STAT MODULATORS AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 63/297,874, filed January 10, 2022 and U.S. Provisional Application No. 63/337,425, filed May 2, 2022, the entire contents of each of which are incorporated herein by reference.

BACKGROUND

[0002] The Signal Transducer and Activator of Transcription (STAT) family of proteins consists of transcription factors that play an essential role in the regulation of cell processes, such as proliferation, differentiation, apoptosis and angiogenesis. Seven STAT genes have been identified in the human genome: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6.

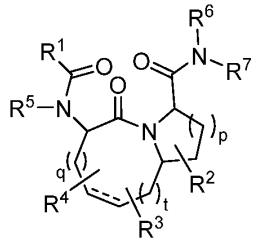
[0003] STAT3 has received particular attention because it is strongly associated with the promotion of tumor growth and immune evasion, and the only STAT family member whose genetic deletion results in embryonic lethality. Indeed, aberrantly elevated STAT3 activity has been estimated to occur in more than 70% of human cancers. Activated STAT3 mediates critical gene expression changes and molecular events that dysregulate cell growth and apoptosis, promote angiogenesis, invasion, metastasis, and the development of resistance to apoptosis, and suppress the host's immune surveillance of the tumor, thereby making constitutively-active STAT3 a critical mediator of carcinogenesis and tumor progression.

[0004] Another STAT protein that has gained recent interest is STAT6. Recent studies have shown that STAT6 signaling is essential for IL-4- and IL-13-induced epithelial mesenchymal transition (EMT) and aggressiveness of colorectal cancer cells (CRC) cells. STAT6 is involved in several aspects of inflammatory disease and other related conditions.

[0005] Given their role in the regulation of cell processes, modulating the activity of one or more STAT proteins, particularly STAT3 and/or STAT6, represent a pivotal area of investigation for the treatment of cancer, inflammatory conditions, and other therapeutic needs.

SUMMARY

[0006] Provided herein are modulators of STAT3 and/or STAT6. Such modulators include those having the structural Formula **I**:



(**I**);

and pharmaceutically acceptable salts and compositions thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, q, t and p are as described herein.

[0007] In one aspect, the disclosed compounds of Formula **I** and pharmaceutically acceptable salts thereof inhibit STAT3 and/or STAT6, and are useful in a variety of therapeutic applications such as, for example, in treating cancer and inflammatory conditions.

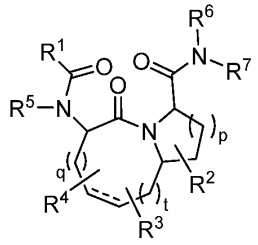
[0008] Pharmaceutical compositions comprising the compounds and pharmaceutically acceptable salts of the disclosed compounds of Formula **I**, as well as methods for their preparation are also included.

[0009] Methods of treating conditions responsive to the modulation of STAT3 and/or STAT6 using the disclosed compounds, pharmaceutically acceptable salts, and compositions thereof are also included.

DETAILED DESCRIPTION

1. *General Description of Compounds*

[0010] In a first embodiment, provided herein is a compound of structural Formula **I**:



(**I**);

or a pharmaceutically acceptable salt thereof, wherein:

q is 0 or 1 and t is 0, 1, or 2, provided that at least one of q or t is 1;

p is 1 or 2;

the dotted line represents a single or double bond;

R^1 is selected from an 8- to 10-membered fused bicyclic heteroaryl substituted with $-CR^{1a}R^{2a}P(O)OR^{1b}OR^{2b}$ or $-CR^{1a}R^{2a}P(O)[OR^{1b}][NH(AA)C(O)OR^T]$, an 8- to 10-membered fused bicyclic heterocyclyl substituted with $-CR^{1a}R^{2a}P(O)OR^{1b}OR^{2b}$ or $-CR^{1a}R^{2a}P(O)[OR^{1b}][NH(AA)C(O)OR^T]$, an aryl substituted with $CR^{1a}R^{2a}P(O)OR^{1b}OR^{2b}$ or –

$CR^{1a}R^{2a}P(O)[OR^{1b}][NH(AA)C(O)OR^{T}]$, a -$(C_1$-$C_4)$alkyl(aryl) wherein said aryl portion of -$(C_1$-$C_4)$alkyl(aryl) is substituted with $–CR^{1a}R^{2a}P(O)OR^{1b}OR^{2b}$ or – $CR^{1a}R^{2a}P(O)[OR^{1b}][NH(AA)C(O)OR^{T}]$, and a -$(C_2$-$C_4)$alkenyl(aryl) wherein said aryl portion of -$(C_2$-$C_4)$alkenyl(aryl) is substituted with $–CR^{1a}R^{2a}P(O)OR^{1b}OR^{2b}$ or – $CR^{1a}R^{2a}P(O)[OR^{1b}][NH(AA)C(O)OR^{T}]$;

R^{1a} and R^{2a} are each absent or are independently selected from hydrogen, cyano, $(C_1$-$C_4)$alkyl, hydroxy$(C_1$-$C_4)$alkyl and fluoro; or R^{1a} and R^{2a} taken together with the carbon they are attached form oxo;

R^{1b} and R^{2b} are each absent or independently selected from hydrogen, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, -[$(C_1$-$C_4)$alkyl]-OC(O)-[$(C_1$-$C_4)$alkyl], -[$(C_1$-$C_4)$alkyl]-C(O)O-[$(C_1$-$C_4)$alkyl], -[$(C_1$-$C_4)$alkyl]-O-[$(C_1$-$C_{20})$alkyl], -[$(C_1$-$C_4)$alkyl]-OC(O)-[halo$(C_1$-$C_4)$alkyl], [$(C_1$-$C_4)$alkyl]-OC(O)O-[5- to 7-membered heterocyclyl], [$(C_1$-$C_4)$alkyl]-OC(O)-[5- to 7-membered heterocyclyl], -[$(C_1$-$C_4)$alkyl]-OC(O)-[$(C_1$-$C_4)$alkyl]-OH, -[$(C_1$-$C_4)$alkyl]-OC(O)-[$(C_1$-$C_4)$alkyl]-O-[$(C_1$-$C_4)$alkyl], -[$(C_1$-$C_4)$alkyl]-OC(O)O-[$(C_1$-$C_4)$alkyl], -[$(C_1$-$C_4)$alkyl]-OC(O)O-[halo$(C_1$-$C_4)$alkyl], -[$(C_1$-$C_4)$alkyl]-OC(O)O-[$(C_1$-$C_4)$alkyl]-OH, -[$(C_1$-$C_4)$alkyl]-OC(O)O-[$(C_1$-$C_4)$alkyl]-O-[$(C_1$-$C_4)$alkyl], -[$(C_1$-$C_4)$alkyl]-SC(O)-[$(C_1$-$C_4)$alkyl], -[$(C_1$-$C_4)$alkyl]-SC(O)-[halo$(C_1$-$C_4)$alkyl], -[$(C_1$-$C_4)$alkyl]-SC(O)-[$(C_1$-$C_4)$alkyl]-OH, -[$(C_1$-$C_4)$alkyl]-SC(O)-[$(C_1$-$C_4)$alkyl]-O-[$(C_1$-$C_4)$alkyl], -[$(C_1$-$C_4)$alkyl]-OC(O)NH$(C_1$-$C_4)$alkyl], -[$(C_1$-$C_4)$alkyl]-OC(O)N[$(C_1$-$C_4)$alkyl]$_2$, 5- to 6- membered heteroaryl, and aryl, wherein said 5- to 6- membered heteroaryl and aryl are each optionally and independently substituted with, as valency permits, 1 to 2 groups selected from halo, cyano, and $(C_1$-$C_4)$alkyl and wherein said 5- to 7-membered heterocyclyl of [$(C_1$-$C_4)$alkyl]-OC(O)O-[5- to 7-membered heterocyclyl] and [$(C_1$-$C_4)$alkyl]-OC(O)-[5- to 7-membered heterocyclyl] are each optionally and independently substituted with, as valency permits 1 to 2 groups selected from $C(O)OR^{h}$;

R^2 is selected from hydrogen, halo, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, hydroxy$(C_1$-$C_4)$alkyl, cyano, and hydroxyl;

R^3 and R^4 are each independently selected from hydrogen, halo, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, hydroxy$(C_1$-$C_4)$alkyl, -$(C_1$-$C_4)$alkylphenyl, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, -$(C_1$-$C_4)$alkyl$(C_1$-$C_4)$alkoxy, hydroxyl, cyano, $-NR^{a}R^{b}$, phenyl, $(C_3$-$C_6)$cycloalkyl, 5- to 6-membered heteroaryl, and 4- to 6-membered heterocyclyl, wherein said phenyl, $(C_3$-$C_6)$cycloalkyl, 5- to 6-membered heteroaryl, and 4- to 6-membered heterocyclyl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^{S};

or R^3 and R^4 are taken together on the same carbon atom to form a $(C_3$-$C_6)$cycloalkyl or a 4- to 6-membered heterocyclyl each optionally substituted with, as valency permits, 1 to

3 groups selected from halo, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, and halo(C_1-C_4)alkoxy;

R^5 and R^6 are each independently selected from hydrogen and (C_1-C_4)alkyl;

R^7 is selected from (C_1-C_4)alkyl, phenyl, 4- to 9-membered monocyclic or bicyclic heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl, wherein said (C_1-C_4)alkyl is optionally substituted with, as valency permits, 1 to 3 groups selected from R^Y and said phenyl, 4- to 9-membered monocyclic or bicyclic heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^Z; or

R^6 and R^7 together with the nitrogen atom to which they are attached form a 4- to 14-membered monocyclic or bicyclic heterocyclyl or a 5- to 12-membered monocyclic or bicyclic heteroaryl, each of which being optionally substituted with, as valency permits, 1 to 3 groups selected from R^Q;

AA is the residue of an alpha or beta natural or non-natural amino acid;

R^T is selected from (C_1-C_4)alkyl, benzyl, and phenyl, wherein said phenyl is optionally substituted with 1 or 2 groups selected from halo, (C_1-C_4)alkyl, and halo(C_1-C_4)alkyl;

R^Q is selected from halo, (C_2-C_4)alkenyl, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, cyano, phenyl, hydroxyl, 4- to 6-membered heterocyclyl, 5- to 10-membered monocyclic or bicyclic heteroaryl, (C_3-C_6)cycloalkyl, oxo, imino, -O(phenyl), -C(O)R^g, -C(O)OR^e, -NHC(O)R^e, -C(O)N$R^c$$R^d$, -N$R^a$$R^b$, -S(O)$R^e$$R^f$, -S(O)$_2$$R^f$, -S(O)=NH($C_1$-$C_4$)alkyl, -S(O)N$R^e$$R^f$, and -S(O)$_2NR^e$$R^f$, wherein said ($C_2$-$C_4$)alkenyl and ($C_1$-$C_4$)alkyl are each optionally and independently substituted with, as valency permits, 1 to 3 groups selected from R^M, and wherein said phenyl, 5- to 10- membered monocyclic or bicyclic heteroaryl, (C_3-C_6)cycloalkyl, and 4- to 6-membered heterocyclyl are each optionally and independently substituted with, as valency permits, 1 to 3 groups selected from R^F;

R^Y is selected from halo, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, cyano, -C(O)R^g, -C(O)OR^e, -NHC(O)R^e, -N$R^a$$R^b$, -S(O)$R^e$$R^f$, -S(O)$_2$$R^f$, -S(O)N$R^e$$R^f$, -S(O)=NH($C_1$-$C_4$)alkyl, -S(O)$_2NR^e$$R^f$, hydroxyl, phenyl, 4- to 6-membered heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl, wherein said phenyl, 4- to 6-membered heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^X;

R^J and R^M are each independently selected from halo, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, cyano, -C(O)R^g, -C(O)OR^e, -NHC(O)R^e, -C(O)N$R^c$$R^d$, -N$R^a$$R^b$, -S(O)$R^e$$R^f$, -

$S(O)_2R^f$, $-S(O)NR^eR^f$, $-S(O)=NH(C_1-C_4)$alkyl, $-S(O)_2NR^eR^f$, hydroxyl, phenyl, 4- to 6-membered heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl, wherein said phenyl, 4- to 6-membered heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^X;

R^F, R^S, R^X, and R^Z are each independently selected from halo, cyano, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, $-(C_1-C_4)$alkyl(C_1-C_4)alkoxy, hydroxy(C_1-C_4)alkyl, $-(C_1-C_4)$alkylphenyl, (C_2-C_4)alkenyl, halo(C_2-C_4)alkenyl, (C_2-C_4)alkynyl, halo(C_2-C_4)alkynyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, hydroxyl, oxo, imino, phenyl, $-S(O)R^eR^f$, $-S(O)_2R^f$, $-S(O)=NH(C_1-C_4)$alkyl, $-S(O)NR^eR^f$, and $-S(O)_2NR^eR^f$, $-C(O)OR^e$, $-NR^cC(O)R^e$, $-C(O)R^g$, $-C(O)NR^cR^d$, and $-NR^aR^b$, wherein said phenyl and said phenyl for the group $-(C_1-C_4)$alkylphenyl are each optionally and independently substituted with, as valency permits 1 to 3 groups selected from halo, cyano, (C_1-C_{10})alkyl, (C_2-C_{10})alkenyl, (C_2-C_{10})alkynyl, halo(C_1-C_{10})alkyl, (C_1-C_{10})alkoxy, and halo(C_1-C_{10})alkoxy, wherein said (C_1-C_{10})alkyl, (C_2-C_{10})alkenyl and (C_2-C_{10})alkynyl are each optionally substituted with, as valency permits a 5-to 10-membered monocyclic or bicyclic heteroaryl or a 4-to 10-membered monocyclic or bicyclic heterocyclyl each of said 5-to 10-membered monocyclic and bicyclic heteroaryl or a 4-to 10-membered monocyclic or bicyclic heterocyclyl being optionally substituted with oxo or a 5- to 7-membered heterocyclyl that is optionally substituted with 1 to 2 oxo; and

R^a, R^b, R^c, R^d, R^e, R^f, R^g, and R^h are each independently selected from, as valency permits, hydrogen, (C_1-C_4)alkyl, phenyl, (C_3-C_6)cycloalkyl, 4- to 6-membered heterocyclyl and 5- to 6-membered heteroaryl, wherein said (C_1-C_4)alkyl is optionally substituted with, as valency permits, 1 to 3 groups selected from R^J, and said phenyl, (C_3-C_6)cycloalkyl, 4- to 6-membered heterocyclyl, and 5- to 6-membered heteroaryl are each independently optionally substituted with, as valency permits, 1 to 3 groups selected from halo, cyano, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, hydroxyl, phenyl, and benzyl.

2. *Definitions*

[0011] When used in connection to describe a chemical group that may have multiple points of attachment, a hyphen (-) designates the point of attachment of that group to the variable to which it is defined. For example, $-NR^cC(O)R^e$ means that the point of attachment for this group occurs on the nitrogen atom.

[0012] The terms "halo" and "halogen" refer to an atom selected from fluorine (fluoro, -F), chlorine (chloro, -Cl), bromine (bromo, -Br), and iodine (iodo, -I).

[0013] Unless otherwise specified, the term "alkyl" when used alone or as part of a larger moiety, such as "haloalkyl", and the like, means saturated straight-chain or branched monovalent hydrocarbon radical.

[0014] The term "haloalkyl" includes mono, poly, and perhaloalkyl groups where the halogens are independently selected from fluorine, chlorine, bromine, and iodine.

[0015] "Alkoxy" means an alkyl radical attached through an oxygen linking atom, represented by –O-alkyl. For example, "(C_1-C_4)alkoxy" includes methoxy, ethoxy, proproxy, and butoxy.

[0016] "Haloalkoxy" is a haloalkyl group which is attached to another moiety via an oxygen atom such as, e.g., $–OCHF_2$ or $–OCF_3$.

[0017] The term "oxo" means the group =O.

[0018] The term "imino" means the group =NH.

[0019] Unless otherwise specified, the term "heteroaryl" refers to a 5- to 12-membered aromatic radical containing 1-4 heteroatoms selected from N, O, and S. In some instances, nitrogen atoms in a heteroaryl may be quaternized. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring", "heteroaryl group", or "heteroaromatic". A heteroaryl group may be mono- or bi-cyclic. Monocyclic heteroaryl includes, for example, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, etc. Bi-cyclic heteroaryls include groups in which a monocyclic heteroaryl ring is fused to one or more aryl or heteroaryl rings. Nonlimiting examples include indolyl, benzooxazolyl, benzooxodiazolyl, indazolyl, benzimidazolyl, benzthiazolyl, benzothiopheneyl, quinolinyl, quinazolinyl, quinoxalinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, pyrrolopyridinyl, thienopyridinyl, thienopyrimidinyl, indolizinyl, purinyl, cinnolinyl, naphthyridinyl, and pteridinyl. It will be understood that when specified, optional substituents on a heteroaryl group may be present on any substitutable position and, include, e.g., the position at which the heteroaryl is attached (where valency permits).

[0020] Unless otherwise specified, the term "heterocyclyl" means a 4- to 12-membered saturated or partially unsaturated heterocyclic ring containing 1 to 4 heteroatoms independently selected from N, O, and S. The terms "heterocycle", "heterocyclyl", "heterocyclyl ring", "heterocyclic group", "heterocyclic moiety", and "heterocyclic radical", are used interchangeably herein. A heterocyclyl ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. A heterocyclyl group may be mono- or bicyclic (e.g., a bridged, fused, or spiro bicyclic ring). Examples of monocyclic

saturated or partially unsaturated heterocyclic radicals include, without limitation, azetidinyl, tetrahydrofuranyl, tetrahydrothienyl, terahydropyranyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, morpholinyl, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, dihydrooxadizolyl, and dihydroisoxazolyl. Bi-cyclic heterocyclyl groups include, *e.g.,* unsaturated heterocyclic radicals fused to another unsaturated heterocyclic radical, cycloalkyl, aryl, or heteroaryl ring, such as for example, benzodioxolyl, dihydrobenzodioxinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, 5-oxa-2,6-diazaspiro[3.4]oct-6-enyl, 6-thia-2,7-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.3]heptanyl, spiro[indoline-3,3'-pyrrolidine]-yl, thiochromanyl, and the like. It will be understood that when specified, optional substituents on a heterocyclyl group may be present on any substitutable position and, include, *e.g*., the position at which the heterocyclyl is attached (where valency permits).

[0021] The term "spiro" refers to two rings that shares one ring atom (e.g., carbon).

[0022] The term "fused" refers to two rings that share two adjacent ring atoms with one another.

[0023] The term "bridged" refers to two rings that share three adjacent ring atoms with one another.

[0024] The term "aryl" refers to an aromatic carbocyclic single ring or two fused ring system containing 6 to 10 carbon atoms. Examples include phenyl, indanyl, tetrahydronaphthalene, and naphthyl. In one aspect, the aryl is phenyl or naphthyl.

[0025] The terms "cycloalkyl", used alone or as part of a larger moiety, refers to a saturated cyclic aliphatic monocyclic or bicyclic ring system, as described herein, having from, unless otherwise specified, 3 to 10 carbon ring atoms. Monocyclic cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, and cyclooctyl. It will be understood that when specified, optional substituents on a cycloalkyl or cycloaliphatic group may be present on any substitutable position and, include, e.g., the position at which the cycloalkyl group is attached.

[0026] The "residue of an amino acid" is the moiety remaining after formation of a bond between a reactive group in another compound (e.g., an amino group) and the carboxylic acid in the amino acid, after formation of a bond between a reactive group in another compound (e.g., a carboxylic acid) and the amino group in the amino acid, or both. As a consequence of the bond(s) formation, the carboxylic acid in the amino acid no longer has the OH group and

instead has a bond between the carbonyl group and the reactive group in the compound; the amino group has only one hydrogen atom and instead has a bond between the reactive group in the other compound and the nitrogen of the amino group; or both. For example, the "residue of an alpha amino acid" can be depicted structurally as $NH_2CR'R$-C(O)-, -NHCR'R-C(O)OH or -NHCR'R-C(O)-; and the "residue of an beta amino acid" can be depicted structurally as or $NH_2CR'RCH_2$-C(O)-, -NHCR'RCH_2-C(O)OH or -NHCR'RCH_2-C(O)-, where R' is H or C_1-C_6 alkyl and R is H or C_1-C_6 alkyl optionally substituted with 1 to 3 groups selected from halo, (C_1-C_3)alkoxy, OH, NH_2, -NH(C_1-C_4 alkyl), -N[(C_1-C_4 alkyl)]$_2$, SH, S(C_1-C_4 alkyl), imino, COOH, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl)phenyl, phenyl, and 5- to 10-membered heteroaryl, wherein said C_1-C_6 alkyl may also be optionally interrupted by a sulfur or nitrogen heteroatom and wherein said phenyl is optionally substituted with 1 to 3 groups selected from OH, cyano, (C_1-C_4 alkyl), and halo(C_1-C_4 alkyl); or R is taken together with the nitrogen atoms from the alpha or beta amino acid residue to form a 4- to 6-membered heterocyclyl. For naturally occurring alpha amino acid (i.e., amino acids that occur in nature), R' is H and R is selected from hydrogen, methyl, isopropyl, -$CH_2CH(CH_3)_2$, -$(CH_2)_2SCH_3$, -$CH(CH_3)(CH_2CH_3)$, CH_2OH, -$CH(OH)(CH_3)$, CH_2SH, -$CH_2C(O)NH_2$, -$(CH_2)_2C(O)NH_2$, benzyl, p-hydroxybenzyl, -CH_2(indolyl), -$(CH_2)_4NH_2$, -$(CH_2)_3NHC(=NH_2)NH_2$, -CH_2(imidazolyl), -(CH_2)COOH, and -$(CH_2)_2$COOH; or R taken together with the nitrogen atom of the alpha or beta amio acid residue forms a pyrrolidinyl ring.

[0027] Non-natural amino acids are known in the art and include e.g., alpha-alkyl amino acids (e.g., alpha methyl), alpha-alkylalkoxy amino acids (e.g., alpha -CH_2OCH_3), N-methyl amino acids, homo-amino acids, etc.

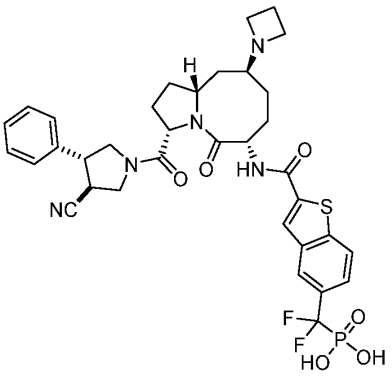
[0028] Compounds having one or more chiral centers can exist in various stereoisomeric forms. Stereoisomers are compounds that differ only in their spatial arrangement. Stereoisomers include all diastereomeric, enantiomeric, and epimeric forms as well as racemates and mixtures thereof. A "geometric isomer" refers to isomers that differ in the orientation of substituent group in relationship to a carbon-carbon double bond, a cycloalkyl ring, or a bridged bicyclic system. Atoms (other than H) on each side of a carbon-carbon double bond may be in an E (substituents are on opposite sides of the carbon-carbon double bond) or Z (substituents are oriented on the same side) configuration. "Cis" refers to substituents oriented on the same side of the ring, whereas "trans" refers to substituents oriented on opposite sides of the ring.

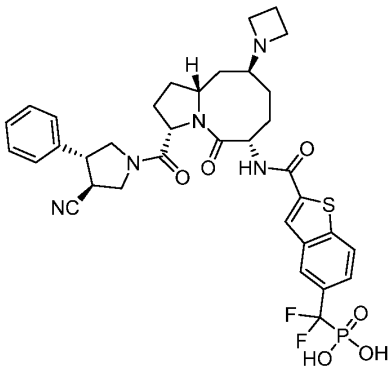
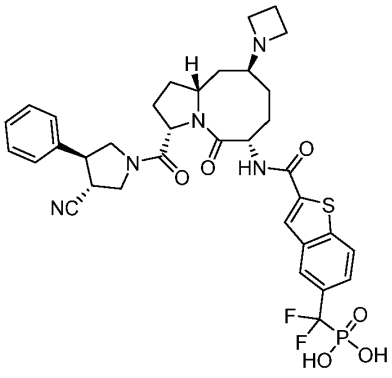
[0029] When the stereochemical configuration at a chiral center in a compound having one or more chiral centers is depicted by its chemical name (e.g., where the configuration is indicated in the chemical name by "R" or "S") or structure (e.g., the configuration is indicated by "wedge" bonds), the enrichment of the indicated configuration relative to the opposite configuration is greater than 50%, 60%, 70%, 80%, 90%, 99% or 99.9%. "Enrichment of the indicated configuration relative to the opposite configuration" is a mole percent and is determined by dividing the number of compounds with the indicated stereochemical configuration at the chiral center(s) by the total number of all of the compounds with the same or opposite stereochemical configuration in a mixture.

[0030] When a geometric isomer is depicted by name or structure, the enrichment of the indicated isomer relative to the opposite isomer is greater than 50%, 60%, 70%, 80%, 90%, 99% or 99.9%. "Enrichment of the indicated isomer relative to the opposite isomer" is a mole percent and is determined by dividing the number of compounds with the indicated geometrical configuration by the total number of all of the compounds with the same or opposite geometrical configuration in a mixture.

[0031] When a disclosed compound is named or depicted by structure without indicating stereochemistry, it is understood that the name or the structure encompasses one of the possible stereoisomers or geometric isomers free of the others, or a mixture of the encompassed stereoisomers or geometric isomers.

[0032] In certain instances, compounds were isolated and tested as a 1:1 mixture of diastereomers. In such cases, the relative stereochemistry is denoted by the term "rel-" in the compound name and by the use of flat bonds instead of wedges. For example, ((2-(((3S,6S,9S,10aR)-9-(azetidin-1-yl)-3-(*rel*-(trans)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid, having the structure:

 means that the substituents about the pyrrolidine ring are trans and encompass a mixture of both diastereomers

 and  .

[0033] The terms "subject" and "patient" may be used interchangeably, and means a mammal in need of treatment, *e.g.*, companion animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, pigs, horses, sheep, goats and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs and the like). Typically, the subject is a human in need of treatment.

[0034] The term "inhibit," "inhibition" or "inhibiting" includes a decrease in the baseline activity of a biological activity or process.

[0035] As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some aspects, treatment may be administered after one or more symptoms have developed, *i.e.*, therapeutic treatment. In other aspects, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of exposure to a particular organism, or other susceptibility factors), *i.e.*, prophylactic treatment. Treatment may also be continued after symptoms have resolved, for example to delay their recurrence.

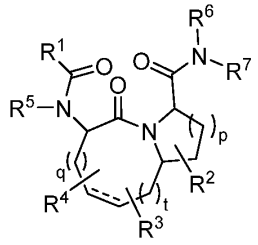
[0036] The term "pharmaceutically acceptable carrier" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions described herein include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0037] For use in medicines, the salts of the compounds described herein refer to non-toxic "pharmaceutically acceptable salts." Pharmaceutically acceptable salt forms include pharmaceutically acceptable acidic/anionic or basic/cationic salts. Suitable pharmaceutically acceptable acid addition salts of the compounds described herein include e.g., salts of inorganic acids (such as hydrochloric acid, hydrobromic, phosphoric, nitric, and sulfuric acids) and of organic acids (such as, acetic acid, benzenesulfonic, benzoic, methanesulfonic, and p-toluenesulfonic acids). Compounds of the present teachings with acidic groups such as carboxylic acids can form pharmaceutically acceptable salts with pharmaceutically acceptable base(s). Suitable pharmaceutically acceptable basic salts include e.g., ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts). Compounds with a quaternary ammonium group also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like. Other examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, benzoates and salts with amino acids such as glutamic acid.

[0038] The term "effective amount" or "therapeutically effective amount" refers to an amount of a compound described herein that is sufficient to achieve the desired therapeutic effect (such as treatment of a condition recited herein) under the conditions of administration e.g., a dosage of between 0.01 - 100 mg/kg body weight/day.

3. ***Compounds***

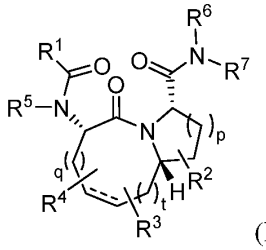
[0039] In a first embodiment, provided is a compound of structural Formula **I**:



(**I**);

or a pharmaceutically acceptable salt thereof, wherein the variables are as described above.

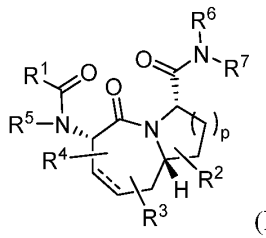
[0040] In a second embodiment, the compound of Formula **I** is of the structural Formula **II**:



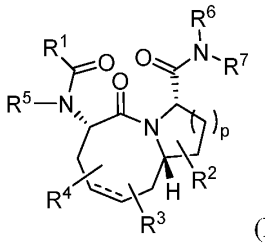
(**II**);

or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula **I**.

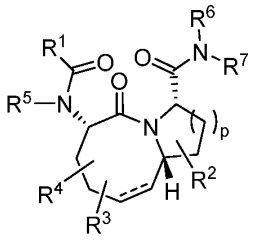
[0041] In a third embodiment, the compound of Formula **I** is of the structural Formula **III**, **IV**, **V**, or **VII**:



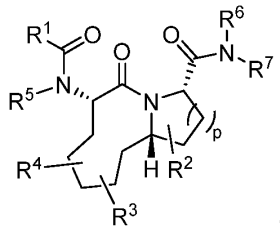
(**III**),



(**IV**),

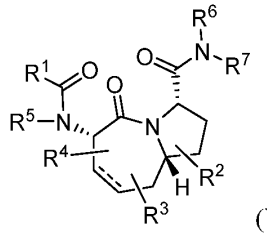
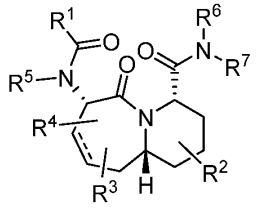
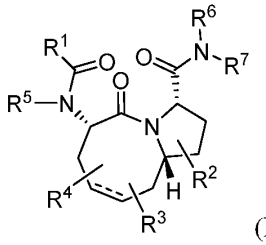
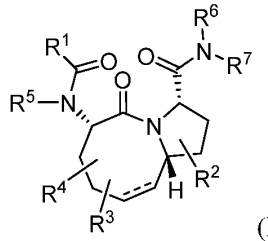
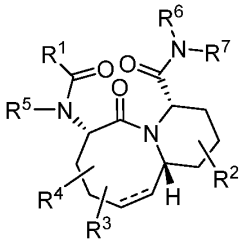
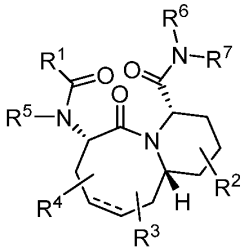
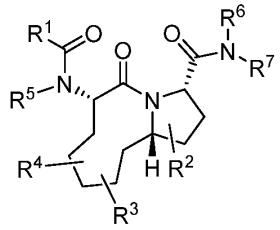


(**V**), or

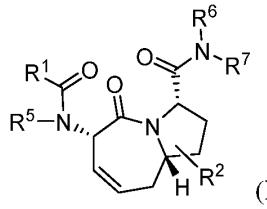
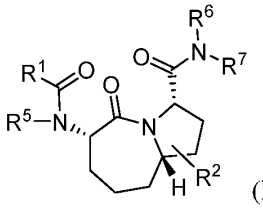
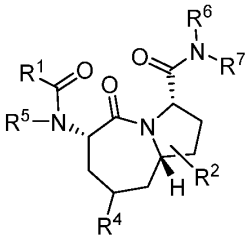
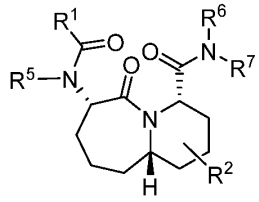
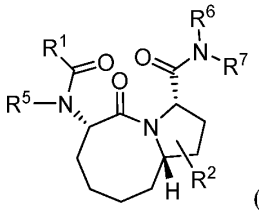
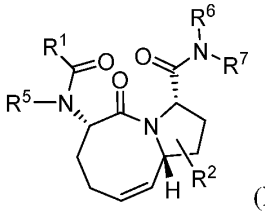


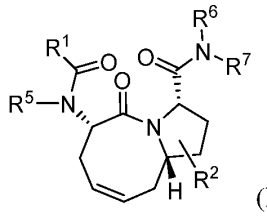
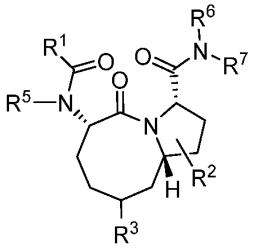
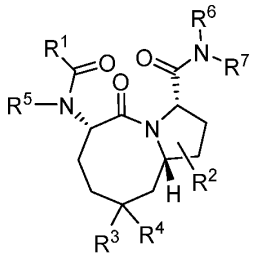
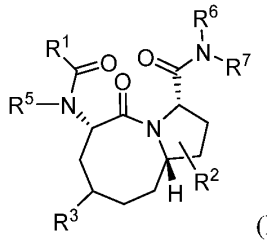
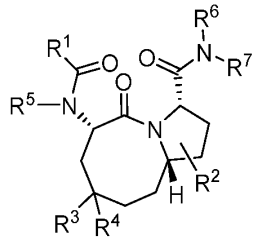
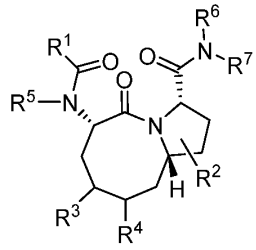
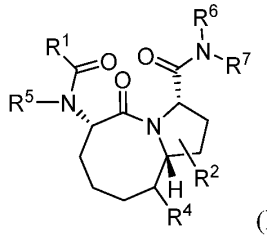
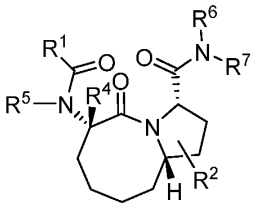
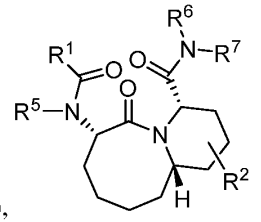
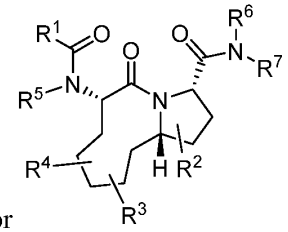
(**VII**); or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula **I**.

[0042] In a fourth embodiment, the compound of Formula **I** is of the structural Formula **VIII**, **VIII'**, **IX**, **X**, **XI, XII**, or **XIII**:

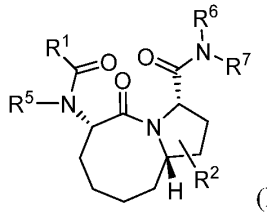
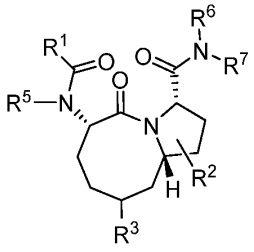
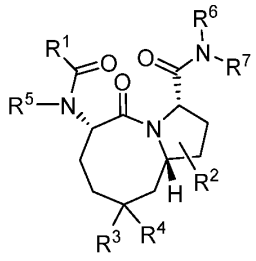
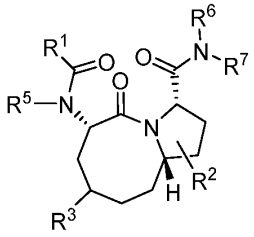
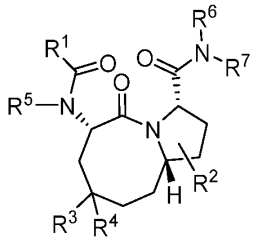
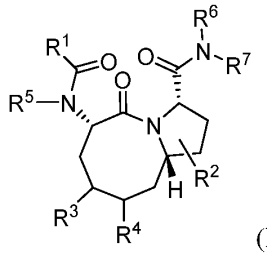
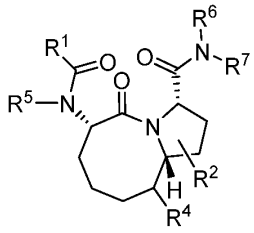
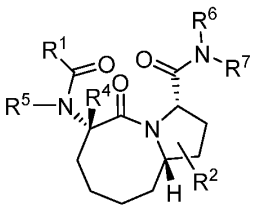

(**VIII**),

(**VIII'**),

(**IX**),

(**X**),

(**XI**),

(**XII**), or

(**XIII**); or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula **I**.

[0043] In a sixth embodiment, the compound of Formula **I** is of the structural Formula **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, or **XXVIII**:


(**XIV**),

(**XV**),

(**XVI**),

(**XVI'**),

(**XVII**),

(**XVIII**),


(**XX**),

(**XXI**),

(**XXII**),

(**XXIII**),

(**XXIV**),

(**XXV**),

(**XXVI**),

(**XXVII**),


(**XXVIII**), or
(**XXIX**); or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula **I**.

[0044] In a seventh embodiment, the compound of Formula **I** is of the structural Formula **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXVII**:


(**XXX**),

(**XXXI**),

(**XXXII**),

(**XXXIII**),

(**XXXIV**),

(**XXXV**),

(**XXXVI**), or

(**XXXVII**); or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula **I**.

[0045] In an eighth embodiment, R^3 in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **IX**, **X**, **XI, XII**, **XIII**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXIX**, **XXXI**, **XXXII**, **XXXIII**, **XXXIV**, and **XXXV** is selected from hydrogen, (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylphenyl, and 4- to 6-membered heterocyclyl, wherein the remaining variables are as described above for Formula **I**. Alternatively, as part of an eighth embodiment, R^3 in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **IX**, **X**, **XI, XII**, **XIII**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXIX**, **XXXI**, **XXXII**, **XXXIII**, **XXXIV**, and **XXXV** is selected from hydrogen, (C_1-C_2)alkyl, hydroxyl, (C_1-C_2)alkoxy, benzyl, and azetidinyl, wherein the remaining variables are as described above for Formula **I**.

[0046] In a ninth embodiment, R^4 in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **IX**, **X**, **XI, XII**, **XIII**, **XVI**, **XXII**, **XXIV**, **XXVI**, **XXIX**, **XXXII**, **XXXIV**, **XXXV**, and **XXXVI** is selected from hydrogen (C_1-C_4)alkyl, and hydroxyl, wherein the remaining variables are as described above for Formula **I**.

[0047] In a tenth embodiment, R^3 and R^4 in the compound of any one of Formulae

I, **II**, **III**, **IV**, **V**, **VII, VIII**, **IX**, **X**, **XI, XII**, **XIII**, **XVI**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXIX**, **XXXI**, **XXXII**, **XXXIII**, **XXXIV**, **XXXV,** and **XXXVI** are hydrogen, wherein the remaining variables are as described above for Formula **I**.

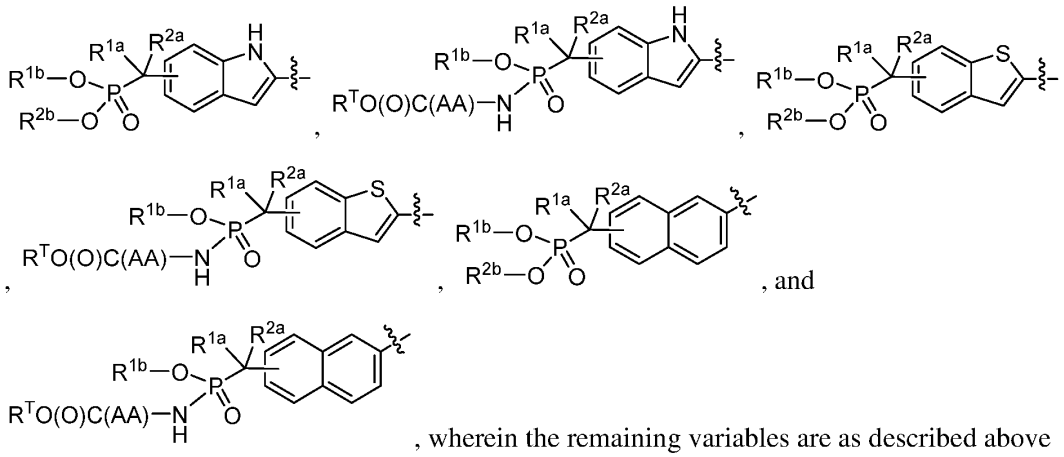
[0048] In an eleventh embodiment, R^3 and R^4 in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **IX**, **X**, **XI, XII**, **XIII**, **XVI**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXIX**, **XXXI**, **XXXII**, **XXXIII**, **XXXIV**, **XXXV,** and **XXXVI** are taken together on the same carbon atom to form a (C_3-C_6)cycloalkyl, wherein the remaining variables are as described above for Formula **I**. Alternatively, as part of an eleventh embodiment, R^3 and R^4 in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **IX**, **X**, **XI, XII**, **XIII**, **XVI**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXIX**, **XXXI**, **XXXII**, **XXXIII**, **XXXIV**, **XXXV,** and **XXXVI** are taken together on the same carbon atom to form cyclopropyl, wherein the remaining variables are as described above for Formula **I**.

[0049] In a twelfth embodiment, R^2 in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is selected from hydrogen and hydroxyl, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through eleventh embodiments. Alternatively, as part of a twelfth embodiment, R^2 in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is hydrogen, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through eleventh embodiments.

[0050] In a thirteenth embodiment, R^5 in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **VIII'**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is hydrogen, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through twelfth embodiments.

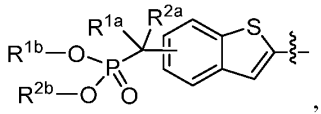
[0051] In a fourteenth embodiment, R^1 in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is selected from 8- to 10-membered fused bicyclic heteroaryl and aryl, each of which are substituted with $-CR^{1a}R^{2a}P(O)OR^{1b}OR^{2b}$ or $-CR^{1a}R^{2a}P(O)[OR^{1b}][NH(AA)C(O)OR^{T}]$, wherein the remaining variables are as described

above for Formula **I** or any one of the eighth through thirteenth embodiments. Alternatively, as part of a fourteenth embodiment, R^1 in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is selected from benzothiophenyl, indolyl, and naphthalenyl, each of which are substituted with $-CR^{1a}R^{2a}P(O)OR^{1b}OR^{2b}$ or $-CR^{1a}R^{2a}P(O)[OR^{1b}][NH(AA)C(O)OR^{T}]$, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through thirteenth embodiments. In another alternative, as part of a fourteenth embodiment, R^1 in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is selected from



, and

, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through thirteenth embodiments. In yet another alternative, as part of a fourteenth embodiment, R^1 in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is



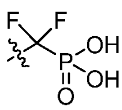
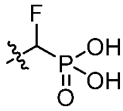
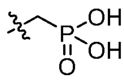
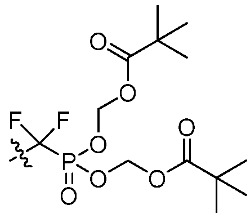
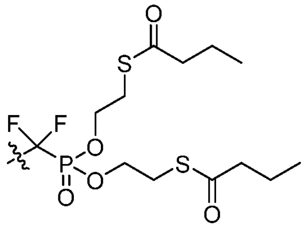
, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through thirteenth embodiments.

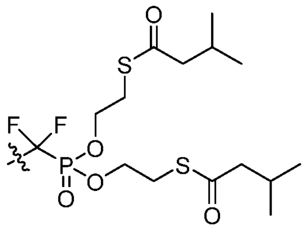
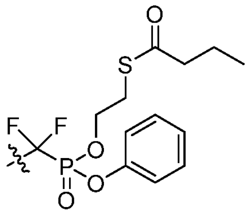
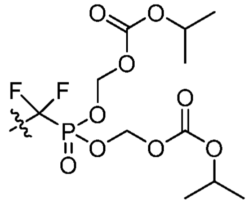
[0052] In a fifteenth embodiment, R^{1a} in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII,**

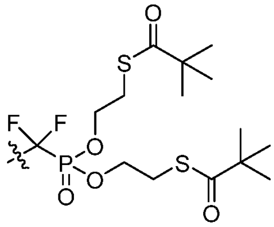
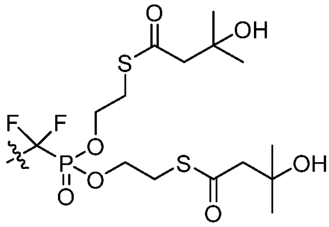
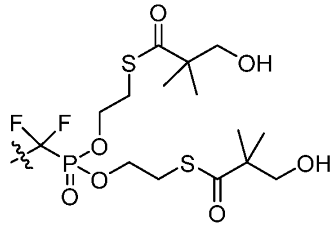
XXXIII XXXIV, **XXXV**, **XXXVI**, or **XXXVII** is hydrogen and R^{2a} is fluoro or R^{1a} is fluoro and R^{2a} is fluoro, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through fourteenth embodiments. Alternatively, as part of a fifteenth embodiment, R^{1a} in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is fluoro and R^{2a} is fluoro, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through fourteenth embodiments.

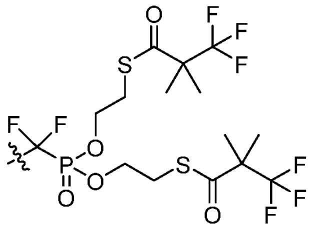
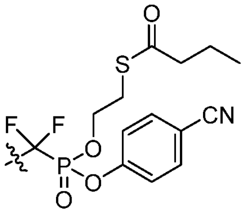
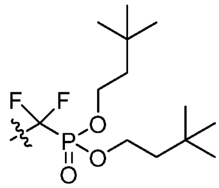
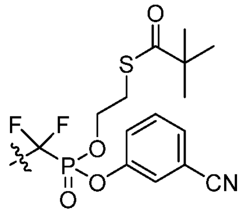
[0053] In a sixteenth embodiment, R^{1b} and R^{2b} in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** are each independently selected from hydrogen, (C_1-C_4)alkyl, -[(C_1-C_4)alkyl]-OC(O)-[(C_1-C_4)alkyl], -[(C_1-C_4)alkyl]-OC(O)O-[(C_1-C_4)alkyl], -[(C_1-C_4)alkyl]-SC(O)-[(C_1-C_4)alkyl], -[(C_1-C_4)alkyl]-SC(O)-[halo(C_1-C_4)alkyl], -[(C_1-C_4)alkyl]-SC(O)-[(C_1-C_4)alkyl]-OH, phenyl, pyridinyl, and naphthalenyl, wherein said phenyl, pyridinyl, and naphthalenyl are each optionally and independently substituted with cyano, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through fifteenth embodiments. Alternatively, as part of a sixteenth embodiment, R^{1b} and R^{2b} in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** are each -[(C_1-C_4)alkyl]-OC(O)-[(C_1-C_4)alkyl], wherein the remaining variables are as described above for Formula **I** or any one of the eighth through fifteenth embodiments. In another alternative, as part of a sixteenth embodiment, R^{1b} and R^{2b} in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** are each hydrogen, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through fifteenth embodiments.

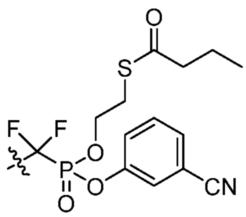
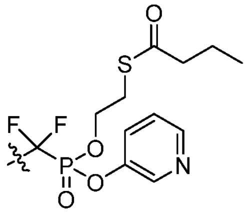
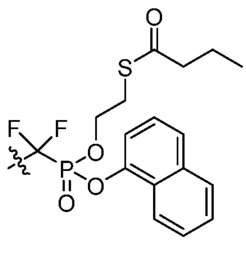
[0054] In a seventeenth embodiment, $-CR^{1a}R^{2a}P(O)OR^{1b}OR^{2b}$ in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is selected from

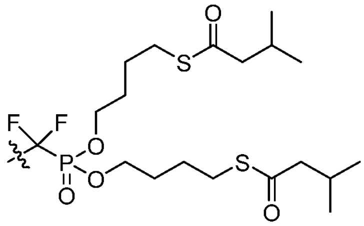
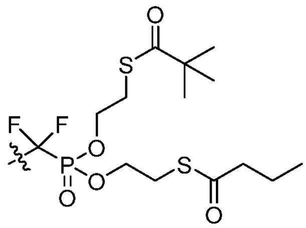
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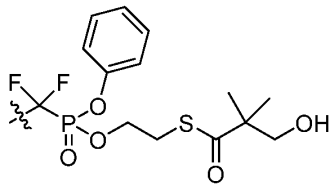
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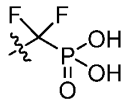
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, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through sixteenth embodiments. Alternatively, as part of a seventeenth embodiment, $-CR^{1a}R^{2a}P(O)OR^{1b}OR^{2b}$ in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is  , wherein the remaining variables are as described above for Formula **I** or any one of the eighth through sixteenth embodiments.

[0055] In an eighteenth embodiment, $-NH[AA]C(O)OR^T$ in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is $-NHC(R')(R)C(O)R^T$ or $-NHC(R')(R)CH_2C(O)R^T$, wherein R' is hydrogen, $(C_1\text{-}C_3)$alkyl, or $(C_1\text{-}C_3)$alkyl$(C_1\text{-}C_3)$alkoxy and R is selected from hydrogen, methyl, isopropyl, $-CH_2CH(CH_3)_2$, $-(CH_2)_2SCH_3$, $-CH(CH_3)(CH_2CH_3)$, CH_2OH, $-CH(OH)(CH_3)$, CH_2SH, $-CH_2C(O)NH_2$, $-(CH_2)_2C(O)NH_2$, benzyl, p-hydroxybenzyl, $-CH_2$(indolyl), $-(CH_2)_4NH_2$, $-(CH_2)_3NHC(=NH_2)NH_2$, $-CH_2$(imidazolyl), $-(CH_2)COOH$, and $-(CH_2)_2COOH$; or R taken together with the nitrogen atom of $-NHC(R')(R)C(O)R^T$ or $-NHC(R')(R)CH_2C(O)R^T$ forms a pyrrolidinyl ring, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through seventeenth embodiments.

[0056] In a nineteenth embodiment, R^7 in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is selected from $(C_1\text{-}C_4)$alkyl, phenyl, 5- or 6-membered monocyclic heterocyclyl, 9- or 10-membered fused bicyclic heterocyclyl, 5- or 6-membered monocyclic heteroaryl, and 9- or 10-membered fused bicyclic heteroaryl, wherein said $(C_1\text{-}C_4)$alkyl is optionally substituted with, as valency permits, 1 to 3 groups selected from R^Y and said phenyl, 5- or 6-membered monocyclic heterocyclyl, 9- or 10-membered fused bicyclic heterocyclyl, 5- or 6-membered monocyclic heteroaryl, and 9- or

10-membered fused bicyclic heteroaryl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^Z, and wherein the remaining variables are as described above for Formula **I** or any one of the eighth through fourteenth and eighteenth embodiments. Alternatively, as part of a nineteenth embodiment, R^7 in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is selected from (C_1-C_4)alkyl, phenyl, pyrrolidinyl, thiochromanyl, dihydrobenzo[b]thiophenyl, pyridinyl, indazolyl, cinnolinyl, and quinolinyl, wherein said (C_1-C_4)alkyl is optionally substituted with, as valency permits, 1 to 3 groups selected from R^Y and said phenyl, pyrrolidinyl, thiochromanyl, dihydrobenzo[b]thiophenyl, pyridinyl, indazolyl, cinnolinyl, and quinolinyl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^Z, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through eighteenth embodiments.

[0057] In a twentieth embodiment, R^Y in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is selected from halo, hydroxyl, phenyl, 4- to 6-membered heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl, wherein said phenyl, 4- to 6-membered heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^X, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through nineteenth embodiments. Alternatively, as part of a a twentieth embodiment, R^Y in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is selected from halo, hydroxyl, 4- to 6-membered heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl, wherein said 4- to 6-membered heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^X, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through nineteenth embodiments.

[0058] In a twenty-first embodiment, R^Y in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**,

XXI, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII**, **XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is selected from -C(O)NH_2, -C(O)N(C_1-C_4)alkyl[phenyl]$_2$, hydroxyl, phenyl, imidazolyl, 1,2-dihydropyridinyl, pyridinyl, and pyrazolo[3,4-b]pyridinyl, wherein said phenyl, imidazolyl, 1,2-dihydropyridinyl, pyridinyl, and pyrazolo[3,4-b]pyridinyl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^X, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through twentieth embodiments. Alternatively, as part of a twenty-first embodiment, R^Y in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is selected from hydroxyl, imidazolyl, 1,2-dihydropyridinyl, pyridinyl, and pyrazolo[3,4-b]pyridinyl, wherein said phenyl, imidazolyl, 1,2-dihydropyridinyl, pyridinyl, and pyrazolo[3,4-b]pyridinyl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^X, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through twentieth embodiments.

[0059] In a twenty-second embodiment, R^Z in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is selected from phenyl, -C(O)(C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkyl, halo, cyano, and (C_1-C_4)alkoxy, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through twentieth-first embodiments.

[0060] In a twenty-third embodiment, R^6 and R^7 in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** together with the nitrogen atom to which they are attached form 4- to 6-membered monocyclic heterocyclyl, 7- to 13-membered spiro bicyclic heterocyclyl, or 9- to 10-membered fused bicyclic heterocyclyl, each of which being optionally substituted with, as valency permits, 1 to 3 groups selected from R^Q, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through eighteenth embodiments. Alternatively, as part of a twenty- third embodiment, R^6 and R^7 in the compound of any one of Formulae **XVI'**, together with the nitrogen atom to which they are attached form pyrrolidinyl, azetidinyl, piperazinyl, 5-oxa-2,6-diazaspiro[3.4]oct-6-enyl, 6-thia-2,7-diazaspiro[3.4]octanyl, 2-thia-6-azaspiro[3.3]heptanyl, 4-azaspiro[2.4]heptanyl,

spiro[indoline-3,3'-pyrrolidinyl], or 1,2,3,4,5,6-hexahydro-2,6-naphthyridinyl, each of which being optionally substituted with, as valency permits, 1 to 3 groups selected from R^Q, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through eighteenth embodiments. In another alternative, as part of a twenty- third embodiment, R^6 and R^7 in the compound of any one of Formulae **XVI'**, together with the nitrogen atom to which they are attached form pyrrolidinyl or azetidinyl, each of which being optionally substituted with, as valency permits, 1 to 3 groups selected from R^Q, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through eighteenth embodiments.

[0061] In a twenty-fourth embodiment, R^Q in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is selected from halo, $(C_2$-$C_4)$alkenyl, $(C_1$-$C_4)$alkyl, cyano, phenyl, hydroxyl, 4- to 6-membered heterocyclyl, 5- to 10-membered monocyclic or bicyclic heteroaryl, $(C_3$-$C_6)$cycloalkyl, oxo, imino, -O(phenyl), $-C(O)R^g$, $-NHC(O)R^e$, $-S(O)=NH(C_1$-$C_4)$alkyl, and $-S(O)_2NR^eR^f$, wherein said $(C_2$-$C_4)$alkenyl and $(C_1$-$C_4)$alkyl are each optionally and independently substituted with, as valency permits, 1 to 3 groups selected from R^M, and wherein said phenyl, 4- to 6-membered heterocyclyl, 5- to 10-membered monocyclic or bicyclic heteroaryl, and $(C_3$-$C_6)$cycloalkyl are each optionally and independently substituted with, as valency permits, 1 to 3 groups selected from R^F, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through twentieth-third embodiments. Alternatively, as part of a twenty- fourth embodiment, R^Q in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is selected from halo, $(C_2$-$C_4)$alkenyl, $(C_1$-$C_4)$alkyl, cyano, phenyl, hydroxyl, morpholinyl, dihydropyridinyl, tetrahydro-2H-thiopyranyl, pyridinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, triazolyl, indazolyl, benzoimidazolyl, pyrazolo[3,4-b]pyridinyl, cyclohexyl, cyclopropyl, oxo, imino, -O(phenyl), $-C(O)R^g$, $-NHC(O)R^e$, $-S(O)=NH(C_1$-$C_4)$alkyl, and $-S(O)_2NR^eR^f$, wherein said $(C_2$-$C_4)$alkenyl and $(C_1$-$C_4)$alkyl are each optionally and independently substituted with, as valency permits, 1 to 3 groups selected from R^M, and wherein said phenyl, morpholinyl, dihydropyridinyl, tetrahydro-2H-thiopyranyl, pyridinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, triazolyl, indazolyl, benzoimidazolyl, pyrazolo[3,4-b]pyridinyl, cyclohexyl, and cyclopropyl are each optionally and independently substituted

with, as valency permits, 1 to 3 groups selected from R^F, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through twentieth-third embodiments.

[0062] In a twenty-fifth embodiment, R^M in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is selected from 4- to 6-membered heterocyclyl, 5- to 6-membered monocyclic heteroaryl, -S(O)=NH(C_1-C_4)alkyl, cyano, and phenyl, wherein said 4- to 6-membered heterocyclyl, 5- to 6-membered monocyclic heteroaryl, and phenyl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^X, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through twentieth-fourth embodiments. Alternatively, as part of a twenty-fifth embodiment, R^M in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is selected from tetrahydropyranyl, pyrazolyl, -S(O)=NH(C_1-C_4)alkyl, cyano, and phenyl, wherein said tetrahydropyranyl, pyrazolyl, and phenyl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^X, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through twentieth-fourth embodiments.

[0063] In a twenty-sixth embodiment, R^X in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, and oxo, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through twentieth-fifth embodiments.

[0064] In a twenty-seventh embodiment, R^F in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is selected from halo, (C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_2-C_4)alkynyl, cyano, oxo, and imino, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through twentieth-sixth embodiments.

[0065] In a twenty-eighth embodiment, R^g in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** is selected from (C_1-C_4)alkyl, morpholinyl, imidazolyl, benzyl, and cyclopropyl, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through twentieth-seventh embodiments.

[0066] In a twenty-ninth embodiment, R^e and R^f in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** are each independently selected from (C_1-C_4)alkyl and halo(C_1-C_4)alkyl, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through twentieth-eighth embodiments.

[0067] In a thirtieth embodiment, R^c and R^d in the compound of any one of Formulae **I**, **II**, **III**, **IV**, **V**, **VII, VIII**, **VIII'**, **IX**, **X**, **XI, XII**, **XIII**, **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXXVII** are each independently selected from hydrogen and (C_1-C_4)alkyl, wherein the remaining variables are as described above for Formula **I** or any one of the eighth through tweny-ninth embodiments. Compounds having the Formula **I** are further disclosed in the Exemplification and are included in the present disclosure. Pharmaceutically acceptable salts thereof as well as the neutral forms are included.

4. *Uses, Formulation and Administration*

[0068] The compounds and compositions described herein are generally useful for modulating the activity of STAT proteins, in particular STAT3 and/or STAT6. In some aspects, the compounds, pharmaceutical acceptable salts, and pharmaceutical compositions described herein inhibit the activity STAT3 and/or STAT6.

[0069] In some aspects, the compounds and pharmaceutical compositions described herein are useful in a condition responsive to the modulation of STAT3 and/or STAT6. Thus, provided herein are methods of treating a condition responsive to the modulation (e.g., inhibition) of STAT3 and/or STAT6 in a subject, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a disclosed compound or pharmaceutically acceptable salt thereof.

[0070] Also provided is the use of a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a disclosed compound or pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a condition responsive to the modulation (e.g., inhibition) of STAT3 and/or STAT6. Also provided is a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a disclosed compound or pharmaceutically acceptable salt thereof, for use in treating a condition responsive to the modulation (e.g., inhibition) of STAT3 and/or STAT6.

[0071] In one aspect, the condition responsive to the modulation (e.g., inhibition) of STAT3 and/or STAT6 include, but are not limited to, cancer, a neurodegenative disorder, a viral disease, an autoimmune disease, an inflammatory disorder, a hereditary disorder, a hormone-related disease, a metabolic disorder, conditions associated with organ transplantation, immunodeficiency disorders, a destructive bone disorder, a proliferative disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, liver disease, pathologic immune conditions involving T cell activation, a cardiovascular disorder, or a CNS disorder.

[0072] In another aspect, the condition responsive to the modulation (e.g., inhibition) of STAT3 and/or STAT6 include, but are not limited to, cancer (see, e.g., Turkson & Jove, Oncogene 2000, 19:6613-6626), diabetes (see. e.g., Gurzov et al., FEBS 2016, 283:3002), cardiovascular disease (see, e.g., Grote et al., Vasc. Pharmacol. 2005, 43:2005), viral disease (see, e.g., Gao et al., J Hepatol. 2012, 57(2):430), autoimmune diseases such as lupus (see, e.g., Goropevsek et al., Clin. Rev. Alleg. & Immun. 2017, 52(2):164), and rheumatoid arthritis (see, e.g., Walker & Smith, J. Rheumat. 2005, 32(9): 1650), autoinflammatory syndromes (see, e.g., Rauch et al., Jak-Stat 2013, 2(l):e23820), atherosclerosis (see, e.g., Ortiz-Munoz et al., Arterio., Thromho., Vase. Bio. 2009, 29:525), psoriasis (see, e.g., Andres et al., Exp. Derm. 2013, 22(5):323), allergic disorders (see, e.g., Oh et al., Eur. Respir. Rev. 2019, 19(115):46), inflammatory bowel disease (see. e.g., Sugimoto, World J Gastroenterol. 2008, 14(33):5110), inflammation (see, e.g., Tamiya et al., Arierio. Thrombo., Vasc. Bio. 2011, 31:980), acute and chronic gout and gouty arthritis, neurological disorders (see, e.g., Campbell, Brain Res. Rev. 2005, 48(2): 166), metabolic syndrome, immunodeficiency disorders such as AIDS and HIV (see, e.g., O'Shea et al., N. Engl. J.Med. 2013, 368:161), destructive bone disorders (see, e.g., Jatiani et al., Genes & Can. 2011, 1(10):979), osteoarthritis, proliferative disorders, Waldenstrom's Macroglobulinemia (see,

e.g., Hodge et al., Blood 2014, 123(7):1055) infectious diseases, conditions associated with cell death, pathologic immune conditions involving T cell activation, and CNS disorders.

[0073] Proliferative disorders, include, but are not limited to a benign or malignant tumor, solid tumor, liquid tumor, carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina, cervix, testis, genitourinary tract, esophagus, larynx, skin, bone or thyroid, sarcoma, glioblastomas, neuroblastomas, multiple myeloma, gastrointestinal cancer, especially colon carcinoma or colorectal adenoma, a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, adenoma, adenocarcinoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small-cell lung carcinoma, lymphomas, Hodgkins and Non-Hodgkins, a mammary carcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, an IL-I driven disorder, an MyD88 driven disorder, Smoldering of indolent multiple myeloma, or hematological malignancies (including leukemia, diffuse large B-cell lymphoma (DLBCL), ABC DLBCL, chronic lymphocytic leukemia (CLL), chronic lymphocytic lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenstrom's macroglobulinemia (WM), splenic marginal zone lymphoma, multiple myeloma, plasmacytoma, intravascular large B-cell lymphoma).

[0074] In some embodiments, the cancer to be treated is selected from glioma, breast cancer, prostate cancer, head and neck squamous cell carcinoma, skin melanomas, ovarian cancer, malignant peripheral nerve sheath tumors (MPNST), and pancreatic cancer. In other embodiments, the cancer to be treated is cancer selected from glioma, breast cancer, prostate cancer, head and neck squamous cell carcinoma, skin melanomas, ovarian cancer, malignant peripheral nerve shealth tumors (MPNST), pancreatic cancer, non-small cell lung cancer (NSCLC) including EGFR-mutant NSCLC, urothelial cancer, liver cancer, bile duct cancer, kidney cancer, colon cancer, esophageal cancer, gastric cancer, gastrointestinal stromal tumors, and hematological malignancies include lymphomas, leukemias, myelomas, myeloproliferative neoplasms and myelodysplastic syndromes. In other embodiments, the cancer is selected from solid tumors (e.g., prostate cancer, renal cancer, hepatic cancer, pancreatic cancer, gastric cancer, breast cancer, lung cancer, cancers of the head and neck, thyroid cancer, glioblastoma, Kaposi's sarcoma, Castleman's disease, uterine leiomyosarcoma, melanoma etc.), hematological cancers (e.g., lymphoma, leukemia Such

as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML) or multiple myeloma), and skin cancer such as cutaneous T-cell lymphoma (CTCL) and cutaneous B-cell lymphoma. Example CTCLs include Sezary syndrome and mycosis fungoides.

[0075] Compounds, salts, and compositions described herein are also useful in the treatment of inflammatory or obstructive airways diseases, resulting, for example, in reduction of tissue damage, airways inflammation, bronchial hyperreactivity, remodeling or disease progression. Inflammatory or obstructive airways diseases include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics.

[0076] Compounds, salts, and compositions described herein are also useful in the treatment of heteroimmune diseases including, but are not limited to, graft versus host disease, transplantation, transfusion, anaphylaxis, allergies (e.g., allergies to plant pollens, latex, drugs, foods, insect poisons, animal hair, animal dander, dust mites, or cockroach calyx), type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, and atopic dermatitis.

[0077] Compounds, salts, and compositions described herein are also useful in the treatment of other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable and include acute lung injury (ALI), adult/acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. Compounds, salts, and compositions described herein are also useful in the treatment of bronchitis including, but not limited to, acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Compounds, salts, and compositions described herein are also useful in the treatment of pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

[0078] Compounds, salts, and compositions described herein are also useful in the treatment of inflammatory or allergic conditions of the skin, for example psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, systemic lupus erythematosus, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acne vulgaris, and other inflammatory or allergic conditions of the skin.

[0079] Compounds, salts, and compositions described herein are also useful in the treatment of other diseases or conditions, such as diseases or conditions having an inflammatory component, for example, treatment of diseases and conditions of the eye such as ocular allergy, conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or etiology, including autoimmune hematological disorders (e.g. hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia), systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), irritable bowel syndrome, celiac disease, periodontitis, hyaline membrane disease, kidney disease, glomerular disease, alcoholic liver disease, multiple sclerosis, endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), Sjogren's syndrome, keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, cryopyrin-associated periodic syndrome, nephritis, vasculitis, diverticulitis, interstitial cystitis, glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minal change nephropathy), chronic granulomatous disease, endometriosis, leptospiriosis renal disease, glaucoma, retinal disease, ageing, headache, pain, complex regional pain syndrome, cardiac hypertrophy, musclewasting, catabolic disorders, obesity, fetal growth retardation, hyperchlolesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ectodermal dysplasia, Behcet's disease, incontinentia pigmenti, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma (allergic and non-allergic, mild, moderate, severe, bronchitic, and exercise-induced), acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, nasal sinusitis, ocular allergy, silica

induced diseases, COPD (reduction of damage, airways inflammation, bronchial hyperreactivity, remodeling or disease progression), pulmonary disease, cystic fibrosis, acidinduced lung injury, pulmonary hypertension, polyneuropathy, cataracts, muscle inflammation in conjunction with systemic sclerosis, inclusion body myositis, myasthenia gravis, thyroiditis, Addison's disease, lichen planus, Type 1 diabetes, or Type 2 diabetes, appendicitis, atopic dermatitis, asthma, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, Crohn's disease, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, encephalomyelitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, ulcerative colitis, uveitis, vaginitis, vasculitis, or vulvitis.

[0080] In some embodiments, cardiovascular diseases which can be treated according to the present methods include, but are not limited to, restenosis, cardiomegaly, atherosclerosis, myocardial infarction, ischemic stroke, congestive heart failure, angina pectoris, reocclusion after angioplasty, restenosis after angioplasty, reocclusion after aortocoronary bypass, restenosis after aortocoronary bypass, stroke, transitory ischemia, a peripheral arterial occlusive disorder, pulmonary embolism, and deep venous thrombosis.

[0081] In some embodiments, the neurodegenerative disease which can be treated according to the present methods include, but are not limited to, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia, and neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity, hypoxia, epilepsy, treatment of diabetes, metabolic syndrome, obesity, organ transplantation and graft versus host disease.

[0082] In certain aspects, a pharmaceutical composition described herein is formulated for administration to a patient in need of such composition. Pharmaceutical compositions described herein may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion

techniques. In some embodiments, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the pharmaceutical compositions described herein may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents.

[0083] In some aspects, the pharmaceutical compositions are administered orally.

[0084] A specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound described herein in the composition will also depend upon the particular compound in the pharmaceutical composition.

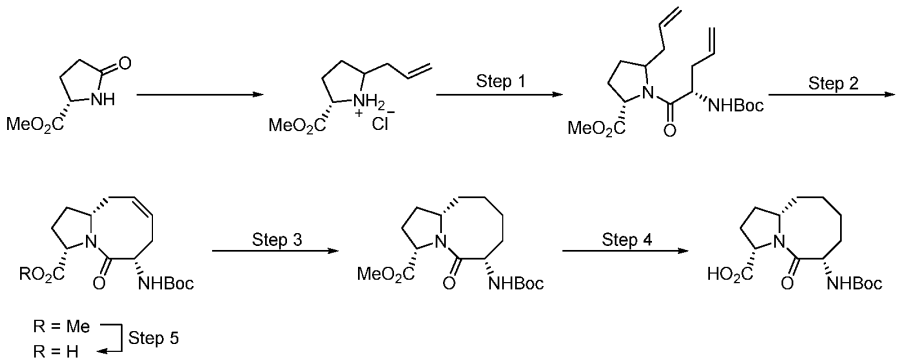
EXEMPLIFICATION

Preparation of Compounds

[0085] The compounds claimed herein were prepared following the procedures outlined in the following schemes. Compound names were generated using the software built into ChemDraw. To the extent that there are discrepancies between the name of a compound and its depicted structure, the depicted chemical structure is to be taken as the appropriate compound.

[0086] **Procedures for Syntheses of Cores:**

Synthesis of (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid

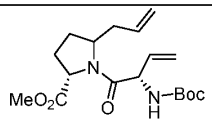
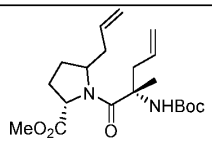


[0087] *Step 1: Preparation of methyl (2S)-5-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-enoyl)pyrrolidine-2-carboxylate*

[0088] To a cooled (0 °C) solution of methyl (2S)-5-allylpyrrolidine-2-carboxylate hydrochloride (200 g, 972 mmol, 1.00 eq) and (S)-2-((tert-butoxycarbonyl)amino)pent-4-enoic acid (209 g, 972 mmol, 1.00 eq) in CH_2Cl_2 (1.60 L) was added Et_3N (406 mL, 2.92 mol, 3.00 eq) and 2-chloro-1-methylpyridinium iodide (CMPI) (273 g, 1.07 mol, 1.10 eq). The solution was warmed to 25 °C and stirred for 1 h. The mixture was poured into water (5.0 L), extracted with CH_2Cl_2 (2.00 L x 3). The combined organic layers were washed with brine (2.0 L), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Six individual batches of equal scale were performed in parallel and combined during work up. The resulting residue was purified by column chromatography (petroleum ether : EtOAc = 100:1 to 10:1) to give methyl (2S)-5-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-enoyl)pyrrolidine-2-carboxylate (1.18 kg, 3.22 mol, 55.2% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 – 5.78 (m, 2H), 5.17 – 4.99 (m, 5H), 4.50 – 4.34 (m, 3H), 3.76 – 3.70 (m, 3H), 2.50 – 2.15 (m, 6H), 1.96 – 1.91 (m, 2H), 1.41 (s, 9H).

[0089] The intermediates shown in **Table 1** were prepared according the protocol outlined in Step 1 above using (S)-5-oxopyrrolidine-2-carboxylic acid, the appropriate N-protected amino acids [(S)-2-((tert-butoxycarbonyl)amino)but-3-enoic acid) or (S)-2-((tert-butoxycarbonyl)amino)-2-methylpent-4-enoic acid], CMPI, triethylamine, and CH_2Cl_2. The intermediate(s) was purified using standard methods.

Table 1

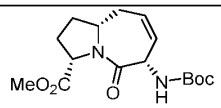
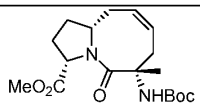
Name	Structure	LCMS	NMR
methyl (2S)-5-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)but-3-enoyl)pyrrolidine-2-carboxylate			^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 – 5.75 (m, 2H), 5.46 – 5.42 (m, 1H), 5.34 – 5.26 (m, 2H), 5.14 – 5.03 (m, 2H), 4.56 – 4.48 (m, 1H), 4.31 – 4.13 (m, 1H), 3.80 – 3.75 (m, 3H), 2.58 – 2.54 (m, 1H), 2.33 – 1.94 (m, 5H), 1.43 (s, 9H)
methyl (2S)-5-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)-2-methylpent-4-enoyl)pyrrolidine-2-carboxylate		281.3 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 – 5.71 (m, 2H), 5.18 – 5.12 (m, 4H), 5.09 – 4.97 (m, 1H), 4.49 (s, 1H), 4.20 (s, 1H), 3.76 (s, 3H), 2.98 (s, 1H), 2.74 – 2.69 (m, 1H), 2.56 (s, 1H), 2.25 (s, 1H), 1.96 – 1.66 (m, 4H), 1.51 (s, 3H), 1.43 (s, 9H)

[0090] *Step 2: Preparation of methyl (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate*

[0091] To a solution of methyl (2S)-5-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-enoyl)pyrrolidine-2-carboxylate (200 g, 546 mmol, 1.00 eq) in CH_2Cl_2 (2.00 L) was added 1st generation Grubbs catalyst (44.9 g, 54.6 mmol, 0.10 eq) at 25 °C. The solution was subsequently heated to 50 °C and stirred for 36 h. Six individual batches of equal scale were performed in parallel and combined during work up. The combined reaction mixtures were concentrated to give a residue. The residue was purified by column chromatography (petroleum ether : EtOAc = 100:1 to 0:1) twice to give a crude product. The crude product was triturated with petroleum ether (2.00 L) for 12 h and filtered. The filter cake was dried under reduced pressure to give methyl (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate (510 g, 1.40 mol, 51.3% yield, 92.9% purity) as a solid. LCMS (ESI) m/z = 361.2 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 – 5.80 (m, 1H), 5.73 – 5.71 (m, 1H), 5.58 –5.56 (m, 1H), 4.88 – 4.85 (m, 1H), 4.52 – 4.49 (m, 1H), 4.16 – 4.14 (m, 1H), 3.71 (s, 3H), 2.81 – 2.74 (m, 2H), 2.45 – 2.38 (m, 1H), 2.33 – 2.24 (m, 1H), 2.14 – 2.05 (m, 2H), 1.98 – 1.93 (m, 2H), 1.43 (s, 9H).

[0092] The intermediates shown in **Table 2** were prepared according to the representative protocol described above in Step 2 with appropriate modifications.

Table 2

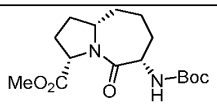
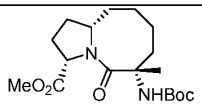
Name	Structure	LCMS	NMR
methyl (3S,6S,9aR)-6-((tert-butoxycarbonyl)amino)-5-oxo-2,3,5,6,9,9a-hexahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate		225.1 $[(M–100)+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 5.75 (d, J = 6.4 Hz, 1H), 5.65 – 5.61 (m, 1H), 5.44 – 5.35 (m, 2H), 4.58 – 4.54 (m, 1H), 4.46 – 4.41 (m, 1H), 3.75 (s, 3H), 2.51 – 2.42 (m, 1H), 2.33 – 2.22 (m, 3H), 2.10 – 2.06 (m, 1H), 1.82 – 1.77 (m, 1H), 1.45 (s, 9H).
methyl (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-6-methyl-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate		353.3 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 6.34 (s, 1H), 5.78 – 5.68 (m, 2H), 4.81 – 4.75 (m, 1H), 4.38 (t, *J* = 8.0 Hz, 1H), 3.73 (s, 3H), 3.46 – 3.41 (m, 1H), 2.63 – 2.50 (m, 2H), 2.33 – 2.12 (m, 3H), 2.97 – 2.82 (m, 2H), 1.59 (s, 3H), 1.41 (s, 9H)

[0093] *Step 3: Preparation of methyl (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate*

[0094] To a solution of methyl (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate (47.9 g, 137 mmol, 96.8% purity, 1.00 *eq*) in EtOAc (500 mL) was added 10% Pd/C (9.58 g) under N_2 (g). The suspension was degassed under vacuum and purged with H_2 (g) several times. The mixture was stirred at 25 °C under H_2 (g) (50 psi) for 16 h. The mixture was filtered, and the filtrate was concentrated to give methyl (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (48.0 g) as brown oil. LCMS (ESI) m/z = 341.0 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (d, J = 8.4 Hz, 1H), 4.69 – 4.57 (m, 1H), 4.50 – 4.41 (m, 1H), 4.27 – 4.18 (m, 1H), 3.76 (s, 3H), 2.34 – 2.25 (m, 1H), 2.21 – 2.11 (m, 1H), 2.04 – 1.68 (m, 8H), 1.64 – 1.57 (m, 2H), 1.43 (s, 9H).

[0095] The intermediates shown in **Table 3** were prepared according to the protocol described above in Step 3 with appropriate modifications.

Table 3

Name	Structure	LCMS	NMR
methyl (3S,6S,9aS)-6-((tert-butoxycarbonyl)amino)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate		327.2 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (dd, J = 8.4, 3.6 Hz, 1H), 4.22 (br d, J = 11.2 Hz, 1H), 3.97 (br d, J = 10.0 Hz, 1H), 3.72 (s, 3H), 2.36 – 2.23 (m, 1H), 2.11 (br dd, J = 8.8, 1.2 Hz, 1H), 2.07 – 1.96 (m, 2H), 1.89 – 1.56 (m, 6H), 1.44 (s, 9H)
methyl (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-6-methyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate		355.2 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (s, 1H), 4.62 – 4.59 (m, 1H), 4.33 (t, *J* = 9.2 Hz, 1H), 3.76 (s, 3H), 2.95 (d, *J* = 16.4 Hz, 1H), 2.24 – 2.02 (m, 3H), 1.94 – 1.77 (m, 4H), 1.72 – 1.66 (m, 2H), 1.64 – 1.57 (m, 1H), 1.55 (s, 3H), 1.52 – 1.44 (m, 1H), 1.41 (s, 9H)

[0096] *Step 4: Preparation of (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid*

[0097] To a cooled (0 °C) solution of methyl (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (17.0 g, 49.9 mmol, 1.00 *eq*) in 1,4-dioxane (85.0 mL) was added a 2 M aqueous solution of $LiOH{\cdot}H_2O$ (74.9 mL, 3.00 eq). The mixture was allowed to gradually warm to room temperature stirred at 25 °C for 16 h. The reaction mixture was acidified with 1.0 N HCl to pH ~4.0. The mixture

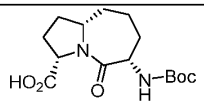
was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4 and concentrated to give a residue. The residue was dissolved with water (150 mL) and acetonitrile (30 mL). The mixture was lyophilized to give (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid (15.5 g, 44.8 mmol, 92.3% yield for two steps, 94.3% purity) as a grey solid. LCMS (ESI) m/z = 327.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1H), 5.53 (d, J = 8.0 Hz, 1H), 4.72 – 4.62 (m, 1H), 4.54 (t, J = 8.6 Hz, 1H), 4.32 – 4.21 (m, 1H), 2.32 – 2.12 (m, 3H), 2.05 – 1.95 (m, 1H), 1.85 – 1.55 (m, 8H), 1.43 (s, 9H).

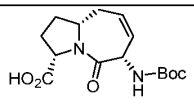
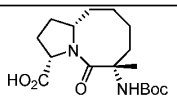
[0098] *Step 5: Preparation of (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylic acid*

[0099] (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylic acid was prepared using the hydrolysis conditions described above in step 4 for the preparation of (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid and starting from methyl (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate. Starting from (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylic acid (35.0 g, 103 mmol, 1.00 equiv), $LiOH \cdot H_2O$ (8.64 g, 3.00 eq), and THF (150 mL) / water (50 mL) afforded (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylic acid (31.1 g, 99.1 mmol, 96.1% yield) as white solids. LCMS (ESI) m/z = 325.2 $[M+H]^+$;

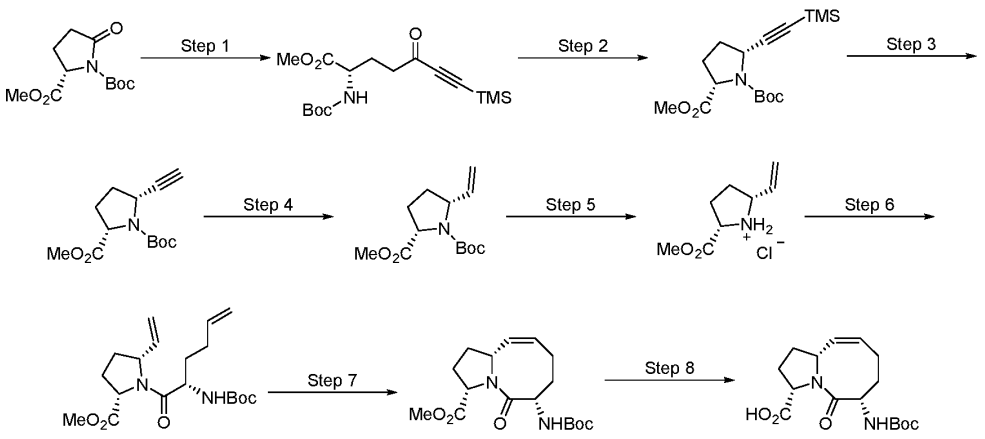
[00100] The intermediate(s) shown in **Table 4** were prepared using the hydrolysis conditions described above in Step 4 for the preparation of (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid and starting from the appropriate starting materials and conditions.

Table 4

Name	Structure	LCMS	NMR
(3S,6S,9aS)-6-((tert-butoxycarbonyl)amino)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic acid		313.2 $[M+H]^+$	^1H NMR (400 MHz, DMSO-d_6) δ 12.33 – 12.61 (m, 1H) 6.59 (d, J = 8.0 Hz, 1H) 4.36 (m, 1H) 4.01 – 4.15 (m, 1H) 3.88 (m, 1H) 2.11 – 2.26 (m, 1H) 1.96 – 2.07 (m, 1H) 1.84 – 1.92 (m, 2H) 1.71 (m, 2H) 1.66 (m, 2H) 1.41 – 1.55 (m, 2H) 1.37 (s, 9H)

(3S,6S,9aR)-6-((tert-butoxycarbonyl)amino)-5-oxo-2,3,5,6,9,9a-hexahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic acid		333.2 $[M+Na]^+$	^1H NMR (400 MHz, methanol-d_4) δ 6.34 – 6.21 (m, 1H), 5.77 – 5.58 (m, 1H), 5.42 – 5.27 (m, 1H), 4.68 – 4.43 (m, 2H), 4.13 – 3.98 (m, 1H), 2.69 – 2.50 (m, 1H), 2.35 – 2.21 (m, 3H), 2.13 – 2.03 (m, 2H), 1.44 (s, 9H)
(3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-6-methyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid		341.1 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 6.15 (s, 1H), 4.65 – 4.60 (m, 1H), 4.48 (t, J = 7.6 Hz, 1H), 2.91 (d, J = 16.0 Hz, 1H), 2.26 – 2.16 (m, 3H), 2.11 – 2.04 (m, 1H), 1.89 – 1.75 (m, 2H), 1.72 – 1.61 (m, 4H), 1.59 (m, 3H), 1.54 – 1.48 (m, 1H), 1.43 (s, 9H)

Synthesis of methyl (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate



[00101] *Step 1: Preparation of methyl (S)-2-((tert-butoxycarbonyl)amino)-5-oxo-7-(trimethylsilyl)hept-6-ynoate*

[00102] To a cooled (0 °C) solution of isopropylmagnesium chloride (2.0 M, 9.04 L, 1.10 eq) and THF (4.00 L) was added ethynyltrimethylsilane (1.86 kg, 18.9 mol, 2.62 L, 1.15 eq). The reaction mixture was stirred for 1 h, followed by slow addition of a solution of 1-(tert-butyl) 2-methyl (S)-5-oxopyrrolidine-1,2-dicarboxylate (4.00 kg, 16.4 mol, 1.00 eq) in THF (8.0 L) over 1.5 h. After stirring for an additional 30 min, the reaction mixture was transferred into a stirred and cooled (0 °C) biphasic mixture of iPAc (5.00 L) and 20% aqueous NH_4Cl (16.0 L). The biphasic mixture was separated, and the aqueous layer was extracted with iPAc (8.00 L). The combined organic layers were washed with 20% aqueous

NH_4Cl solution (8.00 L), brine (8.00 L), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give methyl (S)-2-((tert-butoxycarbonyl)amino)-5-oxo-7-(trimethylsilyl)hept-6-ynoate (5.50 kg) as yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.11 – 5.09 (m, 1H), 4.32 – 4.30 (m, 1H), 3.77 – 3.72 (m, 3H), 2.72 – 2.64 (m, 2H), 2.04 – 2.01 (m, 1H), 1.73 – 1.71 (m, 1H), 1.41 (s, 9H), 0.24 (s, 9H).

[00103] *Step 2: Preparation of 1-(tert-butyl) 2-methyl (2S,5R)-5-((trimethylsilyl)ethynyl)pyrrolidine-1,2-dicarboxylate*

[00104] To a suspension of $NaBH(OAc)_3$ (4.03 kg, 19.0 mol, 1.30 eq) in iPAc (5.00 L) was added a solution of methyl (S)-2-((tert-butoxycarbonyl)amino)-5-oxo-7-(trimethylsilyl)hept-6-ynoate in iPAc (20.0 L). The batch was cooled to (–10 °C), followed by slow addition of TFA (7.18 kg, 62.9 mol, 4.66 L, 4.30 eq) over 1.5 h. The mixture was warmed to 10 °C and stirred for an additional 2 h. The reaction mixture was transferred to a cooled (0 °C) solution of 25% aqueous K_2HPO_4 (40.0 L). The pH of the suspension was adjusted to pH 6 – 7 with aqueous saturated $NaHCO_3$. The biphasic mixture was separated, and the aqueous layer was extracted with iPAc (8.00 L). The combined organic layers were washed with 25% K_2HPO_4 solution (8.00 L), brine (5.00 L), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 30/1 to 3/1) to yield 1-(tert-butyl) 2-methyl (2S,5R)-5-((trimethylsilyl)ethynyl)pyrrolidine-1,2-dicarboxylate (2.27 kg, 6.97 mol, 42.4% yield) as yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 4.49 – 4.32 (m, 1H), 4.16 (s, 1H), 3.63 (s, 3H), 2.16 (s, 2H), 1.95 – 1.88 (m, 2H), 1.40 – 1.32 (m, 9H), 0.13 (s, 9H).

[00105] *Step 3: Preparation of 1-(tert-butyl) 2-methyl (2S,5R)-5-ethynylpyrrolidine-1,2-dicarboxylate*

[00106] To a cooled (0 °C) solution of 1-(tert-butyl) 2-methyl (2S,5R)-5-((trimethylsilyl)ethynyl)pyrrolidine-1,2-dicarboxylate (500 g, 1.54 mol, 1.00 eq) in THF (2.00 L) was added a 1.0 M solution of TBAF (1.84 L, 1.20 eq) in THF and the mixture was subsequently stirred for 1 h. Four batches of equal scale were performed in parallel, and the reaction mixtures were combined and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 1/0 to 0/1) to yield 1-(tert-butyl) 2-methyl (2S,5R)-5-ethynylpyrrolidine-1,2-dicarboxylate (**I-14**) (920 g, 2.95 mol, 48.0% yield, 81.2% purity) as yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.62 – 4.50 (m, 1H), 4.30 – 4.20 (m, 1H), 3.74 – 3.70 (m, 3H), 2.31 – 2.14 (m, 5H), 1.47 – 1.40 (m, 9H).

[00107] *Step 4: Preparation of 1-(tert-butyl) 2-methyl (2S,5R)-5-vinylpyrrolidine-1,2-dicarboxylate*

[00108] To a suspension of 1-(tert-butyl) 2-methyl (2S,5R)-5-ethynylpyrrolidine-1,2-dicarboxylate (150 g, 592 mmol, 1.00 eq) in EtOAc (1.50 L) under N_2 (g) was added Lindlar's catalyst (7.50 g, 1.82 mmol, 5.0% wt) and quinoline (163 g, 1.27 mol, 150 mL, 2.14 eq). The suspension was degassed under vacuum and purged with H_2 (g) (3x). The mixture was stirred under H_2 (g) (50 psi) for 1 h. Six batches of equal scale were performed in parallel, filtered, and the filtrates were combined during workup. The mixture was filtered, the filtrate was washed with aqueous 1N HCl (9.00 L), separated, and concentrated. The combined residues were purified by silica gel column chromatography (petroleum ether/EtOAc = 1/0 to 0/1) to yield 1-(tert-butyl) 2-methyl (2S,5R)-5-vinylpyrrolidine-1,2-dicarboxylate (745 g, 2.23 mol, 62.8% yield, 76.5% purity) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.84 – 5.76 (m, 1H), 5.34 – 5.27 (m, 1H), 5.06 – 5.04 (m, 1H), 4.29 – 4.17 (m, 2H), 3.65 – 3.62 (m, 3H), 2.16 – 2.14 (m, 2H), 1.79 – 1.78 (m, 1H), 1.69 – 1.65 (m, 1H), 1.34 – 1.32 (m, 9H).

[00109] *Step 5: Preparation of methyl (2S,5R)-5-vinylpyrrolidine-2-carboxylate*

[00110] To a solution of 1-(tert-butyl) 2-methyl (2S,5R)-5-vinylpyrrolidine-1,2-dicarboxylate (245 g, 959 mmol, 1.00 eq) in EtOAc (1.25 L) was added a solution of 4.0 M solution of HCl in EtOAc (959 mL, 4.00 eq). Three batches of equal scale were performed in parallel, and the mixture was stirred at 25 °C for 2 h. The reaction mixtures were combined and concentrated under reduced pressure to give product methyl (2S,5R)-5-vinylpyrrolidine-2-carboxylate (520 g, HCl) was obtained as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.03 – 5.95 (m, 1H), 5.44 – 5.33 (m, 2H), 4.49 – 4.45 (m, 1H), 4.11 – 4.05 (m, 1H), 3.76 (s, 3H), 2.31 – 2.28 (m, 1H), 2.16 – 2.10 (m, 1H), 1.81 – 1.76 (m, 1H).

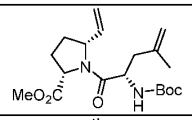
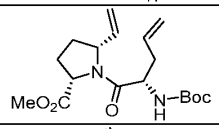
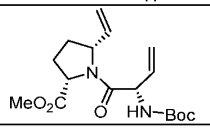
[00111] *Step 6: Preparation of methyl (2S,5R)-1-((S)-2-((tert-butoxycarbonyl)amino)hex-5-enoyl)-5-vinylpyrrolidine-2-carboxylate*

[00112] To a solution of (S)-2-((tert-butoxycarbonyl)amino)hex-5-enoic acid (80.6 g, 352 mmol, 1.00 eq) in CH_2Cl_2 (674 mL) was added methyl (2S,5R)-5-vinylpyrrolidine-2-carboxylate (67.4 g, 352 mmol, 1.00 eq, HCl) and Et_3N (147 mL, 1.06 mol, 3.00 eq). The mixture was cooled to 0 °C and CMPI (98.8 g, 387 mmol, 1.10 eq) was added. The reaction mixture was subsequently warmed to 25 °C and stirred for 3 h. The reaction mixture was poured into water (500 mL), extracted with CH_2Cl_2 (200 mL x 3). The combined organic layers were washed with saturated aqueous NH_4Cl (300 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by

column chromatography (petroleum ether/EtOAc = 50/1 to 5/1) to give methyl (2S,5R)-1-((S)-2-((tert-butoxycarbonyl)amino)hex-5-enoyl)-5-vinylpyrrolidine-2-carboxylate (115 g, 247 mmol, 70.2% yield, 78.9% purity) as yellow oil. LCMS (ESI) m/z = 367.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 6.03 – 5.94 (m, 1H), 5.53 (d, J = 17.2 Hz, 1H), 5.23 (d, J = 10.4 Hz, 1H), 5.03 – 4.94 (m, 3H), 4.81 (t, J = 12.0 Hz, 1H), 4.53 – 4.40 (m, 2H), 3.75 (s, 3H), 2.25 – 2.18 (m, 2H), 2.16 – 2.12 (m, 1H), 2.10 – 2.07 (m, 1H), 2.05 (s, 1H), 2.00-1.97 (m, 1H), 1.89 – 1.84 (m, 1H), 1.80 – 1.73 (m, 1H), 1.43 (s, 9H).

[00113] The intermediates shown in **Table 5** were synthesized using methyl (2S,5R)-5-vinylpyrrolidine-2-carboxylate, appropriate N-protected amino acids, CMPI, triethylamine, and CH_2Cl_2 under the reaction conditions described above. The intermediate(s) was purified using standard methods.

Table 5

Name	Structure	LCMS
(2S,5R)-1-((S)-2-((tert-butoxycarbonyl)amino)-4-methylpent-4-enoyl)-5-vinylpyrrolidine-2-carboxylic acid		367.2 $[M+H]^+$
methyl (2S,5R)-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-enoyl)-5-vinylpyrrolidine-2-carboxylate		353.0 $[M+H]^+$
methyl (2S,5R)-1-((S)-2-((tert-butoxycarbonyl)amino)but-3-enoyl)-5-vinylpyrrolidine-2-carboxylate		239.0 $[(M–100)+H]^+$

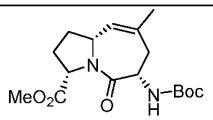
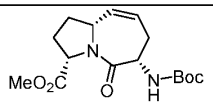
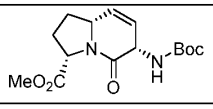
[00114] *Step 7: Preparation of* methyl (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate

[00115] To a solution of methyl (2S,5R)-1-((S)-2-((tert-butoxycarbonyl)amino)hex-5-enoyl)-5-vinylpyrrolidine-2-carboxylate (38.2 g, 104 mmol, 1.00 eq) in CH_2Cl_2 (1.90 L) was added 1st generation Grubb's catalyst (8.58 g, 10.4 mmol, 0.10 eq). The mixture was heated to 50 °C and stirred for 12 h. Three batches of equal scale were performed in parallel. The reaction mixtures were subsequently combined and concentrated to give a residue. The residue was purified by column chromatography (petroleum ether/EtOAc = 100/1 to 7/3) to give the crude product as a gray solid. The crude product (62.0 g) was triturated with petroleum ether (122 mL) for 1.5 h. The mixture was filtered and the filter cake was dried under vacuum to give methyl (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate (50.0 g, 50.3% yield) as a gray solid. LCMS (ESI) m/z = 339.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 – 5.71 (m,

1H), 5.48 (d, J = 12.0 Hz, 1H), 5.28 (d, J = 8.8 Hz, 1H), 4.75 – 4.68 (m, 2H), 4.62 (t, J = 6.4 Hz, 1H), 3.74 (s, 3H), 3.10 – 3.07 (m, 1H), 2.30 – 2.24 (m, 1H), 2.15 – 2.07 (m, 2H), 2.00 – 1.88 (m, 2H), 1.64 – 1.57 (m, 1H), 1.42 (s, 9H).

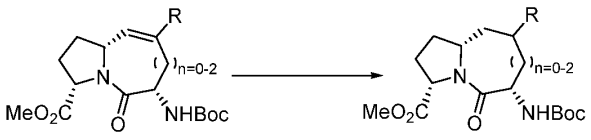
[00116] The intermediates shown in **Table 6** were synthesized using the appropriate starting materials and reagents under conditions described above for the preparation of methyl (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate.

Table 6

Name	Structure	LCMS
methyl (3S,6S,9aR)-6-((tert-butoxycarbonyl)amino)-8-methyl-5-oxo-2,3,5,6,7,9a-hexahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate		361.1 $[M+Na]^+$
methyl (3S,6S,9aR)-6-((tert-butoxycarbonyl)amino)-5-oxo-2,3,5,6,7,9a-hexahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate		347.1 $[M+Na]^+$
methyl (3S,6S,8aR)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,8a-hexahydroindolizine-3-carboxylate		211.2 $[(M–100)+H]^+$

[00117] *Step 8: Preparation of (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylic acid*

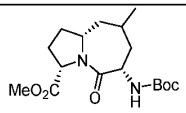
[00118] (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylic acid was prepared using the hydrolysis conditions described previously in Step 4 for the preparation (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid. Using methyl (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate, LiOH (185 mg, 4.41 mmol, 3 eq), and THF/water (9 mL/3mL) afforded (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylic acid (488 mg, 1.50 mmol) as white solids. LCMS (ESI) m/z = 339.1 $[M+H]^+$.

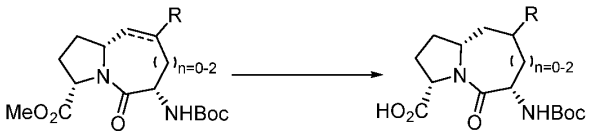


[00119] The intermediates shown in **Table 7** were synthesized using the appropriate starting materials and reagents under the hydrogenation conditions described in Step 3 for the

preparation methyl (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate.

Table 7

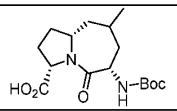
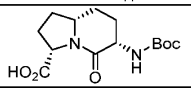
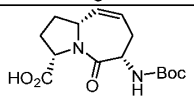
Name	Structure	LCMS
methyl (3S,6S,9aR)-6-((tert-butoxycarbonyl)amino)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate		241.1 $[(M-100)+H]^+$



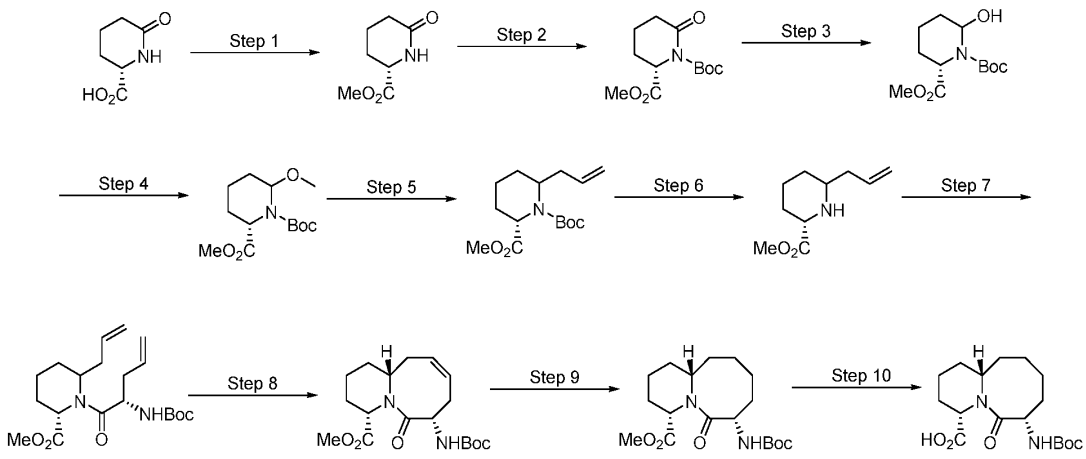
R = H or Me R = H or Me

[00120] The intermediates shown in **Table 8** were synthesized using the appropriate starting materials and reagents under the hydrolysis conditions described in Step 4 for the preparation (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid.

Table 8

Name	Structure
(3S,6S,9aR)-6-((tert-butoxycarbonyl)amino)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic acid	
(3S,6S,8aS)-6-((tert-butoxycarbonyl)amino)-5-oxooctahydroindolizine-3-carboxylic acid	
(3S,6S,9aR)-6-((tert-butoxycarbonyl)amino)-5-oxo-2,3,5,6,7,9a-hexahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic acid	

Synthesis of (4S,7S,11aS)-7-((tert-butoxycarbonyl)amino)-6-oxodecahydro-2H-pyrido[1,2-a]azocine-4-carboxylic acid



[00121] *Step 1: Preparation of methyl (S)-6-oxopiperidine-2-carboxylate*

[00122] To a cooled (0 °C) solution of MeOH (1.50 L) was sequentially added $SOCl_2$ (137 g, 1.15 mol, 83.6 mL, 1.10 eq) and (S)-6-oxopiperidine-2-carboxylic acid (150 g, 1.05 mol, 1.00 eq). The mixture was warmed to 25 °C and stirred for 12 h. Two batches of equal scale were performed in parallel. The reaction mixtures were combined and concentrated *in vacuo*. The resulting residue was dissolved in a mixture of toluene (1.15 L) and Et_3N (292 mL, 2.10 mol, 2.00 eq). The mixture was stirred at 25 °C for 30 mins, then filtered and the filtrate was concentrated to give methyl (S)-6-oxopiperidine-2-carboxylate (282 g) as yellow oil. LCMS (ESI) m/z = 158.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 6.53 (s, 1H), 4.10 (t, J = 5.60 Hz, 1H), 3.77 (s, 3H), 2.43 – 2.33 (m, 2H), 2.20 – 2.15 (m, 1H), 1.89 – 1.77 (m, 3H).

[00123] *Step 2: Preparation of 1-(tert-butyl) 2-methyl (S)-6-oxopiperidine-1,2-dicarboxylate*

[00124] To a solution of methyl (S)-6-oxopiperidine-2-carboxylate (141 g, 897 mmol, 1.00 eq) in acetonitrile (1.41 L) was added Boc_2O (235 g, 1.08 mol, 247 mL, 1.20 eq), DMAP (21.9 g, 179 mmol, 0.20 eq) and Et_3N (136 g, 1.35 mol, 187 mL, 1.50 eq) at 25 °C. The mixture was stirred at 25 °C for 3 h. Two batches of equal scale were performed in parallel, the reaction mixtures were combined, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (petroleum ether/ EtOAc = 100/ 1 to 80/ 1) to give 1-(tert-butyl) 2-methyl (S)-6-oxopiperidine-1,2-dicarboxylate (431 g, 1.67 mol, 79.5% yield over two steps, 99.4% purity) as a yellow solid. LCMS (ESI) m/z = 158.2 $[(M\text{-}Boc)+H]^+$; ^1H NMR: (400 MHz, $CDCl_3$) δ 4.71 – 4.69 (m, 1H), 3.76 (s, 3H), 2.60 – 2.43 (m, 2H), 2.18 – 2.14 (m, 1H), 2.09 – 2.00 (m, 1H), 1.81 – 1.72 (m, 2H), 1.49 (s, 9H).

[00125] *Step 3: Preparation of 1-(tert-butyl) 2-methyl (2S)-6-hydroxypiperidine-1,2-dicarboxylate*

[00126] To a cooled (–78 °C) solution of 1-(tert-butyl) 2-methyl (S)-6-oxopiperidine-1,2-dicarboxylate (120 g, 464 mmol, 99.4% purity, 1.00 eq) in THF (960 mL) was added $LiEt_3BH$ (1 M, 510 mL, 1.10 eq). The mixture was stirred at for 1 h under N_2 (g). The reaction mixture was poured into saturated aqueous NH_4Cl solution (4.50 L) and extracted with EtOAc (2.00 L x 2). Three batches of equal scale were performed and worked-up in a similar manner. The combined organic layers were washed with brine (1.50 L x 2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 1-(tert-butyl) 2-methyl (2S)-6-hydroxypiperidine-1,2-dicarboxylate (487 g) as yellow oil. ^1H NMR (400 MHz,

DMSO-d_6) δ 5.55 (s, 1H), 5.34 (s, 1H), 4.58 (s, 1H), 3.58 (m, 3H), 2.11 (d, J = 13.2 Hz, 1H), 1.83 – 1.73 (m, 1H), 1.65 (d, J = 1.2 Hz, 2H), 1.57 – 1.51 (m, 2H), 1.41 (s, 9H).

[00127] *Step 4: Preparation of 1-(tert-butyl) 2-methyl (2S)-6-methoxypiperidine-1,2-dicarboxylate*

[00128] To a solution of 1-(tert-butyl) 2-methyl (2S)-6-hydroxypiperidine-1,2-dicarboxylate (266 g, 1.03 mol, 1.00 eq) in MeOH (1.33 L) was added TsOH•H_2O (39.1 g, 205 mmol, 0.20 eq). The reaction mixture was stirred at 25 °C for 12 h. Two batches of equal scale were performed. The reaction batches were combined and concentrated under *in vacuo*. The crude residue was dissolved in EtOAc (3.00 L) and washed with saturated aqueous $NaHCO_3$ solution (2.00 L x 2). The combined organic layers were washed with brine (1.50 L x 2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (petroleum ether/ EtOAc = 100/ 0 to 20/ 1) to give 1-(tert-butyl) 2-methyl (2S)-6-methoxypiperidine-1,2-dicarboxylate (427 g) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (m, 1H), 4.74 (m, 1H), 3.71 (s, 3H), 3.30 (s, 3H), 2.33 – 2.25 (m, 1H), 1.92 – 1.81 (m, 2H), 1.69 – 1.58 (m, 2H), 1.50 (s, 9H), 1.47 (s, 1H).

[00129] *Step 5: Preparation of 1-(tert-butyl) 2-methyl (2S)-6-allylpiperidine-1,2-dicarboxylate*

[00130] To a solution of 1-(tert-butyl) 2-methyl (2S)-6-methoxypiperidine-1,2-dicarboxylate (136 g, 496 mmol, 1.00 eq) in CH_2Cl_2 (1.35 L) was added allyltrimethylsilane (113 g, 992 mmol, 158 mL, 2.00 eq). The reaction mixture was cooled to –78 °C, followed by dropwise addition of BF_3·Et_2O (76.1 g, 536 mmol, 66.1 mL, 1.08 eq) and stirred for 1 h. Three batches of equal scale were performed. The reaction mixtures were combined and quenched by pouring into H_2O (10.0 L). The reaction mixture was extracted with CH_2Cl_2 (1.00 L x 2). Combined organic layers were washed with brine (4.00 L x 2), dried over Na_2SO_4, filtered, and concentrated to give 1-(tert-butyl) 2-methyl (2S)-6-allylpiperidine-1,2-dicarboxylate (334 g) as yellow oil.

[00131] *Step 6: Preparation of 1-(tert-butyl) 2-methyl (2S)-6-allylpiperidine-1,2-dicarboxylate*

[00132] To a cooled (0 °C) solution of 1-(tert-butyl) 2-methyl (2S)-6-allylpiperidine-1,2-dicarboxylate (188 g, 662 mmol, 1.00 eq) in MeOH (938 mL) was added a solution of 4 M HCl in 1,4-dioxane (827 mL, 5.00 eq). The mixture was warmed to 25 °C and stirred for 2 h. Two batches of equal scale were performed, and the mixtures were combined and concentrated under vacuum. The resulting residue was suspended in EtOAc (5.00 L) and H_2O (2.50 L). The aqueous layer was removed, and the organic layer was washed with saturated

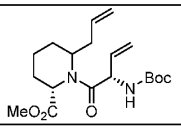
aqueous $NaHCO_3$ solution (5.00 L x 2). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 1-(tert-butyl) 2-methyl (2S)-6-allylpiperidine-1,2-dicarboxylate (76.6 g) as yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 – 5.72 (m, 1H), 5.15 – 5.07 (m, 2H), 3.71 (s, 3H), 3.35 – 3.32 (m, 1H), 2.58 – 2.53 (m, 1H), 2.24 – 2.14 (m, 3H), 2.12 – 2.00 (m, 1H), 1.91 – 1.84 (m, 1H), 1.64 (d, J = 13.2 Hz, 1H), 1.45 – 1.34 (m, 2H), 1.14 – 1.07 (m, 1H).

[00133] *Step 7: Prepa*ration *of methyl (2S)-6-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-enoyl)piperidine-2-carboxylate*

[00134] To a solution of 1-(tert-butyl) 2-methyl (2S)-6-allylpiperidine-1,2-dicarboxylate (56.5 g, 308 mmol, crude purity, 1.00 eq) in THF (1.41 L) was added (S)-2-((tert-butoxycarbonyl)amino)pent-4-enoic acid (67.7 g, 314 mmol, 1.02 eq) and IIDQ (100 g, 330 mmol, 1.07 eq). The mixture was stirred for 12 h and subsequently diluted with EtOAc (2.80 L). The organic layer was washed with aqueous 1 N HCl (2.80 L), followed by saturated aqueous $NaHCO_3$ (2.80 L). The combined organic layers were washed with brine (2.80 L), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (petroleum ether/ EtOAc = 100 / 0 to 5 / 1) to give methyl (2S)-6-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-enoyl)piperidine-2-carboxylate (22.4 g, 54.4 mmol, 4.7% yield over five steps, 92.6% purity) as light yellow oil. LCMS (ESI) m/z = 381.3 $[M+H]^+$.

[00135] The intermediate shown in **Table 9** was synthesized using the procedure described above and starting from 1-(tert-butyl) 2-methyl (2S)-6-allylpiperidine-1,2-dicarboxylate, appropriate N-protected amino acid [(S)-2-((tert-butoxycarbonyl)amino)pent-4-enoic acid], IIDQ, and THF.

Table 9

Name	Structure	LCMS
methyl (2S)-6-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)but-3-enoyl)piperidine-2-carboxylate		367.3 $[M+H]^+$

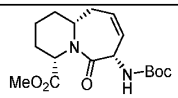
[00136] *Step 8: Preparation of methyl (4S,7S,11aR,Z)-7-((tert-butoxycarbonyl)amino)-6-oxo-1,3,4,6,7,8,11,11a-octahydro-2H-pyrido[1,2-a]azocine-4-carboxylate*

[00137] To a solution of methyl (2S)-6-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-enoyl)piperidine-2-carboxylate (21.8 g, 53.0 mmol, 92.6% purity, 1.00 *eq*) in CH_2Cl_2 (1.09 L) was added 1st generation Grubb's catalyst (8.72 g, 10.6 mmol, 0.20 eq). The mixture was heated to 50 °C. After 5 h, LCMS analysis showed the reaction contained ~14% of starting

material. To the mixture was introduced additional 1st generation Grubb's catalyst (8.72 g, 10.6 mmol, 0.20 eq) and the mixture was allowed to age for another 2 h. The reaction mixture was cooled to room temperature and concentrated to give a residue. The residue was purified by column chromatography (petroleum ether/EtOAc = 100/1 to 20/1) to give methyl (4S,7S,11aR,Z)-7-((tert-butoxycarbonyl)amino)-6-oxo-1,3,4,6,7,8,11,11a-octahydro-2H-pyrido[1,2-a]azocine-4-carboxylate (10.0 g) as brown oil. LCMS (ESI) m/z = 353.3 $[M+H]^+$.

[00138] The intermediate shown in **Table 10** was synthesized via ring closing metathesis using the conditions described above for the preparation of methyl (4S,7S,11aR,Z)-7-((tert-butoxycarbonyl)amino)-6-oxo-1,3,4,6,7,8,11,11a-octahydro-2H-pyrido[1,2-a]azocine-4-carboxylate and starting from methyl (2S)-6-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)but-3-enoyl)piperidine-2-carboxylate and using 1st generation Grubb's catalyst.

Table 10

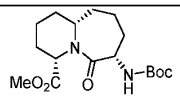
Name	Structure	LCMS
methyl (4S,7S,10aR)-7-((tert-butoxycarbonyl)amino)-6-oxo-1,2,3,4,6,7,10,10a-octahydropyrido[1,2-a]azepine-4-carboxylate		239.2 $[(M-100)+H]^+$

[00139] *Step 9: Preparation of methyl (4S,7S,11aS)-7-((tert-butoxycarbonyl)amino)-6-oxodecahydro-2H-pyrido[1,2-a]azocine-4-carboxylate*

[00140] To a solution of methyl (4S,7S,11aR,Z)-7-((tert-butoxycarbonyl)amino)-6-oxo-1,3,4,6,7,8,11,11a-octahydro-2H-pyrido[1,2-a]azocine-4-carboxylate (10.4 g, 29.5 mmol, 1.00 eq) in EtOAc (100 mL) was added 10% Pd/C (2.08 g) under N_2 (g). The suspension was subjected to three cycles of degassing under vacuum and purging with H_2 (g). The mixture was stirred at 25 °C under H_2 (g) (50 psi). After 12 h, the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by prep-HPLC (Phenomenex luna C18 250*80mm*10 um; mobile phase: [water(TFA)-acetonitrile];B%: 50%-80%). The mixture was adjusted pH to 7 – 8 with aqueous saturated $NaHCO_3$ solution and carefully concentrated under reduced pressure to remove acetonitrile. The aqueous layer was extracted with EtOAc (250 mL x 2). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give methyl (4S,7S,11aS)-7-((tert-butoxycarbonyl)amino)-6-oxodecahydro-2H-pyrido[1,2-a]azocine-4-carboxylate (6.46 g, 18.1 mmol, 31.2% yield over two steps) as dark brown gum. LCMS (ESI) m/z = 355.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (d, J = 7.2 Hz, 1H), 5.20 (t, J = 2.4 Hz, 1H), 4.67 – 4.62 (m, 1H), 4.24 – 4.21 (m, 1H), 3.72 (s, 3H), 3.31 – 3.28 (m, 1H), 2.14 – 2.10 (m, 1H), 2.03 – 1.65 (m, 6H), 1.60 – 1.36 (m, 5H), 1.44 (s, 9H), 1.27 – 1.21 (m, 1H).

[00141] The intermediate shown in **Table 11** was synthesized using the hydrogenation conditions described above for the preparation of methyl (4S,7S,11aS)-7-((tert-butoxycarbonyl)amino)-6-oxodecahydro-2H-pyrido[1,2-a]azocine-4-carboxylate and starting from methyl (4S,7S,10aR)-7-((tert-butoxycarbonyl)amino)-6-oxo-1,2,3,4,6,7,10,10a-octahydropyrido[1,2-a]azepine-4-carboxylate.

Table 11

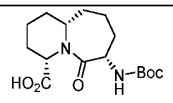
Name	Structure	LCMS
methyl (4S,7S,10aS)-7-((tert-butoxycarbonyl)amino)-6-oxodecahydropyrido[1,2-a]azepine-4-carboxylate		241.2 $[M+H]^+$

[00142] *Step 10: Preparation of (4S,7S,11aS)-7-((tert-butoxycarbonyl)amino)-6-oxodecahydro-2H-pyrido[1,2-a]azocine-4-carboxylic acid*

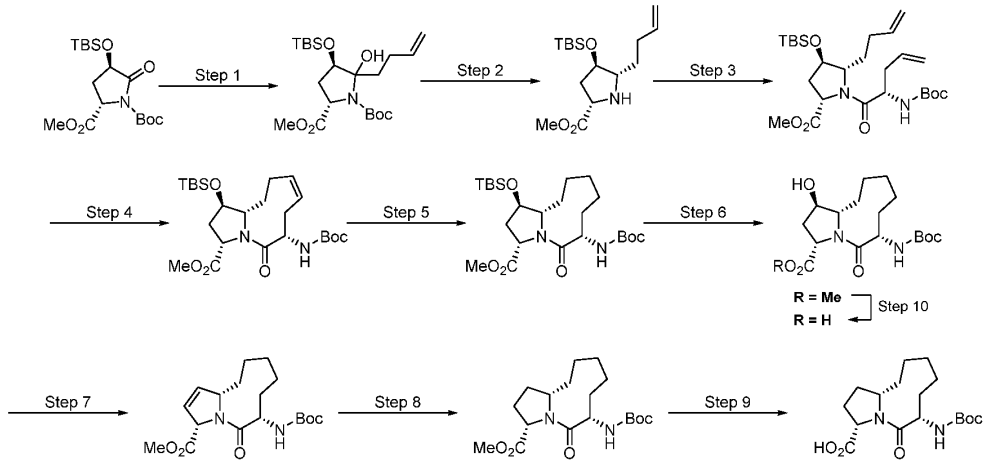
[00143] (4S,7S,11aS)-7-((tert-butoxycarbonyl)amino)-6-oxodecahydro-2H-pyrido[1,2-a]azocine-4-carboxylic acid was prepared using the hydrolysis conditions described previously in Step 4 for the preparation (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid.

[00144] The intermediate shown in **Table 12** was synthesized using the conditions described in Step 4 for the preparation (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid.

Table 12

Name	Structure	LCMS
(4S,7S,10aS)-7-((tert-butoxycarbonyl)amino)-6-oxodecahydropyrido[1,2-a]azepine-4-carboxylic acid		327.3 $[M+H]^+$

[00145] Synthesis of (1R,3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-1-hydroxy-5-oxodecahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylic acid and (3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylic acid



[00146] *Preparation of 1-(tert-butyl) 2-methyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)-5-oxopyrrolidine-1,2-dicarboxylate*

[00147] 1-(tert-butyl) 2-methyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)-5-oxopyrrolidine-1,2-dicarboxylate was prepared according the protocol reported in WO2015010626.

[00148] *Step 1: Preparation of 1-(tert-butyl) 2-methyl (2S,4R)-5-(but-3-en-1-yl)-4-((tert-butyldimethylsilyl)oxy)-5-hydroxypyrrolidine-1,2-dicarboxylate*

[00149] To a cooled (–78 °C) solution of 1-(tert-butyl) 2-methyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)-5-oxopyrrolidine-1,2-dicarboxylate (165 g, 442 mmol, 1.00 eq) in THF (1.50 L) was added a 1 M solution of but-3-en-1-ylmagnesium bromide in THF (552 mL, 1.25 eq). The reaction mixtures were stirred for 1 h. Two batches of equal scale were performed in parallel and combined for work-up. The reaction mixtures were poured into saturated aqueous NH_4Cl (6.00 L) and extracted with EtOAc (5.00 L x 3). The combined organic layers were washed with brine (5.00 L), dried over Na_2SO_4, filtered, and concentrated to give 1-(tert-butyl) 2-methyl (2S,4R)-5-(but-3-en-1-yl)-4-((tert-butyldimethylsilyl)oxy)-5-hydroxypyrrolidine-1,2-dicarboxylate (357 g) as yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 – 5.72 (m, 1H), 5.13 – 4.92 (m, 2H), 4.53 – 4.39 (m, 1H), 4.18 (t, J = 5.2 Hz, 1H), 3.79 – 3.71 (m, 3H), 2.84 – 2.70 (m, 1H), 2.63 – 2.54 (m, 1H), 2.38 – 2.24 (m, 2H), 2.22 – 2.08 (m, 2H), 1.47 – 1.39 (m, 9H), 0.99 – 0.90 (m, 9H), 0.18 – 0.12 (m, 3H), 0.11 – 0.06 (m, 3H).

[00150] *Step 2: Preparation of methyl (2S,4R,5S)-5-(but-3-en-1-yl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate*

[00151] To a cooled (0 °C) solution of 1-(tert-butyl) 2-methyl (2S,4R)-5-(but-3-en-1-yl)-4-((tert-butyldimethylsilyl)oxy)-5-hydroxypyrrolidine-1,2-dicarboxylate (178 g, 414 mmol, 1.00 eq) in CH_2Cl_2 (1.80 L) was sequentially added TFA (472 g, 4.14 mol, 307 mL, 10.0 eq),

followed by Et_3SiH (241 g, 2.07 mol, 331 mL, 5.00 eq). The mixture was stirred 3 h while maintaining the reaction temperature between 0 °C to 25 °C. Two batches of equal scale were performed in parallel and combined during work-up. The combined reaction mixtures were concentrated to give a residue. The resultant residue was dissolved with EtOAc (2.00 L) and saturated aqueous $NaHCO_3$ was added until the aqueous layer was basic (pH ~8). The mixture was extracted with EtOAc (2.00 L x 3). The combined organic layers were washed with brine (2.00 L), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (petroleum ether/EtOAc = 1/0-10/1) to give methyl (2S,4R,5S)-5-(but-3-en-1-yl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate (102 g, 325 mmol, 39.3% yield for four steps) as yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.89 – 5.79 (m, 1H), 5.08 – 5.03 (m, 1H), 5.00 – 4.97 (m, 1H), 3.97 (t, J = 8.0 Hz, 1H), 3.89 – 3.84 (m, 1H), 3.74 (s, 3H), 2.94 – 2.90 (m, 1H), 2.24 – 2.11 (m, 3H), 2.04 – 1.96 (m, 2H), 1.73 – 1.61 (m, 1H), 1.51 – 1.42 (m, 1H), 0.89 (s, 9H), 0.06 (d, J = 1.0 Hz, 6H).

[00152] *Step 3: Preparation of methyl (2S,4R,5S)-5-(but-3-en-1-yl)-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-enoyl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate*

[00153] To a solution of methyl (2S,4R,5S)-5-(but-3-en-1-yl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate in DMF (1.00 L) was sequentially added N,N-diisopropylethylamine (283 mL, 1.63 mol, 5.00 eq), (S)-2-((tert-butoxycarbonyl)amino)pent-4-enoic acid (77.0 g, 358 mmol, 1.10 eq) and HATU (247 g, 651 mmol, 2.00 eq). The mixture was stirred at for 3 h at ambient temperatures and subsequently poured into water (2.00 L). The mixture was extracted with EtOAc (1.00 L x 3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (1.00 L x 3), saturated aqueous NH_4Cl (1.00 L), brine (1.00 L), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (petroleum ether/EtOAc = 1/0-10/1) to give methyl (2S,4R,5S)-5-(but-3-en-1-yl)-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-enoyl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate (121 g, 220 mmol, 67.5% yield, 92.7% purity) as yellow oil. LCMS (ESI) m/z = 511.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 – 5.66 (m, 2H), 5.18 – 5.00 (m, 4H), 4.66 – 4.56 (m, 1H), 4.50 – 4.41 (m, 1H), 4.24 (d, J = 3.2 Hz, 1H), 4.16 – 4.04 (m, 1H), 3.98 – 3.95 (m, 1H), 3.80 – 3.71 (m, 3H), 2.58 – 2.48 (m, 1H), 2.43 – 2.27 (m, 2H), 2.24 – 2.13 (m, 3H), 2.09 – 2.01 (m, 1H), 1.85 – 1.75 (m, 1H), 1.44 – 1.39 (m, 9H), 0.89 – 0.82 (m, 9H), 0.09 – 0.04 (m, 6H).

[00154] *Step 4: Preparation of methyl (1R,3S,6S,11aS,Z)-6-((tert-butoxycarbonyl)amino)-1-((tert-butyldimethylsilyl)oxy)-5-oxo-2,3,5,6,7,10,11,11a-octahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylate*

[00155] To a solution of methyl (2S,4R,5S)-5-(but-3-en-1-yl)-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-enoyl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate (60.5 g, 118 mmol, 1.00 eq) in CH_2Cl_2 (1.20 L) was added 1st generation Grubb's catalyst (9.75 g, 11.9 mmol, 0.10 eq) under N_2 (g). The mixture was heated to 55 °C and stirred for 12 h. Two batches of equal scale were performed in parallel and were combined for work-up. The combined reaction mixtures were cooled to ambient temperatures and concentrated to give a residue. The residue was purified by column chromatography (petroleum ether/EtOAc = 1/0-10/1) to give methyl (1R,3S,6S,11aS,Z)-6-((tert-butoxycarbonyl)amino)-1-((tert-butyldimethylsilyl)oxy)-5-oxo-2,3,5,6,7,10,11,11a-octahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylate (70.8 g, 130 mmol, 54.9% yield, 88.6% purity) as brown oil. LCMS (ESI) m/z = 483.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 6.02 – 5.90 (m, 1H), 5.83 (d, J = 6.8 Hz, 1H), 5.71 – 5.49 (m, 1H), 4.78 (t, J = 9.0 Hz, 1H), 4.34 (t, J = 6.8 Hz, 1H), 4.10 – 4.07 (m, 1H), 3.88 – 3.82 (m, 1H), 3.75 (s, 3H), 2.66 – 2.58 (m, 1H), 2.51 – 2.38 (m, 1H), 2.35 – 2.30 (m, 1H), 2.27 – 2.18 (m, 1H), 2.16 – 2.09 (m, 2H), 1.54 – 1.46 (m, 2H), 1.42 (s, 9H), 0.80 (s, 9H), 0.09 – 0.03 (m, 6H).

[00156] *Step 5: Preparation of methyl (1R,3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-1-((tert-butyldimethylsilyl)oxy)-5-oxodecahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylate*

[00157] To a solution of methyl (1R,3S,6S,11aS,Z)-6-((tert-butoxycarbonyl)amino)-1-((tert-butyldimethylsilyl)oxy)-5-oxo-2,3,5,6,7,10,11,11a-octahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylate (70.8 g, 147 mmol, 1.00 eq) in EtOH (700 mL) was added Pd/C (7.00 g, 10% wt) under a constant stream of N_2 (g). The reaction mixture was degassed under vacuum and purged with H_2 (g) (3x). The reaction mixture was stirred under H_2 (g) (50 psi) for 12 h. The reaction mixture was filtered and the filter cake was washed with EtOH (200 mL x 3). The filtrate was concentrated to give a methyl (1R,3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-1-((tert-butyldimethylsilyl)oxy)-5-oxodecahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylate (65.0 g, 125 mmol, 85.5% yield, 93.5% purity) as an off-white solid. LCMS (ESI) m/z = 485.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 5.17 (d, J = 8.8 Hz, 1H), 4.86 – 4.76 (m, 1H), 4.70 – 4.65 (m, 1H), 4.10 (d, J = 2.0 Hz, 1H), 3.86 (d, J = 10.0 Hz, 1H), 3.77 (s, 3H), 2.20 – 2.15 (m, 1H), 2.13 – 2.03 (m, 1H), 2.02 – 1.94 (m, 1H), 1.88 – 1.73 (m, 5H), 1.59 (s, 2H), 1.54 – 1.44 (m, 2H), 1.41 (s, 9H), 0.85 (s, 9H), 0.08 (d, J = 5.0 Hz, 6H).

[00158] *Step 6: Preparation of methyl (1R,3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-1-hydroxy-5-oxodecahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylate*

[00159] A cooled (-10 °C) solution of methyl (1R,3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-1-((tert-butyldimethylsilyl)oxy)-5-oxodecahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylate (65.0 g, 134 mmol, 1.00 eq) in THF (650 mL) was added in a dropwise manner a 1 M solution of TBAF in THF (268 mL, 2.00 eq). The reaction mixture was stirred at 0 °C for 1 h and subsequently poured into water (1.50 L). The mixture was extracted with EtOAc (1.00 L x 2). The combined organic layers were washed with brine (1.00 L), dried over Na_2SO_4, filtered, and concentrated to give a residue. The residue was purified by column chromatography (petroleum ether/EtOAc = 1/0-3/2) to give methyl (1R,3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-1-hydroxy-5-oxodecahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylate (40.8 g, 107 mmol, 79.9% yield, 97.3% purity) as an off-white solid. LCMS (ESI) m/z = 371.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 5.22 (d, J = 8.0 Hz, 1H), 4.74 – 4.70 (m, 2H), 4.19 (d, J = 3.2 Hz, 1H), 4.01 (d, J = 10.0 Hz, 1H), 3.76 (s, 3H), 2.78 (s, 1H), 2.34 – 2.28 (m, 1H), 2.12 – 1.97 (m, 2H), 1.89 – 1.83 (m, 2H), 1.79 – 1.74 (m, 3H), 1.61 – 1.57 (m, 4H), 1.42 (s, 9H).

[00160] *Step 7: Preparation of methyl (3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-5-oxo-5,6,7,8,9,10,11,11a-octahydro-3H-pyrrolo[1,2-a]azonine-3-carboxylate*

[00161] To a cooled (–78 °C) solution of methyl (1R,3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-1-hydroxy-5-oxodecahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylate (12.0 g, 32.4 mmol, 1.00 eq) in CH_2Cl_2 (120 mL) was slowly added DAST (25.7 mL, 194 mmol, 6.00 eq) under N_2 (g). After complete addition of DAST, the mixture was allowed to warm to 25 °C and stirred for 8 h. The reaction mixture was cooled to at 0 °C and subsequently quenched by addition of saturated aqueous $NaHCO_3$ (300 mL). The biphasic mixture was extracted with CH_2Cl_2 (200 mL x 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated to give a residue. The residue was purified by column chromatography (petroleum ether/EtOAc = 1/0-3/1) to give methyl (3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-5-oxo-5,6,7,8,9,10,11,11a-octahydro-3H-pyrrolo[1,2-a]azonine-3-carboxylate (3.00 g, 8.36 mmol, 25.8% yield, 98.2% purity) as a white solid. LCMS (ESI) m/z = 353.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 – 5.78 (m, 2H), 5.43 (s, 1H), 5.18 (d, J = 8.0 Hz, 1H), 4.88 – 4.74 (m, 2H), 3.77 (s, 3H), 2.04 – 1.93 (m, 2H), 1.89 – 1.76 (m, 4H), 1.63 – 1.55 (m, 4H), 1.43 (s, 9H).

[00162] *Step 8: Preparation of methyl (3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylate*

[00163] To a solution of methyl (3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-5-oxo-5,6,7,8,9,10,11,11a-octahydro-3H-pyrrolo[1,2-a]azonine-3-carboxylate (3.00 g, 8.51 mmol, 1.00 eq) in MeOH (30.0 mL) was added Pd/C (0.60 g, 10% wt) under a constant stream of N_2 (g). The mixture was degassed under vacuum and purged with H_2 (g) (15 psi) (3x). The mixture was heated to 45 °C and stirred at under H_2 (g) (15 psi) for 22 h. The mixture was filtered, and the filter cake was washed with MeOH (50.0 mL x 3). The filtrate was concentrated to give a residue. The residue was dissolved with acetonitrile (5.00 mL) and H_2O (30.0 mL) and subsequently lyophilized to give methyl (3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylate (5.72 g, 15.9 mmol, 94.2% yield, 98.2% purity) as an off-white solid. LCMS (ESI) m/z = 355.1 [M+H[+; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (d, J = 8.8 Hz, 1H), 4.89 – 4.78 (m, 1H), 4.60 – 4.51 (m, 1H), 4.22 – 4.13 (m, 1H), 3.76 (s, 3H), 2.30 – 2.18 (m, 2H), 2.01 (s, 2H), 1.83 – 1.73 (m, 7H), 1.60 – 1.55 (m, 3H), 1.43 (s, 9H).

[00164] *Step 9: Preparation of (3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylic acid*

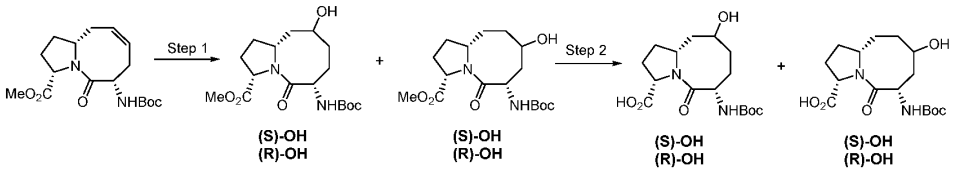
[00165] To a cooled (0 °C) solution of methyl (3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylate (1.00 g, 2.82 mmol, 1.00 eq) in THF (10 mL) was added LiOH▪H_2O (153 mg, 3.66 mmol, 1.3 eq) and water (10 mL). The mixture was stirred for 16 h, and subsequently acidified with $NaHSO_4$. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4 and concentrated to give (3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylic acid (855 mg, 2.51 mmol, 89.1% yield) as a solid. LCMS (ESI) m/z = 341.4 $[M+H]^+$.

[00166] *Step 10: Preparation of methyl (1R,3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-1-hydroxy-5-oxodecahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylate*

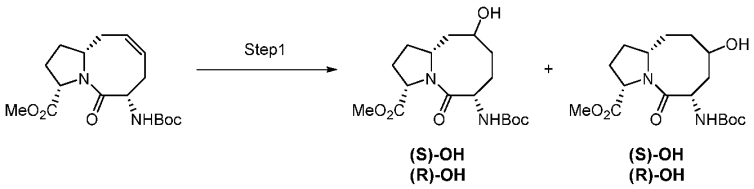
[00167] Methyl (1R,3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-1-hydroxy-5-oxodecahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylate was prepared using the hydrolysis procedure described above for the preparation of (3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylic acid and starting from methyl (1R,3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-1-hydroxy-5-oxodecahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylate. Starting from methyl (1R,3S,6S,11aS)-6-((tert-butoxycarbonyl)amino)-1-hydroxy-5-oxodecahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylate (500 mg, 1.34 mmol. 1.00 eq), LiOH▪H_2O (107 mg, 2.68 mmol, 2.0 eq), THF (12 mL), and water (4 mL) afforded methyl (1R,3S,6S,11aS)-6-

((tert-butoxycarbonyl)amino)-1-hydroxy-5-oxodecahydro-1H-pyrrolo[1,2-a]azonine-3-carboxylate (340 mg, 0.953 mmol, 71.2% yield) as solids. LCMS (ESI) m/z = 357.3 $[M+H]^+$.

Synthesis of (3*S*,6*S*,9*R*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-9-hydroxy-5-oxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylic acid, (3S,6S,9S,10aR)-6-((tert-butoxycarbonyl)amino)-9-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid, (3S,6S,8S,10aR)-6-((tert-butoxycarbonyl)amino)-8-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid, (3S,6S,8R,10aR)-6-((tert-butoxycarbonyl)amino)-8-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid



[00168] *Step 1: Preparation of methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-9-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate and methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-8-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate*



[00169] Methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-9-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate and methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-8-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate were prepared starting from methyl (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate and utilizing similar protocols established in Journal of Medicinal Chemistry (2010), 53(17), 6361-6367.

[00170] The mixture of alcohol diastereoisomers and regioisomers were separated by reverse phase chromatography [C18 cartridge eluting with a gradient of 5-40% MeOH in water (with 0.1% formic acid)] followed by chiral SFC separation [Lux i-Cellulose-5 21.2 x 250 mm 5 um column, column temp = 40°C, flow rate 75 mL/min, 20% MeOH, cycle time: 5 min]. A representative reaction starting from methyl (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate (4.3 g, 12.7 mmol) afforded the following products:

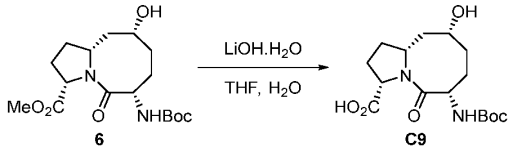
[00171] Peak 1: Methyl (3*S*,6*S*,9*R*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-9-hydroxy-5-oxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylate (760 mg, 2.13 mmol, 16.8% yield) as a white solid. LCMS (ESI) m/z = 357.2 $[M+H]^+$.

[00172] Peak 2: Methyl (3*S*,6*S*,9*S*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-9-hydroxy-5-oxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylate (375 mg, 19% yield) as a clear thick oil. LCMS (ESI) m/z = 357.2 $[M+H]^+$.

[00173] Peak 3: Methyl (3*S*,6*S*,8*R*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-8-hydroxy-5-oxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylate (795 mg, 40% yield) as a white foam. LCMS (ESI) m/z = 357.2 $[M+H]^+$.

[00174] Peak 4: Methyl (3*S*,6*S*,8*S*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-8-hydroxy-5-oxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylate (600 mg, 30% yield) as a white solid. LCMS (ESI) m/z = 357.2 $[M+H]^+$.

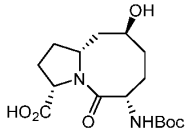
[00175] *Step 2: Preparation of (3S,6S,9R,10aR)-6-{[(tert-Butoxy)carbonyl]amino}-9-hydroxy-5-oxo-decahydropyrrolo[1,2-a]azocine-3-carboxylic acid.*

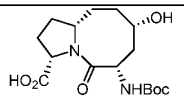
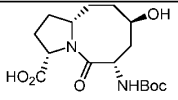


[00176] To a solution of methyl (3*S*,6*S*,9*R*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-9-hydroxy-5-oxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylate (Peak 1) (1.08 g, 3.03 mmol, 1 eq) in a mixture of THF (24 mL) and water (8 mL) was added LiOH▪H_2O (380 mg, 9.08 mmol, 3.0 eq). The reaction mixture was stirred at room temperature for 2 hours. The reaction was subsequently concentrated under reduced pressure to remove tetrahydrofuran. The crude residue was purified by reverse phase chromatography [C18 cartridge eluting with a gradient of 5-60% Acetonitrile in water (with 0.1% formic acid)] to give (3*S*,6*S*,9*R*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-9-hydroxy-5-oxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylic acid (780 mg, 76% yield) as a white solid. LCMS (ESI) m/z = 343.2 $[M+H]^+$.

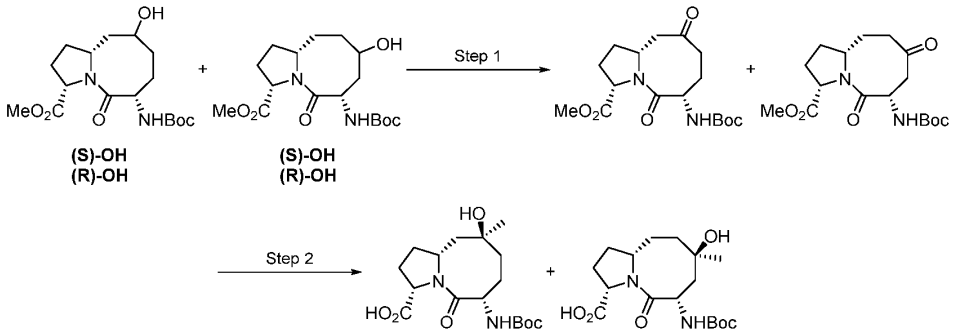
[00177] The following intermediates in **Table 13** were prepared according to the general procedure described above starting from the appropriate starting materials.

Table 13

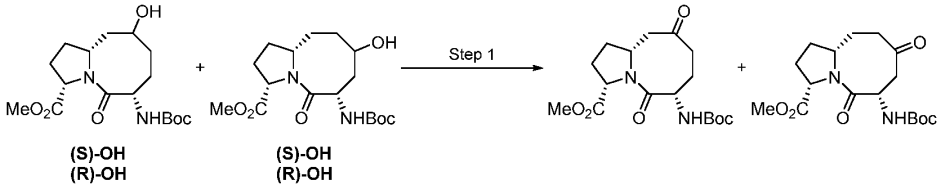
Name	Structure	LCMS
(3S,6S,9S,10aR)-6-((tert-butoxycarbonyl)amino)-9-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid		343.2 $[M+H]^+$

(3S,6S,8S,10aR)-6-((tert-butoxycarbonyl)amino)-8-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid	 Peak 4 of starting material building block used for synthesis	343.2 $[M+H]^+$
(3S,6S,8R,10aR)-6-((tert-butoxycarbonyl)amino)-8-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid	 Peak 3 of starting material building block used for synthesis	343.2 $[M+H]^+$

Synthesis of (3S,6S,9S,10aR)-6-{[(tert-butoxy)carbonyl]amino}-9-hydroxy-9-methyl-5-oxo-decahydropyrrolo[1,2-a]azocine-3-carboxylic acid and (3S,6S,8R,10aR)-6-((tert-butoxycarbonyl)amino)-8-hydroxy-8-methyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid



[00178] *Step 1: Preparation of methyl (3S,6S,10aR)-6-{[(tert-butoxy)carbonyl]amino}-5,9-dioxo-decahydropyrrolo[1,2-a]azocine-3-carboxylate and methyl (3S,6S,10aR)-6-{[(tert-butoxy)carbonyl]amino}-5,8-dioxo-decahydropyrrolo[1,2-a]azocine-3-carboxylate*



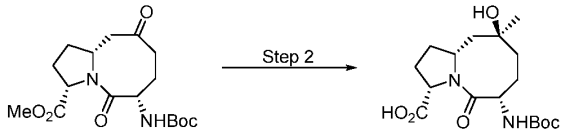
[00179] Methyl (3S,6S,10aR)-6-{[(tert-butoxy)carbonyl]amino}-5,9-dioxo-decahydropyrrolo[1,2-a]azocine-3-carboxylate and methyl (3S,6S,10aR)-6-{[(tert-butoxy)carbonyl]amino}-5,8-dioxo-decahydropyrrolo[1,2-a]azocine-3-carboxylate were prepared using the protocol described in US 2009/0123480. The crude reaction mixture was purified by reverse phase chromatography using a [C18 cartridge eluting with a gradient of 5-

100 % acetonitrile in water (with 0.1% FA)] to give a mixture of ketone isomers (1.2 g) as a beige solid. The resultant ketone isomers were separated chiral SFC separation (Column Lux i-Cellulose-5 21.2 x 250 mm 5 um column, flow rate 75 mL/min, 15% MeOH) to give methyl (3*S*,6*S*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-5,9-dioxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylate (**9**) (424 mg, 35.6% yield) as a white solid and methyl (3*S*,6*S*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-5,8-dioxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylate (433 mg, 36.3% yield) as a white solid.

[00180] Methyl (3*S*,6*S*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-5,9-dioxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylate: LCMS (ESI) m/z = 299.1 $[M+H]^+$; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.27 (d, J = 8.1 Hz, 1H), 4.59 (t, J = 8.7 Hz, 1H), 4.45 – 4.31 (m, 2H), 3.80 (s, 3H), 3.20 (td, J = 12.5, 4.9 Hz, 1H), 3.06 (t, J = 12.0 Hz, 1H), 2.47 – 2.15 (m, 5H), 2.13 – 2.00 (m, 1H), 1.87 (dd, J = 12.1, 7.0 Hz, 1H), 1.68 – 1.62 (m, 1H), 1.41 (s, 9H).

[00181] Methyl (3*S*,6*S*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-5,8-dioxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylate: LCMS (ESI) m/z = 299.1 $[M+H]^+$; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.56 (d, J = 7.6 Hz, 1H), 5.13 (ddd, J = 12.2, 7.6, 4.9 Hz, 1H), 4.51 (t, J = 8.8 Hz, 1H), 4.33 – 4.23 (m, 1H), 3.73 (s, 3H), 3.07 (dd, J = 13.8, 4.5 Hz, 1H), 2.96 (td, J = 11.9, 2.9 Hz, 1H), 2.65 – 2.50 (m, 2H), 2.36 – 1.91 (m, 4H), 1.90 – 1.76 (m, 2H), 1.45 (s, 9H).

[00182] *Step 2: Preparation of (3S,6S,9S,10aR)-6-{[(tert-Butoxy)carbonyl]amino}-9-hydroxy-9-methyl-5-oxo-decahydropyrrolo[1,2-a]azocine-3-carboxylic acid*

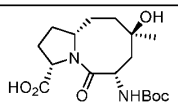


[00183] To a cooled (–78 °C) solution of methyl (3*S*,6*S*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-5,9-dioxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylate (250 mg, 705 µmol, 1 eq) in THF (15 mL) was added a 3 M solution of MeMgCl in THF (480 µL, 1.44 mmol, 2.05 eq). The reaction mixture was slowly warmed to 0 °C with stirring for 2 h and subsequently quenched with saturated aq. NH_4Cl. The product was extracted with EtOAc (2x) and the combined organic layers were dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by reverse phase chromatography [C18 cartridge eluting with a gradient of 5-60% Acetonitrile in water (with 0.1% formic acid)] to yield the resultant tertiary alcohol (240 mg, 647 µmol, 93.3%) as a white solid [as a 1:1 mixture of ketone and tertiary alcohol ratio based on ^{1}H NMR]. This mixture was dissolved in tetrahydrofuran (6 mL) and water (2 mL) and $LiOH{\cdot}H_2O$ (81.4 mg, 1.94 mmol, 3 eq) was

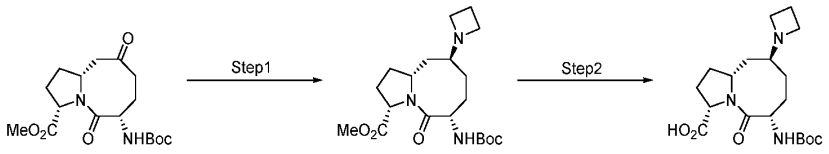
then added. The reaction mixture was stirred for 4 h at room temperature. The reaction was concentrated under reduced pressure and purified by reverse phase chromatography [C18 cartridge, elution gradient: 5-60% Acetonitrile in water (with 0.1% FA)]. The pure fractions were combined and evaporated to dryness to give (3*S*,6*S*,9*S*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-9-hydroxy-9-methyl-5-oxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylic acid (82.0 mg, 230 µmol, 35.6% yield) as a white solid. LCMS (ESI) m/z = 357.2 $[M+H]^+$.

[00184] The following intermediate in **Table 14** was prepared according to the protocol outlined above and starting from methyl (3*S*,6*S*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-5,8-dioxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylate.

Table 14

Name	Structure	LCMS
(3S,6S,8R,10aR)-6-((tert-butoxycarbonyl)amino)-8-hydroxy-8-methyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid		357.2 $[M+H]^+$

Synthesis of (3S,6S,9S,10aR)-9-(azetidin-1-yl)-6-{[(tert-butoxy)carbonyl]amino}-5-oxo-decahydropyrrolo[1,2-a]azocine-3-carboxylic acid



[00185] *Step 1: Preparation of methyl (3S,6S,9S,10aR)-9-(azetidin-1-yl)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate*

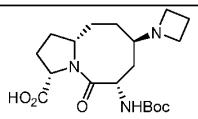
[00186] To a solution of methyl (3*S*,6*S*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-5,9-dioxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylate (150 mg, 0.4232 mmol, 1 eq) and AcOH (26.5 µL, 465 µmol, 1.1 eq) in CH_2Cl_2 (10 mL) was added azetidine (55.7 µL, 846 µmol, 2 eq). The mixture was stirred for 2 h at room temperature. To the mixture was added $NaBH(OAc)_3$ (134 mg, 634 µmol, 1.5 eq) was added and the reaction was stirred for 1.5 h at room temperature. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (10 mL). The product was extracted with CH_2Cl_2 (3x). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure to give crude methyl (3S,6S,9S,10aR)-9-(azetidin-1-yl)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate as a white solid. LCMS (ESI) m/z = 396.3 $[M+H]^+$.

[00187] *Step 2: Preparation of (3S,6S,9S,10aR)-9-(azetidin-1-yl)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid*

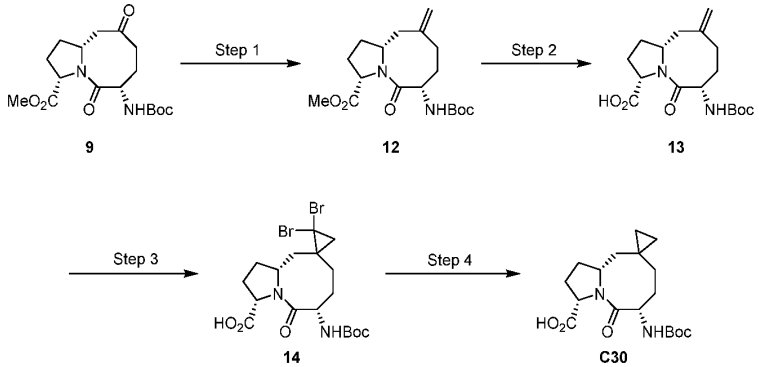
[00188] To a solution of methyl (3S,6S,9S,10aR)-9-(azetidin-1-yl)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (180 mg, 0.4551 mmol) in THF (24 mL) and water (8 mL) was added $LiOH \cdot H_2O$ (57.0 mg, 1.36 mmol). The reaction was stirred for 4 h at room temperature. The reaction was then concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography [C18 cartridge eluting with a gradient of 0-40% acetonitrile in water]. The pure fractions were concentrated to dryness and the product was subsequently lyophilized to give (3S,6S,9S,10aR)-9-(azetidin-1-yl)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid (140 mg, 0.3669 mmol, 80.9% yield) as a white solid. LCMS (ESI) m/z = 382.4 $[M+H]^+$.

[00189] The following intermediate in **Table 15** was prepared according to the procedure outlined above and starting from methyl (3*S*,6*S*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-5,8-dioxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylate.

Table 15

Name	Structure	LCMS
(3S,6S,8R,10aS)-8-(azetidin-1-yl)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid		382.4 $[M+H]^+$

Synthesis of (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-5-oxooctahydro-1H-spiro[cyclopropane-1,9-pyrrolo[1,2-a]azocine]-3-carboxylic acid



[00190] *Step 1: Preparation of methyl (3S,6S,10aR)-6-{[(tert-butoxy)carbonyl]amino}-9-methylidene-5-oxo-decahydropyrrolo[1,2-a]azocine-3-carboxylate*

[00191] To a cooled (0 °C) solution of methyltriphenylphosphonium bromide (628 mg, 1.76 mmol, 2.5 eq) in THF (10 mL) was added a solution of 1.0 M NaHMDS in THF (1.76

mL, 1.76 mmol, 2.5 eq). The resulting yellow suspension was warmed up to room temperature and stirred for 30 min. The yellow suspension was cooled to 0 °C, followed by addition of a solution of methyl (3*S*,6*S*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-5,9-dioxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylate (250 mg, 0.7054 mmol, 1 eq) in THF (10 mL). The resulting reaction mixture was stirred for 10 min and subsequently warmed to ambient temperatures over 1.5 h. The reaction mixture was quenched by the addition of brine (10 mL) and the product was extracted with EtOAc (30 mL x 2). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by reverse phase chromatography [C18 cartridge eluting with a gradient of 5-60% acetonitrile with 10 mM ammonium bicarbonate/ammonium hydroxide buffer pH = 10] to give methyl (3*S*,6*S*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-9-methylidene-5-oxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylate (210 mg, 0.5958 mmol, 84.6% yield) as a white solid. LCMS (ESI) m/z = 353.2 $[M+H]^+$.

[00192] *Step 2: Preparation of (3S,6S,10aR)-6-{[(tert-Butoxy)carbonyl]amino}-9-methylidene-5-oxo-decahydropyrrolo[1,2-a]azocine-3-carboxylic acid*

[00193] To a solution of methyl (3*S*,6*S*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-9-methylidene-5-oxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylate (210 mg, 0.5958 mmol, 1 eq) in THF (6 mL) and water (2 mL) was added $LiOH \cdot H_2O$ (74.6 mg, 1.78 mmol, 3 eq). The reaction was stirred for 20 h at room temperature. The reaction was then concentrated under reduced pressure and purified by reverse phase chromatography [C18 cartridge eluting with a gradient of 5-60% acetonitrile in water (with 0.1% FA)] to give (3*S*,6*S*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-9-methylidene-5-oxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylic acid (186 mg, 0.5496 mmol, 92.5% yield) as a white solid. LCMS (ESI) m/z = 339.2 $[M+H]^+$.

[00194] *Step 3: Preparation of (3S,6S,10aR)-2,2-Dibromo-6-((tert-butoxycarbonyl)amino)-5-oxooctahydro-1H-spiro[cyclopropane-1,9-pyrrolo[1,2-a]azocine]-3-carboxylic acid*

[00195] To a solution of (3*S*,6*S*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-9-methylidene-5-oxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylic acid (186 mg, 0.5496 mmol, 1 eq) in CH_2Cl_2 (2 mL) was added bromoform (384 µL, 4.35 mmol, 7.9 eq) and TEBAC (15.0 mg, 65.9 µmol, 0.12 eq), followed by addition of a 50% wt aqueous solution of NaOH (0.56 mL, 7.0 mmol, 12.7 eq). The reaction was heated at reflux for 21 h. The reaction mixture was then diluted with 1 N aqueous NaOH and the product was extracted with CH_2Cl_2. The organic layer was concentrated under reduced pressure and dried under high vacuum. The resulting

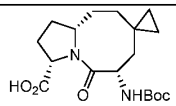
residue was purified by reverse phase chromatography [C18 cartridge using a gradient of 5-80% acetonitrile in water (with 0.1% FA)] to give (3*S*,6*S*,10*aR*)-2,2-dibromo-6-((*tert*-butoxycarbonyl)amino)-5-oxooctahydro-1*H*-spiro[cyclopropane-1,9-pyrrolo[1,2-*a*]azocine]-3-carboxylic acid (175 mg, 0.3429 mmol, 62.5% yield) as a white solid. LCMS (ESI) m/z = 509.0 $[M+H]^+$.

[00196] *Step 4: Preparation of (3S,6S,10aR)-6-((tert-Butoxycarbonyl)amino)-5-oxooctahydro-1H-spiro[cyclopropane-1,9-pyrrolo[1,2-a]azocine]-3-carboxylic acid*

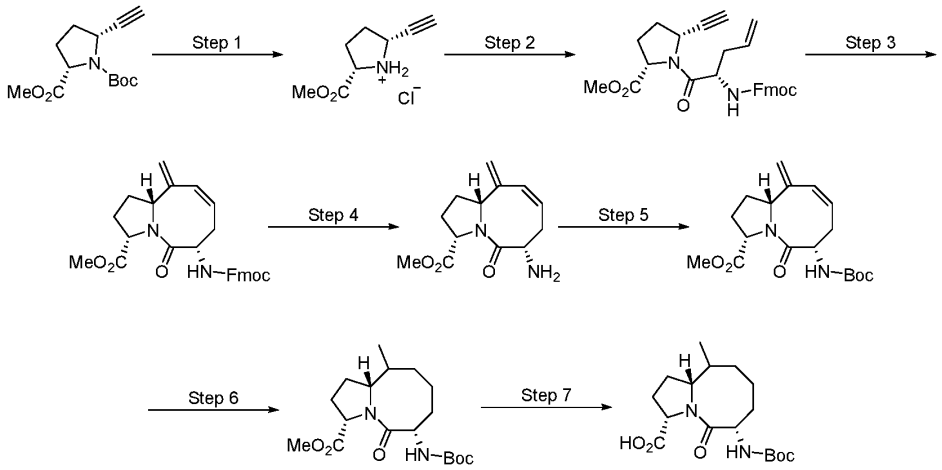
[00197] To a solution of (3*S*,6*S*,10*aR*)-2,2-dibromo-6-((*tert*-butoxycarbonyl)amino)-5-oxooctahydro-1*H*-spiro[cyclopropane-1,9-pyrrolo[1,2-*a*]azocine]-3-carboxylic acid (175 mg, 0.3429 mmol, 1 eq) in 2-propanol (6 mL) under N_2 (g) atmosphere was added KOH (115 mg, 2.05 mmol, 6 eq) and 10% Pd/C (50% wet, 170 mg, 0.1597 mmol, 0.466 eq). The reaction mixture was heated to 70 °C under H_2 (g) (40 psi) for 21 h. The reaction mixture was then diluted with MeOH and filtered over a pad of Celite®. The filtrate was concentrated under reduced pressure and subsequently purified by reverse phase chromatography [C18 cartridge eluting with a gradient of 5-70% acetonitrile in water (with 0.1% FA)] to give (3*S*,6*S*,10*aR*)-6-((*tert*-butoxycarbonyl)amino)-5-oxooctahydro-1*H*-spiro[cyclopropane-1,9-pyrrolo[1,2-*a*]azocine]-3-carboxylic acid (104 mg, 0.2950 mmol, 86.6% yield) as a white solid. LCMS (ESI) m/z = 353.2 $[M+H]^+$.

[00198] The following intermediate in **Table 16** was prepared according to the steps (Steps 1 – 4) outlined above for synthesis of (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-5-oxooctahydro-1H-spiro[cyclopropane-1,9-pyrrolo[1,2-a]azocine]-3-carboxylic acid and starting from methyl (3*S*,6*S*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-5,8-dioxo-decahydropyrrolo[1,2-*a*]azocine-3-carboxylate.

Table 16

Name	Structure	LCMS
(3'S,6'S,10a'S)-6'-((tert-butoxycarbonyl)amino)-5'-oxooctahydro-5'H-spiro[cyclopropane-1,8'-pyrrolo[1,2-a]azocine]-3'-carboxylic acid		382.4 $[M+H]^+$

Synthesis of (3S,6S,10S,10aR)-6-amino-10-methyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid



[00199] *Step 1: Preparation of methyl (2S,5R)-5-ethynylpyrrolidine-2-carboxylate hydrochloride*

[00200] To a solution of 1-(tert-butyl) 2-methyl (2S,5R)-5-ethynylpyrrolidine-1,2-dicarboxylate (52.0 g, 205 mmol, 1.00 eq) in EtOAc (260 mL) was added 4.0 M solution of HCl (154 mL, 3.00 eq) in EtOAc. After 3.5 h, the mixture was concentrated under reduced pressure to give methyl (2S,5R)-5-ethynylpyrrolidine-2-carboxylate hydrochloride (44.0 g, 232 mmol, HCl salt) as brown oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 4.74 – 4.71 (m, 1H), 4.62 (t, J = 7.2 Hz, 1H), 3.91 (s, 3H), 2.69 (d, J = 1.6 Hz, 1H), 2.61 – 2.35 (m, 3H), 2.21 – 2.14 (m, 1H).

[00201] *Step 2: Preparation of methyl (2S,5R)-1-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)pent-4-enoyl)-5-ethynylpyrrolidine-2-carboxylate*

[00202] To a mixture of methyl (2S,5R)-5-ethynylpyrrolidine-2-carboxylate hydrochloride (44.0 g, 232 mmol, 1.00 eq, HCl) and (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)pent-4-enoic acid (62.6 g, 186 mmol, 0.80 eq) in CH_2Cl_2 (880 mL) was added BOPCl (59.1 g, 232 mmol, 1.00 eq) and $NaHCO_3$ (78.0 g, 928 mmol, 36.1 mL, 4.00 eq) under N_2 (g). The mixture was heated to 40 °C and stirred After 2 h, the mixture cooled to ambient temperatures and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether / EtOAc = 100 / 1 to 4 / 1) to give methyl (2S,5R)-1-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)pent-4-enoyl)-5-ethynylpyrrolidine-2-carboxylate (85.0 g, 169 mmol, 93.9% purity) as yellow oil. LCMS (ESI) m/z = 473.0 $[M+H]^+$; ^{1}H NMR (400 MHz $CDCl_3$) δ 7.76 (d, J = 7.6 Hz, 2H), 7.60 – 7.56 (m, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.33 – 7.30 (m, 2H), 5.92 – 5.81 (m, 1H), 5.50 (d, J = 8.4 Hz, 1H), 5.30 – 5.10 (m, 2H), 5.00 – 4.92 (m, 1H), 4.73 – 4.69 (m, 1H), 4.54 – 4.50 (m,

1H), 4.40 – 4.35 (m, 1H), 4.31 – 4.27 (m, 1H) , 4.23 – 4.19 (m, 1H), 3.76 – 3.70 (m, 2H), 2.80 – 2.75 (m, 1H), 2.58 – 2.53 (m, 1H), 2.50 – 2.49 (m, 1H), 2.37 – 2.31 (m, 1H), 2.27 – 2.18 (m, 3H).

[00203] *Step 3: Preparation of methyl (3S,6S,10aR,Z)-6-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-10-methylene-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate*

[00204] A solution of methyl (2S,5R)-1-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)pent-4-enoyl)-5-ethynylpyrrolidine-2-carboxylate in toluene (2.80 L) was sparged with ethylene for 10 min. To the solution was added Grubbs Generation I catalyst (3.65 g, 5.82 mmol, 0.05 eq) and the mixture was stirred under an atmosphere of ethylene. Three batches of equal scale were performed in parallel and combined for work-up. After 3 h, the reaction mixture was concentrated *in vacuo*. The resulting product was purified by reversed phase HPLC (0.10% formic acid condition) to afford methyl (3S,6S,10aR,Z)-6-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-10-methylene-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate (43.0 g, 87.1 mmol, 95.7% purity) as black brown oil. LCMS (ESI) m/z = 473.0 $[M+H]^+$; ^{1}H NMR (400 MHz $CDCl_3$) δ 7.77 (d, J = 7.6 Hz, 2H), 7.62 – 7.58 (m, 2H), 7.41 (t, J = 7.2 Hz, 2H), 7.33 – 7.29 (m, 2H), 6.24 – 6.15 (m, 1H), 5.94 – 5.81 (m, 1H),5.58 (d, J = 8.8 Hz, 1H), 5.27 – 5.16 (m, 1H), 5.04 – 5.01 (m, 1H), 4.81 – 4.69 (m, 1H), .4.54 – 4.50 (m, 1H), 4.40 – 4.20 (m, 3H), 3.77 – 3.70 (m, 3H) , 2.79 – 2.66 (m, 1H), 2.57 – 2.49 (m, 1H), 2.38 – 2.16 (m, 3H), 2.11 – 2.07 (m, 1H).

[00205] *Step 4: Preparation of methyl (3S,6S,10aR,Z)-6-amino-10-methylene-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate*

[00206] To a solution of methyl (3S,6S,10aR,Z)-6-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-10-methylene-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate (13.0 g, 27.5 mmol, 1.00 eq) in THF (260 mL) was added piperidine (7.03 g, 82.5 mmol, 8.15 mL, 3.00 eq). After stirring for 2 h, the mixture was poured into a solution of aqueous 2 N HCl (200 mL) and the biphasic mixture was extracted with EtOAc (200 mL x 2). The combined organic layers were discarded and the aqueous phase was basified with $NaHCO_3$ (adjusted to pH= 8–9). The resulting basic aqueous layer was extracted with EtOAc (200 mL x 2). The combined organic layers were discarded, the aqueous phase was collected to give a crude product. The crude product was purified by prep-HPLC (Phenomenex luna c18 250 mm * 100 mm * 10 um; mobile phase: [water (TFA) – acetonitrile]; B%: 10% – 30%, 20 min) and lyophilizated to give methyl (3S,6S,10aR,Z)-6-amino-10-methylene-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate

(2.65 g, 10.6 mmol, 38.5% yield) as a white solid. LCMS (ESI) m/z = 250.9 $[M+H]^+$; ^1H NMR (400 MHz $CDCl_3$) δ 8.30 (s, 3H), 6.30 – 6.23 (m, 1H), 5.89 (t, J = 4.0 Hz, 1H), 5.29 – 5.25 (m, 1H), 5.04 – 5.01 (m, 1H), 4.88 (s, 1H), 4.63 – 4.61 (m, 1H), 4.46 (s, 1H), 3.61 (s, 3H), .2.49 – 2.43 (m, 1H), 2.39 – 2.03 (m, 1H), 1.93 – 1.92 (m, 1H) , 1.91 – 1.82 (m, 1H).

[00207] *Step 5: Preparation of methyl (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-10-methylene-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate*

[00208] To a solution of methyl (3S,6S,10aR,Z)-6-amino-10-methylene-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate (2.55 g, 10.2 mmol, 1.00 eq) and Et_3N (2.06 g, 20.4 mmol, 2.84 mL, 2.00 eq) in CH_2Cl_2 (25.5 mL) was added Boc_2O (2.45 g, 11.2 mmol, 2.57 mL, 1.10 eq). The reaction was stirred for 2 h and subsequently poured into aqueous saturated NH_4Cl (50.0 mL). The biphasic mixture was extracted with EtOAc (30.0 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc = 100 / 1 to 10 / 1) to give methyl (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-10-methylene-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate (1.52 g, 4.26 mmol, 98.1% purity, 41.8% yield) as colorless oil. LCMS (ESI) m/z = 251.2 $[(M–100)+H]^+$; ^1H NMR (400 MHz $CDCl_3$) δ 6.21 – 6.14 (m, 1H), 5.90 (d, J = 4.0 Hz, 1H), 5.76 (d, J = 3.2 Hz, 1H), 5.20 (d, J = 8.4 Hz, 1H), 4.99 (d, J = 5.4 Hz, 1H),4.79 – 4.72 (m, 3H), 4.65 – 4.61 (m, 1H), 3.71 (s, 3H), .2.61 – 2.59 (m, 1H), 2.53 – 2.38 (m, 2H), 2.07 – 2.04 (m, 2H) , 1.43 (s, 9H).

[00209] *Step 6: Preparation of methyl (3S,6S,10S,10aR)-6-amino-10-methyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate*

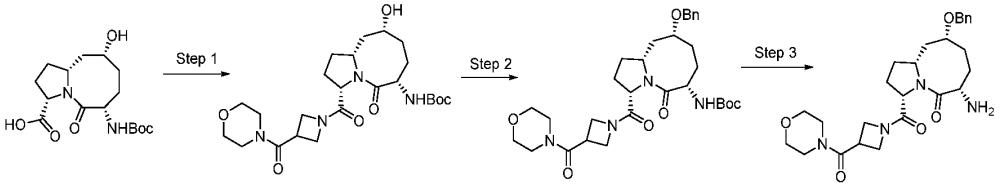
[00210] To a solution (under N_2 (g)) of methyl (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-10-methylene-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate (1.52 g, 4.34 mmol, 1.00 eq) in EtOAc (15.2 mL) was carefully added 10% Pd/C (0.30 g, 868 umol, 0.20 eq) at 25 °C. The suspension was subjected to three cycles of evacuation and purging with H_2 (g). The mixture was stirred under H_2 (g) (50 Psi) at 25 °C. After stirring for 3 h, the reaction vessel was evacuated, and the reaction mixture was subjected to three cycles of evacuation and purging with N_2 (g). The reaction mixture was filtered over Celite® and the filter liquor was concentrated to give methyl (3S,6S,10S,10aR)-6-amino-10-methyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (1.14 g, crude) as colorless oil. LCMS (ESI) m/z = 355.0 $[M+H]^+$.

[00211] *Step 7: Preparation of (3S,6S,10S,10aR)-6-amino-10-methyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid*

[00212] To a solution of methyl (3S,6S,10S,10aR)-6-amino-10-methyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (1.16 g, 3.26 mmol, 1.00 eq) in THF (11.0 mL) was added a solution of $LiOH.H_2O$ (411 mg, 9.79 mmol, 3.00 eq) in H_2O (2.20 mL). After 12 h, H_2O (20.0 mL) was added to the reaction mixture and the solution was acidified with aqueous 1 N HCl to pH 2. The mixture was extracted with EtOAc (20.0 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 * 40 mm * 15 um; mobile phase: [water (TFA) – ACN]; B%: 31% – 61%, 10 min) and lyophilized to give (3S,6S,10S,10aR)-6-amino-10-methyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid (0.80 g, 2.35 mmol, 77.9% over two steps) as a white solid.

[00213] Two batches of equal scale were combined to yield (3S,6S,10S,10aR)-6-amino-10-methyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid (1.12 g, 4.66 mmol, 99.1% purity) as a white solid. LCMS (ESI) m/z = 241.0 $[(M–100)+H]^+$; ^1H NMR (400 MHz $CDCl_3$) δ 5.69 (d, J = 3.0 Hz, 1H), 4.75 – 4.66 (m, 1H), 4.35 – 4.32 (m, 1H), 4.05 (t, J = 8.8 Hz, 1H), 3.66 – 3.51 (m, 1H), 2.55 – 2.47 (m, 1H), 2.41 – 2.07 (m, 3H), 1.97 – 1.67 (m, 3H), 1.69 – 1.55 (m, 2H), 1.46 (s, 9H), 1.36 – 1.20 (m, 1H), 1.10 – 0.95 (m, 1H), 0.89 – 0.84 (m, 3H).

Synthesis of (3S,6S,9R,10aR)-6-amino-9-(benzyloxy)-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)octahydropyrrolo[1,2-a]azocin-5(1H)-one



[00214] *Step 1: Preparation of tert-butyl N-[(3S,6S,9R,10aR)-9-hydroxy-3-[3-(morpholine-4-carbonyl)azetidine-1-carbonyl]-5-oxo-decahydropyrrolo[1,2- a]azocin-6-yl]carbamate*

[00215] To a solution of (3*S*,6*S*,9*R*,10*aR*)-6-{[(*tert*-butoxy)carbonyl]amino}-9-hydroxy-5-oxodecahydropyrrolo[1,2-*a*]azocine-3-carboxylic acid (0.780 g, 2.27 mmol, 1 eq), 4-(azetidine-3-carbonyl)morpholine trifluoroacetic salt (645 mg, 2.27 mmol, 1 eq) and N,N-diisopropylethylamine (2.35 mL, 13.6 mmol, 6 eq) in DMF (10 mL) was added HATU (1.03 g, 2.72 mmol, 1.2 eq). The reaction was stirred at room temperature 2 h. The reaction mixture was then concentrated in vacuo and subsequently purified by reverse phase chromatography [C18 cartridge eluting with a gradient of 5-75% acetonitrile in water (with 0.1% FA)] to give

tert-butyl *N*-[(3*S*,6*S*,9*R*,10*aR*)-9-hydroxy-3-[3-(morpholine-4-carbonyl)azetidine-1-carbonyl]-5-oxo-decahydropyrrolo[1,2- *a*]azocin-6-yl]carbamate (1.16 g, 2.34 mmol, 103% yield) as a beige foam. LCMS (ESI) m/z = 495.3 $[M+H]^+$.

[00216] *Step 2: Preparation of tert-butyl ((3S,6S,9R,10aR)-9-(benzyloxy)-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate*

[00217] To a solution of *tert*-butyl *N*-[(3*S*,6*S*,9*R*,10*aR*)-9-hydroxy-3-[3-(morpholine-4-carbonyl)azetidine-1-carbonyl]-5-oxo-decahydropyrrolo[1,2-*a*]azocin-6-yl]carbamate (75 mg, 0.1516 mmol, 1 eq) in CH_2Cl_2 (3 mL) was added Et_3N (63.2 µL, 454 µmol, 3 eq) and TMSCl (28.7 µL, 227 µmol, 1.5 eq) and the mixture was stirred at room temperature. After 30 min, brine (10 mL) was added, and the organic materials were extracted with CH_2Cl_2 (10 mL x 2). The combined organic extracts were dried with sodium sulfate, filtered and concentrated *in vacuo* to give crude *tert*-butyl *N*-[(3*S*,6*S*,9*R*,10*aR*)-3-[3-(morpholine-4-carbonyl)azetidine-1-carbonyl]-5- oxo-9-[(trimethylsilyl)oxy]-decahydropyrrolo[1,2-*a*]azocin-6-yl]carbamate (85.9 mg, 0.1516 mmol, 100% yield) as a white solid.

[00218] A solution of *tert*-butyl *N*-[(3*S*,6*S*,9*R*,10*aR*)-3-[3-(morpholine-4-carbonyl)azetidine-1-carbonyl]-5-oxo-9-[(trimethylsilyl)oxy]-decahydropyrrolo[1,2-*a*]azocin-6-yl]carbamate (85.9 mg, 0.1516 mmol, 1 eq) in CH_2Cl_2 (5 mL) was cooled to –78 °C, followed by addition of benzaldehyde (22.9 µL, 227 µmol, 1.5 eq), Et_3SiH (36.1 µL, 227 µmol, 1.5 eq) and trimethylsilyl triflate (20.4 µL, 113 µmol, 0.75 eq). The reaction was stirred for 10 min at –78 °C and then stirred for 90 min at 0 °C. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (10 mL) and the product was extracted with in CH_2Cl_2 (10 mL x 3). The combined organic extracts were dried with sodium sulfate and filtered to give a solution of tert-butyl ((3S,6S,9R,10aR)-9-(benzyloxy)-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate

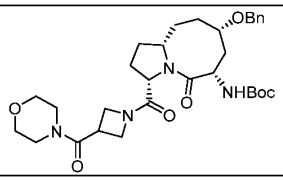
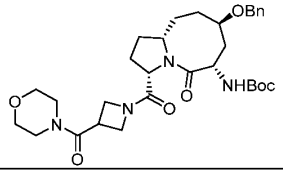
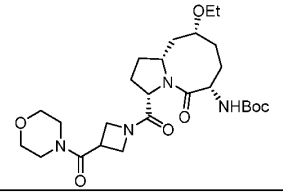
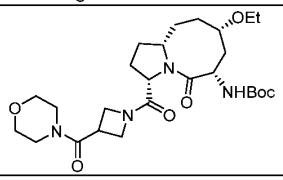
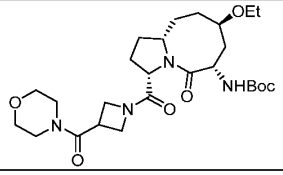
[00219] *Step 3: Preparation of (3S,6S,9R,10aR)-6-amino-9-(benzyloxy)-3-[3-(morpholine-4-carbonyl)azetidine-1-carbonyl]-decahydropyrrolo[1,2-a]azocin-5-one*

[00220] To the solution was added trifluoroacetic acid (0.5 mL) and the reaction was stirred for 30 min at room temperature then concentrated under reduced pressure. The reaction was purified by reverse phase chromatography [C18 cartridge eluting with a gradient of 5-40% Acetonitrile in water (with 0.1% FA)] to give (3*S*,6*S*,9*R*,10*aR*)-6-amino-9-(benzyloxy)-3-[3-(morpholine-4-carbonyl)azetidine-1-carbonyl]-decahydropyrrolo[1,2-

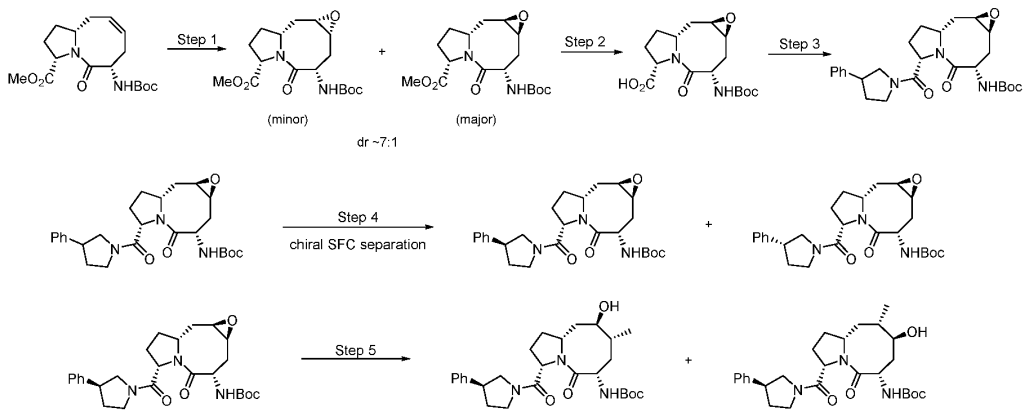
a]azocin-5-one (41.0 mg, 0.08460 mmol, 56.0% yield) as a white solid. LCMS (ESI) m/z = 485.4 $[M+H]^+$.

[00221] The following intermediates in **Table 17** were prepared according to the protocol outlined for synthesis of (3*S*,6*S*,9*R*,10*aR*)-6-amino-9-(benzyloxy)-3-[3-(morpholine-4-carbonyl)azetidine-1-carbonyl]-decahydropyrrolo[1,2-*a*]azocin-5-one and using the appropriate advanced intermediate(s) as starting materials. Where appropriate the final treatment with TFA (Step 3) was omitted and N-Boc protected amines were isolated.

Table 17

Name	Structure	LCMS
tert-butyl ((3S,6S,8S,10aR)-8-(benzyloxy)-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate		485.4 $[M+H]^+$
tert-butyl ((3S,6S,8R,10aR)-8-(benzyloxy)-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate		485.4 $[M+H]^+$
tert-butyl ((3S,6S,9R,10aR)-9-ethoxy-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate		523.3 $[M+H]^+$
tert-butyl ((3S,6S,8S,10aR)-8-ethoxy-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate		523.6 $[M+H]^+$
tert-butyl ((3S,6S,8R,10aR)-8-ethoxy-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate		523.6 $[M+H]^+$

Synthesis of tert-butyl ((3R,6R,8R,9R,10aS)-8,9-dihydroxy-5-oxo-3-(3-phenylpyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamate, tert-butyl ((3S,6S,8R,9R,10aR)-9-hydroxy-8-methyl-5-oxo-3-((S)-3-phenylpyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamate, and tert-butyl ((3S,6S,8S,9S,10aR)-8-hydroxy-9-methyl-5-oxo-3-((S)-3-phenylpyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamate



[00222] *Step 1: Preparation of methyl (1aS,3S,6S,8aR,9aR)-3-((tert-butoxycarbonyl)amino)-4-oxodecahydrooxireno[2,3-d]pyrrolo[1,2-a]azocine-6-carboxylate and methyl (1aR,3S,6S,8aR,9aS)-3-((tert-butoxycarbonyl)amino)-4-oxodecahydrooxireno[2,3-d]pyrrolo[1,2-a]azocine-6-carboxylate*

[00223] To a cooled (0 °C) solution of 1*H*-pyrazole (40.2 mg, 591 µmol, 0.1 eq), methyltrioxorhenium (14.7 mg, 59.1 µmol, 0.01 eq) and H_2O_2 (6.66 g, 59.1 mmol, 10 eq) in CF_3CH_2OH (3 mL) was slowly added methyl (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate (2.00 g, 5.91 mmol, 1 eq). The reaction mixture was warmed to room temperature and stirred for 4 h. To the mixture was added a solution of saturated aqueous $NaHSO_3$ and the mixture was extracted with CH_2Cl_2 (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over with anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by C18 column (gradient 15% to 60% acetonitrile in water) to give methyl (1aS,3S,6S,8aR,9aR)-3-((tert-butoxycarbonyl)amino)-4-oxodecahydrooxireno[2,3-d]pyrrolo[1,2-a]azocine-6-carboxylate (1.50 g, 4.23 mmol, 72% yield) as the major product major adduct and methyl (1aR,3S,6S,8aR,9aS)-3-((tert-butoxycarbonyl)amino)-4-oxodecahydrooxireno[2,3-d]pyrrolo[1,2-a]azocine-6-carboxylate (minor adduct) (190 mg, 0.54 mmol, 9% yield) as the minor adduct

[00224] Methyl (1aS,3S,6S,8aR,9aR)-3-((tert-butoxycarbonyl)amino)-4-oxodecahydrooxireno[2,3-d]pyrrolo[1,2-a]azocine-6-carboxylate (major diastereomer): LCMS (ESI) *m/z* = 355 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 5.51 (d, J = 6.9 Hz, 1H), 4.68 (dd, J = 14.9, 7.6 Hz, 1H), 4.60 – 4.48 (m, 1H), 4.27 – 4.13 (m, 1H), 3.74 (s, 3H), 3.29 – 3.20

(m, 1H), 3.18 – 3.08 (m, 1H), 2.55 – 2.36 (m, 2H), 2.34 – 2.13 (m, 3H), 2.09 – 1.91 (m, 3H), 1.42 (s, 9H).

[00225] Methyl (1aR,3S,6S,8aR,9aS)-3-((tert-butoxycarbonyl)amino)-4-oxodecahydrooxireno[2,3-d]pyrrolo[1,2-a]azocine-6-carboxylate (minor diastereomer): LCMS (ESI) *m/z* = 355 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (d, J = 6.4 Hz, 1H), 4.53 – 4.42 (m, 2H), 4.14 (t, J = 6.3 Hz, 1H), 3.75 (s, 3H), 3.31 – 3.19 (m, 1H), 3.11 – 3.06 (m, 1H), 2.37 – 2.27 (m, 2H), 2.25 – 2.11 (m, 3H), 2.03 – 1.87 (m, 3H), 1.44 (s, 9H).

[00226] *Step 2: Preparation of (1aS,3S,6S,8aR,9aR)-3-((tert-butoxycarbonyl)amino)-4-oxodecahydrooxireno[2,3-d]pyrrolo[1,2-a]azocine-6-carboxylic acid*

[00227] To a solution of methyl (1aS,3S,6S,8aR,9aR)-3-((tert-butoxycarbonyl)amino)-4-oxodecahydrooxireno[2,3-d]pyrrolo[1,2-a]azocine-6-carboxylate (390 mg, 1.10 mmol, 1.0 eq) in a mixture of THF (8 mL) and H_2O (2 mL) was added $LiOH \cdot H_2O$ (138 mg, 3.30 mmol, 3.0 eq). The reaction the mixture was stirred for 4 h at room temperature and subsequently acidified with an aqueous solution of 1 N HCl to pH = 5 – 6. The resulting acidic mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified on C18 column (gradient 15% to 60% acetonitrile in water) to give (1aS,3S,6S,8aR,9aR)-3-((tert-butoxycarbonyl)amino)-4-oxodecahydrooxireno[2,3-d]pyrrolo[1,2-a]azocine-6-carboxylic acid (300 mg, 0.88 mmol, 80% yield) as white solids. LCMS (ESI) *m/z* = 341 $[M+H]^+$.

[00228] *Step 3: Preparation of tert-butyl ((1aS,3S,6S,8aR,9aR)-4-oxo-6-(3-phenylpyrrolidine-1-carbonyl)decahydrooxireno[2,3-d]pyrrolo[1,2-a]azocin-3-yl)carbamate*

[00229] To a solution of (1aS,3S,6S,8aR,9aR)-3-((tert-butoxycarbonyl)amino)-4-oxodecahydrooxireno[2,3-d]pyrrolo[1,2-a]azocine-6-carboxylic acid (300 mg, 0.88 mmol, 1 eq), Et_3N (445 mg, 4.40 mmol, 5 eq) and *rac*-3-phenylpyrrolidine (129 mg, 0.88 mmol, 1 eq) in DMF (10 mL) was added HATU (399 mg, 1.05 mmol, 1.2 eq) in one portion. The resulting mixture was stirred at room temperature for additional 12 h and subsequently diluted with water (5 mL). The biphasic mixture was extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers and washed with brine (20 mL), dried over with anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel to afford tert-butyl ((1aS,3S,6S,8aR,9aR)-4-oxo-6-(3-phenylpyrrolidine-1-carbonyl)decahydrooxireno[2,3-d]pyrrolo[1,2-a]azocin-3-yl)carbamate (200 mg, 0.43 mmol, 48% yield) as clear oil. LCMS (ESI) m/z = 470.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 2H), 7.27 – 7.19 (m, 3H), 5.87 – 5.37 (m, 1H), 4.74 –

4.41 (m, 2H), 4.36 – 4.08 (m, 2H), 4.02 – 3.65 (m, 2H), 3.61 – 3.31 (m, 4H), 2.50 – 2.26 (m, 3H), 2.25 – 1.92 (m, 6H), 1.90 – 1.82 (m, 1H), 1.43 (s, 9H).

[00230] *Step 4: Preparation of tert-butyl ((1aS,3S,6S,8aR,9aR)-4-oxo-6-((S)-3-phenylpyrrolidine-1-carbonyl)decahydrooxireno[2,3-d]pyrrolo[1,2-a]azocin-3-yl)carbamate and tert-butyl ((1aS,3S,6S,8aR,9aR)-4-oxo-6-((R)-3-phenylpyrrolidine-1-carbonyl)decahydrooxireno[2,3-d]pyrrolo[1,2-a]azocin-3-yl)carbamate*

[00231] Rac-tert-butyl ((1aR,3R,6R,8aS,9aS)-4-oxo-6-(3-phenylpyrrolidine-1-carbonyl)decahydrooxireno[2,3-d]pyrrolo[1,2-a]azocin-3-yl)carbamate (600 mg, 1.27 mmol, 1 eq), triethylamine (976 mg, 9.65 mmol, 5 eq) and (3S)-3-phenylpyrrolidine (284 mg, 1.93 mmol, 1 eq) was separated by SFC (ChiralCel OX, 250×21.2mm I.D., 5μm, A for CO_2 and B for MeOH + 0.1% NH_4OH, 40 mL/min) to yield Peak 1: tert-butyl ((1aS,3S,6S,8aR,9aR)-4-oxo-6-((R)- or (S)-3-phenylpyrrolidine-1-carbonyl)decahydrooxireno[2,3-d]pyrrolo[1,2-a]azocin-3-yl)carbamate (400 mg, 0.8518 mmol, 67.1% yield). LCMS (ESI) m/z = 470.3 $[M+H]^+$ and Peak 2: tert-butyl ((1aS,3S,6S,8aR,9aR)-4-oxo-6-((S)- or (R)-3-phenylpyrrolidine-1-carbonyl)decahydrooxireno[2,3-d]pyrrolo[1,2-a]azocin-3-yl)carbamate (130 mg, 0.2768 mmol, 21.8% yield) as clear oil. LCMS (ESI) m/z = 470.3 $[M+H]^+$.

[00232] *Step 5: Preparation of tert-butyl ((3S,6S,8R,9R,10aR)-9-hydroxy-8-methyl-5-oxo-3-((S)-3-phenylpyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamate and tert-butyl ((3S,6S,8S,9S,10aR)-8-hydroxy-9-methyl-5-oxo-3-((S)-3-phenylpyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamate*

[00233] To a cooled (0 °C) solution of tert-butyl ((1aS,3S,6S,8aR,9aR)-4-oxo-6-((R)- or (S)-3-phenylpyrrolidine-1-carbonyl)decahydrooxireno[2,3-d]pyrrolo[1,2-a]azocin-3-yl)carbamate (Peak 1) (200 mg, 0.43 mmol, 1 eq) in toluene (5 mL) was slowly added $AlMe_3$ (613 mg, 8.51 mmol, 20 eq) in a dropwise manner. The reaction mixture was subsequently warmed to room temperature. After 30 min, the reaction mixture was cooled to 0 °C and MeOH (10 mL) was subsequently added to quench excess $AlMe_3$. The resulting mixture was concentrated under reduced pressure and purified on C18 column (gradient 20% to 70% acetonitrile in water) to give an inseparable regioisomeric mixtures of epoxide ring opened products (160 mg, 0.33 mmol, 77% yield). LCMS (ESI) *m/z* = 486.3 $[M+H]^+$; ^1H NMR (400 MHz, mixture of isomers, $CDCl_3$) δ 7.40 – 7.28 (m, 3H), 7.26 – 7.21 (m, 2H), 5.78 – 5.50 (m, 1H), 4.73 – 4.49 (m, 2H), 4.36 – 4.09 (m, 2H), 4.04 – 3.30 (m, 6H), 2.44 – 1.97 (m, 10H), 1.43 (s, 9H), 1.13 – 0.83 (m, 3H).

[00234] The mixture of regioisomeric ring opened products (60 mg, 0.124 mmol) was purified by SFC (ChiralPak R,R-WHELK, 250×21.2mm I.D., 5μm; Mobile phase: A for CO_2 and B for MeOH + 0.1% NH_4OH Gradient: B 25%; flow rate: 40 mL / min) to yield:

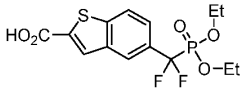
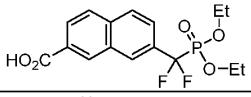
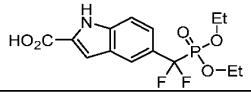
[00235] Peak 1: tert-butyl ((3S,6S,8R,9R,10aR)-9-hydroxy-8-methyl-5-oxo-3-((R)- or (S)-3-phenylpyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamate (3.00 mg, 0.006177 mmol). LCMS (ESI) m/z = 486.3 $[M+H]^+$.

[00236] Peak 2: tert-butyl ((3S,6S,8S,9S,10aR)-8-hydroxy-9-methyl-5-oxo-3-((S)- or (R)-3-phenylpyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamate (5.00 mg, 0.01029 mmol) as white solids. LCMS (ESI) m/z = 486.3 $[M+H]^+$.

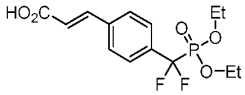
Procedures for Syntheses of Linkers:

[00237] The following intermediates in **Table 18** were prepared according to the protocol described in WO 2020/205467.

Table 18

Name	Structure
5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid	
7-((diethoxyphosphoryl)difluoromethyl)-2-naphthoic acid	
5-((diethoxyphosphoryl)difluoromethyl)-1H-indole-2-carboxylic acid	

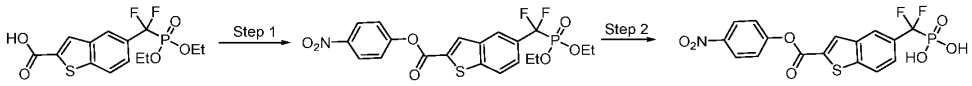
Synthesis of (E)-3-(4-((diethoxyphosphoryl)difluoromethyl)phenyl)acrylic acid



[00238] (E)-3-(4-((diethoxyphosphoryl)difluoromethyl)phenyl)acrylic acid was prepared according to protocol described in US 2004/0225146.

Representative Procedure for Preparation of Activated Ester Phosphonic Acids

Synthesis of (difluoro(2-((4-nitrophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid



[00239] *Step 1: Preparation of 4-nitrophenyl 5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate*

[00240] To a mixture of 5-[(diethoxyphosphoryl)difluoromethyl]-1-benzothiophene-2-carboxylic acid (10.0 g, 27.4 mmol), EDCI (7.85 g, 41.0 mmol) and DMAP (836 mg, 6.85

mmol) in CH_2Cl_2 (80 mL) was stirred at room temperature. After 15 min, 4-nitrophenol (4.75 g, 34.2 mmol) was added and the resulting yellow mixture was stirred at room temperature for 18 h. The reaction was quenched with water (30 mL) and the product was extracted with CH_2Cl_2 (10 mL x 2). The combined organic extracts were washed with brine, dried with sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by reverse phase chromatography [C18 cartridge eluting with a gradient of 5-100% acetonitrile in water] and the appropriate fractions were concentrated to give 4-nitrophenyl 5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (7.80 g, 16.0 mmol, 59.0% yield) as a yellow solid. LCMS m/z = 486.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 – 8.37 (m, 3H), 8.22 (s, 1H), 8.01 (d, J = 9.1 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1 H), 7.51 – 7.45 (m, 2 H), 4.14 – 4.32 (m, 4H), 1.34 (t, J = 7.8 Hz, 6H).

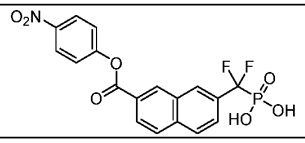
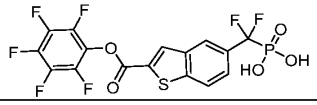
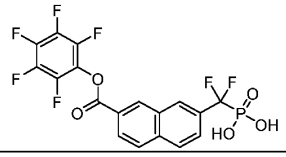
[00241] *Step 2: Preparation of (difluoro(2-((4-nitrophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid*

[00242] To a cooled (0 °C) solution of 4-nitrophenyl 5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (4.47 g, 9.20 mmol) in CH_2Cl_2 (39 mL) was added N,O-bis(trimethylsilyl)trifluoroacetamide (12.1 mL, 46.0 mmol) and iodotrimethylsilane (5.23 mL, 36.8 mmol) as a solution in CH_2Cl_2 (10 mL). The reaction mixture was gradually allowed to warm to ambient temperatures. To the reaction mixture was added a mixture of 2:1 H_2O / acetonitrile (with 0.1% TFA) (50 mL) and precipitation of product was observed. The volatiles were removed in vacuo and the crude residue was suspended in a mixture of acetonitrile/water solution (1:1 v/v, 100 mL). The suspension was filtered, the solids were washed with a 2:1 mixture acetonitrile/water solution, and the solid were dried under reduced pressure to afford [difluoro({2-[(4-nitrophenoxy)carbonyl]-1-benzothiophen-5-yl})methyl]phosphonic acid (6.5 g, 94%) as a beige solid. The filtrate was concentrated to 50% of solvent volume and the resulting suspension was filtered and washed with 1:2 acetonitrile/water solution. The solid was dried under reduced pressure to afford additional [difluoro({2-[(4-nitrophenoxy)carbonyl]-1-benzothiophen-5-yl})methyl]phosphonic acid (0.4 g) as a beige solid. Both products were lyophilized to give (difluoro(2-((4-nitrophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (6.90 g, 16.0 mmol, 98.0% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 – 7.74 (m, 3H), 8.27 (d, J = 8.3 Hz, 1H), 8.30 (s, 1H), 8.36 – 8.41 (m, 2H), 8.66 (s, 1H).

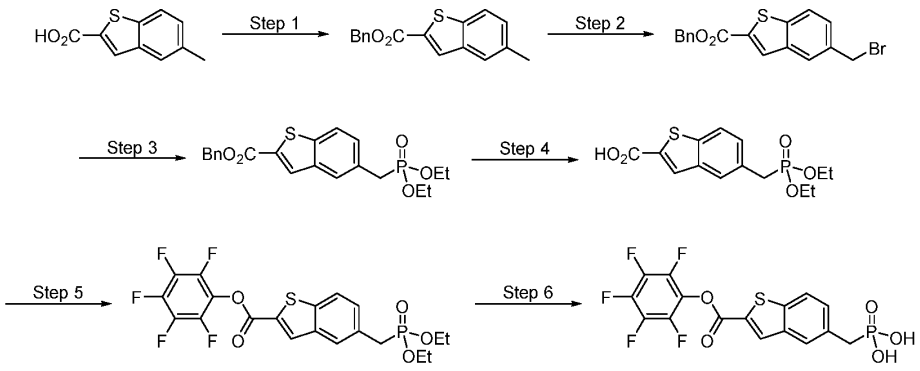
[00243] The following intermediates in **Table 19** were prepared using a similar protocol outlined above for synthesis of [difluoro({2-[(4-nitrophenoxy)carbonyl]-1-benzothiophen-5-

yl})methyl]phosphonic acid and utilizing the appropriate advanced intermediate(s) as starting material(s).

Table 19

Name	Structure	LC-MS
(difluoro(7-((4-nitrophenoxy)carbonyl)naphthalen-2-yl)methyl)phosphonic acid		424.1 $[M+H]^+$
(difluoro(2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		475.0 $[M+H]^+$
(difluoro(7-((perfluorophenoxy)carbonyl)naphthalen-2-yl)methyl)phosphonic acid		467.0 $[M–H]^-$

Synthesis of ((2-((perfluorophenoxy)carbonyl)benzo[*b*]thiophen-5-yl)methyl)phosphonic acid



[00244] *Preparation of 5-methylbenzo[b]thiophene-2-carboxylic acid*

[00245] 5-Methylbenzo[b]thiophene-2-carboxylic acid was prepared according to the procedure described in WO 2016/100184.

[00246] *Step 1: Preparation of benzyl 5-methylbenzo[b]thiophene-2-carboxylate*

[00247] To a solution of 5-methylbenzo[b]thiophene-2-carboxylic acid (21.2 g, 110.0 mmol, 1.0 eq) and K_2CO_3 (30.4 g, 220.0 mmol, 2.0 eq) in DMF (200 mL) was added benzyl bromide (20.6 g, 121.0 mmol, 1.1 eq). The mixture was stirred at room temperature for 14 h. The reaction mixture was poured into ice water (400 mL) and stirred for 5 min. The resulting solids were filtered, and the filter cake was washed with water (50 mL), dried in vacuum to give benzyl 5-methylbenzo[b]thiophene-2-carboxylate (30.1 g, 106.0 mmol, 97% yield) as a

yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.71 (t, *J* = 12.2 Hz, 1H), 7.65 (s, 1H), 7.46 (d, *J* = 6.8 Hz, 2H), 7.42 – 7.35 (m, 3H), 7.29 – 7.26 (m, 1H), 5.38 (s, 2H), 2.47 (s, 3H).

[00248] *Step 2: Preparation of benzyl 5-(bromomethyl)benzo[b]thiophene-2-carboxylate*

[00249] To a solution of benzyl 5-methylbenzo[b]thiophene-2-carboxylate (15.0 g, 53.1 mmol, 1.0 eq) and NBS (10.3 g, 58.4 mmol, 1.1 eq) in CCl_4 (30 mL) was added benzoyl peroxide (1.3 g, 5.31 mmol, 0.1 eq). The reaction flask was subjected to three cycles of evacuation and backfilling with N_2 (g). The mixture was stirred at 80 °C for 16 h under constant atmosphere of N_2 (g). The reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give benzyl 5-(bromomethyl)benzo[b]thiophene-2-carboxylate (6.80 g, 18.8 mmol, 36% yield) as a yellow solid.

[00250] *Step 3: Preparation of benzyl 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00251] A solution of benzyl 5-(bromomethyl)benzo[b]thiophene-2-carboxylate (10.3 g, 28.5 mmol, 1.0 eq) dissolved in triethyl phosphite (30.0 g, 180.0 mmol, 6.3 eq) was stirred at 100 °C for 5 h. The reaction mixture was concentrated under reduced pressure directly, the residue was purified by flash column chromatography on silica gel to give benzyl 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylate (6.5 g, 15.5 mmol, 55% yield) as a colorless oil. LCMS (ESI) *m/z* = 419 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.49 – 7.33 (m, 6H), 5.39 (s, 2H), 4.08 – 3.93 (m, 4H), 3.26 (d, J = 21.5 Hz, 2H), 1.24 (t, J = 7.1 Hz, 6H).

[00252] *Step 4: Preparation of 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid*

[00253] To a solution of benzyl 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylate (5.6 g, 13.3 mmol, 1.0 eq) in dissolved in a mixture of THF (80 mL) and H_2O (10 mL) was added LiOH (1.10 g, 26.6 mmol, 2.0 eq). The mixture was stirred at room temperature for 3 h and subsequently acidified with aqueous solution of 1 N HCl (adjusted to pH ~3-4). The product precipitated out of solution upon acidification. The resulting solids were filtered, the filter cake was washed with water (20 mL x 2), and the solids were dried under vacuum to give 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (3.9 g, 11.8 mmol, 88.9% yield) as a white solid. LCMS (ESI) *m/z* = 329 $[M+H]^+$.

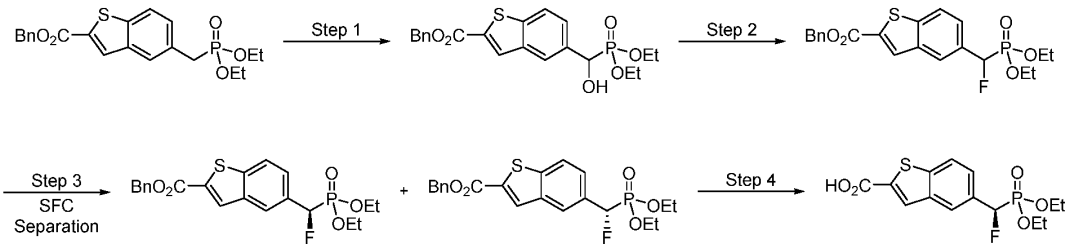
[00254] *Step 5: Preparation of perfluorophenyl 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00255] To a cooled (0 °C) solution of 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (3.9 g, 11.8 mmol, 1.0 eq) in CH_2Cl_2 (50 mL) was added oxalyl chloride (2.2 g, 17.7 mmol, 1.5 eq) followed by addition of two drops of DMF. The mixture was stirred at 0 °C for 30 min, followed by evaporation of the reaction mixture to dryness. The resulting solids were dissolved in CH_2Cl_2 (50 mL), followed by addition of Et_3N (3.6 g, 35.4 mmol, 3.0 eq) and pentafluorophenol (2.6 g, 14.1 mmol, 1.2 eq). The resulting mixture was stirred at room temperature for additional 2 h and subsequently, poured over H_2O (30 mL). The bi-phasic solution was extracted with EtOAc (30 mL x 3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure, the residue was purified by column chromatography on silica gel to give perfluorophenyl 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylate (4.7 g, 9.5 mmol, 81% yield) as a white solid. LCMS (ESI) *m/z* = 419 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.88 (d, J = 9.1 Hz, 2H), 7.51 (d, J = 8.4 Hz, 1H), 4.14 – 3.94 (m, 4H), 3.29 (d, J = 21.5 Hz, 2H), 1.26 (t, J = 7.0 Hz, 6H).

[00256] *Step 6: Preparation of ((2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid*

[00257] To a solution of perfluorophenyl 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylate (4.7 g, 9.5 mmol, 1.0 eq) in CH_2Cl_2 (60 mL) was added bromotrimethylsilane (12 mL). The mixture was stirred at room temperature for 14 h and subsequently concentrated under reduced pressure. The residue was purified by C18 column chromatography to give ((2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (3.7 g, 8.4 mmol, 89% yield) as a white solid. LCMS (ESI) *m/z* = 439 $[M+H]^+$.

Synthesis of (R)- or (S)-5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid and (S)-5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid



[00258] *Step 1: rac-benzyl 5-((diethoxyphosphoryl)(hydroxy)methyl)benzo[b]thiophene-2-carboxylate*

[00259] To a cooled (–78 °C) solution of benzyl 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylate (2.4 g, 5.73 mmol, 1 eq) in THF (75 mL) and 2-(benzenesulfonyl)-3-phenyloxaziridine (2.97 g, 11.4 mmol, 2 eq) was added a 1 M solution of NaHMDS (11.4 mL, 11.4 mmol, 2 eq) in THF. A deep purple solution was observed upon addition of base that changed to orange after complete addition of the base. The mixture was stirred for an additional 10 min, followed by addition of aqueous saturated NH_4Cl (50 mL). The mixture was warmed to ambient temperatures and EtOAc (75 mL) and water (25 mL) was added. After stirring for an additional 30 min, the phases were separated. The aqueous layer was extracted with EtOAc (125 mL x 2). The combined organic extracts were dried with anhydrous sodium sulfate, filtered, concentrated under reduced pressure. Another batch of equal scale was performed and combined for purification. The combined material (6.42 mmol, 12.15 mmol in total) was purified by flash chromatography (20% – 100% = EtOAc : heptane) to give *rac*-benzyl 5-((diethoxyphosphoryl)(hydroxy)methyl)benzo[b]thiophene-2-carboxylate (3.69 g, 8.49 mmol, 70%) as a white sticky solid. LCMS (ESI) m/z = 869.4 $[2M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.04 – 8.00 (m, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.61 (d, *J* = 8.6 Hz, 1H), 7.51 – 7.47 (m, 2H), 7.46 – 7.35 (m, 3H), 5.42 (s, 2H), 5.17 (dd, *J* = 10.4, 4.5 Hz, 1H), 4.18 – 3.95 (m, 4H), 3.10 – 2.99 (m, 1H), 1.33 – 1.20 (m, 6H).

[00260] *Step 2: rac-benzyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate*

[00261] To a cooled (–78 °C) solution (under N_2 (g)) of *rac*-benzyl 5-((diethoxyphosphoryl)(hydroxy)methyl)benzo[b]thiophene-2-carboxylate (**cc**) (1.56 g, 3.59 mmol, 1 eq) in CH_2Cl_2 (30 mL) was added (diethylamino)sulfur trifluoride (568 µL, 4.30 mmol, 1.2 eq). The reaction was stirred for 15 min, followed by addition of aqueous saturated $NaHCO_3$ (50 mL).After warming to room temperature, the product was extracted with CH_2Cl_2 (50 mL x 3). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography on C18 cartridge (eluting with 5-80% acetonitrile in water) to give *rac*-benzyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (650 mg, 1.48 mmol, 41.6 %) as a thick clear oil. LCMS (ESI) m/z = 873.2 $[2M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 8.02 – 7.99 (m, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 1H),

7.51 – 7.51 (m, 2H), 7.46 – 7.36 (m, 3H), 5.82 (dd, *J* = 44.4, 7.5 Hz, 1H), 5.42 (s, 2H), 4.21 – 4.02 (m, 4H), 1.34 – 1.26 (m, 6H).

[00262] *Step 3: Preparation of benzyl (R)-5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate and benzyl (S)-5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate*

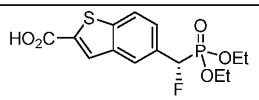
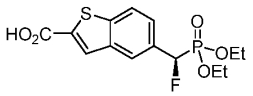
[00263] rac-Benzyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (650 mg, 1.48 mmol) was submitted to chiral SFC separation (Column: Lux *i*-Amylose 3, 21.2 x 250 mm 5 um column, 75 mL/min, 40% MeOH) to give benzyl (R)- or (S)-5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (304 mg, 0.70 mmol, 46.8% recovery, 99.9% ee) as a thick clear oil (Peak 1) and benzyl (R)- or (S)-5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (317 mg, 0.73 mmol, 49% recovery, 99.9% ee) as a thick clear oil (Peak 2). **Note:** Fastest eluting enantiomer by SFC was arbitrarily assigned as (*R*)-5-(fluoro(phosphono)methyl)benzo[*b*]thiophene-2-carboxylic acid and slowest eluting enantiomer by SFC as (*S*)-5-(fluoro(phosphono)methyl)benzo[*b*]thiophene-2-carboxylic acid. HPLC method for analysis of enantiomeric excess: Lux Cellulose-3 150mm 45% H_2O+0.05% TFA / 55% MeCN 1mL/min 8 min.

[00264] *Step 4: Preparation of* (R)- or (S)-*5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid*

[00265] To a mixture of 10% Pd/C (60 mg, 50% wet) and benzyl (R)-5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (Peak 1) (60 mg, 0.1374 mmol, 1 eq) in THF (5 mL) was degassed with N_2 (g) for 5 min. To the mixture was bubbled H_2 (g) for 5 min then the reaction was allowed to stir at room temperature under H_2 (g) (1 atm). The reaction mixture was stirred until consumption of starting material was detected by LCMS. The reaction mixture was subsequently sparged N_2 (g) for 15 min and filtered over a pad of Celite®. The filter cake was washed with 2-MeTHF and the filtrate was concentrated to give (R)- or (S)-5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid (47.4 mg, 0.0137 mmol, 99%) as a thick clear oil. LCMS (ESI) m/z = 347.2 $[M+H]^+$.

[00266] The following intermediate in **Table 20** was prepared using the procedure outlined above (in Step 4) starting from benzyl (S)- or (R)-5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (Peak 2) and using the appropriate reagents.

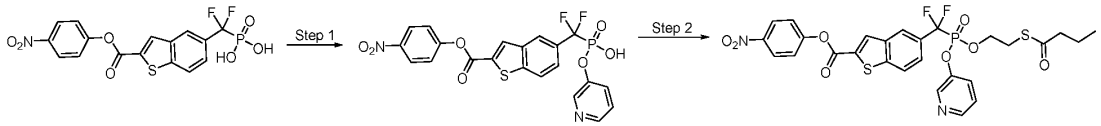
Table 20

Name	Structure	LCMS
(S)-or (R)-5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid	 or 	347.2 $[M+H]^+$

Representative Methods for Synthesis of Activated Linkers

[00267] Method 1: Stepwise Acid Chloride Method for Synthesis of Mixed Linkers

[00268] Representative Procedure for the synthesis of 4-nitrophenyl 5-(((2-(butyrylthio)ethoxy)(pyridin-3-yloxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate



[00269] *Step 1: Preparation of 4-nitrophenyl 5-(difluoro(hydroxy(pyridin-3-yloxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

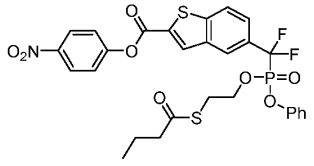
[00270] To a cooled (0 °C) heterogeneous solution of (difluoro(2-((4-nitrophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (100 mg, 0.2329 mmol, 1 eq) in CH_2Cl_2 (4 mL) was added catalytic DMF (2 drops) followed by dropwise addition of oxalyl chloride (198 µL, 2.32 mmol, 10 eq). The homogenous reaction mixture was warmed up to room temperature and stirred for 2 h. The reaction was concentrated *in vacuo* and further dried under high vacuum for 30 min to give a yellow solid. The yellow solid was diluted in CH_2Cl_2 (4 mL) and cooled down to –78 °C. A solution of pyridin-3-ol (22.0 mg, 232 µmol, 1 eq) and triethylamine (64.7 µL, 465 µmol, 2 eq) in CH_2Cl_2 (1 mL) [sonicated for 1 min to allow for solubilization] and was added slowly. The homogeneous reaction mixture was stirred at –78 °C for 2 min, then allowed to warm to ambient temperatures and stirred overnight. After 24 h, the reaction mixture turned heterogeneous and the reaction was concentrated under reduced pressure. The crude product 4-nitrophenyl 5-(difluoro(hydroxy(pyridin-3-yloxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate was used directly in the next step without further purification or manipulation. LCMS m/z = 507.2 $[M+H]^+$.

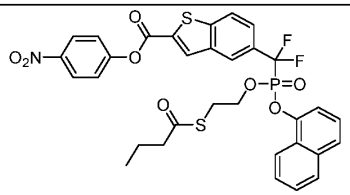
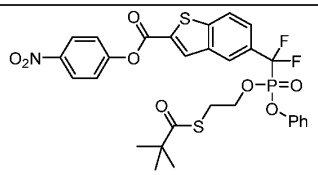
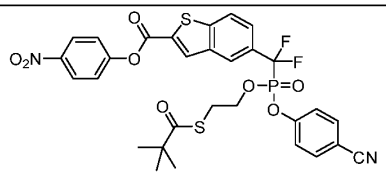
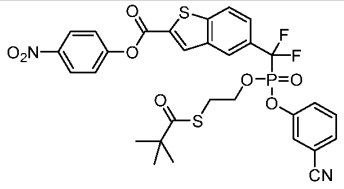
[00271] *Step 2: Preparation of 4-nitrophenyl 5-(((2-(butyrylthio)ethoxy)(pyridin-3-yloxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate*

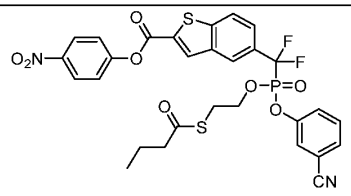
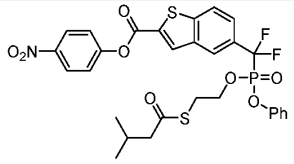
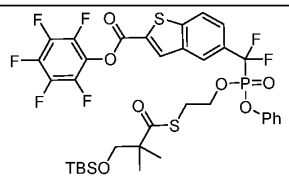
[00272] To a cooled (0 °C) solution of nitrophenyl 5-(difluoro(hydroxy(pyridin-3-yloxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (117 mg, 0.2329 mmol, 1 eq) in CH_2Cl_2 (5 mL) was added 2 drops of DMF followed by dropwise addition of oxalyl chloride (198 µL, 2.32 mmol, 10 eq). The reaction was warmed up to room temperature and stirred for 1.5 h. LCMS analysis showed partial conversion to desired activated intermediate. Additional oxalyl chloride (198 µL, 2.32 mmol, 10 eq) was introduced into the reaction mixture and the mixture was stirred for additional 1 h. The reaction was concentrated *in vacuo* and further dried under high vacuum for 30 min to give a yellow solid. The yellow solid was diluted in CH_2Cl_2 (5 mL) and cooled to –78 °C. To the cooled solution was slowly added a solution of 1-[(2-hydroxyethyl)sulfanyl]butan-1-one (103 mg, 698 µmol, 3 eq) diluted in CH_2Cl_2 (1 mL) [previously dried by passing through anhydrous Na_2SO_4] followed by triethylamine (134 µL, 967 µmol, 2 eq). After stirring for 2 min, the resulting mixture was allowed to warm to ambient temperatures and stirred overnight. To the mixture was added Celite® and the mixture was carefully concentrated *in vacuo*. The crude residue was purified by flash-chromatography (gradient elution 0-60% EtOAc in heptanes) to give 4-nitrophenyl 5-(((2-(butyrylthio)ethoxy)(pyridin-3-yloxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (22.0 mg, 0.03455 mmol, 14.9% yield) as a clear oil. LCMS m/z = 637.2 $[M+H]^+$; ^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.50 – 8.44 (m, 2H), 8.33 – 8.38 (m, 3H), 8.25 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.6 Hz, 1H), 7.57 – 7.53 (m, 1 H), 7.50 – 7.45 (m, 2H), 7.31 – 7.26 (m, 1H), 4.37 – 4.24 (m, 2 H), 3.20 – 3.08 (m, 2H), 2.52 (t, J = 7.6 Hz, 2H), 1.67 (sextet, J = 7.3 Hz, 2H), 0.94 (t, J = 7.6 Hz, 3H).

[00273] The following intermediates in **Table 21** were prepared using a similar protocol described above for synthesis of 4-nitrophenyl 5-(((2-(butyrylthio)ethoxy)(pyridin-3-yloxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate and utilizing the appropriate advanced intermediate(s) as starting material(s).

Table 21

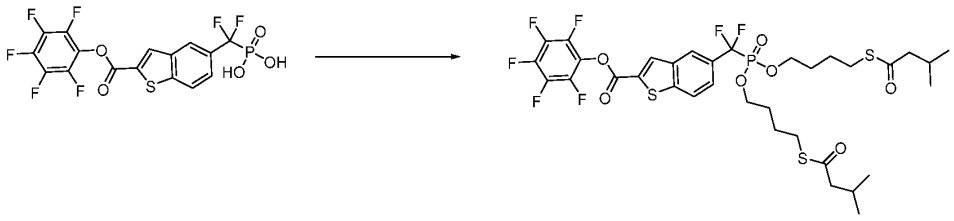
Name	Structure	LCMS	NMR
4-nitrophenyl 5-(((2-(butyrylthio)ethoxy)(phenoxy)phosphoryl)difluoromethyl)benzo[b]t			^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.44 (s, 1H), 8.40 – 8.35 (m, 3H), 7.79 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 9.0 Hz, 2H), 7.44 – 7.37 (m, 2H), 7.29 – 7.23 (m, 1H),

hiophene-2-carboxylate			7.18 (d, J = 8.6 Hz, 2H), 4.36 – 4.20 (m, 2H), 3.15 (t, J = 6.1 Hz, 2H), 2.58 – 2.52 (m, 2H), 1.58 – 1.50 (m, 2H), 0.85 (q, J = 7.3 Hz, 3H)
4-nitrophenyl 5-(((2-(butyrylthio)ethoxy)(naphthalen-1-yloxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate			^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.49 (s, 1H), 8.39 (d, J = 9.3 Hz, 3H), 8.00 (d, J = 8.3 Hz, 1H), 7.87 – 7.80 (m, 3H), 7.70 (d, J = 9.0 Hz, 2H), 7.64 – 7.58 (m, 1H), 7.58 – 7.53 (m, 1H), 7.49 (t, J = 7.9 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 4.35 – 4.23 (m, 2H), 3.11 (t, J = 5.9 Hz, 2H), 2.45 (t, J = 7.3 Hz, 2H), 1.48 (sextet, J = 7.4 Hz, 2H), 0.81 (t, J = 7.5 Hz, 3H)
4-nitrophenyl 5-(difluoro(phenoxy(2-(pivaloylthio)ethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate			^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.49 – 8.34 (m, 4H), 7.80 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 9.0 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.30 – 7.15 (m, 3H), 4.33 – 4.23 (m, 2H), 3.12 (t, J = 5.6 Hz, 2H), 1.12 (s, 9H)
4-nitrophenyl 5-(((4-cyanophenoxy)(2-(pivaloylthio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate			
4-nitrophenyl 5-(((3-cyanophenoxy)(2-(pivaloylthio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate			^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.46 (s, 1H), 8.42 – 8.34 (m, 3H), 7.83 – 7.67 (m, 5H), 7.66 – 7.59 (m, 1H), 7.58 – 7.53 (m, 1H), 4.40 – 4.28 (m, 2H), 3.14 (t, J = 6.2 Hz, 2H), 1.12 (s, 9H)

4-nitrophenyl 5-(((2-(butyrylthio)ethoxy)(3-cyanophenoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate		661.1 $[M+H]^+$	
4-nitrophenyl 5-(difluoro((2-((3-methylbutanoyl)thio)ethoxy)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate			^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.49 – 8.34 (m, 4H), 7.80 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 9.0 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.30 – 7.15 (m, 3H), 4.33 – 4.23 (m, 2H), 3.12 (t, J = 5.6 Hz, 2H), 1.12 (s, 9H)
perfluorophenyl 5-(((2-((3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanoyl)thio)ethoxy)(phenoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate		847.0 $[M+Na]^+$	

[00274] Method 2: One-Pot Acid Chloride Method for the Synthesis of Activated Linkers

[00275] Representative Procedure for the synthesis of Perfluorophenyl 5-((bis(4-((3-methylbutanoyl)thio)butoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate

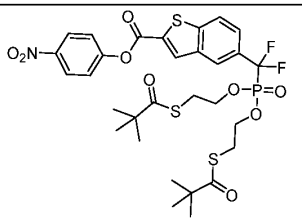
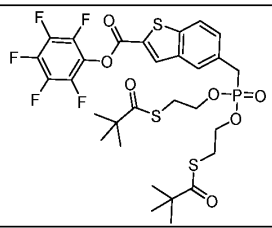


[00276] To a cooled (0 °C) solution of 3 (200 mg, 0.42 mmol, 1.0 eq) in dry CH_2Cl_2 (15 mL) and catalytic DMF (3.2 µL, 42.1 µmol, 0.1 eq) was added in a dropwise manner oxalyl chloride (266 mg, 2.10 mmol, 5.0 eq). The reaction mixture was allowed to warm to 40 °C. After stirring for 2 h, the reaction mixture was concentrated *in vacuo* and dried (to remove excess oxalyl chloride). The resulting solids were re-dissolved in anhydrous CH_2Cl_2 (5 mL)

and cooled to 0 °C. To the cooled solution was added S-(4-hydroxybutyl) 3-methylbutanethioate (239 mg, 1.26 mmol, 3.0 eq), DMAP (5.14 mg, 42.1 µmol, 0.1 eq) and a solution of N,N-diisopropylethylamine (217 mg, 1.68 mmol, 4.0 eq) in anhydrous CH_2Cl_2 (10 mL). The reaction mixture was allowed to warm to room temperature and stirred for additional 18 h. The reaction was quenched by adding H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined and washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography to afford perfluorophenyl 5-((bis(4-((3-methylbutanoyl)thio)butoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (15.0 mg, 18.3 µmol, 4.4% yield). LCMS (ESI) m/z = 819 $[M+H]^+$.

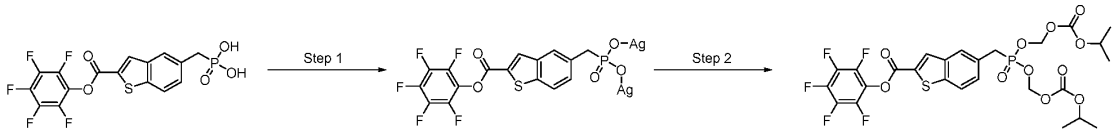
[00277] The following intermediates in **Table 22** were prepared using a similar protocol described above for synthesis of perfluorophenyl 5-((bis(4-((3-methylbutanoyl)thio)butoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate and utilizing the appropriate advanced intermediate(s) as starting material(s).

Table 22

Name	Structure	LC-MS	NMR
4-nitrophenyl 5-((bis(2-(pivaloylthio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate			^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.41 – 8.32 (m, 4H), 7.76 – 7.65 (m, 3H), 4.22 – 4.11 (m, 4H), 3.12 (t, J = 6.4 Hz, 4H), 1.16 (s, 18H)
perfluorophenyl 5-((bis(2-(pivaloylthio)ethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		749.0 $[M+Na]^+$	

[00278] Method 3: One-Pot Silver Salt Method for the Synthesis of Activated Linkers

[00279] Representative procedure for the synthesis of Perfluorophenyl 5-((bis(((isopropoxycarbonyl)oxy)methoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate



[00280] *Step 1: Preparation of silver(I) ((2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonate*

[00281] To a solution of ((2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (300 mg, 684 μmol, 1.0 eq) in a mixture of deionized H_2O (4 mL) and THF (2 mL) was added Amberlite IR120® resin (Na^+ form) (1.5 g). The resulting mixture was stirred at room temperature for 1 h and the suspension was subsequently filtered. To the filtrate was added a solution of $AgNO_3$ (463 mg, 2.73 mmol, 4.0 eq) in deionized H_2O (2 mL) and the resulting mixture was stirred at room temperature for an additional 1 h. Formation of a white precipitate was observed and the solids were collected via filtration. The filter cake was then washed with cold H_2O (3 x 2 mL), and the solid was dried under reduced pressure to yield silver(I) ((2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonate as a dry powder. The silver salt was used without further purification.

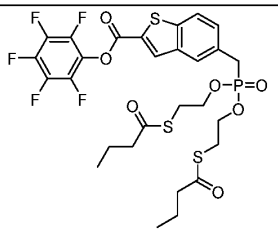
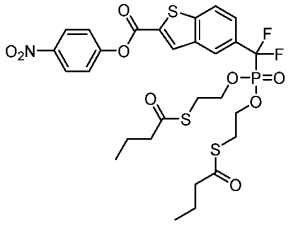
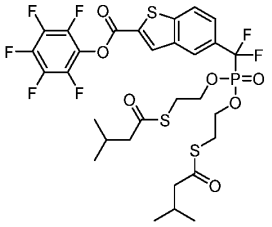
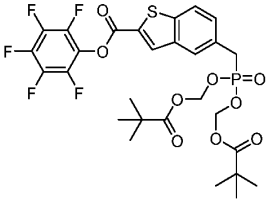
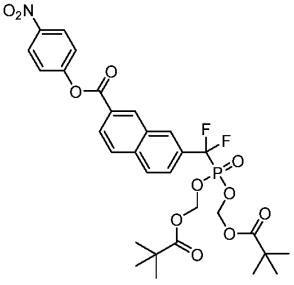
[00282] *Step 2: Preparation of perfluorophenyl 5-((bis(((isopropoxycarbonyl)oxy)methoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

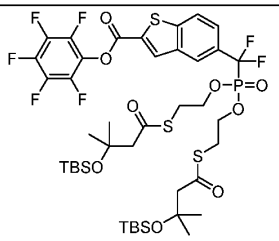
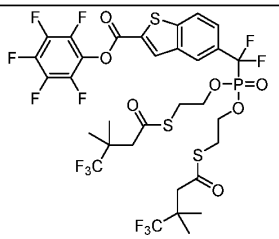
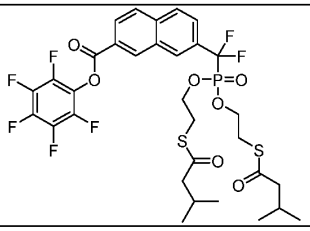
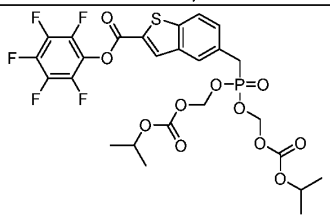
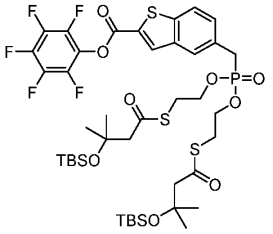
[00283] To a suspension of silver(I) ((2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonate was suspended in anhydrous toluene (10 mL) and iodomethyl 2-methylpropanoate (500 mg, 2.05 mmol, 3.0 eq) was added in a dropwise manner. After addition, the resulting mixture was stirred at room temperature for an additional 12 h. The reaction progress was monitored by LCMS, and after completion, the unreacted silver salt was recovered by filtration. The filtrate solution was concentrated *in vacuo*, and the resulting residue was purified by reverse phase chromatography [C18 column gradient elution water/acetonitrile = 90% to 1%] to give perfluorophenyl 5-((bis(((isopropoxycarbonyl)oxy)methoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (165 mg, 246 μmol, 36% yield) as a white solid. LCMS (ESI) *m/z* = 671 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.96 – 7.80 (m, 2H), 7.48 (d, *J* = 8.5 Hz, 1H), 5.70 – 5.53 (m, 4H), 4.90 (dt, J = 12.6, 6.2 Hz, 2H), 3.42 (d, J = 22.2 Hz, 2H), 1.31 (d, *J* = 6.2 Hz, 12H).

[00284] The following intermediates in **Table 23** were prepared using a similar protocol described above for synthesis of perfluorophenyl 5-((bis(4-((3-methylbutanoyl)thio)butoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate and utilizing the appropriate advanced intermediate(s) as starting material(s).

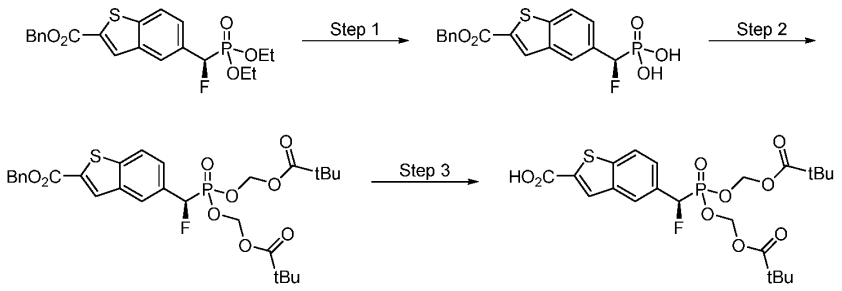
Table 23

Name	Structure	LCMS	NMR

perfluorophenyl 5-((bis(2-(butyrylthio)ethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		699 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.96 – 7.80 (m, 2H), 7.50 (d, J = 8.3 Hz, 1H), 4.08 – 4.03 (m, 4H), 3.33 (d, J_{HP} = 21.6 Hz, 2H), 3.08 (t, J = 6.5 Hz, 4H), 2.52 (t, J = 7.4 Hz, 4H), 1.72 – 1.63 (m, 4H), 0.94 (t, J = 7.4 Hz, 6H)
4-nitrophenyl 5-((bis(2-(butyrylthio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate		690 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 8.35 – 8.34 (m, 3H), 8.23 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.48 (d, J = 9.0 Hz, 2H), 4.29 – 4.19 (m, 4H), 3.27 – 3.03 (m, 4H), 2.54 (t, J = 7.4 Hz, 4H), 1.75 – 1.63 (m, 4H), 0.95 (t, J = 7.4 Hz, 6H)
perfluorophenyl 5-((bis(2-((3-methylbutanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate			^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.24 (s, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.78 (d, J = 8.7 Hz, 1H), 4.34 – 4.08 (m, 4H), 3.25 – 3.05 (m, 4H), 2.43 (d, J = 7.1 Hz, 4H), 2.14 (dt, J = 13.7, 6.8 Hz, 2H), 0.95 (s, 6H), 0.94 (s, 6H)
((((2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		689 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.90 – 7.86 (m, 2H), 7.50 – 7.45 (m, 1H), 5.68 – 5.56 (m, 4H), 3.38 (m, 2H), 1.19 (s, 18H)
(((difluoro(7-((4-nitrophenoxy)carbonyl)naphthalen-2-yl)methyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		674.1 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.40 – 8.34 (m, 2H), 8.34 – 8.26 (m, 2H), 8.04 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 1H), 7.52 – 7.47 (m, 2H), 5.81 – 5.66 (m, 4H), 1.21 (s, 18H)

perfluorophenyl 5-((bis(2-((3-((tert-butyldimethylsilyl)oxy)-3-methylbutanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate			^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 – 8.30 (m, 3H), 8.22 (s, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.47 (d, J = 8.9 Hz, 2H), 4.25 – 4.13 (m, 4H), 3.57 (s, 4H), 3.16 – 3.05 (m, 4H), 1.18 (s, 12H), 0.84 (s, 18H), 0.00 (s, 12H)
perfluorophenyl 5-((bis(2-((3,3,3-trifluoro-2,2-dimethylpropanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate		893.2 $[M+Na]^+$	
perfluorophenyl 7-((bis(2-((3-methylbutanoyl)thio)ethoxy)phosphoryl)difluoromethyl)-2-naphthoate		799 $[M+Na]^+$	
perfluorophenyl 5-((bis(((isopropoxycarbonyl)oxy)methoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate			^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.96 – 7.80 (m, 2H), 7.48 (d, J = 8.5 Hz, 1H), 5.70 – 5.53 (m, 4H), 4.90 (dt, J = 12.6, 6.2 Hz, 2H), 3.42 (d, J = 22.2 Hz, 2H), 1.31 (d, J = 6.2 Hz, 12H)
perfluorophenyl 5-((bis(2-((3-((tert-butyldimethylsilyl)oxy)-3-methylbutanoyl)thio)ethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate			^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.95 – 7.80 (m, 2H), 7.50 (d, J = 8.4 Hz, 1H), 4.01 (dd, J = 14.7, 7.0 Hz, 4H), 3.58 (d, J= 10.6 Hz, 4H), 3.32 (d, J = 21.6 Hz, 2H), 3.04 (t, J = 6.7 Hz, 4H), 1.18 (d, J = 8.5 Hz, 12H), 0.84 (s, 18H), 0.00 (d, J = 3.5 Hz, 12H)

(R)- or (S)-5-((bis((pivaloyloxy)methoxy)phosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid



[00285] *Step 1: Preparation of (R)- or (S)-((2-((benzyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid*

[00286] To a cooled (0 °C) solution of benzyl (R)- or (S)-5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (Peak 1) (205 mg, 0.4697 mmol) in CH_2Cl_2 (8.0 mL) was added BSTFA (746 µL, 2.81 mmol) followed by a 1.0 M solution of trimethylsilyl iodide (1.87 mL, 1.87 mmol) in CH_2Cl_2. After stirring for 1 h, a mixture of acetonitrile (0.66 mL), water (0.33 mL) and 0.1% TFA was added. The solvent was removed under reduced pressure at 0°C. The crude residue was purified by reverse phase chromatography (C18 cartridge eluting with 5-40% acetonitrile in water) to give (R)- or (S)-((2-((benzyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid (163 mg, 0.4285 mmol) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (s, 1H), 8.11 – 8.06 (m, 2H), 7.58 (d, J = 8.6 Hz, 1H), 7.51 – 7.47 (m, 2H), 7.45 – 7.33 (m, 3H), 5.84 (dd, J = 44.6, 8.3 Hz, 1H), 5.40 (s, 2H).

[00287] *Step 2: Preparation of (R)- or (S)-((2-((benzyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid*

[00288] [The following reaction was conducted in foiled covered vessel and in the absence of ambient light]: To a suspension of (R)- or (S)-((2-((benzyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid (163 mg, 0.4285 mmol, 1 eq) in water (5 mL) was added a solution of aqueous sodium hydroxide (34.2 mg, 857 µmol, 2 eq) in water (2 mL). To the yellow solution was added silver(I) nitrate (181 mg, 1.07 mmol, 2.5 eq) and the resulting off-white suspension was stirred for 1.5 h at room temperature. The suspension was cooled to 0 °C, filtered, and dried under high vacuum. The solids were re-suspended in acetonitrile, concentrated under reduced pressure, and further dried under high vacuum (3 h). The resulting dark yellow powder was suspended in toluene (10 mL) and iodomethyl 2,2-dimethylpropanoate (191 µL, 1.28 mmol, 3 eq) was added. After stirring for 20 h, the reaction mixture was stirred for 20 h at room temperature. The reaction mixture was filtered and rinsed with toluene. The filtrate was concentrated under reduced pressure. The crude residue was purified (C18 cartridge eluting with 5-100% acetonitrile in water) to give (R)- or

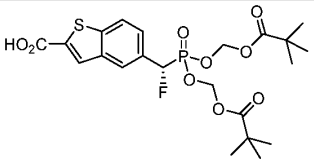
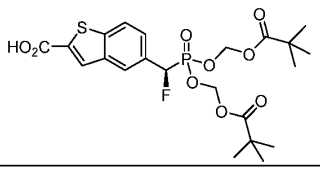
(S)-((((2-((benzyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate) (122 mg, 0.2004 mmol, 46.9 %) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1 H), 8.01 – 7.99 (m, 1 H), 7.92 (d, J = 8.3 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.52 – 7.47 (m, 2 H), 7.46 – 7.36 (m, 3H), 8.87 (dd, J = 44.3, 7.5 Hz, 1H), 5.72 – 5.62 (m, 4H), 5.43 (s, 2H), 1.21 (s, 18H).

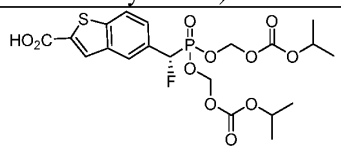
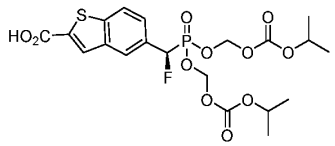
[00289] *Step 3: Preparation of (R)- or (S)-5-((bis((pivaloyloxy)methoxy)phosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid*

[00290] To a solution of (R)-((((2-((benzyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate) (122 mg, 0.200 mmol, 1 eq) in THF (10 mL) under N_2 (g) was added 10% Pd/C (50% wet, 120 mg, 0.1127 mmol, 0.56 eq). To the suspension was bubbled H_2 (g) for 5 min. The reaction mixture was stirred under H_2 (g) (1 atm) at room temperature. After stirring for 22 h, the reaction mixture was purged with N_2 (g) and filtered over Celite®. The filter pad was washed with THF and concentrated under reduced pressure to give (R)-5-((bis((pivaloyloxy)methoxy)phosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid (0.200 mmol, 99.9%) as a thick clear oil. LC-MS (ESI) m/z $[M+H]^+$ = 519.1.

[00291] The following intermediates in **Table 24** were prepared using a similar protocol described above for synthesis of (R)- or (S)-5-((bis((pivaloyloxy)methoxy)phosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid and utilizing the appropriate advanced intermediate(s) as starting material(s). The absolute configuration of the starting material, (R)- or (S)-((2-((benzyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid was not determined, but the elution peak ("Peak 1" or "Peak 2") of the starting material utilized is indicated in the table

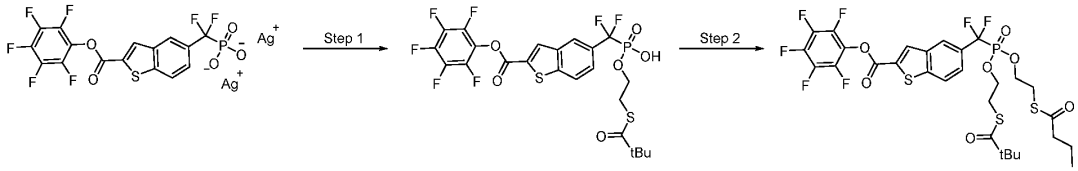
Table 24

Name	Structure	LCMS	NMR
(R)- or (S)-5-((bis((pivaloyloxy)methoxy)phosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid	 or 	519.1 $[M+H]^+$	

	(Peak 2 of phosphonate building block was utilized for synthesis)		
(R)- or (S)-5-((bis(((isopropoxycarbonyl)oxy)methoxy)phosphoryl)fluoromethyl) benzo[b]thiophene-2-carboxylic acid	 or  (Peak 2 of phosphonate building block was utilized for synthesis)	689 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.09 (s, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 8.6 Hz, 1H), 5.93 (dd, J = 44.2, 7.3 Hz, 1H), 5.73-5.54 (m, 4H), 4.97-4.84 (m, 2H), 1.33-1.29 (m, 12H)

[00292] Method 4: Stepwise Silver Salt Method for the Synthesis of Mixed Linkers

[00293] Representative procedure for the Perfluorophenyl 5-(((2-(butyrylthio)ethoxy)(2-(pivaloylthio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate



[00294] *Step 1: Preparation of perfluorophenyl 5-(difluoro(hydroxy(2-(pivaloylthio)ethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00295] *Silver(I) (difluoro(2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonate was synthesized starting from (difluoro(2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid using the method described in Step 1, Method 3 for the synthesis of silver(I) ((2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonate.*

[00296] To a suspension of silver(I) ((2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonate (647 mg, 940 μmol, 1.0 eq) in anhydrous toluene (10 mL) was added in a dropwise manner S-(2-iodoethyl) 2,2-dimethylpropanethioate (310 mg, 1.14 mmol, 1.2 eq). After complete addition of the alcohol, the resulting mixture was stirred at room temperature for an additional 12 h. The heterogeneous mixture was filtered, and the filtrate was concentrated *in vacuo*. The resulting residue was purified by reverse phase

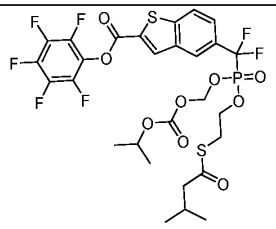
chromatography to give perfluorophenyl 5-(difluoro(hydroxy(2-(pivaloylthio)ethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (240 mg, 388 µmol, 41% yield). LCMS (ESI) *m/z* = 617 [M-H]$^-$.

[00297] *Step 2: Preparation of perfluorophenyl 5-(((2-(butyrylthio)ethoxy)(2-(pivaloylthio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate*

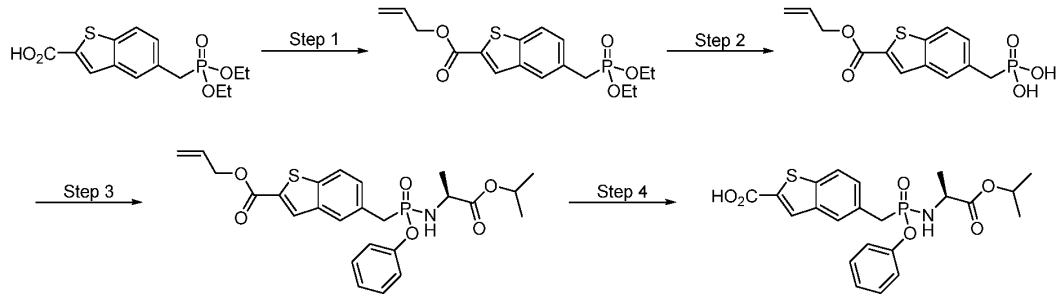
[00298] Perfluorophenyl 5-(((2-(butyrylthio)ethoxy)(2-(pivaloylthio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate was synthesized using similar protocol outlined above. Starting with perfluorophenyl 5-(difluoro(hydroxy(2-(pivaloylthio)ethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (190 mg, 307 µmol, 1.0 eq), $AgNO_3$ (207 mg, 1.22 mmol, 4.0 eq), and S-(2-iodoethyl) butanethioate (94.9 mg, 368 µmol, 1.2 eq) produced perfluorophenyl 5-(((2-(butyrylthio)ethoxy)(2-(pivaloylthio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (55.0 mg, 73.4 µmol, 24%) as a white solid. LCMS (ESI) *m/z* = 749 [M+H]$^+$.

[00299] The following intermediates in **Table 25** were prepared using a similar protocol described above for synthesis of perfluorophenyl 5-(((2-(butyrylthio)ethoxy)(2-(pivaloylthio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate and utilizing the appropriate advanced intermediate(s) as starting material(s).

Table 25

Name	Structure	LCMS	NMR
perfluorophenyl 5-(difluoro((((isopropoxycarbonyl)oxy)methoxy)(2-((3-methylbutanoyl)thio)ethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		757 [M+Na]$^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.24 (s, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.77 (d, J = 8.7 Hz, 1H), 5.69 (ddd, J = 17.8, 12.2, 5.2 Hz, 2H), 4.93 (dt, J = 12.5, 6.3 Hz, 1H), 4.34-4.14 (m, 2H), 3.14 (td, J = 6.6, 3.0 Hz, 2H), 2.42 (d, J = 7.1 Hz, 2H), 2.13 (dt, J = 13.7, 6.8 Hz, 1H), 1.33 (s, 3H), 1.31 (s, 3H), 0.95 (s, 3H), 0.93 (s, 3H)

Preparation of 5-(((((S)-1-isopropoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid



[00300] *Step 1: Preparation of allyl 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00301] To a suspension of 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (1.0 g, 3.0 mmol, 1.0 eq) and K_2CO_3 (839 mg, 6.1 mmol, 2.0 eq) in DMF (20 mL) was added 3-bromoprop-1-ene (440 mg, 3.6 mmol, 1.2 eq). The mixture was stirred at room temperature for 14 h and poured over water (30 mL). The mixture was extracted with EtOAc (25 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure, the residue was purified by column chromatography to give allyl 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylate (0.980 g, 2.7 mmol, 88% yield) as a light-yellow solid. LCMS (ESI) *m/z* = 369 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.84 – 7.77 (m, 2H), 7.45 – 7.37 (m, 1H), 6.18 – 5.94 (m, 1H), 5.49 – 5.39 (m, 1H), 5.36 – 5.28 (m, 1H), 4.87 – 4.83 (m, 2H), 4.08 – 3.97 (m, 4H), 3.27 (d, J = 21.4 Hz, 2H), 1.25 (t, J = 7.1 Hz, 6H).

[00302] *Step 2: Preparation of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid*

[00303] To a solution of allyl 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylate (980 mg, 2.7 mmol, 1.0 eq) in CH_2Cl_2 (15 mL) was added bromotrimethylsilane (3 mL). The mixture was stirred at room temperature for 14 h and subsequently concentrated under reduced pressure. The resulting residue was triturated with H_2O (5 mL) and the resulting precipitates were filtered. The filter cake was washed with H_2O (5 mL x 2) and dried under reduced pressure to give ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (0.710 g, 2.3 mmol, 86% yield) as a white solid. LCMS (ESI) *m/z* = 313 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.92 – 7.83 (m, 1H), 7.50 – 7.38 (m, 1H), 6.12 – 5.98 (m, 1H), 5.46 – 5.38 (m, 1H), 5.32 – 5.27 (m, 1H), 4.85 – 4.80 (m, 2H), 3.08 (d, J = 21.2 Hz, 2H).

[00304] *Step 3: Preparation of allyl 5-(((((S)-1-isopropoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00305] To a cooled (0 °C) solution (under a constant stream of N_2 (g)) of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (2.80 g, 8.96 mmol, 1 eq) and catalytic DMF (1 drop) in dry CH_2Cl_2 (50 mL) was added oxalyl chloride (3.40 g, 26.8 mmol, 3 eq). After effervescence of gas ceased, the mixture was warmed at 40°C. After 2 h, the mixture was cooled to room temperature and concentrated *in* vacuo to give yellow solids. The solids were subsequently diluted CH_2Cl_2 (50 mL) and cooled to 0 °C. To the cooled solution was added phenol (0.843 g, 8.96 mmol, 1 eq) and Et_3N (4.53 g, 44.8 mmol, 5 eq). After complete addition, the mixture was warmed to room temperature and stirred for 1 h, followed by introduction of propan-2-yl (2S)-2-aminopropanoate (1.75 g, 13.4 mmol, 1.5 eq) to the mixture. After stirring for an additional 2 h, the mixture was concentrated to dryness. The residue was purified by C18 column (elution 50% – 80% acetonitrile in water) to give allyl 5-(((((S)-1-isopropoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (2.23 g, 4.44 mmol, 49.6% yield) as white solids. LCMS (ESI) m/z = 502.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 6.9 Hz, 1H), 7.91 – 7.80 (m, 2H), 7.53 – 7.43 (m, 1H), 7.29 (d, J = 8.1 Hz, 2H), 7.18 – 7.09 (m, 3H), 6.05 (ddd, J = 16.1, 10.9, 5.6 Hz, 1H), 5.48 – 5.40 (m, 1H), 5.32 (dd, J = 10.4, 1.2 Hz, 1H), 4.98 – 4.87 (m, 1H), 4.85 (d, J = 5.7 Hz, 2H), 4.04 – 3.85 (m, 1H), 3.44 (dd, J = 20.7, 14.1 Hz, 2H), 3.12 (t, J = 10.9 Hz, 1H), 1.21 – 1.10 (m, 9H).

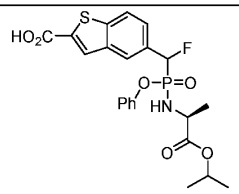
[00306] *Step 4: Preparation of 5-(((((S)-1-isopropoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid*

[00307] A solution of allyl 5-(((((S)-1-isopropoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (90 mg, 0.1794 mmol, 1 eq), pyrrolidine (12.7 mg, 179 µmol, 1 eq), $Pd(PPh_3)_4$ (10.3 mg, 8.97 µmol, 0.05 eq) in CH_2Cl_2 (5 mL) was stirred under N_2 (g). After 2 h, the reaction was concentrated *in* vacuo. The residue was purified by C18 column (elution 30% – 70% acetonitrile in water) to yield 5-(((((S)-1-isopropoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (64.0 mg, 0.1386 mmol, 77.4% yield) as white solids. LCMS (ESI) m/z = 462.1 $[M+H]^+$.

[00308] The following intermediates in **Table 26** were prepared using the described above for synthesis of 5-(((((S)-1-isopropoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid and utilizing the appropriate utilizing the appropriate starting materials and modifications.

Table 26

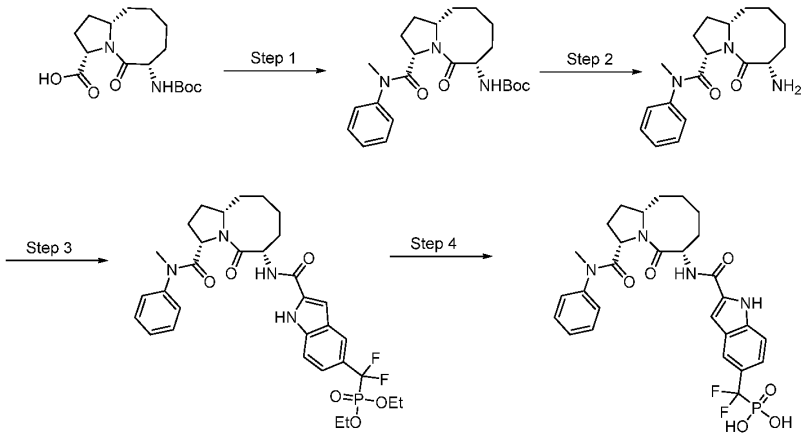
Name	Structure	LCMS	NMR

5-(fluoro((((S)-1-isopropoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		480.1 $[M+H]^+$	

Syntheses of Phosphonic Acid Analogues:

[00309] Method 1: Representative procedure for the Synthesis of Phosphonic Acid Analogues via Amino Acid Coupling of Carboxylic Acid Linkers with Amino Acid Cores.

[00310] (Difluoro(2-(((3S,6S,10aS)-3-(methyl(phenyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)-1H-indol-5-yl)methyl)phosphonic acid (1)



[00311] *Step 1: Preparation of tert-butyl ((3S,6S,10aS)-3-(methyl(phenyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate*

[00312] To a solution of (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid (400 mg, 1.22 mmol, 1.0 eq), *N*-methylaniline (261 mg, 2.44 mmol, 2.0 eq) and Et_3N (246 mg, 2.44 mmol, 2.0 eq) in CH_2Cl_2 (10 mL) was added T_3P (1.55 g, 2.44 mmol, 2 eq). The resulting mixture was stirred for 12 h at 40 °C. The reaction mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (10 mL x 3). The organic layers were combined and washed with brine (20 mL), dried over with anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography to afford tert-butyl ((3S,6S,10aS)-3-(methyl(phenyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate (240 mg, 578 μmol, 47% yield) as a white solid. LCMS (ESI) m/z = 416 $[M+H]^+$.

[00313] *Step 2: Preparation of (3S,6S,10aS)-6-amino-N-methyl-5-oxo-N-phenyldecahydropyrrolo[1,2-a]azocine-3-carboxamide*

[00314] To a solution of tert-butyl ((3S,6S,10aS)-3-(methyl(phenyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate (100 mg, 240 μmol, 1 eq) in CH_2Cl_2 (6 mL) was added trifluoroacetic acid (3 mL). The reaction mixture was stirred for 1 h at room temperature, subsequently cooled to 0 °C, and neutralized carefully with aqueous $NaHCO_3$ until basic (adjusted to pH = 8-9). The resulting mixture was then extracted with CH_2Cl_2 (10 mL x 3 mL), and the combined organic layers were washed with brine (2 x 10 mL), dried over with anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude (3S,6S,10aS)-6-amino-N-methyl-5-oxo-N-phenyldecahydropyrrolo[1,2-a]azocine-3-carboxamide (76 mg, 240 μmol) as a white solid, which was used in the next step directly without further purification. LCMS (ESI) *m/z* = 316 $[M+H]^+$.

[00315] *Step 3: Preparation of diethyl (difluoro(2-(((3S,6S,10aS)-3-(methyl(phenyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)-1H-indol-5-yl)methyl)phosphonate*

[00316] To a solution of (3S,6S,10aS)-6-amino-N-methyl-5-oxo-N-phenyldecahydropyrrolo[1,2-a]azocine-3-carboxamide (76 mg, 240 μmol, 1.0 eq) and 5-[(diethoxyphosphoryl)difluoromethyl]-1H-indole-2-carboxylic acid (83.3 mg, 240 μmol, 1.0 eq) in DMF (3 mL) was added HATU (118 mg, 312 μmol, 1.3 eq) and Et_3N (72.8 mg, 720 μmol, 3.0 eq). The resulting mixture was stirred for an additional 2 h at room temperature. The reaction mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (10 mL x 3). The organic layers were combined and washed with brine (20 mL), dried over with anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography to afford diethyl (difluoro(2-(((3S,6S,10aS)-3-(methyl(phenyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)-1H-indol-5-yl)methyl)phosphonate (100 mg, 155 μmol, 65% yield) as a white solid. LCMS (ESI) *m/z* = 645 $[M+H]^+$.

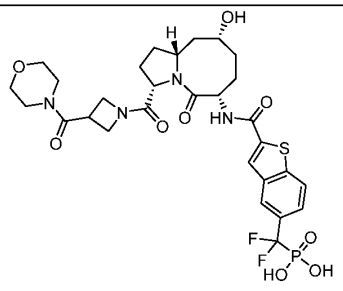
[00317] *Step 4: Preparation of (Difluoro(2-(((3S,6S,10aS)-3-(methyl(phenyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)-1H-indol-5-yl)methyl)phosphonic acid* **(1)**

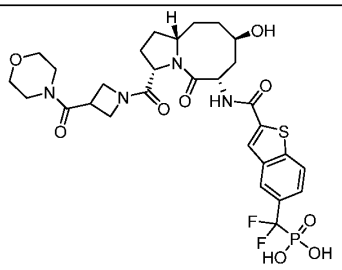
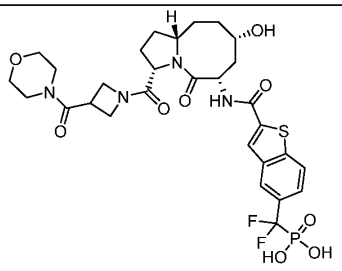
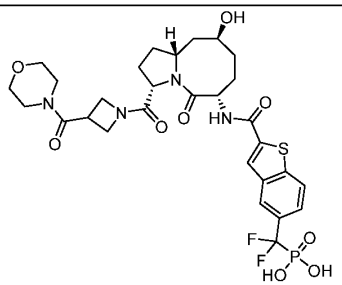
[00318] To a cooled (0 °C) solution of diethyl (difluoro(2-(((3S,6S,10aS)-3-(methyl(phenyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)-1H-indol-5-yl)methyl)phosphonate (100 mg, 155 μmol, 1.0 eq) in CH_2Cl_2 (10 mL) was added in a dropwise manner bromotrimethylsilane (355 mg, 2.32 mmol, 15.0 eq). The reaction was

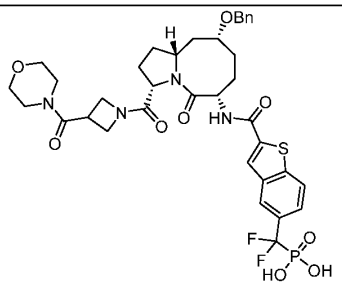
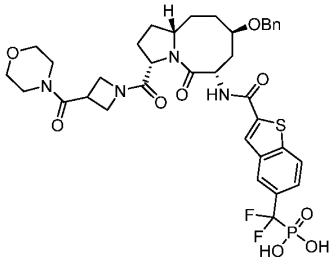
allowed to warm to room temperature and stirred. After 12 h, the reaction mixture was quenched by addition of H_2O (5 mL). The biphasic mixture was extracted using with CH_2Cl_2 (3 x 10 mL). The organic layers were combined and washed with brine (20 mL), dried over with anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by reverse phase HPLC to afford (difluoro(2-(((3S,6S,10aS)-3-(methyl(phenyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)-1H-indol-5-yl)methyl)phosphonic acid **(1)** (8.70 mg, 14.7 µmol, 9.5% yield) as a white solid. LCMS (ESI) *m/z* = 589 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.74 (s, 1H), 8.51 (d, J = 7.1 Hz, 1H), 7.82 (s, 1H), 7.41 (m, 8H), 4.96 (d, J = 5.4 Hz, 1H), 4.17 (m, 4H), 3.16 (s, 3H), 1.93 (m, 8H), 1.57 (m, 4H)

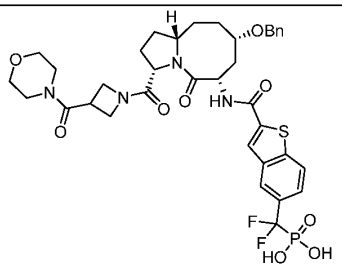
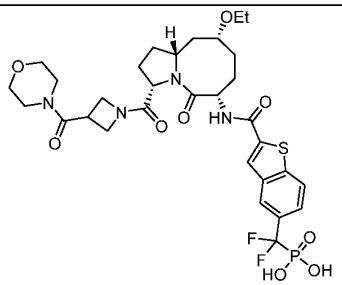
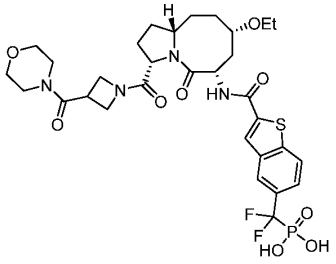
[00319] The following compounds in **Table 27** were prepared according to the representative procedure described above for the synthesis of (difluoro(2-(((3S,6S,10aS)-3-(methyl(phenyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)-1H-indol-5-yl)methyl)phosphonic acid **(1)** and utilizing the appropriate starting materials and modifications.

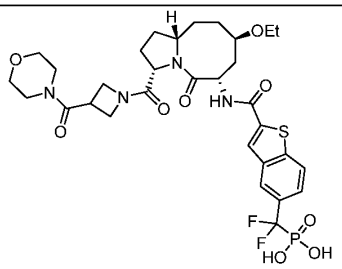
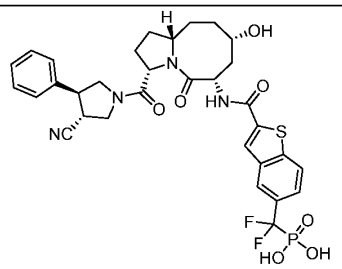
Table 27

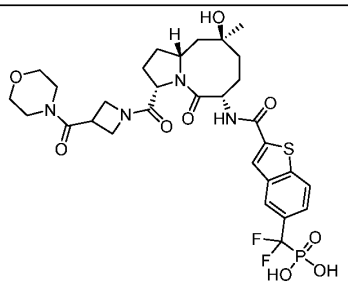
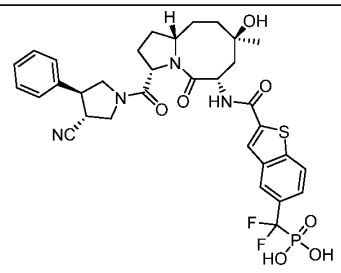
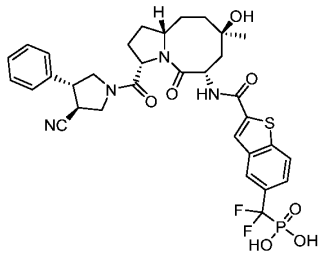
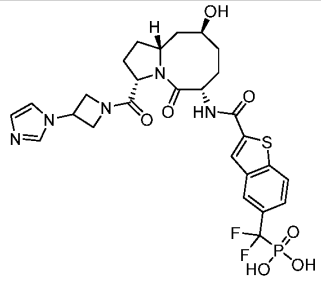
Compound	Name	Structure	LCMS	NMR
2	(difluoro(2-(((3S,6S,9R,10aR)-9-hydroxy-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		685.3 $[M+H]^+$	^1H NMR (400 MHz, methanol-d_4) δ 8.17 – 8.09 (m, 2H), 8.04 – 7.95 (m, 1H), 7.70 – 7.62 (m, 1H), 4.87 – 4.81 (m, 1H), 4.71 – 4.62 (m, 1H), 4.51 – 4.36 (m, 3H), 4.32 – 4.20 (m, 1H), 4.14 – 4.04 (m, 1H), 3.97 – 3.88 (m, 1H), 3.83 – 3.71 (m, 1H), 3.68 – 3.43 (m, 6H), 3.35 (t, *J* = 4.8 Hz, 1H), 3.30 – 3.23 (m, 1H), 2.45 – 2.20 (m, 3H), 2.20 – 1.84 (m, 6H), 1.84 – 1.75 (m, 1H)

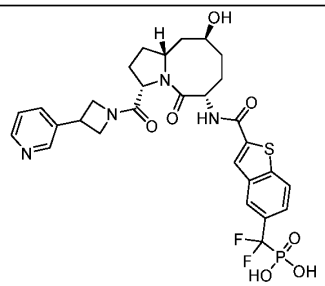
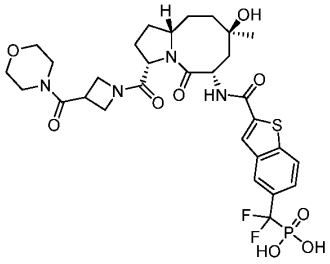
3	(difluoro(2-(((3S,6S,8R,10aR)-8-hydroxy-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		685.2 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.21 – 8.11 (m, 2H), 8.06 – 7.97 (m, 1H), 7.72 – 7.63 (m, 1H), 5.08 – 4.97 (m, 1H), 4.71 – 4.61 (m, 1H), 4.49 – 4.34 (m, 3H), 4.32 – 4.21 (m, 2H), 4.15 – 4.02 (m, 1H), 3.86 – 3.74 (m, 1H), 3.69 – 3.46 (m, 6H), 3.41 – 3.35 (m, 1H), 3.35 – 3.32 (m, 1H), 2.35 – 2.18 (m, 3H), 2.17 – 1.80 (m, 6H), 1.79 – 1.70 (m, 1H)
4	(difluoro(2-(((3S,6S,8S,10aR)-8-hydroxy-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		685.3 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.15 – 8.14 (m, 2H), 8.03 – 8.00 (m, 1H), 7.68 (d, J = 8.8 Hz, 1H), 4.97 – 4.89 (m, 1H), 4.66 (t, J = 8.3 Hz, 1H), 4.46 – 4.31 (m, 3H), 4.34 – 4.23 (m, 1H), 4.15 – 4.05 (m, 1H), 4.04 – 3.96 (m, 1H), 3.85 – 3.74 (m, 1H), 3.68 – 3.48 (m, 6H), 3.40 – 3.32 (m, 2H), 2.35 – 2.14 (m, 4H), 2.13 – 1.83 (m, 5H), 1.82 – 1.71 (m, 1H)
5	(difluoro(2-(((3S,6S,9S,10aR)-9-hydroxy-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-		685.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.18 – 8.11 (m, 2H), 8.05 – 7.97 (m, 1H), 7.71 – 7.63 (m, 1H), 5.21 – 5.08 (m, 1H), 4.74 – 4.57 (m, 2H), 4.51 – 4.37 (m, 2H), 4.32 – 4.20 (m, 2H), 4.14 – 4.04 (m, 1H), 3.84 – 3.73 (m, 1H), 3.69 – 3.47 (m, 6H), 3.41 – 3.32 (m, 2H), 2.34 – 2.10 (m, 5H), 2.09 –

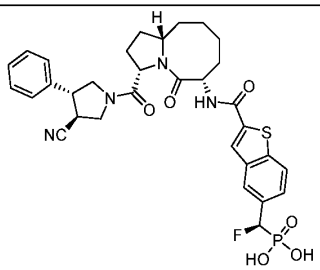
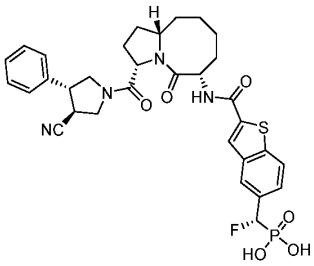
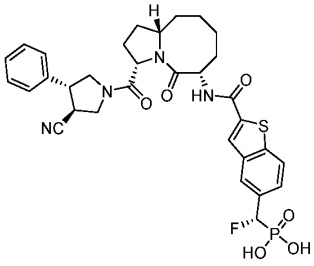
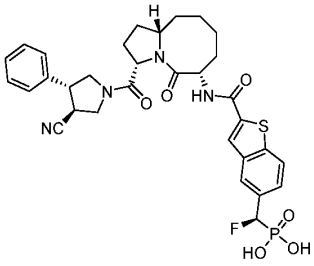
	a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			1.92 (m, 2H), 1.89 – 1.70 (m, 3H)
6	((2-(((3S,6S,9R,10aR)-9-(benzyloxy)-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		775.3 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.17 – 8.09 (m, 2H), 8.05 – 7.95 (m, 1H), 7.71 – 7.63 (m, 1H), 7.40 – 7.22 (m, 5H), 4.86 – 4.78 (m, 1H), 4.71 – 4.63 (m, 1H), 4.63 – 4.51 (m, 2H), 4.49 – 4.37 (m, 3H), 4.31 – 4.20 (m, 1H), 4.13 – 4.05 (m, 1H), 3.83 – 3.44 (m, 9H), 3.38 – 3.34 (m, 1H), 2.43 – 2.22 (m, 3H), 2.22 – 2.10 (m, 1H), 2.08 – 1.87 (m, 6H)
7	((2-(((3S,6S,8R,10aR)-8-(benzyloxy)-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		775.3 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.19 – 8.11 (m, 2H), 8.06 – 7.99 (m, 1H), 7.72 – 7.64 (m, 1H), 7.40 – 7.20 (m, 5H), 5.13 – 5.02 (m, 1H), 4.73 – 4.64 (m, 1H), 4.62 – 4.51 (m, 2H), 4.49 – 4.36 (m, 3H), 4.34 – 4.23 (m, 1H), 4.22 – 4.06 (m, 2H), 3.85 – 3.74 (m, 1H), 3.69 – 3.52 (m, 6H), 3.40 – 3.33 (m, 2H), 2.44 – 2.32 (m, 1H), 2.31 – 1.95 (m, 7H), 1.92 – 1.72 (m, 2H)

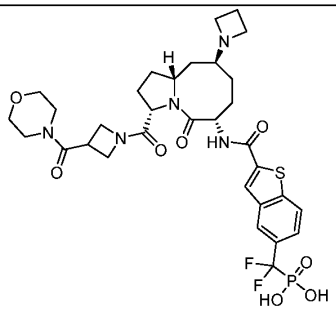
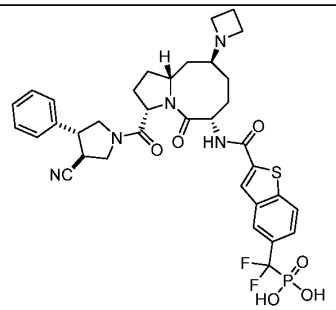
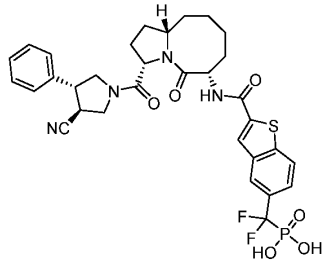
8	((2-(((3S,6S,8S,10aR)-8-(benzyloxy)-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		775.3 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.15 (s, 2H), 8.02 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.39 – 7.22 (m, 5H), 4.85 – 4.81 (m, 1H), 4.70 (t, J = 8.3 Hz, 1H), 4.63 – 4.53 (m, 2H), 4.46 – 4.36 (m, 2H), 4.34 – 4.19 (m, 2H), 4.13 – 4.03 (m, 1H), 3.82 – 3.73 (m, 1H), 3.72 – 3.53 (m, 7H), 3.39 – 3.32 (m, 2H), 2.46 – 2.43 (m, 1H), 2.32 – 1.93 (m, 6H), 1.90 – 1.67 (m, 3H)
9	((2-(((3S,6S,9R,10aR)-9-ethoxy-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		713.2 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.19 – 8.09 (m, 2H), 8.05 – 7.97 (m, 1H), 7.72 – 7.64 (m, 1H), 4.73 – 4.62 (m, 1H), 4.53 – 4.36 (m, 3H), 4.31 – 4.19 (m, 1H), 4.14 – 4.03 (m, 1H), 3.86 – 3.74 (m, 1H), 3.69 – 3.46 (m, 10H), 3.41 – 3.33 (m, 2H), 2.38 – 2.21 (m, 3H), 2.15 – 1.82 (m, 7H), 1.18 (t, J = 7.0 Hz, 3H)
10	((2-(((3S,6S,8S,10aR)-8-ethoxy-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-		713.2 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.16 – 8.14 (m, 2H), 8.02 (d, J = 8.6 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 4.73 – 4.66 (m, 1H), 4.46 – 4.21 (m, 4H), 4.13 – 4.04 (m, 1H), 3.83 – 3.73 (m, 1H), 3.68 – 3.46 (m, 10H), 3.40 – 3.32 (m, 2H), 2.40 – 2.12

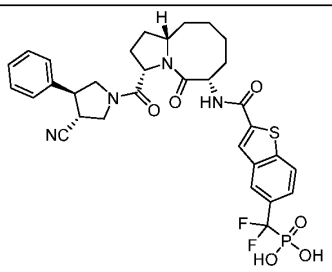
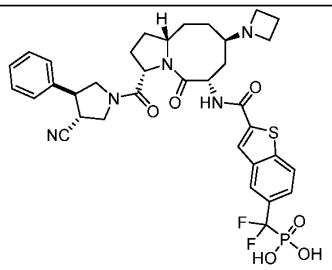
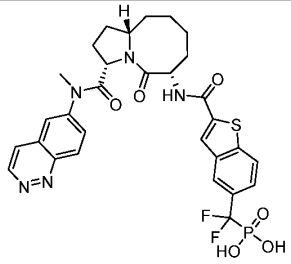
	a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid			(m, 3H), 2.07 – 1.71 (m, 7H), 1.21 – 1.15 (m, 3H)
11	((2-(((3S,6S,8R,10aR)-8-ethoxy-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		713.3 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.20 – 8.10 (m, 2H), 8.02 (d, J = 8.6 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 5.09 – 4.98 (m, 1H), 4.72 – 4.62 (m, 1H), 4.49 – 4.35 (m, 3H), 4.32 – 4.22 (m, 1H), 4.16 – 4.05 (m, 1H), 4.04 – 3.94 (m, 1H), 3.86 – 3.72 (m, 1H), 3.69 – 3.45 (m, 8H), 3.41 – 3.33 (m, 2H), 2.39 – 2.15 (m, 3H), 2.12 – 1.72 (m, 7H), 1.19 (t, J = 7.1 Hz, 3H)
12	((2-(((3S,6S,8S,10aR)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-8-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		687.2 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.22 – 8.11 (m, 2H), 8.07 – 7.96 (m, 1H), 7.67 (d, J = 8.6 Hz, 1H), 7.50 – 7.25 (m, 5H), 5.02 – 4.92 (m, 1H), 4.67 – 4.56 (m, 1H), 4.47 – 4.34 (m, 1H), 4.24 – 4.15 (m, 1H), 4.15 – 3.86 (m, 3H), 3.83 – 3.56 (m, 2H), 3.55 – 3.39 (m, 1H), 2.51 – 2.18 (m, 4H), 2.17 – 2.06 (m, 1H), 2.05 – 1.84 (m, 4H), 1.83 – 1.69 (m, 1H)

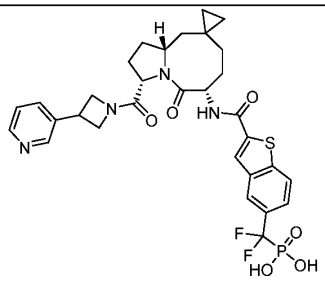
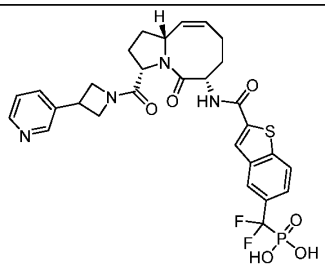
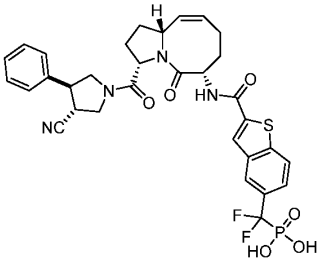
13	(difluoro(2-(((3S,6S,9S,10aR)-9-hydroxy-9-methyl-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		699.3 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.15 – 8.11 (m, 2H), 8.03 – 7.96 (m, 1H), 7.66 (d, J = 7.8 Hz, 1H), 5.32 – 5.23 (m, 1H), 4.72 – 4.57 (m, 2H), 4.50 – 4.36 (m, 2H), 4.30 – 4.20 (m, 1H), 4.13 – 4.05 (m, 1H), 3.83 – 3.73 (m, 1H), 3.67 – 3.46 (m, 6H), 3.38 – 3.32 (m, 2H), 2.38 – 2.10 (m, 5H), 2.04 – 1.89 (m, 1H), 1.85 – 1.72 (m, 2H), 1.71 – 1.55 (m, 2H), 1.28 (s, 3H)
14	((2-(((3S,6S,8R,10aR)-3-((3R,4S or 3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-8-hydroxy-8-methyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid	 or  SFC peak 1 was used for biological testing	701.2 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.18 – 8.13 (m, 2H), 8.06 – 7.99 (m, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.50 – 7.26 (m, 5H), 5.18 – 5.09 (m, 1H), 4.66 – 4.54 (m, 2H), 4.23 – 4.14 (m, 0.8H), 4.13 – 4.05 (m, 1.2H), 3.92 (t, J = 10.1 Hz, 0.5H), 3.83 – 3.75 (m, 0.5H), 3.75 – 3.70 (m, 0.7H), 3.67 – 3.57 (m, 1.3H), 3.52 – 3.37 (m, 1H), 2.44 – 2.33 (m, 1H), 2.33 – 2.13 (m, 2H), 2.10 – 1.93 (m, 3.5H), 1.90 – 1.73 (m, 2.5H), 1.71 – 1.60 (m, 1H), 1.36 – 1.30 (m, 3H)
15	((2-(((3S,6S,9S,10aR)-3-(3-(1H-imidazol-1-yl)azetidine-1-carbonyl)-9-hydroxy-5-oxodecahydr		638.2 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 9.09 – 9.03 (m, 1H), 8.22 – 8.16 (m, 1H), 8.16 – 8.11 (m, 1H), 8.05 – 7.99 (m, 1H), 7.95 – 7.87 (m, 1H), 7.76 – 7.69 (m, 1H), 7.58 – 7.53 (m, 1H), 5.43 – 5.32 (m, 1H), 5.20 – 5.08 (m,

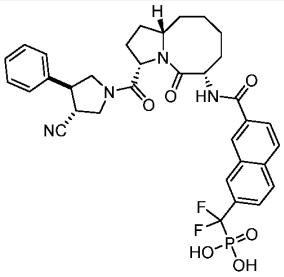
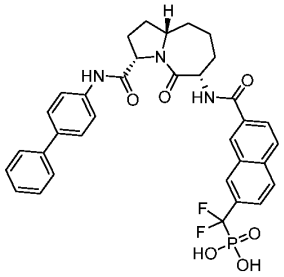
	opyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid			1H), 4.81 – 4.70 (m, 1H), 4.69 – 4.60 (m, 1H), 4.56 – 4.16 (m, 5H), 2.35 – 1.69 (m, 10H)
16	(difluoro(2-(((3S,6S,9S,10aR)-9-hydroxy-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		649.2 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.69 – 8.40 (m, 2H), 8.25 – 7.99 (m, 3H), 7.97 – 7.87 (m, 1H), 7.78 – 7.69 (m, 1H), 7.64 – 7.47 (m, 1H), 5.22 – 5.09 (m, 1H), 5.05 – 4.91 (m, 1H), 4.75 – 4.59 (m, 2H), 4.58 – 4.35 (m, 2H), 4.34 – 4.22 (m, 1H), 4.11 – 3.94 (m, 2H), 2.38 – 2.12 (m, 5H), 2.11 – 1.96 (m, 2H), 1.95 – 1.71 (m, 3H)
17	(difluoro(2-(((3S,6S,8R,10aR)-8-hydroxy-8-methyl-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		699.3 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.16 – 8.10 (m, 2H), 8.03 – 7.96 (m, 1H), 7.69 – 7.64 (m, 1H), 5.15 – 5.09 (m, 1H), 4.71 – 4.64 (m, 1H), 4.59 – 4.51 (m, 1H), 4.48 – 4.35 (m, 2H), 4.32 – 4.20 (m, 1H), 4.12 – 4.05 (m, 1H), 3.82 – 3.72 (m, 1H), 3.67 – 3.43 (m, 6H), 3.37 – 3.33 (m, 1H), 3.29 – 3.20 (m, 1H), 2.30 – 2.10 (m, 3H), 2.08 – 1.91 (m, 4H), 1.85 – 1.58 (m, 3H), 1.31 (s, 3H)

18	((2-(((3S,6S,10aS)-3-((3S,4R or 3R, 4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 or  SFC peak 1 was used for biological testing	653.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.11 (s, 1H), 8.07 – 8.00 (m, 1H), 7.98 – 7.91 (m, 1H), 7.64 – 7.55 (m, 1H), 7.45 – 7.27 (m, 5H), 5.82 (m, 1H), 5.09 – 4.97 (m, 1H), 4.74 – 4.63 (m, 1H), 4.58 – 4.38 (m, 2H), 4.13 – 3.91 (m, 1H), 3.90 – 3.64 (m, 2H), 3.63 – 3.46 (m, 2H), 2.43 – 2.16 (m, 2H), 2.13 – 1.93 (m, 6H), 1.91 – 1.75 (m, 2H), 1.73 – 1.55 (m, 2H)
19	((2-(((3S,6S,10aS)-3-((3S,4R or 3R, 4S))-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 or  SFC peak 2 was used for biological testing	653.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.12 (s, 1H), 8.06 – 8.00 (m, 1H), 7.99 – 7.91 (m, 1H), 7.63 – 7.55 (m, 1H), 7.45 – 7.26 (m, 5H), 5.83 (m, 1H), 5.09 – 4.99 (m, 1H), 4.75 – 4.64 (m, 1H), 4.58 – 4.37 (m, 2H), 4.12 – 3.92 (m, 1H), 3.89 – 3.65 (m, 2H), 3.64 – 3.50 (m, 2H), 2.40 – 2.18 (m, 2H), 2.11 – 1.93 (m, 6H), 1.91 – 1.77 (m, 2H), 1.71 – 1.58 (m, 2H)

20	((2-(((3S,6S,9S,10aR)-9-(azetidin-1-yl)-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		724.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.22 – 8.13 (m, 2H), 8.13 – 8.04 (m, 1H), 7.78 – 7.71 (m, 1H), 4.81 – 4.58 (m, 1H), 4.57 – 4.37 (m, 1H), 4.36 – 4.21 (m, 2H), 4.19 – 3.88 (m, 4H), 3.82 – 3.67 (m, 2H), 3.66 – 3.54 (m, 6H), 3.53 – 3.43 (m, 1H), 3.42 – 3.32 (m, 2H), 3.14 – 3.01 (m, 1H), 2.54 – 2.37 (m, 1H), 2.35 – 2.23 (m, 1H), 2.22 – 2.04 (m, 2H), 2.02 – 1.79 (m, 2H), 1.78 – 1.49 (m, 4H), 1.47 – 1.36 (m, 1H), 0.66 – 0.52 (m, 1H), 0.44 – 0.30 (m, 1H)
21	((2-(((3S,6S,9S,10aR)-9-(azetidin-1-yl)-3-(*rel*-(trans)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		726.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.27 – 8.12 (m, 2H), 8.10 – 8.01 (m, 1H), 7.81 – 7.73 (m, 1H), 7.51 – 7.21 (m, 5H), 4.63 – 4.48 (m, 1H), 4.46 – 4.30 (m, 1H), 4.16 – 3.36 (m, 10H), 3.24 – 3.11 (m, 1H), 2.51 – 1.84 (m, 6H), 1.82 – 1.49 (m, 4H), 1.49 – 1.36 (m, 1H), 0.69 – 0.54 (m, 1H), 0.44 – 0.27 (m, 1H)
22	((2-(((3S,6S,10aS)-3-((3S,4R or 3R, 4S))-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-	 or	671.0 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.19 – 8.13 (m, 2H), 8.02 (t, J = 7.5 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.43 – 7.29 (m, 5H), 5.08 – 4.99 (m, 1H), 4.75 – 4.65 (m, 1H), 4.58 – 4.50 (m, 0.5H), 4.49 – 4.39 (m, 1.5H), 4.07 (dd, J = 11.5, 8.1 Hz, 0.5H), 3.96 (dd, J = 11.7,

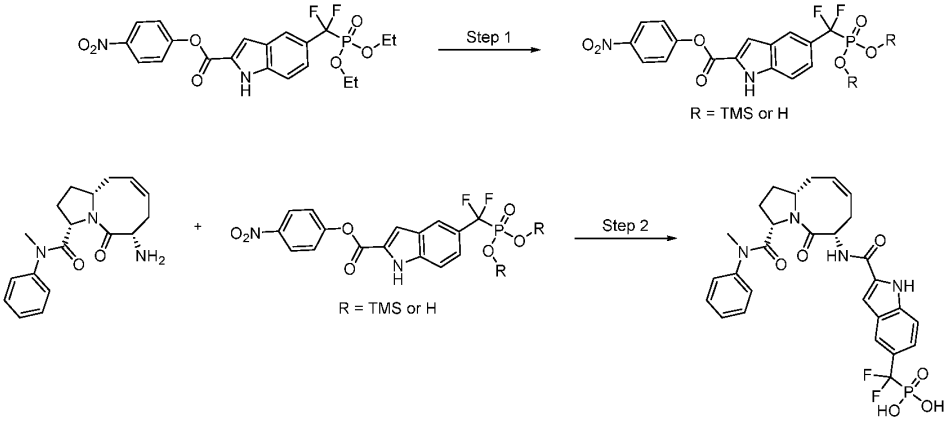
	yl)carbamoyl)benzo[b]thio phen-5-yl)difluorom ethyl)phosph onic acid	 SFC peak 2 was used for biological testing		7.6 Hz, 0.5H), 3.85 (t, J = 9.7 Hz, 0.5H), 3.80 – 3.66 (m, 1.5H), 3.66 – 3.50 (m, 2H), 2.42 – 2.17 (m, 2H), 2.13 – 1.93 (m, 6H), 1.92 – 1.75 (m, 2H), 1.75 – 1.58 (m, 2H)
23	((2-(((3S,6S,8R, 10aS)-8-(azetidin-1-yl)-3-(*rel*-trans) -3-cyano-4-phenylpyrroli dine-1-carbonyl)-5-oxodecahydr opyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thio phen-5-yl)difluorom ethyl)phosph onic acid		726.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.19 – 8.14 (m, 1H), 8.13 – 8.07 (m, 1H), 7.97 – 7.91 (m, 1H), 7.79 – 7.70 (m, 1H), 7.44 – 7.24 (m, 5H), 4.71 – 4.56 (m, 1H), 4.45 – 3.38 (m, 13H), 2.63 – 2.46 (m, 1H), 2.46 – 2.18 (m, 3H), 2.13 – 1.74 (m, 6H), 1.73 – 1.56 (m, 1H), 1.17 – 1.02 (m, 1H)
24	((2-(((3S,6S,10a S)-3-(cinnolin-6-yl(methyl)car bamoyl)-5-oxodecahydr opyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thio phen-5-yl)difluorom ethyl)phosph onic acid		658.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 9.29 (d, J = 5.9 Hz, 1H), 8.52 (d, J = 9.3 Hz, 1H), 8.30 (d, J = 5.9 Hz, 1H), 8.16 – 8.13 (m, 1H), 8.13 – 8.06 (m, 3H), 7.96 (d, J = 8.6 Hz, 1H), 7.67 (d, J = 8.6 Hz, 1H), 5.00 (t, J = 8.7 Hz, 1H), 4.63 – 4.48 (m, 1H), 4.44 – 4.31 (m, 1H), 3.45 (s, 3H), 2.22 – 1.95 (m, 8H), 1.92 – 1.75 (m, 2H), 1.73 – 1.57 (m, 2H)

25	(difluoro(2-(((3'S,6'S,10a'R)-5'-oxo-3'-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1'H-spiro[cyclopropane-1,9'-pyrrolo[1,2-a]azocin]-6'-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		659.2 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4 + 1 drop NaOD) δ 8.59 – 8.53 (m, 1H), 8.50 – 8.42 (m, 1H), 8.33 – 8.26 (m, 1H), 8.19 – 8.13 (m, 1H), 8.12 – 8.06 (m, 0.4H), 7.98 – 7.92 (m, 0.6H), 7.90 – 7.82 (m, 2H), 7.53 – 7.44 (m, 1H), 5.23 – 5.13 (m, 1H), 5.05 – 4.97 (m, 1H), 4.75 – 4.61 (m, 1H), 4.60 – 4.27 (m, 3H), 4.17 – 3.94 (m, 2H), 2.72 – 2.51 (m, 2H), 2.35 – 2.17 (m, 2H), 2.10 – 1.99 (m, 1H), 1.98 – 1.85 (m, 2H), 1.84 – 1.71 (m, 1H), 1.36 – 1.19 (m, 1H), 0.81 – 0.68 (m, 2H), 0.61 – 0.47 (m, 2H), 0.43 – 0.34 (m, 1H)
26	(difluoro(2-(((3S,6S,10aR,Z)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		631.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.57 – 8.51 (m, 1H), 8.49 – 8.40 (m, 1H), 8.30 – 8.24 (m, 1H), 8.15 (s, 1H), 8.10 – 7.92 (m, 1H), 7.91 – 7.80 (m, 2H), 7.53 – 7.41 (m, 1H), 5.88 – 5.75 (m, 1H), 5.68 – 5.57 (m, 1H), 5.03 – 4.95 (m, 2H), 4.87 – 4.79 (m, 1H), 4.74 – 4.58 (m, 2H), 4.57 – 4.37 (m, 1H), 4.33 – 3.96 (m, 2H), 3.24 – 3.11 (m, 1H), 2.44 – 2.31 (m, 1H), 2.25 – 1.87 (m, 6H)
27	((2-(((3S,6S,10aR,Z)-3-(*rel*-trans)3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxo-1,2,3,5,6,7,8,10a-		669.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.20 – 8.12 (m, 2H), 8.06 – 7.99 (m, 1H), 7.68 – 7.66 (m, 1H), 7.46 – 7.28 (m, 5H), 5.85 – 5.75 (m, 1H), 5.65 – 5.62 (m, 1H), 5.01 – 4.96 (m, 1H), 4.85 – 4.77 (m, 2H), 4.52 – 3.98 (m, 2H), 3.97 – 3.39 (m, 4H), 3.27 – 3.17 (m, 1H), 2.43

	octahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid			– 2.34 (m, 1H), 2.28 – 2.15 (m, 1H), 2.13 – 1.89 (m, 5H), 1.40 – 1.09 (m, 1H)
28	((7-(((3S,6S,10aS)-3-(*rel*-trans)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphonic acid		665.4 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.55 – 8.50 (m, 1H), 8.27 (s, 1H), 8.01 – 7.92 (m, 3H), 7.90 – 7.83 (m, 1H), 7.49 – 7.27 (m, 5H), 5.14 – 5.05 (m, 1H), 4.75 – 4.62 (m, 1H), 4.60 – 4.41 (m, 2H), 4.17 – 4.03 (m, 1H), 4.02 – 3.84 (m, 1H), 3.84 – 3.68 (m, 1H), 3.67 – 3.45 (m, 2H), 2.42 – 2.20 (m, 2H), 2.14 – 1.93 (m, 6H), 1.92 – 1.77 (m, 2H), 1.76 – 1.60 (m, 2H)
29	((7-(((3S,6S,9aS)-3-([1,1'-biphenyl]-4-ylcarbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphonic acid		648.2 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.53 (s, 1H), 8.24 (s, 1H), 8.07 – 7.93 (m, 3H), 7.78 (d, J = 8.8 Hz, 1H), 7.70 – 7.62 (m, 2H), 7.61 – 7.52 (m, 4H), 7.41 (t, J = 7.6 Hz, 2H), 7.35 – 7.26 (m, 1H), 4.86 (s, 1H), 4.74 (dd, J = 8.0, 4.0 Hz, 1H), 4.12 (d, J = 5.6 Hz, 1H), 2.34 (dd, J = 12.4, 5.6 Hz, 1H), 2.26 – 2.02 (m, 4H), 2.00 – 1.82 (m, 5H)

[00320] Method 2: Representative Procedure for the Synthesis of Phosphonic Acid Analogues by Direct Coupling of Perfluorophenyl or p-Nitrophenyl Activated Linker Esters with Amino Acid Cores

[00321] Synthesis of difluoro(2-(((3S,6S,10aR,Z)-3-(methyl(phenyl)carbamoyl)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)-1H-indol-5-yl)methyl)phosphonic acid (30)



[00322] *Step 1: Preparation of 4-nitrophenyl 5-((bis((trimethylsilyl)oxy)phosphoryl)difluoromethyl)-1H-indole-2-carboxylate*

[00323] To a solution of 4-nitrophenyl 5-((diethoxyphosphoryl)difluoromethyl)-1H-indole-2-carboxylate (70 mg, 149 µmol, 1.0 eq.) in CH_2Cl_2 (4 mL) was added TMSBr (228 mg, 1.49 mmol, 10.0 eq.) dropwise at room temperature. The mixture was stirred at room temperature for 5 hrs. After completion, the reaction was concentrated under reduced pressure to afford 4-nitrophenyl 5-((bis((trimethylsilyl)oxy)phosphoryl)difluoromethyl)-1H-indole-2-carboxylate (77.0 mg, 146 µmol, 99 %) as a yellow solid, which was used in next step directly without further purification. LCMS (ESI) *m/z* = 413 $[(M-144)+H]^+$. (TMS ester was hydrolysis when LCMS, only detected parent acid mass).

[00324] *Step 2: Preparation of* (3S,6S,10aR,Z)-6-amino-N-methyl-5-oxo-N-phenyl-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxamide

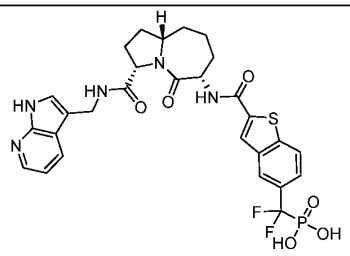
[00325] (3S,6S,10aR,Z)-6-amino-N-methyl-5-oxo-N-phenyl-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxamide was synthesized starting from (3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylic acid and using similar protocol described above for the preparation of (3S,6S,10aS)-6-amino-N-methyl-5-oxo-N-phenyldecahydropyrrolo[1,2-a]azocine-3-carboxamide.

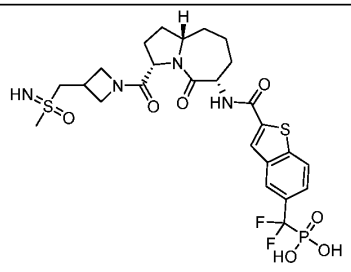
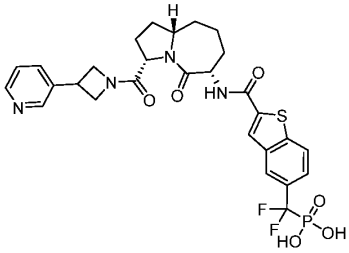
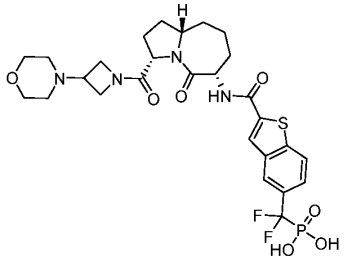
[00326] *Step 1: Preparation of difluoro(2-(((3S,6S,10aR,Z)-3-(methyl(phenyl)carbamoyl)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)-1H-indol-5-yl)methyl)phosphonic acid (**30**)*

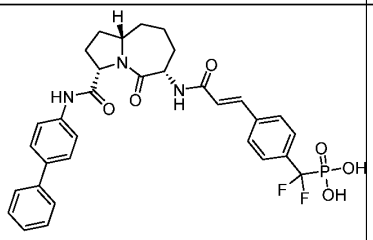
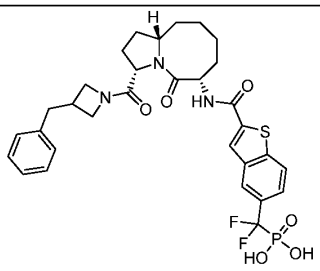
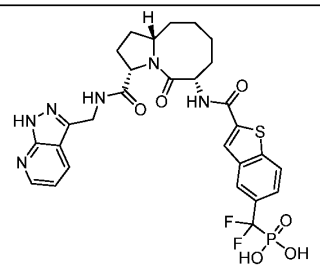
[00327] To a solution of (3S,6S,10aR,Z)-6-amino-N-methyl-5-oxo-N-phenyl-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxamide (137 mg, 440 µmol, 1.1 eq) [previously synthesized using similar protocol detailed in step 1 and step2 of Method 1 for the preparation of difluoro(2-(((3S,6S,10aS)-3-(methyl(phenyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)-1H-indol-5-yl)methyl)phosphonic acid (**1**)] and DMAP (146 mg, 1.20 mmol, 3 eq) in DMF (3 mL) was added 4-nitrophenyl 5-({bis[(trimethylsilyl)oxy]phosphoryl}difluoromethyl)-1H-indole-2-carboxylate (223 mg, 400 µmol, 1 eq). The resulting mixture was stirred 40 °C for 12 h. The reaction mixture was cooled to ambient temperatures and H_2O (10 mL) was subsequently introduced. The biphasic mixture was extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were washed with brine (2 x 20 mL), dried over with anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by reverse phase HPLC to afford (difluoro(2-(((3S,6S,10aR,Z)-3-(methyl(phenyl)carbamoyl)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)-1H-indol-5-yl)methyl)phosphonic acid (**30**) (77 mg, 132 µmol, 33% yield) as a white solid. LCMS (ESI) m/z = 587 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1H), 8.55 (d, J = 7.6 Hz, 1H), 7.83 (s, 1H), 7.52-7.34 (m, 8H), 5.88-5.73 (m, 2H), 5.03-4.93 (m, 1H), 4.26-4.11 (m, 1H), 3.18-3.11 (m, 4H), 2.67-2.56 (m, 2H), 2.54-2.40 (m, 2H), 1.97-1.73 (m, 4H).

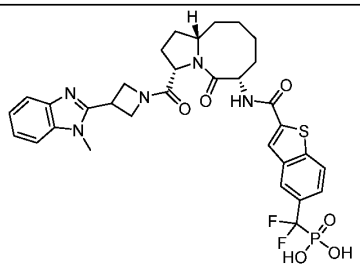
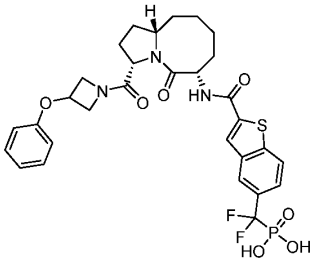
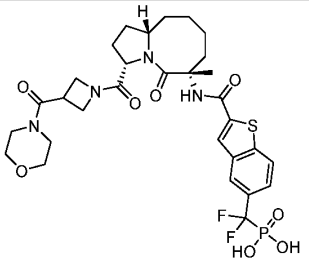
[00328] The following compounds in **Table 28** were prepared according to the representative procedure described above for the synthesis of (difluoro(2-(((3S,6S,10aR,Z)-3-(methyl(phenyl)carbamoyl)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)-1H-indol-5-yl)methyl)phosphonic acid and utilizing appropriate starting materials and modifications.

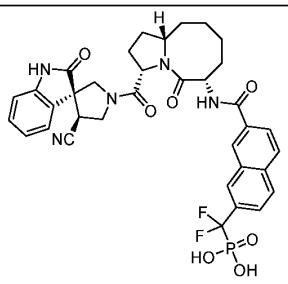
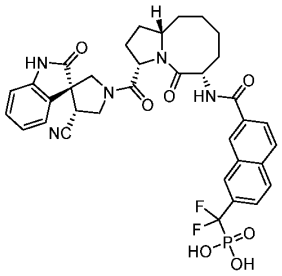
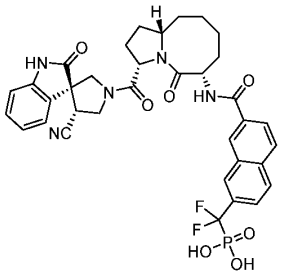
Table 28

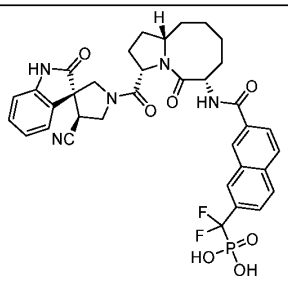
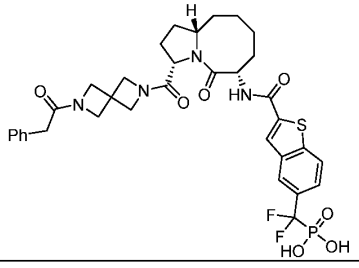
Compound	Name	Structure	LCMS	NMR
31	((2-(((3S,6S,9aS)-3-(((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl		632.1 $[M+H]^+$	^1H NMR (400 MHz, methanol-d_4) δ 8.27 – 8.14 (m, 2H), 8.10 – 8.05 (m, 2H), 7.91 (d, J = 8.5 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.38 (s, 1H), 7.12 – 7.08 (m, 1H), 4.71 (d, J = 11.2 Hz, 1H), 4.61 – 4.50 (m, 3H), 4.06 – 3.97 (m, 1H), 2.31 – 2.21 (m, 1H), 2.07 – 1.97 (m,

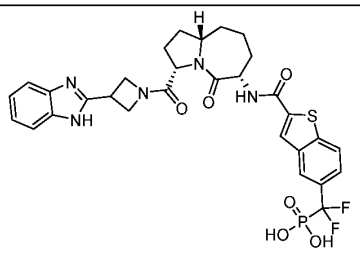
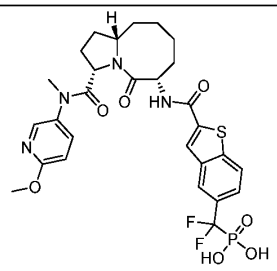
	)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid			4H), 1.93 – 1.81 (m, 3H), 1.80 – 1.67 (m, 2H)
32	(difluoro(2-(((3S,6S,9aS)-3-(3-((S-methylsulfonimidoyl)methyl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		633.3 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.21 – 8.07 (m, 2H), 7.98 (d, J = 8.4 Hz, 1H), 7.74 – 7.66 (m, 1H), 4.49 – 4.36 (m, 2H), 4.45 – 4.35 (m, 2H), 4.24 – 4.11 (m, 3H), 4.09 – 4.03 (m, 1H), 3.97 – 3.85 (m, 1H), 3.64 – 3.54 (m, 3H), 2.29 (m, 1H), 2.12 – 1.99 (m, 3H), 1.98 – 1.74 (m, 7H)
33	(difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		619.0 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.54 (d, J = 1.6 Hz, 1H), 8.49 – 8.40 (m, 1H), 8.22 (s, 1H), 8.16 – 7.89 (m, 3H), 7.78 (d, J = 8.4 Hz, 1H), 7.55 – 7.39 (m, 1H), 4.80 – 4.65 (m, 2H), 4.63 – 4.47 (m, 2H), 4.45 – 4.24 (m, 1H), 4.15 – 3.92 (m, 3H), 2.31 (d, J = 6.4 Hz, 1H), 2.22 – 1.77 (m, 9H), 1.38 – 1.29 (m, 3H)
34	(difluoro(2-(((3S,6S,9aS)-3-(3-morpholinoazetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl		627.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (dd, J = 7.6, 14.4 Hz, 1H), 8.28 (d, J = 6.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.07 (s, 1H), 7.59 (d, J = 8.4 Hz, 1H), 4.63 (d, J = 5.2 Hz, 1H), 4.55 – 4.48 (m, 1H), 4.40 (dd, J = 8.4, 4.8 Hz, 1H), 4.31 (d, J = 3.2 Hz, 1H), 3.97 (dd, J = 4.8,

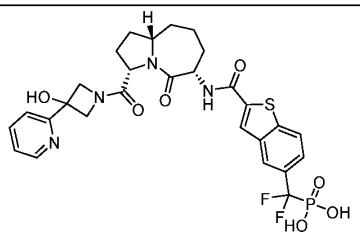
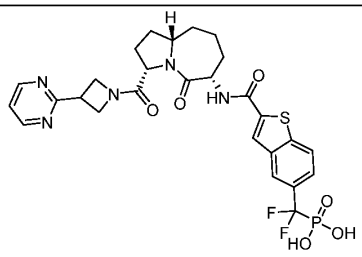
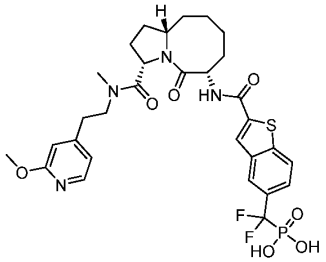
	)benzo[b]thiophen-5-yl)methyl)phosphonic acid			10.0 Hz, 4H), 3.75 – 3.68 (m, 4H), 2.92 – 2.81 (m, 2H), 2.68 (d, J = 11.2 Hz, 2H), 2.23 – 2.17 (m, 1H), 2.01 – 1.93 (m, 2H), 1.91 – 1.82 (m, 2H), 1.78 (d, J = 4.0 Hz, 2H), 1.64 (s, 3H)
35	((4-((E)-3-(((3S,6S,9aS)-3-([1,1'-biphenyl]-4-ylcarbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)amino)-3-oxoprop-1-en-1-yl)phenyl)difluoromethyl)phosphonic acid		624.5 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 7.70 – 7.51 (m, 11H), 7.41 (t, J = 7.6 Hz, 2H), 7.34 – 7.24 (m, 1H), 6.80 (d, J = 15.6 Hz, 1H), 4.75 – 4.65 (m, 2H), 4.17 – 3.95 (m, 1H), 2.40 – 2.26 (m, 1H), 2.23 – 2.02 (m, 3H), 1.98 – 1.73 (m, 6H)
36	((2-(((3S,6S,10aS)-3-(3-benzylazetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		646.4 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.21 – 8.10 (m, 2H), 7.98 – 7.91 (m, 1H), 7.78 – 7.70 (m, 1H), 7.30 – 7.12 (m, 5H), 5.07 – 4.98 (m, 1H), 4.82 (s, 1H), 4.46 – 4.35 (m, 2H), 4.26 (d, J = 5.6 Hz, 1H), 4.02 – 3.90 (m, 1H), 3.82 – 3.62 (m, 1H), 3.03 – 2.88 (m, 3H), 2.29 – 2.13 (m, 2H), 2.06 – 1.91 (m, 6H), 1.88 – 1.73 (m, 2H), 1.72 – 1.54 (m, 2H)
37	((2-(((3S,6S,10aS)-3-(((1H-pyrazolo[3,4-b]pyridin-3-yl)methyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-		647.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.50 – 8.43 (m, 1H), 8.40 – 8.34 (m, 1H), 8.16 (s, 1H), 8.10 (s, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.23 – 7.15 (m, 1H), 5.08 – 5.01 (m, 1H), 4.74 (m, 2H), 4.49 – 4.38 (m, 2H), 2.26 – 2.15

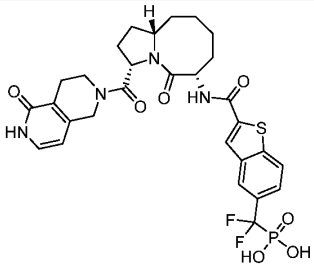
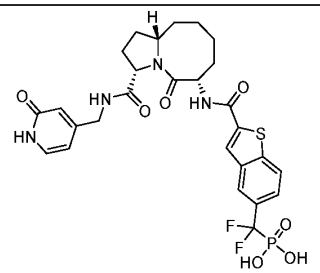
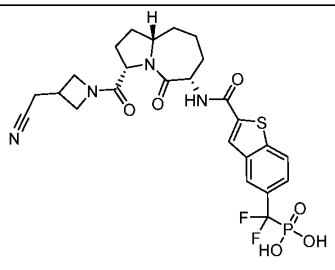
	yl)carbamoyl)benzo[b]thio phen-5-yl)difluorom ethyl)phosph onic acid			(m, 2H), 2.08 – 1.93 (m, 6H), 1.86 – 1.76 (m, 2H), 1.73 – 1.58 (m, 2H)
38	(difluoro(2-(((3S,6S,10a S)-3-(3-(1-methyl-1H-benzo[d]imid azol-2-yl)azetidine-1-carbonyl)-5-oxodecahydr opyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thio phen-5-yl)methyl)ph osphonic acid		686.2 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.21 (s, 1H), 8.16 – 8.07 (m, 1H), 7.94 – 7.83 (m, 1H), 7.79 – 7.71 (m, 1H), 7.67 – 7.56 (m, 1H), 7.50 – 7.37 (m, 1H), 7.32 – 7.18 (m, 2H), 5.05 – 4.98 (m, 1H), 4.79 – 4.70 (m, 1H), 4.65 – 4.52 (m, 2H), 4.52 – 4.39 (m, 2H), 4.38 – 4.27 (m, 2H), 3.77 – 3.65 (m, 3H), 2.35 – 2.17 (m, 2H), 2.11 – 1.89 (m, 6H), 1.88 – 1.74 (m, 2H), 1.73 – 1.57 (m, 2H)
39	(difluoro(2-(((3S,6S,10a S)-5-oxo-3-(3-phenoxyazeti dine-1-carbonyl)dec ahydropyrrol o[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thio phen-5-yl)methyl)ph osphonic acid		648.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.21 – 8.07 (m, 2H), 7.95 – 7.90 (m, 1H), 7.79 – 7.69 (m, 1H), 7.32 – 7.21 (m, 2H), 7.00 – 6.86 (m, 1H), 6.82 – 7.79 (m, 2H), 5.10 – 4.88 (m, 3H), 4.71 – 4.52 (m, 1H), 4.50 – 4.39 (m, 2H), 4.37 – 4.18 (m, 1H), 4.06 – 3.88 (m, 1H), 2.32 – 2.16 (m, 2H), 2.08 – 1.90 (m, 6H), 1.89 – 1.73 (m, 2H), 1.72 – 1.55 (m, 2H)
40	(difluoro(2-(((3S,6S,10a S)-6-methyl-3-(3-(morpholine-4-carbonyl)azet idine-1-carbonyl)-5-oxodecahydr		683.2 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.34 – 8.13 (m, 1H), 8.05 – 7.91 (m, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.63 – 7.34 (m, 1H), 4.74 – 4.65 (m, 1H), 4.54 – 4.28 (m, 2H), 4.23 – 4.02 (m, 1H), 3.97 – 3.57 (m, 6H), 3.46 – 3.37 (m, 1H), 3.24 – 3.15 (m,

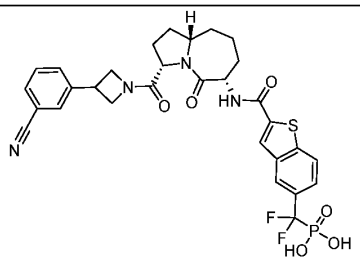
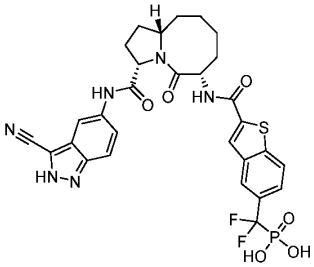
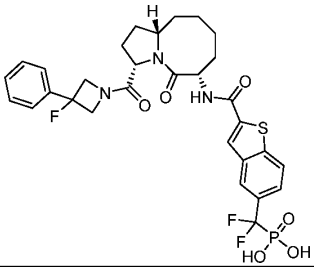
	opyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			1H), 3.09 – 2.94 (m, 1H), 2.48 – 2.29 (m, 1H), 2.25 – 2.09 (m, 1H), 2.07 – 1.67 (m, 6H), 1.65 – 1.48 (m, 2H), 1.46 – 1.29 (m, 10H)
41	((7-(((3S,6S,10aS)-3-((3S,4'S)-4'-cyano-2-oxospiro[indoline-3,3'-pyrrolidine]-1'-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphonic acid or ((7-(((3S,6S,10aS)-3-((3R,4'R)-4'-cyano-2-oxospiro[indoline-3,3'-pyrrolidine]-1'-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphonic acid	 or  or  or	706.0 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.55 – 8.44 (m, 1H), 8.27 (d, J = 13.6 Hz, 1H), 8.01 – 7.84 (m, 4H), 7.49 – 7.35 (m, 1H), 7.35 – 7.28 (m, 1H), 7.17 – 7.07 (m, 1H), 7.04 – 6.94 (m, 1H), 5.17 – 5.06 (m, 1H), 4.79 (m, 1H), 4.71 – 4.61 (m, 1H), 4.56 – 4.41 (m, 1H), 4.32 – 4.22 (m, 1H), 4.21 – 3.98 (m, 1H), 3.90 (s, 1H), 3.84 – 3.76 (m, 1H), 2.57 – 2.20 (m, 2H), 2.18 – 1.97 (m, 6H), 1.92 – 1.78 (m, 2H), 1.77 – 1.61 (m, 2H)

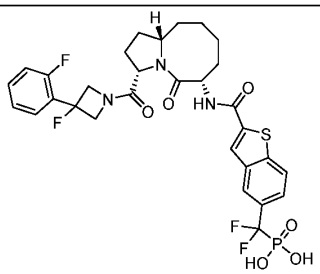
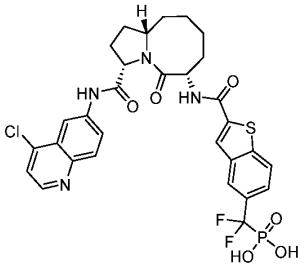
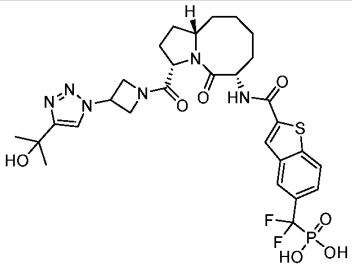
	or ((7-(((3S,6S,10aS)-3-((3R,4'S)-4'-cyano-2-oxospiro[indoline-3,3'-pyrrolidine]-1'-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphonic acid or ((7-(((3S,6S,10aS)-3-((3S,4'R)-4'-cyano-2-oxospiro[indoline-3,3'-pyrrolidine]-1'-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphonic acid	 SFC Peak 2 was used for biological testing		
42	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-(6-(2-phenylacetyl)-2,6-diazaspiro[3.3]heptane-2-		715.2 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.15 (d, J = 2.0 Hz, 2H), 8.02 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.35 – 7.13 (m, 5H), 5.04 – 4.93 (m, 1H), 4.69 – 4.59 (m, 1H), 4.38 (d, J = 4.8 Hz, 3H),

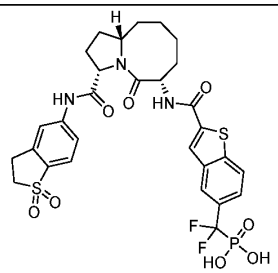
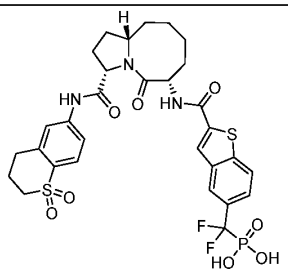
	carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			4.36 – 4.32 (m, 2H), 4.17 (s, 1H), 4.14 (d, J = 6.0 Hz, 2H), 4.07 (d, J = 10.4 Hz, 1H), 3.47 (d, J = 8.0 Hz, 2H), 2.25 – 2.16 (m, 2H), 2.04 – 1.90 (m, 6H), 1.87 – 1.76 (m, 2H), 1.72 – 1.54 (m, 2H)
43	((2-(((3S,6S,9aS)-3-(3-(1H-benzo[d]imidazol-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		658.2 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.78 (d, J = 8.1 Hz, 1H), 8.27 (app. d, J = 21.1 Hz, 1H), 8.16 – 7.99 (m, 2H), 7.70 – 7.55 (m, 2H), 7.50 (d, J = 7.3 Hz, 1H), 7.24 (dd, J = 6.4, 3.1 Hz, 1H), 7.13 (t, J = 4.3 Hz, 1H), 4.79 (s, 1H), 4.64 (m, 2H), 4.45 (m, 2H), 4.32 – 4.25 (m, 1H), 4.25 – 4.13 (m, 3H), 4.00 (s, 2H), 2.21 (s, 1H), 1.97 (m, 2H), 1.79 (m, 7H)
44	(difluoro(2-(((3S,6S,10aS)-3-((6-methoxypyridin-3-yl)(methyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		637.2 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.84 (d, J = 7.0 Hz, 1H), 8.32 (s, 1H), 8.22 (d, J = 2.7 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 8.06 (s, 1H), 7.74 (dd, J = 8.7, 2.7 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 4.96 – 4.87 (m, 1H), 4.26 – 4.08 (m, 3H), 3.83 (s, 4H), 2.04 (s, 1H), 1.85 (m, 7H), 1.65 (m, 2H), 1.53 (m, 2H)

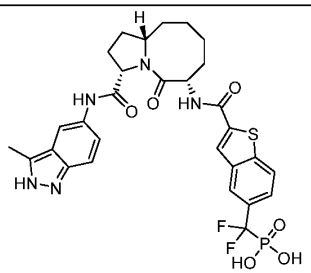
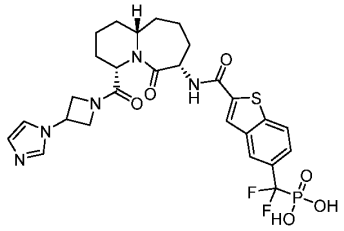
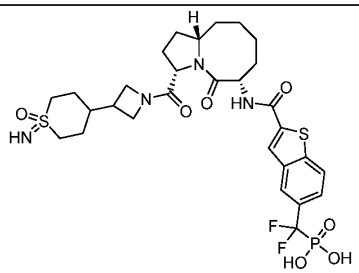
45	(difluoro(2-(((3S,6S,9aS)-3-(3-hydroxy-3-(pyridin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		635.2 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.76 (d, J = 7.6 Hz, 1H), 8.64 – 8.53 (m, 1H), 8.29 (dd, J = 5.8, 2.5 Hz, 1H), 8.12 (dd, J = 8.4, 3.0 Hz, 1H), 8.07 (d, J = 6.6 Hz, 1H), 7.82 (q, J = 7.5 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 8.6 Hz, 1H), 7.32 (dd, J = 9.7, 5.2 Hz, 1H), 4.79 – 4.60 (m, 2H), 4.59 – 4.46 (m, 2H), 4.35 (m, 2H), 4.18 (m, 2H), 3.96 (s, 2H), 3.88 (d, J = 10.2 Hz, 1H), 2.24 – 2.15 (m, 1H), 2.07 – 1.93 (m, 2H), 1.88 – 1.68 (m, 6H)
46	(difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyrimidin-2-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		620.2 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.78 (m, 2H), 8.28 (app. d, J = 20.5 Hz, 1H), 8.22 – 8.07 (m, 1H), 8.05 (d, J = 13.5 Hz, 1H), 7.56 (dd, J = 9.0, 4.1 Hz, 1H), 7.39 (dt, J = 17.1, 4.9 Hz, 1H), 4.80 – 4.36 (m, 4H), 4.29 – 3.94 (m, 4H), 3.04 (pd, J = 7.2, 3.6 Hz, 1H), 2.18 (dt, J = 13.7, 6.6 Hz, 1H), 2.10 – 1.89 (m, 2H), 1.85 – 1.64 (m, 5H), 1.13 (app. t, J = 7.3 Hz, 2H)
47	(difluoro(2-(((3S,6S,10aS)-3-((2-(2-methoxypyridin-4-yl)ethyl)(methyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)ph		665.2 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d$_6$) δ 8.85 (d, J = 6.6 Hz, 1H), 8.31 (s, 1H), 8.12 (d, J = 8.6 Hz, 1H), 8.04 (t, J = 4.5 Hz, 2H), 7.57 (d, J = 8.6 Hz, 1H), 6.90 (dd, J = 23.6, 5.3 Hz, 1H), 6.72 (d, J = 28.9 Hz, 1H), 4.96 (app. s, 1H), 4.71 (m, 1H), 4.26 (m, 1H), 3.64 (s, 2H), 3.41 – 3.36 (m, 1H), 3.00 (s, 2H), 2.91 (s, 1H), 2.72 (m, 3H), 2.27 – 1.77 (m, 7H), 1.74 – 1.39 (m, 5H)

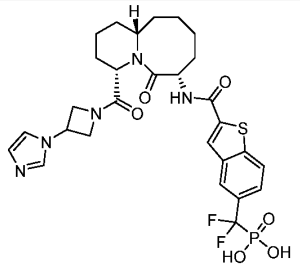
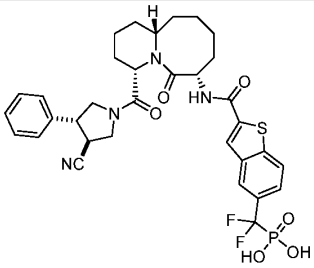
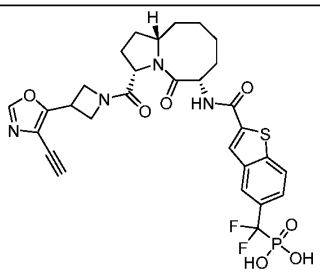
	osphonic acid			
48	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-(5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-2-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		649.0 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 11.41 (s, 1H), 8.83 (dd, J = 16.6, 7.0 Hz, 1H), 8.29 (s, 1H), 8.11 (d, J = 8.7 Hz, 1H), 8.04 (s, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.19 (d, J = 6.7 Hz, 1H), 6.01 (t, J = 8.4 Hz, 1H), 5.01 – 4.82 (m, 2H), 4.76 – 4.49 (m, 2H), 4.27 (m, 2H), 3.89 (m, 1H), 3.63 (s, 4H), 2.30 (m, 2H), 2.08 (m, 2H), 1.77 (m, 5H), 1.56 (m, 3H)
49	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-(((2-oxo-1,2-dihydropyridin-4-yl)methyl)carbamoyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		623.2 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 11.38 (s, 1H), 8.93 (d, J = 6.8 Hz, 1H), 8.49 (t, J = 6.1 Hz, 1H), 8.32 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 8.06 (s, 1H), 7.57 (d, J = 8.6 Hz, 1H), 7.27 (d, J = 6.7 Hz, 1H), 6.18 (s, 1H), 6.06 (d, J = 6.8 Hz, 1H), 4.94 (dt, J = 11.6, 5.9 Hz, 1H), 4.35 (t, J = 8.5 Hz, 1H), 4.28 (t, J = 9.8 Hz, 1H), 4.16 (dd, J = 16.8, 6.1 Hz, 2H), 4.05 (dd, J = 16.8, 5.2 Hz, 2H), 2.16 (m, 1H), 2.06 (m, 1H), 1.97 – 1.68 (m, 7H), 1.57 (m, 3H)
50	((2-(((3S,6S,9aS)-3-(3-(cyanomethyl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl		581.0 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.75 (t, J = 6.2 Hz, 1H), 8.27 (d, J = 1.9 Hz, 1H), 8.10 (d, J = 8.6 Hz, 1H), 8.05 (s, 1H), 7.59 – 7.53 (m, 1H), 4.62 (t, J = 9.4 Hz, 1H), 4.46 (t, J = 8.4 Hz, 1H), 4.38 (dd, J = 8.1, 4.2 Hz, 1H), 4.29 (t, J = 8.5 Hz, 1H), 4.05 – 3.92 (m, 3H), 3.88 (dd, J

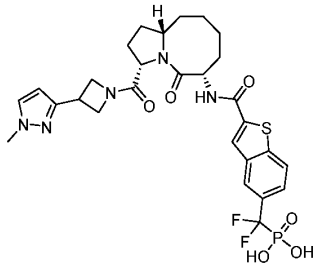
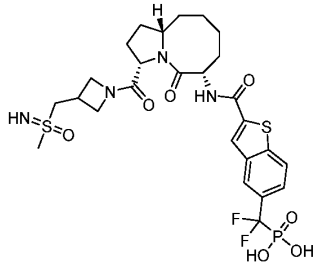
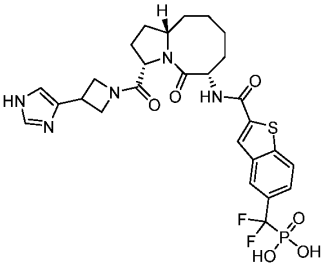
	)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid			= 8.9, 4.8 Hz, 1H), 3.56 (ddd, J = 21.0, 10.0, 5.5 Hz, 2H), 2.99 – 2.83 (m, 3H), 2.79 (dd, J = 7.1, 2.8 Hz, 1H), 2.23 – 2.13 (m, 1H), 2.01 – 1.89 (m, 2H), 1.84 (m, 1H), 1.80 – 1.55 (m, 6H)
51	((2-(((3S,6S,9aS)-3-(3-(3-cyanophenyl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		643.2 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.77 (t, J = 7.1 Hz, 1H), 8.29 (dd, J = 13.1, 2.3 Hz, 1H), 8.12 (t, J = 6.5 Hz, 1H), 8.07 (s, 1H), 7.92 – 7.82 (m, 1H), 7.77 – 7.67 (m, 2H), 7.61 – 7.50 (m, 2H), 4.76 (t, J = 8.9 Hz, 1H), 4.71 – 4.62 (m, 1H), 4.59 (t, J = 8.8 Hz, 1H), 4.39 (dt, J = 21.7, 6.9 Hz, 2H), 4.31 – 4.16 (m, 2H), 3.95 (d, J = 7.8 Hz, 2H), 3.87 (t, J = 8.6 Hz, 1H), 2.18 (d, J = 6.5 Hz, 1H), 2.04 – 1.92 (m, 2H), 1.89 – 1.63 (m, 7H)
52	((2-(((3S,6S,10aS)-3-((3-cyano-2H-indazol-5-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		657.4 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 14.29 (s, 1H), 10.41 (s, 1H), 8.83 (d, J = 6.7 Hz, 1H), 8.35 (s, 1H), 8.27 (s, 1H), 8.09 (d, J = 8.5 Hz, 1H), 8.02 (s, 1H), 7.70 (d, J = 9.1 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.53 – 7.46 (m, 1H), 4.93 (s, 1H), 4.46 (t, J = 8.8 Hz, 1H), 4.33 (d, J = 10.5 Hz, 1H), 2.22 (d, J = 11.8 Hz, 1H), 2.11 (s, 1H), 2.04 – 1.27 (m, 11H)
53	(difluoro(2-(((3S,6S,10aS)-3-(3-fluoro-3-phenylazetidine-1-carbonyl)-5-oxodecahydr		650.0 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.90 (dd, J = 20.5, 7.1 Hz, 1H), 8.30 (d, J = 26.9 Hz, 1H), 8.09 (t, J = 8.4 Hz, 1H), 8.04 (d, J = 10.5 Hz, 1H), 7.60 – 7.54 (m, 1H), 7.45 (m, 4H), 5.00 – 4.86 (m, 2H),

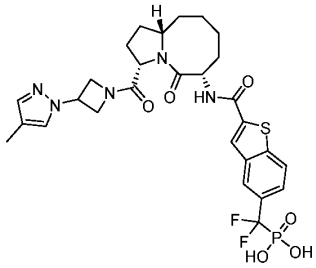
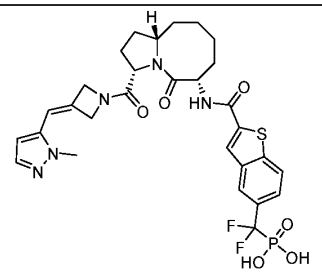
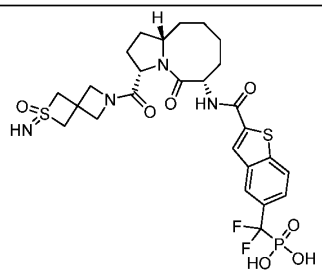
	opyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			4.66 (dt, J = 21.4, 11.1 Hz, 1H), 4.41 – 4.31 (m, 2H), 4.27 (m, 2H), 2.07 – 1.99 (m, 1H), 1.95 – 1.71 (m, 6H), 1.69 – 1.42 (m, 4H)
54	(difluoro(2-(((3S,6S,10aS)-3-(3-fluoro-3-(2-fluorophenyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		666.2 $[M-H]^-$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.88 (dd, J = 38.1, 7.2 Hz, 1H), 8.28 (d, J = 51.2 Hz, 1H), 8.10 (t, J = 10.1 Hz, 1H), 8.03 (d, J = 22.5 Hz, 1H), 7.56 (tt, J = 28.9, 7.3 Hz, 3H), 7.30 (tt, J = 15.7, 9.1 Hz, 2H), 5.09 – 4.69 (m, 4H), 4.50 (ddd, J = 35.5, 22.6, 11.8 Hz, 2H), 4.39 – 4.21 (m, 3H), 2.25 – 2.11 (m, 1H), 2.08 – 1.99 (m, 1H), 1.82 (dd, J = 45.1, 31.7 Hz, 6H), 1.69 – 1.55 (m, 2H), 1.48 (s, 1H)
55	((2-(((3S,6S,10aS)-3-((4-chloroquinolin-6-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		677.2 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 10.68 (s, 1H), 8.85 (d, J = 6.7 Hz, 1H), 8.77 – 8.62 (m, 2H), 8.29 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 3.8 Hz, 2H), 7.93 (d, J = 9.5 Hz, 1H), 7.72 (d, J = 4.7 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 5.00 – 4.92 (m, 1H), 4.52 (t, J = 8.8 Hz, 1H), 4.34 (s, 1H), 2.27 (s, 1H), 2.14 (d, J = 10.5 Hz, 1H), 1.87 (s, 7H), 1.76 – 1.47 (m, 4H)
56	(difluoro(2-(((3S,6S,10aS)-3-(3-(4-(2-hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)azetidine-1-carbonyl)-		679.2 $[M-H]^-$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.86 (d, J = 7.7 Hz, 1H), 8.45 (d, J = 8.0 Hz, 1H), 8.29 (d, J = 12.6 Hz, 1H), 8.13 – 7.98 (m, 2H), 7.57 (d, J = 8.8 Hz, 1H), 5.64 (d, J = 15.4 Hz, 1H), 5.50 (d, J = 8.0 Hz, 1H), 5.04 (d, J = 19.7 Hz, 1H), 5.02 – 4.91 (m,

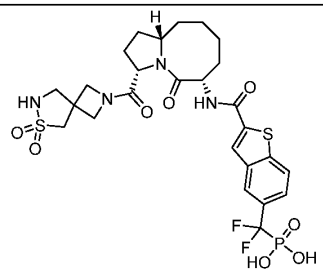
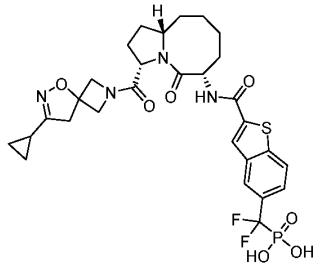
	5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			1H), 4.73 (d, J = 6.8 Hz, 1H), 4.54 – 4.43 (m, 1H), 4.34 (p, J = 9.8, 9.1 Hz, 1H), 4.26 (dd, J = 11.1, 6.4 Hz, 1H), 4.16 (dd, J = 10.9, 4.9 Hz, 1H), 2.52 (s, 7H), 2.17 (d, J = 11.1 Hz, 1H), 2.03 (d, J = 20.2 Hz, 2H), 1.86 (dd, J = 26.3, 13.9 Hz, 3H), 1.75 (d, J = 11.4 Hz, 1H), 1.70 – 1.55 (m, 2H), 1.51 (s, 1H), 1.47 – 1.35 (m, 1H), 1.15 (q, J = 7.4 Hz, 1H)
57	((2-(((3S,6S,10aS)-3-((1,1-dioxido-2,3-dihydrobenzo[b]thiophen-5-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		682.2 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 10.57 (s, 1H), 8.86 (d, J = 6.7 Hz, 1H), 8.29 (s, 1H), 8.12 (d, J = 8.6 Hz, 1H), 8.05 (s, 1H), 7.89 (s, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 4.99 – 4.90 (m, 1H), 4.46 (t, J = 8.6 Hz, 1H), 4.33 (t, J = 9.6 Hz, 1H), 3.54 (t, J = 6.9 Hz, 2H), 3.31 (t, J = 6.9 Hz, 2H), 2.24 (dt, J = 11.8, 7.3 Hz, 1H), 2.18 – 2.06 (m, 1H), 2.00 – 1.49 (m, 10H)
58	((2-(((3S,6S,10aS)-3-((1,1-dioxidothiochroman-6-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		696.2 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 10.46 (s, 1H), 8.86 (d, J = 6.7 Hz, 1H), 8.29 (s, 1H), 8.12 (d, J = 8.5 Hz, 1H), 8.05 (s, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 4.93 (q, J = 8.4, 7.7 Hz, 1H), 4.44 (t, J = 8.6 Hz, 1H), 4.33 (d, J = 9.9 Hz, 1H), 3.48 – 3.40 (m, 2H), 2.95 (m, 2H), 2.45 – 2.18 (m, 4H), 2.09 (m, 1H), 2.03 – 1.43 (m, 11H)

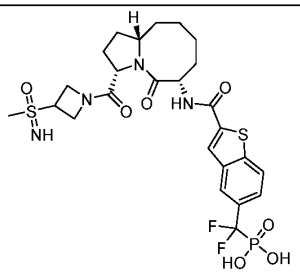
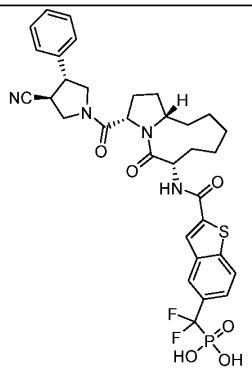
59	(difluoro(2-(((3S,6S,10aS)-3-((3-methyl-2H-indazol-5-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		646.0 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 12.52 (s, 1H), 10.08 (s, 1H), 8.84 (d, J = 6.8 Hz, 1H), 8.30 (s, 1H), 8.12 (t, J = 8.2 Hz, 1H), 8.10 – 7.83 (m, 2H), 7.57 (d, J = 8.6 Hz, 1H), 7.48 – 7.24 (m, 2H), 5.02 – 4.90 (m, 1H), 4.47 (m, 1H), 4.32 (t, J = 9.7 Hz, 1H), 2.44 (s, 3H), 2.23 (m, 1H), 2.10 (m, 1H), 2.08 – 1.27 (m, 10H)
60	((2-(((4S,7S,10aS)-4-(3-(1H-imidazol-1-yl)azetidine-1-carbonyl)-6-oxodecahydropyrido[1,2-a]azepin-7-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		622.2 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.53 (app. d, J = 35.4 Hz, 1H), 8.26 (m, 1H), 8.04 (m, 2H), 7.81 – 7.60 (m, 1H), 7.55 (s, 1H), 7.25 (d, J = 15.5 Hz, 1H), 5.24 (m, 1H), 5.02 (s, 1H), 4.85 – 4.50 (m, 3H), 4.31 (m, 1H), 4.06 (m, 4H), 2.28 (s, 1H), 1.91 (s, 2H), 1.75 (m, 4H), 1.60 (m, 2H), 1.42 (m, 2H)
61	(difluoro(2-(((3S,6S,10aS)-3-(3-(1-imino-1-oxidohexahydro-1l6-thiopyran-4-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)ph		687.2 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.81 (app. m, 1H), 8.34 – 8.27 (m, 1H), 8.09 (d, J = 8.6 Hz, 1H), 8.05 (d, J = 7.0 Hz, 1H), 7.57 (d, J = 8.6 Hz, 1H), 4.90 (m, 1H), 4.49 – 4.38 (m, 1H), 4.29 – 4.21 (m, 2H), 4.16 (m, 1H), 4.05 (dt, J = 16.7, 7.4 Hz, 1H), 3.89 (m, 1H), 3.85 (m, 1H), 3.79 (m, 2H), 3.58 (m, 2H), 3.51 (m, 1H), 3.22 (m, 2H), 3.10 – 3.01 (m, 2H), 2.10 (m, 1H), 2.05 – 1.97 (m, 1H), 1.84 (m, 7H), 1.71 (m, 1H), 1.62 (m, 1H), 1.58 –

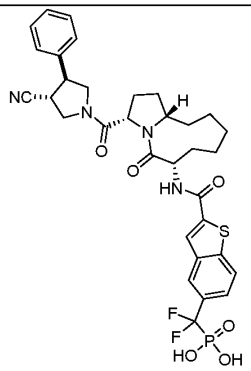
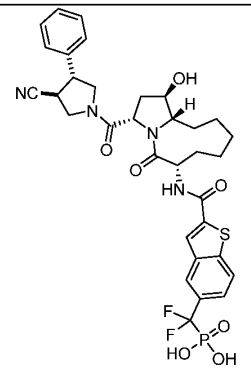
	osphonic acid			1.52 (m, 1H), 1.48 (m, 3H)
62	((2-(((4S,7S,11aS)-4-(3-(1H-imidazol-1-yl)azetidine-1-carbonyl)-6-oxodecahydro-2H-pyrido[1,2-a]azocin-7-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		636.2 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 9.04 (app. m, 1H), 8.61 (s, 1H), 8.39 – 7.61 (m, 4H), 7.59 – 7.28 (m, 2H), 5.17 (m, 2H), 4.60 (s, 1H), 4.42 (s, 1H), 4.22 (s, 1H), 4.11 – 3.85 (m, 2H), 3.78 (m, 1H), 2.13 (s, 2H), 1.87 (s, 3H), 1.64 (m, 6H), 1.44 – 1.11 (m, 2H), 1.04 (s, 1H)
63	((2-(((4S,7S,11aS)-4-(*rel*-(trans)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-6-oxodecahydro-2H-pyrido[1,2-a]azocin-7-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		683.2 $[M-H]^-$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.87 – 8.69 (m, 1H), 8.38 – 8.27 (m, 1H), 8.15 – 8.01 (m, 2H), 7.63 – 7.52 (m, 1H), 7.38 (m, 5H), 5.04 (m, 1H), 4.88 (m, 1H), 4.41 – 4.24 (m, 2H), 4.16 – 3.88 (m, 5H), 2.11 – 1.56 (m, 10H), 1.41 (m, 4H)
64	((2-(((3S,6S,10aS)-3-(3-(4-ethynyloxazol-5-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thio		647.0 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.86 (app. m, 1H), 8.44 – 8.01 (m, 4H), 7.56 (d, J = 8.5 Hz, 1H), 4.93 (s, 1H), 4.78 (s, 1H), 4.49 (d, J = 15.6 Hz, 2H), 4.28 (s, 3H), 4.14 (s, 1H), 4.04 (s, 1H), 3.97 (s, 1H), 2.14 (s, 1H), 2.02 (s, 1H), 1.83 (s, 6H), 1.72 (s, 1H), 1.63 (s, 1H), 1.57 (s, 1H), 1.49 (s, 1H)

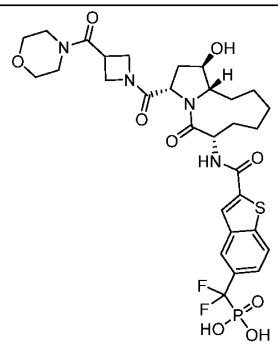
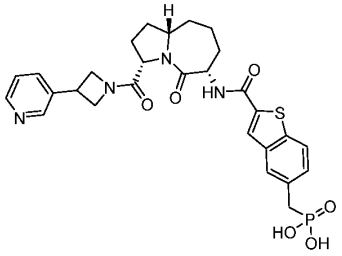
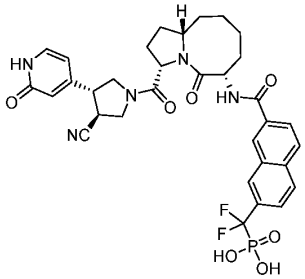
	phen-5-yl)difluoromethyl)phosphonic acid			
65	(difluoro(2-(((3S,6S,10aS)-3-(3-(1-methyl-1H-pyrazol-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		636.2 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.85 (d, J = 6.9 Hz, 1H), 8.31 (d, J = 8.0 Hz, 1H), 8.11 (dd, J = 8.6, 3.6 Hz, 1H), 8.05 (d, J = 6.1 Hz, 1H), 7.65 – 7.50 (m, 2H), 6.17 (dd, J = 12.1, 2.2 Hz, 1H), 4.92 (m, 1H), 4.60 (m, 1H), 4.41 – 4.19 (m, 3H), 4.18 – 4.08 (m, 1H), 3.96 – 3.78 (m, 2H), 3.75 (app. d, 3H), 2.14 (m, 1H), 2.02 (m, 1H), 1.99 – 1.73 (m, 6H), 1.71 (m, 1H), 1.63 (m, 1H), 1.56 (m, 1H), 1.49 (m, 1H)
66	(difluoro(2-(((3S,6S,10aS)-3-(3-((S-methylsulfonimidoyl)methyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		647.2 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.83 (dd, J = 17.3, 7.0 Hz, 1H), 8.30 (s, 1H), 8.09 (d, J = 8.5 Hz, 1H), 8.04 (s, 1H), 7.56 (d, J = 8.6 Hz, 1H), 4.92 (m, 1H), 4.55 – 4.31 (m, 1H), 4.24 (m, 2H), 4.10 – 3.92 (m, 2H), 3.72 (m, 2H), 3.53 (app. d, J = 7.5 Hz, 1H), 3.42 (m, 1H), 3.09 (m, 1H), 2.96 (app. d, J = 5.8 Hz, 3H), 2.30 – 1.89 (m, 3H), 1.82 (m, 5H), 1.71 (m, 1H), 1.63 (dm, 1H), 1.55 (m, 1H), 1.49 (m, 1H)
67	((2-(((3S,6S,10aS)-3-(3-(1H-imidazol-4-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thio		622.2 $[M+H]^+$	

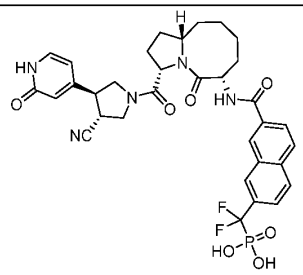
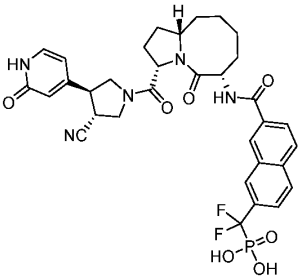
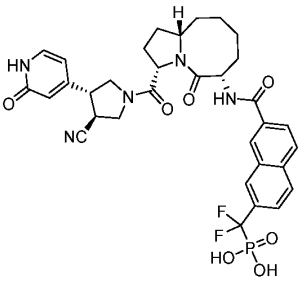
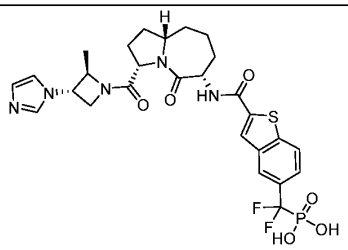
	phen-5-yl)difluoromethyl)phosphonic acid			
68	(difluoro(2-(((3S,6S,10aS)-3-(3-(4-methyl-1H-pyrazol-1-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		636.0 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.87 (dd, J = 17.7, 7.0 Hz, 1H), 8.31 (s, 1H), 8.12 – 8.03 (m, 2H), 7.57 (m, 2H), 7.33 (d, J = 16.8 Hz, 1H), 5.17 (m, 1H), 4.93 (s, 1H), 4.87 – 4.50 (m, 2H), 4.43 – 3.96 (m, 6H), 2.15 (s, 1H), 2.07 – 2.00 (m, 1H), 1.98 (app. m, 4H), 1.83 (m, 6H), 1.73 (m, 1H), 1.56 (m, 3H)
69	(difluoro(2-(((3S,6S,10aS)-3-(3-((1-methyl-1H-pyrazol-5-yl)methylene)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		648.0 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.84 (d, J = 7.1 Hz, 1H), 8.29 (d, J = 6.5 Hz, 1H), 8.10 (app. dd, J = 8.5, 3.7 Hz, 1H), 8.03 (d, J = 4.9 Hz, 1H), 7.60 – 7.51 (m, 1H), 7.34 (d, J = 15.8 Hz, 1H), 6.55 (s, 1H), 6.08 (d, J = 36.3 Hz, 1H), 5.19 (s, 1H), 4.91 (m, 2H), 4.76 – 4.48 (m, 2H), 4.36 (m, 1H), 4.25 (s, 1H), 3.77 (d, J = 4.1 Hz, 3H), 2.17 (m, 1H), 2.09 – 1.99 (m, 1H), 1.93 – 1.70 (m, 7H), 1.57 (m, 3H)
70	(difluoro(2-(((3S,6S,10aS)-3-(2-imino-2-oxido-2l6-thia-6-azaspiro[3.3]heptane-6-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-		645.2 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.91 – 8.80 (m, 1H), 8.30 (s, 1H), 8.11 (d, J = 8.6 Hz, 1H), 8.05 (s, 1H), 7.57 (d, J = 8.6 Hz, 1H), 4.92 (br. s, 1H), 4.56 (t, J = 8.5 Hz, 1H), 4.35 (dd, J = 12.2, 8.9 Hz, 1H), 4.29 – 4.19 (m, 4H), 4.15 – 3.96 (m, 4H), 2.16 – 2.09 (m, 1H), 2.02 (m, 1H), 1.81 (m,

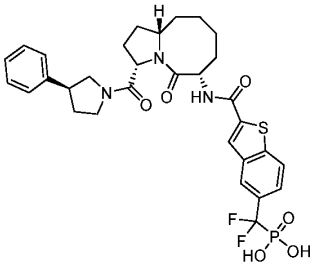
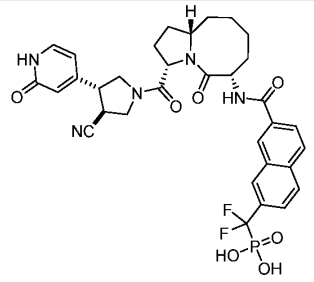
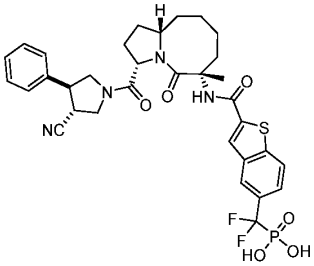
	yl)carbamoyl)benzo[b]thio phen-5-yl)methyl)ph osphonic acid			6H), 1.71 (m, 1H), 1.62 (s, 1H), 1.55 (m, 1H), 1.48 (s, 1H)
71	((2-(((3S,6S,10a S)-3-(6,6-dioxido-6-thia-2,7-diazaspiro[3.4]octane-2-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		661.0 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.87 (app. t, J = 6.3 Hz, 1H), 8.30 (s, 1H), 8.10 (d, J = 8.6 Hz, 1H), 8.05 (s, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.12 (dt, J = 13.3, 6.3 Hz, 1H), 4.92 (dt, J = 11.8, 6.1 Hz, 1H), 4.40 (m, 2H), 4.24 (m, 3H), 4.15 (d, J = 8.9 Hz, 1H), 3.96 (d, J = 10.1 Hz, 1H), 3.89 (m, 2H), 3.41 (d, J = 5.7 Hz, 1H), 3.37 (d, J = 6.1 Hz, 1H), 3.33 (t, J = 6.0 Hz, 1H), 2.17 – 2.09 (m, 1H), 2.08 – 1.99 (m, 1H), 1.81 (m, 6H), 1.71 (m, 1H), 1.62 (m, 1H), 1.56 (m, 1H), 1.48 (s, 1H)
72	((2-(((3S,6S,10a S)-3-(7-cyclopropyl-5-oxa-2,6-diazaspiro[3.4]oct-6-ene-2-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		651.0 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.85 (m, 1H), 8.30 (d, J = 7.1 Hz, 1H), 8.08 (m, 2H), 7.58 (d, J = 8.6 Hz, 1H), 4.92 (s, 1H), 4.55 (app. t, J = 10.6 Hz, 1H), 4.25 (m, 3H), 4.09 (d, J = 10.9 Hz, 1H), 3.96 (s, 1H), 3.87 (d, J = 10.9 Hz, 1H), 3.12 (m, 2H), 2.08 (m, 2H), 1.97 – 1.27 (m, 10H), 0.81 (m, 2H), 0.72 (m, 2H)

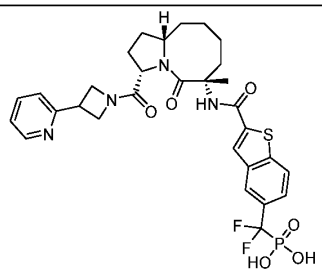
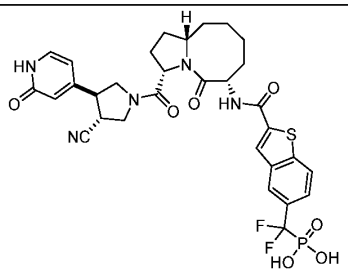
73	(difluoro(2-(((3S,6S,10aS)-3-(3-(S-methylsulfonimidoyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		633.2 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.87 (m, 1H), 8.31 (d, J = 4.8 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 8.05 (s, 1H), 7.56 (d, J = 8.6 Hz, 1H), 4.91 (t, J = 9.0 Hz, 1H), 4.70 – 4.51 (m, 2H), 4.46 – 4.36 (m, 1H), 4.31 (dd, J = 9.4, 5.2 Hz, 1H), 4.25 (q, J = 7.8, 6.9 Hz, 2H), 4.20 – 4.15 (m, 1H), 4.12 – 4.07 (m, 1H), 4.03 (m, 1H), 3.98 – 3.94 (m, 1H), 2.90 (m, 3H), 2.20 – 2.10 (m, 1H), 2.03 (m, 1H), 1.93 – 1.69 (m, 6H), 1.69 – 1.17 (m, 4H)
74	((2-(((3S,6S,11aS)-3-((*rel*-trans)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydro-1H-pyrrolo[1,2-a]azonin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		685.0 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.88 (m, 1H), 8.31 (d, J = 16.6 Hz, 1H), 8.12 – 8.00 (m, 3H), 7.56 (t, J = 8.4 Hz, 1H), 7.45 – 7.27 (m, 4H), 6.91 (d, J = 9.1 Hz, 1H), 5.00 (m, 1H), 4.59 (m, 1H), 4.29 – 4.23 (m, 1H), 4.23 – 4.16 (m, 1H), 4.11 (dd, J = 10.2, 7.6 Hz, 1H), 4.02 (m, 1H), 3.94 (app. t, J = 10.0 Hz, 1H), 3.83 – 3.75 (m, 1H), 3.67 (t, J = 10.2 Hz, 1H), 3.61 – 3.53 (m, 1H), 3.48 (dd, J = 11.5, 9.5 Hz, 1H), 3.25 (app, t, J = 11.0 Hz, 1H), 3.04 (m, 1H), 2.21 (m, 1H), 2.07 (m, 1H), 1.98 (m, 1H), 1.92 (m, 2H), 1.83 – 1.60 (m, 4H), 1.51 (s, 1H), 1.41 (s, 1H)

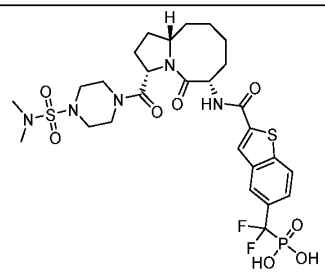
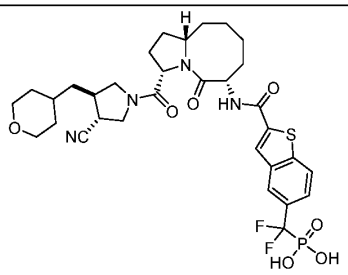
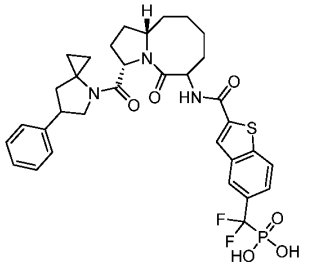
75	((2-(((3S,6S,11aS)-3-(*rel*-(trans)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydro-1H-pyrrolo[1,2-a]azonin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		685.0 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.89 (m, 1H), 8.32 (d, J = 2.9 Hz, 1H), 8.12 (app. t, J = 9.3 Hz, 1H), 8.05 (d, J = 5.4 Hz, 1H), 7.57 (app. t, J = 7.5 Hz, 1H), 7.42 (t, J = 8.6 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.31 (dd, J = 8.3, 5.9 Hz, 1H), 4.99 (m, 1H), 4.62 (m, 1H), 4.34 (m, 1H), 4.24 (m, 1H), 3.95 (dd, J = 11.6, 7.1 Hz, 1H), 3.89 – 3.81 (m, 1H), 3.74 – 3.62 (m, 3H), 3.56 – 3.49 (m, 1H), 3.33 (dd, J = 11.8, 9.7 Hz, 1H), 2.20 (m, 1H), 2.12 – 2.03 (m, 1H), 2.00 – 1.86 (m, 4H), 1.83 – 1.71 (m, 3H), 1.71 – 1.61 (m, 2H), 1.52 – 1.48 (m, 1H), 1.44 – 1.38 (m, 1H)
76	((2-(((1R,3S,6S,11aS)-3-(*rel*-(trans)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-1-hydroxy-5-oxodecahydro-1H-pyrrolo[1,2-a]azonin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		701.0 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.88 – 8.78 (m, 1H), 8.37 – 8.31 (m, 1H), 8.10 (app. t, J = 9.3 Hz, 1H), 8.04 (d, J = 9.0 Hz, 1H), 7.56 (app. t, J = 7.7 Hz, 1H), 7.45 – 7.36 (m, 4H), 7.35 – 7.29 (m, 1H), 5.16 (m, 1H), 5.09 – 5.01 (m, 1H), 4.75 – 4.64 (m, 1H), 4.45 – 4.32 (m, 1H), 4.09 – 3.98 (m, 2H), 3.95 – 3.85 (m, 1H), 3.84 – 3.74 (m, 1H), 3.75 – 3.68 (m, 1H), 3.61 – 3.49 (m, 2H), 2.15 – 2.00 (m, 2H), 1.98 – 1.90 (m, 1H), 1.86 (m, 3H), 1.61 (m, 2H), 1.54 – 1.45 (m, 2H), 1.45 – 1.36 (m, 1H)

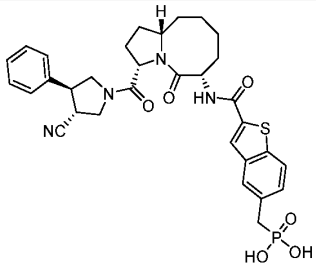
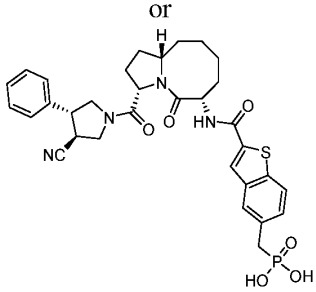
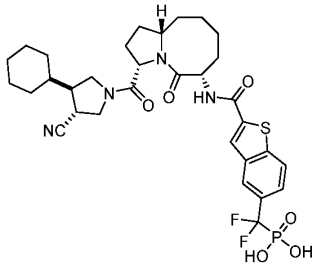
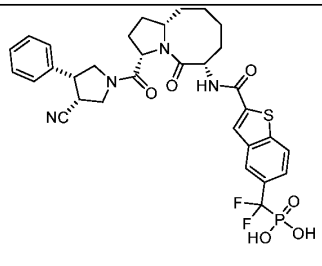
77	(difluoro(2-(((1R,3S,6S,11aS)-1-hydroxy-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydro-1H-pyrrolo[1,2-a]azonin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		699.0 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.89 – 8.77 (m, 2H), 8.33 (d, J = 5.6 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 8.03 (s, 1H), 7.57 (d, J = 8.6 Hz, 1H), 7.16 – 6.98 (m, 1H), 5.17 (app. d, J = 13.6 Hz, 1H), 5.03 (m, 1H), 4.62 (t, J = 8.7 Hz, 1H), 4.52 (t, J = 7.5 Hz, 1H), 4.42 (m, 1H), 4.35 – 4.24 (m, 1H), 4.08 (t, J = 9.4 Hz, 1H), 4.00 (m, 1H), 3.95 – 3.83 (m, 2H), 3.74 – 3.64 (m, 1H), 3.52 (m, 3H), 3.45 (m, 2H), 2.04 – 1.91 (m, 3H), 1.87 – 1.75 (m, 3H), 1.66 – 1.55 (m, 2H), 1.53 – 1.43 (m, 3H), 1.39 (s, 1H)
78	((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		583.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 – 8.69 (m, 1H), 8.61 – 8.54 (m, 1H), 8.51 – 8.42 (m, 1H), 8.19 (s, 1H), 7.96 – 7.83 (m, 2H), 7.84 – 7.76 (m, 1H), 7.47 – 7.30 (m, 2H), 4.86 – 4.58 (m, 2H), 4.45 – 4.38 (m, 1H), 4.35 – 4.18 (m, 2H), 4.02 – 3.97 (m, 1H), 3.95 – 3.88 (m, 2H), 3.11 (d, J = 21.1 Hz, 2H), 2.24 – 2.15 (m, 1H), 2.09 – 1.93 (m, 2H), 1.88 – 1.66 (m, 7H)
79	((7-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-	 or	682.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 – 8.52 (m, 2H), 8.26 – 8.14 (m, 1H), 8.14 – 7.98 (m, 3H), 7.80 – 7.65 (m, 1H), 7.44 – 7.29 (m, 1H), 6.42 – 6.33 (m, 1H), 6.30 – 6.18 (m, 1H), 5.07 – 4.92 (m, 1H), 4.58 – 4.49 (m, 1H), 4.39 – 4.28 (m, 1H), 4.20 – 4.07 (m, 1H), 4.02 – 3.91 (m, 1H), 3.87 – 3.78 (m, 1H), 3.68 – 3.59 (m, 1H), 3.53 – 3.42 (m, 1H),

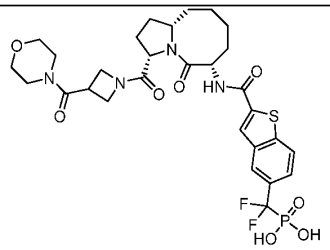
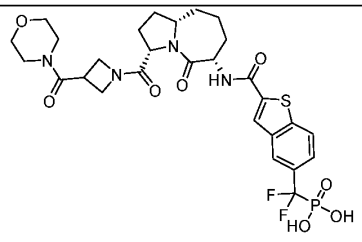
	yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphonic acid	 SFC peak 1 was used for biological testing		3.32 – 3.14 (m, 1H), 2.36 – 2.18 (m, 1H), 2.16 – 2.01 (m, 1H), 2.00 – 1.73 (m, 7H), 1.70 – 1.45 (m, 3H)
80	((7-(((3S,6S,10aS)-3-((3R,4S or 3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphonic acid	 or  SFC peak 2 was used for biological testing	682.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 – 8.57 (m, 2H), 8.20 (s, 1H), 8.15 – 7.99 (m, 3H), 7.78 – 7.66 (m, 1H), 7.39 (d, J = 6.6 Hz, 1H), 6.43 – 6.20 (m, 2H), 5.09 – 4.95 (m, 1H), 4.61 – 4.52 (m, 1H), 4.37 – 4.21 (m, 1H), 3.98 – 3.94 (m, 1H), 3.91 – 3.87 (m, 1H), 3.83 – 3.79 (m, 1H), 3.71 – 3.67 (m, 1H), 3.61 – 3.56 (m, 1H), 3.52 – 3.44 (m, 1H), 3.36 – 3.17 (m, 1H), 2.35 – 1.99 (m, 3H), 1.97 – 1.74 (m, 6H), 1.70 – 1.50 (m, 3H)
81	((2-(((3S,6S,9aS)-3-((2R,3S)-3-(1H-imidazol-1-yl)-2-methylazetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		622.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 – 8.66 (m, 2H), 8.28 (s, 1H), 8.15 – 7.99 (m, 2H), 7.91 – 7.74 (m, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.42 – 7.15 (m, 1H), 4.90 – 4.86 (m, 1H), 4.71 – 4.61 (m, 3H), 4.42 – 4.36 (m, 1H), 4.34 – 4.28 (m, 1H), 4.08 – 3.95 (m, 1H), 2.28 – 2.13 (m, 1H), 2.09 – 1.67 (m, 9H), 2.09 – 1.61 (m, 10H), 1.67 – 1.58 (m, 1H), 1.44 (d, J = 6.2 Hz, 2H)

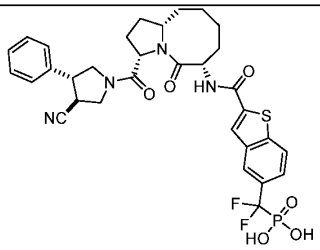
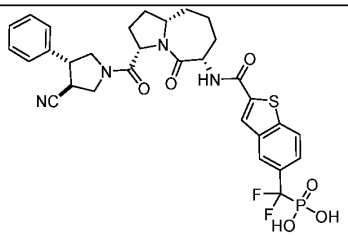
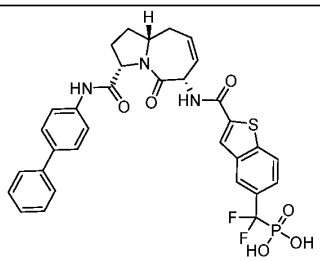
	yl)difluoromethyl)phosphonic acid			
82	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-((S)-3-phenylpyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		646.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 – 8.77 (m, 1H), 8.36 – 8.01 (m, 3H), 7.58 (d, J = 8.1 Hz, 1H), 7.38 – 6.90 (m, 5H), 5.02 – 4.90 (m, 1H), 4.63 – 4.53 (m, 1H), 4.30 – 4.23 (m, 1H), 3.80 – 3.72 (m, 2H), 3.60 – 3.53 (m, 1H), 3.43 – 3.21 (m, 2H), 2.36 – 2.16 (m, 2H), 2.15 – 1.43 (m, 12H)
83	((7-(((3S,6S,10aS)-3-(*rel*-(trans)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphonic acid		682.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 – 8.57 (m, 2H), 8.20 (s, 1H), 8.13 – 7.95 (m, 3H), 7.72 (d, J = 8.3 Hz, 1H), 7.43 – 7.32 (m, 1H), 6.45 – 6.15 (m, 2H), 5.08 – 4.96 (m, 1H), 4.60 – 4.49 (m, 1H), 4.39 – 4.29 (m, 1H), 4.19 – 4.11 (m, 1H), 4.03 – 3.98 (m, 1H), 3.92 – 3.88 (m, 1H), 3.85 – 3.78 (m, 1H), 3.67 – 3.59 (m, 1H), 3.53 – 3.42 (m, 1H), 2.35 – 2.17 (m, 1H), 2.16 – 2.02 (m, 1H), 2.01 – 1.75 (m, 7H), 1.71 – 1.49 (m, 3H)
84	((2-(((3S,6S,10aS)-3-(*rel*-(trans)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-6-methyl-5-oxodecahydropyrrolo[1,2-		685.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (m, 4H), 7.59 (m, 1H), 7.48 (m, 2H), 7.42 (m, 2H), 7.38 – 7.31 (m, 1H), 4.66 – 4.60 (m, 1H), 4.59 – 4.52 (m, 1H), 4.29 (m, 1H), 4.07 (m, 2H), 3.41–3.33 (m, 2H), 3.35 – 3.27 (m, 1H), 2.85 – 2.77 (m, 1H), 2.30 (m, 2H), 2.06

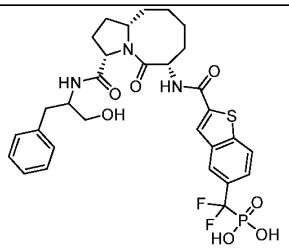
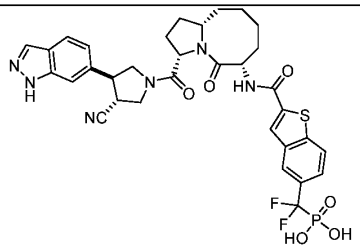
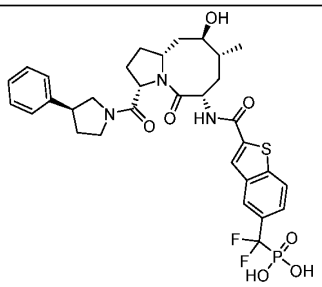
	a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid			(m, 3H), 1.76 (m, 2H), 1.73 – 1.68 (m, 3H), 1.50 – 1.44 (m, 2H), 1.24 (s, 2H)
85	(difluoro(2-(((3S,6S,10aS)-6-methyl-5-oxo-3-(3-(pyridin-2-yl)azetidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		647.0 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 – 8.58 (m, 1H), 8.27 – 8.05 (m, 4H), 7.93 – 7.80 (m, 1H), 7.64 – 7.31 (m, 3H), 4.79 – 4.69 (m, 1H), 4.57 – 4.53 (m, 1H), 4.36 – 4.31 (m, 2H), 4.26 – 4.12 (m, 3H), 2.88 – 2.78 (m, 1H), 2.35 – 2.27 (m, 1H), 2.22 – 2.05 (m, 2H), 2.01 – 1.92 (m, 1H), 1.81 – 1.71 (m, 2H), 1.68 – 1.60 (m, 5H), 1.52 – 1.41 (m, 2H), 1.30 – 1.19 (m, 1H) (TFA salt)
86	((2-(((3S,6S,10aS)-3-(*rel*-(trans)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		688.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 – 8.71 (m, 1H), 8.37 – 8.27 (m, 1H), 8.18 – 8.10 (m, 1H), 8.07 (s, 1H), 7.58 (d, J = 8.3 Hz, 1H), 7.44 – 7.31 (m, 1H), 6.43 – 6.09 (m, 2H), 5.02 – 4.87 (m, 1H), 4.64 – 4.52 (m, 1H), 4.33 – 4.27 (m, 1H), 4.18 – 4.12 (m, 1H), 4.04 – 3.96 (m, 1H), 3.94 – 3.87 (m, 1H), 3.85 – 3.77 (m, 1H), 3.65 – 3.54 (m, 1H), 3.44 – 3.17 (m, 1H), 2.37 – 2.15 (m, 1H), 2.13 – 1.44 (m, 11H)

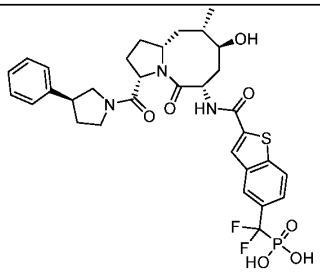
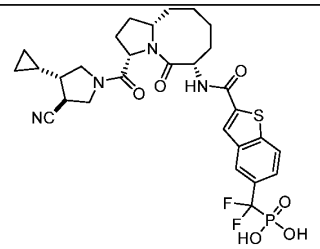
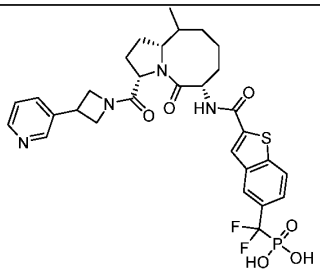
87	((2-(((3S,6S,10aS)-3-(4-(N,N-dimethylsulfamoyl)piperazine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		692.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 – 8.85 (m, 1H), 8.30 (s, 1H), 8.11 – 7.99 (m, 2H), 7.57 (d, J = 8.5 Hz, 1H), 4.97 – 4.95 (m, 1H), 4.84 – 4.80 (m, 1H), 4.32 – 4.28 (m, 1H), 3.74 – 3.39 (m, 5H), 3.28 – 3.00 (m, 5H), 2.76 (s, 6H), 2.25 – 1.44 (m, 12H)
88	((2-(((3S,6S,10aS)-3-(*rel*-(trans)-3-cyano-4-((tetrahydro-2H-pyran-4-yl)methyl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		693.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 – 8.76 (m, 1H), 8.38 – 8.24 (m, 1H), 8.13 (d, J = 8.5 Hz, 1H), 8.06 (s, 1H), 7.58 (d, J = 8.6 Hz, 1H), 5.02 – 4.82 (m, 1H), 4.62 – 2.62 (m, 14H), 2.37 – 0.98 (m, 17H)
89	(difluoro(2-(((3S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)ph		672.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (t, J = 7.4 Hz, 1H), 8.30 (d, J = 3.9 Hz, 1H), 8.15 – 7.94 (m, 2H), 7.58 (d, J = 8.2 Hz, 1H), 7.41 – 7.18 (m, 5H), 5.04 – 4.86 (m, 1H), 4.71 – 4.35 (m, 2H), 4.29 – 4.17 (m, 1H), 4.16 – 4.08 (m, 1H), 4.00 – 3.90 (m, 1H), 2.34 – 2.16 (m, 2H), 2.12 – 1.53 (m, 14H), 0.56 – 0.40 (m, 2H)

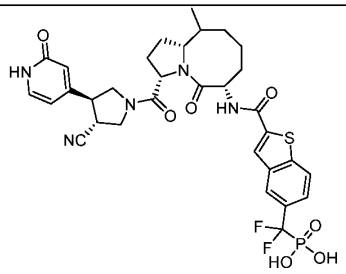
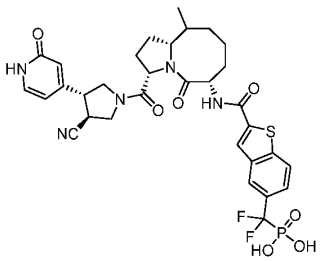
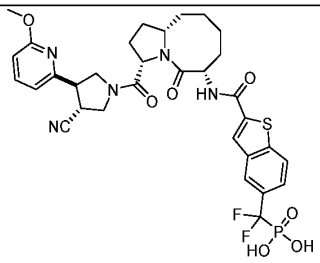
	osphonic acid			
90	((2-(((3S,6S,10aS)-3-((3R,4S or 3S, 4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid	 or  SFC peak 2 was used for biological testing	635.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 – 8.69 (m, 1H), 8.20 (d, J = 10.4 Hz, 1H), 7.95 – 7.86 (m, 1H), 7.79 (s, 1H), 7.56 – 7.21 (m, 6H), 5.01 – 4.87 (m, 1H), 4.57 – 4.49 (m, 1H), 4.32 – 4.24 (m, 1H), 4.22 – 4.12 (m, 1H), 4.02 – 3.95 (m, 1H), 3.83 – 3.77 (m, 1H), 3.70 – 3.63 (m, 1H), 3.57 – 3.52 (m, 1H), 3.33 – 3.23 (m, 1H), 3.10 (d, J = 20.9 Hz, 2H), 2.32 – 2.19 (m, 1H), 2.14 – 2.00 (m, 1H), 2.01 – 1.68 (m, 7H), 1.69 – 1.43 (m, 3H)
91	((2-(((3S,6S,10aS)-3-(*rel*-(trans)-3-cyano-4-cyclohexylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		677.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 – 8.78 (m, 1H), 8.37 – 8.27 (m, 1H), 8.13 (d, J = 8.5 Hz, 1H), 8.06 (s, 1H), 7.58 (d, J = 8.5 Hz, 1H), 5.02 – 4.86 (m, 1H), 4.58 – 4.46 (m, 1H), 4.29 – 4.24 (m, 1H), 3.88 – 3.81 (m, 3H), 3.24 – 3.17 (m, 2H), 2.30 – 2.16 (m, 2H), 1.97 – 1.54 (m, 16H), 1.25 – 0.96 (m, 6H)
92	((2-(((3S,6S,10aS)-3-(*rel*-(trans)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydr		671.0 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 – 8.81 (m, 1H), 8.36 – 8.27 (m, 1H), 8.14 – 8.12 (m, 1H), 8.07 (s, 1H), 7.59 – 7.57 (m, 1H), 7.42 – 7.25 (m, 5H), 4.99 – 4.94 (m, 1H), 4.62 – 4.55 (m, 1H), 4.39 – 4.28 (m, 2H), 4.15 –

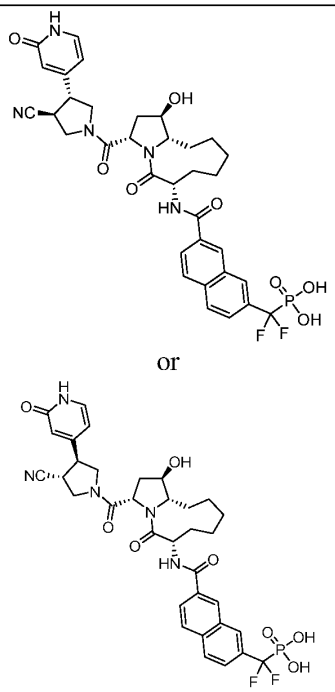
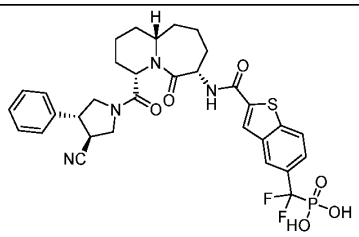
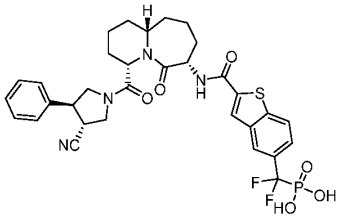
	opyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid			4.11 (m, 1H), 4.06 – 4.00 (m, 1H), 3.97 – 3.92 (m, 2H), 3.69 – 3.64 (m, 2H), 2.38 – 2.31 (m, 1H), 2.14 – 2.07 (m, 2H), 1.91 – 1.80 (m, 5H), 1.66 – 1.55 (m, 3H), 1.26 – 1.21 (m, 1H)
93	(difluoro(2-(((3S,6S,10aS)-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		669.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (dd, J = 21.4, 6.9 Hz, 1H), 8.33 (s, 1H), 8.14 (d, J = 8.7 Hz, 1H), 8.07 (s, 1H), 7.59 (d, J = 8.5 Hz, 1H), 4.99 – 4.89 (m, 2H), 4.64 – 4.40 (m, 4H), 4.29 (s, 1H), 4.10 – 3.85 (m, 6H), 3.78 – 3.61 (m, 3H), 3.47 – 3.39 (m, 2H), 2.14 (d, J = 7.6 Hz, 1H), 2.01 (d, J = 7.5 Hz, 1H), 1.94 – 1.75 (m, 6H), 1.75 – 1.44 (m, 4H)
94	(difluoro(2-(((3S,6S,9aS)-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		655.1 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 – 8.77 (m, 1H), 8.30 (s, 1H), 8.24 – 8.03 (m, 2H), 7.72 – 7.45 (m, 1H), 4.72 – 4.14 (m, 4H), 4.09 – 3.95 (m, 4H), 3.65 – 3.17 (m, 8H), 2.21 – 1.15 (m, 10H)

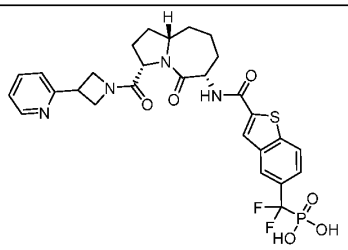
95	((2-(((3S,6S,10aS)-3-(*rel*-(trans)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		671.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89 – 8.79 (m, 1H), 8.36 – 8.25 (m, 1H), 8.13 – 8.03 (m, 2H), 7.60 (d, J = 9.1 Hz, 1H), 7.47 – 7.30 (m, 5H), 5.01 – 4.89 (m, 1H), 4.63 – 4.51 (m, 1H), 4.40 – 4.22 (m, 2H), 4.03 – 3.91 (m, 2H), 3.56 – 3.51 (m, 3H), 2.32 – 2.18 (m, 1H), 2.08 – 1.75 (m, 8H), 1.68 – 1.49 (m, 3H)
96	((2-(((3S,6S,9aS)-3-(*rel*-trans)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		657.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 – 8.70 (m, 1H), 8.31 – 8.25 (m, 1H), 8.12 – 8.03 (m, 2H), 7.59 (d, J = 8.4 Hz, 1H), 7.46 – 7.31 (m, 5H), 4.74 – 4.58 (m, 2H), 4.03 – 3.93 (m, 2H), 3.62 – 3.49 (m, 5H), 2.27 – 2.06 (m, 2H), 1.90 – 1.59 (m, 8H)
97	((2-(((3S,6S,9aR)-3-([1,1'-biphenyl]-4-ylcarbamoyl)-5-oxo-2,3,5,6,9,9a-hexahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluorom		652.1 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 9.09 (d, J = 8.0 Hz, 1H), 8.32 (s, 1H), 8.19 – 7.98 (m, 2H), 7.72 – 7.56 (m, 7H), 7.43 (t, J = 7.6 Hz, 2H), 7.32 (t, J = 7.3 Hz, 1H), 5.88 – 5.68 (m, 2H), 5.54 – 5.38 (m, 1H), 4.68 – 4.46 (m, 2H), 2.49 – 1.71 (m, 6H)

	ethyl)phosphonic acid			
98	(difluoro(2-(((3S,6S,10aS)-3-((1-hydroxy-3-phenylpropan-2-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		650.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 – 8.88 (m, 1H), 8.54 – 8.50 (m, 1H), 8.35 – 8.30 (m, 1H), 8.11 – 8.04 (m, 1H), 7.95 (d, J = 7.1 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.45 – 7.01 (m, 5H), 4.98 – 4.90 (m, 1H), 4.38 – 4.31 (m, 2H), 4.08 – 4.03 (m, 2H), 3.42– 2.57 (m, 4H), 2.38 – 1.37 (m, 12H)
99	((2-(((3S,6S,10aS)-3-(*rel*-(trans)-3-cyano-4-(1H-indazol-6-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		711.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 9.31 – 8.76 (m, 1H), 8.39 – 8.27 (m, 1H), 8.19 – 8.01 (m, 3H), 7.82 – 7.70 (m, 1H), 7.62 – 7.41 (m, 2H), 7.25 – 7.05 (m, 1H), 5.05 – 4.91 (m, 1H), 4.80 – 4.47 (m, 2H), 4.42 – 4.28 (m, 2H), 4.07 – 3.95 (m, 4H), 2.36 – 2.06 (m, 2H), 2.03 – 1.74 (m, 7H), 1.70 – 1.47 (m, 3H)
100	(difluoro(2-(((3S,6S,8R,9R,10aR)-9-hydroxy-8-methyl-5-oxo-3-((S)-3-phenylpyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-		676.0 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 – 8.78 (m, 1H), 8.34 (d, J = 1.9 Hz, 1H), 8.12 (d, J = 9.0 Hz, 1H), 8.07 (s, 1H), 7.59 (d, J = 8.6 Hz, 1H), 7.35 – 7.19 (m, 5H), 4.99 – 4.88 (m, 1H), 4.59 (t, J = 8.2 Hz, 1H), 4.33 – 4.16 (m, 2H), 4.08 – 4.00 (m, 1H), 3.98 – 3.92 (m, 1H), 3.82 – 3.78 (m, 1H), 3.25

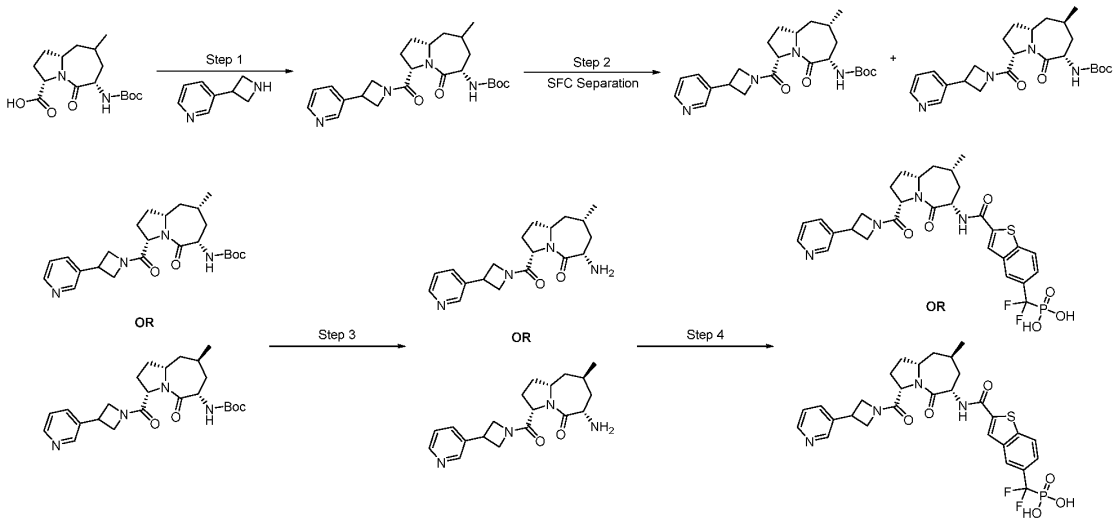
	yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			– 3.17 (m, 2H), 2.25 – 2.11 (m, 3H), 2.02 – 1.89 (m, 3H), 1.88 – 1.67 (m, 4H), 1.59 – 1.50 (m, 1H), 0.96 (d, J = 6.1 Hz, 3H)
101	(difluoro(2-(((3S,6S,8S,9S,10aR)-8-hydroxy-9-methyl-5-oxo-3-((S)-3-phenylpyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		676.1 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 – 8.66 (m, 1H), 8.28 (s, 1H), 8.05 (s, 2H), 7.60 (d, J = 8.8 Hz, 1H), 7.36 – 7.22 (m, 5H), 5.00 – 4.92 (m, 1H), 4.62 – 4.58 (m, 1H), 4.45 – 4.35 (m, 1H), 4.26 – 3.95 (m, 1H), 3.82 – 3.77 (m, 1H), 3.59 – 3.53 (m, 2H), 3.18 – 3.17 (m, 2H), 2.23 – 2.14 (m, 3H), 1.95 – 1.83 (m, 3H), 1.76 – 1.61 (m, 3H), 1.56 – 1.50 (m, 1H), 1.47 – 1.44 (m, 1H), 0.98 (d, J = 4.7 Hz, 3H)
102	((2-(((3S,6S,10aS)-3-(*rel*-(trans)-3-cyano-4-cyclopropylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		635.1 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 – 8.80 (m, 1H), 8.33 – 8.30 (m, 1H), 8.14 (d, J = 8.5 Hz, 1H), 8.07 (s, 1H), 7.58 (d, J = 8.6 Hz, 1H), 5.00 – 4.90 (m, 1H), 4.57 – 4.48 (m, 1H), 4.30 – 4.25 (m, 1H), 3.81 – 3.61 (m, 2H), 3.55 – 3.40 (m, 2H), 2.33 – 2.21 (m, 1H), 2.06 – 1.52 (m, 12H), 1.28 – 1.21 (m, 1H), 0.87 – 0.78 (m, 1H), 0.57 – 0.48 (m, 2H), 0.32 – 0.24 (m, 2H)
103	(difluoro(2-(((3S,6S,10aR)-10-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)dec		647.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 – 8.77 (m, 1H), 8.59 (s, 1H), 8.53 – 8.40 (m, 1H), 8.31 (s, 1H), 8.16 – 8.05 (m, 2H), 8.01 – 7.89 (m, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.51 – 7.30 (m, 1H), 4.86 – 4.63 (m, 2H), 4.62 –

	ahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			4.55 (m, 1H), 4.45 – 4.39 (m, 1H), 4.30 – 4.27 (m, 1H), 4.21 – 4.17 (m, 1H), 3.95 – 3.83 (m, 2H), 2.27 – 2.13 (m, 1H), 2.06 – 1.93 (m, 3H), 1.92 – 1.39 (m, 7H), 0.93 – 0.83 (m, 3H)
104	((2-(((3S,6S,10aR)-3-((3R,4S or 3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-10-methyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid	 or  SFC peak 2 was used for biological testing	702.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO- d_6) δ 8.88 – 8.64 (m, 1H), 8.29 (d, J = 6.0 Hz, 1H), 8.17 – 8.01 (m, 2H), 7.66 – 7.49 (m, 1H), 7.45 – 7.29 (m, 1H), 6.47 – 6.32 (m, 1H), 6.32 – 6.18 (m, 1H), 4.75 – 4.58 (m, 1H), 4.53 – 4.38 (m, 1H), 4.23 – 4.12 (m, 1H), 4.09 – 3.99 (m, 1H), 3.95 – 3.88 (m, 1H), 3.87 – 3.82 (m, 1H), 3.80 – 3.76 (m, 1H), 3.17 (dd, J = 25.0, 10.2 Hz, 2H), 2.28 – 1.91 (m, 5H), 1.88 – 1.47 (m, 7H), 1.36 – 1.18 (m, 1H), 0.99 – 0.75 (m, 3H)
105	((2-(((3S,6S,10aS)-3-(*rel*-(trans) 3-cyano-4-(6-methoxypyridin-2-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		702.1 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 – 8.72 (m, 2H), 8.41 – 8.24 (m, 1H), 8.20 – 7.98 (m, 2H), 7.79 – 7.66 (m, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.11 – 6.96 (m, 1H), 6.82 – 6.66 (m, 1H), 5.02 – 4.88 (m, 1H), 4.62 – 4.48 (m, 1H), 4.45 – 4.22 (m, 3H), 4.17 – 3.91 (m, 3H), 3.88 – 3.80 (m, 3H), 3.75 – 3.62 (m, 1H), 3.56 – 3.38 (m, 1H), 2.36 – 2.18 (m, 1H), 2.16 – 2.01 (m, 1H), 2.00 – 1.70 (m, 7H), 1.70 – 1.44 (m, 3H)

106	((7-(((1R,3S,6S,11aS)-3-((3S,4R or 3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-1-hydroxy-5-oxodecahydro-1H-pyrrolo[1,2-a]azonin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphonic acid	 or SFC peak 2 was used for biological testing	712.1 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 – 8.58 (m, 2H), 8.20 – 8.19 (m, 1H), 8.09 – 8.04 (m, 4H), 7.72 – 7.70 (m,, 1H), 7.40 – 7.37 (m, 1H), 6.38 – 6.36 (m, 1H), 6.29 – 6.22 (m, 1H), 5.20 – 5.13 (m, 1H), 4.70 – 4.66 (m, 1H), 4.14 – 4.10 (m, 1H), 4.07 – 4.04 (m, 1H), 3.99 – 3.97 (m, 1H), 3.82 – 3.78 (m, 1H), 3.67 – 3.66 (m, 1H), 3.63 – 3.61 (m, 1H), 3.50 – 3.47 (m, 1H), 3.24 – 3.19 (m, 1H), 2.16 – 1.94 (m, 4H), 1.88 – 1.85 (m, 3H), 1.65 (m, 3H), 1.58 – 1.53 (m, 2H), 1.44 – 1.40 (m, 1H)
107	((2-(((4S,7S,10aS)-4-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-6-oxodecahydropyrido[1,2-a]azepin-7-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid	 or  SFC peak 2 used for biological testing	669.0 $[M-H]^-$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.85 – 8.71 (m, 1H), 8.34 – 8.24 (m, 1H), 8.12 (dd, J = 8.7, 6.0 Hz, 1H), 8.06 (s, 1H), 7.63 – 7.53 (m, 1H), 7.46 – 7.35 (m, 3H), 7.31 (t, J = 7.7 Hz, 1H), 5.02 (d, J = 8.9 Hz, 1H), 4.88 (ddt, J = 14.0, 11.0, 5.2 Hz, 1H), 4.14 – 4.04 (m, 2H), 3.95 (ddd, J = 18.2, 11.2, 7.3 Hz, 2H), 3.69 – 3.66 (m, 2H), 3.56 – 3.43 (m, 3H), 3.23 (dt, J = 30.9, 10.8 Hz, 1H), 2.39 (s, 1H), 1.99 – 1.47 (m, 9H), 1.47 – 1.32 (m, 2H)

108	(difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-2-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		618.9 $[M+H]^+$	^1H NMR (400 MHz, methanol-d_4) δ 8.75 – 8.55 (m, 1H), 8.43 – 8.22 (m, 1H), 8.21 – 8.15 (m, 1H), 8.13 (d, J = 2.8 Hz, 1H), 8.05 – 7.96 (m, 1H), 7.90 – 7.85 (m, 1H), 7.80 – 7.65 (m, 1H), 7.58 – 7.37 (m, 1H), 4.79 – 4.69 (m, 2H), 4.61 – 4.39 (m, 2H), 4.30 – 4.00 (m, 3H), 3.53 – 3.45 (m, 1H), 2.25 – 2.45 (m, 1 H), 2.21 – 1.74 (m, 8H), 1.40 – 1.19 (m, 1H)

Synthesis of (difluoro(2-(((3S,6S,8R,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid or (difluoro(2-(((3S,6S,8S,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (109/110)



[00329] *Step 1: Preparation of tert-butyl ((3S,6S,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate*

[00330] To a solution of 3-(azetidin-3-yl)pyridine (0.16 g, 1.2 mmol, 1 eq) and N,N-diisopropylethylamine (0.47 g, 3.7 mmol, 3.0 eq) in DMF (1.0 mL) was sequentially added a solution of (3S,6S,9aR)-6-{[(tert-butoxy)carbonyl]amino}-8-methyl-5-oxo-octahydro-

1Hpyrrolo[1,2-a]azepine-3-carboxylic acid (0.40 g, 1.2 mmol, 1 eq) in DMF (1.0 mL). To this mixture was introduced HATU (0.7 g, 1.8 mmol, 1.5 eq), N,N-diisopropylethylamine (0.47 g, 3.7 mmol, 3.0 eq). The yellow solution was stirred for 1 h, and subsequently diluted with water (50 mL). The aqueous phase was extracted with EtOAc (50 mL × 2). The combined organic layers were washed with saturated aqueous brine (50 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (elution with CH_2Cl_2 / MeOH) to give tert-butyl ((3S,6S,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (0.29 mg, 53% yield) as a yellow oil. LCMS (ESI) m/z = 443.1 $[M+H]^+$.

[00331] *Step 2: Preparation of tert-butyl ((3S,6S,8R,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate and tert-butyl ((3S,6S,8S,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate*

[00332] tert-Butyl ((3S,6S,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (0.29 mg) was purified by SFC (Column: DAICEL CHIRALPAK AD 250 mm × 30 mm, 10 um, Mobile phase: Phase A for CO_2, and Phase B for Neu-IPA; Gradient elution: B in A 30%) to yield

[00333] Peak 1: tert-butyl ((3S,6S,8R,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate or tert-butyl ((3S,6S,8S,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (0.14 g, 48% yield, tR = 1.536 min) as a white solid. LCMS (ESI) m/z = 443.1 $[M+H]^+$.

[00334] Peak 2: tert-butyl ((3S,6S,8S,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate or tert-butyl ((3S,6S,8R,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (80 mg, 28% yield, tR = 1.662 min) as a white solid. LCMS (ESI) m/z = 443.1 $[M+H]^+$.

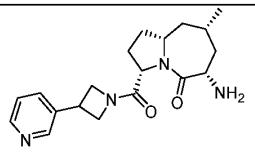
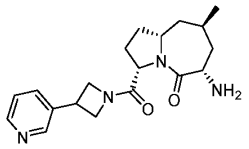
[00335] *Step 3: Preparation of (3S,6S,8R,9aR)-6-amino-8-methyl-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-5H-pyrrolo[1,2-a]azepin-5-one or (3S,6S,8S,9aR)-6-amino-8-methyl-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-5H-pyrrolo[1,2-a]azepin-5-one*

[00336] To a solution of tert-butyl ((3S,6S,8R,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate or tert-butyl ((3S,6S,8S,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-

pyrrolo[1,2-a]azepin-6-yl)carbamate [Peak 1] (1 eq) in CH_2Cl_2 (0.3 mL) was added trifluoroacetic acid (0.1 mL). The resulting yellow reaction mixture was stirred for 15 min and subsequently concentrated *in vacuo* and dried to give (3S,6S,8R,9aR)-6-amino-8-methyl-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-5H-pyrrolo[1,2-a]azepin-5-one or (3S,6S,8S,9aR)-6-amino-8-methyl-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-5H-pyrrolo[1,2-a]azepin-5-one (140 mg, TFA salt) as a yellow oil. LCMS (ESI) m/z = 343.1 $[M+H]^+$.

[00337] The intermediate in **Table 29** was prepared according to the method described above starting from tert-butyl ((3S,6S,8S,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate or tert-butyl ((3S,6S,8R,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate [Peak 2] and using the appropriate conditions.

Table 29

Name	Structure	LCMS
(3S,6S,8S,9aR)-6-amino-8-methyl-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-5H-pyrrolo[1,2-a]azepin-5-one or (3S,6S,8S,9aR)-6-amino-8-methyl-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-5H-pyrrolo[1,2-a]azepin-5-one or (3S,6S,8R,9aR)-6-amino-8-methyl-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-5H-pyrrolo[1,2-a]azepin-5-one or (3S,6S,8S,9aR)-6-amino-8-methyl-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-5H-pyrrolo[1,2-a]azepin-5-one	 or 	343.1 $[M+H]^+$

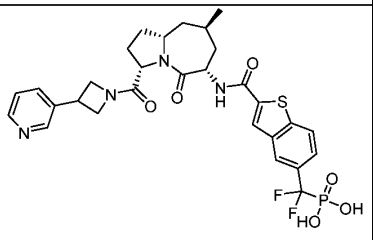
[00338] *Step 4: Preparation of (difluoro(2-(((3S,6S,8R,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid or (difluoro(2-(((3S,6S,8S,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (**109/110**)*

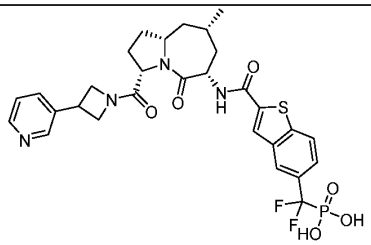
[00339] To a solution of (difluoro(2-((4-nitrophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (1 eq) in DMF (1 mL) was added HOBt (1.5 eq) and N,N-

diisopropylethylamine (3 eq). After stirring for 30 min, the solution of (3S,6S,8R,9aR)-6-amino-8-methyl-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-5H-pyrrolo[1,2-a]azepin-5-one or (3S,6S,8S,9aR)-6-amino-8-methyl-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-5H-pyrrolo[1,2-a]azepin-5-one [from Step 3 and derived from Peak 1] (1.2 eq) in DMF (1 mL) and N,N-diisopropylethylamine (3 eq) was added to the reaction mixture. The resulting yellow reaction mixture was stirred for 30 min, and subsequently purified by prep-HPLC (column: Phenomenex Luna C18 150 × 25 mm ×10 um, mobile phase: water (NH_4HCO_3)-acetonitrile; B%: 4% – 34%, 8 min) to give (difluoro(2-(((3S,6S,8R,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid or (difluoro(2-(((3S,6S,8S,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (**109**) (21 mg, 14% yield). LCMS (ESI) m/z = 633.3 $[M+H]^+$; ^1H NMR (400 MHz, methanol-d_4) δ 8.69 – 8.40 (m, 2H), 8.22 – 8.06 (m, 3H), 7.94 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.48 (s, 1H), 4.77 (d, J = 10.0 Hz, 1H), 4.69 (s, 1H), 4.62 – 4.47 (m, 2H), 4.45 – 4.24 (m, 1H), 4.14 – 3.93 (m, 3H), 2.31 (s, 1H), 2.18 – 2.03 (m, 2H), 1.96 (d, J = 9.6 Hz, 3H), 1.86 – 1.72 (m, 1H), 1.70 – 1.52 (m, 2H), 1.05 (s, 3H).

[00340] The compound in **Table 30** was prepared according to the method described above starting from (3S,6S,8S,9aR)-6-amino-8-methyl-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-5H-pyrrolo[1,2-a]azepin-5-one or (3S,6S,8R,9aR)-6-amino-8-methyl-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-5H-pyrrolo[1,2-a]azepin-5-one [derived from Peak 2]and using the appropriate conditions.

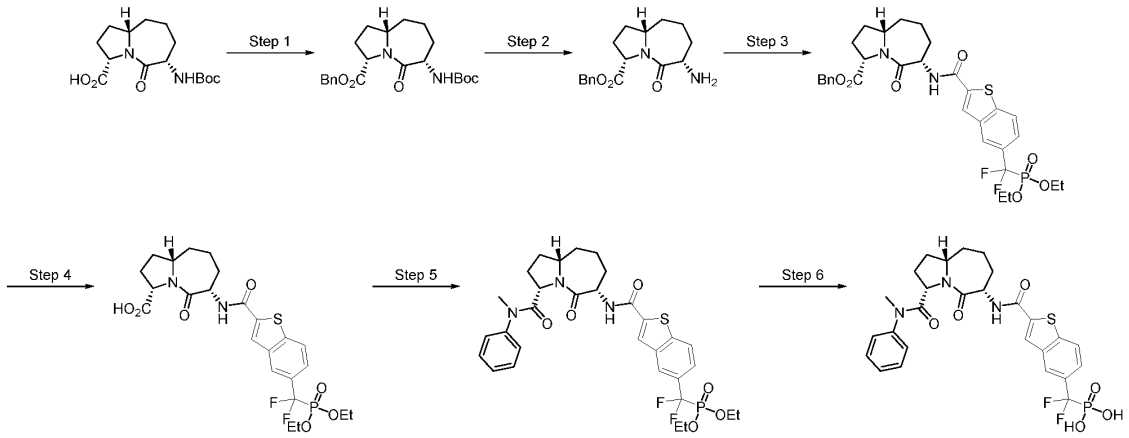
Table 30

Compound	Name	Structure	LCMS	^1H NMR
110	(difluoro(2-(((3S,6S,8R,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid or	 or	633.1 $[M+H]^+$	^1H NMR (400 MHz, methanol-d_4) δ 8.54 (d, J = 8.0 Hz, 1H), 8.47 – 8.42 (m, 1H), 8.28 – 8.10 (m, 3H), 7.95 – 7.90 (m, 1H), 7.85 – 7.78 (m, 1H), 7.50 – 7.42 (m, 1H), 5.02 – 4.96 (m, 2H), 4.73 – 4.66 (m, 1H), 4.64 – 4.58 (m, 1H), 4.56 – 4.51 (m, 1H), 4.32 – 4.26 (m, 1H), 4.08 – 3.96 (m, 2H), 2.38 – 2.27 (m, 2H), 2.21 – 2.00 (m, 6H), 1.98 –

	(difluoro(2-(((3S,6S,8S,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			1.81 (m, 2H), 1.65 – 1.55 (m, 2H)

[00341] Method 3: Representative Procedure for the Synthesis of Phosphonic Acid Analogues via Amino Acid Coupling of Core Carboxylic Acids with Amines

[00342] Synthesis of (Difluoro(2-(((3S,6S,9aS)-3-(methyl(phenyl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (111)



[00343] *Step 1: Preparation of benzyl (3S,6S,9aS)-6-((tert-butoxycarbonyl)amino)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate*

[00344] To a solution of (3S,6S,9aS)-6-((tert-butoxycarbonyl)amino)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic acid (590 mg, 1.88 mmol, 1 eq) and Cs_2CO_3 (1.22 g, 3.76 mmol, 2 eq) in THF (15 mL) was added benzyl bromide (352 mg, 2.06 mmol, 1.1 eq). The resulting mixture was stirred for an additional 12 h at room temperature, followed by addition of H_2O (10 mL). The resulting suspension was extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography to yield benzyl (3S,6S,9aS)-6-((tert-butoxycarbonyl)amino)-5-

oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate (633 mg, 1.57 mmol, 84% yield) as a white solid. LCMS (ESI) *m/z* = 403 $[M+H]^+$.

[00345] *Step 2: Preparation of benzyl (3S,6S,9aS)-6-amino-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate*

[00346] To a solution of benzyl (3S,6S,9aS)-6-((tert-butoxycarbonyl)amino)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate (663 mg, 1.64 mmol, 1.0 eq) in CH_2Cl_2 (16 mL) was added trifluoroacetic acid (8 mL), and the resulting mixture was stirred for 2 h at room temperature. The reaction mixture was subsequently cooled (0 °C) and saturated aqueous $NaHCO_3$ was carefully added to basify the mixture (adjusted to pH = 8-9). The resulting mixture was extracted with CH_2Cl_2 (10 mL x 3), and the combined organic layers were washed with brine (10 mL x 2), dried over with anhydrous Na_2SO_4, then concentrated under reduced pressure to give crude benzyl (3S,6S,9aS)-6-amino-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate (498 mg, 1.64 mmol, quant) as a white solid, which was used in next step directly without further purification. LCMS (ESI): *m/z* = 303 $[M+H]^+$.

[00347] *Step 3: Preparation of benzyl (3S,6S,9aS)-6-(5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxamido)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate*

[00348] A solution of 5-[(diethoxyphosphoryl)difluoromethyl]-1-benzothiophene-2-carboxylic acid (597 mg, 1.64 mmol, 1 eq), EDCI (412 mg, 2.13 mmol, 1.3 eq), HOBt (287 mg, 2.13 mmol, 1.3 eq) and N,N-diisopropylethylamine (635 mg, 4.92 mmol, 3 eq) in CH_2Cl_2 (15 mL) was stirred for 30 min, followed by addition of benzyl (3S,6S,9aS)-6-amino-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate (498 mg, 1.64 mmol, 1 eq). The mixture was stirred over 12 h at room temperature, followed by addition of H_2O (10 mL). The biphasic mixture was extracted with CH_2Cl_2 (10 mL x 3). The organic layers were combined and washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford benzyl (3S,6S,9aS)-6-(5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxamido)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate (530 mg, 817 μmol, 50%) as a white solid. LCMS (ESI): *m/z* = 649 $[M+H]^+$.

[00349] *Step 4: Preparation of (3S,6S,9aS)-6-(5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxamido)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic acid*

[00350] A mixture of benzyl (3S,6S,9aS)-6-(5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxamido)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate (510 mg, 786 µmol, 1 eq) and 10% wt wet Pd/C (50 mg) in MeOH (15 mL) was stirred under H_2 (g) atmosphere. After complete consumption of starting material (as judged by LCMS), the reaction mixture filtered by passing through a pad of Celite®. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography to afford (3S,6S,9aS)-6-(5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxamido)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic acid (376 mg, 673 µmol, 86 % yield) as an off-white solid. LCMS (ESI): *m/z* = 559 $[M+H]^+$.

[00351] *Step 5: Preparation of diethyl (difluoro(2-(((3S,6S,9aS)-3-(methyl(phenyl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonate*

[00352] A solution of (3S,6S,9aS)-6-(5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxamido)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic acid (120 mg, 214 µmol, 1 eq), 2-chloro-1-methylpyridinium iodide (164 mg, 642 µmol, 3.0 eq), and N,N-diisopropylethylamine (82.9 mg, 642 µmol, 3.0 eq) in CH_2Cl_2 (15 mL) was stirred for 30 min at room temperature, followed by addition of N-methylaniline (22.9 mg, 214 µmol, 1.0 eq). After stirring for 12 h, The reaction mixture was diluted with H_2O (10 mL) and the resulting biphasic mixture was extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford diethyl (difluoro(2-(((3S,6S,9aS)-3-(methyl(phenyl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonate (90 mg, 138 µmol, 65% yield) as a white solid. LCMS (ESI) *m/z* = 648 $[M+H]^+$.

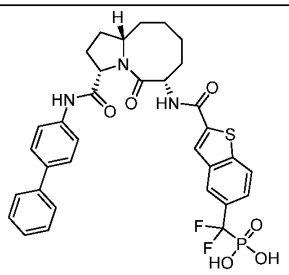
[00353] *Step 6: Preparation of (difluoro(2-(((3S,6S,9aS)-3-(methyl(phenyl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (111)*

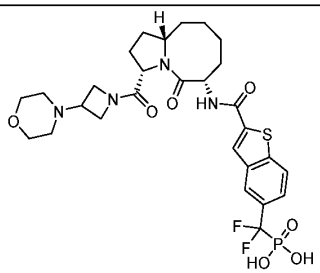
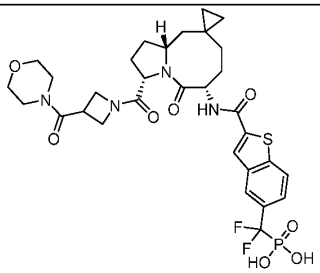
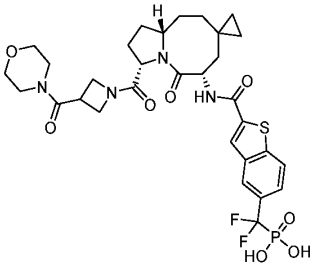
[00354] To a cooled (0 °C) solution of diethyl (difluoro(2-(((3S,6S,9aS)-3-(methyl(phenyl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonate (50 mg, 77.1 µmol, 1.0 eq) in CH_2Cl_2 (15 mL) was added bromo trimethylsilane (235 mg, 1.54 mmol, 20.0 eq) in a dropwise manner. After the addition, the reaction mixture was allowed to warm to room

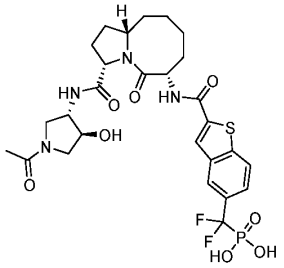
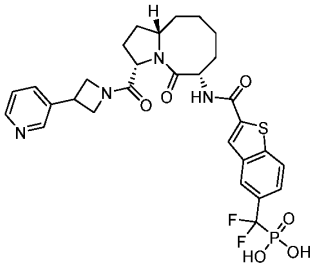
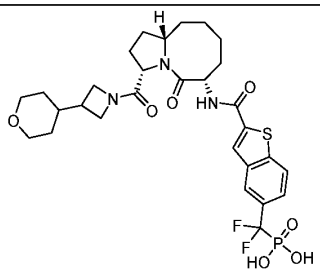
temperature and stirred for an additional 12 h. After completion consumption of starting material (as judged by LCMS), the reaction mixture was quenched by adding H_2O (5 mL) and the resulting biphasic mixture was extracted with CH_2Cl_2 (10 mL x 3). The organic layers were combined and washed with brine (20 mL), dried over with anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by reverse phase HPLC to afford (difluoro(2-(((3S,6S,9aS)-3-(methyl(phenyl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (**111**) (2.1 mg, 3.5 μmol, 4.5% yield) as a white solid. LCMS (ESI) *m/z* =592 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, J = 6.7 Hz, 1H), 8.29 (s, 1H), 8.13 – 7.96 (m, 2H), 7.65 (d, J = 7.3 Hz, 1H), 7.53 – 7.25 (m, 5H), 4.67 – 4.55 (m, 1H), 4.41 – 4.27 (m, 1H), 3.99 – 3.85 (m, 1H), 3.15 (s, 3H), 2.16 – 1.62 (m, 10H).

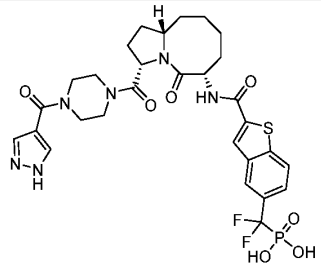
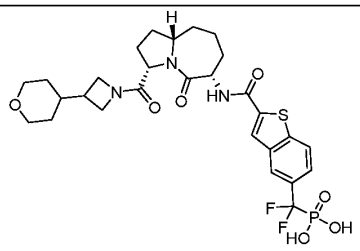
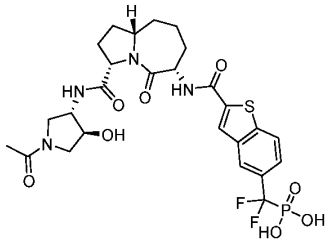
[00355] The following compounds in **Table 31** were prepared according to the representative procedure described above for the synthesis of (difluoro(2-(((3S,6S,9aS)-3-(methyl(phenyl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid and utilizing the appropriate starting materials and modifications.

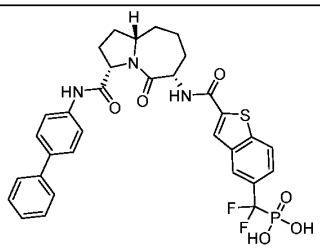
Table 31

Compound	Name	Structure	LCMS	NMR
112	((2-(((3S,6S,10aS)-3-([1,1'-biphenyl]-4-ylcarbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		668.4 $[M+H]^+$	^1H NMR (400 MHz, methanol-d_4) δ 8.15 (s, 2H), 8.00 (d, J = 8.4 Hz, 1H), 7.73 – 7.64 (m, 3H), 7.63 – 7.57 (m, 4H), 7.43 (t, J = 7.6 Hz, 2H), 7.35 – 7.29 (m, 1H), 5.09 (t, J = 8.8 Hz, 1H), 4.60 (t, J = 8.4 Hz, 1H), 4.48 (m, 1H), 2.42 – 2.27 (m, 2H), 2.24 – 1.95 (m, 6H), 1.93 – 1.81 (m, 2H), 1.80 – 1.61 (m, 2H)

113	(difluoro(2-(((3S,6S,10aS)-3-(3-morpholinoazetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		641.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.20 (s, 1H), 8.13 (s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 5.07 – 4.97 (m, 1H), 4.54 (t, J = 8.0 Hz, 1H), 4.47 – 4.38 (m, 2H), 4.15 – 4.05 (m, 1H), 3.95 – 3.92 (m, 1H), 3.82 – 3.78 (m, 1H), 3.72 – 3.66 (m, 4H), 3.27 – 3.16 (m, 1H), 2.41 (s, 4H), 2.30 – 2.14 (m, 2H), 2.08 – 1.90 (m, 6H), 1.88 – 1.75 (m, 2H), 1.73 – 1.55 (m, 2H)
114	(difluoro(2-(((3'S,6'S,10a'R)-3'-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5'-oxooctahydro-1'H-spiro[cyclopropane-1,9'-pyrrolo[1,2-a]azocin]-6'-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		695.3 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.19 – 8.14 (m, 1H), 8.14 – 8.09 (m, 1H), 7.96 – 7.88 (m, 1H), 7.74 (d, J = 8.4 Hz, 1H), 5.19 – 5.07 (m, 1H), 4.70 – 4.63 (m, 1H), 4.50 – 4.43 (m, 2H), 4.42 – 4.36 (m, 1H), 4.33 – 4.20 (m, 1H), 4.15 – 4.04 (m, 1H), 3.86 – 3.71 (m, 1H), 3.70 – 3.54 (m, 6H), 3.40 – 3.34 (m, 1H), 2.66 – 2.46 (m, 2H), 2.31 – 2.16 (m, 2H), 2.09 – 1.66 (m, 5H), 1.24 (d, J = 11.6 Hz, 1H), 0.78 – 0.66 (m, 2H), 0.58 – 0.44 (m, 2H), 0.36 (d, J = 9.2 Hz, 1H)
115	(difluoro(2-(((3'S,6'S,10a'S)-3'-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5'-oxooctahydro-5'H-spiro[cyclopropane-1,8'-pyrrolo[1,2-a]azocin]-6'-		695.3 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.20 – 8.12 (m, 1H), 8.10 – 8.03 (m, 1H), 7.94 – 7.85 (m, 1H), 7.74 (d, J = 8.4 Hz, 1H), 5.04 – 4.94 (m, 1H), 4.78 – 4.69 (m, 1H), 4.51 – 4.42 (m, 2H), 4.42 – 4.35 (m, 1H), 4.34 – 4.20 (m, 1H), 4.13 – 4.05 (m, 1H), 3.84 – 3.71 (m, 1H), 3.68 – 3.48 (m, 6H), 3.36 (m, 1H), 2.28 – 2.15 (m, 2H), 2.11 – 1.96 (m, 1H),

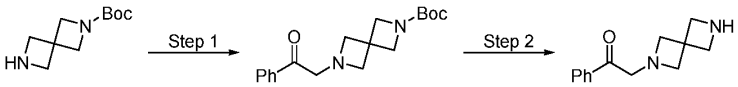
	yl)carbamoyl)benzo[b]thio phen-5-yl)methyl)ph osphonic acid			1.95 – 1.80 (m, 4H), 1.78 – 1.54 (m, 3H), 1.36 – 1.27 (m, 1H), 0.62 – 0.42 (m, 4H)
116	((2-(((3S,6S,10a S)-3-(((3S,4S)-1-acetyl-4-hydroxypyrr olidin-3-yl)carbamoyl)-5-oxodecahydr opyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thio phen-5-yl)difluorom ethyl)phosph onic acid		643.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.19 (s, 1H), 8.12 (s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 5.06 – 4.98 (m, 1H), 4.45 – 4.33 (m, 2H), 4.20 (d, J = 2.4 Hz, 1H), 4.16 – 4.11 (m, 1H), 3.90 – 3.86 (m, 1H), 3.78 – 3.70 (m, 1H), 3.60 – 3.56 (m, 1H), 3.52 – 3.39 (m, 2H), 2.27 – 2.15 (m, 2H), 2.06 (d, J = 4.0 Hz, 3H), 2.02 – 1.94 (m, 5H), 1.87 – 1.76 (m, 2H), 1.73 – 1.58 (m, 2H)
117	(difluoro(2-(((3S,6S,10a S)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)dec ahydropyrrol o[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thio phen-5-yl)methyl)ph osphonic acid		633.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.59 (d, J = 17.2 Hz, 1H), 8.47 (s, 1H), 8.26 – 8.09 (m, 3H), 7.97 – 7.85 (m, 1H), 7.80 – 7.67 (m, 1H), 7.61 – 7.38 (m, 1H), 5.11 – 4.96 (m, 1H), 4.73 – 4.59 (m, 2H), 4.57 – 4.38 (m, 3H), 3.82 (s, 2H), 2.33 – 2.18 (m, 2H), 2.15 – 1.93 (m, 6H), 1.92 – 1.56 (m, 4H)
118A	(difluoro(2-(((3S,6S,10a S)-5-oxo-3-(3-(tetrahydro-2H-pyran-4-yl)azetidine-1-carbonyl)dec		640.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.23 – 8.12 (m, 2H), 7.95 (d, J = 8.4 Hz, 1H), 7.84 – 7.67 (m, 1H), 5.13 – 4.99 (m, 1H), 4.64 – 4.39 (m, 3H), 4.28 (d, J = 7.2 Hz, 1H), 4.01 – 3.87 (m, 2H), 3.85 – 3.62 (m, 2H), 3.52 –

	ahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			3.35 (m, 1H), 2.53 – 2.16 (m, 3H), 2.11 – 1.94 (m, 6H), 1.91 – 1.75 (m, 4H), 1.73 – 1.57 (m, 4H), 1.41 – 1.07 (m, 2H)
118B	((2-(((3S,6S,10aS)-3-(4-(1H-pyrazole-4-carbonyl)piperazine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		679.4 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.18 (s, 1H), 8.13 (s, 1H), 7.94 – 7.89 (m, 3H), 7.74 (d, J = 8.8 Hz, 1H), 5.08 – 5.01 (m, 1H), 4.50 – 4.39 (m, 1H), 3.93 – 3.74 (m, 6H), 3.73 – 3.51 (m, 3H), 2.37 – 2.22 (m, 2H), 2.21 – 2.09 (m, 1H), 2.07 – 1.93 (m, 5H), 1.89 – 1.75 (m, 2H), 1.73 – 1.59 (m, 2H)
119	(difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(tetrahydro-2H-pyran-4-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		626.5 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.20 (s, 1H), 8.12 (d, J = 1.6 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H) , 4.74 (d, J = 10.8 Hz, 1H), 4.58 – 4.50 (m, 1H), 4.32 – 4.18 (m, 1H), 4.15 – 4.00 (m, 2H), 3.99 – 3.87 (m, 3H), 3.80 – 3.66 (m, 1H), 3.47 – 3.37 (m, 2H) , 2.50 – 2.37 (m, 1H), 2.34 – 2.23 (m, 1H), 2.16 – 2.02 (m, 3H), 1.97 – 1.73 (m, 7H), 1.68 – 1.55 (m, 2H), 1.24 – 1.13 (m, 2H)
120	((2-(((3S,6S,9aS)-3-(((3S,4S)-1-acetyl-4-hydroxypyrrolidin-3-yl)carbamoyl)-5-		629.2 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.20 (s, 1H), 8.10 (d, J = 4.0 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 4.72 (d, J = 10.8 Hz, 1H), 4.57 – 4.44 (m, 1H), 4.24 – 4.10 (m, 2H), 4.09

	oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid			– 4.00 (m, 1H), 3.93 – 3.75 (m, 1H), 3.74 – 3.55 (m, 1H), 3.52 – 3.38 (m, 2H), 2.33 – 2.24 (m, 1H), 2.09 (d, J = 2.8 Hz, 1H), 2.06 (d, J = 1.6 Hz, 3H), 2.06 – 1.93 (m, 3H), 1.93 – 1.73 (m, 5H)
121	((2-(((3S,6S,9aS)-3-([1,1'-biphenyl]-4-ylcarbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		654.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 8.79 (d, J = 7.5 Hz, 1H), 8.28 (s, 1H), 8.16 – 7.98 (m, 2H), 7.75 – 7.55 (m, 7H), 7.49 – 7.39 (m, 2H), 7.37 – 7.24 (m, 1H), 4.71 – 4.54 (m, 2H), 4.08 – 4.01 (m, 1H), 2.30 – 2.07 (m, 2H), 2.05 – 1.71 (m, 8H)

[00356] Azetidine Building Block Syntheses:

[00357] Synthesis of 1-phenyl-2-(2,6-diazaspiro[3.3]heptan-2-yl)ethan-1-one



[00358] *Step 1: Preparation of tert-butyl 6-(2-oxo-2-phenylethyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate*

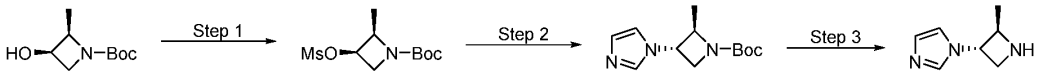
[00359] To a solution of 2-phenylacetic acid (500 mg, 3.67 mmol, 1 eq) in DMF (4 mL) was added N,N-diisopropylethylamine (1.42 g, 11.0 mmol, 3 eq) and HATU (2.09 g, 5.50 mmol, 1.5 eq). After stirring for 10 min, a solution of tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate (945 mg, 4.77 mmol, 1.3 eq) in DMF (4 mL) and N,N-diisopropylethylamine (1.42 g, 11.0 mmol, 3 eq) was added. The mixture was stirred for an additional 1 h and subsequently diluted with water (20 mL). The mixture was extracted with EtOAc (10 mL × 2). The combined organic layers were washed with saturated aqueous brine (10 mL × 2), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (eluent of 0% – 5 % = CH_2Cl_2 : MeOH) to give tert-butyl 6-(2-phenylacetyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (1.00

g, 3.16 mmol, 86.2% yield) was obtained as a white solid. LCMS (ESI) m/z = 317.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.28 – 7.22 (m, 3H), 4.18 (s, 2H), 4.11 (s, 2H), 3.47 (s, 2H), 2.81 (s, 4H), 1.72 (s, 4H), 1.43 (s, 9H).

[00360] *Step 2: Preparation of 1-phenyl-2-(2,6-diazaspiro[3.3]heptan-2-yl)ethan-1-one*

[00361] To a solution of tert-butyl 6-(2-phenylacetyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (1.00 g, 3.16 mmol) in CH_2Cl_2 (6 mL) was added trifluoroacetic acid (2 mL, 0.0175 mmol, 0.006 eq) and the reaction mixture as stirred for 1 h. The resulting yellow reaction mixture was concentrated under reduced pressure to give a residue. The product 1-phenyl-2-(2,6-diazaspiro[3.3]heptan-2-yl)ethan-1-one (~1 g, TFA salt) was obtained as a yellow oil and was used without further purification.

Synthesis of 1-((2R,3S)-2-methylazetidin-3-yl)-1H-imidazole



[00362] *Step 1: Preparation of tert-butyl (2R,3R)-2-methyl-3-((methylsulfonyl)oxy)azetidine-1-carboxylate*

[00363] To a solution of tert-butyl (2R,3R)-3-hydroxy-2-methylazetidine-1-carboxylate (500 mg, 2.67 mmol, 1.0 eq) and Et_3N (810 mg, 8.01 mmol, 3.0 eq) in CH_2Cl_2 (20 mL) was added methanesulfonyl chloride (335 mg, 2.93 mmol, 1.1 eq). The reaction mixture was stirred at room temperature for 14 h, followed by addition of H_2O (10 mL). The resulting biphasic mixture was extracted with CH_2Cl_2 (20 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Biotage® C18 column to afford tert-butyl (2R,3R)-2-methyl-3-((methylsulfonyl)oxy)azetidine-1-carboxylate (710 mg, 2.67 mmol, 100% yield) as a colorless oil. LCMS (ESI) *m/z* = 210 $[(M-56)+H]^+$.

[00364] *Step 2: Preparation of tert-butyl (2R,3S)-3-(1H-imidazol-1-yl)-2-methylazetidine-1-carboxylate*

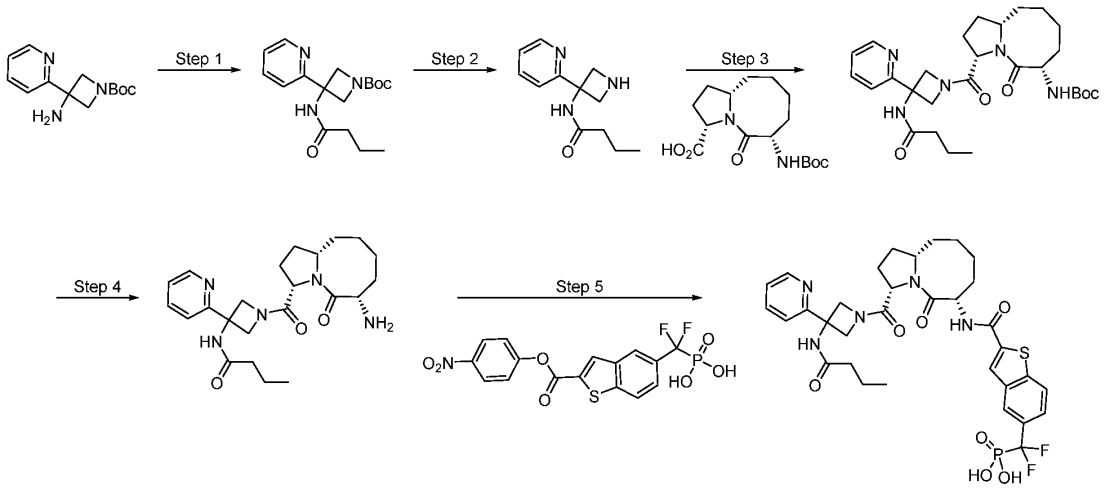
[00365] To a cooled (0 °C) solution of 1*H*-imidazole (599 mg, 8.81 mmol, 3.3 eq) in DMF (10 mL) under a constant stream of N_2 (g), was added NaH (352 mg, 8.81 mmol, 3.3 eq) in portions. The mixture was stirred until gas evolution ceased (~30 min). To the mixture as added a solution of tert-butyl (2R,3R)-2-methyl-3-((methylsulfonyl)oxy)azetidine-1-carboxylate (710 mg, 2.67 mmol, 1.0 eq) in DMF (3 mL). The reaction mixture was subsequently heated to 80 °C. After stirring for 72 h, the reaction mixture was cooled to 0 °C and saturated aqueous NH_4Cl (10 mL) was added. The mixture was extracted with EtOAc (20 mL x 3). The organic layers were combined, washed with brine (10 mL), dried over

anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Biotage® C18 column to afford tert-butyl (2R,3S)-3-(1H-imidazol-1-yl)-2-methylazetidine-1-carboxylate (73.0 mg, 0.31 mmol, 12% yield) as a colorless oil. LCMS (ESI) *m/z* = 238 $[M+H]^+$.

[00366] *Step 3: Preparation of 1-((2R,3S)-2-methylazetidin-3-yl)-1H-imidazole*

[00367] To a solution of tert-butyl (2R,3S)-3-(1H-imidazol-1-yl)-2-methylazetidine-1-carboxylate (73.0 mg, 0.31 mmol, 1.0 eq) in CH_2Cl_2 (3 mL) was added TFA (1 mL), and the resulting mixture was stirred at room temperature. After stirring for 16 h, the reaction mixture was concentrated under reduced pressure to give 1-((2R,3S)-2-methylazetidin-3-yl)-1H-imidazole (40 mg, TFA salt) as a white solid, which was used without further purification. LCMS (ESI) *m/z* = 138 $[M+H]^+$.

[00368] **((2-(((3S,6S,10aS)-3-(3-butyramido-3-(pyridin-2-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid (122)**



[00369] *Step 1: Preparation of tert-butyl 3-butyramido-3-(pyridin-2-yl)azetidine-1-carboxylate*

[00370] To a solution of butyric acid (95 mg, 1.1 mmol, 0.9 eq) in DMF (3 mL) was added HATU (0.69 g, 1.8 mmol, 1.5 eq) and N,N-diisopropylethylamine (0.46 g, 3.6 mmol, 3 eq). The mixture was stirred for 10 minutes, followed by addition of tert-butyl 3-amino-3-(pyridin-2-yl)azetidine-1-carboxylate (0.30 g, 1.2 mmol, 1 eq). After stirring for an additional 1 h, the reaction mixture turned brown. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with saturated aqueous brine (30 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel

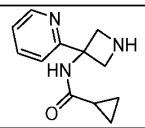
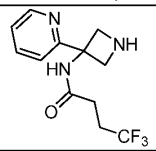
chromatography (SepaFlash Column, 0% – 100% EtOAc / petroleum ether gradient) to give tert-butyl 3-butyramido-3-(pyridin-2-yl)azetidine-1-carboxylate (0.26 g, 68% yield) as white solids. LCMS (ESI) m/z = 320.1 $[M+H]^+$.

[00371] *Step 2: Preparation of N-(3-(pyridin-2-yl)azetidin-3-yl)butyramide*

[00372] A solution of tert-butyl 3-butyramido-3-(pyridin-2-yl)azetidine-1-carboxylate (0.24 g, 0.75 mmol, 1 eq) in CH_2Cl_2 (2 mL) and TFA (1 mL) was stirred at room temperature. After 1 h, the resulting yellow solution concentrated under reduced pressure to give N-(3-(pyridin-2-yl)azetidin-3-yl)butyramide (0.24 g, TFA salt) which was used into the next step without further purification.

[00373] The following intermediates in **Table 32** were prepared according to the representative procedures (Step1 and Step 2) described above starting from tert-butyl 3-butyramido-3-(pyridin-2-yl)azetidine-1-carboxylate and utilizing appropriate starting materials and modifications.

Table 32

Name	Structure	LCMS
N-(3-(pyridin-2-yl)azetidin-3-yl)cyclopropanecarboxamide		218.1 $[M+H]^+$
4,4,4-trifluoro-N-(3-(pyridin-2-yl)azetidin-3-yl)butanamide		218.1 $[M+H]^+$

[00374] *Step 3: Preparation of tert-butyl ((3S,6S,10aS)-3-(3-butyramido-3-(pyridin-2-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate*

[00375] To a solution of (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid (0.36 g, 1.1 mmol, 1 eq) in DMF (3 mL) was added N,N-diisopropylethylamine (0.43 g, 3.3 mmol, 3 eq) and HATU (0.63 g, 1.6 mmol, 1.5 eq). After 10 min, N-(3-(pyridin-2-yl)azetidin-3-yl)butyramide (0.24 g, 1.1 mmol, 1 eq) was added. After 1 h, the brown solution was diluted with water (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with saturated aqueous brine 60 mL (20 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (SepaFlash Silica Flash Column, 0% – 100% EtOAc / petroleum ether) to give tert-butyl ((3S,6S,10aS)-3-(3-butyramido-3-(pyridin-2-yl)azetidine-1-carbonyl)-5-

oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate (0.29 g, 51% yield) as a white solid. LCMS (ESI) m/z = 528.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 9.11 – 8.95 (m, 1H), 8.61 (d, J = 4.4 Hz, 1H), 7.82 – 7.73 (m, 1H), 7.43 – 7.26 (m, 2H), 6.76 – 6.67 (m, 1H), 4.66 – 4.53 (m, 1H), 4.32 (td, J = 8.8, 9.2 Hz, 2H), 4.19 – 4.08 (m, 2H), 4.07 – 3.99 (m, 1H), 2.25 – 2.13 (m, 3H), 1.99 (s, 1H), 1.87 – 1.65 (m, 6H), 1.54 (dt, J = 7.8, 11.2 Hz, 6H), 1.38 – 1.30 (m, 9H), 1.17 (t, J = 7.2 Hz, 1H), 0.88 (td, J = 5.2, 5.2 Hz, 3H)

[00376] *Step 4: Preparation of N-(1-((3S,6S,10aS)-6-amino-5-oxodecahydropyrrolo[1,2-a]azocine-3-carbonyl)-3-(pyridin-2-yl)azetidin-3-yl)butyramide*

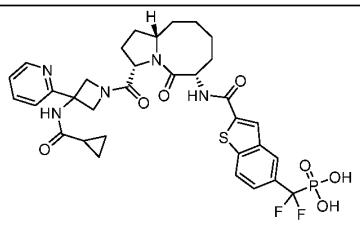
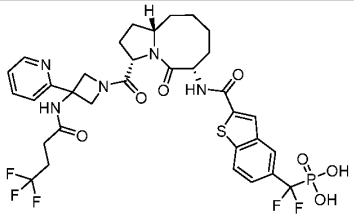
[00377] A solution of tert-butyl ((3S,6S,10aS)-3-(3-butyramido-3-(pyridin-2-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate (0.22 g, 0.42 mmol, 1 eq) in CH_2Cl_2 (1 mL) and TFA (0.5 mL) was stirred at room temperature. After 1 h, the resulting yellow solution was concentrated under reduced pressure to give N-(1-((3S,6S,10aS)-6-amino-5-oxodecahydropyrrolo[1,2-a]azocine-3-carbonyl)-3-(pyridin-2-yl)azetidin-3-yl)butyramide (0.22 g, TFA salt) which was used into the next step without further purification.

[00378] *Step 5: Preparation of ((2-(((3S,6S,10aS)-3-(3-butyramido-3-(pyridin-2-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid (**122**)*

[00379] To a solution of N-(1-((3S,6S,10aS)-6-amino-5-oxodecahydropyrrolo[1,2-a]azocine-3-carbonyl)-3-(pyridin-2-yl)azetidin-3-yl)butyramide (80 mg, 0.19 mmol, 1 eq) in DMF (1 mL) was added (difluoro(2-((4-nitrophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (80 mg, 0.19 mmol, 1 eq), N,N-diisopropylethylamine (73 mg, 0.57 mmol, 3 eq) and HOBt (25 mg, 0.19 mmol, 1 eq). The mixture was stirred at 25 °C for 10 min and the yellow mixture was subsequently filtered. The filtrate was purified by prep-HPLC (Phenomenex Luna C18 150 × 25 mm × 10 um; water (0.1% TFA) – ACN; B%: 32% – 62% over 10 min) to yield ((2-(((3S,6S,10aS)-3-(3-butyramido-3-(pyridin-2-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid (**122**) (40 mg, 5.6% yield) as a white solid. LCMS (ESI) m/z = 718.4 $[M+H]^+$; ^1H NMR (400 MHz, methanol-d_4) δ 8.67 – 8.33 (m, 1H), 8.21 – 8.12 (m, 1H), 8.03 (s, 1H), 8.02 – 7.93 (m, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.67 (dd, J = 8.4, 6.4 Hz, 1H), 7.58 – 7.51 (m, 1H), 5.06 – 4.93 (m, 2H), 4.84 – 4.77 (m, 1H), 4.68 – 4.60 (m, 1H), 4.55 – 4.47 (m, 1H), 4.55 – 4.47 (m, 1H), 4.45 (d, J = 10.0 Hz, 1H), 4.36 – 4.26 (m, 1H), 2.34 – 2.21 (m, 4H), 2.14 – 1.92 (m, 6H), 1.91 – 1.79 (m, 2H), 1.75 – 1.68 (m, 1H), 1.68 – 1.51 (m, 3H), 0.90 (td, J = 7.2, 12.0 Hz, 3H).

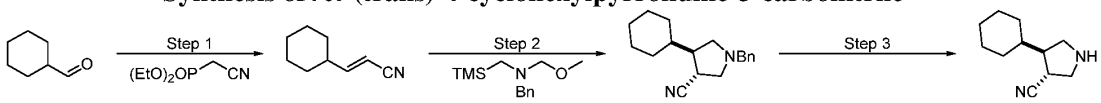
[00380] The following compounds in **Table 33** were prepared according to the representative procedures described above starting from (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid and utilizing appropriate starting materials and modifications.

Table 33

Compound	Name	Structure	LCMS	NMR
123	((2-(((3S,6S,10aS)-3-(3-(cyclopropanecarboxamido)-3-(pyridin-2-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		716.4 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.65 – 8.47 (m, 1H), 8.19 – 8.08 (m, 2H), 7.98 – 7.87 (m, 1H), 7.85 – 7.61 (m, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.32 – 7.29 (m, 1H), 5.05 – 4.99 (m, 1H), 4.79 – 4.66 (m, 1H), 4.61 – 4.48 (m, 1H), 4.47 – 4.37 (m, 2H), 4.28 (d, J = 10.4 Hz, 1H), 2.38 – 2.20 (m, 2H), 2.14 – 1.93 (m, 6H), 1.90 – 1.77 (m, 2H), 1.74 – 1.71(m, 1H), 1.69 – 1.60 (m, 1H), 1.37 – 1.33 (m, 2H), 0.90 – 0.71 (m, 4H)
124	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-(3-(pyridin-2-yl)-3-(4,4,4-trifluorobutanamido)azetidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		772.4 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.64 – 8.45 (m, 1H), 8.21 – 8.06 (m, 2H), 7.98 – 7.88 (m, 1H), 7.86 – 7.76 (m, 1H), 7.75 – 7.67 (m, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.36 – 7.27 (m, 1H), 5.07 – 4.98 (m, 2H), 4.78 – 4.71 (m, 1H), 4.62 – 4.50 (m, 1H), 4.48 – 4.40 (m, 2H), 4.29 (d, J = 10.4 Hz, 1H), 2.64 – 2.57 (m, 2H), 2.54 – 2.42 (m, 2H), 2.33 – 2.19 (m, 2H), 2.10 – 1.95 (m, 6H), 1.90 – 1.77 (m, 2H), 1.75 – 1.54 (m, 2H).

[00381] **Pyrrolidine Building Block Synthesis:**

Synthesis of *rel*-(trans)-4-cyclohexylpyrrolidine-3-carbonitrile



[00382] *Step 1*: *Preparation of (E)-3-cyclohexylacrylonitrile*

[00383] To a solution of cyclohexanecarbaldehyde (500 mg, 4.45 mmol, 1.0 eq) in THF (15 mL) were added *t*-BuOK (998 mg, 8.90 mmol, 2.0 eq) and diethyl (cyanomethyl)phosphonate (788 mg, 4.45 mmol, 1.0 eq) at room temperature. The solution was stirred at room temperature for 1 h. After completion, the reaction mixture was quenched by adding H_2O (10 mL), then extracted with EtOAc (10 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford (E)-3-cyclohexylacrylonitrile (300 mg, 2.21 mmol, 50% yield) as a colorless oil. LC-MS (ESI) *m/z* = 136 $[M+H]^+$.

[00384] *Step 2*: *Preparation of* rel-*(trans)-1-benzyl-4-cyclohexylpyrrolidine-3-carbonitrile*

[00385] To a solution of (E)-3-cyclohexylacrylonitrile (300 mg, 2.21 mmol, 1.0 eq) in CH_2Cl_2 (5 mL) were added N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine (524 mg, 2.21 mmol, 1.0 eq) and TFA (25.1 mg, 221 μmol, 0.1 eq). The reaction mixture was stirred at room temperature for 12 h. After completion, the reaction mixture was dilute with CH_2Cl_2 (10 mL) and washed with aqueous saturated $NaHCO_3$ (5 mL), the organic layer was separated and concentrated under reduced pressure to afford crude rel-(trans)-1-benzyl-4-cyclohexylpyrrolidine-3-carbonitrile (700 mg) as a colorless oil. LC-MS (ESI) *m/z* = 269 $[M+H]^+$.

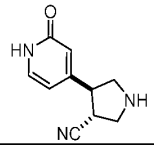
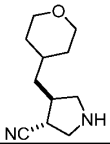
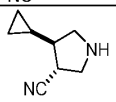
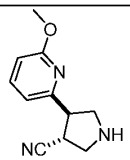
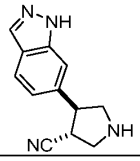
[00386] *Step 3: Preparation of rel-(trans)-4-cyclohexylpyrrolidine-3-carbonitrile*

[00387] To a solution of (trans)-1-benzyl-4-cyclohexylpyrrolidine-3-carbonitrile (700 mg) in dry 1,2-dichloroethane (15 mL) was added 1-chloroethyl carbonochloridate (3.71 g, 26.0 mmol, 10.0 eq). The resulting mixture was stirred at 70 °C for 12 h, then concentrated under reduced pressure, the crude product was dissolved in MeOH (5 mL) and stirred at 70 °C for 1 hr. After completion, the reaction solution was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford rel-(trans)-4-cyclohexylpyrrolidine-3-carbonitrile (211 mg, 1.18 mmol, 46% yield) as a colorless oil. LC-MS (ESI) *m/z* = 179 $[M+H]^+$.

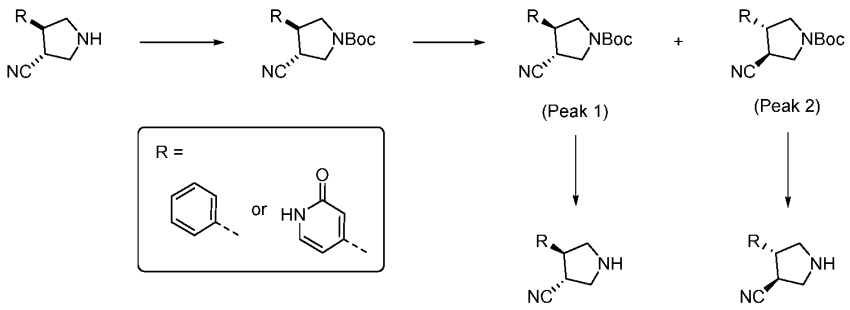
[00388] The following intermediates in **Table 34** were prepared according to the representative procedures (Step1 through Step 3) described for *rel*-(trans)-4-cyclohexylpyrrolidine-3-carbonitrile utilizing appropriate starting materials and

modifications. Compounds were prepared as racemates with trans stereochemical configuration relative to the C3 and C4 stereocenters within the pyrrolidine ring.

Table 34

Name	Structure	LCMS
rel-(trans)-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-3-carbonitrile		190 $[M+H]^+$
rel-(trans)-4-((tetrahydro-2H-pyran-4-yl)methyl)pyrrolidine-3-carbonitrile		195 $[M+H]^+$
rel-(trans)-4-cyclopropylpyrrolidine-3-carbonitrile		137 $[M+H]^+$
rel-(trans)-4-(6-methoxypyridin-2-yl)pyrrolidine-3-carbonitrile		204 $[M+H]^+$
rel-(trans)-4-(1H-indazol-6-yl)pyrrolidine-3-carbonitrile		213 $[M+H]^+$

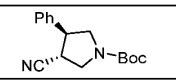
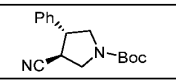
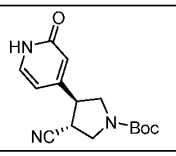
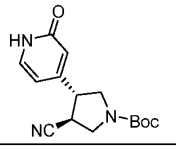
[00389] tert-Butyl rel-(trans)-3-cyano-4-phenylpyrrolidine-1-carboxylate and tert-butyl (trans)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate were prepared according to the method describe above for the synthesis of rel-(trans)-4-cyclohexylpyrrolidine-3-carbonitrile. The racemic mixture of trans-isomers were purified under SFC conditions and the absolute stereochemistry was arbitrarily assigned as drawn.



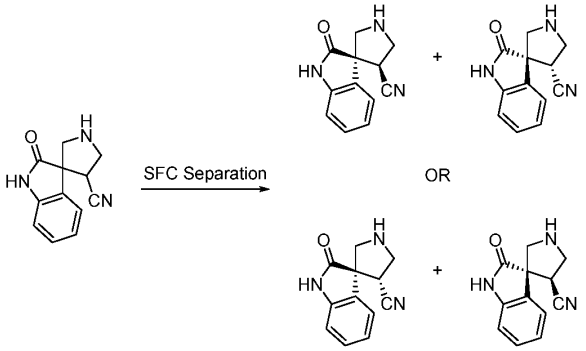
[00390] Preparative separation method:

[00391] Instrument: Waters Thar 80 preparative SFC; Column: ChiralPak C-IG, 100 ×4.6mm I.D., 5μm; Mobile phase: A for CO_2 and B for methanol (0.05% diethylamine); Gradient: 10% to 40% B in 8 min; Flow rate: 2.5 mL/min; Back pressure: 100 bar; Column temperature: 40 °C; Wavelength: 210 nm; Cycle-time: 2 min

Table 35

Name	Structure	LCMS
tert-butyl (3R,4S)-3-cyano-4-phenylpyrrolidine-1-carboxylate (Peak 1)		217 $[(M–56)+1]^+$
tert-butyl (3S,4R)-3-cyano-4-phenylpyrrolidine-1-carboxylate (Peak 2)		217 $[(M–56)+1]^+$
tert-butyl (3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate (Peak 1)		190 $[M+H]^+$
tert-butyl (3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate (Peak 2)		190 $[M+H]^+$

Separation of 2-oxospiro[indoline-3,3'-pyrrolidine]-4'-carbonitrile

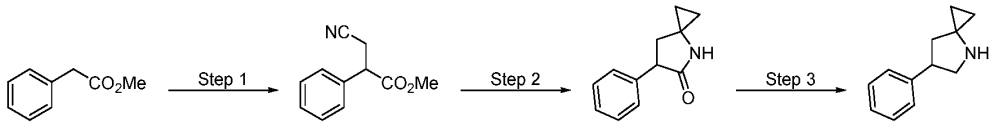


[00392] 2-oxospiro[indoline-3,3'-pyrrolidine]-4'-carbonitrile (1.00 g, single diastereomer with relative stereochemistry unknown, CAS# 1423027-48-8) was purchased and separated under SFC conditions (Column Lux-Cellulose-5 21.2 x 250 mm, 5 um column, 3.7 mg/inj, concentration 36.9 mg/mL, Column T = 40°C, Flow rate 75 mL/min, 15% MeOH (with 0.1% diethylamine), cycle time: 4.9 min) to give Peak 1 or Peak 2.

[00393] Peak 1: (3S,4'S)-2-oxospiro[indoline-3,3'-pyrrolidine]-4'-carbonitrile and (3R,4'R)-2-oxospiro[indoline-3,3'-pyrrolidine]-4'-carbonitrile (230 mg each enantiomer) or (3S,4'R)-2-oxospiro[indoline-3,3'-pyrrolidine]-4'-carbonitrile or (3R,4'S)-2-oxospiro[indoline-3,3'-pyrrolidine]-4'-carbonitrile (220 mg each enantiomer)

[00394] Peak 2: (3S,4'S)-2-oxospiro[indoline-3,3'-pyrrolidine]-4'-carbonitrile and (3R,4'R)-2-oxospiro[indoline-3,3'-pyrrolidine]-4'-carbonitrile (220 mg each enantiomer) or (3S,4'R)-2-oxospiro[indoline-3,3'-pyrrolidine]-4'-carbonitrile or (3R,4'S)-2-oxospiro[indoline-3,3'-pyrrolidine]-4'-carbonitrile (220 mg each enantiomer)

Synthesis of 6-phenyl-4-azaspiro[2.4]heptane



[00395] *Step 1: Preparation of methyl 3-cyano-2-phenylpropanoate*

[00396] To a cooled (–78 °C) solution of methyl 2-phenylacetate (5.0 g, 33.3 mmol, 1.0 eq) in dry THF (50 mL) was slowly added a solution of 2 M LDA (20 mL, 40.0 mmol, 1.2 eq) in THF. After 1 h, 2-bromoacetonitrile (4.2 g, 35.0 mmol, 1.1 eq) slowly in a dropwise manner and the reaction was further aged for additional 1 h at –78 °C. To the mixture was added saturated aqueous NH_4Cl (5 mL) and the mixture was warmed to room temperature. The mixture was with EtOAc (20 mL x 3). The organic layers were combined, washed with brine (150 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to methyl 3-cyano-2-phenylpropanoate (5.0 g, 26.5 mmol, 79 %) as a white solid. LCMS (ESI) m/z = 190.1 $[M+H]^+$.

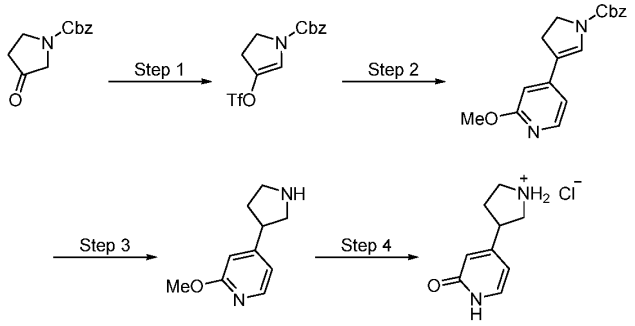
[00397] *Step 2: Preparation of 6-phenyl-4-azaspiro[2.4]heptan-5-one*

[00398] To a cooled (0 °C) solution of methyl 3-cyano-2-phenylpropanoate (5.0 g, 26.5 mmol, 1.0 eq) and $Ti(OiPr)_4$ (9.0 g, 31.7 mmol, 1.2 eq) in dry THF (100 mL) was slowly added a 3 M solution of EtMgBr (20 mL, 59.6 mmol, 2.25 eq), while maintaining inner temperature between -5 °C to 0 °C. After complete addition of EtMgBr, the mixture was stirred at 0 °C for additional 1 h. The reaction mixture was quenched by addition of aqueous 2 N HCl (60 mL). The resulting acidic solution was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (20 mL x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on to afford 6-phenyl-4-azaspiro[2.4]heptan-5-one (2.1 g, 11.2 mmol, 42% yield) as a white solid. LCMS (ESI) m/z = 188 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.24 (m, 6H), 3.86 (dd, J = 9.4, 7.6 Hz, 1H), 2.51 (dd, J = 12.9, 9.4 Hz, 1H), 2.29 (dd, J = 12.9, 7.6 Hz, 1H), 0.85 – 0.88 (m, 1H), 0.87 – 0.81 (m, 1H), 0.76 – 0.64 (m, 2H).

[00399] *Step 3: Preparation of 6-phenyl-4-azaspiro[2.4]heptane*

[00400] To a cooled (10 °C) solution of 6-phenyl-4-azaspiro[2.4]heptan-5-one (2.1 g, 11.2 mmol, 1.0 eq) in dry THF (50 mL) was added $NaBH_4$ (2.1 g, 56.0 mmol, 5.0 eq) in several portions. To the mixture was added in a dropwise manner $BF_3 \cdot Et_2O$ (6.7 mL, 56.0 mmol, 5.0 eq). The reaction mixture was heated at 60 °C for 16 h. The mixture was cooled to ambient temperature and aqueous 2 N HCl (30 mL) was introduced slowly. The acidic mixture was extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Biotage® C18 column to afford 6-phenyl-4-azaspiro[2.4]heptane (1.5 g, 8.7 mmol, 78 %) as a colorless oil. LCMS (ESI) m/z = 174 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) 8.59 (s, 1H), δ 7.38 – 7.27 (m, 5H), 3.85 – 3.57 (m, 2H), 3.40 – 3.17 (m, 1H), 2.43 – 2.09 (m, 2H), 1.46 – 1.18 (m, 2H), 0.98 – 0.66 (m, 2H).

Synthesis of 3-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidin-1-ium chloride



[00401] *Step 1: Preparation of benzyl 4-(((trifluoromethyl)sulfonyl)oxy)-2,3-dihydro-1H-pyrrole-1-carboxylate*

[00402] To a cooled (–78 °C) solution of benzyl 3-oxopyrrolidine-1-carboxylate (5.0 g, 22.8 mmol, 1 eq) in dry THF (80 mL) was slowly added a solution of LDA (25.0 mmol, 1.1 eq) in THF. The mixture was stirred for additional 30 min, followed by addition of a solution of 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (8.93 g, 25.0 mmol, 1.1 eq) in THF (70 mL) . After complete addition of 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide, the reaction mixture was allowed to warm to room temperature and stirred for 14 h. The reaction mixture was quenched by adding H_2O (20 mL) and extracted with EtOAc (150 mL x 3). The organic layers were combined, washed with brine (150 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford benzyl 4-(((trifluoromethyl)sulfonyl)oxy)-2,3-dihydro-1H-pyrrole-1-carboxylate (3.00 g, 8.53 mmol, 37.5% yield) as a yellow oil. LCMS (ESI) *m/z* = 352 $[M+H]^+$.

[00403] *Step 2: Preparation of benzyl 4-(2-methoxypyridin-4-yl)-2,3-dihydro-1H-pyrrole-1-carboxylate*

[00404] A solution of benzyl 4-(((trifluoromethyl)sulfonyl)oxy)-2,3-dihydro-1H-pyrrole-1-carboxylate (3.0 g, 8.53 mmol, 1.0 eq), (2-methoxypyridin-4-yl)boronic acid (1.55 g, 10.2 mmol, 1.2 eq), and K_2CO_3 (2.94 g, 21.3 mmol, 2.5 eq) in a mixture of toluene (60.0 mL), EtOH (15.0 mL) and H_2O (15.0 mL) was added $Pd(PPh_3)_4$ (492 mg, 426 μmol, 0.05 eq). The reaction mixture was subsequently heated at 100 °C under N_2 (g) for 12 h. The reaction mixture was cooled to room temperature, diluted with H_2O (40 mL), and extracted with EtOAc (100 mL x 3). The organic layers were combined, washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford benzyl 4-(2-methoxypyridin-4-yl)-2,3-dihydro-1H-pyrrole-1-carboxylate (750 mg, 2.41 mmol, 28.4% yield) as a white solid. LCMS (ESI) m/z = 311 $[M+H]^+$.

[00405] *Step 3: Preparation of 2-methoxy-4-(pyrrolidin-3-yl)pyridine*

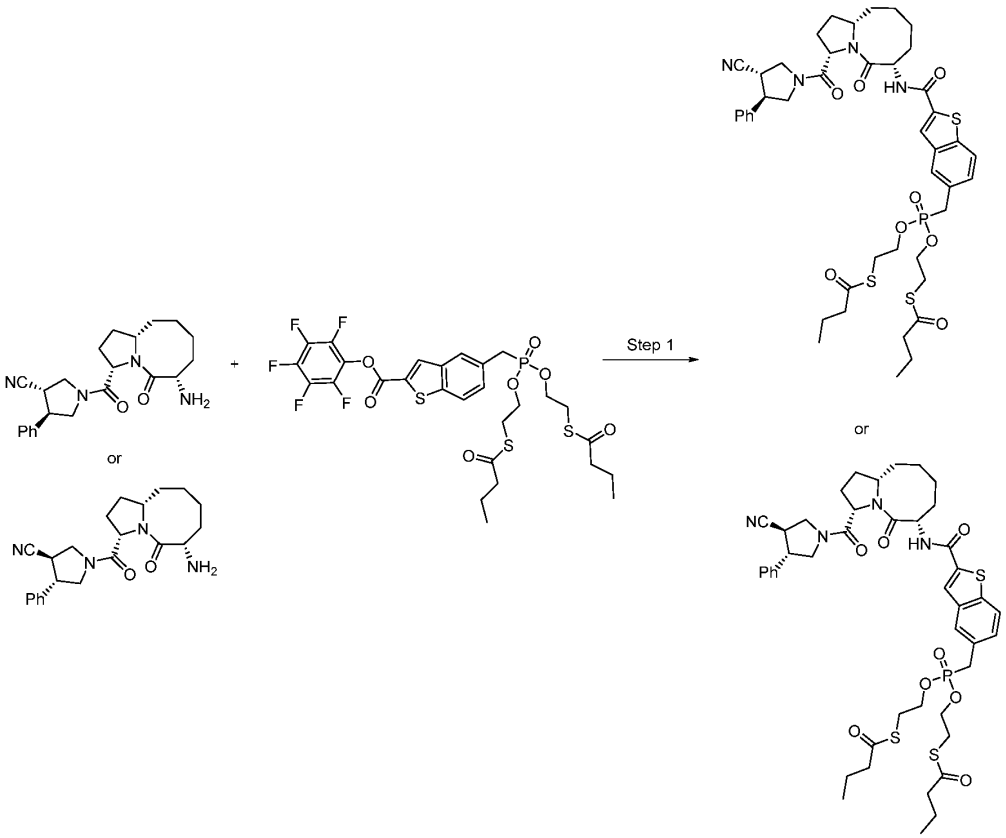
[00406] To a solution of benzyl 4-(2-methoxypyridin-4-yl)-2,3-dihydro-1H-pyrrole-1-carboxylate (750 mg, 2.41 mmol, 1 eq) in MeOH (50 mL) under N_2 (g) was added 10% Pd/C (100 mg). The suspension was subjected to three cycles to evacuation and purging with H_2 (g). The resulting mixture was stirred at room temperature for 14 h under H_2 (g) (1 atm). The reaction mixture was subsequently subjected to three cycles to evacuation and purging with N_2 (g) and the suspension was filtered through a pad of Celite®. The filter cake was carefully washed with MeOH (20 mL) and the combined filtrate was concentrated to dryness to give 2-methoxy-4-(pyrrolidin-3-yl)pyridine (375 mg, 2.10 mmol, 87.4% yield) as off white solid. LCMS (ESI) m/z = 179 $[M+H]^+$.

[00407] *Step 4: Preparation of 3-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidin-1-ium chloride*

[00408] A solution of 2-methoxy-4-(pyrrolidin-3-yl)pyridine (375 mg, 2.10 mmol, 1 eq) in a solution of 1 N HCl (4 mL) 1,4-dioxane was heated and stirred at 100 °C in a sealed tube. After 24 h, the reaction mixture was concentrated under reduced pressure to afford 3-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidin-1-ium chloride (400 mg, HCl salt) as a white solid, which was used directly without further purification. LCMS (ESI) m/z = 165 $[M+H]^+$.

[00409] Representative Procedure for Direct Coupling of Perfluorophenyl or p-Nitrophenyl Activated Linker Esters with Amino Acid Cores for Construction of Analogues

S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl) bis(oxy)) bis(ethane-2,1-diyl)) dibutanethioate (125)



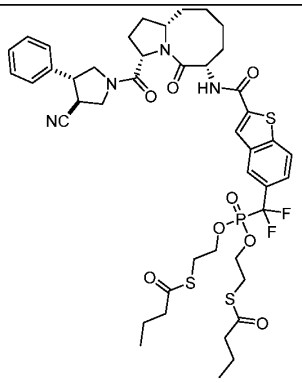
[00410] *Step 1: Preparation of S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl) bis(oxy)) bis(ethane-2,1-diyl)) dibutanethioate*

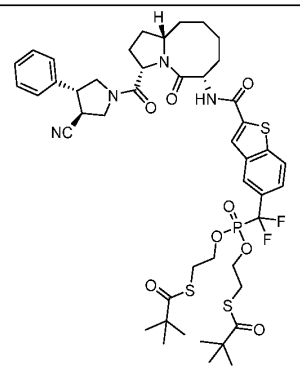
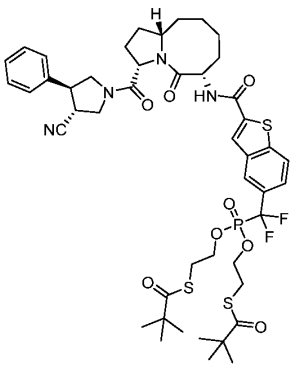
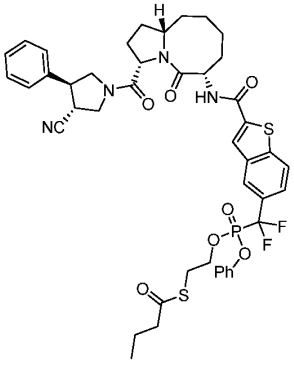
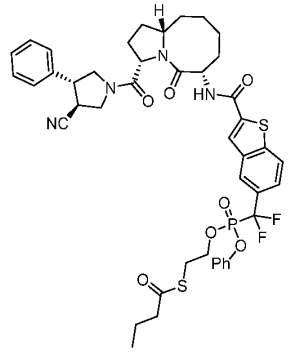
[00411] To a solution of perfluorophenyl 5-((bis(2-(butyrylthio)ethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (30 mg, 42.9 μmol, 1.0 eq) and (3S,4R or 3R,4S)-1-((3S,6S,10aS)-6-amino-5-oxodecahydropyrrolo[1,2-a]azocine-3-carbonyl)-4-phenylpyrrolidine-3-carbonitrile (16 mg, 42.0 μmol, 1.0 eq) (pyrrolidine SFC peak 2 used) in CH2Cl2 (2 mL) was added N,N-diisopropylethylamine (10.8 mg, 84 μmol, 2.0 eq) at room temperature. After stirring for 48 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase HPLC to give S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R, 4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-

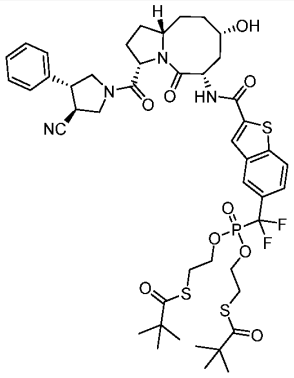
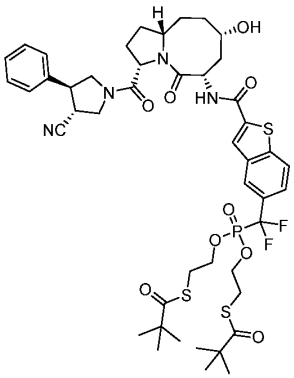
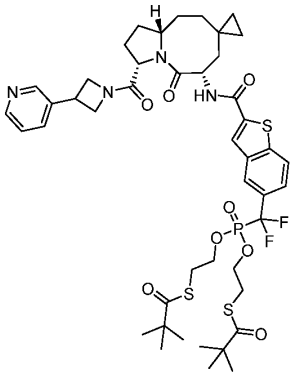
yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) dibutanethioate (35 mg, 39 μmol, 94% yield) as a white solid. LCMS (ESI) m/z =895 [M+H]+; 1H NMR (400 MHz, CDCl3) δ 7.86-7.71 (m, 3H), 7.45-7.29 (m, 6H), 7.22-7.13 (m, 1H), 5.19-5.08 (m, 1H), 4.60-4.49 (m, 1H), 4.39-4.23 (m, 2H), 4.11-3.93 (m, 6H), 3.81-3.60 (m, 2H), 3.28 (d, JHP = 21.2 Hz, 2H), 3.22-3.12 (m, 1H), 3.06 (t, J = 6.3 Hz, 4H), 2.52 (t, J = 7.4 Hz, 4H), 2.29-1.58 (m, 16H), 0.94 (t, J= 8.0 Hz, 6H).

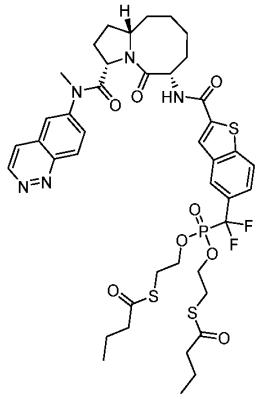
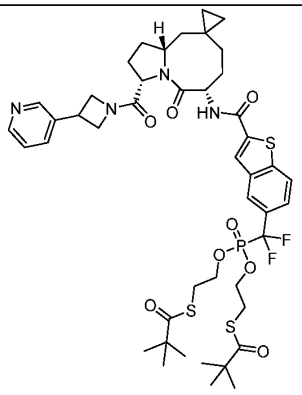
[00412] The following compounds in **Table 36** were prepared using the representative protocol described above for the synthesis S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) dibutanethioate and utilizing the appropriate starting materials and modifications.

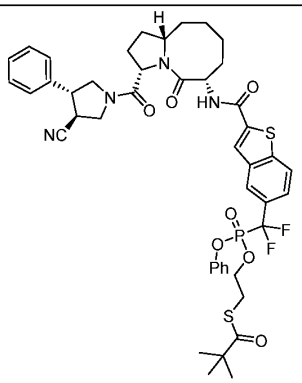
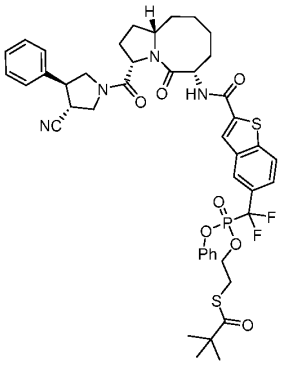
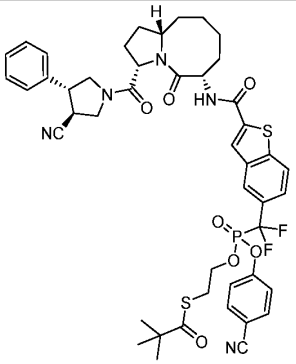
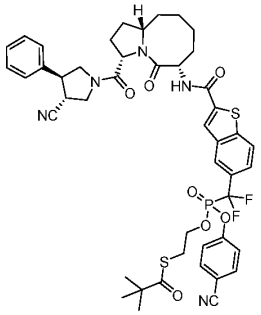
Table 36

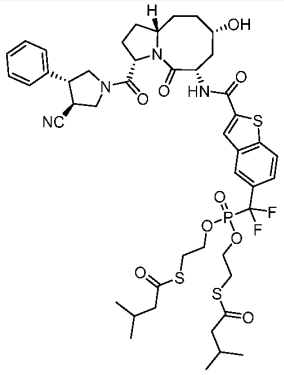
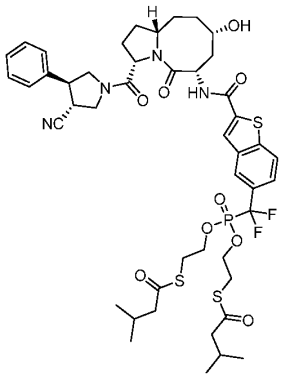
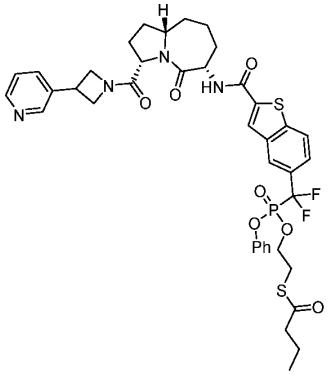
Compound	Name	Structure	LCMS	NMR
126	S,S'-(((((2-(((3S,6S,10aS)-3-(*rel*-trans)--3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) dibutanethioate		931.7 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.98 – 7.90 (m, 1H), 7.89 – 7.82 (m, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.44 – 7.29 (m, 5H), 7.25 – 7.21 (m, 1H), 5.21 – 5.05 (m, 1H), 4.61 – 4.49 (m, 1H), 4.38 – 4.11 (m, 6H), 4.10 – 3.96 (m, 1H), 3.92 – 3.04 (m, 8H), 2.53 (t, J = 7.4 Hz, 4H), 2.31 – 1.76 (m, 10H), 1.74 – 1.65 (m, 4H), 1.44 – 1.23 (m, 2H), 0.94 (t, J = 7.4 Hz, 6H)

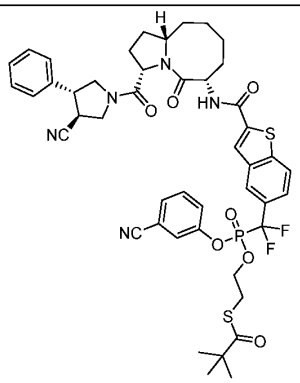
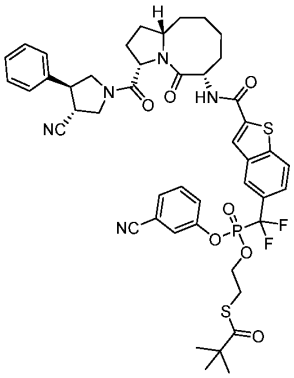
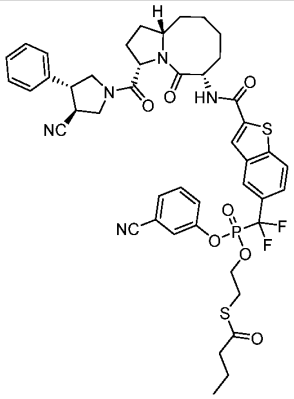
127	S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2,2-dimethylpropanethioate)	 or  SFC peak 2 was used for biological testing	959.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.20 (d, J = 2.9 Hz, 1H), 8.18 – 8.14 (m, 1H), 8.08 (t, J = 9.2 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.44 – 7.28 (m, 5H), 5.09 – 5.00 (m, 1H), 4.74 – 4.65 (m, 1H), 4.60 – 4.50 (m, 0.5H), 4.50 – 4.38 (m, 1.5H), 4.30 – 4.13 (m, 4H), 4.06 (dd, J = 11.5, 8.1 Hz, 0.5H), 3.96 (dd, J = 11.6, 7.5 Hz, 0.5H), 3.85 (t, J = 9.8 Hz, 0.5H), 3.79 – 3.64 (m, 1.5H), 3.64 – 3.50 (m, 2H), 3.20 – 3.08 (m, 4H), 2.41 – 2.18 (m, 2H), 2.11 – 1.93 (m, 6H), 1.92 – 1.75 (m, 2H), 1.75 – 1.57 (m, 2H), 1.20 (s, 18H)
128	S-(2-((((2-(((3S,6S,10aS)-3-((3R,4S or 3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(phenoxy)phosphoryl)oxy)ethyl) butanethioate	 or 	877.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.22 – 8.17 (m, 2H), 8.14 – 8.07 (m, 1H), 7.72 – 7.67 (m, 1H), 7.47 – 7.27 (m, 7H), 7.27 – 7.20 (m, 1H), 7.15 (d, J = 7.6 Hz, 2H), 5.09 – 5.00 (m, 1H), 4.69 – 4.60 (m, 1H), 4.50 – 4.39 (m, 1H), 4.35 – 4.15 (m, 3H), 4.15 – 4.06 (m, 1H), 3.92 (t, J = 10.3 Hz, 0.5H), 3.84 – 3.75 (m, 0.5H), 3.68 – 3.59 (m, 1H), 3.52 – 3.38 (m, 1H), 3.17 – 3.10 (m, 2H), 2.52 – 2.45 (m, 2H), 2.42 – 2.18 (m, 2H), 2.13 – 1.93 (m, 6H), 1.92 – 1.76 (m, 2H), 1.75 – 1.55 (m, 4H), 1.46 – 1.40 (m, 1H), 0.94 – 0.86 (m, 3H)

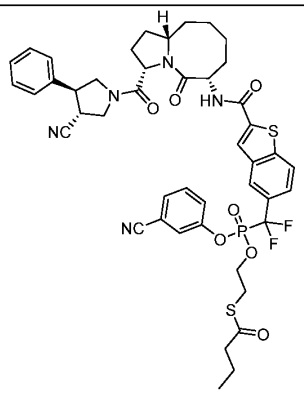
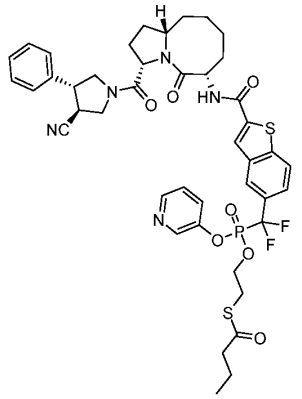
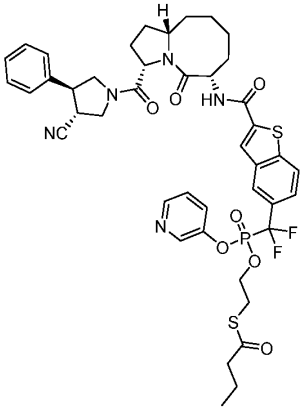
		SFC peak 1 was used for biological testing		
129	S,S'-(((((2-(((3S,6S,8S,10aR)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-8-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2,2-dimethylpropanethioate)	 or  SFC peak 2 was used for biological testing	975.2 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.20 – 8.18 (m, 2H), 8.12 – 8.06 (m, 1H), 7.67 – 7.65 (m, 1H), 7.42 – 7.28 (m, 5H), 4.99 – 4.96 (m, 1H), 4.73 – 4.64 (m, 1H), 4.53 – 4.33 (m, 2H), 4.29 – 4.13 (m, 4H), 4.10 – 3.93 (m, 2H), 3.88 – 3.51 (m, 4H), 3.20 – 3.07 (m, 4H), 2.45 – 2.18 (m, 4H), 2.17 – 1.73 (m, 6H), 1.20 (s, 18H)
130	S,S'-((((difluoro(2-(((3'S,6'S,10a'S)-5'-oxo-3'-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-5'H-spiro[cyclopropane-1,8'-pyrrolo[1,2-a]azocin]-6'-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl))		947.2 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.64 – 8.59 (m, 0.6H), 8.56 – 8.51 (m, 0.4H), 8.49 – 8.42 (m, 1H), 8.17 (s, 2H), 8.12 – 8.02 (m, 1.6H), 7.98 – 7.92 (m, 0.4H), 7.69 – 7.62 (m, 1H), 7.51 – 7.41 (m, 1H), 5.08 – 4.97 (m, 1.6H), 4.70 (d, J = 8.1 Hz, 1H), 4.61 – 4.45 (m, 2.4H), 4.42 (t, J = 9.4 Hz, 0.6H), 4.34 – 4.12 (m, 4.4H), 4.11 – 3.94 (m, 2H), 3.20 – 3.07 (m, 4H), 2.32 – 2.16 (m, 2H), 2.15 – 2.03 (m, 1H), 2.02 – 1.83 (m, 4H), 1.78 – 1.57 (m, 3H), 1.19 (d, J = 5.9 Hz, 18H), 0.65 – 0.45 (m, 4H)

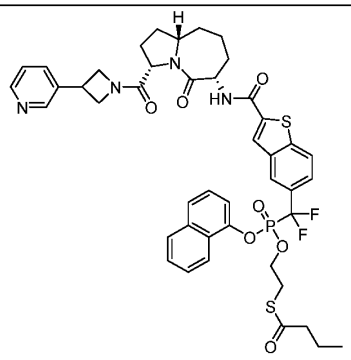
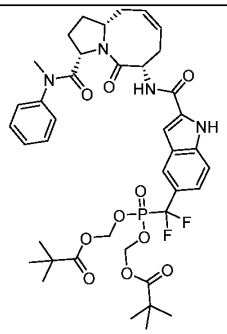
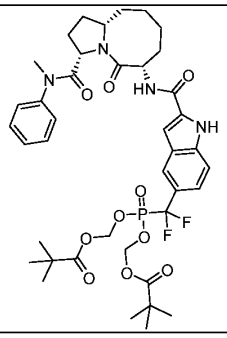
	bis(2,2-dimethylpropanethioate)			
131	S,S'-(((((2-(((3S,6S,10aS)-3-(cinnolin-6-yl(methyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl))dibutanethioate		918.1 [M+H]$^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 9.25 (d, J = 5.9 Hz, 1H), 8.49 (d, J = 9.0 Hz, 1H), 8.15 – 8.00 (m, 6H), 7.62 (d, J = 8.6 Hz, 1H), 5.04 – 4.98 (m, 1H), 4.61 – 4.33 (m, 2H), 4.32 – 4.16 (m, 4H), 3.48 – 3.38 (m, 3H), 3.24 – 3.13 (m, 4H), 2.56 – 2.52 (m, 4H), 2.20 – 1.97 (m, 8H), 1.88 – 1.75 (m, 2H), 1.70 – 1.58 (m, 6H), 0.92 – 0.90 (m, 6H)
132	S,S'-((((difluoro(2-(((3'S,6'S,10a'R)-5'-oxo-3'-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1'H-spiro[cyclopropane-1,9'-pyrrolo[1,2-a]azocin]-6'-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl))bis(2,2-dimethylpropanethioate)		947.2 [M+H]$^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.61 – 8.52 (m, 1H), 8.50 – 8.40 (m, 1H), 8.25 – 8.20 (m, 1H), 8.19 – 8.15 (m, 1H), 8.14 – 7.91 (m, 2H), 7.70 – 7.61 (m, 1H), 7.52 – 7.39 (m, 1H), 5.23 – 5.14 (m, 1H), 5.02 – 4.97 and 4.73 – 4.39 (m, 5H), 4.33 – 4.14 (m, 4H), 4.10 – 3.95 (m, 2H), 3.23 – 3.03 (m, 4H), 2.72 – 2.49 (m, 2H), 2.38 – 2.15 (m, 2H), 2.13 – 1.98 (m, 1H), 1.97 – 1.71 (m, 3H), 1.37 – 1.25 (m, 1H), 1.23 – 1.14 (m, 18H), 0.82 – 0.74 (m, 1H), 0.73 – 0.65 (m, 1H), 0.60 – 0.47 (m, 2H), 0.44 – 0.33 (m, 1H)

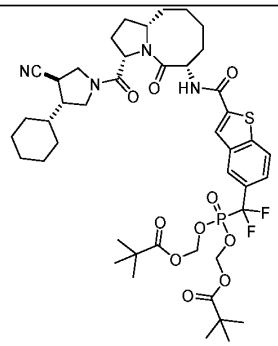
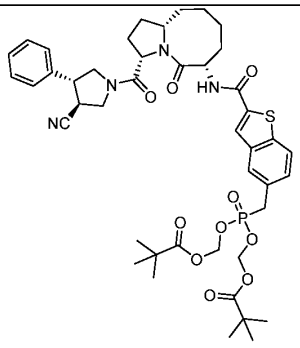
133	S-(2-((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(phenoxy)phosphoryl)oxy)ethyl) 2,2-dimethylpropanethioate	 or  SFC peak 2 was used for biological testing	891.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.22 – 8.18 (m, 2H), 8.11 – 8.07 (m, 1H), 7.71 – 7.68 (m, 1H), 7.42 – 7.31 (m, 7H), 7.26 – 7.13 (m, 3H), 5.08 – 5.00 (m, 1H), 4.73 – 4.65 (m, 1H), 4.56 – 4.39 (m, 2H), 4.34 – 4.19 (m, 2H), 4.10 – 3.93 (m, 1H), 3.88 – 3.50 (m, 4H), 3.11 – 3.08 (m, 2H), 2.41 – 2.18 (m, 2H), 2.11 – 1.94 (m, 6H), 1.92 – 1.77 (m, 2H), 1.73 – 1.59 (m, 2H), 1.16 (s, 9H)
134	S-(2-((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(4-cyanophenoxy)phosphoryl)oxy)ethyl) 2,2-dimethylpropanethioate	 or 	916.2 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.21 – 8.17 (m, 2H), 8.13 – 8.08 (m, 1H), 7.76 (d, J = 8.6 Hz, 2H), 7.70 – 7.66 (m, 1H), 7.45 – 7.35 (m, 7H), 5.07 – 5.01 (m, 1H), 4.72 – 4.66 (m, 1H), 4.56 – 4.38 (m, 2H), 4.37 – 4.26 (m, 2H), 4.10 – 3.93 (m, 1H), 3.73 – 3.46 (m, 4H), 3.16 – 3.09 (m, 2H), 2.40 – 2.19 (m, 2H), 2.08 – 1.93 (m, 6H), 1.91 – 1.79 (m, 2H), 1.74 – 1.62 (m, 2H), 1.15 (s, 9H)

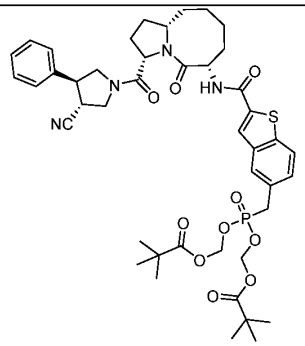
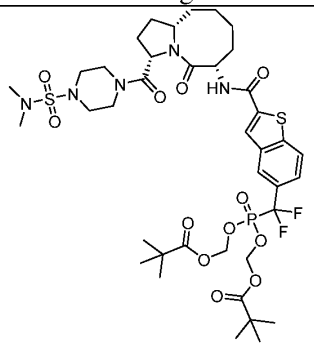
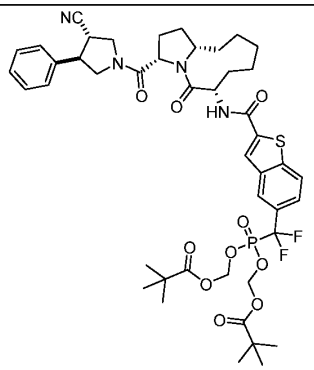
		SFC peak 2 was used for biological testing		
135	S,S'-(((((2-(((3S,6S,8S,10aR)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-8-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methylbutanethioate)	 or  SFC peak 2 was used for biological testing	975.0 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.20 – 8.17 (m, 2H), 8.11 – 8.08 (m, 1H), 7.66 – 7.64 (m, 1H), 7.44 – 7.29 (m, 5H), 4.99 – 4.96 (m, 1H), 4.73 – 4.64 (m, 1H), 4.61 – 4.35 (m, 2H), 4.30 – 4.15 (m, 4H), 4.11 – 3.94 (m, 2H), 3.88 – 3.50 (m, 4H), 3.20 – 3.13 (m, 4H), 2.45 – 2.41 (m, 4H), 2.40 – 2.15 (m, 4H), 2.14 – 1.84 (m, 7H), 1.83 – 1.74 (m, 1H), 0.94 – 0.91 (m, 12H)
136	S-(2-(((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)oxy)ethyl) butanethioate		825.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.59 – 5.54 (m, 1H), 8.47 – 8.41 (m, 1H), 8.25 – 8.17 (m, 2H), 8.13 – 7.93 (m, 2H), 7.70 (d, J = 8.6 Hz, 1H), 7.50 – 7.32 (m, 3H), 7.27 – 7.20 (m, 1H), 7.16 – 7.14 (m, 2H), 4.79 – 4.75 (m, 1H), 4.73 – 4.67 (m, 1H), 4.62 – 4.50 (m, 2H), 4.49 – 4.36 (m, 1H), 4.34 – 4.23 (m, 2H), 4.11 – 3.97 (m, 3H), 3.14 (t, J = 6.2 Hz, 2H), 2.53 – 2.44 (m, 2H), 2.37 – 2.26 (m, 1H), 2.20 – 2.06 (m, 2H), 2.05 – 1.81 (m, 7H), 1.67 – 1.54 (m, 2H), 0.93 – 0.86 (m, 3H)

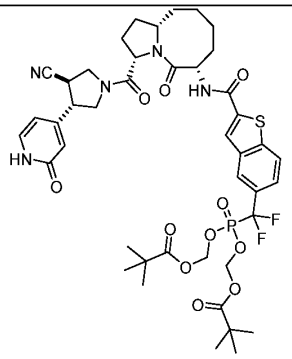
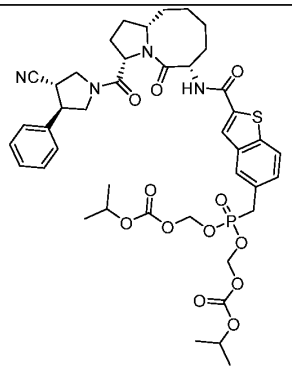
137	S-(2-((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(3-cyanophenoxy)phosphoryl)oxy)ethyl) 2,2-dimethylpropanethioate	 or  SFC peak 2 was used for biological testing	916.0 $[M+H]^+$	^{1}H NMR (400 MHz, CD_3CN) δ 8.20 – 8.13 (m, 1H), 8.07 – 7.94 (m, 2H), 7.79 – 7.60 (m, 2H), 7.60 – 7.55 (m, 1H), 7.54 – 7.43 (m, 3H), 7.42 – 7.28 (m, 5H), 5.08 – 4.99 (m, 1H), 4.61 – 4.57 (m, 1H), 4.40 – 4.19 (m, 4H), 4.10 – 3.92 (m, 1H), 3.82 – 3.32 (m, 4H), 3.16 – 3.04 (m, 2H), 2.35 – 2.20 (m, 1H), 2.13 – 1.96 (m, 5H), 1.89 – 1.60 (m, 6H), 1.15 (s, 9H)
138	S-(2-((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(3-cyanophenoxy)phosphoryl)oxy)ethyl) butanethioate	 or	902.1 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.23 – 8.18 (m, 2H), 8.12 – 8.07 (m, 1H), 7.72 – 7.65 (m, 1H), 7.63 – 7.46 (m, 4H), 7.42 – 7.27 (m, 5H), 5.05 – 5.00 (m, 1H), 4.73 – 4.65 (m, 1H), 4.63 – 4.24 (m, 5H), 4.10 – 3.83 (m, 1H), 3.77 – 3.66 (m, 1H), 3.63 – 3.48 (m, 2H), 3.22 – 3.10 (m, 2H), 2.50 (t, J = 7.3 Hz, 2H), 2.39 – 2.19 (m, 2H), 2.10 – 1.94 (m, 6H), 1.92 – 1.76 (m, 2H), 1.74 – 1.54 (m, 4H), 0.90 (t, J = 7.3 Hz, 3H)

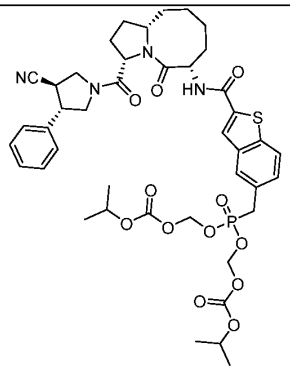
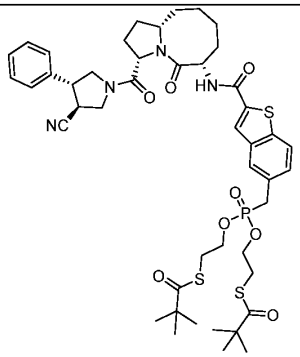
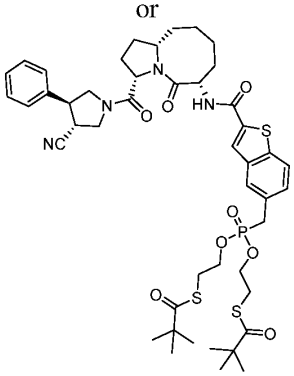
		 SFC peak 2 was used for biological testing		
139	S-(2-((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(pyridin-3-yloxy)phosphoryl)oxy)ethyl) butanethioate	 or  SFC peak 2 was used for biological testing	878.1 $[M+H]^+$	^{1}H NMR (400 MHz, acetonitrile-d_3) δ 8.46 – 8.41 (m, 2H), 8.22 – 8.15 (m, 1H), 8.10 – 8.02 (m, 1H), 8.00 (s, 1H), 7.75 – 7.60 (m, 2H), 7.60 – 7.52 (m, 1H), 7.45 – 7.26 (m, 6H), 5.09 – 4.98 (m, 1H), 4.66 – 4.49 (m, 1H), 4.42 – 4.18 (m, 4H), 4.12 – 3.95 (m, 1H), 3.85 – 3.32 (m, 4H), 3.13 (t, J = 6.2 Hz, 2H), 2.49 (t, J = 7.3 Hz, 2H), 2.38 – 2.21 (m, 1H), 2.12 – 1.96 (m, 5H), 1.84 – 1.51 (m, 8H), 0.88 (t, J = 7.3 Hz, 3H)

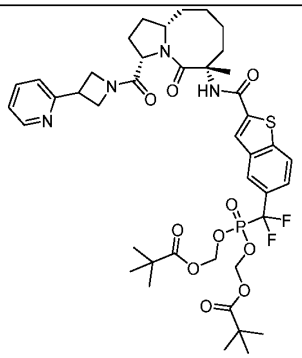
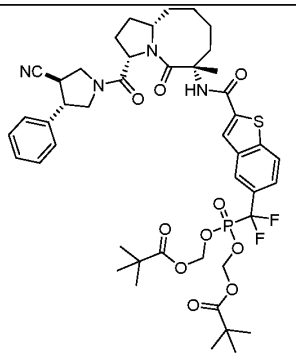
140	S-(2-(((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(naphthalen-1-yloxy)phosphoryl)oxy)ethyl) butanethioate		875.0 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.57 – 8.52 (m, 1H), 8.48 – 8.36 (m, 1H), 8.25 – 8.20 (m, 1H), 8.14 – 8.08 (m, 2H), 8.06 – 7.93 (m, 1H), 7.91 – 7.88 (m, 1H), 7.83 – 7.81 (m, 1H), 7.77 – 7.71 (m, 2H), 7.57 – 7.50 (m, 1H), 7.49 – 7.33 (m, 4H), 4.97 – 4.88 (m, 1H), 4.78 – 4.67 (m, 1H), 4.62 – 4.37 (m, 3H), 4.34 – 4.24 (m, 2H), 4.11 – 3.95 (m, 3H), 3.08 (t, J = 5.9 Hz, 2H), 2.43 – 2.37 (m, 2H), 2.35 – 2.26 (m, 1H), 2.17 – 1.78 (m, 9H), 1.60 – 1.48 (m, 2H), 0.90 – 0.82 (m, 3H)
141	(((difluoro(2-(((3S,6S,10aR,Z)-3-(methyl(phenyl)carbamoyl)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)-1H-indol-5-yl)methyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		815.0 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.68 (s, 1H), 7.75 (s, 1H), 7.40 – 7.22 (m, 6H), 7.16 (d, J = 8.6 Hz, 1H), 6.91 (s, 1H), 6.03 – 5.90 (m, 2H), 5.82 – 5.63 (m, 4H), 5.25 – 5.15 (m, 1H), 4.53 – 4.46 (m, 1H), 4.30 – 4.20 (m, 1H), 3.27 (s, 3H), 2.82 – 2.57 (m, 4H), 2.30 – 2.02 (m, 2H), 2.01 – 1.89 (m, 2H), 1.22 (d, J = 2.7 Hz, 18H)
142	(((difluoro(2-(((3S,6S,10aS)-3-(methyl(phenyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl		816.8 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 – 9.18 (m, 1H), 8.19 – 7.62 (m, 2H), 7.55 – 7.05 (m, 7H), 6.85 – 6.95 (m, 1H), 5.80 – 5.60 (m, 4H), 5.13 – 5.01 (m, 1H), 4.42 – 4.35 (m, 1H), 4.31 – 4.17 (m, 1H), 3.30 (d, J = 5.8 Hz, 3H),

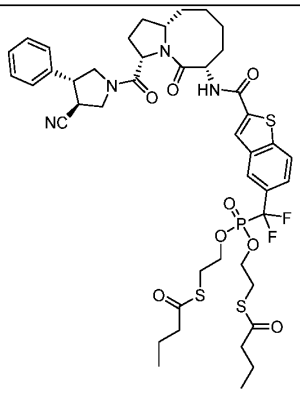
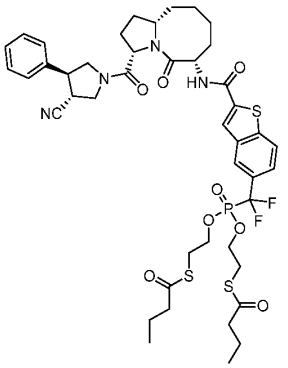
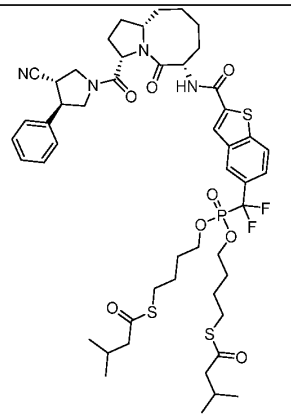
	)-1H-indol-5-yl)methyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)			2.22 – 1.71 (m, 12H), 1.22 (s, 18H)
143	((((2-(((3S,6S,10aS)-3-(*rel*-(trans)-3-cyano-4-cyclohexylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		905.3 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 – 9.18 (m, 1H), 8.19 – 7.62 (m, 2H), 7.55 – 7.05 (m, 7H), 6.85 – 6.95 (m, 1H), 5.80 – 5.60 (m, 4H), 5.13 – 5.01 (m, 1H), 4.42 – 4.35 (m, 1H), 4.31 – 4.17 (m, 1H), 3.30 (d, J = 5.8 Hz, 3H), 2.22 – 1.71 (m, 12H), 1.22 (s, 18H)
144	((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)	 or	863.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 – 7.61 (m, 3H), 7.33 – 7.27 (m, 8.0 Hz, 6H), 7.13 – 7.09 (m, 1H), 5.65 – 5.50 (m, 4H), 5.12 – 5.01 (m, 1H), 4.54 – 4.45 (m, 1H), 4.30 – 4.22 (m, 2H), 4.06 – 3.92 (m, 2H), 3.71- 3.56 (m, 2H), 3.30 - 3.25 (m, 2H), 3.17 – 3.05 (m, 1H), 2.12 (d, J = 17.9 Hz, 4H), 1.83 – 1.54 (m, 6H), 1.49 (d, J = 6.5 Hz, 1H), 1.42 (d, J = 6.6 Hz, 1H), 1.11 (s, 18H)

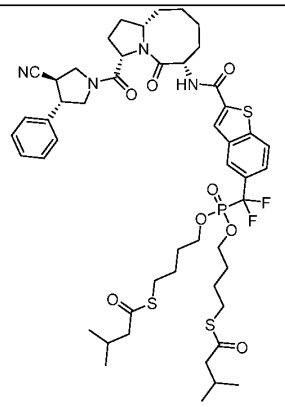
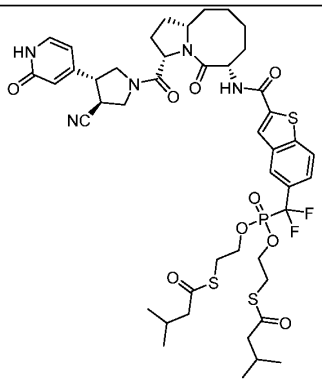
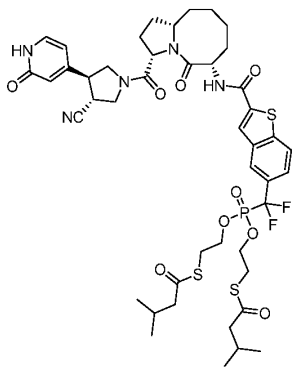
		 SFC peak 2 was used for synthesis and biological testing		
145	((((2-(((3S,6S,10aS)-3-(4-(N,N-dimethylsulfamoyl)piperazine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		920.3 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.77 (s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 5.68 – 5.55 (s, 4H), 5.13 – 5.01 (m, 1H), 4.79 – 4.68 (m, 1H), 4.33 – 4.20 (m, 1H), 3.86 – 3.48 (m, 4H), 3.41 – 3.13 (m, 4H), 2.78 (s, 6H), 2.16 – 1.89 (m, 8H), 1.80 – 1.71 (m, 2H), 1.63 – 1.55 (m, 2H), 1.13 (s, 18H)
146	((((2-(((3S,6S,11aS)-3-(*rel*-(trans)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydro-1H-pyrrolo[1,2-a]azonin-6-yl)carbamoyl)benzo[b]thiophen-5-		913.3 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.03 (m, 1H), 7.98 – 7.88 (m, 1H), 7.87 – 7.77 (m, 1H), 7.67 – 7.59 (m, 1H), 7.44 – 7.28 (m, 5H), 7.02 – 6.80 (m, 1H), 5.77 – 5.69 (m, 2H), 5.69 – 5.61 (m, 2H), 5.38 – 5.25 (m, 1H), 4.66 – 4.57 (m, 1H), 4.32 – 4.22 (m, 1H), 4.09 – 3.96 (m, 1H), 3.85 – 3.51 (m, 2H), 3.36 – 3.08 (m, 1H), 2.28 – 2.08 (m, 5H), 2.03 – 1.87 (m, 4H), 1.87 –

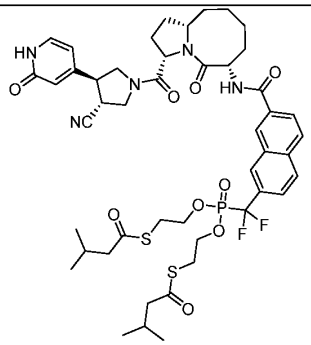
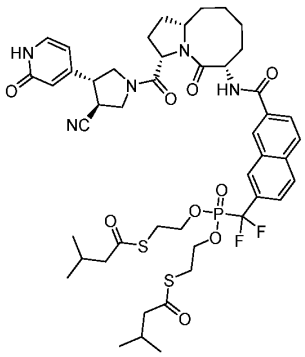
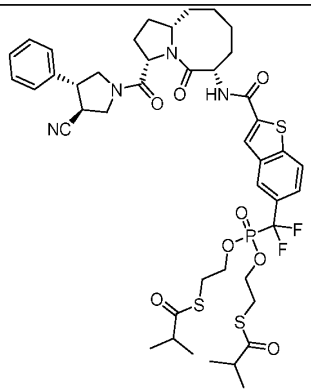
	yl)difluorom ethyl)phosph oryl)bis(oxy))bis(methyle ne) bis(2,2-dimethylprop anoate)			1.82 (m, 2H), 1.79 – 1.73 (m, 2H), 1.70 – 1.55 (m, 3H), 1.20 (s, 18H)
147	((((2-(((3S,6S,10a S)-3-(*rel*-trans) -3-cyano-4-(2-oxo-1,2-dihydropyrid in-4-yl)pyrrolidin e-1-carbonyl)-5-oxodecahydr opyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thio phen-5-yl)difluorom ethyl)phosph oryl)bis(oxy))bis(methyle ne) bis(2,2-dimethylprop anoate)		916.3 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.02 (m, 1H), 8.01 – 7.79 (m, 2H), 7.69 – 7.53 (m, 1H), 7.44 – 7.29 (m, 1H), 6.74 – 6.42 (m, 1H), 6.22 (s, 1H), 5.81 – 5.58 (m, 4H), 5.26 – 5.04 (m, 1H), 4.65 – 4.47 (m, 1H), 4.42 – 4.26 (m, 1H), 4.23 – 4.02 (m, 1H), 4.01 – 3.73 (m, 2H), 3.71 – 3.39 (m, 2H), 3.38 – 3.09 (m, 1H), 2.29 – 2.06 (m, 5H), 2.03 – 1.83 (m, 4H), 1.82 – 1.73 (m, 1H), 1.72 – 1.57 (m, 2H), 1.19 (s, 18H)
148	((((2-(((3S,6S,10a S)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrroli dine-1-carbonyl)-5-oxodecahydr opyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thio phen-5-yl)methyl)ph osphoryl)bis(oxy))bis(met hylene) diisopropyl	 or	867.3 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.75 (m, 3H), 7.41 – 7.30 (m, 7H), 5.68 – 5.54 (m, 4H), 5.21 – 5.09 (m, 1H), 4.96 – 4.83 (m, 2H), 4.61 – 4.50 (m, 1H), 4.40 – 4.31 (m, 2H), 4.09 – 3.92 (m, 2H), 3.78 – 3.63 (m, 2H), 3.39 (d, J = 22.4 Hz, 2H), 3.33 – 3.23 (m, 1H), 2.30 – 1.59 (m, 12H), 1.30 (d, J = 6.0 Hz, 12H)

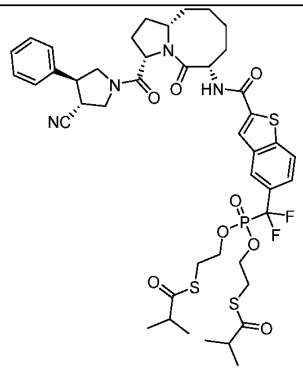
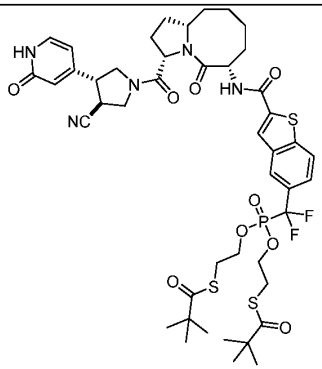
	bis(carbonate)	 SFC peak 2 was used for biological testing		
149	S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl))bis(2,2-dimethylpropanethioate)	 or  SFC peak 2 was used for biological testing	923.4 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.74 (m, 3H), 7.45 – 7.17 (m, 8H), 5.19 – 5.08 (m, 1H), 4.61 – 4.52 (m, 1H), 4.37 – 4.26 (m, 2H), 4.11 – 3.95 (m, 6H), 3.76 – 3.67 (m, 2H), 3.36 – 3.20 (m, 3H), 3.09 – 3.00 (m, 4H), 2.25 – 1.87 (m, 10H), 1.75 – 1.66 (m, 2H), 1.22 (s, 18H)

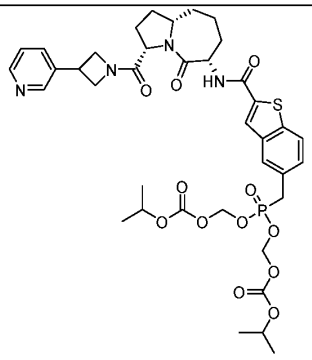
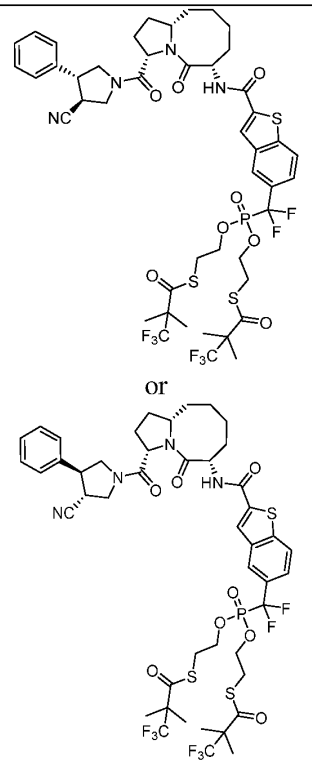
150	(((difluoro(2-(((3S,6S,10aS)-6-methyl-5-oxo-3-(3-(pyridin-2-yl)azetidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		875.0 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 – 8.47 (m, 1H), 8.23 – 7.96 (m, 2H), 7.87 (d, J = 8.5 Hz, 1H), 7.80 – 7.51 (m, 3H), 7.24 – 7.12 (m, 2H), 5.79 – 5.44 (m, 4H), 4.97 – 4.68 (m, 1H), 4.62 – 4.46 (m, 2H), 4.45 – 3.96 (m, 4H), 3.19 – 3.02 (m, 1H), 2.20 – 2.14 (m, 1H), 2.11 – 1.87 (m, 7H), 1.86 – 1.76 (m, 3H), 1.65 – 1.50 (m, 3H), 1.12 (s, 18H)
151	((((2-(((3S,6S,10aS)-3-(*rel*-trans)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-6-methyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		913.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 – 7.99 (m, 4H), 7.68 – 7.25 (m, 6H), 5.90 – 5.32 (m, 4H), 4.69 – 4.50 (m, 2H), 4.33 – 3.69 (m, 6H), 2.88 – 2.72 (m, 1H), 2.34 – 1.61 (m, 12H), 1.54 – 1.41(m, 2H), 1.20 – 1.06 m, 18H)

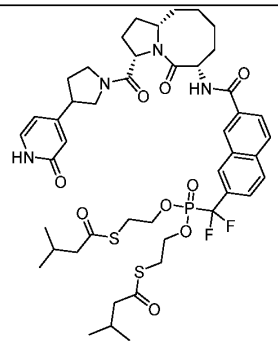
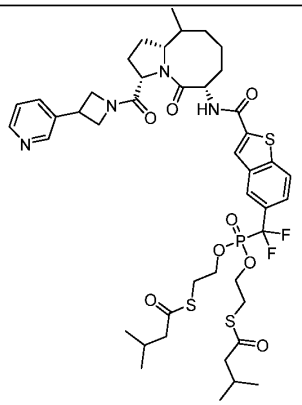
152	S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl))dibutanethioate	 or  SFC peak 2 was used for biological testing		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.01 (m, 1H), 7.97 – 7.77 (m, 2H), 7.69 – 7.56 (m, 1H), 7.46 – 7.27 (m, 5H), 5.18 – 5.06 (m, 1H), 4.63 – 4.50 (m, 1H), 4.39 – 3.95 (m, 8H), 3.81 – 3.45 (m, 2H), 3.36 – 3.05 (m, 5H), 2.53 (t, J = 7.4 Hz, 4H), 2.31 – 1.95 (m, 7H), 1.91 – 1.80 (m, 2H), 1.78 – 1.60 (m, 7H), 0.94 (t, J = 7.4 Hz, 6H)
153	S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(butane-4,1-diyl))bis(3-methylbutanethioate)	 or	1015.2 $[M+H]^+$	^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.10 – 8.04 (m, 1H), 7.96 – 7.90 (m, 1H), 7.87 and 7.84 (s, 1H), 7.66 – 7.60 (m, 1H), 7.44 – 7.21 (m, 6H), 5.18 – 5.06 (m, 1H), 4.61 – 4.50 (m, 1H), 4.38 – 4.23 (m, 2H), 4.21 – 3.95 (m, 6H), 3.80 – 3.45 (m, 2H), 3.45 – 3.12 (m, 1H), 2.85 (t, J = 7.1 Hz, 4H), 2.41 (d, J = 7.1 Hz, 4H), 2.28 – 1.92 (m, 8H), 1.90 – 1.56(m, 14H), 0.94 (d, J = 6.7 Hz, 12H)

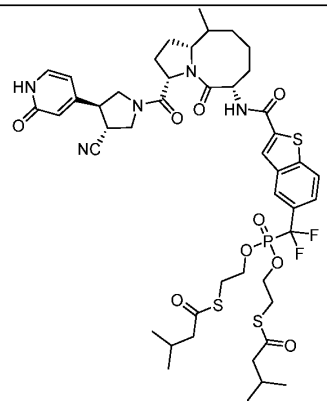
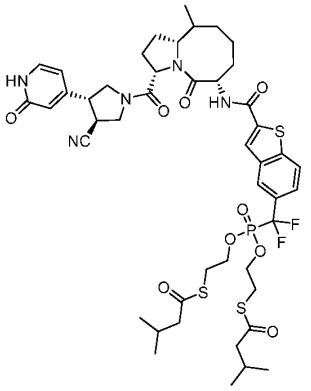
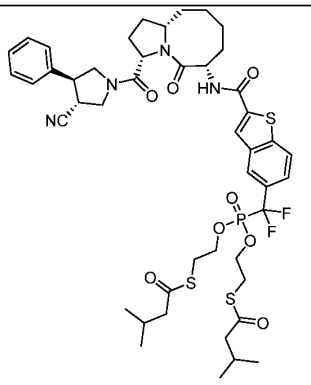
		 SFC peak was 2 used for biological testing		
154	S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methylbutanethioate)	 or  SFC peak 2 was used for biological testing	976.3 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 7.83 (m, 1H), 7.69 – 7.54 (m, 1H), 7.44 – 7.30 (m, 1H), 6.80 – 6.49 (m, 1H), 6.38 – 6.17 (m, 1H), 5.18 – 5.05 (m, 1H), 4.63 – 4.46 (m, 1H), 4.44 – 4.31 (m, 1H), 4.31 – 4.06 (m, 6H), 4.04 – 3.92 (m, 1H), 3.84 – 3.60 (m, 2H), 3.56 – 3.04 (m, 6H), 2.48 – 2.37 (m, 4H), 2.30 – 2.03 (m, 9H), 2.02 – 1.87 (m, 3H), 1.85 – 1.74 (m, 1H), 1.65 (dd, J = 12.0, 6.7 Hz, 1H), 1.03 – 0.87 (m, 12H)

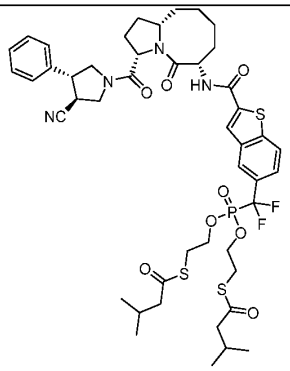
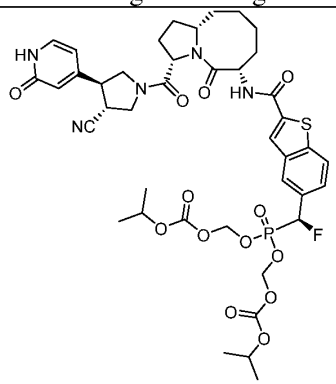
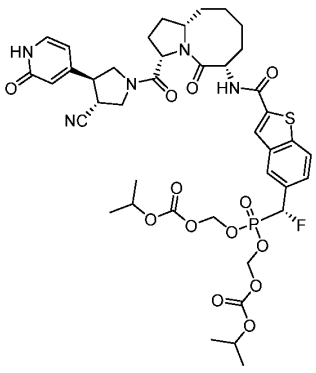
155	S,S'-(((((7-(((3S,6S,10aS)-3-((3R,4S or 3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methylbutanethioate)	 or  SFC peak 1 was used for biological testing	970.3 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 – 8.39 (m, 5H), 8.38 – 8.16 (m, 1H), 8.09 – 7.68 (m, 5H), 7.44 – 7.31 (m, 1H), 6.69 – 6.46 (m, 1H), 6.28 – 6.10 (m, 1H), 5.27 – 5.04 (m, 1H), 4.64 – 4.44 (m, 2H), 4.40 – 4.05 (m, 6H), 3.99 – 3.62 (m, 3H), 3.57 – 3.24 (m, 2H), 3.21 – 3.05 (m, 5H), 2.46 – 2.37 (m, 4H), 2.28 – 2.00 (m, 9H), 2.00 – 1.85 (m, 3H), 1.83 – 1.70 (m, 2H), 0.93 (d, J = 6.6 Hz, 12H)
156	S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2-	 or	931.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 – 8.85 (m, 1H), 8.35 (d, J = 11.4 Hz, 1H), 8.25 – 8.07 (m, 2H), 7.67 – 7.26 (m, 6H), 5.07 – 4.83 (m, 1H), 4.57 – 4.51 (m, 1H), 4.36 – 3.53 (m, 11H), 3.14 – 3.11 m, 4H), 2.77 – 2.67 (m, 2H), 2.28 – 1.51 (m, 12H), 1.18 – 0.95 (m, 12H)

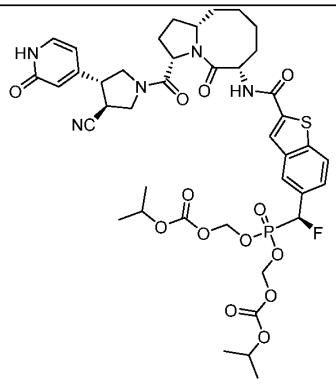
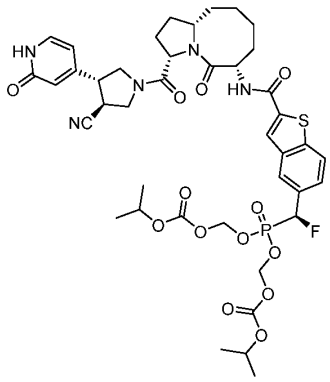
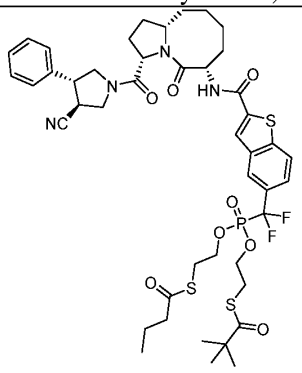
	methylpropanethioate)	 SFC peak 2 was used for biological testing		
157	S,S'-(((((2-(((3S,6S,10aS)-3-(*rel*-(trans)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2,2-dimethylpropanethioate)		976.3 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 7.81 (m, 4H), 7.79 – 7.55 (m, 1H), 7.49 – 7.29 (m, 1H), 6.76 – 6.40 (m, 1H), 6.35 – 6.14 (m, 1H), 5.22 – 5.03 (m, 1H), 4.67 – 4.28 (m, 3H), 4.28 – 3.84 (m, 6H), 3.84 – 3.25 (m, 3H), 3.23 – 2.98 (m, 1H), 2.34 – 1.84 (m, 9H), 1.83 – 1.61 (m, 3H), 1.22 (s, 18H)

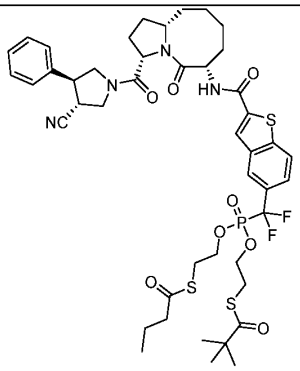
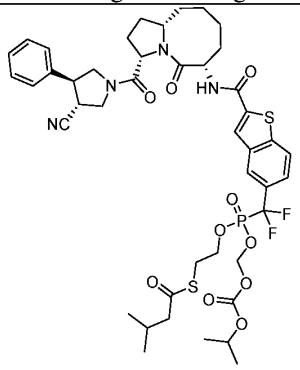
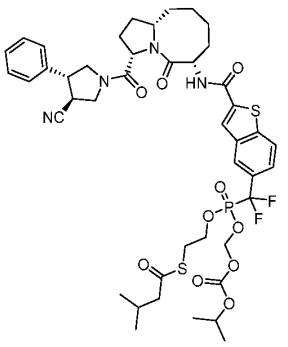
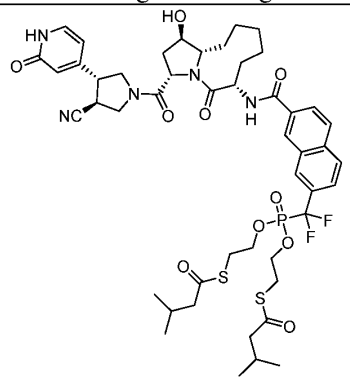
158	diisopropyl (((((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(methylene)) bis(carbonate)		814.9 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 8.83 – 8.45 (m, 2H), 7.99 – 7.34 (m, 7H), 5.64 – 5.59 (m, 4H), 5.05 – 3.92 (m, 10H), 3.53 – 3.30 (m, 2H), 2.41 – 2.07 (m, 6H), 1.98 – 1.69 (m, 4H), 1.30 (d, J = 5.3 Hz, 12H)
159	S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3,3,3-trifluoro-2,2-dimethylpropanethioate)	 or SFC peak was 2 used for biological testing	1067.3 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (m, 1H), 7.97 – 7.81 (m, 2H), 7.64 – 7.60 (m,1H), 7.42 – 7.30 (m, 6H), 5.20 – 5.10 (m, 1H), 4.58 – 4.55 (m, 1H), 4.31 4.25 (m, 2H), 4.26 – 4.18 (m, 3H), 4.16 – 3.96 (m, 3H), 3.79 – 3.47 (m, 2H), 3.12 – 3.14 (m, 4H), 2.31 – 2.06 (m, 5H), 1.92 – 1.62 (m, 8H), 1.46 (s, 12H), 1.26 (m, 2H)

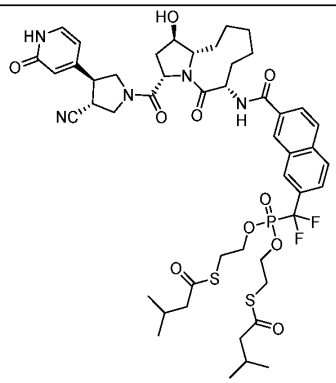
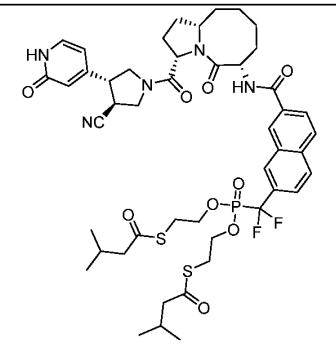
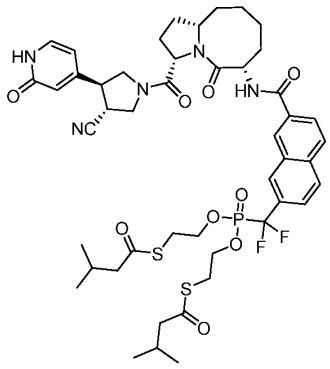
160	S,S'-((((difluoro(7-(((3S,6S,10aS)-5-oxo-3-(3-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl))bis(3-methylbutanethioate)		945.4 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 8.48 – 8.42 (m, 1H), 8.22 – 8.19 (m, 1H), 8.01 – 7.91 (m, 3H), 7.76 -7.74 (m, 1H), 7.76 – 7.41 (m, 2H), 6.89 – 6.49 (m, 2H), 5.20 – 5.17 (m, 1H), 4.61 (t, J = 7.9 Hz, 1H), 4.39 – 4.35 (m, 1H), 4.27 – 4.14 (m, 5H), 3.86 – 3.67 (m, 2H), 3.58 – 3.36 (m, 2H), 3.20 – 3.08 (m, 4H), 2.46 – 2.20 (m, 5H), 2.16 – 2.01 (m, 10H), 1.99 – 1.66 (m, 5H), 0.93 (d, J = 6.6, 1.3 Hz, 12H)
161	S,S'-((((difluoro(2-(((3S,6S,10aR)-10-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl))bis(3-methylbutanethioate)		934.9 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 9.00 – 8.84 (m, 1H), 8.69 – 8.52 (m, 1H), 8.24 – 8.09 (m, 2H), 8.08 – 7.84 (m, 2H), 7.83 – 7.60 (m, 2H), 7.60 – 7.37 (m, 1H), 5.09 – 4.73 (m, 1H), 4.72 – 4.33 (m, 3H), 4.29 – 4.01 (m, 6H), 4.01 – 3.79 (m, 1H), 3.24 – 3.05 (m, 4H), 2.46 – 2.40 (m, 4H), 2.32 – 2.20 (m, 3H), 2.20 – 1.95 (m, 7H), 1.95 – 1.76 (m, 2H), 1.73 – 1.66 (m, 2H), 0.97 – 0.93 (m, 12H), 0.93 – 0.89 (m, 3H)

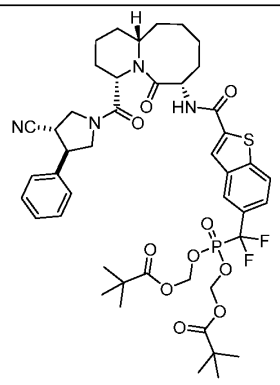
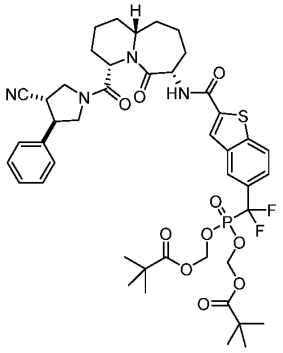
162	S,S'-(((((2-(((3S,6S,10aR)-3-((3R,4S or 3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-10-methyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methylbutanethioate)	 or  SFC peak 2 was used for biological testing	990.3 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.03 (m, 2H), 7.97 – 7.76 (m, 2H), 7.68 – 7.56 (m, 1H), 7.42 – 7.31 (m, 1H), 6.96 – 6.52 (m, 1H), 6.32 – 6.19 (m, 1H), 4.75 – 4.57 (m, 1H), 4.56 – 4.42 (m, 1H), 4.41 – 4.03 (m, 8H), 4.01 – 3.68 (m, 2H), 3.66 – 3.25 (m, 2H), 3.22 – 3.05 (m, 5H), 2.46 – 2.38 (m, 4H), 2.34 – 2.24 (m, 1H), 2.23 – 2.04 (m, 8H), 1.97 – 1.87 (m, 1H), 1.86 – 1.78 (m, 1H), 1.77 – 1.71 (m, 1H), 1.69 – 1.61 (m, 1H), 0.97 – 0.88 (m, 15H)
163	S,S'-(((((2-(((3S,6S,10aS)-3-((3R,4S or 3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methylbutanethioate)	 or	958.8 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.01 (m, 1H), 7.97 – 7.89 (m, 1H), 7.88 – 7.79 (m, 1H), 7.66 – 7.59 (m, 1H), 7.44 – 7.30 (m, 5H), 5.20 – 5.05 (m, 1H), 4.64 – 4.49 (m, 1H), 4.39 – 3.97 (m, 8H), 3.81 – 3.49 (m, 2H), 3.31 – 3.05 (m, 5H), 2.43 (d, J = 7.1 Hz, 4H), 2.30 – 2.10 (m, 6H), 2.09 – 1.76 (m, 6H), 1.72 – 1.61 (m, 2H), 0.94 (d, J = 6.7 Hz, 12H)

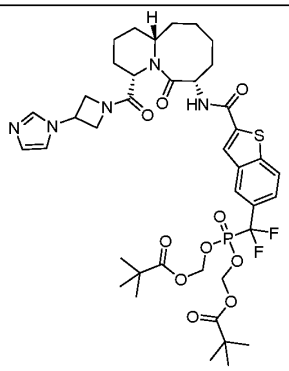
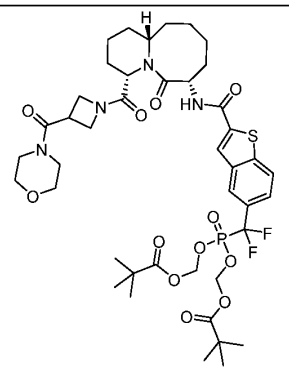
		 SFC peak 2 was used for biological testing		
164	((((S)-(2-(((3S,6S,10aS)-3-((3R,4S or 3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphoryl)bis(oxy))bis(methylene) diisopropyl bis(carbonate) or ((((R)-(2-(((3S,6S,10aS)-3-((3R,4S or 3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydr	 or  or	902.3 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.92 (m, 1H), 7.91 – 7.79 (m, 2H), 7.64 – 7.29 (m, 3H), 7.03 – 6.73 (m, 1H), 6.70 – 6.53 (m, 1H), 5.90 (dd, J = 44.1, 6.9 Hz, 1H), 5.71 – 5.59 (m, 4H), 5.21 – 5.03 (m, 1H), 4.97 – 4.83 (m, 2H), 4.60 – 4.45 (m, 1H), 4.39 – 3.93 (m, 4H), 3.79 – 3.12 (m, 3H), 2.29 – 1.94 (m, 6H), 1.93 – 1.55 (m, 6H), 1.36 – 1.23 (m, 12H)

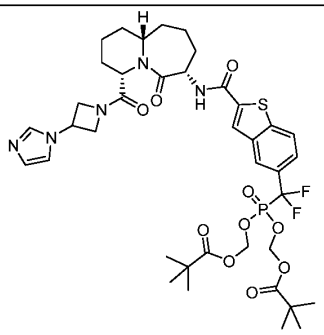
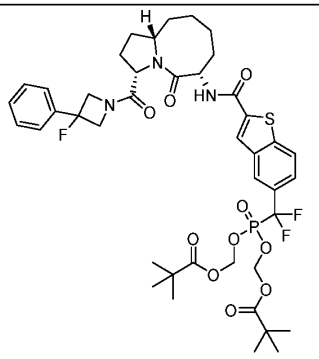
	opyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphoryl)bis(oxy))bis(methylene) diisopropyl bis(carbonate)	 or  (SFC peak 1 was used for biological testing, Peak 2 of phosphonate building block was used for synthesis)		
165	S-(2-((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(2-(pivaloylthio)ethoxy)phosphoryl)oxy)ethyl) butanethioate	 or	967.4 $[M+Na]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 – 8.88 (m, 1H), 8.38 – 8.31 (m, 1H), 8.24 – 8.18 (m, 1H), 8.17 – 8.12 (m, 1H), 7.62 – 7.55 (m, 1H), 7.47 – 7.26 (m, 5H), 5.02 – 4.89 (m, 1H), 4.54 (q, J = 9.0 Hz, 1H), 4.36 – 3.90 (m, 7H), 3.86 – 3.77 (m, 1H), 3.70 – 3.47 (m, 2H), 3.34 – 3.24 (m, 1H), 3.17 – 3.06 (m, 4H), 2.57 – 2.50 (m, 2H), 2.33 – 2.22 (m, 1H), 2.13 – 1.76 (m, 8H), 1.69 – 1.47 (m, 5H), 1.16 – 1.13 (m, 9H), 0.88 – 0.81 (m, 3H)

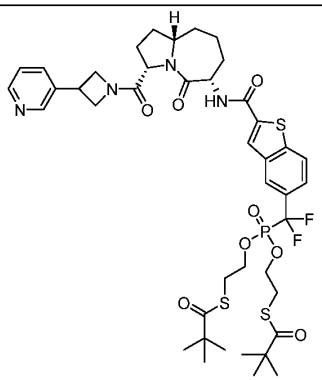
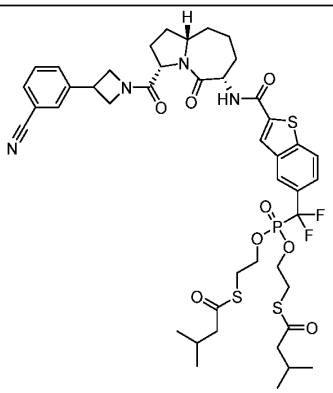
		 SFC peak 2 was used for biological testing		
166	S-(2-((((2-(((3S,6S,10aS)-3-((3R,4S or 3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(((isopropoxycarbonyl)oxy)methoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate	 or  SFC peak 2 was used for biological testing	931.3 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.06 (m, 1H), 7.97 – 7.90 (m, 1H), 7.89 – 7.81 (m, 1H), 7.67 – 7.61 (m, 1H), 7.44 – 7.27 (m, 5H), 7.26 – 7.20 (m, 1H), 5.73 – 5.59 (m, 2H), 5.19 – 5.06 (m, 1H), 4.98 – 4.86 (m, 1H), 4.61 – 4.50 (m, 1H), 4.40 – 3.03 (m, 12H), 2.44 – 2.39 (m, 2H), 2.30 – 1.70 (m, 11H), 1.32 (d, J = 6.0 Hz, 6H), 0.94 (d, J = 6.0 Hz, 6H)
167	S,S'-(((((7-(((1R,3S,6S,11aS)-3-((3S,4R or 3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-1-	 or	999.9 $[M+H]^+$	^{1}H (400 MHz, $CDCl_3$) δ 8.44 – 8.40 (m, 1H), 8.28 – 8.05 (m, 2H), 7.98 – 7.61 (m, 4H), 7.16 (m, 1H), 6.50 – 6.42 (m, 1H), 6.12 – 5.95 (m, 1H), 5.36– 5.10 (m, 1H), 4.97 – 4.73 (m, 1H), 4.32 – 3.97 (m, 8H), 4.02 – 3.90 (m, 1H), 3.60 – 3.19 (m, 2H), 3.17 – 3.11 (m, 4H), 3.09 – 3.01 (m, 1H), 2.57

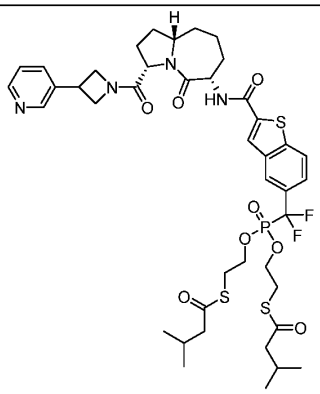
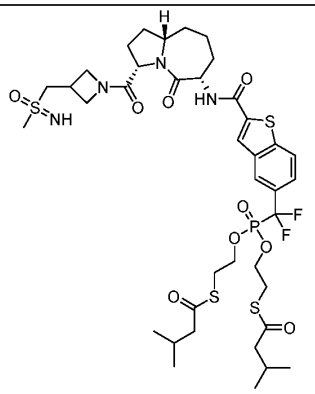
	hydroxy-5-oxodecahydro-1H-pyrrolo[1,2-a]azonin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methylbutanethioate)	 SFC peak 2 was used for biological testing		– 2.43 (m, 1H), 2.43 – 2.40 (m, 4H), 2.26 – 2.20 (m, 1H), 2.16 – 2.11 (m, 5H), 1.92 – 1.62 (m, 8H), 0.94 – 0.91 (m, 12H)
168	S,S'-(((((7-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methylbutanethioate)	 or  SFC peak 2 was used for biological testing	970.4 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 – 8.41 (m, 2H), 8.35 – 8.15 (m, 1H), 8.09 – 7.68 (m, 5H), 7.47 – 7.27 (m, 2H), 6.79 – 6.43 (m, 1H), 6.37 – 6.11 (m, 1H), 5.27 – 5.04 (m, 1H), 4.61 – 4.47 (m, 1H), 4.44 – 4.12 (m, 7H), 4.11 – 3.89 (m, 1H), 3.79 – 3.42 (m, 2H), 3.30 – 3.07 (m, 5H), 2.49 – 2.35 (m, 4H), 2.30 – 2.05 (m, 7H), 2.05 – 1.65 (m, 9H), 1.04 – 0.84 (m, 12H)

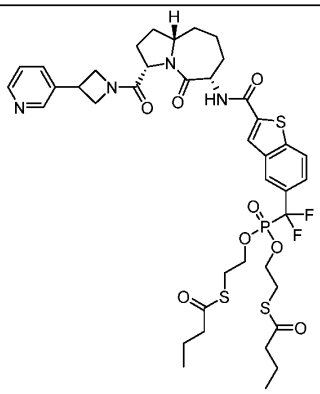
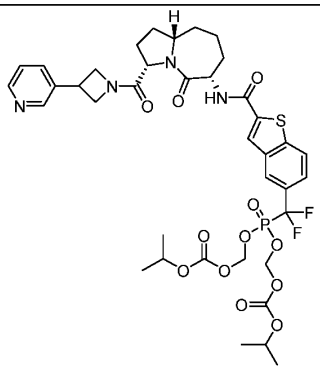
169	((((2-(((4S,7S,11aS)-4-((*rel*-trans)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-6-oxodecahydro-2H-pyrido[1,2-a]azocin-7-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		911.0 [M-H]$^-$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.09 (d, J = 15.9 Hz, 1H), 7.93 (t, J = 7.1 Hz, 1H), 7.88 – 7.78 (m, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.53 – 7.29 (m, 6H), 5.73 (dd, J = 12.6, 5.0 Hz, 2H), 5.69 – 5.60 (m, 2H), 5.10 (s, 1H), 4.91 (dd, J = 7.7, 4.2 Hz, 1H), 4.37 – 4.21 (m, 2H), 4.15 – 3.78 (m, 3H), 3.72 – 3.61 (m, 1H), 3.27 – 3.13 (m, 1H), 2.22 (s, 1H), 1.93 (s, 3H), 1.83 (s, 4H), 1.69 (d, J = 37.4 Hz, 2H), 1.51 (q, J = 16.3, 12.6 Hz, 3H), 1.41 (d, J = 6.9 Hz, 1H), 1.20 (s, 18H)
170	((((2-(((4S,7S,10aS)-4-(*rel*-(trans)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-6-oxodecahydropyrido[1,2-a]azepin-7-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)			^{1}H NMR (600 MHz, DMSO-d_6) δ 8.09 (s, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.71 (app m, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.50 – 7.30 (m, 5H), 5.78 – 5.69 (m, 2H), 5.65 (m, 2H), 5.07 – 4.96 (m, 2H), 4.58 – 4.07 (m, 1H), 4.07 – 3.99 (m, 2H), 3.90 – 3.62 (m, 2H), 3.58 – 3.17 (m, 1H), 2.61 – 2.39 (m, 1H), 2.28 – 2.07 (m, 1H), 1.92 (dt, J = 34.5, 17.1 Hz, 5H), 1.78 (s, 3H), 1.70 (s, 1H), 1.20 (s, 18H)

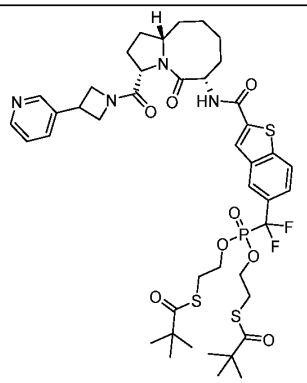
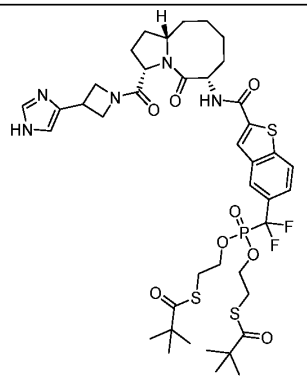
171	((((2-(((4S,7S,11aS)-4-(3-(1H-imidazol-1-yl)azetidine-1-carbonyl)-6-oxodecahydro-2H-pyrido[1,2-a]azocin-7-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		864.4 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.17 – 7.49 (m, 7H), 6.05 (s, 2H), 5.74 – 5.48 (m, 3H), 4.98 (s, 1H), 4.63 (s, 2H), 4.39 (s, 1H), 4.24 (s, 1H), 4.06 (s, 1H), 2.41 (s, 1H), 2.18 (s, 1H), 1.84 (s, 5H), 1.45 (s, 4H), 1.34 – 0.88 (m, 18H)
172	(((difluoro(2-(((4S,7S,11aS)-4-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-6-oxodecahydro-2H-pyrido[1,2-a]azocin-7-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		911.2 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.05 (app. m, 1H), 7.99 – 7.86 (m, 1H), 7.86 – 7.76 (m, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.54 (m, 1H), 5.72 (m, 2H), 5.69 – 5.59 (m, 2H), 5.18 – 5.06 (m, 1H), 4.78 (m, 1H), 4.68 (m, 1H), 4.60 – 4.41 (m, 1H), 4.27 (m, 2H), 4.16 – 4.04 (m, 1H), 3.75 – 3.60 (m, 7H), 3.57 (s, 1H), 1.99 – 1.77 (m, 6H), 1.77 – 1.59 (m, 3H), 1.59 – 1.28 (m, 5H), 1.23 – 1.18 (s, 18H)

173	((((2-(((4S,7S,10aS)-4-(3-(1H-imidazol-1-yl)azetidine-1-carbonyl)-6-oxodecahydropyrido[1,2-a]azepin-7-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		850.2 $[M+H]^+$	
174	(((difluoro(2-(((3S,6S,10aS)-3-(3-fluoro-3-phenylazetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		878.2 $[M+H]^+$	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.99 (dd, J = 17.9, 7.1 Hz, 1H), 8.32 (d, J = 28.3 Hz, 1H), 8.20 (t, J = 8.1 Hz, 1H), 8.09 (d, J = 11.2 Hz, 1H), 8.02 (d, J = 8.7 Hz, 1H), 7.46 (m, 6H), 5.81 – 5.64 (m, 4H), 4.98 – 4.86 (m, 2H), 4.67 (m, 1H), 4.41 – 4.31 (m, 2H), 4.27 (m, 2H), 2.20 (m, 1H), 2.09 – 2.00 (m, 1H), 1.90 – 1.74 (m, 6H), 1.64 (m, 1H), 1.59 (m, 1H), 1.50 (s, 1H), 1.10 (s, 18H)

175	S,S'-((((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2,2-dimethylpropanethioate)			^{1}H NMR (600 MHz, DMSO-d_6) δ 9.14 (s, 1H), 8.64 (d, J = 20.8 Hz, 1H), 8.40 (s, 1H), 8.29 – 8.07 (m, 2H), 8.03 – 7.83 (m, 2H), 7.74 – 7.61 (m, 2H), 4.88 (m, 1H), 4.70 (m, 1H), 4.51 (m, 2H), 4.25 – 4.19 (m, 2H), 4.15 (m, 2H), 3.94 (m, 2H), 3.13 (m, 4H), 2.41 – 2.14 (m, 4H), 2.04 (m, 4H), 1.91 (m, 4H), 1.23 (s, 18H)
176	S-(2-((((2-(((3S,6S,9aS)-3-(3-(3-cyanophenyl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(((3-methylbutanoyl)thio)methoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate		931.2 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.28 – 8.18 (m, 2H), 8.15 – 8.09 (m, 1H), 7.97 (s, 1H), 7.79 – 7.73 (m, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.60 – 7.49 (m, 1H), 4.93 (d, J = 1.6 Hz, 1H), 4.78 (d, J = 10.4 Hz, 1H), 4.70 (t, J = 8.0 Hz, 1H), 4.63 – 4.54 (m, 2H), 4.41 (t, J = 8.0 Hz, 1H), 4.26 – 4.16 (m, 4H), 4.11 – 4.07 (m, 1H), 4.05 – 3.94 (m, 1H), 3.17 – 3.07 (m, 4H), 2.81 (s, 1H), 2.22 – 2.15 (m, 4H), 2.10 – 1.96 (m, 7H), 1.94 – 1.80 (m, 4H), 1.24 (t, J = 7.2 Hz, 1H), 0.93 (d, J = 4.8 Hz, 12H)

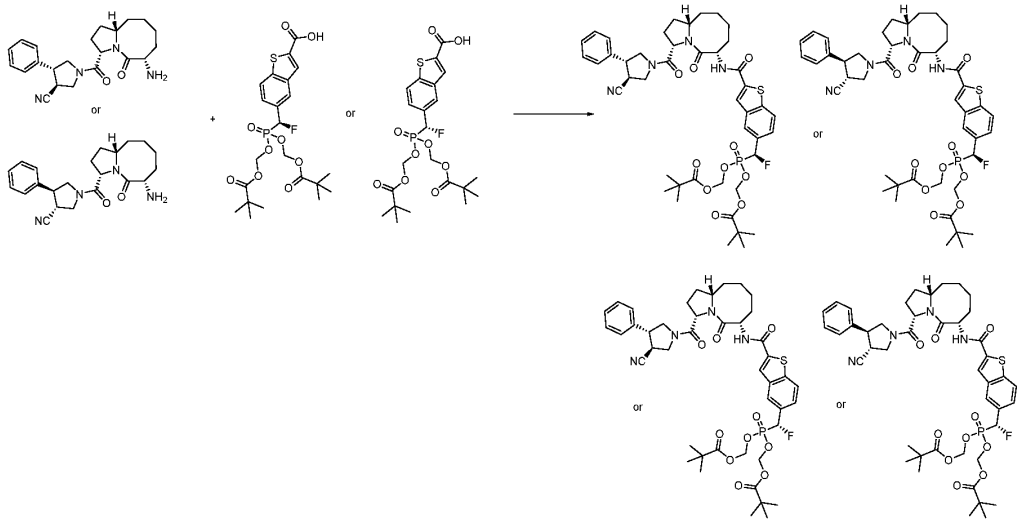
177	S,S'-((((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methylbutanethioate)		907.3 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 – 8.55 (m, 2H), 8.15 (d, J = 11.6 Hz, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.92 – 7.87 (m, 1H), 7.74 – 7.68 (m, 2H), 7.42 – 7.32 (m, 1H), 5.10 (m, 1H), 4.74 – 4.58 (m, 3H), 4.57 – 4.39 (m, 1H), 4.29 – 4.18 (m, 5H), 4.12 – 4.05 (m, 1H), 4.01 – 3.88 (m, 2H), 3.19 – 2.96 (m, 4H), 2.35 – 2.21 (m, 2H), 2.21 – 2.17 (m, 4H), 2.13 – 2.06 (m, 5H), 2.03 (s, 1H), 1.96 (t, J = 10.0 Hz, 2H), 1.86 – 1.70 (m, 2H), 0.95 (d, J = 6.4 Hz, 12H)
178	S-(2-(((difluoro(2-(((3S,6S,9aS)-3-(3-((S-methylsulfonimidoyl)methyl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(((3-methylbutanoyl)thio)methoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate		921 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 6.8 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 10.8 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 4.71 – 4.62 (m, 1H), 4.52 – 4.44 (m, 2H), 4.27 – 4.16 (m, 5H), 3.97 – 3.88 (m, 2H), 3.61 – 3.44 (m, 2H), 3.39 – 3.27 (m, 1H), 3.07 – 3.02 (m, 4H), 2.29 – 2.21 (m, 2H), 2.21 – 2.18 (m, 4H), 2.13 – 2.04 (m, 3H), 2.04 – 1.98 (m, 3H), 1.97 – 1.89 (m, 2H), 1.84 – 1.77 (m, 2H), 1.26 (s, 3H), 0.95 (d, J = 6.8 Hz, 12H), 0.91 – 0.82 (m, 2H)

179	S,S'-((((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl))dibutanethioate		879.3 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 – 8.54 (m, 2H), 8.15 (d, J = 11.6 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.92 – 7.66 (m, 4H), 7.44 – 7.31 (m, 1H), 5.07 – 4.38 (m, 4H), 4.30 – 4.03 (m, 6H), 4.02 – 3.87 (m, 2H), 3.19 – 2.98 (m, 4H), 2.29 (t, J = 7.2 Hz, 4H), 2.25 – 2.19 (m, 1H), 2.06 (d, J = 3.2 Hz, 4H), 1.96 (t, J = 10.0 Hz, 2H), 1.86 – 1.80 (m, 1H), 1.74 (d, J = 11.6 Hz, 1H), 1.67 – 1.63 (m, 3H), 1.32 (m, 2H), 0.95 (t, J = 7.2 Hz, 6H)
180	(((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(methylene) diisopropyl bis(carbonate)		851.4 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 – 8.54 (m, 2H), 8.12 (d, J = 9.2 Hz, 1H), 7.95 (m, 1H), 7.92 – 7.85 (m, 1H), 7.75 – 7.70 (m, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.47 – 7.33 (m, 1H), 5.78 – 5.62 (m, 4H), 4.98 – 4.84 (m, 2H), 4.75 – 4.50 (m, 4H), 4.26 – 4.18 (m, 1H), 4.12 – 4.04 (m, 1H), 4.03 – 3.87 (m, 2H), 2.34 – 2.18 (m, 2H), 1.78 – 1.55 (m, 8H), 1.32 (d, J = 6.0 Hz, 12H)

181	S,S'-((((difluoro(2-(((3S,6S,10aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl))bis(2,2-dimethylpropanethioate)		921.1 $[M+H]^+$	^{1}H NMR (400 MHz, acetonitrile-d_3) δ 8.30 – 8.12 (m, 2H), 7.82 (d, J = 9.2 Hz, 1H), 7.76 – 7.62 (m, 3H), 7.55 – 7.48 (m, 1H), 7.32 (app. t, J = 7.6 Hz, 1H), 7.09 – 6.95 (m, 1H), 4.79 – 4.71 (m, 1H), 4.35 – 4.20 (m, 2H), 4.16 – 4.07 (m, 2H), 4.01 (d, J = 8.8 Hz, 1H), 3.91 – 3.82 (m, 4H), 3.66 – 3.58 (m, 2H), 2.81 (t, J = 6.4 Hz, 4H), 1.85 – 1.76 (m, 4H), 1.53 – 1.45 (m, 3H), 1.45 – 1.24 (m, 5H), 0.88 (s, 18H)
182	S,S'-((((((2-(((3S,6S,10aS)-3-(3-(1H-imidazol-4-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl))bis(2,2-dimethylpropanethioate)		910.3 $[M+H]^+$	^{1}H NMR (400 MHz, acetonitrile-d_3) δ 8.11 (s, 1H), 8.04 – 7.96 (m, 2H), 7.77 (d, J = 6.8 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.53 (s, 1H), 6.89 (d, J = 3.2 Hz, 1H), 5.07 – 4.97 (m, 1H), 4.46 (d, J = 7.6 Hz, 1H), 4.42 – 4.36 (m, 1H), 4.32 – 4.07 (m, 7H), 4.00 – 3.78 (m, 2H), 3.10 (t, J = 6.2 Hz, 4H), 2.23 – 2.03 (m, 3H), 2.02 – 1.96 (m, 2H), 1.92 – 1.86 (m, 1H), 1.80 – 1.72 (m, 2H), 1.71 – 1.64 (m, 1H), 1.64 – 1.54 (m, 2H), 1.18 (s, 18H)

[00413] Representative Procedure for Amino Acid Coupling Conditions of Linker Acids Esters with Amino Acid Cores for Construction of Analogues

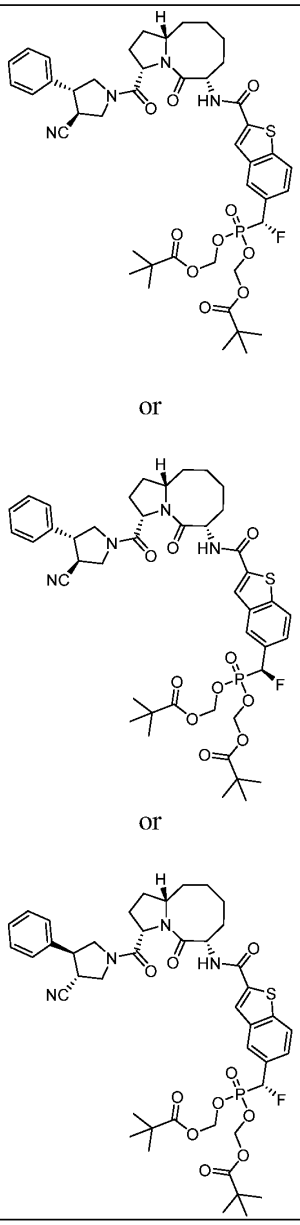
[00414] *Preparation of (((((R)- or (S)-(2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)) (**183**)*

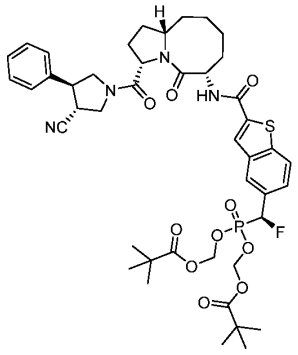
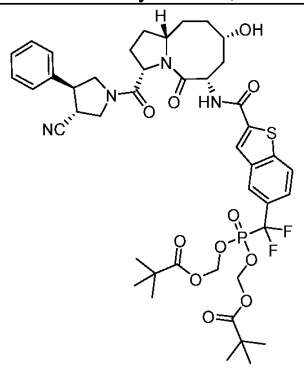
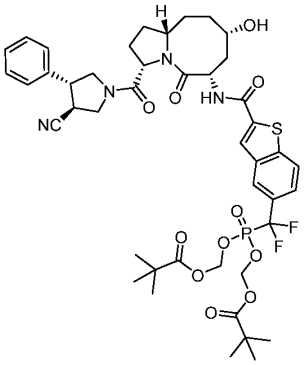


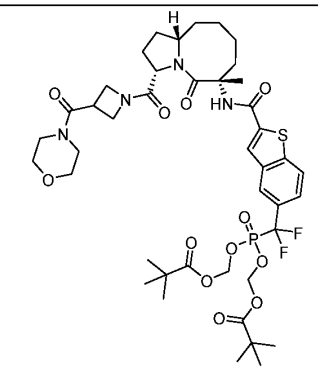
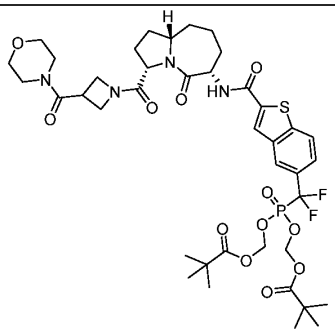
[00415] To a solution of (3S,4R or 3R,4S)-1-[(3S,6S,10aS)-6-amino-5-oxo-decahydropyrrolo[1,2-a]azocine-3-carbonyl]-4-phenylpyrrolidine-3-carbonitrile (pyrrolidine peak 2) (45.6 mg, 120 µmol, 1.2 eq), 5-[(S)-[bis({[(2,2-dimethylpropanoyl)oxy]methoxy})phosphoryl](fluoro)methyl]-1-benzothiophene-2-carboxylic acid (phosphonate peak 2) (51.8 mg, 0.10 mmol, eq) and N,N-diisopropylethylamine (104 µL, 600 µmol, 6 eq) in DMF (3 mL) was added HATU (45.6 mg, 120 µmol, 1.2 eq). The reaction mixture was stirred at room temperature for 15 min and the solution was subsequently purified by reverse phase chromatography using a C18 column (gradient 5% to 100% acetonitrile in water) to yield ({[(R)- or (S)-(2-{[(3S,6S,10aS)-3-[(3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl]-5-oxo-decahydropyrrolo[1,2-a]azocin-6-yl]carbamoyl}-1-benzothiophen-5-yl)(fluoro)methyl]({[(2,2-dimethylpropanoyl)oxy]methoxy})phosphoryl}oxy)methyl 2,2-dimethylpropanoate (182) (36.4 mg, 0.04136 mmol, 41.3 %) as a white solid. LCMS (ESI) m/z = 881.2 $[M+H]^+$; ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 8.03 – 7.91 (m, 3H), 7.56 – 7.46 (m, 2H), 7.46 – 7.29 (m, 5H), 5.99 (dd, J = 43.0, 7.8 Hz, 1H), 5.67 – 5.52 (m, 4H), 5.10 – 4.96 (m, 1H), 4.63 – 4.53 (m, 1H), 4.42 – 4.23 (m, 2H), 4.13 – 3.95 (m, 1H), 3.85 – 3.68 (m, 1H), 3.65 – 3.31 (m, 3H), 2.35 – 2.21 (m, 1H), 2.12 – 1.96 (m, 5H), 1.91 – 1.66 (m, 4H), 1.65 – 1.54 (m, 2H), 1.12 (s, 18H).

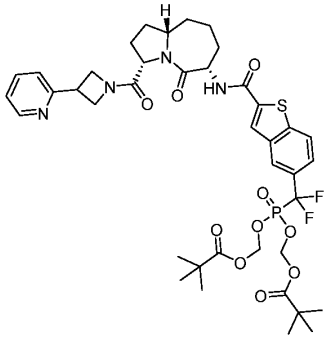
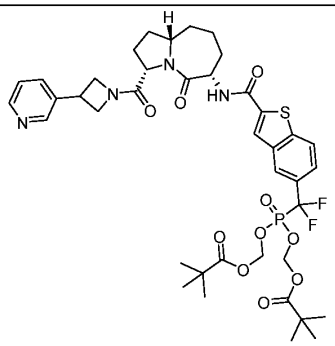
[00416] The following compounds in **Table 37** were prepared according to the representative procedure described above for the synthesis of ({[(R)- or (S)-(2-{[(3S,6S,10aS)-3-[(3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl]-5-oxo-decahydropyrrolo[1,2-a]azocin-6-yl]carbamoyl}-1-benzothiophen-5-yl)(fluoro)methyl]({[(2,2-dimethylpropanoyl)oxy]methoxy})phosphoryl}oxy)methyl 2,2-dimethylpropanoate (182) and using the appropriate starting materials and modifications.

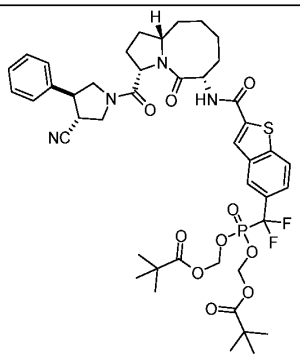
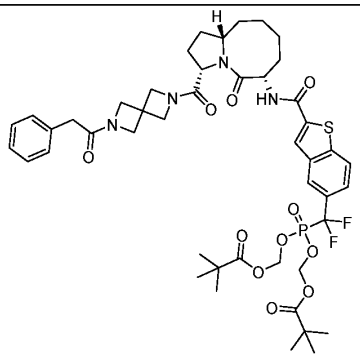
Table 37

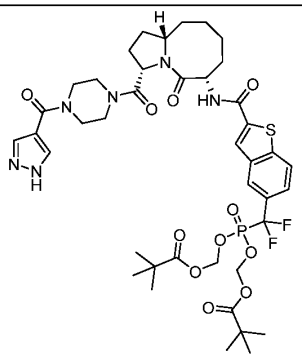
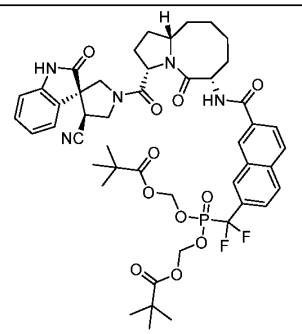
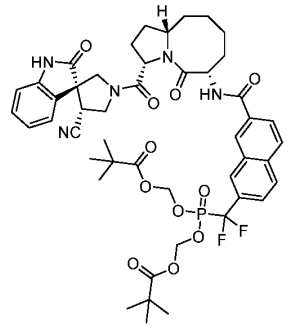
Compound	Name	Structure	LCMS	NMR
184	((((S)- or (R)-(2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		881.2 $[M+H]^+$	^{1}H NMR (400 MHz, acetonitrile-d_3) δ 8.02 – 7.95 (m, 2H), 7.94 (s, 1H), 7.59 – 7.47 (m, 2H), 7.45 – 7.29 (m, 5H), 5.99 (dd, J = 44.7, 8.8 Hz, 1H), 5.65 – 5.54 (m, 4H), 5.11 – 4.93 (m, 1H), 4.63 – 4.51 (m, 1H), 4.44 – 4.22 (m, 2H), 4.13 – 3.93 (m, 1H), 3.84 – 3.68 (m, 1H), 3.67 – 3.29 (m, 3H), 2.39 – 2.20 (m, 1H), 2.13 – 1.96 (m, 5H), 1.90 – 1.67 (m, 4H), 1.65 – 1.50 (m, 2H), 1.10 (s, 18H)

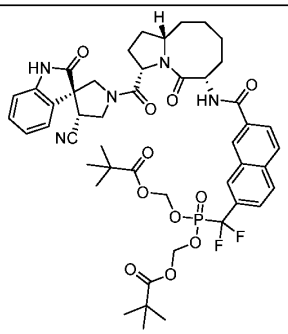
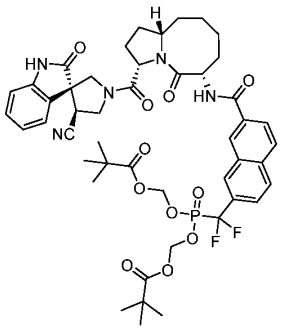
		or  (SFC peak 2 was used for biological testing, Peak 1 of phosphonate building block was used for synthesis)		
185	((((2-(((3S,6S,8S,10aR)-3-((3R,4S or 3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-8-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)	 or  SFC peak 1 was used for biological testing	915.4 $[M+H]^+$	^{1}H NMR (400 MHz, acetonitrile-d_3) δ 8.16 – 7.94 (m, 3H), 7.65 – 7.55 (m, 2H), 7.48 – 7.28 (m, 5H), 5.72 – 5.58 (m, 4H), 5.09 – 4.97 (m, 1H), 4.58 – 4.42 (m, 2H), 4.34 – 4.22 (m, 1H), 4.15 – 3.87 (m, 3H), 3.81 – 3.33 (m, 4H), 2.40 – 2.29 (m, 2H), 2.27 – 2.15 (m, 2H), 2.11 – 1.98 (m, 3H), 1.89 – 1.75 (m, 2H), 1.74 – 1.63 (m, 1H), 1.16 (s, 18H)

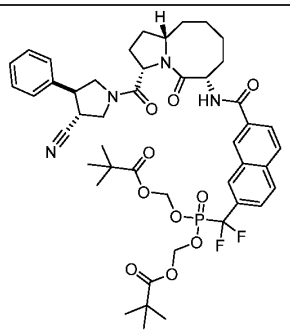
186	(((difluoro(2-(((3S,6S,10aS)-6-methyl-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		911.3 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.03 (m, 1H), 8.00 – 7.91 (m, 1H), 7.88 – 7.78 (m, 1H), 7.69 – 7.59 (m, 1H), 5.77 – 5.61 (m, 4H), 4.74 – 4.64 (m, 1H), 4.63 – 4.53 (m, 1H), 4.52 – 4.37 (m, 1H), 4.35 – 4.24 (m, 1H), 4.20 – 4.03 (m, 1H), 3.92 – 3.44 (m, 5H), 3.42 – 3.24 (m, 2H), 3.22 – 2.79 (m, 1H), 2.31 – 2.19 (m, 1H), 2.18 – 2.05 (m, 2H), 2.05 – 1.94 (m, 2H), 1.88-1.85 (m, 1H), 1.72 (s, 3H), 1.70 – 1.58 (m, 5H), 1.55 (d, J = 10.8 Hz, 1H), 1.42 – 1.29 (m, 2H), 1.20 (s, 18H)
187	(((difluoro(2-(((3S,6S,9aS)-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		883.4 $[M+H]^+$	^1H NMR (400 MHz, methanol-d_4) δ 8.19 – 8.04 (m, 1H), 7.97 – 7.82 (m, 2H), 7.70 – 7.60 (m, 1H), 5.88 – 5.48 (m, 4H), 4.77 – 4.49 (m, 3H), 4.44 – 4.25 (m, 1H), 4.24 – 4.06 (m, 1H), 4.00 – 3.81 (m, 1H), 3.78 – 3.50 (m, 7H), 3.40 – 3.17 (m, 2H), 2.34 (s, 2H), 2.10 – 1.78 (m, 9H), 1.21 (s, 18H)

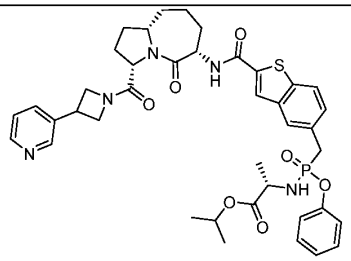
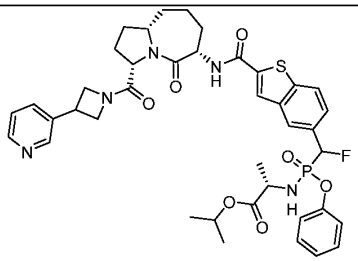
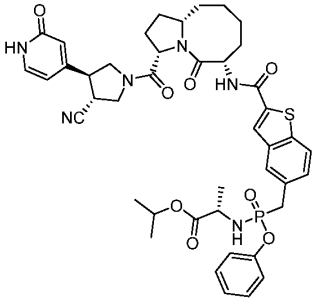
188	(((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-2-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		847.2 $[M+H]^+$	^1H NMR (400 MHz, methanol-d_4) δ 8.69 – 8.60 (m, 1H), 8.09 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.87 – 7.81 (m, 1H), 7.77 – 7.61 (m, 3H), 7.24 – 7.18 (m, 1H), 5.88 – 5.55 (m, 4H), 4.92 – 4.75 (m, 1H), 4.71 – 4.49 (m, 3H), 4.45 – 4.18 (m, 1H), 4.12 – 3.87 (m, 2H), 2.34 – 1.71 (m, 11H), 1.21 (s, 18H)
189	(((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		847.1 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 9.11 (d, J = 4.0 Hz, 1H), 8.75 – 8.53 (m, 1H), 8.42 – 8.28 (m, 1H), 8.23 – 8.05 (m, 2H), 7.97 – 7.83 (m, 1H), 7.74 – 7.55 (m, 2H), 5.79 – 5.58 (m, 4H), 4.94 – 4.79 (m, 1H), 4.76 – 4.62 (m, 1H), 4.51 – 4.39 (m, 5H), 4.26 – 4.11 (m, 1H), 4.07 – 3.89 (m, 2H), 2.17 (s, 2H), 2.04 (dd, J = 12.0, 5.6 Hz, 3H), 1.92 (d, J = 7.2 Hz, 3H), 1.21 (s, 18H)

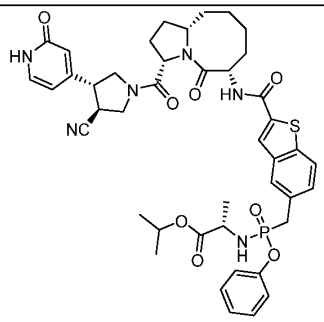
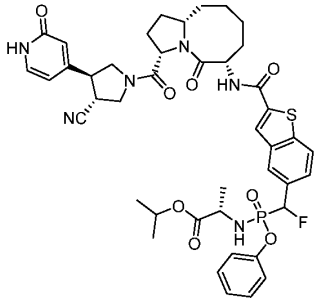
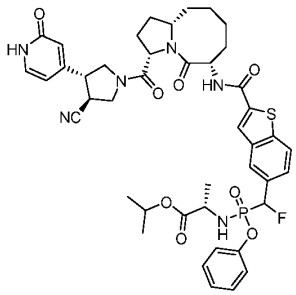
190	((((2-(((3S,6S,10aS)-3-(*rel*-trans)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		899.2 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.23 – 8.02 (m, 3H), 7.65 – 7.59 (m, 1H), 7.46 – 7.36 (m, 4H), 7.34 (s, 1H), 5.80 – 5.66 (m, 4H), 5.05 (d, J = 10.4 Hz, 1H), 4.70 (d, J = 8.8 Hz, 1H), 4.58 – 4.39 (m, 2H), 4.20 – 4.07 (m, 1H), 4.01 – 3.81 (m, 1H), 3.78 – 3.69 (m, 1H), 3.65 – 3.52 (m, 2H), 2.39 – 2.19 (m, 2H), 2.10 – 1.96 (m, 6H), 1.92 – 1.78 (m, 2H), 1.75 – 1.59 (m, 2H), 1.18 (s, 18H)
191	(((difluoro(2-(((3S,6S,10aS)-5-oxo-3-(6-(2-phenylacetyl)-2,6-diazaspiro[3.3]heptane-2-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		943.3 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.82 (s, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.25 (s, 3H), 5.78 – 5.62 (m, 4H), 5.17 – 5.05 (m, 1H), 4.70 (dd, J = 16.0, 8.8 Hz, 1H), 4.37 – 4.12 (m, 8H), 4.10 – 3.98 (m, 1H), 3.48 (d, J = 4.4 Hz, 2H), 2.18 – 2.04 (m, 4H), 2.04 – 1.87 (m, 3H), 1.87 – 1.76 (m, 2H), 1.71 – 1.68 (m, 1H), 1.67 – 1.59 (m, 2H), 1.21 (s, 18H)

192	((((2-(((3S,6S,10aS)-3-(4-(1H-pyrazole-4-carbonyl)piperazine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		907.1 $[M+H]^+$	^{1}H NMR (400 MHz, acetonitrile-d_3) δ 8.08 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 7.79 – 7.74 (m, 2H), 7.57 (d, J = 8.4 Hz, 1H), 5.71 – 5.58 (m, 4H), 5.03 (m, 1H), 4.82 (t, J = 8.8 Hz, 1H), 4.37 – 4.24 (m, 1H), 3.78 – 3.54 (m, 8H), 2.23 (s, 1H), 2.16 – 2.13 (m, 2H), 2.04 – 1.97 (m, 2H), 1.91 – 1.87 (m, 1H), 1.77 (dd, J = 6.4, 11.6 Hz, 2H), 1.72 – 1.66 (m, 1H), 1.60 (dd, J = 12.4, 6.8 Hz, 2H), 1.32 – 1.25 (m, 1H), 1.15 (s, 18H)
193	((((7-(((3S,6S,10aS)-3-((3S,4'S)-4'-cyano-2-oxospiro[indoline-3,3'-pyrrolidine]-1'-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate) or ((((7-(((3S,6S,10aS)-3-((3R,4'R)-4'-	 or  or	934.5 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 – 8.26 (m, 1H), 8.25 – 8.14 (m, 1H), 8.00 – 7.90 (m, 3H), 7.82 – 7.65 (m, 2H), 7.43 – 7.33 (m, 2H), 7.25 – 7.20 (m, 1H), 7.04 – 6.98 (m, 1H), 5.78 – 5.72 (m, 2H), 5.71 – 5.64 (m, 2H), 5.25 – 5.09 (m, 1H), 4.55 – 4.27 (m, 3H), 4.18 – 4.00 (m, 1H), 3.99 – 3.91 (m, 1H), 3.91 – 3.78 (m, 1H), 3.65 (t, J = 9.2 Hz, 1H), 2.28 – 2.12 (m, 4H), 2.11 – 1.90 (m, 4H), 1.85 – 1.68 (m, 4H), 1.21 (s, 18H)

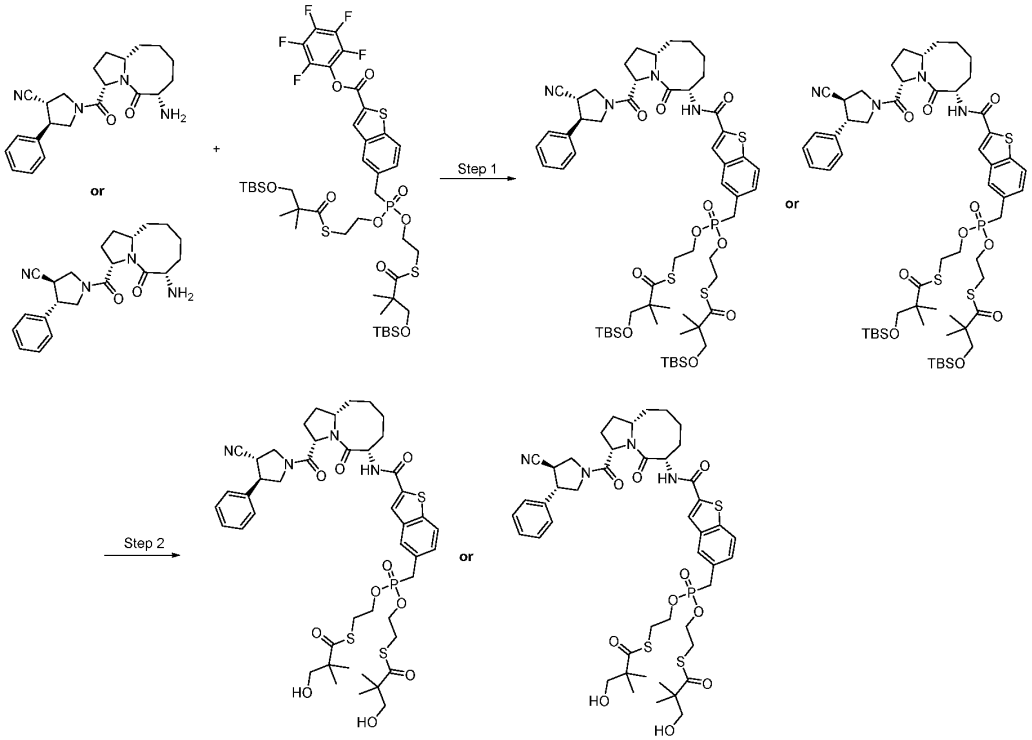
	cyano-2-oxospiro[indoline-3,3'-pyrrolidine]-1'-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate) or ((((7-(((3S,6S,10aS)-3-((3R,4'S)-4'-cyano-2-oxospiro[indoline-3,3'-pyrrolidine]-1'-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate) or ((((7-(((3S,6S,10a	 or  (SFC Peak 2 of pyrrolidine building block used for synthesis and biological testing)		

	S)-3-((3S,4'R)-4'-cyano-2-oxospiro[indoline-3,3'-pyrrolidine]-1'-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)			
194	((((7-(((3S,6S,10aS)-3-(*rel*-(trans)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		893.3 $[M+H]^+$	^{1}H NMR (400 MHz, methanol-d_4) δ 8.64 – 8.52 (m, 1H), 8.26 (s, 1H), 8.13 – 8.02 (m, 3H), 7.74 (d, J = 8.4 Hz, 1H), 7.50 – 7.26 (m, 5H), 5.82 – 5.67 (m, 4H), 5.15 – 5.06 (m, 1H), 4.74 – 4.63 (m, 1H), 4.56 (s, 1H), 4.52 – 4.44 (m, 1H), 4.22 – 4.06 (m, 1H), 4.02 – 3.79 (m, 1H), 3.79 – 3.66 (m, 1H), 3.65 – 3.46 (m, 2H), 2.41 – 2.23 (m, 2H), 2.13 – 1.96 (m, 6H), 1.93 – 1.79 (m, 2H), 1.76 – 1.62 (m, 2H), 1.35 – 1.12 (m, 18H)

195	isopropyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		772.4 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 – 8.70 (m, 1H), 8.61 – 8.52 (m, 1H), 8.51 – 8.39 (m, 1H), 8.21 (s, 1H), 7.98 – 7.82 (m, 3H), 7.48 – 7.27 (m, 4H), 7.19 – 7.08 (m, 3H), 5.74 – 5.48 (m, 1H), 4.88 – 4.52 (m, 3H), 4.46 – 4.16 (m, 3H), 4.04 – 3.70 (m, 4H), 3.53 – 3.39 (m, 2H), 2.27 – 2.12 (m, 1H), 2.08 – 1.92 (m, 2H), 1.90 – 1.59 (m, 7H), 1.14 – 0.95 (m, 9H)
196	isopropyl ((fluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		790.8 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 – 8.45 (m, 2H), 8.04 – 7.64 (m, 5H), 7.63 – 7.51 (m, 1H), 7.45 – 7.29 (m, 2H), 7.27 – 7.02 (m, 4H), 6.07 – 5.85 (m, 1H), 5.05 – 4.91 (m, 1H), 4.75 – 4.34 (m, 4H), 4.24 – 3.05 (m, 6H), 2.34 – 2.15 (m, 2H), 2.12 – 1.87 (m, 6H), 1.86 – 1.68 (m, 2H), 1.42 – 1.08 (m, 9H)
197	isopropyl (((2-(((3S,6S,10aS)-3-((3R,4S or 3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-	 or	841.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 8.87 – 8.67 (m, 1H), 8.25 – 8.15 (m, 1H), 8.00 – 7.90 (m, 1H), 7.90 – 7.83 (m, 1H), 7.48 – 7.36 (m, 2H), 7.36 – 7.26 (m, 2H), 7.18 – 7.09 (m, 3H), 6.41 – 6.30 (m, 1H), 6.29 – 6.17 (m, 1H), 5.71 – 5.50 (m, 1H), 4.99 – 4.88 (m, 1H), 4.85 – 4.73 (m, 1H), 4.59 – 4.50 (m, 1H), 4.36 – 4.19 (m, 2H), 3.95

	a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 SFC peak 2 was used for biological testing		– 3.42 (m, 7H), 3.24 – 3.15 (m, 1H), 2.34 – 2.18 (m, 1H), 2.10 – 2.02 (m, 1H), 1.92 – 1.74 (m, 6H), 1.64 – 1.51 (m, 2H), 1.24 – 1.15 (m, 1H), 1.14 – 0.94 (m, 10H)
198	isopropyl (((2-(((3S,6S,10aS)-3-((3R,4S or 3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 or  SFC peak 1 was used for biological testing	859.2 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.48 (m, 5H), 7.37 – 7.27 (m, 2H), 7.25 – 6.95 (m, 4H), 6.57 – 6.39 (m, 1H), 6.17 – 5.84 (m, 2H), 5.20 – 5.07 (m, 1H), 5.06 – 4.88 (m, 1H), 4.63 – 4.42 (m, 2H), 4.39 – 4.28 (m, 1H), 4.21 – 3.51 (m, 5H), 3.49 – 3.37 (m, 1H), 3.32 – 3.07 (m, 1H), 2.26 – 1.73 (m, 10H), 1.69 – 1.57 (m, 2H), 1.29 – 1.09 (m, 9H)

S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-hydroxy-2,2-dimethylpropanethioate) trifluoroacetate (199)



[00417] Step 1: Preparation of S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanethioate)

[00418] S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanethioate) was prepared using the procedure described for the synthesis of S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl) bis(oxy)) bis(ethane-2,1-diyl)) dibutanethioate and starting from perfluorophenyl 5-((bis(2-((3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanoyl)thio)ethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate and (3S,4R or 3R,4S)-1-((3S,6S,10aS)-6-amino-5-oxodecahydropyrrolo[1,2-a]azocine-3-carbonyl)-4-phenylpyrrolidine-3-carbonitrile (SFC peak 2 was used). The product was purified using standard chromatographic techniques.

[00419] The reaction with perfluorophenyl 5-((bis(2-(butyrylthio)ethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (25.0 mg, 25.3

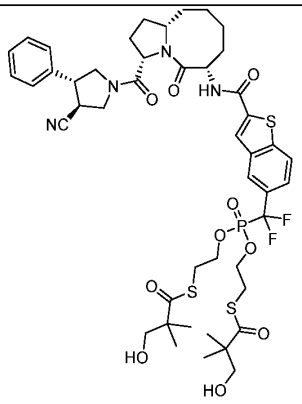
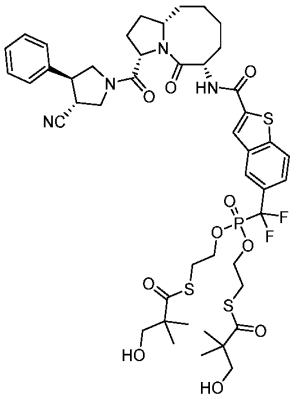
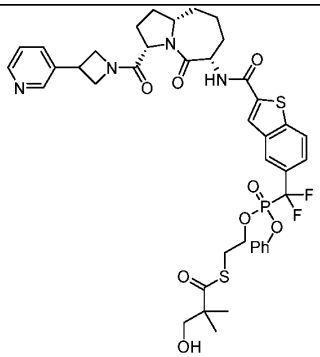
μmol, 1.0 eq) and (3S,4R or 3R,4S)-1-((3S,6S,10aS)-6-amino-5-oxodecahydropyrrolo[1,2-a]azocine-3-carbonyl)-4-phenylpyrrolidine-3-carbonitrile (9.62 mg, 25.3 μmol, 1.0 eq) afforded S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanethioate) (14.0 mg, 11.8 μmol, 46.8% yield) as a colorless oil after prep-HPLC purification.

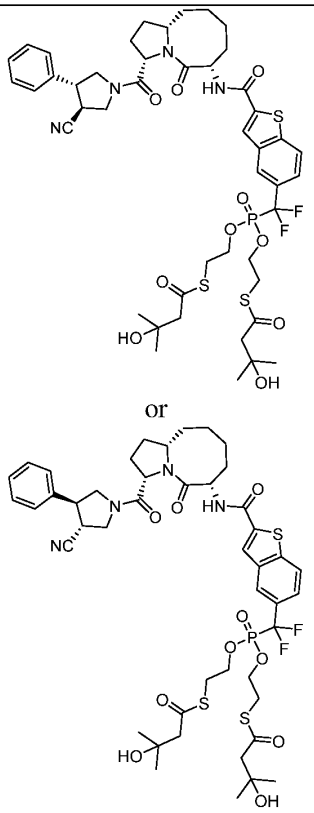
[00420] Step 2: *Preparation of S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-hydroxy-2,2-dimethylpropanethioate) trifluoroacetate (**199**)*

[00421] To a solution of S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanethioate) (14 mg, 11.8 μmol, 1.0 eq) in CH2Cl2 (0.5 mL) added TFA (13.4 mg, 118 μmol, 10.0 eq). The reaction mixture was stirred at 25 °C for 0.5 h and subsequently concentrated in vacuo. The crude product was pre-purified by column chromatography followed by prep-HPLC purification to afford S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-hydroxy-2,2-dimethylpropanethioate) trifluoroacetate (**199**) (4.90 mg, 5.13 μmol, 43.7% yield). LCMS ESI (m/z) = 955.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (m, 1H), 8.21 (m, 1H), 7.98 – 7.91 (m, 1H), 7.84 (s, 1H), 7.41 (m, 5H), 7.34 – 7.26 (m, 1H), 5.08 – 4.91 (m, 1H), 4.54 (m, 1H), 4.29 (m, 1H), 3.98 (m, 4H), 3.84 – 3.62 (m, 3H), 3.47 – 3.38 (m, 8H), 3.04 (m, 4H), 2.30 – 2.22 (m, 1H), 1.84 (m, 6H), 1.59 (m, 3H), 1.24 (s, 2H), 1.10 (s, 12H)

[00422] The following compounds in **Table 38** were prepared using the representative protocol described above for the synthesis S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-hydroxy-2,2-dimethylpropanethioate) trifluoroacetate (**199**) and utilizing the appropriate starting materials and modifications.

Table 38

Compound	Name	Structure	LCMS	NMR
200	S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-hydroxy-2,2-dimethylpropanethioate)	 or  SFC peak 2 was used for biological testing	990.8 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.02 (m, 1H), 8.00 – 7.85 (m, 2H), 7.61 (d, J = 8.5 Hz, 1H), 7.45 – 7.29 (m, 6H), 5.23 – 5.09 (m, 1H), 4.61 – 4.49 (m, 1H), 4.37 – 3.95 (m, 8H), 3.79 – 3.47 (m, 6H), 3.35 – 3.03 (m, 5H), 2.25 – 2.17 (m, 3H), 2.15 – 2.10 (m, 3H), 2.03 – 2.00 (m, 1H), 1.90 – 1.75 (m, 3H), 1.72 – 1.61 (m, 2H), 1.25 – 1.14 (m, 12H)
201	S-(2-(((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)oxy)ethyl) 3-hydroxy-2,2-		854.9 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 – 8.51 (m, 2H), 8.15 (d, J = 16.3 Hz, 1H), 8.05 – 7.84 (m, 3H), 7.77 – 7.63 (m, 2H), 7.48 – 7.29 (m, 3H), 7.22 – 7.12 (m, 3H), 5.02 – 4.44 (m, 5H), 4.32 – 4.16 (m, 3H), 4.09 – 3.88 (m, 2H), 3.53 (s, 2H), 3.16 – 2.99 (m, 2H), 2.32 – 2.16 (m, 3H), 2.09 – 2.04 (m, 3H), 1.96 – 1.92 (m, 2H), 1.85 – 1.79 (m, 2H), 1.17 (dd, J = 5.8, 2.4 Hz, 6H)

	dimethylpropanethioate			
202	S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R or 3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-hydroxy-3-methylbutanethioate)	 SFC peak 2 was used for biological testing	991.3 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 – 8.79 (m, 1H), 8.35 (d, J = 10.1 Hz, 1H), 8.28 – 8.07 (m, 2H), 7.60 (s, 1H), 7.39 (m, 5H), 4.96 (s, 1H), 4.66 (s, 1H), 4.60 – 4.48 (m, 1H), 4.39 – 3.91 (m, 8H), 3.88 – 3.77 (m, 1H), 3.70 – 3.50 (m, 2H), 3.12 (s, 4H), 2.66 (s, 4H), 2.27 (s, 1H), 2.07 – 1.54 (m, 11H), 1.17 (s, 12H)

List of SFC Methods:

[00423] A listing of certain SFC conditions are shown in **Table 39**.

Table 39

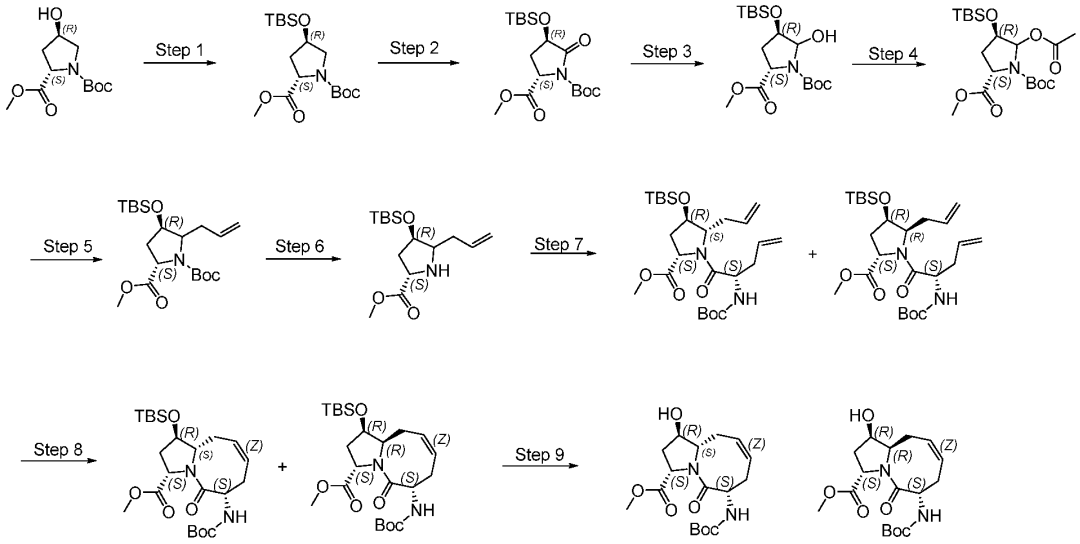
Method	Preparative SFC conditions for separation	Used for
1	Lux i-Cellulose-5 21.2 x 250 mm 5 um column, column temp = 40°C, flow rate 75 mL/min, 20% MeOH, cycle time: 5 min	• methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-9-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate and methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-8-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate
2	ChiralCel OX, 250×21.2mm I.D., 5μm, A for CO_2 and	• tert-butyl ((1aS,3S,6S,8aR,9aR)-4-oxo-6-((S)-3-phenylpyrrolidine-1-carbonyl)decahydrooxireno[2,3-d]pyrrolo[1,2-a]azocin-3-yl)carbamate and tert-butyl ((1aS,3S,6S,8aR,9aR)-4-oxo-6-((R)-3-

	B for MeOH + 0.1% NH_4OH, 40 mL/min	phenylpyrrolidine-1-carbonyl)decahydrooxireno[2,3-d]pyrrolo[1,2-a]azocin-3-yl)carbamate
3	ChiralPak R,R-WHELK, 250×21.2mm I.D., 5µm; Mobile phase: A for CO_2 and B for MeOH + 0.1% NH_4OH Gradient: B 25%; flow rate: 40 mL / min	• tert-butyl ((3S,6S,8R,9R,10aR)-9-hydroxy-8-methyl-5-oxo-3-((S)-3-phenylpyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamate and tert-butyl ((3S,6S,8S,9S,10aR)-8-hydroxy-9-methyl-5-oxo-3-((S)-3-phenylpyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamate
4	Lux *i*-Amylose 3, 21.2 x 250 mm 5 um column, 75 mL/min, 40% MeOH	• benzyl (R)-5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate and benzyl (S)-5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate
5	DAICEL CHIRALPAK AD 250 mm × 30 mm, 10 um, Mobile phase: Phase A for CO_2, and Phase B for Neu-IPA; Gradient elution: B in A 30%	• tert-butyl ((3S,6S,8R,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate and tert-butyl ((3S,6S,8S,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate
6	ChiralPak C-IG, 100 ×4.6mm I.D., 5µm; Mobile phase: A for CO_2 and B for methanol (0.05% diethylamine); Gradient: 10% to 40% B in 8 min; Flow rate: 2.5 mL/min; Back pressure: 100 bar; Column temperature: 40 ºC; Wavelength: 210 nm; Cycle-time: 2 min	Trans pyrrolidines: • tert-butyl (3R,4S)-3-cyano-4-phenylpyrrolidine-1-carboxylate • tert-butyl (3S,4R)-3-cyano-4-phenylpyrrolidine-1-carboxylate • tert-butyl (3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate • tert-butyl (3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate
7	Column Lux-Cellulose-5 21.2 x 250 mm, 5 um column, 3.7 mg/inj, concentration 36.9 mg/mL, Column T = 40 °C, Flow rate 75 mL/min, 15% MeOH (with 0.1% diethylamine), cycle time: 4.9 min	• (3S,4'S)-2-oxospiro[indoline-3,3'-pyrrolidine]-4'-carbonitrile and (3R,4'R)-2-oxospiro[indoline-3,3'-pyrrolidine]-4'-carbonitrile or (3S,4'R)-2-oxospiro[indoline-3,3'-pyrrolidine]-4'-carbonitrile or (3R,4'S)-2-oxospiro[indoline-3,3'-pyrrolidine]-4'-carbonitrile

Further Compounds and Methods

Procedures for Syntheses of Cores:

Synthesis of methyl (1R,3S,6S,10aS,Z)-6-((tert-butoxycarbonyl)amino)-1-hydroxy-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate and methyl (1R,3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-1-hydroxy-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate



[00424] *Step 1: 1-(tert-butyl) 2-methyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate*

[00425] To a solution of 1-(tert-butyl) 2-methyl (2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate (330 g, 1.35 mol, 1.00 eq) in DMF (2.50 L) was added imidazole (183 g, 2.69 mol, 2.00 eq) at 25 °C under N_2. The mixture was cooled to 0 °C and stirred for 0.50 hr. To the mixture was added TBSCl (243 g, 1.61 mol, 198 mL, 1.20 eq) at 0 °C and the mixture was stirred at 0 °C for 0.5 hr. The mixture was allowed to warm to 25 °C and stirred at 25 °C for 12 h. TLC (petroleum ether/ethyl acetate = 1/3) showed that 1-(tert-butyl) 2-methyl (2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate (R_f = 0.50) was consumed completely and a major new spot (R_f = 0.80) was formed. Three batches were combined. The mixture was poured into 15.0 L water and extracted with ethyl acetate (5.00 L * 2). The organic layer was washed with saturated $NaHCO_3$ (5.00 L * 2), saturated NH_4Cl (5.00 L * 2), brine (5.00 L), dried over Na_2SO_4, filtered and concentrated to give *1-(tert-butyl) 2-methyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate* (1.54 kg, crude) as colorless oil. ^1H NMR:

(400 MHz, $CDCl_3$) δ 4.49 - 4.29 (m, 2H), 3.80 - 3.69 (m, 3H), 3.67 - 3.54 (m, 1H), 3.47 - 3.28 (m, 1H), 2.25 - 2.12 (m, 1H), 2.08 - 1.96 (m, 1H), 1.52 - 1.38 (m, 9H), 0.88 (s, 9H), 0.07 (s, 6H).

[00426] *Step 2: Synthesis of 1-(tert-butyl) 2-methyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)-5-oxopyrrolidine-1,2-dicarboxylate*

[00427] To a solution of $NaIO_4$ (250 g, 1.17 mol, 64.7 mL, 3.00 eq) in H_2O (2.20 L) was added $RuO_2.H_2O$ (11.8 g, 77.9 mmol, 0.20 eq) at 25 °C under N_2. The mixture was stirred at 25 °C for 0.50 hr. To the mixture was added a solution of *1-(tert-butyl) 2-methyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate* (140 g, 389 mmol, 1.00 eq) in ethyl acetate (1.20 L) at 25 °C. The mixture was stirred at 25 °C for 12 h. TLC (petroleum ether/ethyl acetate = 10/1) showed that *1-(tert-butyl) 2-methyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate* (R_f = 0.40) was consumed and a major new spot (R_f = 0.45) was formed. Six batches were combined. The mixture was filtered. The filtrate was extracted with ethyl acetate (10.0 L * 3). The combined organic layer was washed with $Na_2S_2O_3$ (10.0 L * 2), brine (10.0 L), dried over Na_2SO_4, filtered and concentrated to give *1-(tert-butyl) 2-methyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)-5-oxopyrrolidine-1,2-dicarboxylate* (822 g, crude) as yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.60 - 4.57 (m, 1H), 4.45 - 4.40 (m, 1H), 3.79 (s, 3H), 2.39 - 2.34 (m, 1H), 2.25 - 2.17 (m, 1H), 1.51 (s, 9H), 0.90 (s, 9H), 0.18 (s, 3H), 0.13 (s, 3H).

[00428] *Step 3: Synthesis of 1-(tert-butyl) 2-methyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)-5-hydroxypyrrolidine-1,2-dicarboxylate*

[00429] To a solution of *1-(tert-butyl) 2-methyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)-5-oxopyrrolidine-1,2-dicarboxylate* (450 g, 1.20 mol, 1.00 eq) in THF (1.35 L) was added $LiBHEt_3$ (1 M, 1.33 L, 1.10 eq) at -78 °C, then stirred at -78 °C for 3 h. TLC (petroleum ether/ethyl acetate = 3/1) showed *1-(tert-butyl) 2-methyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)-5-oxopyrrolidine-1,2-dicarboxylate* (R_f = 0.60) remained and the desired spots (R_f = 0.45, 0.50) were detected. The resulting mixture was quenched by saturated $NaHCO_3$ (1000 mL), then extracted with ethyl acetate (1500 mL * 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. *1-(tert-butyl) 2-methyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)-5-hydroxypyrrolidine-1,2-dicarboxylate* (450 g, Crude) was obtained as a light-yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.50 - 5.15 (m, 1H), 4.56 - 4.18 (m, 2H), 3.76 - 3.68 (m, 3H), 2.28 - 2.09 (m, 2H), 1.46 - 1.38 (m, 9H), 0.87 (d, J = 3.0 Hz, 9H), 0.10 - 0.04 (m, 6H).

[00430] *Step 4: Synthesis of 1-(tert-butyl) 2-methyl (2S,4R)-5-acetoxy-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate*

[00431] To a solution of *1-(tert-butyl) 2-methyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)-5-hydroxypyrrolidine-1,2-dicarboxylate* (384 g, 1.02 mol, 1.00 eq) , Ac_2O (156 g, 1.53 mol, 143 mL, 1.50 eq) and TEA (156 g, 1.54 mol, 215 mL, 1.51 eq) in DCM (2.00 L) was added DMAP (25.0 g, 204 mmol, 0.20 eq) at 25 °C, then stirred at 25 °C for 2 h. TLC (petroleum ether/ethyl acetate =4/1) showed *1-(tert-butyl) 2-methyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)-5-hydroxypyrrolidine-1,2-dicarboxylate* (R_f = 0.40, 0.45) was consumed and the desired spot (R_f = 0.45, 0.55) was detected. The combined reaction mixture was poured into saturate $NaHCO_3$ (2000 mL) and extracted with DCM (1000 mL * 2). The combined organic phase was concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate = 10/1, R_f = 0.45). 1-(tert-butyl) 2-methyl (2S,4R)-5-acetoxy-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate (220 g, 527 mmol, 51.5% yield, 100% purity) was obtained as a light-yellow oil. ^{1}H NMR: EW28523-2-P1A1 (400 MHz, $CDCl_3$) δ 6.17 (s, 1H), 4.56 - 4.37 (m, 1H), 4.14 (d, J = 7.2 Hz, 1H), 3.77 (s, 3H), 2.18 - 2.07 (m, 5H), 1.45 (d, J = 6.8 Hz, 9H), 0.87 (s, 9H), 0.16 - 0.07 (m, 6H).

[00432] *Step 5: Synthesis of 1-(tert-butyl) 2-methyl (2S,4R)-5-allyl-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate*

[00433] To a solution of *1-(tert-butyl) 2-methyl (2S,4R)-5-acetoxy-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate* (100 g, 239 mmol, 1.00 eq) in DCM (1.00 L) was added BF_3•Et_2O (85.1 g, 599 mmol, 74.0 mL, 2.50 eq) and allyltrimethylsilane (123 g, 1.08 mol, 172 mL, 4.50 eq) at -70 °C under N_2. The reaction mixture was stirred at -70 °C for 3 h. LCMS (EW28523-3-P1A) showed *1-(tert-butyl) 2-methyl (2S,4R)-5-acetoxy-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate* was consumed and the desired mass (RT = 1.153 mins) was detected. The reaction was quenched by saturated $NaHCO_3$ (1000 mL), then extracted with DCM (1000 mL * 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. *1-(tert-butyl) 2-methyl (2S,4R)-5-allyl-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate* (200 g, crude) was obtained as a yellow oil. The crude product was used for the next step without purification. LCMS: product RT = 1.153 mins, m/z = 300.1 $[M\text{-}Boc]^+$. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.97 - 5.74 (m, 1H), 5.17 - 4.95 (m, 1H), 4.67 - 3.94 (m, 3H), 3.81 - 3.70 (m, 3H), 2.65 - 2.42 (m, 1H), 2.37 - 2.15 (m, 1H), 2.12 - 1.92 (m, 2H), 1.60 - 1.36 (m, 8H), 0.92 - 0.83 (m, 9H), 0.09 - 0.03 (m, 6H)

[00434] *Step 6: Synthesis of methyl (2S,4R)-5-allyl-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate*

[00435] To a solution of *1-(tert-butyl) 2-methyl (2S,4R)-5-allyl-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate* (200 g, 500 mmol, Crude purity, 1.00 eq) in DCM (1.50 mL) was added TFA (571 g, 5.01 mol, 370 mL, 10.0 eq) at 0 °C, then stirred at 25 °C for 16 h. TLC (petroleum ether/ethyl acetate = 2/1) showed *1-(tert-butyl) 2-methyl (2S,4R)-5-allyl-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate* (R_f = 0.50, 0.55) was consumed and the desired spot (R_f = 0.35) was detected. The resulting mixture was quenched by saturated $NaHCO_3$ (3000 mL) then extracted with DCM (2000 mL * 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by fast silica gel chromatography (petroleum ether/ethyl acetate = 10/1, R_f = 0.35). *methyl (2S,4R)-5-allyl-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate* (135 g, crude) was obtained as a yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.89 - 5.76 (m, 1H), 5.19 - 5.03 (m, 3H), 4.30 - 4.21 (m, 1H), 4.07 (t, J = 8.2 Hz, 1H), 3.73 (s, 3H), 3.18 (dt, J = 3.4, 7.0 Hz, 1H), 2.35 - 2.27 (m, 2H), 2.21 - 2.11 (m, 2H), 2.08 - 1.99 (m, 2H), 0.91 - 0.89 (m, 9H), 0.08 (d, J = 5.4 Hz, 6H).

[00436] *Step 7: Synthesis of methyl (2S,4R,5S)-5-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-enoyl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate and methyl (2S,4R,5R)-5-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-enoyl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate*

[00437] To a solution of *methyl (2S,4R)-5-allyl-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate* (135 g, 451 mmol, crude purity, 1.00 eq) and (S)-2-((tert-butoxycarbonyl)amino)pent-4-enoic acid (111 g, 518 mmol, 1.15 eq) in DMF (1.30 L) was added HATU (343 g, 902 mmol, 2.00 eq) and DIEA (291 g, 2.25 mol, 393 mL, 5.00 eq) at 0 °C, then stirred at 25 °C for 16 h. TLC (petroleum ether/ethyl acetate = 3/1) showed *methyl (2S,4R)-5-allyl-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate* (R_f = 0.40, 0.45) was consumed and the desired spot (R_f = 0.50) was detected. The reaction was poured into water (4.00 L), then extracted with ethyl acetate (2.00 L * 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by pre-HPLC (column: Phenomenex Luna C18 (250*80mm*15um);mobile phase: [water(0.1%TFA)-ACN];B%: 80%-100%,35min]). The aqueous was concentrated under vacuum to give product. *methyl (2S,4R,5S)-5-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-enoyl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate* (84.0 g, 163 mmol, 32.2% yield over three steps, 96.5% purity) was obtained as a

light-yellow oil. *methyl (2S,4R,5R)-5-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-enoyl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate* (24.0 g, 48.3 mmol, 10.7% yield over three steps) was obtained as a light-yellow oil. HPLC *methyl (2S,4R,5S)-5-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-enoyl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate*: product RT = 4.394 mins, 96.5% purity under 220 nm. ^{1}H NMR *methyl (2S,4R,5S)-5-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-enoyl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate*: (400 MHz, $CDCl_3$) δ 5.98 - 5.76 (m, 2H), 5.28 - 5.05 (m, 5H), 4.63 - 4.48 (m, 2H), 4.43 - 4.31 (m, 1H), 4.14 - 4.01 (m, 1H), 3.74 (s, 3H), 2.71 - 2.59 (m, 1H), 2.48 - 2.35 (m, 2H), 2.31 (s, 1H), 2.24 - 2.14 (m, 1H), 2.08 - 2.00 (m, 1H), 1.48 - 1.40 (m, 9H), 0.94 - 0.88 (m, 9H), 0.09 (d, J = 3.2 Hz, 6H).

[00438] *Step 8a: Synthesis of methyl (1R,3S,6S,10aS,Z)-6-((tert-butoxycarbonyl)amino)-1-((tert-butyldimethylsilyl)oxy)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate*

[00439] To a solution of *methyl (2S,4R,5S)-5-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-enoyl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate* (30.0 g, 58.3 mmol, 96.5% purity, 1.00 eq) in DCM (1.50 L) was added Grubbs 1st (9.59 g, 11.7 mmol, 0.20 eq) at 25 °C, then heated to reflux (55 °C) for 16 h. LCMS (EW28523-6-P1A) showed methyl (2S,4R,5S)-5-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-enoyl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate remained (RT = 1.138 mins) and the desired mass (RT = 1.065 mins) was detected. The mixture was concentrated in vacuo. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 10/1, petroleum ether/ethyl acetate = 3/1, R_f = 0.40). *methyl (1R,3S,6S,10aS,Z)-6-((tert-butoxycarbonyl)amino)-1-((tert-butyldimethylsilyl)oxy)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate* (23.0 g, crude) was obtained as a brown oil. LCMS: product RT = 1.065 mins, m/z = 469.1 $(M+H)^+$

[00440] *Step 8b: Synthesis of methyl (1R,3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-1-((tert-butyldimethylsilyl)oxy)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate*

[00441] To a solution of *methyl (2S,4R,5R)-5-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-enoyl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate* (16.3 g, 32.8 mmol, 1.00 eq) in DCM (800 mL) was added Grubb's 1st (2.70 g, 3.28 mmol, 0.10 eq) at 25 °C, then heated to reflux (60 °C) for 16 h. LCMS (EW21491-265-P1A) showed *methyl (2S,4R,5R)-5-allyl-1-((S)-2-((tert-butoxycarbonyl)amino)pent-4-*

enoyl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate was consumed and the desired mass (RT = 1.077 mins) was detected. The resulting mixture was concentrated under vacuum. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 10/1 to 5/1, R_f = 0.50, Plate: petroleum ether/ethyl acetate = 1/1). *methyl (1R,3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-1-((tert-butyldimethylsilyl)oxy)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate* (18.0 g, crude) was obtained as a brown oil. LCMS: product RT = 1.077 mins, m/z = 469.1 $(M+H)^+$

[00442] *Step 9a: Synthesis of methyl (1R,3S,6S,10aS,Z)-6-((tert-butoxycarbonyl)amino)-1-hydroxy-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate*

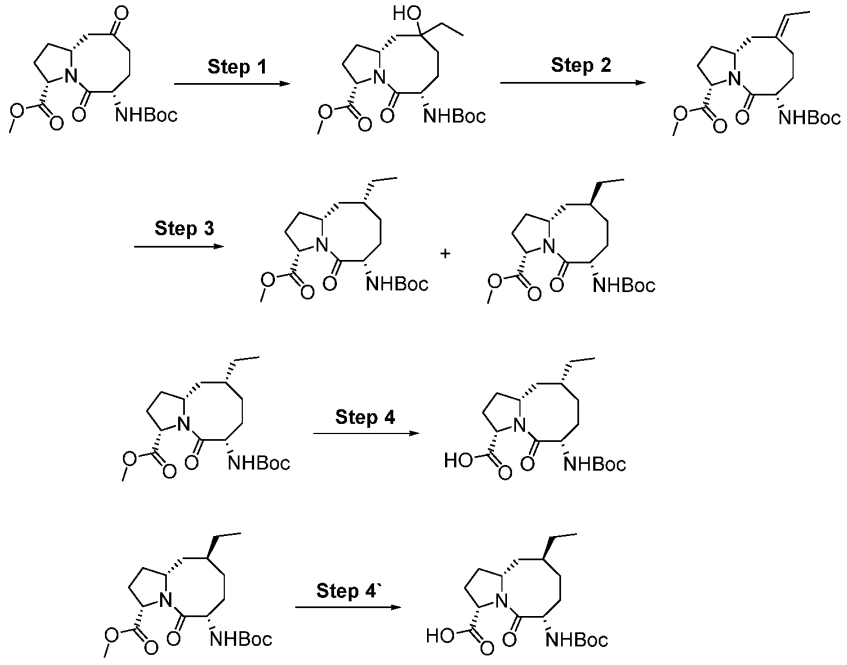
[00443] To a solution of *methyl (1R,3S,6S,10aS,Z)-6-((tert-butoxycarbonyl)amino)-1-((tert-butyldimethylsilyl)oxy)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate* (23.0 g, 49.1 mmol, CRUDE purity, 1.00 eq) in THF (220 mL) was added TBAF (1 M, 98.1 mL, 2.00 eq) at -10 °C, then stirred at 0 °C for 1 hr. TLC (petroleum ether/ethyl acetate = 3/1, Plate 1) showed *methyl (1R,3S,6S,10aS,Z)-6-((tert-butoxycarbonyl)amino)-1-((tert-butyldimethylsilyl)oxy)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate* (R_f = 0.30) was consumed and the desired spot (R_f = 0.00) was detected. The reaction was poured into water (50.0 mL) then extracted with ethyl acetate (50.0 mL * 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was triturated with petroleum ether/ethyl acetate = 2/1 (80.0 mL) at 20 °C for 0.5 h, then filtered. The filter cake was dried under vacuum. *methyl (1R,3S,6S,10aS,Z)-6-((tert-butoxycarbonyl)amino)-1-hydroxy-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate* (5.20 g, 14.2 mmol, 12.1% yield over two step, 96.7% purity) was obtained as a light-yellow solid. LCMS: product RT = 0.774 min, m/z = 299.0 $[M-55]^+$ HPLC product RT = 1.910 mins, 96.7% purity under 220 nm SFC: RT = 1.218 mins, ee% = 100% (220 nm) ^1H NMR: (400 MHz, $CDCl_3$) δ 6.05 - 5.71 (m, 3H), 4.77 - 4.62 (m, 2H), 4.41 (d, J = 3.2 Hz, 1H), 4.30 - 4.22 (m, 1H), 3.75 (s, 3H), 2.89 - 2.78 (m, 1H), 2.71 - 2.55 (m, 2H), 2.46 (ddd, J = 3.0, 8.2, 16.8 Hz, 1H), 2.26 (ddd, J = 3.8, 9.2, 13.4 Hz, 1H), 2.16 - 1.95 (m, 2H), 1.44 (s, 9H)

[00444] *Step 9b: Synthesis of methyl (1R,3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-1-hydroxy-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate*

[00445] To a solution of *methyl (1R,3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-1-((tert-butyldimethylsilyl)oxy)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate* (18.0 g, 38.4 mmol, CRUDE purity, 1.00 eq) in THF (100 mL) was added TBAF (1 M, 76.8 mL, 2.00 eq) at -10 °C, then stirred at 0 °C for 1 hr. TLC (petroleum ether/ethyl

acetate = 3/1, Plate 1) showed *methyl (1R,3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-1-((tert-butyldimethylsilyl)oxy)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate* (R_f = 0.30) was consumed and the desired spot (R_f = 0.00) was detected. The reaction was poured into water (200 mL) then extracted with ethyl acetate (100 mL * 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by prep-HPLC (TFA condition), then adjusted pH about 7 with saturated $NaHCO_3$ aqueous (50.0 mL), extracted with ethyl acetate (500 mL * 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. *methyl (1R,3S,6S,10aR,Z)-6-((tert-butoxycarbonyl)amino)-1-hydroxy-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate* (4.20 g, 11.4 mmol, 36.0% yield over two step, 96.2% purity) was obtained as a yellow solid LCMS: product RT = 0.776 min, m/z = 299.0 $(M-55)^+$ HPLC: product RT = 1.960 mins, 96.2% purity under 220 nm SFC: RT = 1.483 mins, ee% = 100% (220 nm) ^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.96 - 5.81 (m, 1H), 5.78 - 5.63 (m, 2H), 4.84 - 4.65 (m, 1H), 4.58 (t, J = 7.2 Hz, 1H), 4.16 (d, J = 4.6 Hz, 1H), 3.89 (d, J = 4.6 Hz, 1H), 3.72 (s, 3H), 3.40 - 2.82 (m, 1H), 2.65 (t, J = 16.8 Hz, 2H), 2.55 - 2.34 (m, 2H), 2.27 - 2.07 (m, 2H), 1.42 (s, 9H).

Synthesis of (3S,6S,9R,10aR)-6-((tert-butoxycarbonyl)amino)-9-ethyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid and (3S,6S,9S,10aR)-6-((tert-butoxycarbonyl)amino)-9-ethyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid

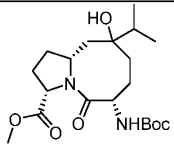


[00446] *Step 1: Preparation of methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-9-ethyl-9-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate*

[00447] To a solution of methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-5,9-dioxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (250 mg, 705 µmol, 1 eq) in anhydrous tetrahydrofuran (10 mL) was added ethyl magnesium chloride solution (2 M in THF) (720 µL, 1.44 mmol, 2.05 eq) at 0 °C. The reaction mixture was stirred at 0°C for 2 h, then quenched with saturated aq. NH_4Cl. The mixture was extracted with EtOAc (2 x 15 mL) and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by reverse phase chromatography on a 30 g C_{18} cartridge eluting with 5-60% MeCN in water (with 0.1% formic acid). The combined fractions were concentrated under reduced pressure and then freeze-dried to give methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-9-ethyl-9-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (197 mg, 72.6%) as a white solid. LCMS (ESI): m/z = 385.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 5.38 (d, *J* = 7.8 Hz, 1H), 5.08 - 4.96 (m, 1H), 4.58 (dd, *J* = 11.7, 7.6 Hz, 1H), 4.53 - 4.43 (m, 1H), 3.78 - 3.71 (m, 3H), 2.41 - 2.29 (m, 1H), 2.26 - 2.12 (m, 3H), 2.06 - 1.91 (m, 2H), 1.73 (dd, *J* = 12.1, 6.7 Hz, 1H), 1.68 - 1.57 (m, 2H), 1.54 - 1.46 (m, 4H), 1.44 - 1.38 (m, 9H), 0.91 (t, *J* = 7.5 Hz, 3H).

[00448] The intermediates shown in **Table 40** were prepared according to the protocol described above in Step 1 with appropriate modifications.

Table 40

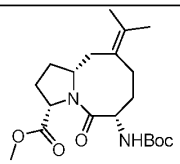
Name	Structure	LCMS	NMR
methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-9-hydroxy-9-isopropyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate		399.4 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 5.40 (d, *J* = 7.8 Hz, 1H), 5.08 - 4.95 (m, 1H), 4.59 (dd, *J* = 11.1, 8.2 Hz, 1H), 4.53 - 4.42 (m, 1H), 3.76 (s, 3H), 2.39 - 2.29 (m, 1H), 2.25 - 2.10 (m, 3H), 2.08 - 1.94 (m, 2H), 1.78 - 1.47 (m, 6H), 1.43 (s, 9H), 0.91 (dd, *J* = 6.7, 3.3 Hz, 6H)

[00449] *Step 2: Preparation of methyl (3S,6S,10aR,E)-6-((tert-butoxycarbonyl)amino)-9-ethylidene-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate*

[00450] To a solution of methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-9-ethyl-9-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (197 mg, 512 μmol, 1 eq) in anhydrous toluene (5 mL) was added Burgess' reagent (486 mg, 2.04 mmol, 4 eq). The reaction mixture was warmed up to 70°C and stirred for 1 h. Solvent was evaporated. The crude product was purified by reverse phase chromatography on a 50 g C_{18} cartridge eluting with 5-100% MeCN in water (with 0.1% formic acid). The combined fractions were concentrated under reduced pressure to give methyl (3S,6S,10aR,E)-6-((tert-butoxycarbonyl)amino)-9-ethylidene-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (158 mg, 84.4%) as a yellow oil. LCMS (ESI): m/z = 367.4 $[M+H]^+$.

[00451] The intermediates shown in **Table 41** were prepared according to the protocol described above in Step 2 with appropriate modifications.

Table 41

Name	Structure	LCMS
methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-5-oxo-9-(propan-2-ylidene)decahydropyrrolo[1,2-a]azocine-3-carboxylate		381.2 $[M+H]^+$

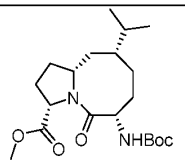
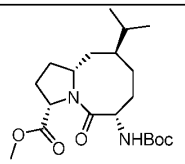
[00452] *Step 3: Preparation of methyl (3S,6S,9R,10aR)-6-((tert-butoxycarbonyl)amino)-9-ethyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate and methyl (3S,6S,9S,10aR)-6-((tert-butoxycarbonyl)amino)-9-ethyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate*

[00453] To a solution of methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-9-ethylidene-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (158 mg, 431 μmol, 1 eq) in methanol (5 mL) under nitrogen bubbling was added 10% palladium on carbon (50% wet) (136 mg, 129 μmol, 0.3 eq). Hydrogen was bubbled for 5 min. into the suspension and then the reaction mixture was stirred at room temperature for 20 h under hydrogen atmosphere (1 atm). Nitrogen was bubbled into the suspension for 5 min. The reaction mixture was filtered over Celite (rinsing with MeOH) and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography on a 100 g C_{18} cartridge eluting with 5-100% MeCN in water (with 0.1% formic acid). The combined fractions were concentrated under reduced pressure and then freeze-dried to give methyl (3S,6S,9R,10aR)-6-((tert-butoxycarbonyl)amino)-9-ethyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (86.0 mg, 54.4%, major isomer) as a white solid. LCMS (ESI): m/z = 369.2 $[M+H]^+$. ^1H NMR (400 MHz, C_6D_6) δ 5.69 (d, J = 8.3 Hz,

1H), 4.91 - 4.84 (m, 1H), 4.45 (t, *J* = 8.7 Hz, 1H), 3.66 - 3.62 (m, 1H), 3.37 - 3.29 (m, 3H), 2.18 - 2.15 (m, 1H), 1.96 - 1.68 (m, 1H), 1.72 - 1.65 (m, 1H), 1.65 - 1.50 (m, 3H), 1.44 (s, 9H), 1.33 - 1.30 (m, 1H), 1.25 - 1.14 (m, 2H), 1.11 - 1.02 (m, 2H), 1.00 - 0.90 (m, 2H), 0.74 (t, *J* = 7.3 Hz, 3H). Methyl (3S,6S,9S,10aR)-6-((tert-butoxycarbonyl)amino)-9-ethyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (10.0 mg, 6.32%, minor isomer) was also isolated as a white solid. LCMS (ESI): m/z = 369.2 $[M+H]^+$. ^{1}H NMR (400 MHz, C_6D_6) δ 6.20 (d, *J* = 6.8 Hz, 1H), 4.57 - 4.45 (m, 1H), 4.36 (t, *J* = 9.0 Hz, 1H), 3.62 - 3.50 (m, 1H), 3.31 (s, 3H), 2.27 - 2.22 (m, 1H), 1.77 - 1.65 (m, 2H), 1.63 - 1.47 (m, 3H), 1.45 (s, 9H), 1.37 - 1.29 (m, 1H), 1.25 - 1.12 (m, 3H), 1.11 - 1.01 (m, 1H), 0.95 - 0.88 (m, 1H), 0.83 (t, *J* = 7.5 Hz, 3H), 0.75 - 0.64 (m, 1H). **Note:** Absolute stereochemistry on carbon bearing ethyl group is unknown for both isomers.

[00454] The intermediates shown in **Table 42** were prepared according to the protocol described above in Step 3 with appropriate modifications. **Note:** Absolute stereochemistry on carbon bearing isopropyl group is unknown for both isomers.

Table 42

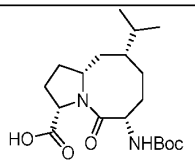
Name	Structure	LCMS	NMR
methyl (3S,6S,9R,10aR)-6-((tert-butoxycarbonyl)amino)-9-isopropyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (Major Isomer)		383.2 $[M+H]^+$	^{1}H NMR (400 MHz, C_6D_6) δ 5.70 (d, *J* = 8.6 Hz, 1H), 4.95 - 4.82 (m, 1H), 4.46 (t, *J* = 8.8 Hz, 1H), 3.65 (dd, *J* = 11.6, 7.9 Hz, 1H), 3.35 -3.30 (m, 3H), 2.11 - 1.98 (m, 1H), 1.95 - 1.84 (m, 1H), 1.73 - 1.65 (m, 1H), 1.64 - 1.51 (m, 3H), 1.45 - 1.41 (m, 9H), 1.37 - 1.31 (m, 2H), 1.28 - 1.18 (m, 2H), 1.00 - 0.90 (m, 2H), 0.73 (t, *J* = 6.4 Hz, 6H)
methyl (3S,6S,9S,10aR)-6-((tert-butoxycarbonyl)amino)-9-isopropyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (Minor Isomer)		383.2 $[M+H]^+$	^{1}H NMR (400 MHz, C_6D_6) δ 6.25 (d, *J* = 6.8 Hz, 1H), 4.50 - 4.42 (m, 1H), 4.35 (t, *J* = 9.0 Hz, 1H), 3.54 - 3.49 (m, 1H), 2.30 - 2.21 (m, 1H), 1.76 - 1.66 (m, 2H), 1.61 - 1.47 (m, 3H), 1.46 - 1.42 (m, 10H), 1.42 - 1.27 (m, 4H), 1.14 - 1.02 (m, 2H), 0.95 - 0.89 (m, 1H), 0.81 - 0.77 (m, 7H)

[00455] *Step 4: Preparation of (3S,6S,9R,10aR)-6-((tert-butoxycarbonyl)amino)-9-ethyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid*

[00456] To a solution of methyl (3S,6S,9R,10aR)-6-((tert-butoxycarbonyl)amino)-9-ethyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (40 mg, 108 µmol, 1 eq) in tetrahydrofuran (6 mL) and water (2 mL) was added lithium hydroxide monohydrate (13.5 mg, 324 µmol, 3 eq). The reaction mixture was stirred 4 h at room temperature. The reaction mixture was concentrated under reduced pressure (to remove THF). The crude product was purified by reverse phase chromatography on a 50 g C_{18} cartridge eluting with 5-60% MeCN in water (with 0.1% formic acid). The combined fractions were concentrated under reduced pressure and then freeze-dried to give (3S,6S,9R,10aR)-6-((tert-butoxycarbonyl)amino)-9-ethyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid (32.0 mg, 83.7%) as a white solid. LCMS (ESI): m/z = 355.2 $[M+H]^+$.

[00457] The intermediates shown in **Table 43** were prepared according to the protocol described above in Step 4 with appropriate modifications.

Table 43

Name	Structure	LCMS	NMR
(3S,6S,9R,10aR)-6-((tert-butoxycarbonyl)amino)-9-isopropyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid		369.2 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (d, *J* = 8.8 Hz, 1H), 4.81 - 4.70 (m, 1H), 4.62 (t, *J* = 8.1 Hz, 1H), 4.29 - 4.25 (m, 1H), 2.45 - 2.32 (m, 1H), 2.29 - 2.20 (m, 2H), 1.98 - 1.82 (m, 2H), 1.72 - 1.51 (m, 5H), 1.45 (s, 9H), 1.37 - 1.26 (m, 1H), 0.85 - 0.80 (m, 6H)

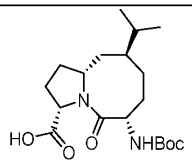
[00458] *Step 4': Preparation of (3S,6S,9S,10aR)-6-((tert-butoxycarbonyl)amino)-9-ethyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid*

[00459] To a solution of methyl (3S,6S,9S,10aR)-6-((tert-butoxycarbonyl)amino)-9-ethyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (10 mg, 27.1 µmol, 1 eq) in tetrahydrofuran (1 mL) and water (0.2 mL) was added lithium hydroxide monohydrate (3.41 mg, 81.3 µmol, 3 eq). The reaction mixture was stirred for 18 h at room temperature. 1 N HCl (1 mL) was added. The reaction mixture was concentrated under reduced pressure to give crude (3S,6S,9S,10aR)-6-((tert-butoxycarbonyl)amino)-9-ethyl-5-oxodecahydropyrrolo[1,2-

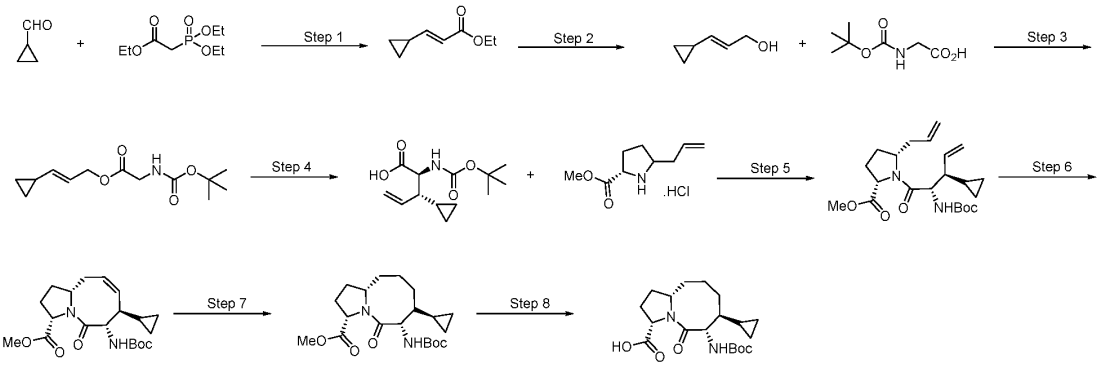
a]azocine-3-carboxylic acid (9.6 mg, 100%) as a white solid. LCMS (ESI): m/z = 355.2 $[M+H]^+$.

[00460] The intermediates shown in **Table 44** were prepared according to the protocol described above in Step 4 and Step 4' with appropriate modifications.

Table 44

Name	Structure	LCMS
(3S,6S,9S,10aR)-6-((tert-butoxycarbonyl)amino)-9-isopropyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid		369.2 $[M+H]^+$

Synthesis of (3S,6S,7S,10aS)-6-((tert-butoxycarbonyl)amino)-7-cyclopropyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid



[00461] *Step 1: Preparation of ethyl (E)-3-cyclopropylacrylate*

[00462] To a suspension of 60% sodium hydride in mineral oil (658 mg, 16.5 mmol, 1.1 eq) in tetrahydrofuran (25 mL) at 0 °C was slowly added ethyl 2-(diethoxyphosphoryl)acetate (3.69 g, 16.5 mmol, 1.1 eq). The reaction was warmed up to room temperature and stirred for 30 min. A solution was observed. Cyclopropanecarbaldehyde (1.05 g, 15 mmol, 1 eq) was added dropwise at room temperature. An exotherm was observed and the formation of a thick paste. Stirring was difficult and the thick paste precipitated at the bottom of the flask. The reaction was stirred for 20 h at room temperature. The reaction was quenched with the addition of saturated $NaHCO_3$ aqueous solution (50 mL) and diluted with EtOAc (100 mL) and water (50 mL). The phases were separated and the aqueous layer was re-extracted with EtOAc (2 x 75 mL). The combined organic layers were dried with sodium sulfate, filtered, adsorbed on silica gel and carefully concentrated under reduced pressure (product is volatile

and care should be taken during concentration in vacuo). The crude residue was purified by flash-chromatography on silica gel eluting with 1-25% DCM in pentane to give ethyl (E)-3-cyclopropylacrylate (1.25 g, 59.5%) as a clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (dd, J = 15.3, 9.7 Hz, 1H), 5.91 (d, J = 15.7 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 1.64 - 1.53 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H), 0.99 - 0.93 (m, 2H), 0.69 - 0.62 (m, 2H).

[00463] *Step 2: Preparation of (E)-3-cyclopropylprop-2-en-1-ol*

[00464] To a solution of ethyl (E)-3-cyclopropylacrylate (1.59 g, 11.3 mmol, 1 eq) in diethyl ether (50 mL) at -78 °C was slowly added 1 M DIBAL-H (24.0 mL, 24.0 mmol, 2.13 eq) in *n*-hexanes. The reaction was stirred for 1 h at -78 °C and 2.25 h at room temperature. The reaction was cooled down to 0°C and quenched with the addition of MeOH (15 mL) and then 10% Rochelle salt aqueous solution (70 mL). The mixture was vigorously stirred for 1.5 h at room temperature and then the phases were separated. The organic layer was washed with brine, dried with sodium sulfate, filtered and concentrated under reduced pressure to give (E)-3-cyclopropylprop-2-en-1-ol (986 mg, 89.6%) as a clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (dt, J = 15.2, 6.1 Hz, 1H), 5.29 - 5.21 (m, 1H), 4.09 (d, J = 5.8 Hz, 2H), 1.48 - 1.38 (m, 1H), 0.78 - 0.72 (m, 2H), 0.43 - 0.38 (m, 2H).

[00465] *Step 3: Preparation of (E)-3-cyclopropylallyl (tert-butoxycarbonyl)glycinate*

[00466] To solution of (E)-3-cyclopropylprop-2-en-1-ol (1.05 g, 10.6 mmol, 1 eq) and (tert-butoxycarbonyl)glycine (1.85 g, 10.6 mmol, 1 eq) in methylene chloride (50 mL) at 0 °C were added dicyclohexylcarbodiimide (2.18 g, 10.6 mmol, 1.0 eq) followed by DMAP (403 mg, 1.05 mmol, 0.1 eq). The reaction was warmed up to room temperature and stirred overnight.

[00467] The white precipitate was filtered off and the filtrate was washed with 1 N HCl (50 mL) and then saturated $NaHCO_3$ aqueous solution (50 mL). The organic layer was adsorbed on silica gel and concentrated under reduced pressure. The crude residue was purified by flash-chromatography on silica gel eluting with 0-50% EtOAc in heptane to give (E)-3-cyclopropylallyl (tert-butoxycarbonyl)glycinate (1.49 g, 55.1%) as a sticky off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (dt, J = 15.4, 7.1 Hz, 1H), 5.34 - 5.29 (m, 1H), 5.05 - 4.97 (m, 1H), 4.61 - 4.57 (m, 2H), 3.98 - 3.82 (m, 2H), 1.47 (s, 9H), 1.44 - 1.39 (m, 1H), 0.80 - 0.74 (m, 2H), 0.46 - 0.40 (m, 2H).

[00468] *Step 4: Preparation of racemic-(2S,3S)-2-((tert-butoxycarbonyl)amino)-3-cyclopropylpent-4-enoic acid*

[00469] To a solution of (E)-3-cyclopropylallyl (tert-butoxycarbonyl)glycinate (1 g, 3.91 mmol, 1 eq) in tetrahydrofuran (40 mL) at -78 °C were added chlorotrimethylsilane (1.48 mL, 11.7 mmol, 3 eq) followed by the dropwise addition of a solution of 1 M LiHMDS (11.7 mL, 11.7 mmol, 3 eq) in THF. The reaction was kept in an ice-bath and stirred overnight while slowly warming up to room temperature. The reaction was quenched with 1 N HCl (3 mL) and concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography on a C_{18} cartridge eluting with 5-80% MeCN in water (with 0.1% formic acid) to give racemic-(2S,3S)-2-((tert-butoxycarbonyl)amino)-3-cyclopropylpent-4-enoic acid (730 mg, 73.1%) as a yellowish thick oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 - 5.68 (m, 1H), 5.28 - 5.10 (m, 3H), 4.51 - 4.43 (m, 1H), 1.93 - 1.82 (m, 1H), 1.45 (s, 9H), 0.94 - 0.82 (m, 1H), 0.62 - 0.49 (m, 2H), 0.34 - 0.24 (m, 1H), 0.19 - 0.08 (m, 1H).

[00470] *Step 5: Preparation of methyl (2S,5R)-5-allyl-1-((2S,3S)-2-((tert-butoxycarbonyl)amino)-3-cyclopropylpent-4-enoyl)pyrrolidine-2-carboxylate*

[00471] HATU (977 mg, 2.57 mmol, 1.2 eq) was added to a solution of crude methyl (2S)-5-allylpyrrolidine-2-carboxylate (434 mg, 2.57 mmol, eq) HCl salt, racemic-(2S,3S)-2-((tert-butoxycarbonyl)amino)-3-cyclopropylpent-4-enoic acid (550 mg, 2.15 mmol, eq) and DIPEA (2.23 mL, 12.9 mmol, 6 eq) in *N,N*-dimethylformamide (2 mL). The reaction was stirred at room temperature for 15 min. The product was purified directly by reverse phase chromatography on a C_{18} cartridge eluting with 5-80% MeCN in water (with 0.1% formic acid) to give methyl (2S,5R)-5-allyl-1-((2S,3S)-2-((tert-butoxycarbonyl)amino)-3-cyclopropylpent-4-enoyl)pyrrolidine-2-carboxylate (525 mg, 60.0%) as a thick clear oil. LCMS (ESI) m/z = 407.2 $[M+H]^+$.

[00472] *Step 6: Preparation of methyl (3S,6S,7R,10aR,Z)-6-((tert-butoxycarbonyl)amino)-7-cyclopropyl-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate*

[00473] To a solution of methyl (2S,5R)-5-allyl-1-((2S,3S)-2-((tert-butoxycarbonyl)amino)-3-cyclopropylpent-4-enoyl)pyrrolidine-2-carboxylate (525 mg, 1.29 mmol, 1 eq) in methylene chloride (75 mL) under nitrogen was added Grubbs II catalyst (109 mg, 0.129 mmol, 0.1 eq). The reaction was heated to reflux for 48 h. The reaction was concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography on a 100 g C_{18} cartridge eluting with 5-80% MeCN in water (with 0.1% formic acid) to give methyl (3S,6S,7R,10aR,Z)-6-((tert-butoxycarbonyl)amino)-7-cyclopropyl-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate (218

mg, 44.6%) as a brownish oil (complex mixture of diastereomers). LCMS (ESI) m/z = 379.2 $[M+H]^+$.

[00474] *Step 7: Preparation of methyl (3S,6S,7R,10aS)-6-((tert-butoxycarbonyl)amino)-7-cyclopropyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate*

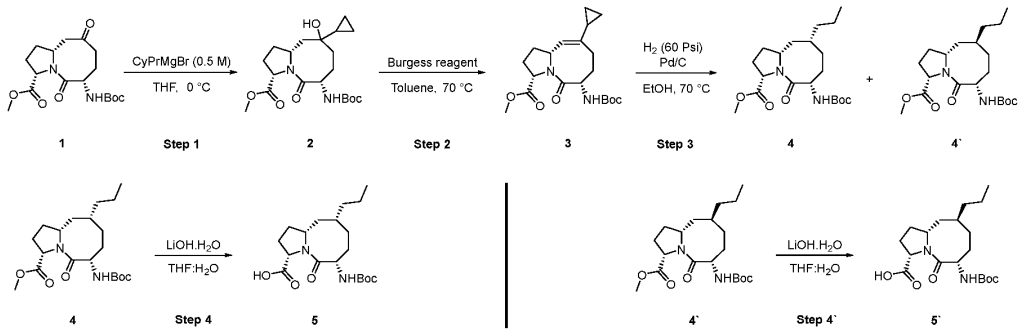
[00475] To a solution of methyl (3S,6S,7R,10aR,Z)-6-((tert-butoxycarbonyl)amino)-7-cyclopropyl-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate (218 mg, 0.5760 mmol, 1 eq) in ethanol (25 mL) under nitrogen was added 10% palladium on carbon (50% wet) (120 mg, 0.05638 mmol, 0.10 eq). Hydrogen was bubbled for 2 min. into the suspension and then the reaction was stirred at room temperature for 40 h under hydrogen atmosphere (1 atm). Nitrogen was bubbled into the suspension and the reaction was filtered over Celite (rinsed with MeOH). The filtrate was concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography on a C_{18} cartridge eluting with 5-80% MeCN in water (0.1% formic acid) to give methyl (3S,6S,7R,10aS)-6-((tert-butoxycarbonyl)amino)-7-cyclopropyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (122 mg, 56%) as a white solid. LCMS (ESI) m/z = 381.4 $[M+H]^+$. ^{1}H NMR (400 MHz, C_6D_6) δ 5.56 (d, J = 9.1 Hz, 1H), 4.95 (t, J = 9.5 Hz, 1H), 4.39 (t, J = 8.6 Hz, 1H), 3.74 - 3.65 (m, 1H), 3.36 (s, 3H), 2.39 - 2.29 (m, 1H), 1.80 - 1.70 (m, 1H), 1.68 - 1.50 (m, 5H), 1.46 (s, 9H), 1.20 - 1.06 (m, 1H), 1.05 - 0.78 (m, 4H), 0.74 - 0.61 (m, 1H), 0.27 - 0.16 (m, 2H), -0.23 - -0.31 (m, 1H).

[00476] *Step 8: Preparation of (3S,6S,7S,10aS)-6-((tert-butoxycarbonyl)amino)-7-cyclopropyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid*

[00477] To a solution of methyl (3S,6S,7R,10aS)-6-((tert-butoxycarbonyl)amino)-7-cyclopropyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (122 mg, 0.3206 mmol, 1 eq) in tetrahydrofuran (3 mL) and water (1 mL) was added lithium hydroxide monohydrate (26.9 mg, 0.6412 mmol, 2 eq). The reaction was stirred for 20 h. The reaction was quenched with the addition of 1 N HCl (1 mL) and concentrated under reduced pressure to remove THF. The crude product was purified by reverse phase chromatography on a C_{18} cartridge eluting with 5-80% MeCN in water (with 0.1% formic acid) to give (3S,6S,7S,10aS)-6-((tert-butoxycarbonyl)amino)-7-cyclopropyl-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid (100 mg, 85.4%) as a white solid. LCMS (ESI) m/z = 367.1 $[M+H]^+$. ^{1}H NMR (400 MHz, C_6D_6) δ 5.72 - 5.59 (m, 1H), 4.92 - 4.81 (m, 1H), 4.35 - 4.25 (m, 1H), 3.73 - 3.57 (m, 1H), 2.01 - 1.83 (m, 2H), 1.67 - 1.49 (m, 3H), 1.46 (s, 9H), 1.42 - 1.28 (m, 3H), 1.19 - 1.04

(m, 1H), 0.99 - 0.87 (m, 2H), 0.87 - 0.75 (m, 2H), 0.71 - 0.57 (m, 1H), 0.30 - 0.12 (m, 2H), -0.19 - -0.31 (m, 1H).

Synthesis of (3S,6S,9R,10aR)-6-((tert-butoxycarbonyl)amino)-5-oxo-9-propyldecahydropyrrolo[1,2-a]azocine-3-carboxylic acid and (3S,6S,9S,10aR)-6-((tert-butoxycarbonyl)amino)-5-oxo-9-propyldecahydropyrrolo[1,2-a]azocine-3-carboxylic acid



[00478] *Step 1: Preparation of methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-9-cyclopropyl-9-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate*

[00479] To a solution of methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-5,9-dioxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (490 mg, 1.38 mmol, 1 eq) in anhydrous tetrahydrofuran (10 mL) was added cyclopropyl magnesium bromide solution (0.5 M in THF) (5.52 mL, 2.76 mmol, 2 eq) at 0°C. The reaction mixture was stirred at 0°C for 2 h. Cyclopropyl magnesium bromide solution (0.5 M in THF) (5.52 mL, 2.76 mmol, 2 eq) was added. The reaction mixture was stirred at 0°C for 2 h, then quenched with saturated aq. NH_4Cl. The product was extracted with EtOAc (2 x 15 mL) and the combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by reverse phase chromatography on a 50 g C_{18} cartridge eluting with 5-60% MeCN in water (with 0.1% formic acid). The combined fractions were concentrated under reduced pressure and then freeze-dried to give methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-9-cyclopropyl-9-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (420 mg, 76.7%) as a beige solid. LCMS (ESI): m/z = 397.2 $[M+H]^+$.

[00480] *Step 2: Preparation of methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-9-cyclopropyl-5-oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate*

[00481] To a solution of methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-9-cyclopropyl-9-hydroxy-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylate (420 mg, 1.05 mmol, 1 eq) in anhydrous toluene (15 mL) was added Burgess' reagent (1 g, 4.20 mmol, 4

eq). The reaction mixture was warmed up to 70 °C and stirred for 1 h. Solvent was evaporated. The crude product was purified by reverse phase chromatography on a 100 g C_{18} cartridge eluting with 5-100% MeCN in water (with 0.1% formic acid). The combined fractions were concentrated under reduced pressure to give methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-9-cyclopropyl-5-oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate (285 mg, 71.7%) as a beige solid. LCMS (ESI): m/z = 379.2 $[M+H]^+$.

[00482] *Step 3: Preparation of methyl (3S,6S,9R,10aR)-6-((tert-butoxycarbonyl)amino)-5-oxo-9-propyldecahydropyrrolo[1,2-a]azocine-3-carboxylate* and *methyl (3S,6S,9S,10aR)-6-((tert-butoxycarbonyl)amino)-5-oxo-9-propyldecahydropyrrolo[1,2-a]azocine-3-carboxylate*

[00483] To a solution of methyl (3S,6S,10aR)-6-((tert-butoxycarbonyl)amino)-9-cyclopropyl-5-oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylate (190 mg, 502 µmol, 1 eq) in ethanol (10 mL) under nitrogen bubbling was added 10% palladium on carbon (50% wet) (159 mg, 150 µmol, eq). Hydrogen was bubbled into the suspension for 5 min. and then the reaction was stirred at 70°C for 18 h under hydrogen pressure (60 psi). Nitrogen was bubbled for 5 min. into the suspension. The reaction mixture was filtered over Celite (rinsing with EtOH) and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase chromatography on a 100 g C_{18} cartridge eluting with 5-100% MeCN in water (with 0.1% formic acid). The combined fractions were concentrated under reduced pressure and then freeze-dried to give methyl (3S,6S,9R,10aR)-6-((tert-butoxycarbonyl)amino)-5-oxo-9-propyldecahydropyrrolo[1,2-a]azocine-3-carboxylate (107 mg, 55.7%, major isomer) as a white solid. LCMS (ESI): m/z = 383.2 $[M+H]^+$. ^1H NMR (400 MHz, C_6D_6) δ 5.71 (d, *J* = 8.3 Hz, 1H), 4.94 - 4.82 (m, 1H), 4.45 (t, *J* = 8.7 Hz, 1H), 3.69 - 3.60 (m, 1H), 3.34 (s, 3H), 2.22 - 2.11 (m, 1H), 2.02 - 1.91 (m, 1H), 1.71 - 1.52 (m, 3H), 1.44 - 1.42 (m, 9H), 1.43 (s, 9H), 1.35 - 1.25 (m, 2H), 1.22 - 1.16 (m, 1H), 1.15 - 1.05 (m, 2H), 1.04 - 0.89 (m, 5H), 0.83 (t, *J* = 7.1 Hz, 3H). Methyl (3S,6S,9S,10aR)-6-((tert-butoxycarbonyl)amino)-5-oxo-9-propyldecahydropyrrolo[1,2-a]azocine-3-carboxylate (16.0 mg, 8.33%, minor isomer) was also isolated as a white solid. LCMS (ESI): m/z = 383.2 $[M+H]^+$. ^1H NMR (400 MHz, C_6D_6) δ 6.21 (d, *J* = 7.1 Hz, 1H), 4.57 - 4.46 (m, 1H), 4.36 (t, *J* = 9.0 Hz, 1H), 3.63 - 3.53 (m, 1H), 3.31 (s, 3H), 2.30 - 2.21 (m, 1H), 1.85 - 1.75 (m, 1H), 1.74 - 1.64 (m, 1H), 1.62 - 1.53 (m, 2H), 1.52 - 1.47 (m, 1H), 1.45 (s, 9H), 1.29 - 1.19 (m, 3H), 1.13 - 1.05 (m, 3H), 0.95 - 0.85 (m, 5H), 0.71 - 0.64 (m, 1H).

Note: Absolute stereochemistry on carbon bearing n-propyl group is unknown for both isomers

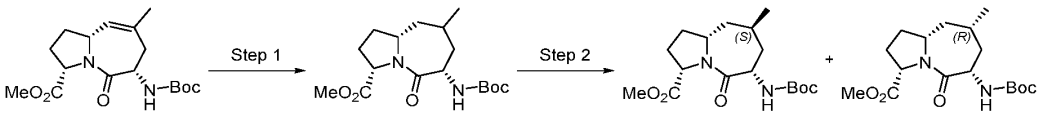
[00484] *Step 4: Preparation of (3S,6S,9R,10aR)-6-((tert-butoxycarbonyl)amino)-5-oxo-9-propyldecahydropyrrolo[1,2-a]azocine-3-carboxylic acid*

[00485] To a solution of methyl (3S,6S,9R,10aR)-6-((tert-butoxycarbonyl)amino)-5-oxo-9-propyldecahydropyrrolo[1,2-a]azocine-3-carboxylate (90 mg, 235 µmol, 1 eq) in tetrahydrofuran (6 mL) and water (2 mL) was added lithium hydroxide monohydrate (17 mg, 405 µmol, 1.7 eq). The reaction mixture was stirred overnight at room temperature. 1 N HCl (1 mL) was added. The reaction was concentrated under reduced pressure (to remove THF). The crude product was purified by reverse phase chromatography on a 30 g C_{18} cartridge eluting with 5-100% MeCN in water (with 0.1% formic acid). The pure fractions were evaporated and lyophilized to give (3S,6S,9R,10aR)-6-((tert-butoxycarbonyl)amino)-5-oxo-9-propyldecahydropyrrolo[1,2-a]azocine-3-carboxylic acid (65.0 mg, 75.1%) as a white solid. LCMS (ESI): m/z = 369.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.79 (d, J = 7.6 Hz, 1H), 4.55 - 4.28 (m, 1H), 4.25 - 4.15 (m, 2H), 2.25 - 1.99 (m, 2H), 1.94 - 1.78 (m, 2H), 2.28 - 1.78 (m, 4H), 1.76 - 1.44 (m, 6H), 1.40 - 1.28 (m, 11H), 1.22 - 1.14 (m, 2H), 0.86 (t, J = 7.2 Hz, 3H).

[00486] *Step 4': Preparation of (3S,6S,9S,10aR)-6-((tert-butoxycarbonyl)amino)-5-oxo-9-propyldecahydropyrrolo[1,2-a]azocine-3-carboxylic acid*

[00487] To a solution of methyl (3S,6S,9S,10aR)-6-((tert-butoxycarbonyl)amino)-5-oxo-9-propyldecahydropyrrolo[1,2-a]azocine-3-carboxylate (15 mg, 39.2 µmol, 1 eq) in tetrahydrofuran (1 mL) and water (0.2 mL) was added lithium hydroxide monohydrate (4.90 mg, 117 µmol, 3 eq). The reaction mixture was stirred for 18 h at room temperature. 1 N HCl (1 mL) was added. The reaction was concentrated under reduced pressure (to remove THF). The crude product was purified by reverse phase chromatography on a 50 g C_{18} cartridge eluting with 5-60% MeCN in water (with 0.1% formic acid). The pure fractions were evaporated and lyophilized to give (3S,6S,9S,10aR)-6-((tert-butoxycarbonyl)amino)-5-oxo-9-propyldecahydropyrrolo[1,2-a]azocine-3-carboxylic acid (13.0 mg, 90.2%) as a beige solid. **LCMS** (ESI): m/z = 369.2 $[M+H]^+$.

Synthesis of methyl (3S,6S,8S,9aR)-6-((tert-butoxycarbonyl)amino)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate and methyl (3S,6S,8R,9aR)-6-((tert-butoxycarbonyl)amino)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate



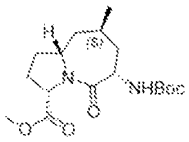
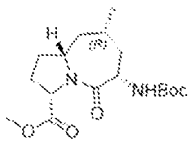
[00488] *Step 1: Preparation of methyl (3S,6S,9aR)-6-((tert-butoxycarbonyl)amino)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate*

[00489] To a solution of Pd/C (wet) (0.50 g, 4.85 mmol, 0.3 eq) in MeOH (50 mL) was added methyl (3S,6S,9aR)-6-((tert-butoxycarbonyl)amino)-8-methyl-5-oxo-2,3,5,6,7,9a-hexahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate (5.5 g, 16 mmol, 1 eq), the mixture was stirred at 25 °C for 2 hours under H_2 (15 Psi). The reaction mixture was filtered to give filtrate and concentrated under reduced pressure to give methyl (3S,6S,9aR)-6-((tert-butoxycarbonyl)amino)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate (5.70 g, crude) as a yellow oil. ^{1}H NMR (400 MHz, CD_3OD) δ 4.57 - 4.46 (m, 1H), 4.24 - 4.10 (m, 1H), 4.00 - 3.89 (m, 1H), 3.68 (d, J = 1.2 Hz, 3H), 2.32 - 2.18 (m, 2H), 2.14 - 2.06 (m, 1H), 1.99 - 1.93 (m, 1H), 1.84 - 1.65 (m, 4H), 1.60 - 1.53 (m, 1H), 1.40 (s, 9H), 1.15 (d, J = 7.2 Hz, 1H), 0.96 (d, J = 6.4 Hz, 2H).

[00490] *Step 2: Preparation of methyl (3S,6S,8S,9aR)-6-((tert-butoxycarbonyl)amino)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate and methyl (3S,6S,8R,9aR)-6-((tert-butoxycarbonyl)amino)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate*

[00491] Methyl (3S,6S,9aR)-6-((tert-butoxycarbonyl)amino)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate (5.70 g, 16.70 mmol, 1 eq) was purified by SFC (Method\IC-3-MeOH (DEA)-5-40-3 mL-35T.lcm) to give methyl (3S,6S,8S,9aR)-6-((tert-butoxycarbonyl)amino)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate (1.2 g, 3.5 mmol, 21% yield, **Peak 2**) as a light yellow oil. SFC (Rt = 1.342 min). ^{1}H NMR (400 MHz, CD_3OD) δ 4.53 (d, J = 4.0 Hz, 1H), 4.44 (d, J = 3.2 Hz, 1H), 4.20 - 4.13 (m, 1H), 3.77 - 3.67 (m, 3H), 2.33 - 2.19 (m, 2H), 2.18 - 2.09 (m, 1H), 2.05 - 1.97 (m, 1H), 1.92 - 1.79 (m, 2H), 1.77 - 1.66 (m, 2H), 1.65 - 1.57 (m, 1H), 1.44 (s, 9H), 1.23 - 1.15 (m, 3H) and methyl (3S,6S,8R,9aR)-6-((tert-butoxycarbonyl)amino)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate (3.0 g, 8.8 mmol, 53% yield, **Peak 1**) as a light yellow oil. SFC (Rt = 1.138 min). ^{1}H NMR (400 MHz, CD_3OD) δ 4.58 (d, J = 3.6 Hz, 1H), 4.23 (d, J = 11.2 Hz, 1H), 3.98 (d, J = 10.4 Hz, 1H), 3.72 (s, 3H), 2.35 - 2.25 (m, 1H), 2.18 - 2.08 (m, 1H), 2.06 - 1.91 (m, 3H), 1.89 - 1.79 (m, 2H), 1.79 - 1.69 (m, 2H), 1.44 (s, 9H), 1.00 (d, J = 6.4 Hz, 3H).

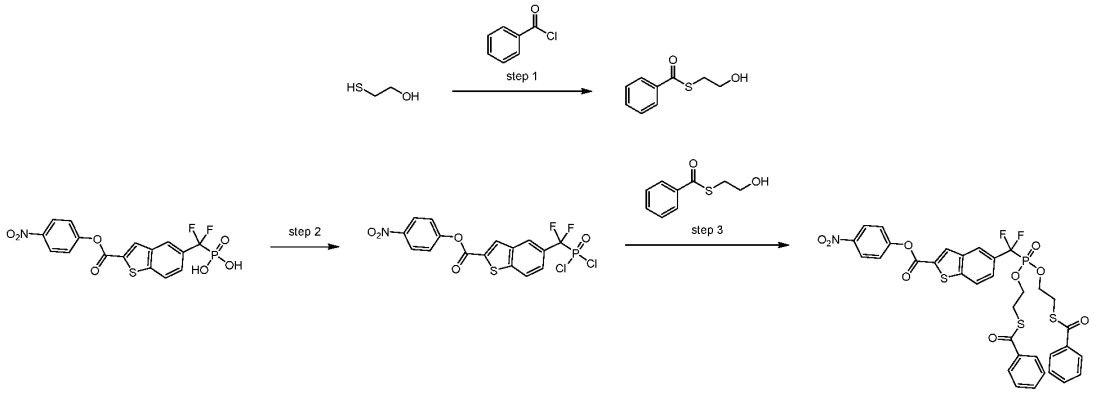
Name	Structure	LCMS	NMR

methyl (3S,6S,8S,9aR)-6-((tert-butoxycarbonyl)amino)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate*	 Peak 2 (stereochemistry confirmed via 2D NMR)		SFC (Rt = 1.342 min). ^{1}H NMR (400 MHz, CD_3OD) δ 4.53 (d, J = 4.0 Hz, 1H), 4.44 (d, J = 3.2 Hz, 1H), 4.20 - 4.13 (m, 1H), 3.77 - 3.67 (m, 3H), 2.33 - 2.19 (m, 2H), 2.18 - 2.09 (m, 1H), 2.05 - 1.97 (m, 1H), 1.92 - 1.79 (m, 2H), 1.77 - 1.66 (m, 2H), 1.65 - 1.57 (m, 1H), 1.44 (s, 9H), 1.23 - 1.15 (m, 3H)
methyl (3S,6S,8R,9aR)-6-((tert-butoxycarbonyl)amino)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate*	 Peak 1 (stereochemistry confirmed via 2D NMR)		SFC (Rt = 1.138 min). ^{1}H NMR (400 MHz, CD_3OD) δ 4.58 (d, J = 3.6 Hz, 1H), 4.23 (d, J = 11.2 Hz, 1H), 3.98 (d, J = 10.4 Hz, 1H), 3.72 (s, 3H), 2.35 - 2.25 (m, 1H), 2.18 - 2.08 (m, 1H), 2.06 - 1.91 (m, 3H), 1.89 - 1.79 (m, 2H), 1.79 - 1.69 (m, 2H), 1.44 (s, 9H), 1.00 (d, J = 6.4 Hz, 3H)

* The individual isomers were separated by chiral SFC utilizing the following conditions: Column: Chiralpak IC-3 50 x 4.6 mm, I.D. 3 um. Mobile phase: CO_2/MeOH/0.05% DEA). Peak 1 r.t.=1 minute, Peak 2 r.t. = 1.135 minute.

Procedures for Syntheses of Linkers:

Synthesis of 4-nitrophenyl 5-((bis(2-(benzoylthio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate

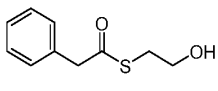


[00492] *Step 1: Preparation of S-(2-hydroxyethyl) benzothioate*

[00493] To a solution of 2-mercaptoethanol (5.0 g, 64 mmol) and triethylamine (6.7 g, 64 mmol) in DCM (50 mL), then benzoyl chloride (8.1 g, 58 mmol) in DCM (10 mL) was added in it at -70 °C. The mixture solution was stirred at 25 °C for 12 h to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give S-(2-hydroxyethyl) benzothioate (5.60 g, 30.73 mmol, 48% yield) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 - 8.03 (m, 2H), 7.63 - 7.55 (m, 1H), 7.50 - 7.42 (m, 2H), 4.46 (t, J = 6.4 Hz, 2H), 2.90 (td, J = 6.8, 8.4 Hz, 2H)

[00494] The following intermediates in **Table 45** were prepared using the described above in step 1 for the preparation of S-(2-hydroxyethyl) benzothioate and utilizing the appropriate starting materials and modifications.

Table 45

Name	Structure	NMR
S-(2-hydroxyethyl) 2-phenylethanethioate		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 - 7.37 (m, 5H), 4.23 (t, J=4.00 Hz, 2H), 3.66 (s, 2H), 2.73 (m, 2H).

[00495] *Step 2: Preparation of 4-nitrophenyl 5-((dichlorophosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate*

[00496] To a solution of (difluoro(2-((4-nitrophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (0.50 g, 1.2 mmol) and DMF (42 mg, 0.58 mmol) in DCM (5 mL) was added oxalic dichloride (0.44 g, 3.5 mmol) in DCM (5 mL) at 0 °C, then the mixture solution was stirred at 40 °C for 1 h to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give 4-nitrophenyl 5-((dichlorophosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (0.54 g, crude) as a yellow oil

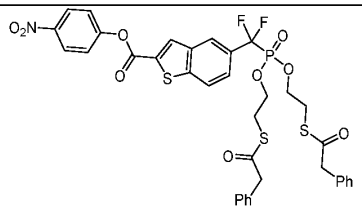
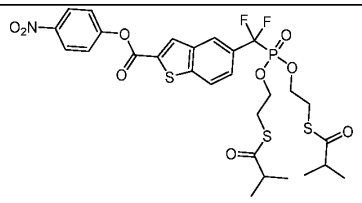
[00497] *Step 3: Preparation of 4-nitrophenyl 5-((bis(2-(benzoylthio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate*

[00498] To a solution of 4-nitrophenyl 5-((dichlorophosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (0.54 g, 1.1 mmol) in DCM (5 mL) was dropwise S-(2-hydroxyethyl) benzothioate (0.35 g, 1.9 mmol) at -78 °C, then triethylamine (0.27 g, 2.7 mmol) in DCM (5 mL) was dropwise added in it at -78 °C and stirred at -78 °C for 5 min to give a yellow solution. The mixture was purified by column

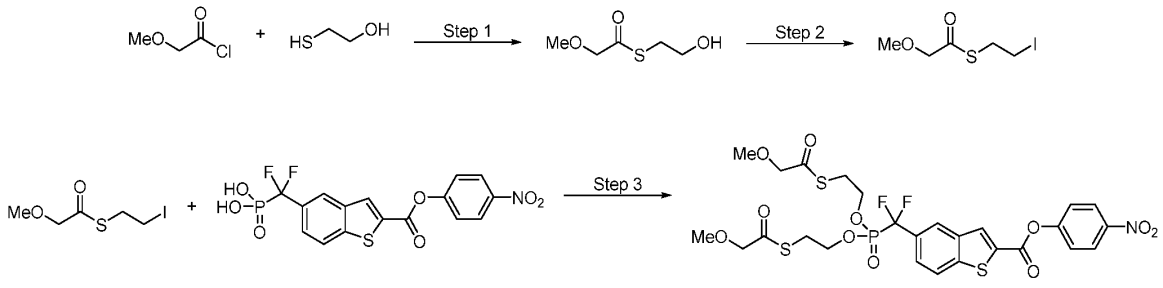
chromatography to give 4-nitrophenyl 5-((bis(2-(benzoylthio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (0.20 g, 0.26 mmol, 25% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 - 8.26 (m, 3H), 8.23 - 8.06 (m, 1H), 8.06 - 7.95 (m, 5H), 7.85 - 7.73 (m, 1H), 7.62 - 7.54 (m, 2H), 7.53 - 7.40 (m, 6H), 4.52 – 4.40 (m, 4H), 3.39 - 3.15 (m, 4H).

[00499] The following intermediates in **Table 46** were prepared using the method described above in step 1 for the preparation of 4-nitrophenyl 5-((bis(2-(benzoylthio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate and utilizing the appropriate starting materials and modifications.

Table 46

Name	Structure	LCMS
4-nitrophenyl 5-((bis(2-((2-phenylacetyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate		786.2 $[M+H]^+$
4-nitrophenyl 5-((bis(2-(isobutyrylthio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate		712.0 $[M+Na]^+$

Synthesis of 4-nitrophenyl 5-((bis(2-((2-methoxyacetyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate



[00500] *Step 1: Preparation of S-(2-hydroxyethyl) 2-methoxyethanethioate*

[00501] A solution of 2-methoxyacetyl chloride (1.5 g, 13.8 mmol, 1 eq) and triethylamine (1.91 mL, 13.8 mmol, 1.0 eq) in DCM (20 mL) was cooled down to -78 °C under nitrogen

then 2-sulfanylethan-1-ol (1.07 g, 13.8 mmol, 1 eq) was added dropwise. The reaction was stirred for 1 h at -78 °C and then warmed up to room temperature and stirred for 1 h. The reaction was filtered and rinsed with DCM (20 mL) then the filtrate was washed with water (30 mL). The organic layer was washed with DCM (2 x 20 mL) and the combined organic extracts were adsorbed on silica gel and concentrated under reduced pressure. The residue was purified by flash-chromatography on silica gel eluting with 0-60% EtOAc in heptane to give S-(2-hydroxyethyl) 2-methoxyethanethioate (1.27 g, 61.3%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) d 4.11 (s, 2H), 3.78 (t, J = 6.2 Hz, 2H), 3.49 (s, 3H), 3.12 (t, J = 6.2 Hz, 2H).

[00502] *Step 2: Preparation o f S-(2-iodoethyl) 2-methoxyethanethioate*

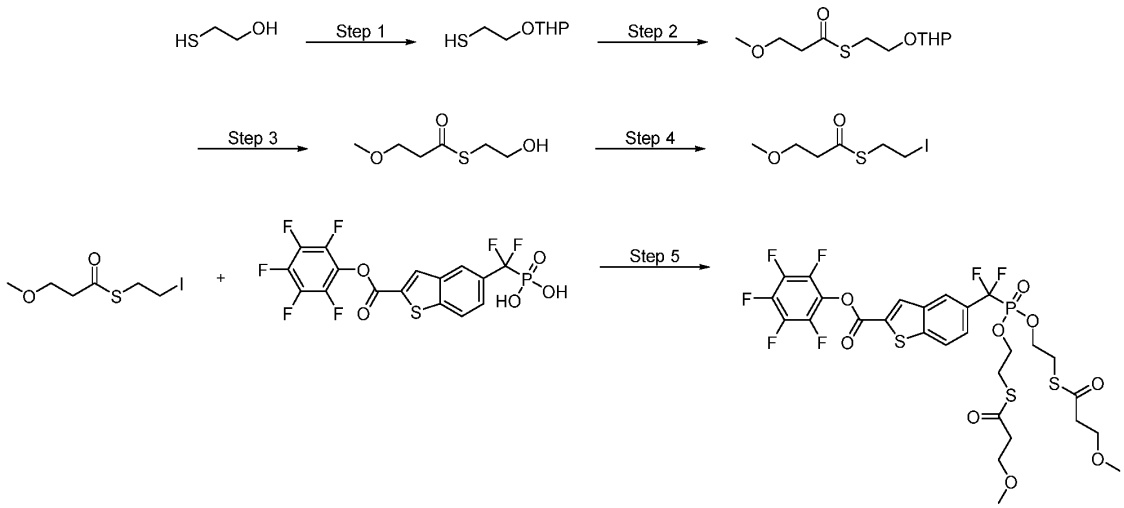
[00503] To a solution of S-(2-hydroxyethyl) 2-methoxyethanethioate (500 mg, 3.32 mmol, 1 eq) in THF (10 mL) at 0 °C were added triphenylphosphine (870 mg, 3.32 mmol, 1.0 eq), imidazole (452 mg, 6.64 mmol, 2.0 eq) and iodine (842 mg, 3.32 mmol, 1.0 eq). The resulting brown solution was stirred for 1 h at 0 °C. The solution was adsorbed on silica gel and concentrated under reduced pressure. The crude product was flash-chromatography on silica gel eluting with 0-30% EtOAc in heptane to give S-(2-iodoethyl) 2-methoxyethanethioate (757 mg, 87.7%) as clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) d 4.09 (s, 2H), 3.49 (s, 3H), 3.40 - 3.34 (m, 2H), 3.29 - 3.23 (m, 2H).

[00504] *Step 3: Preparation of 4-nitrophenyl 5-((bis(2-((2-methoxyacetyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate*

[00505] Sodium hydroxide (74.3 mg, 1.86 mmol) in water (1 mL) was added dropwise to a stirred suspension of (difluoro(2-((4-nitrophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (400 mg, 0.9317 mmol) in water (10 mL). When the mixture became pH~8, a clear yellowish solution was obtained and silver nitrate (473 mg, 2.79 mmol) was added. A white precipitate was observed. After 2 h at room temperature, the white mixture was cooled down to 0°C and the white precipitate was collected by filtration, washed with water and transferred with MeCN in a 100 mL flask. The solvent was removed under reduced pressure and the resulting beige solid was dried under vacuum. The powder was suspended in dry toluene (10 mL), and S-(2-iodoethyl) 2-methoxyethanethioate (787 mg, 3.02 mmol, 3.24 eq) was added. The mixture was stirred for 16 h at 50°C. The reaction was adsorbed on Celite and concentrated under reduced pressure. The crude residue was purified by flash-chromatography on silica gel eluting with a gradient of EtOAc in heptane (0 to 60%) to give 4-nitrophenyl 5-((bis(2-((2-methoxyacetyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (178 mg, 27.5%) as a thick clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) d 8.39 - 8.34 (m, 3H), 8.23

(s, 1H), 8.02 (d, J = 8.7 Hz, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.48 (d, J = 9.1 Hz, 2H), 4.35 - 4.17 (m, 4H), 4.09 (s, 4H), 3.49 (s, 6H), 3.26 - 3.11 (m, 4H).

Synthesis of perfluorophenyl 5-((bis(2-((3-methoxypropanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate



[00506] *Step 1: Preparation of 2-((tetrahydro-2H-pyran-2-yl)oxy)ethane-1-thiol*

[00507] To a solution of 2-mercaptoethan-1-ol (9 g, 115 mmol, 1 eq.) and 3,4-dihydro-2H-pyran (14.5 g, 173 mmol, 1.5 eq.) in EtOH (200 mL) was added PPTS (2.9 g, 11.5 mmol, 0.1 eq). The reaction solution was stirred at 70 °C for 2 h under N_2. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 2-((tetrahydro-2H-pyran-2-yl)oxy)ethane-1-thiol (12 g, 74.0 mmol, 64%) as a colorless oil. LCMS (ESI) m/z = 163 $[M+H]^+$.

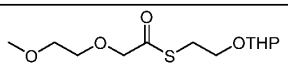
[00508] *Step 2: Preparation of S-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl) 3-methoxypropanethioate*

[00509] To a solution of 3-methoxypropanoic acid (5.5 g, 52.8 mmol, 1 eq.) in DCM (30 mL) was added CDI (9.39 g, 58.0 mmol, 1.1 eq.) at 0 °C. The solution was stirred at room temperature for 30 min, then 2-((tetrahydro-2H-pyran-2-yl)oxy)ethane-1-thiol (8.56 g, 52.8 mmol, 1 eq.) was added to the solution. The solution was stirred at room temperature for 2 h. After completion, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford S-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl) 3-methoxypropanethioate (8.00 g, 32.2 mmol, 61%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65-4.60 (m, 1H), 3.92-3.74 (m, 3H), 3.71-3.64 (m, 2H), 3.62-

3.46 (m, 2H), 3.38-3.30 (m, 3H), 3.21-3.08 (m, 2H), 2.88-2.78 (m, 2H), 1.82 (ddd, J = 15.1, 10.1, 3.4 Hz, 2H), 1.76-1.65 (m, 1H), 1.64-1.46 (m, 4H).

[00510] The following intermediates in **Table 47** were prepared using the method described above in step 2 for the preparation of S-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl) 3-methoxypropanethioate and utilizing the appropriate starting materials and modifications.

Table 47

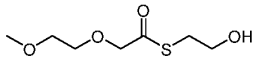
Name	Structure	LCMS
perfluorophenyl 5-((bis(2-((2-(2-methoxyethoxy)acetyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate		279 $[M+H]^+$

[00511] *Step 3: Preparation of S-(2-hydroxyethyl) 3-methoxypropanethioate*

[00512] To a solution of S-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl) 3-methoxypropanethioate (8 g, 32.2 mmol, 1 eq.) in EtOH (40 mL) was added PPTS (809 mg, 3.22 mmol, 0.1 eq). The reaction solution was stirred at 50 °C for 2 h under N_2. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford S-(2-hydroxyethyl) 3-methoxypropanethioate (4.00 g, 24.3 mmol, 76%) as a colorless oil. LCMS (ESI) *m/z* = 165 $[M+H]^+$.

[00513] The following intermediates in **Table 48** were prepared using the method described above in step 3 for the preparation of S-(2-hydroxyethyl) 3-methoxypropanethioate and utilizing the appropriate starting materials and modifications.

Table 48

Name	Structure	LCMS
S-(2-hydroxyethyl) 2-(2-methoxyethoxy)ethanethioate		195 $[M+H]^+$

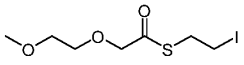
[00514] *Step 4: Preparation of S-(2-iodoethyl) 3-methoxypropanethioate*

[00515] To a solution of S-(2-hydroxyethyl) 3-methoxypropanethioate (1.4 g, 8.54 mmol, 1 eq.) and triphenylphosphine (2.2 g, 8.54 mmol, 1.0 eq.) in DCM (50 mL) was added 1-iodopyrrolidine-2,5-dione (1.92 g, 8.54 mmol, 1.0 eq.) at 0 °C. The solution was stirred at room temperature for 1 hr. After completion, the reaction solution was concentrated under

reduced pressure. The residue was purified by flash column chromatography on silica gel to afford S-(2-iodoethyl) 3-methoxypropanethioate (1.3 g, 4.74 mmol, 56%) as a yellow oil. LCMS (ESI) *m/z* = 163 $[M+H]^+$.

[00516] The following intermediates in **Table 49** were prepared using the method described above in step 4 for the preparation of S-(2-iodoethyl) 3-methoxypropanethioate and utilizing the appropriate starting materials and modifications.

Table 49

Name	Structure	LCMS
S-(2-iodoethyl) 2-(2-methoxyethoxy)ethanethioate		305 $[M+H]^+$

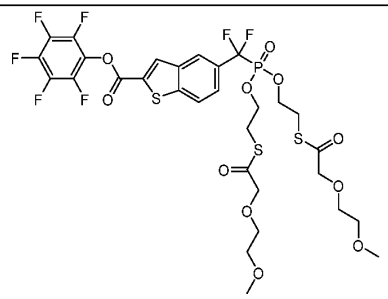
[00517] *Step 5: Preparation of perfluorophenyl 5-((bis(2-((3-methoxypropanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate*

[00518] Amberlite IR120® (2.92 g, 127 mmol, 10 eq) in water (2 mL) was added dropwise to a stirred suspension of (difluoro(2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (6 g, 12.7 mmol, 1 eq.) in H_2O (60 mL). When the mixture became clear (pH~9), silver(I) nitrate (4.75 g, 27.9mmol, 2.2 eq.) was added. After stirring at 0 °C for 2 h, the gray precipitate was collected by filtration and dried under vacuum. To a solution of gray precipitate (2.2 g, 3.19 mmol, 1 eq.) in MeCN (10 mL) was added 1 S-(2-iodoethyl) 3-methoxypropanethioate (**5**, 2.00 g, 7.33 mmol, 2.3 eq). The solution was stirred at room temperature for 48 h. After completion, the mixture was filtered and the filtrate was purified by Prep-HPLC to afford perfluorophenyl 5-((bis(2-((3-methoxypropanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (500 mg, 652 µmol, 20%) as a yellow oil. LCMS (ESI) *m/z* = 767 $[M+H]^+$.

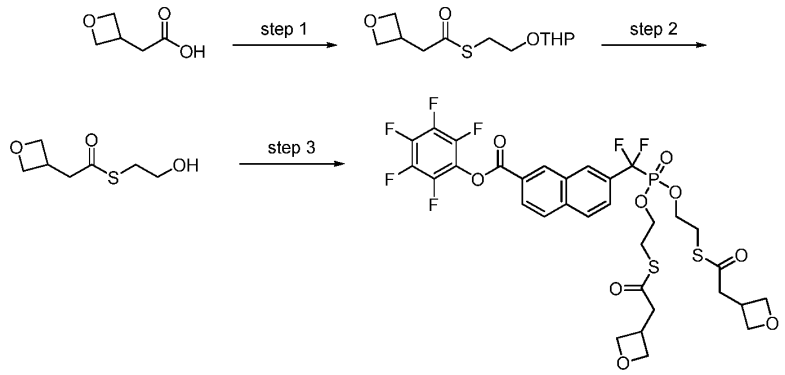
[00519] The following intermediates in **Table 50** were prepared using the method described above in step 5 for the preparation of perfluorophenyl 5-((bis(2-((3-methoxypropanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate and utilizing the appropriate starting materials and modifications.

Table 50

Name	Structure	LCMS

perfluorophenyl 5-((bis(2-((2-(2-methoxyethoxy)acetyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate		827 $[M+H]^+$

Synthesis of perfluorophenyl 7-((bis(2-((2-(oxetan-3-yl)acetyl)thio)ethoxy)phosphoryl)difluoromethyl)-2-naphthoate:



[00520] *Step 1: Preparation of S-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl) 2-(oxetan-3-yl)ethanethioate*

[00521] To a solution of 2-(oxetan-3-yl)acetic acid (1.0 g, 8.62 mmol, 1.0 eq.) and 2-((tetrahydro-2H-pyran-2-yl)oxy)ethane-1-thiol (1.5 g, 9.50 mmol, 1.1 eq.) in DCM (30 mL) was added CDI (2.79 g, 17.2 mmol, 2.0 eq.). The mixture was stirred at room temperature for 1 hr. After completion, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford S-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl) 2-(oxetan-3-yl)ethanethioate (1.1 g, 4.23 mmol, 49%) as a white solid. LCMS (ESI) m/z = 261 $[M+H]^+$.

[00522] *Step 2: Preparation of S-(2-hydroxyethyl) 2-(oxetan-3-yl)ethanethioate*

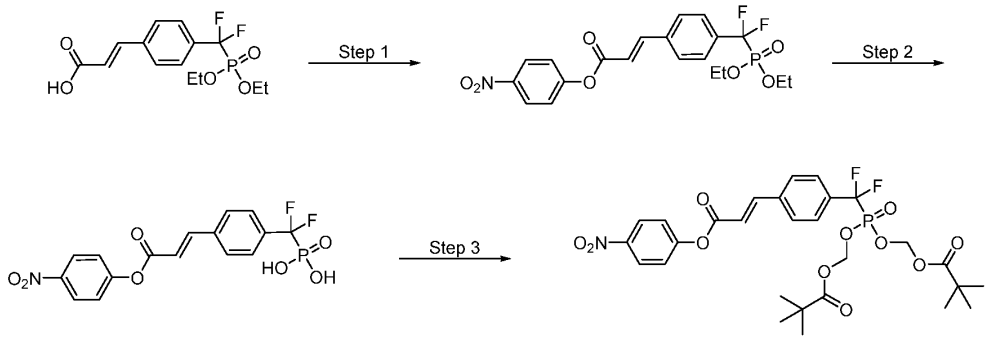
[00523] To a solution of S-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl) 2-(oxetan-3-yl)ethanethioate (1.1 g, 4.23 mmol, 1 eq.) in EtOH (15 mL) was added 4-methylbenzene-1-sulfonic acid; pyridine (106 mg) at room temperature. The reaction solution was stirred at 50 °C for 5 h under N_2. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford S-

(2-hydroxyethyl) 2-(oxetan-3-yl)ethanethioate (600 mg, 3.40 mmol, 81%) as an oil. LCMS (ESI) *m/z* = 177 $[M+H]^+$.

[00524] *Step 3: Preparation of perfluorophenyl 7-((bis(2-((2-(oxetan-3-yl)acetyl)thio)ethoxy)phosphoryl)difluoromethyl)-2-naphthoate*

[00525] Oxalyl chloride (243 mg, 1.92 mmol, 3 eq.) was added dropwise to the solution of (difluoro(7-((perfluorophenoxy)carbonyl)naphthalen-2-yl)methyl)phosphonic acid (300 mg, 0.64 mmol, 1 eq.) in dry DCM (15 mL) and DMF (4.68 mg, 64 µmol, 0.1 eq.) at 20 °C. The reaction mixture was stirred at 40 °C for an additional 1 hr. The reaction was monitored by pipetting out a small amount of crude sample and quenching it with MeOH to ensure bis-Cl phosphoryl chloride had been formed completely (bis-methoxy phosphonate was observed by LCMS). After completion, the excess oxalyl chloride and solvent were removed under reduced pressure. The residue was re-dissolved in anhydrous DCM (2 mL), then added to a mixture of S-(2-hydroxyethyl) 2-(oxetan-3-yl)ethanethioate (**3**, 281 mg, 1.60 mmol, 2.5 eq.) and DIEA (330 mg, 2.56 mmol, 4 eq.) in anhydrous DCM (2 mL) at 0 °C. The reaction was allowed to warm to 25 °C and stirred for an additional 2 h. After completion, the reaction mixture was quenched with HCl (0.3 mL, 2N) and concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give to get perfluorophenyl 7-((bis(2-((2-(oxetan-3-yl)acetyl)thio)ethoxy)phosphoryl)difluoromethyl)-2-naphthoate (50.0 mg, 63 µmol, 10%). LCMS (ESI) *m/z* = 785.0 $[M+H]^+$.

Synthesis of (E)-(((difluoro(4-(3-(4-nitrophenoxy)-3-oxoprop-1-en-1-yl)phenyl)methyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate):



[00526] *Step 1: Preparation of 4-nitrophenyl (E)-3-(4-((diethoxyphosphoryl)difluoromethyl)phenyl)acrylate*

[00527] Oxalyl chloride (1.13 g, 8.98 mmol, 3 eq.) was added dropwise to the solution of (E)-3-(4-((diethoxyphosphoryl)difluoromethyl)phenyl)acrylic acid (1 g, 2.99 mmol, 1 eq.) in

dry DCM (20 mL) and DMF (0.1 mL) at 0 °C. The reaction mixture was stirred at 40 °C for an additional 1 hr. After completion, the excess oxalyl chloride and solvent were removed under reduced pressure. The residue was re-dissolved in anhydrous DCM (10 mL), then added to a mixture of 4-nitrophenol (457 mg, 3.29 mmol, 1.1 eq.) and TEA (1.5 g, 15.0 mmol, 5 eq.) in anhydrous DCM (10 mL) at 0 °C. The reaction was allowed to warm to 25 °C and stirred for an additional 2 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 4-nitrophenyl (E)-3-(4-((diethoxyphosphoryl)difluoromethyl)phenyl)acrylate (1 g, 2.20 mmol, 74%) as a white solid. LCMS (ESI): *m/z* = 456 $[M+H]^+$.

[00528] *Step 2: Preparation of (E)-(difluoro(4-(3-(4-nitrophenoxy)-3-oxoprop-1-en-1-yl)phenyl)methyl)phosphonic acid*

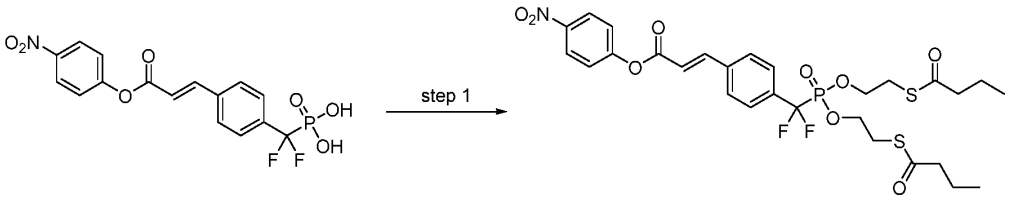
[00529] To a solution of 4-nitrophenyl (E)-3-(4-((diethoxyphosphoryl)difluoromethyl)phenyl)acrylate (1 g, 2.20 mmol, 1.0 eq.) in DCM (15 mL) was added TMSBr (6.7 g, 44 mmol, 20.0 eq.) dropwise at 0 °C. After the addition, the reaction mixture was allowed to warm to room temperature and stirred for an additional 12 h. The reaction progress was monitored by LCMS. After completion, the reaction was quenched by adding H_2O (5 mL) and extracted with DCM (10 mL x 3). The organic layers were combined and washed with brine (20 mL), dried over with anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by RP-prep-HPLC to afford (E)-(difluoro(4-(3-(4-nitrophenoxy)-3-oxoprop-1-en-1-yl)phenyl)methyl)phosphonic acid (443 mg, 1.11 mmol, 50%) as a white solid. LCMS (ESI): *m/z* = 400 $[M+H]^+$.

[00530] *Step31: Preparation of (E)-(((difluoro(4-(3-(4-nitrophenoxy)-3-oxoprop-1-en-1-yl)phenyl)methyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)*

[00531] To a solution of (E)-(difluoro(4-(3-(4-nitrophenoxy)-3-oxoprop-1-en-1-yl)phenyl)methyl)phosphonic acid (443 mg, 1.11 mmol, 1.0 eq.) in a mixture of deionized H_2O (6 mL) and THF (3 mL) was added Amberlite IR120® resin (Na^+ form) (2.5 g). The resulting mixture was stirred at room temperature for 1 h, then the excess of the resin was removed by filtration. $AgNO_3$ (755 mg, 4.44 mmol, 4.0 eq.) in deionized H_2O (2 mL) was then added to the resulting solution. After addition, the resulting mixture was stirred at room temperature for an additional 1 hr. During this period, the silver salt formed as a white precipitate, which was collected via filtration. The filter cake was washed with cool H_2O (2 mL x3), and the silver salt was further dried under reduced pressure to give a dry powder, which was used without further purification.

[00532] The isolated Ag salt was suspended in anhydrous toluene (10 mL), and iodomethyl pivalate (806 mg, 3.33 mmol, 3.0 eq.) was added dropwise. After addition, the resulting mixture was stirred at room temperature for an additional 12 h. The reaction progress was monitored by LCMS, and after completion, the unreacted silver salt was recovered by filtration, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel to afford (E)-(((difluoro(4-(3-(4-nitrophenoxy)-3-oxoprop-1-en-1-yl)phenyl)methyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate) (297 mg, 0.47 mmol, 43%) as a white solid. LCMS (ESI) *m/z* =628 $[M+H]^+$.

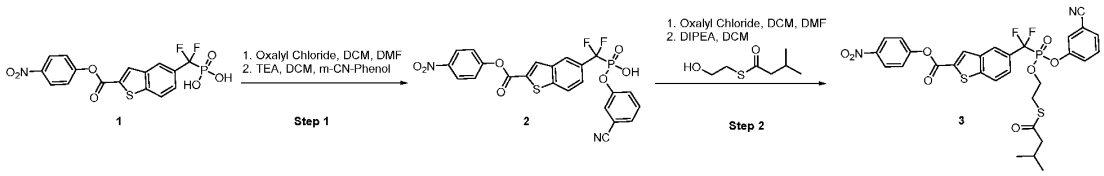
Synthesis of 4-nitrophenyl (E)-3-(4-((bis(2-(butyrylthio)ethoxy)phosphoryl)difluoromethyl)phenyl)acrylate



[00533] *Step 1: Preparation of 4-nitrophenyl (E)-3-(4-((bis(2-(butyrylthio)ethoxy)phosphoryl)difluoromethyl)phenyl)acrylate*

[00534] Oxalyl chloride (284 mg, 2.26 mmol, 3 eq.) was added dropwise to the solution of (E)-(difluoro(4-(3-(4-nitrophenoxy)-3-oxoprop-1-en-1-yl)phenyl)methyl)phosphonic acid (300 mg, 0.75 mmol, 1 eq.) (prepared according procedures adapted from JMC (2011) 54, 3549-3563) in dry DCM (5 mL) and DMF (0.1 mL) at 0 °C. The reaction mixture was stirred at 40 °C for an additional 1 hr. The reaction was monitored by pipetting out a small amount of crude sample and quenching it with MeOH to ensure bis-Cl phosphoryl chloride had been formed completely (bis-methoxy phosphonate was observed by LCMS). After completion, the excess oxalyl chloride and solvent were removed under reduced pressure. The residue was re-dissolved in anhydrous DCM (10 mL), then added to a mixture of S-(2-hydroxyethyl) butanethioate (334 mg, 2.26 mmol, 3 eq.) and TEA (379 mg, 3.75 mmol, 5 eq.) in anhydrous DCM (10 mL) at 0 °C. The reaction was allowed to warm to 25 °C and stirred for an additional 2 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 4-nitrophenyl (E)-3-(4-((bis(2-(butyrylthio)ethoxy)phosphoryl)difluoromethyl)phenyl)acrylate (208 mg, 0.32 mmol, 43%) as a colorless oil. LCMS (ESI): *m/z* = 660 $[M+H]^+$.

Synthesis of 4-nitrophenyl 5-(((3-cyanophenoxy)(2-((3-methylbutanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate



[00535] *Step 1:Preparation of 4-nitrophenyl 5-(((3-cyanophenoxy)(hydroxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate*

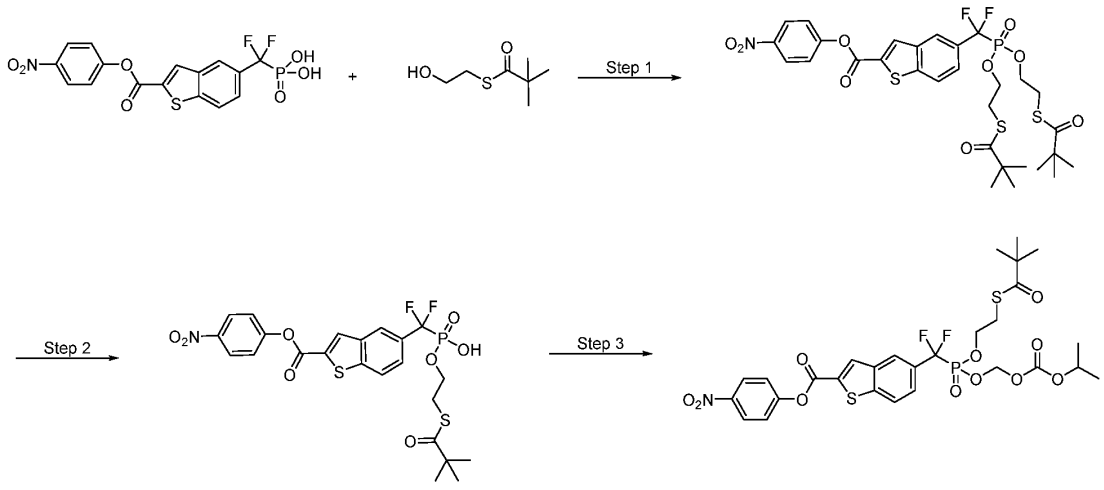
[00536] To a solution of (difluoro(2-((4-nitrophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (600 mg, 1.39 mmol, 1 eq) in DCM (10 mL) at 0 °C were added 3 drops of DMF (cat) followed by dropwise addition of oxalyl chloride (1.77 mL, 20.8 mmol, 15 eq) The reaction was warmed up to room temperature and stirred for 2 h. The reaction was concentrated under reduced pressure and dried completely under high vacuum to give a beige solid which was diluted in DCM (10 mL) and cooled down to -78 °C. A solution of 3-hydroxybenzonitrile (165 mg, 1.39 mmol, 1 eq) and triethylamine (387 µL, 2.78 mmol, 2 eq) in DCM (1 mL) was slowly added over 5 min. The reaction mixture was stirred at -78 °C for 20 min. and then warmed up to room temperature and stirred for 18 h. More triethylamine (190 µL, 1 eq) was added as a solution in DCM (1.5 mL) and the reaction was stirred for 3 h. More triethylamine (190 µL,1 eq) was added as a solution in DCM (1.5 mL) and the reaction was stirred for 18 h. Water (2-3 drops) was added and the reaction was concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography on a 100 g C_{18} cartridge eluting with a gradient of 5-100% acetonitrile in water to give 4-nitrophenyl 5-(((3-cyanophenoxy)(hydroxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (372 mg, 42.4%) as a yellow solid. LCMS (ESI) m/z = 528.8 $(M-H)^-$. ^1H NMR (400 MHz, $CDCl_3$) δ 11.66 - 11.40 (m, 1H), 8.39 - 8.32 (m, 2H), 8.31 - 8.22 (m, 2H), 7.96 - 7.82 (m, 2H), 7.53 - 7.46 (m, 3H), 7.45 - 7.39 (m, 1H), 7.32 - 7.28 (m, 2H), 3.09 - 2.96 (m, 6H), 1.27 (t, J = 7.3 Hz, 9H).

[00537] *Step 2: Preparation of 4-nitrophenyl 5-(((3-cyanophenoxy)(2-((3-methylbutanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate*

[00538] To a solution of 4-nitrophenyl 5-(((3-cyanophenoxy)(hydroxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (372

mg, 588 µmol, 1 eq) in DCM (6 mL) at 0 °C were added 1 drop of DMF (cat) followed by dropwise addition of oxalyl chloride (750 µL, 8.82 mmol, 15 eq). The reaction was warmed up to room temperature and stirred for 1.5 h. The reaction was concentrated under reduced pressure and dried completely under high vacuum for 30 min to give a yellow solid. The yellow solid was diluted in DCM (6 mL) and cooled down to 0 °C. A solution of 1-[(2-hydroxyethyl)sulfanyl]-3-methylbutan-1-one (95.4 mg, 588 µmol, 1 eq) and *N*,*N*-diisopropylethylamine (0.3 mL, 1.76 mmol, 3 eq) in DCM (1 mL) was dried on sodium sulfate and slowly added on the yellow solution. The reaction mixture was stirred at 0°C for 5 min. and warmed up to room temperature and stirred for 18 h. A solution of *N*,*N*-diisopropylethylamine (0.30 mL, 1.76 mmol, 3 eq) and 1-[(2-hydroxyethyl)sulfanyl]-3-methylbutan-1-one (300 mg, 1.76 mmol, 3 eq) in DCM (4 mL) was added dropwise at 0°C and stirred for 1.5 h at room temperature. Water (2 mL) was added and the reaction was concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography on a 50 g C_{18} cartridge eluting with a gradient of 5-100% acetonitrile in water to give 4-nitrophenyl 5-(((3-cyanophenoxy)(2-((3-methylbutanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (133 mg, 33.5%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 - 8.29 (m, 3H), 8.28 - 8.23 (m, 1H), 8.11 - 8.00 (m, 1H), 7.86 - 7.72 (m, 1H), 7.55 - 7.40 (m, 6H), 4.44 - 4.19 (m, 2H), 3.25 - 3.02 (m, 2H), 2.54 - 2.33 (m, 2H), 2.22 - 2.06 (m, 1H), 0.95 (d, J = 6.8 Hz, 6H).

Synthesis of 4-nitrophenyl 5-(difluoro((((isopropoxycarbonyl)oxy)methoxy)(2-(pivaloylthio)ethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate



[00539] *Step 1: Preparation of 4-nitrophenyl 5-((bis(2-(pivaloylthio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate*

[00540] To a solution of (difluoro(2-((4-nitrophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (1 g, 2.32 mmol, 1 eq) in DCM (25 mL) at 0 °C were added 5 drops of DMF (cat.) followed by dropwise addition of oxalyl chloride (1.98 mL, 23.2 mmol, 10 eq). The reaction mixture was warmed up to room temperature and stirred for 2 h. The reaction mixture was not soluble at first (yellow solid floating on surface) but became a clear solution upon adding oxalyl chloride and warming up to room temperature. The reaction mixture was concentrated under reduced pressure and dried completely under high vacuum for 30 min. to give a yellow solid. The yellow solid was diluted in DCM (25 mL) and cooled down to 0 °C. A solution of S-(2-hydroxyethyl) 2,2-dimethylpropanethioate (1.12 g, 6.96 mmol, 3 eq) in DCM (2 mL, dried on Na_2SO_4) was added dropwise and then triethylamine (969 µL, 6.96 mmol, 3 eq) in DCM (2 mL, dried on Na_2SO_4) was slowly added on the yellow solution over 1 min. The reaction mixture was stirred at 0 °C for 5 min., then warmed up to room temperature and stirred for 20 h. Water (1 mL) was added and the reaction mixture was concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography on a 100 g C_{18} cartridge eluting with 5-100% MeCN in water to give 4-nitrophenyl 5-((bis(2-(pivaloylthio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (1.19 g, 71.6%) as a yellow semi-solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 – 8.63 (m, 1H), 8.42 – 8.34 (m, 4H), 7.75 – 7.64 (m, 3H), 4.23 – 4.09 (m, 4H), 3.17 – 3.07 (m, 4H), 1.18 – 1.13 (m, 18H).

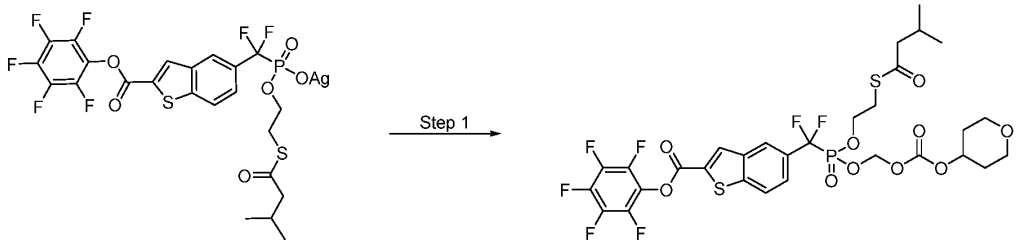
[00541] *Step 2: Preparation of 4-nitrophenyl 5-(difluoro(hydroxy(2-(pivaloylthio)ethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00542] A solution of 4-nitrophenyl 5-((bis(2-(pivaloylthio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (1.19 g, 1.65 mmol, 1 eq) in acetonitrile (3 mL) and water (3 mL) was heated to 75 °C for 48 h. The crude product was purified by reverse phase chromatography on a 100 g C_{18} cartridge eluting with 5-100% MeCN in water. The pure fractions were concentrated under reduced pressure and freeze-dried to give 4-nitrophenyl 5-(difluoro(hydroxy(2-(pivaloylthio)ethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (512 mg, 54.1%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 – 8.62 (m, 1H), 8.42 – 8.24 (m, 4H), 7.77 – 7.65 (m, 3H), 3.98 – 3.93 (m, 2H), 3.03 (t, J = 6.5 Hz, 2H), 1.17 (s, 9H).

[00543] *Step 3: Preparation of 4-nitrophenyl 5-(difluoro((((isopropoxycarbonyl)oxy)methoxy)(2-(pivaloylthio)ethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00544] A mixture of 4-nitrophenyl 5-(difluoro(hydroxy(2-(pivaloylthio)ethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (350 mg, 0.6102 mmol, 1 eq) and Amberlite® IR120 Na^+ form (1.75 g) in deionized water (10 mL) and THF (10 mL) was stirred at room temperature for 4 h. The mixture was filtered. Silver nitrate (414 mg, 2.44 mmol, 4 eq) was added into the filtrate. After addition, the reaction mixture was stirred at room temperature for 1 h. The mixture was filtered and the filter cake was transferred in a separate flask with acetonitrile (20 mL), concentrated under reduced pressure and dried under high vacuum for 2 h. The solid was suspended in acetonitrile (10 mL) and chloromethyl propan-2-yl carbonate (465 mg, 3.05 mmol, 5 eq) was added. After addition, the reaction mixture was stirred at room temperature overnight. Additional chloromethyl propan-2-yl carbonate (465 mg, 3.05 mmol, 5 eq) was added and the reaction was stirred at 45 °C for 5 h. Celite was added and the reaction was concentrated under reduced pressure. The crude residue was purified by flash-chromatography on silica gel eluting with 0-50% EtOAc in heptane to give 4-nitrophenyl 5-(difluoro((((isopropoxycarbonyl)oxy)methoxy)(2-(pivaloylthio)ethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (92.0 mg, 21.9%) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) d 8.04 - 8.34 (m, 3H), 8.25 (s, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 9.3 Hz, 2H), 5.79 - 5.65 (m, 2H), 8.00 - 4.93 (m, 1H), 4.32 - 4.20 (m, 2H), 3.17 - 3.11 (m, 2H), 1.36 (d, *J* = 6.2 Hz, 6H), 1.25 (s, 9H).

Synthesis of perfluorophenyl 5-(difluoro((2-((3-methylbutanoyl)thio)ethoxy)(((((tetrahydro-2H-pyran-4-yl)oxy)carbonyl)oxy)methoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate

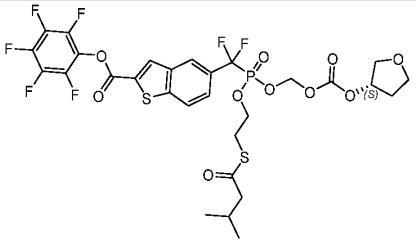
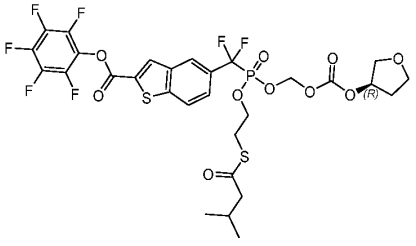


[00545] *Step 1: Preparation of perfluorophenyl 5-(difluoro((2-((3-methylbutanoyl)thio)ethoxy)(((((tetrahydro-2H-pyran-4-yl)oxy)carbonyl)oxy)methoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

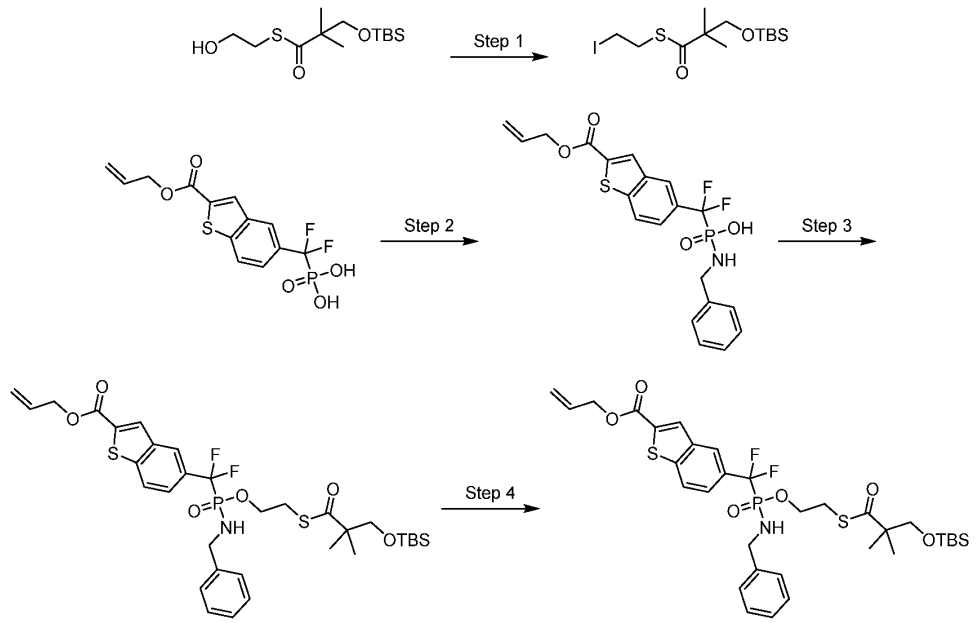
[00546] To a solution of (((difluoro(2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)(2-((3-methylbutanoyl)thio)ethoxy)phosphoryl)oxy)silver [prepared using the protocols shown in step 1 and 2 from the synthesis of 4-nitrophenyl 5-(difluoro((((isopropoxycarbonyl)oxy)methoxy)(2-(pivaloylthio)ethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate and utilizing the appropriate starting materials and modifications] (150 mg, 0.21 mmol, 1.0 eq.) in MeCN (3 mL) was added chloromethyl (tetrahydro-2H-pyran-4-yl) carbonate (62 mg, 0.32 mmol, 1.5 eq.) was added. The mixture was stirred at room temperature for 24 h. After filtration, the solvent was removed in vacuo. The crude residue was directly purified by flash column chromatography on silica gel to give perfluorophenyl 5-(difluoro((2-((3-methylbutanoyl)thio)ethoxy)(((((tetrahydro-2H-pyran-4-yl)oxy)carbonyl)oxy)methoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (15 mg, 19 μmol, 9%) as a white solid. LCMS (ESI): *m/z* = 777 $[M+H]^+$.

[00547] The following intermediates in **Table 51** were prepared using the method described above for the synthesis of perfluorophenyl 5-(difluoro((2-((3-methylbutanoyl)thio)ethoxy)(((((tetrahydro-2H-pyran-4-yl)oxy)carbonyl)oxy)methoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate and utilizing the appropriate starting materials and modifications.

Table 51

Name	Structure	LCMS
perfluorophenyl 5-(difluoro((2-((3-methylbutanoyl)thio)ethoxy)((((((S)-THF-3-yl)oxy)carbonyl)oxy)methoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		785 $[M+Na]^+$
perfluorophenyl 5-(difluoro((2-((3-methylbutanoyl)thio)ethoxy)((((((R)-THF-3-yl)oxy)carbonyl)oxy)methoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		763 $[M+H]^+$

Synthesis of 5-(((benzylamino)(2-((3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid:



[00548] *Step 1: Preparation of S-(2-iodoethyl) 3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanethioate*

[00549] To a solution of S-(2-hydroxyethyl) 3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanethioate (700 mg, 2.39 mmol, 1 eq.) in DCM (20 mL) was added PPh_3 (626 mg, 2.39 mmol, 1.0 eq.) portionwise at 0 °C and the resulting mixture was stirred for 30 min. Then NIS (537 mg, 2.39 mmol, 1.0 eq) was added dropwise at 0 °C and the reaction mixture was stirred at 0 °C for 1 hr. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give S-(2-iodoethyl) 3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanethioate (700 mg, 1.73 mmol, 73%) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.57 (s, 2H), 3.31-3.24 (m, 2H), 3.23-3.15 (m, 2H), 1.17 (s, 6H), 0.84 (s, 9H), 0.00 (s, 6H).

[00550] *Step 2: Preparation of P-((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)difluoromethyl)-N-benzylphosphonamidic acid*

[00551] Oxalyl chloride (1.01 g, 8.00 mmol, 5 eq.) was added dropwise to the solution of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid (150 mg, 0.4307 mmol, 1 eq.) in dry DCM (10 mL) and DMF (1 drop) at 0 ºC. The reaction mixture was stirred at 40 °C for an additional 2 h. The reaction was monitored by pipetting out a

small amount of crude sample and quenching it with MeOH to ensure bis-Cl phosphoryl chloride had been formed completely (bis-methoxy phosphonate was observed by LCMS). After completion, the excess oxalyl chloride and solvent were removed under reduced pressure. The residue was re-dissolved in anhydrous DCM (10 mL), then added to a mixture of phenylmethanamine (46.0 mg, 430 μmol, 1 eq.) and TEA (217 mg, 2.15 mmol, 5 eq.) in anhydrous DCM (10 mL) at 0 °C. The reaction was allowed to warm to 25 °C and stirred for an additional 2 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give P-((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)difluoromethyl)-N-benzylphosphonamidic acid (100 mg, 0.23 mmol, 53%) as a colorless oil. LCMS (ESI): *m/z* = 438 $[M+H]^+$.

[00552] *Step 3: Preparation of allyl 5-(((benzylamino)(2-((3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate*

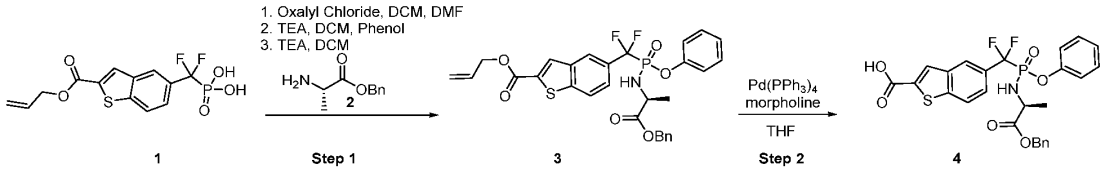
[00553] Amberlite IR120® (18.2 mg, 457 μmol, 2 eq) in water (2 mL) was added dropwise to a stirred suspension of P-((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)difluoromethyl)-N-benzylphosphonamidic acid (100 mg, 0.23 mmol, 1 eq.) in H_2O (6 mL). When the mixture became clear (pH~9), silver(I) nitrate (85.2 mg, 502 μmol, 2.2 eq.) was added. After stirring at 0 °C for 2 h, the gray precipitate was collected by filtration and dried under vacuum. The powder was suspended in dry Toluene (1 mL) and S-(2-iodoethyl) 3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanethioate (1.68 g, 6.96 mmol, 30 eq.) was added. The mixture was stirred at 80 °C for 24 h. After filtration, the solvent was removed in vacuo. The crude residue was directly purified by flash column chromatography on silica gel to give allyl 5-(((benzylamino)(2-((3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (40.0 mg, 56 μmol, 25%) as a white solid. LCMS (ESI): *m/z* = 734.2 $[M+Na]^+$.

[00554] *Step 4: Preparation of 5-(((benzylamino)(2-((3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid*

[00555] To a solution of allyl 5-(((benzylamino)(2-((3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (35 mg, 49 μmol, 1 eq.) in DCM (1 mL) were added $Pd(PPh_3)_4$ (2.83 mg, 2.45 μmol, 0.05 eq.) and pyrrolidine (3 mg, 49.1 μmol, 1 eq.). The mixture was purged and degassed with N_2 (three times), then stirred at 25 °C for 2 h. After completion, the mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography

to give 5-(((benzylamino)(2-((3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid (20.0 mg, 30 µmol, 61%) as a colorless oil. LCMS (ESI): *m/z* = 672.1 $[M+H]^+$.

Synthesis of 5-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid

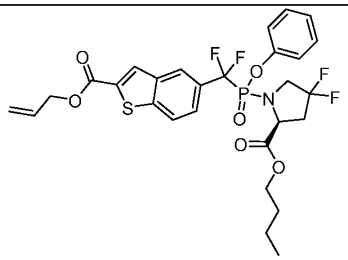
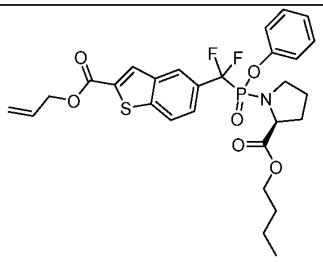


[00556] *Step 1: Preparation of allyl 5-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate*

[00557] To a solution of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid (300 mg, 861 µmol, 1 eq) in DCM (5 mL) at 0 °C were added 2 drops of DMF (cat.) followed by dropwise addition of oxalyl chloride (220 µL, 2.58 mmol, 3 eq). The reaction was warmed up to room temperature and stirred for 16 h. The reaction mixture was concentrated under reduced pressure and dried completely under high vacuum for 30 min. to give a yellow solid. The yellow solid was diluted in DCM (5 mL) and cooled to 0°C. A solution of phenol (89.1 mg, 947 µmol, 1.1 eq) and triethylamine (599 µL, 4.30 mmol, 5 eq) in DCM (1 mL, dried on Na_2SO_4) was slowly added to the yellow solution. The reaction mixture was stirred at 0°C for 2 min. and then warmed up to room temperature and stirred for 2 h. A solution of *L*-alanine benzyl ester p-toluenesulfonate salt (453 mg, 1.29 mmol, 1.5 eq) in DCM (1 mL, dried on Na_2SO_4) was slowly added to the yellow solution. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed *in vacuo*. The crude product was purified by reverse phase chromatography on a 50 g C_{18} cartridge eluting with a gradient of 5-100% acetonitrile in water. The pure fractions were combined and concentrated under reduced pressure to give allyl 5-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (196 mg, 38.8%) as a yellow oil. LCMS (ESI) m/z = 586.2.

[00558] The following intermediates in **Table 52** were prepared using the method described above in step 1 for the preparation of allyl 5-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate and utilizing the appropriate starting materials and modifications.

Table 52

Name	Structure	LCMS	NMR
butyl (2S)-1-(((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)difluoromethyl)(phenoxy)phosphoryl)-4,4-difluoropyrrolidine-2-carboxylate		614.2 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.12 (s, 1H), 7.99 - 7.91 (m, 1H), 7.79 - 7.73 (m, 1H), 7.35 - 7.02 (m, 5H), 6.12 - 5.98 (m, 1H), 5.50 - 5.41 (m, 1H), 5.38 - 5.28 (m, 1H), 4.89 - 4.84 (m, 2H), 4.81 - 4.73 (m, 0.8H), 4.47 - 4.38 (m, 0.2H), 4.29 - 3.96 (m, 2H), 3.88 - 3.64 (m, 2H), 2.76 - 2.43 (m, 2H), 1.61 - 1.50 (m, 2H), 1.39 - 1.23 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H)
butyl (((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)difluoromethyl)(phenoxy)phosphoryl)-L-prolinate		542.3 $[M+H]^+$	

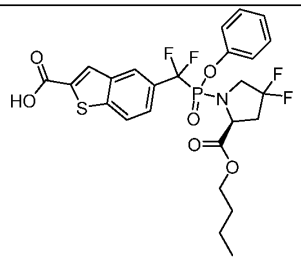
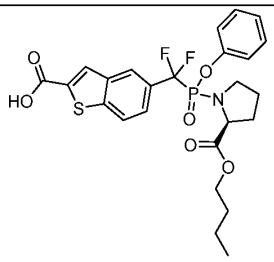
[00559] *Step 2:Preparation of 5-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid*

[00560] To a stirred solution of allyl 5-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (196 mg, 334 µmol, 1 eq) in THF (5 mL) were added morpholine (143 µL, 1.67 mmol, 5 eq) and $Pd(PPh_3)_4$ (38.5 mg, 33.4 µmol, 0.10 eq) under nitrogen. The reaction mixture was stirred 1 h at room temperature. The reaction mixture was directly purified by reverse phase chromatography on a 50 g C_{18} cartridge eluting with a gradient of 5-100% acetonitrile in water (with 0.1% formic acid). The pure fractions were concentrated under reduced pressure to give 5-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid (164 mg, 90.1%) as a light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 - 8.09 (m, 1H), 7.88 -

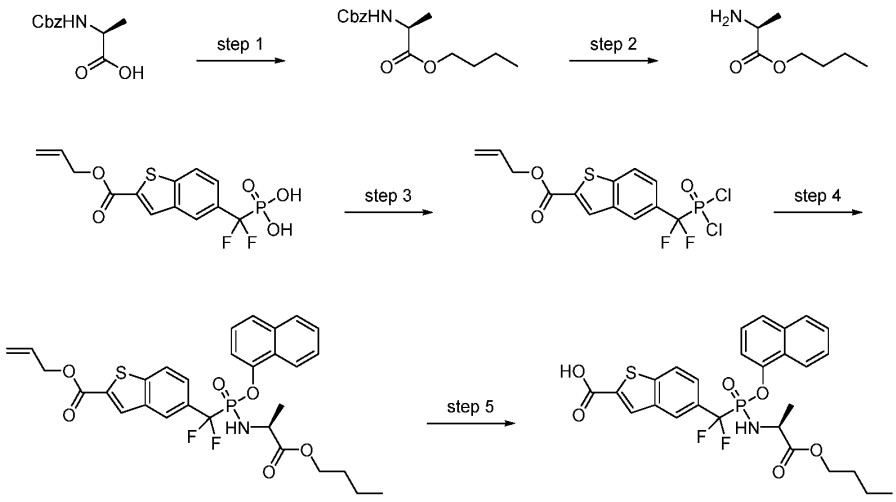
7.76 (m, 2H), 7.66 - 7.59 (m, 1H), 7.43 - 7.29 (m, 7.6H), 7.26 - 7.15 (m, 2.4H), 5.24 (s, 1H), 5.13 (s, 1H), 4.83 - 4.67 (m, 0.5H), 4.62 - 4.44 (m, 0.5H), 4.39 - 4.14 (m, 1H), 1.50 - 1.35 (m, 3H).

[00561] The following intermediates in **Table 53** were prepared using the method described above in step 2 for the preparation of 5-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid and utilizing the appropriate starting materials and modifications.

Table 53

Name	Structure	LCMS
5-((((S)-2-(butoxycarbonyl)-4,4-difluoropyrrolidin-1-yl)(phenoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid		574.2 $[M+H]^+$
5-((((S)-2-(butoxycarbonyl)pyrrolidin-1-yl)(phenoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid		537.8 $[M+H]^+$

Synthesis of 5-(((((S)-1-butoxy-1-oxopropan-2-yl)amino)(naphthalen-1-yloxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid



[00562] *Step 1: Preparation of butyl ((benzyloxy)carbonyl)-L-alaninate*

[00563] To a solution of ((benzyloxy)carbonyl)-L-alanine (5 g, 22 mmol, 1 eq) in DMF (50 mL) was added 1-chlorobutane (2.1 g, 22 mmol, 1 eq) and dipotassium carbonate (6.2 g, 45 mmol, 2 eq), the mixture was stirred at 60 °C for 1 h to give yellow solution. The mixture was diluted with water (200 mL) and extracted with EtOAc (200 mL × 2), the combined organic layers were washed with saturated brine (200 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give butyl ((benzyloxy)carbonyl)-L-alaninate (3.6 g, 13 mmol, 57.8% yield) as a yellow oil. LCMS (ESI) m/z = 280.0

[00564] *Step 2: Preparation of butyl L-alaninate*

[00565] To a solution of butyl ((benzyloxy)carbonyl)-L-alaninate (3 g, 11 mmol, 1 eq) in THF (30 mL) was added Pd/C (3 g, 10%) under N_2, the mixture was stirred at 25 °C for 2 h under H_2 (15 Psi). The reaction mixture was filtered and the filter was concentrated to give butyl L-alaninate (1.7 g, crude) as a yellow oil. LCMS (ESI) m/z = 146.1 $[M+H]^+$.

[00566] *Step 3: Preparation of allyl 5-((dichlorophosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate*

[00567] To a solution of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid (0.2 g, 0.57 mmol, 1 eq) in DCM (5 mL) was added dimethylformamide (0.42 mg, 5.7 μmol, 0.01 eq), the mixture was stirred at 0 °C for 5 min, then a solution of oxalyl chloride (0.22 g, 1.7 mmol, 3 eq) in DCM (5 mL) was added to the mixture, the mixture was stirred at 40 °C for 15 min to give yellow solution. The reaction mixture was concentrated under reduced pressure to give allyl 5-

((dichlorophosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (0.2 g, crude) as a yellow oil. LCMS (ESI) m/z = 377.0 $[M+H]^+$.

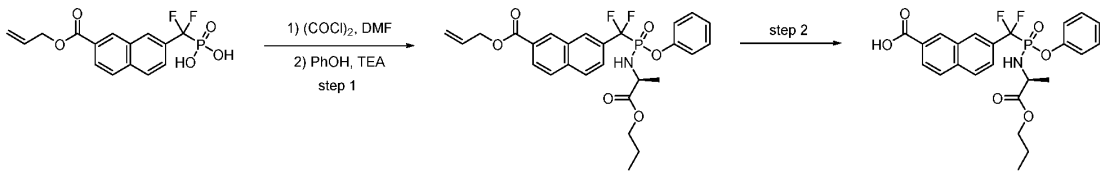
[00568] *Step 4: Preparation of allyl 5-(((((S)-1-butoxy-1-oxopropan-2-yl)amino)(naphthalen-1-yloxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate*

[00569] To a solution of allyl 5-((dichlorophosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (0.2 g, 0.52 mmol, 1 eq) in DCM (10 mL) was added naphthalen-1-ol (60 mg, 0.42 mmol, 0.8 eq), the mixture was stirred at 0 °C for 5 min, then a solution of N,N-diisopropylethylamine (0.2 g, 1.6 mmol, 3.0 eq) in DCM (10 mL) was added to the mixture, then a solution of butyl L-alaninate (75 mg, 0.52 mmol, 1 eq) in DCM (10 mL) was added to the mixture, the mixture was stirred at 0 °C for 30 min to give yellow solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give allyl 5-(((((S)-1-butoxy-1-oxopropan-2-yl)amino)(naphthalen-1-yloxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (0.15 g, 0.24 mmol, 46.4% yield) as a yellow oil. LCMS (ESI) m/z = 602.1 $[M+H]^+$.

[00570] *Step 5: Preparation of 5-(((((S)-1-butoxy-1-oxopropan-2-yl)amino)(naphthalen-1-yloxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid*

[00571] To a solution of allyl 5-(((((S)-1-butoxy-1-oxopropan-2-yl)amino)(naphthalen-1-yloxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (0.14 g, 0.23 mmol, 1 eq) in DCM (1.0 mL) was added $Pd(PPh_3)_4$ (27 mg, 23 μmol, 0.1 eq), the mixture was stirred at 0 °C for 5 min, then pyrrolidine (17 mg, 0.23 mmol, 1 eq) was added to the mixture, the mixture was stirred at 25 °C for 5 min to give yellow solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by reversed phase (TFA) to give 5-(((((S)-1-butoxy-1-oxopropan-2-yl)amino)(naphthalen-1-yloxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid (97 mg, 0.17 mmol, 74.6% yield) as a yellow oil. LCMS (ESI) m/z = 562.1 $[M+H]^+$.

Synthesis of 7-(difluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoic acid:

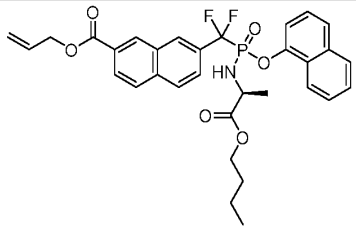


[00572] *Step 1: Preparation of allyl 7-(difluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoate*

[00573] Oxalyl chloride (10 mL) was added dropwise to the solution of ((7-((allyloxy)carbonyl)naphthalen-2-yl)difluoromethyl)phosphonic acid (1.5 g, 4.38 mmol, 1 eq.) in dry DCM (10 mL) and DMF (1 drop) at 0 °C. The reaction mixture was stirred at 40 °C for an additional 1 hr. The reaction was monitored by pipetting out a small amount of crude sample and quenching it with MeOH to ensure bis-Cl phosphoryl chloride had been formed completely (bis-methoxy phosphonate was observed by LCMS). After completion, the excess oxalyl chloride and solvent were removed under reduced pressure. The residue was re-dissolved in anhydrous DCM (5 mL), then added to a mixture of phenol (412 mg, 4.38 mmol, 1 eq.) and triethylamine (2.21 g, 21.9 mmol, 5 eq.) in anhydrous DCM (10 mL) at 0 °C. The reaction was allowed to warm to 25 °C and stirred for an additional 1 hr. Then propyl L-alaninate (1.14 g, 8.76 mmol, 2 eq.) was added at 0 °C and the resulting mixture was stirred at 20 °C for 1 h under N_2. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give allyl 7-(difluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoate (510 mg, 0.96 mmol, 22%) as a white solid. LCMS (ESI): *m/z* = 532.2 $[M+H]^+$.

[00574] The following intermediates in **Table 54** were prepared using the method described above in step 1 for the preparation of 5-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid and utilizing the appropriate starting materials and modifications.

Table 54

Name	Structure	LCMS
allyl 7-(((((S)-1-butoxy-1-oxopropan-2-yl)amino)(naphthalen-1-yloxy)phosphoryl)difluoromethyl)-2-naphthoate		596 $[M+H]^+$

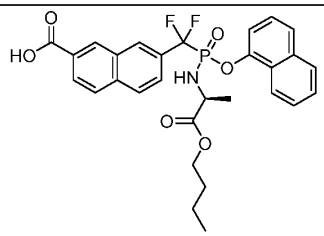
[00575] *Step 2: Preparation of 7-(difluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoic acid*

[00576] To a solution of allyl 7-(difluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoate (2, 510 mg, 0.96 mmol, 1 eq) in DCM (2 mL) were added $Pd(PPh_3)_4$ (22.3 mg, 0.01932 mmol, 0.05 eq.) and pyrrolidine (27.4 mg, 0.3864 mmol, 1.0 eq.). The mixture was purged and degassed with N_2 (three times), then

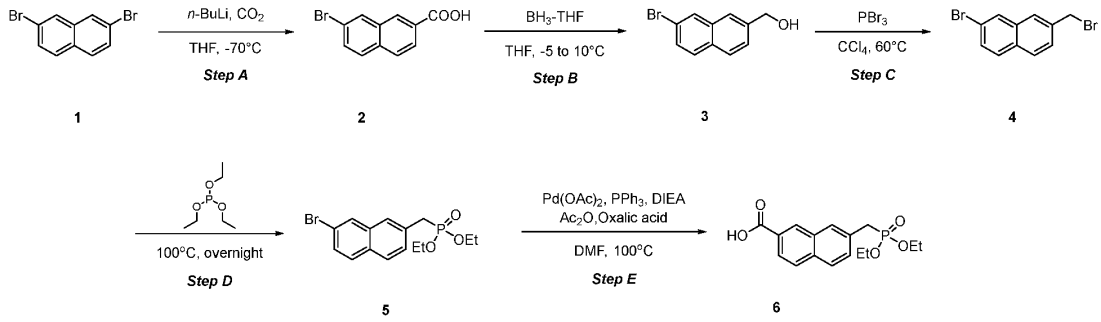
stirred at 25 °C for 1 hr. After completion, the mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give 7-(difluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoic acid (1150 mg, 0.3142 mmol, 82%) as a white solid. LCMS (ESI): *m/z* = 492 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 8.75 (d, *J* = 9.7 Hz, 1H), 8.44-8.38 (m, 1H), 8.21-8.14 (m, 1H), 8.13-8.06 (m, 2H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.40-7.31 (m, 2H), 7.26-7.10 (m, 3H), 6.88-6.78 (m, 1H), 4.00-3.90 (m, 1H), 3.90-3.76 (m, 2H), 1.55-1.38 (m, 2H), 1.25-1.17 (m, 3H), 0.86-0.74 (m, 3H).

[00577] The following intermediates in **Table 55** were prepared using the method described above in step 2 for the preparation of 5-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid and utilizing the appropriate starting materials and modifications.

Table 55

Name	Structure	LCMS
7-(((((S)-1-butoxy-1-oxopropan-2-yl)amino)(naphthalen-1-yloxy)phosphoryl)difluoromethyl)-2-naphthoic acid		556 $[M+H]^+$

Synthesis of 7-((diethoxyphosphoryl)methyl)-2-naphthoic acid



[00578] *STEP A: 7-bromo-2-naphthoic acid*

[00579] To a solution of 2,7-dibromonaphthalene (**1,** 400 g, 1.4 mol, 1.0 eq.) in THF (6000 mL) was added *n*-BuLi (560 mL, 1.4 mol, 2.5 M in hexane, 1.0 eq.) by dropping funnel over a period of 2.5 h at -70 °C under N_2. Then the reaction mixture was stirred at -70 °C for an

additional 1 hr. The reaction was monitored by pipetting out a small amount of crude sample and quenching it with acetone to ensure **1** was consumed completely (observed by TLC). After completion, CO_2(g) was bubbled into the reaction mixture at -70 °C to -60 °C for 30 minutes (3L / min). The reaction progress was monitored by TLC (DCM:EA=1:1, Rf =0.2). After completion, the reaction mixture was quenched by adding H_2O (5000 mL), the suspension was filtered through a pad of celite and the filter cake was washed with H_2O (1000 mL). The combined filtrates were extracted with PE (3000 mL). The aqueous phase was acidified with 6 N HCl until the pH was adjusted to pH = 3. The mixture was filtered and the filter cake was washed with H_2O (600 mL), then dried in vacuum to afford 7-bromo-2-naphthoic acid (**2,** 240 g, 0.96 mol, 68%) as a white solid. LCMS (ESI): *m/z* = 251 $[M+H]^+$.

[00580] *STEP B: (7-bromonaphthalen-2-yl)methanol*

[00581] To a solution of 7-bromo-2-naphthoic acid (**2,** 480 g, 1.92 mol, 1.0 eq.) in THF(1000 mL) was added BH_3/THF (4800 mL, 4.8 mol, 1 M in THF, 2.5 eq.) by dropping funnel over a period of 3 h at -20 °C to -5 °C under N_2. Then the reaction mixture was stirred at -5 °C to 10 °C overnight. The reaction progress was monitored by TLC (DCM:EA =5:1, Rf =0.3). After completion, the reaction mixture was quenched by adding HCl aqueous solution (1N, 400mL) at 0 °C. The mixture was diluted with H_2O (2000 mL) and extracted with EtOAc (2000 mL x 2). The combined organic layers were washed with water (3000 mL), brine(2000 mL) and dried over anhydrous Na_2SO_4. The organic layers were concentrated under reduced pressure. The residue was purified by re-crystallization from DCE (2000 mL). The mixture was filtered and the filter cake was washed with PE (200 mL), then dried in vacuum to afford (7-bromonaphthalen-2-yl)methanol (**3,** 405 g, 1.70 mol, 89%) as a white solid.

[00582] *STEP C: 2-bromo-7-(bromomethyl)naphthalene*

[00583] To a solution of (7-bromonaphthalen-2-yl)methanol (**3,** 40.0 g, 0.17 mol, 1.0 eq.) in CCl_4 (400 mL) was added PBr_3 (16.1 g, 0.06 mol, 0.35 eq.) at 60 °C. After addition, the reaction mixture was stirred at 60 °C for 3 h. After completion, the reaction mixture was concentrated under reduced pressure to give a solid. The solid was triturated with PE/EA=8/1 (400 mL) to afford 2-bromo-7-(bromomethyl)naphthalene (**4,** 48.5 g, 0.16 mol, 96 %) as a white solid. ^{1}H NMR(400 MHz, DMSO-d_6) δ 8.26 (d, *J* = 1.7 Hz, 1H), 8.08-7.90 (m, 3H), 7.75-7.56 (m, 2H), 4.93 (s, 2H).

[00584] *STEP D: diethyl ((7-bromonaphthalen-2-yl)methyl)phosphonate*

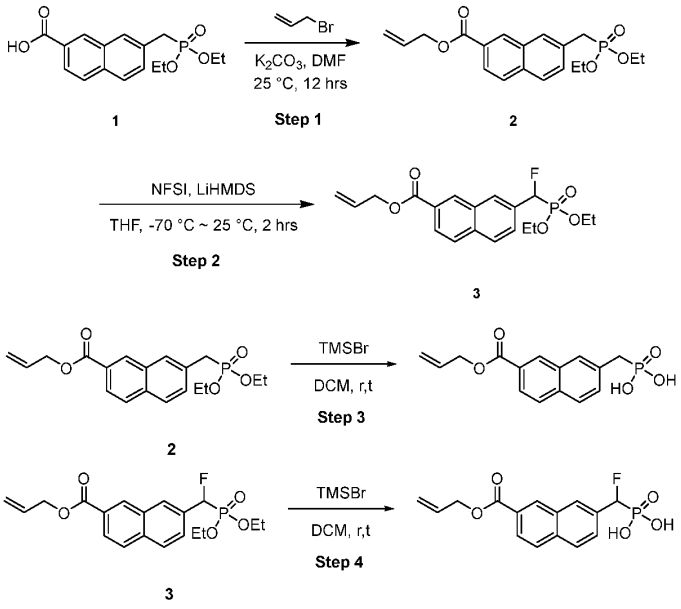
[00585] A solution of 2-bromo-7-(bromomethyl)naphthalene (**4,** 48.5 g, 0.16 mol, 1.0 eq.) in triethyl phosphite (100 mL) was stirred at 100 °C overnight under nitrogen atmosphere.

After completion, the reaction mixture was concentrated under reduced pressure to remove triethyl phosphite. The residue was triturated with IPA (100 mL) to afford diethyl ((7-bromonaphthalen-2-yl)methyl)phosphonate (**5,** 40.0 g, 0.11 mol, 69%) as a white solid. LCMS (ESI): *m/z* = 357.1 $[M+H]^+$. ^1H NMR(400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.69-7.65 (m, 2H), 7.57-7.39 (m, 2H), 4.13 -3.90 (m, 4H), 3.31 (d, *J* = 21.8 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 6H).

[00586] *STEP E: 7-((diethoxyphosphoryl)methyl)-2-naphthoic acid*

[00587] To a solution of diethyl ((7-bromonaphthalen-2-yl)methyl)phosphonate (**5,** 10.0 g, 27.9 mmol, 1.0 eq.), oxalic acid (10.9 g, 122.0 mmol, 4.4 eq.), Ac_2O (10.5 g, 103.0 mmol, 3.7 eq.) and DIEA (19.3 g, 150.0 mmol, 5.4 eq.) in DMF (60.0 mL) was added $Pd(OAc)_2$ (625 mg, 2.79 mmol, 0.1 eq.) and PPh_3 (2.2 g, 8.37 mmol, 0.3 eq.). The resulting mixture was stirred at 100 °C overnight under nitrogen atmosphere. After completion, the reaction mixture was cooled to room temperature and acidified with 1 N HCl aqueous solution until the pH was adjusted to pH = 3. The mixture was filtered. The filtrate was diluted with H_2O (40 mL) and extracted with EtOAc (200 mL x 3). The organic layers were combined, washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford 7-((diethoxyphosphoryl)methyl)-2-naphthoic acid (**6,** 8.0 g, 24.8 mmol, 89%) as a yellow solid. LCMS (ESI): *m/z* = 323.2 $[M+H]^+$.

Synthesis of ((7-((allyloxy)carbonyl)naphthalen-2-yl)methyl)phosphonic acid and ((7-((allyloxy)carbonyl)naphthalen-2-yl)fluoromethyl)phosphonic acid



[00588] *Step 1: allyl 7-((diethoxyphosphoryl)methyl)-2-naphthoate*

[00589] Four batches of the reactions were carried out in parallel.

To a solution of 7-((diethoxyphosphoryl)methyl)-2-naphthoic acid (Compound 1, 150 g, 465 mmol, 1.00 *eq*) and K_2CO_3 (129 g, 931 mmol, 2.00 *eq*) in DMF (1.50 L) was added allyl bromide (67.6 g, 559 mmol, 1.20 *eq*) at 25 °C. After addition, the reaction mixture was stirred at 25 °C for 12 h, at which time LCMS indicated reaction was complete. Four batches of reaction mixture were combined for work-up. The reaction mixture was poured into water (18.0 L) and extracted with ethyl acetate (6.00 L x 2). The organic layers were combined, washed with water (6.00 L) and brine (6.00 L), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (Petroleum ether: Ethyl acetate = 50: 1 to 0: 1, Petroleum ether: Ethyl acetate = 0: 1, $R_f = 0.50$) to give allyl 7-((diethoxyphosphoryl)methyl)-2-naphthoate (Compound 2 568 g, 1.54 mol, 82.7% yield) as a light-yellow solid. LCMS (ESI): *m/z* = 363.1 $[M+H]^+$. ^1H NMR(400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.07 - 8.06 (d, *J* = 7.60 Hz, 1H), 7.88 - 7.84 (m, 3H), 7.58 - 7.56 (m, 1H), 6.13 - 6.06 (m, 1H), 5.49 - 5.44 (m, 1H), 5.35 - 5.32 (m, 1H), 4.91 - 4.89 (m, 2H), 4.06 - 4.02 (m, 4H), 3.36 - 3.31 (d, *J* = 22.0 Hz 1H), 1.27 - 1.23 (m, 6H).

[00590] *Step 2: allyl 7-((diethoxyphosphoryl)fluoromethyl)-2-naphthoate*

[00591] Eight batches of the reactions were carried out in parallel.

[00592] To a solution of allyl 7-((diethoxyphosphoryl)methyl)-2-naphthoate (Compound 2**,** 100 g, 276 mmol, 1.00 *eq*) in THF (1.50 L) was added NFSI (87.0 g, 276 mmol, 1.00 *eq*) at 25 °C slowly. The mixture was cooled to -70 °C. A solution of LiHMDS (1.00 M, 276 mL, 1.00 *eq*) was added to the above mixture drop-wise under N_2. After addition, the reaction mixture was stirred at -70 °C for 2 h under N_2. The reaction mixture was poured into saturated NH_4Cl aqueous solution (2.00 L) slowly at 0 °C. The mixture was extracted with ethyl acetate (1.00 L * 2). The organic layers were combined, washed with brine (4.00 L), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was diluted with ethyl acetate (4.00 L) and filtered; the filtrate was concentrated under reduced pressure to give a crude yellow oil (779 g). The product was purified by silica gel column chromatography (Petroleum ether: Ethyl acetate = 50: 1 to 0: 1) to give allyl 7-((diethoxyphosphoryl)fluoromethyl)-2-naphthoate (Compound 3, 418 g, 1.07 mol, 52.3% yield, 97.4% purity) as yellow oil. LCMS (ESI): *m/z* = 381.1 $[M+H]^+$. ^1H NMR(400 MHz, DMSO) δ 8.71 (s, 1H), 8.23 (s, 1H), 8.10 - 8.04 (m, 3H), 7.74 - 7.72 (d, *J* = 8.80 Hz, 1H),

6.39 - 6.26 (m, 1H), 6.14 - 6.10 (m, 1H), 5.49 - 5.44 (m, 1H), 5.33 - 5.30 (m, 1H), 4.89 - 4.87 (m, 2H), 4.07 - 4.01 (m, 4H), 1.22 - 1.15 (m, 6H).

[00593] *Step 3: ((7-((allyloxy)carbonyl)naphthalen-2-yl)methyl)phosphonic acid*

[00594] To a solution of allyl 7-((diethoxyphosphoryl)methyl)-2-naphthoate (Compound 2**,** 4 g, 11.0 mmol, 1.0 eq.) in DCM (40 mL) was added TMSBr (8 mL) at room temperature. After addition, the reaction mixture was stirred at room temperature for 12 h. After completion, the reaction mixture was poured into H_2O (30 mL) and the suspension was filtered. The filter cake was dried under vacuum to afford ((7-((allyloxy)carbonyl)naphthalen-2-yl)methyl)phosphonic acid (3.0 g, 9.79 mmol, 89%) as a yellow solid. LCMS (ESI): *m/z* = 307 $[M+H]^+$.

^1H NMR(400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.04-7.87 (m, 4H), 7.64-7.56 (m, 1H), 6.21-5.96 (m, 1H), 5.53 -5.23 (m, 2H), 4.93-4.82 (m, 2H), 3.17 (d, *J* = 21.5 Hz, 2H).

[00595] *Step 4: ((7-((allyloxy)carbonyl)naphthalen-2-yl)fluoromethyl)phosphonic acid:*

[00596] To a solution of allyl 7-((diethoxyphosphoryl)fluoromethyl)-2-naphthoate (Compound 3, 27 g, 71.1 mmol, 1.0 eq.) in DCM (300 mL) was added TMSBr (50 mL) at room temperature. After addition, the reaction mixture was stirred at room temperature for 12 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to afford ((7-((allyloxy)carbonyl)naphthalen-2-yl)fluoromethyl)phosphonic acid (17.6 g, 54.2 mmol, 76%) as a white solid.

^1H NMR(400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.16 (s, 1H), 8.10-7.96 (m, 3H), 7.73 (d, *J* = 8.5 Hz, 1H), 6.18-6.04 (m, 1H), 5.89 (dd, *J* = 44.5, 8.6 Hz, 1H), 5.52-5.42 (m, 1H), 5.36-5.26 (m, 1H), 4.88 (d, *J* = 5.4 Hz, 2H). LCMS (ESI): *m/z* =325.1 $[M+H]^+$.

Chiral separation of allyl 7-((diethoxyphosphoryl)fluoromethyl)-2-naphthoate

[00597] *Rac*-allyl 7-((diethoxyphosphoryl)fluoromethyl)-2-naphthoate (617 g, 1.62 mol, 1.00 *eq*) was purified by SFC to give allyl (S)-7-((diethoxyphosphoryl)fluoromethyl)-2-naphthoate (Peak 1) and allyl (R)-7-((diethoxyphosphoryl)fluoromethyl)-2-naphthoate (Peak 2).

[00598] Preparative SFC method: Instrument: Waters 350 Preparative SFC. Column: REGIS (S,S) WHELK-O1, 250×50 mm I.D., 10 μm. Mobile phase: A for CO_2 and B for MeOH (Neu). Gradient: B 15 % Flow rate: 220 g/min. Back pressure: 100 bar. Column temperature: 35 °C. Wavelength: 254 nm. Cycle-time: 7.3 min.

[00599] Analytical SFC method: Column: Kromasil (S,S) WHELK-O1, 50×4.6 mm I.D., 3.5 µm. Mobile phase: A for CO_2 and B for MEOH (0.05% DEA). Gradient: B 5 to 40 % Flow rate: 3 mL/min. Back pressure: 100 bar. Column temperature: 35 °C. Wavelength: 220 nm.

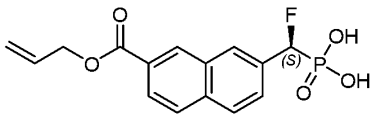
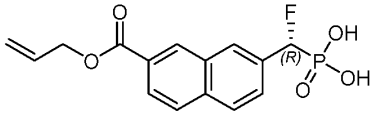
[00600] allyl (S)-7-((diethoxyphosphoryl)fluoromethyl)-2-naphthoate (Peak 1, 286 g, 745 mmol, 45.9% yield, >99 %ee, RT= 1.31min) was obtained as yellow oil. **LCMS (ESI)**: *m/z* = 381.1 $[M+H]^+$.

[00601] allyl (R)-7-((diethoxyphosphoryl)fluoromethyl)-2-naphthoate (Peak 2, 288 g, 748 mmol, 46.1% yield, >99 %ee, RT= 1.52min) was obtained as yellow oil. **LCMS (ESI)**: *m/z* = 381.1 $[M+H]^+$.

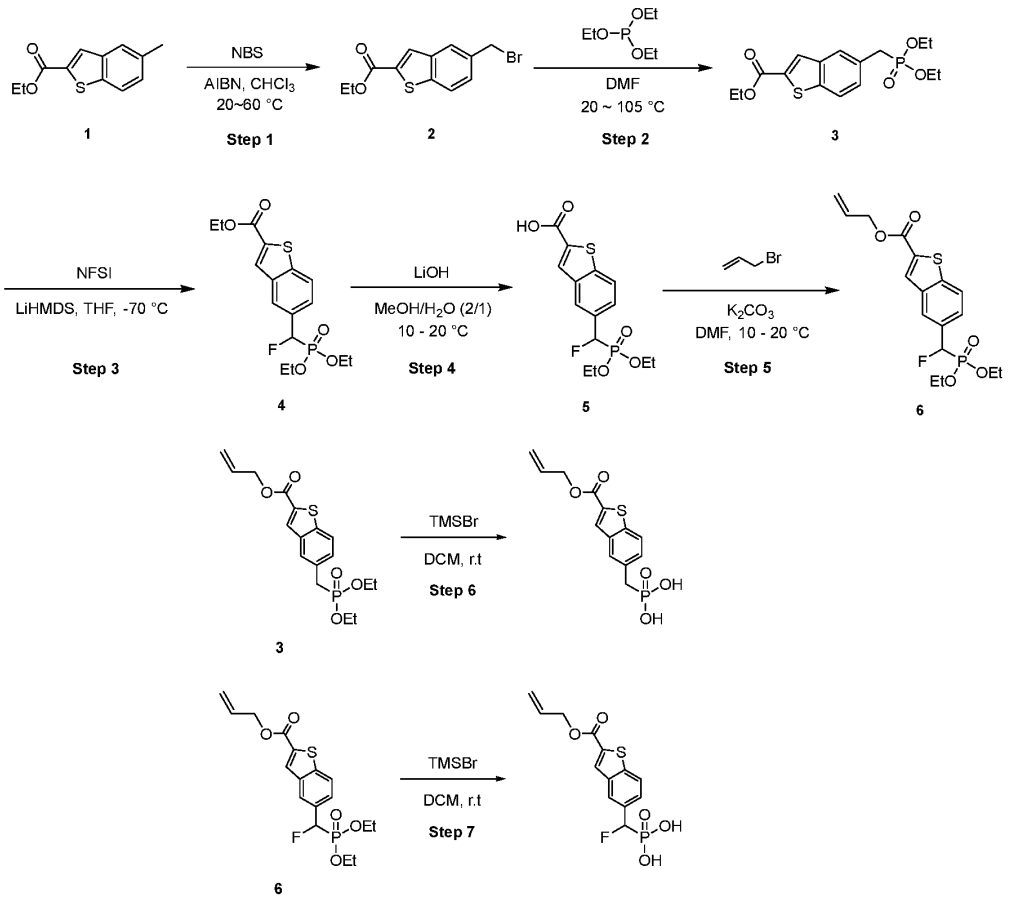
[00602] Assignment of absolute stereochemical configuration was made by comparison of experimental vibrational circular dichroism (VCD) spectra with theoretical VCD spectra obtained from DFT calculations.

[00603] The following intermediates in **Table 56** were prepared using the method described above in step 4 for the preparation of ((7-((allyloxy)carbonyl)naphthalen-2-yl)fluoromethyl)phosphonic acid and utilizing the appropriate starting materials and modifications.

Table 56

Name	Structure	LCMS
(S)-((7-((allyloxy)carbonyl)naphthalen-2-yl)fluoromethyl)phosphonic acid		325.1 $[M+H]^+$
(R)-((7-((allyloxy)carbonyl)naphthalen-2-yl)fluoromethyl)phosphonic acid		325.1 $[M+H]^+$

Synthesis of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid and ((2-((allyloxy)carbonyl)benzo[*b*]thiophen-5-yl)fluoromethyl)phosphonic acid:



[00604] Ethyl 5-methylbenzo[*b*]thiophene-2-carboxylate was prepared according to the procedure described in WO 2016/100184.

[00605] *STEP 1: ethyl 5-(bromomethyl)benzo[b]thiophene-2-carboxylate*

[00606] To a solution of ethyl 5-methylbenzo[*b*]thiophene-2-carboxylate (**1,** 7.3 kg, 33.1 mol, 1.0 eq.) in $CHCl_3$ (58 L) stirred at 20 °C was added AIBN (544 g, 3.31 mol, 0.10 eq.) and NBS (6.19 kg, 34.8 mol, 1.05 eq.). The mixture was heated from 30 °C to 50 °C over 4 h and was then heated to 60 °C and stirred for 12 hours. After completion, the reaction mixture was cooled to 10 °C and 15% Na_2SO_3 (20 L) was added. The organic layers were washed with H_2O (20 L * 2), dried over Na_2SO_4, and concentrated under reduced pressure at 45 °C to afford ethyl 5-(bromomethyl)benzo[*b*]thiophene-2-carboxylate (**2**, 9.50 kg, 23.5 mol, 70.9% yield, 74.0% purity) as a yellow solid. LCMS (ESI): *m/z* = 298.9 $[M+H]^+$.
^1H NMR (400 MHz, $CDCl_3$) δ 8.034 (s, 1H), 7.89 – 7.84 (m, 2H), 7.50 (d, J = 9.6 Hz, 1H), 4.64 (s, 2H), 4.45 - 4.40 (m, 2H), 1.45 – 1.41 (m, 3H).

[00607] *STEP 2: ethyl 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00608] To a solution of ethyl 5-(bromomethyl)benzo[b]thiophene-2-carboxylate (**2,** 9.50 kg, 31.8 mol, 1.0 eq.) in DMF (28.5 L) stirred at 20 °C was added triethyl phosphite (5.8 kg, 34.9 mol, 1.1 equiv). The mixture was heated to 100 °C and stirred for 5 h. After completion, the reaction mixture was cooled to 15 °C, poured into H_2O (50.0 L), and extracted with EtOAc (20 L *2). The combined organics were washed with H2O (20 L * 2) and brine (10 L), dried over Na2SO4, and concentrated under reduced pressure at 45 °C to give a residue. Crude residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate = 100/1 to 1/1, Petroleum ether/Ethyl acetate = 0/1) to afford ethyl 5-((diethoxyphosphoryl)methyl)benzo[*b*]thiophene-2-carboxylate (**3,** 5.24 kg, 14 mol, 44.4% yield) as yellow solid. LCMS (ESI): *m/z* = 356.9 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.82 – 7.80 (m, 2H), 7.41 (d, J = 2.0 Hz, 1H), 4.44 – 4.41 (m, 2H), 4.05 - 4.01 (m, 4H), 3.27 (d, J = 21.6 Hz, 2H), 1.46 – 1.42 (m, 3H), 1.27 – 1.23 (m, 6H).

[00609] STEP 3: *ethyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate*

[00610] Three batches were carried out in parallel.

[00611] To a solution of ethyl 5-((diethoxyphosphoryl)methyl)benzo[*b*]thiophene-2-carboxylate (**3**, 250 g, 702 mmol, 1.00 *eq*) and *N*-(benzenesulfonyl)-*N*-fluorobenzenesulfonamide (221 g, 702 mmol, 1.00 *eq*) in THF (2.50 L) was added dropwise LiHMDS (1 M, 702 mL, 1.00 *eq*) at -70 °C under N_2. The mixture was stirred at -70 °C for 3 h. Following completion, the reaction mixture was poured into saturated NH_4Cl aqueous solution (5.00 L) slowly at 0 °C and the mixture was stirred at 0 °C for 0.5 hr. Then three batches were combined to workup. The mixture was extracted with ethyl acetate (5.00 L * 3). The organic layers were combined, washed with brine (5.00 L), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 - 3/1, R_f = 0.30, petroleum ether/ethyl acetate = 1/1) to give ethyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (**4**, 357 g, 928 mmol, 44.1% yield) as yellow oil. LCMS (ESI): *m/z* = 375.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 8.00 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 5.88 - 5.75 (m, 1H), 4.45 - 4.40 (m, 2H), 4.15 - 4.05 (m, 4H), 1.45 - 1.41 (m 3H), 1.31 - 1.28 (m, 6H).

[00612] *STEP 4: 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid*

[00613] To a solution of ethyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (**4**, 252 g, 673 mmol, 1.00 *eq*) in MeOH (1.80 L) was added H_2O (760 mL) and

$LiOH•H_2O$ (56.5 g, 1.35 mol, 2.00 *eq*) at 10 - 20 °C under N_2. The mixture was stirred at 10 - 20 °C for 1 hr. TLC (petroleum ether/ethyl acetate = 1/1) showed that compound **4** was consumed ($R_f = 0.30$) and desired spot ($R_f = 0.10$) was formed. The reaction mixture was quenched by H_2O (2.50 L) and then adjusted pH to 3 - 4 with HCl (aq.1M). The mixture was extracted with dichloromethane (2.50 L * 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid (**5**, 222 g, 626 mmol, 93.0% yield) as a white solid.

[00614] *STEP 5: allyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate*

[00615] Two batches were carried out in parallel.

[00616] To a solution of 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid (**5**, 178 g, 514 mmol, 1.00 eq) in DMF (1.78 L) was added K_2CO_3 (142 g, 1.03 mol, 2.00 eq) and allyl bromide (68.4 g, 565 mmol, 1.10 eq) at 10 - 20 °C. The mixture was stirred at 10 - 20 °C for 12 h. TLC (petroleum ether/ethyl acetate = 0/1) showed that compound **5** was consumed ($R_f = 0.60$) and a new spot ($R_f = 0.70$) was formed. The reaction mixture was diluted with H_2O (6.00 L), extracted with ethyl acetate (2.00 L * 3). The organic layers were combined. The mixture was washed with brine (2.00 L) and NH_4Cl (2.00 L), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give allyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (**6**, 388 g, 985 mmol, 95.8% yield) as yellow oil.

[00617] *STEP 6: ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid*

[00618] To a solution of allyl 5-((diethoxyphosphoryl)methyl)benzo[*b*]thiophene-2-carboxylate (**3**, 50 g, 136 mmol, 1.0 eq.) in DCM (5 L) was added TMSBr (411 g, 2.71 mol, 20.0 eq.) dropwise at 0 °C. After addition, the reaction mixture was allowed to warm to room temperature and stirred for an additional 12 h. The reaction progress was monitored by LCMS. After completion, the reaction mixture was concentrated under reduced pressure and water was added. The resulting mixture was filtered and the filter cake was washed with water (2 L), then dried in vacuum to afford ((2-((allyloxy)carbonyl)benzo[*b*]thiophen-5-yl)methyl)phosphonic acid (40.3 g, 129 mmol, 95%) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.87 (s, 1H), 7.43 (d, J = 8.4 Hz, 1H), 6.10-5.98 (m, 1H), 5.46-5.37 (m, 1H), 5.33-5.24 (m, 1H), 4.86-4.77 (m, 2H), 3.08 (d, J = 21.2 Hz, 2H). LCMS (ESI) m/z = 313.1 $[M+H]^+$.

[00619] *STEP 7: ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid*

[00620] To a solution of allyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[*b*]thiophene-2-carboxylate (**6**, 5.2 g, 13.5 mmol, 1.0 eq.) in DCM (500 mL) was added TMSBr (41.1 g, 270 mmol, 20.0 eq.) dropwise at 0 °C. After the addition, the reaction mixture was allowed to warm to room temperature and stirred for an additional 12 h. The reaction progress was monitored by LCMS. After completion, the reaction mixture was concentrated under reduced pressure and water was added. The resulting mixture was filtered and the filter cake was washed with water (200 mL), then dried in vacuum to afford ((2-((allyloxy)carbonyl)benzo[*b*]thiophen-5-yl)fluoromethyl)phosphonic acid (3.1 g, 9.37 mmol, 69%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.14-8.05 (m, 2H), 7.59 (d, J = 8.4 Hz, 1H), 6.12-5.99 (m, 1H), 5.84 (dd, J = 44.3, 8.2 Hz, 1H), 5.49-5.40 (m, 1H), 5.35-5.27 (m, 1H), 4.88-4.81 (m, 2H). LCMS (ESI): m/z = 329.1 $[M-H]^-$.

Chiral separation of allyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate

[00621] *Rac*- allyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (617 g, 1.62 mol, 1.00 *eq*) was purified by SFC to give allyl (S)-5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (Peak 1) and allyl (R)-5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (Peak 2).

[00622] Preparative SFC method: Instrument: Waters 350 Preparative SFC. Column: REGIS (S,S) WHELK-O1, 250×50 mm I.D., 10 μm. Mobile phase: A for CO_2 and B for MEOH (Neu). Gradient: B 30 %. Flow rate: 220 g/min. Back pressure: 100 bar. Column temperature: 35 °C. Wavelength: 220 nm. Cycle-time: 3.3 min.
Analytical SFC method: Column: Kromasil (S,S) WHELK-O1, 50×4.6 mm I.D., 3.5 μm. Mobile phase: A for CO_2 and B for MEOH (0.05% DEA). Gradient: B 5 to 40 % Flow rate: 3 mL/min. Back pressure: 100 bar. Column temperature: 35 °C. Wavelength: 220 nm.

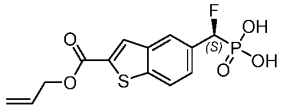
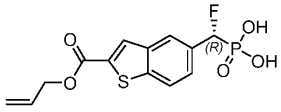
[00623] allyl (S)-5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (Peak 1, 267 g, 685 mmol, 39.7% yield, >99 %ee, RT= 1.36 min) was obtained as yellow oil. LCMS (ESI): m/z = 387.1 $[M+H]^+$.

[00624] allyl (R)-5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (Peak 2, 270 g, 676 mmol, 39.2% yield, >99 %ee, RT= 1.55 min) was obtained as yellow oil. LCMS (ESI): m/z = 387.1 $[M+H]^+$.

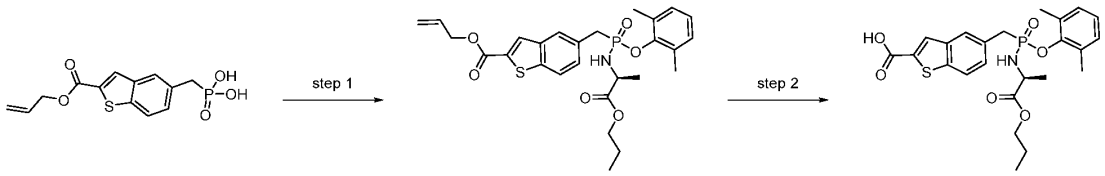
[00625] Assignment of absolute stereochemical configuration was made by comparison of experimental vibrational circular dichroism (VCD) spectra with theoretical VCD spectra obtained from DFT calculations.

[00626] The following intermediates in **Table 57** were prepared using the method described above in step 7 for the preparation of ((2-((allyloxy)carbonyl)benzo[*b*]thiophen-5-yl)fluoromethyl)phosphonic acid and utilizing the appropriate starting materials and modifications.

Table 57

Name	Structure	LCMS
(S)-((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		329 [M-H]$^-$
(R)-((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		329 [M-H]$^-$

Synthesis of 5-(((2,6-dimethylphenoxy)(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid



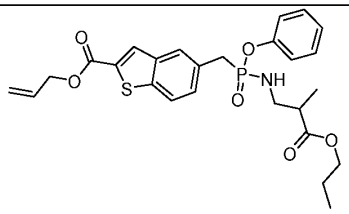
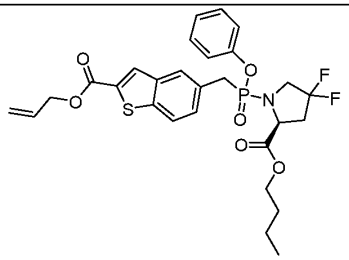
[00627] *Step 1: Preparation of allyl 5-(((2,6-dimethylphenoxy)(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

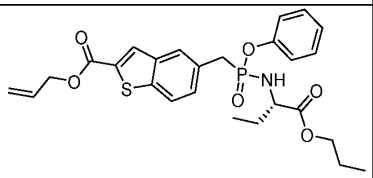
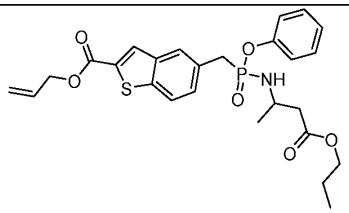
[00628] To a suspension of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (0.150 g, 480 µmol, 1 eq) and 1 drop of DMF (cat.) in DCM (4 mL) at 0 °C was added oxalyl chloride (122 µL, 1.44 mmol, 3 eq) and the mixture was stirred for 2 days at room temperature. The reaction was concentrated under reduced pressure and then dried under high vacuum for 20 min. The crude residue was diluted in toluene (5 mL). A solution of 2,6-dimethylphenol (58.6 mg, 480 µmol, 1 eq) and triethylamine (333 µL, 2.40 mmol, 5 eq) in toluene (2 mL, dried with sodium sulfate) was added to the mixture and stirred at 90 °C for 3 h. Propyl (2*S*)-2-aminopropanoate hydrochloride (80.4 mg, 480 µmol, 1 eq) was added at once at 90 °C and the reaction was stirred at 90°C for 2 h. The reaction was cooled down to room temperature and quenched with 2 drops of water and

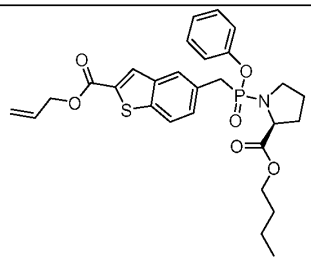
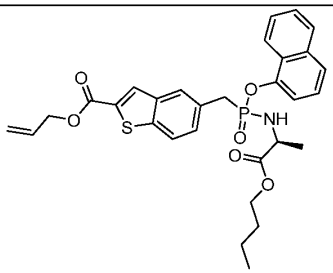
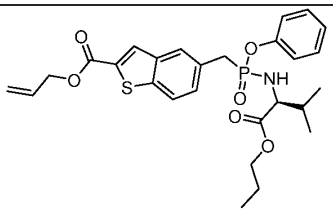
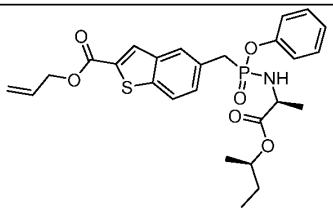
toluene was removed under reduced pressure. The product was purified by reverse phase chromatography on a 100 g C_{18} cartridge eluting with a gradient of 5-100% acetonitrile in water (with 0.1% formic acid) to afford allyl 5-(((2,6-dimethylphenoxy)(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (50.0 mg, 19.6%) as a pale yellow oil. LCMS (ESI) m/z = 530.4 $[M+H]^+$.

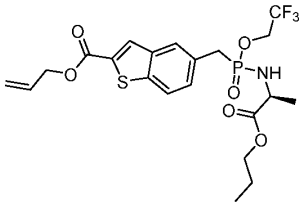
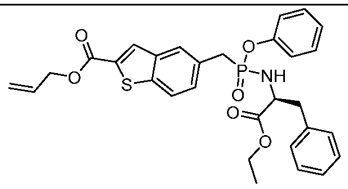
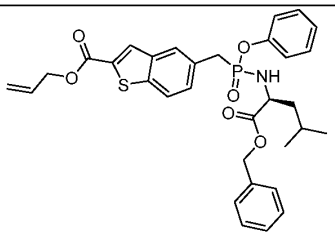
[00629] The following intermediates in **Table 58** were prepared using the method described above in step 1 for the preparation of allyl 5-(((2,6-dimethylphenoxy)(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate and utilizing the appropriate starting materials and modifications.

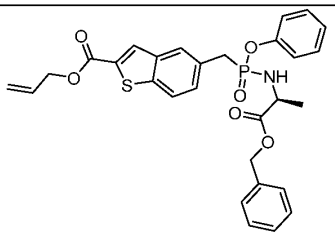
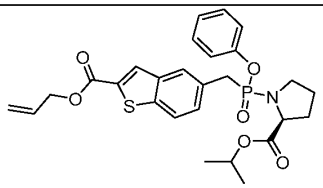
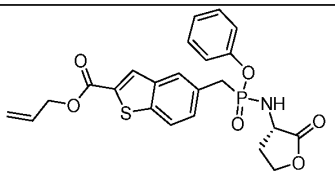
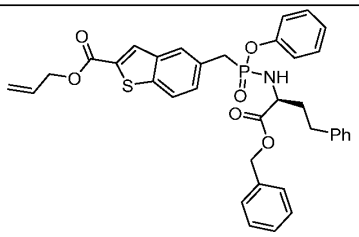
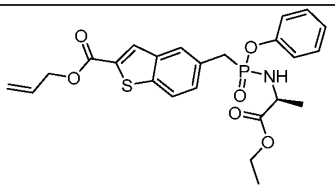
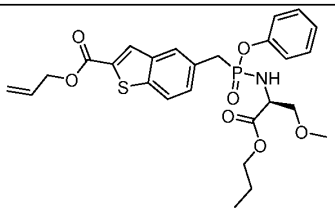
Table 58

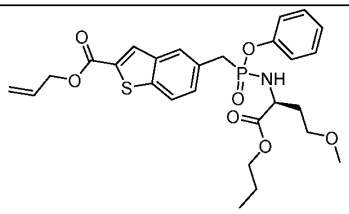
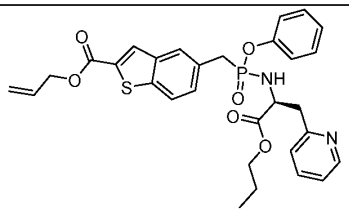
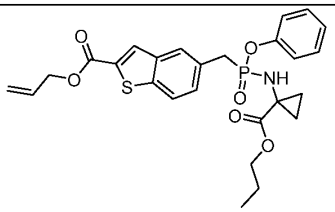
Name	Structure	LCMS	NMR
allyl 5-((((2-methyl-3-oxo-3-propoxypropyl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		516.4 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 - 8.02 (m, 1H), 7.88 - 7.80 (m, 2H), 7.50 - 7.43 (m, 1H), 7.33 - 7.27 (m, 2H), 7.19 - 7.10 (m, 3H), 6.11 - 5.99 (m, 1H), 5.49 - 5.41 (m, 1H), 5.36 - 5.30 (m, 1H), 4.89 - 4.83 (m, 2H), 4.03 - 3.85 (m, 2H), 3.47 - 3.36 (m, 2H), 3.14 - 2.95 (m, 3H), 2.43 - 2.31 (m, 1H), 1.64 - 1.51 (m, 2H), 1.01 (d, J = 7.3 Hz, 3H), 0.92 - 0.83 (m, 3H)
butyl (2S)-1-(((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-4,4-difluoropyrrolidine-2-carboxylate		578.4 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 - 8.02 (m, 1H), 8.00 - 7.89 (m, 1H), 7.88 - 7.80 (m, 1H), 7.63 - 7.50 (m, 1H), 7.37 - 7.10 (m, 5H), 6.14 - 5.98 (m, 1H), 5.49 - 5.42 (m, 1H), 5.39 - 5.28 (m, 1H), 4.89 - 4.83 (m, 2H), 4.73 - 4.67 (m, 0.4H), 4.30 - 4.23 (m,

			0.6H), 4.23 - 4.02 (m, 2H), 3.82 - 3.59 (m, 1H), 3.58 - 3.41 (m, 2H), 3.31 - 3.04 (m, 1H), 2.54 - 2.20 (m, 2H), 1.70 - 1.48 (m, 2H), 1.45 - 1.15 (m, 2H), 0.98 - 0.88 (m, 3H)
allyl 5-(((((S)-1-oxo-1-propoxybutan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		516.2 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 - 8.00 (m, 1H), 7.93 - 7.81 (m, 2H), 7.56 - 7.44 (m, 1H), 7.33 - 7.27 (m, 2H), 7.19 - 7.04 (m, 3H), 6.12 - 6.00 (m, 1H), 5.49 - 5.42 (m, 1H), 5.37 - 5.30 (m, 1H), 4.89 - 4.82 (m, 2H), 4.05 - 3.87 (m, 3H), 3.51 - 3.39 (m, 2H), 3.33 - 3.07 (m, 1H), 1.63 - 1.46 (m, 4H), 0.93 - 0.83 (m, 3H), 0.78 - 0.59 (m, 3H)
allyl 5-((((4-oxo-4-propoxybutan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		516.2 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 - 8.02 (m, 1H), 7.90 - 7.78 (m, 2H), 7.50 - 7.44 (m, 1H), 7.34 - 7.27 (m, 2H), 7.21 - 7.08 (m, 3H), 6.13 - 5.99 (m, 1H), 5.49 -5.41 (m, 1H), 5.36 - 5.30 (m, 1H), 4.89 (m, 2H) 4.03 - 3.86 (m, 2H), 3.80 - 3.64 (m, 1H), 3.48 - 3.36 (m, 2H), 3.33 - 3.12 (m, 1H), 2.34 - 2.14 (m, 2H), 1.67 - 1.50 (m, 2H), 1.10 - 0.97 (m, 3H), 0.95 - 0.85 (m, 3H)

butyl (((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-prolinate		542.3 $[M+H]^+$	
allyl 5-(((((S)-1-butoxy-1-oxopropan-2-yl)amino)(naphthalen-1-yloxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		566.1 $[M+H]^+$	
allyl 5-(((((S)-3-methyl-1-oxo-1-propoxybutan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate			^{1}H NMR (400 MHz, CDCl3) δ 8.05 (d, J = 6.0 Hz, 1H), 7.92 - 7.80 (m, 2H), 7.55 - 7.45 (m, 1H), 7.30 - 7.27 (m, 1H), 7.27 - 7.24 (m, 1H), 7.15 - 7.08 (m, 3H), 6.13 - 5.99 (m, 1H), 5.45 (td, J = 1.2, 17.2 Hz, 1H), 5.36 - 5.31 (m, 1H), 5.31 (s, 1H), 4.86 (d, J = 5.6 Hz, 2H), 4.03 - 3.90 (m, 1H), 3.86 - 3.75 (m, 1H), 3.50 - 3.39 (m, 2H), 3.21 - 3.03 (m, 1H), 1.94 - 1.83 (m, 1H), 1.59 - 1.50 (m, 2H), 0.91 - 0.86 (m, 3H), 0.85 - 0.78 (m, 3H), 0.67 (dd, J = 4.0, 6.8 Hz, 3H)
allyl 5-(((((S)-1-((R)-sec-butoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate			^{1}H NMR (400 MHz, CDCl3) δ 8.04 (d, J = 6.4 Hz, 1H), 7.90 - 7.79 (m, 2H), 7.48 (m, 1H), 7.30 - 7.27 (m, 1H), 7.25 (d, J = 2.0 Hz, 1H), 7.17 - 7.09 (m,

			3H), 6.09 - 5.99 (m, 1H), 5.47 - 5.40 (m, 1H), 5.33 - 5.29 (m, 1H), 4.85 (d, J = 5.6 Hz, 2H), 4.81 - 4.71 (m, 1H), 4.01 - 3.90 (m, 1H), 3.48 - 3.38 (m, 2H), 1.55 - 1.43 (m, 2H), 1.18 - 1.14 (m, 3H), 1.14 - 1.09 (m 3H), 0.83 (s, 3H)
allyl 5-(((((S)-1-oxo-1-propoxypropan-2-yl)amino)(2,2,2-trifluoroethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate			^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 - 8.01 (m, 1H), 7.86 - 7.79 (m, 2H), 7.47 - 7.37 (m, 1H), 6.12 - 5.98 (m, 1H), 5.45 (dd, J = 1.6, 17.2 Hz, 1H), 5.33 (dd, J = 1.2, 10.4 Hz, 1H), 4.86 (d, J = 5.6 Hz, 2H), 4.33 - 4.16 (m, 2H), 4.10 - 3.93 (m, 2H), 3.43 - 3.31 (m, 2H), 3.21 - 2.96 (m, 1H), 1.66 - 1.54 (m, 3H), 1.35 (d, J = 7.2 Hz, 2H), 1.26 (d, J = 7.2 Hz, 1H), 0.95 - 0.88 (m, 3H)
allyl 5-(((((S)-1-ethoxy-1-oxo-3-phenylpropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		564 $[M+H]^+$	
allyl 5-(((((S)-1-(benzyloxy)-4-methyl-1-oxopentan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		592 $[M+H]^+$	

allyl 5-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		550 $[M+H]^+$	
isopropyl (((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-prolinate		528 $[M+H]^+$	
allyl 5-(((((S)-2-oxoTHF-3-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		472.1 $[M+H]^+$	
allyl 5-(((((S)-1-(benzyloxy)-1-oxo-4-phenylbutan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		640 $[M+H]^+$	
allyl 5-(((((S)-1-ethoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		488 $[M+H]^+$	
allyl 5-(((((S)-3-methoxy-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		532 $[M+H]^+$	

allyl 5-(((((S)-4-methoxy-1-oxo-1-propoxybutan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		546 $[M+H]^+$	
allyl 5-(((((S)-1-oxo-1-propoxy-3-(pyridin-2-yl)propan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		579 $[M+H]^+$	
allyl 5-((phenoxy((1-(propoxycarbonyl)cyclopropyl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		514.1 $[M+H]^+$	

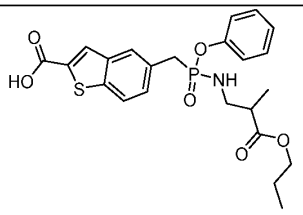
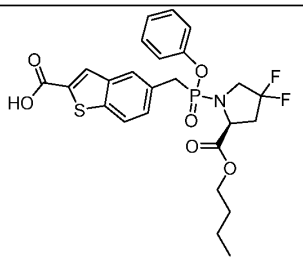
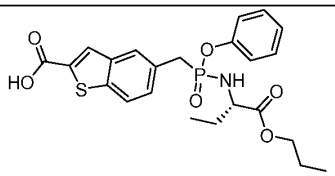
[00630] *Step 2: Preparation of 5-(((2,6-dimethylphenoxy)(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid*

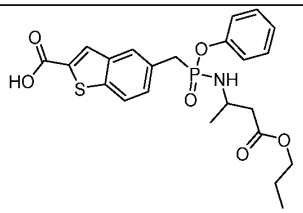
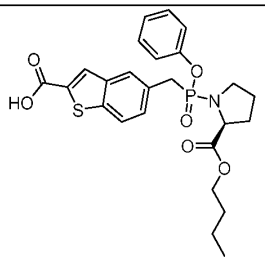
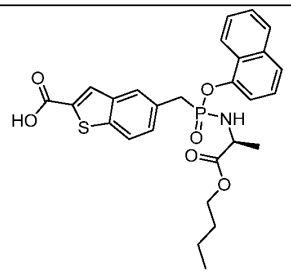
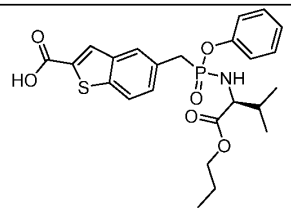
[00631] To a stirred solution of allyl 5-(((2,6-dimethylphenoxy)(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (50 mg, 94.4 µmol, 1 eq) in THF (4 mL) were added morpholine (40.6 µL, 472 µmol, 5 eq) and $Pd(PPh_3)_4$ (3.27 mg, 2.83 µmol, 0.03 eq) under nitrogen. The reaction mixture was stirred at room temperature 1 h. The solvent was removed under reduced pressure and the product was directly purified by reverse phase chromatography on a 100 g C_{18} cartridge eluting with a gradient of 5-80% acetonitrile in water (with 0.1% formic acid) to afford 5-(((2,6-dimethylphenoxy)(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (36.0 mg, 77.9%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 - 7.84 (m, 1H), 7.83 - 7.71 (m, 2H), 7.48 - 7.36 (m, 1H), 7.08 - 6.93 (m, 3H), 4.17 - 3.98 (m, 3H), 3.59 - 3.42 (m, 2H), 2.37 (s, 3H), 2.30 (s, 3H), 1.65 - 1.57 (m, 2H), 1.27 - 1.22 (m, 3H), 1.15 - 1.11 (m, 1H), 0.94 - 0.88 (m, 3H).

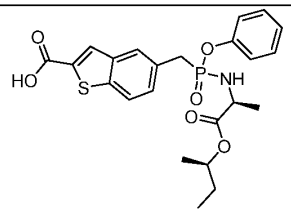
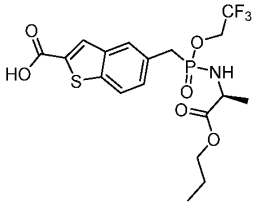
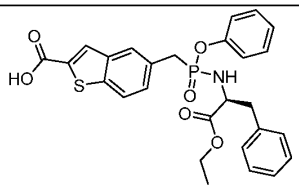
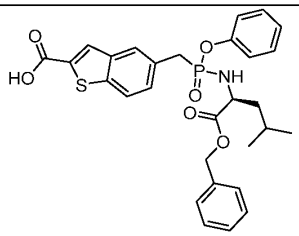
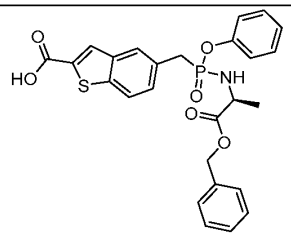
[00632] The following intermediates in **Table 59** were prepared using the method described above in step 2 for the preparation of 5-(((2,6-dimethylphenoxy)(((S)-1-oxo-1-

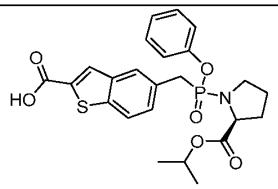
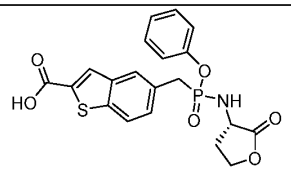
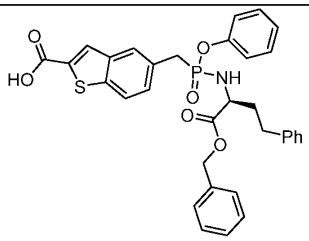
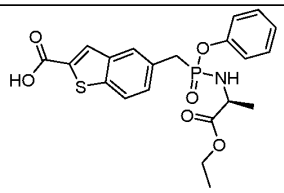
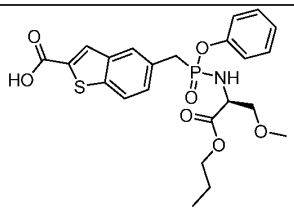
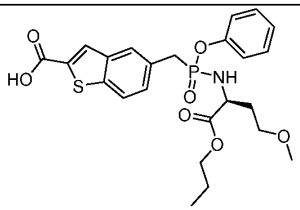
propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid and utilizing the appropriate starting materials and modifications.

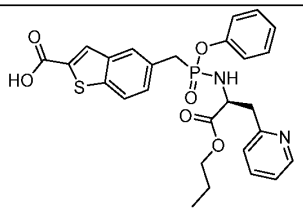
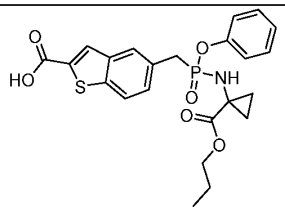
Table 59

Name	Structure	LCMS	NMR
5-((((2-methyl-3-oxo-3-propoxypropyl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		476.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.39 (br. s., 1H), 8.10 - 8.05 (m, 1H), 8.01 - 7.88 (m, 2H), 7.51 - 7.44 (m, 1H), 7.39 - 7.28 (m, 2H), 7.22 - 7.05 (m, 3H), 5.22 - 5.10 (m, 1H), 3.96 - 3.82 (m, 2H), 3.47 - 3.36 (m, 2H), 3.10 - 2.94 (m, 1H), 2.86 - 2.70 (m, 1H), 2.36 - 2.22 (m, 1H), 1.56 - 1.45 (m, 2H), 0.90 (dd, J = 10.3, 7.1 Hz, 3H), 0.86 - 0.78 (m, 3H)
5-((((S)-2-(butoxycarbonyl)-4,4-difluoropyrrolidin-1-yl)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		538.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.49 (br. s., 1H), 8.14 - 8.06 (m, 1H), 8.04 - 7.91 (m, 2H), 7.55 - 7.47 (m, 1H), 7.40 - 7.28 (m, 2H), 7.25 - 7.06 (m, 3H), 4.67 - 4.56 (m, 0.4H), 4.35 - 4.28 (m, 0.6H), 4.08 - 3.69 (m, 3H), 3.68 - 3.42 (m, 3H), 2.73 - 2.30 (m, 2H), 1.55 - 1.37 (m, 2H), 1.35 - 1.18 (m, 2H), 0.91 - 0.77 (m, 3H)
5-(((((S)-1-oxo-1-propoxybutan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		476.2 $[M+H]^+$	^{1}H NMR (400 MHz, CD_3OD) δ 8.01 (s, 1H), 7.97 - 7.83 (m, 2H), 7.54 - 7.47 (m, 1H), 7.36 - 7.25 (m, 2H), 7.21 - 7.11 (m, 3H),

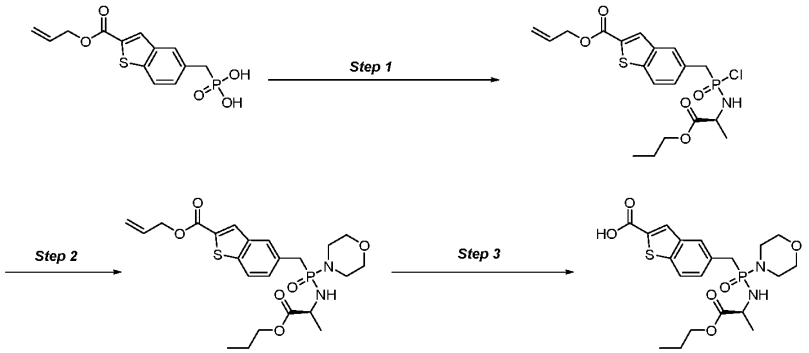
			3.95 - 3.65 (m, 3H), 3.61 - 3.43 (m, 2H), 1.59 - 1.40 (m, 4H), 0.86 (q, *J* = 7.6 Hz, 3H), 0.73 - 0.63 (m, 3H)
5-((((4-oxo-4-propoxybutan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		476.2 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.47 (br. s., 1H), 8.08 (s, 1H), 8.02 - 7.89 (m, 2H), 7.53 - 7.45 (m, 1H), 7.39 - 7.27 (m, 2H), 7.17 - 7.09 (m, 3H), 5.22 - 5.04 (m, 1H), 3.92 - 3.80 (m, 2H), 3.61 - 3.45 (m, 1H), 3.45 - 3.25 (m, 3H), 2.30 - 2.13 (m, 2H), 1.55 - 1.44 (m, 2H), 0.93 - 0.86 (m, 3H), 0.85 - 0.79 (m, 3H)
5-((((S)-2-(butoxycarbonyl)pyrrolidin-1-yl)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		502.1 $[M+H]^+$	
5-(((((S)-1-butoxy-1-oxopropan-2-yl)amino)(naphthalen-1-yloxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		526.1 $[M+H]^+$	
5-(((((S)-3-methyl-1-oxo-1-propoxybutan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		490.3 $[M+H]^+$	

5-(((((S)-1-((R)-sec-butoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		476.8 $[M+H]^+$	
5-(((((S)-1-oxo-1-propoxypropan-2-yl)amino)(2,2,2-trifluoroethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid			^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.81 - 7.75 (m, 2H), 7.32 (dd, J = 2.0, 8.4 Hz, 1H), 4.50 - 4.29 (m, 2H), 4.18 - 3.98 (m, 2H), 3.87 - 3.62 (m, 1H), 3.46 - 3.32 (m, 2H), 1.72 - 1.64 (m, 2H), 1.42 (dd, J = 7.2, 17.2 Hz, 3H), 0.96 (q, J = 7.2 Hz, 3H)
5-(((((S)-1-ethoxy-1-oxo-3-phenylpropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		524 $[M+H]^+$	
5-(((((S)-1-(benzyloxy)-4-methyl-1-oxopentan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		552 $[M+H]^+$	
5-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		510 $[M+H]^+$	

5-((((S)-2-(isopropoxycarbonyl)pyrrolidin-1-yl)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		488 $[M+H]^+$	
5-(((((S)-2-oxoTHF-3-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		432 $[M+H]^+$	
5-(((((S)-1-(benzyloxy)-1-oxo-4-phenylbutan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		600 $[M+H]^+$	
5-(((((S)-1-ethoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		448 $[M+H]^+$	
5-(((((S)-3-methoxy-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		492 $[M+H]^+$	
5-(((((S)-4-methoxy-1-oxo-1-propoxybutan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		546 $[M+H]^+$	

5-(((((S)-1-oxo-1-propoxy-3-(pyridin-2-yl)propan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		539 $[M+H]^+$	
5-((phenoxy((1-(propoxycarbonyl)cyclopropyl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		474.0 $[M+H]^+$	

Synthesis of 5-((morpholino(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid



[00633] *STEP 1: Synthesis of allyl 5-((chloro(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00634] Oxalyl chloride (10 mL) was added dropwise to the solution of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (1 g, 3.20 mmol, 1.0 eq.) in dry DCM (20 mL) and DMF (1 drop) at 20 °C. The reaction mixture was stirred at 25 °C for an additional 1 hr. The reaction was monitored by pipetting out a small amount of crude sample and quenching it with MeOH to ensure bis-Cl phosphoryl chloride had been formed completely (bis-methoxy phosphonate was observed by LCMS). After completion, the excess oxalyl chloride and solvent were removed under reduced pressure to afford allyl 5-((dichlorophosphoryl)methyl)benzo[*b*]thiophene-2-carboxylate (960 mg, 2.74 mmol, 86%). allyl 5-((dichlorophosphoryl)methyl)benzo[*b*]thiophene-2-carboxylate (100 mg, 251 µmol, 1.0 eq.) was re-dissolved in anhydrous DCM (2 mL), then added to a mixture of propyl *L*-

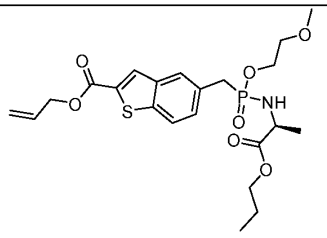
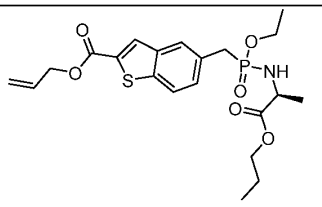
alaninate (36 mg, 276 µmol, 1.1 eq.) and triethylamine (101 mg, 1.00 mmol, 4.0 eq.) in anhydrous DCM (2 mL) at 0 °C. The reaction was allowed to warm to 25 °C, and stirred for an additional 15 min. The reaction progress was monitored by LCMS, and after completion, the reaction mixture was used in next step directly without further purification.

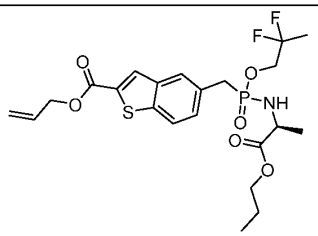
[00635] *STEP 2: Synthesis of allyl 5-((morpholino(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00636] allyl 5-((chloro(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (200 mg, 450 µmol, 1.0 eq.) as a solution in DCM (5 mL) was added to a solution of morpholine (196 mg, 2.25 mmol, 5 eq.) and TEA (273 mg, 2.7 mmol, 6 eq.) in DCM (1 mL). The mixture was stirred at 25 °C for 15 min, at which time LCMS showed formation of product. The mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give allyl 5-((morpholino(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (82 mg, 0.17 mmol, 38%) as a white solid. LCMS (ESI): *m/z* = 495 $[M+H]^+$.

[00637] The following intermediates in **Table 60** were prepared using the method described above in step 2 for the preparation of allyl 5-((morpholino(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate and utilizing the appropriate starting materials and modifications.

Table 60

Name	Structure	LCMS
allyl 5-(((2-methoxyethoxy)(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		484 $[M+H]^+$
allyl 5-((ethoxy(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		438 $[M+H]^+$

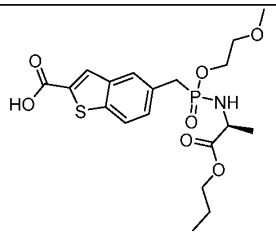
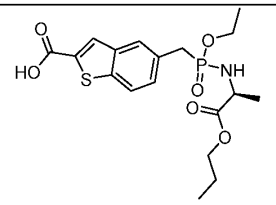
allyl 5-(((2,2-difluoropropoxy)(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		490 $[M+H]^+$

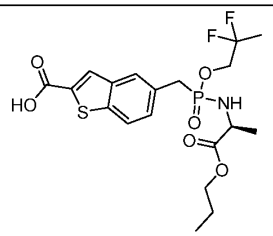
[00638] *STEP 3: Synthesis of 5-((morpholino(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid*

[00639] To a solution of allyl 5-((morpholino(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (82 mg, 0.17 mmol, 1.0 eq) in DCM (3 mL) were added $Pd(PPh_3)_4$ (20 mg, 17 μmol, 0.1 eq.) and pyrrolidine (12 mg, 0.17 mmol, 1.0 eq.). The mixture was purged and degassed with N_2 (three times), then stirred at 25 °C for 0.5 h. After completion, the mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give 5-((morpholino(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (50 mg, 0.11 mmol, 65%) as a white solid. LCMS (ESI): *m/z* = 455 $[M+H]^+$.

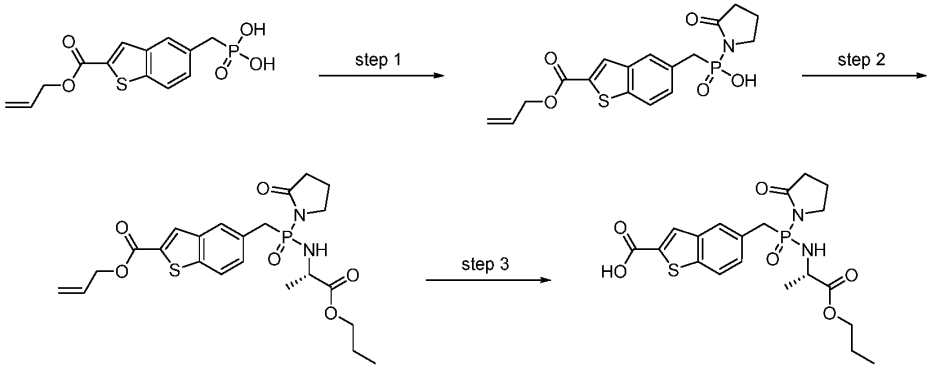
[00640] The following intermediates in **Table 61** were prepared using the method described above in step 3 for the preparation of 5-((morpholino(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid and utilizing the appropriate starting materials and modifications.

Table 61

Name	Structure	LCMS
5-(((2-methoxyethoxy)(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		444 $[M+H]^+$
5-((ethoxy(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		414 $[M+H]^+$

5-(((2,2-difluoropropoxy)(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		450 $[M+H]^+$

Synthesis of 5-(((((S)-4-methoxy-1-oxo-1-propoxybutan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid



[00641] *Step 1: Preparation of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)(2-oxopyrrolidin-1-yl)phosphinic acid*

[00642] Oxalyl chloride (10 mL) was added dropwise to the solution of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (300 mg, 960 µmol, 1 eq.) in dry DCM (20 mL) and DMF (0.1 mL) at 0 °C. The reaction mixture was stirred at 40 °C for an additional 1 hr. The reaction was monitored by pipetting out a small amount of crude sample and quenching it with MeOH to ensure bis-Cl phosphoryl chloride had been formed completely (bis-methoxy phosphonate was observed by LCMS). After completion, the excess oxalyl chloride and solvent were removed under reduced pressure to afford allyl 5-((dichlorophosphoryl)methyl)benzo[b]thiophene-2-carboxylate (300 mg). The residue (300 mg, 859 µmol, 1 eq.) was re-dissolved in anhydrous DCM (5 mL), then added to a mixture of pyrrolidin-2-one (218 mg, 2.57 mmol, 3 eq.) and TEA (259 mg, 2.57 mmol, 3 eq.) in anhydrous DCM (10 mL) at 0 °C. The reaction was allowed to warm to 25 °C and stirred for an additional 2 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give ((2-

((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)(2-oxopyrrolidin-1-yl)phosphinic acid (100 mg, 263 µmol, 31%) as a colorless oil. LCMS (ESI): *m/z* = 380 $[M+H]^+$.

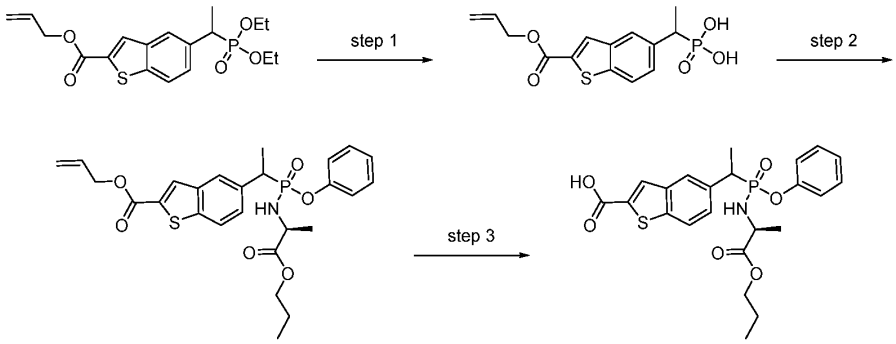
[00643] *Step 2: Preparation of allyl 5-(((((S)-1-oxo-1-propoxypropan-2-yl)amino)(2-oxopyrrolidin-1-yl)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00644] Oxalyl chloride (201 mg, 1.59 mmol, 5 eq.) was added dropwise to the solution of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)(2-oxopyrrolidin-1-yl)phosphinic acid (100 mg, 320 µmol, 1 eq.) in dry DCM (5 mL) and DMF (0.1 mL) at 0 °C. The reaction mixture was stirred at 40 °C for an additional 1 hr. The reaction was monitored by pipetting out a small amount of crude sample and quenching it with MeOH to ensure mono-Cl phosphoryl chloride had been formed completely (mono-methoxy phosphonate was observed by LCMS). After completion, the excess oxalyl chloride and solvent were removed under reduced pressure to afford allyl 5-((chloro(2-oxopyrrolidin-1-yl)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (100 mg). The residue (100 mg, 251 µmol, 1 eq.) was re-dissolved in anhydrous DCM (10 mL), then added to a mixture of propyl L-alaninate (65.8 mg, 502 µmol, 2 eq.) and TEA (101 mg, 1.00 mmol, 4 eq.) in anhydrous DCM (10 mL) at 0 °C. The reaction was allowed to warm to 25 °C and stirred for an additional 2 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give allyl 5-(((((S)-1-oxo-1-propoxypropan-2-yl)amino)(2-oxopyrrolidin-1-yl)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (23.0 mg, 46.6 µmol, 19%) as a colorless oil. LCMS (ESI): *m/z* = 493 $[M+H]^+$.

[00645] *Step 3: Preparation of 5-(((((S)-1-oxo-1-propoxypropan-2-yl)amino)(2-oxopyrrolidin-1-yl)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid*

[00646] To a solution of allyl 5-(((((S)-1-oxo-1-propoxypropan-2-yl)amino)(2-oxopyrrolidin-1-yl)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (22 mg, 44.6 µmol, 1 eq) in DCM (2 mL) were added $Pd(PPh_3)_4$ (5 mg, 4.46 µmol, 0.1 eq.) and pyrrolidine (3 mg, 44.6 µmol, 1.0 eq.). The mixture was purged and degassed with N_2 (three times), then stirred at 25 °C for 0.5 h. After completion, the mixture was quenched with HCl aqueous solution (1 N) and extracted with DCM (10 mL x 3). The organic layers were combined and washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give 5-(((((S)-4-methoxy-1-oxo-1-propoxybutan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (13.0 mg, 28.7 µmol, 65%) as a colorless oil. LCMS (ESI): *m/z* = 453 $[M+H]^+$.

Synthesis of 5-(1-((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)ethyl)benzo[b]thiophene-2-carboxylic acid



[00647] *Step 1: Preparation of allyl 5-(1-(diethoxyphosphoryl)ethyl)benzo[b]thiophene-2-carboxylate*

[00648] To a solution of (1-(2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)ethyl)phosphonic acid (400 mg, 1.05 mmol, 1.0 eq.) in DCM (10 mL) were added TMSBr (1.6 g, 10.5 mmol, 10.0 eq.). The mixture was stirred at room temperature for 16 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford allyl 5-(1-(diethoxyphosphoryl)ethyl)benzo[b]thiophene-2-carboxylate (310 mg, 0.95 mmol, 90%) as a colorless oil. LCMS (ESI): *m/z* = 327 $[M+H]^+$.

[00649] *Step 2: Preparation of allyl 5-(1-((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)ethyl)benzo[b]thiophene-2-carboxylate*

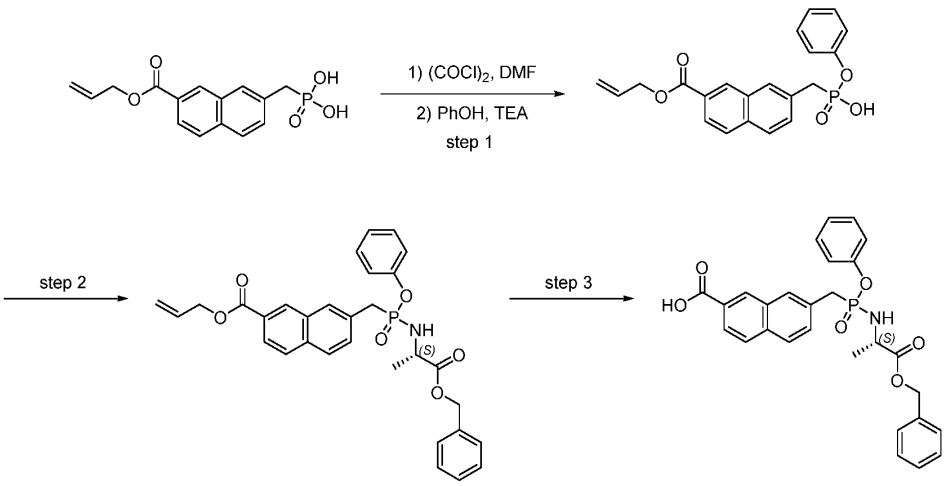
[00650] Oxalyl chloride (599 mg, 4.75 mmol, 5 eq.) was added dropwise to the solution of allyl 5-(1-(diethoxyphosphoryl)ethyl)benzo[b]thiophene-2-carboxylate (310 mg, 0.95 mmol, 1 eq.) in dry DCM (20 mL) and DMF (0.1 mL) at 25 °C. The reaction mixture was stirred at 40 °C for an additional 1 hr. The reaction was monitored by pipetting out a small amount of crude sample and quenching it with MeOH to ensure bis-Cl phosphoryl chloride had been formed completely (bis-methoxy phosphonate was observed by LCMS). After completion, the excess oxalyl chloride and solvent were removed under reduced pressure. The residue was re-dissolved in anhydrous DCM (20 mL), then added to a mixture of phenol (89 mg, 0.95 mmol, 1.0 eq.) and TEA (960 mg, 9.5 mmol, 10 eq.) in anhydrous DCM (20 mL) at -20 °C. The reaction was stirred at -20 °C for an additional 1 hr. Then, propyl L-alaninate (249 mg, 1.90 mmol, 2.0 eq.) was added into the above mixture at 0 °C. The reaction was stirred at 25 °C for an additional 1 hr. After completion, the reaction was poured into ice-water (10 mL)

and extracted with DCM (10 mL x 2). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to afford allyl 5-(1-((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)ethyl)benzo[b]thiophene-2-carboxylate (110 mg, 0.21 mmol, 22%) as a brown solid. LCMS (ESI): *m/z* = 516 $[M+H]^+$.

[00651] *Step 3: Preparation of 5-(1-((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)ethyl)benzo[b]thiophene-2-carboxylic acid*

[00652] To a solution of allyl 5-(1-((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)ethyl)benzo[b]thiophene-2-carboxylate (110 mg, 0.21 mmol, 1.0 eq) in DCM (10 mL) were added $Pd(PPh_3)_4$ (24 mg, 0.02 mmol, 0.1 eq.) and pyrrolidine (15 mg, 0.21 mmol, 1.0 eq.). The mixture was purged and degassed with N_2 (three times), then stirred at 25 °C for 0.5 h. After completion, the mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give 5-(1-((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)ethyl)benzo[b]thiophene-2-carboxylic acid (68 mg, 0.13 mmol, 62%) as a yellow solid. LCMS (ESI): *m/z* = 516 $[M+H]^+$.

Synthesis of 7-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoic acid



[00653] *Step 1: Preparation of allyl 7-((hydroxy(phenoxy)phosphoryl)methyl)-2-naphthoate*

[00654] Oxalyl chloride (208 mg, 1.65 mmol, 5 eq.) was added dropwise to the solution of ((7-((allyloxy)carbonyl)naphthalen-2-yl)methyl)phosphonic acid (100 mg, 0.33 mmol, 1 eq.)

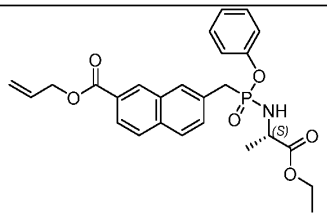
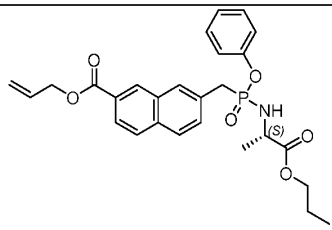
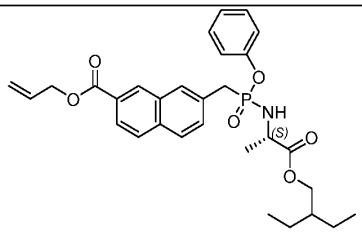
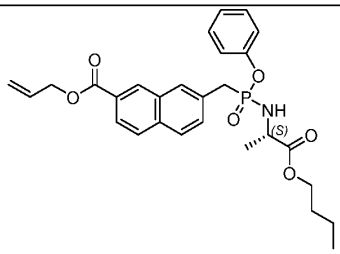
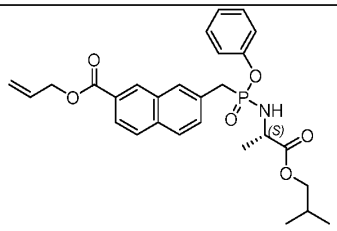
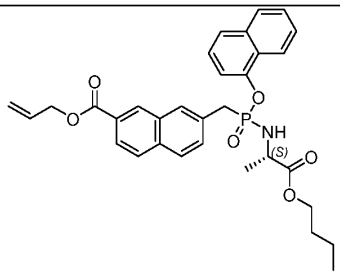
in dry DCM (20 mL) and DMF (0.1 mL) at 25 °C. The reaction mixture was stirred at 40 °C for an additional 1 hr. The reaction was monitored by pipetting out a small amount of crude sample and quenching it with MeOH to ensure bis-Cl phosphoryl chloride had been formed completely (bis-methoxy phosphonate was observed by LCMS). After completion, the excess oxalyl chloride and solvent were removed under reduced pressure. The residue was re-dissolved in anhydrous DCM (20 mL), then added to a mixture of phenol (31 mg, 0.33 mmol, 1.0 eq.) and TEA (333 mg, 3.3 mmol, 10 eq.) in anhydrous DCM (20 mL) at -20 °C. The reaction was stirred at 25 °C for an additional 1 hr. After completion, the reaction was poured into ice-water (50 mL) and extracted with DCM (50 mL x 2). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to afford allyl 7-((hydroxy(phenoxy)phosphoryl)methyl)-2-naphthoate (100 mg, 0.26 mmol, 79%) as a yellow oil. LCMS (ESI): *m/z* = 383 $[M+H]^+$.

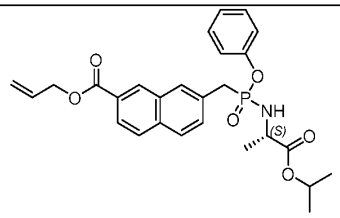
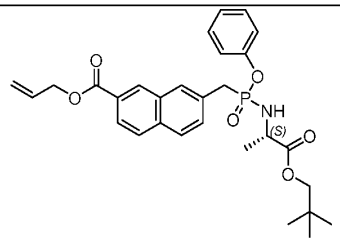
[00655] *Step 2: Preparation of allyl 7-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoate*

[00656] Oxalyl chloride (330 mg, 2.62 mmol, 5 eq.) was added dropwise to the solution of allyl 7-((hydroxy(phenoxy)phosphoryl)methyl)-2-naphthoate (200 mg, 0.52 mmol, 1 eq.) in dry DCM (10 mL) and DMF (0.1 mL) at 25 °C. The reaction mixture was stirred at 40 °C for an additional 1 hr. After completion, the excess oxalyl chloride and solvent were removed under reduced pressure. The residue was re-dissolved in anhydrous DCM (10 mL), then added to a mixture of benzyl L-alaninate (186 mg, 1.04 mmol, 2.0 eq.) and triethylamine (525 mg, 5.2 mmol, 10 eq.) in anhydrous DCM (20 mL) at 0 °C. The reaction was stirred at 25 °C for an additional 1 hr. After completion, the reaction was poured into ice-water (10 mL) and extracted with DCM (10 mL x 2). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to afford allyl 7-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoate (50 mg, 92 μmol,18%) as a brown solid. LCMS (ESI): *m/z* = 544 $[M+H]^+$.

[00657] The following intermediates in **Table 62** were prepared using the method described above in step 2 for the preparation of allyl 7-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoate and utilizing the appropriate starting materials and modifications.

Table 62

Name	Structure	LCMS
allyl 7-(((((S)-1-ethoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoate		482 $[M+H]^+$
allyl 7-(((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoate		496 $[M+H]^+$
allyl 7-(((((S)-1-(2-ethylbutoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoate		538.3 $[M+H]^+$
allyl 7-(((((S)-1-butoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoate		510 $[M+H]^+$
allyl 7-(((((S)-1-isobutoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoate		510.1 $[M+H]^+$
allyl 7-(((((S)-1-butoxy-1-oxopropan-2-yl)amino)(naphthalen-1-yloxy)phosphoryl)methyl)-2-naphthoate		560 $[M+H]^+$

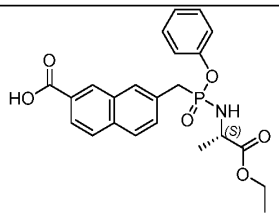
allyl 7-(((((S)-1-isopropoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoate		496 $[M+H]^+$
allyl 7-(((((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoate		524.0 $[M+H]^+$

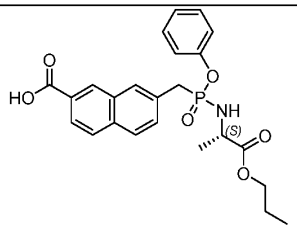
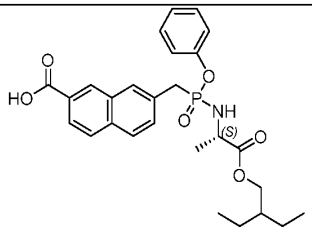
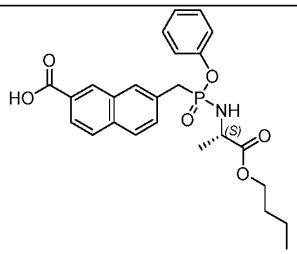
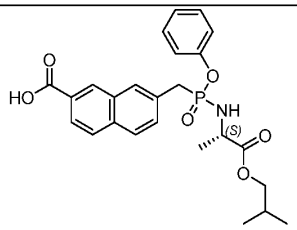
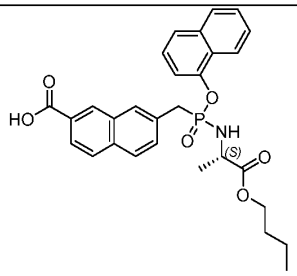
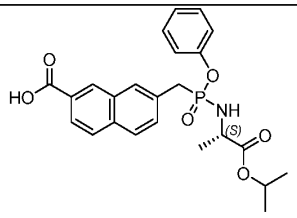
[00658] *Step 3: Preparation of 7-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoic acid*

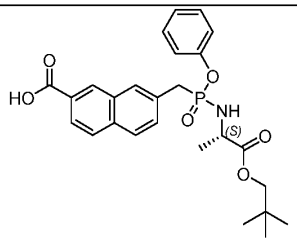
[00659] To a solution of allyl 7-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoate (50 mg, 92 µmol, 1.0 eq) in DCM (10 mL) were added $Pd(PPh_3)_4$ (11 mg, 9.2 µmol, 0.1 eq.) and pyrrolidine (7 mg, 92 µmol, 1.0 eq.). The mixture was purged and degassed with N_2 (three times), then stirred at 25 °C for 0.5 h. After completion, the mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give 7-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoic acid (40 mg, 80 µmol, 87%) as a yellow solid. LCMS (ESI): *m/z* = 504 $[M+H]^+$.

[00660] The following intermediates in **Table 63** were prepared using the method described above in step 3 for the preparation of allyl 7-(((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoate and utilizing the appropriate starting materials and modifications.

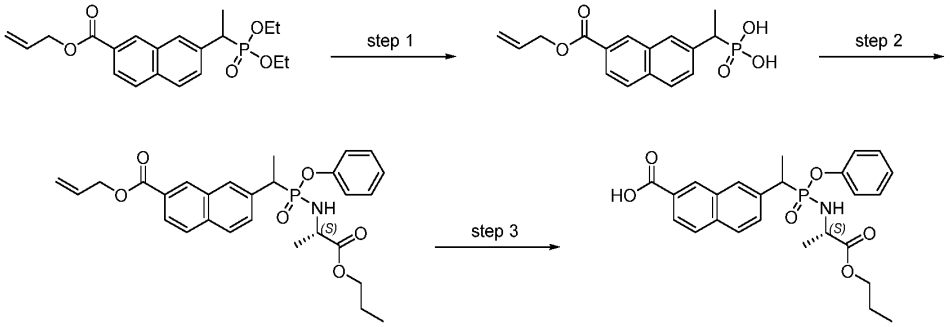
Table 63

Name	Structure	LCMS
7-(((((S)-1-ethoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoic acid		442 $[M+H]^+$

7-(((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoic acid		456 $[M+H]^+$
7-(((((S)-1-(2-ethylbutoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoic acid		498.2 $[M+H]^+$
7-(((((S)-1-butoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoic acid		470 $[M+H]^+$
7-(((((S)-1-isobutoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoic acid		470.1 $[M+H]^+$
7-(((((S)-1-butoxy-1-oxopropan-2-yl)amino)(naphthalen-1-yloxy)phosphoryl)methyl)-2-naphthoic acid		520 $[M+H]^+$
7-(((((S)-1-isopropoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoic acid		456 $[M+H]^+$

7-(((((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoic acid		484.2 $[M+H]^+$

Synthesis of 7-(1-((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)ethyl)-2-naphthoic acid



[00661] *Step 1: Preparation of (1-(7-((allyloxy)carbonyl)naphthalen-2-yl)ethyl)phosphonic acid*

[00662] To a solution allyl 7-(1-(diethoxyphosphoryl)ethyl)-2-naphthoate (600 mg, 1.60 mmol, 1 eq.) in DCM (5 mL) was added TMSBr (2.5 g, 16.0 mmol, 10 eq.). The mixture was stirred at room temperature for 2 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford (1-(7-((allyloxy)carbonyl)naphthalen-2-yl)ethyl)phosphonic acid (400 mg, 1.25 mmol, 78%) as a white solid. LCMS (ESI): *m/z* = 321 $[M+H]^+$.

[00663] *Step 2: Preparation of allyl 7-(1-((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)ethyl)-2-naphthoate*

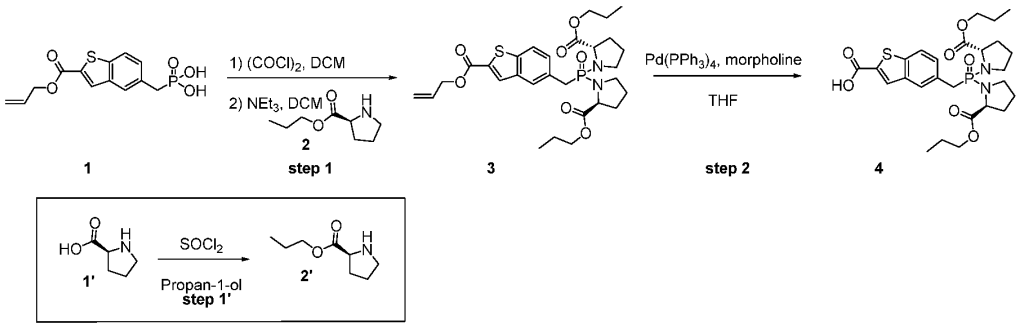
[00664] Oxalyl chloride (616 mg, 4.89 mmol, 3 eq.) was added dropwise to the solution of a (1-(7-((allyloxy)carbonyl)naphthalen-2-yl)ethyl)phosphonic acid (520 mg, 1.63 mmol, 1 eq.) in dry DCM (5 mL) and DMF (0.1 mL) at 0 °C. The reaction mixture was stirred at 40 °C for an additional 1 hr. The reaction was monitored by pipetting out a small amount of crude sample and quenching it with MeOH to ensure bis-Cl phosphoryl chloride had been formed completely (bis-methoxy phosphonate was observed by LCMS). After completion, the excess oxalyl chloride and solvent were removed under reduced pressure. The residue

was re-dissolved in anhydrous DCM (10 mL), then added to a mixture of phenol (460 mg, 4.89 mmol, 3 eq.) and TEA (1.4 g, 13.0 mmol, 8 eq.) in anhydrous DCM (10 mL) at 0 °C. The reaction was allowed to warm to 25 °C and stirred for an additional 2 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give allyl 7-(1-((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)ethyl)-2-naphthoate (120 mg, 0.24 mmol, 15%) as a colorless oil. LCMS (ESI): *m/z* = 510 $[M+H]^+$.

[00665] *Step 3: Preparation of 7-(1-((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)ethyl)-2-naphthoic acid*

[00666] To a solution of allyl 7-(1-((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)ethyl)-2-naphthoate (120 mg, 0.24 mmol, 1.0 eq) in DCM (1 mL) were added $Pd(PPh_3)_4$ (28 mg, 24 μmol, 0.1 eq.) and pyrrolidine (17 mg, 0.24 mmol, 1.0 eq.). The mixture was purged and degassed with N_2 (three times), then stirred at 25 °C for 0.5 h. After completion, the mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give 7-(1-((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)ethyl)-2-naphthoic acid (82 mg, 0.17 mmol, 71%) as a white solid. LCMS (ESI): *m/z* = 470 $[M+H]^+$.

Synthesis of 5-((bis((S)-2-(propoxycarbonyl)pyrrolidin-1-yl)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid



[00667] *STEP 1: Preparation of propyl L-prolinate*

[00668] To a solution of (2*S*)-pyrrolidine-2-carboxylic acid (2.00 g, 17.3 mmol, 1 eq) in propan-1-ol (13.0 mL, 266 mmol) at -78 °C was added dropwise thionyl chloride (3.76 mL, 51.9 mmol, 3 eq). The mixture was allowed to warm to room temperature and then heated at 80 °C overnight. The reaction mixture was concentrated under reduced pressure and the crude

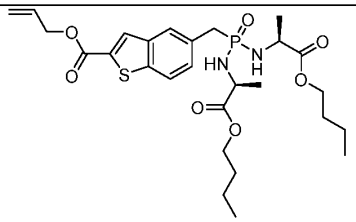
propyl L-prolinate (2.62 g, 16.6 mmol, 96.6%) was isolated as an orange sticky oil that was used directly in the next step. LCMS (ESI): m/z = 158.1 $[M+H]^+$.

[00669] *STEP 2: Preparation of dipropyl (((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)(S)-di-L-prolinate*

[00670] To a solution of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (300 mg, 0.9606 mmol, 1 eq) in DCM (10 mL) at 0 °C were added 2 drops of DMF (cat) and oxalyl chloride (246 µL, 2.88 mmol, 3 eq). The solution was stirred at 0 °C and was allowed to warm slowly to room temperature overnight. The reaction was concentrated under reduced pressure and then dried under high vacuum during 30 min. The crude residue was diluted in DCM (10 mL, dried with Na_2SO_4) and cooled down to 0 °C. A solution of propyl L-prolinate (603 mg, 3.84 mmol, 4 eq) and triethylamine (668 µL, 4.80 mmol, 5 eq) in DCM (3 mL, dried with Na_2SO_4) was added and the mixture was stirred at room temperature for 3 d. The reaction was concentrated under reduced pressure and the crude residue was purified by reverse phase chromatography on a 150 g C_{18} cartridge eluting with 5-100% MeCN in water (with 0.1% formic acid) to give propyl dipropyl (((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)(S)-di-L-prolinate (274 mg, 48.3%) as an orange oil. LCMS (ESI): m/z = 591.2 $[M+H]^+$.

[00671] The following intermediates in **Table 64** were prepared using the method described above in step 2 for the preparation of dipropyl (((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)(S)-di-L-prolinate and utilizing the appropriate starting materials and modifications.

Table 64

Name	Structure	LCMS
dibutyl 2,2'-((((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(azanediyl))(2S,2'S)-dipropionate		567 $[M+H]^+$

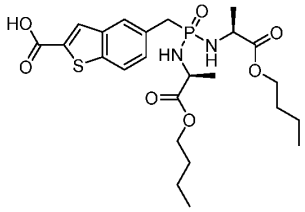
[00672] *STEP 3: Preparation of 5-((bis((S)-2-(propoxycarbonyl)pyrrolidin-1-yl)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid*

[00673] To a solution of propyl dipropyl (((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)(S)-di-L-prolinate (274 mg, 0.4638 mmol, 1 eq) in THF (30 mL) were added morpholine (199 µL, 2.31 mmol, 5 eq) and $Pd(PPh_3)_4$ (53.5 mg, 0.04638 mmol, 0.10

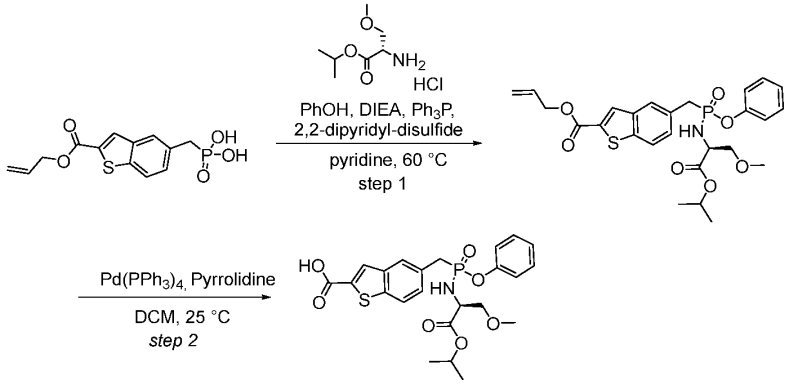
eq). The reaction mixture was stirred at room temperature for 2 h and THF was removed under reduced pressure. The crude residue was purified by reverse phase chromatography on a 100 g C_{18} cartridge eluting with 5-100% MeCN in water (with 0.1% formic acid) to give 5-((bis((S)-2-(propoxycarbonyl)pyrrolidin-1-yl)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (203 mg, 79.6%) as a white solid. LCMS (ESI): m/z = 551.2 $[M+H]^+$.

[00674] The following intermediates in **Table 65** were prepared using the method described above in step 2 for the preparation of 5-((bis((S)-2-(propoxycarbonyl)pyrrolidin-1-yl)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid and utilizing the appropriate starting materials and modifications.

Table 65

Name	Structure	LCMS
5-((bis(((S)-1-butoxy-1-oxopropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		527 $[M+H]^+$

Synthesis of 5-(((((S)-1-isopropoxy-3-methoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid:



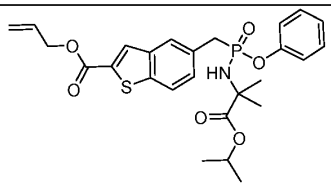
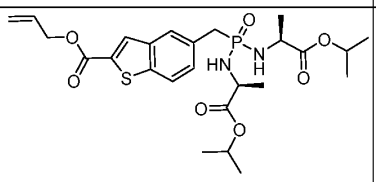
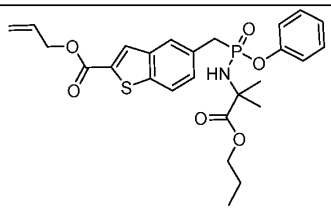
[00675] *Step 1: Preparation of allyl 5-(((((S)-1-isopropoxy-3-methoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00676] To a solution of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (49.3 mg, 158 µmol, 1 eq.), propan-2-yl (2S)-2-amino3-methoxypropanoate hydrochloride (31.2 mg, 158 µmol, 1 eq.) and phenol (19.3 mg, 206

μmol, 1.3 eq.) in pyridine (3 mL) were added N,N-diisopropylethylamine (162 mg, 1.26 mmol, 8 eq.), 2,2-dipyridyl-disulfide (140 mg, 635 μmol, 4 eq.) and triphenylphosphine (166 mg, 635 μmol, 4 eq.) at 25 °C. The mixture was heated to 60 °C and stirred at 60 °C for 48 h under N_2 atmosphere. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to afford allyl 5-(((((S)-1-isopropoxy-3-methoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (35.0 mg, 65.8 μmol, 42%) as a yellow solid. LCMS (ESI): *m/z* = 532 $[M+H]^+$.

[00677] The following intermediates in **Table 66** were prepared using the method described above in step 1 for the preparation of allyl 5-(((((S)-1-isopropoxy-3-methoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate and utilizing the appropriate starting materials and modifications.

Table 66

Name	Structure	LCMS
allyl 5-((((1-isopropoxy-2-methyl-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		516.2 $[M+H]^+$
diisopropyl 2,2'-((((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(azanediyl))(2S,2'S)-dipropionate		539 $[M+H]^+$
allyl 5-((((2-methyl-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		516.1 $[M+H]^+$

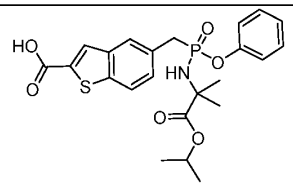
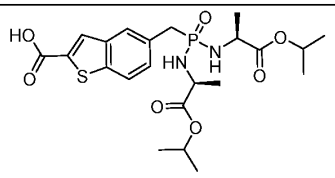
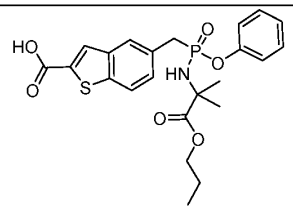
[00678] *Step 2: Preparation of 5-(((((S)-1-isopropoxy-3-methoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid*

[00679] To a solution of allyl 5-(((((S)-1-isopropoxy-3-methoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (**2**, 150 mg, 282 μmol, 1 eq) in DCM (5 mL) were added $Pd(PPh_3)_4$ (65.1 mg, 56.4 μmol, 0.2 eq.) and

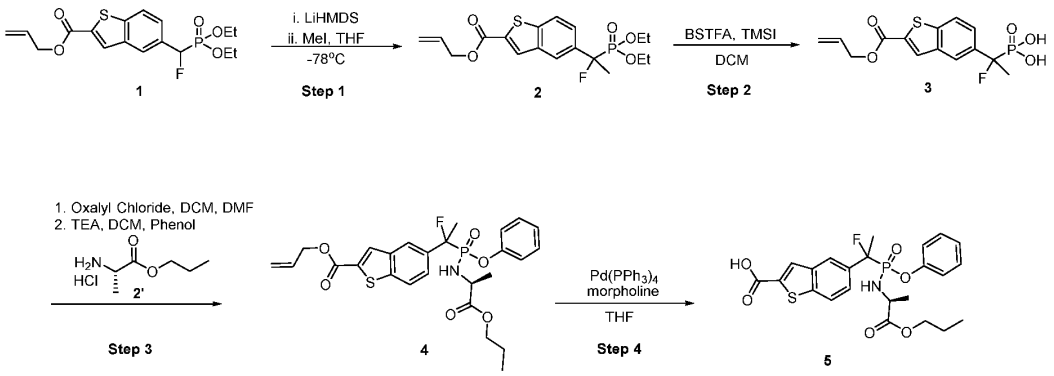
pyrrolidine (20.0 mg, 282 μmol, 1.0 eq.). The mixture was purged and degassed with N_2 (three times), then stirred at 25 °C for 1 hr. After completion, the mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give 5-(((((S)-1-isopropoxy-3-methoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (120 mg, 244 μmol, 87%) as a yellow solid. LCMS (ESI): m/z = 492.1 $[M+H]^+$.

[00680] The following intermediates in **Table 67** were prepared using the method described above in step 2 for the preparation of 5-(((((S)-1-isopropoxy-3-methoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid and utilizing the appropriate starting materials and modifications.

Table 67

Name	Structure	LCMS
5-((((1-isopropoxy-2-methyl-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		476.5 $[M+H]^+$
5-((bis(((S)-1-isopropoxy-1-oxopropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		499 $[M+H]^+$
5-((((2-methyl-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		476.2 $[M+H]^+$

Synthesis of 5-(1-fluoro-1-((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)ethyl)benzo[b]thiophene-2-carboxylic acid



[00681] *Step 1: Preparation of allyl 5-(1-(diethoxyphosphoryl)-1-fluoroethyl)benzo[b]thiophene-2-carboxylate*

[00682] To a solution of allyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (2.66 g, 6.88 mmol, 1 eq) in THF (50 mL) at -78 °C were added 1 M LiHMDS in THF (6.88 mL, 6.88 mmol, 1 eq) and methyl iodide (850 µL, 13.7 mmol, 2 eq) dropwise. The mixture was stirred at -78 °C for 5 min. The reaction was quenched with a saturated aqueous solution of ammonium chloride (30 mL), warmed up to room temperature and the product was extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried with sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by reverse phase chromatography on a 150 g C_{18} cartridge eluting with a gradient of 5-80% acetonitrile in water (with 0.1% formic acid). The fractions were combined and concentrated under reduced pressure to give allyl 5-(1-(diethoxyphosphoryl)-1-fluoroethyl)benzo[b]thiophene-2-carboxylate (1.44 g, 52.3%) as a brown oil. LCMS (ESI) m/z = 401.2

[00683] *Step 2: Preparation of (1-(2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)-1-fluoroethyl)phosphonic acid*

[00684] To a solution of allyl 5-(1-(diethoxyphosphoryl)-1-fluoroethyl)benzo[b]thiophene-2-carboxylate (1.44 g, 3.59 mmol, 1 eq) in DCM (30 mL) at 0 °C were added *N,O*-bis(trimethylsilyl)trifluoroacetamide (4.74 mL, 17.9 mmol) followed by slow addition of trimethylsilyl iodide (1.52 mL, 10.7 mmol, 3 eq) in DCM (2 mL). The solution was stirred at 0 °C for 1 h. The reaction was quenched with the addition of a 2:1 solution of water and acetonitrile (with 0.1% TFA) (2 mL). The solvent was removed under reduced pressure. The crude residue was purified by reverse phase chromatography on a 150 g C_{18} cartridge eluting with a gradient of 5-60% acetonitrile in water (with 0.1% formic acid). The combined fractions were concentrated and freeze-dried to give (1-(2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)-1-fluoroethyl)phosphonic acid (887 mg,

72.1%) as a pale-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) 11.84 - 11.05 (m, 2H), 8.34 - 8.28 (m, 1H), 8.12 - 8.02 (m, 2H), 7.66 - 7.56 (m, 1H), 6.12 - 5.98 (m, 1H), 5.49 - 5.39 (m, 1H), 5.35 - 5.27 (m, 1H), 4.89 - 4.81 (m, 2H), 1.96 - 1.78 (m, 3H).

[00685] *Step 3:Preparation of allyl 5-(1-fluoro-1-((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)ethyl)benzo[b]thiophene-2-carboxylate*

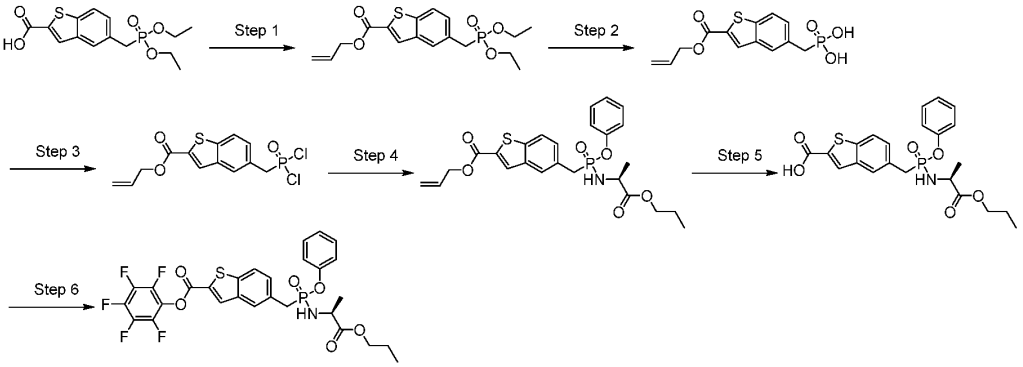
[00686] To a suspension of (1-(2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)-1-fluoroethyl)phosphonic acid (160 mg, 464 µmol, 1 eq) and 1 drop of DMF (cat) in DCM (30 mL) at 0°C was added oxalyl chloride (118 µL, 1.39 mmol, 3 eq) and the reaction was stirred for 20 h. The reaction was concentrated under reduced pressure and then dried under high vacuum during 10 min. The crude residue was diluted in 1,2-dichloroethane (3 mL) and a solution of phenol (43.6 mg, 464 µmol, 1 eq) and triethylamine (322 µL, 2.32 mmol, 5 eq) in 1,2-dichloroethane (3 mL, dried with Na_2SO_4) was added to the mixture which was stirred at 45°C for 3 h. Propyl (2*S*)-2-aminopropanoate hydrochloride (77.7 mg, 464 µmol, 1 eq) in dichloromethane (10 mL, dried with Na_2SO_4) was added directly to the solution and stirred at room temperature overnight. The reaction mixture was quenched with water and the dichloromethane was removed *in vacuo*. The product was purified by reverse phase chromatography on a 50 g C_{18} cartridge eluting with a gradient of 5-100% acetonitrile in water (with 0.1% formic acid) to afford allyl 5-(1-fluoro-1-((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)ethyl)benzo[b]thiophene-2-carboxylate (30.0 mg, 12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 - 8.02 (m, 2H), 7.93 - 7.82 (m, 1H), 7.72 - 7.64 (m, 1H), 7.38 - 7.28 (m, 1H), 7.25 - 7.13 (m, 2H), 7.09 - 7.00 (m, 1H), 7.00 - 6.92 (m, 1H), 6.13 - 5.98 (m, 1H), 5.45 (br d, J = 17.1 Hz, 1H), 5.33 (br d, J = 10.5 Hz, 1H), 4.86 (br d, J = 4.9 Hz, 2H), 4.25 - 4.11 (m, 0.5H), 4.10 - 4.00 (m, 1H), 3.95 - 3.76 (m, 1H), 3.68 - 3.48 (m, 1.25H), 3.45 - 3.36 (m, 0.25H), 2.44 - 2.74 (m, 1H), 2.17 - 2.01 (m, 3H), 1.70 - 1.59 (m, 1H), 1.56 - 1.46 (m, 0.5H), 1.45 - 1.33 (m, 0.5H), 1.32 - 1.23 (m, 1.5H), 1.13 - 1.05 (m, 0.5H), 0.97 - 0.89 (m, 1.5H), 0.87 - 0.80 (m, 0.5H), 0.80 - 0.72 (m, 1H).

[00687] *Step 4:Preparation of 5-(1-fluoro-1-((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)ethyl)benzo[b]thiophene-2-carboxylic acid*

[00688] To a stirred solution of allyl 5-(1-fluoro-1-((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)ethyl)benzo[b]thiophene-2-carboxylate (30 mg, 56.2 µmol, 1 eq) in THF (3 mL) were added morpholine (24.1 µL, 281 µmol, 5 eq) and $Pd(PPh_3)_4$ (3.24 mg, 2.81 µmol, 0.05 eq) under nitrogen. The reaction mixture was stirred at room temperature for 1 h. The reaction was concentrated and the crude was directly purified by reverse phase chromatography on a 50 g C_{18} cartridge eluting with a gradient of 5-100%

acetonitrile in water (with 0.1% formic acid) to afford 5-(1-fluoro-1-((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)ethyl)benzo[b]thiophene-2-carboxylic acid (30.0 mg, 108%) as a beige solid. LCMS (ESI) m/z = 494.2 $[M+H]^+$.

Synthesis of perfluorophenyl 5-(((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate



[00689] *Step 1: Preparation of allyl 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00690] To a solution of 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (25 g, 76 mmol,1eq) in DMF (250 mL) was added Na_2CO_3 (20 g, 190 mmol, 2.5 eq) and 3-bromoprop-1-ene (23 g, 190 mmol, 2.5 eq), the mixture was stirred at 25 °C for 12 h. The mixture was diluted with water (500 mL) and extracted with EtOAc (500 mL × 3). The combined organic layers were washed with brine (500 mL × 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give allyl 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylate (25 g, 68 mmol, 89% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.79 - 7.67 (m, 2H), 7.39 - 7.28 (m, 1H), 6.05 - 5.88 (m, 1H), 5.43 - 5.33 (m, 1H), 5.29 - 5.20 (m, 1H), 4.83 - 4.73 (m, 2H), 4.00 - 3.88 (m, 4H), 3.29 - 3.11 (m, 2H), 1.18 (d, J = 6.4 Hz, 6H)

[00691] *Step 2: Preparation of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid*

[00692] To a solution of allyl 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylate (25 g, 68 mmol, 1 eq) in DCM (250 mL) was added TMSI (54 g, 272 mmol, 4 eq) in a dropwise manner at 0 °C, the mixture was stirred at 0 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a yellow oil. The oil was purified by reversed phase (TFA) to lyophilized to give ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-

yl)methyl)phosphonic acid (13 g, 42 mmol, 61% yield) as a white solid. LCMS (ESI) m/z = 313.2 $[M+H]^+$.

[00693] *Step 3: Preparation of allyl 5-((dichlorophosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00694] To a solution of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (2.0 g, 6.4 mmol, 1 eq) in DCM (30 mL) was added DMF (0.09 mL) and was cooled to 0 °C, then oxalic dichloride (2.4 g, 19.2 mmol, 3 eq) was dropwise, after that the reaction was warmed to 40 °C and was stirred 1 h to give a yellow clean solution. The reaction mixture was concentrated under reduced pressure to give allyl 5 ((dichlorophosphoryl)methyl)benzo[b]thiophene-2-carboxylate (2.0 g, crude) as a brassy yellow solid. LCMS (ESI) m/z = 341.2 $[M+H]^+$.

[00695] *Step 4: Preparation of allyl 5-(((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00696] To a solution of allyl 5-((dichlorophosphoryl)methyl)benzo[b]thiophene-2-carboxylate (2.0 g, crude, 1 eq) in DCM (40 mL) was cooled to 0 °C and was added a solution of phenol (0.43 g, 4.58 mmol, 1 eq) in DCM (8 mL), then ethylbis(propan-2-yl)amine (2.2 g, 17 mmol, 3 eq) in DCM (50 mL) was dropwise over 0.5 h. Then propyl L-alaninate hydrochloride (1.44 g, 1.58 mmol, 1.5 eq) in DCM (8 mL) was added, the mixture was stirred at 0 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give allyl 5-(((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (1.4 g, 2.8 mmol, 43.8% yield) as a yellow oil. LCMS (ESI) m/z = 502.2 $[M+H]^+$.

[00697] *Step 5: Preparation of 5-(((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid*

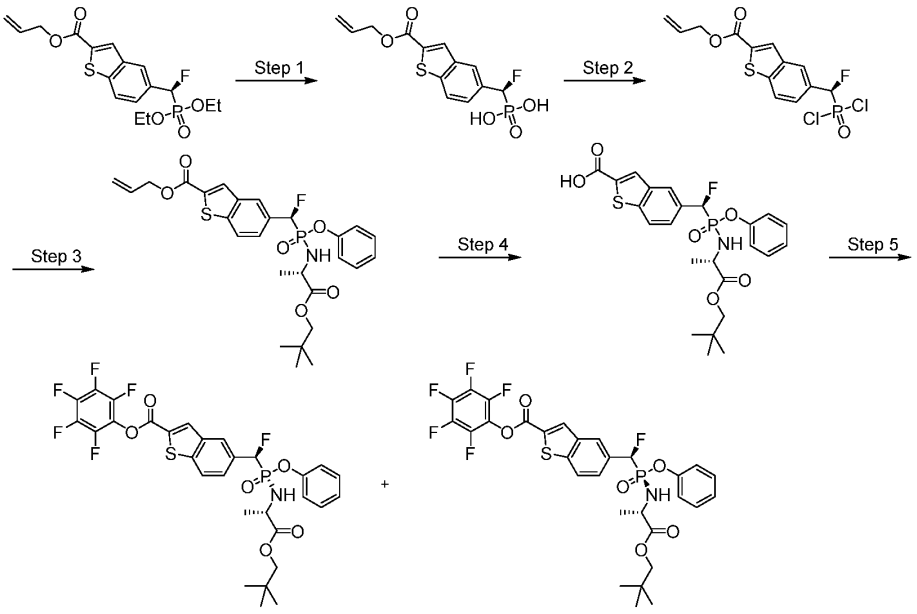
[00698] To a solution of allyl 5-(((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (1.4 g, 2.8 mmol) in DCM (20 mL) was added $Pd(PPh_3)_4$ (0.3 g, 0.3 mmol, 0.1 eq) and pyrrolidine (0.4 g, 5.6 mmol, 2 eq). Then the reaction was stirred at 25 °C for 15 min to give a yellow clean solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by reversed phase (TFA) to freeze-drying to give 5-(((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (1.1 g, 2.4 mmol, 85.9% yield) as a yellow oil. LCMS (ESI) m/z = 461.9 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 - 7.86 (m, 1H), 7.84 - 7.76 (m, 2H), 7.45 - 7.38 (m, 1H),

7.38 - 7.31 (m, 2H), 7.27 - 7.15 (m, 3H), 4.28 - 3.95 (m, 3H), 3.56 - 3.42 (m, 2H), 1.64 (td, J = 7.2, 14.0 Hz, 2H), 1.33 - 1.18 (m, 3H), 0.93 (dt, J = 4.8, 7.2 Hz, 3H)

[00699] *Step 6: Preparation of perfluorophenyl 5-((((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00700] To a solution of 5-(((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (19 g, 41 mmol, 1 eq) and pyridine (11 g, 0.14 mol, 3.5 eq) in DMF (100 mL) was cooled to 0 °C, then the solution of perfluorophenyl 2,2,2-trifluoroacetate (57 g, 0.21 mol, 5 eq) was dropwise added to the mixture at 0 °C. Then the mixture was stirred at 0 °C for 1 h to give a yellow solution. The mixture was diluted with water (500 mL) and extracted with EtOAc (500 mL × 3), the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give perfluorophenyl 5-(((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (17 g, 27 mmol, 65% yield) was obtained as a yellow oil. LCMS (ESI) m/z = 628.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 - 8.23 (m, 1H), 8.03 - 7.85 (m, 2H), 7.60-7.53 (m, 1H), 7.28 (s, 2H), 7.20 - 7.05 (m, 3H), 4.08 - 3.87 (m, 3H), 3.55 - 3.42 (m, 2H), 1.63-1.52 (m, 2H), 1.19-1.15 (m, 3H), 0.95 - 0.83 (m, 3H).

Synthesis of perfluorophenyl 5-((S)-fluoro((R)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate



[00701] *Step 1: Preparation of (S)-((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid*

[00702] To a solution of allyl (S)-5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (20 g, 52 mmol, 1 eq) in methylene chloride (500 mL) was added trimethylsilyl iodide (21 g, 0.10 mol, 2 eq). The mixture was stirred at 0 °C for 1 hour to give a brown solution. The reaction mixture was concentrated under reduced pressure to give a residue. The reaction residue was purified by prep-HPLC (TFA) to lyophilized to give (S)-((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid (12 g, 36 mmol, 70% yield) as a brown solid. LCMS (ESI) m/z = 330.9

[00703] *Step 2: Preparation of allyl (S)-5-((dichlorophosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate*

[00704] To a solution of (S)-((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid (11 g, 33 mmol, 1 eq) in methylene chloride (200 mL) was added dimethylformamide (0.24 g, 3.3 mmol, 0.1 eq) at 0 °C under N2 atmosphere, then oxalyl chloride (13 g, 0.10 mol, 3 eq) was added dropwise and stirred at 0 °C for 30 minutes and warmed to 40 °C for 1 hour to give a brown solution. The reaction mixture was concentrated under reduced pressure to give allyl (S)-5-((dichlorophosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (11 g crude) as a yellow solid. LCMS (ESI) m/z = 358.9.

[00705] *Step 3: Preparation of allyl 5-((1S)-fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

To a solution of (S)-5-((dichlorophosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (11 g, 30 mmol, 1 eq) in methylene chloride (150 mL) was added phenol (2.2 g, 24 mmol, 0.8 eq) in methylene chloride (20 mL) in 10 minutes at 0 °C, then the solution of N,N-diisopropylethylamine (12 g, 90 mmol, 3 eq) in methylene chloride (200 mL) was dropwise over 1.5 hours and the mixture was stirred at 25 °C for 5 minutes to give a yellow clean solution then the solution of propyl (2S)-2-aminopropanoate (3.9 g, 30 mmol, 1 eq) in methylene chloride (20 mL) was added, the mixture was stirred at 25 °C for 1 hour to give a yellow clean solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give allyl 5-((1S)-fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (7.4 g, 14.2 mmol, 47% yield) as a yellow solid. LCMS (ESI) m/z = 520.2

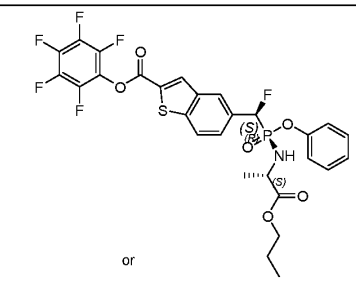
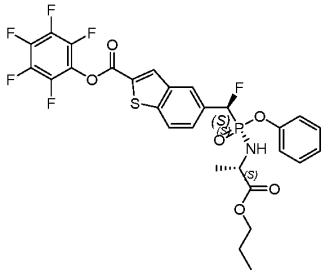
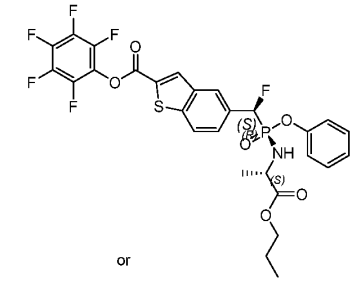
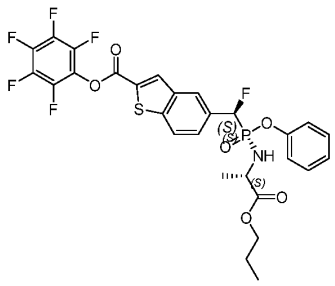
[00706] *Step 4: Preparation of 5-((1S)-fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid*

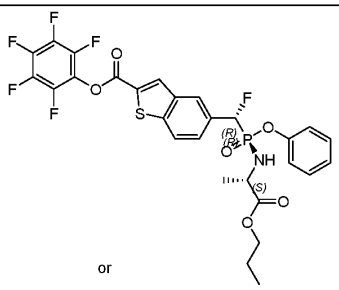
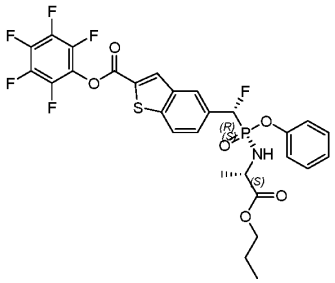
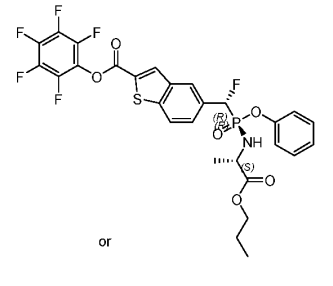
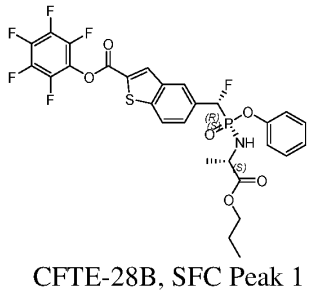
[00707] To a solution of allyl 5-((1S)-fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (3.5 g, 6.7 mmol, 1 eq) in methylene chloride (40 mL) at 0 °C under N2 atmosphere, then pyrrolidine (0.38 g, 5.4 mmol, 0.8 eq) and $Pd(PPh_3)_4$ (0.7 g, 0.67 mmol, 0.11 eq) was added dropwise and stirred at 0 °C for 10 minutes and warmed to 25 °C for 10 minutes to give a brown solution. The reaction mixture was concentrated under reduced pressure to give a residue. The reaction residue was purified by prep-HPLC (TFA) to lyophilized to give 5-((1S)-fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (2.8 g, 5.9 mmol, 87% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 11.2 Hz, 2H), 7.97 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.38 - 7.30 (m, 2H), 7.19 (d, J = 7.6 Hz, 3H), 6.20 - 5.99 (m, 1H), 4.05 - 3.77 (m, 3H), 1.68 - 1.42 (m, 2H), 1.22 (d, J = 7.2 Hz, 3H), 0.89 - 0.85 (m, 3H)

[00708] *Step 5: Preparation of perfluorophenyl 5-((S)-fluoro((R)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate and perfluorophenyl 5-((S)-fluoro((S)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00709] To a solution of 5-((1S)-fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (3.0 g, 6.3 mmol, 1 eq) in pyridine (15 mL) at 0 °C under N2 atmosphere, then 2,3,4,5,6-pentafluorophenyl 2,2,2-trifluoroacetate (5.2 g, 19 mmol, 3 eq) was added dropwise and stirred at 0 °C for 10 minutes and warmed to 25 °C for 1 hour to give a brown solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography in 3:1 Petroleum ether/ethyl acetate to give the separated Phos isomers. The analogous (*R*)-F isomer was made in a similar manner. Analytical data for all 4 isomers are listed in the table below. SFC conditions used in the peak assignments are as follows: Chiralpak AS-3 50x4.6mm I.D., 3um. Mobile phase: Phase A for CO2, and Phase B for EtOH (0.05%DEA); Gradient elution: B in A from 5% to 40%. Flow rate: 3mL/min; Detector: PDA;Column Temp: 35C;Back Pressure: 100Bar.

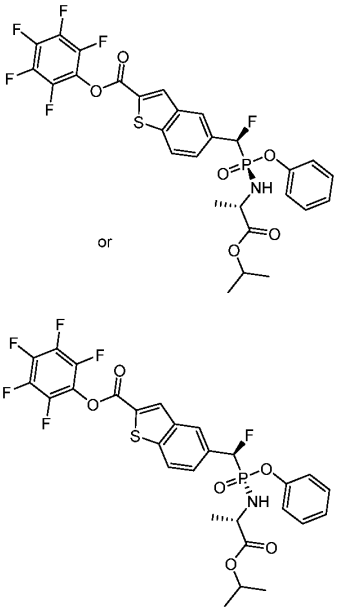
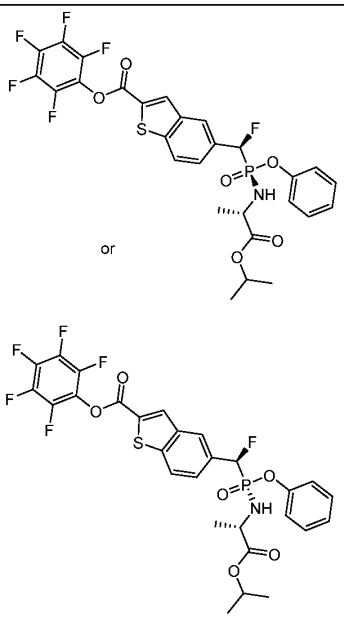
Name	Structure	LCMS	NMR

perfluorophenyl 5-((S)-fluoro((R)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate or perfluorophenyl 5-((S)-fluoro((S)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate	 or  CFTE-27B, SFC Peak 2 Ret. Time = 1.46 Minutes	645.9 $[M+H]^+$	^1H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1H), 8.25 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.39 - 7.32 (m, 2H), 7.27 - 7.16 (m, 3H), 6.25 - 6.01 (m, 1H), 4.00 (t, J = 6.8 Hz, 2H), 3.92 - 3.82 (m, 1H), 1.63 - 1.52 (m, 2H), 1.14 (d, J = 7.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H)
perfluorophenyl 5-((S)-fluoro((R)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate or perfluorophenyl 5-((S)-fluoro((S)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate	 or  CFTE-27A, SFC Peak 1 Ret. Time = 0.89 Minutes	646.0 $[M+H]^+$	^1H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.27 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.40 - 7.33 (m, 2H), 7.25 - 7.18 (m, 3H), 6.27 - 6.08 (m, 1H), 4.03 - 3.85 (m, 3H), 1.63 - 1.51 (m, 2H), 1.25 (d, J = 7.2 Hz, 3H), 0.89 (t, J = 7.6 Hz, 3H)

perfluorophenyl 5-((R)-fluoro((R)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate or perfluorophenyl 5-((R)-fluoro((S)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate	 or  CFTE-28A, SFC Peak 2 Ret. Time = 1.95 Minutes	645.9 $[M+H]^+$	^{1}H NMR (400 MHz, CD_3OD) δ 8.50 - 8.44 (m, 1H), 8.26 - 8.18 (m, 1H), 8.13 - 8.03 (m, 1H), 7.81 - 7.72 (m, 1H), 7.41 - 7.28 (m, 2H), 7.27 - 7.11 (m, 3H), 6.22 - 6.00 (m, 1H), 4.01 - 3.94 (m, 2H), 3.93 - 3.83 (m, 1H), 1.63 - 1.51 (m, 2H), 1.23 (d, J = 7.2 Hz, 3H), 0.93 - 0.83 (m, 3H)
perfluorophenyl 5-((R)-fluoro((R)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate or perfluorophenyl 5-((R)-fluoro((S)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate	 or  CFTE-28B, SFC Peak 1 Ret. Time = 1.51 Minutes	646.1 $[M+H]^+$	^{1}H NMR (400 MHz, METHANOL-d4) δ 8.40 (s, 1H), 8.17 - 8.06 (m, 1H), 8.04 - 7.95 (m, 1H), 7.75 - 7.64 (m, 1H), 7.29 - 7.18 (m, 2H), 7.14 - 6.98 (m, 3H), 6.18 - 5.93 (m, 1H), 3.87 - 3.79 (m, 1H), 3.79 - 3.67 (m, 2H), 1.48 - 1.36 (m, 2H), 1.15 - 1.09 (m, 3H), 0.76 (t, J = 7.6 Hz, 3H)

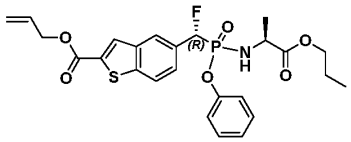
[00710] The following intermediates in **Table 68** were prepared using the synthetic procedure described above *Synthesis of perfluorophenyl 5-((S)-fluoro((R)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate* and utilizing the appropriate starting materials and modifications.

Table 68

Name	Structure	LCMS	NMR
perfluorophenyl 5-((S)-fluoro((R)-(((S)-1-isopropoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate or perfluorophenyl 5-((S)-fluoro((S)-(((S)-1-isopropoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		646.2 $[M+H]^+$	
perfluorophenyl 5-((S)-fluoro((R)-(((S)-1-isopropoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate or perfluorophenyl 5-((S)-fluoro((S)-(((S)-1-isopropoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		646.2 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.14 (s, 1H), 8.02 - 7.95 (m, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.32 - 7.28 (m, 2H), 7.18 - 7.14 (m, 1H), 7.12 (d, J = 8.0 Hz, 2H), 6.10 - 5.94 (m, 1H), 5.05 (m, 1H), 4.20 - 4.09 (m, 1H), 3.68 (t, J = 10.4 Hz, 1H), 1.32 (d, J = 7.2 Hz, 3H), 1.30 - 1.24 (m, 6H)

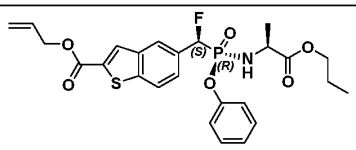
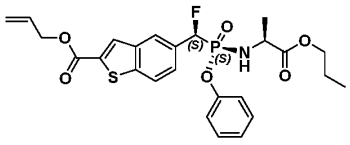
[00711] The following intermediates in **Table 69** were prepared using the synthetic procedure described above for *allyl 5-((1S)-fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate* and utilizing the appropriate starting materials and modifications.

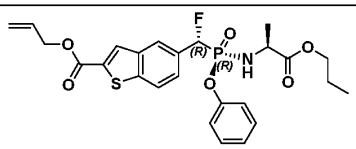
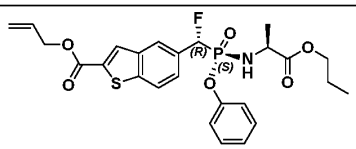
Table 69

Name	Structure	LCMS
allyl 5-((1R)-fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		520.1 $[M+H]^+$

[00712] The following phosphorus chiral intermediates in **Table 70** were obtained by chiral SFC separation of the corresponding P-isomer mixtures, which were prepared using the synthetic procedure described above for *allyl 5-((1S)-fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate* and utilizing the appropriate starting materials and modifications. Absolute stereochemical configuration at phosphorus is arbitrarily assigned as drawn.

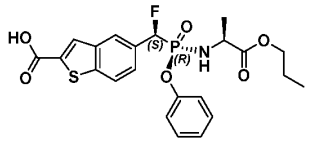
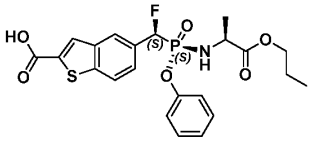
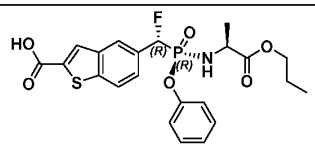
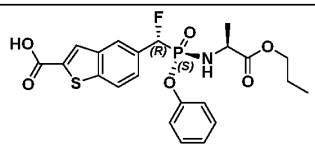
Table 70

Name	Structure	LCMS	Preparative SFC conditions for separation
allyl 5-((S)-fluoro((R)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate	 (Peak 1, RT = 4.46 min)	520.2 $[M+H]^+$	ChiralPak R,R-WHELK 250×21.2mm 5 µm column; Mobile phase: A for CO_2 and B for MeOH + 0.1% NH_3H_2O; Gradient: B 50%; Flow rate: 40 mL/min; Back pressure: 100 bar; Column temperature: 35 °C; Wavelength: 220 nm; Cycle-time: 11 min
allyl 5-((S)-fluoro((S)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate	 (Peak 2, RT = 6.54 min)	520.2 $[M+H]^+$	

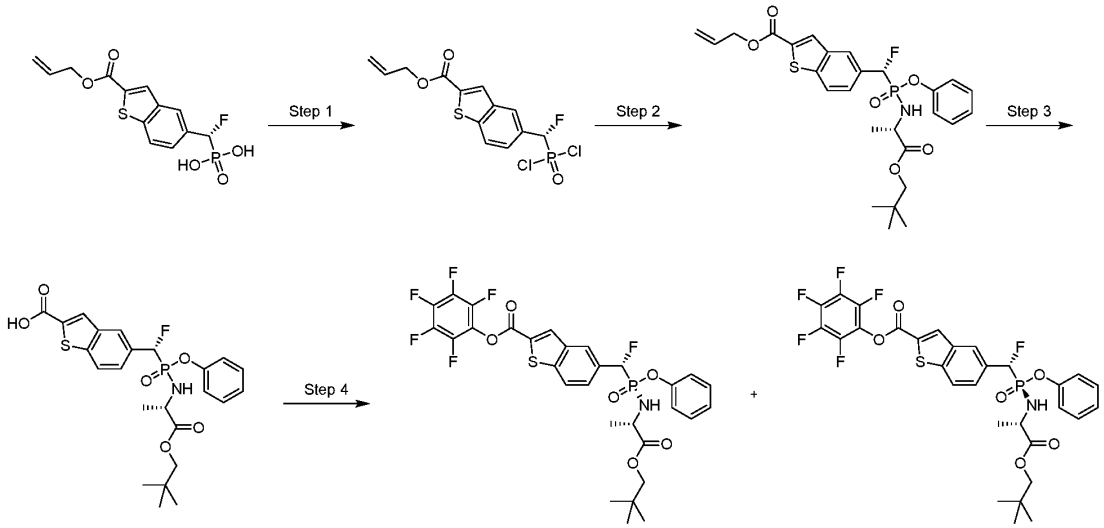
allyl 5-((R)-fluoro((R)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate	 (Peak 1, RT = 2.72 min)	520.2 $[M+H]^+$	ChiralPak IH 250×21.2 mm 5 µm column; Mobile phase: A for CO_2 and B for MeOH + 0.1% NH_3H_2O; Gradient: B 35%; Flow rate: 40 mL/min; Back pressure: 100 bar; Column temperature: 35 °C; Wavelength: 220 nm; Cycle-time: 5 min
allyl 5-((R)-fluoro((S)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate	 (Peak 2, RT = 4.11 min)	520.2 $[M+H]^+$	

[00713] The following intermediates in **Table 71** were prepared using the synthetic procedure described above for *5-((1S)-fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid* and utilizing the appropriate starting materials and modifications.

Table 71

Name	Structure	LCMS
5-((S)-fluoro((R)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		480.1 $[M+H]^+$
5-((S)-fluoro((S)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		480.1 $[M+H]^+$
5-((R)-fluoro((R)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		480.1 $[M+H]^+$
5-((R)-fluoro((S)-(((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		480.1 $[M+H]^+$

Synthesis of perfluorophenyl 5-((R)-fluoro((S)-(((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate and perfluorophenyl 5-((R)-fluoro((R)-(((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate



[00714] *Step 1: Preparation of allyl (R)-5-((dichlorophosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate*

[00715] To a solution of (R)-((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid (2.0 g, 6.1 mmol, 1.0 eq) in DCM (30 mL) was added 3 drops of DMF (0.03 mL) cooled to 0 °C, then the reaction was added oxalyl chloride (2.3 g, 18.1 mmol, 3 eq) slowly, after that the reaction was warmed to 45 °C and stirred 20 min to give a yellow clean solution. The reaction mixture was concentrated under reduced pressure to give allyl (R)-5-((dichlorophosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (2.0 g, crude) as a yellow oil and was used into the next step without further purification. LCMS (ESI) m/z=358.9 $[M+H]^+$.

[00716] *Step 2:Preparation of allyl 5-((1R)-fluoro((((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00717] To a solution of allyl (R)-5-((dichlorophosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (2.0 g, 5.4 mmol, 1.0 eq) in DCM (40 mL) was cooled to 0 °C and was added a solution of phenol (0.5 g, 5.4 mmol, 1.0 eq) in DCM (10 mL), then the mixture was added N,N-diisopropylethylamine (2.1 g, 16 mmol, 3.0 eq) in DCM (40 mL) dropwise. The reaction was stirred at 0 °C for 10 min and was added 2,2-dimethylpropyl (2S)-2-aminopropanoate (0.9 g, 5.4 mmol, 1.0 eq) in

DCM (20 mL). Then the reaction was warmed to 25 °C and stirred for 1 h to give a light-yellow clean solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography on silica gel to get allyl 5-((1R)-fluoro((((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (1.7 g, 3.1 mmol, 57% yield) was obtained as a yellow oil. LCMS (ESI) m/z=548.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.07 - 7.99 (m, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.68 - 7.59 (m, 1H), 7.41 - 7.25 (m, 3H), 7.23 - 7.06 (m, 3H), 6.12 - 5.90 (m, 2H), 5.48 - 5.44 (m, 1H), 5.39 - 5.30 (m, 1H), 4.87 (d, J = 5.6 Hz, 2H), 4.22 - 4.07 (m, 2H), 3.90 - 3.83 (m, 1H), 3.74 - 3.63 (m, 2H), 1.38 - 1.30 (m, 3H), 0.92 (s, 9H).

[00718] *Step 3: Preparation of 5-((1R)-fluoro((((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid*

[00719] To a solution of allyl 5-((1R)-fluoro((((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (1.7 g, 3.1 mmol, 1.0 eq) in DCM (20 mL) was added pyrrolidine (0.4 g, 6.2 mmol, 2.0 eq) and $Pd(PPh_3)_4$ (0.4 g, 0.3 mmol, 0.1 eq). Then the reaction stirred for 15 min to give a yellow clean solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by reversed phase (TFA) to lyophilized to give 5-((1R)-fluoro((((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (1.3 g, 2.6 mmol, 83% yield) as a white solid. LCMS (ESI) m/z=508.2

[00720] *Step 4: Preparation of perfluorophenyl 5-((R)-fluoro((S)-(((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate and perfluorophenyl 5-((R)-fluoro((R)-(((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

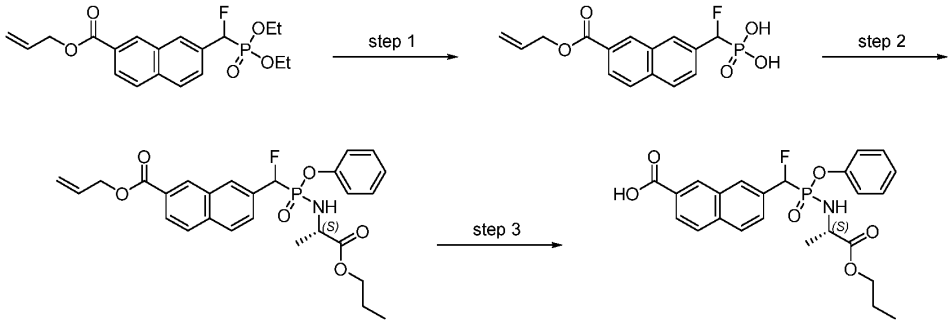
[00721] To a solution of 5-((1R)-fluoro((((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (1.2 g, 2.4 mmol, 1.0 eq) in pyridine (100 mL) was added 2,3,4,5,6-pentafluorophenyl 2,2,2-trifluoroacetate (0.66 g, 2.4 mmol, 1.0 eq) at 0 °C, the mixture was stirred at 25 °C for 10 min to give a yellow clean solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography on silica gel to give perfluorophenyl 5-((R)-fluoro((S)-(((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate or perfluorophenyl 5-((R)-fluoro((R)-(((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (0.4 g, 0.59 mmol,

25% yield, Rt = 1.883 min, **Peak 2**) as a yellow oil and perfluorophenyl 5-((R)-fluoro((R)-(((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate or perfluorophenyl 5-((R)-fluoro((S)-(((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (0.50 g, 0.74 mmol, 32% yield, Rt = 1.442 min, **Peak 1**) as a yellow oil.

[00722] **Peak 2:** perfluorophenyl 5-((R)-fluoro((S)-(((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate: LCMS (ESI) m/z = 674.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.09 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.40 - 7.35 (m, 2H), 7.32 - 7.27 (m, 2H), 7.24 - 7.19 (m, 1H), 6.07 - 5.89 (m, 1H), 4.16 - 4.05 (m, 1H), 3.88 - 3.76 (m, 2H), 3.72 - 3.64 (m, 1H), 1.15 (d, J = 7.2 Hz, 3H), 0.91 (s, 9H)

[00723] **Peak 1:** perfluorophenyl 5-((R)-fluoro((R)-(((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate or perfluorophenyl 5-((R)-fluoro((S)-(((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate: LCMS (ESI) m/z=674.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.12 (s, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.29 (s, 1H), 7.25 (s, 1H), 7.16 - 7.05 (m, 3H), 6.13 - 5.96 (m, 1H), 4.22 - 4.10 (m, 1H), 3.89 – 3.83 (m, 1H), 3.73 - 3.66 (m, 1H), 3.62 - 3.54 (m, 1H), 1.33 (d, J = 7.2 Hz, 3H), 0.92 (s, 9H).

Synthesis of 7-(fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoic acid



[00724] *Step 1: Preparation of ((7-((allyloxy)carbonyl)naphthalen-2-yl)fluoromethyl)phosphonic acid*

[00725] To a solution of allyl 7-((diethoxyphosphoryl)fluoromethyl)-2-naphthoate (1 g, 2.63 mmol, 1.0 eq.) in DCM (10 mL) were added TMSBr (4.0 g, 26.3 mmol, 10.0 eq.). The

mixture was stirred at room temperature for 16 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford ((7-((allyloxy)carbonyl)naphthalen-2-yl)fluoromethyl)phosphonic acid (680 mg, 2.10 mmol, 80%) as a colorless oil. LCMS (ESI): *m/z* = 325 $[M+H]^+$.

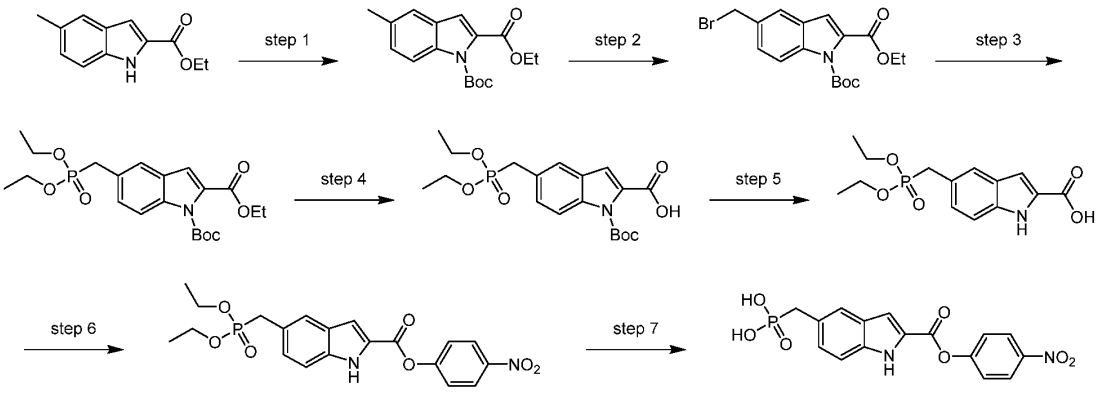
[00726] *Step 2: Preparation of allyl 7-(fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoate*

[00727] Oxalyl chloride (1.32 g, 10.5 mmol, 5 eq.) was added dropwise to the solution of afford ((7-((allyloxy)carbonyl)naphthalen-2-yl)fluoromethyl)phosphonic acid (680 mg, 2.10 mmol, 1 eq.) in dry DCM (20 mL) and DMF (0.1 mL) at 25 °C. The reaction mixture was stirred at 40 °C for an additional 1 hr. The reaction was monitored by pipetting out a small amount of crude sample and quenching it with MeOH to ensure bis-Cl phosphoryl chloride had been formed completely (bis-methoxy phosphonate was observed by LCMS). After completion, the excess oxalyl chloride and solvent were removed under reduced pressure. The residue was re-dissolved in anhydrous DCM (20 mL), then added to a mixture of phenol (197 mg, 2.10 mmol, 1.0 eq.) and TEA (2.12 g, 21.0 mmol, 10 eq.) in anhydrous DCM (20 mL) at -20 °C. The reaction was stirred at -20 °C for an additional 1 hr. Then, propyl L-alaninate (550 mg, 4.2 mmol, 2.0 eq.) was added into the above mixture at 0 °C. The reaction was stirred at 25 °C for an additional 1 hr. After completion, the reaction was poured into ice-water (10 mL) and extracted with DCM (10 mL x 2). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to afford allyl 7-(fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoate (323 mg, 0.63 mmol, 30%) as a brown solid. LCMS (ESI): *m/z* = 514 $[M+H]^+$.

[00728] *Step 3: Preparation of 7-(fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoic acid*

[00729] To a solution of allyl 7-(fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoate (323 mg, 0.63 mmol, 1.0 eq) in DCM (10 mL) were added $Pd(PPh_3)_4$ (69 mg, 0.06 mmol, 0.1 eq.) and pyrrolidine (45 mg, 0.63 mmol, 1.0 eq.). The mixture was purged and degassed with N_2 (three times), then stirred at 25 °C for 0.5 h. After completion, the mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give 7-(fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)-2-naphthoic acid (228 mg, 0.48 mmol,76%) as a yellow solid. LCMS (ESI): *m/z* = 474 $[M+H]^+$.

Synthesis of ((2-((4-nitrophenoxy)carbonyl)-1H-indol-5-yl)methyl)phosphonic acid



[00730] *Step 1: Preparation of 1-(tert-butyl) 2-ethyl 5-methyl-1H-indole-1,2-dicarboxylate*

[00731] To a solution of 1-tert-butyl 2-ethyl 5-[(diethoxyphosphoryl)methyl]-1H-indole-1,2-dicarboxylate (10 g, 5.2 mmol) in THF (100 mL) was added NaH (0.12 g, 4.9 mmol) at 0 °C and stirred for 0.5 h, then di-tert-butyl dicarbonate (13.0 g, 59.0 mmol) was added in it and stirred at 25 °C for 12 h to give a white suspension. The reaction mixture was quenched by water (100 mL) at 0 °C , then extracted with EtOAc (150 mL × 2), the combined organic layers were washed with saturated brine (200 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give 1-(tert-butyl) 2-ethyl 5-methyl-1H-indole-1,2-dicarboxylate (15 g, 49 mmol, 90% yield) as a yellow oil. LCMS (ESI) m/z = 304.5 $[M+H]^+$.

[00732] *Step 2: Preparation of 1-(tert-butyl) 2-ethyl 5-(bromomethyl)-1H-indole-1,2-dicarboxylate*

[00733] To a solution of 1-(tert-butyl) 2-ethyl 5-methyl-1H-indole-1,2-dicarboxylate (15 g, 49 mmol, 1.0 eq) in chloroform (120 mL) was added BPO (477 mg, 2.0 mmol, 0.04 eq) and N-bromosuccinimide (8.8 g, 49 mmol, 1.0 eq), the mixture was stirred at 120 °C for 12 h to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give 1-(tert-butyl) 2-ethyl 5-(bromomethyl)-1H-indole-1,2-dicarboxylate (15 g, 39 mmol, 79% yield) as a yellow oil. LCMS (ESI) m/z = 281.9 $[M+H]^+$.

[00734] *Step 3: Preparation of 1-(tert-butyl) 2-ethyl 5-((diethoxyphosphoryl)methyl)-1H-indole-1,2-dicarboxylate*

[00735] A solution of 1-(tert-butyl) 2-ethyl 5-(bromomethyl)-1H-indole-1,2-dicarboxylate (3.2 g, 8.4 mmol) in triethyl phosphite (14 g, 84 mmol) was stirred at 100 °C for 12 h to give a colorless solution. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL × 2), the combined organic layers were washed with saturated brine (150 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give 1-(tert-butyl) 2-ethyl 5-((diethoxyphosphoryl)methyl)-1H-indole-1,2-dicarboxylate (2.3 g, 5.2 mmol, 62% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.8 Hz, 1H), 7.52 (s, 1H), 7.39 - 7.33 (m, 1H), 7.04 (s, 1H), 4.45 - 4.44 (m, 1H), 4.37 (q, J = 7.2 Hz, 1H), 4.03 - 3.90 (m, 4H), 3.28 - 3.16 (m, 2H), 1.62 (s, 9H), 1.27 - 1.21 (m, 6H), 1.16 - 1.12 (m, 3H).

[00736] *Step 4: Preparation of 1-(tert-butoxycarbonyl)-5-((diethoxyphosphoryl)methyl)-1H-indole-2-carboxylic acid*

[00737] To a solution of 1-tert-butyl 2-ethyl 5-[(diethoxyphosphoryl)methyl]-1H-indole-1,2-dicarboxylate (4.6 g, 5.2 mmol) in MeOH (15 mL), THF (15 mL) and H_2O (15 mL) was added $LiOH{\cdot}H_2O$ (1.8 g, 42 mmol) and stirred at 25 °C for 1 h to give a white suspension. The reaction mixture was used saturated 2 M HCl to adjust the pH = 4 ~ 5, the reaction mixture was concentrated under reduced pressure to give 1-(tert-butoxycarbonyl)-5-((diethoxyphosphoryl)methyl)-1H-indole-2-carboxylic acid (7.0 g, crude) as a yellow oil. LCMS (ESI) m/z = 412.2 $[M+H]^+$.

[00738] *Step 5: Preparation of 5-((diethoxyphosphoryl)methyl)-1H-indole-2-carboxylic acid*

[00739] To a solution of 1-(tert-butoxycarbonyl)-5-((diethoxyphosphoryl)methyl)-1H-indole-2-carboxylic acid (7.0 g, 17 mmol) in DCM (30 mL) was added TFA (30 mL) and stirred at 25 °C for 1 h to give a brown solution. The reaction mixture was concentrated under reduced pressure to give 5-((diethoxyphosphoryl)methyl)-1H-indole-2-carboxylic acid (7.0 g, crude) as a brown oil. LCMS (ESI) m/z = 311.9 $[M+H]^+$.

[00740] *Step 6: Preparation of 4-nitrophenyl 5-((diethoxyphosphoryl)methyl)-1H-indole-2-carboxylate*

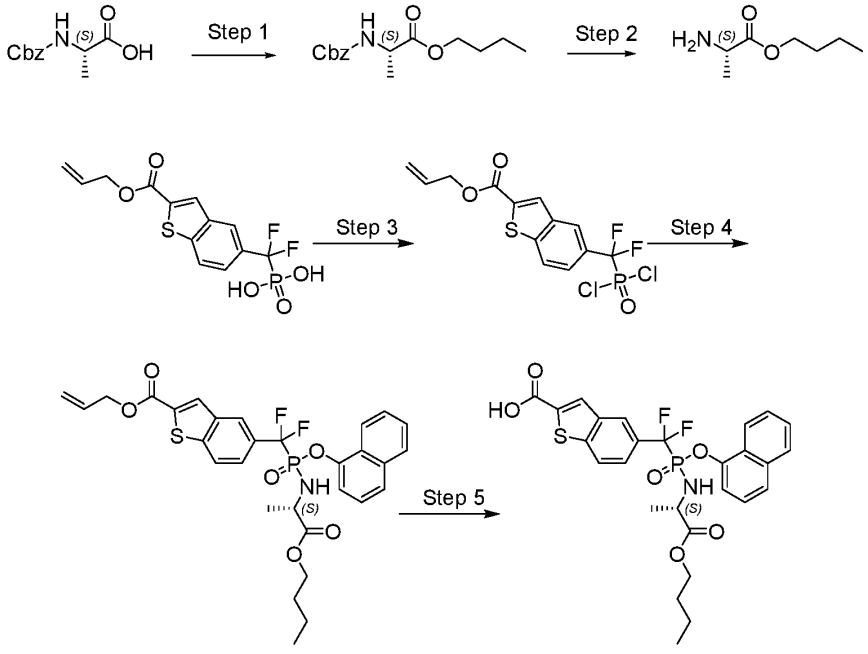
[00741] To a solution of 5-((diethoxyphosphoryl)methyl)-1H-indole-2-carboxylic acid (1.2 g, 3.9 mmol) in EtOAc (70 mL) was added 4-nitrophenol (0.64 g, 4.6 mmol), dicyclohexylcarbodiimide (0.95 g, 4.6 mmol) and 4-dimethylaminopyridine (0.70 g, 5.8 mmol), then the mixture was stirred at 25 °C for 3 h to give a white suspension. The reaction mixture was filtered and the filter was concentrated to give a residue. The residue was purified by column chromatography to give 4-nitrophenyl 5-((diethoxyphosphoryl)methyl)-

1H-indole-2-carboxylate (0.90 g, 2.1 mmol, 54% yield) as a yellow solid. LCMS (ESI) m/z = 433.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.35 (d, J = 9.2 Hz, 2H), 7.65 (d, J = 2.4 Hz, 1H), 7.58 - 7.53 (m, 2H), 7.46 (d, J = 8.8 Hz, 1H), 7.40 (s, 1H), 7.30 (m, 1H), 4.07 - 3.99 (m, 4H), 1.25 (t, J = 7.2 Hz, 6H).

[00742] *Step 7: Preparation of ((2-((4-nitrophenoxy)carbonyl)-1H-indol-5-yl)methyl)phosphonic acid*

[00743] To a solution of 4-nitrophenyl 5-((diethoxyphosphoryl)methyl)-1H-indole-2-carboxylate (25 mg, 58 μmol) and BSTFA (59 mg, 0.23 mmol) in DCM (0.5 mL) was dropwise added a solution of trimethylsilyl iodide (69 mg, 0.35 mmol) in DCM (0.5 mL) at 0 °C, then the mixture solution was stirred at 0 °C for 1 h to give a brown solution. The reaction mixture was concentrated under reduced pressure to give ((2-((4-nitrophenoxy)carbonyl)-1H-indol-5-yl)methyl)phosphonic acid (25 mg, crude) as a brown solid. LCMS (ESI) m/z = 377.0 $[M+H]^+$.

Synthesis of 5-(difluoro((((S)-1-isopropoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid



[00744] *Step 1: Preparation of allyl 5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate*

[00745] To a solution of 5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid (5 g, 14 mmol, 1 eq) in dimethyl sulfoxide (40 mL) was added disodium carbonate (4.3 g, 41 mmol, 3 eq) and 3-bromoprop-1-ene (1.7 g, 14 mmol, 1 eq), the mixture was stirred at 25 ºC for 12 h to give a white suspension. The mixture was diluted with water (200 mL) and extracted with EtOAc (200 mL × 2), the combined organic layers were washed with saturated brine (200 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give allyl 5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (4.6 g, 11.3 mmol, 83% yield) as a white oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 - 8.13 (m, 2H), 7.96 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 6.13 - 5.99 (m, 1H), 5.50 - 5.42 (m, 1H), 5.37 - 5.32 (m, 1H), 4.87 (d, J = 5.6 Hz, 2H), 4.27 - 4.12 (m, 4H), 1.33 (t, J = 7.2 Hz, 6H).

[00746] *Step 2: Preparation of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid*

[00747] To a solution of allyl 5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (4.6 g, 11.3 mmol, 1 eq) in DCM (40 mL) was added iodotrimethylsilane (9.0 g, 45 mmol, 4 eq) at 0 ºC, the mixture was stirred at 0 ºC for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by reversed phase (TFA) to give ((2-((allyloxy) carbonyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid (2.3 g, 6.6 mmol, 58% yield) as a white solid. LCMS (ESI) m/z = 348.7

[00748] *Step 3: Preparation of allyl 5-((dichlorophosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate*

[00749] To a solution of ((2-((allyloxy) carbonyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid (1 g, 2.9 mmol, 1 eq) in DCM (3 mL) was added DMF (21 mg, 0.29 mmol, 0.1 eq), oxalic dichloride (1.2 g, 28 mmol, 3 eq) was dropwise at 0 ºC, the mixture was stirred at 40 ºC for 1 h to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give allyl 5-((dichlorophosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (1 g, crude) as a yellow solid. LCMS (ESI) m/z = 376.6.

[00750] *Step 4: Preparation of allyl 5-(((((S)-1-butoxy-1-oxopropan-2-yl)amino)(naphthalen-1-yloxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate*

[00751] To a solution of prop-2-en-1-yl 5-[(dichlorophosphoryl)difluoromethyl]-1-benzothiophene-2-carboxylate (0.2 g, 0.52 mmol, 1 eq) in methylene chloride (10 mL) was added naphthalen-1-ol (60 mg, 0.42 mmol, 0.8 eq), the mixture was stirred at 0 ºC for 5 min,

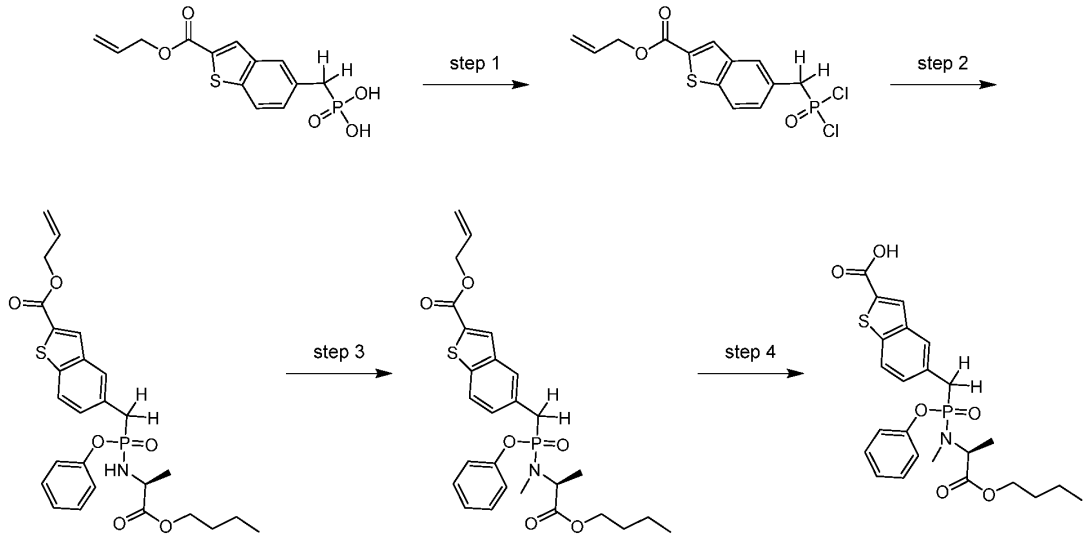
then a solution of N,N-diisopropylethylamine (0.2 g, 1.6 mmol, 3.0 eq) in methylene chloride (10 mL) was added to the mixture, then a solution of butyl (2S)-2-aminopropanoate (75 mg, 0.52 mmol, 1 eq) in methylene chloride (10 mL) was added to the mixture, the mixture was stirred at 0 °C for 30 min to give yellow solution. The reaction mixture was concentrated under reduced pressure to give a residue.

[00752] The residue was purified by column chromatography to give prop-2-en-1-yl 5-[({[(2S)-1-butoxy-1-oxopropan-2-yl]amino}(naphthalen-1-yloxy)phosphoryl)difluoromethyl]-1-benzothiophene-2-carboxylate (0.15 g, 0.24 mmol, 46.4% yield) as a yellow oil. LCMS (ESI) m/z = 602.1

[00753] *Step 5: Preparation of 5-(((((S)-1-butoxy-1-oxopropan-2-yl)amino)(naphthalen-1-yloxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid*

[00754] To a solution of prop-2-en-1-yl 5-[({[(2S)-1-butoxy-1-oxopropan-2-yl]amino}(naphthalen-1-yloxy)phosphoryl)difluoromethyl]-1-benzothiophene-2-carboxylate (0.14 g, 0.23 mmol, 1 eq) in methylene chloride (1.0 mL) was added $Pd(PPh_3)_4$ (27 mg, 23 μmol, 0.1 eq), the mixture was stirred at 0 °C for 5 min, then pyrrolidine (17 mg, 0.23 mmol, 1 eq) was added to the mixture, the mixture was stirred at 25 °C for 5 min to give yellow solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by reversed phase (TFA) to give 5-[({[(2S)-1-butoxy-1-oxopropan-2-yl]amino}(naphthalen-1-yloxy)phosphoryl)difluoromethyl]-1-benzothiophene-2-carboxylic acid (97 mg, 0.17 mmol, 74.6% yield) as a yellow oil . LCMS (ESI) m/z = 562.1

Synthesis of 5-(((((S)-1-butoxy-1-oxopropan-2-yl)(methyl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid



[00755] *Step 1: Preparation of allyl 5-((dichlorophosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00756] To a solution of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (0.1 g, 0.32 mmol, 1 eq) in DCM (2 mL) was added DMF (2.3 mg, 32 µmol, 0.1 eq). The mixture was stirred at 0 ºC for 5 min, then a solution of oxalyl chloride (0.12 g, 0.96 mmol, 3 eq) in DCM (2 mL) was added to the mixture, the mixture was stirred at 40 ºC for 1 h to give yellow solution. The reaction mixture was concentrated under reduced pressure to give allyl 5-((dichlorophosphoryl)methyl)benzo[b]thiophene-2-carboxylate (0.100 g, crude) as a yellow oil. LCMS (ESI) m/z =341.0 (MeOH quench)

[00757] *Step 2: Preparation of allyl 5-(((((S)-1-butoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00758] To a solution of allyl 5-((dichlorophosphoryl)methyl)benzo[b]thiophene-2-carboxylate (0.10 g, 0.29 mmol, 1 eq) in DCM (2 mL) was added phenol (22 mg, 0.23 mmol, 0.8 eq) at 0 ºC for 30 min, then a solution of DIEA (0.1 g, 0.86 mmol, 3.0 eq) in DCM (2 mL) was added to the mixture at 0 ºC for 15 min, then a solution of butyl L-alaninate (42 mg, 0.29 mmol, 1 eq) in DCM (2 mL) was added to the mixture at 0 ºC for 15 min to give yellow solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give allyl 5-(((((S)-1-butoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (80 mg, 0.15 mmol, 80% yield,) as a yellow oil. LCMS (ESI) m/z =516.2 $[M+H]^+$.

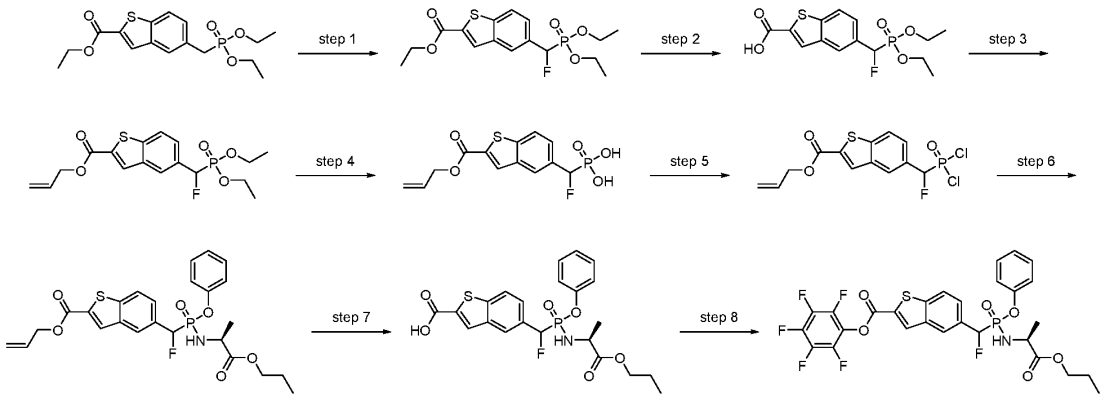
[00759] *Step 3: Preparation of allyl 5-(((((S)-1-butoxy-1-oxopropan-2-yl)(methyl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00760] To a solution of allyl 5-(((((S)-1-butoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (0.2 g, 0.39 mmol, 1 eq) in THF (5 mL) was added LDA (83 mg, 0.77 mmol, 2 eq) and methyl iodide (0.55 g, 3.9 mmol, 10 eq), the mixture was stirred at -70 oC for 15 min to give yellow solution. The reaction mixture was added water (0.5 mL) and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give allyl 5-(((((S)-1-butoxy-1-oxopropan-2-yl)(methyl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (60 mg, 0.11 mmol, 28% yield) as a yellow oil. LCMS (ESI) m/z =530.2 $[M+H]^+$.

[00761] *Step 4: Preparation of 5-(((((S)-1-butoxy-1-oxopropan-2-yl)(methyl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid*

[00762] To a solution of allyl 5-(((((S)-1-butoxy-1-oxopropan-2-yl)(methyl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (60 mg, 0.11 mmol, 1 eq) in DCM (2 mL) was added pyrrolidine (6.4 mg, 90 µmol, 0.8 eq) and $Pd(PPh_3)_4$ (1.3 mg, 1.1 µmol, 0.01 eq), the mixture was stirred at 25 oC for 5 min to give yellow solution. The reaction mixture was added water and concentrated under reduced pressure to give a residue. The residue was purified by reversed phase (TFA) then lyophilized to give 5-(((((S)-1-butoxy-1-oxopropan-2-yl)(methyl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (49 mg, 99 µmol, 88% yield) as a yellow oil. LCMS (ESI) m/z =490.1 $[M+H]^+$.

Synthesis of perfluorophenyl 5-(fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate



[00763] *Step 1: Preparation of ethyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate*

[00764] To a solution of ethyl 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylate (58 g, 0.16 mol, 1 eq) in THF (600 mL) was added lithium bis(trimethylsilyl)azanide (170 mL, 0.17 mol, 1.1 eq, 1.0 M in THF) at -70 °C ,then N-(benzenesulfonyl)-N-fluorobenzenesulfonamide (54 g, 0.17 mol, 1.1 eq) was added at -70 °C, then stirred at -70 °C for 0.5 h. The reaction mixture was quenched by water (500 mL) at -70 °C, then extracted with EtOAc (500 mL × 2), the combined organic layers were washed with saturated brine (400 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give ethyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (26 g, 67 mmol, 43% yield) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.92 (s, 1H),

7.83 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 5.84 - 5.63 (m, 1H), 4.39 - 4.29 (m, 2H), 4.09 - 3.96 (m, 4H), 1.35 (t, J = 7.1 Hz, 3H), 1.23 - 1.19 (m, 6H).

[00765] *Step 2: Preparation of 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid*

[00766] To a solution of ethyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (15 g, 40 mmol, 1 eq) in THF (40 mL) was dropwise added $LiOH \cdot H_2O$ (1.8 g, 44 mmol, 1.1 eq) in H_2O (40 mL) at 0 °C and stirred at 25 °C for 1 h to give a yellow solution. The reaction mixture was extracted with EtOAc (80 mL), then the aqueous phase was used 1M HCl to adjust the pH = 4~3 extracted with EtOAc (100 mL × 2), the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid (11 g, crude) as a white solid. LCMS (ESI) m/z = 346.8 $[M+H]^+$.

[00767] *Step 3: Preparation of allyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate*

[00768] To a solution of 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid (11 g, 32 mmol, 1 eq) in DMF (120 mL) was added sodium carbonate (6.7 g, 63 mmol, 2 eq) and stirred at 25 °C for 30 min, then 3-bromoprop-1-ene (7.7 g, 63 mmol, 2 eq) was added in it and stirred at 25 °C for 5 h to give a white suspension. The reaction mixture was diluted with water (300 mL) and extracted with EtOAc (400 mL × 3), the combined organic layers were washed with saturated brine (500 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give allyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (10 g, 26 mmol, 82% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.05 - 7.98 (m, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 6.13 - 5.97 (m, 1H), 5.91 - 5.71 (m, 1H), 5.52 - 5.40 (m, 1H), 5.33 (dd, J = 1.2, 10.4 Hz, 1H), 4.86 (dd, J = 1.2, 5.6 Hz, 2H), 4.19 - 4.03 (m, 4H), 1.33 - 1.24 (m, 6H).

[00769] *Step 4: Preparation of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid*

[00770] To a solution of allyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (9 g, 23 mmol, 1 eq) and (E)-(trimethylsilyl 2,2,2-trifluoro-N-(trimethylsilyl)ethanimidate) (18 g, 70 mmol, 3 eq) in DCM (100 mL) was added iodotrimethylsilane (16 g, 93 mmol, 4 eq) at 0 °C and stirred at 0 °C for 1 h to give a brown solution. The reaction mixture was concentrated under reduced pressure to give a residue.

The crude was purified by reverse phase chromatography (TFA) then lyophilization to give ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid (6.0 g, 18 mmol, 78% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 1H), 8.14 - 8.05 (m, 2H), 7.59 (d, J = 8.4 Hz, 1H), 6.13 - 5.98 (m, 1H), 5.90 - 5.76 (m, 1H), 5.44 (dd, J = 1.6, 17.2 Hz, 1H), 5.31 (dd, J = 1.6, 10.4 Hz, 1H), 4.86 - 4.83 (m, 2H).

[00771] *Step 5: Preparation of allyl 5-((dichlorophosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate*

[00772] To a solution of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid (2 g, 6.0 mmol, 1 eq) and DMF (88 mg, 1.2 mmol, 0.2 eq) in DCM (20 mL) was added oxalic dichloride (2.7 g, 21 mmol, 3.5 eq) at 0 °C and stirred at 40 °C for 0.5 h to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give allyl 5-((dichlorophosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (2.2 g, crude) as a yellow solid. LCMS (ESI) m/z = 717.1 (MeOH quench)

[00773] *Step 6: Preparation of allyl 5-(fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00774] To a solution of allyl 5-((dichlorophosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (2.2 g, 6.0 mmol, 1 eq) in DCM (20 mL), the solution was under N_2 and cooled to 0 °C, then phenol (0.56 g, 6.0 mmol, 1 eq) in DCM (10 mL) was added in it, ethylbis(propan-2-yl)amine (3.1 g, 24 mmol, 4 eq) in DCM (60 mL) was dropwise added in it and stirred at 0 °C for 5 min, 3,3,3-trifluoropropyl (2S)-2-aminopropanoate (0.91 g, 6.0 mmol, 1 eq) in DCM (20 mL) was added in it and stirred at 0 °C for 10 min to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give allyl 5-(fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (1.1 g, 1.9 mmol, 33% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 - 8.07 (m, 1H), 8.05 - 7.99 (m, 1H), 7.93 - 7.86 (m, 1H), 7.67 - 7.58 (m, 1H), 7.40 - 7.32 (m, 1H), 7.27 - 7.17 (m, 2H), 7.15 - 7.05 (m, 2H), 6.10 - 5.89 (m, 2H), 5.50 - 5.42 (m, 1H), 5.34 (dd, J = 1.2, 10.4 Hz, 1H), 4.87 (d, J = 5.6 Hz, 2H), 4.22 - 4.08 (m, 1H), 4.00 - 3.76 (m, 1H), 3.69 - 3.51 (m, 1H), 1.67 - 1.59 (m, 2H), 1.33 - 1.26 (m, 3H), 0.96 - 0.89 (m, 3H).

[00775] *Step 7: Preparation of 5-(fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid*

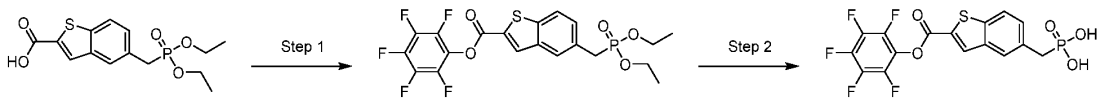
[00776] To a solution of allyl 5-(fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (1 g, 1.9 mmol, 1 eq) and pyrrolidine (82 mg, 1.2 mmol, 0.6 eq) in DCM (10 mL) was added $Pd(PPh_3)_4$ (0.22 g,

0.19 mmol, 0.1 eq) and stirred at 25 °C for 1 h to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give a residue. The crude was purified by reverse phase chromatography (TFA) then lyophilized to give 5-(fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (0.70 g, 1.5 mmol, 76% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 - 7.91 (m, 1H), 7.90 - 7.79 (m, 2H), 7.70 - 7.51 (m, 1H), 7.46 - 7.29 (m, 3H), 7.25 - 7.15 (m, 2H), 6.15 - 5.98 (m, 1H), 4.24 - 4.05 (m, 3H), 1.79 - 1.58 (m, 2H), 1.41 - 1.22 (m, 3H), 0.96 (dd, J = 12.4, 19.6 Hz, 3H).

[00777] *Step 8: Preparation of perfluorophenyl 5-(fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00778] To a solution of 5-(fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (0.70 g, 1.5 mmol, 1 eq) and pyridine (0.57 g, 7.2 mmol, 5 eq) in DMF (10 mL) was added 2,3,4,5,6-pentafluorophenyl 2,2,2-trifluoroacetate (2.0 g, 7.2 mmol, 5 eq) and stirred at 25 °C for 0.5 h to give a yellow solution. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL × 2), the combined organic layers were washed with saturated brine (40 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give perfluorophenyl 5-(fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (0.80 g, 1.2 mmol, 86% yield) as a white solid. LCMS (ESI) m/z = 646.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 - 8.30 (m, 1H), 8.15 - 8.07 (m, 1H), 8.02 - 7.91 (m, 1H), 7.78 - 7.63 (m, 1H), 7.43 - 7.34 (m, 1H), 7.31 - 7.28 (m, 1H), 7.25 - 7.17 (m, 1H), 7.16 - 7.06 (m, 2H), 6.13 - 5.89 (m, 1H), 4.11 - 4.01 (m, 2H), 3.70 - 3.51 (m, 1H), 1.72 - 1.59 (m, 3H), 1.32 (d, J = 7.2 Hz, 2H), 0.99 - 0.87 (m, 3H).

Synthesis of ((2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid



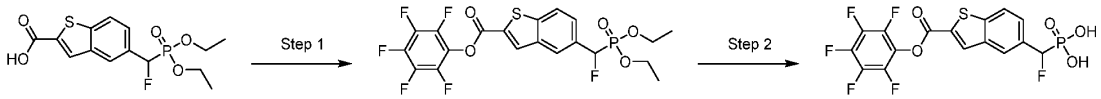
[00779] *Step 1: Preparation of ((2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid*

[00780] To a solution of 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (2 g, 6.1 mmol, 1 eq) in dimethylformamide (100 mL) was added pyridine (1.9 g, 24 mmol, 4 eq), the mixture was stirred at 0 °C for 5 min, then 2,3,4,5,6-pentafluorophenyl 2,2,2-trifluoroacetate (6.8 g, 24 mmol, 4 eq) was added to the mixture, the mixture was stirred at 25 °C for 15 min to give yellow solution. The mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL × 2), the combined organic layers were washed with saturated brine (40 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give perfluorophenyl 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylate (1.4 g, 2.9 mmol, 47% yield) as a yellow oil. LCMS (ESI) m/z =495.0

[00781] *Step 2: Preparation of ((2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid*

[00782] To a solution of perfluorophenyl 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylate (1.4 g, 2.8 mmol, 1 eq) in DCM (10 mL) was added trimethylsilyl iodide (2.3 g, 11 mmol, 4 eq), the mixture was stirred at 0 °C for 15 min to give yellow solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by reversed phase (TFA) to give ((2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (0.9 g, 2.1 mmol, 74% yield) as a white solid. LCMS (ESI) m/z = 438.9 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.41 (s, 1H), 8.01 - 7.94 (m, 2H), 7.60 - 7.55 (m, 1H), 3.32 - 3.32 (m, 1H), 3.26 (s, 1H).

Synthesis of (fluoro(2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid



[00783] *Step 1: Preparation of perfluorophenyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate*

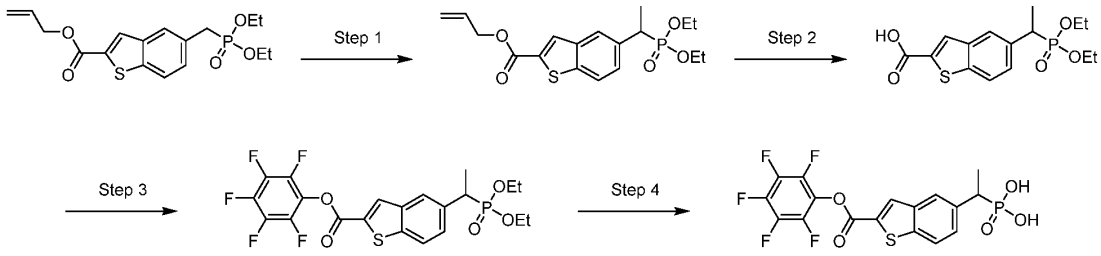
[00784] To a solution of 5-[(diethoxyphosphoryl)(fluoro)methyl]-1-benzothiophene-2-carboxylic acid (5 g, 14.40 mmol, 1 eq) in piperidine (6.13 g, 72 mmol, 5 eq) was added 2,3,4,5,6-pentafluorophenyl 2,2,2-trifluoroacetate (12 g, 43.20 mmol, 3 eq), the mixture was stirred at 0 °C for 30 min to give a brown clean solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (200 mL) and extracted with EtOAc (500 mL × 2), the combined organic layers were washed

with saturated brine (500 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give perfluorophenyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (6.50 g, 11.70 mmol, 81.40%) as a yellow oil. LCMS (ESI) m/z = 513.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.08 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 5.93 - 5.77 (m, 1H), 4.22 - 4.17 (m, 1H), 4.16 - 4.13 (m, 1H), 4.13 - 4.11 (m, 1H), 4.10 - 4.06 (m, 1H), 1.34 - 1.31 (m, 3H), 1.30 - 1.27 (m, 3H).

[00785] *Step 2: Preparation of (fluoro(2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid*

[00786] To a solution of perfluorophenyl 5-((diethoxyphosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (6 g,12 mmol, 1 eq) in DCM (60 mL) was dropwise TMSI (9.3 g,47 mmol,4 eq) at 0 C, the mixture was stirred at 0 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a yellow oil. The oil was purified by reversed phase (TFA) to lyophilized to give (fluoro(2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (3.0 g, 6.6 mmol, 56% yield) as a white solid. LCMS (ESI) m/z = 457.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.17 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 5.97 - 5.78 (m, 1H).

Synthesis of (1-(2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)ethyl)phosphonic acid



[00787] *Step 1: Preparation of allyl 5-(1-(diethoxyphosphoryl)ethyl)benzo[b]thiophene-2-carboxylate*

[00788] To a solution of allyl 5-((diethoxyphosphoryl)methyl)benzo[b]thiophene-2-carboxylate (1.4 g, 3.80 mmol, 1 eq.) and CH_3I (809 mg, 5.7 mmol, 1.5 eq.) in THF (3 mL) was added LiHMDS (3.99 mmol, 1.05 eq.) dropwise at -78 °C for 10 min. The reaction mixture was stirred at room temperature for 2 h. After completion, the reaction mixture was

quenched with NH_4Cl (aq, sat.) and extracted with EtOAc (20 mL x 2). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to afford allyl 5-(1-(diethoxyphosphoryl)ethyl)benzo[b]thiophene-2-carboxylate (520 mg, 1.36 mmol, 36%) as a colorless oil. **LCMS (ESI)** *m/z* = 383 $[M+H]^+$.

[00789] *Step 2: Preparation of 5-(1-(diethoxyphosphoryl)ethyl)benzo[b]thiophene-2-carboxylic acid*

[00790] To a solution of allyl 5-(1-(diethoxyphosphoryl)ethyl)benzo[b]thiophene-2-carboxylate (120 mg, 0.31 mmol, 1.0 eq) in DCM (5 mL) were added $Pd(PPh_3)_4$ (36 mg, 31 μmol, 0.1 eq.) and pyrrolidine (22 mg, 0.31 mmol, 1.0 eq.). The mixture was purged and degassed with N_2 (three times), then stirred at 25 °C for 0.5 h. After completion, the mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give 5-(1-(diethoxyphosphoryl)ethyl)benzo[b]thiophene-2-carboxylic acid (95 mg, 0.28 mmol, 90%) as a colorless oil. LCMS (ESI): *m/z* = 343 $[M+H]^+$.

[00791] *Step 3: Preparation of perfluorophenyl 5-(1-(diethoxyphosphoryl)ethyl)benzo[b]thiophene-2-carboxylate*

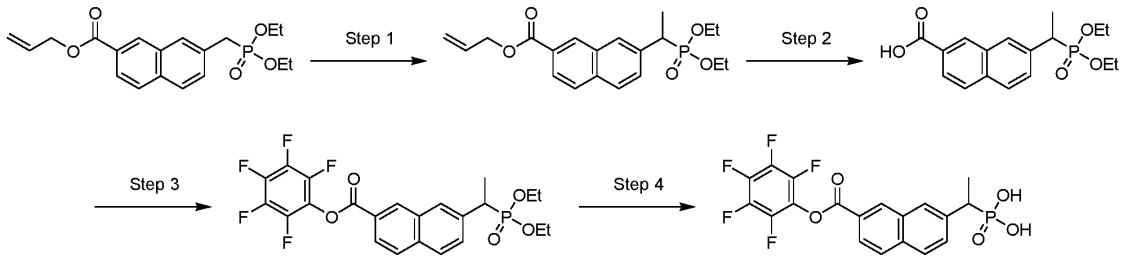
[00792] Oxalyl chloride (127 mg, 1.05 mmol, 1.5 eq.) was added dropwise to the solution of 5-(1-(diethoxyphosphoryl)ethyl)benzo[b]thiophene-2-carboxylic acid (240 mg, 0.70 mmol, 1.0 eq.) in dry DCM (10 mL) and DMF (1 drop) at 0 °C. The reaction mixture was stirred at room temperature for an additional 2 h. After completion, the excess oxalyl chloride and solvent were removed under reduced pressure. The residue was re-dissolved in anhydrous DCM (10 mL), then added to a mixture of PFPOH (193 mg, 1.05 mmol, 1.5 eq.) and TEA (212 mg, 2.1 mmol, 3 eq.) in anhydrous DCM (10 mL). The reaction was stirred for an additional 0.5 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford perfluorophenyl 5-(1-(diethoxyphosphoryl)ethyl)benzo[b]thiophene-2-carboxylate (320 mg, 0.63 mmol, 90%) as a yellow solid. LCMS (ESI): *m/z* = 509 $[M+H]^+$.

[00793] *Step 1: Preparation of (1-(2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)ethyl)phosphonic acid*

[00794] To a solution perfluorophenyl 5-(1-(diethoxyphosphoryl)ethyl)benzo[b]thiophene-2-carboxylate (320 mg, 0.63 mmol, 1 eq.) in DCM (5 mL) was added TMSBr (964 mg, 6.3 mmol, 10 eq.). The mixture was stirred at room temperature for 2 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford (1-(2-

((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)ethyl)phosphonic acid (230 mg, 0.51 mmol, 81%) as a white solid. LCMS (ESI): *m/z* = 453 $[M+H]^+$.

Synthesis of (1-(7-((perfluorophenoxy)carbonyl)naphthalen-2-yl)ethyl)phosphonic acid



[00795] *Step 1: Preparation of allyl 7-(1-(diethoxyphosphoryl)ethyl)-2-naphthoate*

[00796] To a solution of allyl 7-((diethoxyphosphoryl)methyl)-2-naphthoate (2.0 g, 5.52 mmol, 1 eq.) and CH_3I (1.18 g, 8.28 mmol, 1.5 eq.) in THF (3 mL) was added LiHMDS (5.80 mmol, 1.05 eq.) dropwise at -78 °C for 10 min. The reaction mixture was stirred at room temperature for 2 h. After completion, the reaction mixture was quenched with NH_4Cl (aq, sat.) and extracted with EtOAc (20 mL x 2). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to afford allyl 7-(1-(diethoxyphosphoryl)ethyl)-2-naphthoate (1.05 g, 2.79 mmol, 51%) as a colorless oil. LCMS (ESI) *m/z* = 377 $[M+H]^+$.

[00797] *Step 2: Preparation of 7-(1-(diethoxyphosphoryl)ethyl)-2-naphthoic acid*

[00798] To a solution of allyl 7-(1-(diethoxyphosphoryl)ethyl)-2-naphthoate (300 mg, 0.80 mmol, 1.0 eq) in DCM (5 mL) were added $Pd(PPh_3)_4$ (92 mg, 80 μmol, 0.1 eq.) and pyrrolidine (57 mg, 0.80 mmol, 1.0 eq.). The mixture was purged and degassed with N_2 (three times), then stirred at 25 °C for 0.5 h. After completion, the mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give 7-(1-(diethoxyphosphoryl)ethyl)-2-naphthoic acid (240 mg, 0.71 mmol, 89%) as a colorless oil. LCMS (ESI): *m/z* = 337 $[M+H]^+$.

[00799] *Step 3: Preparation of perfluorophenyl 7-(1-(diethoxyphosphoryl)ethyl)-2-naphthoate*

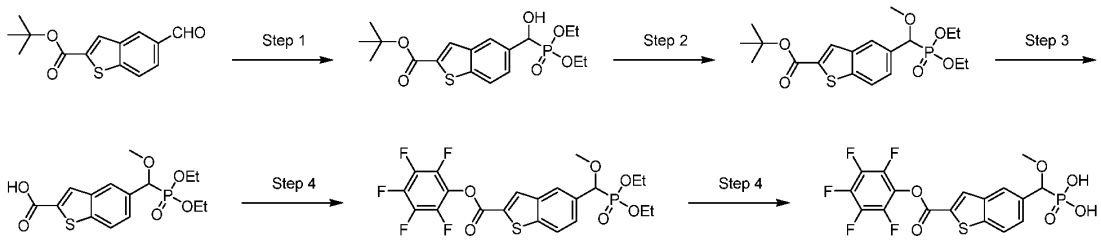
[00800] Oxalyl chloride (134 mg, 1.07 mmol, 1.5 eq.) was added dropwise to the solution of 7-(1-(diethoxyphosphoryl)ethyl)-2-naphthoic acid (240 mg, 0.71 mmol, 1.0 eq.) in dry DCM (10 mL) and DMF (1 drop) at 0 °C. The reaction mixture was stirred at room temperature for an additional 2 h. After completion, the excess oxalyl chloride and solvent

were removed under reduced pressure. The residue was re-dissolved in anhydrous DCM (10 mL), then added to a mixture of PFPOH (197 mg, 1.07 mmol, 1.5 eq.) and TEA (212 mg, 2.1 mmol, 3 eq.) in anhydrous DCM (10 mL). The reaction was stirred for an additional 0.5 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford perfluorophenyl 7-(1-(diethoxyphosphoryl)ethyl)-2-naphthoate (320 mg, 0.64 mmol, 90%) as a yellow solid. LCMS (ESI): *m/z* = 503 $[M+H]^+$.

[00801] *Step 4: Preparation of (1-(7-((perfluorophenoxy)carbonyl)naphthalen-2-yl)ethyl)phosphonic acid*

[00802] To a solution perfluorophenyl 7-(1-(diethoxyphosphoryl)ethyl)-2-naphthoate (320 mg, 0.64 mmol, 1 eq.) in DCM (5 mL) was added TMSBr (979 mg, 6.4 mmol, 10 eq.). The mixture was stirred at room temperature for 2 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford (1-(7-((perfluorophenoxy)carbonyl)naphthalen-2-yl)ethyl)phosphonic acid (220 mg, 0.49 mmol, 77%) as a white solid. LCMS (ESI): *m/z* = 447 $[M+H]^+$.

Synthesis of (methoxy(2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid



[00803] *Step 1: Preparation of tert-butyl 5-((diethoxyphosphoryl)(hydroxy)methyl)benzo[b]thiophene-2-carboxylate*

[00804] To a solution of tert-butyl 5-formylbenzo[b]thiophene-2-carboxylate (50 mg, 190 µmol, 1 eq.) and diethyl phosphonate (28.8 mg, 209 µmol, 1.1 eq.) in DCM (15 mL) was added DBU (2.89 mg, 19.0 µmol, 0.1 eq.). The reaction solution was stirred at room temperature for 18 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford tert-butyl 5-((diethoxyphosphoryl)(hydroxy)methyl)benzo[b]thiophene-2-carboxylate (60.0 mg, 149 µmol, 79%) as a colorless oil. LCMS (ESI) *m/z* = 401.2 $[M+H]^+$.

[00805] *Step 2: Preparation of tert-butyl 5-((diethoxyphosphoryl)(methoxy)methyl)benzo[b]thiophene-2-carboxylate*

[00806] To a solution of tert-butyl 5-((diethoxyphosphoryl)(hydroxy)methyl)benzo[b]thiophene-2-carboxylate (150 mg, 374 μmol, 1 eq.) and CH_3I (79.6 mg, 561 μmol, 1.5 eq.) in DMF (3 mL) was added LiHMDS (65.5 mg, 392 μmol, 1.05 eq.) dropwise at -18 °C for 10 min. The reaction mixture was stirred at room temperature for 2h. After completion, the reaction mixture was quenched with NH_4Cl(aq, sat.) and extracted with EtOAc (20 mL x 2). The organic layers were combined and washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to afford tert-butyl 5-((diethoxyphosphoryl)(methoxy)methyl)benzo[b]thiophene-2-carboxylate (40.0 mg, 96.5 μmol, 26%) as a colorless oil. LCMS (ESI) *m/z* = 415.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 16.2 Hz, 2H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 1H), 4.64 (d, *J* = 15.4 Hz, 1H), 4.18- 3.88 (m, 4H), 3.43 (s, 3H), 1.63 (s, 9H), 1.32-1.19 (m, 6H).

[00807] *Step 3: Preparation of 5-((diethoxyphosphoryl)(methoxy)methyl)benzo[b]thiophene-2-carboxylic acid*

[00808] To a solution of tert-butyl 5-((diethoxyphosphoryl)(methoxy)methyl)benzo[b]thiophene-2-carboxylate (40 mg, 96.5 μmol, 1 eq.) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at room temperature for 2 h. After completion, the reaction mixture was concentrated under reduced pressure to afford 5-((diethoxyphosphoryl)(methoxy)methyl)benzo[b]thiophene-2-carboxylic acid (30 mg, quant.) as a colorless oil, which was used in next step directly without further purification. LCMS (ESI) *m/z* = 359 $[M+H]^+$.

[00809] *Step 4: Preparation of perfluorophenyl 5-((diethoxyphosphoryl)(methoxy)methyl)benzo[b]thiophene-2-carboxylate*

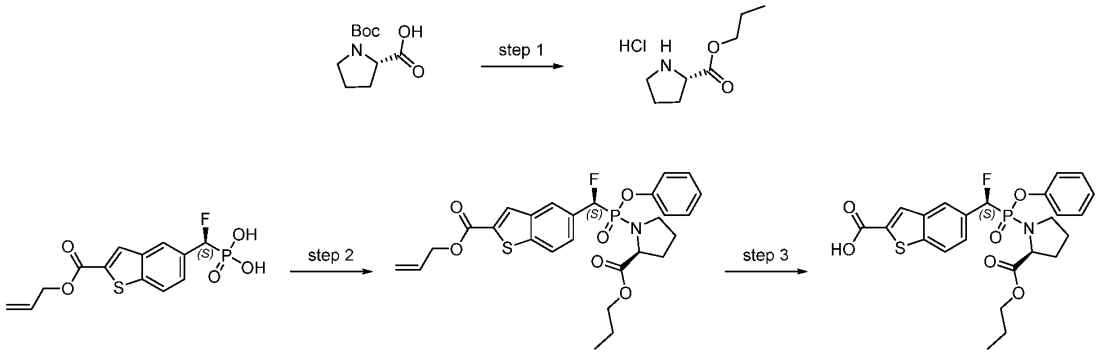
[00810] Oxalyl chloride (15.8 mg, 125 μmol, 1.5 eq.) was added dropwise to the solution of 5-((diethoxyphosphoryl)(methoxy)methyl)benzo[b]thiophene-2-carboxylic acid (30 mg, 83.7 μmol, 1.0 eq.) in dry DCM (10 mL) and DMF (2 drops) at 0 °C. The reaction mixture was stirred at room temperature for an additional 2 h. After completion, the excess oxalyl chloride and solvent were removed under reduced pressure. The residue was re-dissolved in anhydrous DCM (10 mL), then added to a mixture of PFPOH (23.0 mg, 125 μmol, 1.5 eq.) and TEA (25.3 mg, 251 μmol, 3 eq.) in anhydrous DCM (10 mL). The reaction was stirred for an additional 0.5 h. After completion, the reaction mixture was concentrated under

reduced pressure. The residue was purified by flash column chromatography on silica gel to afford perfluorophenyl 5-((diethoxyphosphoryl)(methoxy)methyl)benzo[b]thiophene-2-carboxylate (38.0 mg, 72.4 µmol, 87%) as a yellow solid. LCMS (ESI): *m/z* = 525.0 $[M+H]^+$.

[00811] *Step 5: Preparation of (methoxy(2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid*

[00812] To a solution perfluorophenyl 5-((diethoxyphosphoryl)(methoxy)methyl)benzo[b]thiophene-2-carboxylate (38.0 mg, 72.4 µmol, 1 eq.) in DCM (1 mL) was added TMSBr (110 mg, 0.72 mmol, 10 eq.). The mixture was stirred at room temperature for 2 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford (methoxy(2-((perfluorophenoxy)carbonyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (17 mg, 36 µmol, 50%) as a white solid. LCMS (ESI): *m/z* = 469 $[M+H]^+$.

Synthesis of 5-((1S)-fluoro(phenoxy((S)-2-(propoxycarbonyl)pyrrolidin-1-yl)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid

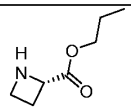


[00813] *Step 1: Preparation of propyl L-prolinate hydrochloride*

[00814] Thionyl chloride (2.01 mL, 27.8 mmol, 3 eq) was added dropwise to a solution of (tert-butoxycarbonyl)-L-proline (2.00 g, 9.29 mmol, 1 eq) in propan-1-ol (20 mL, 332 µmol, eq) at 0°C. The mixture was allowed to warm to ambient temperature and then heated at 80 °C overnight. The reaction mixture was concentrated under reduced pressure to give crude propyl L-prolinate hydrochloride (1.85 g, 103%) as a brown oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.36 - 4.33 (m, 1H), 4.18 - 4.07 (m, 2H), 3.26 - 3.14 (m, 2H), 2.32 - 2.22 (m, 1H), 2.01 - 1.85 (m, 3H), 1.66 - 1.59 (m, 2H), 0.92 - 0.89 (m, 3H).

[00815] The following intermediates in **Table 72** were prepared using the method described above in step 1 for the preparation of propyl L-prolinate hydrochloride and utilizing the appropriate starting materials and modifications.

Table 72

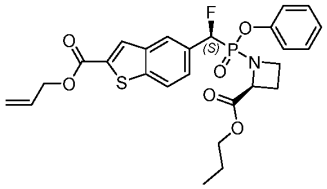
Name	Structure	LCMS
propyl (S)-azetidine-2-carboxylate (HCl salt)		144.2 $[M+H]^+$

[00816] *Step 2: Preparation of propyl (((S)-(2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-prolinate*

[00817] To a solution of (S)-((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid (500 mg, 1.51 mmol, 1 eq) and DMF (2 drops) in DCM (15 mL) was added dropwise oxalyl chloride (1.02 mL, 12.0 mmol, 8 eq). The reaction mixture was stirred 2 h at room temperature under N_2. The reaction mixture was concentrated under reduced pressure and dried completely under high vacuum for 30 min. to give a yellow solid. The yellow solid was diluted in DCM (15 mL, dried on Na_2SO_4) and cooled down to 0°C. A solution of phenol (134 mg, 1.43 mmol, 0.95 eq) and triethylamine (1.26 mL, 9.06 mmol, 6.0 eq) in DCM (5 mL, dried on Na_2SO_4) was slowly added onto the solution. The reaction mixture was stirred at 0°C for 2 min. and then warmed up to room temperature and stirred for 18 h. A solution of propyl L-prolinate hydrochloride (584 mg, 3.02 mmol, 2 eq) in DCM (5 mL, dried on Na_2SO_4) was slowly added onto the orange solution. The reaction mixture was stirred at room temperature for 4 h. Water (1 mL) was added. The solvent was removed under reduced pressure. The crude residue was purified by reverse phase chromatography on a 150 g C_{18} cartridge eluting with 5-100% MeCN in water. The pure fractions were then concentrated under reduced pressure to give propyl (((S)-(2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-prolinate (320 mg, 38.8%) as a yellow oil. LCMS (ESI): m/z = 546.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 - 8.04 (m, 2H), 7.94 - 7.86 (m, 1H), 7.79 - 7.62 (m, 1H), 7.34 - 7.28 (m, 2H), 7.24 - 7.20 (m, 1H), 7.19 - 7.03 (m, 2H), 6.10 - 6.00 (m, 1H), 5.49 - 5.31 (m, 2H), 4.89 - 4.84 (m, 2H), 4.57 - 4.22 (m, 1H), 4.15 - 3.96 (m, 2H), 3.66 - 3.21 (m, 1H), 3.13 - 2.67 (m, 1H), 2.18 - 2.04 (m, 1H), 1.97 - 1.86 (m, 1H), 1.83 - 1.46 (m, 5H), 1.00 - 0.86 (m, 3H).

[00818] The following intermediates in **Table 73** were prepared using the method described above in step 2 for the preparation of propyl (((S)-(2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-prolinate and utilizing the appropriate starting materials and modifications.

Table 73

Name	Structure	LCMS
propyl (2S)-1-(((S)-(2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)azetidine-2-carboxylate		532.2 $[M+H]^+$

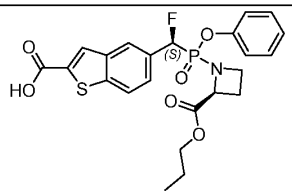
[00819] *Step 3: Preparation of 5-((1S)-fluoro(phenoxy((S)-2-(propoxycarbonyl)pyrrolidin-1-yl)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid*

[00820] To a solution of propyl (((S)-(2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-prolinate (320 mg, 586 µmol, 1 eq) in THF (6 mL) were added morpholine (251 µL, 2.92 mmol, 5 eq) and $Pd(PPh_3)_4$ (13.5 mg, 11.7 µmol, 0.02 eq). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated to a volume of 2 mL under N_2. The crude product was purified by reverse phase chromatography on a 100 g C_{18} cartridge eluting with 5-80% MeCN in water (with 0.1% formic acid). The combined fractions were concentrated under reduced pressure and then freeze dried to give 5-((1S)-fluoro(phenoxy((S)-2-(propoxycarbonyl)pyrrolidin-1-yl)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (172 mg) as a white solid which was re-purified by reverse phase chromatography on a 275 g C_{18} cartridge eluting with 5-80% MeCN in water (with 0.1% formic acid). The combined fractions were concentrated under reduced pressure and then freeze dried to give 5-((1S)-fluoro(phenoxy((S)-2-(propoxycarbonyl)pyrrolidin-1-yl)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (75.0 mg, 25.3%) as a white solid. LCMS (ESI): m/z = 506.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.58 (br. s., 1H), 8.21 - 8.10 (m, 2H), 7.73 - 7.63 (m, 1H), 7.41 - 7.31 (m, 3H), 7.30 - 7.16 (m, 2H), 7.12 - 7.08 (m, 1H), 6.86 - 6.28 (m, 1H), 4.43 - 3.41 (m, 4H), 3.19 - 2.82 (m, 1H), 2.10 - 1.61 (m, 4H), 1.57 - 1.45 (m, 2H), 0.92 - 0.72 (m, 3H).

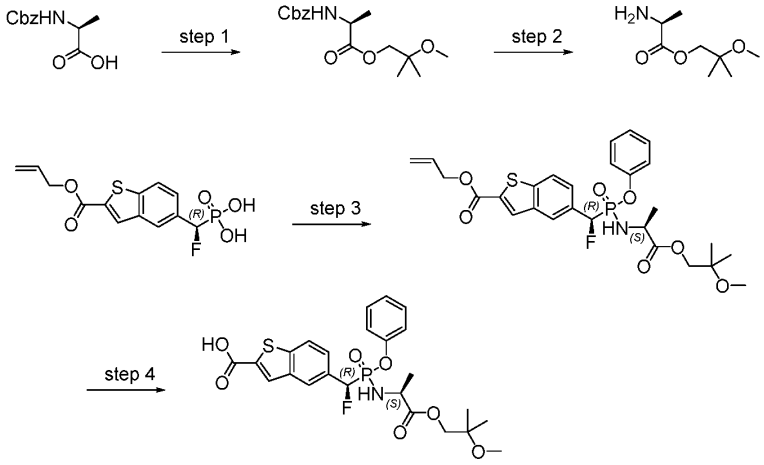
[00821] The following intermediates in **Table 74** were prepared using the method described above in step 3 for the preparation of 5-((1S)-fluoro(phenoxy((S)-2-(propoxycarbonyl)pyrrolidin-1-yl)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid and utilizing the appropriate starting materials and modifications.

Table 74

Name	Structure	LCMS

5-((1S)-fluoro(phenoxy((S)-2-(propoxycarbonyl)azetidin-1-yl)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		492.2 $[M+H]^+$

Synthesis of 5-((1R)-fluoro((((S)-1-(2-methoxy-2-methylpropoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid

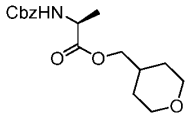
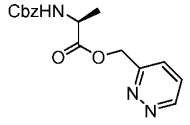
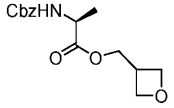
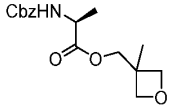


[00822] *Step 1: Preparation of 2-methoxy-2-methylpropyl ((benzyloxy)carbonyl)-L-alaninate*

[00823] To a solution of ((benzyloxy)carbonyl)-L-alanine (1.64 g, 7.34 mmol, 1 eq.) and 2-methoxy-2-methylpropan-1-ol (916 mg, 8.80 mmol, 1.2 eq.) in ACN (20 ml) were added EDCI (1.68 g, 8.80 mmol, 1.2 eq.) and DMAP (1.07 g, 8.80 mmol, 1.2 eq.). The mixture was stirred at 25 °C for 16 h. After completion, the reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 2-methoxy-2-methylpropyl ((benzyloxy)carbonyl)-L-alaninate (2, 1.63 g, 5.27 mmol, 72%) as a colorless oil. LCMS (ESI): *m/z* = 310 $[M+H]^+$.

[00824] The following intermediates in **Table 75** were prepared using the method described above in step 1 for the preparation of 2-methoxy-2-methylpropyl ((benzyloxy)carbonyl)-L-alaninate and utilizing the appropriate starting materials and modifications.

Table 75

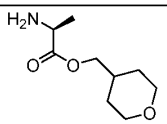
Name	Structure	LCMS
(tetrahydro-2H-pyran-4-yl)methyl ((benzyloxy)carbonyl)-L-alaninate		322 $[M+H]^+$
pyridazin-3-ylmethyl ((benzyloxy)carbonyl)-L-alaninate		282 $[M+H]^+$
oxetan-3-ylmethyl ((benzyloxy)carbonyl)-L-alaninate		294 $[M+H]^+$
(3-methyloxetan-3-yl)methyl ((benzyloxy)carbonyl)-L-alaninate		308 $[M+H]^+$

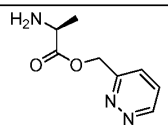
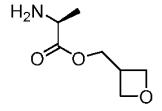
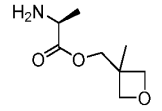
[00825] *Step 2: Preparation of 2-methoxy-2-methylpropyl L-alaninate*

[00826] To a solution of 2-methoxy-2-methylpropyl ((benzyloxy)carbonyl)-L-alaninate (1.5 g, 4.84 mmol, 1.0 eq.) in EtOAc (15 ml) was added Pd/C (150 mg) under nitrogen. The suspension was degassed under vacuum and purged with H_2 several times. The resulting mixture was stirred at room temperature for 14 h. After completion, the suspension was filtered through a pad of Celite®, the filter cake was washed with MeOH (20 mL). The combined filtrates were concentrated to dryness to give 2-methoxy-2-methylpropyl L-alaninate (640 mg, 3.65 mmol, 75%) as a colorless oil. LCMS (ESI): *m/z* = 176 $[M+H]^+$.

[00827] The following intermediates in **Table 76** were prepared using the method described above in step 2 for the preparation of 2-methoxy-2-methylpropyl ((benzyloxy)carbonyl)-L-alaninate and utilizing the appropriate starting materials and modifications.

Table 76

Name	Structure	LCMS
(tetrahydro-2H-pyran-4-yl)methyl L-alaninate		188 $[M+H]^+$

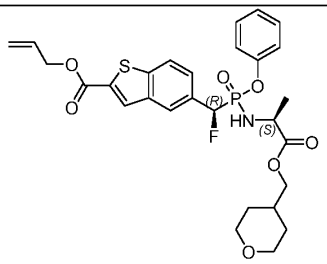
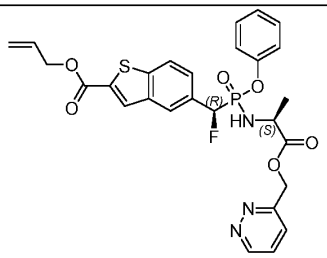
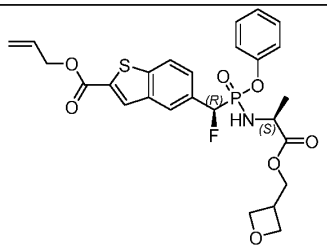
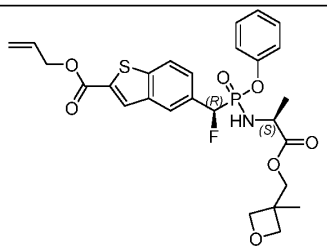
pyridazin-3-ylmethyl L-alaninate		182 $[M+H]^+$
oxetan-3-ylmethyl L-alaninate		160 $[M+H]^+$
(3-methyloxetan-3-yl)methyl L-alaninate		147.1 $[M+H]^+$

[00828] *Step 3: Preparation of allyl 5-((1R)-fluoro((((S)-1-(2-methoxy-2-methylpropoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00829] Oxalyl chloride (576 mg, 4.54 mmol, 5 eq.) was added dropwise to the solution of (R)-((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid (300 mg, 0.91 mmol, 1 eq.) in dry DCM (10 mL) and DMF (1 drop) at 25 °C. The reaction mixture was stirred at 40 °C for an additional 0.5 hr. The reaction was monitored by pipetting out a small amount of crude sample and quenching it with MeOH to ensure bis-Cl phosphoryl chloride had been formed completely (bis-methoxy phosphonate was observed by LCMS). After completion, the excess oxalyl chloride and solvent were removed under reduced pressure. The residue was re-dissolved in anhydrous DCM (10 mL), then added to a mixture of phenol (88.8 mg, 0.94mmol, 1.05 eq.) and TEA (908 mg, 8.98 mmol, 10.0 eq.) in anhydrous DCM (5 mL) at 0 °C. The reaction was stirred for 0.5 h. Then 2-methoxy-2-methylpropyl L-alaninate (313 mg, 1.79 mmol, 2 eq.) was added at 0 °C and the resulting mixture was stirred at 20 °C for 1 h under N_2. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give allyl 5-((1R)-fluoro((((S)-1-(2-methoxy-2-methylpropoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (45.0 mg, 80 μmol, 9%) as a yellow solid. LCMS (ESI): *m/z* = 564.0 $[M+H]^+$.

[00830] The following intermediates in **Table 77** were prepared using the method described above in step 3 for the preparation of allyl 5-((1R)-fluoro((((S)-1-(2-methoxy-2-methylpropoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate and utilizing the appropriate starting materials and modifications.

Table 77

Name	Structure	LCMS
allyl 5-((1R)-fluoro((((S)-1-oxo-1-((tetrahydro-2H-pyran-4-yl)methoxy)propan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		576 $[M+H]^+$
allyl 5-((1R)-fluoro((((S)-1-oxo-1-(pyridazin-3-ylmethoxy)propan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		570 $[M+H]^+$
allyl 5-((1R)-fluoro((((S)-1-(oxetan-3-ylmethoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		548 $[M+H]^+$
allyl 5-((1R)-fluoro((((S)-1-((3-methyloxetan-3-yl)methoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		562 $[M+H]^+$

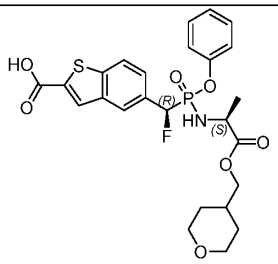
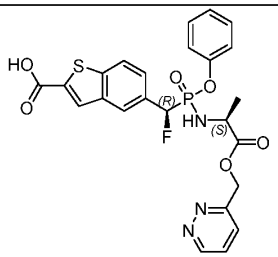
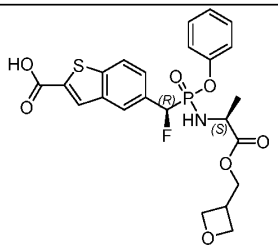
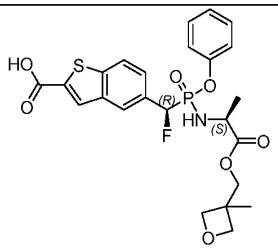
[00831] *Step 4: Preparation of 5-((1R)-fluoro((((S)-1-(2-methoxy-2-methylpropoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid*

[00832] To a solution of allyl 5-((1R)-fluoro((((S)-1-(2-methoxy-2-methylpropoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (45.0 mg, 80 µmol, 1.0 eq) in DCM (6 mL) were added $Pd(PPh_3)_4$ (5 mg, 8 µmol, 0.1 eq.) and pyrrolidine (6 mg, 80 µmol, 1.0 eq.). The mixture was purged and degassed with N_2 (three times), then stirred at 25 °C for 1 hr. After completion, the mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give

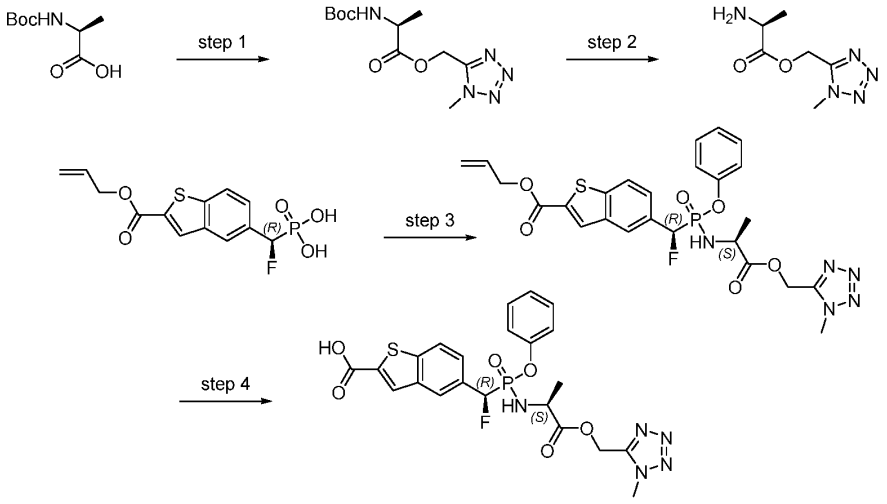
5-((1R)-fluoro((((S)-1-(2-methoxy-2-methylpropoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (40 mg, 76 µmol, 95%) as a colorless oil. LCMS (ESI): *m/z* = 524 $[M+H]^+$.

[00833] The following intermediates in **Table 78** were prepared using the method described above in step 4 for the preparation of 5-((1R)-fluoro((((S)-1-(2-methoxy-2-methylpropoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid and

Table 78

Name	Structure	LCMS
5-((1R)-fluoro((((S)-1-oxo-1-((tetrahydro-2H-pyran-4-yl)methoxy)propan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		536 $[M+H]^+$
5-((1R)-fluoro((((S)-1-oxo-1-(pyridazin-3-ylmethoxy)propan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		530 $[M+H]^+$
5-((1R)-fluoro((((S)-1-(oxetan-3-ylmethoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		508 $[M+H]^+$
5-((1R)-fluoro((((S)-1-((3-methyloxetan-3-yl)methoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		522 $[M+H]^+$

Synthesis of 5-((1R)-fluoro((((S)-1-((1-methyl-1H-tetrazol-5-yl)methoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid



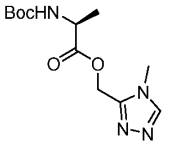
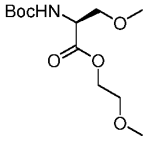
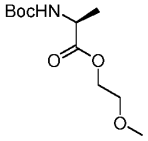
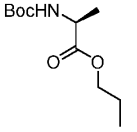
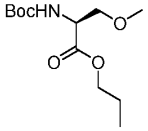
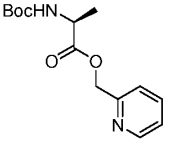
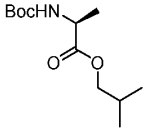
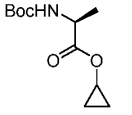
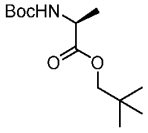
[00834] *Step 1: Preparation of (1-methyl-1H-tetrazol-5-yl)methyl (tert-butoxycarbonyl)-L-alaninate*

[00835] To a solution of (tert-butoxycarbonyl)-L-alanine (1 g, 5.28 mmol, 1 eq.) and (1-methyl-1H-1,2,3,4-tetrazol-5-yl)methanol (903 mg, 7.92 mmol, 1.5 eq.) in DCM (15 ml) were added T_3P (50%) (5.02 g, 15.8 mmol, 3 eq.), DMAP (32.2 mg, 264 µmol, 0.05 eq.) and 4-methylmorpholine (1.59 g, 15.8 mmol, 3 eq.). The mixture was stirred at room temperature for 2 h. After completion, the reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford (1-methyl-1H-tetrazol-5-yl)methyl (tert-butoxycarbonyl)-L-alaninate (900 mg, 3.15 mmol, 60%) as a colorless oil. LCMS (ESI): m/z = 286 $[M+H]^+$.

[00836] The following intermediates in **Table 79** were prepared using the method described above in step 1 for the preparation of (1-methyl-1H-tetrazol-5-yl)methyl (tert-butoxycarbonyl)-L-alaninate and utilizing the appropriate starting materials and modifications.

Table 79

Name	Structure	LCMS	NMR

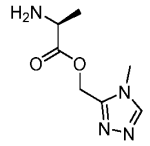
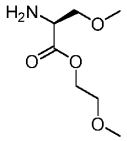
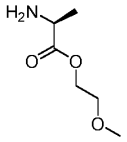
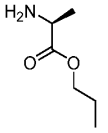
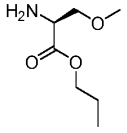
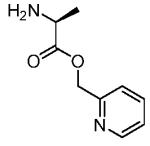
(4-methyl-4H-1,2,4-triazol-3-yl)methyl (tert-butoxycarbonyl)-L-alaninate		285 $[M+H]^+$	
2-methoxyethyl N-(tert-butoxycarbonyl)-O-methyl-L-serinate		278 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19-7.07 (m, 1H), 4.28-4.10 (m, 3H), 3.61-3.46 (m, 4H), 3.28-3.19 (m, 6H), 1.38 (s, 9H).
2-methoxyethyl (tert-butoxycarbonyl)-L-alaninate		248 $[M+H]^+$	
propyl (tert-butoxycarbonyl)-L-alaninate			
propyl N-(tert-butoxycarbonyl)-O-methyl-L-serinate		262 $[M+H]^+$	
pyridin-2-ylmethyl (tert-butoxycarbonyl)-L-alaninate		281 $[M+H]^+$	
isobutyl (tert-butoxycarbonyl)-L-alaninate		246 $[M+H]^+$	
cyclopropyl (tert-butoxycarbonyl)-L-alaninate		230 $[M+H]^+$.	
neopentyl (tert-butoxycarbonyl)-L-alaninate		260 $[M+H]^+$	

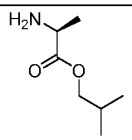
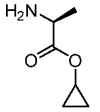
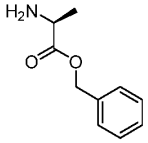
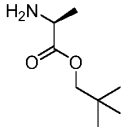
[00837] *Step 2: Preparation of (1-methyl-1H-tetrazol-5-yl)methyl L-alaninate*

[00838] A solution of (1-methyl-1H-tetrazol-5-yl)methyl (tert-butoxycarbonyl)-L-alaninate (600 mg, 2.10 mmol, 1 eq) in HCl / EA (10 mL) was stirred at room temperature for 1 hr. After completion, the reaction mixture was concentrated under reduced pressure to give crude (1-methyl-1H-tetrazol-5-yl)methyl L-alaninate (390 mg, quant.)(HCl salt) as a white solid, which was used in next step directly without further purification. LCMS (ESI): *m/z* = 186 $[M+H]^+$.

[00839] The following intermediates in **Table 80** were prepared using the method described above in step 2 for the preparation of (1-methyl-1H-tetrazol-5-yl)methyl L-alaninate and utilizing the appropriate starting materials and modifications.

Table 80

Name	Structure	LCMS	NMR
(4-methyl-4H-1,2,4-triazol-3-yl)methyl L-alaninate (HCl Salt)		185 $[M+H]^+$	
2-methoxyethyl O-methyl-L-serinate (HCl salt)			^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (s, 2H), 4.29-4.22 (m, 2H), 3.87-3.75 (m, 2H), 3.58-3.56 (m, 3H), 3.31-3.25 (m, 6H)
2-methoxyethyl L-alaninate (HCl salt)		148 $[M+H]^+$	
propyl L-alaninate (HCl salt)			
propyl O-methyl-L-serinate (HCl salt)		162 $[M+H]^+$	
pyridin-2-ylmethyl L-alaninate (HCl salt)		181 $[M+H]^+$	

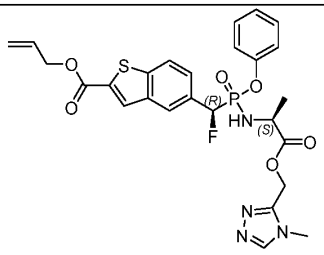
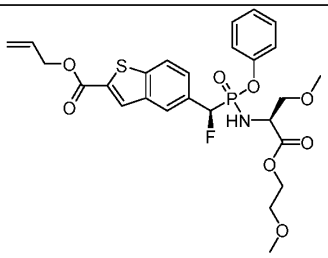
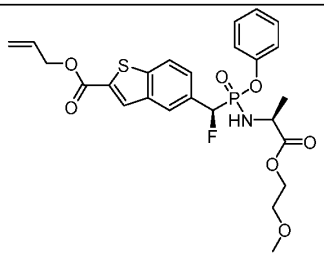
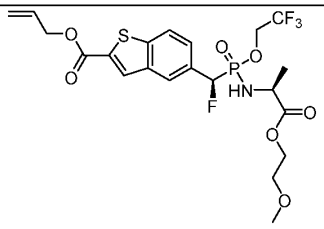
isobutyl L-alaninate (HCl salt)		146 $[M+H]^+$	
cyclopropyl L-alaninate (HCl salt)		130 $[M+H]^+$	
benzyl L-alaninate (HCl salt)		180 $[M+H]^+$	
neopentyl L-alaninate (HCl salt)		160 $[M+H]^+$	

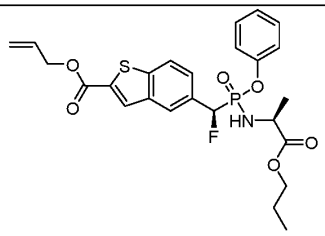
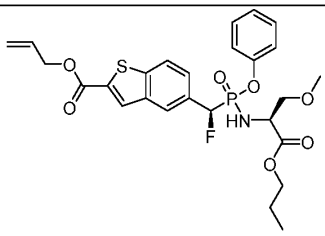
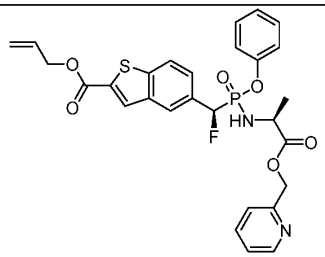
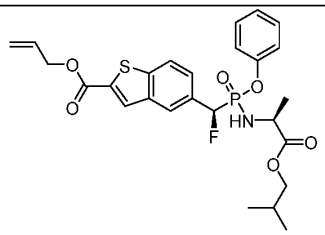
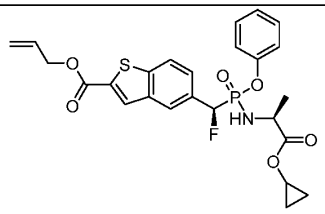
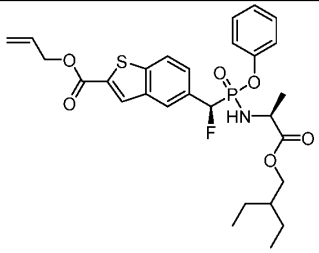
[00840] *Step 3: Preparation of allyl 5-((1R)-fluoro((((S)-1-((1-methyl-1H-tetrazol-5-yl)methoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

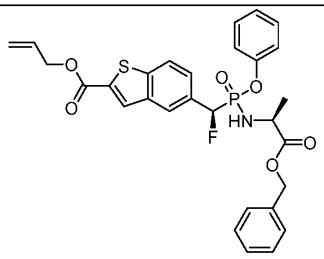
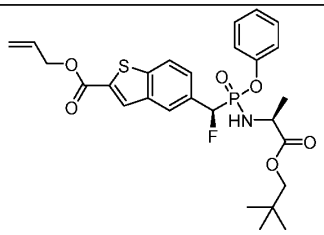
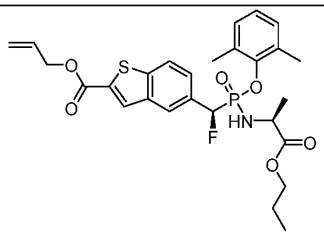
[00841] Oxalyl chloride (1.05 g, 8.35 mmol, 5 eq.) was added dropwise to a solution of (R)-((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid (550 mg, 1.67 mmol, 1 eq.) in dry DCM (10 mL) and DMF (1 drop) at 25 °C. The reaction mixture was stirred at 40 °C for an additional 0.5 hr. The reaction was monitored by pipetting out a small amount of crude sample and quenching it with MeOH to ensure bis-Cl phosphoryl chloride had been formed completely (bis-methoxy phosphonate was observed by LCMS). After completion, the excess oxalyl chloride and solvent were removed under reduced pressure. The residue was re-dissolved in anhydrous DCM (10 mL), then added to a mixture of phenol (146 mg, 1.56 mmol, 1.05 eq.) and TEA (752 mg, 7.45 mmol, 5 eq.) in anhydrous DCM (5 mL) at 0 °C. The reaction was stirred for 0.5 h. Then (1-methyl-1H-tetrazol-5-yl)methyl L-alaninate (3, 551 mg, 2.98 mmol, 2 eq.) was added at 0 °C and the resulting mixture was stirred at 20 °C for 1 h under N_2. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give allyl 5-((1R)-fluoro((((S)-1-((1-methyl-1H-tetrazol-5-yl)methoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (90.0 mg, 156 µmol, 11%) as a yellow oil. LCMS (ESI): *m/z* = 574 $[M+H]^+$.

[00842] The following intermediates in **Table 81** were prepared using the method described above in step 3 for the preparation of allyl 5-((1R)-fluoro((((S)-1-((1-methyl-1H-tetrazol-5-yl)methoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate and utilizing the appropriate starting materials and modifications.

Table 81

Name	Structure	LCMS
allyl 5-((1R)-fluoro((((S)-1-((4-methyl-4H-1,2,4-triazol-3-yl)methoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		573 $[M+H]^+$
allyl 5-((1R)-fluoro((((S)-3-methoxy-1-(2-methoxyethoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		566 $[M+H]^+$
allyl 5-((1R)-fluoro((((S)-1-(2-methoxyethoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		536 $[M+H]^+$
allyl 5-((1R)-fluoro((((S)-1-(2-methoxyethoxy)-1-oxopropan-2-yl)amino)(2,2,2-trifluoroethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		542 $[M+H]^+$

allyl 5-((1R)-fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		520 $[M+H]^+$
allyl 5-((1R)-fluoro((((S)-3-methoxy-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		550 $[M+H]^+$
allyl 5-((1R)-fluoro((((S)-1-oxo-1-(pyridin-2-ylmethoxy)propan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		569 $[M+H]^+$
allyl 5-((1R)-fluoro((((S)-1-isobutoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		534 $[M+H]^+$
allyl 5-((1R)-((((S)-1-cyclopropoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate		518 $[M+H]^+$
allyl 5-((1R)-((((S)-1-(2-ethylbutoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate		562 $[M+H]^+$

allyl 5-((1R)-((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate		568 $[M+H]^+$
allyl 5-((1R)-fluoro((((S)-1-(neopentyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate		548 $[M+H]^+$
allyl 5-((1R)-((2,6-dimethylphenoxy)(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate		548 $[M+H]^+$

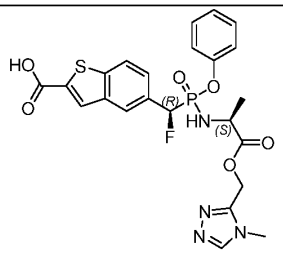
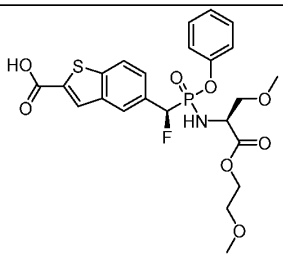
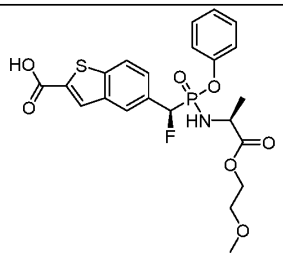
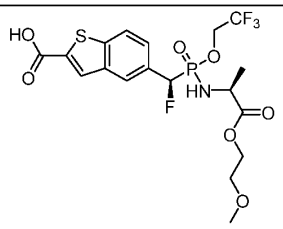
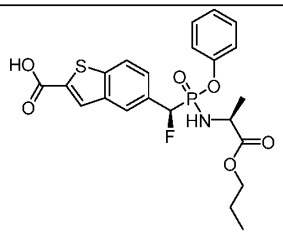
[00843] *Step 4: Preparation of 5-((1R)-fluoro((((S)-1-((1-methyl-1H-tetrazol-5-yl)methoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid*

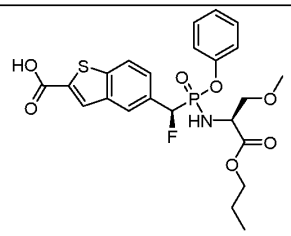
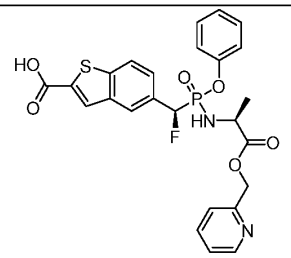
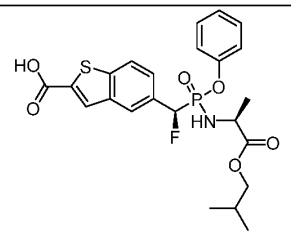
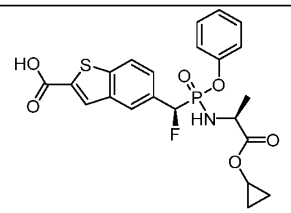
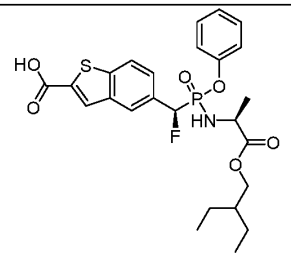
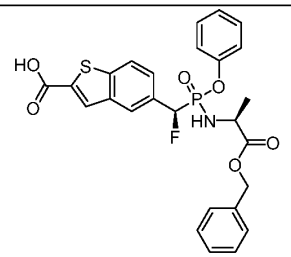
[00844] To a solution of allyl 5-((1R)-fluoro((((S)-1-((1-methyl-1H-tetrazol-5-yl)methoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (90 mg, 156 µmol, 1 eq.) in DCM (5 mL) were added $Pd(PPh_3)_4$ (9.0 mg, 7.8 µmol, 0.05 eq.) and pyrrolidine (11.0 mg, 156 µmol, 1.0 eq.). The mixture was purged and degassed with N_2 (three times), then stirred at 25 °C for 1 hr. After completion, the mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give 5-((1R)-fluoro((((S)-1-((1-methyl-1H-tetrazol-5-yl)methoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (50.0 mg, 93.7 µmol, 60%) as a yellow oil. LCMS (ESI): *m/z* = 534 $[M+H]^+$.

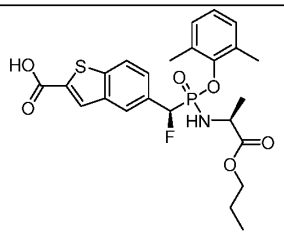
[00845] The following intermediates in **Table 82** were prepared using the method described above in step 4 for the preparation of 5-((1R)-fluoro((((S)-1-((1-methyl-1H-tetrazol-5-yl)methoxy)-1-oxopropan-2-

yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid and utilizing the appropriate starting materials and modifications.

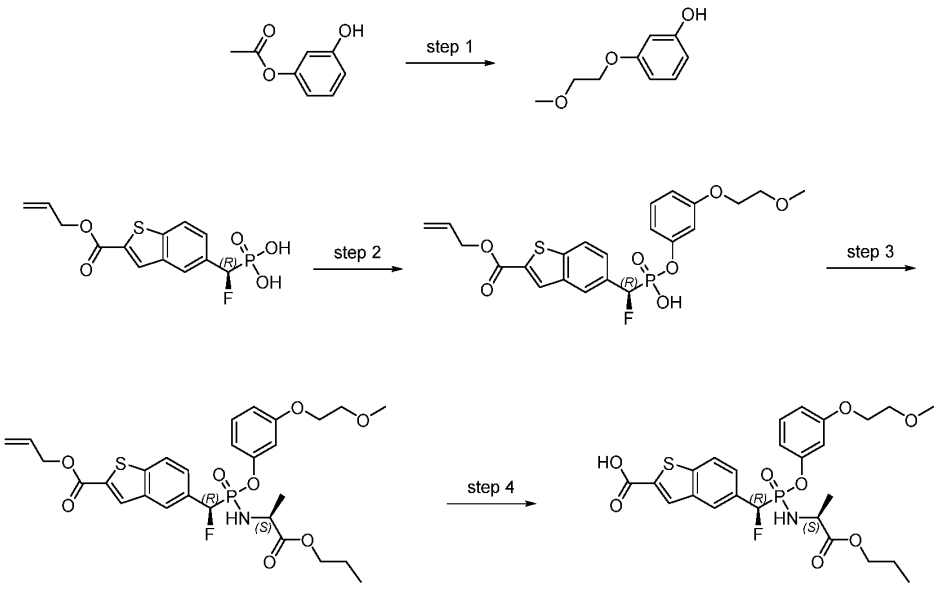
Table 82

Name	Structure	LCMS
5-((1R)-fluoro((((S)-1-((4-methyl-4H-1,2,4-triazol-3-yl)methoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		533 $[M+H]^+$
5-((1R)-fluoro((((S)-3-methoxy-1-(2-methoxyethoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		526 $[M+H]^+$
5-((1R)-fluoro((((S)-1-(2-methoxyethoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		496 $[M+H]^+$
5-((1R)-fluoro((((S)-1-(2-methoxyethoxy)-1-oxopropan-2-yl)amino)(2,2,2-trifluoroethoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		502 $[M+H]^+$
5-((1R)-fluoro((((S)-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		480 $[M+H]^+$

5-((1R)-fluoro((((S)-3-methoxy-1-oxo-1-propoxypropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		510 $[M+H]^+$
5-((1R)-fluoro((((S)-1-oxo-1-(pyridin-2-ylmethoxy)propan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		529 $[M+H]^+$
5-((1R)-fluoro((((S)-1-isobutoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid		494 $[M+H]^+$
5-((1R)-((((S)-1-cyclopropoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid		478 $[M+H]^+$
5-((1R)-((((S)-1-(2-ethylbutoxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid		522 $[M+H]^+$
5-((1R)-((((S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid		528 $[M+H]^+$.

5-((1R)-((2,6-dimethylphenoxy)(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylic acid		508 $[M+H]^+$

Synthesis of 5-((1R)-fluoro((3-(2-methoxyethoxy)phenoxy)(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid



[00846] *Step 1: Preparation of 3-(2-methoxyethoxy)phenol*

[00847] To a solution of 3-hydroxyphenyl acetate (5 g, 32.9 mmol, 1.0 eq.) and K_2CO_3 (13.6 g, 98.7 mmol, 3.0 eq.) in DMF (100 ml) was added 2-methoxyethyl 4-methylbenzenesulfonate (11.4 g, 49.4 mmol, 1.5 eq.). The mixture was stirred at 80 °C for 4 h. After completion, the reaction was cooled to room temperature and 20% NaOH (aq.) was added into the reaction mixture. The resulting mixture was stirred for 0.5 h and then quenched with HCl (1 N, aq.), diluted with H_2O (100 mL) and extracted with DCM (100 mL x 3). The organic layers were combined and washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 3-(2-methoxyethoxy)phenol (4 g, 23.8 mmol, 72%) as a colorless oil. LCMS (ESI): *m/z* = 169 $[M+H]^+$.

[00848] *Step 2: Preparation of allyl 5-((1R)-fluoro(hydroxy(3-(2-methoxyethoxy)phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00849] Oxalyl chloride (3.82 g, 30.3 mmol, 5 eq.) was added dropwise to a solution of (R)-((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid (3, 2 g, 6.06 mmol, 1 eq.) in dry DCM (30 mL) and DMF (1 drop) at 25 °C. The reaction mixture was stirred at 40 °C for an additional 0.5 h. The reaction was monitored by pipetting out a small amount of crude sample and quenching it with MeOH to ensure bis-Cl phosphoryl chloride had been formed completely (bis-methoxy phosphonate was observed by LCMS). After completion, the excess oxalyl chloride and solvent were removed under reduced pressure. The residue was re-dissolved in anhydrous DCM (20 mL), then added to a mixture of 3-(2-methoxyethoxy)phenol (1.07 g, 6.36 mmol, 1.05 eq.) and TEA (6.12 g, 60.6 mmol, 10.0 eq.) in anhydrous DCM (10 mL) at 0 °C. The reaction was stirred for 0.5 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give allyl 5-((1R)-fluoro(hydroxy(3-(2-methoxyethoxy)phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (2.00 g, 4.17 mmol, 69%) as a yellow solid. LCMS (ESI): m/z = 481 $[M+H]^+$.

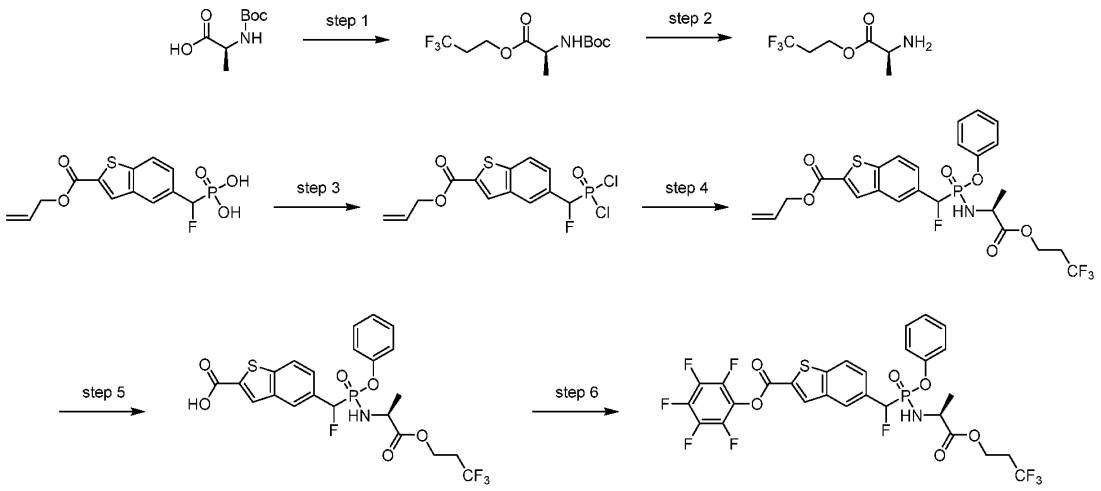
[00850] *Step 3: Preparation of allyl 5-((1R)-fluoro((3-(2-methoxyethoxy)phenoxy)(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00851] Oxalyl chloride (2.63 g, 20.85 mmol, 5 eq.) was added dropwise to the solution of allyl 5-((1R)-fluoro(hydroxy(3-(2-methoxyethoxy)phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (2 g, 4.17 mmol, 1 eq.) in dry DCM (10 mL) and DMF (1 drop) at 25 °C. The reaction mixture was stirred at 40 °C for an additional 0.5 h. The reaction was monitored by pipetting out a small amount of crude sample and quenching it with MeOH to ensure mono-Cl phosphoryl chloride had been formed completely (mono-methoxy phosphonate was observed by LCMS). After completion, the excess oxalyl chloride and solvent were removed under reduced pressure. The residue was re-dissolved in anhydrous DCM (20 mL), then added to a mixture of propyl L-alaninate (1.09 g, 8.34 mmol, 2.0 eq.) and TEA (4.21 g, 41.7 mmol, 10.0 eq.) in anhydrous DCM (20 mL) at 0 °C. The reaction was stirred for 0.5 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give allyl 5-((1R)-fluoro((3-(2-methoxyethoxy)phenoxy)(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (1.8 g, 3.04 mmol, 73%) as a yellow solid. LCMS (ESI): m/z = 594 $[M+H]^+$.

[00852] *Step 4: 5-((1R)-fluoro((3-(2-methoxyethoxy)phenoxy)(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid*

[00853] To a solution of allyl 5-((1R)-fluoro((3-(2-methoxyethoxy)phenoxy)(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (900 mg, 1.52 mmol, 1.0 eq) in DCM (6 mL) were added $Pd(PPh_3)_4$ (175 mg, 152 μmol, 0.1 eq.) and pyrrolidine (109 mg, 1.52 mmol, 1.0 eq.). The mixture was purged and degassed with N_2 three times, then stirred at 25 °C for 1 hr. After completion, the mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give 5-((1R)-fluoro((3-(2-methoxyethoxy)phenoxy)(((S)-1-oxo-1-propoxypropan-2-yl)amino)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (370 mg, 0.67 mmol, 44%) as a white solid. LCMS (ESI): *m/z* = 554 $[M+H]^+$.

Synthesis of perfluorophenyl 5-(fluoro((((S)-1-oxo-1-(3,3,3-trifluoropropoxy)propan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate



[00854] *Step 1: Preparation of (S)-3,3,3-trifluoropropyl 2-((tert-butoxycarbonyl)amino)propanoate*

[00855] To a solution of (S)-2-((tert-butoxycarbonyl)amino)propanoic acid (5 g, 26.4 mmol, 1 eq) in dimethylformamide (50 mL) was added 3-chloro-1,1,1-trifluoropropane (10 g, 79 mmol, 3 eq) and K_2CO_3 (7.3 g, 53 mmol, 2 eq). The mixture was stirred at 60 °C for 16 h to give a white suspension. The mixture was diluted with water (250 mL) and extracted with EtOAc (1 L × 3), the combined organic layers were washed with saturated brine (1 L × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give a (S)-3,3,3-trifluoropropyl 2-

((tert-butoxycarbonyl)amino)propanoate (4.5 g, 15 mmol, 20% yield) as an off-white solid. LCMS (ESI) m/z =286.1 $[M+H]^+$.

[00856] *Step 2: Preparation of (S)-3,3,3-trifluoropropyl 2-aminopropanoate*

[00857] The (S)-3,3,3-trifluoropropyl 2-((tert-butoxycarbonyl)amino)propanoate (2 g, 7.0 mmol, 1 eq) was dissolved in DCM (20 mL) and HCL/dioxane (20 mL), the reaction solution was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a (S)-3,3,3-trifluoropropyl 2-aminopropanoate (1.1 g, crude) as an off-white solid. ^1H NMR (400 MHz, CD_3OD) δ 4.59 - 4.40 (m, 2H), 4.15 (q, J = 7.2 Hz, 1H), 2.75 - 2.61 (m, 2H), 1.56 (d, J = 7.2 Hz, 3H).

[00858] *Step 3: Preparation of allyl 5-((dichlorophosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate*

[00859] To a solution of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid (0.90 g, 2.7 mmol, 1 eq) in DCM (9 mL) was added N,N-dimethylformamide (20 mg, 0.27 mmol, 0.1 eq) at 25 °C, then cooled to 0 °C, then oxalic dichloride (1.2 g, 9.5 mmol, 3.5 eq) was added at 0 °C, then stirred at 40 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give 5-((dichlorophosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (1.0 g, crude) as a yellow oil. LCMS (ESI) m/z =368.0 $[M+H]^+$.

[00860] *Step 4: Preparation of allyl 5-(fluoro((((S)-1-oxo-1-(3,3,3-trifluoropropoxy)propan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00861] To a solution of allyl 5-((dichlorophosphoryl)fluoromethyl)benzo[b]thiophene-2-carboxylate (1.0 g, 2.7 mmol, 1eq) in DCM (4 mL), the solution was under N_2 and cooled to 0 °C, then phenol (0.20 g, 2.2 mmol, 0.8 eq) in DCM (4 mL) was added in it, ethylbis(propan-2-yl)amine (1.4 g, 11 mmol, 4 eq) in DCM (20 mL) was dropwise added in it and stirred at 0 °C for 5 min, (S)-3,3,3-trifluoropropyl 2-aminopropanoate (0.60 g, 3.3 mmol, 1.2 eq) in DCM (4 mL) was added in it and stirred at 0 °C for 10 min to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give a product 5-(fluoro((((S)-1-oxo-1-(3,3,3-trifluoropropoxy)propan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (0.70 g, 1.2 mmol, 44% yield) as a white solid. LCMS (ESI) m/z = 574.1

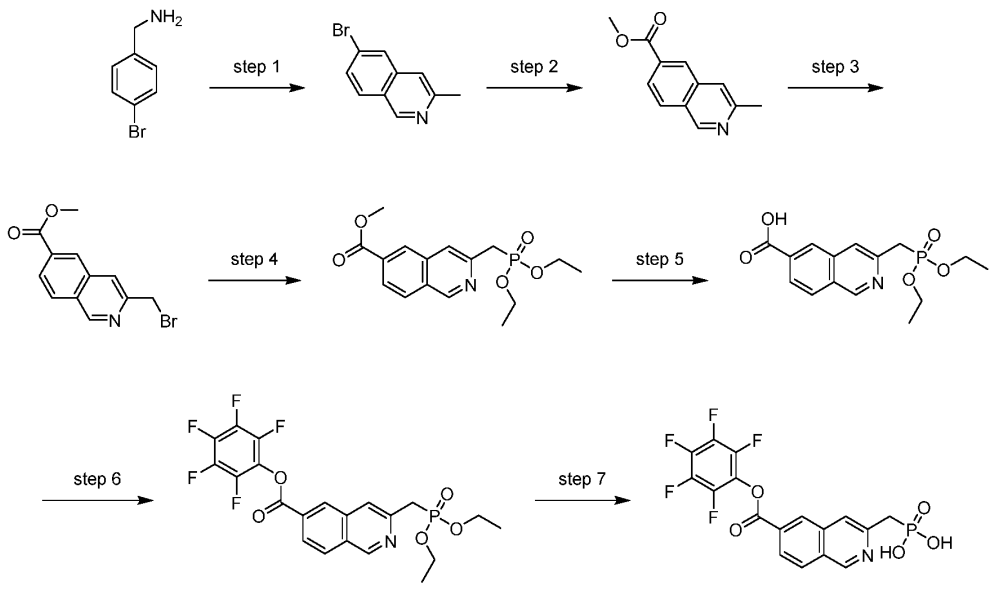
[00862] *Step 5: Preparation of 5-(fluoro((((S)-1-oxo-1-(3,3,3-trifluoropropoxy)propan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid*

[00863] To a solution of 5-(fluoro((((S)-1-oxo-1-(3,3,3-trifluoropropoxy)propan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (0.58 g, 1.0 mmol, 1 eq) and $Pd(PPh_3)_4$ (0.17 g, 0.15 mmol, 1.5 eq) in DCM (5 mL) was added pyrrolidine (50 mg, 0.71 mmol, 0.7 eq) at 0 °C. The mixture was stirred at 25°C for 0.5 h to give a yellow suspension. The reaction mixture was filtrated. The filtered and concentrated under reduced pressure to give a residue. The residue was purified by reverse phase (TFA) to lyophilized to give 5-(fluoro((((S)-1-oxo-1-(3,3,3-trifluoropropoxy)propan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (0.38 g, 0.71 mmol, 70% yield) as a yellow solid. LCMS (ESI) m/z = 534.1 $[M+H]^+$.

[00864] *Step 6: Preparation of perfluorophenyl 5-(fluoro((((S)-1-oxo-1-(3,3,3-trifluoropropoxy)propan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate*

[00865] To a solution of 5-(fluoro((((S)-1-oxo-1-(3,3,3-trifluoropropoxy)propan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylic acid (0.40 g, 0.75 mmol, 1 eq) in dimethylformamide (4 mL) was added pyridine (0.18 g, 2.2 mmol, 3 eq), then perfluorophenyl 2,2,2-trifluoroacetate (1.0 g, 3.7 mmol, 5 eq) was added in the mixture at 0 °C to give a yellow solution. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL × 2), the combined organic layers were washed with saturated brine (20 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give a product perfluorophenyl 5-(fluoro((((S)-1-oxo-1-(3,3,3-trifluoropropoxy)propan-2-yl)amino)(phenoxy)phosphoryl)methyl)benzo[b]thiophene-2-carboxylate (0.45 mg, 0.64 mmol, 86% yield) as a white solid. LCMS (ESI) m/z = 700.0 $[M+H]^+$.

Synthesis of ((6-((perfluorophenoxy)carbonyl)isoquinolin-3-yl)methyl)phosphonic acid



[00866] *Step 1: Preparation of 6-bromo-3-methylisoquinoline*

[00867] To a solution of (4-bromophenyl)methanamine (10 g, 54 mmol, 1 eq) in DCM (5 mL) was added 1,1-dimethoxypropan-2-one (7.0 g, 59 mmol, 1.1 eq) and magnesium(2+) sulfate (10 g, 83 mmol, 1.6 eq), the mixture was stirred at 40 °C for 12 h. Then sodium (boranylidenemethylidene)azanide (3.9 g, 64 mmol, 1.2 eq) was added, the mixture was stirred at 25 °C for 5 h. The mixture was filtered. The filtrate was concentrated to give a yellow oil. Then chlorosulfuric acid (6 mL) was slowly added to the crude product at 0 °C slowly, the reaction mixture was heated to 100 °C for 1 h, then the reaction mixture was cooled to room temperature and poured into ice water. The mixture was neutralized with 2M NaOH and extracted with EtOAc (100 mL × 2), the combined organic layers were washed with saturated brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give 6-bromo-3-methylisoquinoline (1.8 g, 8.1 mmol, 15% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.91 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.39 (s, 1H), 2.71 (s, 3H)

[00868] *Step 2: Preparation of methyl 3-methylisoquinoline-6-carboxylate*

[00869] To a solution of 6-bromo-3-methylisoquinoline (1.5 g, 6.8 mmol, 1 eq) in methanol (10 mL) was added triethylamine (1.4 g, 14 mmol, 2 eq) and Pd(dppf)Cl_2 (0.5 g, 0.68 mmol, 0.1 eq) under N_2, the mixture was stirred at 70 °C for 16 h under CO (50 psi). The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give methyl 3-methylisoquinoline-6-carboxylate (1.40

g, 7.0 mmol, 95% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.49 (s, 1H), 8.14 - 8.07 (m, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.59 (s, 1H), 4.01 (s, 3H), 2.74 (s, 3H)

[00870] *Step 3: Preparation of methyl 3-(bromomethyl)isoquinoline-6-carboxylate*

[00871] To a solution of methyl 3-methylisoquinoline-6-carboxylate (0.40 g, 2.0 mmol, 1 eq) in CCl_4 (6 mL) was added 1-bromopyrrolidine-2,5-dione (35 mg, 0.19 mmol, 0.1 eq) and 2-[(1E)-2-(1-cyano-1-methylethyl)diazen-1-yl]-2-methylpropanenitrile (0.33 g, 2.0 mmol, 1.0 eq), the mixture was stirred at 65 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc = 100: 1 to 10: 1) to give methyl 3-(bromomethyl)isoquinoline-6-carboxylate (0.33 g, 1.2 mmol, 60% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.59 (s, 1H), 8.27 - 8.20 (m, 1H), 8.12 - 8.02 (m, 1H), 7.89 (s, 1H), 4.78 (s, 2H), 4.04 (s, 3H)

[00872] *Step 4: Preparation of methyl 3-((diethoxyphosphoryl)methyl)isoquinoline-6-carboxylate*

[00873] A solution of methyl 3-(bromomethyl)isoquinoline-6-carboxylate (0.3 g, 1.07 mmol, 1 eq) in triethyl phosphite (3 mL) was stirred at 120 °C for 12 h. The reaction mixture was purified by reversed phase (TFA) then lyophilized to give methyl 3-((diethoxyphosphoryl)methyl)isoquinoline-6-carboxylate (0.35 g, 1.04 mmol, 97% yield) as a yellow oil. LCMS (ESI) m/z = 338.3.

[00874] *Step 5: Preparation of 3-((diethoxyphosphoryl)methyl)isoquinoline-6-carboxylic acid*

[00875] To a solution of methyl 3-((diethoxyphosphoryl)methyl)isoquinoline-6-carboxylate (0.13 g, 0.39 mmol, 1 eq) in THF (0.5 mL) was added sodium hydroxide (30.70 mg, 770 μmol, 2 eq) in water (0.5 mL), the mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give 3-((diethoxyphosphoryl)methyl)isoquinoline-6-carboxylic acid (0.13 g, crude) as a yellow solid. LCMS (ESI) m/z = 324.0

[00876] *Step 6: Preparation of perfluorophenyl 3-((diethoxyphosphoryl)methyl)isoquinoline-6-carboxylate*

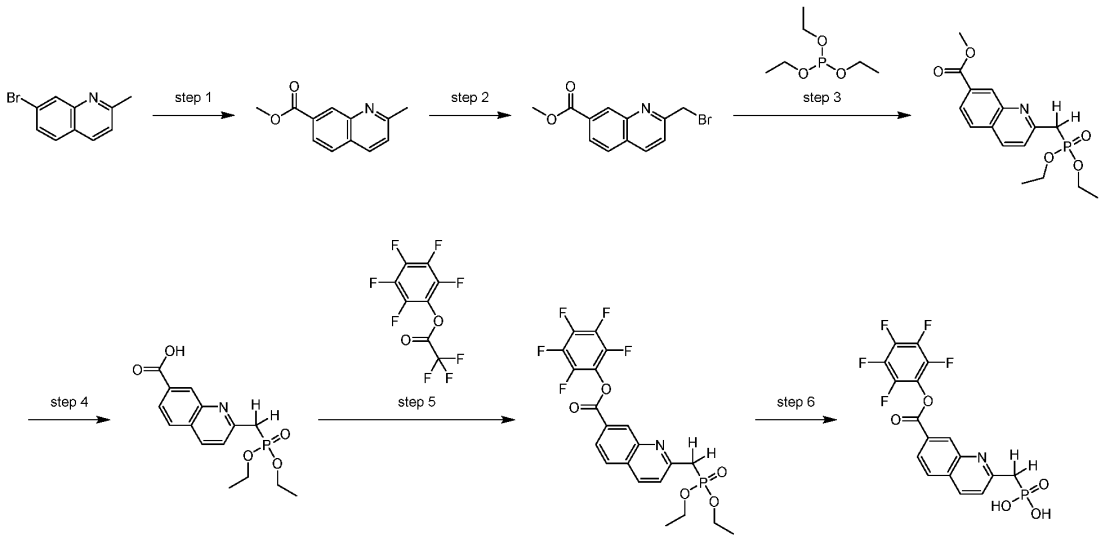
[00877] To a solution of 3-((diethoxyphosphoryl)methyl)isoquinoline-6-carboxylic acid (0.13 g, 0.40 mol, 1 eq) in DMF (1 mL) was added pyridine (0.13 g, 1.60 mmol, 4 eq), then 2,3,4,5,6-pentafluorophenyl 2,2,2-trifluoroacetate (2.25 g, 8.04 mmol, 20 eq) was added at 0 °C, the mixture was stirred at 25 °C for 1 h to give a yellow solution. The mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL × 2), the combined organic layers were

washed with saturated brine (40 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give perfluorophenyl 3-((diethoxyphosphoryl)methyl)isoquinoline-6-carboxylate (80 mg, 0.16 mmol, 40.80% yield) as a yellow solid. LCMS (ESI) m/z = 490.2

[00878] *Step 7: Preparation of ((6-((perfluorophenoxy)carbonyl)isoquinolin-3-yl)methyl)phosphonic acid*

[00879] To a solution of perfluorophenyl 3-((diethoxyphosphoryl)methyl)isoquinoline-6-carboxylate (80 mg, 0.16 mmol, 1 eq) in DCM (1 mL) was added iodotrimethylsilane (0.13 g, 0.65 mmol, 4 eq) at 0 °C, the mixture was stirred at 0 °C for 10 min. The reaction mixture was concentrated under reduced pressure to remove DCM, then was immediately purified by reversed phase (TFA) to lyophilized to give ((6-((perfluorophenoxy)carbonyl)isoquinolin-3-yl)methyl)phosphonic acid (30.00 mg, 0.07 mmol, 42.40% yield) as a red solid. ^{1}H NMR (400 MHz, CD_3OD) δ 9.69 - 9.61 (m, 1H), 9.03 (s, 1H), 8.52 - 8.47 (m, 1H), 8.46 - 8.42 (m, 1H), 8.35 - 8.30 (m, 1H), 3.72 - 3.59 (m, 2H)

Synthesis of ((7-((perfluorophenoxy)carbonyl)quinolin-2-yl)methyl)phosphonic acid



[00880] *Step 1: Preparation of methyl 2-methylquinoline-7-carboxylate*

[00881] To a solution of 7-bromo-2-methylquinoline (1 g, 4.50 mmol, 1 eq) in MeOH (100 mL) was added TEA (910 mg, 9.00 mmol, 2 eq) and $Pd(dppf)Cl_2$ (330 mg, 450 μmol, 0.1 eq), and the reaction was stirred for 16 h at 70 °C under CO (50 Psi). The reaction solution was concentrated directly to give a residue. The residue was purified by column chromatography to give methyl 2-methylquinoline-7-carboxylate (850 mg, 4.22 mmol, 93.9%

yield) as a white solid. LCMS (ESI) m/z = 202.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 3.98 (s, 3H), 2.73 (s, 3H)

[00882] *Step 2: Preparation of methyl 2-(bromomethyl)quinoline-7-carboxylate*

[00883] To a solution of methyl 2-methylquinoline-7-carboxylate (850 mg, 4.22 mmol, 1 eq) in chloroform (10 mL) was added NBS (825 mg, 4.64 mmol, 1.1 eq) and AIBN (825 mg, 4.64 mmol, 0.1 eq), the mixture was stirred at 70°C for 12 h. The mixture was diluted with water (10 mL) and extracted with DCM (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give methyl 2-(bromomethyl)quinoline-7-carboxylate (320 mg, 1.14 mmol, 27.1% yield) as a white solid. LCMS (ESI) m/z = 279.8 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.66 (s, 1H), 8.40 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 4.77 (s, 2H), 4.00 (s, 3H).

[00884] *Step 3: Preparation of methyl 2-((diethoxyphosphoryl)methyl)quinoline-7-carboxylate*

[00885] A mixture of methyl 2-(bromomethyl)quinoline-7-carboxylate (320 mg, 1.14 mmol, 1 eq) in triethyl phosphite (0.5 mL), the mixture was stirred at 120 °C for 2 h. The mixture was purified by prep-HPLC (column: Welch Xtimate C18 150 × 25 mm × 5 um ; mobile phase: [water (TFA)-ACN]; B%: 20%-50%, 10 min) to lyophilized to give methyl 2-((diethoxyphosphoryl)methyl)quinoline-7-carboxylate (350 mg, 1.03 mmol, 91.1% yield) as a white solid. LCMS (ESI) m/z = 338.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.44 (d, *J* = 8.8 Hz, 1H), 8.14 - 8.02 (m, 2H), 7.65 (d, *J* = 8.4 Hz, 1H), 4.05 - 3.99 (m, 4H), 3.94 (s, 3H), 3.78 - 3.63 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 6H)

[00886] *Step 4: Preparation of 2-((diethoxyphosphoryl)methyl)quinoline-7-carboxylic acid*

[00887] To a solution of methyl 2-((diethoxyphosphoryl)methyl)quinoline-7-carboxylate (350 mg, 1.03 mmol, 1 eq) in THF (4 mL) was added and lithium(1+) hydrate hydroxide (86.4 mg, 2.06 mmol, 2 eq, 1 M), the mixture was stirred at 25 °C for 1 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL × 3). The combined aqueous phase was used 1 N HCl to adjust PH=3-4, then extracted with EtOAc (20 mL × 3), the combined organic layers were washed with brine (20 mL × 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 2-((diethoxyphosphoryl)methyl)quinoline-7-carboxylic acid (300 mg, crude) as a white solid. LCMS (ESI) m/z = 324.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.43 (d, *J*

= 8.4 Hz, 1H), 8.10 - 8.02 (m, 2H), 7.68 - 7.58 (m, 1H), 4.03-3.96 (m, 4H), 3.73 - 3.66 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 6H)

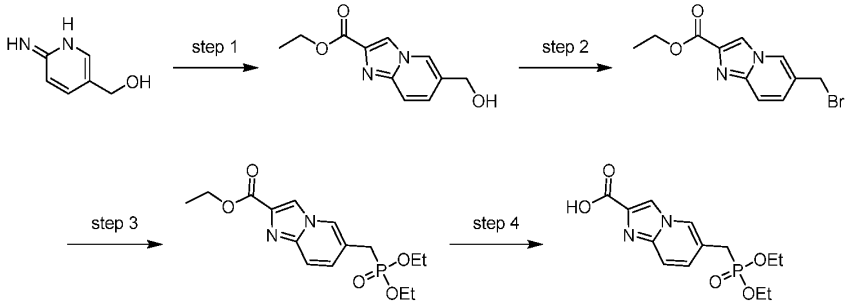
[00888] *Step 5: Preparation of perfluorophenyl 2-((diethoxyphosphoryl)methyl)quinoline-7-carboxylate*

[00889] To a solution of 2-((diethoxyphosphoryl)methyl)quinoline-7-carboxylic acid (300 mg, 927 µmol, 1 eq) in DMA (3 mL) was added pyridine (366 mg, 4.63 mmol, 5 eq), then perfluorophenyl 2,2,2-trifluoroacetate (1.29 g, 4.63 mmol, 5 eq) was dropwise at 0 °C, the mixture was stirred at 25 °C for 2 h to give a yellow solution. The mixture solution was purified by prep-HPLC (column: Phenomenex Luna C18 200 × 40 mm × 10 um; mobile phase: [water (TFA)-ACN]; B%: 46%-76%, 10 min) to lyophilized to give perfluorophenyl 2-((diethoxyphosphoryl)methyl)quinoline-7-carboxylate (400 mg, 817 µmol, 88.3%) yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.52 (d, *J* = 8.8 Hz, 1H), 8.30 - 8.10 (m, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 4.08 - 4.01 (m, 4H), 3.83 - 3.63 (m, 2H), 1.36 - 1.07 (m, 6H)

[00890] *Step 6: Preparation of ((7-((perfluorophenoxy)carbonyl)quinolin-2-yl)methyl)phosphonic acid*

[00891] To a solution of perfluorophenyl 2-((diethoxyphosphoryl)methyl)quinoline-7-carboxylate (200 mg, 408 µmol, 1 eq) in DCM (5 mL) was added iodotrimethylsilane (326 mg, 1.63 mmol, 4 eq), the mixture was stirred at 0 °C for 0.5 h. The mixture was concentrated directly to give the residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150 × 25 mm × 5 um; mobile phase: [water (TFA)-ACN]; B%: 20%-50%, 8 min) to lyophilized to give ((7-((perfluorophenoxy)carbonyl) quinolin-2-yl)methyl)phosphonic acid (70 mg, 161 µmol, 39.7% yield) as a yellow solid. LCMS (ESI) m/z = 433.7 $[M+H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 8.96 - 8.80 (m, 1H), 8.72 - 8.58 (m, 1H), 8.38 - 8.19 (m, 2H), 8.06 - 7.87 (m, 1H), 3.33 (d, *J* = 1.2 Hz, 2H)

Synthesis of 6-((diethoxyphosphoryl)methyl)imidazo[1,2-a]pyridine-2-carboxylic acid



[00892] *Step 1: Preparation of ethyl 6-(hydroxymethyl)imidazo[1,2-a]pyridine-2-carboxylate*

[00893] To a solution of (6-imino-1,6-dihydropyridin-3-yl)methanol (2 g, 16.1 mmol, 1 eq) in THF (20 mL) was added ethyl 3-bromo-2-oxopropanoate (4.4 g, 22.5 mmol, 1.4 eq) at 25 °C, then the mixture was stirred at 80 °C for 12 h to give a yellow suspension. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give ethyl 6-(hydroxymethyl)imidazo[1,2-a]pyridine-2-carboxylate (0.7 g, 2.2 mmol, 18% yield) as a yellow oil. LCMS (ESI) m/z =221.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.40 (d, J = 16.0 Hz, 2H), 7.56 (d, J = 8.0 Hz, 1H), 7.44 - 7.34 (m, 1H), 4.49 - 4.32 (m, 2H), 3.35 (s, 2H), 1.40 (t, J = 7.2 Hz, 3H)

[00894] *Step 2: Preparation of ethyl 6-(bromomethyl)imidazo[1,2-a]pyridine-2-carboxylate*

[00895] To a solution of ethyl 6-(hydroxymethyl)imidazo[1,2-a]pyridine-2-carboxylate (0.7 g, 2.2 mmol, 1 eq) in DCM (5 mL) was added triphenylphosphine (0.8 g, 2.9 mmol, 1.3 eq) at 25 °C, then the mixture was cooled to 0 °C, then a solution of CBr_4 (0.7 g, 2.2 mmol, 1.0 eq) in DCM (1 mL) was slowly dropwise added to the mixture at 0 °C, then the mixture was stirred at 25 °C for 1 h to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give ethyl 6-(bromomethyl)imidazo[1,2-a]pyridine-2-carboxylate (0.5 g, 1.8 mmol, 80% yield) as a white oil. LCMS (ESI) m/z =284.8 $[M+H]^+$.

[00896] *Step 3: Preparation of ethyl 6-((diethoxyphosphoryl)methyl)imidazo[1,2-a]pyridine-2-carboxylate*

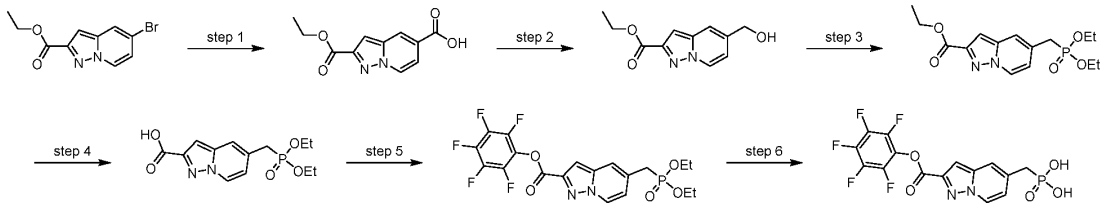
[00897] A solution of ethyl 6-(bromomethyl)imidazo[1,2-a]pyridine-2-carboxylate (0.5 g, 1.8 mmol, 1 eq) in triethyl phosphite (4 mL) was stirred at 100 °C for 12 h to give a white solution. The reaction mixture was purified by reverse phase (TFA) to lyophilized to give ethyl 6-((diethoxyphosphoryl)methyl)imidazo[1,2-a]pyridine-2-carboxylate (0.4 g, 1.0 mmol, 58% yield) as a white oil. LCMS (ESI) m/z =341.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 4.0 Hz, 1H), 8.16 (s, 1H), 8.06 (d, J = 12.0 Hz, 1H), 7.45 (d, J = 12.0 Hz, 1H), 4.52 - 4.41 (m, 2H), 4.14 - 4.10 (m, 4H), 3.25 - 3.10 (m, 2H), 1.43 (t, J = 8.0 Hz, 3H), 1.30 (t, J = 8.0 Hz, 6H).

[00898] *Step 4: Preparation of 6-((diethoxyphosphoryl)methyl)imidazo[1,2-a]pyridine-2-carboxylic acid*

[00899] To a solution of ethyl 6-((diethoxyphosphoryl)methyl)imidazo[1,2-a]pyridine-2-carboxylate (0.4 g, 1.0 mmol, 1 eq) in EtOH (0.5 mL) and THF (0.5 mL) was added

lithium(1+) hydroxide (5 mL, 2 M), then the mixture was stirred at 25 °C for 2 h to give a white solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by reverse phase (TFA) to lyophilized to give 6-((diethoxyphosphoryl)methyl)imidazo[1,2-a]pyridine-2-carboxylic acid (0.2 g, 0.6 mmol, 62.8% yield) as a white oil. LCMS (ESI) m/z =312.9 $[M+H]^+$.

Synthesis of (((2-((perfluorophenoxy)carbonyl)pyrazolo[1,5-a]pyridin-5-yl)methyl)phosphonic acid



[00900] *Step 1: Preparation of 2-(ethoxycarbonyl)pyrazolo[1,5-a]pyridine-5-carboxylic acid*

[00901] To a solution of ethyl 5-bromopyrazolo[1,5-a]pyridine-2-carboxylate (4 g, 15 mmol, 1 eq) in THF (35 mL) and H_2O (7 mL) was added $Pd(DPPF)Cl_2$ (2.2 g, 3 mmol, 0.20 eq) and TEA (15 g, 0.15 mol. 10 eq) under CO (45 Psi), the mixture was stirred at 65 °C for 16 h to give black solution. The reaction mixture was filtered and the filter was concentrated to give a residue. The residue was diluted with water (40 mL) and extracted with EtOAc (40 mL × 1), the combined organic layers were washed with saturated brine (40 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition; (column: Welch Ultimate C18 150 × 25 mm × 5 um, mobile phase: water (TFA)-ACN; B%:B%: 30% - 40%, 30 min) to lyophilized to give 2-(ethoxycarbonyl)pyrazolo[1,5-a]pyridine-5-carboxylic acid (1.3 g, 37% yield) as white solid

[00902] *Step 2: Preparation of ethyl 5-(hydroxymethyl)pyrazolo[1,5-a]pyridine-2-carboxylate*

[00903] To a solution of 2-(ethoxycarbonyl)pyrazolo[1,5-a]pyridine-5-carboxylic acid (1.2 g, 5.1 mmol, 1 eq) in THF (12 mL) was added BH_3.THF (13 mL, 13 mmol, 2.5 eq) at 0 °C, the mixture was stirred at 60 °C for 12 h to give a yellow clean solution, the mixture reaction was diluted with water (13 mL × 2) at 0 °C, and then was extracted with EtOAc (13 mL × 2), the combined organic layers were washed with saturated brine (26 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was

purified by flash silica gel chromatography (12 g SepaFlash® Silica Flash Column, Eluent of 0~30 % DCM/MeOH ethergradient @ 12 mL/min) and then was collected and concentrated in vacuo to give ethyl 5-(hydroxymethyl)pyrazolo[1,5-a]pyridine-2-carboxylate (0.40 g, 35% yield) as white solid

[00904] *Step 3: Preparation of ethyl 5-((diethoxyphosphoryl)methyl)pyrazolo[1,5-a]pyridine-2-carboxylate*

[00905] To a solution of ethyl 5-(hydroxymethyl)pyrazolo[1,5-a]pyridine-2-carboxylate (0.35 g, 1.6 mmol, 1 eq) in triethyl phosphite (2.6 g, 16 mmol, 10 eq) was added tetrabutylammonium ion iodide (0.17 g, 0.47 mmol, 0.30 eq), the mixture was stirred at 120 °C for 16 h to give a yellow clean solution. The reaction was diluted with NaCl (2 mL), and then the reaction was purified by prep-HPLC (TFA condition; (column: Welch Ultimate C18 150 × 25 mm × 5 um, mobile phase: water (TFA)-ACN; B%:B%: 30% - 50%, 10 min) to lyophilized to give ethyl 5-((diethoxyphosphoryl)methyl)pyrazolo[1,5-a]pyridine-2-carboxylate (0.35 g, 65% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 7.2 Hz, 1H), 7.49 (d, J = 3.2 Hz, 1H), 7.02 (s, 1H), 6.87 (td, J = 1.6, 7.2 Hz, 1H), 4.47 (q, J = 7.2 Hz, 2H), 4.13 - 4.02 (m, 4H), 3.21 - 3.12 (m, 2H), 1.44 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 6H)

[00906] *Step 4: Preparation of 5-((diethoxyphosphoryl)methyl)pyrazolo[1,5-a]pyridine-2-carboxylic acid*

[00907] To a solution of 5-((diethoxyphosphoryl)methyl)pyrazolo[1,5-a]pyridine-2-carboxylic acid (0.35 g, 1.0 mmol, 1 eq) in THF (1 mL), MeOH (1 mL), H_2O (1 mL) was added lithium(1+) hydrate hydroxide (43 mg, 1.0 mmol, 1 eq), the mixture was stirred at 25 °C for 0.5 h to give a yellow clean solution, the reaction mixture was concentrated under reduced pressure to give a residue. the residue was diluted with water (5 mL) and extracted with 1 M HCl to pH=5~6, the combined organic layers were washed with EtOAc (5 mL × 4), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 5-((diethoxyphosphoryl)methyl)pyrazolo[1,5-a]pyridine-2-carboxylic acid (0.30 g, 94% yield) as white solid. LCMS (ESI) m/z = 313.1

[00908] *Step 5: Preparation of perfluorophenyl 5-((diethoxyphosphoryl)methyl)pyrazolo[1,5-a]pyridine-2-carboxylate*

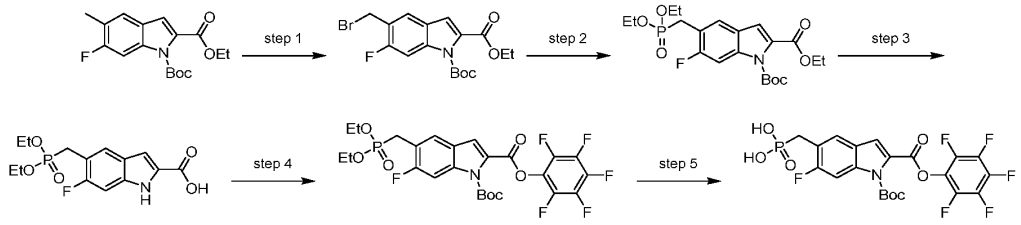
[00909] To a solution of 5-((diethoxyphosphoryl)methyl)pyrazolo[1,5-a]pyridine-2-carboxylic acid (0.10 g, 0.32 mmol, 1 eq) in DMF (1 mL) was added pyridine (25 mg, 0.32 mmol, 1 eq), 2,3,4,5,6-pentafluorophenyl 2,2,2-trifluoroacetate (90 mg, 0.32 mmol, 1 eq) at 0 °C, the mixture was stirred at 0 °C for 0.5 h to give a yellow clean solution. The reaction was

diluted with water (2 mL) and extracted with EtOAc (2 mL × 2), the combined organic layers were washed with saturated brine (4 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, the residue was purified by flash silica gel chromatography (4 g SepaFlash® Silica Flash Column, Eluent of 0~30 % PE:EA @ 22 mL/min) and then was collected and concentrated in vacuo to give perfluorophenyl 5-((diethoxyphosphoryl)methyl)pyrazolo[1,5-a]pyridine-2-carboxylate (0.10 g, 65% yield) as a white solid. LCMS (ESI) m/z = 479.0

[00910] *Step 6: Preparation of ((2-((perfluorophenoxy)carbonyl)pyrazolo[1,5-a]pyridin-5-yl)methyl)phosphonic acid*

[00911] To a solution of perfluorophenyl 5-((diethoxyphosphoryl)methyl)pyrazolo[1,5-a]pyridine-2-carboxylate (0.10 g, 0.21 mmol, 1 eq) in DCM (1 mL) was added BSTFA (0.16 g, 0.63 mmol, 3 eq), trimethylsilyl iodide (42 mg, 0.21 mmol, 1 eq) at 0 °C, the mixture was stirred at 0 °C for 10 min to give a yellow clean solution, the reaction mixture was concentrated under reduced pressure to give a residue, the residue was purified by prep-HPLC (TFA condition; (column: Welch Ultimate C18 150 × 25 mm × 5 um, mobile phase: water (TFA)-ACN; B%:B%: 20% - 40%, 10 min) to lyophilized to give ((2-((perfluorophenoxy)carbonyl)pyrazolo[1,5-a]pyridin-5-yl)methyl)phosphonic acid (60 mg, 68% yield) as a white solid. LCMS (ESI) m/z = 422.9

Synthesis of ({6-fluoro-2-[(2,3,4,5,6-pentafluorophenoxy)carbonyl]-1H-indol-5-yl}methyl)phosphonic acid



[00912] *Step 1: Preparation of 1-(tert-butyl) 2-ethyl 5-(bromomethyl)-6-fluoro-1H-indole-1,2-dicarboxylate*

[00913] To a solution of 1-(tert-butyl) 2-ethyl 6-fluoro-5-methyl-1H-indole-1,2-dicarboxylate (600 mg, 1.86 mmol, 1 eq.) in CCl_4 (10 mL) were added NBS (331 mg, 1.86 mmol, 1.0 eq.) and BPO (45.0 mg, 186 μmol, 0.1 eq.). The mixture was stirred at 80 °C for 6 h under N_2. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 1-(tert-

butyl) 2-ethyl 5-(bromomethyl)-6-fluoro-1H-indole-1,2-dicarboxylate (260 mg, 649 µmol, 35%) as a yellow oil. LCMS (ESI) *m/z* = 400 $[M+H]^+$.

[00914] *Step 2: Preparation of 1-(tert-butyl) 2-ethyl 5-((diethoxyphosphoryl)methyl)-6-fluoro-1H-indole-1,2-dicarboxylate*

[00915] 1-(tert-butyl) 2-ethyl 5-(bromomethyl)-6-fluoro-1H-indole-1,2-dicarboxylate (260 mg, 649 µmol, 1 eq.) was dissolved in triethyl phosphite (322 mg, 1.94 mmol, 3 eq.). The mixture was stirred at 120 °C for 4 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel and prep-HPLC to afford 1-(tert-butyl) 2-ethyl 5-((diethoxyphosphoryl)methyl)-6-fluoro-1H-indole-1,2-dicarboxylate (230 mg, 502 µmol, 78%) as a colorless oil. LCMS (ESI) *m/z* = 458 $[M+H]^+$.

[00916] *Step 3: Preparation of 5-((diethoxyphosphoryl)methyl)-6-fluoro-1H-indole-2-carboxylic acid*

[00917] To a solution of 1-(tert-butyl) 2-ethyl 5-((diethoxyphosphoryl)methyl)-6-fluoro-1H-indole-1,2-dicarboxylate (230 mg, 502 µmol, 1.0 eq.) in MeOH (3 mL) and H_2O (1 mL) was added $LiOH.H_2O$ (97.8 mg, 2.51 mmol, 5 eq.). The mixture was stirred at 25 °C for 16 h. After completion, the reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford 1-(tert-butoxycarbonyl)-5-((diethoxyphosphoryl)methyl)-6-fluoro-1H-indole-2-carboxylic acid (120 mg, quant.) as a white solid, which was used in next step directly without further purification. LCMS (ESI) *m/z* = 430 $[M+H]^+$.

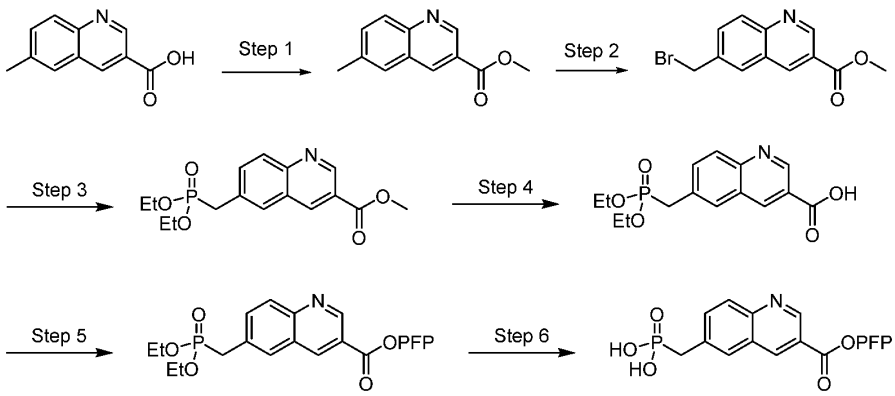
[00918] *Step 4: Preparation of perfluorophenyl 5-((diethoxyphosphoryl)methyl)-6-fluoro-1H-indole-2-carboxylate*

[00919] To a solution of 1-(tert-butoxycarbonyl)-5-((diethoxyphosphoryl)methyl)-6-fluoro-1H-indole-2-carboxylic acid (40 mg, 121 µmol, 1 eq.) in DCM (2 mL) were added DCC (49.8 mg, 242 µmol, 2 eq.), DMAP (11.8 mg, 96.8 µmol, 0.8 eq.) and pentafluorophenol (55.5 mg, 302 µmol, 2.5 eq.). The mixture was stirred at 25 °C for 16 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was pre-purified by flash column chromatography on silica gel and prep-HPLC to afford perfluorophenyl 5-((diethoxyphosphoryl)methyl)-6-fluoro-1H-indole-2-carboxylate (28.0 mg, 56.5 µmol, 47%) as a white solid. LCMS (ESI): *m/z* = 496 $[M+H]^+$.

[00920] *Step 5: Preparation of ((6-fluoro-2-((perfluorophenoxy)carbonyl)-1H-indol-5-yl)methyl)phosphonic acid*

[00921] To a solution perfluorophenyl 5-((diethoxyphosphoryl)methyl)-6-fluoro-1H-indole-2-carboxylate (28 mg, 56.5 μmol, 1 eq.) in DCM (1 mL) was added TMSBr (86.4 mg, 565 μmol, 10 eq.). The mixture was stirred at 25 °C for 2 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was pre-purified by flash column chromatography on silica gel and prep-HPLC to afford ({6-fluoro-2-[(2,3,4,5,6-pentafluorophenoxy)carbonyl]-1H-indol-5-yl}methyl)phosphonic acid (13.0 mg, 29.5 μmol, 52%) as a white solid. LCMS (ESI): *m/z* = 440 $[M+H]^+$.

Synthesis of ((3-((perfluorophenoxy)carbonyl)quinolin-6-yl)methyl)phosphonic acid:



[00922] *STEP 1: Preparation of methyl 6-methylquinoline-3-carboxylate*

[00923] To a solution of 6-methylquinoline-3-carboxylic acid (**1**, 220 mg, 1.17 mmol, 1.0 eq.) and K_2CO_3 (322 mg, 2.34 mmol, 2.0 eq.) in DMF (10 mL) was added CH_3I (332 mg, 2.34 mmol, 2.0 eq.), and the resulting mixture was stirred at room temperature overnight. After completion, the reaction was diluted with H_2O (10 mL) and extracted with EtOAc (20 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford methyl 6-methylquinoline-3-carboxylate (**2**, 210 mg, 1.04 mmol, 89%) as a yellow solid. LCMS (ESI): *m/z* = 202.1 $[M+H]^+$.

[00924] *STEP 2: Preparation of methyl 6-(bromomethyl)quinoline-3-carboxylate*

[00925] To a solution of methyl 6-methylquinoline-3-carboxylate (**2**, 210 mg, 1.04 mmol, 1.0 eq.) and NBS (220 mg, 1.24 mmol, 1.2 eq.) in CCl_4 (10 mL) was added BPO (25.1 mg, 0.10 mmol, 0.1 eq.) under N_2, and the resulting mixture was stirred at 70 °C overnight under N_2. After completion, the reaction was cooled to room temperature, diluted with H_2O (10 mL) and extracted with DCM (20 mL x 2). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure.

The residue was purified by flash column chromatography on silica gel to afford methyl 6-(bromomethyl)quinoline-3-carboxylate (**3**, 225 mg, 803 μmol, 77%) as a white solid. LCMS (ESI): *m/z* = 280.0 $[M+H]^+$.

[00926] *STEP 3: Preparation of methyl 6-((diethoxyphosphoryl)methyl)quinoline-3-carboxylate*

[00927] A solution of methyl 6-(bromomethyl)quinoline-3-carboxylate (**3**, 225 mg, 803 μmol, 1.0 eq.) in Triethyl phosphite (5 mL) was stirred at 100 °C overnight. After completion, the reaction was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give methyl 6-[(diethoxyphosphoryl)methyl]quinoline-3-carboxylate (**4**, 220 mg, 652 μmol, 81%) as a colorless oil. LCMS (ESI): *m/z* = 338.1 $[M+H]^+$.

^{1}H NMR(400 MHz, $CDCl_3$) δ 9.45 (d, *J* = 1.1 Hz, 1H), 8.84 (s, 1H), 8.15 (s, 1H), 7.89 (s, 1H), 7.82 (s, 1H), 4.11-4.05 (m, 4H), 4.04 (s, 3H), 3.38 (d, *J* = 21.9 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 6H).

[00928] *STEP 4: Preparation of 6-((diethoxyphosphoryl)methyl)quinoline-3-carboxylic acid*

[00929] To a solution of methyl 6-[(diethoxyphosphoryl)methyl]quinoline-3-carboxylate (**4**, 220 mg, 652 μmol, 1 eq.) in THF/H_2O (6mL, v/v = 5:1) was added $LiOH{\cdot}H_2O$ (84.9 mg, 1.95 mmol, 3.0 eq.), and the resulting mixture was stirred at room temperature for 2 h. After completion, the reaction mixture was cooled down in an ice bath, then neutralized carefully with HCl (2 N, aq.) until the pH was adjusted to pH = 3. The resulting mixture was extracted with DCM (10 mL x 3), and the combined organic layers were washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure to afford 6-((diethoxyphosphoryl)methyl)quinoline-3-carboxylic acid (**5**, 180 mg, 556 μmol, 86%) as a yellow solid, which was used in next step directly without further purification. LCMS (ESI): *m/z* = 324.1 $[M+H]^+$.

[00930] *STEP 5: Preparation of perfluorophenyl 6-((diethoxyphosphoryl)methyl)quinoline-3-carboxylate*

[00931] Oxalyl chloride (82.3 mg, 649 μmol, 1.5 eq.) was added dropwise to the solution of 6-((diethoxyphosphoryl)methyl)quinoline-3-carboxylic acid (**5**, 140 mg, 433 μmol, 1.0 eq.) in dry DCM (5 mL) and DMF (2 drops) at 0 °C. The reaction mixture was warmed to room temperature, then stirred for 2 h. The reaction was monitored by pipetting out a small amount of crude sample and quenching it with MeOH to ensure acyl chloride had been

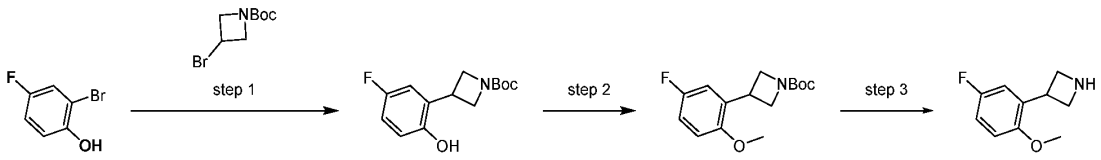
formed completely. After completion, the excess oxalyl chloride and solvent were removed under reduced pressure. The residue was re-dissolved in anhydrous DCM (5 mL), then added to a mixture of 2,3,4,5,6-pentafluorophenol (143 mg, 779 µmol, 1.8 eq.) and triethylamine (175 mg, 1.73 mmol, 4 eq.) in anhydrous DCM (2 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature, and stirred for an additional 30 min. The reaction progress was monitored by LCMS, and after completion, the reaction was quenched by adding H_2O (10 mL) and extracted with DCM (10 mL x 3). The organic layers were combined and washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford perfluorophenyl 6-((diethoxyphosphoryl)methyl)quinoline-3-carboxylate (**6**, 140 mg, 286 µmol, 66%) as a yellow solid. LCMS (ESI): *m/z* = 490 $[M+H]^+$.

[00932] *STEP 6: Preparation of ((3-((perfluorophenoxy)carbonyl)quinolin-6-yl)methyl)phosphonic acid*

[00933] To a solution of perfluorophenyl 6-((diethoxyphosphoryl)methyl)quinoline-3-carboxylate (**6**, 140 mg, 286 µmol, 1.0 eq.) in DCM (5 mL) was added TMSBr (1 mL), and the resulting mixture was stirred at room temperature for 16 h. After completion, the reaction mixture was concentrated under reduced pressure to give crude ((3-((perfluorophenoxy)carbonyl)quinolin-6-yl)methyl)phosphonic acid (**7**, 98.0 mg, 226 µmol, 80%) as a yellow solid, which was used in next step directly without further purification. LCMS (ESI): *m/z* = 434.1 $[M+H]^+$.

Syntheses of Building Blocks:

Synthesis of 3-(5-fluoro-2-methoxyphenyl)azetidine



[00934] *Step 1: Preparation of tert-butyl 3-(5-fluoro-2-hydroxyphenyl)azetidine-1-carboxylate*

[00935] A reaction vial containing a solution of tert-butyl 3-(5-fluoro-2-hydroxyphenyl)azetidine-1-carboxylate (1 g, 0.2 mmol, 1 eq), tert-butyl 3-bromoazetidine-1-carboxylate (1.24 g, 0.26 mmol, 1.3 eq) $Ir[dF(CF_3)ppy]_2(dtbpy)(PF_6)$ (1.12 g, 0.002 mmol, 0.01 eq), $NiCl_2$.dtbbpy (595 mg, 0.003 mmol , 0.015 eq), TTMSS (2.48 g, 0.2 mmol, 1 eq), Na_2CO_3 (2.12 g, 0.4 mmol, 2 eq) in DME (10 mL, 1 M) was sealed and placed under an

atmosphere of nitrogen. The reaction was stirred and irradiated with a 30 W blue LED lamp (3 cm away), with cooling water to keep the reaction temperature at 25 °C for 14 h. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL × 2), the combined organic layers were washed with saturated brine (100 mL × 2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give tert-butyl 3-(5-fluoro-2-hydroxyphenyl)azetidine-1-carboxylate (0.7 g, 67% yield) as a yellow oil.

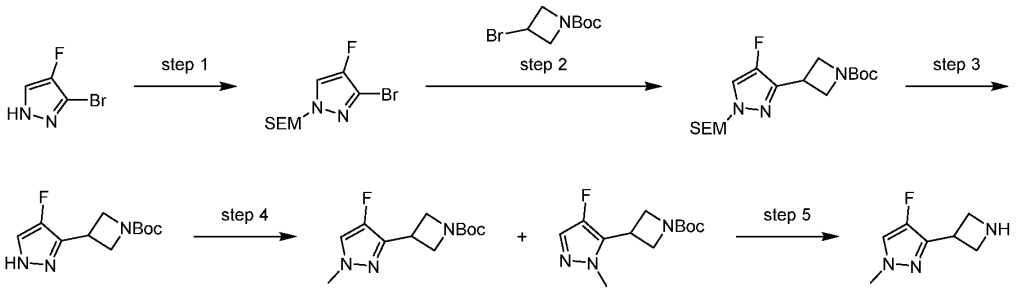
[00936] *Step 2: Preparation of tert-butyl 3-(5-fluoro-2-methoxyphenyl)azetidine-1-carboxylate*

[00937] To a solution of *tert-butyl 3-(5-fluoro-2-hydroxyphenyl)azetidine-1-carboxylate* (0.7 g, 2.61 mmol, 1 eq) in acetone (10 mL) was added iodomethane (0.41 g, 2.87 mmol, 1.1 eq) and potassium carbonate (0.54 g, 3.9 mmol, 1.5 eq). The mixture was stirred at 25 °C for 12 h. The reaction was diluted with water (100 mL) and extracted with EtOAc (100 mL × 2), the combined organic layers were washed with saturated brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 3-(5-fluoro-2-methoxyphenyl)azetidine-1-carboxylate (0.3 g, 1.1 mmol, 41% yield) as a yellow oil. LCMS (ESI) m/z = 226.3 $[M+H]^+$.

[00938] *Step 3: Preparation of 3-(5-fluoro-2-methoxyphenyl)azetidine*

[00939] To a solution of *tert-butyl 3-(5-fluoro-2-methoxyphenyl)azetidine-1-carboxylate* (0.3 g, 1.06 mmol , 1 eq) in DCM/TFA=3:1 (2 mL). The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give 3-(5-fluoro-2-methoxyphenyl)azetidine (0.2 g, crude) as a white solid. LCMS (ESI) m/z = 182.4 $[M+H]^+$.

Synthesis of 3-(azetidin-3-yl)-4-fluoro-1-methyl-1H-pyrazole



[00940] *Step 1: Preparation of 3-bromo-4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole*

[00941] To a solution of 3-bromo-4-fluoro-1H-pyrazole (1.5 g, 9.1 mmol, 1 eq) in THF (15 mL) was added NaH (0.5 g, 13.6 mmol, 1.5 eq) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h, followed by addition of SEMCl (2.7 g, 9.9 mmol, 1.1 eq) at 0 °C, the

mixture was stirred at 25 °C for 0.5 h to give a heterogenous solution with white precipitates. The reaction mixture was quenched by water (10 mL) at 0 °C and concentrated under reduced pressure to remove the THF. The mixture was purified by reverse phase (TFA) to lyophilized to give 3-bromo-4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (2.2 g, 7.5 mmol, 82% yield) as a yellow oil. LCMS (ESI) m/z =295.2

[00942] *Step 2: Preparation of tert-butyl 3-(4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)azetidine-1-carboxylate.*

[00943] To a 15 mL vial equipped with a stir bar was added 3-bromo-4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (2.0 g, 6.8 mmol, 1 eq), tert-butyl 3-bromoazetidine-1-carboxylate (1.9 g, 8.1 mmol, 1.2 eq), $Ir[dF(CF_3)ppy]_2(dtbpy)(PF_6)$ (0.8 g, 0.7 mmol, 0.1 eq), $NiCl_2$·dtbbpy (0.3 g, 0.7 mmol, 0.1 eq), TTMSS (1.7 g, 6.8 mmol, 1 eq), Na_2CO_3 (1.4 g, 13.5 mmol, 2 eq) and DME (20 mL). The vial was sealed and placed under nitrogen was added. The reaction was stirred and irradiated with a 10 W blue LED lamp (3 cm away), with cooling water to keep the reaction temperature at 25 ℃ for 14 h to give a brown suspension solution. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by reverse phase (TFA) to lyophilized to give tert-butyl 3-(4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)azetidine-1-carboxylate (0.8 g, 2.2 mmol, 31.8 % yield) as a yellow oil. LCMS (ESI) m/z =315.7 $[M+H]^+$. ^1H NMR (400 MHz, CDCl3) δ 7.43 - 7.33 (m, 1H), 5.34 - 5.27 (m, 2H), 4.36 - 4.14 (m, 5H), 3.57 - 3.43 (m, 2H), 1.47 - 1.44 (m, 9H), 0.91 - 0.79 (m, 2H), 0.00 - -0.05 (m, 9H).

[00944] *Step 3: Preparation of tert-butyl 3-(4-fluoro-1H-pyrazol-3-yl)azetidine-1-carboxylate*

[00945] To a solution of tert-butyl 3-(4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)azetidine-1-carboxylate (0.5 g, 1.5 mmol, 1 eq) in THF (1 mL) was added a solution of TBAF (7.4 mL, 7.5 mmol, 5 eq) in THF at 25 °C, then then mixture was stirred at 50 °C for 12 h to give a brown solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by reverse phase (TFA) to lyophilized to give tert-butyl 3-(4-fluoro-1H-pyrazol-3-yl)azetidine-1-carboxylate (0.3 g, 1.2 mmol, 84% yield) as a yellow oil. LCMS (ESI) m/z =242.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 4.6 Hz, 1H), 4.34 - 4.24 (m, 2H), 4.20 - 4.12 (m, 2H), 3.92 - 3.77 (m, 1H), 1.45 (s, 9H)

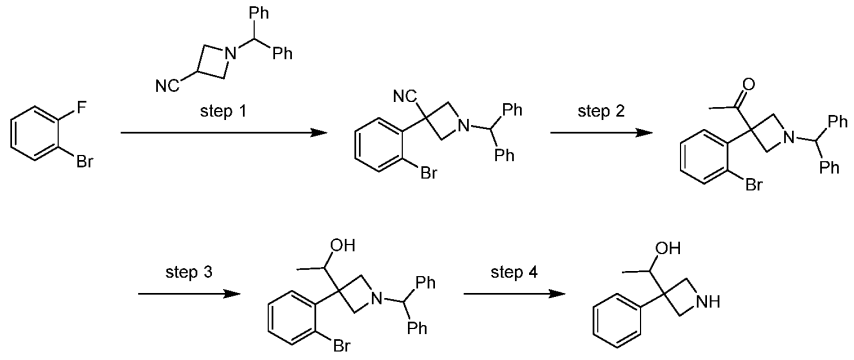
[00946] *Step 4: Preparation of tert-butyl 3-(4-fluoro-1-methyl-1H-pyrazol-3-yl)azetidine-1-carboxylate and tert-butyl 3-(4-fluoro-1-methyl-1H-pyrazol-5-yl)azetidine-1-carboxylate*

[00947] To a solution of tert-butyl 3-(4-fluoro-1H-pyrazol-3-yl)azetidine-1-carboxylate (0.3 g, 1.0 mmol, 1 eq) in THF (3 mL) was added Cs_2CO_3 (0.5 g, 1.5 mmol, 1.5 eq), then cooled to 0 °C, then iodomethane (0.3 g, 2.1 mmol, 2 eq) was added to the mixture at 0 °C. Then the mixture was stirred at 25 ° C for 2 h to give a white suspension. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150 X 25 mm X 5 um; mobile phase: water (TFA) - ACN; B%: 32%-52%,10 min) then lyophilized to give tert-butyl 3-(4-fluoro-1-methyl-1H-pyrazol-3-yl)azetidine-1-carboxylate (80 mg, 0.3 mmol, 30% yield) as a yellow oil. LCMS (ESI) m/z =200.0 $[M+H]^+$. ^1H NMR (400 MHz, CDCl3) δ 7.26 (s, 1H), 4.30 (m, 2H), 4.22 (m, 2H), 3.91 - 3.87 (m, 1H), 3.85 (s, 3H), 1.51 (s, 9H). Additionally, tert-butyl 3-(4-fluoro-1-methyl-1H-pyrazol-5-yl)azetidine-1-carboxylate (40 mg, 0.1 mmol, 15% yield) was isolated as a yellow oil. LCMS (ESI) m/z =256.0 $[M+H]^+$. ^1H NMR (400 MHz, CDCl3) δ 7.26 (s, 1H), 4.33 - 4.25 (m, 2H), 4.24 - 4.16 (m, 2H), 3.87 - 3.77 (m, 1H), 3.71 (s, 3H), 1.45 (s, 9H)

[00948] Step 5: *Preparation of 3-(azetidin-3-yl)-4-fluoro-1-methyl-1H-pyrazole*

[00949] To a solution of tert-butyl 3-(4-fluoro-1-methyl-1H-pyrazol-3-yl)azetidine-1-carboxylate (60 mg, 0.2 mmol, 1 eq) in DCM (1 mL) was added TFA (0.3 mL). Then the mixture was stirred at 25 °C for 1 h to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give 3-(azetidin-3-yl)-4-fluoro-1-methyl-1H-pyrazole (60.0 mg) as a yellow oil. LCMS (ESI) m/z =156.1 $[M+H]^+$.

Synthesis of 1-(3-phenylazetidin-3-yl)ethan-1-ol



[00950] *Step 1: Preparation of 3-(2-bromophenyl)-1-(diphenylmethyl)azetidine-3-carbonitrile.*

[00951] To a cooled (0 °C) solution of 1-bromo-2-fluorobenzene (10 g, 57 mmol, 1.0 eq) and 1-(diphenylmethyl)azetidine-3-carbonitrile (14 g, 57 mmol, 1.0 eq) in THF (120 mL) was added a solution of KHMDS (85 mL, 85 mmol, 1.5 eq) in THF. The mixture was stirred and

warmed to 25 °C for 12 h to give a brown solution. The reaction mixture was quenched by H_2O (50 mL) at 0 °C and extracted with EtOAc 150 mL (50 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give 3-(2-bromophenyl)-1-(diphenylmethyl)azetidine-3-carbonitrile (5.0 g, 12.4 mmol, 22% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.45 (d, J=8.0 Hz, 2H), 3.98 (d, J=8.0 Hz, 2H), 4.55 (s, 1H), 7.23 (d, J=8.0 Hz, 2H), 7.32 (t, J=8.0 Hz, 5H), 7.40 - 7.49 (m, 6H), 7.69 (d, J=8.0 Hz, 1H).

[00952] *Step 2: Preparation of 1-[3-(2-bromophenyl)-1-(diphenylmethyl)azetidin-3-yl]ethan-1-one*

[00953] To a solution of 3-(2-bromophenyl)-1-(diphenylmethyl)azetidine-3-carbonitrile (4.5 g, 11 mmol, 1.0 eq) in THF (30 mL) was added a solution of methylmagnesium bromide (2.7 g, 22 mol, 2.0 eq) at 0 °C. Then mixture was stirred warmed to 40 °C over 12 h. The reaction mixture was quenched by water (100 mL) at 0 °C and extracted with EtOAc (100 mL ×3) .The combined organic layer was washed with brine (200 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give 1-[3-(2-bromophenyl)-1-(diphenylmethyl)azetidin-3-yl]ethan-1-one (1.8 g, 3.7 mmol, 38% yield) as a white solid. ^{1}H NMR (400 MHz, CDCl3) δ 7.57 (m, 1H), 7.49 (d, J=8.0 Hz, 4H), 7.31 - 7.38 (m, 5H), 7.26 (s, 4H), 4.44 (s, 1H), 4.07 (d, J=8.0 Hz, 2H), 3.48 (d, J=8.0 Hz, 2H), 2.38 (s, 3H).

[00954] *Step 3: Preparation of 1-[3-(2-bromophenyl)-1-(diphenylmethyl)azetidin-3-yl]ethan-1-ol*

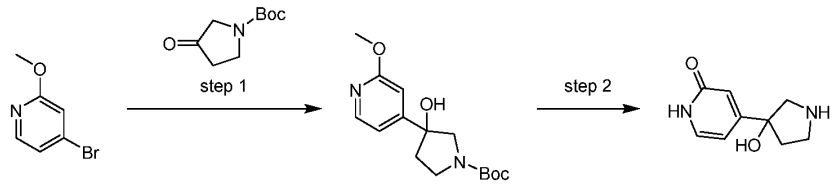
[00955] To a solution of 1-[3-(2-bromophenyl)-1-(diphenylmethyl)azetidin-3-yl]ethan-1-one (1.8 g, 3.7 mmol, 1.0 eq) in EtOH (20 mL) was added $NaBH_4$ (828 mg, 22 mmol, 6.0 eq) at 0 °C. The mixture was stirred at 25 °C for 4 h to give a suspension. The reaction mixture was quenched by MeOH (50 mL) at 0 °C, after stirring 2 h, the mixture was concentrated to give residue. The residue was purified by column chromatography to give 1-[3-(2-bromophenyl)-1-(diphenylmethyl)azetidin-3-yl]ethan-1-ol (1.4 g, 3.3 mmol, 92% yield) as a white solid. LCMS (ESI) m/z = 423.9 $[M+H]^+$.

[00956] *Step 4: Preparation of 1-(3-phenylazetidin-3-yl)ethan-1-ol*

[00957] To a solution of 1-[3-(2-bromophenyl)-1-(diphenylmethyl)azetidin-3-yl]ethan-1-ol (0.75 g, 1.8 mmol, 1.0 eq) in MeOH (10 mL) was added Pd/C (0.4 g) under N_2, then mixture was stirred at 25 °C for 24 h under H_2 (15 Psi) to give black suspension. The reaction mixture was filtered and concentrated under reduced pressure to give 1-(3-phenylazetidin-3-yl)ethan-1-ol (0.35 g, crude) as a green solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 (d, J=8.0 Hz, 2H)

7.30 (d, J=8.0 Hz, 1H) 7.15 - 7.20 (m, 2H) 4.29 - 4.35 (m, 1H) 4.24 (s, 1H) 4.17 - 4.22 (m, 1H) 3.99 (d, J=12.0 Hz, 1H) 3.86 - 3.94 (m, 1 H) 0.75 (d, J=8.0 Hz, 3H).

Synthesis of 4-(3-hydroxypyrrolidin-3-yl)pyridin-2(1H)-one



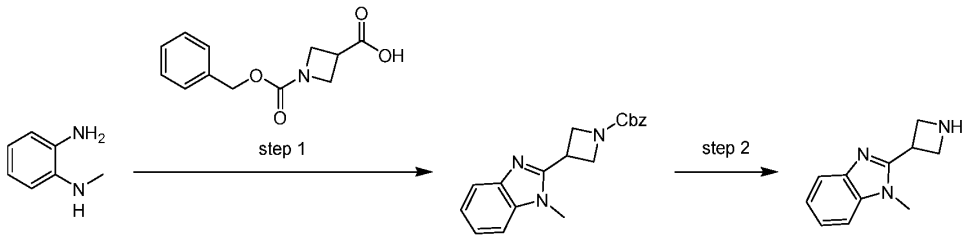
[00958] *Step 1: Preparation of tert-butyl 3-hydroxy-3-(2-methoxypyridin-4-yl)pyrrolidine-1-carboxylate*

[00959] To a cooled (-40 °C) solution (under N_2) of 4-bromo-2-methoxypyridine (1.5 g, 8.0 mmol) in THF (10 mL) was added n-BuLi (7.2 mL, 18 mmol). The mixture was stirred at -40 °C for 2 h, followed by addition of tert-butyl 3-oxopyrrolidine-1-carboxylate (1.5 g, 8.0 mmol). The mixture was stirred at -40 °C for 30 min, allowed to warm to 20 °C over 12 h. The resulting orange mixture was quenched by H_2O (50 mL), then was extracted with EtOAc (80 mL × 3), the combined organic layers were washed with saturated brine (80 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give tert-butyl 3-hydroxy-3-(2-methoxypyridin-4-yl)pyrrolidine-1-carboxylate (0.40 g, 1.36 mmol, 17% yield) as a yellow oil. ^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (d, J = 5.6 Hz, 1H), 7.07 (d, J = 5.6 Hz, 1H), 6.96 (s, 1H), 3.91 (s, 3H), 3.64 - 3.50 (m, 4H), 2.38 - 2.27 (m, 1H), 2.13 - 2.05 (m, 1H), 1.48 (d, J = 7.6 Hz, 9H).

[00960] *Step 2: Preparation of 4-(3-hydroxypyrrolidin-3-yl)pyridin-2(1H)-one*

[00961] To a solution of tert-butyl 3-hydroxy-3-(2-methoxypyridin-4-yl)pyrrolidine-1-carboxylate (0.1 g, 0.40 mmol) was added HBr/AcOH (3 mL). The mixture was stirred at 80 °C for 12 h to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give 4-(3-hydroxypyrrolidin-3-yl)pyridin-2(1H)-one (0.10 g, crude) as a black oil. LCMS (ESI) m/z = 181.0 $[M+H]^+$.

Synthesis of 2-(azetidin-3-yl)-1-methyl-1H-benzo[d]imidazole



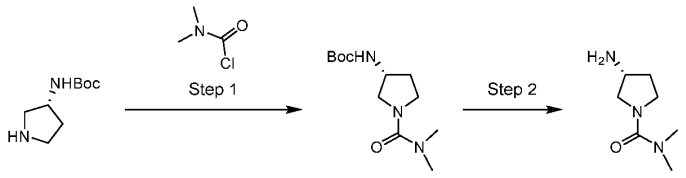
[00962] *Step 1: Preparation of benzyl 3-(1-methyl-1H-benzo[d]imidazol-2-yl)azetidine-1-carboxylate*

[00963] To a solution of N1-methylbenzene-1,2-diamine (0.73 g, 6.0 mmol, 1.4 eq) and 1-[(benzyloxy)carbonyl]azetidine-3-carboxylic acid (1 g, 4.3 mmol, 1 eq) in THF (20 mL) was sequentially added EDCI (0.98 g, 5.1 mmol, 1.2 eq) and N,N-diisopropylethylamine (1.6 g, 13 mmol, 3 eq) and 1-hydroxy-7-azabenzotriazole (0.69 g, 5.1 mmol, 1.2 eq). The mixture was stirred at 25 °C for 18 h. the reaction solution was concentrated. The residue was dissolved in acetic acid (10 mL). After stirring at ambient temperature for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give benzyl 3-(1-methyl-1H-benzo[d]imidazol-2-yl)azetidine-1-carboxylate (1.3 g, 4.0 mmol, 70% yield) as a yellow solid. LCMS (ESI) m/z = 322.1 $[M+H]^+$.

[00964] *Step 2: Preparation of 2-(azetidin-3-yl)-1-methyl-1H-benzo[d]imidazole*

[00965] To a solution of benzyl 3-(1-methyl-1H-1,3-benzodiazol-2-yl)azetidine-1-carboxylate (1.30 g, 4.0 mmol, 1 eq) in MeOH (20 mL) was added Pd/C (0.40 g) under N_2, the mixture was stirred at 25 °C under H_2 (15 psi) for 16 h to give a black mixture. The reaction mixture filtered and the filtrate was concentrated under reduced pressure to give 2-(azetidin-3-yl)-1-methyl-1H-benzo[d]imidazole (0.9 g crude) as a black solid. LCMS (ESI) m/z = 188.2 $[M+H]^+$.

Synthesis of (R)-3-amino-N,N-dimethylpyrrolidine-1-carboxamide



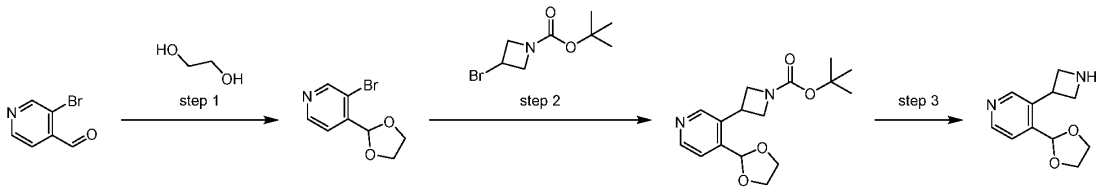
[00966] *Step 1: Preparation of (R)-tert-butyl (1-(dimethylcarbamoyl)pyrrolidin-3-yl)carbamate*

[00967] To a solution of tert-butyl N-[(3R)-pyrrolidin-3-yl]carbamate (300 mg, 1.61 mmol, 1 eq) in methylene chloride (3 mL) was added triethylamine (488 mg, 4.83 mmol, 3 eq) was stirred at 25 °C for 10 min. The mixture was subsequently cooled to 0 °C and dimethylcarbamic chloride (207 mg, 1.93 mmol, 1.2 eq) was dropwise at 0 °C. The reaction mixture was stirred at 25 °C for 1 h to give a white suspension. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL × 2), the combined organic layers were washed with saturated brine (10 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give (R)-tert-butyl (1-(dimethylcarbamoyl)pyrrolidin-3-yl)carbamate (0.3 g, 0.99 mmol, 62% yield) as a yellow oil. LCMS (ESI) m/z = 257.9 $[M+H]^+$. ^1H NMR (400 MHz, CDCl3) δ 4.24 - 4.06 (m, 1H), 3.58 (dd, J = 6.0, 10.9 Hz, 1H), 3.46 - 3.46 (m, 1H), 3.53 - 3.46 (m, 1H), 3.46 - 3.37 (m, 1H), 3.24 (d, J = 4.0 Hz, 1H), 2.84 (s, 6H), 2.08 (dd, J = 5.6, 12.9 Hz, 1H), 1.87 - 1.73 (m, 1H), 1.45 (s, 9H).

[00968] *Step 2: Preparation of (R)-3-amino-N,N-dimethylpyrrolidine-1-carboxamide (2).*

[00969] To a solution of (R)-tert-butyl (1-(dimethylcarbamoyl)pyrrolidin-3-yl)carbamate (150 mg, 0.58 mmol, 1 eq) in methylene chloride (3 mL) was added TFA (1 mL) and the mixture was stirred at 25°C for 1 h. The yellow suspension was concentrated under reduced pressure to give (R)-3-amino-N,N-dimethylpyrrolidine-1-carboxamide (150 mg, crude) as a yellow oil. LCMS (ESI) m/z = 158.0 $[M+H]^+$.

Synthesis of 3-(azetidin-3-yl)-4-(1,3-dioxolan-2-yl)pyridine



[00970] *Step 1: Preparation of 3-bromo-4-(1,3-dioxolan-2-yl)pyridine*

[00971] To a solution of 3-bromoisonicotinaldehyde (1 g, 5.4 mmol, 1 eq) in toluene (15 mL) was added 4-methylbenzene-1-sulfonic acid (0.28 g, 1.62 mmol, 0.30 eq) and ethane-1,2-diol (0.66 g, 11 mmol, 2 eq). The mixture was stirred at 110 °C for 12 h to give a yellow clean solution. The mixture was purified by flash silica gel chromatography to give 3-bromo-4-(1,3-dioxolan-2-yl)pyridine (0.80 g, 3.48 mmol, 65% yield) as a white solid. ^1H NMR (400 MHz, CDCl3) δ 8.71 - 8.68 (m, 1H), 8.51 (d, J = 4.8 Hz, 1H), 7.45 (d, J = 5.2 Hz, 1H), 5.99 (s, 1H), 4.13 - 4.08 (m, 2H), 4.07 - 4.03 (m, 2H).

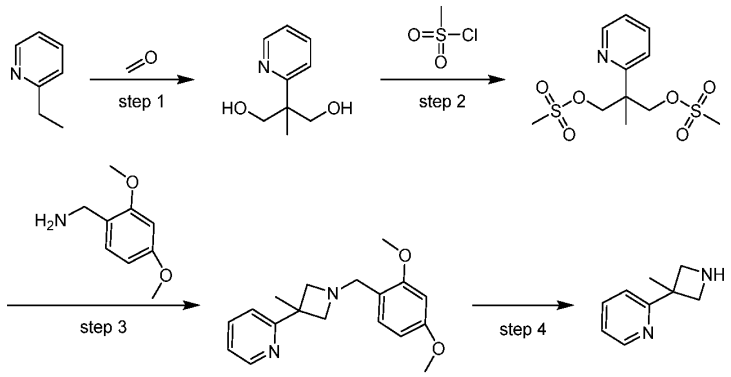
[00972] *Step 2: Preparation of tert-butyl 3-(4-(1,3-dioxolan-2-yl)pyridin-3-yl)azetidine-1-carboxylate*

[00973] To a solution of 3-bromo-4-(1,3-dioxolan-2-yl)pyridine (0.20 g, 0.87 mmol, 1 eq) in DME (5 mL) was added tert-butyl 3-bromoazetidine-1-carboxylate (0.26 g, 1.1 mmol, 1.3 eq), $Ir[dF(CF_3)ppy]_2(dtbpy)(PF_6)$ (11 mg, 8.7 μmol, 0.010 eq), $NiCl_2$·dtbbpy (5.2 mg, 13 μmol, 0.015 eq), TTMSS (0.22 g, 0.87 mmol, 1 eq) and Na_2CO_3 (0.18 g, 1.7 mmol, 2 eq). The mixture was stirred at 25 °C for 14 h. The resulting homogeneous red solution was concentrated under reduced pressure to give a residue. The residue was diluted with water (20 mL) and extracted with EtOAc (20 mL × 2), the combined organic layers were washed with saturated brine (20 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, the residue was purified by flash silica gel chromatography to give tert-butyl 3-(4-(1,3-dioxolan-2-yl)pyridin-3-yl)azetidine-1-carboxylate (100 mg, 0.33 mmol, 37% yield) as yellow oil. LCMS (ESI) m/z = 307.1 [M+H]+.

[00974] *Step 3: Preparation of 3-(azetidin-3-yl)-4-(1,3-dioxolan-2-yl)pyridine*

[00975] To a solution of tert-butyl 3-(4-(1,3-dioxolan-2-yl)pyridin-3-yl)azetidine-1-carboxylate (0.10 g, 0.33 mmol, 1 eq) in DCM (1 mL) was added TFA (0.30 mL). The mixture was stirred at 25 °C for 30 min to give a yellow clean solution and the reaction mixture was subsequently concentrated under reduced pressure to give 3-(azetidin-3-yl)-4-(1,3-dioxolan-2-yl)pyridine (0.10 g, crude) as yellow solid.

Synthesis of 2-(3-methylazetidin-3-yl)pyridine



[00976] *Step 1: Preparation of 2-methyl-2-(pyridin-2-yl)propane-1,3-diol*

[00977] A solution of 2-ethylpyridine (25 g, 0.23 mol, 1.0 eq) in formaldehyde (188 mL, 2.3 mol, 10 eq, 37% aqueous solution) was stirred at 140 °C for 68 h under N2. The mixture was filter and the filtrate was purified by reversed phase (basic system) to lyophilized to give desired 2-methyl-2-(pyridin-2-yl)propane-1,3-diol (0.38 g, 2.3 mmol, 0.98% yield) as a

colorless oil. 1H NMR (400 MHz, CD3OD) δ 8.59 - 8.45 (m, 1H), 7.78 (dt, J = 2.0, 8.0 Hz, 1H), 7.55 - 7.45 (m, 1H), 7.33 - 7.21 (m, 1H), 3.87 - 3.83 (m, 4H), 1.33 (s, 3H).

[00978] *Step 2: Preparation of 3-(methanesulfonyloxy)-2-methyl-2-(pyridin-2-yl)propylmethanesulfonate*

[00979] To a cooled (0 °C) solution of 2-methyl-2-(pyridin-2-yl)propane-1,3-diol (0.5 g, 3.0 mmol, 1.0 eq) triethylamine (1.5 g, 15 mmol, 5.0 eq) in DCM (10 mL) was added MsCl (1.4 g, 12 mmol, 4.0 eq) in a dropwise manner. After stirring 1 h, the resulting yellow suspension was quenched by ice water (20 mL) and then was extracted with DCM (30 mL × 2). The combined organic layers were washed with saturated $NaHCO_3$ (30 mL), saturated brine (40 mL × 2), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give 3-(methanesulfonyloxy)-2-methyl-2-(pyridin-2-yl)propyl methanesulfonate (0.6 g, crude) as a yellow oil. 1H NMR (400 MHz, CDCl3) δ 8.67 - 8.46 (m, 1H), 7.73 (dt, J = 1.6, 7.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.26 - 7.20 (m, 1H), 4.67 - 4.51 (m, 4H), 2.96 (s, 6H), 1.51 (s, 3H).

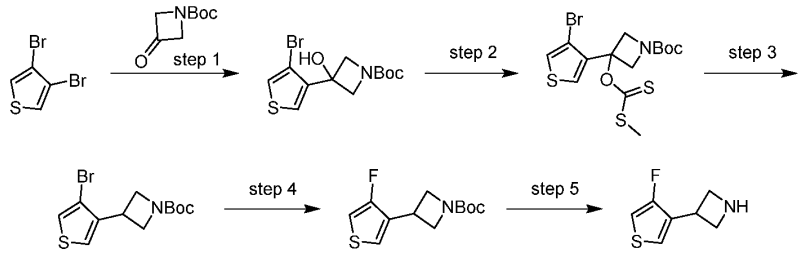
[00980] *Step 3: Preparation of 2-(1-(2,4-dimethoxybenzyl)-3-methylazetidin-3-yl)pyridine*

[00981] To a solution of 3-(methanesulfonyloxy)-2-methyl-2-(pyridin-2-yl)propyl methanesulfonate (0.42 g, 1.3 mmol, 1 eq) in MeCN (6 mL) was added 1-(2,4-dimethoxyphenyl)methanamine (0.26 g, 1.5 mmol, 1.2 eq) and ethylbis(propan-2-yl)amine (0.5 g, 3.9 mmol, 3.0 eq). The mixture was stirred at 80 °C for 12 h to get a yellow solution. The reaction was concentrated in vacuum to get a residue. The residue was purified by silica gel column to get product 2-(1-(2,4-dimethoxybenzyl)-3-methylazetidin-3-yl)pyridine (0.33 g, 1.1 mmol, 86.1% yield) as a yellow oil. 1H NMR (400 MHz, CDCl3) δ 8.62 (d, J = 4.0 Hz, 1H), 7.69 (dt, J = 2.0, 7.6 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.24 - 7.16 (m, 2H), 6.50 (dd, J = 2.4, 8.4 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 4.27 - 4.06 (m, 4H), 3.85 - 3.79 (m, 6H), 2.84 (s, 2H), 1.80 (s, 3H).

[00982] *Step 4: Preparation of 2-(3-methylazetidin-3-yl)pyridine*

[00983] To a suspension of 2-(1-(2,4-dimethoxybenzyl)-3-methylazetidin-3-yl)pyridine (0.25 g, 0.84 mol, 1.0 eq) in MeCN/H2O (20 mL) was added λ^4-cerium(4+) bis(nitric acid) diamine tetranitrate (2.8 g, 5.0 mmol, 6 eq). The mixture was stirred at 60 °C for 4 h to give a yellow solution. The mixture was filter and the filtrate was purified by reversed phase (TFA system) to lyophilized to give 2-(3-methylazetidin-3-yl)pyridine (0.13 g, 0.84 mmol, 90% yield) as a yellow solid. 1H NMR (400 MHz, CD3OD) δ 8.75 - 8.66 (m, 1H), 8.11 (dt, J = 2.0, 8.0 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.62 - 7.50 (m, 1H), 4.64 (d, J = 11.2 Hz, 2H), 4.21 (d, J = 11.2 Hz, 2H), 1.82 (s, 3H).

Synthesis of 3-(4-fluorothiophen-3-yl)azetidine



[00984] *Step 1: Preparation of tert-butyl 3-(4-bromothiophen-3-yl)-3-hydroxyazetidine-1-carboxylate*

[00985] A solution of 3,4-dibromothiophene (10 g, 41.3 mmol, 1 eq) in THF (100 mL) was cooled it to -78 °C under N2. To the mixture was slowly added butyllithium (18 mL, 45.4 mmol, 1 eq). The mixture was stirred at -78 °C for 10 min. To the mixture was added tert-butyl 3-oxoazetidine-1- carboxylate (7.77 g, 45.4 mmol, 1.2 eq) solution in THF (100 mL) dropwise over 30 min. The mixture was stirred at -78 °C for 2 h and subsequently warmed to 0 °C. The reaction mixture was quenched by saturated NH4Cl (50 mL), then was diluted with water (200 mL) and extracted with EtOAc (200 mL × 2). The combined organic layers were washed with saturated brine (200 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give tert-butyl 3-(4-bromothiophen-3-yl)-3-hydroxyazetidine-1-carboxylate tert-butyl 3-(4-bromothiophen-3-yl)-3-hydroxyazetidine-1-carboxylate (4.40 g, 13.1 mmol, 31.8% yield) as yellow. LCMS (ESI) m/z = 357.8 [M+H]+.

[00986] *Step 2: Preparation of tert-butyl 3-(4-bromothiophen-3-yl)-3-(((methylthio)carbonothioyl)oxy)azetidine-1-carboxylate*

[00987] To a cooled (0 °C) solution of tert-butyl 3-(4-bromothiophen-3-yl)-3-hydroxyazetidine-1-carboxylate tert-butyl 3-(4-bromothiophen-3-yl)-3-hydroxyazetidine-1-carboxylate (5 g, 14.9 mmol, 1 eq) in THF (50 mL) under N2 was added NaH (1.78 g, 44.7 mmol, 3 eq). The mixture stirred at 25 °C for 1.5 h, subsequently cooled to 0 °C and CS2 (2.04 g, 26.8 mmol, 1.8 eq) was slowly added. The mixture was stirred at 0 °C for 1 h, followed was added iodomethane (4.64 g, 32.7 mmol, 2.2 eq) and stirred at 25 °C. After stirring for 1.5 h, the reaction mixture was quenched with saturated NH_4Cl (50 mL). The reaction was diluted with water (100 mL) and extracted with DCM (100 mL × 2). The combined organic layers were washed with saturated brine (100 mL × 2), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified

by flash silica gel chromatography to give tert-butyl 3-(4-bromothiophen-3-yl)-3-(((methylthio)carbonothioyl)oxy)azetidine-1-carboxylate (4.50 g, 10.6 mmol, 71.2% yield) as a white solid.

[00988] *Step 3: Preparation of tert-butyl 3-(4-bromothiophen-3-yl)azetidine-1-carboxylate*

[00989] To a solution of tert-butyl 3-(4-bromothiophen-3-yl)-3-(((methylthio)carbonothioyl)oxy)azetidine-1-carboxylate (1 g, 2.35 mmol, 1 eq) in toluene (10 mL) was added 2-[(1E)-2-(1-cyano-1-methylethyl)diazen-1-yl]-2-methylpropanenitrile (38.5 mg, 235 μmol, 0.1 eq) and tributyltin hydride (1.03 g, 3.52 mmol, 1.5 eq). The mixture was stirred at 25°C for 12 h. The reaction was diluted with water (100 mL) and extracted with EtOAc (100 mL × 2). The combined organic layers were washed with saturated brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/EtOAc = 10: 1 to 3: 1) to give tert-butyl 3-(4-bromothiophen-3-yl)azetidine-1-carboxylate (0.5 g, 1.57 mmol, 66.9% yield) as a white solid. LCMS (ESI) m/z = 263.9 [M+H]+.

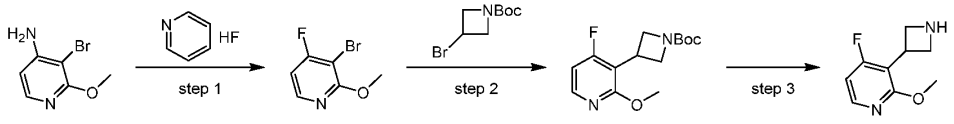
[00990] *Step 4: Preparation of tert-butyl 3-(4-fluorothiophen-3-yl)azetidine-1-carboxylate*

[00991] To a solution of tert-butyl 3-(4-bromothiophen-3-yl)azetidine-1-carboxylate (0.2 g, 628 μmol, 1 eq) in THF (4 mL) was added N-(benzenesulfonyl)-N-fluorobenzenesulfonamide (472 mg, 1.50 mmol, 2.4 eq) and butyllithium (0.5 mL, 1.38 mmol, 2.2 eq). The mixture was stirred at -78°C for 3 h. The reaction mixture was quenched by saturated NH_4Cl (50 mL). The reaction was diluted with water (50 mL) and extracted with EtOAc (50 mL × 2), the combined organic layers were washed with saturated brine (50 mL × 2), dried over Na2SO4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give tert-butyl 3-(4-fluorothiophen-3-yl)azetidine-1-carboxylate (100 mg, 388 μmol, 62.1% yield) as a white solid. LCMS (ESI) m/z = 257.8 [M+H]+.

[00992] *Step 5: Preparation of 3-(4-fluorothiophen-3-yl)azetidine*

[00993] To a solution of tert-butyl 3-(4-fluorothiophen-3-yl)azetidine-1-carboxylate (100 mg, 388 μmol, 1 eq) in DCM/TFA=3:1 (2 mL). The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give 3-(4-fluorothiophen-3-yl)azetidine (80 mg, crude) as a yellow oil. LCMS (ESI) m/z = 158.1 $[M+H]^+$.

Synthesis of 3-(azetidin-3-yl)-4-fluoro-2-methoxypyridine



[00994] *Step 1: Preparation of 3-bromo-4-fluoro-2-methoxypyridine*

[00995] A mixture of 3-bromo-2-methoxypyridin-4-amine (500 mg, 2.5 mmol, 1 eq) in pyridine hydrofluoride salt (4 mL) was stirred at -10 °C. to the mixture as added sodium nitrite (253 mg, 3.7 mmol, 1.5 eq) in portions (10 batch) to the solution at 0 °C. Then the mixture was stirred at 60 °C for 1 h. The reaction mixture was adjusted to pH = 7-8 by aqueous solution of 1N Na2CO3 at 20 °C, then extracted with EtOAc (40 mL × 2). Combined organic layers were washed with brine (40 mL × 2), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give compound 3-bromo-4-fluoro-2-methoxypyridine (300 mg, 1.5 mmol, 59% yield) as a white solid. 1H NMR (400 MHz, CDCl3) δ 8.03 (dd, J = 5.6, 7.6 Hz, 1H), 6.72 (dd, J = 5.6, 7.2 Hz, 1H), 4.03 (s, 3H).

[00996] *Step 2: Preparation of tert-butyl 3-(4-fluoro-2-methoxypyridin-3-yl)azetidine-1-carboxylate*

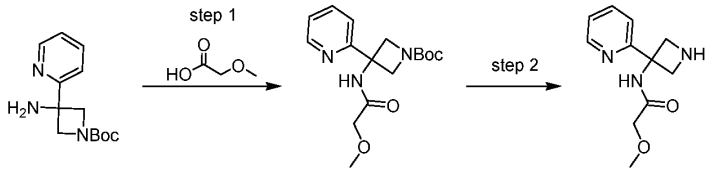
[00997] To an 15 mL vial equipped with a stir bar was added 3-bromo-4-fluoro-2-methoxypyridine (41 mg, 0.19 mmol, 1 eq), tert-butyl 3-bromoazetidine-1-carboxylate (61 mg, 0.26 mmol, 1.3 eq), sodium carbonate (42 mg, 0.39 mmol, 2 eq), 1,1,1,3,3,3-hexamethyl-2-(trimethylsilyl)trisilane (49 mg, 0.19 mmol, 1.0 eq), $Ir[dF(CF_3)ppy]_2(dtbpy)(PF_6)$ (2.2 mg, 2.0 μmol, 0.01 eq), $NiCl_2$·dtbbpy (1.2 mg, 3.0 μmol, 0.02 eq) in DME (2 mL). The vial was sealed and placed under nitrogen was added. The reaction was stirred and irradiated with a 10 W blue LED lamp (3 cm away), with cooling water to keep the reaction temperature at 25 °C for 14 h. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC to give compound tert-butyl 3-(4-fluoro-2-methoxypyridin-3-yl)azetidine-1-carboxylate (20 mg, 71 μmol, 36% yield) as a colorless oil. 1H NMR (400 MHz, CDCl3) δ 7.95 - 7.91 (m, 1H), 6.60 - 6.57 (m, 1H), 4.14 (d, J = 8.0 Hz, 4H), 3.98 - 3.96 (m, 1H), 3.92 - 3.89 (m, 3H), 1.40 (s, 9H)).

[00998] *Step 3: Preparation of 3-(azetidin-3-yl)-4-fluoro-2-methoxypyridine*

[00999] A mixture of tert-butyl 3-(4-fluoro-2-methoxypyridin-3-yl)azetidine-1-carboxylate (20 mg, 71 μmol, 1 eq) in methylene chloride (0.6 mL) and TFA (0.2 mL) was stirred at 20 °C for 0.5 h. The mixture was concentrated under reduced pressure to give compound 3-

(azetidin-3-yl)-4-fluoro-2-methoxypyridine (20 mg, crude) as a colorless oil. LCMS (ESI) m/z = 183.2 $[M+H]^+$.

Synthesis of 2-methoxy-N-(3-(pyridin-2-yl)azetidin-3-yl)acetamide



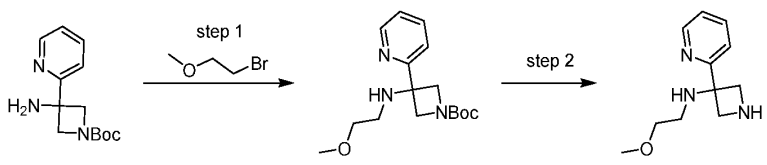
[001000] *Step 1: Preparation of tert-butyl 3-(2-methoxyacetamido)-3-(pyridin-2-yl)azetidine-1-carboxylate*

[001001] To a solution of tert-butyl 3-amino-3-(2-pyridyl)azetidine-1-carboxylate (150 mg, 601 µmol, 1 eq), 2-methoxyacetic acid (108 mg, 1.20 mmol, 92 µL, 2 eq) in DMF (2 mL) was added HATU (251 mg, 661 µmol, 1.1 eq) and DIEA (233 mg, 1.80 mmol, 314 µL, 3 eq). The mixture was stirred at 25 °C for 1 h to give a colorless solution. The mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give tert-butyl 3-[(2-methoxyacetyl)amino]-3-(2-pyridyl)azetidine-1-carboxylate (150 mg, 457 µmol, 76% yield) as an off-white solid. LCMS: (ES+) m/z = 322.3 [M+H]+.

[001002] *Step 2: Preparation of 2-methoxy-N-(3-(pyridin-2-yl)azetidin-3-yl)acetamide*

[001003] To a solution of tert-butyl 3-[(2-methoxyacetyl)amino]-3-(2-pyridyl)azetidine-1-carboxylate (150 mg, 466 µmol, 1 eq) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at 25 °C for 1 h to give a colorless solution. The reaction mixture was concentrated under reduced pressure to give 2-methoxy-N-[3-(2-pyridyl)azetidin-3-yl]acetamide (180 mg, crude) as a colorless oil.

Synthesis of N-(2-methoxyethyl)-3-(pyridin-2-yl)azetidin-3-amine



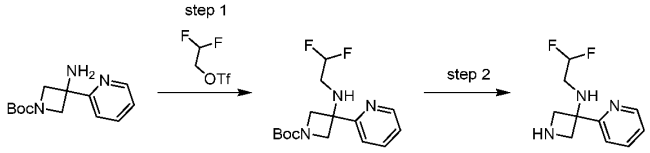
[001004] *Step 1: Preparation of tert-butyl 3-((2-methoxyethyl)amino)-3-(pyridin-2-yl)azetidine-1-carboxylate*

[001005] To a solution of tert-butyl 3-amino-3-(2-pyridyl)azetidine-1-carboxylate (150 mg, 601 μmol, 1 eq), 1-bromo-2-methoxy-ethane (167 mg, 1.20 mmol, 113 μL, 2 eq) in CH3CN (2 mL) was added K2CO3 (249 mg, 1.80 mmol, 3 eq) and KI (199 mg, 1.20 mmol, 2 eq). The mixture was stirred at 80 °C for 12 h to give a colorless solution. The mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give tert-butyl 3-(2-methoxyethylamino)-3-(2-pyridyl)azetidine-1-carboxylate (100 mg, 286 μmol, 48% yield) as an off-white solid. LCMS (ESI) m/z = 308.2 [M+H]+.

[001006] *Step 2: Preparation of N-(2-methoxyethyl)-3-(pyridin-2-yl)azetidin-3-amine*

[001007] To a solution of tert-butyl 3-(2-methoxyethylamino)-3-(2-pyridyl)azetidine-1-carboxylate (100 mg, 286 μmol, 1 eq) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at 25 °C for 2 h to give a colorless solution. The reaction mixture was concentrated under reduced pressure to give N-(2-methoxyethyl)-3-(pyridin-2-yl)azetidin-3-amine (100 mg, crude) as a colorless oil.

Synthesis of N-(2,2-difluoroethyl)-3-(pyridin-2-yl)azetidin-3-amine



[001008] *Step 1: Preparation of tert-butyl 3-((2,2-difluoroethyl)amino)-3-(pyridin-2-yl)azetidine-1-carboxylate*

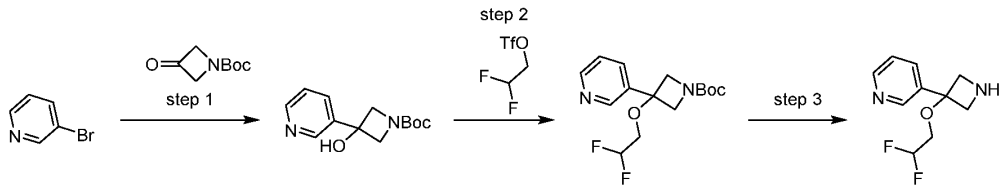
[001009] To a solution of tert-butyl 3-amino-3-(pyridin-2-yl)azetidine-1-carboxylate (120 mg, 481 μmol, 1 eq), 2,2-difluoroethyl trifluoromethanesulfonate (103 mg, 481 μmol, 1 eq) in CH3CN (2 mL) was added DIEA (124 mg, 962 μmol, 2 eq). The mixture was stirred at 80 °C for 3 h to give a colorless solution. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give tert-butyl 3-((2,2-difluoroethyl)amino)-3-(pyridin-2-yl)azetidine-1-carboxylate (140 mg, 447 μmol, 92% yield) as an off-white oil. LCMS (ESI) m/z = 314.2 [M+H]+.

[001010] *Step 2: Preparation of N-(2,2-difluoroethyl)-3-(pyridin-2-yl)azetidin-3-amine*

[001011] To a solution of tert-butyl 3-((2,2-difluoroethyl)amino)-3-(pyridin-2-yl)azetidine-1-carboxylate (100 mg, 319 μmol, 1 eq) in DCM (3 mL) was added TFA (1 mL).

The mixture was stirred at 25 °C for 2 h to give a colorless solution. The reaction mixture was concentrated under reduced pressure to give N-(2,2-difluoroethyl)-3-(pyridin-2-yl)azetidin-3-amine (100 mg, crude) as a colorless oil.

Synthesis of 3-(3-(2,2-difluoroethoxy)azetidin-3-yl)pyridine



[001012] *Step 1: Preparation of tert-butyl 3-hydroxy-3-(pyridin-3-yl)azetidine-1-carboxylate*

[001013] To a cooled (-25 °C) solution of 3-bromopyridine (0.5 g, 3.16 mmol, 1 eq) in THF (15 mL) was added iPrMgCl·LiCl (0.5 g, 3.47 mmol, 1.1 eq) slowly under N2. The reaction mixture was stirred at -25 °C for 0.5 h. To the mixture was added tert-butyl 3-oxoazetidine-1-carboxylate (0.54 g, 3.16 mmol, 1 eq) slowly under N2. The reaction was stirred for 40 min to give a yellow clean solution. The reaction mixture was quenched with saturated NH4Cl (30 mL) and extracted with EtOAc (30 mL × 3), the combined organic layers were washed with saturated brine (40 mL × 2), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give tert-butyl 3-hydroxy-3-(pyridin-3-yl)azetidine-1-carboxylate (0.35 g, 1.39 mmol, 44.3% yield) as a yellow oil. LCMS (ESI) m/z =251.21 [M+H]+.

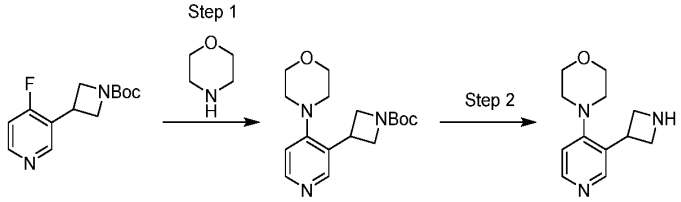
[001014] *Step 2: Preparation of tert-butyl 3-(2,2-difluoroethoxy)-3-(pyridin-3-yl)azetidine-1-carboxylate*

[001015] To a solution of tert-butyl 3-hydroxy-3-(pyridin-3-yl)azetidine-1-carboxylate (0.35 g, 1.39 mmol, 1 eq) and 2,2-difluoroethyl trifluoromethanesulfonate (0.36 g, 1.66 mmol, 1.2 eq) in THF (8 mL), and the mixture was cooled to 0 °C, then was added NaH (0.2 g, 8.34 mmol, 6 eq). The reaction mixture stirred at 25 °C for 2 h. The reaction mixture quenched with saturated NH4Cl (30 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with saturated brine (40 mL × 2), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give tert-butyl 3-(2,2-difluoroethoxy)-3-(pyridin-3-yl)azetidine-1-carboxylate (0.31 g, 990 µmol, 71.3% yield) as a yellow solid. LCMS (ESI) m/z =315.2 [M+H]+.

[001016] *Step 3: Preparation of 3-(3-(2,2-difluoroethoxy)azetidin-3-yl)pyridine*

[001017] To a solution of tert-butyl 3-(2,2-difluoroethoxy)-3-(pyridin-3-yl)azetidine-1-carboxylate (0.2 g, 636 µmol, 1 eq) in DCM (3 mL) and TFA (1 mL). The mixture stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give 3-(3-(2,2-difluoroethoxy)azetidin-3-yl)pyridine (0.13 g, crude) as a yellow oil. LCMS (ESI) m/z =215.0 $[M+H]^+$.

Synthesis of 4-(3-(azetidin-3-yl)pyridin-4-yl)morpholine



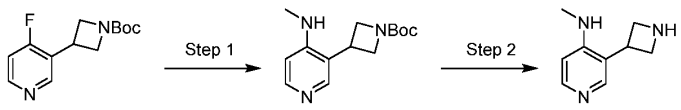
[001018] *Step 1: Preparation of tert-butyl 3-(4-morpholinopyridin-3-yl)azetidine-1-carboxylate*

[001019] To a solution of tert-butyl 3-(4-fluoropyridin-3-yl) azetidine-1-carboxylate (0.1 g, 0.4 mmol, 1 eq) in morpholine (1 mL). The mixture was stirred at 160 °C for 5 h under microwave to give a yellow solution. The mixture was purified by flash silica gel chromatography to give tert-butyl 3-(4-morpholinopyridin-3-yl) azetidine-1-carboxylate (0.1 g, 0.28 mmol, 71% yield) as a yellow oil. LCMS (ESI) m/z = 320.2 [M+H]+. 1H NMR (400 MHz, CDCl3) δ 8.57 - 8.53 (m, 1H), 8.48 - 8.39 (m, 1H), 6.95 - 6.85 (m, 1H), 4.45 - 4.30 (m, 2H), 4.11 - 4.05 (m, 2H), 3.88 - 3.82 (m, 4H), 3.50 (s, 1H), 2.96 - 2.86 (m, 4H), 1.48 (s, 9H).

[001020] *Step 2: Preparation of 4-(3-(azetidin-3-yl)pyridin-4-yl)morpholine.*

[001021] To a solution of tert-butyl 3-[4-(morpholin-4-yl)pyridin-3-yl] azetidine-1-carboxylate (50 mg, 156 µmol, 1 eq) in DCM (1 mL) was added TFA (0.5 mL). The mixture was stirred at 25 °C for 0.5 h to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give 4-(3-(azetidin-3-yl) pyridin-4-yl) morpholine (50 mg, crude) as a yellow oil. LCMS (ESI) m/z =220.2 [M+H]+.

Synthesis of 3-(azetidin-3-yl)-N-methylpyridin-4-amine



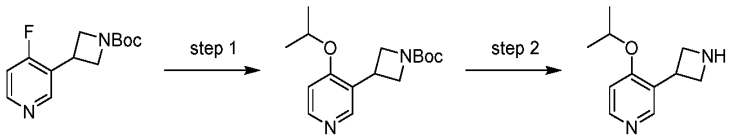
[001022] *Step 1: Preparation of tert-butyl 3-(4-(methylamino)pyridin-3-yl)azetidine-1-carboxylate*

[001023] To a solution of tert-butyl 3-(4-fluoropyridin-3-yl)azetidine-1-carboxylate (0.19 g, 0.75 mmol, 1 eq), methanamine hydrochloride (0.15 g, 2.3 mmol, 3 eq), DIEA (0.29 g, 2.3 mmol, 3 eq) in DMA (2 mL), the mixture was stirred at 100 °C for 16 h. The mixture solution was diluted with water (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (10 mL × 3), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give tert-butyl 3-[4-(methylamino)p-yridin-3-yl]azetidine-1-carboxylate (0.11 g, 0.42 mmol, 56% yield) as a yellow oil. 1H NMR (400 MHz, DMSO-d6) δ 8.16 - 8.09 (m, 2H), 6.55 (d, J = 6.0 Hz, 1H), 5.75 (s, 2H), 3.87 (t, J = 7.4 Hz, 2H), 3.76 (d, J = 7.2 Hz, 1H), 2.77 (d, J = 4.6 Hz, 3H), 1.38 (s, 9H).

[001024] *Step 2: Preparation of 3-(azetidin-3-yl)-N-methylpyridin-4-amine*

[001025] To a solution of tert-butyl 3-[4-(methylamino)pyridin-3-yl]azetidine-1-carboxylate (80 mg, 0.30 mmol, 1 eq) in DCM (1.5 mL) was added TFA (0.5 mL). After stirring at 25 °C for 1 h, the mixture was concentrated directly to give 3-(azetidin-3-yl)-N-methylpyri-din-4-amine (50 mg, crude) as a yellow oil.

Synthesis of 3-(azetidin-3-yl)-4-isopropoxypyridine



[001026] *Step 1: Preparation of tert-butyl 3-(4-isopropoxypyridin-3-yl)azetidine-1-carboxylate*

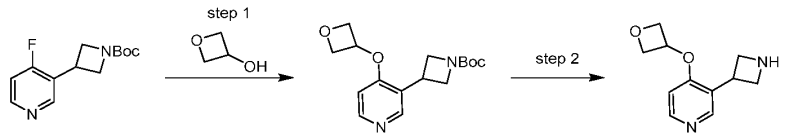
[001027] To a solution of tert-butyl 3-(4-fluoropyridin-3-yl)azetidine-1-carboxylate (100 mg, 396 µmol, 1 eq) in isopropyl alcohol (1 mL) was added tBuOK (80 mg, 712 µmol, 1.8 eq). The mixture was stirred at 60 °C for 3 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give tert-butyl 3-[4-(propan-2-yloxy)pyridin-3-yl]azetidine-1-carboxylate (90 mg, crude) as a yellow oil. LCMS (ESI) m/z = 293.1 [M+H]+.

[001028] *Step 2: Preparation of 3-(azetidin-3-yl)-4-isopropoxypyridine*

[001029] To a solution of tert-butyl 3-[4-(propan-2-yloxy)pyridin-3-yl]azetidine-1-carboxylate (90 mg, 307 µmol, 1 eq) in methylene chloride (1 mL) was added TFA (0.3 mL). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under

reduced pressure to give 3-(azetidin-3-yl)-4-(propan-2-yloxy)pyridine (60.0 mg, crude) as a yellow oil. LCMS (ESI) m/z = 193.1 [M+H]+.

Synthesis of (3-(azetidin-3-yl)-4-(oxetan-3-yloxy)pyridine



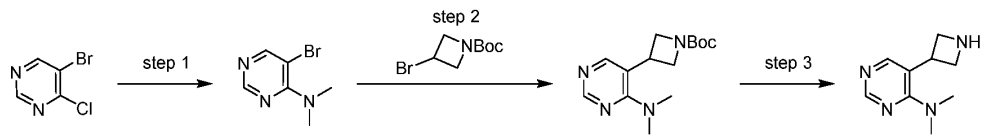
[001030] *Step 1: Preparation of tert-butyl 3-(4-(oxetan-3-yloxy)pyridin-3-yl)azetidine-1-carboxylate (1).*

[001031] To a solution of tert-butyl 3-(4-fluoropyridin-3-yl)azetidine-1-carboxylate (0.12 g, 0.48 mmol, 1 eq) in THF (2 mL) was added NaH (36 mg, 1.4 mmol, 3.0 eq) in portions at 0 °C, the reaction mixture was stirred for 30 min, then oxetan-3-ol (35 mg, 0.48 mmol, 1 eq) was added to the mixture. The reaction mixture was slowly heated to 80 °C and stirred for 1 h. The reaction was quenched with water (30 mL) and extracted (30 mL × 3), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The organic layer was dried over anhydrous Na2SO4 and concentrated in vacuum to give crude product. The residue was purified by flash silica gel chromatography to give tert-butyl 3-(4-(oxetan-3-yloxy)pyridin-3-yl)azetidine-1-carboxylate (0.13 g, 0.42 mmol, 90% yield) was obtained as a yellow oil. 1H NMR (400 MHz, CDCl3) δ 8.40 (s, 1H), 8.39 - 8.35 (m, 1H), 6.33 (d, J = 5.6 Hz, 1H), 5.30 - 5.26 (m, 1H), 5.04 - 4.98 (m, 2H), 4.75 - 4.71 (m, 2H), 4.36 - 4.26 (m, 2H), 4.17 - 4.10 (m, 2H), 4.01 - 3.90 (m, 1H), 1.49 - 1.41 (m, 9H)

[001032] *Step 2: Preparation of 3-(azetidin-3-yl)-4-(oxetan-3-yloxy)pyridine*

[001033] To a solution of tert-butyl 3-(4-(oxetan-3-yloxy)pyridin-3-yl)azetidine-1-carboxylate (0.10 g, 0.33 mmol, 1 eq) in DCM (1 mL) was added TFA (0.30 mL). The mixture was stirred at 25 °C for 1 h to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give 3-(azetidin-3-yl)-4-(oxetan-3-yloxy)pyridine (100 mg, crude) as a yellow oil.

Synthesis of 5-(azetidin-3-yl)-N,N-dimethylpyrimidin-4-amine



[001034] *Step 1: Preparation of 5-bromo-N,N-dimethylpyrimidin-4-amine*

[001035] To a solution of 5-bromo-4-chloropyrimidine (0.85 g, 4.39 mmol, 1 eq) in THF (4 mL) was added dimethylamine (4 mL, 4.39 mmol, 1.0 eq). The mixture was stirred at 65 °C for 4 h to give a yellow mixture. The mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL × 2), the combined organic layers were washed with saturated brine (40 mL × 2), dried over Na2SO4, filtered, and concentrated under reduced pressure to give 5-bromo-N,N-dimethylpyrimidin-4-amine (735 mg, 3.64 mmol, 83% yield) as a yellow oil. LCMS (ESI) m/z = 204.1 [M+H]+. 1H NMR (400 MHz, CD3OD) 8.38 (s, 1H), 8.29 (s, 1H), 3.24 (s, 6H).

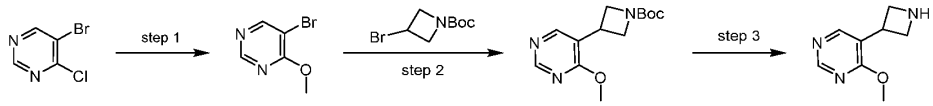
[001036] *Step 2: Preparation of tert-butyl 3-(4-(dimethylamino)pyrimidin-5-yl)azetidine-1-carboxylate*

[001037] To a 15 mL vial equipped with a stir bar was added tert-butyl 3-bromoazetidine-1-carboxylate (0.11 g, 0.49 mmol, 1 eq), 5-bromo-N,N-dimethylpyrimidin-4-amine (0.10 g, 0.49 mmol, 1 eq), $Ir[dF(CF_3)ppy]_2(dtbpy)(PF_6)$ (2.24 mg, 0.01 eq), $NiCl_2$·dtbbpy (1.19 mg, 0.015 eq), TTMSS (49.73 mg, 1 eq), Na_2CO_3 (42.40 mg, 2 eq) in DME (2 mL, 0.1 M). The vial was sealed and placed under nitrogen was added. The reaction was stirred and irradiated with a 10 W blue LED lamp (3 cm away), with cooling water to keep the reaction temperature at 25 °C for 14 h. The mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL × 2). The combined organic layers were washed with saturated brine (40 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep - TLC and concentrated under reduced pressure to give tert-butyl 3-(4-(dimethylamino)pyrimidin-5-yl)azetidine-1-carboxylate (40 mg, 0.14 mmol, 29% yield) as a yellow oil. LCMS (ESI) m/z = 279.1 [M+H]+. 1H NMR (400 MHz, ^c) 8.57 (s, 1H), 8.31 (s, 1H), 4.35 - 4.26 (m, 2H), 3.97 - 3.93 (m, 2H), 3.37 - 3.34 (m, 1H), 3.25 (s, 6H), 1.42 (s, 9H).

[001038] *Step 3: Preparation of 5-(azetidin-3-yl)-N,N-dimethylpyrimidin-4-amine*

[001039] To a solution of tert-butyl 3-(4-(dimethylamino)pyrimidin-5-yl)azetidine-1-carboxylate (40 mg, 0.14 mmol, 1 eq) in methylene chloride (0.60 mL) was added TFA (0.20 mL). The mixture was stirred at 25 °C for 1 h to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give 5-(azetidin-3-yl)-N,N-dimethylpyrimidin-4-amine (26 mg, crude) as a yellow oil.

Synthesis of 5-(azetidin-3-yl)-4-methoxypyrimidine



[001040] *Step 1: Preparation of 5-bromo-4-methoxypyrimidine*

[001041] To a solution of 5-bromo-4-chloropyrimidine (1 g, 5.16 mmol, 1 eq) in MeOH (10 mL) was added tBuOK (694 mg, 6.19 mmol, 1.2 eq), the mixture was stirred at 25 °C for 2 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL × 3), the combined organic layers were washed with saturated brine (20 mL × 2), dried over Na2SO4, filtered and concentrated under reduced pressure to give a white solids. The residue was purified by prep-TLC to give 5-bromo-4-methoxypyrimidine (864 mg, 4.57 mmol, 88.6% yield) as a white solid. LCMS (ESI) m/z = 190.1 [M+H]+.

[001042] *Step 2: Preparation of tert-butyl 3-(4-methoxypyrimidin-5-yl)azetidine-1-carboxylate*

[001043] To an 60 mL vial equipped with a stir bar was added 5-bromo-4-methoxypyrimidine (450 mg, 2.38 mmol,1eq), tert-butyl 3-bromoazetidine-1-carboxylate (561 mg, 2.38 mmol, eq), TTMSS (49.8 mg, 200 μmol, 1.0 eq), Na2CO3 (504 mg, 4.76 mmol, 2 eq), Ir[dF(CF_3)ppy]$_2$(dtbpy)(PF_6) (29.5 mg, 23.8 μmol, 0.01 eq), TTMSS (592 mg, 2.38 mmol, 1 eq) in DME (20 mL). The vial was sealed and placed under nitrogen was added. The reaction was stirred and irradiated with a 10 W blue LED lamp (3 cm away), with cooling water to keep the reaction temperature at 25 °C for 14 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give tert-butyl 3-(4-methoxypyrimidin-5-yl)azetidine-1-carboxylate (350 mg, 1.31 mmol, 55.4% yield) as a yellow oil. LCMS (ESI) m/z = 266.2 $[M+H]^+$.

[001044] *Step 3: Preparation of 5-(azetidin-3-yl)-4-methoxypyrimidine*

[001045] To a solution of tert-butyl 3-(4-methoxypyrimidin-5-yl)azetidine-1-carboxylate (350 mg, 1.31 mmol, 1 eq) in DCM (0.3 mL) and TFA (0.1 mL), the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give 5-(azetidin-3-yl)-4-methoxypyrimidine (216 mg, crude) as a yellow oil. LCMS (ESI) m/z = 166.2 [M+H]+.

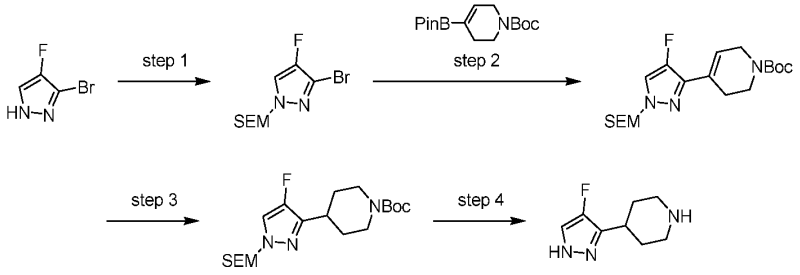
Synthesis of 5-(azetidin-3-yl)pyrimidin-4-ol



[001046] *Step 1: Preparation of 5-(azetidin-3-yl)pyrimidin-4-ol*

[001047] To a solution of tert-butyl 3-(4-methoxypyrimidin-5-yl)azetidine-1-carboxylate (0.14 g, 0.53 mmol, 1 eq) in ACN (3 mL) was added 40% HBr/AcOH (1 mL, 0.53 mmol, 1.0 eq) to the mixture at 25°C, the mixture was stirred at 70 °C for 12 h to give a yellow suspension. The mixture was filtrated and the filtrate was concentrated under reduced pressure to give crude product as white solids. The solid was trituration by DCM (10 mL× 3), then the mixture was filtered to give a white solid. The solid was concentrated under reduced pressure to give 5-(azetidin-3-yl)pyrimidin-4-ol (30 mg, crude) as a white solid. 1HNMR (400 MHz, DMSO-d6) δ 8.95 - 8.58 (m, 1H), 8.05 - 7.98 (m, 1H), 8.54 - 7.96 (m, 1H), 4.27 - 4.07 (m, 4H), 3.98 - 3.81 (m, 1H), 2.50 (s, 1H).

Synthesis of 4-(4-fluoro-1H-pyrazol-3-yl)piperidine



[001048] *Step 1: Preparation of 3-bromo-4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole*

[001049] To a solution of 3-bromo-4-fluoro-1H-pyrazole (1.80 g, 11 mmol, 1 eq) in DMF (18 mL) was added NaH (0.34 g, 14 mmol, 1.3 eq) and SEMCl (2.4 g, 14 mmol, 1.3 eq) at 0 °C. The mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched by ice water. The mixture was diluted with water (0 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (50 mL × 3), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give 3-bromo-4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (406 mg, 1.4 mmol, 13% yield) as a colorless oil. 1H NMR (400 MHz, CDCl3) δ 7.45 (d, J = 4.8 Hz, 1H), 5.41 (d, J = 1.2 Hz, 2H), 3.57 (dd, J = 7.6, 8.8 Hz, 2H), 0.92 - 0.88 (m, 2H), -0.03 (s, 9H).

[001050] *Step 2: Preparation of tert-butyl 4-(4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate*

[001051] A mixture of 3-bromo-4-fluoro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole (350 mg, 1.18 mmol, 1 eq), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)-3,6-dihydropyridine-1(2H)-carboxylate (435 mg, 1.41 mmol, 1.2 eq), palladium(2+) bis((cyclopenta-1,3-dien-1-yl)diphenylphosphane) dichloromethane iron dichloride (193 mg, 236 µmol, 0.2 eq) and K2CO3 (489 mg, 3.54 mmol, 3.0 eq) in dioxane (3.5 mL) and water (0.9 mL) was degassed and purged with N2 (3 times). The mixture was stirred at 60 °C for 2 h under N2 atmosphere. The mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give tert-butyl 4-(4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate (305 mg, 767 µmol, 65% yield) as a yellow oil. 1H NMR (400 MHz, CDCl3) δ 7.35 (d, J = 4.4 Hz, 1H), 6.18 (s, 1H), 5.34 (s, 2H), 4.12 - 4.10 (m, 2H), 3.66 - 3.61 (m, 4H), 2.50 (s, 2H), 1.49 (s, 9H), 0.91 - 0.87 (m, 2H), -0.02 (s, 9H).

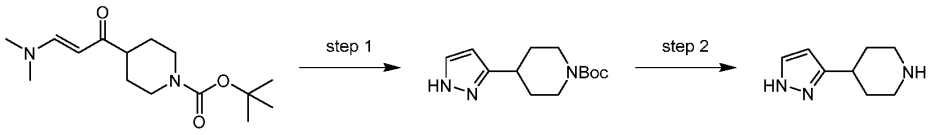
[001052] *Step 3: Preparation of tert-butyl 4-(4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)piperidine-1-carboxylate*

[001053] To a solution of tert-butyl 4-(4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate (300 mg, 754 µmol, 1.0 eq) in methanol (3 mL) was added wet Pd/C (10%, 30 mg) under N2 atmosphere. The suspension was degassed and purged with H2 (3 times). The mixture was stirred under H2 (15 Psi) at 25 °C for 2 h. The reaction solution was filtered and filtrate was concentrated under pressure to give tert-butyl 4-(4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)piperidine-1-carboxylate (230 mg, crude) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.36 (d, J = 4.0 Hz, 1H), 5.42 (s, 2H), 4.85 (s, 2H), 4.19 (d, J = 13.2 Hz, 2H), 3.55 - 3.50 (m, 1H), 3.34 - 3.28 (m, 2H), 3.13 - 3.05 (m, 1H), 2.91 - 2.79 (m, 2H), 1.77 (d, J = 4.0 Hz, 1H), 1.48 (s, 9H), 0.89 - 0.85 (m, 2H), -0.02 (s, 9H).

[001054] *Step 4: Preparation of 4-(4-fluoro-1H-pyrazol-3-yl)piperidine*

[001055] To a solution of tert-butyl 4-(4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)piperidine-1-carboxylate (100 mg, 250 µmol, 1.0 eq) in DCM (1 mL) was added TFA (0.3 mL). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give 4-(4-fluoro-1H-pyrazol-3-yl)piperidine (60 mg, crude) as a yellow oil.

Synthesis of 4-(1H-pyrazol-3-yl)piperidine



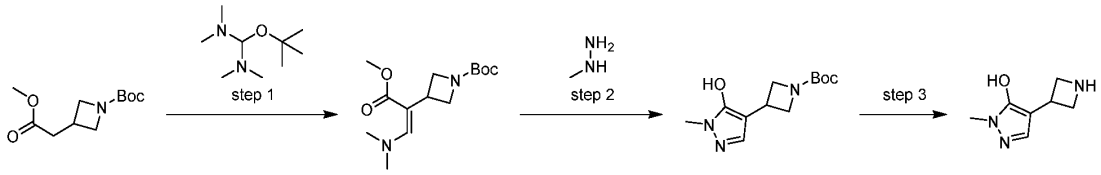
[001056] *Step 1: Preparation of tert-butyl 4-(1H-pyrazol-3-yl)piperidine-1-carboxylate*

[001057] To a solution of tert-butyl 4-[(2E)-3-(dimethylamino)prop-2-enoyl]piperidine-1-carboxylate (0.5 g, 1.8 mmol, 1 eq) in EtOH (10 mL) was added hydrazine hydrate (0.13 g, 2.7 mmol, 1.5 eq) at 0 °C, the mixture was stirred at 80 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (50 mL) and extracted with EtOAc (50 mL × 2), the combined organic layers were washed with saturated brine (50 mL × 2), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give tert-butyl 4-(1H-pyrazol-3-yl)piperidine-1-carboxylate (0.4 g, 1.6 mmol, 90 % yield) as a yellow oil. LCMS (ESI) m/z = 196.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 2.0 Hz, 1H), 6.13 (d, J = 2.0 Hz, 1H), 2.86 (ddd, J = 3.7, 8.0, 15.4 Hz, 4H), 2.05 (s, 1H), 2.00 - 1.92 (m, 2H), 1.70 - 1.58 (m, 2H), 1.48 (s, 9H)

[001058] *Step 2: Preparation of 4-(1H-pyrazol-3-yl)piperidine*

[001059] To a solution of tert-butyl 4-(1H-pyrazol-3-yl)piperidine-1-carboxylate (50 mg, 0.20 mmol, 1 eq) in DCM (0.6 mL) was added TFA (0.2 mL), the mixture was stirred at 25 °C for 10 min to give a colorless clean solution. The reaction mixture was concentrated under reduced pressure to give 4-(1H-pyrazol-3-yl)piperidine (30 mg, crude) as a white oil. LCMS (ESI) m/z = 152.0 [M+H]+.

Synthesis of 4-(azetidin-3-yl)-1-methyl-1H-pyrazol-5-ol



[001060] *Step 1: Preparation of tert-butyl (Z)-3-(1-(dimethylamino)-3-methoxy-3-oxoprop-1-en-2-yl)azetidine-1-carboxylate*

[001061] To a solution of tert-butyl 3-(2-methoxy-2-oxoethyl)azetidine-1-carboxylate (2.5 g, 11 mmol, 1 eq), 1-tert-butoxy-N,N,N',N'-tetramethylmethanediamine (1.9 g, 11 mmol, 1 eq) in DMF (20 ml). The mixture was stirred at 100 ℃ for 12 h. The mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL × 3). The combined organic layers

were washed with brine (100 mL × 3), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give tert-butyl 3-[(1Z)-1-(dimethylamino)-3-methoxy-3-oxoprop-1-en-2-yl]azetidine-1-carboxylate (1.30 g, 4.6 mmol, 42% yield) as a yellow solid. 1H NMR (400 MHz, CDCl3) δ 7.64 (s, 1H), 3.92 (s, 4H), 3.62 - 3.57 (m, 3H), 3.33 (s, 7H), 31 - 1.17 (m, 9H)

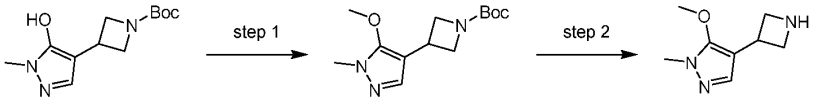
[001062] *Step 2: Preparation of tert-butyl 3-(5-hydroxy-1-methyl-1H-pyrazol-4-yl)azetidine-1-carboxylate*

[001063] To a solution of tert-butyl 3-[(1Z)-1-(dimethylamino)-3-methoxy-3-oxoprop-1-en-2-yl]azetidine-1-carboxylate (1.5 g, 5.28 mmol, 1 eq), methylhydrazine (530 mg, 11.6 mmol, 2.2 eq) in EtOH (12 mL). The mixture was stirred at 80 ℃ for 3 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by reversed phase (TFA) then lyophilized to give tert-butyl 3-(5-hydroxy-1-methyl-1H-pyrazol-4-yl)azetidine-1-carboxylate (0.75 g, 3.0 mmol, 56% yield) as a yellow solid. LCMS (ESI) m/z = 254.2 [M+H]+.

[001064] *Step 3: Preparation of 4-(azetidin-3-yl)-1-methyl-1H-pyrazol-5-ol*

[001065] To a solution of tert-butyl 3-(5-hydroxy-1-methyl-1H-pyrazol-4-yl)azetidine-1-carboxylate (750 mg, 2.96 mmol, 1 eq) in methylene chloride (1 mL) was added TFA (0.3 mL). The mixture was stirred at 25 ℃ for 1 h. The reaction mixture was concentrated under reduced pressure to give 4-(azetidin-3-yl)-1-methyl-1H-pyrazol-5-ol (450 mg, crude) as a yellow oil. LCMS (ESI) m/z = 154.2 $[M+H]^+$.

Synthesis of 4-(azetidin-3-yl)-5-methoxy-1-methyl-1H-pyrazole



[001066] *Step 1: Preparation of tert-butyl 3-(5-methoxy-1-methyl-1H-pyrazol-4-yl)azetidine-1-carboxylate*

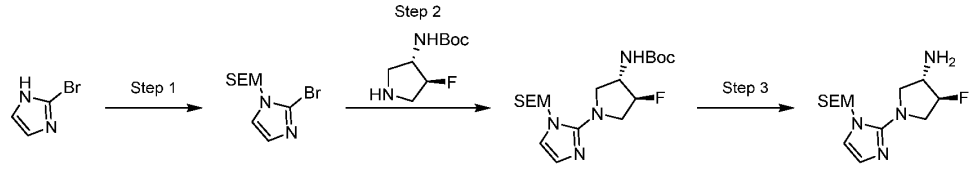
[001067] To a solution of tert-butyl 3-(5-hydroxy-1-methyl-1H-pyrazol-4-yl)azetidine-1-carboxylate (1.1 g, 4.2 mmol, 1 eq) in ACN (10 mL) was added K2CO3 (1.2 g, 8. mmol, 2.0 eq) and iodomethane (0.60 g, 4.2 mmol, 1 eq). The mixture was stirred at 25 ℃ for 3 h. The reaction mixture was filter and the filtrate was concentrated to give a residue. The residue was purified by reversed phase (TFA) then lyophilized to give tert-butyl 3-(5-methoxy-1-methyl-1H-pyrazol-4-yl)azetidine-1-carboxylate (60 mg, 0.22 mmol, 5.4% yield)

as a yellow oil. 1H NMR (400 MHz, CDCl3) δ 7.38 (s, 1H), 4.25 (t, J = 8.6 Hz, 2H), 3.94 (dd, J = 6.5, 8.4 Hz, 3H), 3.86 (s, 3H), 3.68 (s, 3H), 1.46 (s, 9H).

[001068] *Step 2: Preparation of 4-(azetidin-3-yl)-5-methoxy-1-methyl-1H-pyrazole*

[001069] To a solution of tert-butyl 3-(5-methoxy-1-methyl-1H-pyrazol-4-yl) azetidine-1-carboxylate (60 mg, 224 µmol, 1 eq) in methylene chloride (1 mL) was added TFA (0.3 mL). The mixture was stirred at 25 ºC for 1 h and subsequently concentrated under reduced pressure to give 4-(azetidin-3-yl)-5-methoxy-1-methyl-1H-pyrazole (30 mg, crude) as a yellow oil.

Synthesis of (3S,4S)-4-fluoro-1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyrrolidin-3-amine



[001070] *Step 1: Preparation of 2-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole*

[001071] A solution of 2-bromo-1H-imidazole (4 g, 27.2 mmol, 1 eq) in THF (50 mL) was added NaH (1.3 g, 33 mmol, 1.20 eq) at 0 °C. To the mixture was added SEMCl (5.9 g, 35 mmol, 1.3 eq) and stirred at 25 °C for 1 h. The reaction mixture was quenched with H2O (20 mL) at 0 °C and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over anhydrous Na2SO4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give 2-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (1.3 g, 4.7 mmol, 17% yield) as a yellow oil. 1H NMR (400 MHz, CDCl3) δ 7.27 - 7.21 (m, 2H), 5.43 (s, 2H), 3.72 - 3.67 (m, 2H), 1.09 - 1.06 (m, 2H), 0.15 (s, 9H).

[001072] *Step 2: Preparation of tert-butyl ((3S,4S)-4-fluoro-1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyrrolidin-3-yl)carbamate*

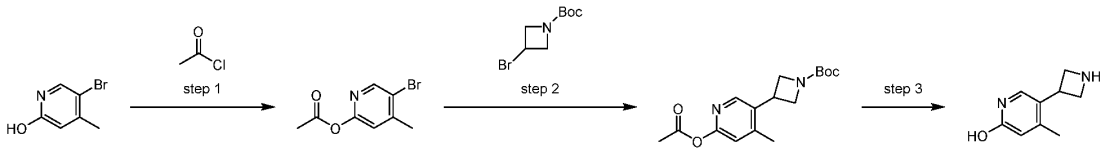
[001073] A solution of 2-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (800 mg, 2.88 mmol, 1 eq), tert-butyl N-[(3S,4S)-4-fluoropyrrolidin-3-yl]carbamate (1.17 g, 5.76 mmol, 2 eq), tBuONa (690 mg, 7.19 mmol, 2.5 eq) in toluene (10 mL) was added {1,3-bis[2,6-bis(pentan-3-yl)phenyl]-4,5-dichloro-2,3-dihydro-1H-imidazol-2-ylidene}dichloro(3-chloropyridin-1-ium-1-yl)palladium (123 mg, 144 µmol, 0.05 eq). The mixture was stirred at 85 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a

residue. The residue was purified by flash silica gel chromatography to give tert-butyl N-[(3S,4S)-4-fluoro-1-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl)pyrrolidin-3-yl]carbamate (918 mg, 2.29 mmol, 79.8% yield) as a yellow oil. LCMS (ESI) m/z = 401.1 [M+H]+.

[001074] *Step 3: Preparation of (3S,4S)-4-fluoro-1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyrrolidin-3-amine*

[001075] A solution of tert-butyl N-[(3S, 4S)-4-fluoro-1-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl)pyrrolidin-3-yl]carbamate (900 mg, 2.24 mmol, 1 eq) in DCM (9 mL) was added TFA (3 mL). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give (3S,4S)-4-fluoro-1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyrrolidin-3-amine (918 mg, crude) as a yellow oil. LCMS (ESI) m/z = 301.1 $[M+H]^+$.

Synthesis of 5-(azetidin-3-yl)-4-methylpyridin-2-ol



[001076] *Step 1: Preparation of 5-bromo-4-methylpyridin-2-yl acetate*

[001077] To a solution of 5-bromo-4-methylpyridin-2-ol (1.0 g, 5.3 mmol, 1.0 eq) in DCM (10 mL) was added triethylamine (1.3 g, 13 mmol, 2.5 eq), then a solution of acetyl chloride (2.1 g, 26 mmol, 5.0 eq) in DCM (10 mL) was added at 0 °C, the mixture was stirred at 25 °C for 12 h to give a brown suspension. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give 5-bromo-4-methylpyridin-2-yl acetate (0.69 g, 3 mmol, 57% yield) as a white oil. 1H NMR (400 MHz, CDCl3) δ 8.42 (s, 1H) 6.98 (s, 1H) 2.42 (s, 3H) 2.33 (s, 3H).

[001078] *Step 2: Preparation of tert-butyl 3-(6-acetoxy-4-methylpyridin-3-yl)azetidine-1-carboxylate*

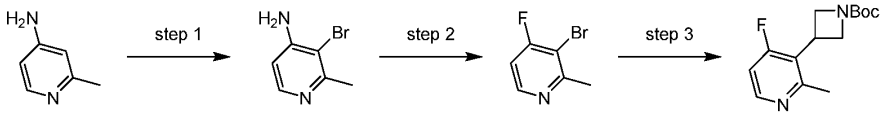
[001079] To an 15 mL vial equipped with a stir bar was added 5-bromo-4-methylpyridin-2-yl acetate (0.50 g, 2.2 mmol, 1.0 eq), tert-butyl 3-bromoazetidine-1-carboxylate (0.67 g, 2.8 mmol, 1.3 eq), Ir[dF(CF3)ppy]2(dtbpy)(PF6) (0.27 g, 0.22 mmol, 0.10 eq), NiCl2·dtbbpy (13 mg, 33 μmol, 0.015 eq), TTMSS (0.54 g, 2.2 mmol, 1.0 eq), Na2CO3 (0.46 g, 4.3 mmol, 2.0 eq) in DME (22 mL). The vial was sealed and placed under

nitrogen. The reaction was stirred and irradiated with a 10 W blue LED lamp (3 cm away), with cooling water to keep the reaction temperature at 25 °C for 14 h to give a brown suspension solution. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give tert-butyl 3-(6-acetoxy-4-methylpyridin-3-yl)azetidine-1-carboxylate (0.40 g, 1.3 mmol, 60% yield) as a yellow oil. 1H NMR (400 MHz, CDCl3) δ 7.22 - 7.26 (m, 1H) 6.40 (s, 1H) 4.23 (t, J=8.00 Hz, 2H) 3.84 - 3.88 (m, 2H) 3.68 (m, 1H) 2.18 - 2.32 (m, 3H) 2.10 (s, 3H) 1.44 (s, 9H).

[001080] *Step 3: Preparation of 5-(azetidin-3-yl)-4-methylpyridin-2-ol*

[001081] To a solution of tert-butyl 3-[6-(acetyloxy)-4-methylpyridin-3-yl]azetidine-1-carboxylate (0.20 g, 0.65 mmol, 1.0 eq) in ACN (5.0 mL) was added 1 M HCl (5.0 mL). Then the mixture was stirred at 80 °C for 12 h to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give 5-(azetidin-3-yl)-4-methylpyridin-2-ol (0.20 g, crude) as a yellow oil. LCMS (ESI) m/z =165.1 [M+H]+.

Synthesis of tert-butyl 3-(4-fluoro-2-methylpyridin-3-yl)azetidine-1-carboxylate



[001082] *Step 1: Preparation of 3-bromo-2-methylpyridin-4-amine*

[001083] To a solution of 2-methylpyridin-4-amine (10 g, 92 mmol, 1 eq) in hydrogen bromide (100 mL, 40% in water) was dropwise added peroxol (21 g, 0.18 mol, 2 eq, 30% wt) at 40 °C, then the mixture solution was stirred at 60 °C for 1 h to give a red suspension. To the mixture was added sufficient saturated NaHCO3 (300 mL) to adjust pH~8. The resulting mixture was extracted with EtOAc (400 mL × 2), the combined organic layers were dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give a 3-bromo-2-methylpyridin-4-amine (10 g, 53 mmol, 58% yield) as a white solid. 1H NMR (400 MHz, CDCl3) δ 7.98 (d, J = 5.6 Hz, 1H), 6.45 (d, J = 5.6 Hz, 1H), 4.71 (s, 2H), 2.59 (s, 3H)

[001084] *Step 2: Preparation of 3-bromo-4-fluoro-2-methylpyridine*

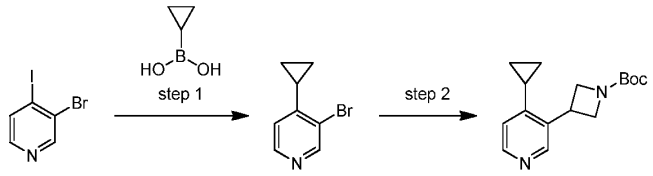
[001085] To cooled (0 °C) pyridine·HF (2 mL) was added 3-bromo-2-methylpyridin-4-amine (0.22 g, 1.2 mmol, 1 eq) slowly, followed by slow portion wise addition of sodium nitrite (0.11 g, 1.6 mmol, 1.4 eq). The mixture solution was stirred at 60 °C for 2 h to give a yellow suspension. The reaction mixture was diluted with NaHCO3 (20 mL) and extracted

with EtOAc (20 mL × 2). The combined organic layers were dried over Na2SO4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give 3-bromo-4-fluoro-2-methylpyridine (0.11 g, 0.63 mmol, 54% yield) as a yellow oil. LCMS (ESI) m/z = 191.9 [M+H]+.

[001086] *Step 3: Preparation of tert-butyl 3-(4-fluoro-2-methylpyridin-3-yl)azetidine-1-carboxylate*

[001087] To a solution of 5-bromo-4-fluoro-2-methylpyridine (0.10 g, 0.53 mmol, 1 eq), tert-butyl 3-bromoazetidine-1-carboxylate (0.16 g, 0.68 mmol, 1.3 eq) in DME (10 mL) was added Ir[dF(CF3)ppy]2(dtbpy)(PF6) (27 mg, 24 μmol, 0.05 eq), iridium(1+) bis(2-phenylpyridine) 4,4 (33 mg, 36 μmol, 0.068 eq), K2CO3 (86 mg, 1.06 mmol, 2 eq) and TTMSS (0.60 g, 0.53 mmol, 1.0 eq). The resulting solution was stirred and irradiated with a 10 W blue LED lamp ((3 cm away), with cooling water to keep the reaction temperature at 25 °C. After stirring for 14 h, the reaction mixture produced brown suspension. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL × 2), the combined organic layers were washed with saturated brine (10 mL × 2), dried over Na2SO4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give tert-butyl 3-(4-fluoro-2-methylpyridin-3-yl)azetidine-1-carboxylate (50 mg, 0.19 mmol, 36% yield) as a yellow oil. LCMS (ESI) m/z = 267.2 [M+H]+.

Synthesis of tert-butyl 3-(4-cyclopropylpyridin-3-yl)azetidine-1-carboxylate



[001088] *Step 1: Preparation of 3-bromo-4-cyclopropylpyridine*

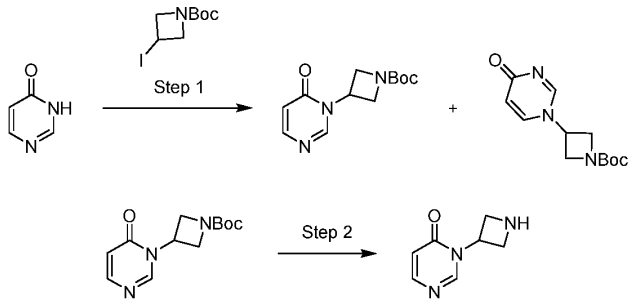
[001089] To a solution of 3-bromo-4-iodopyridine (2.0 g, 7.0 mmol, 1 eq) and cyclopropylboronic acid (0.6 g, 7.0 mmol, 1 eq) in mixture of 1,4-dioxane (40 mL) and water (10 mL) was added Na2CO3 (2.22 g, 21 mmol, 3 eq) and palladium(4+) bis((cyclopenta-2,4-dien-1-ylidene)diphenylphosphanuide) iron dichloride (0.5 g, 0.7 mmol, 0.1 eq) under N2 atmosphere. The mixture solution was stirred at 100 °C for 12 h to give a green suspension. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (30 mL) and extracted with EtOAc (50 mL × 2), the combined organic layers were washed with saturated brine (60 mL × 2), dried over Na2SO4, filtered, and

concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give 3-bromo-4-cyclopropylpyridine (480 mg, 2.4 mmol, 34% yield) as a yellow oil. 1H NMR (400 MHz, CDCl3) δ 8.63 (s, 1H), 8.40 - 8.28 (m, 1H), 6.73 (d, J = 5.2 Hz, 1H), 2.23 (dd, J = 5.2, 8.4 Hz, 1H), 1.19 - 1.12 (m, 2H), 0.82 - 0.76 (m, 2H).

[001090] *Step 2: Preparation of tert-butyl 3-(4-cyclopropylpyridin-3-yl)azetidine-1-carboxylate*

[001091] To a solution of 3-bromo-4-cyclopropylpyridine (0.48 g, 2.4 mmol, 1 eq), tert-butyl 3-bromoazetidine-1-carboxylate (0.73 g, 3.1 mmol, 1.3 eq) in DME (20 mL) was added Ir[dF(CF3)ppy]2(dtbpy)(PF6) (27 mg, 24 μmol, 0.01 eq), iridium(1+) bis(2-phenylpyridine) 4,4 (33 mg, 36 μmol, 0.015 eq), Na2CO3 (0.51 g, 4.8 mmol, 2 eq) and TTMSS (0.60 g, 2.4 mmol, 1.0 eq). The resulting solution was stirred and irradiated with a 10 W blue LED lamp (3 cm away), with cooling water to keep the reaction temperature at 25 °C. After stirring for 14 h, the formation of brown suspension was observed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (60 mL) and extracted with EtOAc (60 mL × 2). The combined organic layers were washed with saturated brine (80 mL × 2), dried over Na2SO4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give tert-butyl 3-(4-cyclopropylpyridin-3-yl)azetidine-1-carboxylate (0.32 g, 1.2 mmol, 49% yield) as a yellow oil. LCMS (ESI) m/z = 275.1 [M+H]+.

Synthesis of 3-(azetidin-3-yl)pyrimidin-4(3H)-one



[001092] *Step 1: Preparation of tert-butyl 3-(6-oxopyrimidin-1(6H)-yl)azetidine-1-carboxylate*

[001093] To a solution of pyrimidin-4(3H)-one (0.5 g, 5.2 mmol, 1 eq) in DMF (10 mL) was added tert-butyl 3-iodoazetidine-1-carboxylate (1.5 g, 5.2 mmol, 1 eq) and K2CO3 (1.1 g, 7.8 mmol, 1.5 eq). The mixture was stirred at 80 °C for 12 h to give a yellow solution under N2. The mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL ×

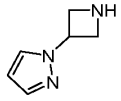
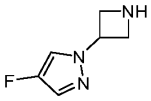
2). The combined organic layers were washed with saturated brine (30 mL × 2), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give tert-butyl 3-(6-oxopyrimidin-1(6H)-yl)azetidine-1-carboxylate (0.25 g , 0.85 mmol, 16% yield) as yellow solid and tert-butyl 3-(4-oxopyrimidin-1(4H)-yl)azetidine-1-carboxylate (0.7 g, 2.6 mmol, 49% yield) as yellow solid.

[001094] tert-butyl 3-(6-oxopyrimidin-1(6H)-yl)azetidine-1-carboxylate: LCMS (ESI) m/z =252.1 [M+H]+. 1H NMR (400 MHz, CD3OD) δ 8.41 (s, 1H), 7.94 (d, J = 6.4 Hz, 1H), 6.45 - 6.48 (m, 1H), 5.09 - 5.12 (m, 1H), 4.49 - 4.21 (m, 4H), 1.47 (s, 9H).

[001095] tert-butyl 3-(4-oxopyrimidin-1(4H)-yl)azetidine-1-carboxylate: LCMS (ESI) m/z =252.1 [M+H]+. 1H NMR (400 MHz, CDCl3) δ 8.77 (s, 1H), 8.50 (d, J = 5.6 Hz, 1H), 6.83 (d, J = 5.6 Hz, 1H), 5.42 - 5.39 (m, 1H), 4.38 - 4.33 (m, 2H), 4.06 - 3.95 (m, 2H), 1.46 (s, 9H).

[001096] The following intermediates in Table **83** were prepared using the method described above in step 1 for the preparation of tert-butyl 3-(6-oxopyrimidin-1(6H)-yl)azetidine-1-carboxylate and utilizing the appropriate starting materials and modifications.

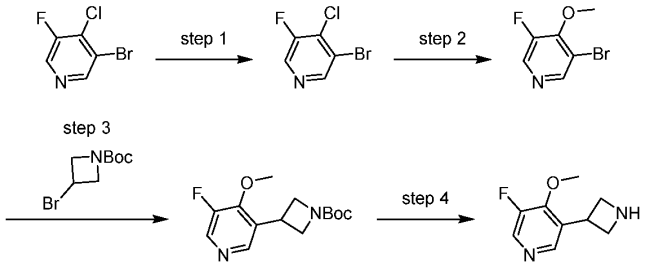
Table 83

Name	Structure	LCMS
1-(azetidin-3-yl)-1H-pyrazole		124.2 $[M+H]^+$
1-(azetidin-3-yl)-4-fluoro-1H-pyrazole		142.3 $[M+H]^+$

[001097] *Step 2: Preparation of 3-(azetidin-3-yl)pyrimidin-4(3H)-one*

[001098] To a solution of tert-butyl 3-(6-oxopyrimidin-1(6H)-yl)azetidine-1-carboxylate (100 mg, 0.40 mmol, 1 eq) in DCM (1.5 mL) was added TFA (0.5 mL). The mixture was stirred at 25 °C for 1 h to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give 3-(azetidin-3-yl)pyrimidin-4(3H)-one (100 mg, crude) as a yellow oil. LCMS (ESI) m/z =152.1 $[M+H]^+$.

Synthesis of 3-(azetidin-3-yl)-5-fluoro-4-methoxypyridine



[001099] *Step 1: Preparation of 3-bromo-4-chloro-5-fluoropyridine*

[001100] To a cooled (-78 ℃) solution of 3-bromo-5-fluoropyridine (10 g, 57 mmol, 1 eq) in THF (100 mL) was slowly added LiHMDS (25 mL, 62 mmol, 1.1 eq) over 0.5 h. The mixture was stirred at -78 ℃ for another 0.5 h, followed by slow addition of a solution of hexachloroethane (15 g, 62 mmol, 1.1 eq) in THF (100 mL). The mixture was stirred at -78 ℃ for 1 h and allowed to warm to 25 ℃. The mixture was stirred at 25 ℃ for 0.5 h and quenched by sat NH4Cl (50 mL) and extracted with EtOAc 90 mL (30 mL × 3). The combined organic layers were washed with saturated brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give 3-bromo-4-chloro-5-fluoropyridine (5.4 g, 26 mmol, 45% yield) as colorless oil was obtained. LCMS (ESI) m/z = 210.1 [M+H]+.

[001101] *Step 2: Preparation of 3-bromo-5-fluoro-4-methoxypyridine*

[001102] To a solution of 3-bromo-4-chloro-5-fluoropyridine (2.0 g, 9.5 mmol, 1.0 eq) in THF (10 mL) and MeOH (10 mL) was added NaOMe (0.5 g, 9.5 mmol, 1.0 eq). The mixture was stirred at 25 °C for 12 h. The reaction was filter and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give 3-bromo-5-fluoro-4-methoxypyridine (900 mg, 4.4 mmol, 46% yield) was obtained as a yellow solid. LCMS (ESI) m/z = 207.8 [M+H]+.

[001103] *Step 3: Preparation of tert-butyl 3-(5-fluoro-4-methoxypyridin-3-yl)azetidine-1-carboxylate*

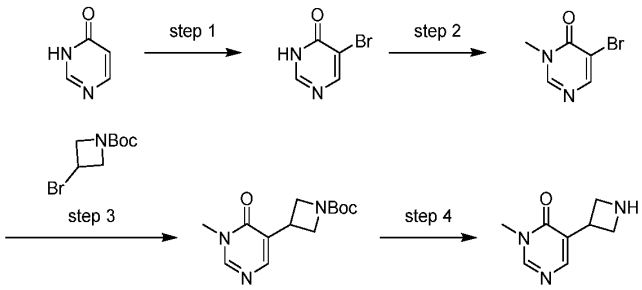
[001104] To a solution of 3-bromo-5-fluoro-4-methoxypyridine (0.7 g, 3.4 mmol, 1.0 eq) in DME (10 mL) was added tert-butyl 3-bromoazetidine-1-carboxylate (1.0 g, 4.4 mmol, 1.3 eq), Ir[dF(CF3)ppy]2(dtbpy)(PF6) (38 mg, 0.034 mmol, 0.01 eq), NiCl2·dtbbpy (11.1 mg, 0.051 mmol, 0.015 eq), TTMSS (842 mg, 3.4 mmol, 1.00 eq), Na2CO3 (718 mg, 6.8 mmol, 2 eq). The vial was sealed and placed under nitrogen was added. The reaction was stirred and irradiated with a 10 W blue LED lamp (3 cm away), with cooling water to keep the reaction temperature at 25 °C for 14 h. The reaction was diluted with water (30 mL) and

extracted with EtOAc (30 mL × 2). The combined organic layers were washed with saturated brine (50 mL × 2), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give tert-butyl 3-(5-fluoro-4-methoxypyridin-3-yl)azetidine-1-carboxylate (0.6 g, 2.1 mmol, 63% yield) as a white solid. LCMS (ESI) m/z = 183.0 [M+H]+.

[001105] *Step 4: Preparation of 3-(azetidin-3-yl)-5-fluoro-4-methoxypyridine*

[001106] To a solution of tert-butyl 3-(5-fluoro-4-methoxypyridin-3-yl)azetidine-1-carboxylate (50 mg, 177 μmol, 1 eq) in DCM (0.3 mL) and TFA (0.1 mL). The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue 3-(azetidin-3-yl)-5-fluoro-4-methoxypyridine (32 mg, crude) as a yellow oil. LCMS (ESI) m/z = 183.1 [M+H]+.

Synthesis of 5-(azetidin-3-yl)-3-methylpyrimidin-4(3H)-one



[001107] *Step 1: Preparation of 5-bromopyrimidin-4(3H)-one*

[001108] To a solution of pyrimidin-4(3H)-one (3 g, 31 mmol, 1.0 eq) in chloroform (15 mL) was added bromine (1.6 mL, 31 mmol, 1 eq). The mixture was stirred at 20 °C for 12 h. The reaction was diluted with water (60 mL) and extracted with EtOAc (60 mL × 2). The combined organic layers were washed with saturated brine (60 mL × 2), dried over Na2SO4, filtered and concentrated under reduced pressure to give 5-bromopyrimidin-4(3H)-one (4.2 g, crude) as a yellow solid.

[001109] *Step 2: Preparation of 5-bromo-3-methylpyrimidin-4(3H)-one*

[001110] To a solution of 5-bromopyrimidin-4(3H)-one5-bromopyrimidin-4(3H)-one (0.5 g, 2.9 mmol, 1.0 eq) in acetone (10 mL) was added K_2CO_3 (0.59 g, 4.3 mmol, 1.5 eq) and iodomethane (0.45 g, 3.1 mmol, 1.1 eq). The mixture was stirred at 25 °C for 12 h. The reaction was diluted with water (50 mL) and extracted with EtOAc (50 mL × 2), the combined organic layers were washed with saturated brine (50 mL × 2), dried over Na2SO4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified

by column chromatography to give 5-bromo-3-methylpyrimidin-4(3H)-one (100 mg, 529 µmol, 19% yield) as a white solid. LCMS (ESI) m/z =189.1 [M+H]+.

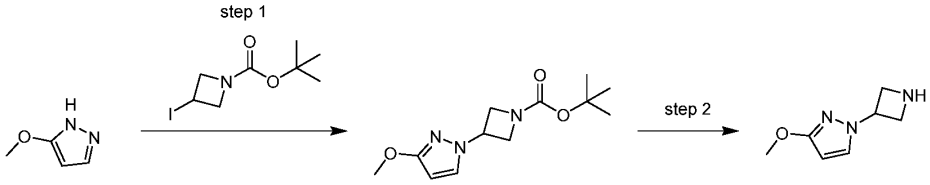
[001111] *Step 3: Preparation of tert-butyl 3-(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)azetidine-1-carboxylate*

[001112] To a solution of 5-bromo-3-methylpyrimidin-4(3H)-one (100 mg, 264 µmol, 1 eq) in DME (2 mL) was added tert-butyl 3-bromoazetidine-1-carboxylate (162 mg, 343 µmol, 1.3 eq), $Ir[dF(CF_3)ppy]_2(dtbpy)(PF_6)$ (5.9 mg, 2.6 µmol,0.01 eq), $NiCl_2$·dtbbpy (1.7 mg, 3.7 µmol, 0.015 eq), TTMSS (131 mg, 264 µmol, 1.00 eq), Na_2CO_3 (112 mg, 264 µmol, 2 eq). The vial was sealed and placed under nitrogen was added. The reaction was stirred and irradiated with a 10 W blue LED lamp (3 cm away), with cooling water to keep the reaction temperature at 25 °C for 14 h. The reaction was diluted with water (10 mL) and extracted with EtOAc (10 mL × 2), the combined organic layers were washed with saturated brine (10 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give tert-butyl 3-(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)azetidine-1-carboxylate (106 mg, 199 µmol, 76% yield) as a white solid. LCMS (ESI) m/z = 266.3 [M+H]+.

[001113] *Step 4: Preparation of 5-(azetidin-3-yl)-3-methylpyrimidin-4(3H)-one*

[001114] To a solution of tert-butyl 3-(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)azetidine-1-carboxylate (106 mg, 199 µmol, 1 eq) in DCM (0.3 mL) and TFA (0.1 mL). The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give 5-(azetidin-3-yl)-3-methylpyrimidin-4(3H)-one (100 mg, crude) was obtained as a yellow oil.

Synthesis of 1-(azetidin-3-yl)-3-methoxy-1H-pyrazole



[001115] *Step 1: Preparation of tert-butyl 3-(3-methoxy-1H-pyrazol-1-yl)azetidine-1-carboxylate*

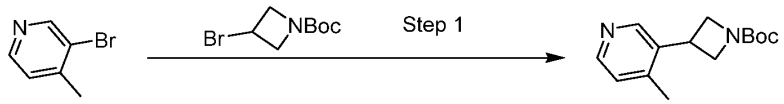
[001116] To a solution of 5-methoxy-1H-pyrazole (0.10 mg, 1.0 mmol, 1 eq) in dimethylformamide (1 mL) was added Cs2CO3 (0.49 g, 1.5 mmol, 1.50 eq), the mixture was stirred at 25 °C for 10 min, then tert-butyl 3-iodoazetidine-1-carboxylate (0.28 g, 1.01 mmol,

1 eq) was added. After stirring for 1 h, the yellow reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL × 2). The combined organic layers were washed with saturated brine (10 mL × 2), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC to give tert-butyl 3-(3-methoxy-1H-pyrazol-1-yl)azetidine-1-carboxylate (20 mg, 79 μmol, 25% yield). LCMS (ESI) m/z =254.2 [M+H]+. 1H NMR (400 MHz, CDCl3) 7.28 (d, J = 2.4 Hz, 1H), 5.69 (d, J = 2.4 Hz, 1H), 4.90 - 4.79 (m, 1H), 4.31 (s, 2H), 4.29 (d, J = 1.6 Hz, 2H), 3.89 (s, 3H), 1.46 (s, 9H).

[001117] *Step 2: Preparation of 1-(azetidin-3-yl)-3-methoxy-1H-pyrazole*

[001118] To a solution of tert-butyl 3-(3-methoxy-1H-pyrazol-1-yl)azetidine-1-carboxylate (20 mg, 79 μmol, 1.0 eq) in DCM (0.3 mL) and TFA (0.1 mL). The mixture was stirred at 25 °C for 1 h. The resulting yellow solution was concentrated under reduced pressure to give 1-(azetidin-3-yl)-3-methoxy-1H-pyrazole (12 mg, crude) as a yellow oil.

Synthesis of tert-butyl 3-(4-methylpyridin-3-yl)azetidine-1-carboxylate

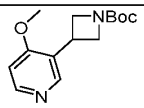
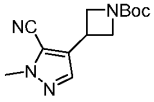
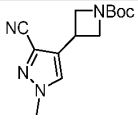
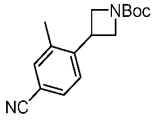
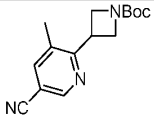
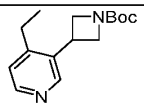
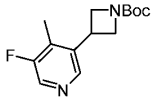
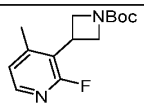
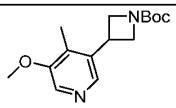


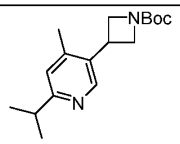
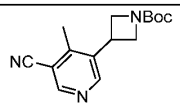
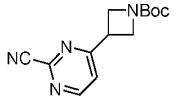
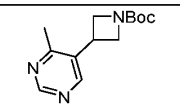
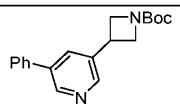
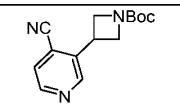
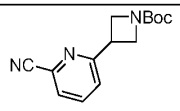
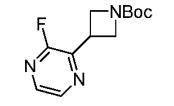
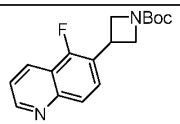
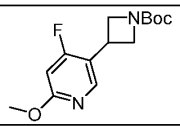
[001119] *Step 1: Preparation of tert-butyl 3-(4-methylpyridin-3-yl)azetidine-1-carboxylate:*

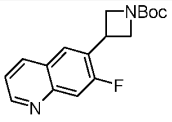
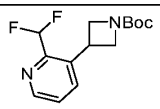
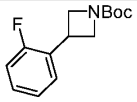
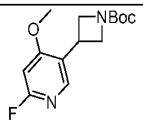
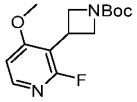
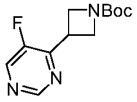
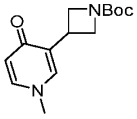
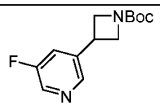
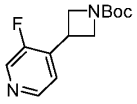
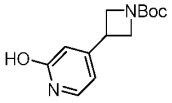
[001120] To a 15 mL vial equipped with a stir bar was added 3-bromo-4-methylpyridine (3.0 g, 1.0 eq), tert-butyl 3-bromoazetidine-1-carboxylate (8.2 g, 2.0 eq), $Ir[dF(CF_3)ppy]_2(dtbpy)(PF_6)$ (0.22 g, 0.010 eq), $NiCl_2$.dtbbpy (0.10 g, 0.015 eq), TTMSS (4.3 g, 1.0 eq), Na_2CO_3 (3.7 g, 2.0 eq) was added in DME (0.17 L). The vial was sealed and placed under nitrogen. The reaction was stirred and irradiated with a 10 W blue LED lamp, with cooling water to keep the reaction temperature at 25 °C for 14 h to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give tert-butyl 3-(4-methylpyridin-3-yl)azetidine-1-carboxylate (2.9 g, 69% yield) as a yellow oil.

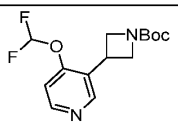
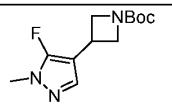
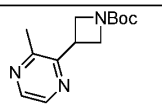
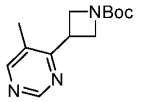
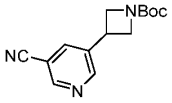
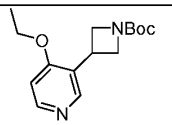
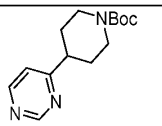
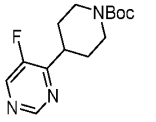
[001121] The following intermediates in Table **84** were prepared using the method described above in step 1 for the preparation of tert-butyl 3-(4-methylpyridin-3-yl)azetidine-1-carboxylate and utilizing the appropriate starting materials and modifications.

Table 84

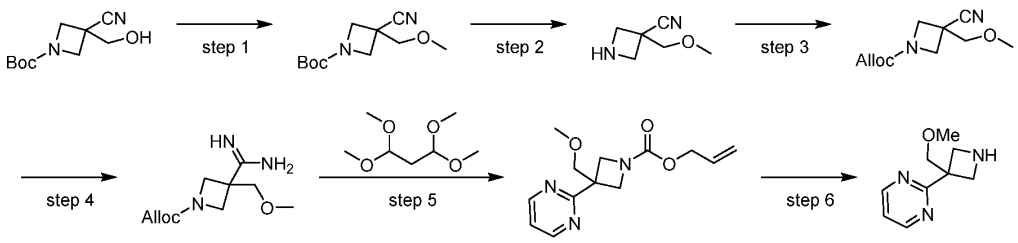
Name	Structure	LCMS	H-NMR data
tert-butyl 3-(4-methoxypyridin-3-yl)azetidine-1-carboxylate		265.0 $[M+H]^+$	1H NMR (400 MHz, CD_3OD) δ 8.40 - 8.30 (m, 2 H), 7.08 (d, J = 5.6 Hz, 1 H), 4.32 - 4.23 (m, 2 H), 4.09 (t, J= 7.6 Hz, 2 H), 3.94 (s, 3 H), 3.89 (s, 1 H), 1.46 (s, 9 H)
tert-butyl 3-(5-cyano-1-methyl-1H-pyrazol-4-yl)azetidine-1-carboxylate		285.1 $[M+H]^+$	^1H NMR (400 MHz, CD_3OD) 7.66 (s, 1H), 4.34 (t, J = 8.8 Hz, 2H), 4.01 (s, 3H), 4.00 - 3.94 (m, 2H), 3.90 - 3.82 (m, 1H), 1.46 (s, 9H)
tert-butyl 3-(3-cyano-1-methyl-1H-pyrazol-4-yl)azetidine-1-carboxylate		263.1 $[M+H]^+$	
tert-butyl 3-(4-cyano-2-methylphenyl)azetidine-1-carboxylate		273.1 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.51 (m, 1H), 7.49 - 7.36 (m, 2H), 4.39 - 4.28 (m, 2H), 4.03 - 3.91 (m, 3H), 2.25 (s, 3H), 1.45 (s, 9H)
tert-butyl 3-(5-cyano-3-methylpyridin-2-yl)azetidine-1-carboxylate		218.0 $[M+H]^+$	^1H NMR (400 MHz, CD_3OD) δ 8.76 (d, *J* = 1.8 Hz, 1H), 7.93 (d, *J* = 0.9 Hz, 1H), 4.23 - 4.18 (m, 2H), 4.13 - 3.99 (m, 2H), 3.63 - 3.54 (m, 1H), 2.31 (s, 3H), 1.45 (s, 9H)
tert-butyl 3-(4-ethylpyridin-3-yl)azetidine-1-carboxylate		263.2 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.25 (d, *J* = 5.2 Hz, 1H), 6.94 (d, *J* = 4.8 Hz, 1H), 4.20 - 4.13 (m, 2H), 3.92 - 3.87 (m, 2H), 3.85 - 3.76 (m, 1H), 2.41 - 2.34 (m, 2H), 1.28 (s, 9H), 1.03 (t, *J* = 7.6 Hz, 3H)
tert-butyl 3-(5-fluoro-4-methylpyridin-3-yl)azetidine-1-carboxylate		267.2 $[M+H]^+$	
tert-butyl 3-(2-fluoro-4-methylpyridin-3-yl)azetidine-1-carboxylate		267.1 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 7.93 - 7.99 (m, 1 H) 6.94 - 6.99 (m, 1 H) 4.18 - 4.32 (m, 5 H) 2.34 (s, 3 H) 1.44 (d, J=4.0 Hz, 9 H)
tert-butyl 3-(5-methoxy-4-methylpyridin-3-yl)azetidine-1-carboxylate		279.0 $[M+H]^+$	1H NMR (400 MHz, CD_3OD) δ 8.21 - 8.12 (m, 2H), 4.38 (t, J = 8.0 Hz, 2H), 4.13 - 4.08 (m, 2H), 3.95 (s, 3H), 3.64 - 3.55 (m, 1H), 2.15 (s, 3H), 1.47 - 1.43 (m, 9H)

tert-butyl 3-(6-isopropyl-4-methylpyridin-3-yl)azetidine-1-carboxylate		292.1 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.15 - 8.07 (m, 1H), 5.51 - 5.30 (m, 2H), 5.08 - 4.95 (m, 1H), 4.87 (d, *J* = 5.6 Hz, 2H), 4.14 (s, 3H), 3.91 - 3.76 (m, 1H), 1.29 - 1.23 (m, 15H)
tert-butyl 3-(5-cyano-4-methylpyridin-3-yl)azetidine-1-carboxylate		273.3 $[M+H]^+$	
tert-butyl 3-(2-cyanopyrimidin-4-yl)azetidine-1-carboxylate		282.9 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 5.2 Hz, 1H), 7.34 (d, J = 5.2 Hz, 1H), 4.94 - 4.65 (m, 1H), 4.59 - 4.26 (m, 2H), 4.23 - 4.14 (m, 1H), 4.00 - 3.88 (m, 1H), 1.42 (s, 9H).
tert-butyl 3-(4-methylpyrimidin-5-yl)azetidine-1-carboxylate		250.1 $[M+H]^+$	^{1}H NMR (400 MHz, CD_3OD) δ 8.90 (s, 1H), 8.70 (s, 1H), 4.42 - 4.34 (m, 2H), 4.12 - 4.05 (m, 3H), 2.47 (s, 3H), 1.46 (s, 9H)
tert-butyl 3-(5-phenylpyridin-3-yl)azetidine-1-carboxylate		311.2 $[M+H]^+$	
tert-butyl 3-(4-cyanopyridin-3-yl)azetidine-1-carboxylate		260.1 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 - 8.98 (m, 1H) 8.69 - 8.76 (m, 1H) 7.51 (d, J=4.88 Hz, 1H) 4.44 - 4.53 (m, 2H) 4.09 - 4.18 (m, 2H) 3.40 (s, 1H) 1.40 - 1.57 (m, 9H)
tert-butyl 3-(6-cyanopyridin-2-yl)azetidine-1-carboxylate		282.2 $[M+H]^+$	^{1}H NMR (400 MHz, CD_3OD) δ 7.97 - 7.91 (m, 1H), 7.77 – 7.74 (m, 1H), 7.60 – 7.58 (m, 1H), 4.36 - 4.25 (m, 2H), 4.13 (t, *J* = 6.4 Hz, 2H), 4.05 - 3.99 (m, 1H), 1.49 - 1.46 (m, 9H)
tert-butyl 3-(3-fluoropyrazin-2-yl)azetidine-1-carboxylate		254.3 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 - 8.49 (m, 1H), 8.12 (t, J = 2.0 Hz, 1H), 4.35 - 4.30 (m, 2H), 4.29 - 4.25 (m, 2H), 4.16 - 4.08 (m, 1H), 1.47 (s, 9H)
tert-butyl 3-(5-fluoroquinolin-6-yl)azetidine-1-carboxylate		303.3 $[M+H]^+$	^{1}H NMR (400 MHz, CD_3OD) δ 8.94 - 8.87 (m, 1H), 8.61 - 8.54 (m, 1H), 7.95 - 7.85 (m, 2H), 7.59 (m, 1H), 4.48 - 4.41 (m, 2H), 4.34 - 4.25 (m, 1H), 4.17 - 4.10 (m, 2H), 1.49 (s, 9H)
tert-butyl 3-(4-fluoro-6-methoxypyridin-3-		283.2 $[M+H]^+$	^{1}H NMR (400 MHz, CD_3OD) δ 8.18 - 8.05 (m, 1H), 6.65 - 6.51 (m, 1H), 4.35 - 4.28 (m, 2H), 4.05 (t, J =

yl)azetidine-1-carboxylate			7.6 Hz, 2H), 3.97 - 3.92 (m, 1H), 3.91 (s, 3H), 1.46 (s, 9H).
tert-butyl 3-(7-fluoroquinolin-6-yl)azetidine-1-carboxylate		303.2 $[M+H]^+$	
tert-butyl 3-(2-(difluoromethyl)pyridin-3-yl)azetidine-1-carboxylate		285.1 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 4.4 Hz, 1H), 8.07 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 4.8, 7.8 Hz, 1H), 6.68 (t, J = 54.4 Hz, 1H), 4.43 - 4.29 (m, 3H), 3.96 (s, 2H), 1.47 (s, 9H)
tert-butyl 3-(2-fluorophenyl)azetidine-1-carboxylate		196.0 $[M+H]^+$	^{1}H NMR (400 MHz, CD_3OD) δ 7.40 (dt, J = 1.8, 7.8 Hz, 1H), 7.32 - 7.25 (m, 1H), 7.22 - 7.16 (m, 1H), 7.09 (ddd, J = 1.2, 8.2, 10.8 Hz, 1H), 4.38 - 4.26 (m, 2H), 4.08 - 3.98 (m, 3H), 1.46 (s, 9H)
tert-butyl 3-(6-fluoro-4-methoxypyridin-3-yl)azetidine-1-carboxylate		283.1 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 6.40 (d, *J*=3.6 Hz, 1H), 4.09 - 4.01 (m, 4H), 3.90 (s, 3H), 3.62 - 3.59 (m, 1H), 1.47 (s, 9H).
tert-butyl 3-(2-fluoro-4-methoxypyridin-3-yl)azetidine-1-carboxylate		283.1 $[M+H]^+$	
tert-butyl 3-(5-fluoropyrimidin-4-yl)azetidine-1-carboxylate		254.3 $[M+H]^+$	^{1}H NMR (400 MHz, CD_3OD) *δ* 9.02 (d, *J* = 2.8 Hz, 1H), 8.74 - 8.61 (m, 1H), 4.31 - 4.23 (m, 5H), 1.46 (s, 9H).
tert-butyl 3-(1-methyl-4-oxo-1,4-dihydropyridin-3-yl)azetidine-1-carboxylate		265.2 $[M+H]^+$	
tert-butyl 3-(5-fluoropyridin-3-yl)azetidine-1-carboxylate		253.1 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 - 8.43 (m, 2H), 7.82 (d, J = 8.0 Hz, 1H), 4.45 (t, J = 8.4 Hz, 2H), 3.96 (dd, J = 5.6, 8.8 Hz, 2H), 3.92 - 3.81 (m, 1H), 1.49 (s, 9H)
tert-butyl 3-(3-fluoropyridin-4-yl)azetidine-1-carboxylate		253.4 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.43 - 8.42 (m, 2H), 7.35 (t, *J* = 6.0 Hz, 1H), 4.38 - 4.32 (m, 2H), 4.04 - 3.98 (m, 3H), 1.46 (s, 9H)
tert-butyl 3-(2-hydroxypyridin-4-yl)azetidine-1-carboxylate		251.1 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 6.4 Hz, 1H), 6.47 (s, 1H), 6.33 (d, *J* = 6.4 Hz, 1H), 4.29 (t, *J* = 8.8 Hz, 2H), 4.12 (s, 1H), 3.76 (s, 1H), 3.58 (s, 1H), 1.47 (s, 9H)

tert-butyl 3-(4-(difluoromethoxy)pyridin-3-yl)azetidine-1-carboxylate		301.4 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) 8.77 (s, 1H), 8.71 (d, *J* = 6.4 Hz, 1H), 7.41 (d, *J* = 6.4 Hz, 1H), 6.84 - 6.63 (m, 1H), 5.31 (s, 1H), 4.47 - 4.35 (m, 2H), 4.11 - 4.06 (m, 2H), 1.47 (s, 9H)
tert-butyl 3-(5-fluoro-1-methyl-1H-pyrazol-4-yl)azetidine-1-carboxylate		256.3 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 4.25 (t, J = 8.8 Hz, 2H), 3.92 (dd, J = 6.5, 8.1 Hz, 2H), 3.72 (s, 3H), 3.64 - 3.54 (m, 1H), 1.46 (s, 9H)
tert-butyl 3-(3-methylpyrazin-2-yl)azetidine-1-carboxylate		250.2 $[M+H]^+$	^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (d, J = 2.4 Hz, 1H), 8.15 (d, J = 2.4 Hz, 1H), 4.11 - 4.01 (m, 5H), 2.31 (s, 3H), 1.27 (s, 9H)
tert-butyl 3-(5-methylpyrimidin-4-yl)azetidine-1-carboxylate		250.1 $[M+H]^+$	^{1}H NMR (400 MHz, DMSO) δ 9.02 (s, 1H), 8.54 (s, 1H), 4.10 (d, J = 4.8 Hz, 5H), 2.17 (s, 3H), 1.39 (s, 9H)
tert-butyl 3-(5-cyanopyridin-3-yl)azetidine-1-carboxylate		259.8 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 9.03 (s, 1H), 8.87 - 8.83 (m, 1H), 3.74 - 3.69 (m, 1H), 3.65 - 3.59 (m, 2H), 3.55 - 3.46 (m, 2H), 1.26 (s, 9H)
tert-butyl 3-(4-ethoxypyridin-3-yl)azetidine-1-carboxylate			^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 - 8.30 (m, 2H), 6.97 - 6.80 (m, 1H), 4.35 - 4.24 (m, 2H), 4.22 - 4.06 (m, 4H), 4.02 - 3.85 (m, 1H), 1.55 - 1.40 (m, 12H).
tert-butyl 4-(pyrimidin-4-yl)piperidine-1-carboxylate		264.1 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 - 9.13 (m, 1H), 8.66 (d, *J* = 5.2 Hz, 1H), 7.19 (dd, *J* = 1.2, 5.2 Hz, 1H), 3.80 - 3.61 (m, 1H), 3.50 - 3.34 (m, 2H), 2.88 - 2.80 (m, 2H), 1.96 - 1.90 (m, 2H), 1.71 (dq, *J* = 4.4, 12.4 Hz, 2H), 1.48 (s, 9H)
tert-butyl 4-(5-fluoropyrimidin-4-yl)piperidine-1-carboxylate		282.3 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) 8.96 (d, *J* = 2.8 Hz, 1H), 8.49 (d, *J* = 2.0 Hz, 1H), 3.41 (d, *J* = 11.2 Hz, 1H), 3.26 - 3.14 (m, 1H), 2.87 (t, *J* = 11.6 Hz, 2H), 2.69 - 2.60 (m, 1H), 1.94 - 1.85 (m, 2H), 1.83 (s, 2H), 1.49 (s, 9H).

Synthesis of 2-(3-(methoxymethyl)azetidin-3-yl)pyrimidine



[001122] *Step 1: Preparation of tert-butyl 3-cyano-3-(methoxymethyl)azetidine-1-carboxylate*

[001123] To a cooled (0 ºC) solution of tert-butyl 3-cyano-3-(hydroxymethyl)azetidine-1-carboxylate (2.5 g, 12 mmol, 1 eq) in THF (200 mL) was added NaH (0.36 g, 15 mmol, 1.3 eq). The mixture was stirred at 25 ºC for 30 min, followed by addition of iodomethane (3.3 g, 24 mmol, 2 eq). The mixture was stirred at 25 ºC for 1 h to give a gray suspension. The reaction mixture was quenched by H2O (10 mL) at 0 ºC, subsequently diluted with water (20 mL) and extracted with EtOAc (100 mL × 2). The combined organic layers were washed with saturated brine (100 mL × 2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give tert-butyl 3-cyano-3-(methoxymethyl)azetidine-1-carboxylate (1 g, 4.4 mmol, 38% yield) as a white oil. 1H NMR (400 MHz, CDCl3) δ 4.14 (d, J = 8.8 Hz, 2H), 3.88 (d, J = 8.8 Hz, 2H), 3.60 (s, 2H), 3.40 (s, 3H), 1.38 (s, 9H).

[001124] *Step 2: Preparation of 3-(methoxymethyl)azetidine-3-carbonitrile*

[001125] A solution of tert-butyl 3-cyano-3-(methoxymethyl)azetidine-1-carboxylate (1 g, 1.7 mmol, 1.0 eq) in methylene chloride (6 mL) and TFA (3 mL) was stirred at 25 ºC for 30 min to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give 3-(methoxymethyl)azetidine-3-carbonitrile (1 g, crude) as a clear oil.

[001126] *Step 3: Preparation of allyl 3-cyano-3-(methoxymethyl)azetidine-1-carboxylate*

[001127] To a solution of 3-(methoxymethyl)azetidine-3-carbonitrile (1 g, 7.9 mmol, 1.0 eq) in methylene chloride (1 mL) was added triethylamine (3.2 g, 32 mmol, 4 eq), followed by dropwise addition of AllocCl (0.95 g, 7.9 mmol, 1 eq) at 0 oC. The mixture was stirred at 25 oC for 3 h to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to afford allyl 3-cyano-3-(methoxymethyl)azetidine-1-carboxylate (0.85 g, 4.0 mmol, 51% yield) as a yellow oil. 1H NMR (400 MHz, CDCl3) δ 5.97 - 5.85 (m, 1H),

5.35 - 5.28 (m, 1H), 5.28 - 5.24 (m, 1H), 4.60 (d, J = 6.0 Hz, 2H), 4.31 (d, J = 9.2 Hz, 2H), 4.08 (d, J = 8.8 Hz, 2H), 3.68 (s, 2H), 3.48 (s, 3H).

[001128] *Step 4: Preparation of allyl 3-carbamimidoyl-3-(methoxymethyl)azetidine-1-carboxylate*

[001129] Acetyl chloride (9.0 g, 0.14 mol, 30 eq) was slowly added to a cooled (0 ℃) mixture of EtOH (6 mL) and CH3Cl (8 mL). The mixture was stirred for 2 h, followed by slow addition of a solution of allyl 3-cyano-3-(methoxymethyl)azetidine-1-carboxylate (0.80 g, 3.8 mmol, 1 eq) in CH3Cl (8 mL). The resulting mixture was stirred at 25 ℃ for 12 h and subsequently concentrated in vacuo to give a residue. The residue was redissolved by EtOH (6 mL), followed by addition of NH_3/MeOH (1.9 g, 0.14 mol, 30 eq, 7 M). The mixture was stirred at 25 °C for 12 h to give a white suspension. The reaction mixture was concentrated under reduced pressure to give allyl 3-carbamimidoyl-3-(methoxymethyl)azetidine-1-carboxylate (0.8 g, crude) as a white oil. LCMS (ESI) m/z = 228.1 [M+H]+.

[001130] *Step 5: Preparation of allyl 3-(methoxymethyl)-3-(pyrimidin-2-yl)azetidine-1-carboxylate*

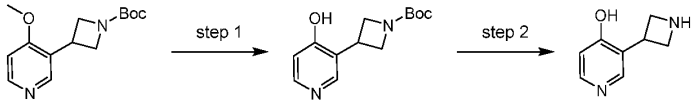
[001131] To a solution of allyl 3-carbamimidoyl-3-(methoxymethyl)azetidine-1-carboxylate (0.8 g, 3.5 mmol, 1 eq) in pyridine (10 mL) was added 1,1,3,3-tetramethoxypropane (1.2 g, 7.0 mmol, 2 eq). The mixture was heated to 170 ℃ under MW for 1 h to give a black solution. The reaction mixture was concentrated under reduced pressure to give allyl 3-(methoxymethyl)-3-(pyrimidin-2-yl)azetidine-1-carboxylate (0.4 g, 1.52 mmol, 43% yield) as a black oil. 1H NMR (400 MHz, CDCl3) δ 8.76 (d, J = 4.8 Hz, 2H), 7.22 (t, J = 4.8 Hz, 1H), 6.00 - 5.89 (m, 1H), 5.37 - 5.29 (m, 1H), 5.25 - 5.19 (m, 1H), 4.59 - 4.57 (m, 2H), 4.20 (d, J = 8.8 Hz, 2H), 3.90 (s, 2H), 3.82 (s, 2H), 3.37 (s, 3H).

[001132] *Step 6: Preparation of 2-(3-(methoxymethyl)azetidin-3-yl)pyrimidine*

[001133] To a solution of allyl 3-(methoxymethyl)-3-(pyrimidin-2-yl)azetidine-1-carboxylate (0.4 g, 1.5 mmol, 1 eq) in methylene chloride (5 mL) was added pyrrolidine (0.21 g, 3.0 mmol, 2 eq) and $Pd(PPh_3)_4$ (0.17 g, 0.15 mmol, 0.1 eq) under N2, the mixture was stirred at 25 ℃ for 1 h to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in H2O (3 mL) and purified by reversed phase (TFA) to lyophilized to give a residue. The residue was re-purification by prep-HPLC (column: Phenomenex Luna C18 150 × 25 mm ×10 um, mobile phase: water (TFA) - ACN; B%: 13% - 43%, 11.5 min) to lyophilized to give 2-(3-(methoxymethyl)azetidin-3-yl)pyrimidine (70 mg, 0.39 mmol, 26% yield) as a yellow oil. 1H

NMR (400 MHz, CDCl3) δ 8.78 - 8.71 (m, 2H), 7.26 (s, 1H), 4.56 (s, 2H), 4.33 (s, 2H), 3.86 (s, 2H), 3.47 (s, 3H).

Synthesis of 3-(azetidin-3-yl)pyridin-4-ol



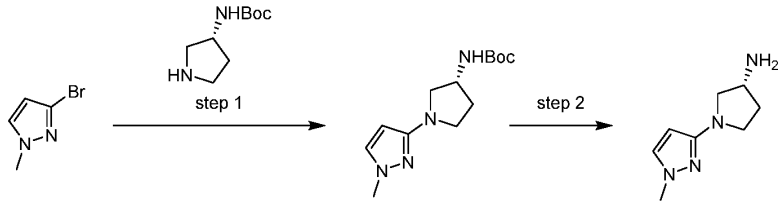
[001134] *Step 1: Preparation of tert-butyl 3-(4-hydroxypyridin-3-yl)azetidine-1-carboxylate*

[001135] To a solution of tert-butyl 3-(4-methoxypyridin-3-yl)azetidine-1-carboxylate (0.3 g, 1.1 mmol, 1 eq) in dimethylformamide (3.0 mL) was added NaOEt (0.19 g, 2.3 mmol, 2 eq). The mixture was stirred at 100 ºC for 2 h. The resulting yellow solution was cooled to room temperature and diluted with water (50 mL) and extracted with EtOAc (50 mL × 2). To the aqueous phase was added saturated $NaHCO_3$ (to adjust the pH = 7~8) and extracted with EtOAc (50 mL × 2). The combined organic layers were washed with saturated brine (40 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 3-(4-hydroxypyridin-3-yl)azetidine-1-carboxylate (0.1 g, crude) as a white solid. LCMS (ESI) m/z =251.1 [M+H]+.

[001136] *Step 2: Preparation of 3-(azetidin-3-yl)pyridin-4-ol*

[001137] To a solution of tert-butyl 3-(4-hydroxypyridin-3-yl)azetidine-1-carboxylate (90 mg, 0.36 mmol, 1 eq) in methylene chloride (1.0 mL) was added TFA (0.3 mL). The mixture was stirred at 25 ºC for 15 min to give yellow solution. The reaction mixture was concentrated under reduced pressure to give 3-(azetidin-3-yl)pyridin-4-ol (90 mg, crude) as a yellow oil which was used to next step without any purification. LCMS (ESI) m/z =151.2 [M+H]+.

Synthesis of (R)-1-(1-methyl-1H-pyrazol-3-yl)pyrrolidin-3-amine

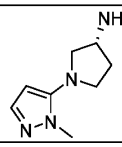
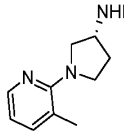
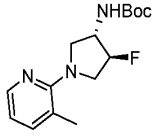


[001138] *Step 1: Preparation of tert-butyl (R)-(1-(1-methyl-1H-pyrazol-3-yl)pyrrolidin-3-yl)carbamate*

[001139] A mixture of (R)-tert-butyl pyrrolidin-3-ylcarbamate tert-butyl N-[(3R)-pyrrolidin-3-yl]carbamate (0.80 mg, 4.3 mmol, 2 eq), 3-bromo-1-methyl-1H-pyrazole (0.35 g, 2.16 mmol, 1 eq), CuI (0.13 g, 0.65 mmol, 0.3 eq), L-Proline (74.6 mg, 648 µmol, 0.3 eq) and K2CO3 (0.89 g, 6.5 mmol, 3 eq) in DMSO (4 mL) was degassed and purged with N2 (3 times). The reaction mixture was stirred at 100 ºC for 12 h under N2 atmosphere. The mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over anhydrous Na2SO4, filtered, and concentrated in vacuo to give a residue. The residue was purified by flash silica gel chromatography to give tert-butyl (R)-(1-(1-methyl-1H-pyrazol-3-yl)pyrrolidin-3-yl)carbamate (0.67 g, 2.5 mmol, 50% yield) as a yellow oil. 1H NMR (400 MHz, CD3OD) δ 7.28 (d, J = 2.0 Hz, 1H), 5.49 (d, J = 2.0 Hz, 1H), 4.21 - 4.12 (m, 1H), 3.69 (s, 3H), 3.52 - 3.45 (m, 1H), 3.40 - 3.33 (m, 2H), 3.29 - 3.20 (m, 1H), 3.10 - 3.03 (m, 1H), 2.25 - 2.17 (m, 1H), 1.45 (s, 9H).

[001140] The following intermediates in Table **85** were prepared using the method described above in step 1 for the preparation of tert-butyl (R)-(1-(1-methyl-1H-pyrazol-3-yl)pyrrolidin-3-yl)carbamate and utilizing the appropriate starting materials and modifications.

Table 85

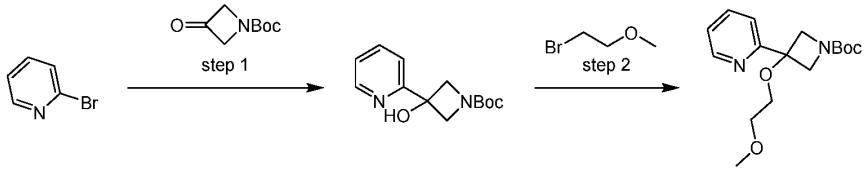
Name	Structure	LCMS
tert-butyl (R)-(1-(1-methyl-1H-pyrazol-5-yl)pyrrolidin-3-yl)carbamate		267.1 $[M+H]^+$
tert-butyl (R)-(1-(3-methylpyridin-2-yl)pyrrolidin-3-yl)carbamate		278.0 $[M+H]^+$
tert-butyl ((3S,4S)-4-fluoro-1-(3-methylpyridin-2-yl)pyrrolidin-3-yl)carbamate		296.0 $[M+H]^+$

[001141] *Step 2: Preparation of (R)-1-(1-methyl-1H-pyrazol-3-yl)pyrrolidin-3-amine*

[001142] To a solution of tert-butyl (R)-(1-(1-methyl-1H-pyrazol-3-yl)pyrrolidin-3-yl)carbamate (300 mg, 1.12 mmol, 1 eq) in DCM (3 mL) was added TFA (1 mL). The

mixture was stirred at 25 ºC for 0.5 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give (R)-1-(1-methyl-1H-pyrazol-3-yl)pyrrolidin-3-amine (0.13 g, 0.79 mmol, 70% yield) as a yellow oil. 1H NMR (400 MHz, CD3OD) δ 7.35 (d, J = 2.4 Hz, 1H), 5.60 (d, J = 2.4 Hz, 1H), 3.99 - 3.91 (m, 1H), 3.73 (s, 3H), 3.57 - 3.45 (m, 2H), 3.42 - 3.36 (m, 1H), 3.28 - 3.21 (m, 1H), 2.48 - 2.38 (m, 1H), 2.11 - 2.02 (m, 1H).

Synthesis of tert-butyl 3-(2-methoxyethoxy)-3-(pyridin-2-yl)azetidine-1-carboxylate



[001143] *Step 1: Preparation of tert-butyl 3-hydroxy-3-(pyridin-2-yl)azetidine-1-carboxylate*

[001144] To a cooled (-78 ºC) solution of 2-bromopyridine (5 g, 31.6 mmol, 1 eq) and tert-butyl 3-oxoazetidine-1-carboxylate (5.40 g, 31.6 mmol, 1 eq) in THF (50 mL) was added n-BuLi (14 mL, 34.81 mmol, 1.1 eq). After stirring for 2 h, the reaction mixture quenched by H2O (50 mL), then extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give tert-butyl 3-hydroxy-3-(pyridin-2-yl)azetidine-1-carboxylate (2.90 g, 11.5 mmol, 36.7% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 - 8.51 (m, 1H), 7.81 (dt, J = 1.8, 7.7 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.31 (ddd, J = 1.1, 4.8, 7.5 Hz, 1H), 6.56 (s, 1H), 4.35 - 4.10 (m, 2H), 3.92 (s, 2H), 1.41 (s, 9H).

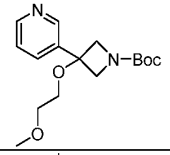
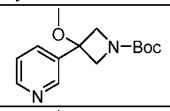
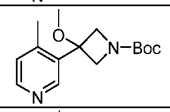
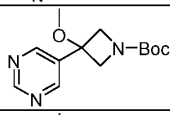
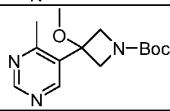
[001145] *Step 2: Preparation of tert-butyl 3-(2-methoxyethoxy)-3-(pyridin-2-yl)azetidine-1-carboxylate*

[001146] To a solution of tert-butyl 3-hydroxy-3-(pyridin-2-yl) azetidine-1-carboxylate (500 mg, 1.99 mmol, 1 eq), 1-bromo-2-methoxyethane (414 mg, 2.98 mmol, 1.5 eq), TBAI (735 mg, 1.99 mmol, 1 eq) in DMF (5 mL) added NaH (119 mg, 4.97 mmol, 2.5 eq) at 0 ºC. The mixture was stirred at 25 ºC for 12 h. The reaction mixture was quenched with NH4Cl aq (50 mL) and extracted with EtOAc (50 mL × 2), the combined organic layers were washed with saturated brine (40 mL × 2), dried over Na2SO4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to

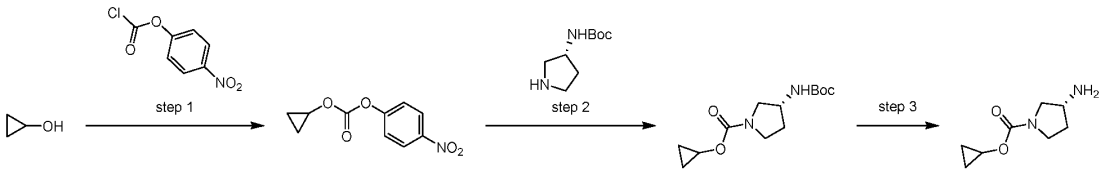
give tert-butyl 3-(2-methoxyethoxy)-3-(pyridin-2-yl)azetidine-1-carboxylate (426 mg, 1.38 mmol, 69.4% yield) as a yellow solid. LCMS (ESI) m/z =308.8 [M+H]+.

[001147] The following intermediates in **Table 86** were prepared using the method described above in step 2 for the preparation of tert-butyl 3-(2-methoxyethoxy)-3-(pyridin-2-yl)azetidine-1-carboxylate and utilizing the appropriate starting materials and modifications.

Table 86

Name	Structure	LCMS
tert-butyl 3-(2-methoxyethoxy)-3-(pyridin-3-yl)azetidine-1-carboxylate		309.5 $[M+H]^+$
tert-butyl 3-methoxy-3-(pyridin-3-yl)azetidine-1-carboxylate		265.1 $[M+H]^+$
tert-butyl 3-methoxy-3-(4-methylpyridin-3-yl)azetidine-1-carboxylate		279.1 $[M+H]^+$
tert-butyl 3-methoxy-3-(pyrimidin-5-yl)azetidine-1-carboxylate		266.2 $[M+H]^+$
tert-butyl 3-methoxy-3-(4-methylpyrimidin-5-yl)azetidine-1-carboxylate		279.8 $[M+H]^+$

Synthesis of cyclopropyl (R)-3-aminopyrrolidine-1-carboxylate



[001148] *Step 1: Preparation of cyclopropyl (4-nitrophenyl) carbonate*

[001149] To a solution of cyclopropanol (0.33 g, 5.8 mmol, 1.2 eq) in DCM (10 mL) was added 4-nitrophenyl carbonochloridate (1 g, 4.9 mmol, 1 eq). After stirring for 2h, the yellow solution was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give cyclopropyl (4-nitrophenyl) carbonate (1 g, 4.48 mmol, 91% yield) as white solid. 1H NMR (400 MHz, CDCl3) δ 8.31 - 8.24 (m, 2H), 7.42 - 7.36 (m, 2H), 4.28 (tt, J = 3.2, 6.4 Hz, 1H), 0.93 - 0.87 (m, 2H), 0.86 - 0.80 (m, 2H).

[001150] *Step 2: Preparation of cyclopropyl (R)-3-((tert-butoxycarbonyl)amino)pyrrolidine-1-carboxylate*

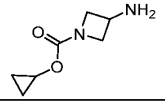
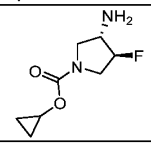
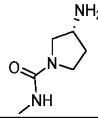
[001151] To a solution of cyclopropyl (4-nitrophenyl) carbonate (0.10 g, 0.45 mmol, 1.3 eq) in DCM (2 mL) was added tert-butyl N-[(3R)-pyrrolidin-3-yl]carbamate (64 mg, 0.34 mmol, 1 eq) and N,N-diisopropylethylamine (44 mg, 0.34 mmol, 1 eq), the mixture was stirred at 25 ℃ for 30 min to give a yellow clean solution. The reaction mixture was concentrated in vacuo to give cyclopropyl (R)-3-((tert-butoxycarbonyl)amino)pyrrolidine-1-carboxylate (0.10 g, crude) as a yellow solid. LCMS (ESI) m/z =271.5 [M+H]+.

[001152] *Step 3: Preparation of cyclopropyl (R)-3-aminopyrrolidine-1-carboxylate*

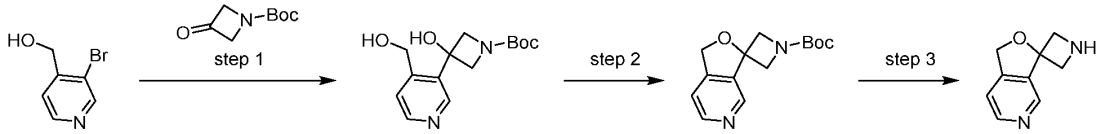
[001153] To a solution of cyclopropyl (R)-3-((tert-butoxycarbonyl)amino)pyrrolidine-1-carboxylate (80 mg, 0.29 mmol, 1 eq) in DCM (1 mL) was added TFA (0.10 g, 0.88 mmol, 3 eq), the mixture was stirred at 25 ℃ for 30 min to give a yellow clean solution, the reaction mixture was concentrated under reduced pressure to give cyclopropyl (R)-3-aminopyrrolidine-1-carboxylate (50 mg, crude) as a white solid. LCMS (ESI) m/z =171.4 [M+H]+.

[001154] The following intermediates in Table **87** were prepared using the method described above for the synthesis of cyclopropyl (R)-3-aminopyrrolidine-1-carboxylate and utilizing the appropriate starting materials and modifications.

Table 87

Name	Structure	LCMS
cyclopropyl 3-aminoazetidine-1-carboxylate		157.2 $[M+H]^+$
cyclopropyl (3S,4S)-3-amino-4-fluoropyrrolidine-1-carboxylate		189.2 $[M+H]^+$
(R)-3-amino-N-methylpyrrolidine-1-carboxamide		144.1 $[M+H]^+$

Synthesis of 1'H-spiro[azetidine-3,3'-furo[3,4-c]pyridine]



[001155] *Step 1: Preparation of tert-butyl 3-hydroxy-3-(4-(hydroxymethyl)pyridin-3-yl)azetidine-1-carboxylate*

[001156] To a cooled (-40 ℃) solution of (3-bromopyridin-4-yl)methanol (1 g, 5.3 mmol, 1 eq) in THF (10 mL) was slowly added i-PrMgCl·LiCl (13 mL, 13 mmol, 2.4 eq, 1.0 M in THF). The mixture was stirred at -40 ℃ for 0.5 h, followed by addition of a solution of tert-butyl 3-oxoazetidine-1-carboxylate (1.1 g, 6.4 mmol, 1.2 eq) in THF (10 mL). The mixture was allowed to warm to ambient temperatures. After 16 h, the reaction mixture was quenched by water (20 mL) and extracted with EtOAc 90 mL (30 mL × 3). The combined organic layer was washed with brine 90 mL (30 mL × 3), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to give tert-butyl 3-hydroxy-3-(4-(hydroxymethyl)pyridin-3-yl)azetidine-1-carboxylate (0.12 g, 0.43 mmol, 8.1% yield) as a yellow solid. 1H NMR (400 MHz, DMSO-d6) δ 8.56 - 8.44 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 5.38 (t, J = 5.6 Hz, 1H), 4.53 (d, J = 5.6 Hz, 2H), 4.40 (d, J = 9.2 Hz, 2H), 4.05 - 3.92 (m, 2H), 3.31 - 3.28 (m, 1H), 1.38 (s, 9H).

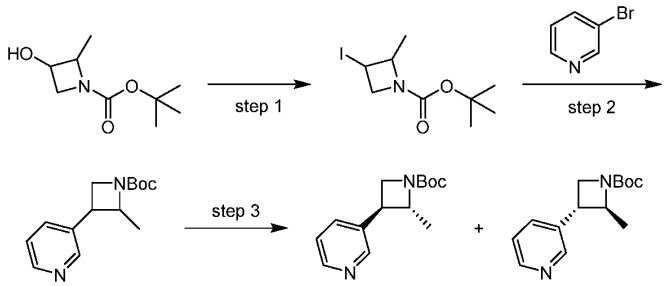
[001157] *Step 2: Preparation of tert-butyl 1'H-spiro[azetidine-3,3'-furo[3,4-c]pyridine]-1-carboxylate*

[001158] To a cooled (0 ℃) solution of tert-butyl 3-hydroxy-3-(4-(hydroxymethyl)pyridin-3-yl)azetidine-1-carboxylate (70 mg, 0.25 mmol, 1 eq) in THF (1 mL) was added sequentially added DIAD (60 mg, 0.30 mmol, 1.2 eq) and PPh3 (78 mg, 0.30 mmol, 1.2 eq). the mixture was stirred at 40 ℃ for 16 h and subsequently quenched by water (30 mL). The mixture was extracted with EtOAc 90 mL (30 mL× 3). The combined organic layer was washed with brine 30 mL (30 mL × 3), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC to give tert-butyl 1'H-spiro[azetidine-3,3'-furo[3,4-c]pyridine]-1-carboxylate (50 mg, 0.19 mmol, 77% yield) as a yellow oil. 1H NMR (400 MHz, DMSO-d6) δ 8.80 (d, J = 0.4 Hz, 1H), 8.55 (d, J = 4.8 Hz, 1H), 7.39 (d, J = 4.8 Hz, 1H), 5.08 (s, 2H), 4.26 - 4.09 (m, 4H), 1.42 (s, 9H).

[001159] *Step 3: Preparation of 1'H-spiro[azetidine-3,3'-furo[3,4-c]pyridine]*

[001160] To a solution of tert-butyl 1'H-spiro[azetidine-3,3'-furo[3,4-c]pyridine]-1-carboxylate (50 mg, 0.19 mmol, 1 eq) in DCM (0.6 mL) was added TFA (0.2 mL). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated directly to give 1'H-spiro[azetidine-3,3'-furo[3,4-c]pyridine] (30 mg, crude) as a yellow oil.

Synthesis of tert-butyl (2R,3S)-2-methyl-3-(pyridin-3-yl)azetidine-1-carboxylate and tert-butyl (2S,3R)-2-methyl-3-(pyridin-3-yl)azetidine-1-carboxylate



[001161] *Step 1: Preparation of tert-butyl 3-iodo-2-methylazetidine-1-carboxylate*

[001162] To a solution of tert-butyl 3-hydroxy-2-methylazetidine-1-carboxylate (5.0 g, 26.7 mmol, 1.0 eq) in DCE (80 mL) was added imidazole (3.6 g, 53.4 mmol, 2.0 eq), PPh3 (10.5 g, 40.0 mmol, 1.5 eq) and iodine (10.2 g, 40.0 mmol, 1.5 eq). The mixture was stirred at 80 °C for 3 h to get black solution. The mixture was added water (100 mL), extracted with EtOAc (150 mL x 2), and organic layer was washed with brine (100 mL). The organic layer was combined and dried with anhydrous sodium sulfate. The solid was filtered, solvent was dried under vacuum. The reaction was concentrated in vacuum to get crude product. The residue was purified by silica gel column to give tert-butyl 3-iodo-2-methylazetidine-1-carboxylate (3.5 g, 26.7 mmol, 44% yield) as a colorless oil. 1H NMR (400 MHz, CDCl3) δ 4.56 (t, J = 6.0 Hz, 1H), 4.50 - 4.45 (m, 1H), 4.24 - 4.14 (m, 1H), 3.99 - 3.95 (m, 1H), 1.45 (s, 9H), 1.38 (d, J = 6.4 Hz, 3H).

[001163] *Step 2: Preparation of tert-butyl 2-methyl-3-(pyridin-3-yl)azetidine-1-carboxylate.*

[001164] To a 100 mL vial was added 3-bromopyridine (1.0 g, 6.3 mmol, 1 eq), tert-butyl 3-iodo-2-methylazetidine-1-carboxylate (3.8 g, 13 mmol, 2 eq), Ir[dF(CF3)ppy]2(dtbpy)(PF6) (70 mg, 0.063 mmol, 0.01 eq), NiCl2·dtbbpy (56 mg, 0.095 mmol, 0.015 eq), TTMSS (1.5 g, 6.3 mmol, 1.0 eq), Na2CO3 (1.3 g, 13 mmol, 2 eq) in DME (60 mL). The vial was sealed under nitrogen. The reaction was stirred and irradiated with a 10 W blue LED lamp (3 cm away), with cooling water to keep the reaction temperature at 25 °C for 14 h. The mixture was concentrated in vacuo. The residue was purified by silica gel column to give tert-butyl 2-methyl-3-(pyridin-3-yl)azetidine-1-carboxylate (550 mg, 2.2 mmol, 35% yield) as a white solid. LCMS (ESI) m/z = 249.2 [M+H]+. 1H NMR (400 MHz, CDCl3) δ 8.78 (s, 1H), 8.75 (d, J = 5.2 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H), 7.85 (dd, J = 5.6,

8.0 Hz, 1H), 4.40 - 4.25 (m, 2H), 3.92 (dd, J = 6.8, 8.8 Hz, 1H), 3.50 - 3.40 (m, 1H), 1.57 (d, J = 6.4 Hz, 3H), 1.48 (s, 9H).

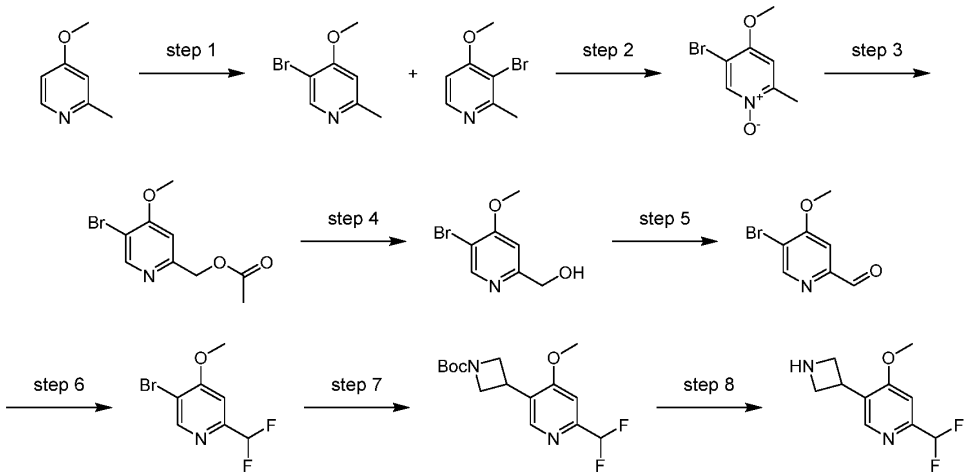
[001165] *Step 3: Preparation of tert-butyl (2R,3S)-2-methyl-3-(pyridin-3-yl)azetidine-1-carboxylate and tert-butyl (2S,3R)-2-methyl-3-(pyridin-3-yl)azetidine-1-carboxylate*

[001166] tert-butyl 2-methyl-3-(pyridin-3-yl)azetidine-1-carboxylate (550 mg, 2.2 mmol, 1.0 eq) was separated by SFC (Column: Chiralpak IC-3 50×4.6mm I.D., 3um, Mobile phase: Phase A for CO2, and Phase B for MeOH (0.05%DEA); Gradient elution:B in A from 5% to 40%, Flow rate: 3mL/min; Detector: PDA; Column Temp: 35C;Back Pressure: 100Bar).

[001167] **Peak 1** (RT = 1.178 min): tert-butyl (2R,3S)-2-methyl-3-(pyridin-3-yl)azetidine-1-carboxylate or tert-butyl (2S,3R)-2-methyl-3-(pyridin-3-yl)azetidine-1-carboxylate (170 mg, 0.68 mmol, 31% yield) as a colorless oil. LCMS (ESI) m/z = 249.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.58 (d, J = 4.4 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.58 (dd, J = 5.2, 8.0 Hz, 1H), 4.21 (t, J = 6.2 Hz, 1H), 4.12 (s, 1H), 3.84 (d, J = 7.6 Hz, 1H), 3.51 - 3.41 (m, 1H), 1.44 (d, J = 6.4 Hz, 3H), 1.41 (s, 9H).

[001168] **Peak 2** (RT = 1.407 min) as a colorless oil: tert-butyl (2S,3R)-2-methyl-3-(pyridin-3-yl)azetidine-1-carboxylate or tert-butyl (2R,3S)-2-methyl-3-(pyridin-3-yl)azetidine-1-carboxylate (120 mg, 0.48 mmol, 22% yield) as a colorless oil. LCMS (ESI) m/z = 249.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.58 (d, J = 4.4 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.58 (dd, J = 5.2, 8.0 Hz, 1H), 4.21 (t, J = 6.0 Hz, 1H), 4.12 (s, 1H), 3.84 (d, J = 7.6 Hz, 1H), 3.51 - 3.41 (m, 1H), 1.44 (d, J = 6.4 Hz, 3H), 1.41 (s, 9H).

Synthesis of 5-(azetidin-3-yl)-2-(difluoromethyl)-4-methoxypyridine



[001169] *Step 1: Preparation of 5-bromo-4-methoxy-2-methylpyridine*

[001170] To a cooled (0 °C) solution of 4-methoxy-2-methylpyridine (10 g, 81 mmol, 1 eq) in AcOH (100 mL) was added bromine (32 g, 0.20 mmol, 2.5 eq). The mixture was subsequently heated to 70 °C for 3 h. The mixture was added cold water (300 mL), the reaction mixture was diluted with water (200 mL) and extracted with EtOAc (500 mL × 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuo. The residue was purified by column chromatography to give 5-bromo-4-methoxy-2-methylpyridine (4 g, 20 mmol, 25% yield) as a yellow solid and 3-bromo-4-methoxy-2-methylpyridine (2 g, 9.9 mmol, 12% yield) as a yellow solid. 5-bromo-4-methoxy-2-methylpyridine: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 6.69 (s, 1H), 3.94 (s, 3H), 2.52 (s, 3H). 3-bromo-4-methoxy-2-methylpyridine: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 5.6 Hz, 1H), 6.69 (d, J = 5.6 Hz, 1H), 3.94 (s, 3H), 2.66 (s, 3H)

[001171] *Step 2: Preparation of 5-bromo-4-methoxy-2-methylpyridine 1-oxide*

[001172] To a cooled (0 °C) solution of 5-bromo-4-methoxy-2-methylpyridine (4.0 g, 20 mmol, 1.0 eq) in DCM (40 mL) was added mCPBA (5.1 g, 30 mmol, 1.5 eq) and the mixture was subsequently stirred at 20 °C. After 3h, the reaction mixture was quenched by addition sat. sodium sulfite (100 mL), diluted with water (100 mL), and extracted with DCM/MeOH = 10 / 1 (200 mL × 3). The combined organic layers were washed with sat. brine (100 mL × 3), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give compound 5-bromo-4-methoxy-2-methylpyridine 1-oxide (4.0 g, crude) as a white solid. 1H NMR (400 MHz, CD3OD) δ 8.48 (s, 1H), 7.26 (s, 1H), 4.00 (s, 3H), 2.50 (s, 3H).

[001173] *Step 3: Preparation of (5-bromo-4-methoxypyridin-2-yl)methyl acetate*

[001174] A mixture of 5-bromo-4-methoxy-2-methylpyridine 1-oxide (2 g, 9.17 mmol, 1 eq), acetyl acetate (5.4 g, 53 mmol, 2.0 eq) in AcOH (15 mL) was stirred at 120 °C for 3 h. The mixture was concentrated under reduced pressure to give compound (5-bromo-4-methoxypyridin-2-yl)methyl acetate (1.50 g, crude) as a yellow oil. LCMS (ESI) m/z = 261.8 [M+H]+.

[001175] *Step 4: Preparation of (5-bromo-4-methoxypyridin-2-yl)methanol*

[001176] A mixture of (5-bromo-4-methoxypyridin-2-yl)methyl acetate (2 g, 7.68 mmol, 1 eq), NaOH (10 mL, 2N in water) in MeOH (20 mL) was stirred for 1 h. The mixture was concentrated under reduced pressure to remove MeOH, diluted with water (30 mL), and extracted with EtOAc/ MeOH (50 mL ×4). The combined organic layer was dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure. The residue was

purified by column chromatography to give compound (5-bromo-4-methoxypyridin-2-yl)methanol (1 g, 4.58 mmol, 59.8% yield) as a white solid. 1H NMR (400 MHz, CDCl3) δ 8.47 (s, 1H), 6.85 (s, 1H), 4.69 (s, 2H), 3.95 (s, 3H).

[001177] *Step 5: Preparation of 5-bromo-4-methoxypicolinaldehyde*

[001178] A mixture of (5-bromo-4-methoxypyridin-2-yl)methanol (0.5 g, 2.3 mmol, 1.0 eq), manganese(IV) oxide (4.2 g, 46 mmol, 20 eq) in DCM (5 mL) was stirred for 1 h. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography to give compound 5-bromo-4-methoxypicolinaldehyde (0.25 g, 1.2 mmol, 51% yield) as a white solid. 1H NMR (400 MHz, CDCl3) δ 9.93 (s, 1H), 8.74 (s, 1H), 7.47 (s, 1H), 4.03 (s, 3H).

[001179] *Step 6: Preparation of 5-bromo-2-(difluoromethyl)-4-methoxypyridine*

[001180] To a cooled (0 °C) solution of 5-bromo-4-methoxypicolinaldehyde (0.22 g, 1.0 mmol, 1.0 eq) in DCM (0.5 mL) was added a solution of DAST (0.33 g, 2.0 mmol, 2.0 eq) in DCM (5 mL), After 0.5 h, the reaction mixture was poured into sat.NaHCO3 (5 mL), diluted with water (5 mL) and extracted with DCM (5 mL × 2). The combined organic layer was dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to give compound 5-bromo-2-(difluoromethyl)-4-methoxypyridine (150 mg, 0.63 mmol, 63% yield) as a colorless oil. 1H NMR (400 MHz, CDCl3) δ 8.60 (s, 1H), 7.14 (s, 1H), 6.71 - 6.43 (m, 1H), 4.02 (s, 3H).

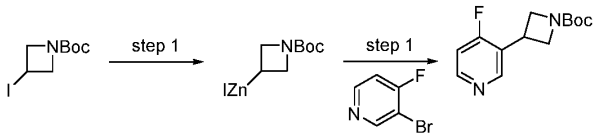
[001181] *Step 7: Preparation of tert-butyl 3-(6-(difluoromethyl)-4-methoxypyridin-3-yl)azetidine-1-carboxylate*

[001182] To an 15 mL vial equipped with a stir bar was added, 5-bromo-2-(difluoromethyl)-4-methoxypyridine (40 mg, 0.17 mmol, 1 eq), tert-butyl 3-bromoazetidine-1-carboxylate (51 mg, 0.22 mmol, 1.3 eq), Ir[dF(CF3)ppy]2(dtbpy)(PF6) (1.9 mg, 1.7 μmol, 0.01 eq), Na2CO3 (36 mg, 0.34 mmol, 2 eq), NiCl2·dtbbpy (1 mg, 2.5 μmol, 0.02 eq), 1,1,1,3,3,3-hexamethyl-2-(trimethylsilyl)trisilane (42 mg, 0.17 mmol, 1.0 eq) in DME (2 mL). The vial was sealed and placed under nitrogen was added. The reaction was stirred and irradiated with a 10 W blue LED lamp (3 cm away), with cooling water to keep the reaction temperature at 25 °C for 14 h. The mixture was concentrated under reduced pressure. The residue was purified by prep-TLC to give tert-butyl 3-(6-(difluoromethyl)-4-methoxypyridin-3-yl)azetidine-1-carboxylate (30 mg, 95 μmol, 57% yield) as a yellow oil. 1H NMR (400 MHz, CDCl3) δ 8.36 (s, 1H), 7.12 (s, 1H), 6.73 - 6.45 (m, 1H), 4.32 - 4.26 (m, 2H), 4.02 - 4.00 (m, 1H), 3.95 - 3.90 (m, 4H), 3.61 - 3.57 (m, 1H), 1.46 (s, 9H).

[001183] *Step 8: Preparation of 5-(azetidin-3-yl)-2-(difluoromethyl)-4-methoxypyridine*

[001184] A mixture of tert-butyl 3-(6-(difluoromethyl)-4-methoxypyridin-3-yl)azetidine-1-carboxylate (30 mg, 95 µmol, 1 eq) in DCM (0.6 mL) and TFA (0.2 mL) was stirred at 20 °C for 0.5 h. The mixture was concentrated under reduced pressure to give 5-(azetidin-3-yl)-2-(difluoromethyl)-4-methoxypyridine (25 mg, crude) as yellow oil. LCMS (ESI) m/z = 215.1 [M+H]+.

Synthesis of tert-butyl 3-(4-fluoropyridin-3-yl)azetidine-1-carboxylate



[001185] *Step 1: Preparation of (1-(tert-butoxycarbonyl)azetidin-3-yl)zinc(II) iodide*

[001186] A suspension of Zn (50 g, 764 mmol, 1.3 eq) in aqueous 1M HCl (40 mL) was stirred at 25 °C for 12 h. The suspension was filtered and the filtrate cake was sequentially washed with H2O (40 mL × 3), EtOH (40 mL× 3), and acetone (40 mL × 3). The solid was dried to give a freshly pre-activated Zinc.

[001187] A heated (65 °C) suspension Zn (40 g, 611 mmol, 5 eq) in DMF (50 mL) under N2 was stirred at for 0.5 h, followed by dropwise addition of TMSCl (22 g, 196 mmol, 0.32 eq) and 1,2-dibromoethane (17 g, 92 mmol, 0.15 eq). The resulting mixture was stirred at 60 °C for 0.5 h. A solution of tert-butyl 3-iodoazetidine-1-carboxylate (173 g, 612 mmol, 1 eq) in DMF (300 mL) was added to the mixture and stirred at 60 °C for 0.5 h. The resulting clear yellow solution was cooled to room temperature, filtered and used for the next step without further manipulation.

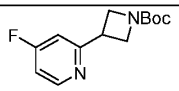
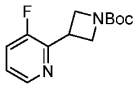
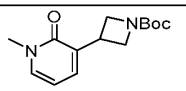
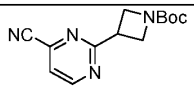
[001188] *Step 2: Preparation of tert-butyl 3-(4-fluoropyridin-3-yl)azetidine-1-carboxylate*

[001189] To a cooled (0 °C) solution of 3-bromo-4-fluoropyridine (20 g, 114 mmol, 1 eq) and Pd(PPh3)Cl2 (8.0 g, 11 mmol, 0.1 eq) in DMF (200 mL) was added a solution of (1-(tert-butoxycarbonyl)azetidin-3-yl)zinc(II) iodide (350 mL, 570 mmol, 5 eq) in a dropwise manner. The mixture was warmed and stirred at 50 °C for 12 h. The reaction mixture was quenched with water (2 L) and extracted with EtOAc (2 L × 3). The combined organic layers were washed with saturated brine (1 L × 2), dried over Na2SO4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography and was collected and concentrated in vacuo to give tert-butyl 3-(4-fluoropyridin-3-yl)azetidine-1-carboxylate (20 g, 79 mmol, 70 % yield) as yellow oil. LCMS (ESI) m/z =252.9 [M+H]+. 1H

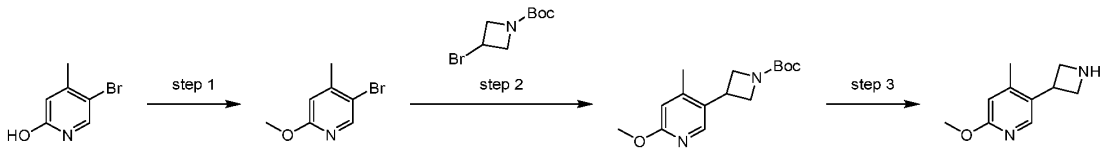
NMR (400 MHz, CDCl3) δ 8.60 (d, J = 10.0 Hz, 1H), 8.52 (dd, J = 5.6, 8.0 Hz, 1H), 7.04 (dd, J = 5.6, 10.0 Hz, 1H), 4.41 - 4.33 (m, 2H), 4.17 - 4.08 (m, 3H), 1.47 (s, 9H).

[001190] The following intermediates in Table **88** were prepared using the method described above for the synthesis of tert-butyl 3-(4-fluoropyridin-3-yl)azetidine-1-carboxylate utilizing the appropriate starting materials and modifications.

Table 88

Name	Structure	LCMS	NMR data
tert-butyl 3-(4-fluoropyridin-2-yl)azetidine-1-carboxylate		197 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1 H) 8.38 - 8.40 (m, 1 H) 7.08 - 7.11 (m, 1 H) 4.32 - 4.37 (m, 2 H) 4.09 (dd, J=8.0, 6.8 Hz, 2 H) 3.56 - 3.63 (m, 1 H), 1.46 (s, 9 H)
tert-butyl 3-(3-fluoropyridin-2-yl)azetidine-1-carboxylate		252.2 $[M+H]^+$	^1H NMR (400 MHz, CD_3OD) δ 8.46 - 8.38 (m, 1H), 7.60 - 7.50 (m, 1H), 7.36 (d, J = 4.4 Hz, 1H), 4.30 - 4.19 (m, 4H), 3.31 (s, 1H), 1.46 (s, 9H)
tert-butyl 3-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)azetidine-1-carboxylate		209.1 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 7.2 Hz, 1H), 7.22 - 7.25 (m, 1H), 6.20 (t, J = 6.8 Hz, 1H), 4.64 - 4.54 (m, 1H), 4.33 - 4.25 (m, 2H), 4.20 - 4.12 (m, 2H), 3.56 (s, 3H), 1.45 (s, 9H).
tert-butyl 3-(4-cyanopyrimidin-2-yl)azetidine-1-carboxylate		205.1 $[M+H]^+$	^1H NMR (400 MHz, $CDCl_3$) δ 8.97 (d, J=4.0 Hz, 1H) 7.54 (d, J=4.0 Hz, 1H) 4.33 (m, 2H) 4.22 - 4.29 (m, 2H) 4.04 - 4.14 (m, 1H) 1.47 (s, 9H)

Synthesis of 5-(azetidin-3-yl)-2-methoxy-4-methylpyridine



[001191] *Step 1: Preparation of 5-bromo-4-methylpyridin-2-yl acetate*

[001192] To a solution of 5-bromo-4-methylpyridin-2-ol (1.0 g, 5.3 mmol, 1.0 eq) in THF (3.0 mL) was added NaH (0.66 g, 27 mmol, 5.0 eq) at 0 °C, the mixture was stirred at 0 °C for 0.5 h, then iodomethane (7.7 g, 53 mmol, 10 eq) was added. The mixture was stirred at 25 °C for 4 h to give a white suspension. The reaction mixture was quenched by water 4 mL at 0 °C, then the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by reversed phase to lyophilized to give 5-bromo-2-methoxy-4-

methylpyridine (0.70 g, 3.46 mmol, 65% yield) as a white solid. 1H NMR (400 MHz, CD3OD) δ 7.90 (s, 1 H) 6.50 (s, 1 H) 3.52 (s, 3 H) 2.27 (s, 3 H).

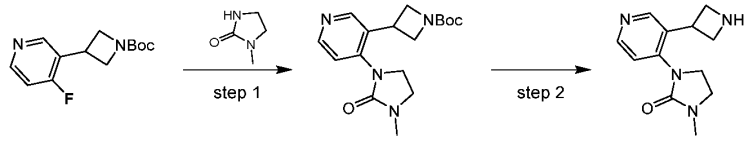
[001193] *Step 2: Preparation of tert-butyl 3-(6-methoxy-4-methylpyridin-3-yl)azetidine-1-carboxylate*

[001194] To an 15 mL vial equipped with a stir bar was added 5-bromo-2-methoxy-4-methylpyridine (0.50 g, 2.5 mmol, 1.0 eq), tert-butyl 3-bromoazetidine-1-carboxylate (0.76 g, 3.2 mmol, 1.3 eq), $Ir[dF(CF_3)ppy]_2(dtbpy)(PF_6)$ (5.8 mg, 24 μmol, 0.010 eq), $NiCl_2$·dtbbpy (15 mg, 37 μmol, 0.015 eq), TTMSS (0.62 g, 2.5 mmol, 1.0 eq), Na_2CO_3 (0.52 g, 4.9 mmol, 2.0 eq) in DME (25 mL). The vial was sealed and placed under nitrogen was added. The reaction was stirred and irradiated with a 10 W blue LED lamp (3 cm away), with cooling water to keep the reaction temperature at 25 °C for 14 h to give a brown suspension. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to tert-butyl 3-(6-methoxy-4-methylpyridin-3-yl)azetidine-1-carboxylate (0.17 g, 0.61 mmol, 25% yield) as a yellow oil. 1H NMR (400 MHz, CD3OD) δ 7.58 (s, 1H) 6.41 (s, 1H) 4.26 (s, 2H) 3.90 - 4.02 (m, 2H) 3.80 - 3.89 (m, 1H) 3.56 (s, 3H) 2.12 (s, 3H) 1.45 (s, 9H).

[001195] *Step 3: Preparation of 5-(azetidin-3-yl)-4-methylpyridin-2-ol*

[001196] The tert-butyl 3-(6-methoxy-4-methylpyridin-3-yl)azetidine-1-carboxylate (0.10 g, 0.36 mmol, 1.0 eq) was dissolved in DCM (1 mL) and TFA (0.5 mL) and stirred at 25 oC for 1 h to give a yellow solution. The reaction mixture was concentrated under reduced pressure to give 5-(azetidin-3-yl)-2-methoxy-4-methylpyridine (0.10 g, crude) as a yellow oil. LCMS (ESI) m/z = 179.1 $[M+H]^+$.

Synthesis of 1-(3-(azetidin-3-yl)pyridin-4-yl)-3-methylimidazolidin-2-one



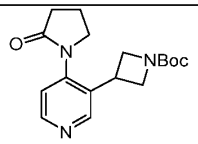
[001197] *Step 1: Preparation of tert-butyl 3-(4-(3-methyl-2-oxoimidazolidin-1-yl)pyridin-3-yl)azetidine-1-carboxylate*

[001198] To a solution of 1-methylimidazolidin-2-one (0.36 g, 3.6 mmol, 3.0 eq) in DMF (5.0 mL) at 0 °C was added NaH (0.14 mg, 3.6 mmol, 60% purity, 3.0 eq) under N2 atmosphere, the mixture stirred for 1 h, and then tert-butyl 3-(4-fluoro-3-pyridyl)azetidine-1-carboxylate (0.30 mg, 1.2 mmol, 1.0 eq) was added. The mixture was stirred at 50 °C for 6 h.

[001199] The reaction mixture was quenched by addition H2O (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with aqueous NaCl (10 mL × 3), dried over Na2SO4, filtered, and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (0.1% FA), then lyophilized to give tert-butyl 3-[4-(3-methyl-2-oxoimidazolidin-1-yl)pyridin-3-yl]azetidine-1-carboxylate (0.18 g, 0.54 mmol, 68% yield) as a yellow solid. LCMS (ESI) m/z =333.3 [M+H]+. 1H NMR (400 MHz, CDCl3) δ 8.52 (s, 1H) 8.35 (d, J = 5.6 Hz, 1H) 6.87 (d, J = 5.6 Hz, 1H) 4.35 - 4.38 (m, 2H) 4.04 - 4.06 (m, 2H) 3.53 (m, 1H) 3.34 (m, 2H) 3.14 (t, J = 5.6 Hz, 2H) 2.81 (s, 3H) 1.48 (s, 9H).

[001200] The following intermediates in Table **89** were prepared using the method described above in Step 1 for the preparation of tert-butyl 3-(4-(3-methyl-2-oxoimidazolidin-1-yl)pyridin-3-yl)azetidine-1-carboxylate utilizing the appropriate starting materials and modifications.

Table 89

Name	Structure	LCMS	NMR data
tert-butyl 3-(4-(2-oxopyrrolidin-1-yl)pyridin-3-yl)azetidine-1-carboxylate		318.1 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.44 (s, 1H), 6.98 (d, *J* = 4.8 Hz, 1H), 4.24 (t, *J* = 8.0 Hz, 2H), 3.95 - 3.89 (m, 2H), 3.88 - 3.83 (m, 1H), 3.80 - 3.65 (m, 2H), 2.54 - 2.45 (m, 2H), 2.23 - 2.13 (m, 2H), 1.36 (s, 9H)

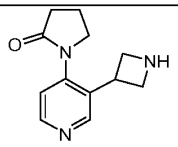
[001201] *Step 2: Preparation of 1-(3-(azetidin-3-yl)pyridin-4-yl)-3-methylimidazolidin-2-one*

[001202] To a solution of tert-butyl 3-[4-(3-methyl-2-oxoimidazolidin-1-yl)pyridin-3-yl]azetidine-1-carboxylate (0.18 g, 0.54 mmol, 1.0 eq) in methylene chloride (3.0 mL) was added TFA (1.0 mL). The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give 1-[3-(azetidin-3-yl)pyridin-4-yl]-3-methylimidazolidin-2-one (0.12 g, crude, TFA salt) as a yellow liquid. LCMS (ESI) m/z =233.2 [M+H]+.

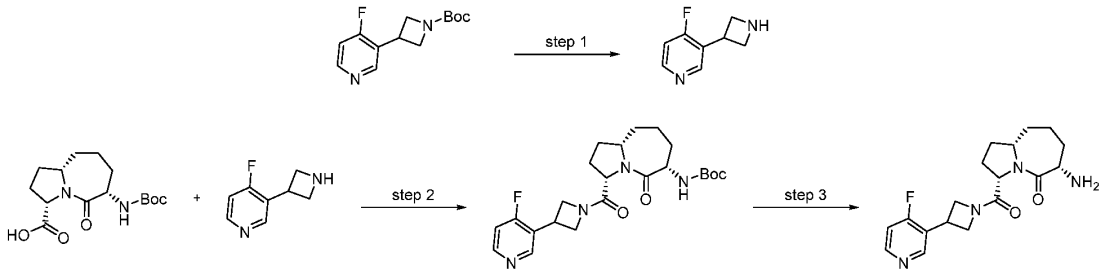
[001203] The following intermediates in Table **90** were prepared using the method described above in Step 2 for the preparation of 1-(3-(azetidin-3-yl)pyridin-4-yl)-3-methylimidazolidin-2-one utilizing the appropriate starting materials and modifications.

Table 90

Name	Structure	LCMS

1-(3-(azetidin-3-yl)pyridin-4-yl)pyrrolidin-2-one (TFA salt)		218.0 $[M+H]^+$

Synthesis of (3*S*,6*S*,9*aS*)-6-amino-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one



[001204] Step 1: Preparation of 3-(azetidin-3-yl)-4-fluoropyridine

[001205] To a stirred solution of tert-butyl 3-(4-fluoropyridin-3-yl)azetidine-1-carboxylate (1.6 g, 6.34 mmol, 1 eq) in CH2Cl2 (20 mL) was added TFA (3 mL). The resulting yellow solution was stirred for 1 h at room temperature. More TFA (0.5 mL) was added and reaction mixture was stirred for 0.5 h at room temperature. The reaction was concentrated to dryness to give the TFA salt of 3-(azetidin-3-yl)-4-fluoropyridine (964 mg, 100%) that was directly in the next step.

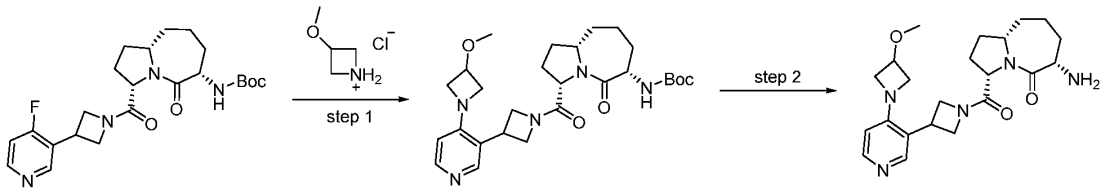
[001206] Step 2: Preparation of tert-butyl ((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate

[001207] To a solution of 3-(azetidin-3-yl)-4-fluoropyridine TFA salt (964 mg, 6.34 mmol, 1.15 eq) in N,N-dimethylformamide (15 mL) were respectively added DIPEA (9 mL, 51.6 mmol, 9.3 eq), (3S,6S,9aS)-6-((tert-butoxycarbonyl)amino)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic acid (1.73 g, 5.53 mmol, 1 eq) and HATU (2.31 g, 6.08 mmol, 1.1 eq). The reaction was stirred at room temperature 16 h. The reaction mixture was concentrated and purified directly by reverse phase chromatography on a 100 g C18 cartridge eluting with 5-60 % MeCN in water to afford tert-butyl ((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (1.75 g, 71.1% yield). LCMS (ESI) m/z = 447.4 [M+H]+.

[001208] STEP 3: Preparation of (3S,6S,9aS)-6-amino-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)hexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one

[001209] To a stirred solution of tert-butyl ((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (1.3 g, 2.91 mmol, 1 eq) in CH_2Cl_2 (20 mL) was added TFA (5 mL). The resulting yellow solution was stirred for 1.5 h at room temperature. The reaction was concentrated to dryness to give the TFA salt of (3S,6S,9aS)-6-amino-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)hexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (1.00 g, 100% yield) that was used directly in the next step.

Synthesis of (3S,6S,9aS)-6-amino-3-(3-(4-(3-methoxyazetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)octahydro-5H-pyrrolo[1,2-a]azepin-5-one



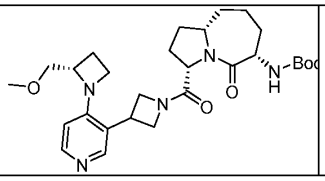
[001210] Step 1: Preparation of tert-butyl ((3S,6S,9aS)-3-(3-(4-(3-methoxyazetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate

[001211] To a solution of tert-butyl N-[(3S,6S,9aS)-3-[3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl]-5-oxo-octahydro-1H-pyrrolo[1,2-a]azepin-6-yl]carbamate (20 mg, 44.7 μmol, 1 eq) and 3-methoxyazetidine hydrochloride (11.0 mg, 89.4 μmol, 2 eq) in dimethyl sulfoxide (2 mL) was added DIPEA (100 μL, 573 μmol, 13 eq). The resulting solution was heated at 95°C under nitrogen during 20 h. The crude mixture was purified by reverse phase chromatography on a 50 g C18 cartridge eluting with 5-60% MeCN in water. The pure fractions were concentrated under reduced pressure to give tert-butyl ((3S,6S,9aS)-3-(3-(4-(3-methoxyazetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (19 mg, 82%) was obtained as a yellow solid. LCMS (ESI) m/z = 514.4 [M+H]+.

[001212] The following intermediates in Table **91** were prepared using the method described above in Step 1 for the preparation of tert-butyl ((3S,6S,9aS)-3-(3-(4-(3-methoxyazetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate utilizing the appropriate starting materials and modifications.

Table 91

Name	Structure	LCMS

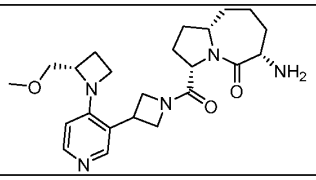
tert-butyl ((3S,6S,9aS)-3-(3-(4-((S)-2-(methoxymethyl)azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate		528.4 $[M+H]^+$

[001213] *Step 2: Preparation of (3S,6S,9aS)-6-amino-3-(3-(4-(3-methoxyazetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)octahydro-5H-pyrrolo[1,2-a]azepin-5-one*

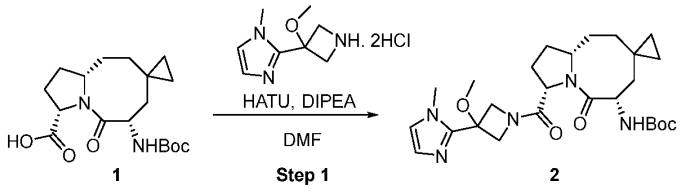
[001214] To a stirred solution of tert-butyl ((3S,6S,9aS)-3-(3-(4-(3-methoxyazetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (50 mg, 97.3 µmol, 1 eq) in CH2Cl2 (2.5 mL) was added TFA (800 µL). The resulting yellow solution was stirred for 1 h at room temperature. The reaction was concentrated to dryness to give the TFA salt of (3S,6S,9aS)-6-amino-3-(3-(4-(3-methoxyazetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)octahydro-5H-pyrrolo[1,2-a]azepin-5-one. LCMS (ESI) m/z = 207.8 (M+2H)2+.

[001215] The following intermediates in Table **92** were prepared using the method described above in Step 2 for the preparation of (3S,6S,9aS)-6-amino-3-(3-(4-(3-methoxyazetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)octahydro-5H-pyrrolo[1,2-a]azepin-5-one utilizing the appropriate starting materials and modifications.

Table 92

Name	Structure	LCMS
(3S,6S,9aS)-6-amino-3-(3-(4-((S)-2-(methoxymethyl)azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)octahydro-5H-pyrrolo[1,2-a]azepin-5-one (TFA salt)		218.4 $(M+2H)^{2+}$

Synthesis of *tert*-butyl ((3'*S*,6'*S*,10*a*'*S*)-3'-(3-methoxy-3-(1-methyl-1*H*-imidazol-2-yl)azetidine-1-carbonyl)-5'-oxooctahydro-5'*H*-spiro[cyclopropane-1,8'-pyrrolo[1,2-*a*]azocin]-6'-yl)carbamate

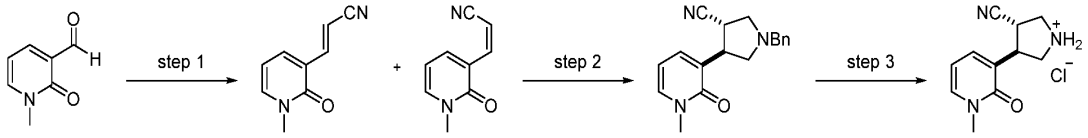


1 Step 1 2

[001216] *Step 1: tert-butyl ((3'S,6'S,10a'S)-3'-(3-methoxy-3-(1-methyl-1H-imidazol-2-yl)azetidine-1-carbonyl)-5'-oxooctahydro-5'H-spiro[cyclopropane-1,8'-pyrrolo[1,2-a]azocin]-6'-yl)carbamate*

[001217] To a solution of (3'S,6'S,10a'S)-6'-((tert-butoxycarbonyl)amino)-5'-oxooctahydro-5'H-spiro[cyclopropane-1,8'-pyrrolo[1,2-a]azocine]-3'-carboxylic acid (20 mg, 56.7 µmol, 1 eq), 2-(3-methoxyazetidin-3-yl)-1-methyl-1H-imidazole dihydrochloride (14.2 mg, 59.5 µmol, 1.05 eq) and HATU (25.8 mg, 68.0 µmol, 1.2 eq) in DMF (3 mL) was added DIPEA (68.8 µL, 396 µmol, 7 eq). The reaction was stirred at room temperature 1 h. The product was purified directly by reverse phase chromatography on a 50 g C18 cartridge eluting with a gradient of 5-60% acetonitrile in water to afford after freeze drying tert-butyl ((3'S,6'S,10a'S)-3'-(3-methoxy-3-(1-methyl-1H-imidazol-2-yl)azetidine-1-carbonyl)-5'-oxooctahydro-5'H-spiro[cyclopropane-1,8'-pyrrolo[1,2-a]azocin]-6'-yl)carbamate (26.0 mg, 91.5%) as a white solid. LCMS (ESI) m/z = 502.4 $[M+H]^+$.

Synthesis of racemic-(3S,4R)-4-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidine-3-carbonitrile



[001218] *Step 1: Preparation of Cis- and Trans-3-(2-methoxypyridin-3-yl)prop-2-enenitrile*

[001219] To a solution of diethyl (cyanomethyl)phosphonate (676 mg, 3.82 mmol, 1.05 eq) in THF (20 mL) was added KOtBu (448 mg, 4.0 mmol, 1.1 eq) at 0 °C. The solution was stirred for 10 min at 0°C, followed by addition of 2-methoxypyridine-3-carbaldehyde (500 mg, 3.64 mmol, 1 eq). The reaction was stirred 1 h. Water (100 mL) was added and the product was extracted with EtOAc (2 x 70 mL). The organic layers were dried with sodium sulfate, filtered and concentrated under reduced pressure to afford a mixture of cis- and trans-3-(2-methoxypyridin-3-yl)prop-2-enenitrile (560 mg, 96.0% yield) as an oil. LCMS (ESI) m/z = 161.2 [M+H]+.

[001220] *Step 2: Preparation of racemic-(3S,4R)-1-benzyl-4-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidine-3-carbonitrile*

[001221] To a solution of cis- and trans-3-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)prop-2-enenitrile (0.56 g, 3.49 mmol, 1 eq) and benzyl(methoxymethyl)[(trimethylsilyl)methyl]amine (1.33 mL, 5.23 mmol, 1.5 eq)

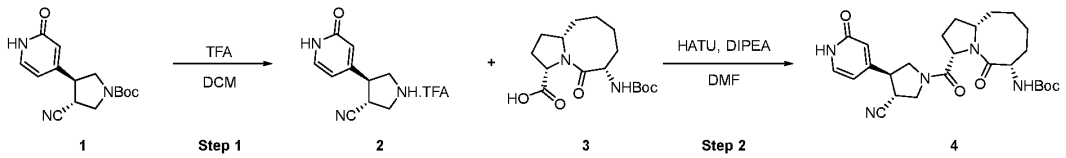
in DCM (15 mL) was added TFA (4 mL, 52.2 mmol, 10 eq) dropwise at room temperature. After the addition, the solution was stirred 15 min at room temperature. The reaction was quenched with saturated aqueous solution of $NaHCO_3$ with vigorous stirring and the product was extracted with DCM (2 x 50 mL). The combined organic layers were concentrated to dryness and the product was purified twice by reverse phase chromatography on a 150 g C_{18} cartridge eluting with 5-70% acetonitrile in water (10 mM NH_4HCO_3 (pH = 10) buffer) to afford racemic-(3S,4R)-1-benzyl-4-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidine-3-carbonitrile (238 mg, 23.3%) as an off-white solid. 1H NMR (400 MHz, acetone-d6) δ 7.57 (dd, J = 6.8, 2.0 Hz, 1H), 7.46 (dd, J = 7.0, 1.8 Hz, 1H), 7.40 - 7.35 (m, 2H), 7.35 - 7.29 (m, 2H), 7.28 - 7.20 (m, 1H), 6.18 (t, J = 6.8 Hz, 1H), 3.70 (s, 2H), 3.66 - 3.57 (m, 1H), 3.50 (s, 3H), 3.49 - 3.44 (m, 1H), 3.09 - 3.03 (m, 1H), 3.02 - 2.96 (m, 2H), 2.70 - 2.62 (m, 1H). LCMS (ESI) m/z = 294.2 [M+H]+.

[001222] racemic-(3S,4S)-1-Benzyl-4-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidine-3-carbonitrile (88 mg, 8.6%) was also isolated as an oil. LCMS (ESI) m/z = 294.2 [M+H]+.

[001223] *Step 3: Preparation of (3S,4R)-4-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidine-3-carbonitrile*

[001224] To a solution of (3S,4R)-1-benzyl-4-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidine-3-carbonitrile (75 mg, 0.2556 mmol, 1 eq) in 1,1-dichloroethane (3 mL) at 0 oC was slowly added 1-chloroethyl chloroformate (35.7 µL, 0.3322 mmol, 1.3 eq). The reaction mixture was stirred for 20 min. at 0 oC and subsequently warmed to room temperature and stirred for 30 min. Additional 1-chloroethyl chloroformate (35.7 µL, 0.3322 mmol, 1.3 eq) was added and the reaction was stirred for 2 h at room temperature. The reaction was heated to reflux for 30 min. and then cooled to room temperature and stirred for 20 h. The reaction was concentrated under reduced pressure. The crude residue was dissolved in methanol (3 mL) and heated to reflux for 1.5 h. The reaction was concentrated under reduced pressure to give crude (3S,4R)-4-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidine-3-carbonitrile (61 mg, 99%, HCl) as a thick oil. LCMS (ESI) m/z = 204.2 [M+H]+.

Synthesis of *tert*-butyl *N*-[(3S,6S,10*a*S)-3-[(*rel*-trans)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl]-5-oxo-decahydropyrrolo[1,2-*a*]azocin-6-yl]carbamate



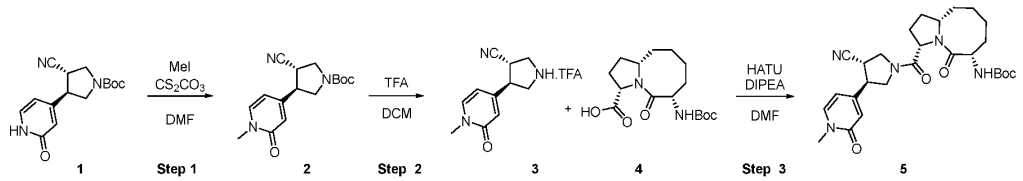
[001225] *Step 1: Preparation of (rel-trans)-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-3-carbonitrile*

[001226] To a solution of tert-butyl (rel-trans)-3-cyano-4-(2-oxo-1,2-dihydropyridin-3-yl)pyrrolidine-1-carboxylate (635 mg, 2.19 mmol, 1 eq) in DCM (7 mL) was added TFA (3.34 mL, 43.8 mmol, 20 eq). The solution was stirred at room temperature for 2 h. The reaction was concentrated to dryness to give the crude TFA salt of (rel-trans)-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-3-carbonitrile (665 mg, 100%). LCMS (ESI): m/z = 190.2 [M+H]+.

[001227] *Step 2: Preparation of tert-butyl N-[(3S,6S,10aS)-3-[(3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl]-5-oxo-decahydropyrrolo[1,2-a]azocin-6-yl]carbamate.*

[001228] To a solution of (rel-trans)-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-3-carbonitrile TFA salt (665 mg, 3.36 mmol, 1.1 eq) in DMF (30 mL) were added (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid (1 g, 3.06 mmol, 1 eq), DIPEA (3.15 g, 24.4 mmol, 8 eq) and HATU (1.16 g, 3.06 mmol, 1 eq). The reaction was stirred at room temperature for 0.5 h. The crude mixture was concentrated and purified directly by reverse phase chromatography on a 100 g C_{18} cartridge using a gradient of 5-80% MeCN in water (with 0.1% formic acid) to give *tert*-butyl *N*-[(3*S*,6*S*,10*aS*)-3-[(*rel*-trans)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl]-5-oxo-decahydropyrrolo[1,2-*a*]azocin-6-yl]carbamate (500 mg, 32.8%) as a beige solid. LCMS (ESI): m/z = 498.4 $[M+H]^+$.

Synthesis of *tert*-butyl *N*-[(3*S*,6*S*,10*aS*)-3-[(*rel*-trans)- 3-cyano-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl]-5-oxo-decahydropyrrolo[1,2-*a*]azocin-6-yl]carbamate



[001229] *Step 1: tert-Butyl (rel-trans)-3-cyano-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate*

[001230] To a solution of tert-butyl (rel-trans)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate (500 mg, 1.72 mmol, 1 eq) and cesium carbonate (781 mg, 2.40 mmol, 1.4 eq) in N,N-dimethylformamide (8 mL) at 0°C was added dropwise methyl iodide (159 μL, 2.57 mmol, 1.5 eq). The reaction mixture was stirred at room temperature for 6 h. The crude material was filtered and purified by reverse phase chromatography on a 100 g C18 cartridge eluting with 5-100% MeCN in water (with 0.1% formic acid). The combined fractions were concentrated under reduced pressure to give tert-butyl (rel-trans)-3-cyano-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate (405 mg, 77.7%) as a white solid. LCMS (ESI): m/z = 304.3 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 7.71 (d, J = 6.8 Hz, 1H), 6.40 (s, 1H), 6.29 (d, J = 6.6 Hz, 1H), 3.83 (br. s., 1H), 3.69 (d, J = 8.3 Hz, 2H), 3.57 - 3.45 (m, 1H), 3.40 (s, 3H), 3.18 (d, J = 7.8 Hz, 1H), 2.50 (s., 1H), 1.40 (s, 9H).

[001231] *Step 2: (rel-trans)-4-(1-Methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-3-carbonitrile*

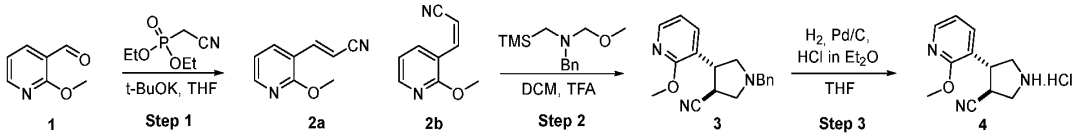
[001232] To a solution of tert-butyl (rel-trans)-3-cyano-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate (400 mg, 1.31 mmol, 1 eq) in methylene chloride (3 mL) was added TFA (1 mL, 13.1 mmol, 10 eq). The resulting yellow solution was stirred for 30 min. at room temperature. The reaction mixture was concentrated under reduced pressure. Crude TFA salt (418 mg, 100%) was used directly in the next step. LCMS (ESI): m/z = 204.2 [M+H]+.

[001233] *Step 3: tert-Butyl N-[(3S,6S,10aS)-3-[(rel-trans)- 3-cyano-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl]-5-oxo-decahydropyrrolo[1,2-a]azocin-6-yl]carbamate*

[001234] HATU (577 mg, 1.52 mmol, 1.2 eq) was added to a solution of (rel-trans)-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-3-carbonitrile TFA salt (260 mg, 1.27 mmol, 1 eq), (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid (453 mg, 1.39 mmol, 1.1 eq) and N,N-diisopropylethylamine (1.32 mL, 7.62 mmol, 6 eq) in N,N-dimethylformamide (10 mL). The reaction mixture was stirred at room temperature for 2 h. The crude product was purified directly by reverse phase chromatography with a 100 g C18 cartridge using a gradient of MeCN in water. The combined fractions were concentrated under reduced pressure and freeze-dried to afford tert-butyl N-[(3S,6S,10aS)-3-[(rel-trans)-3-cyano-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-

yl)pyrrolidine-1-carbonyl]-5-oxo-decahydropyrrolo[1,2-a]azocin-6-yl]carbamate (595 mg, 91.6%) as a white solid. LCMS (ESI): m/z = 512.4 [M+H]+.

Synthesis of (*rel*-trans)-4-(2-methoxypyridin-3-yl)pyrrolidine-3-carbonitrile hydrochloride



[001235] *Step 1: 3-(2-methoxypyridin-3-yl)acrylonitrile*

[001236] To a solution of diethyl (cyanomethyl)phosphonate (3.38 g, 19.1 mmol, 1.05 eq) in THF (100 mL) was added potassium t-butoxide (2.24 g, 20.0 mmol, 1.1 eq) at 0°C. The solution was stirred for 10 min. at 0°C and then 2-methoxynicotinaldehyde (2.5 g, 18.2 mmol, 1 eq) was added to the solution. The reaction was stirred 3.5 h. Water (250 mL) was added and the product was extracted with EtOAc (2 x 150 mL). The organic layers were dried with sodium sulfate, filtered and concentrated under reduced pressure to afford a mixture of cis- and trans-3-(2-methoxypyridin-3-yl)acrylonitrile (3.20 g, 109%) as an oil. LCMS (ESI) m/z = 161.2

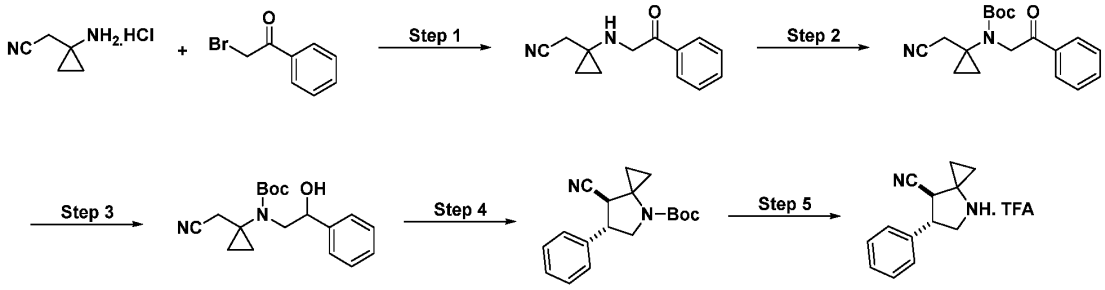
[001237] *Step 2: trans-1-benzyl-4-(2-methoxypyridin-3-yl)pyrrolidine-3-carbonitrile*

[001238] To a solution of cis- and trans-3-(2-methoxypyridin-3-yl)acrylonitrile (4.84 g, 30.2 mmol, 1 eq) and benzyl(methoxymethyl)[(trimethylsilyl)methyl]amine (9.3 g, 39.2 mmol, 1.3 eq) in DCM (50 mL) was added TFA (4 mL, 52.2 mmol, eq) dropwise at room temperature. After the addition, the solution was stirred 15 min. at room temperature. The reaction was quenched with a saturated aqueous solution of sodium bicarbonate with vigorous stirring and the product was extracted with DCM (3 x 75 mL). The combined organic layers were concentrated to dryness and the product was purified twice by reverse phase chromatography on a 275 g C18 cartridge eluting with a gradient of 5-70% acetonitrile in basic water (10 mM NH_4HCO_3 (pH = 10) buffer) to afford trans-1-benzyl-4-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidine-3-carbonitrile (2.37 g, 26.7%) as an off-white solid (racemic trans product). 1H NMR (400 MHz, $(CD_3)_2CO$) δ ppm 8.07 (dd, J = 5.0, 1.6 Hz, 1H), 7.71 (dd, J = 7.3, 1.2 Hz, 1H), 7.43 - 7.30 (m, 4H), 7.29 - 7.23 (m, 1H), 6.94 (dd, J = 7.2, 5.0 Hz, 1H), 3.94 (s, 3H), 3.82 - 3.69 (m, 3H), 3.34 - 3.26 (m, 1H), 3.08 (dt, J = 12.5, 8.7 Hz, 2H), 2.95 (dd, J = 9.3, 5.4 Hz, 1H), 2.72 (dd, J = 9.2, 7.2 Hz, 1H).

[001239] *Step 3: trans-4-(2-methoxypyridin-3-yl)pyrrolidine-3-carbonitrile hydrochloride*

[001240] To a solution of trans-1-benzyl-4-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidine-3-carbonitrile (100 mg, 340 µmol, 1 eq) in THF (5 mL) under nitrogen atmosphere were added 2 M HCl in diethyl ether (170 µL, 340 µmol, 1.0 eq) and 10% palladium on carbon (50% wet) (75 mg, 35 µmol, 0.1 eq). The suspension was stirred 16 h under hydrogen atmosphere (1 atm). The reaction mixture was filtered through Celite. The filter cake was washed with THF and the filtrate was concentrated to dryness to provide crude *trans*-4-(2-methoxypyridin-3-yl)pyrrolidine-3-carbonitrile hydrochloride that was used directly in the next step.

Synthesis of (*rel*-trans)-6-phenyl-4-azaspiro[2.4]heptane-7-carbonitrile TFA salt



[001241] *Step 1: 2-{1-[(2-oxo-2-phenylethyl)amino]cyclopropyl}acetonitrile*

[001242] To a solution of 2-(1-aminocyclopropyl)acetonitrile hydrochloride (10.7 g, 81.0 mmol, 1 eq) in N,N-dimethylformamide (250 mL) were added 2-bromo-1-phenylethan-1-one (16.1 g, 81.0 mmol, 1 eq) followed by potassium phosphate tribasic (42.8 g, 202 mmol, 2.5 eq). The mixture was stirred at room temperature for 4 h. A yellowish mixture was observed over time. The reaction was quenched with the addition of 1 N HCl (600 mL, pH = 1) at room temperature. The aqueous solution was washed with EtOAc (2 x 500 mL) then basified with 1 N NaOH aqueous solution (until pH = 9, 600 mL) then extracted with EtOAc (2 x 600 mL). The combined organic extracts were washed with brine (2 x 300 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give crude 2-{1-[(2-oxo-2-phenylethyl)amino]cyclopropyl}acetonitrile (12.5 g, 72%) as a clear pale orange liquid. **LCMS** (ESI) m/z = 215.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 7.97 (d, J = 7.6 Hz, 2H), 7.66 (t, J = 7.1 Hz, 1H), 7.54 (t, J = 7.1 Hz, 2H), 4.25 (s, 2H), 2.79 (s, 2H), 0.76 - 0.70 (m, 2H), 0.61 - 0.56 (m, 1H).

[001243] *Step 2: tert-butyl N-[1-(cyanomethyl)cyclopropyl]-N-(2-oxo-2-phenylethyl)carbamate*

[001244] To a solution of 2-{1-[(2-oxo-2-phenylethyl)amino]cyclopropyl}acetonitrile (12.5 g, 58.3 mmol, 1 eq) in THF (150 mL) were added water (150 mL) and sodium bicarbonate (4.89 g, 58.3 mmol, 1.0 eq) followed by di-tert-butyl dicarbonate (25.3 g, 116 mmol, 2 eq). The reaction was stirred for 48 h at room temperature. The reaction was concentrated under reduced pressure (to remove THF) then diluted with EtOAc (250 mL) and water (50 mL). The phases were separated and the aqueous phase was back-extracted with EtOAc (2 x 250 mL). The combined organic layers were dried with sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified flash-chromatography on silica gel eluting with 1-25% EtOAc in heptane to give *tert*-butyl *N*-[1-(cyanomethyl)cyclopropyl]-*N*-(2-oxo-2-phenylethyl)carbamate (14.3 g, 78%) as a white solid. **LCMS** (ESI) m/z = 215.2 (M-Boc+2H), 259.2 (M-*t*-Bu+2H). **^{1}H NMR** (400 MHz, DMSO-d_6 at 80°C) δ 7.97 (d, *J* = 7.2 Hz, 2H), 7.67 (t, *J* = 7.1 Hz, 1H), 7.55 (t, *J* = 7.1 Hz, 2H), 4.73 (s, 2H), 2.87 (s, 2H), 1.54 - 1.24 (m, 9H), 1.04 - 0.99 (m, 2H), 0.94 - 0.90 (m, 2H).

[001245] *Step 3: tert-butyl N-[1-(cyanomethyl)cyclopropyl]-N-(2-hydroxy-2-phenylethyl)carbamate*

[001246] To a solution of tert-butyl N-[1-(cyanomethyl)cyclopropyl]-N-(2-oxo-2-phenylethyl)carbamate (14.33 g, 45.4 mmol, 1 eq) in methanol (260 mL) at 0°C was added sodium borohydride (1.71 g, 45.4 mmol, 1.0 eq) portion wise over 10 min. The reaction was stirred for 20 min at room temperature. The reaction was quenched with 1 N HCl (100 mL) and concentrated under reduced pressure (to remove MeOH). The crude residue was extracted with EtOAc (3 x 200 mL). The combined organic layers were over sodium sulfate, filtered and concentrated under reduced pressure to give tert-butyl N-[1-(cyanomethyl)cyclopropyl]-N-(2-hydroxy-2-phenylethyl)carbamate (14.7 g, 100%) as a clear pale pink oil. 1H NMR (400 MHz, DMSO-d6 at 80°C) δ 7.38 - 7.23 (m, 5H), 5.51 (br. s, 1H), 4.89 - 4.72 (m, 1H), 3.39 - 3.27 (m, 1H), 3.21 - 3.13 (m, 1H), 3.04 - 2.90 (m, 1H), 2.68 - 2.60 (m, 1H), 1.48 (s, 9H), 0.83 - 0.65 (m, 4H).

[001247] *Step 4: tert-butyl (rel-trans)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate*

[001248] To a solution of *tert*-butyl *N*-[1-(cyanomethyl)cyclopropyl]-*N*-(2-hydroxy-2-phenylethyl)carbamate (12 g, 37.9 mmol, 1 eq) in THF (650 mL) at -15°C were added diethyl phosphorochloridate (5.74 mL, 39.7 mmol, 1.05 eq) followed by dropwise addition of 1 M

LiHMDS in THF (94.7 mL, 94.7 mmol, 2.5 eq) over 30 min. The reaction was stirred at -15°C for 30 min. The reaction was quenched with 1N HCl (200 mL) and concentrated under reduced pressure (to remove THF). The crude residue was purified flash-chromatography on silica gel eluting with 1-8% EtOAc in heptane to give rac-*tert*-butyl (*rel*-trans)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate (3.7 g, 33%) as a clear oil. **LCMS** (ESI) m/z = 243.2 (M-*t*-Bu+2H)$^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.59 - 7.21 (m, 5H), 4.01 (d, J = 10.5 Hz, 1H), 3.90 (dd, J = 10.5, 7.8 Hz, 1H), 3.69 (q, J = 10.2 Hz, 1H), 3.45 (t, J = 10.0 Hz, 1H), 1.96 - 1.83 (m, 1H), 1.48 - 1.41 (m, 1H), 1.40 - 1.32 (m, 9H), 0.92 - 0.77 (m, 1H), 0.74 - 0.61 (m, 1H).

[001249] rac-*tert*-butyl (6*R*,7*S*)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate was submitted to chiral SFC separation (SFC conditions: Column Lux Amylose 1, 30 x 250 mm 5 um column, 9.25 mg/inj, concentration 18.5 mg/mL, Column T = 40°C, Flow rate 100 mL/min, 10% MeOH, cycle time: 2 min) to give *tert*-butyl (6*R*,7*S*)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate (1.57 g, 5.26 mmol, 42% recovery, 99.9% ee) as a white solid and *tert*-butyl (6*S*,7*R*)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate (1.57 g, 0.70 mmol, 42% recovery, 99.9% ee) as a white solid.

[001250] The assignment of absolute stereochemical configuration was made by comparing experimental vibrational circular dichroism (VCD) spectra with theoretical VCD spectra obtained from DFT calculations.

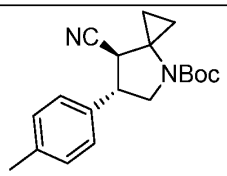
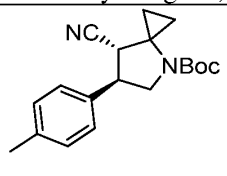
[001251] Step 5: (rel-trans)-6-phenyl-4-azaspiro*[2.4]heptane-7-carbonitrile TFA salt*

[001252] To a solution of a tert-butyl (rel-trans)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate (32 mg, 0.1072 mmol, 1 eq) in methylene chloride (4 mL) was added TFA (1 mL). The reaction was stirred at room temperature for 2 h. The reaction was concentrated under reduced pressure to give crude (rel-trans)-6-phenyl-4-azaspiro[2.4]heptane-7-carbonitrile TFA salt (21.2 mg, 99%) as a thick oil. LCMS (ESI) m/z = 229.2 [M+H]+.

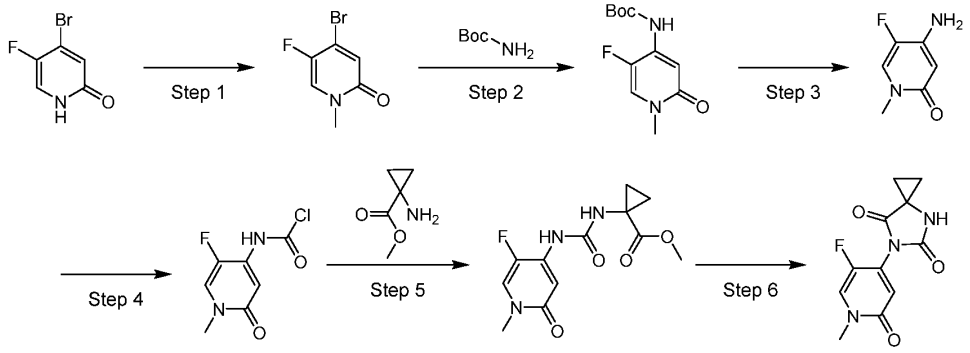
[001253] The compounds in Table **93** were prepared with the procedures described for tert-butyl (rel-trans)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate utilizing the appropriate starting materials.

Table 93

Name	Structure	LCMS

tert-butyl (6S,7R)-7-cyano-6-(p-tolyl)-4-azaspiro[2.4]heptane-4-carboxylate	 SFC Peak 1 (absolute configuration arbitrarily assigned)	313 $[M+H]^+$
tert-butyl (6R,7S)-7-cyano-6-(p-tolyl)-4-azaspiro[2.4]heptane-4-carboxylate	 SFC Peak 2 (absolute configuration arbitrarily assigned)	313 $[M+H]^+$

Synthesis of 6-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione



[001254] *Step 1: Preparation of 4-bromo-5-fluoro-1-methylpyridin-2(1H)-one*

[001255] To a solution of 4-bromo-5-fluoropyridin-2(1H)-one (1.5 g, 7.8 mmol, 1 eq) in DMF (20 mL) was added dipotassium carbonate (1.4 g, 10 mmol, 1.3 eq) and iodomethane (1.1 g, 7.8 mmol, 1.0 eq), the mixture was stirred at 25 °C for 16 h. The reaction was diluted with water (100 mL) and extracted with EtOAc (100 mL × 2), the combined organic layers were washed with saturated brine (50 mL × 2), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography to give 4-bromo-5-fluoro-1-methylpyridin-2(1H)-one (1.4 g, 6.8 mmol, 87% yield) as a white solid. LCMS (ESI) m/z = 206.1 [M+H]+. 1H NMR (400 MHz, CD_3OD) δ 7.87 (d, J = 4.4 Hz, 1H), 6.88 (d, J = 6.4 Hz, 1H), 3.51 (s, 3H).

[001256] *Step 2: Preparation of tert-butyl (5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)carbamate*

[001257] To a solution of 4-bromo-5-fluoro-1-methylpyridin-2(1H)-one (1.4 g, 6.8 mmol, 1 eq) in dioxane (20 mL) was added [5-(diphenylphosphanyl)-9,9- dimethyl-9H-xanthen-4-yl]diphenylphosphane (0.8 g, 1.4 mmol, 0.2 eq), tert-butyl carbamate (1.6 g, 13.5 mmol, 2 eq), Cs_2CO_3 (6.6 g, 20.3 mmol, 3 eq) and $Pd_2(dba)_3$ (621 mg, 679 μmol, 0.1 eq). The mixture was degassed and purged with N_2 (3 times), and then the mixture was stirred at 100 °C for 12 h. The reaction mixture was filtered and the filter was concentrated to give a residue. The residue was purified by flash column chromatography to give a residue. The residue was purified by reversed phase (TFA) then lyophilization to give tert-butyl (5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)carbamate (1.4 g, 5.8 mmol, 85% yield) as a white solid. LCMS (ESI) m/z =242.9 $[M+H]^+$.

[001258] *Step 3: Preparation of 4-amino-5-fluoro-1-methylpyridin-2(1H)-one*

[001259] To a solution of tert-butyl (5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)carbamate (1.4 g, 5.8 mmol, 1 eq) in DCM (12 mL) was added TFA (3 mL), the mixture was stirred at 25 °C for 1 h to give a clear brown solution. The reaction mixture was concentrated under reduced pressure to give 4-amino-5-fluoro-1-methylpyridin-2(1H)-one (1.4 g, crude) as brownness oil. LCMS (ESI) m/z 143.3 [M+H]+.

[001260] *Step 4: Preparation of (5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)carbamic chloride*

[001261] To a cooled (0 °C) solution of ditrichloromethyl carbonate (0.6 g, 1.9 mmol, 0.3 eq) in DCM (10 mL) was added a solution of 4-amino-5-fluoro-1-methylpyridin-2(1H)-one (0.8 g, crude, 1 eq) in DCM and triethylamine (1.2 g, 11.5 mmol, 2.0 eq). The mixture was stirred at 0 °C for 30 min. The mixture was used next step without work up.

[001262] *Step 5: Preparation of methyl 1-(3-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)ureido)cyclopropane-1-carboxylate*

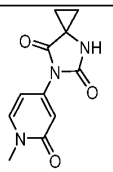
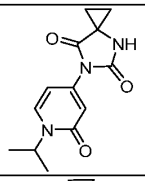
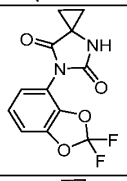
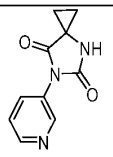
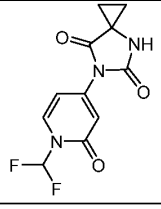
[001263] To a solution of (5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)carbamic chloride (1.2 g, crude) in DCM (10 mL) was added a solution of methyl 1-aminocyclopropane-1-carboxylate (1.0 g, 8.6 mmol, 1.5 eq) in DCM (2 mL) and triethylamine (1.7 g, 17 mmol, 3 eq). The mixture was stirred at 0 °C for 1 h to give a clear brown solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by reversed phase (TFA) then lyophilization to give a methyl 1-(3-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)ureido)cyclopropane-1-carboxylate (1.0 g, 3.5 mmol, 62% yield) as a white solid. LCMS (ESI) m/z =283.7 $[M+H]^+$.

[001264] *Step 6: 6-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione*

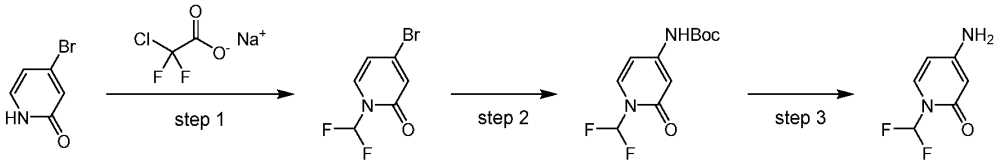
[001265] To a solution of methyl 1-(3-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)ureido)cyclopropane-1-carboxylate (1.0 g, 3.5 mmol, 1 eq) in MeCN (20 mL) was added 1H,2H,3H,4H,6H,7H,8H-[1,3]diazino[1,2-a]pyrimidine (2.0 g, 14 mmol, 4 eq), the mixture was stirred at 25 °C for 1 h to give a yellow clean solution. The mixture was purified by reversed phase (TFA) then lyophilization to give 6-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione (0.4 g, 1.4 mmol, 41% yield) as a white solid. LCMS (ESI) m/z =252.1 $[M+H]^+$.

[001266] The following intermediates in **Table 94** were prepared using the method described above for the synthesis of 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione, utilizing the appropriate starting materials and modifications.

Table 94

Name	Structure	LCMS
6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione		234.1 $[M+H]^+$
6-(1-isopropyl-2-oxo-1,2-dihydropyridin-4-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione		262.1 $[M+H]^+$
6-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione		283.1 $[M+H]^+$
6-(pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione		204 $[M+H]^+$
6-(1-(difluoromethyl)-2-oxo-1,2-dihydropyridin-4-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione		270.2 $[M+H]^+$

Synthesis of 4-amino-1-(difluoromethyl)pyridin-2(1H)-one



[001267] *Step 1: Preparation of 4-bromo-1-(difluoromethyl)pyridin-2(1H)-one*

[001268] To a solution of 4-bromopyridin-2(1H)-one (5.0 g, 29 mmol, 1.0 eq) in DMF (50 mL) was added Cs_2CO_3 (14 g, 43 mmol, 1.5 eq) and sodium 2-chloro-2,2-difluoroacetate (4.4 g, 29 mmol, 1.0 eq). The mixture was stirred at 80 °C for 6 h. The reaction mixture was added to H_2O (100 mL) and extracted with EtOAc (100 mL × 2). The combined organic layer was washed with brine (100 mL × 2), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash silica gel chromatography to give 4-bromo-1-(difluoromethyl)pyridin-2(1H)-one (1.0 g, 4.5 mmol, 15% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 - 7.37 (m, 1H), 7.25 (d, J = 7.6 Hz, 1H), 6.77 (s, 1H), 6.45 - 6.34 (m, 1H).

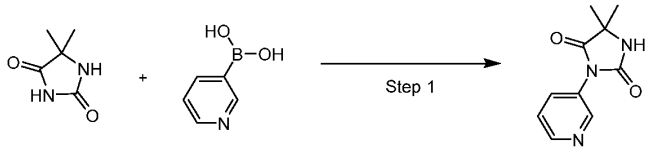
[001269] *Step 2: Preparation of tert-butyl (1-(difluoromethyl)-2-oxo-1,2-dihydropyridin-4-yl)carbamate*

[001270] A mixture of 4-bromo-1-(difluoromethyl)pyridin-2(1H)-one (0.9 g, 4.0 mmol, 1.0 eq) and tert-butyl carbamate (0.94 g, 8.0 mmol, 2.0 eq), [5-(diphenylphosphanyl)-9,9-dimethyl-9H-xanthen-4-yl]diphenylphosphane (0.46 g, 0.80 mmol, 0.2 eq), bis((1Z,4Z)-1,5-diphenylpenta-1,4-dien-3-one) (4Z)-1,5-diphenylpenta-1,4-dien-3-one dipalladium (0.37 g, 0.40 mmol, 0.1 eq) and Cs_2CO_3 (3.9 g, 12 mmol, 3 eq) in dioxane (30 mL) was degassed and purged with N2 (3 times). The mixture was stirred at 100 °C for 12 h under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure. The yellow residue was purified by column chromatography to give tert-butyl (1-(difluoromethyl)-2-oxo-1,2-dihydropyridin-4-yl)carbamate (0.6 g, 2.2 mmol, 57% yield) as a yellow solid. LCMS (ESI) m/z = 261.0

[001271] *Step 3: Preparation of 4-amino-1-(difluoromethyl)pyridin-2(1H)-one*

[001272] To a solution of tert-butyl (1-(difluoromethyl)-2-oxo-1,2-dihydropyridin-4-yl)carbamate (0.4 g , 1.5 mmol, 1.0 eq) in DCM (4 mL) was added HCl/dioxane (3.82 mL, 4 M), the mixture was stirred at 25 °C for 1 h. The mixture was concentrated in vacuo to give 4-amino-1-(difluoromethyl)pyridin-2(1H)-one (240 mg, crude) as a yellow solid. LCMS (ESI) m/z = 161.0 $[M+H]^+$.

Synthesis of 5,5-dimethyl-3-(pyridin-3-yl)imidazolidine-2,4-dione

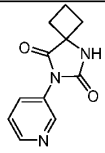


[001273] *Step 1: Preparation of 5,5-dimethyl-3-(pyridin-3-yl) imidazolidine-2,4-dione*

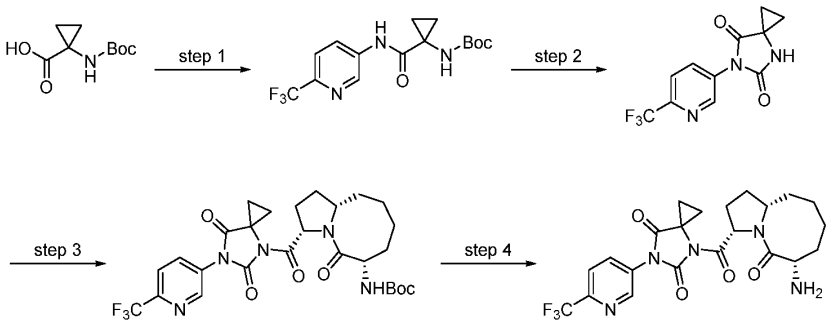
[001274] To a solution of 5,5-dimethylimidazolidine-2,4-dione (1.4 g, 11 mmol, 1.4 eq) and copper diacetate (0.15 g, 0.81 mmol, 0.1 eq) in MeOH (40 mL) was added pyridin-3-ylboronic acid (1 g, 8.1 mmol, 1 eq) under an atmosphere of O_2. The mixture was heated at 70 °C for 16 h. The solvent was then filtered through silica gel to remove copper, and the resulting cake was washed with methanol (200 mL). The reaction mixture was concentrated under reduced pressure to give a residue. The filtrate was purified by reversed phase ($NH_3.H_2O$) then lyophilized to give 5,5-dimethyl-3-(pyridin-3-yl) imidazolidine-2,4-dione (0.6 g, 2.9 mmol, 35% yield) as a yellow oil. LCMS (ESI) m/z =206.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.67 (d, J = 2.0 Hz, 1H), 8.57 - 8.51 (m, 1H), 8.00 - 7.92 (m, 1H), 7.53 - 7.57 (m, 1H), 1.52 (s, 6H).

[001275] The following intermediates in **Table 95** were prepared using the method described above for the synthesis of 5,5-dimethyl-3-(pyridin-3-yl) imidazolidine-2,4-dione, utilizing the appropriate starting materials and modifications.

Table 95

Name	Structure	LCMS	NMR
7-(pyridin-3-yl)-5,7-diazaspiro[3.4]octane-6,8-dione		218.2 $[M+H]^+$	^1H NMR (400 MHz, CD_3OD) δ 8.67 (d, J = 1.8 Hz, 1H), 8.53 (d, J = 4.4 Hz, 1H), 8.00 - 7.91 (m, 1H), 7.53 - 7.57 (m, 1H), 2.69 - 2.61 (m, 2H), 2.53 - 2.44 (m, 2H), 2.11 – 2.14 (m, 1H), 1.99 - 1.84 (m, 1H)

Synthesis of 4-((3S,6S,10aS)-6-amino-5-oxodecahydropyrrolo[1,2-a]azocine-3-carbonyl)-6-(6-(trifluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione

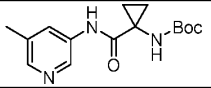
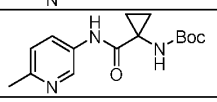


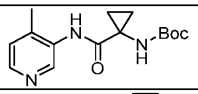
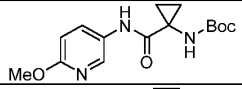
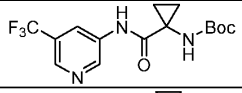
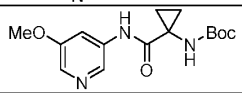
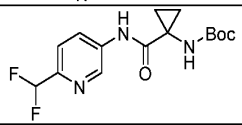
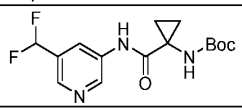
[001276] *Step 1: Preparation of tert-butyl (1-((6-(trifluoromethyl)pyridin-3-yl)carbamoyl)cyclopropyl)*carbamate

[001277] To a solution of 1-((tert-butoxycarbonyl)amino)cyclopropane-1-carboxylic acid (250 mg, 1.24 mmol, 1 eq) and EDC·HCl (283 mg, 1.48 mmol, 1.2 eq) in CH_2Cl_2 (60 mL) were respectively added 6-(trifluoromethyl)pyridin-3-amine (220 mg, 1.36 mmol, 1.1 eq) and DMAP (151 mg, 1.24 mmol, 1 eq). The resulting mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the crude mixture was dissolved in DMSO and purified by reverse phase chromatography on a 100 g C_{18} cartridge eluting with 5-100% MeCN in water (with 0.1% formic acid). The pure fractions were concentrated were lyophilized to give tert-butyl (1-((6-(trifluoromethyl)pyridin-3-yl)carbamoyl)cyclopropyl)carbamate (320 mg, 74.7% yield) was obtained as a white solid LCMS (ESI) m/z = 346.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.96 (br. s., 1H), 8.64 - 8.52 (m, 1H), 8.37 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 5.18 (br. s., 1H), 1.73 - 1.66 (m, 2H), 1.50 (s, 9H), 1.20 - 1.12 (m, 2H).

[001278] The following intermediates in **Table 96** were prepared using the method described above in Step 1 for the preparation of tert-butyl (1-((6-(trifluoromethyl)pyridin-3-yl)carbamoyl)cyclopropyl)carbamate utilizing the appropriate starting materials and modifications.

Table 96

Name	Structure	LCMS
tert-butyl (1-((5-methylpyridin-3-yl)carbamoyl)cyclopropyl)carbamate		292.2 $[M+H]^+$
tert-butyl (1-((6-methylpyridin-3-yl)carbamoyl)cyclopropyl)carbamate		292.2 $[M+H]^+$

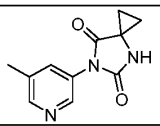
tert-butyl (1-((4-methylpyridin-3-yl)carbamoyl)cyclopropyl)carbamate		292.2 $[M+H]^+$
tert-butyl (1-((6-methoxypyridin-3-yl)carbamoyl)cyclopropyl)carbamate		308.2 $[M+H]^+$
tert-butyl (1-((5-(trifluoromethyl)pyridin-3-yl)carbamoyl)cyclopropyl)carbamate		346.2 $[M+H]^+$
tert-butyl (1-((5-methoxypyridin-3-yl)carbamoyl)cyclopropyl)carbamate		308.4 $[M+H]^+$
tert-butyl (1-((6-(difluoromethyl)pyridin-3-yl)carbamoyl)cyclopropyl)carbamate		328.2 $[M+H]^+$
tert-butyl (1-((5-(difluoromethyl)pyridin-3-yl)carbamoyl)cyclopropyl)carbamate		328.2 $[M+H]^+$

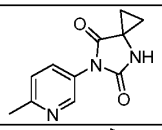
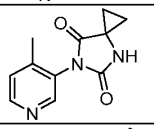
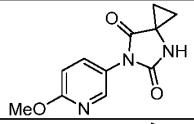
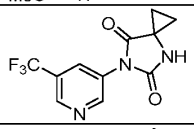
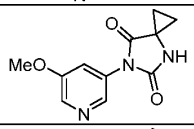
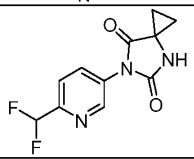
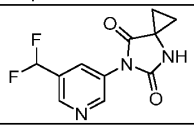
[001279] *Step 2: Preparation of 6-(6-(trifluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione*

[001280] To a stirred solution of tert-butyl (1-((6-(trifluoromethyl)pyridin-3-yl)carbamoyl)cyclopropyl)carbamate (115 mg, 333 µmol, 1 eq) and DTBMP (143 mg, 699 µmol, 2.1 eq) in CH_2Cl_2 (5 mL) at 0°C was added Tf_2O (197 mg, 699 µmol, 2.1 eq) under nitrogen. The reaction mixture was stirred for 1 h. CH_2Cl_2 was removed with a nitrogen stream and the resulting mixture was purified by reverse phase chromatography on a 50 g C_{18} cartridge eluting with 5-100% MeCN in water (with 0.1% formic acid). The pure fractions lyophilized to give 6-(6-(trifluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione (50.0 mg, 55.3% yield) a white solid LCMS (ESI) m/z = 272.2 $[M+H]^+$.

[001281] The following intermediates in **Table 97** were prepared using the method described above in Step 2 for the preparation of 6-(6-(trifluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione utilizing the appropriate starting materials and modifications.

Table 97

Name	Structure	LCMS
6-(5-methylpyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione		218.1 $[M+H]^+$

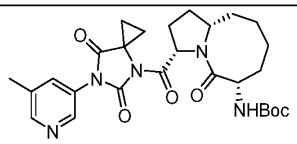
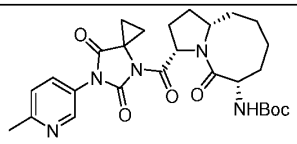
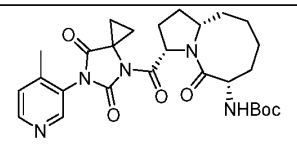
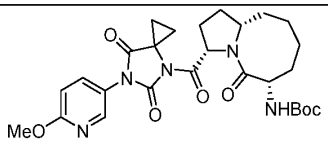
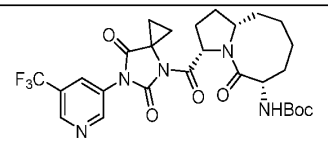
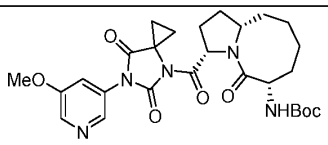
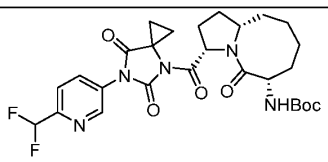
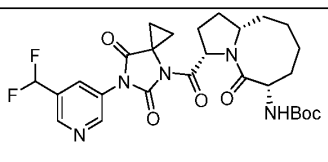
6-(6-methylpyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione		218.1 $[M+H]^+$
6-(4-methylpyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione		218.1 $[M+H]^+$
6-(6-methoxypyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione		234.2 $[M+H]^+$
6-(5-(trifluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione		272.2 $[M+H]^+$
6-(5-methoxypyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione		234.2 $[M+H]^+$
6-(6-(difluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione		254.2 $[M+H]^+$
6-(5-(difluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione		254.2 $[M+H]^+$

[001282] *Step 3: Preparation of tert-butyl ((3S,6S,10aS)-3-(5,7-dioxo-6-(6-(trifluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate*

[001283] To a stirred solution of 6-(6-(trifluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione (30 mg, 110 µmol, 1 eq) and DIPEA (71.0 mg, 550 µmol, 5.0 eq) in *N,N*-dimethylformamide (6 mL) were respectively added (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid (35.9 mg, 110 µmol, 1 eq) and PyBOP (68.6 mg, 132 µmol, 1.2 eq) under nitrogen. The reaction mixture was stirred at room temperature for 24 h and 3 h at 50°C. Then, the crude mixture was purified by reverse phase chromatography on a 50 g C_{18} cartridge eluting with 5-100% MeCN in basic water (10 mM NH_4HCO_3 (pH = 10) buffer). The pure fractions were lyophilized to yield tert-butyl ((3S,6S,10aS)-3-(5,7-dioxo-6-(6-(trifluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate (34.6 mg, 54%) as a white solid. LCMS (ESI) m/z = 480.4 $[(M\text{-Boc})+2H]^+$.

[001284] The following intermediates in **Table 98** were prepared using the method described above in Step 3 for the preparation of tert-butyl ((3S,6S,10aS)-3-(5,7-dioxo-6-(6-(trifluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate utilizing the appropriate starting materials and modifications.

Table 98

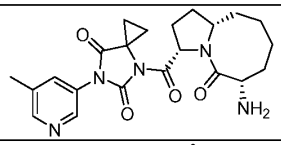
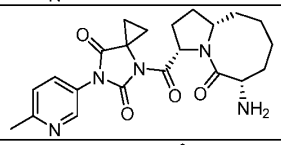
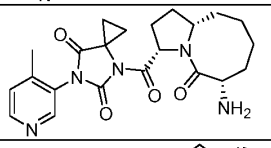
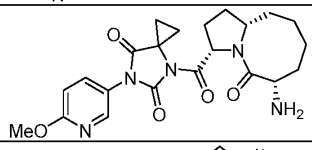
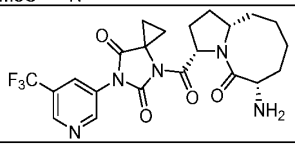
Name	Structure	LCMS
tert-butyl ((3S,6S,10aS)-3-(6-(5-methylpyridin-3-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate		526.3 $[M+H]^+$
tert-butyl ((3S,6S,10aS)-3-(6-(6-methylpyridin-3-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate		526.3 $[M+H]^+$
tert-butyl ((3S,6S,10aS)-3-(6-(4-methylpyridin-3-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate		526.3 $[M+H]^+$
tert-butyl ((3S,6S,10aS)-3-(6-(6-methoxypyridin-3-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate		542.4 $[M+H]^+$
tert-butyl ((3S,6S,10aS)-3-(5,7-dioxo-6-(5-(trifluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate		580.4 $[M+H]^+$
tert-butyl ((3S,6S,10aS)-3-(6-(5-methoxypyridin-3-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate		542.4 $[M+H]^+$
tert-butyl ((3S,6S,10aS)-3-(6-(6-(difluoromethyl)pyridin-3-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate		562.4 $[M+H]^+$
tert-butyl ((3S,6S,10aS)-3-(6-(5-(difluoromethyl)pyridin-3-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate		562.4 $[M+H]^+$

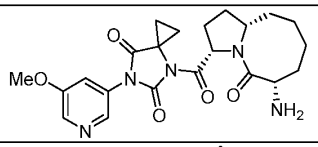
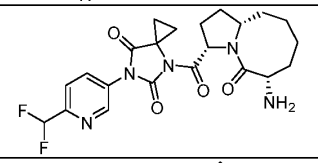
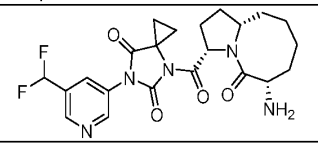
[001285] *Step 4: Preparation of 4-((3S,6S,10aS)-6-amino-5-oxodecahydropyrrolo[1,2-a]azocine-3-carbonyl)-6-(6-(trifluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione*

[001286] To a stirred solution of tert-butyl ((3S,6S,10aS)-3-(5,7-dioxo-6-(6-(trifluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate (21.6 mg, 37.4 μmol, 1 eq) in CH_2Cl_2 (1.5 mL) was added TFA (500 μL). The resulting yellow solution was stirred for 1 h at room temperature. The reaction was concentrated under reduced pressure to dryness to give the TFA salt of 4-((3S,6S,10aS)-6-amino-5-oxodecahydropyrrolo[1,2-a]azocine-3-carbonyl)-6-(6-(trifluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione (22.1 mg, 100%) that was used directly in the next step. LCMS (ESI) m/z = 480.2 $[M+H]^+$.

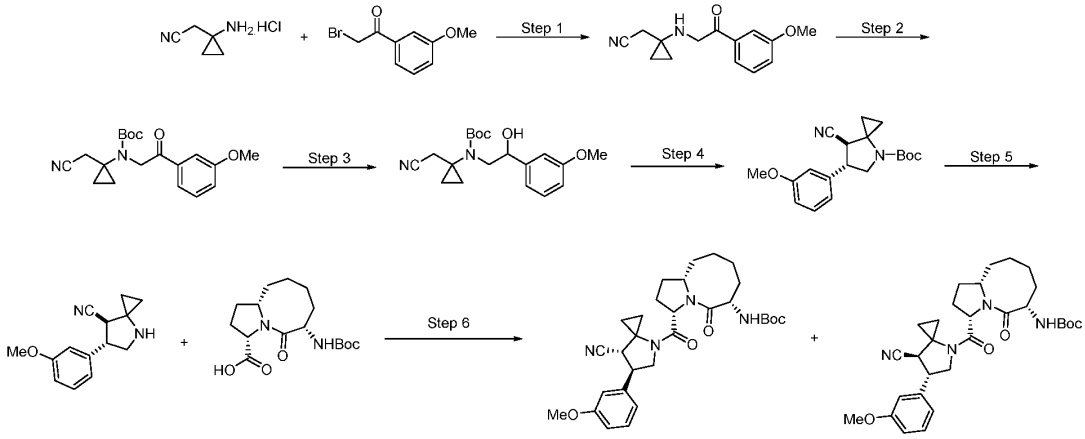
[001287] The following intermediates in **Table 99** were prepared using the method described above in Step 4 for the preparation of 4-((3S,6S,10aS)-6-amino-5-oxodecahydropyrrolo[1,2-a]azocine-3-carbonyl)-6-(6-(trifluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione utilizing the appropriate starting materials and modifications.

Table 99

Name	Structure	LCMS
4-((3S,6S,10aS)-6-amino-5-oxodecahydropyrrolo[1,2-a]azocine-3-carbonyl)-6-(5-methylpyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione (TFA salt)		426.2 $[M+H]^+$
4-((3S,6S,10aS)-6-amino-5-oxodecahydropyrrolo[1,2-a]azocine-3-carbonyl)-6-(6-methylpyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione (TFA salt)		426.2 $[M+H]^+$
4-((3S,6S,10aS)-6-amino-5-oxodecahydropyrrolo[1,2-a]azocine-3-carbonyl)-6-(4-methylpyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione (TFA salt)		426.2 $[M+H]^+$
4-((3S,6S,10aS)-6-amino-5-oxodecahydropyrrolo[1,2-a]azocine-3-carbonyl)-6-(6-methoxypyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione (TFA salt)		442.2 $[M+H]^+$
4-((3S,6S,10aS)-6-amino-5-oxodecahydropyrrolo[1,2-a]azocine-3-carbonyl)-6-(5-(trifluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione (TFA salt)		480.2 $[M+H]^+$

4-((3S,6S,10aS)-6-amino-5-oxodecahydropyrrolo[1,2-a]azocine-3-carbonyl)-6-(5-methoxypyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione (TFA salt)		221.6 $[M+2H]^{2+}$
4-((3S,6S,10aS)-6-amino-5-oxodecahydropyrrolo[1,2-a]azocine-3-carbonyl)-6-(6-(difluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione (TFA salt)		462.2 $[M+H]^{+}$
4-((3S,6S,10aS)-6-amino-5-oxodecahydropyrrolo[1,2-a]azocine-3-carbonyl)-6-(5-(difluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione (TFA salt)		462.2 $[M+H]^{+}$

Synthesis of *tert*-butyl ((3*S*,6*S*,10*aS*)-3-((6*R*,7*S*)-7-cyano-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-*a*]azocin-6-yl)carbamate and *tert*-butyl ((3*S*,6*S*,10*aS*)-3-((6*S*,7*R*)-7-cyano-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-*a*]azocin-6-yl)carbamate



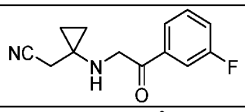
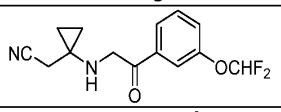
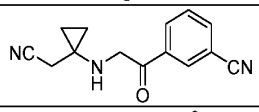
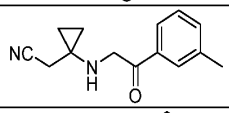
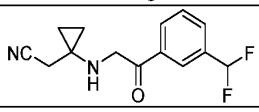
[001288] *Step 1: Preparation of 2-(1-((2-(3-methoxyphenyl)-2-oxoethyl)amino)cyclopropyl)acetonitrile*

[001289] To a solution of 2-(1-aminocyclopropyl)acetonitrile hydrochloride (367 mg, 3.82 mmol, 1.0 eq) in DMF (10 mL) were added 2-bromo-1-(3-methoxyphenyl)ethan-1-one (918 mg, 4.01 mmol, 1.05 eq) and $NaHCO_3$ (801 mg, 9.54 mmol, 2.5 eq). The mixture was stirred at room temperature for 20 h. The reaction was diluted with MeCN and filtered. The filtrate was concentrated under reduced pressure. The crude solution was purified by reverse phase chromatography on a C_{18} cartridge eluting with 5-60% MeCN in basic water (10 mM NH_4HCO_3 (pH = 10) buffer). The pure fractions were concentrated under reduced pressure to give 2-(1-((2-(3-methoxyphenyl)-2-oxoethyl)amino)cyclopropyl)acetonitrile (522 mg, 55.9

%) as an orange oil. LCMS (ESI) m/z = 245.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 - 7.51 (m, 1H), 7.49 - 7.46 (m, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.16 - 7.10 (m, 1H), 4.25 (s, 2H), 3.86 (s, 3H), 2.58 (s, 2H), 0.89 - 0.84 (m, 2H), 0.74 - 0.70 (m, 2H).

[001290] The following intermediates in **Table 100** were prepared using the method described above in Step 1 for the preparation of 2-(1-((2-(3-methoxyphenyl)-2-oxoethyl)amino)cyclopropyl)acetonitrile utilizing the appropriate starting materials and modifications.

Table 100

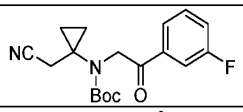
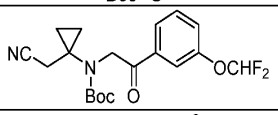
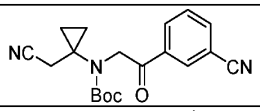
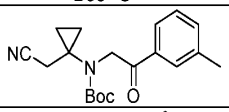
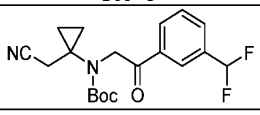
Name	Structure	LCMS
2-(1-((2-(3-fluorophenyl)-2-oxoethyl)amino)cyclopropyl)acetonitrile		233.2 $[M+H]^+$
2-(1-((2-(3-(difluoromethoxy)phenyl)-2-oxoethyl)amino)cyclopropyl)acetonitrile		281.2 $[M+H]^+$
3-((1-(cyanomethyl)cyclopropyl)glycyl)benzonitrile		240.2 $[M+H]^+$
2-(1-((2-oxo-2-(m-tolyl)ethyl)amino)cyclopropyl)acetonitrile		229.2 $[M+H]^+$
2-(1-((2-(3-(difluoromethyl)phenyl)-2-oxoethyl)amino)cyclopropyl)acetonitrile		265.2 $[M+H]^+$

[001291] *Step 2: Preparation of tert-butyl (1-(cyanomethyl)cyclopropyl)(2-(3-methoxyphenyl)-2-oxoethyl)carbamate*

[001292] To a solution of 2-(1-((2-(3-methoxyphenyl)-2-oxoethyl)amino)cyclopropyl)acetonitrile (522 mg, 2.13 mmol, 1 eq) in THF (1 mL) were added water (1 mL) and $NaHCO_3$ (178 mg, 2.13 mmol, 1.0 eq) followed by di-*tert*-butyl dicarbonate (929 mg, 4.26 mmol, 2 eq) at 0°C. The reaction was warmed up to room temperature and stirred for 48 h at room temperature. The reaction was diluted with MeCN and filtered. The filtrate was concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography on a C_{18} cartridge eluting with 5-80% MeCN in water (with 0.1% formic acid) to give tert-butyl (1-(cyanomethyl)cyclopropyl)(2-(3-methoxyphenyl)-2-oxoethyl)carbamate (400 mg, 54.5%) as a sticky oil. LCMS (ESI) m/z = 245.2 $[(M-Boc)+2H]^+$.

[001293] The following intermediates in Table **101** were prepared using the method described above in Step 2 for the preparation of tert-butyl (1-(cyanomethyl)cyclopropyl)(2-(3-methoxyphenyl)-2-oxoethyl)carbamat*e* utilizing the appropriate starting materials and modifications.

Table 101

Name	Structure	LCMS
tert-butyl (1-(cyanomethyl)cyclopropyl)(2-(3-fluorophenyl)-2-oxoethyl)carbamate		277.2 [(M-*t*Bu)+2H]$^+$
tert-butyl (1-(cyanomethyl)cyclopropyl)(2-(3-(difluoromethoxy)phenyl)-2-oxoethyl)carbamate		281.2 [(M-Boc)+2H)$^+$
tert-butyl (1-(cyanomethyl)cyclopropyl)(2-(3-cyanophenyl)-2-oxoethyl)carbamate		240.2 [(M-Boc)+2H]$^+$
tert-butyl (1-(cyanomethyl)cyclopropyl)(2-oxo-2-(m-tolyl)ethyl)carbamate		273.2 [(M-*t*Bu)+2H]$^+$
tert-butyl (1-(cyanomethyl)cyclopropyl)(2-(3-(difluoromethyl)phenyl)-2-oxoethyl)carbamate		309 [(M-*t*Bu)+2H]$^+$

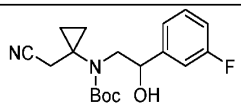
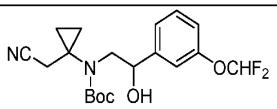
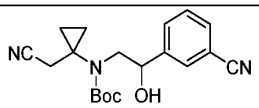
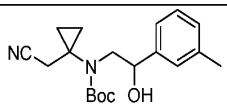
[001294] *Step 3: Preparation of tert-butyl (1-(cyanomethyl)cyclopropyl)(2-hydroxy-2-(3-methoxyphenyl)ethyl)carbamate*

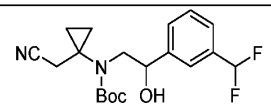
[001295] To a solution of tert-butyl (1-(cyanomethyl)cyclopropyl)(2-(3-methoxyphenyl)-2-oxoethyl)carbamate (193 mg, 0.5603 mmol, 1 eq) in methanol (10 mL) at 0 °C was added $NaBH_4$ (21.1 mg, 0.5603 mmol, 1.0 eq). The reaction was stirred for 2 h at room temperature. The reaction was quenched with 1 N HCl (1 mL) and concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography on a C_{18} cartridge eluting with 5-60% MeCN in water (with 0.1% formic acid) to give tert-butyl (1-(cyanomethyl)cyclopropyl)(2-hydroxy-2-(3-methoxyphenyl)ethyl)carbamate (144 mg, 74.2%) as a thick clear oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.26 (t, J = 7.8 Hz, 1H), 6.91 - 6.80 (m, 3H), 5.56 - 5.48 (m, 1H), 4.88 - 4.71 (m, 1H), 3.75 (s, 3H), 3.40 - 3.30 (m, 1H), 3.19 - 3.10 (m, 1H), 3.04 - 2.92 (m, 1H), 2.73 - 2.61 (m, 1H), 1.46 (s, 9H), 1.32 - 1.20 (m, 1H), 0.84 - 0.62 (m, 3H).

[001296] The following intermediates in **Table 102** were prepared using the method described above in Step 3 for the preparation of tert-butyl (1-(cyanomethyl)cyclopropyl)(2-

hydroxy-2-(3-methoxyphenyl)ethyl)carbamate utilizing the appropriate starting materials and modifications.

Table 102

Name	Structure	LCMS	NMR
tert-butyl (1-(cyanomethyl)cyclopropyl)(2-(3-fluorophenyl)-2-hydroxyethyl)carbamate		261.2 [(M-*t*Bu-OH)+2H]$^+$	
tert-butyl (1-(cyanomethyl)cyclopropyl)(2-(3-(difluoromethoxy)phenyl)-2-hydroxyethyl)carbamate			^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.8 Hz, 1H), 7.22 - 7.18 (m, 1H), 7.17 - 7.13 (m, 1H), 7.07 - 7.02 (m, 1H), 6.53 (t, *J* = 73.8 Hz, 1H), 5.00 - 4.91 (m, 1H), 3.63 - 3.42 (m, 2H), 2.83 - 2.45 (m, 1H), 1.65 - 1.56 (m, 2H), 1.54 (s, 9H), 0.90 - 0.78 (m, 4H).
tert-butyl (1-(cyanomethyl)cyclopropyl)(2-(3-cyanophenyl)-2-hydroxyethyl)carbamate			^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 - 7.68 (m, 1H), 7.64 - 7.61 (m, 1H), 7.60 - 7.56 (m, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 5.03 - 4.93 (m, 1H), 4.68 - 4.25 (m, 1H), 3.61 - 3.40 (m, 2H), 2.89 - 2.37 (m, 2H), 1.54 (s, 9H), 1.02 - 0.89 (m, 4H).
tert-butyl (1-(cyanomethyl)cyclopropyl)(2-hydroxy-2-(m-tolyl)ethyl)carbamate			^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 - 7.22 (m, 1H), 7.19 - 7.07 (m, 3H), 4.95 - 4.87 (m, 1H), 4.31 - 3.97 (m, 1H), 3.62 - 3.41 (m, 2H), 2.88 - 2.49 (m, 2H), 2.36 (s, 3H), 1.54 (s, 9H), 1.03 - 0.87 (m, 4H)

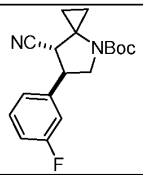
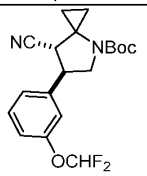
tert-butyl (1-(cyanomethyl)cyclopropyl)(2-(3-(difluoromethyl)phenyl)-2-hydroxyethyl)carbamate		293.2 [(M-*t*Bu-OH)+2H]$^+$	

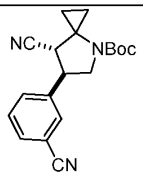
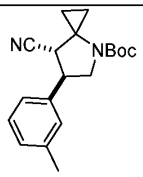
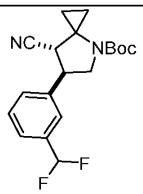
[001297] *Step 4: Preparation of racemic-tert-butyl (6S,7R)-7-cyano-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-4-carboxylate*

[001298] To a solution of tert-butyl (1-(cyanomethyl)cyclopropyl)(2-hydroxy-2-(3-methoxyphenyl)ethyl)carbamate (115 mg, 0.3319 mmol, 1 eq) in THF (10 mL) at -15 °C were added diethyl phosphorochloridate (50.3 µL, 0.3484 mmol, 1.05 eq) followed by dropwise addition of 1 M LiHMDS in THF (829 µL, 0.8297 mmol, 2.5 eq). The reaction was stirred at -15 °C for 2 h. The reaction was quenched with 1 N HCl (1 mL) and concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography on a C_{18} cartridge eluting with 5-70% MeCN in water (with 0.1% formic acid) to give racemic-tert-butyl (6S,7R)-7-cyano-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-4-carboxylate (50.0 mg, 46.2%) as a white solid. LCMS (ESI) m/z = 273.2 [(M-*t*-Bu)+2H]$^+$. ^{1}H NMR (400 MHz, C_6D_6) δ 7.03 - 6.98 (m, 1H), 6.66 - 6.61 (m, 2H), 6.53 - 6.49 (m, 1H), 3.72 - 3.62 (m, 1H), 3.29 (s, 3H), 3.25 - 3.18 (m, 1H), 3.04 - 2.96 (m, 1H), 2.71 (d, *J* = 10.5 Hz, 1H), 2.38 - 1.93 (m, 1H), 1.75 - 1.47 (m, 1H), 1.37 (s, 9H), 1.09 - 1.02 (m, 1H), 0.45 - 0.39 (m, 1H).

[001299] The following intermediates in **Table 103** were prepared using the method described above in Step 4 for the preparation of racemic-tert-butyl (6S,7R)-7-cyano-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-4-carboxylate utilizing the appropriate starting materials and modifications.

Table 103

Name	Structure	LCMS	NMR
Racemic-tert-butyl (6R,7S)-7-cyano-6-(3-fluorophenyl)-4-azaspiro[2.4]heptane-4-carboxylate			
Racemic-tert-butyl (6R,7S)-7-cyano-6-(3-(difluoromethoxy)phenyl)-4-azaspiro[2.4]heptane-4-carboxylate			^{1}H NMR (400 MHz, C_6D_6) δ 6.85 - 6.77 (m, 1H), 6.73 - 6.65 (m, 2H), 6.59 - 6.53 (m, 1H), 5.82 (t, *J* = 73.6 Hz, 1H), 3.64 - 3.50 (m, 1H), 3.12 - 3.03 (m, 1H), 2.92 - 2.80 (m, 1H), 2.55 (d, *J* = 10.3 Hz, 1H), 2.32 - 2.00 (m, 1H), 1.80 - 1.52 (m, 1H), 1.38 (s, 9H), 1.07 - 0.98 (m, 1H), 0.41 - 0.36 (m, 1H).

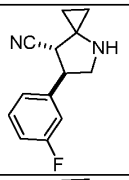
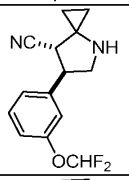
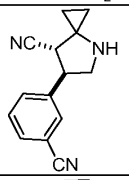
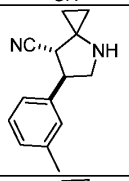
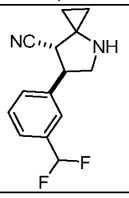
Racemic-tert-butyl (6R,7S)-7-cyano-6-(3-cyanophenyl)-4-azaspiro[2.4]heptane-4-carboxylate		268.1 [(M-*t*-Bu)+2H]$^+$	^{1}H NMR (400 MHz, C_6D_6) δ 6.87 (d, *J* = 7.6 Hz, 1H), 6.77 (s, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.58 (t, *J* = 7.6 Hz, 1H), 3.60 - 3.38 (m, 1H), 2.96 - 2.80 (m, 1H), 2.72 (q, *J* = 9.0 Hz, 1H), 2.40 (d, *J* = 10.3 Hz, 1H), 2.29 - 2.03 (m, 1H), 1.76 - 1.50 (m, 1H), 1.38 (s, 9H), 1.07 - 0.96 (m, 1H), 0.41 - 0.31 (m, 1H)
Racemic-tert-butyl (6R,7S)-7-cyano-6-(m-tolyl)-4-azaspiro[2.4]heptane-4-carboxylate		257.2 [(M-*t*-Bu)+2H]$^+$	^{1}H NMR (400 MHz, C_6D_6) δ 7.06 - 6.98 (m, 1H), 6.92 - 6.86 (m, 1H), 6.76 - 6.68 (m, 2H), 3.76 - 3.60 (m, 1H), 3.28 - 3.15 (m, 1H), 3.11 - 2.99 (m, 1H), 2.74 (d, *J* = 10.8 Hz, 1H), 2.43 - 2.15 (m, 1H), 2.07 (s, 3H), 1.77 - 1.57 (m, 1H), 1.38 (s, 9H), 1.14 - 1.05 (m, 1H), 0.51 - 0.41 (m, 1H)
Racemic-tert-butyl (6R,7S)-7-cyano-6-(3-(difluoromethyl)phenyl)-4-azaspiro[2.4]heptane-4-carboxylate			^{1}H NMR (400 MHz, C_6D_6) δ 7.07 (d, *J* = 7.6 Hz, 1H), 7.02 (s, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.10 (t, *J* = 56.2 Hz, 1H), 3.65 - 3.48 (m, 1H), 3.14 - 3.02 (m, 1H), 2.90 (td, *J* = 10.3, 8.1 Hz, 1H), 2.53 (d, *J* = 10.3 Hz, 1H), 1.38 (s, 9H), 1.08 - 0.98 (m, 1H), 0.49 - 0.36 (m, 3H)

[001300] *Step 5: Preparation of racemic-(6S,7R)-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-7-carbonitrile*

[001301] To a solution of a *tert*-butyl (6*R*,7*S*)-7-cyano-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-4-carboxylate (44 mg, 0.1339 mmol, 1 eq) in methylene chloride (2 mL) was added TFA (0.5 mL). The reaction was stirred at room temperature for 2 h. The reaction was concentrated under reduced pressure to give crude racemic-(6S,7R)-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-7-carbonitrile (30.5 mg, 99%, TFA salt) as a thick oil. LCMS (ESI) m/z = 229.2 [M+H]$^+$.

[001302] The following intermediates in **Table 104** were prepared using the method described above in Step 5 for the preparation of racemic-(6S,7R)-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-7-carbonitrile utilizing the appropriate starting materials and modifications.

Table 104

Name	Structure	LCMS
Racemic-(6R,7S)-6-(3-fluorophenyl)-4-azaspiro[2.4]heptane-7-carbonitrile (TFA salt)		217.2 $[M+H]^+$
(6R,7S)-6-(3-(difluoromethoxy)phenyl)-4-azaspiro[2.4]heptane-7-carbonitrile (TFA salt)		265.2 $[M+H]^+$
(6R,7S)-6-(3-cyanophenyl)-4-azaspiro[2.4]heptane-7-carbonitrile (TFA salt)		224.2 $[M+H]^+$
(6R,7S)-6-(m-tolyl)-4-azaspiro[2.4]heptane-7-carbonitrile (TFA salt)		213.2 $[M+H]^+$
(6R,7S)-6-(3-(difluoromethyl)phenyl)-4l4-azaspiro[2.4]heptane-7-carbonitrile (TFA salt)		249.2 $[M+H]^+$

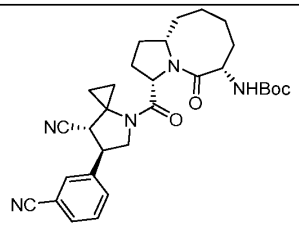
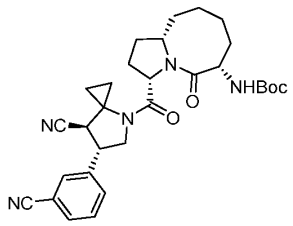
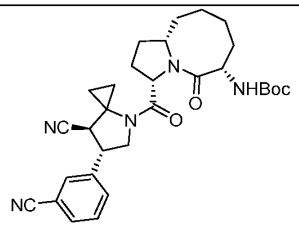
[001303] *Step 6: Preparation of tert-butyl ((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate and tert-butyl ((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate*

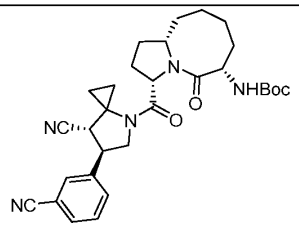
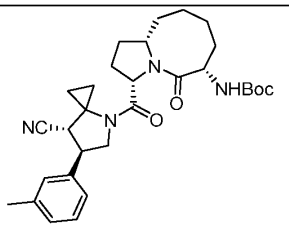
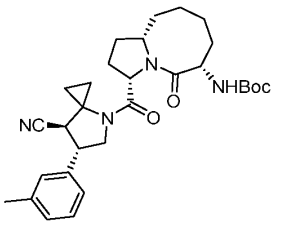
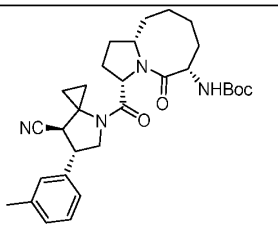
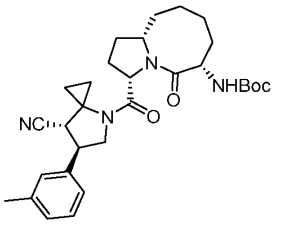
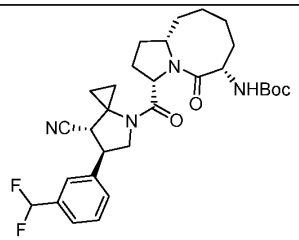
[001304] To a solution of (6*R*,7*S*)-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-7-carbonitrile TFA salt (30.5 mg, 0.134 mmol, 1 eq) in DMF (3 mL) were respectively added DIPEA (159 µL, 0.913 mmol, 6.8 eq), (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid (52.1 mg, 0.160 mmol, 1.20 eq) and HATU (63.6 mg, 0.167 mmol, 1.25 eq). The reaction was stirred at room temperature 3 h. The reaction mixture was purified directly by reverse phase chromatography on a 50 g C_{18} cartridge eluting with 5-60% MeCN in water (with 0.1% formic acid) to afford a 1:1 mixture of two diastereomers (62 mg, 80.4%) as a white solid. LCMS (ESI) m/z = 537.2 $[M+H]^+$. The mixture of diastereomers was submitted to chiral SFC separation (SFC conditions: Column Lux Cellulose 1, 21.2 x 150 mm 5 um column, 3.78 mg/inj, concentration 12.3 mg/mL,

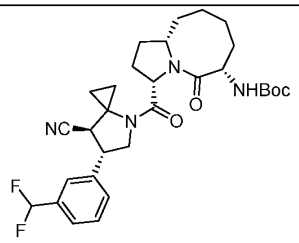
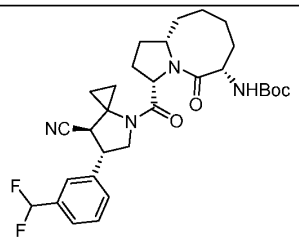
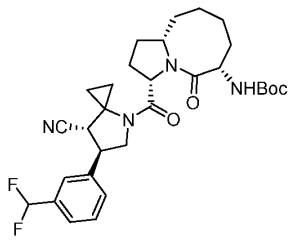
Column T = 40°C, Flow rate 55 mL/min, 10% MeOH, cycle time: 12 min) to give the fastest eluting (**Peak 1**) diastereomer arbitrarily assigned to *tert*-butyl ((3*S*,6*S*,10*aS*)-3-((6*R*,7*S*)-7-cyano-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-*a*]azocin-6-yl)carbamate (27 mg, 0.051 mmol, 44% recovery). The slowest eluting (**Peak 2**) diastereomer was arbitrarily assigned to *tert*-butyl ((3*S*,6*S*,10*aS*)-3-((6*S*,7*R*)-7-cyano-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-*a*]azocin-6-yl)carbamate (29 mg, 0.054 mmol, 47% recovery).

[001305] The following intermediates in **Table 105** were prepared using the method described above in Step 6 for the preparation of tert-butyl ((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate and tert-butyl ((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate utilizing the appropriate starting materials and modifications. Compounds were purified by chiral SFC separation.

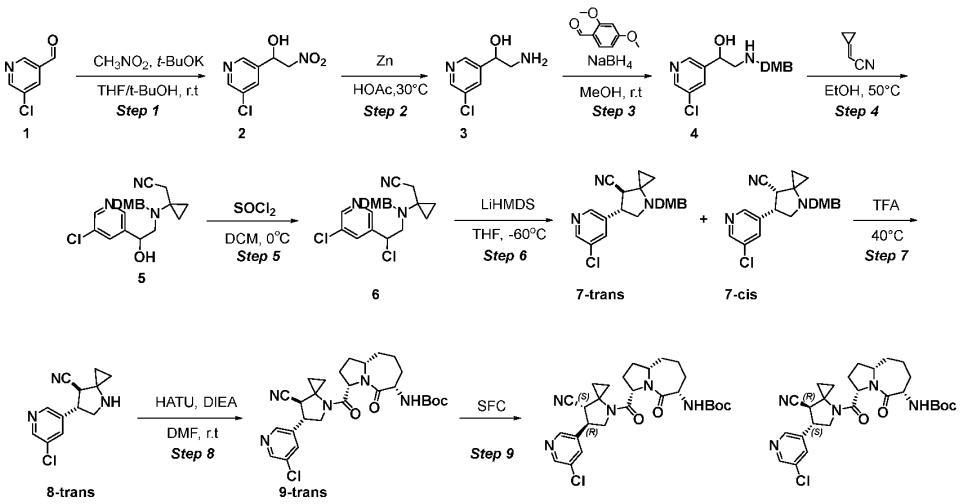
Table 105

Name	Structure	LCMS
tert-butyl ((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(3-cyanophenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate or tert-butyl ((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(3-cyanophenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate **Peak 1** (SFC conditions: Column Lux Cellulose 1, 30 x 250 mm 5 um column, 11 mg/inj, concentration 4.4 mg/mL, Column T = 40°C, Flow rate 100 mL/min, 10% EtOH, cycle time: 30 min)	 Or 	432.1 [(M-Boc)+2H]$^+$
tert-butyl ((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(3-cyanophenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate or tert-butyl ((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(3-cyanophenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate	 Or	432.2 [(M-Boc)+2H]$^+$

Peak 2 (SFC conditions: Column Lux Cellulose 1, 30 x 250 mm 5 um column, 11 mg/inj, concentration 4.4 mg/mL, Column T = 40°C, Flow rate 100 mL/min, 10% EtOH, cycle time: 30 min)		
tert-butyl ((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(m-tolyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate or tert-butyl ((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(m-tolyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate **Peak 1** (SFC conditions: Column Lux Cellulose 1, 30 x 250 mm 5 um column, 11.3 mg/inj, concentration 22.5 mg/mL, Column T = 40°C, Flow rate 100 mL/min, 10% MeOH, cycle time: 8 min)	 Or 	407.4 $[(M-Boc)+2H]^+$
tert-butyl ((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(m-tolyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate or tert-butyl ((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(m-tolyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate **Peak 2** (SFC conditions: Column Lux Cellulose 1, 30 x 250 mm 5 um column, 11.3 mg/inj, concentration 22.5 mg/mL, Column T = 40°C, Flow rate 100 mL/min, 10% MeOH, cycle time: 8 min)	 Or 	407.4 $[(M-Boc)+2H]^+$
tert-butyl ((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(3-(difluoromethyl)phenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate or tert-butyl ((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(3-(difluoromethyl)phenyl)-4-	 Or	557.4 $[M+H]^+$

azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate **Peak 1** (SFC conditions: Column Lux Cellulose 1, 30 x 250 mm 5 um column, 4.1 mg/inj, concentration 13.7 mg/mL, Column T = 40°C, Flow rate 75 mL/min, 10% 2-propanol, cycle time: 2.5 min)		
tert-butyl ((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(3-(difluoromethyl)phenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate or tert-butyl ((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(3-(difluoromethyl)phenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate **Peak 2** (SFC conditions: Column Lux Cellulose 1, 30 x 250 mm 5 um column, 4.1 mg/inj, concentration 13.7 mg/mL, Column T = 40°C, Flow rate 75 mL/min, 10% 2-propanol, cycle time: 2.5 min)	 Or 	557.4 $[M+H]^+$

Synthesis of tert-butyl ((3S,6S,9aS)-3-((6R,7S)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate and tert-butyl ((3S,6S,9aS)-3-((6S,7R)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate



[001306] *Step 1: Preparation of 1-(5-chloropyridin-3-yl)-2-nitroethan-1-ol*

[001307] To a solution of 5-chloropyridine-3-carbaldehyde (1, 1.0 g, 7.06 mmol, 1 eq.) in THF (10 mL) and t-BuOH (10 mL) were added nitromethane (683 mg, 11.2 mmol, 1.6 eq.) and *t*-BuOK (79 mg, 706 μmol, 0.1 eq.). The resulting mixture was stirred at room temperature for 2 h. After completion, the reaction mixture was quenched by adding NH_4Cl (10 mL, aq., sat.), then extracted with EtOAc (10 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 1-(5-chloropyridin-3-yl)-2-nitroethan-1-ol (2, 1.1 g, 5.42 mmol, 77%) as a yellow solid. LCMS (ESI) *m/z* = 203 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.61 (d, *J* = 14.3 Hz, 2H), 8.01 (s, 1H), 6.38 (s, 1H), 5.39 (s, 1H), 4.97 (d, *J* = 12.8 Hz, 1H), 4.75 (t, *J* = 11.1 Hz, 1H).

[001308] *Step 2: Preparation of 2-amino-1-(5-chloropyridin-3-yl)ethan-1-ol*

A mixture of 1-(5-chloropyridin-3-yl)-2-nitroethan-1-ol (2, 4.2 g, 20.7 mmol, 1.0 eq.) and Zn (6.69 g, 103 mmol, 5.0 eq.) in AcOH (40 mL) was stirred at 30 °C for 10 h. After completion, the suspension was filtered through a pad of Celite®, the filter cake was washed with MeOH (10 mL). The combined filtrates were concentrated to afford 2-amino-1-(5-chloropyridin-3-yl)ethan-1-ol (**3**, 3.20 g, quant.) as a yellow oil, which was used directly in next step without further purification. LCMS (ESI) *m/z* = 173 $[M+H]^+$.

[001309] *Step 3: Preparation of 1-(5-chloropyridin-3-yl)-2-((3,4-dimethylbenzyl)amino)ethan-1-ol*

[001310] To a solution of 2-amino-1-(5-chloropyridin-3-yl)ethan-1-ol (3, 5.0 g, 28.9 mmol, 1.0 eq.) in MeOH (100 mL) was added 2,4-dimethoxybenzaldehyde (4.8 g, 28.9 mmol, 1.0 eq.). The resulting mixture was stirred at room temperature for 2 h. $NaBH_4$ (3.63 g, 57.8 mmol, 2.0 eq.) was added and the resulting mixture was stirred at room temperature for 2 h. After completion, the reaction mixture was quenched by adding NH_4Cl (100 mL, aq., sat.), then extracted with EtOAc (100 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 1-(5-chloropyridin-3-yl)-2-((3,4-dimethylbenzyl)amino)ethan-1-ol (4, 4.20 g, 13.0 mmol, 45%) as a yellow oil. LCMS (ESI) m/z = 323 $[M+H]^+$.

[001311] *Step 4: Preparation of 2-(1-((2-(5-chloropyridin-3-yl)-2-hydroxyethyl)(3,4-dimethylbenzyl)amino)cyclopropyl)acetonitrile*

[001312] To a solution of 1-(5-chloropyridin-3-yl)-2-((3,4-dimethylbenzyl)amino)ethan-1-ol (4, 4.2 g, 13.0 mmol, 1 eq.) in EtOH (50 mL) was added 2-cyclopropylideneacetonitrile (1.02 g, 13.0 mmol, 1.0 eq.). The resulting mixture was stirred at 50 °C for 10 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 2-(1-((2-(5-chloropyridin-3-yl)-2-hydroxyethyl)(3,4-dimethylbenzyl)amino)cyclopropyl)acetonitrile (5, 3.8 g, 9.45 mmol, 73%) as a yellow oil. LCMS (ESI) m/z = 402 $[M+H]^+$.

[001313] *Step 5: Preparation of 2-(1-((2-chloro-2-(5-chloropyridin-3-yl)ethyl)(3,4-dimethylbenzyl)amino)cyclopropyl)acetonitrile*

[001314] To a solution of 2-(1-((2-(5-chloropyridin-3-yl)-2-hydroxyethyl)(3,4-dimethylbenzyl)amino)cyclopropyl)acetonitrile (**5**, 3.8 g, 9.45 mmol, 1.0 eq.) in DCM (50 mL) was added $SOCl_2$ (19 mL, 18.9 mmol, 2.0 eq.) at 0 °C. The resulting mixture was stirred at 0 °C for 1 hr. After completion, the reaction mixture was quenched with $NaHCO_3$ (40 mL, aq., sat.), then extracted with DCM (40 mL x 3). The organic layers were combined and washed with brine (40 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 2-(1-((2-chloro-2-(5-chloropyridin-3-yl)ethyl)(3,4-dimethylbenzyl)amino)cyclopropyl)acetonitrile (**6**, 3.20 g, 7.61 mmol, 81%) as a yellow oil. LCMS (ESI) m/z = 420 $[M+H]^+$.

[001315] *Step 6: Preparation of racemic-trans-6-(5-chloropyridin-3-yl)-4-(3,4-dimethylbenzyl)-4-azaspiro[2.4]heptane-7-carbonitrile*

[001316] To a solution of 2-(1-((2-chloro-2-(5-chloropyridin-3-yl)ethyl)(3,4-dimethylbenzyl)amino)cyclopropyl)acetonitrile (6, 2.6 g, 6.18 mmol, 1.0 eq.) in THF (40 mL) was added LiHMDS (12 mL, 12.3 mmol, 2.0 eq., 1 M in THF) slowly -60 °C. The resulting mixture was stirred at -60 °C for 3 min. After completion, the reaction mixture was quenched with NH_4Cl (20 mL, aq., sat.), then extracted with EtOAc (30 mL x 3). The organic layers were combined and washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford racemic-trans-6-(5-chloropyridin-3-yl)-4-(3,4-dimethylbenzyl)-4-azaspiro[2.4]heptane-7-carbonitrile (7-trans, 1.35 g, 3.51 mmol, 57%) as a yellow oil. LCMS (ESI) *m/z* = 384 $[M+H]^+$.

[001317] *Step 7: Preparation of racemic-trans-6-(5-chloropyridin-3-yl)-4-azaspiro[2.4]heptane-7-carbonitrile*

[001318] A solution of racemic-trans-6-(5-chloropyridin-3-yl)-4-(3,4-dimethylbenzyl)-4-azaspiro[2.4]heptane-7-carbonitrile (7-trans, 1.35 g, 3.51 mmol, 1.0 eq.) in TFA (8 mL) was stirred at 40 °C for 5 h. After completion, the reaction mixture was quenched with $NaHCO_3$ (10 mL, aq., sat.) until the pH was adjusted pH = 8, then extracted with EtOAc (10 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford racemic-trans-6-(5-chloropyridin-3-yl)-4-azaspiro[2.4]heptane-7-carbonitrile (8-trans, 700 mg, quant.) as a yellow oil, which was used directly in next step without further purification. LCMS (ESI) *m/z* = 234 $[M+H]^+$.

[001319] *Step 8: Preparation of trans-tert-butyl ((3S,6S,9aS)-3-(6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate*

[001320] To a solution of trans-6-(5-chloropyridin-3-yl)-4-azaspiro[2.4]heptane-7-carbonitrile (8-trans, 200 mg, 855 µmol, 1.0 eq.) in DMF (5 mL) were added (3S,6S,9aS)-6-((tert-butoxycarbonyl)amino)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic acid (267 mg, 855 µmol, 1.0 eq.), HATU (486 mg, 1.28 mmol, 1.5 eq.) and DIEA (330 mg, 2.56 mmol, 3.0 eq.). The resulting mixture was stirred at room temperature for 1 hr. After completion, the mixture was purified by C18 column chromatography to give diastereomeric mixture of trans-tert-butyl ((3S,6S,9aS)-3-(6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (9-trans, 250 mg, 473 µmol, 55%) as a yellow oil. LCMS (ESI) *m/z* = 528 $[M+H]^+$.

[001321] *Step 9: Preparation of tert-butyl ((3S,6S,9aS)-3-((6R,7S)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate and tert-butyl ((3S,6S,9aS)-3-((6S,7R)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate*

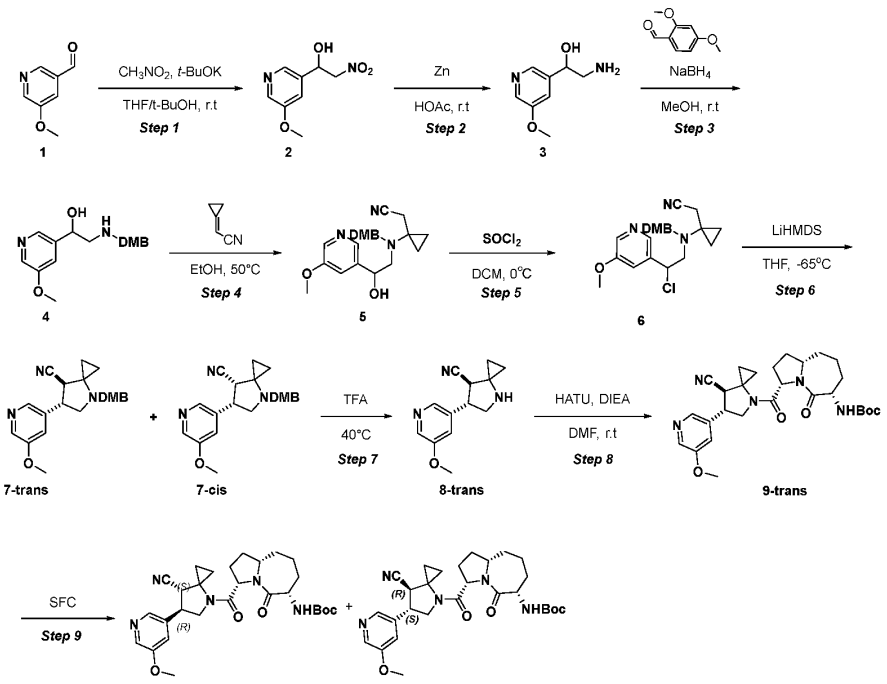
[001322] trans-tert-butyl ((3S,6S,9aS)-3-(6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (9-trans, 280 mg, 530 µmol, 1 eq.) was purified by Chiral separation. Absolute trans stereochemistry was arbitrarily assigned.

[001323] **Peak 1:** tert-butyl ((3S,6S,9aS)-3-((6R,7S)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate or tert-butyl ((3S,6S,9aS)-3-((6S,7R)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (110 mg, 208 µmol, 39%, >99% *ee*, Retention time: 1.683 min) as a yellow oil. LCMS (ESI): $m/z = 528$ $[M+H]^+$.

[001324] **Peak 2:** tert-butyl ((3S,6S,9aS)-3-((6S,7R)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate or tert-butyl ((3S,6S,9aS)-3-((6R,7S)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (110 mg, 208 µmol, 39%, >99% *ee*, Retention time: 2.797 min) as a yellow oil. LCMS (ESI): $m/z = 528$ $[M+H]^+$.

[001325] Analytical method: Column: ChiralCel OZ, 100×4.6mm I.D., 5µm; Mobile phase: A for CO_2 and B for methanol (0.05%DEA); Gradient: 8 min @ 40% B; Flow rate: 2.5 mL/min; Column temperature: 40 °C. SFC method: Instrument: SHIMADZU PREP SOLUTION SFC, Column: ChiralCel OZ, 250×21.2 mm I.D., 5 µm, Mobile phase: A for CO_2 and B for MEOH+0.1%MEA, Gradient: B 40% Flow rate: 40 mL/min Back pressure: 100 bar Column temperature: 35 °C, Wavelength: 220 nm, Cycle-time: 5.5 min, Eluted time: 2 h.

Synthesis of tert-butyl ((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate and tert-butyl ((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate



[001326] *Step 1: Preparation of 1-(5-methoxypyridin-3-yl)-2-nitroethan-1-ol*

[001327] To a solution of 5-methoxynicotinaldehyde (1, 3.0 g, 21.8 mmol, 1 eq.) in THF (10 mL) and t-BuOH (10 mL) were added nitromethane (2.12 g, 34.8 mmol, 1.6 eq.) and *t*-BuOK (244 mg, 2.18 mmol, 0.1 eq.). The resulting mixture was stirred at room temperature for 3 h. After completion, the reaction mixture was quenched by adding NH_4Cl (20 mL, aq., sat.), then extracted with EtOAc (30 mL x 3). The organic layers were combined and washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 1-(5-methoxypyridin-3-yl)-2-nitroethan-1-ol (2, 3.40 g, 17.1 mmol, 79%) as a yellow solid. LCMS (ESI) *m/z* = 199 $[M+H]^+$.

[001328] *Step 2: Preparation of 2-amino-1-(5-methoxypyridin-3-yl)ethan-1-ol*

[001329] A mixture of 1-(5-methoxypyridin-3-yl)-2-nitroethan-1-ol (**2**, 1.0 g, 5.04 mmol, 1.0 eq.) and Zn (1.64 g, 25.2 mmol, 5.0 eq.) in AcOH (10 mL) was stirred at room temperature for 16 h. After completion, the suspension was filtered through a pad of Celite®, the filter cake was washed with MeOH (10 mL). The combined filtrates were concentrated to dryness. The residue was purified by flash column chromatography on silica gel to afford 2-amino-1-(5-methoxypyridin-3-yl)ethan-1-ol (3, 500 mg, 2.97 mmol, 59%) as a yellow oil. LCMS (ESI) *m/z* = 169 $[M+H]^+$.

[001330] *Step 3: Preparation of 2-((3,4-dimethylbenzyl)amino)-1-(5-methoxypyridin-3-yl)ethan-1-ol*

[001331] To a solution of 2-amino-1-(5-methoxypyridin-3-yl)ethan-1-ol (**3**, 800 mg, 4.75 mmol, 1.0 eq.) in MeOH (15 mL) was added 2,4-dimethoxybenzaldehyde (789 mg, 4.75 mmol, 1.0 eq.). The resulting mixture was stirred at room temperature for 2 h. $NaBH_4$ (596 mg, 9.50 mmol, 2.0 eq.) was added and the resulting mixture was stirred at room temperature for 1 hr. After completion, the reaction mixture was quenched by adding NH_4Cl (10 mL, aq., sat.), then extracted with EtOAc (10 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 2-((3,4-dimethylbenzyl)amino)-1-(5-methoxypyridin-3-yl)ethan-1-ol (**4**, 780 mg, 2.44 mmol, 52%) as a yellow oil. LCMS (ESI) m/z = 319 $[M+H]^+$.

[001332] *Step 4: Preparation of 2-(1-((3,4-dimethylbenzyl)(2-hydroxy-2-(5-methoxypyridin-3-yl)ethyl)amino)cyclopropyl)acetonitrile*

[001333] To a solution of 2-((3,4-dimethylbenzyl)amino)-1-(5-methoxypyridin-3-yl)ethan-1-ol (4, 780 mg, 4.66 mmol, 1 eq.) in EtOH (8 mL) was added 2-cyclopropylideneacetonitrile (368 mg, 4.66 mmol, 1.0 eq.). The resulting mixture was stirred at 50 °C overnight. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 2-(1-((3,4-dimethylbenzyl)(2-hydroxy-2-(5-methoxypyridin-3-yl)ethyl)amino)cyclopropyl)acetonitrile (5, 1 g, 4.04 mmol, 87%) as a yellow oil. LCMS (ESI) m/z = 398 $[M+H]^+$.

[001334] *Step 5: Preparation of 2-(1-((2-chloro-2-(5-methoxypyridin-3-yl)ethyl)(3,4-dimethylbenzyl)amino)cyclopropyl)acetonitrile*

[001335] To a solution of 2-(1-((3,4-dimethylbenzyl)(2-hydroxy-2-(5-methoxypyridin-3-yl)ethyl)amino)cyclopropyl)acetonitrile (**5**, 1.46 g, 3.67 mmol, 1.0 eq.) in DCM (10 mL) was added $SOCl_2$ (873 mg, 7.34 mmol, 2.0 eq.) at 0 °C. The resulting mixture was stirred at 0 °C for 1 hr. After completion, the reaction mixture was quenched with $NaHCO_3$ (10 mL, aq., sat.), then extracted with DCM (10 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 2-(1-((2-chloro-2-(5-methoxypyridin-3-yl)ethyl)(3,4-dimethylbenzyl)amino)cyclopropyl)acetonitrile (6, 1 g, 2.40 mmol, 66%) as a yellow oil. LCMS (ESI) m/z = 416 $[M+H]^+$.

[001336] *Step 6: Preparation of racemic-trans-4-(3,4-dimethylbenzyl)-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-7-carbonitrile and racemic-cis-4-(3,4-dimethylbenzyl)-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-7-carbonitrile*

[001337] To a solution of 2-(1-((2-chloro-2-(5-methoxypyridin-3-yl)ethyl)(3,4-dimethylbenzyl)amino)cyclopropyl)acetonitrile (**6**, 1 g, 2.40 mmol, 1.0 eq.) in THF (30 mL) was added LiHMDS (2.9 mL, 2.88 mmol, 1.2 eq., 1 M in THF) slowly -65 °C. The resulting mixture was stirred at -65 °C for 15 min. After completion, the reaction mixture was quenched with NH_4Cl (10 mL, aq., sat.), then extracted with EtOAc (10 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford racemic-trans-4-(3,4-dimethylbenzyl)-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-7-carbonitrile (**7**-trans, 800 mg, 2.10 mmol, 88%). LCMS (ESI) m/z = 380 $[M+H]^+$.

[001338] *Step 7: Preparation of racemic-trans-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-7-carbonitrile*

[001339] A solution of trans-4-(3,4-dimethylbenzyl)-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-7-carbonitrile (**7**-trans, 880 mg, 2.31 mmol, 1.0 eq.) in TFA (4 mL) was stirred at 40 °C for 4 h. After completion, the reaction mixture was quenched with $NaHCO_3$ (10 mL, aq., sat.), then extracted with EtOAc (10 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford racemic-trans-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-7-carbonitrile (8-trans, 570 mg, quant.), which was used directly in next step without further purification. LCMS (ESI) m/z = 230 $[M+H]^+$.

[001340] *Step 8: Preparation of trans-tert-butyl ((3S,6S,9aS)-3-(7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate*

[001341] To a solution of trans-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-7-carbonitrile (8-trans, 130 mg, 566 µmol, 1.0 eq.) in DMF (3 mL) were added (3S,6S,9aS)-6-((tert-butoxycarbonyl)amino)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic acid (176 mg, 566 µmol, 1.0 eq.), HATU (322 mg, 849 µmol, 1.5 eq.) and DIEA (292 mg, 2.26 mmol, 4.0 eq.). The resulting mixture was stirred at room temperature for 1 hr. After completion, the mixture was purified by C18 column chromatography to give trans-tert-butyl ((3S,6S,9aS)-3-(7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-

oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (9-trans, 170 mg, 324 µmol, 57%) as a yellow oil. LCMS (ESI) *m/z* = 524 $[M+H]^+$.

[001342] *Step 9: Preparation of tert-butyl ((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate and tert-butyl ((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate*

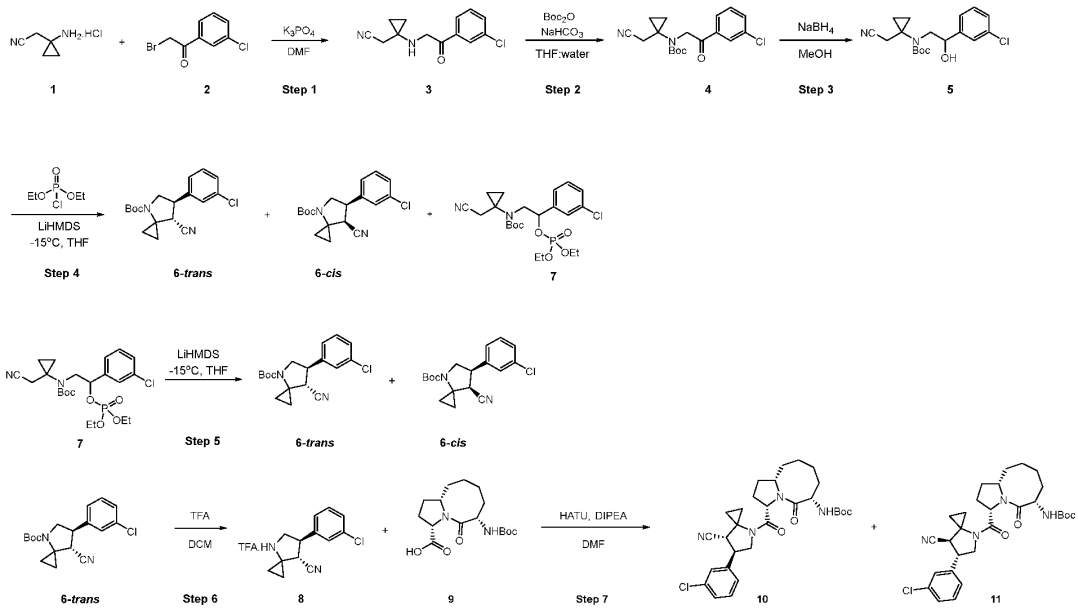
[001343] trans-tert-butyl ((3S,6S,9aS)-3-(7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (9-trans, 190 mg, 362 µmol, 1.0 eq.) was purified by Chiral separation. Absolute trans stereochemistry arbitrarily assigned.

[001344] **Peak 1:** tert-butyl ((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate or tert-butyl ((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (74 mg, 141 µmol, 39%, >99% *ee*, Retention time: 1.144 min) as a yellow oil. LCMS (ESI): *m/z* 524.3 $[M+H]^+$.

[001345] **Peak 2:** tert-butyl ((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate or tert-butyl ((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (69 mg, 131 µmol, 37%, >99% *ee*, Retention time: 1.654 min) as a yellow oil. LCMS (ESI): *m/z* 524.3 $[M+H]^+$.

[001346] Analytical method: Instrument: Waters UPC2 analytical SFC (SFC-H) Column: ChiralCel OX, 100×4.6mm I.D., 3µm, Mobile phase: A for CO_2 and B for Ethanol (0.05%DEA), Gradient: B 40% Flow rate: 2.5 mL/min, Back pressure: 100 bar, Column temperature: 35 °C, Wavelength: 220 nm. SFC method: Instrument: MG II preparative SFC(SFC-13), Column: Cellulose-4, 250×30mm I.D.,10µm, Mobile phase: A for CO_2 and B for Ethanol (0.1%NH3H2O), Gradient: B 40% Flow rate: 80 mL /min, Back pressure: 100 bar, Column temperature: 38 °C, Wavelength: 220 nm, Cycle time: ~6 min.

Synthesis of *tert*-butyl ((3*S*,6*S*,10*aS*)-3-((6*R*,7*S*)-7-cyano-6-(3-chlorophenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-*a*]azocin-6-yl)carbamate and *tert*-butyl ((3*S*,6*S*,10*aS*)-3-((6*S*,7*R*)-7-cyano-6-(3-chlorophenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-*a*]azocin-6-yl)carbamate



[001347] *Step 1: Preparation of 2-(1-{[2-(3-Chlorophenyl)-2-oxoethyl]amino}cyclopropyl)acetonitrile*

[001348] To a solution of 2-(1-aminocyclopropyl)acetonitrile hydrochloride (500 mg, 3.77 mmol, 1 eq) in *N*,*N*-dimethylformamide (8 mL) were added 2-bromo-1-(3-chlorophenyl)ethan-1-one (880 mg, 3.77 mmol, 1 eq) followed by potassium phosphate tribasic (1.99 g, 9.42 mmol, 2.5 eq). The mixture was stirred at room temperature for 2 h. An orange mixture was observed over time. The reaction mixture was quenched with the addition of 1 N HCl (25 mL, pH = 1) at room temperature. The aqueous solution was washed with EtOAc (2 x 30 mL) then basified with 1 N NaOH aqueous solution (until pH = 9, 25 mL). The product was then extracted with EtOAc (2 x 60 mL). The combined organic extracts were washed with brine (30 mL), dried with sodium sulfate, filtered and concentrated under reduced pressure to give crude 2-(1-{[2-(3-chlorophenyl)-2-oxoethyl]amino}cyclopropyl)acetonitrile (550 mg, 58.6%) as an orange oil. LCMS (ESI): m/z = 249.2 $[M+H]^+$.

[001349] *Step 2: Preparation of tert-Butyl-N-[2-(3-chlorophenyl)-2-oxoethyl]-N-[1-(cyanomethyl)cyclopropyl]carbamate*

[001350] To a solution of 2-(1-{[2-(3-chlorophenyl)-2-oxoethyl]amino}cyclopropyl)acetonitrile (550 mg, 2.21 mmol, 1 eq) in THF (4 mL) were added water (4 mL) and sodium bicarbonate (185 mg, 2.21 mmol, 1.0 eq) followed by di-*tert*-butyl dicarbonate (964 mg, 4.42 mmol, 2 eq). The reaction mixture was stirred for 3 days

(over weekend) at room temperature. The reaction mixture was concentrated under reduced pressure (to remove THF). The crude residue was purified by reverse phase chromatography on a 100 g C_{18} cartridge eluting with 5-80% MeCN in water (with 0.1% formic acid). The combined fractions were concentrated under reduced pressure to give *tert*-butyl-*N*-[2-(3-chlorophenyl)-2-oxoethyl]-*N*-[1-(cyanomethyl)cyclopropyl]carbamate (400 mg, 51.9%) as a yellow oil. LCMS (ESI): m/z = 249.2 (M-Boc+2H)$^+$, 293.2 (M-*t*-Bu+2H)$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 - 7.90 (m, 1H), 7.82 (t, *J* = 7.8 Hz, 1H), 7.61 - 7.54 (m, 1H), 7.44 (dt, *J* = 11.7, 7.9 Hz, 1H), 4.70 (d, *J* = 2.0 Hz, 2H), 1.62 - 1.57 (m, 1H), 1.49 - 1.45 (m, 1H), 1.38 - 1.23 (m, 9H), 1.10 (br. s., 2H), 0.97 (br. s., 2H).

[001351] *Step 3: Preparation of tert-Butyl N-[2-(3-chlorophenyl)-2-hydroxyethyl]-N-[1-(cyanomethyl)cyclopropyl]carbamate*

[001352] To a solution of *tert*-butyl-*N*-[2-(3-chlorophenyl)-2-oxoethyl]-*N*-[1-(cyanomethyl)cyclopropyl]carbamate (440 mg, 1.26 mmol, 1 eq) in methanol (10 mL) at 0 °C was added sodium borohydride (47.6 mg, 1.26 mmol, 1.0 eq). The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was quenched with 1 N HCl (1 mL) and concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography on a 50 g C_{18} cartridge eluting with 5-60% MeCN in water (with 0.1% formic acid). The combined fractions were concentrated under reduced pressure to give *tert*-butyl-*N*-[2-(3-chlorophenyl)-2-hydroxyethyl]-*N*-[1-(cyanomethyl)cyclopropyl]carbamate (115 mg, 26.0%) as a thick yellow oil. LCMS (ESI): m/z = 277.2 (M-*t*-Bu-OH+H)$^+$.

[001353] *Step 4: Preparation of tert-Butyl (6R,7S)-6-(3-chlorophenyl)-7-cyano-4-azaspiro[2.4]heptane-4-carboxylate, tert-butyl (6R,7R)-6-(3-chlorophenyl)-7-cyano-4-azaspiro[2.4]heptane-4-carboxylate and tert-butyl-N-[2-(3-chlorophenyl)-2-[(diethoxyphosphoryl)oxy]ethyl]-N-[1-(cyanomethyl)cyclopropyl]carbamate*

[001354] To a solution of *tert*-butyl-*N*-[2-(3-chlorophenyl)-2-hydroxyethyl]-*N*-[1-(cyanomethyl)cyclopropyl]carbamate (115 mg, 327 µmol, 1 eq) in anhydrous THF (10 mL) at -15°C were added diethyl phosphorochloridate (49.4 µL, 343 µmol, 1.05 eq) followed by dropwise addition of LiHMDS 1 M in THF (817 µL, 817 µmol, 2.5 eq). The reaction mixture was stirred at -15°C for 2 h. The reaction mixture was quenched with 1 N HCl (1 mL) and concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography on a 100 g C_{18} cartridge eluting with 5-70% MeCN in water (with 0.1% formic acid). The combined fractions were concentrated under reduced pressure to give *tert*-butyl (6*R*,7*S*)-6-(3-chlorophenyl)-7-cyano-4-azaspiro[2.4]heptane-4-carboxylate (19.0 mg, 17.5%) as a white solid. LCMS (ESI): m/z = 277.2 (M-*t*-Bu+2H)$^+$. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.36 - 7.30 (m, 3H), 7.24 - 7.20 (m, 1H), 4.10 - 3.98 (m, 1H), 3.66 - 3.55 (m, 2H), 3.36 - 3.34 (m, 1H), 2.10 - 2.00 (m, 1H), 1.50 - 1.41 (m, 9H), 1.28 - 1.20 (m, 1H), 1.07 - 1.01 (m, 1H), 0.73 - 0.67 (m, 1H). *tert*-Butyl (6*R*,7*R*)-6-(3-chlorophenyl)-7-cyano-4-azaspiro[2.4]heptane-4-carboxylate (6.00 mg, 5.55%) was also isolated as a thick clear oil. LCMS (ESI): m/z = 277.2 (M-*t*-Bu+2H)$^+$. *tert*-Butyl-*N*-[2-(3-chlorophenyl)-2-[(diethoxyphosphoryl)oxy]ethyl]-*N*-[1-(cyanomethyl)cyclopropyl]carbamate (75.0 mg, 47.1%) was also isolated as a beige solid. LCMS (ESI): m/z = 431.2 (M-*t*-Bu+2H)$^+$.

[001355] *Step 5: Preparation of tert-Butyl (6R,7S)-6-(3-chlorophenyl)-7-cyano-4-azaspiro[2.4]heptane-4-carboxylate*

[001356] To a solution of *tert*-butyl-*N*-[2-(3-chlorophenyl)-2-[(diethoxyphosphoryl)oxy]ethyl]-*N*-[1-(cyanomethyl)cyclopropyl]carbamate (75 mg, 154 µmol, 1 eq) in THF (5 mL) at -15°C was added LiHMDS 1 M in THF (231 µL, 231 µmol, 1.5 eq). The reaction mixture was stirred at -15°C for 2 h. The reaction mixture was quenched with 1 N HCl (1 mL) and concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography on a 50 g C_{18} cartridge eluting with 5-70% MeCN in water (with 0.1% formic acid). The combined fractions were concentrated under reduced pressure to give *tert*-butyl (6*R*,7*S*)-6-(3-chlorophenyl)-7-cyano-4-azaspiro[2.4]heptane-4-carboxylate (24.0 mg, 46.8%) as a clear oil. LCMS (ESI): m/z = 277.2 (M-*t*-Bu+2H)$^+$, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.30 (m, 3H), 7.24 - 7.20 (m, 1H), 4.10 - 3.98 (m, 1H), 3.66 - 3.55 (m, 2H), 3.36 - 3.34 (m, 1H), 2.10 - 2.00 (m, 1H), 1.50 - 1.41 (m, 9H), 1.28 - 1.20 (m, 1H), 1.07 - 1.01 (m, 1H), 0.73 - 0.67 (m, 1H).

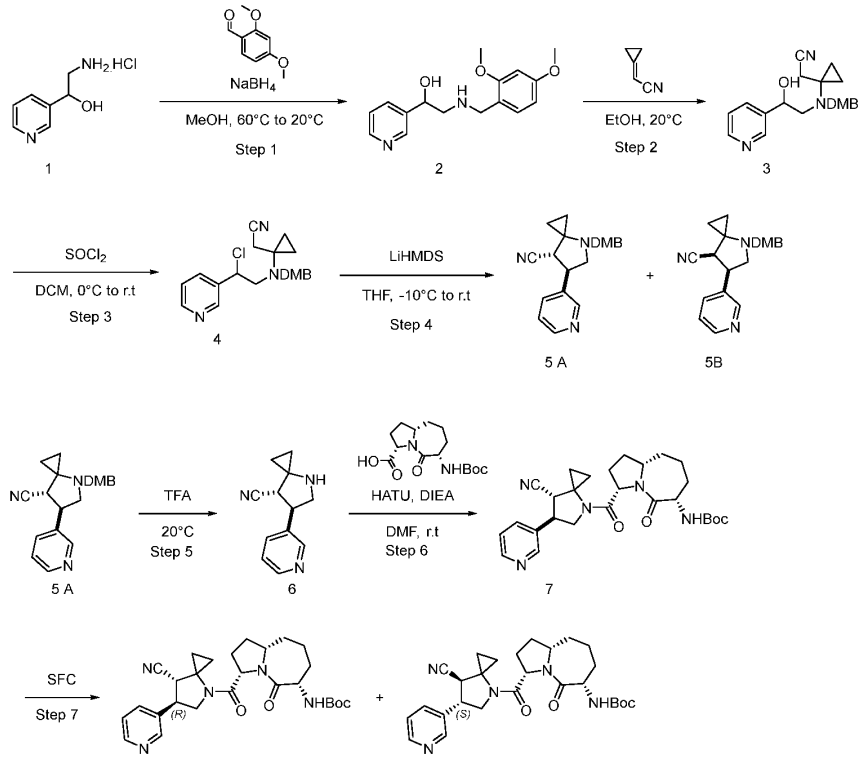
[001357] *Step 6: Preparation of (6R,7S)-6-(3-Chlorophenyl)-4-azaspiro[2.4]heptane-7-carbonitrile TFA salt*

[001358] To a solution of a *tert*-butyl (6*R*,7*S*)-6-(3-chlorophenyl)-7-cyano-4-azaspiro[2.4]heptane-4-carboxylate (40 mg, 120 µmol, 1 eq) in methylene chloride (2 mL) was added TFA (0.5 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure. The crude TFA salt (41.6 mg, 100%) was used for the next step without further purifications. LCMS (ESI): m/z = 233.2 [M+H]$^+$.

[001359] *Step 7: Preparation of tert-butyl ((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(3-chlorophenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate and tert-butyl ((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(3-chlorophenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate*

[001360] To a solution of (6*R*,7*S*)-6-(3-chlorophenyl)-4-azaspiro[2.4]heptane-7-carbonitrile TFA salt (27 mg, 0.116 mmol, 1 eq) in *N,N*-dimethylformamide (2 mL) were respectively added DIPEA (121 µL, 0.696 mmol, 6.0 eq), (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid (37.8 mg, 0.116 mmol, 1 eq) and HATU (48.2 mg, 0.127 mmol, 1.1 eq). The reaction was stirred at room temperature 3 h. The reaction mixture was purified directly by reverse phase chromatography on a 50 g C_{18} cartridge eluting with 5-60% MeCN in water (with 0.1% formic acid) to afford a 1:1 mixture of two diastereomers (40 mg, 63.7%) as a white solid. LCMS (ESI) m/z = 541.4 $[M+H]^+$. The mixture of diastereomers was submitted to chiral SFC separation (SFC conditions: Column Lux Amylose 1, 21.2 x 250 mm 5 um column, 8 mg/inj, concentration 10 mg/mL, Column T = 40°C, Flow rate 75 mL/min, 10% MeOH, cycle time: 22 min) to give the fastest eluting diastereomer arbitrarily assigned to *tert*-butyl ((3*S*,6*S*,10*aS*)-3-((6*R*,7*S*)-7-cyano-6-(3-chlorophenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-*a*]azocin-6-yl)carbamate or *tert*-butyl ((3*S*,6*S*,10*aS*)-3-((6*S*,7*R*)-7-cyano-6-(3-chlorophenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-*a*]azocin-6-yl)carbamate (11 mg, 0.020 mmol, 27.5% recovery, **Peak 1**). LCMS (ESI) m/z = 541.4 $[M+H]^+$. The slowest eluting diastereomer was arbitrarily assigned to *tert*-butyl ((3*S*,6*S*,10*aS*)-3-((6*S*,7*R*)-7-cyano-6-(3-chlorophenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-*a*]azocin-6-yl)carbamate or *tert*-butyl ((3*S*,6*S*,10*aS*)-3-((6*R*,7*S*)-7-cyano-6-(3-chlorophenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-*a*]azocin-6-yl)carbamate (17 mg, 0.031 mmol, 42.5% recovery, **Peak 2**). LCMS (ESI) m/z = 541.4 $[M+H]^+$.

Synthesis of tert-butyl ((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate and tert-butyl ((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate



[001361] *Step 1: Preparation of 2-((2,4-dimethoxybenzyl)amino)-1-(pyridin-3-yl)ethan-1-ol*

[001362] A solution of 2-amino-1-(pyridin-3-yl)ethan-1-ol dihydrochloride (1, 2.8 g, 13.2 mmol, 1 eq.) and 2,4-dimethoxybenzaldehyde (2.19 g, 13.2 mmol, 1 eq.) in MeOH (10 mL) was stirred at 60 °C for 0.5 h, then $NaBH_4$ (1.50 g, 39.5 mmol, 3 eq.) was added at 20 °C and the reaction mixture was stirred at 20 °C for 16 h under N_2 atmosphere. After completion, the reaction mixture was poured into ice-NH_4Cl (100 mL), then extracted with EtOAc (50 mL x 3). The organic layers were combined and washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford 2-((2,4-dimethoxybenzyl)amino)-1-(pyridin-3-yl)ethan-1-ol (2, 2.50 g, 8.67 mmol, 66%) as a yellow oil. LCMS (ESI): *m/z* = 289.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 8.52 (d, *J* = 2.0 Hz, 1H), 8.44 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.71 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.33 (dd, *J* = 7.7, 4.9 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 6.52 (d, *J* = 2.3 Hz, 1H), 6.45 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.46 (s, 1H), 4.70 (t, *J* = 6.0 Hz, 1H), 3.74 (d, *J* = 3.2 Hz, 6H), 3.64 (d, *J* = 4.7 Hz, 2H), 3.17 (d, *J* = 5.1 Hz, 1H), 2.70-2.62 (m, 2H).

[001363] *Step 2: Preparation of 2-(1-((3,4-dimethylbenzyl)(2-hydroxy-2-(pyridin-3-yl)ethyl)amino)cyclopropyl)acetonitrile*

[001364] To a mixture of 2-((2,4-dimethoxybenzyl)amino)-1-(pyridin-3-yl)ethan-1-ol (2, 2.5g, 8.67 mmol, 1 eq.) in EtOH(5 mL) was added 2-cyclopropylideneacetonitrile in PE solution (1.36 g, 17.3 mmol, 2 eq.) and the resulting mixture was stirred at 20 °C for 1 h under N_2 atmosphere. After completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography on silica gel to get 2-(1-((3,4-dimethylbenzyl)(2-hydroxy-2-(pyridin-3-yl)ethyl)amino)cyclopropyl)acetonitrile (3, 2.40 g, 6.53 mmol, 75%) as a pale-yellow oil. LCMS (ESI): *m/z* = 368.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 8.40 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.30 (d, *J* = 1.8 Hz, 1H), 7.54 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.28 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 6.54 (d, *J* = 2.3 Hz, 1H), 6.47 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.99 (d, *J* = 3.1 Hz, 1H), 4.28 (dd, *J* = 9.8, 6.6 Hz, 1H), 3.85-3.71 (m, 8H), 2.94-2.71 (m, 4H), 0.60-0.31 (m, 3H), 0.06 (s, 1H).

[001365] *Step 3: Preparation of 2-(1-((2-chloro-2-(pyridin-3-yl)ethyl)(3,4-dimethylbenzyl)amino)cyclopropyl)acetonitrile*

[001366] $SOCl_2$ in DCM solution (3, 281 mg, 2.37 mmol, 1.2 eq.) was added to a solution 2-(1-((3,4-dimethylbenzyl)(2-hydroxy-2-(pyridin-3-yl)ethyl)amino)cyclopropyl)acetonitrile (3, 730 mg, 1.98 mmol, 1 eq.) in DCM (10 mL) at 0 °C. The solution was stirred at room temperature for 0.5 h. After completion, the reaction mixture was quenched with $NaHCO_3$ (aq., sat.) (20 mL), then extracted with EtOAc (50 mL x 2). The organic layers were combined and washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 2-(1-((2-chloro-2-(pyridin-3-yl)ethyl)(3,4-dimethylbenzyl)amino)cyclopropyl)acetonitrile (4, 310 mg, 0.80 mmol, 41%) as an oil. LCMS (ESI): *m/z* = 386.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 8.50 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.31 (d, *J* = 1.9 Hz, 1H), 7.64-7.57 (m, 1H), 7.37 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 1H), 6.55 (d, *J* = 2.3 Hz, 1H), 6.49 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.62 (t, *J* = 7.2 Hz, 1H), 3.81-3.72 (m, 8H), 3.36-3.23 (m, 2H), 2.91-2.75 (m, 2H), 0.61-0.38 (m, 3H), 0.06--0.04 (m, 1H).

[001367] *Step 4: Preparation of racemic-trans-4-(3,4-dimethylbenzyl)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-7-carbonitrile* & racemic-*cis-4-(3,4-dimethylbenzyl)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-7-carbonitrile*

[001368] To a solution of 2-(1-((2-chloro-2-(pyridin-3-yl)ethyl)(3,4-dimethylbenzyl)amino)cyclopropyl)acetonitrile (4, 310 mg, 0.80 mmol, 1 eq.) in THF (10 mL) was added LiHMDS (202 mg, 2.00 mmol, 2.5 eq.) dropwise at -10 °C and the solution was stirred at room temperature for 1 hr. After completion, the reaction mixture was quenched with NH_4Cl (aq., sat.) (15 mL), then extracted with EtOAc (15 mL x 2). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford racemic-trans-4-(3,4-dimethylbenzyl)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-7-carbonitrile (5A, 75 mg, 0.21 mmol, 27%) and cis-4-(3,4-dimethylbenzyl)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-7-carbonitrile (5B, 55.0 mg, 0.16 mmol, 20%) as a yellow oil. LCMS (ESI): *m/z* = 350.2 $[M+H]^+$.

[001369] *Step 5: Preparation of racemic-trans-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-7-carbonitrile*

[001370] A solution of racemic-trans-4-(3,4-dimethylbenzyl)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-7-carbonitrile (5A, 100 mg, 0.29 mmol, 1 eq.) in TFA (5 mL) was stirred at 20 °C overnight under N_2. After completion, the reaction mixture was quenched with $NaHCO_3$ (aq., sat.) (20 mL), then extracted with EtOAc (20 mL x 2). The organic layers were combined and washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford racemic-trans-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-7-carbonitrile (6, 55.0 mg, quant.) as an oil for next step without further purification. LCMS (ESI): *m/z* = 199.9 $[M+H]^+$.

[001371] *Step 6: Preparation of trans-tert-butyl ((3S,6S,9aS)-3-(7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate*

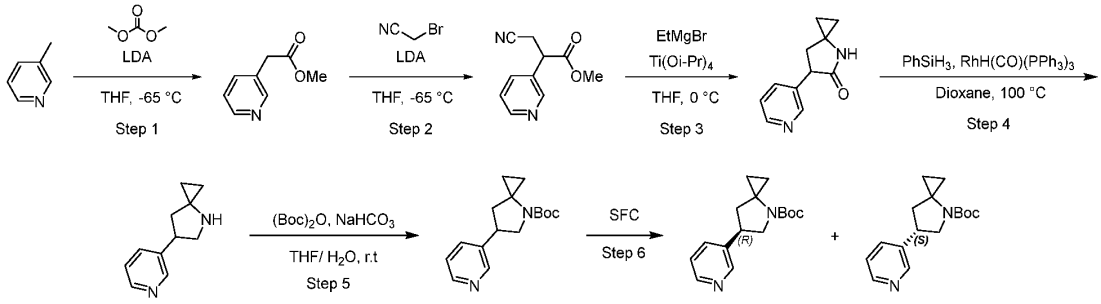
[001372] To a solution of racemic-trans-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-7-carbonitrile (6, 900 mg, 4.52 mmol, 1.0 eq.) and DIEA (2.92 g, 22.6 mmol, 5.0 eq.) in DMF (40 mL) were added HATU (1.72 g, 4.52 mol, 1.0 eq.) and (3S,6S,9aS)-6-((tert-butoxycarbonyl)amino)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic acid (1.55 g, 4.97 mol, 1.1 eq.). The solution was stirred at room temperature for 1 hr. After completion, the reaction mixture was diluted with H_2O (50 mL), then extracted with EtOAc (50 mL x 2). The organic layers were combined and washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford trans-tert-butyl ((3S,6S,9aS)-3-(7-cyano-6-(pyridin-3-

yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (**7**, 450 mg, 0.91 mmol, 20%) as a white solid. LCMS (ESI): *m/z* = 494 $[M+H]^+$.

[001373] *Step 7: Preparation of tert-butyl ((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate and tert-butyl ((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate*

[001374] trans-tert-butyl ((3S,6S,9aS)-3-(7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (7, 450 mg, 0.91 mmol) was separated by SFC to give tert-butyl ((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate or tert-butyl ((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (**Peak 1**, 120 mg, 27%) and tert-butyl ((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate or tert-butyl ((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (**Peak 2**, 220 mg, 49%) as a white solid. LCMS (ESI): *m/z* = 494 $[M+H]^+$. SFC method: Instrument: Waters Thar 80 preparative SFC Column: ChiralCel OX, 250×21.2mm I.D., 5 μm Mobile phase: A for CO_2 and B for 0.1% 7mol/L NH_3 in MeOH, Gradient: B 40%, Flow rate: 40mL /min, Back pressure: 100 bar, Column temperature: 35°C, Wavelength: 254 nm, Cycle-time:4.2 min, Eluted time: 2H.

Synthesis of tert-butyl (*R*)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carboxylate and tert-butyl (*S*)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carboxylate



[001375] *Step 1: Preparation of methyl 2-(pyridin-3-yl)acetate*

[001376] To a solution of 3-methylpyridine (**1,** 30 g, 322 mmol, 1.0 eq.) in THF (600 mL) was added dropwise LDA (193 mL, 386 mmol, 2M, 1.2 eq.) at -65 °C under N_2

atmosphere. The reaction solution was stirred at -65 °C for 1 h and dimethyl carbonate (57 g, 483mmol, 1.5 eq.) was added into the reaction mixture. After addition, the mixture was stirred at -65 °C for an additional 1 hr. After completion, the reaction mixture was quenched with saturated NH_4Cl (aq.) solution (500 mL) at 0 °C, then extracted with EtOAc (500 mL x 2). The organic layers were combined and washed with brine (150 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford methyl 2-(pyridin-3-yl)acetate (**2,** 25.0 g, 165 mmol, 51%) as a yellow oil. LCMS (ESI): *m/z* = 152 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.60-8.48 (m, 2H), 7.68-7.60 (m, 1H), 7.29-7.23 (m, 1H), 3.71 (s, 3H), 3.64 (s, 2H).

[001377] *Step 2: Preparation of methyl 3-cyano-2-(pyridin-3-yl)propanoate*

[001378] To a solution of LDA (99.0 mL, 198 mmol, 2M, 1.5 eq.) in THF (400 mL) was added dropwise a solution of methyl 2-(pyridin-3-yl)acetate (**2,** 20 g, 132 mmol, 1.0 eq.) at -65 °C under N_2 atmosphere. The reaction solution was stirred at -65 °C for 1 h and 2-bromoacetonitrile (18.9 g, 158 mmol, 1.2 eq.) was added into the reaction mixture. After addition, the mixture was stirred at -65 °C for an additional 1 h. After completion, the reaction mixture was quenched with saturated ice-NH_4Cl (aq.) solution (500 mL), then extracted with EtOAc (500 mL x 3). The organic layers were combined and washed with brine (500 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford methyl 3-cyano-2-(2-methoxypyridin-4-yl)propanoate (**3,** 20.5 g, 107 mmol, 82%) as a yellow oil. LCMS (ESI): *m/z* = 191 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.57 (d, *J* = 2.2 Hz, 1H), 7.69-7.61 (m, 1H), 7.34 (dd, *J* = 7.9, 4.8 Hz, 1H), 4.00 (t, *J* = 7.5 Hz, 1H), 3.75 (s, 3H), 3.07 (dd, *J* = 16.9, 7.1 Hz, 1H), 2.88 (dd, *J* = 16.9, 7.9 Hz, 1H).

[001379] *Step 3: Preparation of 6-(pyridin-3-yl)-4-azaspiro[2.4]heptan-5-one*

[001380] To a solution of methyl 3-cyano-2-(pyridin-3-yl)propanoate (**3,** 20.5 g, 107 mmol, 1.0 eq.) and Titanium tetraisopropanolate (36.8 g, 128 mmol, 1.2 eq.) in THF (400 mL) was added dropwise EtMgBr (80 mL, 240 mmol, 3M, 2.25 eq.) at 0 °C. After addition, the reaction mixture was stirred at 0 °C for 1 hr. After completion, the reaction mixture was quenched by addition of HCl aqueous solution (140 mL, 2N) at 0 °C. The suspension was warmed to room temperature and filtered. The filtrate was poured into ice–water (500 mL) and extracted with EtOAc (200 mL x 2). The organic layers were combined, washed with brine (500 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 6-(pyridin-3-yl)-4-azaspiro[2.4]heptan-5-one (**4,** 9.2 g, 48.8 mmol, 46%) as a yellow solid. LCMS (ESI): *m/z*

= 189 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 2.1 Hz, 1H), 8.53 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.74-7.65 (m, 1H), 7.29 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.00 (s, 1H), 3.91 (t, *J* = 8.7 Hz, 1H), 2.53 (dd, *J* = 12.9, 9.3 Hz, 1H), 2.33 (dd, *J* = 12.9, 8.2 Hz, 1H), 1.00-0.68 (m, 4H).

[001381] *Step 4: Preparation of 6-(pyridin-3-yl)-4-azaspiro[2.4]heptane*

[001382] To a solution of 6-(pyridin-3-yl)-4-azaspiro[2.4]heptan-5-one (**4,** 3.0 g, 15.9 mmol, 1.0 eq.) and methanidylidyneoxidanium tris(triphenylphosphane) hydrogen rhodium (729 mg, 795 mmol, 0.05 eq.) in dioxane (60 mL) was added phenylsilane (10.32 g, 95.4 mmol, 6.0 eq.). The reaction solution was stirred at 100 °C for 12 h. After completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was triturated with 1N HCl (200 mL) at 25 °C for 0.5 h and then filtered. The filtrate was extracted with EtOAc (100 mL x 2). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to afford 6-(pyridin-3-yl)-4-azaspiro[2.4]heptane (**5,** 2.2 g, 12.62 mmol, 79%) as a brown solid. LCMS (ESI): *m/z* = 175$[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.55-8.46 (m, 2H), 7.72-7.62 (m, 1H), 7.31-7.25 (m, 1H), 3.84-3.71 (m, 2H), 3.40-3.28 (m, 1H), 2.32-2.17 (m, 2H), 1.52-1.37 (m, 2H), 0.91-0.76 (m, 2H).

[001383] *Step 5: Preparation of tert-butyl 6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carboxylate*

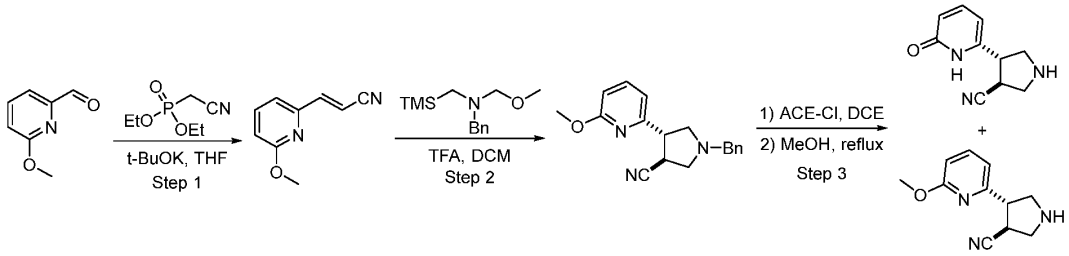
[001384] To a solution of 6-(pyridin-3-yl)-4-azaspiro[2.4]heptane (**5,** 8 g, 45.9 mmol, 1 eq.) in THF / H_2O (80 mL / 10 mL) were added $NaHCO_3$ (7.7 g, 91.7 mmol, 2 eq.) and Boc_2O (12 g, 55.1 mmol, 1.2 eq.). The solution was stirred at room temperature for 4 h. After completion, the reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (100 mL x 3). The organic layers were combined and washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford tert-butyl 6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carboxylate (**6,** 6.7 g, 24.5 mmol, 53%) as a white solid. **LCMS (ESI)**: *m/z* = 275 $[M+H]^+$.

[001385] *Step 6: Preparation of tert-butyl (R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carboxylate and tert-butyl (S)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carboxylate*

[001386] tert-butyl 6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carboxylate (**6,** 6.7 g) was separated by chiral SFC to afford tert-butyl (R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carboxylate (**Peak 1,** 3 g, 45%) and tert-butyl (S)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carboxylate (**Peak 2,** 3.1 g, 46%). **LCMS (ESI)**: *m/z* = 275 $[M+H]^+$. SFC method: Instrument: Waters Thar 80 preparative SFC Column: ChiralPak C-IG, 250×21.2 mm I.D., 5

μm Mobile phase: A for CO_2 and B for MEOH + 0.1%NH_3H_2O, Gradient: B 45 % Flow rate: 40 mL/min , Back pressure: 100 bar, Column temperature: 35 °C, Wavelength: 220 nm Cycle-time: 25 min Eluted time: 7H. The assignment of absolute stereochemical configuration was made by comparison of experimental vibrational circular dichroism (VCD) spectra with theoretical VCD spectra obtained from DFT calculations.

Synthesis of racemic-(3S,4S)-4-(6-oxo-1,6-dihydropyridin-2-yl)pyrrolidine-3-carbonitrile and racemic-(3S,4S)-4-(6-methoxypyridin-2-yl)pyrrolidine-3-carbonitrile



[001387] *Step 1: Preparation of (E)-3-(6-methoxypyridin-2-yl)acrylonitrile*

[001388] To a solution of diethyl (cyanomethyl)phosphonate (1.35 g, 7.65 mmol, 1.05 eq.) in THF (10 mL) was added *t*-BuOK (897 mg, 8.01 mmol, 1.1 eq.) at 0 °C, the solution was stirred for 30 min, then 6-methoxypicolinaldehyde (1 g, 7.29 mmol, 1 eq.) was added to the solution. The solution was stirred at room temperature for 30 min. After completion, H_2O (20 mL) was added to the solution, the solution was extracted with EtOAc (20 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford (E)-3-(6-methoxypyridin-2-yl)acrylonitrile (810 mg, 5.05 mmol, 70%) as a white solid. LCMS (ESI) *m/z* = 161[M+H]$^+$. ^{1}H NMR (400 MHz, DMSO) δ 7.75 (dd, *J* = 8.3, 7.2 Hz, 1H), 7.62 (d, *J* = 16.1 Hz, 1H), 7.15 (d, *J* = 7.1 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.64 (d, *J* = 16.1 Hz, 1H), 3.86 (s, 3H).

[001389] *Step 2: Preparation of racemic (3S,4S)-1-benzyl-4-(6-methoxypyridin-2-yl)pyrrolidine-3-carbonitrile*

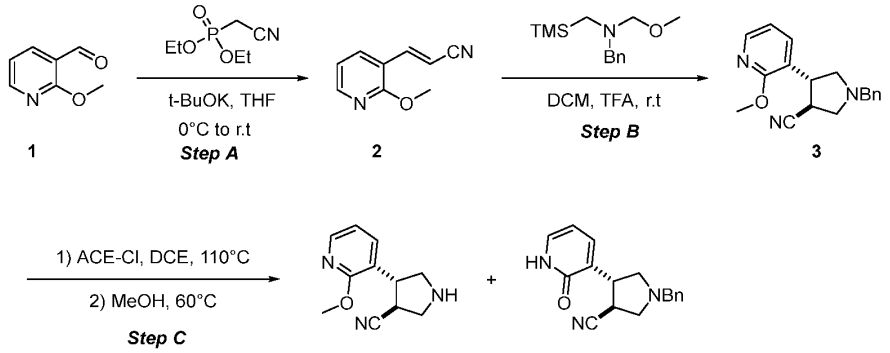
[001390] To a solution of N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine (1.19 g, 5.05 mmol, 1 eq.) in DCM (10 mL) were added (E)-3-(6-methoxypyridin-2-yl)acrylonitrile (810 mg, 5.05 mmol, 1 eq.) and TFA (115 mg, 1.01 mmol, 0.2 eq.). The solution was stirred at room temperature overnight. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford racemic-(3S,4S)-1-benzyl-4-(6-methoxypyridin-2-

yl)pyrrolidine-3-carbonitrile (1.10 g, 3.74 mmol, 74%) as a yellow oil. LCMS (ESI) *m/z* = 294 $[M+H]^+$.

[001391] *Step 3: Preparation of racemic-(3S,4S)-4-(6-oxo-1,6-dihydropyridin-2-yl)pyrrolidine-3-carbonitrile and racemic-(3S,4S)-4-(6-methoxypyridin-2-yl)pyrrolidine-3-carbonitrile*

[001392] To a solution of racemic-(3S,4S)-1-benzyl-4-(6-methoxypyridin-2-yl)pyrrolidine-3-carbonitrile (**3**, 1.4 g, 4.77 mmol, 1 eq.) in DCE (14 mL) was added 1-chloroethyl carbonochloridate (4.43 g, 31.0 mmol, 6.5 eq.). The solution was stirred at 110 °C for 12 h. After completion, the solution was concentrated under reduced pressure. The residue was dissolved in MeOH (10 mL). The solution was stirred at 60 °C for 30 min. After completion, the reaction mixture was concentrated under reduced pressure to give mixture of racemic-(3S,4S)-4-(6-oxo-1,6-dihydropyridin-2-yl)pyrrolidine-3-carbonitrile and racemic-(3S,4S)-4-(6-methoxypyridin-2-yl)pyrrolidine-3-carbonitrile (900 mg) as a yellow solid. LCMS (ESI) *m/z* = 190 & 204 $[M+H]^+$.

Synthesis of racemic-(3S,4R)-4-(2-oxo-1,2-dihydropyridin-3-yl)pyrrolidine-3-carbonitrile and racemic-(3S,4R)-4-(2-methoxypyridin-3-yl)pyrrolidine-3-carbonitrile



[001393] *Step 1: Preparation of (E)-3-(2-methoxypyridin-3-yl)acrylonitrile*

[001394] To a solution of diethyl (cyanomethyl)phosphonate (2.69 g, 15.2 mmol, 1.05 eq.) in THF (40 mL) was added *t*-BuOK (1.78 g, 15.9 mmol, 1.1 eq.) at 0 °C, the solution was stirred for 30 min, then 2-methoxynicotinaldehyde (1, 2 g, 14.5 mmol, 1 eq.) was added to the solution. The solution was stirred at room temperature for 30 min. After completion, H_2O (40 mL) was added to the solution, the solution was extracted with EtOAc (40 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford (E)-3-(2-methoxypyridin-3-

yl)acrylonitrile (2, 2.10 g, quant.) as a yellow solid, which was used in next step without further purification. LCMS (ESI) *m/z* = 161 $[M+H]^+$.

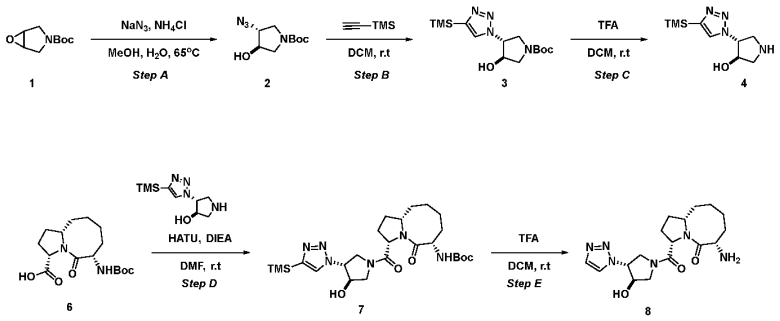
[001395] *Step 2: Preparation of racemic-(3S,4R)-1-benzyl-4-(2-methoxypyridin-3-yl)pyrrolidine-3-carbonitrile*

[001396] To a solution of (E)-3-(2-methoxypyridin-3-yl)acrylonitrile (2, 2 g, 12.4 mmol, 1 eq.) in DCM (20 mL) were added N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine (3.22 g, 13.6 mmol, 1.1 eq.) and TFA (282 mg, 2.48 mmol, 0.2 eq.). The reaction solution was stirred at room temperature for 2 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give racemic-(3S,4R)-1-benzyl-4-(2-methoxypyridin-3-yl)pyrrolidine-3-carbonitrile (3, 2.50 g, 8.52 mmol, 69%) as a yellow oil. LCMS (ESI) *m/z* = 294 $[M+H]^+$.

[001397] *Step 3: Preparation of racemic-(3S,4R)-4-(2-oxo-1,2-dihydropyridin-3-yl)pyrrolidine-3-carbonitrile and racemic-(3S,4R)-4-(2-methoxypyridin-3-yl)pyrrolidine-3-carbonitrile*

[001398] To a solution of racemic-(3S,4R)-1-benzyl-4-(2-methoxypyridin-3-yl)pyrrolidine-3-carbonitrile (**3,** 2.5 g, 8.52 mmol, 1 eq.) in DCE (25 mL) was added 1-chloroethyl carbonochloridate (7.90 g, 55.3 mmol, 6.5 eq.). The solution was stirred at 110 °C for 12 h. After completion, the solution was concentrated under reduced pressure. The residue was dissolved in MeOH (10 mL). The solution was stirred at 60 °C for 30 min. After completion, the reaction mixture was concentrated under reduced pressure to give a mixture of racemic-(3S,4R)-4-(2-oxo-1,2-dihydropyridin-3-yl)pyrrolidine-3-carbonitrile and racemic-(3S,4R)-4-(2-methoxypyridin-3-yl)pyrrolidine-3-carbonitrile (1.6 g, mixture, quant.) as a yellow solid. LCMS (ESI) *m/z* = 190 & 204 $[M+H]^+$.

Synthesis of (3S,6S,10aS)-6-amino-3-((rel-3R,4R)-3-hydroxy-4-(1H-1,2,3-triazol-1-yl)pyrrolidine-1-carbonyl)octahydropyrrolo[1,2-a]azocin-5(1H)-one:



[001399] *Step 1: Preparation of tert-butyl (rel-3R,4R)-3-azido-4-hydroxypyrrolidine-1-carboxylate*

[001400] To a solution of tert-butyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (**1**, 3 g, 16.1 mmol, 1 eq.) and ammonium chloride (3.87 g, 72.4 mmol, 4.5 eq.) in MeOH (96 mL) and H_2O (12 mL) were added NaN_3 (5.23 g, 80.5 mmol, 5 eq.) at room temperature. The resulting mixture was stirred at 60 °C for an additional 18 h. After completion, the reaction mixture was diluted with water and extracted with EtOAc (100 mL x 2). The combined organic layers were washed with $NaHCO_3$ solution, followed by water and then brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford tert-butyl (rel-3R,4R)-3-azido-4-hydroxypyrrolidine-1-carboxylate (**2**, 3.60 g, quant.) as a colorless oil, which was used in next step directly without further purification. LCMS (ESI) *m/z* = 173.2 $[M-56+H]^+$.

[001401] *Step 2: Preparation of tert-butyl (rel-3R,4R)-3-hydroxy-4-(4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl)pyrrolidine-1-carboxylate*

[001402] To a solution of tert-butyl (rel-3R,4R)-3-azido-4-hydroxypyrrolidine-1-carboxylate (**2**, 3.6 g, 15.7 mmol, 1 eq.) and ethynyltrimethylsilane (3.85 g, 39.2 mmol, 2.5 eq.) in DCM (40 mL) was added bis(1,5-cyclooctadiene, (Z,Z)-) diiridium dichloride (105 mg, 157 µmol, 0.01 eq.) in portions under N_2. The reaction mixture was stirred at room temperature for 24 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford tert-butyl (rel-3R,4R)-3-hydroxy-4-(4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl)pyrrolidine-1-carboxylate (**3**, 2.5 g, 7.67 mmol, 49%) as a brown oil, LCMS (ESI) *m/z* = 327.2 $[M+H]^+$.

Step 3: Preparation of (rel-3R,4R)-4-(4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl)pyrrolidin-3-ol

[001403] To a solution of tert-butyl (rel-3R,4R)-3-hydroxy-4-(4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl)pyrrolidine-1-carboxylate (**3**, 500 mg, 1.53 mmol, 1 eq.) in DCM (20 mL) was added TFA (1.74 g, 15.3 mmol, 10 eq.). The reaction mixture was stirred at room temperature for 1 hr. After completion, the reaction mixture was concentrated under reduced pressure to give (rel-3R,4R)-4-(4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl)pyrrolidin-3-ol (**4**, 346 mg, quant.) as a brown solid, which was used in next step without further purification. LCMS (ESI) *m/z* = 227.1 $[M+H]^+$.

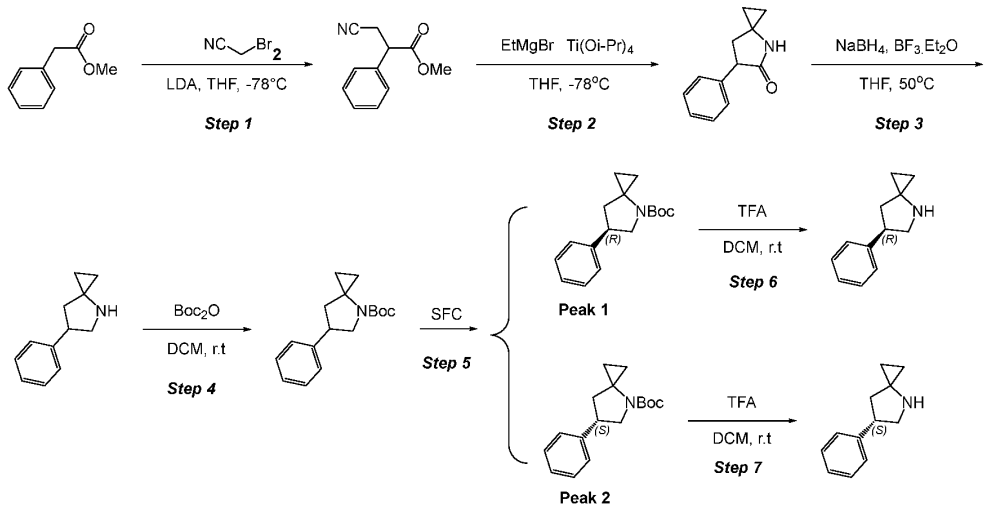
[001404] *Step 4: Preparation of tert-butyl ((3S,6S,10aS)-3-((rel-3R,4R)-3-hydroxy-4-(4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate*

[001405] To a solution of (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid (**6**, 100 mg, 0.31 mmol, 1 eq.), DIEA (200 mg, 1.55 mmol, 5 eq.) and (rel-3R,4R)-4-(4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl)pyrrolidin-3-ol (**4, 70** mg, 0.31 mmol, 1 eq.) in DMF (1 mL) was added HATU (118 mg, 0.31 mmol, 1.0 eq.) and the reaction mixture was stirred at room temperature overnight under N_2. After completion, the reaction mixture was purified by C18 column chromatography to afford tert-butyl ((3S,6S,10aS)-3-((rel-3R,4R)-3-hydroxy-4-(4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate (**7,** 80 mg, 0.16 mmol, 50%). LCMS (ESI): *m/z* = 535 $[M+H]^+$.

[001406] *Step 5: Preparation of (3S,6S,10aS)-6-amino-3-((rel-3R,4R)-3-hydroxy-4-(1H-1,2,3-triazol-1-yl)pyrrolidine-1-carbonyl)octahydropyrrolo[1,2-a]azocin-5(1H)-one*

[001407] A solution of tert-butyl ((3S,6S,10aS)-3-((rel-3R,4R)-3-hydroxy-4-(4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate (**7,** 80 mg, 0.16 mmol, 1 eq.) in TFA (1 mL) and DCM (3 mL) was stirred at room temperature for 30 min under N_2. After completion, the reaction mixture was concentrated under reduced pressure to afford (3S,6S,10aS)-6-amino-3-((rel-3R,4R)-3-hydroxy-4-(1H-1,2,3-triazol-1-yl)pyrrolidine-1-carbonyl)octahydropyrrolo[1,2-a]azocin-5(1H)-one (**8**, 80 mg, quant.) as a colorless oil. LCMS (ESI): *m/z* = 363 $[M+H]^+$.

Synthesis of (R)-6-phenyl-4-azaspiro[2.4]heptane and (S)-6-phenyl-4-azaspiro[2.4]heptane:



[001408] *Step 1: Preparation of methyl 3-cyano-2-phenylpropanoate*

[001409] To a solution of LDA (5.95 mL, 47.8 mmol, 1.2 eq) in THF (80 mL) was added dropwise methyl 2-phenylacetate (6 g, 39.9 mmol, 1.0 eq) at -78 °C under N_2 atmosphere. The reaction solution was stirred at -78 °C for 0.5 h and 2-bromoacetonitrile (5.25 g, 43.8 mmol, 1.1 eq) was introduced into the reaction. After addition, the mixture was stirred at -78 °C for 0.5 h. After completion, the reaction mixture was quenched with saturated ice-NH_4Cl (aq.) solution (500 mL), then extracted with EtOAc (500 mL x 3). The organic layers were combined and washed with brine (500 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford methyl 3-cyano-2-phenylpropanoate (6.20 g, 32.7 mmol, 82%) as a yellow oil. LCMS (ESI): *m/z* = 190 $[M+H]^+$.

[001410] *Step 2: Preparation of 6-phenyl-4-azaspiro[2.4]heptan-5-one*

[001411] To a solution of methyl 3-cyano-2-phenylpropanoate (6.2 g, 32.7 mmol, 1 eq) in THF (50 mL) was added dropwise $Ti(Oi\text{-}Pr)_4$ (10.2 g, 35.9 mmol, 1.1 eq) at -78 °C. The reaction solution was stirred at -78 °C for 10 min and EtMgBr (72 mL, 71.9 mmol, 2.2 eq) was added dropwise into the reaction mixture. The reaction was stirred at -78 °C for 10 min then warmed up to room temperature for 0.5 h. After completion, the reaction mixture was quenched with H_2O (5 mL), followed by 10% aqueous HCl (50 mL) and EtOAc (500 mL). And 10 % aq. NaOH solution was added to the resulting clear mixture until the pH was adjusted pH = 8-9. The filtrate was extracted with EtOAc (200 mL x 2). The organic layers were combined, washed with brine (500 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 6-phenyl-4-azaspiro[2.4]heptan-5-one (9.2 g, 48.8 mmol, 46%) as a yellow solid. LCMS (ESI): *m/z* = 188.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.24 (m, 6H), 3.86 (dd, *J* = 9.4, 7.6 Hz, 1H), 2.51 (dd, *J* = 12.9, 9.4 Hz, 1H), 2.29 (dd, *J* = 12.9, 7.6 Hz, 1H), 0.85-0.88 (m, 1H), 0.87-0.81 (m, 1H), 0.76-0.64 (m, 2H).

[001412] *Step 3: Preparation of 6-phenyl-4-azaspiro[2.4]heptane*

[001413] To a solution of 6-phenyl-4-azaspiro[2.4]heptan-5-one (2.2 g, 11.7 mmol, 1 eq) in THF (100 mL) was added $NaBH_4$ (2.21 g, 58.5 mmol, 5 eq) at 0 °C, then Boron trifluoride etherate (8.30 g, 58.5 mmol, 5 eq) was added dropwise to the mixture. The mixture was stirred at room temperature for 5 h and then stirred at 50 °C overnight. After completion, the reaction mixture was quenched with $NaHCO_3$ aqueous solution (20 mL) and extracted with EtOAc(20 mL x 2). The organic layers were combined, washed with brine (500 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was

purified by C18 column chromatography to afford 6-phenyl-4-azaspiro[2.4]heptane (1.50 g, 8.65 mmol, 74%) as an oil. LCMS (ESI): *m/z* = 174.3 $[M+H]^+$.

[001414] *Step 4: Preparation of tert-butyl 6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate*

[001415] To a solution of 6-phenyl-4-azaspiro[2.4]heptane (1.2 g, 6.92 mmol, 1 eq), DIEA (1.78 g, 13.8 mmol, 2 eq) and DMAP (84.5 mg, 692 μmol, 0.1 eq) in DCM (20 mL) was added di-tert-butyl dicarbonate (301 mg, 1.38 mmol, 1.2 eq) at room temperature. The reaction solution was stirred at room temperature for 5 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to get tert-butyl 6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate (1.50 g, 5.48 mmol, 79%) as a white solid. LCMS (ESI): *m/z* = 218.3 $[(M\text{-}tBu)+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.19 (m, 5H), 3.98 (s, 1H), 3.54-3.39 (m, 2H), 2.48-2.27 (m, 1H), 1.95 (dd, *J* = 12.2, 5.5 Hz, 1H), 1.52 (s, 2H), 1.43 (s, 9H), 0.55-0.42 (m, 2H)

[001416] *Step 5: Preparation of tert-butyl (R)-6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate and tert-butyl (S)-6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate*

tert-butyl 6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate (1.50 g, 5.48 mmol) was further separated by Chiral SFC to give: SFC Method: Instrument: SHIMADZU PREP SOLUTION SFC , Column: ChiralPak IH, 250×21.2mm I.D., 5μm, Mobile phase: A for CO_2 and B for MeOH+0.1%NH_3H_2O, Gradient: B 10%, Flow rate: 10 mL/min, Back pressure: 100 bar, Column temperature: 35 °C, Wavelength: 220 nm, Cycle-time: 4 min, Eluted time: 4 h. Absolute stereochemistry was arbitrarily assigned.

[001417] **Peak 1:** tert-butyl (R)-6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate or tert-butyl (S)-6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate (600 mg, 40%); Retention time: 3.287 min, 99% *ee*. LCMS (ESI): *m/z* = 218.3 $[(M\text{-}tBu)+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.21 (m, 5H), 3.99 (s, 1H), 3.54-3.40 (m, 2H), 2.37 (dd, J = 13.9, 8.8 Hz, 1H), 1.96 (dd, J = 12.1, 5.5 Hz, 1H), 1.43 (s, 9H), 0.57-0.41 (m, 2H).

[001418] **Peak 2:** tert-butyl (S)-6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate or tert-butyl (R)-6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate (600 mg, 40%); Retention time: 3.582 min, 97% *ee*. LCMS (ESI): *m/z* = 218.3 $[(M\text{-}tBu)+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.20 (m, 5H), 3.99 (s, 1H), 3.56-3.38 (m, 2H), 2.37 (dd, *J* = 13.8, 8.8 Hz, 1H), 1.96 (dd, *J* = 12.1, 5.5 Hz, 1H), 1.43 (s, 9H), 0.58-0.42 (m, 2H).

[001419] **Analytical method**: Column: (R,R)-Whelk-O1, 250×4.6mm I.D., 5um, Mobile phase: A for CO_2 and B for IPA (0.05%DEA), Gradient: 10 min @ B 20%, Flow rate: 2.0 mL/min, Back pressure: 100 bar, Column temperature: 35 °C.

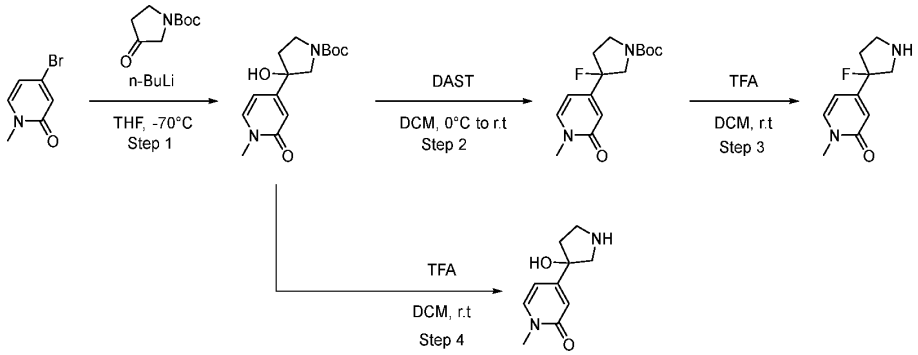
[001420] *Step 6: Preparation of (R)-6-phenyl-4-azaspiro[2.4]heptane or (S)-6-phenyl-4-azaspiro[2.4]heptane*

[001421] To the solution of tert-butyl (R)-6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate or tert-butyl (S)-6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate (60 mg, 219 µmol, 1 eq, **Peak 1**) in DCM (2 mL) was added TFA (1 mL) at room temperature. The solution was stirred at room temperature. for 2 h. After completion, the reaction mixture was concentrated under reduced pressure to give (R)-6-phenyl-4-azaspiro[2.4]heptane or (S)-6-phenyl-4-azaspiro[2.4]heptane (70.0 mg, quant.) as an oil, which was used in next step directly without further purification. LCMS (ESI): *m/z* = 174.2 $[M+H]^+$.

[001422] *Step 7: Preparation of (S)-6-phenyl-4-azaspiro[2.4]heptane or (R)-6-phenyl-4-azaspiro[2.4]heptane*

[001423] To the solution of tert-butyl (6S)-6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate or tert-butyl (R)-6-phenyl-4-azaspiro[2.4]heptane-4-carboxylate (60 mg, 219 µmol, 1 eq, **Peak 2**) in DCM (2 mL) was added TFA (1 mL) at room temperature. The solution was stirred at room temperature. for 2 h. After completion, the reaction mixture was concentrated under reduced pressure to give (S)-6-phenyl-4-azaspiro[2.4]heptane or (R)-6-phenyl-4-azaspiro[2.4]heptane (70.0 mg, quant.) as an oil, which was used in next step directly without further purification. LCMS (ESI): *m/z* = 174.2 $[M+H]^+$.

Synthesis of 4-(3-fluoropyrrolidin-3-yl)-1-methylpyridin-2(1H)-one & 4-(3-hydroxypyrrolidin-3-yl)-1-methylpyridin-2(1H)-one



[001424] *Step 1: Preparation of tert-butyl 3-hydroxy-3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate*

[001425] To a solution of 4-bromo-1-methylpyridin-2(1H)-one (400 mg, 2.12 mmol, 1 eq.) and tert-butyl 3-oxopyrrolidine-1-carboxylate (392 mg, 2.12 mmol, 1 eq.) in THF (6 mL) was added *n*-BuLi (1.6 M in THF solution) (222 mg, 2.22 mmol, 1.05 eq.) at -70 °C dropwise slowly and stirred at -70 °C for 30 min under N_2. After completion, the reaction mixture was poured into saturate NH_4Cl aqueous solution (20 mL). The mixture was extracted with EtOAc (20 mL x 3). The organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford tert-butyl 3-hydroxy-3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate (460 mg, 1.56 mmol, 74%) as a yellow solid. LCMS (ESI): *m/z* = 295.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 7.62 (d, *J* = 7.0 Hz, 1H), 6.47 (s, 1H), 6.32 (d, *J* = 7.1 Hz, 1H), 5.52 (s, 1H), 3.51 -3.41 (m, 4H), 3.38 (s, 3H), 2.22-2.11 (m, 1H), 1.94-1.86 (m, 1H), 1.42-1.39 (m, 9H).

[001426] *Step 2: Preparation of tert-butyl 3-fluoro-3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate*

[001427] To a solution of tert-butyl 3-hydroxy-3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate (300 mg, 1.02 mmol, 1 eq.) in DCM (5 mL) was added DAST (165 mg, 1.02 mmol, 1 eq.) at 0 °C. The solution was stirred at room temperature for 2 h. After completion, the reaction mixture was quenched with $NaHCO_3$ (aq.) and extracted with DCM (10 mL x 3). The organic phase was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford tert-butyl 3-fluoro-3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate (300 mg, quant.), which was used in next step directly without further purification. LCMS (ESI): *m/z* = 297 $[M+H]^+$.

[001428] *Step 3: Preparation of 4-(3-fluoropyrrolidin-3-yl)-1-methylpyridin-2(1H)-one*

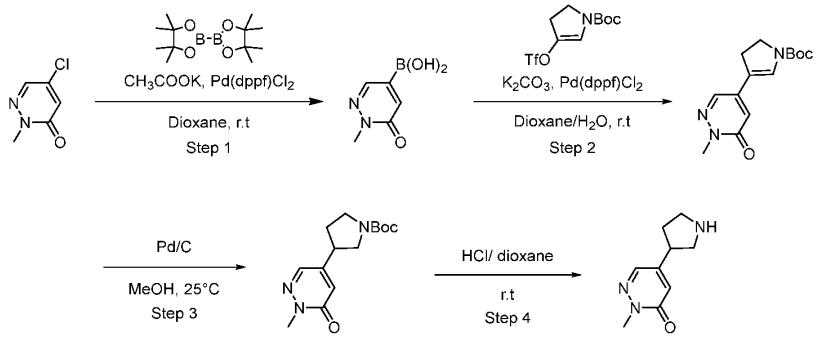
[001429] To a solution of tert-butyl 3-fluoro-3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate (300 mg, 1.01 mmol, 1 eq.) in DCM (3 mL) was added TFA (0.6 mL). The solution was stirred at room temperature for 1 h. After completion, the reaction mixture was concentrated under reduced pressure to afford 4-(3-fluoropyrrolidin-3-yl)-1-methylpyridin-2(1H)-one (250 mg, quant., TFA salt) as a white solid. LCMS (ESI) *m/z* = 197 $[M+H]^+$.

[001430] *Step 4: Preparation of 4-(3-hydroxypyrrolidin-3-yl)-1-methylpyridin-2(1H)-one*

[001431] To a solution of tert-butyl 3-hydroxy-3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate (130 mg, 0.33 mmol, 1 eq.) in DCM (3 mL) was added TFA (0.6 mL). The solution was stirred at room temperature for 1 h. After completion, the reaction

mixture was concentrated under reduced pressure to afford 4-(3-hydroxypyrrolidin-3-yl)-1-methylpyridin-2(1H)-one (120 mg, quant., TFA salt) as a white solid. LCMS (ESI) *m/z* = 295 $[M+H]^+$.

Synthesis of 2-methyl-5-(pyrrolidin-3-yl)pyridazin-3(2H)-one:



[001432] *Step 1: Preparation of (1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)boronic acid*

[001433] Add 5-chloro-2-methyl-2,3-dihydropyridazin-3-one (500 mg, 3.45 mmol, 1 eq.) to a vial containing 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (876 mg, 3.45 mmol, 1.0 eq.), $Pd(dppf)Cl_2$ (2.52 g, 3.45 mmol, 1.0 eq.), AcOK (1.04 g, 10.3 mmol, 3 eq) in dioxane (3 mL) with an N_2 atmosphere. Allow the mixture to react at room temperature for 24-48 h. Quench the reaction with water. Extract the reaction mixture with EtOAc. Wash the organic layer with brine. Evaporate the organic layer under vacuum. Purify the product by flash chromatography on silica gel to get (1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)boronic acid (400 mg, 2.59 mmol, 75%) as yellow solid. ^1H NMR (400 MHz, DMSO-d6) δ 7.83 (d, *J* = 1.4 Hz, 1H), 7.01 (d, *J* = 1.3 Hz, 1H), 3.64 (s, 3H), 1.30 (s, 12H).

[001434] *Step 2: Preparation of tert-butyl 4-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)-2,3-dihydro-1H-pyrrole-1-carboxylate*

[001435] Add(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)boronic acid (359 mg, 2.33 mmol, 1 eq.) to a vial containing tert-butyl 4-(trifluoromethanesulfonyloxy)-2,3-dihydro-1H-pyrrole-1-carboxylate (885 mg, 2.79 mmol, 1.2 eq.), $Pd(dppf)Cl_2$ (84.4 mg, 116 µmol, 0.05 eq.), K_2CO_3 (971 mg, 6.98 mmol, 3 eq.) in dioxane (10 mL) and H_2O (2 mL) with N_2 atmosphere. Allow the mixture to react at room temperature for 24-48 h. Quench the reaction with water. Extract the reaction mixture with EtOAc. Wash the organic layer with brine. Evaporate the organic layer under vacuum. Purify the product by flash chromatography on

silica gel to get tert-butyl 4-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)-2,3-dihydro-1H-pyrrole-1-carboxylate (279 mg, 1.00 mmol, 43%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.27 (d, *J* = 2.0 Hz, 1H), 6.86 (d, *J* = 11.1 Hz, 1H), 6.70 (d, *J* = 2.0 Hz, 1H), 4.42-4.31 (m, 2H), 4.29-4.21 (m, 2H), 3.63 (s, 3H), 1.44 (d, *J* = 3.8 Hz, 9H).

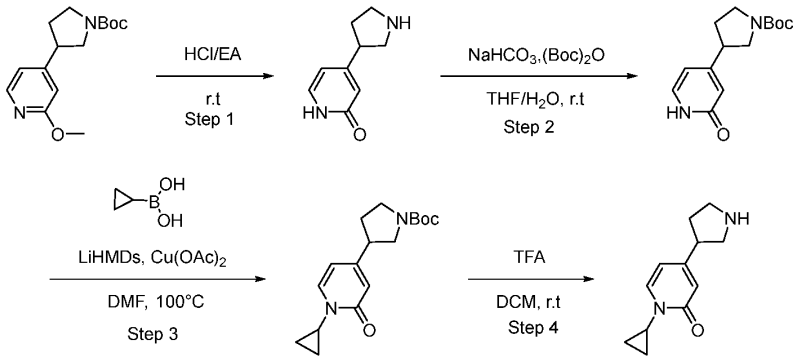
[001436] *Step 3: Preparation of tert-butyl 3-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrrolidine-1-carboxylate*

[001437] To a solution of tert-butyl 4-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)-2,3-dihydro-1H-pyrrole-1-carboxylate (285 mg, 1.02 mmol, 1 eq.) in MeOH (3 mL) was added Pd/C (5.42 mg, 51 μmol, 0.05 eq.). The mixture was stirred at 25 °C for 12 h under H_2. After completion, the suspension was filtered through a pad of Celite®, the filter cake was washed with MeOH (20 mL). The combined filtrates were concentrated to dryness to give tert-butyl 3-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrrolidine-1-carboxylate (280 mg, quant.) as a white solid, which was used in next step without further purification. LCMS (ESI): *m/z* = 559.2 $[M+H]^+$.

[001438] *Step 4: Preparation of 2-methyl-5-(pyrrolidin-3-yl)pyridazin-3(2H)-one*

[001439] A solution of tert-butyl 3-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrrolidine-1-carboxylate (285 mg, 1.02 mmol, 1 eq.) in HCl/dioxane (6 mL, 4 M) was stirred at room temperature overnight under N_2. The reaction was concentrated under reduced pressure to afford 2-methyl-5-(pyrrolidin-3-yl)pyridazin-3(2H)-one (180 mg, quant., HCl salt) as a yellow oil. LCMS (ESI): *m/z* = 180.2 $[M+H]^+$.

Synthesis of 1-cyclopropyl-4-(pyrrolidin-3-yl)pyridin-2(1H)-one:



[001440] *Step 1: Preparation of 4-(pyrrolidin-3-yl)pyridin-2(1H)-one*

[001441] A solution of tert-butyl 3-(2-methoxypyridin-4-yl)pyrrolidine-1-carboxylate (400 mg, 1.43 mmol, 1 eq.) in HCl/EA (5 mL) was stirred at room temperature for 2 h. After completion, the reaction mixture was concentrated under reduced pressure to afford 4-

(pyrrolidin-3-yl)pyridin-2(1H)-one (230 mg, quant., HCl salt) as a yellow oil. LCMS (ESI): *m/z* = 165 $[M+H]^+$.

[001442] *Step 2: Preparation of tert-butyl 3-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate*

[001443] To a solution of 4-(pyrrolidin-3-yl)pyridin-2(1H)-one (230 mg, 1.40 mmol, 1 eq., HCl salt) in THF / H_2O (5 mL / 1 mL) were added $NaHCO_3$ (235 mg, 2.80 mmol, 2 eq.) and Boc_2O (732 mg, 3.36 mmol, 1.2 eq.). The solution was stirred at room temperature for 4 h. After completion, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford tert-butyl 3-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate (330 mg, 1.38 mmol, 98%) as a white solid. LCMS (ESI): *m/z* = 265 $[M+H]^+$.

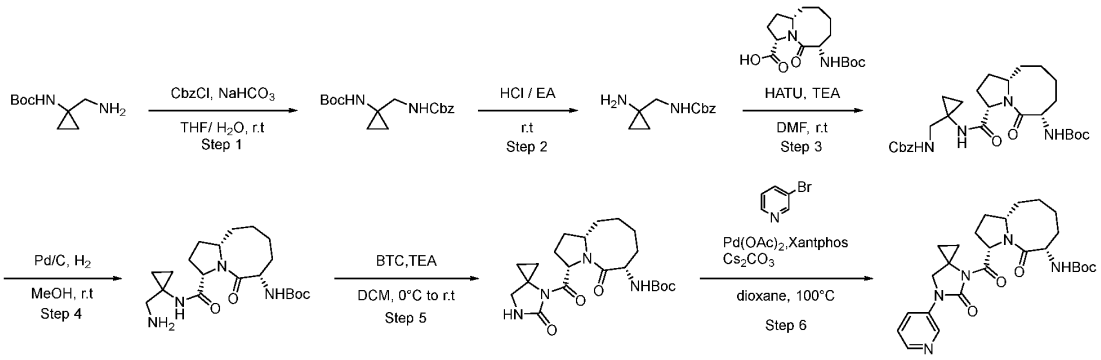
[001444] *Step 3: Preparation of tert-butyl 3-(1-cyclopropyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate*

[001445] A solution of tert-butyl 3-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate (250 mg, 0.94 mmol, 1.0 eq.), cyclopropylboronic acid (202 mg, 2.35 mmol, 2.5 eq.), $Cu(OAc)_2$ (257 mg, 1.41 mmol, 1.5 eq.) and LiHMDS (4.23 mmol, 3.0 eq.) in DMF (5 mL), was stirred at 100 °C for additional 2 h by microwave. After completion, the reaction mixture was diluted with H_2O (10 mL), extracted with EtOAc (10 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford tert-butyl 3-(1-cyclopropyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate (33 mg, 108 μmol, 11%) as a white solid. LCMS (ESI): *m/z* = 305 $[M+H]^+$.

[001446] *Step 4: Preparation of 1-cyclopropyl-4-(pyrrolidin-3-yl)pyridin-2(1H)-one*

[001447] To a solution of tert-butyl 3-(1-cyclopropyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carboxylate (360 mg, 1.18 mmol, 1 eq.) in DCM (1 mL) was added TFA (1 mL) . The solution was stirred at room temperature for 2 h. After completion, the reaction mixture was concentrated under reduced pressure to afford 1-cyclopropyl-4-(pyrrolidin-3-yl)pyridin-2(1H)-one (217 mg, quant.) as a yellow oil. LCMS (ESI): *m/z* = 205 $[M+H]^+$.

Synthesis of tert-butyl ((3S,6S,10aS)-5-oxo-3-(5-oxo-6-(pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamate:



[001448] *Step 1: Preparation of tert-butyl (1-((((benzyloxy)carbonyl)amino)methyl)cyclopropyl)carbamate*

[001449] To a solution of tert-butyl (1-(aminomethyl)cyclopropyl)carbamate (400 mg, 2.14 mmol, 1 eq.) in THF / H_2O (5 mL / 5 mL) were added $NaHCO_3$ (359 mg, 4.28 mmol, 2 eq.) and benzyl carbonochloridate (436 mg, 2.56 mmol, 1.2 eq.). The solution was stirred at room temperature for 4 h. After completion, the reaction mixture was diluted with H_2O (10 mL), extracted with EtOAc (10 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford tert-butyl (1-((((benzyloxy)carbonyl)amino)methyl)cyclopropyl)carbamate (600 mg, 1.87 mmol, 88%) as a white solid. LCMS (ESI): m/z = 321 $[M+H]^+$.

[001450] *Step 2: Preparation of benzyl (1-aminocyclopropyl)methyl)carbamate*

[001451] To a solution of tert-butyl (1-((((benzyloxy)carbonyl)amino)methyl)cyclopropyl)carbamate (600 mg, 1.87 mmol, 1 eq.) in DCM (5 mL) was added TFA (5 mL) . The solution was stirred at room temperature for 2 h. After completion, the reaction mixture was concentrated under reduced pressure to afford benzyl (1-aminocyclopropyl)methyl)carbamate (380 mg, quant.) as a yellow oil. LCMS (ESI): m/z = 221 $[M+H]^+$.

[001452] *Step 3: Preparation of tert-butyl ((3S,6S,10aS)-3-((1-((((benzyloxy)carbonyl)amino)methyl)cyclopropyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate*

[001453] To a solution of (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid (700 mg, 2.14 mmol, 1..0 eq.) in DMF (10 mL) were added HATU (824 mg, 2.17 mmol, 1.02 eq.), TEA (430 mg, 4.26 mmol, 2 eq.) and benzyl (1-aminocyclopropyl)methyl)carbamate (**3**, 470 mg, 2.13 mmol, 1 eq.). The solution was stirred at room temperature for 1 hr. After completion, the reaction mixture was

concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to afford tert-butyl ((3S,6S,10aS)-3-((1-((((benzyloxy)carbonyl)amino)methyl)cyclopropyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate (1.10 g, 2.08 mmol, 98%) as a brown solid. LCMS (ESI): *m/z* = 529 $[M+H]^+$.

[001454] *Step 4: Preparation of tert-butyl ((3S,6S,10aS)-3-((1-(aminomethyl)cyclopropyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate*

[001455] To a solution of tert-butyl ((3S,6S,10aS)-3-((1-((((benzyloxy)carbonyl)amino)methyl)cyclopropyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate (0.2 g, 2.26 mmol, 1 eq.) in MeOH (10 mL) was added Pd/C (300 mg) under nitrogen. The suspension was degassed under vacuum and purged with H_2 several times. The resulting mixture was stirred at room temperature for 12 h. After completion, the suspension was filtered through a pad of Celite®, the filter cake was washed with MeOH (20 mL). The combined filtrates were concentrated to dryness to give tert-butyl ((3S,6S,10aS)-3-((1-(aminomethyl)cyclopropyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate (850 mg, quant.) as a brown solid. LCMS (ESI): *m/z* = 395 $[M+H]^+$.

[001456] *Step 5: Preparation of tert-butyl ((3S,6S,10aS)-5-oxo-3-(5-oxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamate*

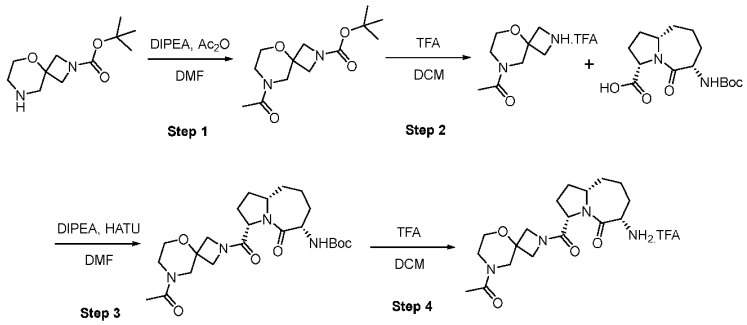
[001457] To a solution of tert-butyl ((3S,6S,10aS)-3-((1-(aminomethyl)cyclopropyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate (800 mg, 2.03 mmol, 1 eq.) and TEA (410 mg, 4.06 mmol, 2 eq.) in DCM (10 mL) was added BTC (238 mg, 0.81 mmol, 0.4 eq.). The solution was stirred at room temperature for 1 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford tert-butyl ((3S,6S,10aS)-5-oxo-3-(5-oxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamate (120 mg, 0.29 mmol, 14%) as a white solid. LCMS (ESI) *m/z* = 421 $[M+H]^+$.

[001458] *Step 6: Preparation of tert-butyl ((3S,6S,10aS)-5-oxo-3-(5-oxo-6-(pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamate*

[001459] A solution of tert-butyl ((3S,6S,10aS)-5-oxo-3-(5-oxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamate (120 mg, 0.29 mmol, 1.0 eq.), 3-bromopyridine (45 mg, 0.29 mmol, 1.0 eq.), and Cs_2CO_3 (284 mg, 0.87 mmol, 2.5 eq.) in dioxane (5 mL), was stirred under N_2, then $Pd(OAc)_2$ (6 mg, 29 μmol, 0.1 eq.) and XantPhos (33 mg, 58 μmol, 0.2 eq.) were added, and the resulting mixture was

stirred at 100°C for additional 12 h. After completion, the reaction mixture was diluted with H_2O (10 mL), extracted with EtOAc (10 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford tert-butyl ((3S,6S,10aS)-5-oxo-3-(5-oxo-6-(pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamate (40 mg, 80 µmol, 28%) as a white solid. LCMS (ESI): *m/z* = 498 $[M+H]^+$.

Synthesis of (3*S*,6*S*,9*aS*)-3-{8-acetyl-5-oxa-2,8-diazaspiro[3.5]nonane-2-carbonyl}-6-amino-octahydro-1*H*-pyrrolo[1,2-*a*]azepin-5-one trifluoroacetic salt



[001460] *Step 1: Preparation of tert-butyl 8-acetyl-5-oxa-2,8-diazaspiro[3.5]nonane-2-carboxylate*

[001461] To an ice-bath cooled solution tert-butyl 5-oxa-2,8-diazaspiro[3.5]nonane-2-carboxylate (40 mg, 175 µmol, 1 eq) and *N*,*N*-diisopropylethylamine (152 µL, 875 µmol, 5 eq) in methylene chloride (2.5 mL) at 0°C was slowly added acetic anhydride (26.7 mg, 262 µmol, 1.5 eq) in methylene chloride (2.5 mL). The mixture was stirred at 0°C for 5 min. then 2 h at room temperature. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by reverse phase chromatography on a C_{18} cartridge eluting with 5-60% MeCN in water to give tert-butyl 8-acetyl-5-oxa-2,8-diazaspiro[3.5]nonane-2-carboxylate (44.5 mg, 94.0%) as a colorless oil. LCMS (ESI) m/z = 271.1 $[M+H]^+$.

[001462] *Step 2: Preparation of 1-(5-oxa-2l4,8-diazaspiro[3.5]nonan-8-yl)ethan-1-one*

To a solution of a t*ert*-butyl 8-acetyl-5-oxa-2,8-diazaspiro[3.5]nonane-2-carboxylate (44.5 mg, 164 µmol, 1 eq) in methylene chloride (2.5 mL) was added TFA (0.5 mL). The reaction was stirred at room temperature for 1 h. The reaction was concentrated under reduced

pressure to give 1-(5-oxa-2l4,8-diazaspiro[3.5]nonan-8-yl)ethan-1-one (57 mg, 99%, TFA salt) as a thick clear oil. LCMS (ESI) m/z = 171.2 $[M+H]^+$.

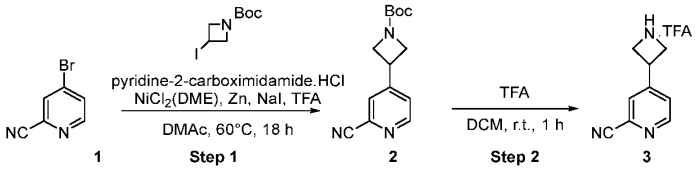
[001463] *Step 3: Preparation of tert-butyl ((3S,6S,9aS)-3-(8-acetyl-5-oxa-2,8-diazaspiro[3.5]nonane-2-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate*

[001464] To a solution of 1-(5-oxa-2l4,8-diazaspiro[3.5]nonan-8-yl)ethan-1-one (57 mg, 164 µmol, 1.1 eq, TFA salt) in *N,N*-dimethylformamide (3 mL) were respectively added *N,N*-diisopropylethylamine (258 µL, 1.49 mmol, 10 eq), (3S,6S,9aS)-6-((tert-butoxycarbonyl)amino)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic acid (46.5 mg, 149 µmol, 1 eq) and HATU (62.3 mg, 164 µmol, 1.1 eq). The reaction was stirred 2 h at room temperature. The reaction mixture was then directly purified by reverse phase chromatography on a C_{18} cartridge eluting with 5-60% MeCN in water to give tert-butyl ((3S,6S,9aS)-3-(8-acetyl-5-oxa-2,8-diazaspiro[3.5]nonane-2-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (63.0 mg, 91.0%) as a white solid. LCMS (ESI) m/z = 365.2 $(M\text{-Boc}+2H)^+$.

[001465] *Step 4: (3S,6S,9aS)-3-{8-acetyl-5-oxa-2,8-diazaspiro[3.5]nonane-2-carbonyl}-6-amino-octahydro-1H-pyrrolo[1,2-a]azepin-5-one trifluoroacetic salt*

[001466] To a solution of tert-butyl ((3S,6S,9aS)-3-(8-acetyl-5-oxa-2,8-diazaspiro[3.5]nonane-2-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamate (33 mg, 71.0 µmol, 1 eq) in methylene chloride (2.5 mL) was added TFA (0.5 mL). The reaction was stirred at room temperature for 1 h. The reaction was concentrated under reduced pressure to give (3S,6S,9aS)-3-(8-acetyl-5-oxa-2,8-diazaspiro[3.5]nonane-2-carbonyl)-6-aminooctahydro-5H-pyrrolo[1,2-a]azepin-5-one (33 mg, 99%, TFA salt) as a thick clear oil. LCMS (ESI) m/z = 365.4 $[M+H]^+$.

Synthesis of 4-(azetidin-3-yl)pyridine-2-carbonitrile TFA salt



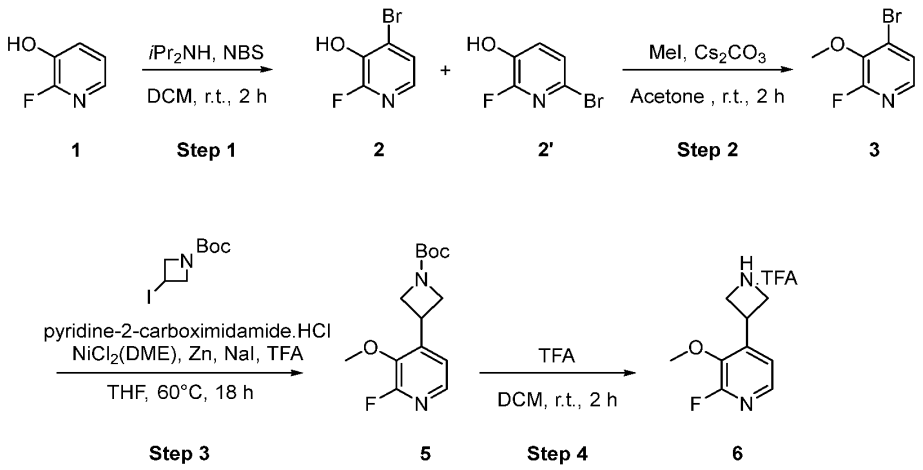
[001467] *Step 1: Preparation of tert-butyl 3-(2-cyanopyridin-4-yl)azetidine-1-carboxylate*

[001468] A flame dried tube was charged with a mixture of 4-bromopyridine-2-carbonitrile (100 mg, 0.54 mmol, 1 eq), tert-butyl 3-iodoazetidine-1-carboxylate (185 mg, 0.66 mmol, 1.2 eq), nickel(II) chloride ethylene glycol dimethyl ether complex (11.9 mg, 0.055 mmol, 0.1 eq), pyridine-2-carboximidamide hydrochloride (8.60 mg, 0.055 mmol, 0.1 eq), sodium iodide (40.9 mg, 0.27 mmol, 0.5 eq), pre-activated zinc (71.2 mg, 1.09 mmol, 2.0 eq) and TFA (5 µL, 0.055 mmol, 0.1 eq) in N,N-dimethylacetamide (2.72 mL). The reaction mixture was degassed with nitrogen for 20 min. and the tube was sealed and placed in a pre-equilibrated bath at 60 °C. The reaction mixture was stirred for 18 h. The mixture was then filtered through a pad of Celite and washed with EtOAc. The filtrate was diluted with water and the product was extracted with EtOAc (3 x). The combined organic layers were washed with brine (2 x), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by reverse phase chromatography on a 50 g C18 cartridge using a gradient of 5-95% MeCN in water (with 0.1% formic acid) to give tert-butyl 3-(2-cyanopyridin-4-yl)azetidine-1-carboxylate (78 mg, 55%) as a yellow oil. LCMS (ESI): m/z = 260.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, J = 4.9 Hz, 1H), 7.69 - 7.65 (m, 1H), 7.49 (dd, J = 5.0, 1.6 Hz, 1H), 4.40 (t, J = 8.7 Hz, 2H), 3.94 (dd, J = 8.8, 5.6 Hz, 2H), 3.82 - 3.68 (m, 1H), 1.48 (s, 9H).

[001469] *Step 2: Preparation of 4-(azetidin-3-yl)pyridine-2-carbonitrile*

[001470] TFA (1 mL, 13 mmol, 45 eq) was added to a solution of tert-butyl 3-(2-cyanopyridin-4-yl)azetidine-1-carboxylate (78 mg, 0.30 mmol, 1 eq) in methylene chloride (3 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under vacuum to give 4-(azetidin-3-yl)pyridine-2-carbonitrile (48.2 mg, quant., TFA salt) as a yellow oil. The crude product was used in the next step without further purification. **LCMS** (ESI): m/z = 160.2 $[M+H]^+$.

Synthesis of 4-(azetidin-3-yl)-2-fluoro-3-methoxypyridine



[001471] *Step 1:* Preparation of *4-bromo-2-fluoropyridin-3-ol*

[001472] In a dried flask under nitrogen was dissolved 2-fluoropyridin-3-ol (500 mg, 4.42 mmol, 1 eq) in methylene chloride (22.1 mL). Diisopropylamine (0.9 mL, 7.07 mmol, 1.6 eq) was slowly added at room temperature followed by N-bromosuccinimide (786 mg, 4.42 mmol, 1.0 eq). The reaction mixture was stirred at room temperature for 2 h. The LCMS showed a 1:1 mixture of 4-bromo and 6-bromo regioisomers. The solvent was removed under vacuum and the crude product was purified by reverse phase chromatography on a 50 g C18 cartridge using a gradient of 5-95% MeCN in water (with 0.1% formic acid) to give 4-bromo-2-fluoropyridin-3-ol (224 mg, 26.4%) as a yellow solid. LCMS (ESI): m/z = 192.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, J = 5.3, 1.3 Hz, 1H), 7.34 (d, J = 5.1 Hz, 1H). 6-Bromo-2-fluoropyridin-3-ol (112 mg, 13.2%) was also isolated.

[001473] *Step 2:* Preparation of *4-bromo-2-fluoro-3-methoxypyridine*

[001474] Cesium carbonate (755 mg, 2.32 mmol, 2.0 eq) was added to a solution of 4-bromo-2-fluoropyridin-3-ol (224 mg, 1.16 mmol, 1 eq) in acetone (5.8 mL). Methyl iodide (79 µL, 1.27 mmol, 1.1 eq) was then added and the reaction mixture was stirred at room temperature for 2 h. Acetone was removed under vacuum and the residue was diluted in DCM and water. The aqueous layer was extracted three times with DCM. The combined organic layers were dried with Na2SO4, filtered and concentrated under vacuum to give 4-bromo-2-fluoro-3-methoxypyridine (193 mg, 81.0%) as a yellow liquid (volatile!). The product was used in the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 5.1, 1.5 Hz, 1H), 7.37 (d, J = 5.4 Hz, 1H), 4.01 (d, J = 2.0 Hz, 3H).

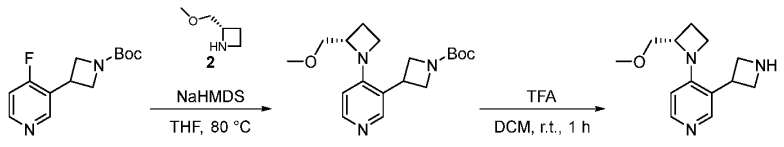
[001475] *Step 3: Preparation of tert-butyl 3-(2-fluoro-3-methoxypyridin-4-yl)azetidine-1-carboxylate*

[001476] A flame dried tube was charged with a mixture of 4-bromo-2-fluoro-3-methoxypyridine (194 mg, 0.94 mmol, 1 eq), tert-butyl 3-iodoazetidine-1-carboxylate (266 mg, 0.94 mmol, 1.2 eq), nickel(II) chloride ethylene glycol dimethyl ether complex (20.6 mg, 0.094 mmol, 0.1 eq), pyridine-2-carboximidamide hydrochloride (14.8 mg, 0.094 mmol, 0.1 eq), sodium iodide (70.4 mg, 0.47 mmol, 0.5 eq), pre-activated zinc (122 mg, 1.88 mmol, 2.0 eq) and TFA (7 µL, 0.094 mmol, 0.1 eq) In THF (4.70 mL). The reaction mixture was degassed with nitrogen for 20 min. and the tube was sealed and placed in a pre-equilibrated bath at 80°C. The reaction mixture was stirred for 18 h. The mixture was filtered through a pad of Celite and washed with EtOAc. The filtrate was diluted with water and the product was extracted with EtOAc (3x). The combined organic layers were washed two times with brine, dried with anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by normal phase chromatography on a 40 g silica gel cartridge using a gradient of 0-100% EtOAc in heptane to give *tert*-butyl 3-(2-fluoro-3-methoxypyridin-4-yl)azetidine-1-carboxylate (27.9 mg, 10.5%) as a yellow oil. LCMS (ESI): m/z = 283.2 $[M+H]^+$.

[001477] *Step 4: Preparation of 4-(azetidine-3-yl)-2-fluoro-3-methoxypyridine*

[001478] TFA (1 mL, 13 mmol, 130 eq) was added to a solution of tert-butyl 3-(2-fluoro-3-methoxypyridin-4-yl)azetidine-1-carboxylate (28 mg, 0.99 mmol, 1 eq) in methylene chloride (1 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under vacuum to give the TFA salt of 4-(azetidine-3-yl)-2-fluoro-3-methoxypyridine (18 mg, quant., TFA salt) as a yellow oil. The crude product was used in the next step without further purification. LCMS (ESI): m/z = 183.2 $[M+H]^+$.

Synthesis of 3-(azetidin-3-yl)-4-[(2*S*)-2-(methoxymethyl)azetidin-1-yl]pyridine



[001479] *Step 1: Preparation of tert-butyl (S)-3-(4-(2-(methoxymethyl)azetidin-1-yl)pyridin-3-yl)azetidine-1-carboxylate*

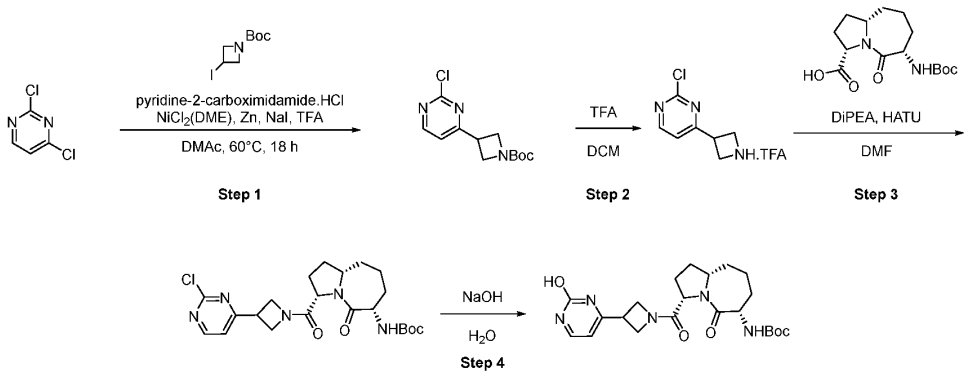
[001480] In a flame dried tube, a solution of NaHMDS (1 M in THF) (1.18 mL, 1.18 mmol, 3.0 eq) was added to a solution of (2S)-2-(methoxymethyl)azetidine (48.0 mg, 0.47 mol, 1.2 eq) in THF (1.97 mL) at room temperature. The reaction was stirred for 5 min. and

tert-butyl 3-(4-fluoropyridin-3-yl)azetidine-1-carboxylate (100 mg, 0.40 mmol, 1 eq) was added. The tube was sealed and placed in a pre-equilibrated bath at 80 °C. The reaction mixture was stirred at this temperature for 3 h. The reaction was quenched with H_2O and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried with Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by reverse phase chromatography on a 50 g C18 cartridge using a gradient of 5-95% MeCN in water (with 0.1% formic acid) to give tert-butyl (S)-3-(4-(2-(methoxymethyl)azetidin-1-yl)pyridin-3-yl)azetidine-1-carboxylate (27.3 mg, 20.6%). LCMS (ESI): m/z = 334.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.22 (d, *J* = 6.4 Hz, 1H), 6.80 (d, *J* = 6.1 Hz, 1H), 4.62 - 4.56 (m, 1H), 4.41 - 4.35 (m, 2H), 4.32 - 4.22 (m, 2H), 4.13 - 4.07 (m, 2H), 4.00 - 3.94 (m, 2H), 3.85 - 3.79 (m, 1H), 3.65 - 3.61 (m, 2H), 3.37 (s, 3H), 1.47 (s, 9H).

[001481] *Step 2: Preparation of (S)-3-(azetidin-3-yl)-4-(2-(methoxymethyl)azetidin-1-yl)pyridine*

[001482] TFA (1 mL, 13 mmol, 150 eq) was added to a solution of tert-butyl (S)-3-(4-(2-(methoxymethyl)azetidin-1-yl)pyridin-3-yl)azetidine-1-carboxylate (27 mg, 0.86 mmol, 1 eq) in methylene chloride (1 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under vacuum to give *(S)-3-(azetidin-3-yl)-4-(2-(methoxymethyl)azetidin-1-yl)pyridine* (20 mg, quant., TFA salt) as a yellow oil. The crude product was used in the next step without further purification. LCMS (ESI): m/z = 234.2 $[M+H]^+$.

Synthesis of *tert*-butyl *N*-[(3*S*,6*S*,9*aS*)-3-[3-(2-hydroxypyrimidin-4-yl)azetidine-1-carbonyl]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepin-6-yl]carbamate.



[001483] *Step 1: Preparation of tert-butyl 3-(2-chloropyrimidin-4-yl)azetidine-1-carboxylate*

[001484] To a solution of 2,4-dichloropyrimidine (150 mg, 1.00 mmol, 1 eq) and *tert*-butyl 3-iodoazetidine-1-carboxylate (185 mg, 0.6556 mmol, 1.2 eq) in *N,N*-dimethylacetamide (5 mL) in a tube were added respectively NaI (74.9 mg, 0.5 mmol, 0.5 eq), pyridine-2-carboximidamide hydrochloride (15.6 mg, 0.1 mmol, 0.1 eq), nickel(II) chloride ethylene glycol dimethyl ether complex (21.9 mg, 0.1 mmol, 0.1 eq), Zn dust (130 mg, 2.00 mmol, 2.0 eq) and TFA (11.4 mg, 0.1 mmol, 0.1 eq). The resulting mixture was degassed with nitrogen for 5 min. The tube was sealed and placed in a pre-equilibrated bath at 60°C and the reaction mixture was stirred overnight. The mixture was then filtered. The filtrate was diluted with water and the product was extracted with EtOAc (3 x). The combined organic layers were washed with water (2 x) and brine (1 x), dried with sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by normal phase chromatography on a 24 g silica gel cartridge eluting with 0-80% EtOAc in heptane to give *tert*-butyl 3-(2-chloropyrimidin-4-yl)azetidine-1-carboxylate (56.0 mg, 20.8%). 2D NOESY confirmed the desired regiochemistry. LCMS (ESI): m/z = 270.1 $[M+H]^+$.

[001485] *Step 2: Preparation of 4-(azetidin-3-yl)-2-chloropyrimidine*

[001486] To a solution of *tert*-butyl 3-(2-chloropyrimidin-4-yl)azetidine-1-carboxylate (56 mg, 0.2076 mmol, 1 eq) in DCM (5 mL) was added TFA (785 µL, 10.3 mmol, 50 eq). The solution was stirred at room temperature for 1 h. The reaction mixture was then concentrated under reduced pressure. Crude TFA salt of 4-(azetidin-3-yl)-2-chloropyrimidine was used as is in the next step. LCMS (ESI): m/z = 170.0 $[M+H]^+$.

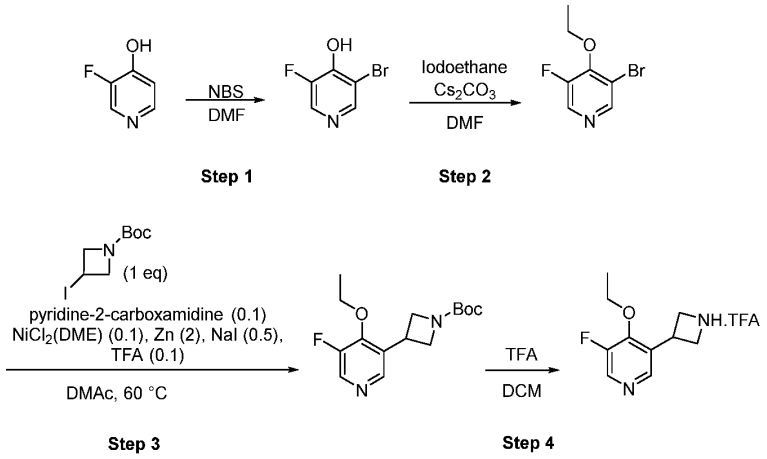
[001487] *Step 3: Preparation of tert-butyl N-[(3S,6S,9aS)-3-[3-(2-chloropyrimidin-4-yl)azetidine-1-carbonyl]-5-oxo-octahydro-1H-pyrrolo[1,2-a]azepin-6-yl]carbamate*

[001488] To a solution of 4-(azetidin-3-yl)-2-chloropyrimidine TFA salt (59 mg, 0.2076 mmol, 1 eq), (3S,6S,9aS)-6-((tert-butoxycarbonyl)amino)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic acid (103 mg, 0.3301 mmol, 1.6 eq) and DIPEA (287 µL, 1.65 mmol, 7.9 eq) in DMF (5 mL) was added HATU (163 mg, 0.4291 mmol, 2.1 eq). The reaction was stirred at room temperature for 1 h. The crude reaction mixture was purified directly by reverse phase chromatography with a 50 g C_{18} cartridge using a gradient of 5-100% MeCN in water (with 0.1% formic acid) to give *tert*-butyl *N*-[(3*S*,6*S*,9*aS*)-3-[3-(2-chloropyrimidin-4-yl)azetidine-1-carbonyl]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepin-6-yl]carbamate (87.0 mg, 90.3%). LCMS (ESI): m/z = 464.2 $[M+H]^+$.

[001489] *Step 4: Preparation of tert-butyl N-[(3S,6S,9aS)-3-[3-(2-hydroxypyrimidin-4-yl)azetidine-1-carbonyl]-5-oxo-octahydro-1H-pyrrolo[1,2-a]azepin-6-yl]carbamate*

[001490] To a solution of sodium hydroxide (7.4 mg, 0.1853 mmol, 2 eq) in water (3 mL) was added *tert*-butyl *N*-[(3*S*,6*S*,9*aS*)-3-[3-(2-chloropyrimidin-4-yl)azetidine-1-carbonyl]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepin-6-yl]carbamate (43 mg, 0.09268 mmol, 1 eq). The solution was stirred at room temperature for 5 days. The reaction mixture was then directly purified by reverse phase chromatography with a 50 g C_{18} cartridge eluting with 5-50% MeCN in water (with 0.1% formic acid) to give *tert*-butyl *N*-[(3*S*,6*S*,9*aS*)-3-[3-(2-hydroxypyrimidin-4-yl)azetidine-1-carbonyl]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepin-6-yl]carbamate (16.0 mg, 50.0%). LCMS (ESI): m/z = 446.2 $[M+H]^+$.

Synthesis of 3-(azetidin-3-yl)-4-ethoxy-5-fluoropyridine



[001491] *Step 1: Preparation of 3-bromo-5-fluoropyridin-4-ol*

[001492] In a solution of 3-fluoropyridin-4-ol (1 g, 8.84 mmol, 1 eq) in *N,N*-dimethylformamide (8 mL) was added *N*-bromosuccinimide (1.57 g, 8.84 mmol, 1.0 eq). The reaction mixture was stirred at room temperature for 2 h. The crude product 3-bromo-5-fluoropyridin-4-ol in DMF was used for the next step without further purification. LCMS (ESI): m/z = 192.0 $[M+H]^+$.

[001493] *Step 2: Preparation of 3-bromo-4-ethoxy-5-fluoropyridine*

[001494] Cesium carbonate (5.40 g, 16.6 mmol, 2.0 eq) was added to a solution of 3-bromo-5-fluoropyridin-4-ol (1.6 g, 8.33 mmol, 1 eq) and iodoethane (2.58 g, 16.6 mmol, 2 eq) in *N,N*-dimethylformamide (6 mL). The reaction mixture was stirred at room temperature for 18 h. The crude product was purified directly by reverse phase chromatography with a 100 g C_{18} cartridge using a gradient of 0-10% MeCN in water to give 3-bromo-4-ethoxy-5-fluoropyridine (858 mg, 46.8%) as a brown oil. LCMS (ESI): m/z = 220.0 $[M+H]^+$. ^1H NMR

(400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 2.2 Hz, 1H), 7.48 (dd, *J* = 6.0, 2.3 Hz, 1H), 3.94 (q, *J* = 7.3 Hz, 2H), 1.52 (t, *J* = 7.3 Hz, 3H).

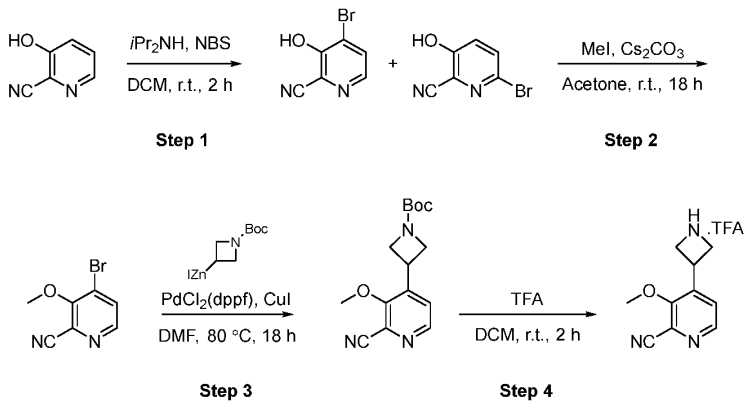
[001495] *Step 3: Preparation of tert-butyl 3-(4-ethoxy-5-fluoropyridin-3-yl)azetidine-1-carboxylate*

[001496] In a sealed tube, a mixture of 3-bromo-4-ethoxy-5-fluoropyridine (160 mg, 636 µmol, 1 eq), *tert*-butyl 3-iodoazetidine-1-carboxylate (180 mg, 636 µmol, 1 eq), nickel(II) chloride ethylene glycol dimethyl ether complex (13.9 mg, 63.6 µmol, 0.1 eq), pyridine-2-carboximidamide hydrochloride (10.0 mg, 63.6 µmol, 0.1 eq), sodium iodide (47.6 mg, 318 µmol, 0.5 eq), zinc (83.0 mg, 1.27 mmol, 2.0 eq) and TFA (7.25 mg, 63.6 µmol, 0.1 eq) in *N,N*-dimethylacetamide (3.5 mL) was degassed with N_2 for 20 min. The tube was placed in a pre-equilibrated bath at 60°C and the reaction mixture was stirred for 18 h. The mixture was filtered. The crude product was purified by reverse phase chromatography on a 50 g C_{18} cartridge eluting with 5-100% MeCN in water (with 0.1% formic acid). The combined fractions were concentrated under reduced pressure to give *tert*-butyl 3-(4-ethoxy-5-fluoropyridin-3-yl)azetidine-1-carboxylate (152 mg, 48.4%, 60% purity) as a white solid. LCMS (ESI): m/z = 297.2 $[M+H]^+$.

[001497] *Step 4: Preparation of 3-(azetidin-3-yl)-4-ethoxy-5-fluoropyridine*

[001498] To a solution of *tert*-butyl 3-(4-ethoxy-5-fluoropyridin-3-yl)azetidine-1-carboxylate (150 mg, 303 µmol) in dichloromethane (1 mL) was added TFA (0.5 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure to give 3-(azetidin-3-yl)-4-ethoxy-5-fluoropyridine (TFA salt). The crude TFA salt was used directly for the next step without further purification. LCMS (ESI): m/z = 197.2 $[M+H]^+$.

Synthesis of 4-(azetidine-3-yl)-3-methoxypyridine-2-carbonitrile



[001499] *Step 1: Preparation of 4-bromo-3-hydroxypyridine-2-carbonitrile*

[001500] In a dried flask under nitrogen was dissolved 3-hydroxypyridine-2-carbonitrile (1.14 g, 9.49 mmol, 1 eq) in methylene chloride (47.1 mL). Diisopropylamine (2.1 mL, 15.1 mmol, 1.6 eq) was slowly added at room temperature followed by *N*-bromosuccinimide (1.68 g, 9.49 mmol, 1.0 eq). The reaction mixture was stirred at room temperature for 2 h. The LCMS showed a 1:3 mixture of 4-bromo and 6-bromo regioisomers. The solvent was removed under vacuum and the crude product was purified by reverse phase chromatography on a 150 g C_{18} cartridge using a gradient of 5-95% MeCN in water (with 0.1% formic acid) to give 4-bromo-3-hydroxypyridine-2-carbonitrile (241 mg, 29 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 5.1 Hz, 1H), 7.69 (d, J = 4.9 Hz, 1H). LCMS (ESI): m/z = 199.0 $[M+H]^+$. 6-Bromo-3-hydroxypyridine-2-carbonitrile (610 mg, 32 %) was also isolated.

[001501] *Step 2: Preparation of 4-bromo-3-methoxypyridine-2-carbonitrile*

[001502] Cesium carbonate (788 mg, 2.42 mmol, 2.0 eq) was added to a solution of 4-bromo-3-hydroxypyridine-2-carbonitrile (241 mg, 1.21 mmol, 1 eq) in acetone (6.1 mL). Methyl iodide (165 µL, 2.66 mmol, 1.1 eq) was then added and the reaction mixture was stirred at room temperature for 2 h. Acetone was removed under vacuum and the residue was absorbed on silica gel. The crude product was purified by normal phase chromatography on a 40 g silica gel cartridge using a gradient of 0-100% EtOAc in heptane to give 4-bromo-3-methoxypyridine-2-carbonitrile (70.9 mg, 27.5%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 5.1 Hz, 1H), 7.75 (d, J = 5.1 Hz, 1H), 4.16 (s, 3H). LCMS (ESI): m/z = 213.0 $[M+H]^+$.

[001503] *Step 3: Preparation of tert-butyl 3-(2-cyano-3-methoxypyridin-4-yl)azetidine-1-carboxylate*

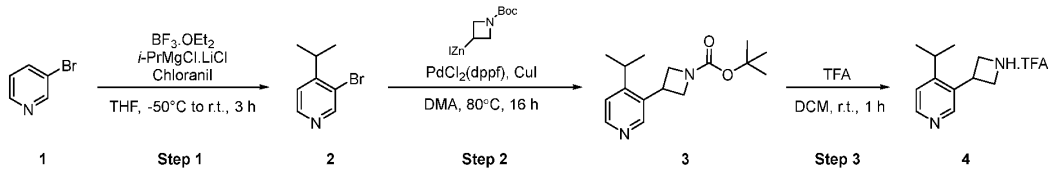
[001504] A flame-dried round bottom flask was charged with zinc (980 mg, 15 mmol, 5.0 eq.) and anhydrous DMF (1.5 mL). 1,2-Dibromoethane (33.5 µL, 0.40 mmol, 0.15 eq.) was added slowly, followed by TMSCl (50 µL, 0.40 mmol, 0.15 eq.) and the reaction was stirred for 15 min. at room temperature. A solution of N-Boc-3-iodoazetidine (849 mg, 3.0 mmol, 1 eq.) in anhydrous DMF (1.5 mL) was added dropwise. The suspension was stirred at room temperature for 1 h. A flame-dried tube was charged with 4-bromo-3-methoxypyridine-2-carbonitrile (71 mg, 0.33 mmol, 1 eq) in anhydrous DMF (3.32 mL) under nitrogen atmosphere followed by the addition of CuI (6.3 mg, 0.033 mmol, 0.1 eq) and $PdCl_2$(dppf) (24.4 mg, 0.033 mmol, 0.1 eq). The reaction was degassed with nitrogen for 10 min. and the previously prepared 1 M solution of zincate (0.6 mL,0.66 mmol, 2.0 eq) was transferred by cannula. The tube was sealed and placed in a pre-equilibrated bath at 80 °C and the reaction

was stirred for 18 h. The reaction mixture was cooled down to room temperature, filtered through a pad of Celite and the pad was washed with EtOAc. The filtrate was concentrated under vacuum. The crude product was purified by reverse phase chromatography on a 50 g C_{18} cartridge using a gradient of 5-95% MeCN in water (with 0.1% formic acid) to give tert-butyl 3-(2-cyano-3-methoxypyridin-4-yl)azetidine-1-carboxylate (65.6 mg, 68.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 4.9 Hz, 1H), 7.51 (d, J = 4.6 Hz, 1H), 4.36 (t, J = 8.2 Hz, 2H), 4.14 (s, 2H), 4.07 - 3.92 (m, 3H), 1.47 (s, 9H). LCMS (ESI): m/z = 290.2 $[M+H]^+$.

[001505] *Step 4: Preparation of 4-(azetidine-3-yl)-3-methoxypyridine-2-carbonitrile*

[001506] TFA (1 mL, 13 mmol, 52 eq) was added to a solution of tert-butyl 3-(2-fluoro-3-methoxypyridin-4-yl)azetidine-1-carboxylate (65 mg, 0.25 mmol, 1 eq) in methylene chloride (1 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under vacuum to give 4-(azetidine-3-yl)-3-methoxypyridine-2-carbonitrile (47 mg, quant., TFA salt) as a yellow oil. The crude product was used in the next step without further purification. LCMS (ESI): m/z = 190.2 $[M+H]^+$.

Synthesis of 3-(azetidin-3-yl)-4-isopropylpyridine



[001507] *Step 1: Preparation of 3-bromo-4-(propan-2-yl)pyridine*

[001508] In a dried flask, boron trifluoride diethyl etherate (492 mg, 3.47 mmol, 1.1 eq) was added to a solution of 3-bromopyridine (500 mg, 3.16 mmol, 1 eq) in THF (6.32 mL) at 0 °C. The reaction mixture was stirred 15 min. at 0°C. The reaction mixture was then cooled down to -50 °C and isopropylmagnesium chloride lithium chloride complex solution (1.3 M in THF) (2.9 mL, 3.79 mmol, 1.2 eq) was added dropwise. The reaction mixture was stirred at -50°C for 30 min. Chloranil (1.55 g, 6.32 mmol, 2 eq) was then added and the mixture was warmed up to room temperature. The mixture was stirred for 2 h at room temperature. A 28% aqueous solution of ammonium hydroxide (5 mL) was then added. The product was extracted with Et_2O (3 x). The combined organic layers were dried with magnesium sulfate and filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure. The crude residue was purified by normal phase chromatography on a silica gel cartridge eluting with a gradient of 0-100% EtOAc in heptane to afford 3-bromo-4-(propan-2-yl)pyridine (210 mg, 33.2%) as a red brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.45 (d, J = 4.9 Hz,

1H), 7.22 (d, J = 5.1 Hz, 1H), 3.33 (m, 1H), 1.27 (d, J = 6.8 Hz, 6H). LCMS (ESI): m/z = 200.0 $[M+H]^+$.

[001509] *Step 2: Preparation of tert-butyl 3-[4-(propan-2-yl)pyridin-3-yl]azetidine-1-carboxylate*

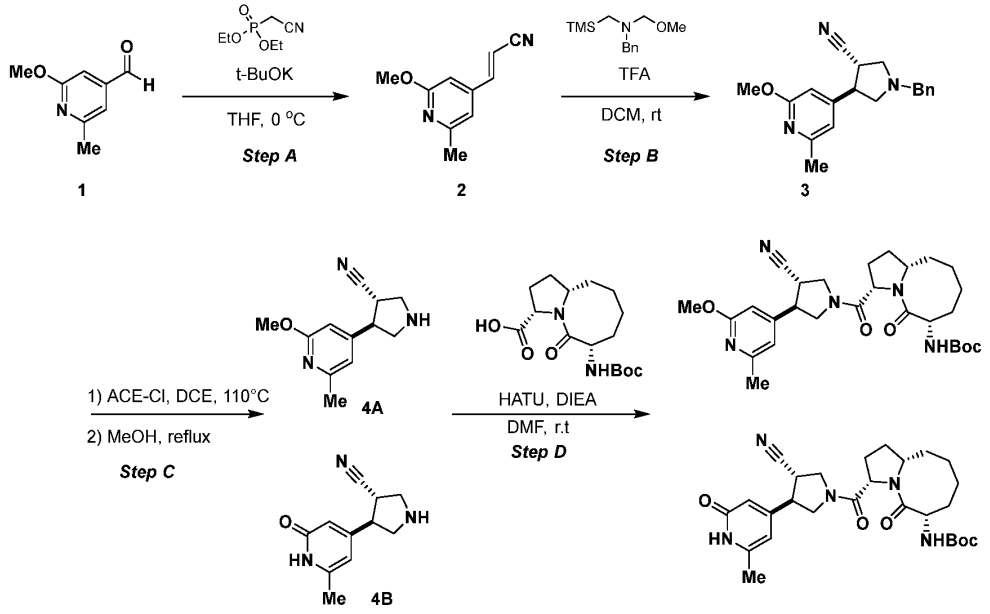
[001510] A flame-dried round bottom flask was charged with zinc (84.3 mg, 1.29 mmol, 2.0 eq.) and anhydrous N,N-dimethylacetamide (1 mL). 1,2-Dibromoethane (24.2 mg, 129 µmol, 0.2 eq.) was added slowly, followed by TMSCl (14 mg, 129 µmol, 0.2 eq.) and the reaction was stirred for 15 min. at room temperature. A solution of N-Boc-3-iodoazetidine (365 mg, 1.29 mmol, 2 eq.) in anhydrous N,N-dimethylacetamide (1 mL) was added dropwise. The suspension was stirred at room temperature for 1 h. A flame-dried tube was charged with 3-bromo-4-(propan-2-yl)pyridine (130 mg, 0.65 mmol, 1 eq) in anhydrous N,N-dimethylacetamide (2 mL) under nitrogen atmosphere followed by the addition of CuI (12.3 mg, 0.065 mmol, 0.1 eq) and $PdCl_2$(dppf) (47.5 mg, 0.065 mmol, 0.1 eq). The reaction was degassed with nitrogen for 15 min. and the previously prepared solution of zincate (2 mL, 1.29 mmol, 2.0 eq) was transferred by cannula. The tube was sealed and placed in a pre-equilibrated bath at 80°C and the reaction was stirred for 16 h. The reaction mixture was cooled down to room temperature, filtered through a pad of Celite and the pad was washed with EtOAc. The filtrate was concentrated under vacuum. The crude product was purified by reverse phase chromatography on a 50 g C18 cartridge using a gradient of 5-95% MeCN in water (with 0.1% formic acid) to give tert-butyl 3-[4-(propan-2-yl)pyridin-3-yl]azetidine-1-carboxylate (64.9 mg, 24.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.49 (d, J = 5.1 Hz, 1H), 8.21 (br. s., 1H), 4.42 - 4.33 (m, 2H), 4.12 - 4.05 (m, 2H), 3.78 - 3.66 (m, 1H), 3.01 - 2.92 (m, 1H), 1.48 (s, 9H), 1.23 (d, J = 6.6 Hz, 6H). LCMS (ESI): m/z = 277.2 $[M+H]^+$.

[001511] *Step 3: Preparation of 3-(azetidin-3-yl)-4-isopropylpyridine*

[001512] TFA (0.73 mL, 9.63 mmol, 41 eq) was added to a solution of tert-butyl 3-[4-(propan-2-yl)pyridin-3-yl]azetidine-1-carboxylate (65 mg, 0.235 mmol, 1 eq) in methylene chloride (2.3 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under vacuum to give 3-(azetidin-3-yl)-4-isopropylpyridine (68 mg, quant., TFA salt) as a yellow oil. The crude product was used in the next step without further purification. LCMS (ESI): m/z = 177.2 $[M+H]^+$.

Synthesis of tert-butyl ((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(2-methoxy-6-methylpyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate, tert-butyl ((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-methoxy-6-methylpyridin-4-yl)pyrrolidine-

1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate, tert-butyl ((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(6-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate, and tert-butyl ((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(6-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate



[001513] *STEP A: Preparation of (E)-3-(2-methoxy-6-methylpyridin-4-yl)acrylonitrile*

[001514] To a solution of diethyl (cyanomethyl)phosphonate (102 mg, 581 µmol, 1.1 eq.) in THF (16 mL) was added t-BuOK (59 mg, 529 µmol, 1.0 eq.) at 0 °C. The solution was stirred at 0 °C for 10 min, then 2-methoxy-6-methylisonicotinaldehyde (80 mg, 529 µmol, 1.0 eq.) was added to the solution at 0 °C. the solution was stirred at 0 °C for 10 min. After completion, the reaction mixture was diluted with H_2O (10 mL), extracted with EtOAc (10 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford (E)-3-(2-methoxy-6-methylpyridin-4-yl)acrylonitrile (135 mg, quant.) as a white solid which was used directly in next step without further purification. LCMS (ESI): m/z =175 $[M+H]^+$.

[001515] *STEP B: Preparation of racemic-(3S,4R)-1-benzyl-4-(2-methoxy-6-methylpyridin-4-yl)pyrrolidine-3-carbonitrile*

[001516] To a solution of (E)-3-(2-methoxy-6-methylpyridin-4-yl)acrylonitrile (183 mg, 774 µmol, 1 eq.) in DCM (10 mL) benzyl(methoxymethyl)[(trimethylsilyl)methyl]amine (183 mg, 774 µmol, 1 eq.) was

added TFA (0.02 mL) at room temperature. The solution was stirred for at 25 °C for 40 min. After completion, the reaction mixture was diluted with H_2O (10 mL), extracted with EtOAc (10 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford racemic-(3S,4R)-1-benzyl-4-(2-methoxy-6-methylpyridin-4-yl)pyrrolidine-3-carbonitrile (230 mg, quant.) as a white solid, which was used directly in next step without further purification. LCMS (ESI): m/z = 308 $[M+H]^+$.

[001517] *STEP C: Preparation of racemic-(3S,4R)-4-(2-methoxy-6-methylpyridin-4-yl)pyrrolidine-3-carbonitrile and racemic-(3S,4R)-4-(6-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-3-carbonitrile*

[001518] To a solution of racemic-(3S,4R)-1-benzyl-4-(2-methoxy-6-methylpyridin-4-yl)pyrrolidine-3-carbonitrile (230 mg, 0.75 mmol, 1 eq.) in DCE (5 mL) was added 1-chloroethyl carbonochloridate (536 mg, 3.8 mmol, 5 eq.). The solution was stirred at 110 °C for 24 h, then concentrated under vacuum, the crude product was dissolved in MeOH (5 mL), the solution was stirred at 60 °C for 1 h. LCMS show that the reaction was completed and DP found. the solution was cooled to room temperature, then under reduced pressure to afford a mixture of racemic-(3S,4R)-4-(2-methoxy-6-methylpyridin-4-yl)pyrrolidine-3-carbonitrile and racemic-(3S,4R)-4-(6-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-3-carbonitrile (mixture of **4A, 4B**, 230 mg, quant.) as a yellow oil which was used directly in next step without further purification. LCMS (ESI): m/z = 218 & 204 $[M+H]^+$

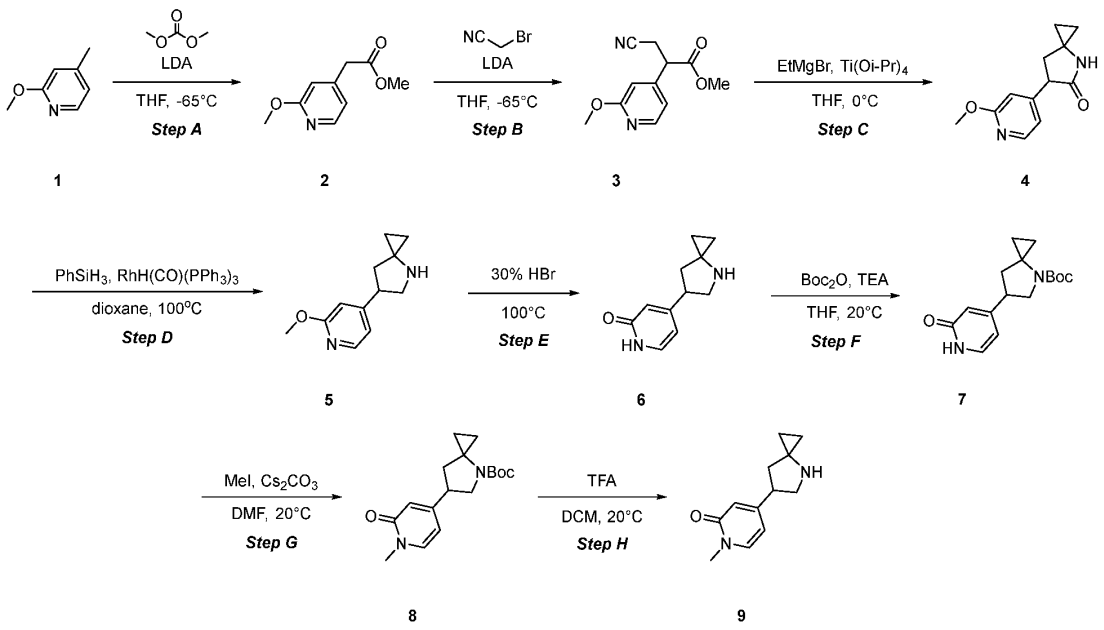
[001519] *STEP D: Preparation tert-butyl ((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(2-methoxy-6-methylpyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate, tert-butyl ((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-methoxy-6-methylpyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate, tert-butyl ((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(6-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate, and tert-butyl ((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(6-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate*

[001520] To a solution of (3S,6S,10aS)-6-((tert-butoxycarbonyl)amino)-5-oxodecahydropyrrolo[1,2-a]azocine-3-carboxylic acid (342 mg, 1.05 mmol, 1 eq.) in DMF (5 mL) were added DIEA (271 mg, 2.1 mmol, 2.0 eq), HATU (441 mg, 1.16 mmol, 1.1 eq.) and afford a mixture of racemic-(3S,4R)-4-(2-methoxy-6-methylpyridin-4-yl)pyrrolidine-3-carbonitrile and racemic-(3S,4R)-4-(6-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-3-carbonitrile (230 mg, 1.05 mmol, 1 eq.). The solution was stirred at 25 °C for 1 hr. After

completion, the reaction mixture was purified by prep-HPLC to afford a mixture of tert-butyl ((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(2-methoxy-6-methylpyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate and tert-butyl ((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-methoxy-6-methylpyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate (94 mg, 178 µmol, 17%) as a yellow oil. LCMS (ESI): m/z = 526 $[M+H]^+$.

[001521] Additionally, tert-butyl ((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(6-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate and tert-butyl ((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(6-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamate (230 mg, 449 µmol, 43%) as a yellow oil. LCMS (ESI): m/z = 512 $[M+H]^+$.

Synthesis of 4-(4-azaspiro[2.4]heptan-6-yl)pyridin-2(1H)-one and 1-methyl-4-(4-azaspiro[2.4]heptan-6-yl)pyridin-2(1H)-one:



[001522] *STEP A: methyl 2-(2-methoxypyridin-4-yl)acetate*

[001523] To a solution of 2-methoxy-4-methylpyridine (**1,** 50 g, 406 mmol, 1.0 eq.) in THF (500 mL) was added dropwise LDA (243 mL, 485 mmol, 2M, 1.2 eq.) at -65 °C. The reaction solution was stirred at -65 °C for 1 h and dimethyl carbonate (40 g, 445 mmol, 1.1 eq.) was added into the reaction mixture. After addition, the mixture was stirred at -65 °C for an additional 1 hr. After completion, the reaction mixture was quenched with saturated NH_4Cl (aq.) solution (500 mL) and extracted with EtOAc (500 mL x 3). The organic layers

were combined and washed with brine (500 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford methyl 2-(2-methoxypyridin-4-yl)acetate (**2,** 35 g, 192 mmol, 47%) as a yellow oil. LCMS (ESI): *m/z* = 182.2 $[M+H]^+$.
^1H NMR (400 MHz, $CDCl_3$) δ 8.14-8.04 (m, 1H), 6.84-6.77 (m, 1H), 6.67 (s, 1H), 3.96-3.90 (m, 3H), 3.73-3.68 (m, 3H), 3.58 (s, 2H).

[001524] *STEP B: methyl 3-cyano-2-(2-methoxypyridin-4-yl)propanoate*

[001525] To a solution of methyl 2-(2-methoxypyridin-4-yl)acetate (**2,** 35 g, 192 mmol, 1.0 eq.) in THF (500 mL) was added dropwise LDA (148 mL, 296 mmol, 2M, 1.5 eq.) at -65 °C under N_2. The reaction solution was stirred at -65 °C for 1 h and 2-bromoacetonitrile (28.4 g, 239 mmol, 1.2 eq.) was added into the reaction mixture. After addition, the mixture was stirred at -65 °C for an additional 1 hr. After completion, the reaction mixture was quenched with saturated NH_4Cl (aq.) solution (500 mL) and extracted with EtOAc (300 mL x 3). The organic layers were combined and washed with brine (500 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford methyl 3-cyano-2-(2-methoxypyridin-4-yl)propanoate (**3,** 39 g, 177 mmol, 92%) as a yellow oil. LCMS (ESI): *m/z* = 221.1 $[M+H]^+$.
^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 5.3 Hz, 1H), 6.79 (dd, *J* = 5.3, 1.5 Hz, 1H), 6.66 (d, *J* = 1.4 Hz, 1H), 3.94 (s, 3H), 3.88 (t, *J* = 7.6 Hz, 1H), 3.75 (s, 3H), 3.06-2.97 (m, 1H), 2.87-2.77 (m, 1H).

[001526] *STEP C: 6-(2-methoxypyridin-4-yl)-4-azaspiro[2.4]heptan-5-one*

[001527] To a solution of methyl 3-cyano-2-(2-methoxypyridin-4-yl)propanoate (**3,** 39 g, 177 mmol, 1.0 eq.) and Titanium tetraisopropanolate (23.3 g, 82 mmol, 0.5 eq.) in THF (800 mL) was added dropwise EtMgBr (134 mL, 402 mmol, 3M, 2.3 eq.) at 0 °C. After addition, the reaction mixture was stirred at 0 °C for 1 hr. After completion, the reaction mixture was quenched with HCl aqueous solution (250 mL, 2N) and filtered, The filtrate was extracted with EtOAc (500 mL x 3). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 6-(2-methoxypyridin-4-yl)-4-azaspiro[2.4]heptan-5-one (**4,** 12 g, 54.8 mmol, 31%) as a white solid. LCMS (ESI): *m/z* = 219.2 $[M+H]^+$.
^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 5.3 Hz, 1H), 6.88 (dd, *J* = 5.3, 1.4 Hz, 1H), 6.81-6.65 (m, 2H), 3.93 (s, 3H), 3.87-3.78 (m, 1H), 2.58-2.48 (m, 1H), 2.38-2.27 (m, 1H), 0.98-0.92 (m, 1H), 0.91-0.85 (m, 1H), 0.81-0.72 (m, 2H).

[001528] *STEP D: 6-(2-methoxypyridin-4-yl)-4-azaspiro[2.4]heptane*

[001529] To a solution of 6-(2-methoxypyridin-4-yl)-4-azaspiro[2.4]heptan-5-one (**4,** 11 g, 50.2 mmol, 1.0 eq.) and methanidylidyneoxidanium tris(triphenylphosphane) hydrogen rhodium (2.31 g, 2.52 mmol, 0.05 eq.) in dioxane (200 mL) was added phenylsilane (33 g, 306 mmol, 6.0 eq.). The reaction solution was stirred at 100 °C for 12 h. After completion, the reaction mixture was cooled to 20 °C and poured into HCl aqueous solution (100 mL, 2N). The resulting solution was stirred at 20 °C for 1 h and filtered. The filtrate was concentrated under reduced pressure to afford 6-(2-methoxypyridin-4-yl)-4-azaspiro[2.4]heptane (**5,** 11 g, 53.7 mmol, quant.) as a brown solid, which was used in next step directly without further purification. LCMS (ESI): *m/z* = 205.2[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 5.3 Hz, 1H), 6.79 (dd, *J* = 5.3, 1.4 Hz, 1H), 6.64 (s, 1H), 3.93 (s, 3H), 3.49-3.36 (m, 2H), 3.03-2.91 (m, 1H), 2.19-2.15 (m, 1H), 1.97-1.87 (m, 1H), 0.85-0.80 (m, 2H), 0.66-0.58 (m, 2H).

[001530] *STEP E: 4-(4-azaspiro[2.4]heptan-6-yl)pyridin-2(1H)-one (HBr salt)*

[001531] A solution of 6-(2-methoxypyridin-4-yl)-4-azaspiro[2.4]heptane (**5,** 11 g, 53.7 mmol, 1.0 eq.) in a mixture of 30% HBr/AcOH (50 mL) and 30% HBr/H_2O (100 mL) was stirred at 100 °C for 12 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was neutralized carefully with $NaHCO_3$ (aq.) until the pH was adjusted to pH = 7. The mixture was concentrated under reduced pressure to afford crude 4-(4-azaspiro[2.4]heptan-6-yl)pyridin-2(1*H*)-one (**6,** 11 g, 57.6 mmol, quant.) as a yellow solid, which was used in next step directly without further purification. LCMS (ESI): *m/z* = 191.2[M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.48 (s, 1H), 7.37 (d, *J* = 6.8 Hz, 1H), 6.29 (d, *J* = 0.6 Hz, 1H), 6.22 (dd, *J* = 6.8, 1.7 Hz, 1H), 3.71-3.62 (m, 1H), 3.56-3.41 (m, 1H), 3.26-3.19 (m, 1H), 2.24-2.03 (m, 2H), 1.21-1.02 (m, 2H), 0.94-0.78 (m, 2H).

[001532] *STEP F: tert-butyl 6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carboxylate*

[001533] To a mixture of 4-(4-azaspiro[2.4]heptan-6-yl)pyridin-2(1*H*)-one (**6,** 11 g, 57.9 mmol, 1.0 eq.) and TEA (15 mL, 108 mmol, 1.9 eq.) in THF (200 mL) was added Boc_2O (20 g, 91.7 mmol, 1.6 eq.). The resulting mixture was stirred at 20 °C for 12 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford *tert*-butyl 6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carboxylate (**7,** 4 g, 13.7 mmol, 24%) as a yellow solid. LCMS (ESI): *m/z* = 291 [M+H]$^+$.

[001534] *STEP G: tert-butyl 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carboxylate*

[001535] To a solution of *tert*-butyl 6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carboxylate (**7,** 4 g, 13.7 mmol, 1.0 eq.) and Cs_2CO_3 (14 g, 42.9 mmol, 3.1 eq.) in DMF (100 mL) was added MeI (2 mL, 32.1 mmol, 2.3 eq.). The resulting mixture was stirred at 20 °C for 12 h. After completion, the mixture was diluted with water (100 mL) and extracted with EtOAc (150 mL ×3). The organic layers were combined and washed with brine (100 mL x 2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford *tert*-butyl 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carboxylate (**8,** 3.0 g, 9.84 mmol, 72%) as a yellow oil. LCMS (ESI) *m/z* = 305 $[M+H]^+$.

[001536] *STEP H: 1-methyl-4-(4-azaspiro[2.4]heptan-6-yl)pyridin-2(1H)-one*

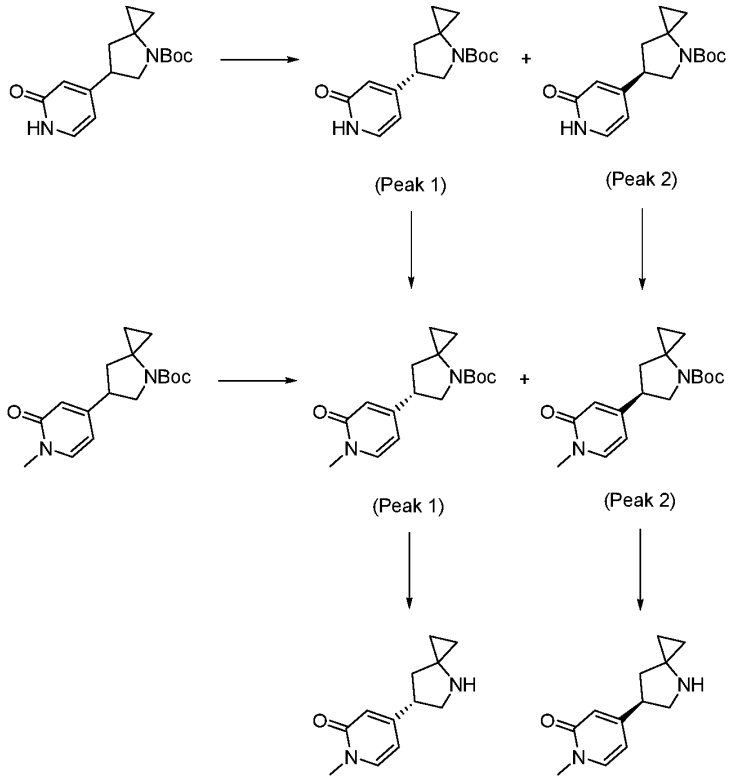
[001537] To a solution of tert-butyl 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carboxylate (**8,** 3.0 g, 9.84 mmol, 1.0 eq.) in DCM (30 mL) was added TFA (6 mL) and the resulting mixture was stirred at 20 °C for 1 hr. After completion, the mixture was concentrated under reduced pressure to give crude 1-methyl-4-(4-azaspiro[2.4]heptan-6-yl)pyridin-2(1*H*)-one (**9,** 2 g, 9.76 mmol, quant.) as a red oil, which was used in next step directly without further purification. LCMS (ESI): *m/z* = 205 $[M+H]^+$.

[001538] *tert*-butyl 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carboxylate was prepared as described above to afford a racemic mixture. The individual stereoisomers were purified by chiral SFC conditions and absolute configuration was assigned as drawn below, based on the comparison of experimental vibrational circular dichroism (VCD) spectra with theoretical VCD spectra obtained from DFT calculations. Preparative separation method for *tert*-butyl 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carboxylate:

[001539] Instrument: Waters Thar 80 preparative SFC; Column: ChiralPak AD, 250×21.2mm I.D., 5μm; Mobile phase: A for CO_2 and B for methanol (0.1% NH_3H_2O); Gradient: B 40%; Flow rate: 40 mL/min; Back pressure: 100 bar; Column temperature: 35 °C; Wavelength: 220 nm; Cycle-time: 10 min.

[001540] (S)-1-methyl-4-(4-azaspiro[2.4]heptan-6-yl)pyridin-2(1H)-one and (R)-1-methyl-4-(4-azaspiro[2.4]heptan-6-yl)pyridin-2(1H)-one were each prepared with the procedure described for racemic 1-methyl-4-(4-azaspiro[2.4]heptan-6-yl)pyridin-2(1H)-one utilizing the appropriate starting materials.

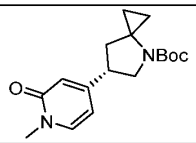
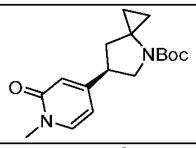
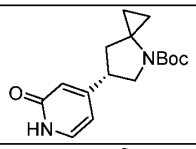
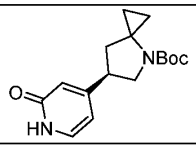
[001541] tert-butyl 6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carboxylate was prepared as described above to afford a racemic mixture. The individual stereoisomers were purified by chiral SFC conditions and absolute configuration was assigned as drawn below. Assignment of absolute configuration was verified by independent synthesis of enantiopure tert-butyl (S)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carboxylate via alkylation of tert-butyl (S)-6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carboxylate, and of enantiopure tert-butyl (R)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carboxylate via alkylation of tert-butyl (R)-6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carboxylate, with the procedures described for racemic *tert*-butyl 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carboxylate.



[001542] Preparative separation method for tert-butyl 6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carboxylate:

[001543] Instrument: SHIMADZU PREP SOLUTION SFC; Column: ChiralPak AD, 250×30mm I.D., 5μm; Mobile phase: A for CO_2 and B for methanol (0.1% NH_3H_2O); Gradient: B 40%; Flow rate: 60 mL/min; Back pressure: 100 bar; Column temperature: 35 °C; Wavelength: 220 nm; Cycle-time: 7 min.

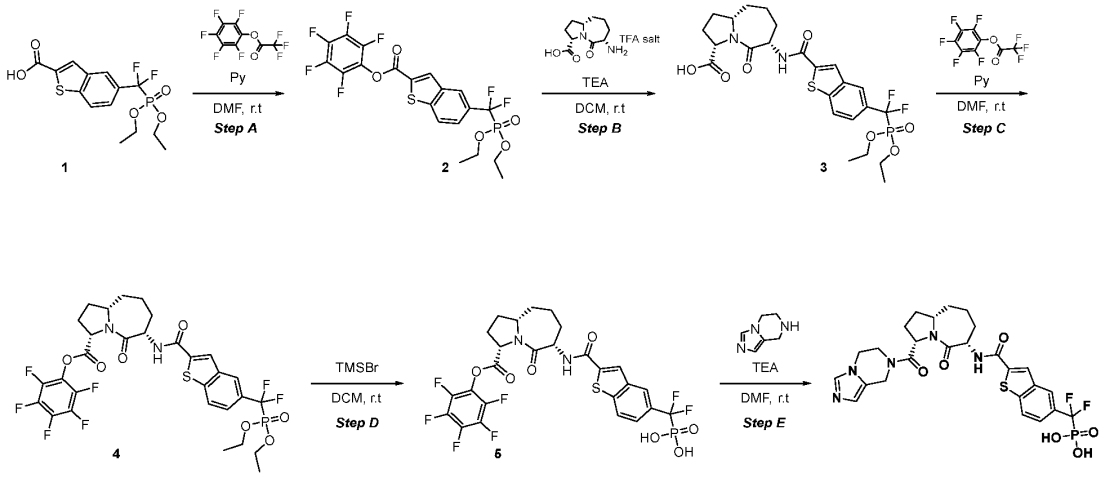
Table 106

Name	Structure	LCMS
tert-butyl (S)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carboxylate (Peak 1)		305 $[M+H]^+$
tert-butyl (R)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carboxylate (Peak 2)		305 $[M+H]^+$
tert-butyl (S)-6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carboxylate (Peak 1)		291 $[M+H]^+$
tert-butyl (R)-6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carboxylate (Peak 2)		291 $[M+H]^+$

[001544] (S)-4-(4-azaspiro[2.4]heptan-6-yl)pyridin-2(1H)-one and (R)-4-(4-azaspiro[2.4]heptan-6-yl)pyridin-2(1H)-one were each prepared with the procedure described for 1-methyl-4-(4-azaspiro[2.4]heptan-6-yl)pyridin-2(1H)-one utilizing the appropriate starting materials.

Syntheses of Phosphonic Acid Analogues: General Scheme 3

Synthesis of (difluoro(2-(((3S,6S,9aS)-5-oxo-3-(5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine-7-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphon2ic acid (203)



[001545] STEP A: *perfluorophenyl 5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate*

[001546] To a solution of 5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid (1, 3.64 g, 9.99 mmol, 1 eq.) in DMF (30 mL) were added pyridine (1.60 mL, 19.9 mmol, 2 eq.) and 2,3,4,5,6-pentafluorophenyl 2,2,2-trifluoroacetate (2.55 mL, 14.9 mmol, 1.5 eq.) under N_2 with stirring. The resulting mixture was stirred at room temperature for 1 hr. After completion, the reaction mixture was poured into H_2O (20 mL), then extracted with EtOAc (50 mL x 3). The organic layers were combined and washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford perfluorophenyl 5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (2, 5.20 g, quant.) as a white solid. LCMS (ESI) *m/z* = 531.0 $[M+H]^+$.

[001547] STEP B: *(3S,6S,9aS)-6-(5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxamido)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic acid*

[001548] To a solution of perfluorophenyl 5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (2, 5.3 g, 9.99 mmol, 1 eq.) in DCM (50 mL) were added TEA (4.05 g, 40.1 mmol, 4.0 eq.) and (3S,6S,9aS)-6-amino-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic acid (2.3 g, 10.8 mmol, 1.1 eq.) under N_2 with stirring. The resulting mixture was stirred at room temperature for 2 h. After completion, the reaction mixture was poured into H_2O (20 mL), then extracted with EtOAc (50 mL x 3). The organic layers were combined and washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford (3S,6S,9aS)-6-{5-[(diethoxyphosphoryl)difluoromethyl]-1-benzothiophene-2-amido}-5-oxo-octahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic acid (**3**, 5.0 g, quant.) as a white solid, which was used in next step directly without further purification. LCMS (ESI) *m/z* = 559.1$[M+H]^+$.

[001549] STEP C: *perfluorophenyl (3S,6S,9aS)-6-(5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxamido)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate*

[001550] To a solution of (3S,6S,9aS)-6-{5-[(diethoxyphosphoryl)difluoromethyl]-1-benzothiophene-2-amido}-5-oxo-octahydro-1H-pyrrolo[1,2-a]azepine-3- carboxylic acid (3, 5.58 g, 9.99 mmol, 1 eq.) in DMF (35 mL) were added pyridine (1.60 mL, 19.9 mmol, 2 eq.) and 2,3,4,5,6-pentafluorophenyl 2,2,2- trifluoroacetate (2.55 mL, 14.9 mmol, 1.5 eq.) under

N_2 with stirring. The resulting mixture was stirred at room temperature for 0.5 h. After completion, the reaction mixture was poured into H_2O (20 mL), then extracted with EtOAc (50 mL x 3). The organic layers were combined and washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford perfluorophenyl (3S,6S,9aS)-6-(5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxamido)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate (4, 5.50 g, 7.59 mmol, 76%) as a white solid. LCMS (ESI) *m/z* = 725.3 $[M+H]^+$.

[001551] STEP D: *(difluoro(2-(((3S,6S,9aS)-5-oxo-3-((perfluorophenoxy)carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid*

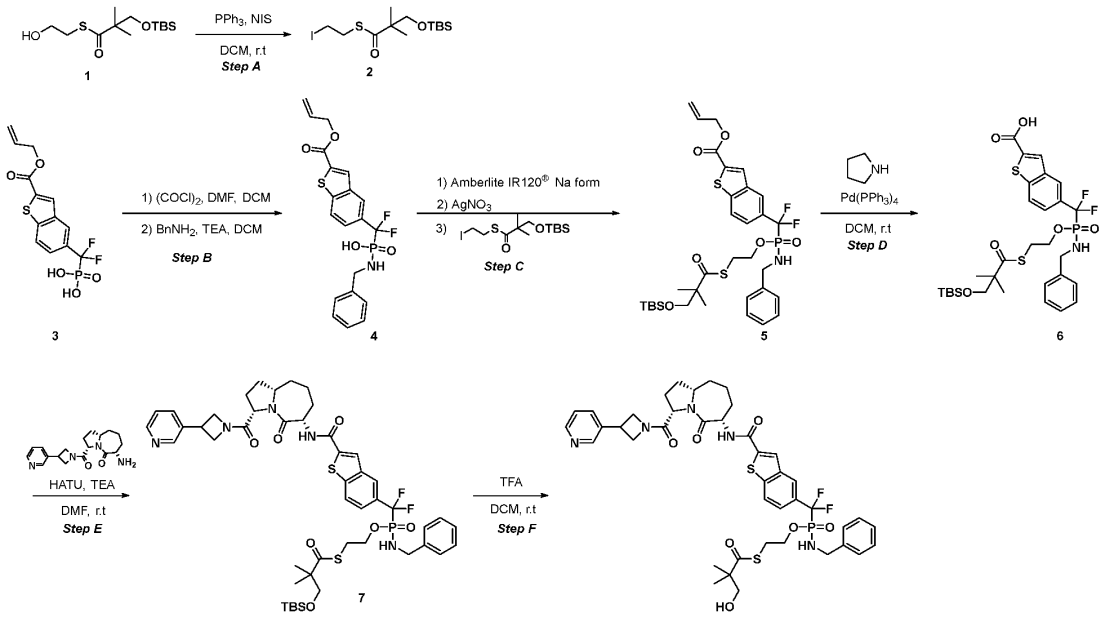
[001552] To a solution of perfluorophenyl (3S,6S,9aS)-6-(5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxamido)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylate (4, 2.5 g, 3.45 mmol, 1 eq.) in DCM (10 mL) was added TMSBr (455 µL, 3.45 mmol, 1.0 eq.) under N_2 with stirring. The resulting mixture was stirred at room temperature overnight. After completion, the reaction mixture was poured into H_2O (20 mL), then extracted with DCM (50 mL x 3). The organic layers were combined and washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford (difluoro(2-(((3S,6S,9aS)-5-oxo-3-((perfluorophenoxy)carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (5, 2.10 g, quant.) as a yellow solid, which was used in next step directly without further purification. LCMS (ESI) *m/z* = 669.2 $[M+H]^+$.

[001553] STEP E: *(difluoro(2-(((3S,6S,9aS)-5-oxo-3-(5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine-7-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid*

[001554] To a solution of 5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine (50 mg, 405 µmol, 1 eq.) in DMF (2 mL) were added (difluoro(2-(((3S,6S,9aS)-5-oxo-3-((perfluorophenoxy)carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (5, 324 mg, 485 µmol, 1.2 eq.) and TEA (168 µL, 1.21 mmol, 3.0 eq.) under N_2 with stirring. The resulting mixture was stirred at room temperature overnight. After completion, the reaction mixture was poured into H_2O (20 mL), then extracted with EtOAc (50 mL x 3). The organic layers were combined and washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced

pressure. The residue was purified by prep-HPLC to afford (difluoro(2-(((3S,6S,9aS)-5-oxo-3-(5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine-7-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (45.2 mg, 74.3 μmol, 18%) as a white solid. ^{1}H NMR (400 MHz, DMSO) δ8.80-8.69 (m, 1H), 8.48-8.33 (m, 1H), 8.23-8.19 (m, 1H), 8.04-7.98 (m, 2H), 7.56 (d, J = 8.3 Hz, 1H), 7.05 (s, 1H), 5.04-4.92 (m, 2H), 4.65 (t, J = 8.7 Hz, 1H), 4.45-4.28 (m, 1H), 4.26-4.00 (m, 4H), 3.86-3.81 (m, 1H), 2.25-1.72 (m, 10H). LCMS (ESI): m/z =608.0 [M+H]$^+$.

Synthesis of S-(2-(((benzylamino)(difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)oxy)ethyl) 3-hydroxy-2,2-dimethylpropanethioate (204)



[001555] *STEP A: S-(2-iodoethyl) 3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanethioate*

[001556] To a solution of S-(2-hydroxyethyl) 3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanethioate (**1**, 700 mg, 2.39 mmol, 1 eq.) in DCM (20 mL) was added PPh_3 (626 mg, 2.39 mmol, 1.0 eq.) in portion wise at 0 °C and the resulting mixture was stirred for 30 min. Then NIS (537 mg, 2.39 mmol, 1.0 eq) was added dropwise at 0 °C and the reaction mixture was stirred at 0 °C for 1 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give S-(2-iodoethyl) 3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanethioate (**2**,

700 mg, 1.73 mmol, 73%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (s, 2H), 3.31-3.24 (m, 2H), 3.23-3.15 (m, 2H), 1.17 (s, 6H), 0.84 (s, 9H), 0.00 (s, 6H).

[001557] *STEP B: P-((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)difluoromethyl)-N-benzylphosphonamidic acid*

[001558] Oxalyl chloride (1.01 g, 8.00 mmol, 5 eq.) was added dropwise to the solution of ((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid (**3,** 150 mg, 0.4307 mmol, 1 eq.) in dry DCM (10 mL) and DMF (1 drop) at 0 °C. The reaction mixture was stirred at 40 °C for an additional 2 h. The reaction was monitored by pipetting out a small amount of crude sample and quenching it with MeOH to ensure bis-Cl phosphoryl chloride had been formed completely (bis-methoxy phosphonate was observed by LCMS). After completion, the excess oxalyl chloride and solvent were removed under reduced pressure. The residue was re-dissolved in anhydrous DCM (10 mL), then added to a mixture of phenylmethanamine (46.0 mg, 430 µmol, 1 eq.) and TEA (217 mg, 2.15 mmol, 5 eq.) in anhydrous DCM (10 mL) at 0 °C. The reaction was allowed to warm to 25 °C and stirred for an additional 2 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give P-((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)difluoromethyl)-N-benzylphosphonamidic acid (**4**, 100 mg, 0.23 mmol, 53%) as a colorless oil. LCMS (ESI): *m/z* = 438 $[M+H]^+$.

[001559] *STEP C: allyl 5-(((benzylamino)(2-((3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate*

[001560] NaOH (18.2 mg, 457 µmol, 2 eq) in water (2 mL) was added dropwise to a stirred suspension of P-((2-((allyloxy)carbonyl)benzo[b]thiophen-5-yl)difluoromethyl)-N-benzylphosphonamidic acid (**4**, 100 mg, 0.23 mmol, 1 eq.) in H_2O (6 mL). When the mixture became clear (pH~9), silver nitrate (85.2 mg, 502 µmol, 2.2 eq.) was added. After stirring at 0 °C for 2 h, the gray precipitate was collected by filtration and dried under vacuum. The powder was suspended in dry Toluene (1 mL) and S-(2-iodoethyl) 3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanethioate (**2**, 1.68 g, 6.96 mmol, 30 eq.) was added. The mixture was stirred at 80 °C for 24 h. After filtration, the solvent was removed in vacuo. The crude residue was directly purified by flash column chromatography on silica gel to give allyl 5-(((benzylamino)(2-((3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (**5**, 40.0 mg, 56 µmol, 25%) as a white solid. LCMS (ESI): *m/z* = 734.2 $[M+Na]^+$.

[001561] *STEP D: 5-(((benzylamino)(2-((3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid*

[001562] To a solution of allyl 5-(((benzylamino)(2-((3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylate (**5**, 35 mg, 49 μmol, 1 eq.) in DCM (1 mL) were added $Pd(PPh_3)_4$ (2.83 mg, 2.45 μmol, 0.05 eq.) and pyrrolidine (3 mg, 49.1 μmol, 1 eq.). The mixture was purged and degassed with N_2 (three times), then stirred at 25 °C for 2 h. After completion, the mixture was concentrated under reduced pressure. The residue was purified by Biotage® C18 column chromatography to give 5-(((benzylamino)(2-((3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid (**6,** 20.0 mg, 30 μmol, 61%) as a colorless oil. LCMS (ESI): *m/z* = 672.1 $[M+H]^+$.

[001563] *STEP E: S-(2-(((benzylamino)(difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)oxy)ethyl) 3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanethioate*

[001564] To a solution of (3S,6S,9aS)-6-amino-3-[3-(pyridin-3-yl)azetidine-1-carbonyl]-octahydro-1H-pyrrolo[1,2-a]azepin-5-one (10 mg, 30 μmol, 1 eq.), TEA (15 mg, 150 μmol, 5 eq.) and 5-(((benzylamino)(2-((3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanoyl)thio)ethoxy)phosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid (**6,** 20 mg, 30 μmol, 1 eq.) in DMF (1 mL) was added HATU (12 mg, 30 μmol, 1.0 eq.) and the reaction mixture was stirred at room temperature overnight under N_2. After completion, the reaction mixture was purified by prep-HPLC to afford S-(2-(((benzylamino)(difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)oxy)ethyl) 3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanethioate (**7,** 5 mg, 6 μmol, 20%). LCMS (ESI): *m/z* = 982 $[M+H]^+$.

[001565] *STEP F: S-(2-(((benzylamino)(difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)oxy)ethyl) 3-hydroxy-2,2-dimethylpropanethioate*

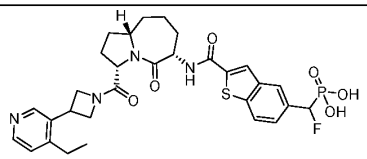
[001566] A solution of S-(2-(((benzylamino)(difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)oxy)ethyl) 3-((tert-

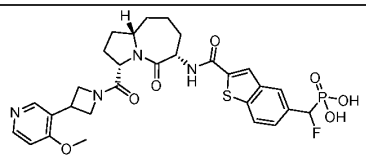
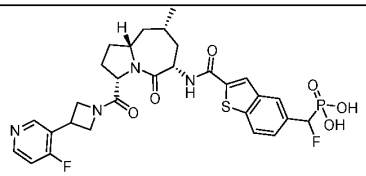
butyldimethylsilyl)oxy)-2,2-dimethylpropanethioate (**7,** 8 mg, 8 μmol, 1 eq.) in TFA (1 mL) and DCM (3 mL) was stirred at room temperature for 30 min under N_2. After completion, the reaction mixture was concentrated under reduced pressure to afford S-(2-(((benzylamino)(difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)oxy)ethyl) 3-hydroxy-2,2-dimethylpropanethioate (6 mg, 7 mmol, 85%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16-8.38 (m, 2H), 8.29-7.98 (m, 3H), 7.97-7.76 (m, 2H), 7.74-7.53 (m, 2H), 7.50-7.27 (m, 6H), 5.10-4.39 (m, 5H), 4.31-4.08 (m, 5H), 4.04-3.88 (m, 2H), 3.60-3.33 (m, 3H), 3.07-2.99 (m, 2H), 2.32-2.25 (m, 1H), 2.21-2.15 (m, 1H), 2.11-1.99 (m, 4H), 1.97-1.80 (m, 4H), 1.19-1.08 (m, 6H). LCMS (ESI): *m/z* =868 $[M+H]^+$.

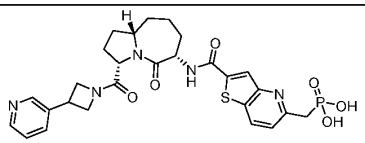
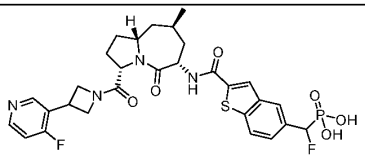
[001567] Compounds prepared according to General Scheme 1: Phosphonic acids

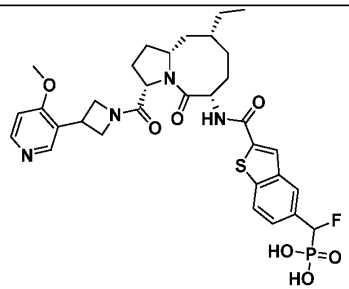
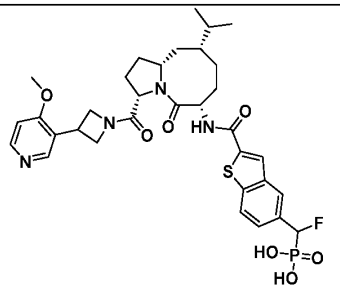
[001568] The following compounds in Table **107** were prepared according to the representative procedure described above for the synthesis of (difluoro(2-(((3S,6S,10aS)-3-(methyl(phenyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)-1H-indol-5-yl)methyl)phosphonic acid (**1**) and utilizing the appropriate starting materials and modifications.

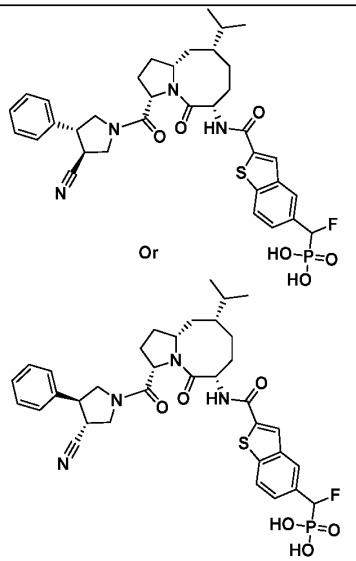
Table 107

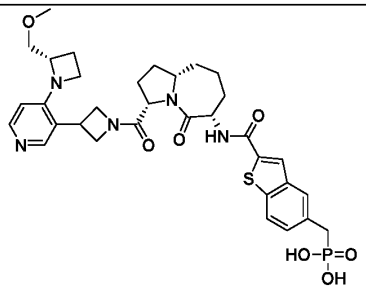
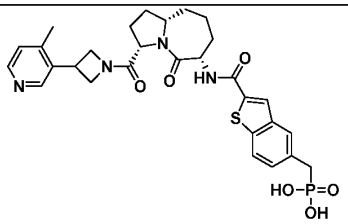
Compound	Name	Structure	LCMS $[M+H]^+$	NMR
205	((2-(((3S,6S,9aS)-3-(3-(4-ethylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		629.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.78 - 8.67 (m, 1H), 8.42 (d, *J* = 11.6 Hz, 1H), 8.02 - 7.91 (m, 2H), 7.89 - 7.83 (m, 1H), 7.79 - 7.73 (m, 1H), 7.64 - 7.52 (m, 1H), 5.86 - 5.68 (m, 1H), 4.78 - 4.71 (m, 2H), 4.67 - 4.51 (m, 2H), 4.48 - 4.40 (m, 1H), 4.35 - 4.28 (m, 1H), 4.17 - 4.06 (m,

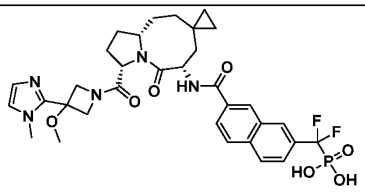
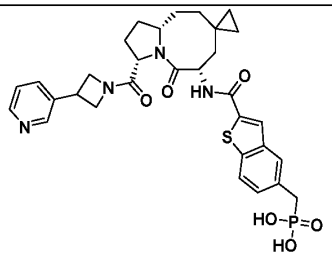
				2H), 2.85 - 2.75 (m, 2H), 2.34 - 1.83 (m, 10H), 1.30 - 1.26 (m, 3H)
206	(fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		631.0	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 - 8.69 (m, 1H), 8.55 - 8.38 (m, 2H), 8.27 - 8.14 (m, 1H), 8.08 - 7.91 (m, 2H), 7.54 – 7.50 (m, 1H), 7.29 - 7.16 (m, 1H), 5.92 - 5.69 (m, 1H), 4.74 - 4.51 (m, 2H), 4.45 - 4.40 (m, 1H), 4.33 - 4.26 (m, 1H), 4.25 - 4.14 (m, 2H), 3.99 (d, *J* = 1.2 Hz, 4H), 3.94 (d, *J* = 4.8 Hz, 3H), 2.23 - 2.15 (m, 1H), 2.08 - 1.92 (m, 2H), 1.90 - 1.63 (m, 7H)
207	(fluoro(2-(((3S,6S,8R,9aR)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		633.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.86 - 8.64 (m, 1H), 8.56 (s, 1H), 8.08 - 7.93 (m, 2H), 7.92 - 7.85 (m, 1H), 7.63 - 7.47 (m, 2H), 5.90 - 5.70 (m, 1H), 4.82 - 4.64 (m, 2H), 4.60 - 4.51 (m, 1H), 4.47 - 3.98 (m, 5H), 2.37 - 2.26 (m, 1H),

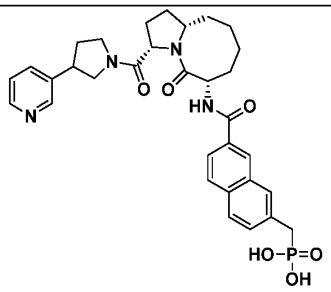
				2.20 - 1.91 (m, 5H), 1.79 (m, 1H), 1.70 - 1.52 (m, 2H), 1.05 (d, J = 6.4 Hz, 3H)
208	((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)thieno[3,2-b]pyridin-5-yl)methyl)phosphonic acid		584.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.59 - 8.50 (m, 1H), 8.46 – 8.42 (m, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.17 - 7.91 (m, 2H), 7.64 – 7.61 (m, 1H), 7.49 – 7.43 (m, 1H), 4.78 – 4.74 (m, 1H), 4.70 (t, J = 8.8 Hz, 1H), 4.63 - 4.55 (m, 2H), 4.44 - 4.28 (m, 1H), 4.14 - 3.93 (m, 3H), 3.40 - 3.33 (m, 2H), 2.38 - 2.27 (m, 1H), 2.19 - 2.07 (m, 2H), 2.06 - 1.95 (m, 3H), 1.94 - 1.79 (m, 4H)
209	(fluoro(2-(((3S,6S,8S,9aR)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		633.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.85 - 8.64 (m, 1H), 8.61 - 8.51 (m, 1H), 8.10 - 7.83 (m, 3H), 7.63 - 7.53 (m, 1H), 7.48 (m, 1H), 5.88 - 5.70 (m, 1H), 5.04 - 4.95 (m, 1H), 4.92 (s, 1H), 4.75 - 4.66 (m, 1H), 4.54 - 4.40 (m, 2H), 4.27 (m, 1H), 4.23 -

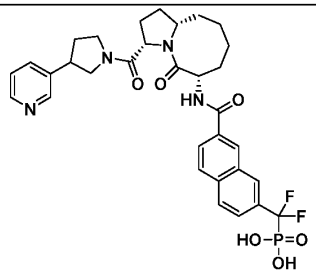
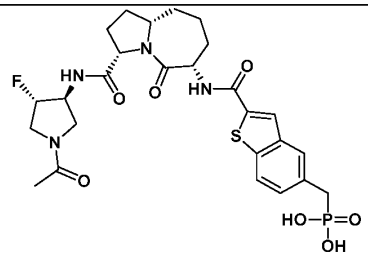
				4.08 (m, 2H), 2.39 - 2.24 (m, 2H), 2.21 - 2.10 (m, 1H), 2.09 - 1.91 (m, 4H), 1.87 - 1.78 (m, 1H), 1.61 (m, 1H), 1.28 - 1.16 (m, 3H)
210	((2-(((3S,6S,9R,10aR)-9-ethyl-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		673.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.69 - 8.21 (m, 2H), 8.10 - 7.73 (m, 3H), 7.63 - 7.52 (m, 1H), 7.33 - 7.17 (m, 1H), 5.78 - 5.54 (m, 1H), 5.09 - 4.93 (m, 1H), 4.65 - 4.62 (m, 1H), 4.48 - 4.38 (m, 2H), 4.35 - 4.28 (m, 1H), 4.20 - 3.92 (m, 6H), 2.31 - 2.21 (m, 2H), 2.07 - 1.85 (m, 6H), 1.67 - 1.50 (m, 3H), 1.43 - 1.33 (m, 2H), 0.99 - 0.94 (m, 3H)
211	(fluoro(2-(((3S,6S,9R,10aR)-9-isopropyl-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		687.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.40 - 8.27 (m, 2H), 8.13 - 7.97 (m, 2H), 7.88 - 7.83 (m, 1H), 7.68 - 7.58 (m, 1H), 7.11 - 6.98 (m, 1H), 5.73 - 5.55 (m, 1H), 5.08 - 5.01 (m, 1H), 4.63 - 4.59 (m,

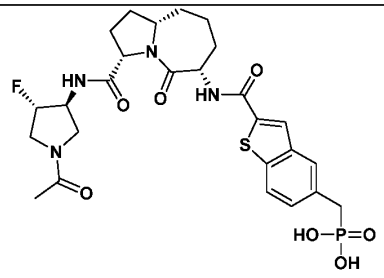
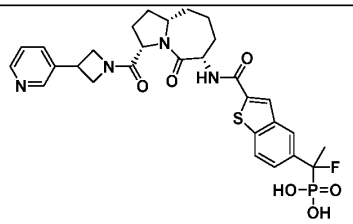
				1H), 4.53 - 4.37 (m, 4H), 4.34 - 4.19 (m, 1H), 4.13 - 4.04 (m, 1H), 3.94 - 3.91 (m, 3H), 2.34 - 2.20 (m, 2H), 2.08 - 1.83 (m, 6H), 1.71 - 1.51 (m, 4H), 0.95 - 0.87 (m, 6H)
212	((2-(((3S,6S,9R,10aR)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-9-isopropyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((2-(((3S,6S,9R,10aR)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-9-isopropyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	695.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (d, J = 2.7 Hz, 1H), 8.02 (br. s., 1H), 7.93 (t, J = 7.9 Hz, 1H), 7.59 - 7.57 (m, 1H), 7.43 - 7.29 (m, 5H), 5.92 - 5.71 (m, 1H), 5.10 - 5.00 (m, 1H), 4.75 - 4.64 (m, 1H), 4.57 - 4.39 (m, 2H), 4.11 - 3.92 (m, 1H), 3.88 - 3.47 (m, 4H), 2.41 - 2.21 (m, 2H), 2.10 - 1.84 (m, 6H), 1.75 - 1.52 (m, 4H), 0.95 - 0.89 (m, 6H)

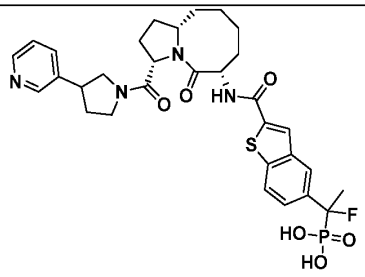
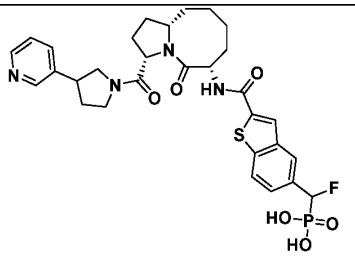
213	((2-(((3S,6S,9aS)-3-(3-(4-((S)-2-(methoxymethyl)azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		682.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.35 - 7.32 (m, 6H), 6.85 - 6.50 (m, 1H), 4.81 - 4.40 (m, 6H), 4.40 - 4.25 (m, 1H), 4.22 - 4.10 (m, 1H), 4.10 - 3.85 (m, 3H), 3.76 - 3.56 (m, 2H), 3.39 - 3.32 (m, 3H), 3.18 - 3.02 (m, 2H), 2.62 - 2.50 (m, 1H), 2.40 - 1.72 (m, 11H).
214	((2-(((3S,6S,9aS)-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		597.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (d, *J* = 17.1 Hz, 1H), 8.36 - 8.31 (m, 1H), 8.00 (d, *J* = 11.2 Hz, 1H), 7.93 (d, *J* = 11.2 Hz, 1H), 7.76 - 7.71 (m, 1H), 7.61 - 7.56 (m, 1H), 7.32 - 7.26 (m, 1H), 5.02 - 4.95 (m, 1H), 4.79 - 4.69 (m, 2H), 4.66 - 4.52 (m, 1H), 4.48 - 4.39 (m, 1H), 4.32 - 4.05 (m, 3H), 3.02 (dd, *J* = 19.6, 3.2 Hz, 2H), 2.34 (s, 4H), 2.24 - 1.74 (m, 9H)

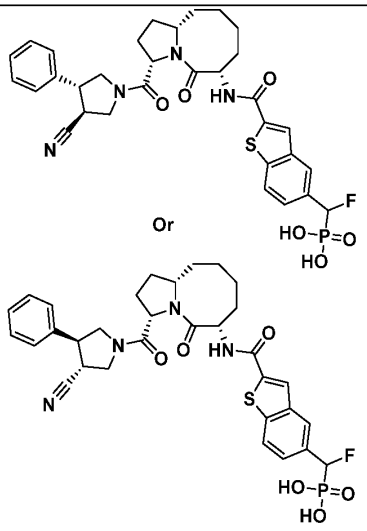
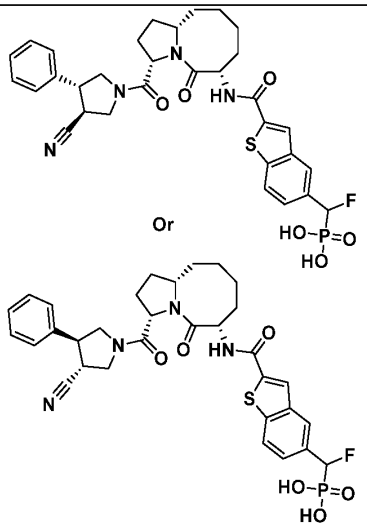
215	(difluoro(7-(((3'S,6'S,10a'S)-3'-(3-methoxy-3-(1-methyl-1H-imidazol-2-yl)azetidine-1-carbonyl)-5'-oxooctahydro-5'H-spiro[cyclopropane-1,8'-pyrrolo[1,2-a]azocin]-6'-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		686.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 - 8.58 (m, 1H), 8.57 - 8.50 (m, 1H), 8.14 (d, J = 13.7 Hz, 1H), 8.05 - 7.90 (m, 3H), 7.77 - 7.69 (m, 1H), 7.22 (d, J = 13.7 Hz, 1H), 6.85 (d, J = 5.4 Hz, 1H), 5.04 - 4.89 (m, 1.5H), 4.72 (q, J = 9.5 Hz, 1H), 4.50 - 4.30 (m, 3.5H), 4.11 - 3.98 (m, 1H), 3.55 (d, J = 7.6 Hz, 3H), 2.90 (d, J = 11.0 Hz, 3H), 2.26 - 2.16 (m, 0.5H), 2.15 - 2.02 (m, 1.5H), 1.98 - 1.80 (m, 3H), 1.80 - 1.67 (m, 2H), 1.64 - 1.46 (m, 3H), 0.53 - 0.28 (m, 4H)
216	((2-(((3'S,6'S,10a'S)-5'-oxo-3'-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-5'H-spiro[cyclopropane-1,8'-pyrrolo[1,2-a]azocin]-6'-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		623.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 - 8.59 (m, 1H), 8.58 - 8.53 (m, 1H), 8.50 - 8.44 (m, 1H), 8.31 (s, 1H), 8.12 (d, J = 6.8 Hz, 1H), 7.88 - 7.75 (m, 2H), 7.72 - 7.66 (m, 1H), 7.40 (dt, J = 7.9, 4.2 Hz, 1H), 7.33 - 7.26 (m, 1H), 4.98 - 4.84 (m,

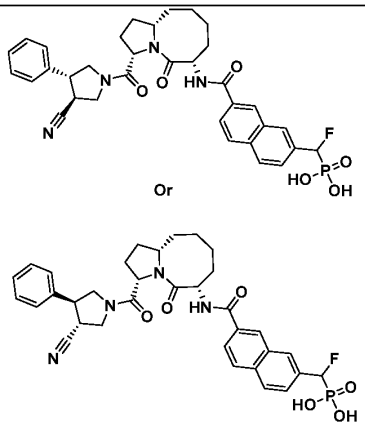
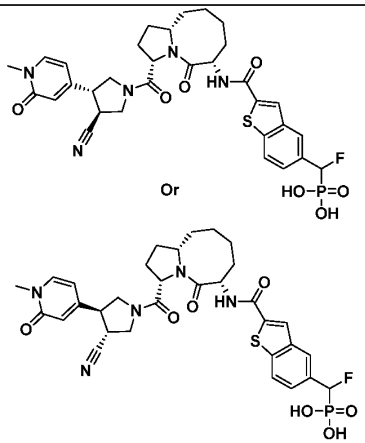
				1.5H), 4.66 - 4.57 (m, 0.5H), 4.56 - 4.48 (m, 0.5H), 4.42 - 4.18 (m, 4H), 3.99 - 3.83 (m, 2.5H), 2.86 - 2.75 (m, 2H), 2.22 - 2.00 (m, 2H), 1.99 - 1.66 (m, 5H), 1.60 - 1.44 (m, 3H), 0.54 - 0.32 (m, 4H)
217	((7-(((3S,6S,10aS)-5-oxo-3-(3-(pyridin-3-yl)pyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		605.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 - 8.50 (m, 2H), 8.48 - 8.36 (m, 2H), 7.98 - 7.79 (m, 4H), 7.77 - 7.69 (m, 1H), 7.57 - 7.48 (m, 1H), 7.40 - 7.25 (m, 1H), 5.09 - 4.92 (m, 1H), 4.64 - 4.49 (m, 1H), 4.39 - 4.20 (m, 1H), 4.06 - 3.89 (m, 1H), 3.87 - 3.71 (m, 1H), 3.65 - 3.47 (m, 2H), 3.15 - 3.06 (m, 2H), 2.32 - 2.17 (m, 2H), 2.14 - 1.69 (m, 10H), 1.66 - 1.47 (m, 3H)

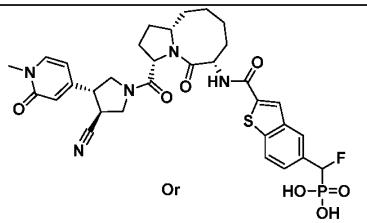
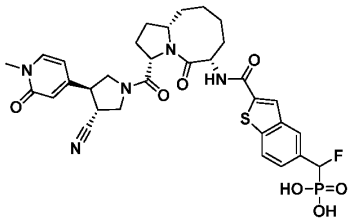
218	(difluoro(7-(((3S,6S,10aS)-5-oxo-3-(3-(pyridin-3-yl)pyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		641.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.70 - 8.15 (m, 5H), 7.99 - 7.74 (m, 5H), 5.19 - 5.06 (m, 1H), 4.76 - 4.66 (m, 1H), 4.55 - 4.43 (m, 1H), 4.13 - 4.00 (m, 1H), 3.98 - 3.65 (m, 3H), 2.40 - 2.23 (m, 3H), 2.13 - 1.96 (m, 7H), 1.94 - 1.78 (m, 3H), 1.71 (br. s., 2H)
219	((2-(((3S,6S,9aS)-3-(((3S,4S)-1-acetyl-4-fluoropyrrolidin-3-yl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		595.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (d, J = 6.6 Hz, 1H), 8.40 (d, J = 5.9 Hz, 1H), 8.00 (d, J = 4.4 Hz, 1H), 7.89 - 7.78 (m, 2H), 7.43 (d, J = 8.6 Hz, 1H), 5.18 - 4.95 (m, 1H), 4.72 (d, J = 10.8 Hz, 1H), 4.54 - 4.35 (m, 2H), 4.11 - 3.99 (m, 1H), 3.95 - 3.80 (m, 1H), 3.80 - 3.60 (m, 3H), 3.28 - 3.20 (m, 2H), 2.35 - 2.22 (m, 1H), 2.18 - 1.75 (m, 12H)

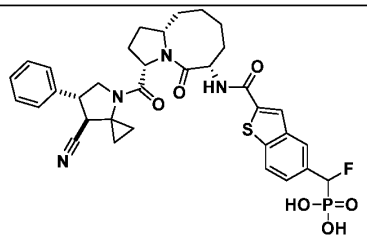
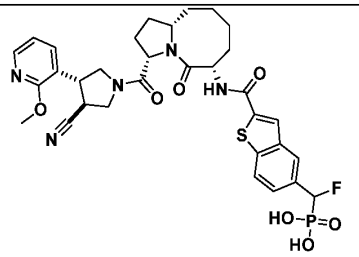
220	((2-(((3S,6S,9aS)-3-(((3S,4S)-1-acetyl-4-fluoropyrrolidin-3-yl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		595.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.51 - 8.44 (m, 1H), 8.02 - 7.97 (m, 1H), 7.88 - 7.80 (m, 2H), 7.46 - 7.38 (m, 1H), 5.28 - 5.03 (m, 1H), 4.73 (d, *J* = 11.0 Hz, 1H), 4.67 - 4.43 (m, 2H), 4.10 - 4.00 (m, 1H), 4.00 - 3.92 (m, 1H), 3.92 - 3.80 (m, 1H), 3.79 - 3.53 (m, 1H), 3.41 (t, *J* = 10.3 Hz, 0.6H), 3.29 - 3.17 (m, 2.4H), 2.36 - 2.24 (m, 1H), 2.20 - 1.72 (m, 12H)
221	(1-fluoro-1-(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)ethyl)phosphonic acid		615.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.58 - 8.41 (m, 2H), 8.14 - 7.93 (m, 3H), 7.85 - 7.83 (m, 1H), 7.72 - 7.70 (m, 1H), 7.50 - 7.44 (m, 1H), 4.99 - 4.94 (m, 1H), 4.72 - 4.68 (m, 1H), 4.62 - 4.53 (m, 2H), 4.46 - 4.28 (m, 1H), 4.11 - 3.97 (m, 3H), 2.37 - 2.25 (m, 1H), 2.20 - 2.07 (m, 2H), 2.05 - 1.79 (m, 10H)

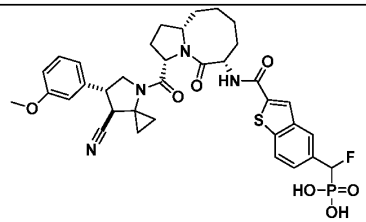
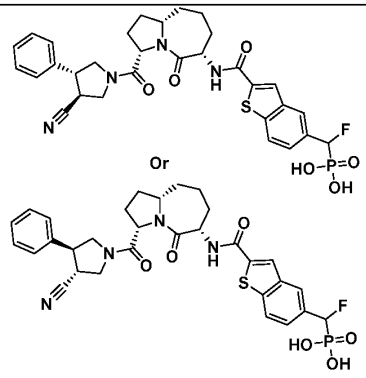
222	(1-fluoro-1-(2-(((3S,6S,10aS)-5-oxo-3-(3-(pyridin-3-yl)pyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)ethyl)phosphonic acid		643.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.54 - 8.48 (m, 1H), 8.45 - 8.37 (m, 1H), 8.14 - 8.05 (m, 2H), 7.91 - 7.73 (m, 3H), 7.47 - 7.37 (m, 1H), 5.09 - 5.00 (m, 1H), 4.76 - 4.66 (m, 1H), 4.48 - 4.36 (m, 1H), 4.18 - 3.75 (m, 2H), 3.74 - 3.34 (m, 3H), 2.51 - 2.20 (m, 3H), 2.20 - 1.76 (m, 12H), 1.75 - 1.59 (m, 2H)
223	(fluoro(2-(((3S,6S,10aS)-5-oxo-3-(3-(pyridin-3-yl)pyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		629.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 - 8.47 (m, 1H), 8.44 - 8.36 (m, 1H), 8.12 - 8.02 (m, 2H), 7.90 - 7.78 (m, 2H), 7.68 - 7.66 (m, 1H), 7.47 - 7.37 (m, 1H), 5.72 - 5.52 (m, 1H), 5.09 - 5.03 (m, 1H), 4.75 - 4.72 (m, 1H), 4.47 - 4.38 (m, 1H), 4.18 - 3.77 (m, 2H), 3.74 - 3.34 (m, 3H), 2.49 - 2.21 (m, 3H), 2.20 - 1.92 (m, 7H), 1.91 - 1.58 (m, 4H)
224	((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-		653.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (s, 1H),

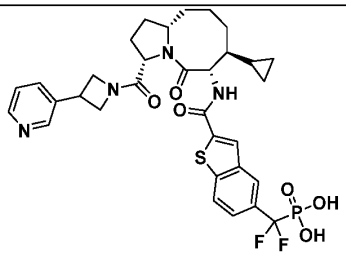
	phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing		8.03 (br. s., 1H), 7.96 - 7.88 (m, 1H), 7.61 - 7.59 (m, 1H), 7.43 - 7.29 (m, 5H), 5.87 - 5.68 (m, 1H), 5.07 - 4.98 (m, 1H), 4.74 - 4.64 (m, 1H), 4.57 - 4.38 (m, 2H), 4.10 - 3.92 (m, 1H), 3.88 - 3.67 (m, 2H), 3.66 - 3.48 (m, 2H), 2.40 - 2.17 (m, 2H), 2.11 - 1.93 (m, 6H), 1.91 - 1.76 (m, 2H), 1.74 - 1.57 (m, 2H)
225	((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 Pyrrolidine building block SFC peak 1 was used for synthesis and biological testing	653.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.15 - 8.07 (m, 1H), 8.03 (br. s., 1H), 7.98 - 7.90 (m, 1H), 7.60 - 7.58 (m, 1H), 7.46 - 7.28 (m, 5H), 5.90 - 5.73 (m, 1H), 5.07 - 4.99 (m, 1H), 4.68 - 4.59 (m, 1H), 4.48 - 4.39 (m, 1H), 4.22 - 4.17 (m, 1H), 4.15 - 4.06 (m, 1H), 3.96 - 3.73 (m, 1H), 3.69 - 3.37 (m, 3H), 2.41 - 2.19 (m, 2H), 2.12 - 1.93 (m, 6H), 1.92 - 1.76 (m, 2H),

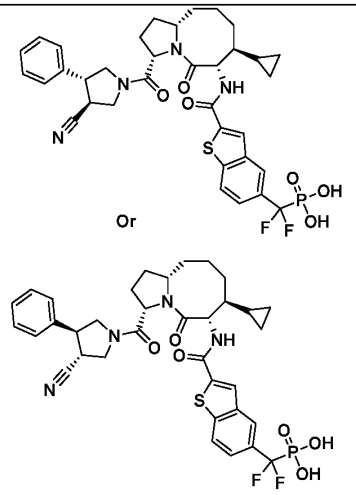
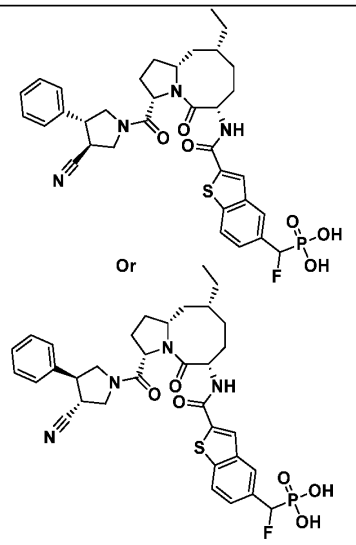
				1.74 - 1.57 (m, 2H)
226	((7-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)fluoromethyl)phosphonic acid Or ((7-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)fluoromethyl)phosphonic acid	 Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	647.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (d, J = 4.4 Hz, 1H), 8.12 - 8.05 (m, 1H), 8.00 - 7.91 (m, 3H), 7.77 - 7.69 (m, 1H), 7.44 - 7.29 (m, 5H), 5.99 - 5.80 (m, 1H), 5.15 - 5.04 (m, 1H), 4.76 - 4.64 (m, 1H), 4.59 - 4.41 (m, 2H), 4.07 (dd, J = 11.5, 8.1 Hz, 0.5H), 3.96 (dd, J = 11.7, 7.8 Hz, 0.5H), 3.85 (t, J = 9.5 Hz, 0.5H), 3.80 - 3.50 (m, 3.5H), 2.42 - 2.18 (m, 2H), 2.13 - 1.94 (m, 6H), 1.93 - 1.76 (m, 2H), 1.76 - 1.59 (m, 2H)
227	((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or		684.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.11 - 8.09 (m, 1H), 8.04 - 8.00 (m, 1H), 7.96 - 7.89 (m, 1H), 7.70 - 7.54 (m, 2H), 6.64 - 6.56 (m, 1H), 6.48 - 6.43 (m, 1H), 5.89 - 5.71 (m, 1H), 5.07 - 4.97 (m, 1H), 4.66 - 4.57 (m, 1H), 4.49 - 4.39 (m, 1H), 4.22 - 4.06

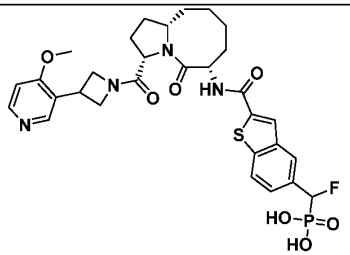
	((2-(((3S,6S,10aS)-3-((3R.4S)-3-cyano-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing		(m, 2H), 3.92 - 3.35 (m, 7H), 2.40 - 2.18 (m, 2H), 2.10 - 1.92 (m, 6H), 1.90 - 1.75 (m, 2H), 1.74 - 1.57 (m, 2H)
228	((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((2-(((3S,6S,10aS)-3-((3R.4S)-3-cyano-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 Or  Pyrrolidine building block SFC peak 1 was used for synthesis and biological testing	684.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (s, 1H), 8.02 (br. s., 1H), 7.96 - 7.89 (m, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.60 - 7.58 (m, 1H), 6.58 (d, *J* = 11.7 Hz, 1H), 6.47 - 6.39 (m, 1H), 5.89 - 5.68 (m, 1H), 5.04 - 4.97 (m, 1H), 4.69 - 4.65 (m, 1H), 4.56 - 4.39 (m, 2H), 4.07 - 3.56 (m, 5H), 3.56- 3.54 (m, 3H), 2.39 - 2.19 (m, 2H), 2.12 - 1.94 (m, 6H), 1.91 - 1.76 (m, 2H), 1.74 - 1.57 (m, 2H)

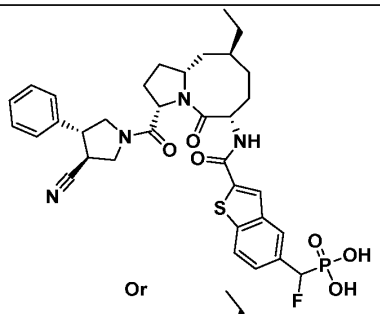
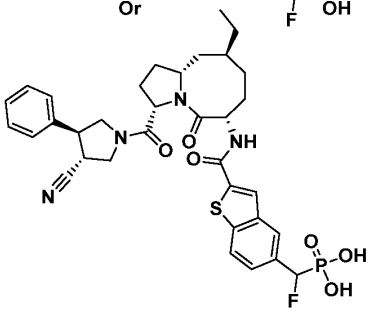
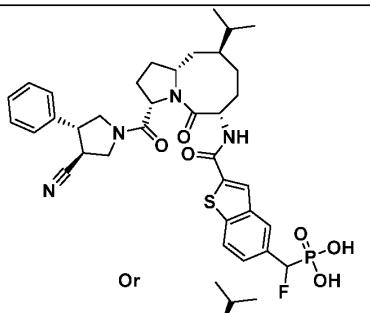
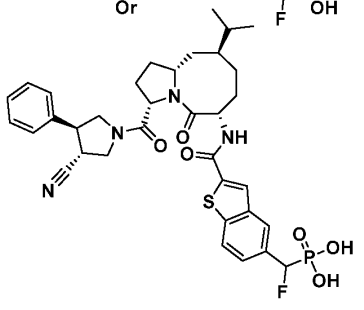
229	((2-(((3S,6S,10aS)-3-((*rel*-trans)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		679.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (s, 1H), 8.04 - 7.97 (m, 1H), 7.92 (d, *J* = 8.8 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.49 - 7.24 (m, 5H), 5.90 - 5.69 (m, 1H), 5.08 - 4.96 (m, 1H), 4.66 - 4.55 (m, 1H), 4.46 - 4.31 (m, 1H), 4.22 - 4.05 (m, 1H), 3.85 - 3.66 (m, 2H), 2.42 - 2.12 (m, 3H), 2.12 - 1.48 (m, 12H), 1.04 - 0.92 (m, 1H), 0.78 - 0.62 (m, 1H)
230	((2-(((3S,6S,10aS)-3-((*rel*-trans)-3-cyano-4-(2-methoxypyridin-3-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		684.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.16 - 8.06 (m, 2H), 8.05 - 7.99 (m, 1H), 7.97 - 7.88 (m, 1H), 7.82 - 7.75 (m, 0.3H), 7.73 - 7.65 (m, 0.7H), 7.63 - 7.55 (m, 1H), 7.03 - 6.94 (m, 1H), 5.87 - 5.69 (m, 1H), 5.09 - 4.98 (m, 1H), 4.72 - 4.61 (m, 1H), 4.49 - 4.36 (m, 1.5H), 4.13 - 3.58 (m, 8.5H), 2.41 - 2.18 (m, 2H), 2.12 - 1.93 (m, 6H), 1.92 - 1.75

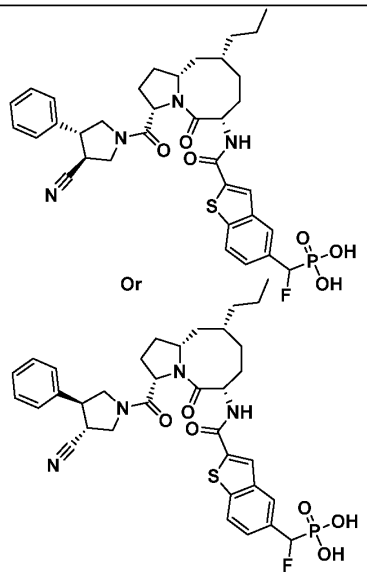
				(m, 2H), 1.74 - 1.58 (m, 2H)
231	((2-(((3S,6S,10aS)-3-((*rel*-trans)-7-cyano-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		709.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 - 8.07 (m, 1H), 8.05 - 7.98 (m, 1H), 7.93 (d, *J* = 7.1 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.33 - 7.22 (m, 1H), 7.07 - 7.00 (m, 1H), 6.99 - 6.94 (m, 1H), 6.90 - 6.82 (m, 1H), 5.91 - 5.70 (m, 1H), 5.05 - 4.96 (m, 1H), 4.67 - 4.55 (m, 1H), 4.45 - 4.33 (m, 1H), 4.20 - 4.06 (m, 1H), 3.83 - 3.68 (m, 5H), 2.43 - 2.12 (m, 3H), 2.08 - 1.73 (m, 9H), 1.71 - 1.53 (m, 2H), 1.38 - 1.24 (m, 1H), 1.02 - 0.93 (m, 1H), 0.79 - 0.65 (m, 1H)
232	((2-(((3S,6S,9aS)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or		639.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 8.04 (s, 1H), 7.98 - 7.92 (m , 1H), 7.63 - 7.57 (m, 1H), 7.46 - 7.30 (m, 5H), 5.90 - 5.73 (m, 1H), 4.83 - 4.72 (m, 2H), 4.53 - 4.33 (m, 1H), 4.14 - 3.95 (m, 2H), 3.89 - 3.49

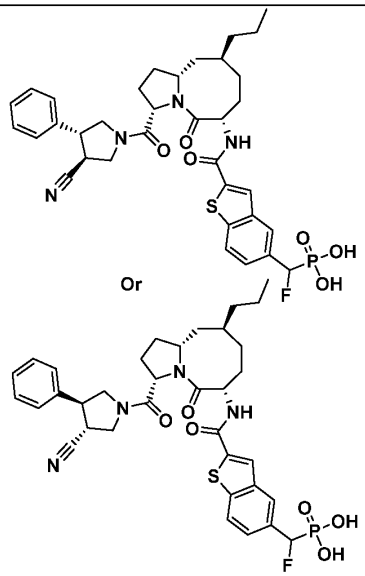
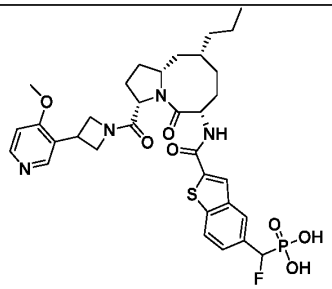
	((2-(((3S,6S,9aS)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing		(m, 4H), 2.39 - 2.25 (m, 1H), 2.25 - 2.06 (m, 2H), 2.06 - 1.97 (m, 2H), 1.97 - 1.78 (m, 5H)
233	((2-(((3S,6S,7S,10aS)-7-cyclopropyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		673.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.63 - 8.50 (m, 1H), 8.48 - 8.41 (m, 1H), 8.29 (s, 1H), 8.13 - 8.10 (m, 1H), 8.09 - 7.92 (m, 1H), 7.90 - 7.83 (m, 2H), 7.56 - 7.41 (m, 1H), 5.29 - 5.15 (m, 1H), 4.73 - 4.57 (m, 1H), 4.50 - 4.22 (m, 3H), 4.12 - 3.91 (m, 2H), 2.33 - 2.00 (m, 5H), 1.94 - 1.82 (m, 4H), 1.75 - 1.64 (m, 1H), 1.28 - 1.17 (m, 1H), 1.09 - 1.01 (m, 1H), 0.98 - 0.84 (m, 1H), 0.67 - 0.51 (m, 2H), 0.46 - 0.34 (m, 1H), 0.09 - -0.03 (m, 1H)

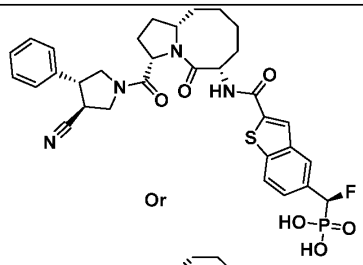
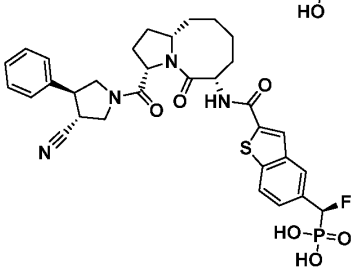
234	((2-(((3S,6S,7S,10aS)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-7-cyclopropyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid Or ((2-(((3S,6S,7S,10aS)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-7-cyclopropyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid	 Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	711.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.21 - 8.15 (m, 1H), 8.12 (s, 1H), 8.06 - 7.95 (m, 1H), 7.74 - 7.63 (m, 1H), 7.45 - 7.28 (m, 5H), 5.29 - 5.19 (m, 1H), 4.72 - 4.62 (m, 1H), 4.54 - 4.38 (m, 2H), 4.13 - 3.92 (m, 1H), 3.89 - 3.49 (m, 4H), 2.43 - 2.15 (m, 3H), 2.14 - 1.79 (m, 6H), 1.75 - 1.63 (m, 1H), 1.29 - 1.13 (m, 1H), 0.98 - 0.83 (m, 1H), 0.65 - 0.50 (m, 2H), 0.46 - 0.34 (m, 1H), 0.08 - -0.04 (m, 1H)
235	((2-(((3S,6S,9R,10aR)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-9-ethyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((2-(((3S,6S,9R,10aR)-3-((3R,4S)-3-		681.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 - 7.87 (m, 3H), 7.60 - 7.58 (m, 1H), 7.43 - 7.29 (m, 5H), 5.90 - 5.67 (m, 1H), 5.09 - 4.98 (m, 1H), 4.75 - 4.65 (m, 1H), 4.58 - 4.40 (m, 2H), 4.09 - 3.90 (m, 1H), 3.88 - 3.47 (m, 4H), 2.39 - 2.22 (m, 2H), 2.16 - 1.83 (m, 6H), 1.70 - 1.48 (m, 3H),

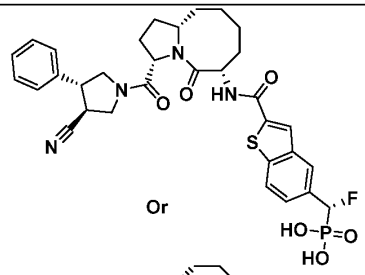
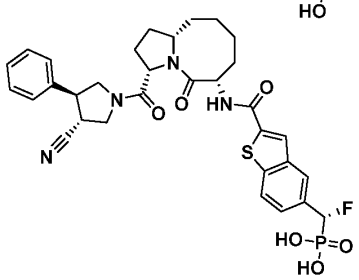
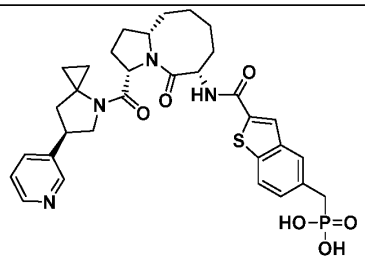
	cyano-4-phenylpyrrolidine-1-carbonyl)-9-ethyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing		1.39 - 1.33 (m, 2H), 1.02 - 0.92 (m, 3H)
236	(fluoro(2-(((3S,6S,10aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		645.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.50 - 8.22 (m, 2H), 8.13 - 7.73 (m, 3H), 7.66 - 7.49 (m, 1H), 7.35 - 7.17 (m, 1H), 5.81 - 5.56 (m, 1H), 5.05 - 4.93 (m, 1H), 4.70 - 4.59 (m, 1H), 4.50 - 4.37 (m, 2H), 4.36 - 4.28 (m, 1H), 4.21 - 4.13 (m, 1H), 4.10 - 4.02 (m, 2H), 3.99 (s, 2H), 2.35 - 2.14 (m, 2H), 2.13 - 1.56 (m, 11H)
237	((2-(((3S,6S,9S,10aR)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-9-ethyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or		681.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.11 - 8.01 (m, 2H), 7.93 - 7.90 (m, 1H), 7.64 - 7.56 (m, 1H), 7.45 - 7.30 (m, 5H), 5.83 - 5.67 (m, 1H), 4.84 - 4.78 (m, 1H), 4.71 - 4.65 (m, 1H), 4.59 - 4.42 (m, 2H), 4.11 - 3.93 (m, 1H), 3.86 - 3.50 (m,

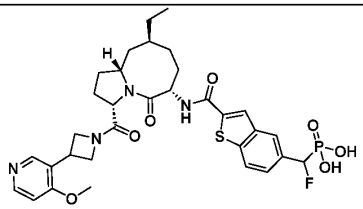
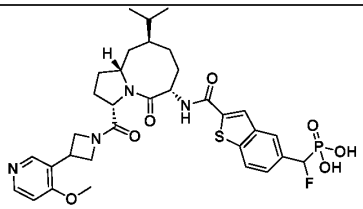
	((2-(((3S,6S,9S,10aR)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-9-ethyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 Or  Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing		4H), 2.46 - 2.29 (m, 1H), 2.21-2.16 (m, 1H), 2.13 - 2.02 (m, 1H), 2.00 - 1.91 (m, 1H), 1.88 - 1.62 (m, 5H), 1.46 - 1.32 (m, 4H), 0.99 - 0.93 (m, 3H)
238	((2-(((3S,6S,9S,10aR)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-9-isopropyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((2-(((3S,6S,9S,10aR)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-9-isopropyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo	 Or  Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	695.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.12 - 7.87 (m, 3H), 7.64 - 7.53 (m, 1H), 7.44 - 7.27 (m, 5H), 5.89 - 5.68 (m, 1H), 4.82 - 4.75 (m, 1H), 4.71 - 4.61 (m, 1H), 4.56 - 4.38 (m, 2H), 4.11 - 3.92 (m, 1H), 3.86 - 3.51 (m, 4H), 2.45 - 2.27 (m, 1H), 2.26 - 1.99 (m, 3H), 1.93 - 1.63 (m, 6H), 1.58 - 1.42 (m, 2H), 0.97 - 0.88 (m, 6H)

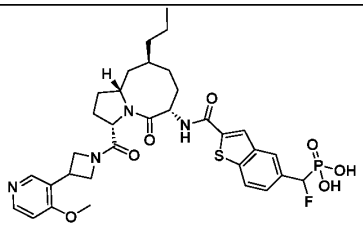
	[b]thiophen-5-yl)fluoromethyl)phosphonic acid			
239	((2-(((3S,6S,9R,10aR)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxo-9-propyldecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((2-(((3S,6S,9R,10aR)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxo-9-propyldecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	695.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.15 - 7.98 (m, 2H), 7.93 (t, *J* = 7.2 Hz, 1H), 7.60 - 7.58 (m, 1H), 7.44 - 7.28 (m, 5H), 5.91 - 5.65 (m, 1H), 5.04 (t, *J* = 9.0 Hz, 1H), 4.75 - 4.66 (m, 1H), 4.57 - 4.37 (m, 2H), 4.10 - 3.93 (m, 1H), 3.86 - 3.48 (m, 4H), 2.38 - 2.20 (m, 2H), 2.14 - 1.82 (m, 6H), 1.73 - 1.61 (m, 2H), 1.57 - 1.50 (m, 1H), 1.45 - 1.30 (m, 4H), 0.96 - 0.92 (m, 3H)

240	((2-(((3S,6S,9S,10aR)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxo-9-propyldecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((2-(((3S,6S,9S,10aR)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxo-9-propyldecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	695.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.12 - 8.01 (m, 2H), 7.95 - 7.92 (m 1H), 7.60 - 7.58 (m, 1H), 7.45 - 7.28 (m, 5H), 5.90 - 5.71 (m, 1H), 4.84 - 4.81 (m, 1H), 4.71 - 4.63 (m, 1H), 4.58 - 4.42 (m, 2H), 4.12 - 3.93 (m, 1H), 3.87 - 3.47 (m, 4H), 2.44 - 2.24 (m, 1H), 2.24 - 1.91 (m, 4H), 1.87 - 1.77 (m, 3H), 1.72 - 1.61 (m, 1H), 1.47 - 1.26 (m, 6H), 0.97 - 0.89 (m, 3H)
241	(fluoro(2-(((3S,6S,9R,10aR)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxo-9-propyldecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		687.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.40 - 8.26 (m, 2H), 8.13 - 7.96 (m, 2H), 7.88 - 7.83 (m, 1H), 7.67 - 7.58 (m, 1H), 7.11 - 6.97 (m, 1H), 5.74 - 5.55 (m, 1H), 5.09 - 5.01 (m, 1H), 4.63 - 4.59 (m, 1H), 4.52 - 4.37 (m, 4H), 4.34 - 4.19 (m, 1H),

				4.14 - 4.05 (m, 1H), 3.94 - 3.91 (m, 3H), 2.34 - 2.19 (m, 2H), 2.13 - 1.76 (m, 6H), 1.71 - 1.59 (m, 2H), 1.56 - 1.28 (m, 5H), 0.94 (t, *J* = 7.0 Hz, 3H)
242	((R)-(2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((R)-(2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 Or  Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	653.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 - 8.09 (m, 1H), 8.06 - 8.00 (m, 1H), 7.99 - 7.91 (m, 1H), 7.63 - 7.55 (m, 1H), 7.46 - 7.29 (m, 5H), 5.93 - 5.73 (m, 1H), 5.09 - 4.99 (m, 1H), 4.75 - 4.63 (m, 1H), 4.58 - 4.37 (m, 2H), 4.12 - 3.91 (m, 1H), 3.89 - 3.65 (m, 2H), 3.63 - 3.49 (m, 2H), 2.43 - 2.15 (m, 2H), 2.12 - 1.90 (m, 6H), 1.90 - 1.78 (m, 2H), 1.73 - 1.59 (m, 2H)

243	((R)-(2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((R)-(2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 Or  Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	653.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 - 8.09 (m, 1H), 8.06 - 7.99 (m, 1H), 7.98 - 7.91 (m, 1H), 7.63 - 7.53 (m, 1H), 7.43 - 7.30 (m, 5H), 5.93 - 5.73 (m, 1H), 5.09 - 4.96 (m, 1H), 4.75 - 4.62 (m, 1H), 4.59 - 4.38 (m, 2H), 4.11 - 3.93 (m, 1H), 3.88 - 3.67 (m, 2H), 3.64 - 3.50 (m, 2H), 2.42 - 2.17 (m, 2H), 2.11 - 1.95 (m, 6H), 1.91 - 1.76 (m, 2H), 1.75 - 1.59 (m, 2H)
244	((2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		637.3	^{1}H NMR (400 MHz, DMSO) δ 8.78 (d, J = 7.3 Hz, 1H), 8.60 – 8.53 (m, 1H), 8.46 – 8.39 (m, 1H), 8.19 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.82 – 7.74 (m, 2H), 7.37 – 7.29 (m, 2H), 4.99 – 4.87 (m, 1H), 4.55 – 4.44 (m, 1H), 4.26 – 4.19 (m, 1H), 4.18 – 4.09 (m, 1H), 3.84 – 3.77 (m, 1H), 3.61 – 3.55 (m, 1H), 3.09 (d, J = 21.2 Hz,

				2H), 2.34 – 2.21 (m, 1H), 2.19 – 2.07 (m, 2H), 2.06 – 1.93 (m, 3H), 1.91 – 1.68 (m, 6H), 1.66 – 1.44 (m, 4H), 0.52 – 0.38 (m, 2H)
245	((2-(((3S,6S,9S,10aR)-9-ethyl-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		673.1	1H NMR (400 MHz, CD_3OD) δ 8.40 - 8.23 (m, 2H), 8.09 - 7.91 (m, 2H), 7.87 - 7.76 (m, 1H), 7.66 - 7.54 (m, 1H), 7.14 - 6.99 (m, 1H), 5.72 - 5.56 (m, 1H), 4.71 - 4.58 (m, 2H), 4.50 - 4.36 (m, 3H), 4.35 - 4.19 (m, 1H), 4.14 - 4.00 (m, 2H), 3.95 - 3.90 (m, 3H), 2.36 - 2.26 (m, 1H), 2.24 - 1.92 (m, 4H), 1.88 - 1.60 (m, 5H), 1.44 - 1.32 (m, 3H), 1.00 - 0.89 (m, 3H)
246	(fluoro(2-(((3S,6S,9S,10aR)-9-isopropyl-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		687.1	1H NMR (400 MHz, CD_3OD) δ 8.38 - 8.29 (m, 2H), 8.11 - 8.02 (m, 2H), 7.83 - 7.69 (m, 2H), 7.10 - 7.04 (m, 1H), 5.68 - 5.54 (m, 1H), 4.77 - 4.57 (m, 3H), 4.49 - 4.36 (m, 3H), 4.34 - 4.21

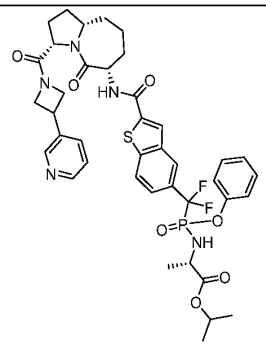
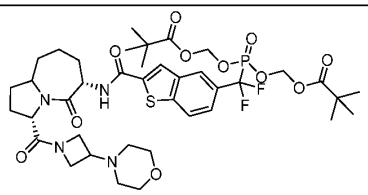
				(m, 1H), 4.15 - 4.06 (m, 1H), 3.95 (s, 3H), 2.38 - 2.28 (m, 1H), 2.25 - 2.12 (m, 2H), 2.10 - 1.99 (m, 1H), 1.89 - 1.73 (m, 4H), 1.73 - 1.62 (m, 2H), 1.58 - 1.42 (m, 2H), 0.93 - 0.88 (m, 6H)
247	(fluoro(2-(((3S,6S,9S,10aR)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxo-9-propyldecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		687.1	1H NMR (400 MHz, CD_3OD) δ 8.39 - 8.25 (m, 2H), 8.12 - 8.01 (m, 2H), 7.83 - 7.67 (m, 2H), 7.10 - 7.05 (m, 1H), 5.69 - 5.51 (m, 1H), 4.95 - 4.88 (m, 2H), 4.73 - 4.57 (m, 1H), 4.49 - 4.20 (m, 4H), 4.17 - 4.06 (m, 1H), 3.97 - 3.93 (m, 3H), 2.38 - 2.26 (m, 1H), 2.24 - 2.08 (m, 2H), 2.07 - 1.88 (m, 2H), 1.86 - 1.72 (m, 4H), 1.75 - 1.61 (m, 1H), 1.46 - 1.26 (m, 5H), 0.95 - 0.91 (m, 3H)

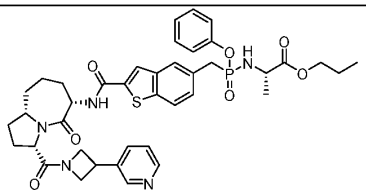
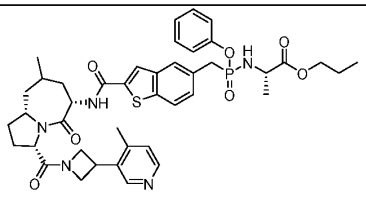
Compounds prepared according to General Scheme 1: Phosphonate Esters

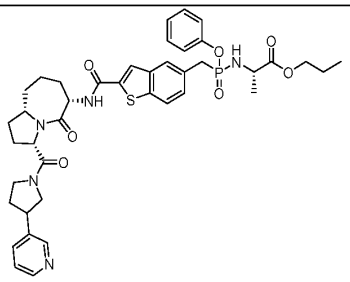
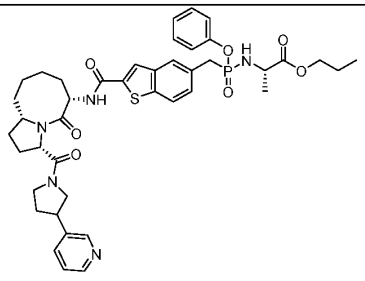
[001569] The following compounds in Table **108** were prepared according to the representative procedure described above for the synthesis of (difluoro(2-(((3S,6S,10aS)-3-(methyl(phenyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)-1H-indol-

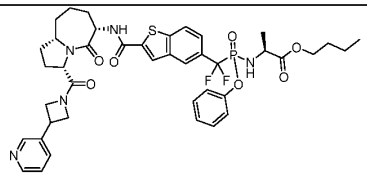
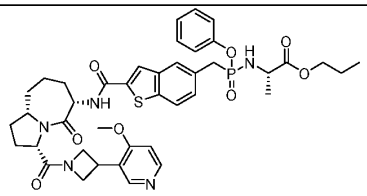
5-yl)methyl)phosphonic acid and utilizing the appropriate starting materials and modifications.

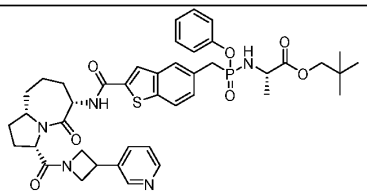
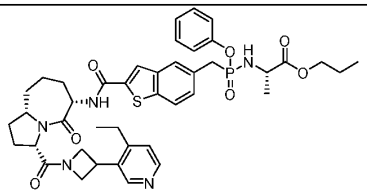
Table 108

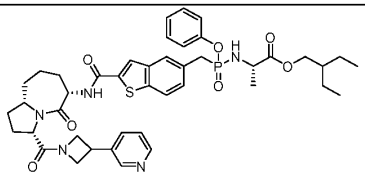
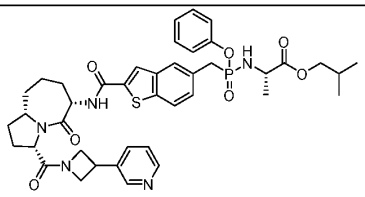
Compound	Name	Structure	LCMS $[M+H]^+$	NMR
248	isopropyl ((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		808.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 - 8.83 (m, 1H), 8.78 - 8.69 (m, 1H), 8.45 (m, 1H), 8.19 - 7.99 (m, 2H), 7.97 - 7.83 (m, 2H), 7.82 - 7.63 (m, 2H), 7.31 - 7.28 (m, 1H), 7.18 - 7.08 (m, 3H), 5.07 - 4.94 (m, 1H), 4.89 - 4.78 (m, 1H), 4.76 - 4.69 (m, 1H), 4.57 - 4.45 (m, 2H), 4.29 - 4.08 (m, 2H), 4.06 - 3.86 (m, 3H), 2.35 - 2.25 (m, 1H), 2.20 - 2.13 (m, 1H), 2.12 - 1.99 (m, 4H), 1.98 - 1.76 (m, 4H), 1.39 - 1.30 (m, 3H), 1.27 - 1.16 (m, 6H)
249	(((difluoro(2-(((3S,6S)-3-(3-morpholinoazetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		855.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (d, J = 5.6 Hz, 2H), 8.13 - 8.05 (m, 1H), 7.64 (d, J = 8.8 Hz, 1H), 5.82 - 5.69 (m, 4H), 4.77 (d, J = 10.8 Hz, 1H), 4.63 - 4.48 (m, 2H), 4.43 - 4.27 (m, 1H), 4.17 - 4.05 (m, 2H), 3.96 - 3.82 (m, 1H), 3.72 (td, J = 4.4, 13.6 Hz, 4H), 3.30 - 3.22 (m, 1H), 2.46 (s, 4H), 2.37 - 2.27 (m, 1H), 2.11 (d, J = 18.0 Hz, 3H), 1.99 - 1.82

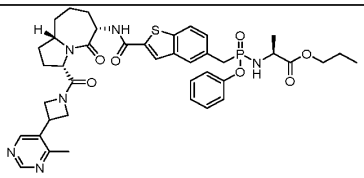
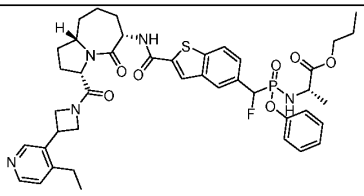
				(m, 6H), 1.22 - 1.17 (m, 18H)
250	propyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		772.6	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 - 8.54 (m, 2H), 8.08 - 7.85 (m, 1H), 7.84 - 7.75 (m, 3H), 7.74 - 7.63 (m, 1H), 7.53 - 7.44 (m, 1H), 7.44 - 7.37 (m, 1H), 7.33 - 7.27 (m, 2H), 7.19 - 7.10 (m, 3H), 4.73 - 4.63 (m, 2H), 4.61 - 4.52 (m, 1H), 4.27 - 4.15 (m, 1H), 4.07 - 3.88 (m, 5H), 3.52 - 3.31 (m, 3H), 3.27 - 3.08 (m, 1H), 2.98 - 2.84 (m, 2H), 2.34 - 2.14 (m, 2H), 2.10 - 2.00 (m, 3H), 1.97 - 1.92 (m, 1H), 1.86 - 1.68 (m, 2H), 1.63 - 1.50 (m, 2H), 1.47 - 1.40 (m, 1H), 1.16 (dd, J = 7.2, 10.4 Hz, 3H), 0.92 - 0.82 (m, 3H)
251	propyl (((2-(((3S,6S,9aR)-8-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		800.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.88 - 8.81 (m, 1H), 8.66 - 8.54 (m, 1H), 8.09 - 7.99 (m, 1H), 7.95 - 7.83 (m, 3H), 7.54 - 7.44 (m, 1H), 7.37 - 7.27 (m, 2H), 7.16 (t, J = 8.4 Hz, 3H), 5.04 - 4.92 (m, 1H), 4.77 - 4.72 (m, 1H), 4.66 (t, J = 7.2 Hz, 1H), 4.59 - 4.52 (m, 1H), 4.49 - 4.41 (m, 1H), 4.41 - 4.33 (m, 1H), 4.22 - 4.05 (m, 2H), 3.98 - 3.81 (m, 3H), 3.58 - 3.45 (m, 2H), 2.57

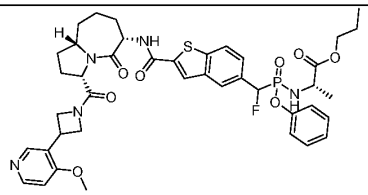
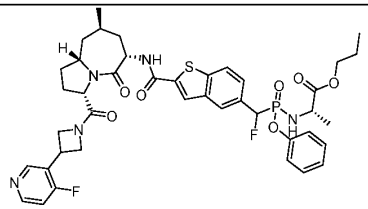
				(d, J = 4.0 Hz, 3H), 2.32 (m, 1H), 2.14 - 1.89 (m, 5H), 1.86 - 1.76 (m, 1H), 1.69 - 1.49 (m, 4H), 1.26 - 1.21 (m, 1H), 1.14 (d, J = 6.8 Hz, 1H), 1.07 (m, 4H), 0.87 (t, J = 7.2 Hz, 3H)
252	propyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)pyrrolidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		786.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 - 8.50 (m, 2H), 8.19 - 7.96 (m, 1H), 7.92 - 7.76 (m, 3H), 7.67 (d, *J* = 4.0 Hz, 1H), 7.54 - 7.30 (m, 4H), 7.21 - 7.11 (m, 3H), 4.83 - 4.68 (m, 2H), 4.39 - 4.13 (m, 1H), 4.01 - 3.86 (m, 4H), 3.75 - 3.60 (m, 1H), 3.54 - 3.40 (m, 3H), 3.33 - 3.10 (m, 1H), 2.56 - 2.40 (m, 1H), 2.33 - 2.25 (m, 1H), 2.22 - 2.18 (m, 1H), 2.12 - 2.03 (m, 4H), 1.96 - 1.83 (m, 3H), 1.79 - 1.68 (m, 2H), 1.66 - 1.48 (m, 1H), 1.23 - 1.12 (m, 3H), 0.89 (d, *J* = 7.4 Hz, 3H)
253	propyl (((2-(((3S,6S,10aS)-5-oxo-3-(3-(pyridin-3-yl)pyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		800.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 - 8.36 (m, 2H), 7.79 - 7.66 (m, 3H), 7.60 - 7.30 (m, 3H), 7.25 - 7.20 (m, 3H), 7.16 - 7.02 (m, 3H), 5.13 - 5.02 (m, 1H), 4.65 - 4.49 (m, 1H), 4.34 - 4.06 (m, 2H), 3.96 - 3.73 (m, 4H), 3.51 - 3.31 (m, 4H), 3.25 - 3.01 (m, 1H), 2.42 - 2.18

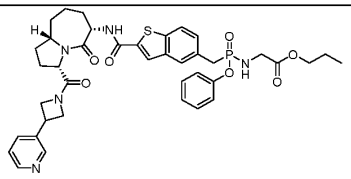
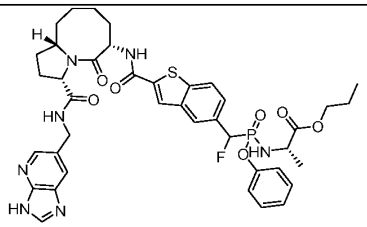
				(m, 2H), 2.14 - 1.94 (m, 7H), 1.79 - 1.58 (m, 3H), 1.47 (s, 2H), 1.12 - 1.03 (m, 3H), 0.88 - 0.76 (m, 3H)
254	butyl ((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		822.0	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 - 9.12 (m, 1H), 8.69 - 8.82 (m, 1H), 8.44 - 8.54 (m, 1H), 8.15 (s, 1H), 7.74 - 7.99 (m, 4H), 7.65 - 7.74 (m, 1H), 7.28 (s, 1H), 7.05 - 7.19 (m, 3H), 4.64 - 4.91 (m, 3H), 4.50 (m, 2H), 4.11 (m, 3H), 3.96 (m, 3H), 2.24 - 2.35 (m, 1H), 2.02 - 2.21 (m, 5H), 1.82 - 1.97 (m, 3H), 1.59 (s, 2H), 1.26 - 1.41 (m, 6H), 0.91 (m, 3H)
255	propyl (((2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		802.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.71 - 8.52 (m, 2H), 8.05 - 7.94 (m, 1H), 7.92 - 7.79 (m, 2H), 7.65 - 7.43 (m, 2H), 7.36 - 7.26 (m, 2H), 7.21 - 7.09 (m, 3H), 4.72 (d, *J* = 9.2 Hz, 1H), 4.64 (d, *J* = 7.6 Hz, 1H), 4.58 - 4.51 (m, 1H), 4.43 (s, 1H), 4.35 (s, 1H), 4.20 - 4.12 (m, 5H), 4.07 (d, *J* = 5.2 Hz, 1H), 4.00 - 3.78 (m, 3H), 3.64 - 3.39 (m, 2H), 2.40 - 2.23 (m, 1H), 2.20 - 1.73 (m, 10H), 1.61 - 1.45 (m, 2H), 1.17 - 1.07 (m, 3H), 0.92 - 0.79 (m, 3H)

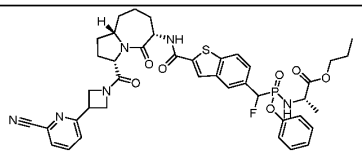
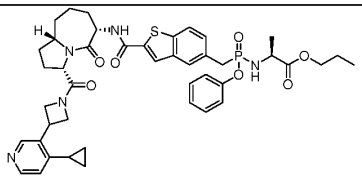
256	neopentyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		800.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 - 8.82 (m, 1H), 8.79 - 8.69 (m, 1H), 8.50 (d, J = 7.6 Hz, 1H), 7.89 - 7.73 (m, 5H), 7.47 - 7.38 (m, 1H), 7.33 - 7.29 (m, 1H), 7.15 (d, J = 8.0 Hz, 3H), 4.84 - 4.68 (m, 3H), 4.56 - 4.46 (m, 2H), 4.27 - 4.15 (m, 1H), 4.10 - 4.02 (m, 1H), 3.99 (d, J = 7.2 Hz, 2H), 3.81 - 3.75 (m, 1H), 3.67 - 3.62 (m, 1H), 3.52 - 3.48 (m, 1H), 3.44 (d, J = 13.2 Hz, 1H), 2.34 - 2.26 (m, 1H), 2.20 - 2.03 (m, 5H), 1.97 - 1.70 (m, 4H), 1.22 - 1.15 (m, 3H), 0.89 - 0.86 (m, 9H)
257	propyl (((2-(((3S,6S,9aS)-3-(3-(4-ethylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		800.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 - 8.82 (m, 1H), 8.63 - 8.52 (m, 1H), 8.19 - 7.89 (m, 1H), 7.60 - 7.51 (m, 1H), 7.87 - 7.50 (m, 3H), 7.48 - 7.35 (m, 1H), 7.32 - 7.28 (m, 1H), 7.20 - 7.08 (m, 3H), 5.08 - 4.90 (m, 1H), 4.86 - 4.61 (m, 2H), 4.54 (t, J = 5.1 Hz, 1H), 4.45 - 4.35 (m, 1H), 4.28 - 4.17 (m, 1H), 4.09 - 3.89 (m, 7H), 3.74 - 3.63 (m, 1H), 3.51 - 3.40 (m, 2H), 2.80 - 2.67 (m, 2H), 2.33 - 2.12 (m, 2H), 2.11 - 1.97 (m, 4H), 1.93 - 1.79 (m, 3H), 1.64 -

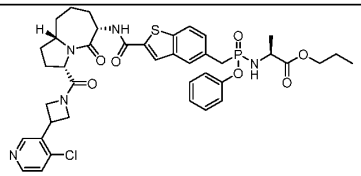
				1.51 (m, 2H), 1.31 - 1.21 (m, 3H), 1.31 - 1.12 (m, 3H), 0.93 - 0.83 (m, 3H)
258	2-ethylbutyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		814.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 15.2 Hz, 1H), 7.98 - 7.76 (m, 4H), 7.73 - 7.64 (m, 1H), 7.50 - 7.42 (m, 1H), 7.41 - 7.34 (m, 1H), 7.32 - 7.27 (m, 2H), 7.20 - 7.10 (m, 3H), 4.72 - 4.40 (m, 4H), 4.21 (m, 1H), 4.10 - 3.98 (m, 2H), 3.97 - 3.93 (m, 2H), 3.92 - 3.86 (m, 1H), 3.51 - 3.40 (m, 2H), 3.36 - 3.10 (m, 1H), 2.33 - 2.26 (m, 1H), 2.25 - 2.19 (m, 1H), 2.10 - 2.03 (m, 4H), 1.96 (t, J = 10.0 Hz, 2H), 1.85 - 1.70 (m, 2H), 1.48 - 1.41 (m, 1H), 1.34 - 1.28 (m, 4H), 1.26 (s, 3H), 0.88 - 0.82 (m, 6H)
259	isobutyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		786.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 - 8.56 (m, 1H), 8.09 - 7.96 (m, 1H), 7.91 - 7.76 (m, 3H), 7.72 - 7.59 (m, 1H), 7.56 - 7.45 (m, 1H), 7.44 - 7.37 (m, 1H), 7.33 - 7.28 (m, 2H), 7.21 - 7.10 (m, 3H), 4.79 - 4.71 (m, 1H), 4.70 - 4.61 (m, 1H), 4.60 - 4.51 (m, 1H), 4.50 - 4.40 (m, 1H), 4.25 - 4.16 (m, 1H), 4.04 - 3.88 (m, 3H), 3.85 - 3.71

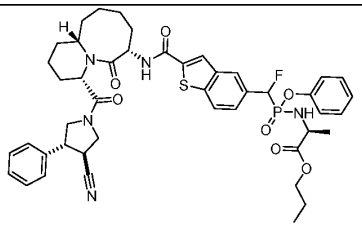
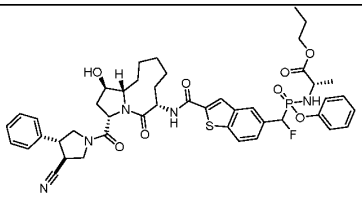
				(m, 2H), 3.52 - 3.39 (m, 2H), 3.37 - 3.25 (m, 1H), 2.31 - 2.19 (m, 2H), 2.10 - 2.01 (m, 4H), 1.98 - 1.91 (m, 3H), 1.88 - 1.82 (m, 2H), 1.21 - 1.13 (m, 3H), 0.90 - 0.83 (m, 6H)
260	propyl (((2-(((3S,6S,9aS)-3-(3-(4-methylpyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		787.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (d, J = 12.0 Hz, 1H), 8.92 - 8.71 (m, 1H), 7.88 - 7.77 (m, 3H), 7.67 - 7.61 (m, 1H), 7.49 - 7.38 (m, 1H), 7.32 - 7.28 (m, 1H), 7.18 - 7.09 (m, 3H), 5.10 - 4.77 (m, 1H), 4.75 - 4.61 (m, 2H), 4.59 - 4.40 (m, 1H), 4.34 - 4.25 (m, 1H), 4.17 - 4.08 (m, 1H), 4.03 - 3.88 (m, 4H), 3.55 - 3.18 (m, 3H), 2.53 (d, J = 5.6 Hz, 3H), 2.34 - 2.13 (m, 2H), 2.12 - 1.99 (m, 4H), 1.931.91 (m, 2H), 1.83 (s, 1H), 1.76 - 1.66 (m, 1H), 1.62 - 1.50 (m, 2H), 1.20 - 1.12 (m, 3H), 0.92 - 0.82 (m, 3H)
261	propyl (((2-(((3S,6S,9aS)-3-(3-(4-ethylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(ph		818.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.76 - 8.61 (m, 1H), 8.42 - 8.33 (m, 1H), 8.15 - 7.94 (m, 3H), 7.70 - 7.58 (m, 1H), 7.38 - 7.29 (m, 3H), 7.24 - 7.14 (m, 3H), 6.21 - 5.99 (m, 1H), 4.99 - 4.93 (m, 1H), 4.78 - 4.70 (m, 2H), 4.63 -

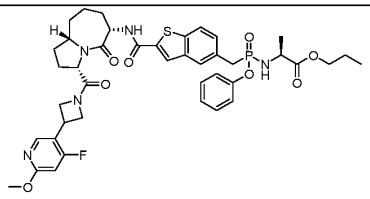
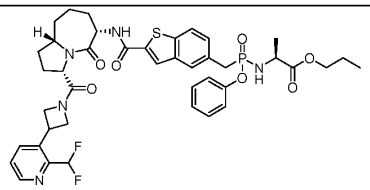
	enoxy)phosphoryl)-L-alaninate			4.49 (m, 2H), 4.45 - 4.37 (m, 1H), 4.32 - 4.24 (m, 1H), 4.16 - 4.06 (m, 2H), 4.00 - 3.93 (m, 1H), 3.88 - 3.79 (m, 1H), 2.71 - 2.65 (m, 2H), 2.32 - 1.98 (m, 6H), 1.93 - 1.80 (m, 4H), 1.61 - 1.48 (m, 2H), 1.30 - 1.20 (m, 6H), 0.93 - 0.83 (m, 3H)
262	propyl ((fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		820.7	^{1}H NMR (400 MHz, ACETONITRILE-d_3) δ 8.62 - 8.49 (m, 2H), 8.07 - 7.91 (m, 3H), 7.90 - 7.73 (m, 1H), 7.65 - 7.56 (m, 1H), 7.37 - 7.14 (m, 5H), 6.14 - 5.93 (m, 1H), 4.67 - 4.60 (m, 1H), 4.59 - 4.49 (m, 2H), 4.39 - 4.22 (m, 2H), 4.06 (s, 5H), 4.00 - 3.78 (m, 4H), 2.24 (d, J = 6.8 Hz, 1H), 2.05 - 1.98 (m, 3H), 1.87 (d, J = 15.6 Hz, 3H), 1.79 (d, J = 6.0 Hz, 2H), 1.65 - 1.49 (m, 3H), 1.23 - 1.17 (m, 2H), 1.08 (d, J = 7.2 Hz, 1H), 0.88 - 0.82 (m, 3H)
263	propyl ((fluoro(2-(((3S,6S,8S,9aR)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		822.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 - 8.98 (m, 1H), 8.78 - 8.61 (m, 1H), 8.03 - 7.95 (m, 1H), 7.92 - 7.85 (m, 1H), 7.83 - 7.74 (m, 1H), 7.62 - 7.47 (m, 2H), 7.41 - 7.31 (m, 2H), 7.30 - 7.28 (m, 1H), 7.25 - 7.18 (m, 2H), 7.13 - 7.05

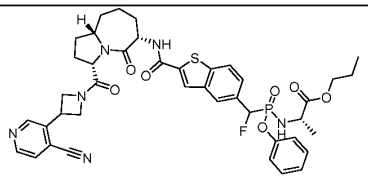
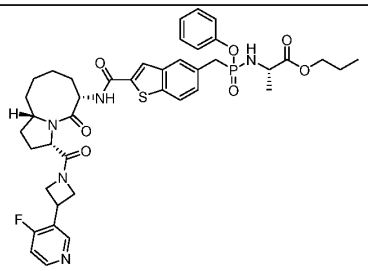
	yl)methyl)(phenoxy)phosphoryl)-L-alaninate			(m, 1H), 6.09 - 5.87 (m, 1H), 5.07 - 4.85 (m, 2H), 4.73 - 4.61 (m, 1H), 4.55 - 4.45 (m, 1H), 4.40 - 4.26 (m, 1H), 4.22 - 4.12 (m, 3H), 4.10 - 3.97 (m, 2H), 3.76 - 3.56 (m, 1H), 2.37 - 2.22 (m, 2H), 2.16 - 2.03 (m, 4H), 2.02 - 1.91 (m, 2H), 1.68 - 1.51 (m, 3H), 1.34 - 1.26 (m, 5H), 1.13 (m, 1H), 0.95 - 0.83 (m, 3H)
264	propyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)glycinate		758.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 - 8.67 (m, 2H) 7.85 - 7.95 (m, 1H) 7.75 - 7.84 (m, 2H) 7.61 - 7.75 (m, 2H) 7.47 (m, 1H) 7.29 - 7.41 (m, 2H) 7.14 (m, 3H) 4.41 - 4.71 (m, 4H) 4.19 (m, 1H) 3.99 - 4.07 (m, 2H) 3.88 - 3.98 (m, 2H) 3.69 - 3.78 (m, 1H) 3.44 - 3.60 (m, 3H) 3.04 - 3.16 (m, 1H) 2.14 - 2.32 (m, 2H) 2.05 (s, 4H) 1.90 - 1.98 (m, 2H) 1.79 - 1.84 (m, 1H) 1.55 - 1.63 (m, 3H) 0.88 (m, 3H)
265	propyl (((2-(((3S,6S,10aS)-3-(((3H-imidazo[4,5-b]pyridin-6-yl)methyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo		818.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.99 (s, 1H), 8.61 (d, J = 1.6 Hz, 1H), 8.33 (s, 1H), 8.15 - 8.04 (m, 2H), 8.02 - 7.94 (m, 1H), 7.64 (t, J = 7.2 Hz, 1H), 7.39 - 7.29 (m, 2H), 7.27 - 7.13

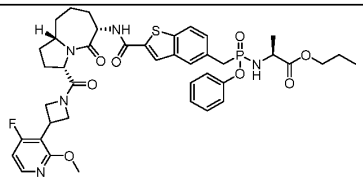
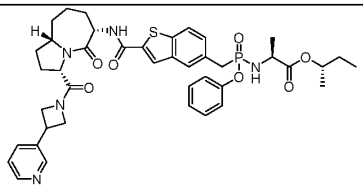
	[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate			(m, 3H), 6.19 - 6.01 (m, 1H), 5.04 - 4.99 (m, 1H), 4.82 - 4.76 (m, 1H), 4.52 - 4.40 (m, 3H), 4.00 - 3.95 (m, 1H), 3.95 - 3.86 (m, 1H), 3.85 - 3.78 (m, 1H), 2.33 - 2.19 (m, 2H), 2.13 - 2.05 (m, 1H), 2.02 - 1.90 (m, 5H), 1.88 - 1.74 (m, 2H), 1.71 - 1.65 (m, 1H), 1.64 - 1.46 (m, 3H), 1.22 (t, J = 7.6 Hz, 2H), 1.08 (d, J = 7.2 Hz, 1H), 0.92 - 0.83 (m, 3H)
266	propyl (((2-(((3S,6S,9aS)-3-(3-(6-cyanopyridin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		815.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.28 (d, J = 11.4 Hz, 1H), 8.12 - 7.89 (m, 4H), 7.77 - 7.56 (m, 2H), 7.39 - 7.31 (m, 2H), 7.23 - 7.10 (m, 3H), 6.30 - 6.08 (m, 2H), 4.78 - 4.52 (m, 2H), 4.48 - 4.43 (m, 1H), 4.37 - 4.27 (m, 1H), 4.26 - 4.16 (m, 1H), 4.15 - 4.03 (m, 2H), 3.97 (d, J = 9.6 Hz, 3H), 3.76 (d, J = 7.6 Hz, 1H), 2.25 - 2.15 (m, 1H), 2.08 - 1.93 (m, 2H), 1.89 - 1.65 (m, 7H), 1.53 - 1.38 (m, 2H), 1.19 - 0.90 (m, 3H), 0.86 - 0.75 (m, 3H)
267	propyl (((2-(((3S,6S,9aS)-3-(3-(4-cyclopropylpyridin-3-yl)azetidine-1-carbonyl)-5-		812.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 - 8.56 (m, 1H), 8.45 (d, J = 4.0 Hz, 1H), 7.91 - 7.77 (m, 3H), 7.67 (d, J = 4.0 Hz, 1H),

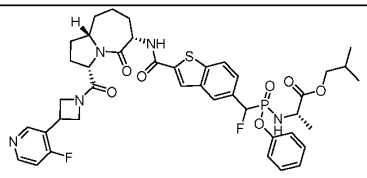
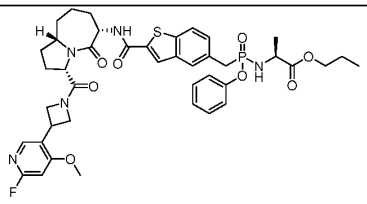
	oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate			7.52 - 7.41 (m, 1H), 7.33 - 7.30 (m, 1H), 7.22 - 7.10 (m, 3H), 6.88 - 6.81 (m, 1H), 5.07 - 4.82 (m, 1H), 4.75 - 4.56 (m, 3H), 4.48 - 4.22 (m, 2H), 3.99 – 3.94 (m, 4H), 3.53 - 3.40 (m, 2H), 3.34 - 3.06 (m, 1H), 2.35 - 2.16 (m, 2H), 2.13 - 2.02 (m, 4H), 2.01 - 1.93 (m, 2H), 1.87 - 1.72 (m, 3H), 1.60 - 1.53 (m, 2H), 1.21 - 1.07 (m, 5H), 0.94 - 0.85 (m, 3H), 0.78 (d, J = 4.0 Hz, 2H)
268	propyl (((2-(((3S,6S,9aS)-3-(3-(4-chloropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		806.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.78 - 8.67 (m, 1H), 8.48 - 8.42 (m, 1H), 8.06 - 8.01 (m, 1H), 7.94 - 7.84 (m, 2H), 7.61 - 7.57 (m, 1H), 7.51 - 7.46 (m, 1H), 7.35 - 7.29 (m, 2H), 7.21 - 7.12 (m, 3H), 4.74 (d, J = 8.4 Hz, 2H), 4.62 - 4.54 (m, 1H), 4.53 - 4.42 (m, 1H), 4.38 - 4.29 (m, 1H), 4.25 - 4.18 (m, 1H), 4.11 - 4.03 (m, 1H), 3.95 - 3.79 (m, 3H), 3.58 - 3.43 (m, 3H), 2.35 - 2.27 (m, 1H), 2.21 - 2.07 (m, 2H), 2.06 - 1.96 (m, 3H), 1.95 - 1.88 (m, 2H), 1.86 - 1.78 (m, 2H), 1.57 - 1.48 (m, 2H), 1.33 - 1.28 (m, 2H), 1.14 (d, J = 7.2 Hz,

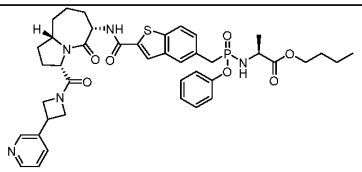
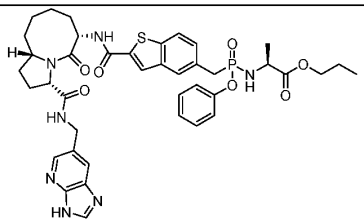
				1H), 0.89 - 0.83 (m, 3H)
269	propyl (((2-(((4S,7S,11aS)-4-((*rel-trans*)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-6-oxodecahydro-2H-pyrido[1,2-a]azocin-7-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		856.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 9.6 Hz, 1H), 7.91 - 7.78 (m, 2H), 7.62 - 7.52 (m, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.44 - 7.30 (m, 6H), 7.28 (s, 1H), 7.25 - 7.18 (m, 1H), 7.14 - 7.05 (m, 1H), 6.08 - 5.86 (m, 1H), 5.20 - 5.06 (m, 1H), 4.91 (s, 1H), 4.41 - 4.20 (m, 2H), 4.12 - 3.99 (m, 3H), 3.88 - 3.49 (m, 4H), 3.42 - 3.14 (m, 1H), 2.65 - 2.54 (m, 1H), 2.26 - 2.20 (m, 1H), 2.03 - 1.91 (m, 4H), 1.90 - 1.80 (m, 2H), 1.77 - 1.71 (m, 1H), 1.62 (J = 7.2, 14.6 Hz, 3H), 1.56 - 1.49 (m, 2H), 1.46 - 1.40 (m, 1H), 1.32 - 1.28 (m, 2H), 1.26 (s, 1H), 1.17 - 1.10 (m, 1H), 0.95 - 0.84 (m, 3H)
270	propyl (((2-(((1R,3S,6S,11aS)-3-((*rel-trans*)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-1-hydroxy-5-oxodecahydro-1H-pyrrolo[1,2-a]azonin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(ph		872.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 - 8.05 (m, 2H), 8.01 - 7.91 (m, 1H), 7.68 - 7.58 (m, 1H), 7.44 - 7.27 (m, 7H), 7.24 - 7.11 (m, 3H), 6.18 - 6.00 (m, 1H), 5.15 (,m, 1H), 4.95 - 4.89 (m, 1H), 4.22 - 4.08 (m, 3H), 4.07 - 3.70 (m, 5H), 3.68 - 3.37 (m, 3H), 2.30 - 2.20 (m, 1H), 2.16 - 2.02

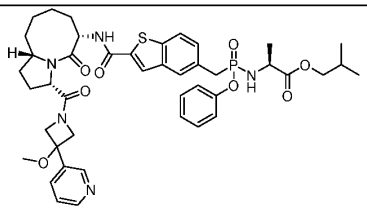
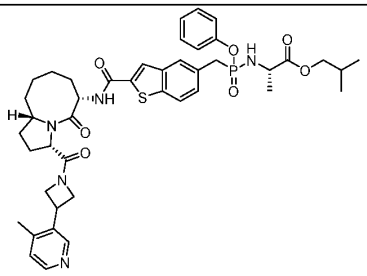
	enoxy)phosphoryl)-L-alaninate			(m, 3H), 2.00 - 1.89 (m, 2H), 1.85 - 1.72 (m, 3H), 1.68 - 1.47 (m, 5H), 1.24 - 1.19 (m, 2H), 1.05 (d, J = 7.2 Hz, 1H), 0.91 - 0.82 (m, 3H)
271	propyl (((2-(((3S,6S,9aS)-3-(3-(4-fluoro-6-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		820.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.23 - 7.90 (m, 2H), 7.88 - 7.70 (m, 2H), 7.59 - 6.95 (m, 6H), 6.64 - 6.40 (m, 1H), 4.67 - 4.45 (m, 3H), 4.37 - 4.24 (m, 1H), 4.12 - 3.69 (m, 9H), 3.54 - 3.33 (m, 3H), 2.27 - 2.15 (m, 1H), 2.10 - 1.65 (m, 9H), 1.55 - 1.35 (m, 2H), 1.16 - 0.92 (m, 3H), 0.89 - 0.68 (m, 3H)
272	propyl (((2-(((3S,6S,9aS)-3-(3-(2-(difluoromethyl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		822.6	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.31 - 7.99 (m, 1H), 7.91 - 7.74 (m, 3H), 7.71 - 7.62 (m, 1H), 7.58 - 7.51 (m, 1H), 7.49 - 7.39 (m, 1H), 7.31 - 7.29 (m, 1H), 7.21 - 7.08 (m, 3H), 6.87 - 6.53 (m, 1H), 4.71 - 4.67 (m, 1H), 4.64 - 4.53 (m, 3H), 4.45 - 4.10 (m, 2H), 4.07 - 3.86 (m, 4H), 3.53 - 3.39 (m, 2H), 3.38 - 3.09 (m, 1H), 2.27 - 2.18 (m, 2H), 2.11 - 2.00 (m, 4H), 1.99 - 1.90 (m, 2H), 1.87 - 1.67 (m, 2H), 1.64 - 1.49 (m, 2H), 1.17 - 1.13 (m,

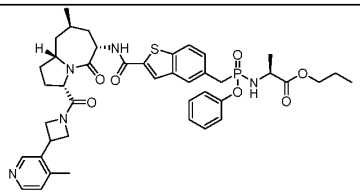
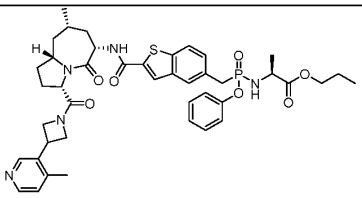
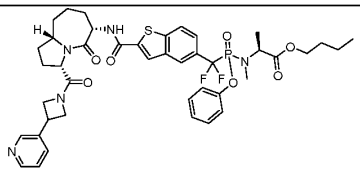
				3H), 0.95 - 0.80 (m, 3H)
273	propyl (((2-(((3S,6S,9aS)-3-(3-(4-cyanopyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		815.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 - 8.63 (m, 1H), 8.52 - 8.42 (m, 1H), 7.75 - 7.67 (m, 1H), 7.63 - 7.51 (m, 2H), 7.43 - 7.20 (m, 3H), 7.09 - 7.03 (m, 1H), 6.94 - 6.88 (m, 1H), 6.86 - 6.69 (m, 2H), 5.81 - 5.55 (m, 1H), 4.55 - 4.45 (m, 1H), 4.41 (t, J = 10.0 Hz, 1H), 4.28 - 4.20 (m, 1H), 4.12 - 3.99 (m, 2H), 3.99 - 3.82 (m, 1H), 3.81 - 3.71 (m, 2H), 3.70 - 3.54 (m, 2H), 3.42 - 3.24 (m, 1H), 2.02 - 1.87 (m, 2H), 1.77 (s, 4H), 1.63 (d, J = 11.6 Hz, 2H), 1.37 - 1.21 (m, 3H), 1.05 - 0.91 (m, 3H), 0.82 (t, J = 6.4 Hz, 1H), 0.65 - 0.54 (m, 3H)
274	propyl (((2-(((3S,6S,10aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		804.4	^{1}H NMR (400 MHz, CD_3OD) δ 9.00 - 8.58 (m, 2H), 8.10 - 7.84 (m, 3H), 7.57 - 7.45 (m, 2H), 7.37 - 7.28 (m, 2H), 7.26 - 7.11 (m, 3H), 5.04 - 4.99 (m, 2H), 4.77 - 4.70 (m, 1H), 4.58 - 4.38 (m, 4H), 4.32 - 4.12 (m, 2H), 3.94 - 3.86 (m, 2H), 3.58 - 3.49 (m, 2H), 2.31 - 2.20 (m, 2H), 2.08 - 1.94 (m, 6H), 1.90 - 1.77 (m, 2H), 1.75 - 1.61 (m, 2H), 1.59 -

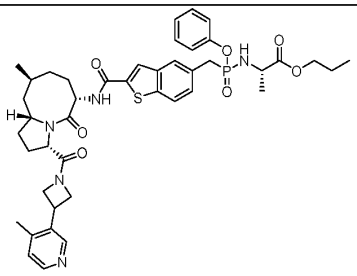
				1.48 (m, 2H), 1.16 - 1.06 (m, 3H), 0.92 - 0.83 (m, 3H)
275	propyl (((2-(((3S,6S,9aS)-3-(3-(4-fluoro-2-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		820.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.07 - 8.00 (m, 2H), 7.88 - 7.86 (m, 2H), 7.50 - 7.45 (m, 1H), 7.31 - 7.29 (m, 2H), 7.19 - 7.13 (m, 3H), 6.80 - 6.79 (m, 1H), 4.76 - 4.72 (m, 2H), 4.60 - 4.58 (m, 2H), 4.28 - 4.27 (m, 3H), 4.09 - 4.04 (m, 1H), 4.00 (d, J = 6.0 Hz, 3H), 3.93 - 3.90 (m, 3H), 3.56 - 3.50 (m, 2H), 2.33 - 2.28 (m, 1H), 2.13 - 1.80 (m, 9H), 1.58 - 1.51 (m, 2H), 1.14 - 1.06 (m, 3H), 0.88 - 0.84 (m, 3H)
276	(S)-sec-butyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		786.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 - 8.81 (m, 1H), 8.78 - 8.67 (m, 1H), 8.52 - 8.10 (m, 1H), 7.86 (s, 1H), 7.85 - 7.77 (m, 3H), 7.77 - 7.60 (m, 1H), 7.48 - 7.37 (m, 1H), 7.32 - 7.28 (m, 1H), 7.20 - 7.07 (m, 3H), 4.80 - 4.66 (m, 4H), 4.58 - 4.42 (m, 2H), 4.28 - 4.13 (m, 1H), 4.10 - 3.92 (m, 3H), 3.53 - 3.40 (m, 2H), 2.35 - 2.24 (m, 1H), 2.24 - 2.13 (m, 1H), 2.12 - 2.00 (m, 4H), 1.98 - 1.68 (m, 4H), 1.59 - 1.42 (m, 2H), 1.24 - 1.09 (m, 6H), 0.88 - 0.78 (m, 3H)

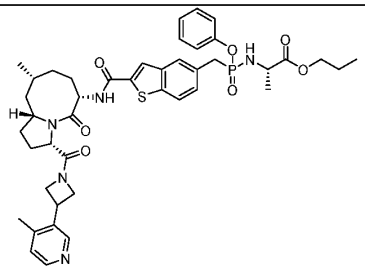
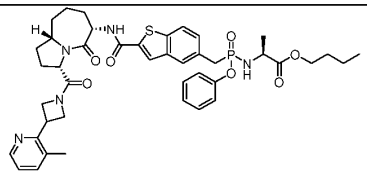
277	isobutyl ((fluoro(2-(((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		822.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 - 8.51 (m, 2H), 7.98 (d, J = 8.8 Hz, 1H), 7.92 - 7.78 (m, 2H), 7.73 - 7.65 (m, 1H), 7.62 - 7.52 (m, 1H), 7.40 - 7.32 (m, 1H), 7.27 - 7.14 (m, 2H), 7.11 - 7.04 (m, 2H), 6.08 - 5.85 (m, 1H), 5.02 - 4.74 (m, 1H), 4.71 - 4.55 (m, 3H), 4.39 - 4.32 (m, 1H), 4.24 - 4.09 (m, 2H), 3.97 - 3.86 (m, 2H), 3.86 - 3.77 (m, 1H), 3.72 - 3.51 (m, 1H), 2.32 - 2.26 (m, 1H), 2.25 - 2.18 (m, 1H), 2.10 - 2.01 (m, 4H), 1.99 - 1.88 (m, 3H), 1.85 - 1.80 (m, 1H), 1.38 - 1.22 (m, 3H), 1.17 - 1.07 (m, 1H), 0.95 - 0.80 (m, 6H)
278	propyl (((2-(((3S,6S,9aS)-3-(3-(6-fluoro-4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		820.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.05 - 7.97 (m, 2H), 8.06 - 7.84 (m, 2H), 7.53 - 7.45 (m, 1H), 7.35 - 7.28 (m, 2H), 7.21 - 7.10 (m, 3H), 6.72 (d, J = 16.6 Hz, 1H), 4.75 - 4.71 (m, 1H), 4.59 - 4.56 (m, 2H), 4.42 - 4.36 (m, 1H), 4.36 - 4.26 (m, 1H), 4.19 - 4.09 (m, 1H), 4.08 - 4.00 (m, 2H), 3.99 - 3.95 (m, 3H), 3.95 - 3.79 (m, 3H), 3.57 - 3.46 (m, 2H), 2.36 - 2.25 (m, 1H), 2.13 - 1.82 (m, 9H), 1.57 - 1.48 (m, 2H),

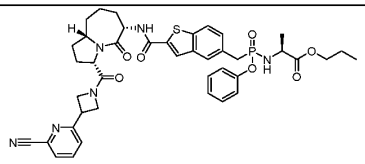
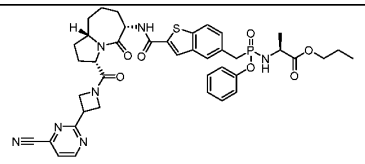
				1.16 - 1.04 (m, 3H), 0.90 - 0.83 (m, 3H)
279	butyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		786.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 - 8.62 (m, 2H), 8.51 (d, J = 6.8 Hz, 1H), 7.88 - 7.74 (m, 4H), 7.49 - 7.35 (m, 1H), 7.29 (s, 2H), 7.18 - 7.02 (m, 3H), 4.81 - 4.37 (m, 5H), 4.28 - 3.89 (m, 6H), 3.71 - 3.36 (m, 3H), 2.33 - 2.10 (m, 3H), 2.06 (d, J = 4.0 Hz, 3H), 1.98 - 1.69 (m, 4H), 1.57 - 1.47 (m, 2H), 1.37 - 1.26 (m, 2H), 1.20 - 1.14 (m, 2H), 0.97 - 0.80 (m, 3H)
280	propyl (((2-(((3S,6S,10aS)-3-(((3H-imidazo[4,5-b]pyridin-6-yl)methyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		800.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 - 8.35 (m, 1H), 8.30 - 8.11 (m, 2H), 8.02 (d, J = 15.2 Hz, 1H), 7.83 (d, J = 2.4 Hz, 1H), 7.71 (d, J = 8.8 Hz, 2H), 7.31 - 7.28 (m, 1H), 7.26 - 7.23 (m, 1H), 7.18 - 7.06 (m, 3H), 5.28 - 5.07 (m, 1H), 4.96 - 4.73 (m, 1H), 4.51 (s, 1H), 4.40 - 4.30 (m, 1H), 4.25 - 4.11 (m, 1H), 4.01 - 3.87 (m, 3H), 3.50 - 3.30 (m, 2H), 2.29 - 1.96 (m, 7H), 1.81 - 1.70 (m, 2H), 1.68 - 1.44 (m, 5H), 1.17 – 1.12 (m, 3H), 0.89 - 0.78 (m, 3H)

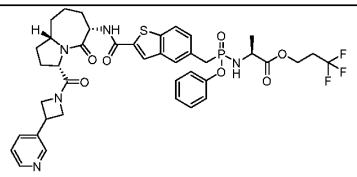
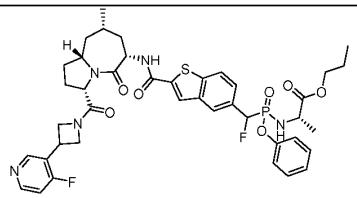
281	isobutyl (((2-(((3S,6S,10aS)-3-(3-methoxy-3-(pyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		830.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 8.87 - 8.63 (m, 1H), 8.48 (d, J = 8.4 Hz, 1H), 8.00 (s, 1H), 7.95 - 7.75 (m, 4H), 7.45 - 7.37 (m, 1H), 7.34 - 7.28 (m, 2H), 7.18 - 7.09 (m, 3H), 5.21 - 5.00 (m, 2H), 4.69 - 4.50 (m, 1H), 4.43 - 4.30 (m, 3H), 4.27 - 4.20 (m, 1H), 4.04 - 3.92 (m, 1H), 3.87 - 3.72 (m, 2H), 3.53 - 3.44 (m, 2H), 3.38 (s, 3H), 2.29 - 2.14 (m, 2H), 2.11 - 1.93 (m, 4H), 1.90 - 1.73 (m, 4H), 1.71 - 1.59 (m, 2H), 1.23 - 1.12 (m, 3H), 0.93 - 0.82 (m, 6H)
282	isobutyl (((2-(((3S,6S,10aS)-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		814.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 - 8.44 (m, 1H), 8.35 - 8.15 (m, 1H), 7.88 - 7.65 (m, 4H), 7.49 - 7.30 (m, 3H), 7.14 (d, J = 7.6 Hz, 3H), 5.13 - 4.92 (m, 1H), 4.52 (s, 2H), 4.45 - 4.27 (m, 3H), 4.13 - 3.94 (m, 3H), 3.87 - 3.72 (m, 2H), 3.66 - 3.56 (m, 1H), 3.54 - 3.38 (m, 2H), 2.37 - 2.25 (m, 3H), 2.18 (d, J = 5.6 Hz, 2H), 2.13 - 2.02 (m, 2H), 1.97 (d, J = 3.6 Hz, 2H), 2.01 - 1.71 (m, 6H), 1.69 - 1.50 (m, 2H), 1.29 - 1.16 (m, 3H), 0.95 - 0.82 (m, 6H)

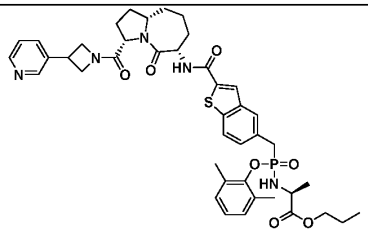
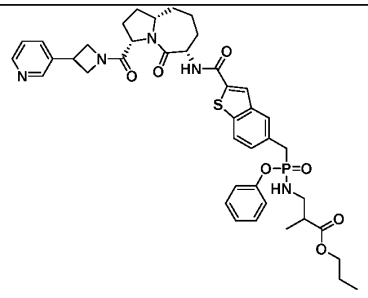
283	propyl (((2-(((3S,6S,8S,9aR)-8-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		800.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 - 8.55 (m, 1H), 8.15 - 7.35 (m, 6H), 7.32 - 7.27 (m, 2H), 7.20 - 7.08 (m, 3H), 5.17 - 4.90 (m, 2H), 4.77 - 4.63 (m, 1H), 4.55 - 4.38 (m, 2H), 4.27 - 4.10 (m, 2H), 4.08 - 3.89 (m, 4H), 3.51 - 3.38 (m, 2H), 2.47 (s, 3H), 2.36 - 2.19 (m, 2H), 2.18 - 1.88 (m, 6H), 1.67 - 1.51 (m, 3H), 1.35 - 1.14 (m, 6H), 0.87 (q, J = 7.2 Hz, 3H)
284	propyl (((2-(((3S,6S,8R,9aR)-8-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		800.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 - 8.87 (m, 1H), 8.71 - 8.57 (m, 1H), 7.98 - 7.75 (m, 3H), 7.62 (m, 1H), 7.57 - 7.36 (m, 2H), 7.32 - 7.27 (m, 2H), 7.17 - 7.10 (m, 3H), 5.13 - 5.02 (m, 1H), 4.86 - 4.64 (m, 2H), 4.58 - 4.40 (m, 2H), 4.15 - 3.83 (m, 6H), 3.51 - 3.39 (m, 2H), 2.49 (s, 3H), 2.34 - 1.98 (m, 6H), 1.84 - 1.46 (m, 5H), 1.22 - 1.12 (m, 3H), 1.06 - 0.98 (m, 3H), 0.91 - 0.83 (m, 3H)
285	butyl N-((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-		836.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 - 8.83 (m, 1H), 8.80 - 8.68 (m, 1H), 8.58 - 8.11 (m, 2H), 8.03 - 7.89 (m, 2H), 7.88 - 7.75 (m, 2H), 7.74 (s, 1H), 7.32 - 7.29 (m, 1H),

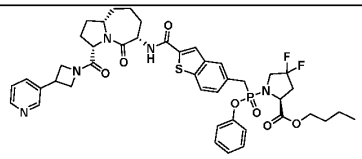
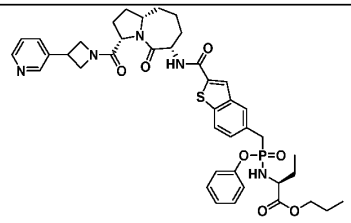
	yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-N-methyl-L-alaninate			7.22 - 7.09 (m, 3H), 4.89 - 4.66 (m, 3H), 4.64 - 4.48 (m, 3H), 4.20 - 4.15 (m, 1H), 4.07 (t, J = 6.4 Hz, 2H), 3.99 (t, J = 6.4 Hz, 2H), 2.88 - 2.76 (m, 3H), 2.17 (d, J = 14.0 Hz, 2H), 2.13 - 1.99 (m, 4H), 1.98 - 1.71 (m, 4H), 1.60 - 1.48 (m, 2H), 1.40 (d, J = 7.2 Hz, 1H), 1.33 (t, J = 7.2 Hz, 4H), 0.96 - 0.82 (m, 3H)
286	propyl (((2-(((3S,6S,9S,10aR)-9-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		814.6	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.69 - 8.53 (m, 1H), 8.23 - 8.07 (m, 1H), 7.99 (d, J = 6.0 Hz, 1H), 7.87 - 7.79 (m, 1H), 7.78 - 7.74 (m, 1H), 7.56 (dd, J = 5.2, 18.0 Hz, 1H), 7.46 - 7.34 (m, 1H), 7.32 - 7.28 (m, 2H), 7.16 - 7.11 (m, 3H), 5.03 (d, J = 4.0 Hz, 1H), 4.97 (d, J = 9.2 Hz, 1H), 4.74 - 4.67 (m, 1H), 4.49 - 4.43 (m, 1H), 4.37 (t, J = 8.0 Hz, 2H), 4.24 - 4.08 (m, 1H), 4.07 - 3.98 (m, 2H), 3.97 - 3.93 (m, 2H), 3.51 - 3.41 (m, 2H), 2.48 (d, J = 12.8 Hz, 3H), 2.32 - 2.18 (m, 2H), 2.16 - 2.08 (m, 2H), 2.06 - 1.90 (m, 2H), 1.88 - 1.80 (m, 2H), 1.75 - 1.65 (m, 2H), 1.61 - 1.53 (m, 2H), 1.37 - 1.29 (m, 1H),

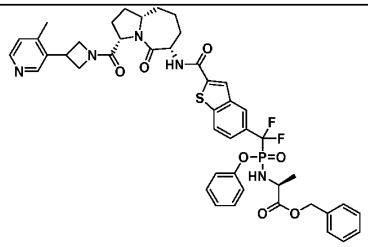
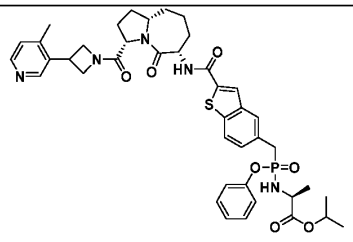
				1.18 (dd, J = 7.2, 16.4 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H), 0.91 - 0.85 (m, 3H)
287	propyl (((2-(((3S,6S,9R,10aR)-9-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		814.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.67 - 8.50 (m, 1H), 8.23 - 8.14 (m, 1H), 8.05 (d, J = 6.4 Hz, 1H), 7.85 - 7.74 (m, 2H), 7.52 (s, 1H), 7.47 - 7.36 (m, 1H), 7.35 - 7.27 (m, 2H), 7.17 - 7.10 (m, 3H), 5.27 - 5.15 (m, 1H), 5.13 - 4.98 (m, 1H), 4.74 - 4.61 (m, 1H), 4.47 - 4.34 (m, 3H), 4.21 - 4.06 (m, 1H), 4.06 - 3.98 (m, 2H), 3.98 - 3.92 (m, 2H), 3.50 - 3.39 (m, 2H), 2.51 - 2.38 (m, 3H), 2.25 - 2.17 (m, 2H), 2.15 - 2.10 (m, 1H), 2.06 - 1.98 (m, 2H), 1.93 (d, J = 11.6 Hz, 1H), 1.89 - 1.80 (m, 3H), 1.62 - 1.53 (m, 3H), 1.45 (d, J = 14.0 Hz, 1H), 1.18 (dd, J = 7.2, 19.2 Hz, 3H), 1.03 (d, J = 6.0 Hz, 3H), 0.92 - 0.84 (m, 3H)
288	butyl (((2-(((3S,6S,9aS)-3-(3-(3-methylpyridin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		800.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.55 - 8.40 (m, 1H), 8.17 - 7.97 (m, 2H), 7.93 - 7.84 (m, 2H), 7.59 - 7.46 (m, 2H), 7.35 - 7.28 (m, 2H), 7.21 - 7.15 (m, 2H), 7.15 - 7.01 (m, 1H), 4.77 - 4.71 (m, 2H), 4.61 -

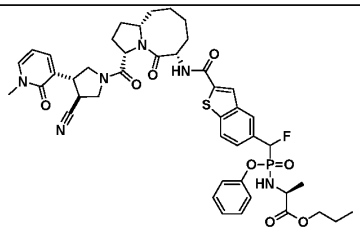
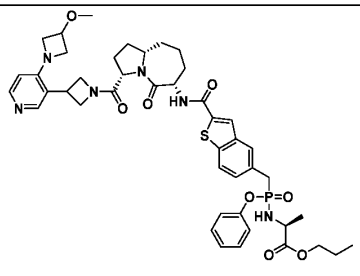
	yl)methyl)(phenoxy)phosphoryl)-L-alaninate			4.41 (m, 4H), 4.35 - 4.24 (m, 1H), 4.13 - 4.04 (m, 1H), 4.03 - 3.90 (m, 2H), 3.89 - 3.78 (m, 1H), 3.59 - 3.44 (m, 2H), 2.40 (d, J = 16.0 Hz, 3H), 2.35 - 2.26 (m, 1H), 2.21 - 2.06 (m, 2H), 2.02 (dd, J = 5.6, 12.0 Hz, 2H), 1.97 (d, J = 4.8 Hz, 2H), 1.89 - 1.79 (m, 3H), 1.55 - 1.45 (m, 2H), 1.34 - 1.25 (m, 2H), 1.16 - 1.06 (m, 3H), 0.94 - 0.86 (m, 3H)
289	propyl (((2-(((3S,6S,9aS)-3-(3-(6-cyanopyridin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		797.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.05 - 8.01 (m, 1H), 7.98 - 7.83 (m, 3H), 7.79 - 7.58 (m, 2H), 7.49 (s, 1H), 7.35 - 7.28 (m, 2H), 7.22 - 7.12 (m, 3H), 4.79 - 4.55 (m, 3H), 4.51 - 4.25 (m, 2H), 4.21 - 4.02 (m, 3H), 3.99 - 3.76 (m, 3H), 3.61 - 3.40 (m, 2H), 2.41 - 2.25 (m, 1H), 2.21 - 2.10 (m, 1H), 2.07 – 1.99 (m, 3H), 1.98 (s, 5H), 1.61 - 1.45 (m, 2H), 1.18 - 1.03 (m, 3H), 0.90 - 0.82 (m, 3H)
290	propyl (((2-(((3S,6S,9aS)-3-(3-(4-cyanopyrimidin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo		798.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 - 9.03 (m, 1H) 7.64 - 7.90 (m, 4H) 7.51 - 7.60 (m, 1H) 7.35 - 7.48 (m, 1H) 7.27 (s, 2H) 7.09 - 7.17 (m, 2H) 4.82 - 5.01 (m, 1H) 4.69 (m, 1H) 4.59

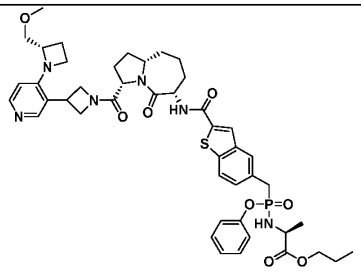
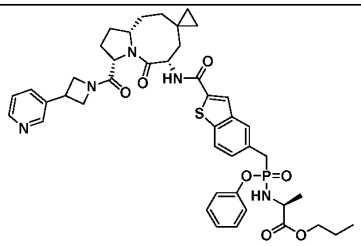
	[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate			(m, 2H) 4.35 - 4.52 (m, 2H) 4.22 - 4.27 (m, 1H) 3.87 - 4.07 (m, 4H) 3.40 - 3.53 (m, 2H) 2.15 - 2.33 (m, 2H) 1.87 - 2.12 (m, 6H) 1.66 - 1.85 (m, 2H) 1.48 - 1.64 (m, 2H) 1.08 - 1.24 (m, 3H) 0.78 - 0.97 (m, 3H)
291	3,3,3-trifluoropropyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		826.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 - 8.82 (m, 1H), 8.78 - 8.67 (m, 1H), 8.52 (s, 1H), 8.28 - 8.02 (m, 2H), 7.87 - 7.78 (m, 4H), 7.45 – 7.39 (m, 1H), 7.18 - 7.09 (m, 3H), 4.81 - 4.45 (m, 4H), 4.29 - 4.11 (m, 3H), 4.09 - 3.93 (m, 3H), 3.66 - 3.35 (m, 3H), 2.43 - 2.25 (m, 3H), 2.19 - 2.01 (m, 5H), 1.97 - 1.67 (m, 4H), 1.22 - 1.10 (m, 3H)
292	propyl ((fluoro(2-(((3S,6S,8R,9aR)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		822.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 - 8.51 (m, 2H), 8.02 - 7.93 (m, 1H), 7.90 - 7.80 (m, 2H), 7.69 (s, 1H), 7.63 - 7.54 (m, 1H), 7.40 - 7.32 (m, 1H), 7.30 - 7.27 (m, 1H), 7.24 (d, J = 2.0 Hz, 1H), 7.15 - 7.06 (m, 3H), 6.08 - 5.84 (m, 1H), 4.70 (m, 1H), 4.66 - 4.54 (m, 2H), 4.42 - 4.30 (m, 1H), 4.23 - 4.09 (m, 2H), 4.06 (m, 2H), 4.01 - 3.91 (m, 2H), 3.75 - 3.57 (m, 1H), 2.29

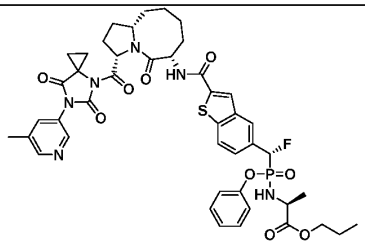
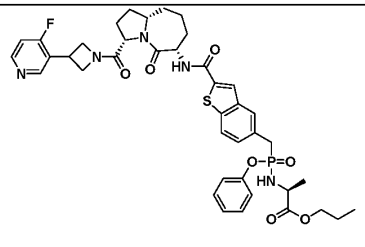
				(m, 1H), 2.16 - 2.01 (m, 5H), 1.80 - 1.68 (m, 2H), 1.67 - 1.58 (m, 2H), 1.56 - 1.49 (m, 1H), 1.35 - 1.28 (m, 3H), 1.02 (d, J = 6.0 Hz, 3H), 0.95 - 0.89 (m, 3H)
293	propyl ((2,6-dimethylphenoxy)((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)-L-alaninate		800.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.60 - 8.52 (m, 1H), 8.49 - 8.38 (m, 1H), 8.12 - 8.03 (m, 1.6H), 7.99 - 7.92 (m, 1.4H), 7.91 - 7.85 (m, 1H), 7.55 - 7.45 (m, 1.4H), 7.44 - 7.38 (m, 0.6H), 7.03 - 6.90 (m, 3H), 4.94 (t, J = 8.4 Hz, 0.4H), 4.80 - 4.73 (m, 1H), 4.72 - 4.66 (m, 0.6H), 4.63 - 4.47 (m, 2H), 4.45 - 4.37 (m, 0.6H), 4.34 - 4.26 (m, 0.4H), 4.13 - 3.76 (m, 6H), 3.69 - 3.48 (m, 2H), 2.36 - 2.25 (m, 5H), 2.22 (s, 2H), 2.20 - 1.78 (m, 9H), 1.59 - 1.46 (m, 2H), 1.15 (d, J = 7.3 Hz, 1H), 1.03 (d, J = 7.1 Hz, 2H), 0.91 - 0.80 (m, 3H)
294	propyl 2-methyl-3-((((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		786.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.60 -8.51 (m, 1H), 8.49 - 8.39 (m, 1H), 8.14 - 7.83 (m, 4H), 7.53 - 7.38 (m, 2H), 7.38 - 7.27 (m, 2H), 7.23 - 7.08 (m, 3H), 4.98 - 4.91 (m, 0.4H), 4.79 - 4.66 (m, 1.6H), 4.62

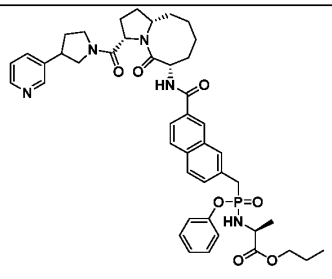
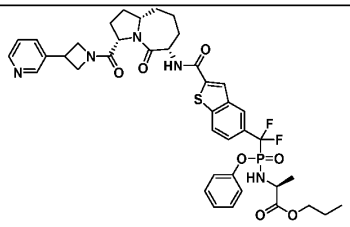
	yl)methyl)(phenoxy)phosphoryl)amino) propanoate			- 4.48 (m, 2H), 4.46 - 4.38 (m, 0.6H), 4.34 - 4.27 (m, 0.4H), 4.13 - 3.84 (m, 5H), 3.57 - 3.42 (m, 2H), 3.15 - 3.00 (m, 1H), 2.98 - 2.80 (m, 1H), 2.39 - 2.26 (m, 2H), 2.20 - 1.78 (m, 9H), 1.61 - 1.50 (m, 2H), 1.01 - 0.92 (m, 3H), 0.92 - 0.83 (m, 3H)
295	butyl (2S)-4,4-difluoro-1-(((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)pyrrolidine-2-carboxylate		848.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.63 - 8.35 (m, 2H), 8.15 - 7.85 (m, 4H), 7.62 - 7.08 (m, 7H), 4.99 - 4.90 (m , 0.4H), 4.80 - 4.38 (m, 4.6H), 4.34 - 4.24 (m, 1H), 4.19 - 3.34 (m, 9H), 2.64 - 2.25 (m, 3H), 2.19 - 1.77 (m, 9H), 1.66 - 1.46 (m, 2H), 1.44 - 1.26 (m, 2H), 1.00 - 0.83 (m, 3H).
296	propyl (2S)-2-((((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)amino) butanoate		786.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.60 - 8.52 (m, 1H), 8.50 - 8.39 (m, 1H), 8.11 - 7.85 (m, 4H), 7.54 - 7.40 (m, 2H), 7.35 - 7.27 (m, 2H), 7.22 - 7.02 (m, 3H), 4.98 - 4.91 (m, 0.4H), 4.79 - 4.66 (m, 1.6H), 4.62 - 4.47 (m, 2H), 4.46 - 4.38 (m, 0.6H), 4.33 - 4.27 (m, 0.4H), 4.12 - 3.97 (m, 3H), 3.96 - 3.80 (m, 2H), 3.79 - 3.68 (m, 1H), 3.62 - 3.44 (m, 2H), 2.37 - 2.26 (m, 1H), 2.19 -

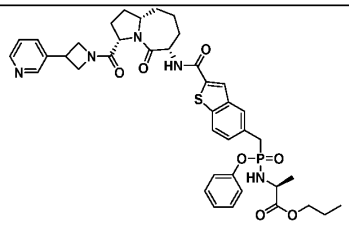
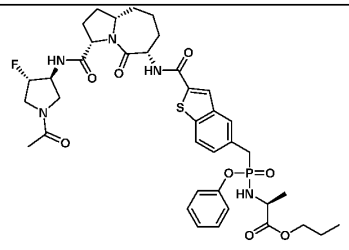
				1.77 (m, 9H), 1.61 - 1.39 (m, 4H), 0.90 - 0.81 (m, 3H), 0.72 - 0.63 (m, 3H)
297	benzyl ((difluoro(2-(((3S,6S,9aS)-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		870.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.64 - 8.52 (m, 1H), 8.34 - 8.25 (m, 1H), 8.23 - 8.17 (m, 1H), 8.17 - 8.10 (m, 1H), 8.09 - 8.02 (m, 0.5H), 8.01 - 7.95 (m, 0.5H), 7.75 - 7.66 (m, 1H), 7.40 - 7.10 (m, 11H), 5.10 - 5.06 (m, 1H), 5.06 - 4.98 (m, 1H), 4.98 - 4.91 (m, 0.5H), 4.79 - 4.68 (m, 2H), 4.64 - 4.56 (m, 1H), 4.54 - 4.47 (m, 0.5H), 4.45 - 4.36 (m, 1H), 4.28 - 4.02 (m, 3H), 4.01 - 3.90 (m, 1H), 2.36 - 2.25 (m, 4H), 2.21 - 1.75 (m, 9H), 1.31 - 1.24 (m, 3H)
298	isopropyl (((2-(((3S,6S,9aS)-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		786.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (t, J = 8.6 Hz, 1H), 8.59 - 8.50 (m, 1H), 8.36 - 8.29 (m, 1H), 8.22 - 8.16 (m, 1H), 7.93 (q, J = 7.1 Hz, 1H), 7.90 - 7.86 (m, 1H), 7.47 - 7.41 (m, 1H), 7.36 - 7.29 (m, 2H), 7.22 - 7.08 (m, 4H), 5.70 - 5.50 (m, 1H), 4.85 - 4.75 (m, 1.5H), 4.70 - 4.59 (m, 1.5H), 4.50 - 4.42 (m, 1.5H), 4.38 - 4.21 (m, 1.5H), 4.17 - 3.96 (m, 3H),

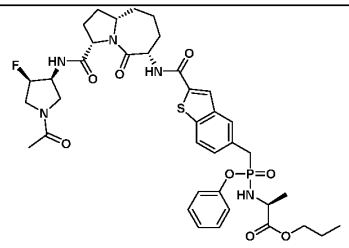
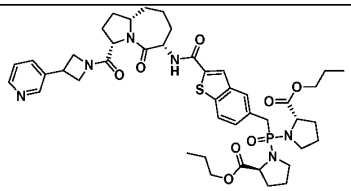
				3.86 - 3.65 (m, 1H), 3.50 - 3.38 (m, 2H), 2.20 (s, 4H), 2.09 - 1.92 (m, 2H), 1.88 - 1.63 (m, 7H), 1.13 - 1.05 (m, 7H), 0.97 (t, *J* = 6.6 Hz, 2H)
299	propyl (((2-(((3S,6S,10aS)-3-(*rel*-(trans)-3-cyano-4-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		873.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.18 - 8.09 (m, 1H), 8.09 - 8.04 (m, 1H), 8.03 - 7.90 (m, 1H), 7.68 - 7.49 (m, 3H), 7.38 - 7.27 (m, 2H), 7.24 - 7.11 (m, 3H), 6.42 - 6.28 (m, 1H), 6.20 - 5.80 (m, 1H), 5.10 - 4.98 (m, 1H), 4.72 - 4.57 (m, 1H), 4.49 - 4.36 (m, 1H), 4.29 - 3.61 (m, 8H), 3.59 - 3.49 (m, 3H), 2.42 - 2.17 (m, 2H), 2.10 - 1.47 (m, 11H), 1.40 - 1.01 (m, 5H), 0.90 - 0.81 (m, 3H)
300	propyl (((2-(((3S,6S,9aS)-3-(3-(4-(3-methoxyazetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		857.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.40 - 8.23 (m, 1H), 8.13 - 7.99 (m, 2H), 7.95 - 7.82 (m, 2H), 7.54 - 7.45 (m, 1H), 7.38 - 7.26 (m, 2H), 7.24 - 7.09 (m, 3H), 6.55 - 6.35 (m, 1H), 4.78 - 4.74 (m, 1H), 4.66 - 4.54 (m, 2H), 4.50 - 4.35 (m, 1H), 4.35 - 4.25 (m, 4H), 4.16 - 4.01 (m, 3H), 4.01 - 3.76 (m, 5H), 3.60 - 3.42 (m, 2H), 3.36 - 3.29 (m, 3H), 2.37 - 2.25 (m, 1H), 2.19 - 1.73 (m, 9H), 1.59 -

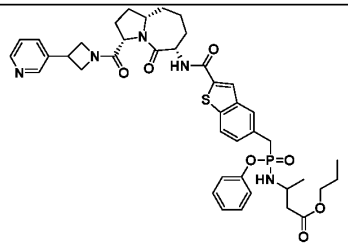
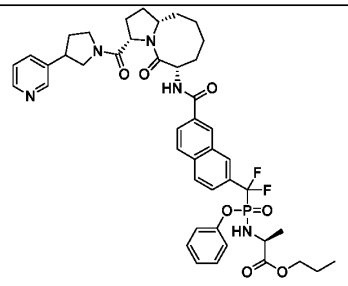
				1.48 (m, 2H), 1.18 - 1.05 (m, 3H), 0.90 - 0.83 (m, 3H)
301	propyl (((2-(((3S,6S,9aS)-3-(3-(4-((S)-2-(methoxymethyl)azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		871.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.37 - 8.24 (m, 1H), 8.12 - 8.00 (m, 2H), 7.96 - 7.83 (m, 2H), 7.53 - 7.44 (m, 1H), 7.36 - 7.27 (m, 2H), 7.21 (m, 3H), 6.81 - 6.72 (m, 1H), 4.78 - 4.54 (m, 4H), 4.52 - 4.43 (m, 1H), 4.38 - 3.99 (m, 5H), 3.98 - 3.77 (m, 3H), 3.75 - 3.64 (m, 1H), 3.64 - 3.41 (m, 4H), 3.37 - 3.32 (m, 3H), 2.46 - 1.74 (m, 12H), 1.62 - 1.47 (m, 2H), 1.18 - 1.05 (m, 3H), 0.90 - 0.82 (m, 3H)
302	propyl (((2-(((3'S,6'S,10a'S)-5'-oxo-3'-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-5'H-spiro[cyclopropane-1,8'-pyrrolo[1,2-a]azocin]-6'-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		812.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.60 (br. s., 0.5H), 8.54 (s, 0.5H), 8.49 - 8.40 (m, 1H), 8.08 - 8.01 (m, 1.5H), 7.97 - 7.82 (m, 2.5H), 7.53 - 7.41 (m, 2H), 7.36 - 7.27 (m, 2H), 7.22 - 7.11 (m, 3H), 5.07 - 4.96 (m, 1.5H), 4.70 (d, *J* = 7.3 Hz, 1H), 4.58 - 4.37 (m, 3H), 4.34 - 4.26 (m, 0.5H), 4.10 - 3.76 (m, 5H), 3.60 - 3.45 (m, 2H), 2.33 - 2.16 (m, 2H), 2.15 - 2.01 (m, 1H), 2.01 - 1.82 (m, 4H), 1.77 - 1.46 (m, 5H), 1.14 (d, *J* = 7.1 Hz, 1H), 1.10 -

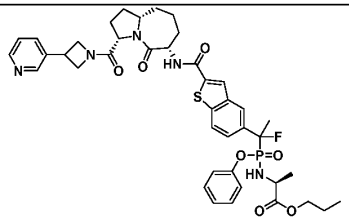
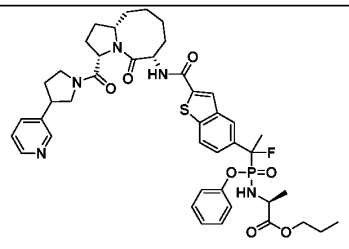
				1.04 (m, 2H), 0.91 - 0.81 (m, 3H), 0.64 - 0.43 (m, 4H)
303	propyl (((R)-fluoro(2-(((3S,6S,10aS)-3-(6-(5-methylpyridin-3-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		887.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.75 - 8.37 (m, 1H), 8.14 - 8.05 (m, 2H), 8.01 - 7.95 (m, 1H), 7.87 - 7.80 (m, 1H), 7.67 - 7.59 (m, 1H), 7.37 - 7.29 (m, 2H), 7.23 - 7.12 (m, 3H), 6.18 - 5.99 (m, 1H), 5.61 - 5.53 (m, 1H), 5.09 - 5.00 (m, 1H), 4.53 - 4.43 (m, 1H), 4.00 - 3.67 (m, 3H), 3.26 - 3.11 (m, 1H), 2.63 - 2.52 (m, 1H), 2.46 - 2.39 (m, 4H), 2.34 - 2.28 (m, 1H), 2.07 - 1.81 (m, 5H), 1.76 - 1.62 (m, 1H), 1.62 - 1.45 (m, 2H), 1.40 - 1.34 (m, 3H), 1.33 - 1.25 (m, 3H), 1.23 - 1.18 (m, 2H), 0.98 - 0.82 (m, 4H)
304	propyl (((2-(((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		790.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.77 - 8.57 (m, 1H), 8.54 - 8.43 (m, 1H), 8.04 (d, *J* = 3.9 Hz, 1H), 7.95 - 7.82 (m, 2H), 7.53 - 7.43 (m, 1H), 7.36 - 7.09 (m, 6H), 4.92 (t, *J* = 8.7 Hz, 0.5H), 4.78 - 4.67 (m, 2H), 4.61 - 4.54 (m, 1H), 4.53 - 4.36 (m, 1.5H), 4.26 - 4.11 (m, 2H), 4.10 - 4.01 (m, 1H), 3.98 - 3.76 (m, 3H), 3.60 - 3.41 (m, 2H), 2.37 -

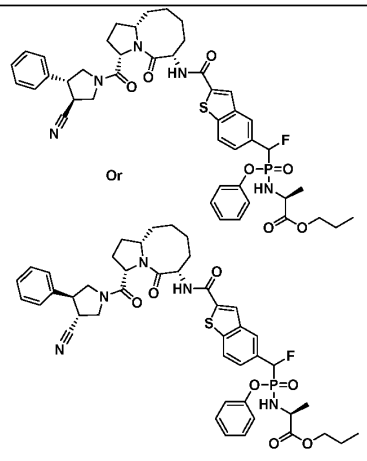
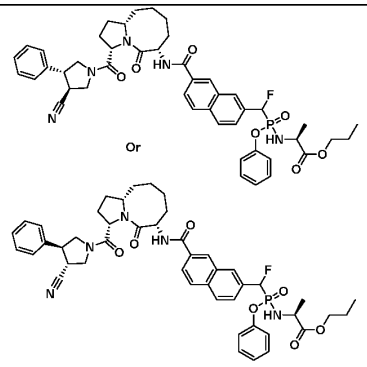
				2.24 (m, 1H), 2.20 - 1.74 (m, 9H), 1.60 - 1.47 (m, 2H), 1.14 (d, *J* = 7.1 Hz, 1.25H), 1.07 (dd, *J* = 7.1, 2.2 Hz, 1.75H), 0.91 - 0.81 (m, 3H)
305	propyl (((7-(((3S,6S,10aS)-5-oxo-3-(3-(pyridin-3-yl)pyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		794.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 - 8.35 (m, 3H), 8.01 - 7.75 (m, 5H), 7.67 - 761 (m, 1H), 7.45 - 7.27 (m, 3H), 7.24 - 7.10 (m, 3H), 5.18 - 5.07 (m, 1H), 4.78 - 4.65 (m, 1H), 4.53 - 4.35 (m, 1H), 4.16 - 3.76 (m, 5H), 3.75 - 3.33 (m, 5H), 2.47 - 1.93 (m, 10H), 1.92 - 1.75 (m, 2H), 1.74 - 1.58 (m, 2H), 1.58 - 1.43 (m, 2H), 1.19 - 1.00 (m, 3H), 0.92 - 0.75 (m, 3H)
306	propyl ((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		809.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.60 - 8.52 (m, 1H), 8.49 - 8.38 (m, 1H), 8.29 - 7.93 (m, 4H), 7.78 - 7.67 (m, 1H), 7.51 - 7.31 (m, 3H), 7.27 - 7.02 (m, 3H), 5.09 - 4.91 (m, 1.4H), 4.80 - 4.74 (m, 1H), 4.73 - 4.66 (m, 0.6H), 4.63 - 4.47 (m, 2H), 4.46 - 4.27 (m, 1H), 4.15 - 3.95 (m, 5H), 2.37 - 2.26 (m, 1H), 2.20 - 1.79 (m, 9H), 1.63 - 1.53 (m, 2H), 1.52 - 1.44 (m, 3H), 0.92 - 0.83 (m, 3H)

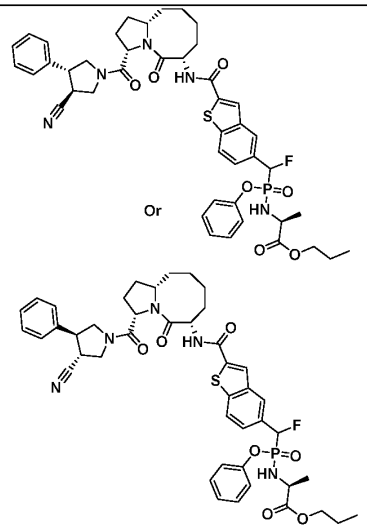
307	propyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		773.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.59 - 8.55 (m, 1H), 8.50 - 8.37 (m, 1H), 8.11 - 7.84 (m, 4H), 7.56 - 7.38 (m, 2H), 7.37 - 7.26 (m, 2H), 7.24 - 7.11 (m, 2H), 7.10 - 7.03 (m, 1H), 4.98 - 4.86 (m, 1.4H), 4.80 - 4.65 (m, 1.6H), 4.62 - 4.37 (m, 2.6H), 4.30 (dd, *J* = 9.4, 5.3 Hz, 0.4H), 4.16 - 3.95 (m, 5H), 3.80 - 3.58 (m, 2H), 2.37 - 2.26 (m, 1H), 2.19 - 1.77 (m, 9H), 1.69 - 1.51 (m, 2H), 1.36 (dd, *J* = 6.8, 1.5 Hz, 3H), 0.98 - 0.80 (m, 3H)
308	propyl (((2-(((3S,6S,9aS)-3-(((3S,4S)-1-acetyl-4-fluoropyrrolidin-3-yl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		784.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.04 - 8.00 (m, 1H), 7.93 - 7.84 (m, 2H), 7.52 - 7.44 (m, 1H), 7.36 - 7.27 (m, 2H), 7.21 - 7.11 (m, 3H), 5.19 - 4.94 (m, 1H), 4.73 (d, *J* = 10.8 Hz, 1H), 4.54 - 4.36 (m, 2H), 4.11 - 3.99 (m, 1H), 3.98 - 3.42 (m, 9H), 2.34 - 2.22 (m, 1H), 2.17 - 1.73 (m, 12H), 1.61 - 1.46 (m, 2H), 1.14 (d, *J* = 7.1 Hz, 1.15H), 1.07 (d, *J* = 7.1 Hz, 1.85H), 0.86 (t, *J* = 7.5 Hz, 3H)

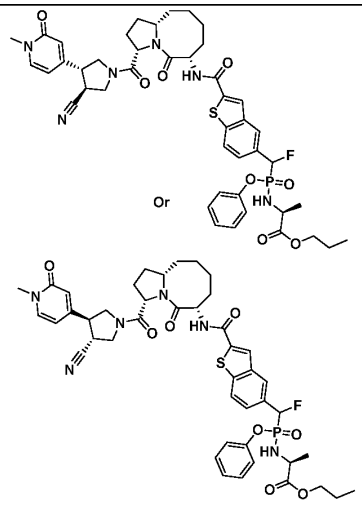
309	propyl (((2-(((3S,6S,9aS)-3-(((3S,4R)-1-acetyl-4-fluoropyrrolidin-3-yl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		784.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.05 - 8.00 (m, 1H), 7.94 - 7.84 (m, 2H), 7.53 - 7.45 (m, 1H), 7.36 - 7.27 (m, 2H), 7.21 - 7.11 (m, 3H), 5.29 - 5.04 (m, 1H), 4.74 (d, *J* = 10.5 Hz, 1H), 4.67 - 4.42 (m, 2H), 4.11 - 4.02 (m, 1H), 4.01 - 3.64 (m, 6H), 3.61 - 3.37 (m, 3H), 2.36 - 2.24 (m, 1H), 2.19 - 1.72 (m, 12H), 1.59 - 1.47 (m, 2H), 1.14 (d, *J* = 7.1 Hz, 1.25H), 1.07 (d, *J* = 7.1 Hz, 1.75H), 0.86 (t, *J* = 7.3 Hz, 3H)
310	dipropyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)(S)-di-L-prolinate		861.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.59 - 8.53 (m, 1H), 8.49 - 8.41 (m, 1H), 8.13 - 8.08 (m, 0.5H), 8.07 - 8.03 (m, 1H), 7.99 - 7.94 (m, 0.5H), 7.93 - 7.86 (m, 2H), 7.51 - 7.40 (m, 2H), 4.98 - 4.93 (m, 0.5H), 4.79 - 4.67 (m, 1H), 4.63 - 4.55 (m, 1.5H), 4.46 - 4.37 (m, 1.5H), 4.35 - 4.26 (m, 0.5H), 4.18 - 3.90 (m, 7H), 3.71 - 3.64 (m, 1H), 3.62 - 3.47 (m, 2H), 3.46 - 3.35 (m, 3H), 2.36 - 1.75 (m, 19H), 1.74 - 1.65 (m, 2H), 1.63 - 1.56 (m, 2H), 1.01 - 0.94 (m, 3H), 0.92 - 0.86 (m, 3H)

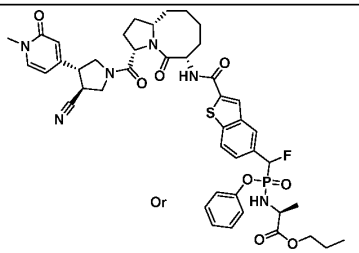
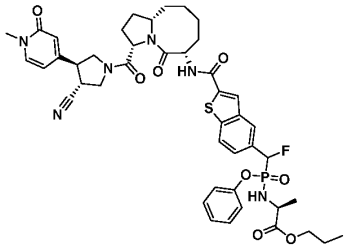
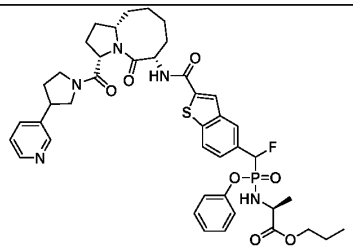
311	propyl 3-((((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)amino)butanoate		786.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.62 - 8.55 (m, 1H), 8.52 - 5.40 (m, 1H), 8.16 - 7.84 (m, 4H), 7.54 - 7.41 (m, 2H), 7.38 - 7.26 (m, 2H), 7.22 - 7.08 (m, 3H), 4.99 - 4.91 (m, 0.4H), 4.80 - 4.66 (m, 1.6H), 4.63 - 4.48 (m, 2H), 4.46 - 4.36 (m, 0.6H), 4.33 - 4.27 (m, 0.4H), 4.13 - 3.84 (m, 5H), 3.74 - 3.38 (m, 3H), 2.39 - 1.74 (m, 12H), 1.62 - 1.49 (m, 2H), 1.00 - 0.92 (m, 3H), 0.91 - 0.83 (m, 3H)
312	propyl ((difluoro(7-(((3S,6S,10aS)-5-oxo-3-(3-(pyridin-3-yl)pyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		830.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.62 - 8.46 (m, 2H), 8.46 - 8.35 (m, 1H), 8.34 - 8.28 (m , 1H), 8.13 - 7.97 (m, 3H), 7.91 - 7.76 (m, 2H), 7.47 - 7.27 (m, 3H), 7.24 - 7.08 (m, 3H), 5.18 - 5.07 (m, 1H), 4.79 - 4.67 (m, 1H), 4.53 - 4.36 (m, 1H), 4.17 - 3.77 (m, 5H), 3.75 - 3.33 (m, 3H), 2.49 - 1.94 (m, 10H), 1.93 - 1.76 (m, 2H), 1.75 - 1.46 (m, 4H), 1.32 - 1.23 (m, 3H), 0.94 - 0.79 (m, 3H)

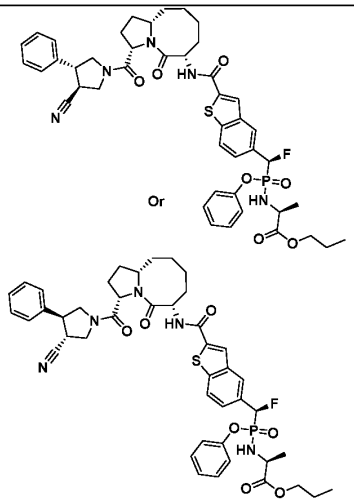
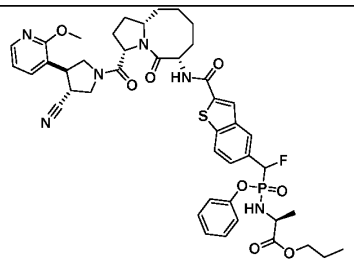
313	propyl ((1-fluoro-1-(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)ethyl)(phenoxy)phosphoryl)-L-alaninate		804.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.60 - 8.52 (m, 1H), 8.50 - 8.39 (m, 1H), 8.16 - 8.05 (m, 2.5H), 8.03 - 7.93 (m, 1.5H), 7.72 - 7.64 (m, 1H), 7.52 - 7.32 (m, 2H), 7.31 - 7.16 (m, 2.5H), 7.15 - 7.00 (m, 1.5H), 4.99 - 4.91 (m, 0.5H), 4.81 - 4.73 (m, 1H), 4.73 - 4.66 (m, 0.5H), 4.64 - 4.50 (m, 2H), 4.46 - 4.37 (m, 0.5H), 4.35 - 4.26 (m, 0.5H), 4.14 - 3.85 (m, 5H), 2.38 - 2.25 (m, 1H), 2.18 - 1.77 (m, 12H), 1.64 - 1.53 (m, 1H), 1.52 - 1.38 (m, 1H), 1.33 - 1.26 (m, 1H), 1.24 (d, J = 7.3 Hz, 1H), 1.20 (d, J = 7.1 Hz, 1H), 1.10 (d, J = 7.1 Hz, 1H), 0.94 - 0.87 (m, 2H), 0.85 - 0.77 (m, 1H)
314	propyl ((1-fluoro-1-(2-(((3S,6S,10aS)-5-oxo-3-(3-(pyridin-3-yl)pyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)ethyl)(phenoxy)phosphoryl)-L-alaninate		832.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.57 - 8.47 (m, 1H), 8.46 - 8.35 (m, 1H), 8.19 - 8.04 (m, 2H), 8.02 - 7.91 (m, 1H), 7.90 - 7.78 (m, 1H), 7.71 - 7.61 (m, 1H), 7.46 - 7.32 (m, 2H), 7.31 - 7.16 (m, 2.4H), 7.16 - 6.98 (m, 1.6H), 5.12 - 5.00 (m, 1H), 4.79 - 4.64 (m, 1H), 4.50 - 4.35 (m, 1H), 4.16 - 3.76 (m, 4H), 3.75 - 3.41 (m, 3H), 2.50 - 2.18 (m, 3H),

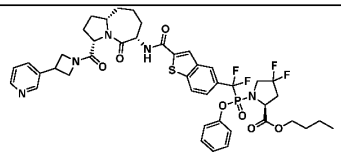
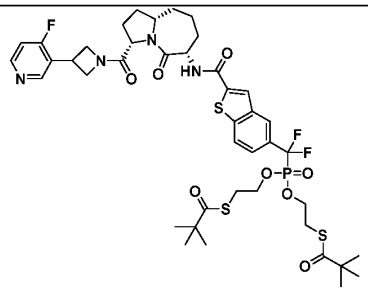
				2.17 - 1.93 (m, 10H), 1.92 - 1.52 (m, 6H), 1.51 - 1.36 (m, 1H), 1.27 - 1.17 (m, 2H), 1.13 - 1.07 (m, 1H), 0.95 - 0.86 (m, 2H), 0.85 - 0.77 (m, 1H)
315	propyl (((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	842.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (s, 1H), 8.08 (br. s., 1H), 8.04 - 7.92 (m, 1H), 7.70 - 7.59 (m, 1H), 7.46 - 7.27 (m, 7H), 7.25 - 7.13 (m, 3H), 6.20 - 5.98 (m, 1H), 5.09 - 4.99 (m, 1H), 4.73 - 4.65 (m, 1H), 4.57 - 4.50 (m, 0.5H), 4.49 - 4.39 (m, 1.5H), 4.10 - 4.02 (m, 0.5H), 4.00 - 3.64 (m, 5.5H), 3.63 - 3.49 (m, 2H), 2.42 - 2.15 (m, 2H), 2.10 - 1.92 (m, 6H), 1.91 - 1.76 (m, 2H), 1.73 - 1.48 (m, 4H), 1.25 - 1.18 (m, 2H), 1.09 - 1.02 (m, 1H), 0.93 - 0.80 (m, 3H)
316	propyl (((7-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)fluoromethyl)(ph		836.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.53 - 8.47 (m, 1H), 8.20 - 8.10 (m, 1H), 8.05 - 7.94 (m, 3H), 7.84 - 7.73 (m, 1H), 7.68 - 7.12 (m, 10H), 6.27 - 6.06 (m, 1H), 5.16 - 5.06 (m, 1H), 4.75 - 4.64 (m, 1H), 4.60 - 4.42 (m, 2H), 4.11 -

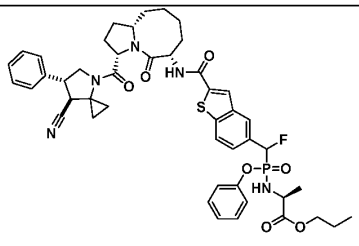
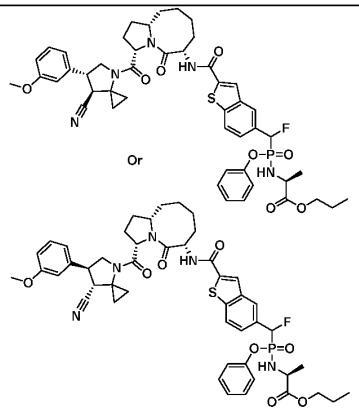
	enoxy)phosphoryl)-L-alaninate Or propyl (((7-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing		3.47 (m, 8H), 2.42 - 2.18 (m, 2H), 2.14 - 1.92 (m, 6H), 1.92 - 1.76 (m, 2H), 1.75 - 1.63 (m, 2H), 1.60 - 1.43 (m, 2H), 1.26 - 1.15 (m, 2H), 1.09 - 1.03 (m, 1H), 0.92 - 0.78 (m, 3H)
317	propyl (((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Pyrrolidine building block SFC peak 1 was used for synthesis and biological testing	842.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.17 - 8.11 (m, 1H), 8.08 (br. s., 1H), 8.03 - 7.92 (m, 1H), 7.69 - 7.58 (m, 1H), 7.48 - 7.26 (m, 7H), 7.24 - 7.12 (m, 3H), 6.19 - 5.98 (m, 1H), 5.09 - 4.98 (m, 1H), 4.69 - 4.57 (m, 1H), 4.49 - 4.38 (m, 1H), 4.24 - 4.15 (m, 1H), 4.14 - 4.04 (m, 1.5H), 4.01 - 3.73 (m, 4H), 3.70 - 3.54 (m, 1.5H), 3.51 - 3.37 (m, 1H), 2.40 - 2.18 (m, 2H), 2.09 - 1.94 (m, 6H), 1.90 - 1.75 (m, 2H), 1.74 - 1.44 (m, 4H), 1.27 - 1.19 (m, 2H), 1.06 (d, *J* = 7.1 Hz, 1H), 0.92 - 0.81 (m, 3H)

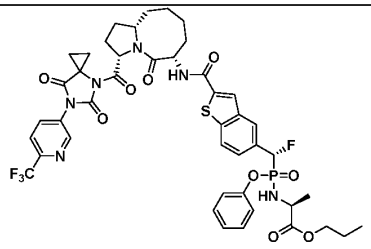
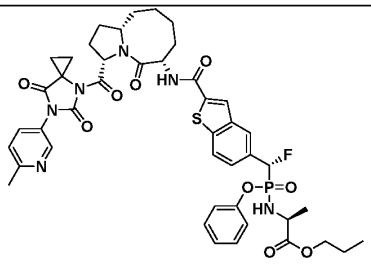
318	propyl (((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	873.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.16 - 8.11 (m, 1H), 8.08 (br. s., 1H), 8.04 - 7.93 (m, 1H), 7.71 - 7.58 (m, 2H), 7.38 - 7.28 (m, 2H), 7.25 - 7.13 (m, 3H), 6.67 - 6.55 (m, 1H), 6.50 - 6.39 (m, 1H), 6.20 - 5.98 (m, 1H), 5.09 - 4.97 (m, 1H), 4.67 - 4.56 (m, 1H), 4.50 - 4.38 (m, 1H), 4.24 - 4.14 (m, 1H), 4.13 - 4.03 (m, 1.5H), 4.01 - 3.77 (m, 3.5H), 3.76 - 3.65 (m, 1H), 3.64 - 3.44 (m, 4.5H), 3.41 - 3.33 (m, 0.5H), 2.41 - 2.18 (m, 2H), 2.11 - 1.91 (m, 6H), 1.91 - 1.75 (m, 2H), 1.74 - 1.47 (m, 4H), 1.22 (t, *J* = 6.5 Hz, 2H), 1.09 - 1.03 (m, 1H), 0.93 - 0.82 (m, 3H)

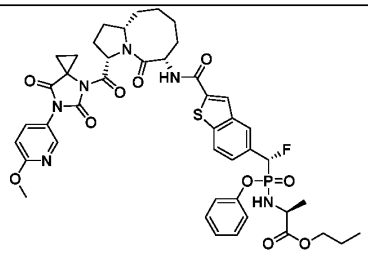
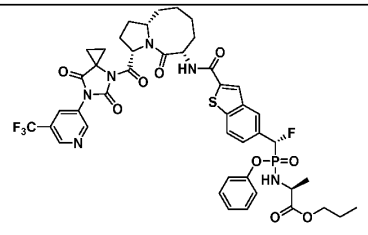
319	propyl (((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Or  Pyrrolidine building block SFC peak 1 was used for synthesis and biological testing	873.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (s, 1H), 8.08 (br. s., 1H), 8.03 - 7.93 (m, 1H), 7.70 - 7.60 (m, 2H), 7.38 - 7.29 (m, 2H), 7.25 - 7.12 (m, 3H), 6.62 - 6.54 (m, 1H), 6.46 - 6.40 (m, 1H), 6.20 - 5.98 (m, 1H), 5.07 - 4.97 (m, 1H), 4.72 - 4.61 (m, 1H), 4.57 - 4.37 (m, 2H), 4.10 - 3.77 (m, 4.5H), 3.76 - 3.45 (m, 6.5H), 2.42 - 2.16 (m, 2H), 2.12 - 1.92 (m, 6H), 1.91 - 1.74 (m, 2H), 1.73 - 1.46 (m, 4H), 1.26 - 1.18 (m, 2H), 1.06 (d, *J* = 6.8Hz, 1H), 0.93 - 0.82 (m, 3H)
320	propyl ((fluoro(2-(((3S,6S,10aS)-5-oxo-3-(3-(pyridin-3-yl)pyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		818.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.57 - 8.46 (m, 1H), 8.45 - 8.35 (m, 1H), 8.17 - 8.10 (m, 1H), 8.10 - 8.04 (m, 1H), 8.02 - 7.91 (m, 1H), 7.87 - 7.75 (m, 1H), 7.68 - 7.59 (m, 1H), 7.45 - 7.28 (m, 3H), 7.24 - 7.12 (m, 3H), 6.20 - 5.97 (m, 1H), 5.12 - 5.00 (m, 1H), 4.78 - 4.64 (m, 1H), 4.50 -

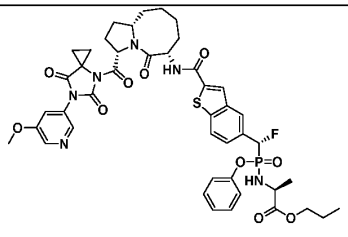
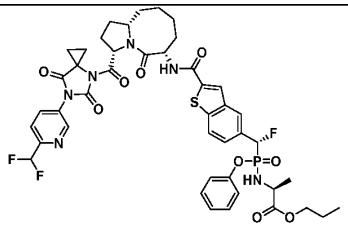
				4.34 (m, 1H), 4.18 - 3.34 (m, 8H), 2.51 - 1.93 (m, 10H), 1.91 - 1.74 (m, 2H), 1.74 - 1.44 (m, 4H), 1.26 - 1.17 (m, 2H), 1.05 (d, J = 7.3 Hz,1H), 0.92 - 0.81 (m, 3H)
321	propyl (((S)-(2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((S)-(2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	842.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.16 - 8.12 (m, 1H), 8.11 - 8.06 (m, 1H), 8.03 - 7.92 (m, 1H), 7.69 - 7.60 (m, 1H), 7.43 - 7.28 (m, 7H), 7.25 - 7.14 (m, 3H), 6.19 - 5.98 (m, 1H), 5.08 - 4.99 (m, 1H), 4.73 - 4.64 (m, 1H), 4.57 - 4.38 (m, 2H), 4.11 - 3.90 (m, 3H), 3.88 - 3.64 (m, 3H), 3.63 - 3.50 (m, 2H), 2.42 - 2.16 (m, 2H), 2.12 - 1.93 (m, 6H), 1.92 - 1.74 (m, 2H), 1.73 - 1.60 (m, 2H), 1.59 - 1.48 (m, 2H), 1.23 and 1.06 (d, J = 7.1 Hz, 3H), 0.87 (t, J = 7.5 Hz, 3H)
322	propyl (((2-(((3S,6S,10aS)-3-((*rel*-trans)-3-cyano-4-(2-methoxypyridin-3-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-		873.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.17 - 8.04 (m, 3H), 8.03 - 7.93 (m, 1H), 7.72 - 7.58 (m, 2H), 7.38 - 7.28 (m, 2H), 7.24 - 7.12 (m, 3H), 7.04 - 6.93 (m, 1H), 6.21 - 5.97 (m, 1H), 5.10 -

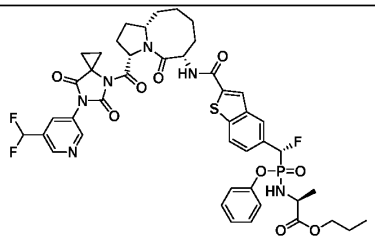
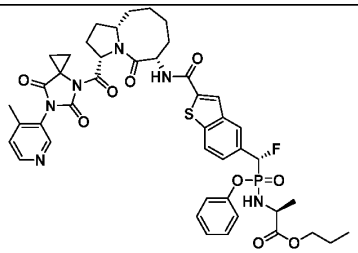
	yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate			4.98 (m, 1H), 4.73 - 4.60 (m, 1H), 4.50 - 4.35 (m, 1.5H), 4.25 - 3.55 (m, 11.5H), 2.44 - 2.17 (m, 2H), 2.11 - 1.92 (m, 6H), 1.91 - 1.75 (m, 2H), 1.74 - 1.45 (m, 4H), 1.27 - 1.17 (m, 2H), 1.09 - 1.03 (m, 1H), 0.92 - 0.82 (m, 3H)
323	butyl (2S)-1-((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-4,4-difluoropyrrolidine-2-carboxylate		884.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.64 - 8.37 (m, 2H), 8.28 - 7.93 (m, 4H), 7.76 - 7.71 (m, 1H), 7.51 - 7.39 (m, 1H), 7.37 - 7.28 (m, 2H), 7.23 - 7.14 (m, 1H), 7.14 - 7.08 (m, 2H), 4.98 - 4.92 (m, 0.5H), 4.80 - 7.74 (m, 1.5H), 4.75 - 4.68 (m, 1H), 4.64 - 4.28 (m, 3H), 4.13 - 3.95 (m, 5H), 3.75 - 3.65 (m, 2H), 2.86 - 2.48 (m, 3H), 2.38 - 2.27 (m, 1H), 2.19 - 2.05 (m, 2H), 2.05 - 1.93 (m, 3H), 1.93 - 1.81 (m, 3H), 1.57 - 1.49 (m, 2H), 1.38 - 1.28 (m, 2H), 0.93 - 0.85 (m, 3H)
324	S,S'-((((difluoro(2-(((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphor		925.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.81 - 8.58 (m, 1H), 8.56 - 8.45 (m, 1H), 8.23 - 8.15 (m, 2H), 8.14 - 8.05 (m, 1H), 7.71 - 7.59 (m, 1H), 7.32 - 7.18 (m, 1H), 4.99 - 4.89 (m, 1H), 4.80 - 4.69 (m, 2H), 4.65 - 4.38 (m, 2H), 4.30 -

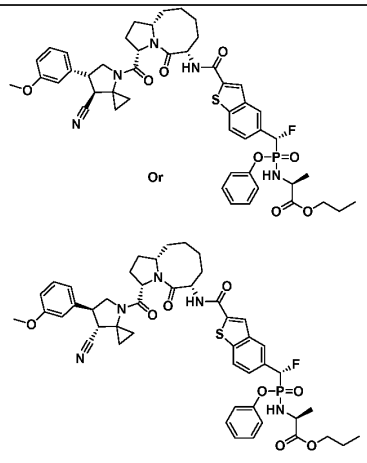
	yl)bis(oxy))bis(ethane-2,1-diyl)) bis(2,2-dimethylpropanethioate)			4.02 (m, 7H), 3.22 - 3.05 (m, 4H), 2.38 - 2.24 (m, 1H), 2.20 - 1.75 (m, 9H), 1.25 - 1.13 (m, 18H)
325	propyl (((2-(((3S,6S,10aS)-3-((*rel*-trans)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		868.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.16 - 8.11 (m, 1H), 8.10 - 8.04 (m, 1H), 8.02 - 7.92 (m, 1H), 7.69 - 7.60 (m, 1H), 7.51 - 7.44 (m, 1H), 7.43 - 7.25 (m, 6H), 7.24 - 7.12 (m, 3H), 6.19 - 5.98 (m, 1H), 5.06 - 4.96 (m, 1H), 4.67 - 4.54 (m, 1H), 4.45 - 4.33 (m, 1H), 4.21 - 4.07 (m, 1H), 4.02 - 3.63 (m, 6H), 2.42 - 2.13 (m, 3H), 2.08 - 1.72 (m, 9H), 1.70 - 1.44 (m, 4H), 1.27 - 1.15 (m, 2H), 1.11 - 1.02 (m, 1H), 1.02 - 0.93 (m, 1H), 0.92 - 0.81 (m, 3H), 0.77 - 0.62 (m, 1H).
326	propyl (((2-(((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or		898.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.15 - 8.10 (m, 1H), 8.10 - 8.05 (m, 1H), 8.02 - 7.91 (m, 1H), 7.69 - 7.58 (m, 1H), 7.40 - 7.12 (m, 6H), 7.06 - 7.00 (m, 1H), 7.00 - 6.94 (m, 1H), 6.91 - 6.81 (m, 1H), 6.21 - 5.96 (m, 1H), 5.06 - 4.97 (m, 1H), 4.67 - 4.56 (m, 1H), 4.45 - 4.33 (m, 1H), 4.20 - 4.07 (m, 1H), 4.02 - 3.64 (m, 9H), 2.42 - 2.14 (m, 3H), 2.07 -

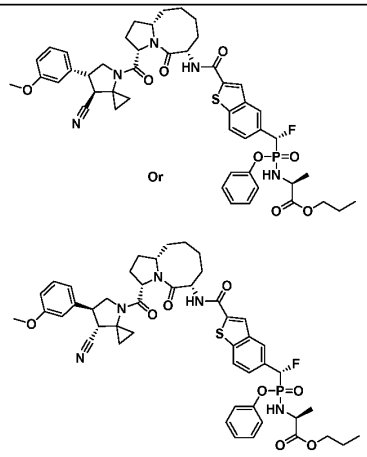
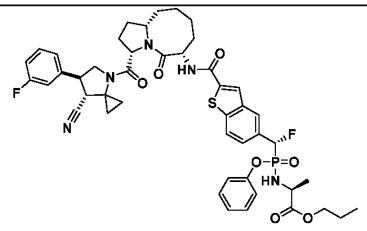
	propyl (((2-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate			1.72 (m, 9H), 1.70 - 1.46 (m, 4H), 1.27 - 1.19 (m, 2H), 1.09 - 1.03 (m, 1H), 1.02 - 0.93 (m, 1H), 0.92 - 0.82 (m, 3H), 0.78 - 0.65 (m, 1H)
327	propyl (((R)-(2-(((3S,6S,10aS)-3-(5,7-dioxo-6-(6-(trifluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		941.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.91 - 8.87 (m, 1H), 8.24 - 8.18 (m, 1H), 8.12 (s, 1H), 8.06 (s, 1H), 8.00 - 7.93 (m, 2H), 7.66 - 7.58 (m, 1H), 7.37 - 7.28 (m, 2H), 7.24 - 7.12 (m, 3H), 6.16 - 5.98 (m, 1H), 5.61 - 5.55 (m, 1H), 5.09 - 5.01 (m, 1H), 4.53 - 4.43 (m, 1H), 3.99 - 3.78 (m, 3H), 2.63 - 2.54 (m, 1H), 2.47 - 2.27 (m, 3H), 2.10 - 1.42 (m, 14H), 1.24 - 1.15 (m, 3H), 0.86 (dt, J = 10.0, 7.5 Hz, 3H)
328	propyl (((R)-fluoro(2-(((3S,6S,10aS)-3-(6-(6-methylpyridin-3-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo		887.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.61 - 8.49 (m, 1H), 8.16 - 8.05 (m, 2H), 8.01 - 7.94 (m, 1H), 7.88 - 7.82 (m, 1H), 7.68 - 7.60 (m, 1H), 7.48 - 7.42 (m, 1H), 7.37 - 7.29 (m, 2H), 7.24 - 7.13 (m, 3H), 6.18 - 5.99 (m, 1H), 5.61 -

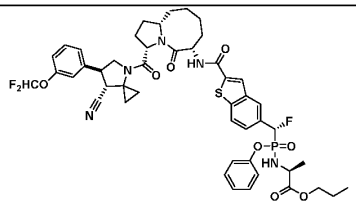
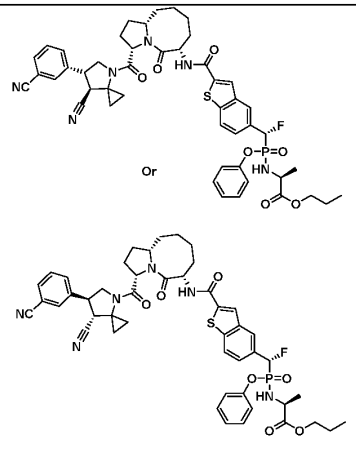
	[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate			5.53 (m, 1H), 5.09 - 5.00 (m, 1H), 4.53 - 4.44 (m, 1H), 4.01 - 3.77 (m, 3H), 2.58 - 2.52 (m, 1H), 2.45 - 2.26 (m, 3H), 2.10 - 1.78 (m, 9H), 1.77 - 1.63 (m, 2H), 1.62 - 1.39 (m, 5H), 1.31 - 1.10 (m, 4H), 0.91 - 0.82 (m, 3H)
329	propyl (((R)-fluoro(2-(((3S,6S,10aS)-3-(6-(6-methoxypyridin-3-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		903.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.23 - 8.18 (m, 1H), 8.11 (s, 1H), 8.07 (s, 1H), 8.00 - 7.94 (m, 1H), 7.76 - 7.70 (m, 1H), 7.67 - 7.59 (m, 1H), 7.38 - 7.28 (m, 2H), 7.24 - 7.13 (m, 3H), 6.92 - 6.86 (m, 1H), 6.17 - 5.98 (m, 1H), 5.60 - 5.54 (m, 1H), 5.08 - 5.00 (m, 1H), 4.52 - 4.41 (m, 1H), 4.01 - 3.78 (m, 6H), 2.61 - 2.49 (m, 1H), 2.45 - 2.23 (m, 3H), 2.12 - 1.37 (m, 14H), 1.25 - 1.17 (m, 3H), 0.86 (dt, *J* = 10.4, 7.4 Hz, 3H)
330	propyl (((R)-(2-(((3S,6S,10aS)-3-(5,7-dioxo-6-(5-(trifluoromethyl)pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(ph		941.0	^{1}H NMR (400 MHz, CD_3OD) δ 9.00 - 8.96 (m, 1H), 8.95 - 8.93 (m, 1H), 8.34 (s, 1H), 8.12 (s, 1H), 8.06 (s, 1H), 7.99 - 7.93 (m, 1H), 7.66 - 7.56 (m, 1H), 7.38 - 7.28 (m, 2H), 7.23 - 7.12 (m, 3H), 6.17 - 5.97 (m, 1H), 5.61 - 5.55 (m, 1H), 5.09 - 5.01 (m, 1H), 4.53 -

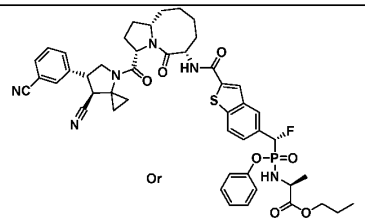
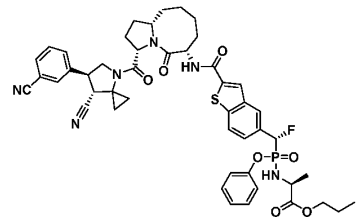
	enoxy)phosphoryl)-L-alaninate			4.43 (m, 1H), 4.01 - 3.77 (m, 3H), 2.64 - 2.54 (m, 1H), 2.47 - 2.39 (m, 1H), 2.39 - 2.27 (m, 2H), 2.10 - 1.78 (m, 8H), 1.76 - 1.42 (m, 6H), 1.23 - 1.17 (m, 3H), 0.86 (dt, *J* = 10.1, 7.5 Hz, 3H)
331	propyl (((R)-fluoro(2-(((3S,6S,10aS)-3-(6-(5-methoxypyridin-3-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		903.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.33 - 8.23 (m, 2H), 8.11 (s, 1H), 8.06 (s, 1H), 7.99 - 7.93 (m, 1H), 7.67 - 7.55 (m, 2H), 7.37 - 7.28 (m, 2H), 7.24 - 7.11 (m, 3H), 6.16 - 5.98 (m, 1H), 5.63 - 5.53 (m, 1H), 5.08 - 5.00 (m, 1H), 4.52 - 4.42 (m, 1H), 4.01 - 3.76 (m, 6H), 2.62 - 2.52 (m, 1H), 2.46 - 2.26 (m, 3H), 2.10 - 1.79 (m, 8H), 1.75 - 1.39 (m, 6H), 1.24 - 1.16 (m, 3H), 0.86 (dt, *J* = 10.0, 7.4 Hz, 3H)
332	propyl (((R)-(2-(((3S,6S,10aS)-3-(6-(6-(difluoromethyl)pyridin-3-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		923.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.82 - 8.78 (m, 1H), 8.18 - 8.11 (m, 2H), 8.07 (s, 1H), 8.00 - 7.94 (m , 1H), 7.87 - 7.81 (m, 1H), 7.67 - 7.59 (m, 1H), 7.37 - 7.28 (m, 2H), 7.24 - 7.12 (m, 3H), 6.93 - 6.62 (m, 1H), 6.17 - 5.98 (m, 1H), 5.63 - 5.53 (m, 1H), 5.09 - 5.01 (m, 1H), 4.53 - 4.43 (m, 1H), 4.01 - 3.77 (m,

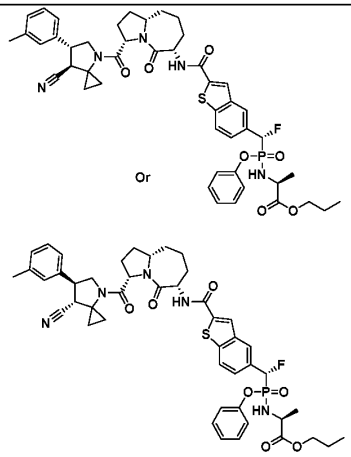
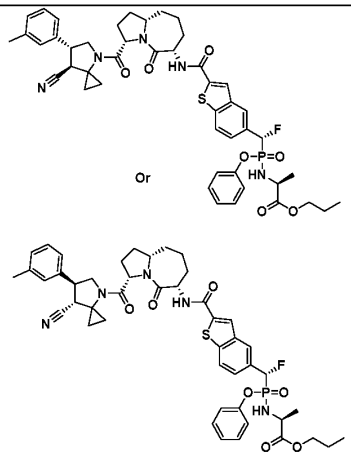
				3H), 2.63 - 2.53 (m, 1H), 2.47 - 2.27 (m, 3H), 2.11 - 1.77 (m, 8H), 1.77 - 1.41 (m, 6H), 1.23 - 1.17 (m, 3H), 0.86 (dt, *J* = 10.3, 7.5 Hz, 3H)
333	propyl (((R)-(2-(((3S,6S,10aS)-3-(6-(5-(difluoromethyl)pyridin-3-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		923.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.86 (s, 1H), 8.77 (s, 1H), 8.19 (s, 1H), 8.12 (s, 1H), 8.07 (s, 1H), 8.00 - 7.93 (m, 1H), 7.66 - 7.59 (m, 1H), 7.39 - 7.27 (m, 2H), 7.24 - 7.13 (m, 3H), 7.13 - 6.83 (m, 1H), 6.16 - 5.98 (m, 1H), 5.62 - 5.54 (m, 1H), 5.09 - 5.00 (m, 1H), 4.54 - 4.42 (m, 1H), 4.01 - 3.76 (m, 3H), 2.63 - 2.53 (m, 1H), 2.47 - 2.39 (m, 1H), 2.39 - 2.27 (m, 2H), 2.11 - 1.79 (m, 8H), 1.77 - 1.42 (m, 6H), 1.24 - 1.16 (m, 3H), 0.86 (dt, *J* = 10.4, 7.4 Hz, 3H)
334	propyl (((R)-fluoro(2-(((3S,6S,10aS)-3-(6-(4-methylpyridin-3-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		887.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.53 - 8.46 (m, 1H), 8.12 (s, 1H), 8.08 (br. s., 1H), 8.02 - 7.95 (m, 1H), 7.67 - 7.60 (m, 1H), 7.52 - 7.45 (m, 1H), 7.37 - 7.31 (m, 1H), 7.24 - 7.02 (m, 3H), 6.86 - 6.70 (m, 1H), 6.15 - 5.99 (m, 1H), 5.59 - 5.49 (m, 1H), 5.07 - 5.00 (m, 1H), 4.61 - 4.55 (m, 1H), 4.52 - 4.43 (m, 1H),

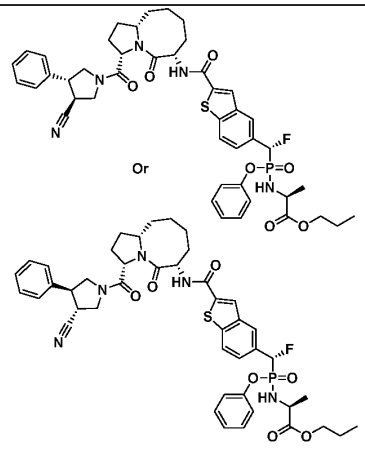
				4.00 - 3.95 (m, 1H), 3.87 - 3.80 (m, 1H), 3.77 - 3.69 (m, 1H), 3.26 - 3.20 (m, 1H), 2.31 - 2.29 (m, 2H), 2.06 - 1.99 (m, 3H), 1.88 - 1.82 (m, 1H), 1.62 - 1.59 (m, 1H), 1.58 - 1.54 (m, 1H), 1.50 - 1.43 (m, 2H), 1.39 - 1.35 (m, 7H), 1.31 - 1.28 (m, 3H), 1.23 - 1.20 (m, 2H), 0.92 - 0.83 (m, 4H)
335	propyl (((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((R)-(2-(((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Pyrrolidine + Core SFC peak 1 was used for synthesis and biological testing	898.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.15 - 8.09 (m, 1H), 8.09 - 8.04 (m, 1H), 7.99 - 7.93 (m, 1H), 7.67 - 7.59 (m, 1H), 7.39 - 7.28 (m, 2H), 7.28 - 7.12 (m, 4H), 7.07 - 6.99 (m, 2H), 6.88 - 6.79 (m, 1H), 6.20 - 5.96 (m, 1H), 5.05 - 4.96 (m, 1H), 4.63 - 4.51 (m, 1H), 4.45 - 4.33 (m, 1H), 4.20 - 4.07 (m, 2H), 3.97 (t, J = 6.6 Hz, 1H), 3.95 - 3.75 (m, 3H), 3.75 (s, 3H), 3.73 - 3.63 (m, 2H), 2.44 - 2.27 (m, 2H), 2.26 - 2.13 (m, 1H), 2.10 - 1.87 (m, 6H), 1.86 - 1.71 (m, 3H), 1.70 - 1.44 (m, 4H), 1.21 (d, J = 7.1 Hz, 3H), 1.02 - 0.92 (m, 1H), 0.92 - 0.81 (m, 3H), 0.77 - 0.62 (m, 1H)

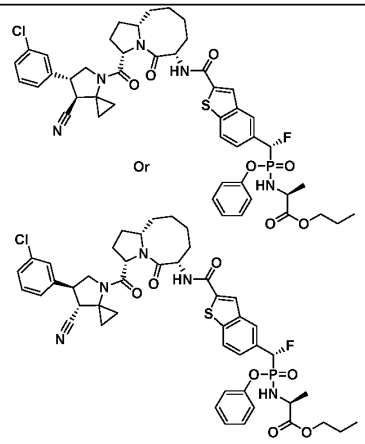
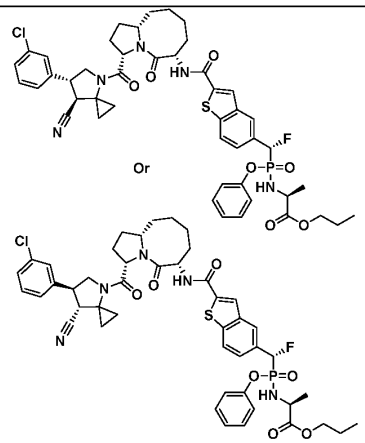
336	propyl (((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((R)-(2-(((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(3-methoxyphenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Or Pyrrolidine + Core SFC peak 2 was used for synthesis and biological testing	898.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.13 - 8.10 (m, 1H), 8.08 - 8.05 (m, 1H), 8.00 - 7.90 (m, 1H), 7.68 - 7.58 (m, 1H), 7.41 - 7.10 (m, 6H), 7.03 - 6.93 (m, 2H), 6.91 - 6.83 (m, 1H), 6.19 - 5.97 (m, 1H), 5.07 - 4.97 (m, 1H), 4.67 - 4.51 (m, 2H), 4.45 - 4.32 (m, 1H), 3.98 (t, *J* = 6.6 Hz, 1H), 3.94 - 3.79 (m, 3H), 3.77 (s, 3H), 3.74 - 3.65 (m, 2H), 2.37 - 2.12 (m, 3H), 2.09 - 1.87 (m, 7H), 1.87 - 1.73 (m, 2H), 1.70 - 1.42 (m, 4H), 1.21 (d, *J* = 7.1 Hz, 3H), 1.03 - 0.93 (m, 1H), 0.92 - 0.82 (m, 3H), 0.79 - 0.65 (m, 1H)
337	propyl (((R)-(2-(((3S,6S,10aS)-3-((*rel*-trans)-7-cyano-6-(3-fluorophenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		886.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.15 - 8.12 (m, 1H), 8.10 - 8.06 (m, 1H), 8.00 - 7.94 (m, 1H), 7.67 - 7.60 (m, 1H), 7.43 - 7.13 (m, 8H), 7.10 - 7.00 (m, 1H), 6.17 - 6.01 (m, 1H), 5.06 - 4.98 (m, 1H), 4.63 - 4.55 (m, 1H), 4.44 - 4.35 (m, 1H), 4.20 - 4.08 (m, 1H), 4.00 - 3.96 (m, 1H), 3.95 - 3.67 (m, 5H), 2.41 - 2.14 (m, 3H), 2.07 -

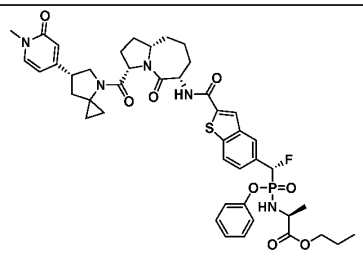
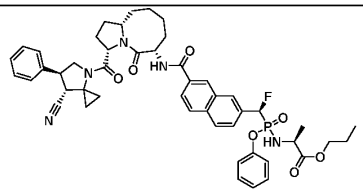
				1.89 (m, 6H), 1.87 - 1.74 (m, 2H), 1.70 - 1.45 (m, 4H), 1.37 - 1.27 (m, 1H), 1.24 - 1.19 (m, 3H), 1.02 - 0.93 (m, 1H), 0.92 - 0.82 (m, 3H), 0.77 - 0.65 (m, 1H)
338	propyl (((R)-(2-(((3S,6S,10aS)-3-((*rel*-trans)-7-cyano-6-(3-(difluoromethoxy)phenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		934.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.18 - 8.04 (m, 2H), 8.01 - 7.91 (m, 1H), 7.69 - 7.57 (m, 1H), 7.45 - 7.27 (m, 5H), 7.26 - 7.08 (m, 4H), 7.06 - 6.62 (m, 1H), 6.20 - 5.97 (m, 1H), 5.06 - 4.96 (m, 1H), 4.63 - 4.56 (m, 1H), 4.46 - 4.33 (m, 1H), 4.23 - 4.11 (m, 1H), 3.98 (t, *J* = 6.6 Hz, 1H), 3.89 - 3.63 (m, 4H), 2.41 - 2.14 (m, 3H), 2.08 - 1.88 (m, 7H), 1.86 - 1.42 (m, 7H), 1.21 (d, *J* = 7.3 Hz, 3H), 1.02 - 0.92 (m, 1H), 0.91 - 0.81 (m, 3H), 0.77 - 0.63 (m, 1H)
339	propyl (((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(3-cyanophenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		893.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (s, 1H), 8.09 - 8.05 (m, 1H), 8.01 - 7.93 (m, 1H), 7.88 - 7.80 (m, 1H), 7.78 - 7.67 (m, 2H), 7.66 - 7.59 (m, 1H), 7.59 - 7.53 (m, 1H), 7.39 - 7.29 (m, 2H), 7.25 - 7.12 (m, 3H), 6.19 - 5.99 (m, 1H), 5.07 - 4.97 (m, 1H), 4.67 - 4.54 (m, 2H), 4.45 - 4.33 (m,

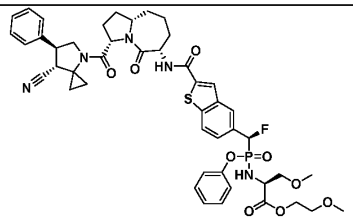
	Or propyl (((R)-(2-(((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(3-cyanophenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	Pyrrolidine + Core SFC peak 1 was used for synthesis and biological testing		1H), 3.98 (t, *J* = 6.6 Hz, 1H), 3.94 - 3.73 (m, 5H), 2.37 - 2.12 (m, 3H), 2.07 - 1.88 (m, 7H), 1.86 - 1.72 (m, 2H), 1.71 - 1.47 (m, 4H), 1.21 (d, *J* = 7.1 Hz, 3H), 1.04 - 0.94 (m, 1H), 0.94 - 0.82 (m, 3H), 0.79 - 0.68 (m, 1H)
340	propyl (((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(3-cyanophenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((R)-(2-(((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(3-cyanophenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Or  Pyrrolidine + Core SFC peak 2 was used for synthesis and biological testing	893.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (s, 1H), 8.10 - 8.06 (m, 1H), 8.01 - 7.94 (m, 2H), 7.87 - 7.79 (m, 1H), 7.69 - 7.60 (m, 2H), 7.58 - 7.52 (m, 1H), 7.39 - 7.29 (m, 2H), 7.25 - 7.13 (m, 3H), 6.18 - 5.99 (m, 1H), 5.07 - 4.99 (m, 1H), 4.65 - 4.57 (m, 1H), 4.45 - 4.35 (m, 1H), 4.28 - 4.16 (m, 2H), 3.98 (t, *J* = 6.6 Hz, 1H), 3.94 - 3.77 (m, 3H), 3.65 (d, *J* = 8.8 Hz, 1H), 2.39 - 2.13 (m, 3H), 2.09 - 1.90 (m, 6H), 1.89 - 1.72 (m, 3H), 1.70 - 1.44 (m, 4H), 1.21 (d, *J* = 7.1 Hz, 3H), 0.98 - 0.91 (m, 1H), 0.90 - 0.82 (m, 3H), 0.70 - 0.60 (m, 1H)

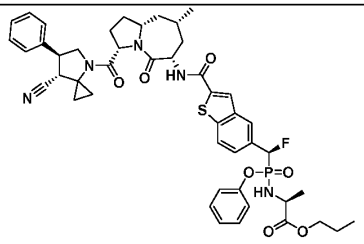
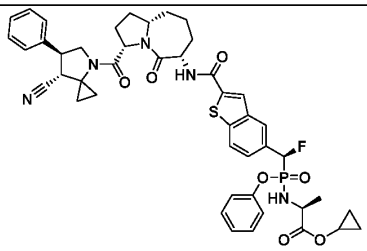
341	propyl (((R)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(m-tolyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(m-tolyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Pyrrolidine + Core SFC peak 1 was used for synthesis and biological testing	868.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.13 - 8.06 (m, 2H), 8.03 - 7.93 (m, 1H), 7.70 - 7.60 (m, 1H), 7.39 - 7.30 (m, 3H), 7.27 - 7.07 (m, 6H), 6.19 - 5.99 (m, 1H), 4.77 - 4.70 (m, 1H), 4.70 - 4.64 (m, 1H), 4.18 - 4.09 (m, 1H), 4.08 - 4.01 (m, 2H), 3.98 (t, *J* = 6.6 Hz, 1H), 3.94 - 3.76 (m, 2H), 3.76 - 3.65 (m, 2H), 2.34 (s, 3H), 2.33 - 2.24 (m, 2H), 2.23 - 2.13 (m, 1H), 2.12 - 1.74 (m, 9H), 1.63 - 1.45 (m, 2H), 1.25 - 1.19 (m, 3H), 1.03 - 0.95 (m, 1H), 0.92 - 0.83 (m, 3H), 0.74 - 0.65 (m, 1H)
342	propyl (((R)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(m-tolyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or		868.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 - 8.07 (m, 2H), 8.02 - 7.96 (m, 1H), 7.70 - 7.61 (m, 1H), 7.39 - 7.11 (m, 9H), 6.20 - 5.99 (m, 1H), 4.78 - 4.66 (m, 2H), 4.50 - 4.38 (m, 1H), 4.08 - 3.79 (m, 5H), 3.78 - 3.66 (m, 2H), 2.36 (s, 3H), 2.34 - 2.21 (m, 2H), 2.17 - 1.92 (m, 4H), 1.91 - 1.74 (m, 6H), 1.63 - 1.45 (m, 2H), 1.25 - 1.17 (m,

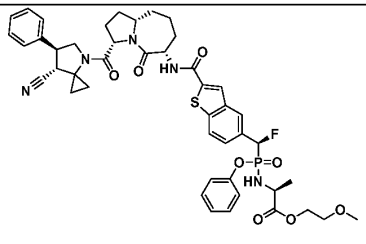
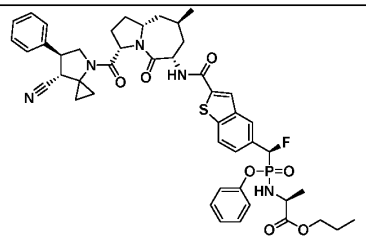
	propyl (((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(m-tolyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	Pyrrolidine + Core SFC peak 2 was used for synthesis and biological testing		3H), 1.04 - 0.97 (m, 1H), 0.94 - 0.81 (m, 3H), 0.79 - 0.68 (m, 1H)
343	propyl (((R)-(2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((R)-(2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	842.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.16 - 8.10 (m, 1H), 8.10 - 8.03 (m, 1H), 8.01 - 7.92 (m, 1H), 7.69 - 7.57 (m, 1H), 7.45 - 7.28 (m, 7H), 7.24 - 7.08 (m, 3H), 6.18 - 5.98 (m, 1H), 5.07 - 4.97 (m, 1H), 4.72 - 4.63 (m, 1H), 4.57 - 4.36 (m, 2H), 4.10 - 3.66 (m, 6H), 3.64 - 3.46 (m, 2H), 2.39 - 2.14 (m, 2H), 2.11 - 1.77 (m, 8H), 1.72 - 1.46 (m, 4H), 1.20 (d, J = 7.3 Hz, 3H), 0.93 - 0.79 (m, 3H)

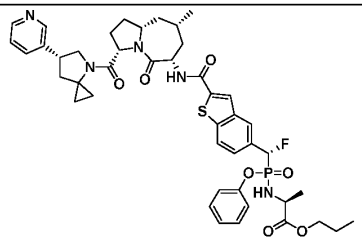
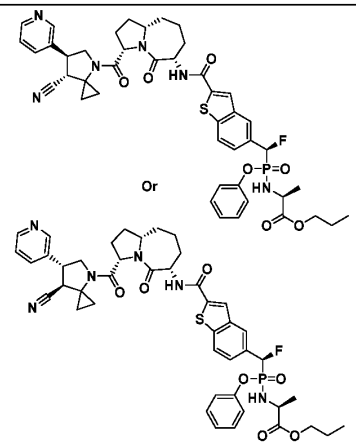
344	propyl (((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-6-(3-chlorophenyl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((R)-(2-(((3S,6S,10aS)-3-((6R,7S)-6-(3-chlorophenyl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Pyrrolidine + Core SFC peak 1 was used for synthesis and biological testing	902.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 - 8.06 (m, 2H), 7.97 - 7.94 (m, 1H), 7.63 (t, J = 8.9 Hz, 1H), 7.47 (s, 1H), 7.39 - 7.29 (m, 5H), 7.24 - 7.12 (m, 3H), 6.19 - 5.97 (m, 1H), 5.06 - 4.98 (m, 1H), 4.67 - 4.54 (m, 2H), 4.43 - 4.34 (m, 1H), 3.98 (t, J = 6.6 Hz, 1H), 3.93 - 3.79 (m, 3H), 3.77 - 3.73 (m, 1H), 2.36 - 2.14 (m, 3H), 2.06 - 1.88 (m, 7H), 1.85 - 1.75 (m, 2H), 1.69 - 1.46 (m, 4H), 1.29 - 1.27 (m, 1H), 1.21 (d, J = 7.1 Hz, 3H), 1.03 - 0.94 (m, 1H), 0.90 - 0.83 (m, 3H), 0.78 - 0.69 (m, 1H)
345	propyl (((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-6-(3-chlorophenyl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or		902.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 - 8.06 (m, 2H), 7.98 - 7.95 (m, 1H), 7.63 (t, J = 8.7 Hz, 1H), 7.54 (s, 1H), 7.45 - 7.39 (m, 1H), 7.37 - 7.27 (m, 4H), 7.24 - 7.11 (m, 3H), 6.19 - 5.98 (m, 1H), 5.06 - 4.96 (m, 1H), 4.62 - 4.53 (m, 1H), 4.44 - 4.34 (m, 1H), 4.20 - 4.07 (m, 2H), 3.98 (t, J = 6.7 Hz, 1H), 3.94 - 3.76 (m, 3H), 3.73 -

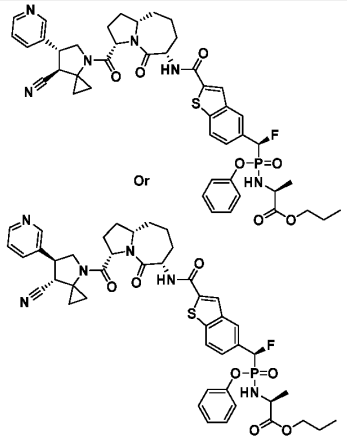
	propyl (((R)-(2-(((3S,6S,10aS)-3-((6R,7S)-6-(3-chlorophenyl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	Pyrrolidine + Core SFC peak 2 was used for synthesis and biological testing		3.68 (m, 1H), 2.42 - 2.15 (m, 3H), 2.07 - 1.89 (m, 6H), 1.86 - 1.73 (m, 3H), 1.69 - 1.46 (m, 4H), 1.35 - 1.27 (m, 1H), 1.21 (d, *J* = 7.1 Hz, 3H), 1.02 - 0.94 (m, 1H), 0.92 - 0.81 (m, 3H), 0.74 - 0.65 (m, 1H)
346	propyl (((R)-fluoro(2-(((3S,6S,9aS)-3-((R)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		860.3	^{1}H NMR (400 MHz, DMSO) δ 8.84-8.75 (m, 1H), 8.27 (s, 1H), 8.13-8.02 (m, 2H), 7.67-7.56 (m, 2H), 7.40-7.30 (m, 2H), 7.24-7.08 (m, 3H), 6.33 (s, 1H), 6.29-6.09 (m, 3H), 4.74-4.53 (m, 2H), 4.20 (s, 1H), 3.91 (s, 3H), 3.77-3.63 (m, 1H), 3.61-3.48 (m, 1H), 3.37 (s, 3H), 2.23-2.13 (m, 2H), 2.10-1.91 (m, 4H), 1.89-1.42 (m, 11H), 1.17 (d, J = 6.6 Hz, 1H), 0.94 (d, J = 6.5 Hz, 2H), 0.81 (t, J = 7.3 Hz, 3H), 0.54-0.41 (m, 2H)
347	propyl (((S)-(7-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)napht		862.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.02 (s, 1H), 7.93-7.82 (m, 3H), 7.74-7.65 (m, 1H), 7.51-7.42 (m, 1H), 7.41-7.34 (m, 3H), 7.34-7.30 (m, 3H), 7.25-7.16 (m, 2H),

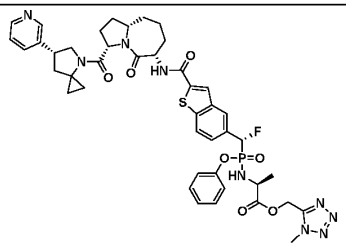
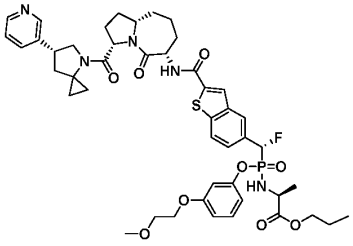
	halen-2-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate			7.12-7.04 (m, 1H), 6.16-5.91 (m, 1H), 5.26-5.09 (m, 1H), 4.77-4.64 (m, 1H), 4.55-4.45 (m, 1H), 4.38-4.26 (m, 1H), 4.08-3.99 (m, 2H), 3.98-3.90 (m, 1H), 3.85-3.78 (m, 2H), 3.69-3.58 (m, 1H), 3.57-3.47 (m, 1H), 2.50-2.37 (m, 1H), 2.26-2.03 (m, 5H), 2.02-1.88 (m, 3H), 1.87-1.74 (m, 3H), 1.74-1.55 (m, 3H), 1.49-1.43 (m, 1H), 1.31-1.24 (m, 3H), 1.18-1.04 (m, 1H), 0.96-0.87 (m, 1H), 0.85-0.77 (m, 2H), 0.77-0.66 (m, 1H)
348	2-methoxyethyl N-(((S)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-O-methyl-L-serinate		900.2	^{1}H NMR (400 MHz, DMSO) δ 8.88-8.78 (m, 1H), 8.28 (s, 1H), 8.13-8.03 (m, 2H), 7.64-7.57 (m, 1H), 7.53-7.46 (m, 2H), 7.42-7.29 (m, 5H), 7.23-7.09 (m, 3H), 6.30-6.08 (m, 2H), 4.70-4.58 (m, 2H), 4.38-4.26 (m, 1H), 4.12-3.66 (m, 7H), 3.49-3.34 (m, 3H), 3.29-2.98 (m, 7H), 2.27-2.11 (m, 2H), 2.08-1.91 (m, 2H), 1.89-1.63 (m, 8H), 0.88-0.63 (m, 2H)

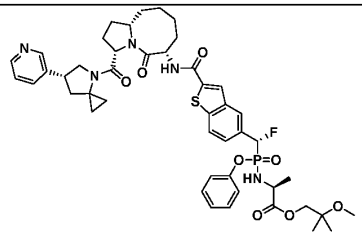
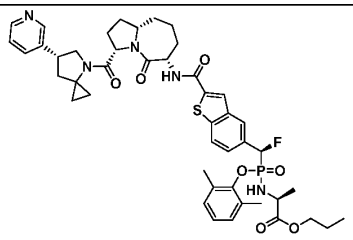
349	propyl (((S)-(2-(((3S,6S,8R,9aR)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		868.5	^{1}H NMR (400 MHz, DMSO) δ 9.04-8.73 (m, 1H), 8.28 (s, 1H), 8.17-7.98 (m, 2H), 7.68-7.57 (m, 1H), 7.55-7.45 (m, 2H), 7.44-7.29 (m, 5H), 7.26-7.09 (m, 3H), 6.44-5.91 (m, 2H), 4.81-4.53 (m, 2H), 4.33 (s, 1H), 4.12-3.62 (m, 7H), 2.31-2.11 (m, 2H), 2.09-1.87 (m, 2H), 1.87-1.75 (m, 2H), 1.74-1.61 (m, 3H), 1.58-1.35 (m, 4H), 1.24-1.10 (m, 2H), 0.99-0.92 (m, 4H), 0.90-0.75 (m, 4H), 0.75-0.60 (m, 1H)
350	cyclopropyl (((S)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		852.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.90-7.83 (m, 1H), 7.83-7.78 (m, 1H), 7.66 (s, 1H), 7.62-7.52 (m, 1H), 7.47-7.30 (m, 6H), 7.26-7.15 (m, 2H), 7.14-7.01 (m, 2H), 6.04-5.87 (m, 1H), 5.30 (s, 1H), 4.75-4.43 (m, 3H), 4.12-4.05 (m, 1H), 3.91-3.77 (m, 2H), 3.70-3.48 (m, 3H), 2.47-1.64 (m, 13H), 1.30-1.01 (m, 4H), 0.78-0.56 (m, 4H)

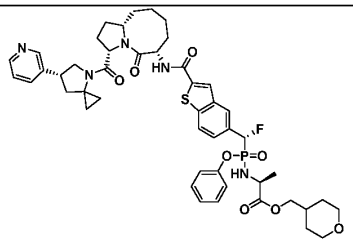
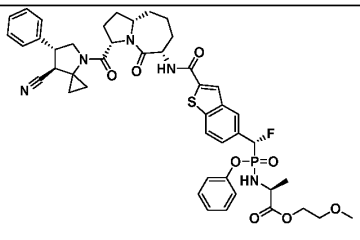
351	2-methoxyethyl (((S)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		870.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.90 (m, 1H), 7.89-7.83 (m, 1H), 7.82-7.78 (m, 1H), 7.73-7.51 (m, 2H), 7.46-7.29 (m, 7H), 7.25-7.23 (m, 1H), 7.21-7.07 (m, 2H), 6.05-5.87 (m, 1H), 4.68-4.53 (m, 2H), 4.37-4.02 (m, 3H), 3.95-3.42 (m, 8H), 3.37-3.29 (m, 3H), 2.45-2.35 (m, 1H), 2.29-2.12 (m, 2H), 2.01-1.64 (m, 9H), 1.33-1.25 (m, 3H), 1.18-1.09 (m, 1H), 0.83-0.69 (m, 1H)
352	propyl (((S)-(2-(((3S,6S,8S,9aR)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		868.3	^{1}H NMR (400 MHz, DMSO) δ 8.90-8.73 (m, 1H), 8.34-8.19 (m, 1H), 8.14-8.00 (m, 2H), 7.69-7.54 (m, 1H), 7.50 (d, J = 7.5 Hz, 2H), 7.43-7.29 (m, 5H), 7.25-7.09 (m, 3H), 6.31-6.03 (m, 2H), 4.92-4.79 (m, 1H), 4.66-4.55 (m, 1H), 4.39-4.28 (m, 1H), 4.13 (d, J = 6.7 Hz, 1H), 4.02 (d, J = 9.9 Hz, 1H), 3.94-3.80 (m, 3H), 3.80-3.60 (m, 3H), 2.30-1.79 (m, 8H), 1.74-1.61 (m, 3H), 1.54-1.41 (m, 3H), 1.21-1.08 (m, 4H), 0.95 (d, J = 7.1 Hz, 2H), 0.88-0.76 (m, 4H), 0.74-0.64 (m, 1H)

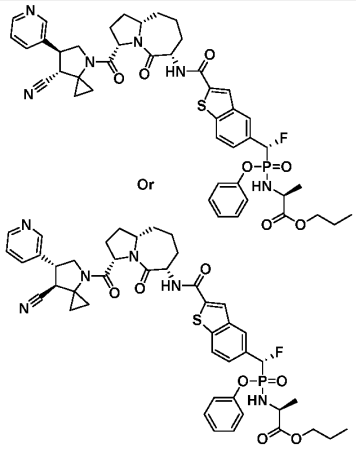
353	propyl (((R)-fluoro(2-(((3S,6S,8R,9aR)-8-methyl-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		844.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86-8.77 (m, 1H), 8.58 (s, 1H), 8.43 (d, J = 4.5 Hz, 1H), 8.27 (s, 1H), 8.07 (d, J = 5.3 Hz, 2H), 7.79 (d, J = 7.9 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.37-7.30 (m, 3H), 7.19-7.13 (m, 3H), 6.28-6.19 (m, 1H), 6.16-6.08 (m, 1H), 4.67-4.58 (m, 2H), 4.09 (t, J = 8.5 Hz, 1H), 4.01-3.89 (m, 2H), 3.85-3.71 (m, 3H), 3.62-3.53 (m, 1H), 2.23-1.94 (m, 6H), 1.85-1.66 (m, 4H), 1.62-1.49 (m, 3H), 1.47-1.37 (m, 2H), 1.13 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H), 0.84-0.76 (m, 3H), 0.52-0.41 (m, 2H)
354	propyl (((S)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((S)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-	 Pyrrolidine + Core SFC peak 2 was used for synthesis and biological testing	855.5	^{1}H NMR (400 MHz, DMSO) δ 8.92-8.77 (m, 1H), 8.71 (s, 1H), 8.60-8.45 (m, 1H), 8.27 (d, J = 3.7 Hz, 1H), 8.17-8.01 (m, 2H), 7.99-7.88 (m, 1H), 7.64-7.51 (m, 1H), 7.46-7.41 (m, 1H), 7.40-7.31 (m, 2H), 7.24-7.10 (m, 3H), 6.34-6.03 (m, 2H), 4.72-4.55 (m, 2H), 4.35 (t, J = 8.4 Hz, 1H), 4.07 (d, J = 9.8 Hz, 1H), 3.99-3.65 (m, 6H), 2.25-2.12 (m, 2H), 2.09-1.91 (m, 2H), 1.88-

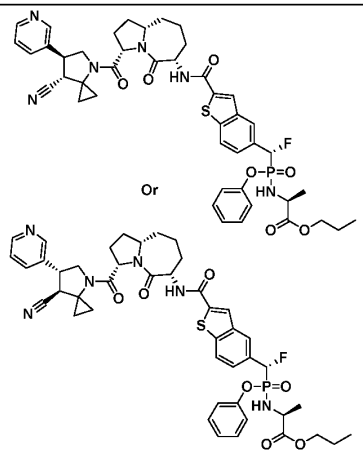
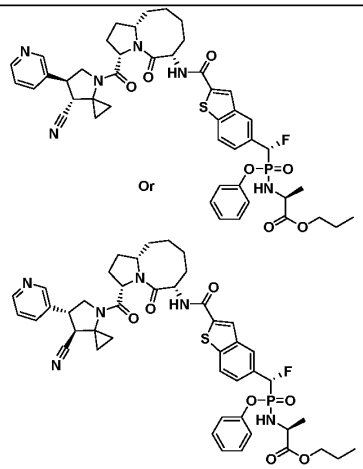
	6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate			1.63 (m, 8H), 1.56-1.41 (m, 2H), 1.19-0.92 (m, 3H), 0.87-0.76 (m, 4H), 0.75-0.64 (m, 1H)
355	propyl (((S)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((S)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Pyrrolidine + Core SFC peak 1 was used for synthesis and biological testing	855.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.67-8.61 (m, 1H), 7.97 (s, 1H), 7.91-7.79 (m, 3H), 7.67-7.54 (m, 2H), 7.50-7.32 (m, 2H), 7.26-7.17 (m, 2H), 7.14-7.06 (m, 2H), 5.95 (dd, J = 44.0, 5.3 Hz, 1H), 4.74-4.60 (m, 2H), 4.26-3.74 (m, 7H), 3.68-3.58 (m, 1H), 3.35-3.27 (m, 1H), 2.50-2.39 (m, 1H), 2.32-2.22 (m, 1H), 2.08-1.70 (m, 12H), 1.34-1.25 (m, 3H), 1.08-0.98 (m, 1H), 0.95-0.82 (m, 3H), 0.78-0.66 (m, 1H)

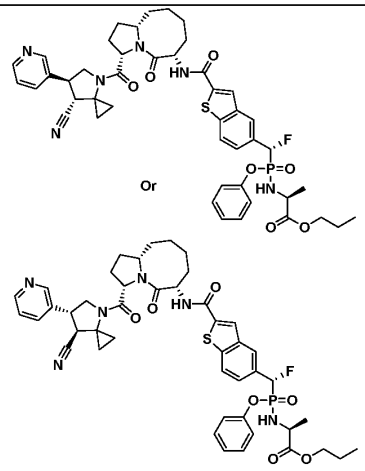
356	(1-methyl-1H-tetrazol-5-yl)methyl (((R)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		884.1	^{1}H NMR (400 MHz, DMSO) δ 8.80 (d, J = 7.5 Hz, 1H), 8.59 (s, 1H), 8.44 (d, J = 4.6 Hz, 1H), 8.38-8.25 (m, 2H), 8.11-8.04 (m, 2H), 7.80 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 8.2 Hz, 1H), 7.37-7.30 (m, 3H), 7.16-7.11 (m, 2H), 6.29-6.13 (m, 2H), 5.41-5.34 (m, 2H), 4.67-4.58 (m, 2H), 4.18-4.06 (m, 2H), 4.04 (s, 3H), 4.00-3.93 (m, 1H), 3.73 (t, J = 9.5 Hz, 1H), 3.60-3.56 (m, 1H), 2.24-1.98 (m, 6H), 1.82-1.68 (m, 6H), 1.23-1.18 (m, 3H), 1.14-1.08 (m, 2H), 0.54-0.42 (m, 2H)
357	propyl (((R)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(3-(2-methoxyethoxy)phenoxy)phosphoryl)-L-alaninate		904.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78-8.43 (m, 2H), 8.01-7.92 (m, 1H), 7.91-7.84 (m, 2H), 7.84-7.75 (m, 2H), 7.62-7.50 (m, 1H), 7.43-7.33 (m, 1H), 7.25-7.09 (m, 1H), 6.90-6.75 (m, 1H), 6.71-6.59 (m, 2H), 6.04-5.85 (m, 1H), 4.75-4.61 (m, 2H), 4.14-3.85 (m, 8H), 3.77-3.67 (m, 2H), 3.66-3.50 (m, 2H), 3.46-3.39 (m, 3H), 2.34-2.13 (m, 5H), 2.11-1.88 (m, 6H), 1.86-1.71 (m, 3H), 1.67-1.55 (m, 2H), 1.30 (d, J = 7.1 Hz, 2H), 1.12 (d,

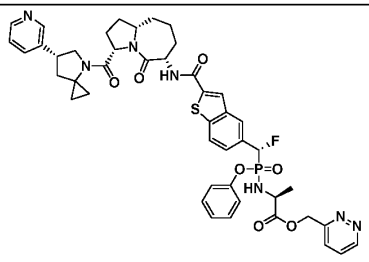
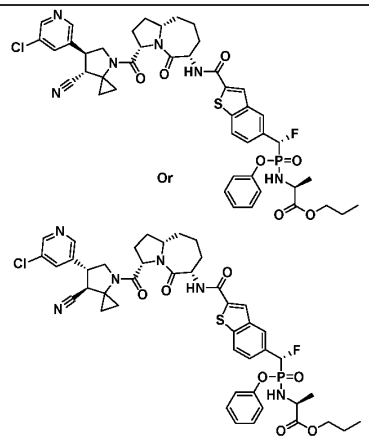
				J = 7.1 Hz, 1H), 0.94-0.87 (m, 3H), 0.57-0.46 (m, 2H)
358	2-methoxy-2-methylpropyl (((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		888.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 8.78-8.65 (m, 1H), 8.34-8.12 (m, 2H), 8.10-7.89 (m, 2H), 7.85-7.70 (m, 2H), 7.60-7.45 (m, 1H), 7.38-7.27 (m, 1H), 7.26-7.14 (m, 2H), 7.14-7.03 (m, 2H), 6.08-5.84 (m, 1H), 5.24-5.14 (m, 1H), 4.81-4.71 (m, 1H), 4.56-4.49 (m, 1H), 4.35-4.29 (m, 1H), 4.08-3.99 (m, 3H), 3.68-3.63 (m, 1H), 3.25-3.12 (m, 3H), 2.77-2.66 (m, 1H), 2.18-1.95 (m, 9H), 1.86-1.68 (m, 4H), 1.67-1.56 (m, 2H), 1.33-1.25 (m, 3H), 1.22-1.08 (m, 7H), 0.48-0.39 (m, 1H), 0.21-0.10 (m, 1H)
359	propyl ((2,6-dimethylphenoxy)((S)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)-L-alaninate		858.9	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69-8.51 (m, 2H), 8.03-7.98 (m, 1H), 7.91-7.74 (m, 4H), 7.66-7.60 (m, 1H), 7.41-7.34 (m, 1H), 7.03-6.91 (m, 3H), 6.05-5.87 (m, 1H), 4.76-4.59 (m, 2H), 4.17-3.86 (m, 6H), 3.65-3.55 (m, 2H), 2.38-2.23 (m, 4H), 2.22-2.18 (m, 6H), 2.17-2.10 (m, 2H), 2.03-1.94

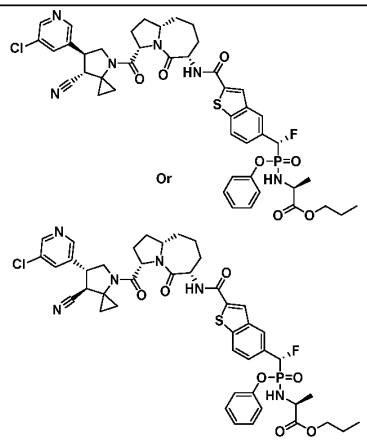
				(m, 5H), 1.83-1.72 (m, 3H), 1.63-1.52 (m, 2H), 1.35-1.23 (m, 3H), 0.90-0.81 (m, 3H), 0.58-0.46 (m, 2H).
360	(tetrahydro-2H-pyran-4-yl)methyl (((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		900.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54-9.36 (m, 1H), 8.79-8.67 (m, 1H), 8.28-8.22 (m, 1H), 8.05-7.96 (m, 2H), 7.94-7.87 (m, 1H), 7.85-7.78 (m, 1H), 7.76-7.67 (m, 1H), 7.61-7.47 (m, 1H), 7.37-7.27 (m, 1H), 7.26-7.16 (m, 2H), 7.13-7.05 (m, 2H), 6.04-5.85 (m, 1H), 5.23-5.10 (m, 1H), 4.63 (d, J = 10.5 Hz, 1H), 4.57-4.48 (m, 1H), 4.38-4.28 (m, 1H), 4.14-3.99 (m, 2H), 3.98-3.90 (m, 3H), 3.91-3.58 (m, 3H), 3.42-3.26 (m, 2H), 2.69-2.62 (m, 1H), 2.25-1.86 (m, 10H), 1.86-1.74 (m, 4H), 1.67-1.46 (m, 4H), 1.36-1.24 (m, 4H), 1.15 (d, J = 7.1 Hz, 1H), 0.51-0.40 (m, 1H), 0.26-0.16 (m, 1H)
361	2-methoxyethyl (((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-		870.3	^{1}H NMR (400 MHz, DMSO) δ 8.84-8.76 (m, 1H), 8.27 (s, 1H), 8.10-8.04 (m, 2H), 7.64-7.58 (m, 1H), 7.52-7.46 (m, 2H), 7.40-7.29 (m, 5H), 7.20-7.11 (m, 3H), 6.30-6.12 (m, 2H),

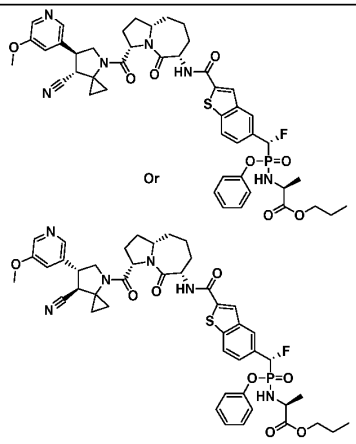
	a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate			4.66-4.57 (m, 2H), 4.19-3.87 (m, 6H), 3.83-3.76 (m, 2H), 3.48-3.39 (m, 2H), 3.23-3.19 (m, 3H), 2.24-2.05 (m, 3H), 1.99-1.92 (m, 1H), 1.86-1.66 (m, 8H), 1.18-1.12 (m, 3H), 0.86-0.77 (m, 1H), 0.70-0.61 (m, 1H)
362	propyl (((R)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Pyrrolidine + Core SFC peak 2 was used for synthesis and biological testing	855.5	^{1}H NMR (400 MHz, DMSO) δ 8.95-8.77 (m, 2H), 8.69 (s, 1H), 8.28 (s, 1H), 8.23 (d, J = 7.7 Hz, 1H), 8.08 (d, J = 4.6 Hz, 2H), 7.75-7.57 (m, 2H), 7.36 (t, J = 7.9 Hz, 2H), 7.18 (t, J = 9.4 Hz, 3H), 6.31-6.04 (m, 2H), 4.72-4.53 (m, 2H), 4.38 (t, J = 8.7 Hz, 1H), 4.10 (d, J = 9.9 Hz, 1H), 4.03-3.89 (m, 3H), 3.88-3.64 (m, 3H), 2.27-2.12 (m, 2H), 2.09-1.91 (m, 2H), 1.89-1.61 (m, 8H), 1.58-1.34 (m, 2H), 1.21-1.03 (m, 3H), 0.92-0.75 (m, 4H), 0.74-0.64 (m, 1H)

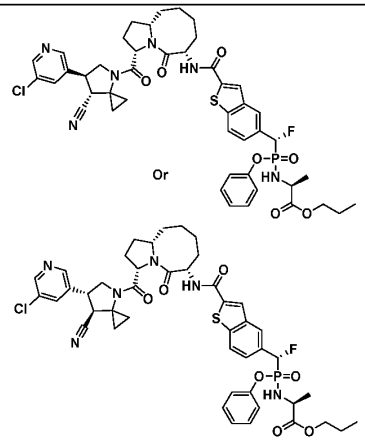
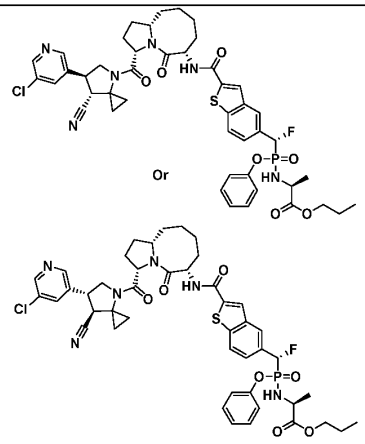
363	propyl (((R)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Pyrrolidine + Core SFC peak 1 was used for synthesis and biological testing	855.5	^{1}H NMR (400 MHz, DMSO) δ 8.88-8.77 (m, 1H), 8.74 (s, 1H), 8.55 (d, J = 4.3 Hz, 1H), 8.27 (s, 1H), 8.19-7.97 (m, 3H), 7.61 (d, J = 8.0 Hz, 1H), 7.47 (dd, J = 7.6, 5.0 Hz, 1H), 7.36 (t, J = 7.8 Hz, 2H), 7.25-7.11 (m, 3H), 6.31-6.02 (m, 2H), 4.71-4.50 (m, 2H), 4.27-4.09 (m, 1H), 4.04-3.89 (m, 5H), 3.85-3.73 (m, 2H), 2.26-1.92 (m, 4H), 1.90-1.65 (m, 8H), 1.58-1.38 (m, 2H), 1.19-1.07 (m, 3H), 0.90-0.72 (m, 4H), 0.70-0.53 (m, 1H)
364	propyl (((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or		869.3	^{1}H NMR (400 MHz, DMSO) δ 8.96-8.82 (m, 1H), 8.70 (s, 1H), 8.59-8.48 (m, 1H), 8.30 (s, 1H), 8.11-8.03 (m, 2H), 7.96-7.87 (m, 1H), 7.65-7.56 (m, 1H), 7.46-7.32 (m, 3H), 7.21-7.13 (m, 3H), 6.27-6.07 (m, 2H), 4.95 (s, 1H), 4.59-4.40 (m, 2H), 4.28-4.18 (m, 1H), 4.11-4.02 (m, 1H), 3.98-3.89 (m, 1H), 3.84-3.72 (m,

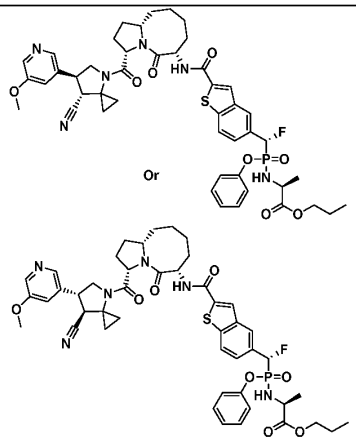
	propyl (((R)-(2-(((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	Pyrrolidine + Core SFC peak 2 was used for synthesis and biological testing		4H), 2.28-2.16 (m, 2H), 2.00-1.46 (m, 14H), 1.13 (d, J = 6.4 Hz, 3H), 0.84-0.67 (m, 5H)
365	propyl (((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((R)-(2-(((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Pyrrolidine + Core SFC peak 1 was used for synthesis and biological testing	869	^{1}H NMR (400 MHz, DMSO) δ 8.95-8.73 (m, 2H), 8.68-8.59 (m, 1H), 8.33-8.25 (m, 1H), 8.23-8.14 (m, 1H), 8.10-8.03 (m, 2H), 7.68-7.56 (m, 2H), 7.39-7.31 (m, 2H), 7.21-7.10 (m, 3H), 6.29-6.19 (m, 1H), 6.17-6.09 (m, 1H), 4.98-4.90 (m, 1H), 4.55-4.47 (m, 1H), 4.32-4.18 (m, 2H), 4.10-3.86 (m, 4H), 3.85-3.75 (m, 2H), 2.35-2.24 (m, 1H), 2.07-1.37 (m, 15H), 1.13 (d, J = 6.1 Hz, 3H), 0.87-0.75 (m, 4H), 0.69-0.55 (m, 1H)

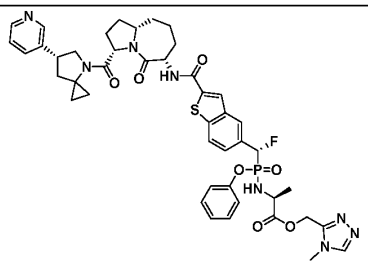
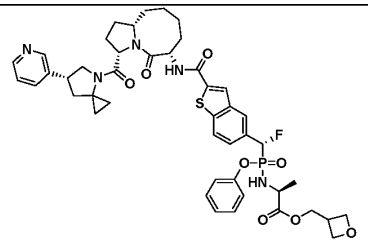
366	pyridazin-3-ylmethyl (((R)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		880.4	^{1}H NMR (400 MHz, DMSO) δ 9.20-9.14 (m, 1H), 8.83-8.74 (m, 1H), 8.61-8.55 (m, 1H), 8.46-8.41 (m, 1H), 8.28-8.23 (m, 1H), 8.09-8.02 (m, 2H), 7.84-7.78 (m, 1H), 7.71-7.55 (m, 3H), 7.37-7.25 (m, 3H), 7.19-7.10 (m, 3H), 6.41-6.14 (m, 2H), 5.36-5.20 (m, 2H), 4.67-4.58 (m, 2H), 4.14-3.84 (m, 3H), 3.77-3.69 (m, 1H), 3.63-3.52 (m, 1H), 2.24-1.94 (m, 6H), 1.88-1.67 (m, 7H), 1.63-1.55 (m, 1H), 1.25-1.16 (m, 3H), 0.54-0.40 (m, 2H)
367	propyl (((R)-(2-(((3S,6S,9aS)-3-((6S,7R)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptan	 Pyrrolidine + Core SFC peak 2 was used for synthesis and biological testing	889	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.54 (s, 1H), 7.97 (d, J = 16.0 Hz, 1H), 7.88-7.85 (m, 1H), 7.82 (s, 1H), 7.69-7.50 (m, 3H), 7.35 (t, J = 7.6 Hz, 1H), 7.27-7.05 (m, 4H), 6.05-5.87 (m, 1H), 4.65 (s, 2H), 4.22-3.55 (m, 9H), 2.46-2.35 (m, 1H), 2.24-2.15 (m, 2H), 2.06-1.89 (m, 7H), 1.84-1.76 (m, 2H), 1.64-1.57 (m, 2H), 1.31-1.28 (m, 2H), 1.19-1.08 (m, 2H), 0.93-0.74 (m, 4H)

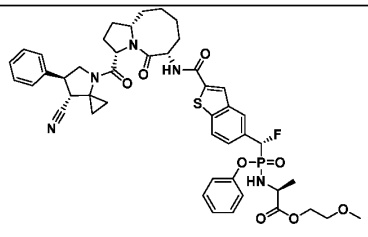
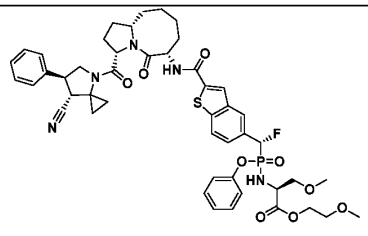
	e-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate			
368	propyl (((R)-(2-(((3S,6S,9aS)-3-((6S,7R)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Pyrrolidine + Core SFC peak 1 was used for synthesis and biological testing	889.2	^{1}H NMR (400 MHz, DMSO) δ 8.87-8.78 (m, 1H), 8.67 (s, 1H), 8.56 (s, 1H), 8.26 (s, 1H), 8.19 (s, 1H), 8.14-8.00 (m, 2H), 7.67-7.57 (m, 1H), 7.42-7.28 (m, 2H), 7.27-7.07 (m, 3H), 6.32-6.05 (m, 2H), 4.71-4.56 (m, 2H), 4.21-4.12 (m, 1H), 4.06-3.89 (m, 5H), 3.86-3.74 (m, 2H), 2.26-1.89 (m, 5H), 1.87-1.67 (m, 7H), 1.54-1.37 (m, 2H), 1.14 (d, J = 5.6 Hz, 3H), 0.91-0.52 (m, 5H)

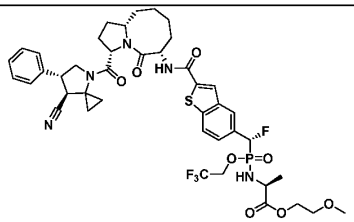
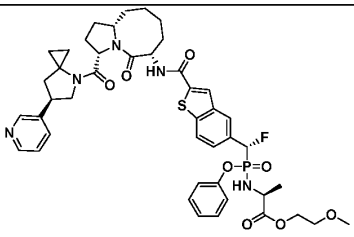
369	propyl (((R)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Pyrrolidine + Core SFC peak 2 was used for synthesis and biological testing	885	^{1}H NMR (400 MHz, DMSO) δ 8.84 (d, J = 7.6 Hz, 1H), 8.34 (d, J = 10.2 Hz, 2H), 8.09-8.05 (m, 2H), 7.73-7.68 (m, 1H), 7.62 (d, J = 8.6 Hz, 1H), 7.38-7.33 (m, 2H), 7.19-7.14 (m, 3H), 6.26-6.08 (m, 2H), 4.67-4.61 (m, 2H), 4.39-4.32 (m, 1H), 4.14 (d, J = 10.1 Hz, 1H), 3.98-3.94 (m, 1H), 3.88-3.78 (m, 8H), 2.23-2.14 (m, 2H), 2.08-1.94 (m, 2H), 1.89-1.64 (m, 9H), 1.46-1.37 (m, 2H), 1.13 (d, J = 7.1 Hz, 3H), 0.85-0.82 (m, 1H), 0.81-0.76 (m, 3H), 0.74-0.68 (m, 1H)

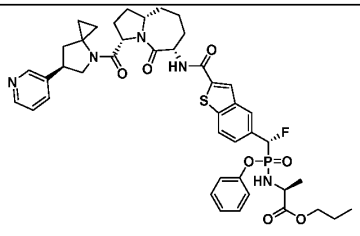
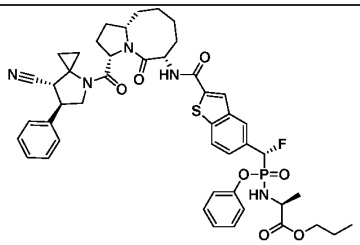
370	propyl (((R)-(2-(((3S,6S,9aS)-3-((6S,7R)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Pyrrolidine + Core SFC peak 2 was used for synthesis and biological testing	903.2	^{1}H NMR (400 MHz, DMSO) δ 8.96-8.84 (m, 1H), 8.67 (d, J = 1.3 Hz, 1H), 8.60 (d, J = 2.2 Hz, 1H), 8.30 (s, 1H), 8.19-8.12 (m, 1H), 8.11-8.02 (m, 2H), 7.66-7.56 (m, 1H), 7.39-7.33 (m, 2H), 7.21-7.13 (m, 3H), 6.29-6.19 (m, 1H), 6.16-6.05 (m, 1H), 5.02-4.87 (m, 1H), 4.56-4.41 (m, 2H), 4.30-4.18 (m, 1H), 4.17-4.09 (m, 1H), 3.96-3.74 (m, 5H), 2.28-2.17 (m, 2H), 2.07-1.97 (m, 1H), 1.92-1.63 (m, 9H), 1.57-1.38 (m, 4H), 1.13 (d, J = 7.1 Hz, 3H), 0.85-0.76 (m, 4H), 0.73-0.63 (m, 1H)
371	propyl (((R)-(2-(((3S,6S,9aS)-3-((6S,7R)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(ph		903.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.68-8.51 (m, 1H), 8.13 (s, 1H), 8.00-7.91 (m, 1H), 7.90-7.77 (m, 2H), 7.60-7.51 (m, 1H), 7.42-7.32 (m, 3H), 7.26-7.10 (m, 2H), 7.08-7.02 (m, 1H), 6.14-5.87 (m, 1H), 5.23-5.07 (m, 1H), 4.67-4.40 (m, 2H), 4.39-4.29 (m, 1H),

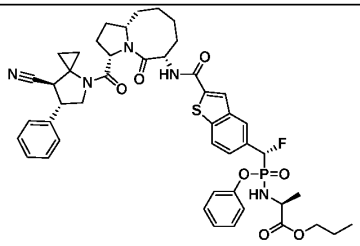
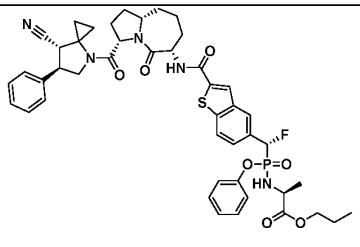
	enoxy)phosphoryl)-L-alaninate Or propyl (((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	Pyrrolidine + Core SFC peak 1 was used for synthesis and biological testing		4.25-3.62 (m, 6H), 3.16 (s, 1H), 2.37-1.76 (m, 12H), 1.72-1.50 (m, 4H), 1.30 (d, J = 7.0 Hz, 2H), 1.15 (d, J = 6.9 Hz, 1H), 1.06-0.83 (m, 4H), 0.70-0.54 (m, 1H)
372	propyl (((R)-(2-(((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-	 Or Pyrrolidine + Core SFC peak 1 was used for synthesis and biological testing	899	^{1}H NMR (400 MHz, DMSO) δ 8.89-8.81 (m, 1H), 8.30-8.25 (m, 2H), 8.21-8.18 (m, 1H), 8.10-8.04 (m, 2H), 7.63-7.54 (m, 2H), 7.39-7.33 (m, 2H), 7.17 (dd, J = 13.8, 7.7 Hz, 3H), 6.27-6.20 (m, 1H), 6.16-6.05 (m, 1H), 4.97-4.87 (m, 1H), 4.55-4.46 (m, 1H), 4.30-4.16 (m, 2H), 4.09-4.01 (m, 1H), 3.97-3.76 (m, 8H), 2.36-2.24 (m, 1H), 2.08-1.98 (m, 2H), 1.90-1.38 (m, 13H), 1.13 (d, J = 7.1 Hz, 3H), 0.85-0.74 (m, 4H), 0.65-0.55 (m, 1H)

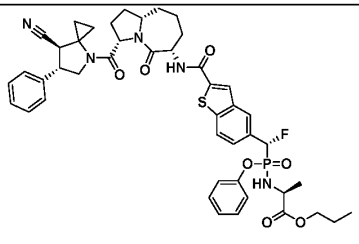
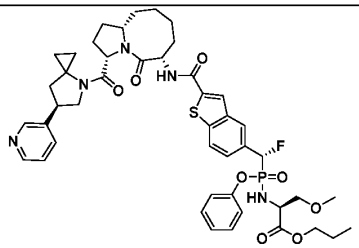
	yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate			
373	(4-methyl-1l2,2l2,4-triazolidin-3-yl)methyl (((1R)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)-2,3-dihydrobenzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		883.2	^{1}H NMR (400 MHz, DMSO) δ 8.80 (d, J = 6.7 Hz, 1H), 8.60 (s, 1H), 8.53-8.40 (m, 2H), 8.28 (s, 1H), 8.14-8.00 (m, 2H), 7.85 (d, J = 7.1 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.42-7.25 (m, 3H), 7.20-7.05 (m, 3H), 6.40-6.05 (m, 2H), 5.24-5.17 (m, 1H), 4.71-4.55 (m, 2H), 4.14-4.04 (m, 1H), 4.02-3.94 (m, 1H), 3.78-3.70 (m, 1H), 3.62-3.58 (m, 3H), 3.31-3.22 (m, 1H), 3.11-3.02 (m, 2H), 2.25-1.94 (m, 6H), 1.83-1.65 (m, 6H), 1.29-1.24 (m, 2H), 1.18 (d, J = 6.0 Hz, 3H), 0.55-0.40 (m, 2H)
374	oxetan-3-ylmethyl (((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		872.6	^{1}H NMR (400 MHz, DMSO) δ 8.92-8.79 (m, 1H), 8.64-8.54 (m, 1H), 8.48-8.38 (m, 1H), 8.33-8.24 (m, 1H), 8.12-8.03 (m, 2H), 7.85-7.74 (m, 1H), 7.67-7.53 (m, 1H), 7.41-7.28 (m, 3H), 7.24-7.10 (m, 3H), 6.33-6.09 (m, 2H), 5.03-4.87 (m, 1H), 4.62-4.44 (m, 3H), 4.32-3.96 (m, 6H), 3.91-3.70

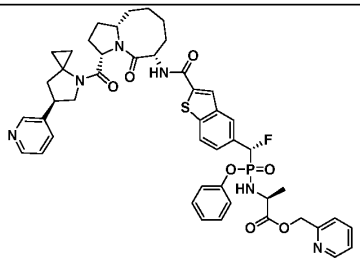
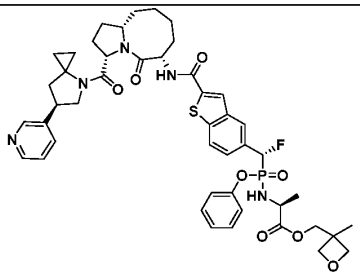
				(m, 2H), 3.65-3.48 (m, 1H), 3.20-2.99 (m, 1H), 2.37-1.40 (m, 16H), 1.21-1.05 (m, 3H), 0.57-0.34 (m, 2H)
375	2-methoxyethyl (((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		884.3	^{1}H NMR (400 MHz, DMSO) δ 8.94-8.85 (m, 1H), 8.31 (s, 1H), 8.10-8.03 (m, 2H), 7.64-7.57 (m, 1H), 7.51-7.44 (m, 2H), 7.41-7.30 (m, 5H), 7.22-7.10 (m, 3H), 6.31-6.11 (m, 2H), 5.01-4.90 (m, 1H), 4.57-4.42 (m, 2H), 4.28-4.17 (m, 1H), 4.17-3.64 (m, 6H), 3.49-3.36 (m, 2H), 3.23-3.18 (m, 3H), 2.26-2.16 (m, 2H), 2.05-1.50 (m, 12H), 1.20-1.10 (m, 3H), 0.84-0.62 (m, 2H)
376	2-methoxyethyl N-(((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-O-methyl-L-serinate		914.2	^{1}H NMR (400 MHz, DMSO) δ 8.93-8.86 (m, 1H), 8.33-8.28 (m, 1H), 8.10-8.04 (m, 2H), 7.63-7.58 (m, 1H), 7.51-7.45 (m, 2H), 7.41-7.31 (m, 5H), 7.22-7.11 (m, 3H), 6.29-6.08 (m, 2H), 5.01-4.90 (m, 1H), 4.56-4.42 (m, 2H), 4.27-4.18 (m, 1H), 4.14-4.09 (m, 1H), 4.06-3.87 (m, 3H), 3.76-3.66 (m, 2H), 3.48-3.37 (m, 3H), 3.32-3.25 (m, 1H), 3.23-3.11 (m, 6H), 2.27-2.16 (m, 2H), 1.98-1.43

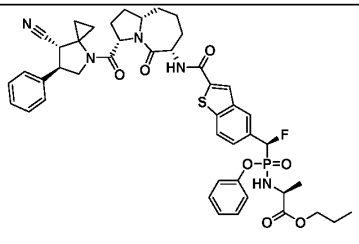
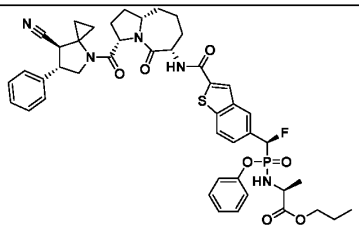
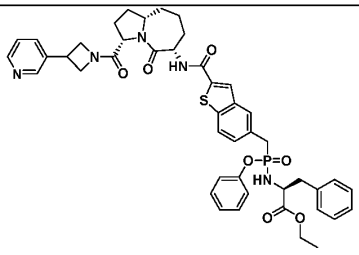
				(m, 12H), 0.85-0.62 (m, 2H).
377	2-methoxyethyl (((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(2,2,2-trifluoroethoxy)phosphoryl)-L-alaninate		890.2	^{1}H NMR (400 MHz, DMSO) δ 8.95-8.87 (m, 1H), 8.32-8.26 (m, 1H), 8.09-8.03 (m, 1H), 8.02-7.96 (m, 1H), 7.55-7.45 (m, 3H), 7.41-7.29 (m, 3H), 6.23-6.00 (m, 2H), 5.01-4.91 (m, 1H), 4.67-4.44 (m, 4H), 4.27-4.00 (m, 4H), 3.94-3.67 (m, 3H), 3.53-3.44 (m, 2H), 3.25-3.19 (m, 3H), 2.26-2.16 (m, 2H), 1.97-1.44 (m, 12H), 1.29-1.20 (m, 3H), 0.85-0.77 (m, 1H), 0.72-0.62 (m, 1H)
378	2-methoxyethyl (((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		860.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61-8.54 (m, 1H), 8.43-8.33 (m, 1H), 7.93-7.79 (m, 3H), 7.77-7.69 (m, 1H), 7.67-7.60 (m, 1H), 7.58-7.51 (m, 1H), 7.51-7.42 (m, 1H), 7.39-7.32 (m, 1H), 7.24-7.17 (m, 2H), 7.14-7.03 (m, 2H), 6.09-5.81 (m, 1H), 5.26-5.04 (m, 1H), 4.59-4.50 (m, 1H), 4.33-4.15 (m, 4H), 4.14-3.96 (m, 3H), 3.62-3.49 (m, 3H), 3.36-3.32 (m, 3H), 2.36-2.16 (m, 3H), 2.15-1.95 (m, 7H), 1.91-1.69 (m, 4H), 1.67-1.53

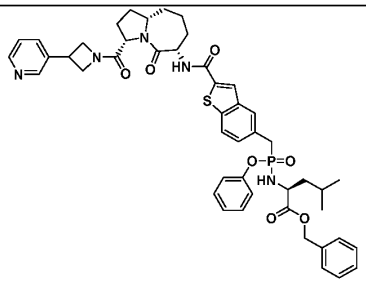
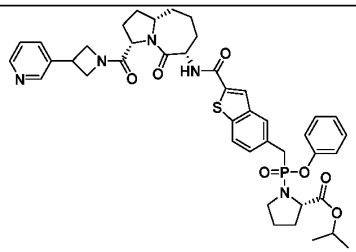
				(m, 2H), 1.37-1.15 (m, 3H), 0.56-0.45 (m, 2H)
379	propyl (((R)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		830.4	^{1}H NMR (400 MHz, DMSO) δ 8.83-8.65 (m, 2H), 8.54 (d, J = 4.7 Hz, 1H), 8.27 (s, 1H), 8.10-8.00 (m, 3H), 7.64-7.49 (m, 2H), 7.41-7.33 (m, 2H), 7.21-7.11 (m, 3H), 6.31-6.02 (m, 2H), 4.68-4.56 (m, 2H), 4.16-3.69 (m, 7H), 2.25-1.43 (m, 16H), 1.19-1.08 (m, 3H), 0.88-0.74 (m, 3H), 0.56-0.41 (m, 2H)
380	propyl (((R)-(2-(((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		868.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.90 (m, 1H), 7.88-7.80 (m, 1H), 7.78 (d, J = 2.2 Hz, 1H), 7.61-7.49 (m, 1H), 7.42-7.27 (m, 8H), 7.25-7.02 (m, 3H), 6.10-5.81 (m, 1H), 5.19-5.03 (m, 1H), 4.80-4.65 (m, 1H), 4.58-4.42 (m, 1H), 4.35-4.21 (m, 1H), 4.14-3.94 (m, 3H), 3.86-3.46 (m, 4H), 2.49-2.34 (m, 1H), 2.21-1.89 (m, 8H), 1.84-1.74 (m, 3H), 1.62-1.55 (m, 2H), 1.36-1.06 (m, 6H), 0.95-0.82 (m, 3H), 0.79-0.67 (m, 1H)

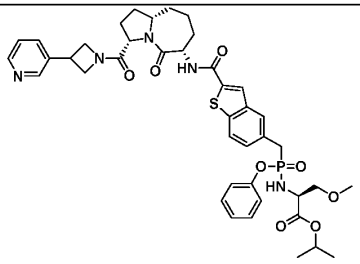
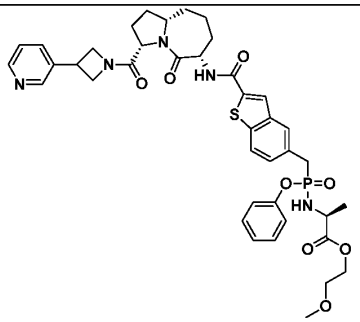
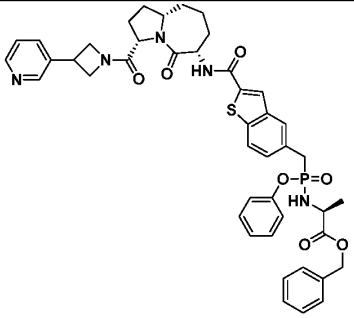
381	propyl (((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		868.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 15.1 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.79 (s, 1H), 7.56 (dd, J = 24.2, 8.8 Hz, 1H), 7.43-7.27 (m, 8H), 7.25-7.02 (m, 3H), 6.11-5.83 (m, 1H), 5.13 (s, 1H), 4.57-4.43 (m, 1H), 4.35-4.24 (m, 1H), 4.22-3.95 (m, 5H), 3.78-3.53 (m, 2H), 3.48-3.40 (m, 1H), 2.59-2.47 (m, 1H), 2.26-2.04 (m, 5H), 1.85-1.72 (m, 4H), 1.67-1.56 (m, 4H), 1.40-1.03 (m, 6H), 0.94-0.69 (m, 4H)
382	propyl (((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		854.5	^{1}H NMR (400 MHz, DMSO) δ 8.83-8.72 (m, 1H), 8.30-8.22 (m, 1H), 8.12-8.02 (m, 2H), 7.67-7.57 (m, 1H), 7.53-7.45 (m, 2H), 7.42-7.26 (m, 5H), 7.24-7.10 (m, 3H), 6.34-5.99 (m, 2H), 4.69-4.55 (m, 2H), 4.19-4.06 (m, 1H), 4.03-3.71 (m, 7H), 2.25-2.02 (m, 3H), 2.00-1.60 (m, 9H), 1.57-1.36 (m, 2H), 1.20-1.10 (m, 3H), 0.88-0.58 (m, 5H)

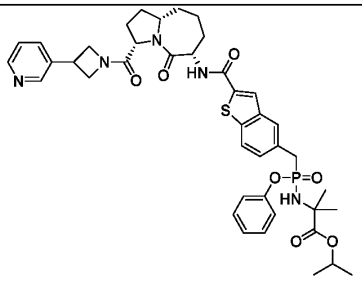
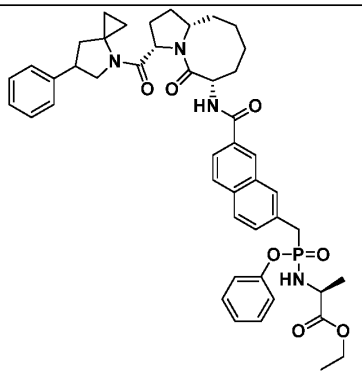
383	propyl (((R)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		854.5	^{1}H NMR (400 MHz, DMSO) δ 8.86-8.75 (m, 1H), 8.30-8.24 (m, 1H), 8.12-8.02 (m, 2H), 7.65-7.57 (m, 1H), 7.56-7.45 (m, 2H), 7.44-7.28 (m, 5H), 7.25-7.09 (m, 3H), 6.28-6.02 (m, 2H), 4.73-4.57 (m, 2H), 4.40-4.27 (m, 1H), 4.07-3.61 (m, 7H), 2.25-2.10 (m, 2H), 2.10-1.61 (m, 10H), 1.58-1.33 (m, 2H), 1.21-1.06 (m, 3H), 0.90-0.60 (m, 5H)
384	propyl N-(((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-O-methyl-L-serinate		874.2	^{1}H NMR (400 MHz, DMSO) δ 8.87-8.79 (m, 1H), 8.61 (mi, 1H), 8.46 (d, J = 4.7 Hz, 1H), 8.29 (s, 1H), 8.10-8.01 (m, 2H), 7.86 (d, J = 7.9 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.42-7.30 (m, 3H), 7.23-7.10 (m, 3H), 6.26-6.00 (m, 2H), 4.99-4.89 (m, 1H), 4.56-4.47 (m, 1H), 4.28-4.11 (m, 2H), 4.02-3.77 (m, 4H), 3.74-3.55 (m, 2H), 3.25-3.20 (m, 1H), 3.17-3.10 (m, 3H), 2.34-2.22 (m, 1H), 2.18-2.11 (m, 2H), 2.06-1.95 (m, 3H), 1.92-1.71 (m, 6H), 1.66-1.46 (m, 5H), 1.41-1.30 (m, 1H), 0.86-0.71 (m, 3H), 0.53-0.40 (m, 2H)

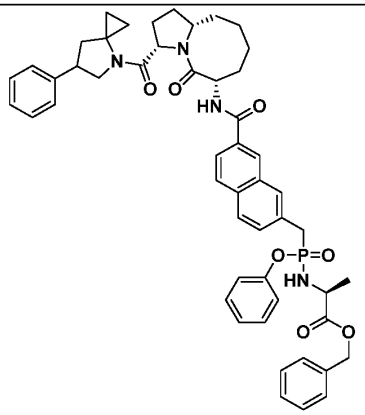
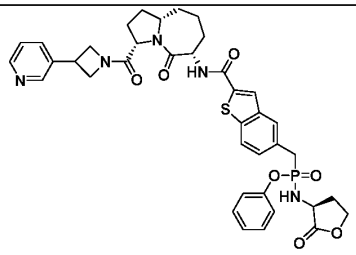
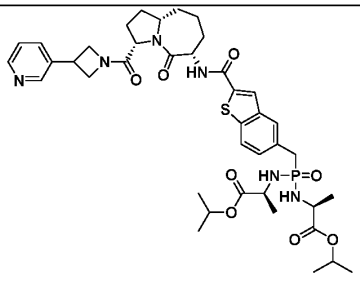
385	pyridin-2-ylmethyl (((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		893.9	^{1}H NMR (400 MHz, DMSO) δ 8.87-8.79 (m, 1H), 8.60-8.55 (m, 1H), 8.54-8.49 (m, 1H), 8.44-8.40 (m, 1H), 8.30-8.26 (m, 1H), 8.08-8.01 (m, 1H), 7.79-7.72 (m, 2H), 7.62-7.56 (m, 2H), 7.36-7.26 (m, 1H), 7.19-7.10 (m, 5H), 6.36-6.12 (m, 3H), 5.15-4.90 (m, 2H), 4.56-4.48 (m, 3H), 4.28-4.10 (m, 1H), 4.06-3.78 (m, 2H), 3.61-3.52 (m, 2H), 2.32-2.23 (m, 1H), 2.19-1.98 (m, 1H), 1.92-1.69 (m, 5H), 1.66-1.44 (m, 6H), 1.24-1.17 (m, 4H), 0.52-0.38 (m, 3H), 0.52-0.38 (m, 2H)
386	(3-methyloxetan-3-yl)methyl (((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		886.4	^{1}H NMR (400 MHz, DMSO) δ 8.96-8.79 (m, 1H), 8.66-8.50 (m, 1H), 8.48-8.37 (m, 1H), 8.34-8.24 (m, 1H), 8.23-7.93 (m, 2H), 7.85-7.72 (m, 1H), 7.66-7.50 (m, 1H), 7.46-7.07 (m, 5H), 6.39-5.91 (m, 2H), 5.10-4.84 (m, 1H), 4.64-4.43 (m, 1H), 4.37-3.97 (m, 7H), 3.94-3.69 (m, 3H), 3.63-3.56 (m, 1H), 2.34-1.46 (m, 16H), 1.29-0.95 (m, 6H), 0.68-0.14 (m, 2H)

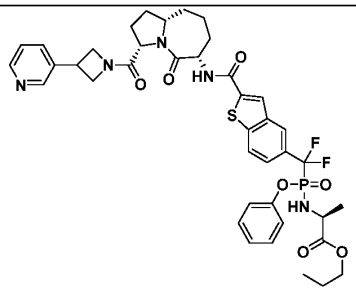
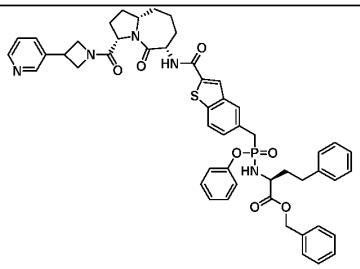
387	propyl (((S)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		854.3	^{1}H NMR (400 MHz, DMSO) δ 8.88-8.73 (m, 1H), 8.31-8.24 (m, 1H), 8.13-8.03 (m, 2H), 7.66-7.58 (m, 1H), 7.53-7.44 (m, 2H), 7.41-7.27 (m, 5H), 7.24-7.09 (m, 3H), 6.33-6.06 (m, 2H), 4.69-4.55 (m, 2H), 4.19-4.07 (m, 1H), 4.01-3.63 (m, 7H), 2.26-2.02 (m, 3H), 2.01-1.59 (m, 9H), 1.57-1.40 (m, 2H), 1.22-0.92 (m, 3H), 0.87-0.76 (m, 4H), 0.72-0.61 (m, 1H)
388	propyl (((S)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		854.3	^{1}H NMR (400 MHz, DMSO) δ 8.89-8.79 (m, 1H), 8.33-8.23 (m, 1H), 8.15-8.03 (m, 2H), 7.66-7.57 (m, 1H), 7.55-7.47 (m, 2H), 7.44-7.29 (m, 5H), 7.26-7.09 (m, 3H), 6.32-6.06 (m, 2H), 4.72-4.58 (m, 2H), 4.40-4.27 (m, 1H), 4.07-3.66 (m, 7H), 2.26-2.13 (m, 2H), 2.10-1.90 (m, 2H), 1.89-1.62 (m, 8H), 1.57-1.40 (m, 2H), 1.21-0.92 (m, 3H), 0.88-0.62 (m, 5H)
389	ethyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-		834.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 – 8.98 (m, 1H), 8.76 – 8.12 (m, 4H), 7.92 – 7.51 (m, 4H), 7.37 – 7.20 (m, 4H), 7.08 – 6.67 (m, 6H), 5.03 – 3.76

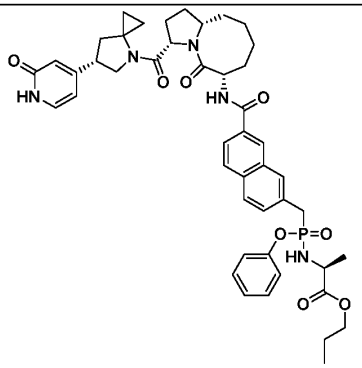
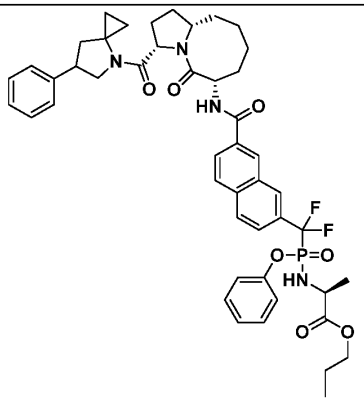
	yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-phenylalaninate			(m, 13H), 3.31 – 3.10 (m, 2H), 2.90 – 2.68 (m, 2H), 2.26 – 2.04 (m, 4H), 1.96 – 1.83 (m, 4H), 1.07 – 0.99 (m, 3H)
390	benzyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-leucinate		862.2	^{1}H NMR (400 MHz, DMSO) δ 8.85 – 8.70 (m, 1H), 8.59 – 8.38 (m, 2H), 8.20 (s, 1H), 7.95 – 7.82 (m, 3H), 7.45 – 7.25 (m, 9H), 7.16 – 7.09 (m, 3H), 5.74 – 5.51 (m, 1H), 5.05 – 4.89 (m, 2H), 4.85 – 4.58 (m, 2H), 4.48 – 4.19 (m, 3H), 4.05 – 3.83 (m, 3H), 3.82 – 3.69 (m, 1H), 3.52 – 3.41 (m, 1H), 2.26 – 2.13 (m, 1H), 2.08 – 1.92 (m, 2H), 1.89 – 1.65 (m, 7H), 1.35 – 1.03 (m, 3H), 0.69 – 0.40 (m, 6H)
391	isopropyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-prolinate		798.2	^{1}H NMR (400 MHz, DMSO) δ 8.85 – 8.70 (m, 1H), 8.60 – 8.40 (m, 2H), 8.22 (s, 1H), 8.01 – 7.84 (m, 3H), 7.51 – 7.05 (m, 7H), 4.93 – 4.58 (m, 3H), 4.47 – 3.80 (m, 7H), 3.70 – 3.49 (m, 2H), 3.44 – 3.37 (m, 1H), 3.15 – 2.96 (m, 1H), 2.25 – 2.14 (m, 1H), 2.08 – 1.64 (m, 13H), 1.20 – 1.04 (m, 6H)

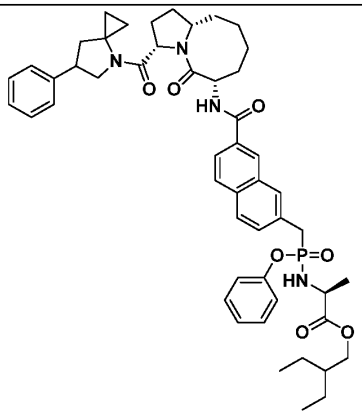
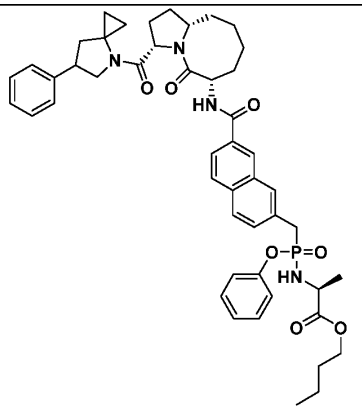
392	isopropyl O-methyl-N-(((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-serinate		802.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 – 8.39 (m, 2H), 8.09 – 7.69 (m, 4H), 7.59 – 7.32 (m, 2H), 7.26 – 7.20 (m, 2H), 7.14 – 6.99 (m, 3H), 5.00 – 4.85 (m, 1H), 4.76 – 4.29 (m, 4H), 4.20 – 4.06 (m, 1H), 4.03 – 3.97 (m, 1H), 3.95 – 3.79 (m, 2H), 3.56 – 3.33 (m, 4H), 3.15 – 3.00 (m, 4H), 2.32 – 1.37 (m, 10H), 1.17 – 1.06 (m, 6H)
393	2-methoxyethyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		788.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 – 8.47 (m, 2H), 8.19 – 7.30 (m, 7H), 7.27 – 7.20 (m, 2H), 7.12 – 7.03 (m, 3H), 5.05 – 4.32 (m, 5H), 4.21 – 4.06 (m, 3H), 4.00 – 3.85 (m, 3H), 3.47 – 3.33 (m, 4H), 3.28 – 3.23 (m, 3H), 2.23 – 1.60 (m, 10H), 1.21 – 1.05 (m, 3H)
394	benzyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		820.2	^{1}H NMR (400 MHz, DMSO) δ 8.86 – 8.37 (m, 3H), 8.25 – 8.12 (m, 1H), 7.96 – 7.80 (m, 3H), 7.49 – 7.24 (m, 9H), 7.22 – 7.05 (m, 3H), 5.82 – 5.61 (m, 1H), 5.10 – 4.96 (m, 2H), 4.85 – 4.57 (m, 2H), 4.48 – 4.19 (m, 3H), 4.05 – 3.81 (m, 4H), 3.48 – 3.44 (m, 1H), 2.25 – 2.14 (m, 1H), 2.09 – 1.94 (m, 2H), 1.93 – 1.62

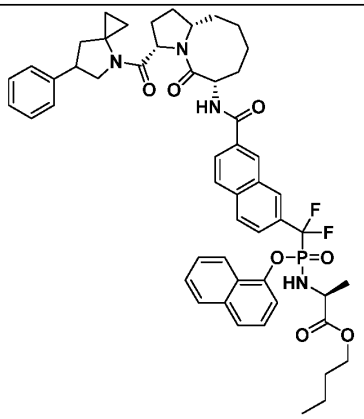
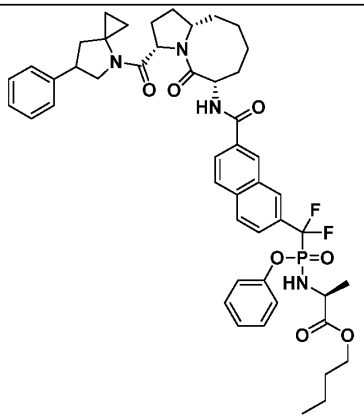
				(m, 7H), 1.15 – 0.98 (m, 3H)
395	isopropyl 2-methyl-2-((((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)amino)propanoate		786.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 – 8.22 (m, 2H), 8.19 – 7.64 (m, 4H), 7.61 – 7.31 (m, 2H), 7.25 – 7.19 (m, 3H), 7.18 – 7.00 (m, 3H), 5.06 – 4.87 (m, 1H), 4.84 – 4.33 (m, 4H), 4.20 – 3.81 (m, 3H), 3.63 – 3.33 (m, 3H), 2.25 – 1.72 (m, 10H), 1.40 – 1.25 (m, 6H), 1.20 – 1.10 (m, 6H)
396	ethyl (((7-(((3S,6S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		805.3	^{1}H NMR (400 MHz, DMSO) δ 8.36 – 8.28 (m, 1H), 7.95 – 7.80 (m, 4H), 7.67 – 7.56 (m, 1H), 7.51 – 7.41 (m, 1H), 7.37 – 7.29 (m, 5H), 7.28 – 7.08 (m, 5H), 5.28 – 5.17 (m, 1H), 4.62 – 4.56 (m, 1H), 4.38 – 4.26 (m, 1H), 4.15 – 3.46 (m, 7H), 3.39 – 3.06 (m, 1H), 2.60 (d, J = 9.1 Hz, 1H), 2.49 – 2.38 (m, 1H), 2.29 – 1.95 (m, 9H), 1.92 – 1.60 (m, 6H), 1.23 – 1.10 (m, 5H), 0.65 – 0.48 (m, 2H)

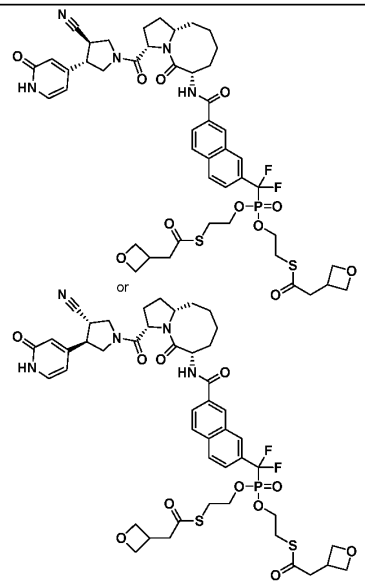
397	benzyl (((7-(((3S,6S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		867.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.84 – 7.69 (m, 4H), 7.53 – 7.45 (m, 1H), 7.29 – 7.21 (m, 6H), 7.20 – 7.12 (m, 7H), 7.10 – 6.98 (m, 3H), 5.20 – 5.09 (m, 1H), 5.04 – 4.84 (m, 2H), 4.55 – 4.45 (m, 1H), 4.31 – 4.17 (m, 1H), 4.06 – 3.83 (m, 2H), 3.61 – 3.39 (m, 3H), 3.33 – 3.00 (m, 1H), 2.45 – 2.29 (m, 2H), 2.19 – 2.10 (m, 2H), 2.03 – 1.87 (m, 5H), 1.76 – 1.53 (m, 5H), 1.12 – 1.04 (m, 3H), 0.86 – 0.72 (m, 2H), 0.56 – 0.38 (m, 2H)
398	phenyl P-((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)-N-((S)-2-oxotetrahydrofuran-3-yl)phosphonamidate		742.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 – 8.27 (m, 2H), 8.27 – 7.48 (m, 5H), 7.44 – 7.20 (m, 4H), 7.19 – 7.00 (m, 3H), 5.01 – 4.44 (m, 3H), 4.42 – 3.72 (m, 7H), 3.66 – 3.34 (m, 3H), 2.40 – 1.59 (m, 12H)
399	diisopropyl 2,2'-((((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-		809.4	^{1}H NMR (400 MHz, DMSO) δ 8.87 – 8.63 (m, 3H), 8.45 – 8.30 (m, 1H), 8.21 – 8.13 (m, 1H), 7.93 – 7.68 (m, 3H), 7.43 – 7.35 (m, 1H), 4.94 – 4.76 (m, 2H), 4.73 – 4.23

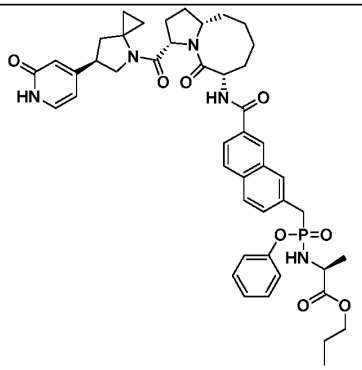
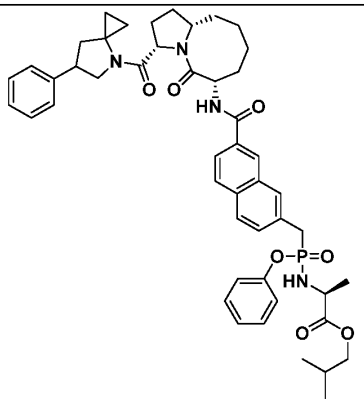
	yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(azanediyl))(2S,2'S)-dipropionate			(m, 6H), 4.16 – 3.88 (m, 3H), 3.85 – 3.54 (m, 2H), 3.29 – 3.04 (m, 2H), 2.27 – 1.62 (m, 10H), 1.28 – 1.04 (m, 18H) (TFA salt)
400	propyl ((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		808.3	^{1}H NMR (400 MHz, DMSO) δ 8.99 – 8.78 (m, 1H), 8.57 (s, 1H), 8.52 – 8.40 (m, 1H), 8.38-8.30 (m, 1H), 8.26-8.12 (m, 2H), 7.91 – 7.80 (m, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.47 – 7.28 (m, 3H), 7.25 – 7.05 (m, 3H), 6.87 – 6.69 (m, 1H), 4.85 – 4.59 (m, 2H), 4.48 – 4.20 (m, 3H), 4.09 – 3.70 (m, 6H), 2.26 – 2.14 (m, 1H), 2.11 – 1.94 (m, 2H), 1.89 – 1.66 (m, 7H), 1.55 – 1.42 (m, 2H), 1.26 – 1.13 (m, 3H), 0.87 – 0.77 (m, 3H)
401	benzyl (2S)-2-((((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)amino)-4-phenylbutanoate		910.4	^{1}H NMR (400 MHz, DMSO) δ 8.83 – 8.69 (m, 1H), 8.64 – 8.38 (m, 2H), 8.24 – 8.16 (m, 1H), 7.95 – 7.79 (m, 3H), 7.50 – 7.24 (m, 9H), 7.23 – 7.02 (m, 6H), 6.93 – 6.87 (m, 1H), 6.79 – 6.71 (m, 1H), 5.89 – 5.65 (m, 1H), 5.08 – 4.89 (m, 2H), 4.83 – 4.56 (m, 2H), 4.49 – 4.18 (m, 3H), 4.06 – 3.75 (m, 4H), 3.51 – 3.42 (m, 2H), 2.38 – 2.09 (m, 3H), 2.06 – 1.51 (m, 11H)

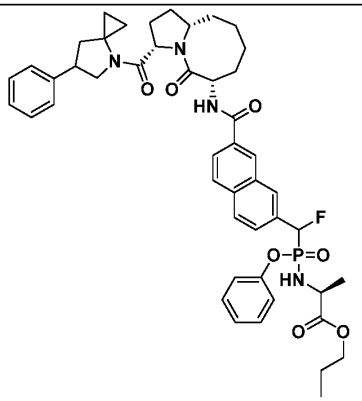
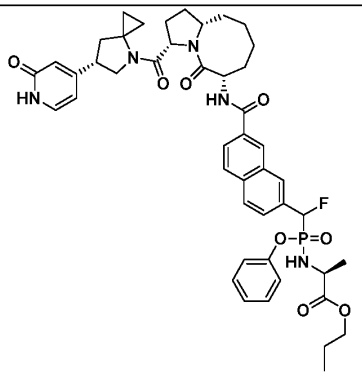
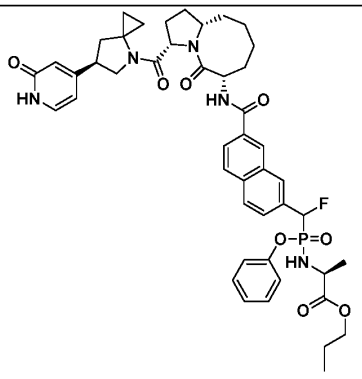
402	propyl (((7-(((3S,6S,10aS)-5-oxo-3-((S)-6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		836.4	^{1}H NMR (400 MHz, DMSO) δ 11.43 (s, 1H), 8.71 – 8.56 (m, 1H), 8.45 (s, 1H), 8.03 – 7.83 (m, 4H), 7.60 (d, J = 8.4 Hz, 1H), 7.40 – 7.23 (m, 3H), 7.18 – 7.06 (m, 3H), 6.24 (s, 1H), 6.18 (d, J = 6.7 Hz, 1H), 5.76 – 5.59 (m, 1H), 5.05 – 4.96 (m, 1H), 4.60 – 4.47 (m, 1H), 4.39 – 4.20 (m, 2H), 3.91 – 3.84 (m, 2H), 3.83 – 3.76 (m, 1H), 3.59 – 3.54 (m, 2H), 3.51 – 3.49 (m, 1H), 2.27 – 2.12 (m, 2H), 2.11 – 2.00 (m, 2H), 1.99 – 1.86 (m, 4H), 1.86 – 1.66 (m, 4H), 1.66 – 1.36 (m, 6H), 1.11 – 1.05 (m, 3H), 0.84 – 0.75 (m, 3H), 0.55 – 0.37 (m, 2H)
403	propyl ((difluoro(7-(((3S,6S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		855.5	^{1}H NMR (400 MHz, DMSO) δ 8.81 – 8.70 (m, 2H), 8.44 – 8.35 (m, 1H), 8.22 (t, J = 7.5 Hz, 1H), 8.17 (s, 2H), 7.88 (d, J = 8.6 Hz, 1H), 7.49 – 7.35 (m, 6H), 7.33 – 7.20 (m, 4H), 6.99 – 6.86 (m, 1H), 5.19 – 5.01 (m, 1H), 4.68 – 4.17 (m, 3H), 4.10 – 3.54 (m, 5H), 2.44 – 2.25 (m, 2H), 2.22 – 1.77 (m, 10H), 1.75 – 1.48 (m, 6H), 1.34 – 1.22 (m, 3H), 0.93 – 0.84

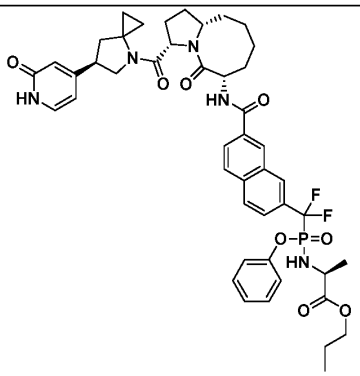
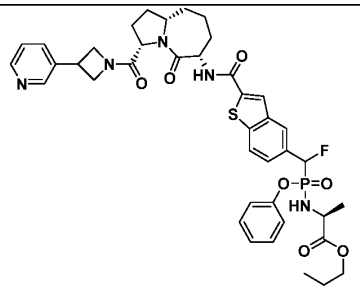
				(m, 3H), 0.67 – 0.46 (m, 2H)
404	2-ethylbutyl (((7-(((3S,6S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		861.6	^{1}H NMR (400 MHz, DMSO) δ 8.74 – 8.55 (m, 1H), 8.46 (d, J = 5.0 Hz, 1H), 8.00 – 7.81 (m, 4H), 7.61 (d, J = 8.3 Hz, 1H), 7.36 – 7.28 (m, 5H), 7.28 – 7.18 (m, 2H), 7.18 – 7.08 (m, 3H), 5.77 – 5.52 (m, 1H), 5.11 – 4.91 (m, 1H), 4.59 – 4.09 (m, 3H), 3.91 – 3.82 (m, 2H), 3.80 – 3.72 (m, 1H), 3.62 – 3.55 (m, 1H), 3.55 – 3.50 (m, 1H), 3.49 – 3.43 (m, 1H), 2.35 – 2.15 (m, 2H), 2.14 – 1.97 (m, 3H), 1.97 – 1.81 (m, 5H), 1.81 – 1.71 (m, 2H), 1.70 – 1.51 (m, 4H), 1.51 – 1.30 (m, 2H), 1.28 – 1.20 (m, 3H), 1.05 (2d, J =7.0 Hz, 3H), 0.83 – 0.69 (m, 6H), 0.54 – 0.39 (m, 2H)
405	butyl (((7-(((3S,6S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		833.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 – 8.26 (m, 1H), 7.93 – 7.80 (m, 4H), 7.64 – 7.55 (m, 1H), 7.47 – 7.36 (m, 1H), 7.35 – 7.26 (m, 6H), 7.24 – 7.02 (m, 4H), 5.26 – 5.13 (m, 1H), 4.60 – 3.45 (m, 10H), 3.37 – 3.04 (m, 1H), 2.55 – 2.37 (m, 1H), 2.25 – 2.18 (m, 1H), 2.13 – 1.42 (m, 16H), 1.36 – 1.10 (m, 5H), 0.95 – 0.76

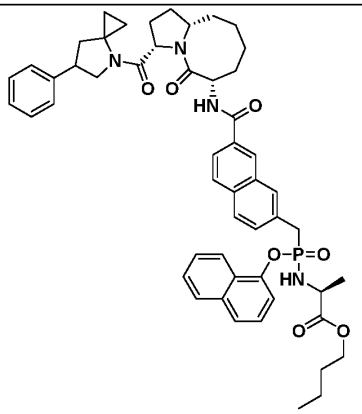
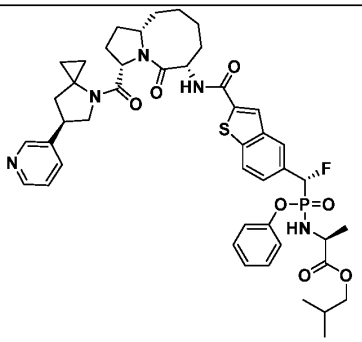
				(m, 3H), 0.63 – 0.47 (m, 2H)
406	butyl ((difluoro(7-(((3S,6S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(naphthalen-1-yloxy)phosphoryl)-L-alaninate		919.0	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 – 8.27 (m, 1H), 8.26 – 8.19 (m, 1H), 8.00 – 7.83 (m, 5H), 7.83 – 7.75 (m, 1H), 7.66 – 7.54 (m, 1H), 7.54 – 7.37 (m, 4H), 7.36 – 7.27 (m, 4H), 7.25 – 7.21 (m, 1H), 5.27 – 5.11 (m, 1H), 4.64 – 4.15 (m, 3H), 4.14 – 3.85 (m, 4H), 3.69 – 3.08 (m, 2H), 2.54 – 2.36 (m, 1H), 2.27 – 1.86 (m, 9H), 1.80 – 1.61 (m, 5H), 1.53 – 1.42 (m, 3H), 1.32 – 1.24 (m, 5H), 0.91 – 0.84 (m, 3H), 0.63 – 0.45 (m, 2H)
407	butyl ((difluoro(7-(((3S,6S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		869.3	^{1}H NMR (400 MHz, DMSO) δ 8.71 – 8.60 (m, 2H), 8.32 – 8.17 (m, 1H), 8.15 – 8.00 (m, 3H), 7.82 – 7.68 (m, 1H), 7.40 – 7.11 (m, 9H), 6.89 – 6.75 (m, 1H), 5.06 – 4.95 (m, 1H), 4.59 – 3.43 (m, 9H), 2.36 – 2.15 (m, 2H), 2.13 – 1.71 (m, 10H), 1.60 – 1.37 (m, 6H), 1.23 – 1.14 (m, 4H), 0.89 – 0.74 (m, 4H), 0.55 – 0.38 (m, 2H)

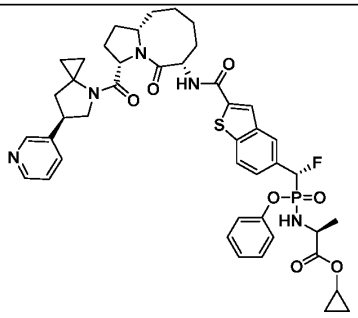
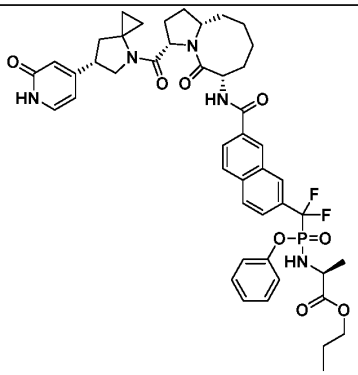
408	S,S'-(((((7-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2-(oxetan-3-yl)ethanethioate) Or S,S'-(((((7-(((3S,6S,10aS)-3-(3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2-(oxetan-3-yl)ethanethioate)	 Pyrrolidine building block SFC peak 1 was used for synthesis and biological testing	998.2	^{1}H NMR (400 MHz, DMSO) δ 11.61 (s, 1H), 8.75 – 8.57 (m, 2H), 8.39 – 8.25 (m, 1H), 8.24 – 8.02 (m, 3H), 7.83 – 7.62 (m, 1H), 7.38 (d, J = 6.7 Hz, 1H), 6.42 – 6.32 (m, 1H), 6.30 – 6.18 (m, 1H), 5.09 – 4.91 (m, 1H), 4.72 – 4.07 (m, 14H), 3.99 – 3.46 (m, 6H), 3.23 – 3.06 (m, 6H), 3.02 – 2.64 (m, 4H), 2.34 – 2.19 (m, 1H), 2.06 – 1.39 (m, 11H) (free base)

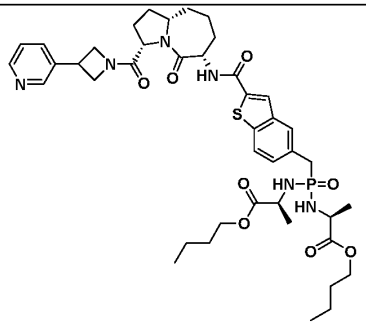
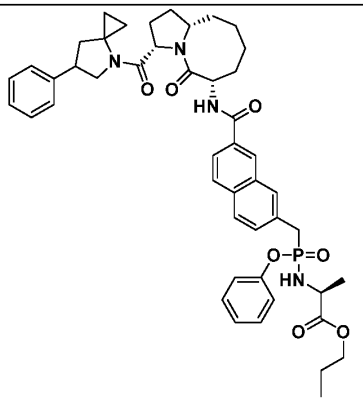
409	propyl (((7-(((3S,6S,10aS)-5-oxo-3-((R)-6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		836.4	^{1}H NMR (400 MHz, DMSO) δ 11.43 (s, 1H), 8.68 – 8.58 (m, 1H), 8.44 (s, 1H), 8.01 – 7.85 (m, 4H), 7.60 (d, J = 8.4 Hz, 1H), 7.36 – 7.20 (m, 3H), 7.18 – 7.07 (m, 3H), 6.26 (s, 1H), 6.18 (d, J = 6.8 Hz, 1H), 5.76 – 5.57 (m, 1H), 5.07 – 4.93 (m, 1H), 4.56 – 4.43 (m, 1H), 4.34 – 4.18 (m, 1H), 4.12 – 4.00 (m, 1H), 3.93 – 3.74 (m, 3H), 3.74 – 3.65 (m, 1H), 3.59 – 3.44 (m, 3H), 2.34 – 2.21 (m, 1H), 2.18 – 1.65 (m, 11H), 1.65 – 1.34 (m, 6H), 1.07 (d, J = 7.1 Hz, 1H), 0.99 (d, J = 7.1 Hz, 2H), 0.83 – 0.75 (m, 3H), 0.54 – 0.39 (m, 2H)
410	isobutyl (((7-(((3S,6S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		833.6	^{1}H NMR (400 MHz, DMSO) δ 8.69 – 8.54 (m, 1H), 8.52 – 8.39 (m, 1H), 8.02 – 7.83 (m, 4H), 7.66 – 7.55 (m, 1H), 7.39 – 7.04 (m, 10H), 5.80 – 5.51 (m, 1H), 5.11 – 4.90 (m, 1H), 4.65 – 4.02 (m, 3H), 3.93 – 3.68 (m, 3H), 3.58 – 3.46 (m, 3H), 2.35 – 2.17 (m, 2H), 2.13 – 1.49 (m, 15H), 1.04 (2d, J = 7.0 Hz, 3H), 0.82-0.79 (m, 6H), 0.55 – 0.38 (m, 2H)

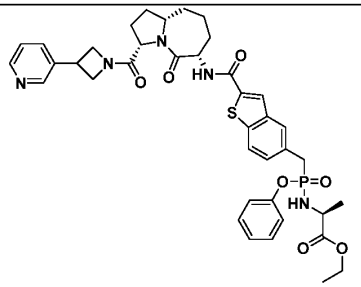
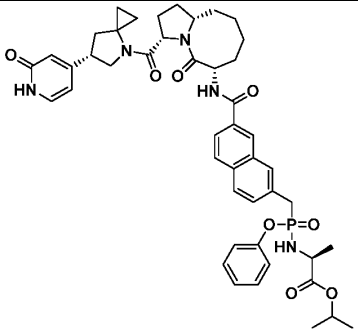
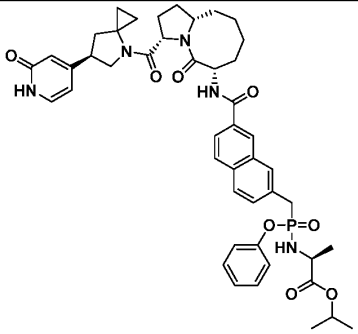
411	propyl ((fluoro(7-(((3S,6S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		837.5	^{1}H NMR (400 MHz, DMSO) δ 8.73 – 8.61 (m, 1H), 8.60 – 8.43 (m, 1H), 8.13 (s, 1H), 8.07 – 7.81 (m, 3H), 7.79 – 7.58 (m, 1H), 7.42 – 7.07 (m, 9H), 6.67 – 6.09 (m, 2H), 5.36 – 4.98 (m, 1H), 4.58 – 4.07 (m, 3H), 4.02 – 3.64 (m, 4H), 3.61 – 3.49 (m, 2H), 2.37 – 2.16 (m, 2H), 2.11 – 1.69 (m, 10H), 1.66 – 1.33 (m, 6H), 1.18 – 1.06 (m, 2H), 1.02 – 0.68 (m, 4H), 0.60 – 0.33 (m, 2H)
412	propyl ((fluoro(7-(((3S,6S,10aS)-5-oxo-3-((S)-6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		854.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 – 7.27 (m, 12H), 7.24 – 6.56 (m, 3H), 6.24 – 5.73 (m, 2H), 5.39 – 5.16 (m, 1H), 4.82 – 4.46 (m, 2H), 4.43 – 4.27 (m, 2H), 4.19 – 3.80 (m, 3H), 3.77 – 3.59 (m, 1H), 3.51 – 3.28 (m, 1H), 2.45 – 2.35 (m, 1H), 2.28 – 1.46 (m, 15H), 1.45 – 1.02 (m, 6H), 1.01 – 0.78 (m, 3H), 0.60 – 0.40 (m, 1H)
413	propyl ((fluoro(7-(((3S,6S,10aS)-5-oxo-3-((R)-6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-		854.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 – 7.29 (m, 12H), 7.25 – 6.99 (m, 3H), 6.19 – 5.87 (m, 1H), 5.38 – 5.02 (m, 1H), 4.72 – 4.13 (m, 5H), 4.11 – 3.99 (m, 2H), 3.95 – 3.81 (m, 1H), 3.72 – 3.54 (m, 1H), 2.42 – 1.92 (m, 9H), 1.89 – 1.45

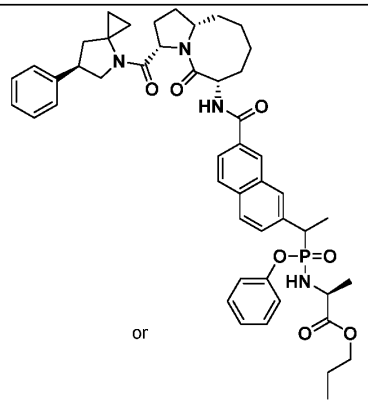
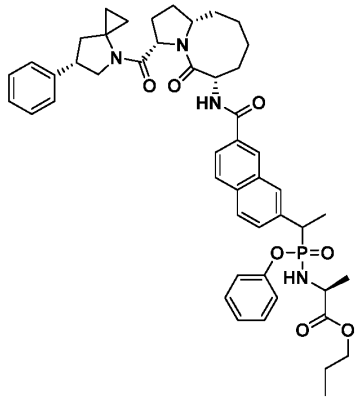
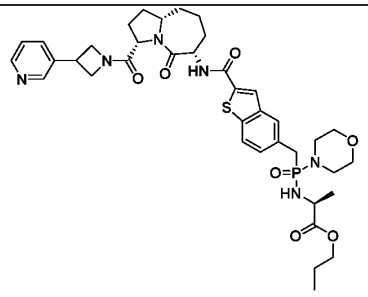
	yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate			(m, 7H), 1.42 – 1.09 (m, 6H), 0.95 – 0.77 (m, 3H), 0.56 – 0.41 (m, 1H) (TFA salt)
414	propyl ((difluoro(7-(((3S,6S,10aS)-5-oxo-3-((R)-6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		872.3	^{1}H NMR (400 MHz, DMSO) δ 11.42 (s, 1H), 8.73 – 8.49 (m, 2H), 8.48 – 8.25 (m, 1H), 8.23 – 8.03 (m, 3H), 7.84 – 7.71 (m, 1H), 7.44 – 7.31 (m, 2H), 7.30 – 7.24 (m, 1H), 7.23 – 7.10 (m, 3H), 6.90 – 6.77 (m, 1H), 6.40 – 6.22 (m, 1H), 6.21 – 6.07 (m, 1H), 5.34 – 4.95 (m, 1H), 4.57 – 4.43 (m, 1H), 4.36 – 3.74 (m, 6H), 3.73 – 3.63 (m, 1H), 2.36 – 2.23 (m, 1H), 2.13 – 1.95 (m, 5H), 1.91 – 1.80 (m, 3H), 1.79 – 1.68 (m, 2H), 1.66 – 1.39 (m, 6H), 1.26 – 1.16 (m, 4H), 0.87 – 0.76 (m, 3H), 0.59 – 0.39 (m, 2H)
415	propyl ((fluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		790.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 – 8.71 (m, 2H), 8.60 – 8.16 (m, 1H), 8.04 – 7.28 (m, 7H), 7.26 – 7.17 (m, 2H), 7.16 – 7.02 (m, 2H), 6.08 – 5.99 (m, 1H), 5.22 – 4.40 (m, 5H), 4.31 – 3.59 (m, 7H), 2.37 – 1.51 (m, 12H), 1.38 – 1.20 (m, 3H), 0.97 – 0.78 (m, 3H) (TFA salt)

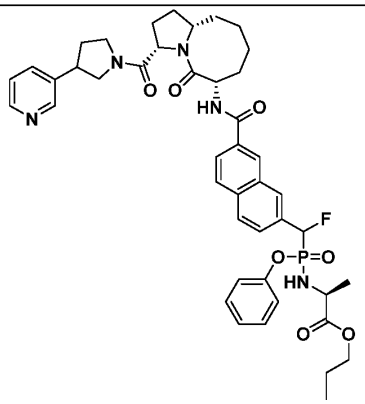
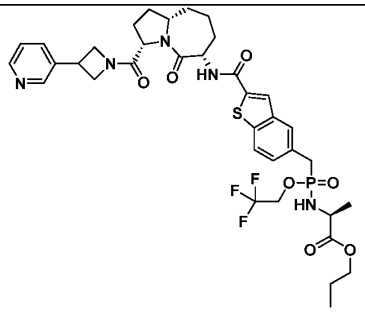
416	butyl ((naphthalen-1-yloxy)((7-(((3S,6S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphoryl)-L-alaninate		883.4	^{1}H NMR (400 MHz, DMSO) δ 8.69 – 8.58 (m, 1H), 8.49 – 8.42 (m, 1H), 8.05 – 7.86 (m, 6H), 7.71 – 7.63 (m, 2H), 7.55 – 7.18 (m, 9H), 5.92 – 5.69 (m, 1H), 5.11 – 4.93 (m, 1H), 4.59 – 4.08 (m, 3H), 4.01 – 3.44 (m, 7H), 2.36 – 2.16 (m, 2H), 2.14 – 1.67 (m, 10H), 1.66 – 1.45 (m, 4H), 1.42 – 1.30 (m, 2H), 1.26 – 1.12 (m, 2H), 1.11 – 0.95 (m, 3H), 0.83 – 0.73 (m, 3H), 0.55 – 0.40 (m, 2H)
417	isobutyl (((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		858.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 – 8.42 (m, 2H), 8.01 – 7.73 (m, 3H), 7.73 – 7.47 (m, 3H), 7.46 – 7.28 (m, 2H), 7.26 – 7.16 (m, 2H), 7.15 – 7.02 (m, 2H), 6.11 – 5.80 (m, 1H), 5.26 – 5.10 (m, 1H), 4.64 – 4.46 (m, 1H), 4.39 – 4.23 (m, 1H), 4.20 – 3.69 (m, 6H), 3.65 – 3.49 (m, 1H), 2.45 – 1.94 (m, 12H), 1.90 – 1.63 (m, 5H), 1.38 – 1.09 (m, 3H), 1.02 – 0.82 (m, 6H), 0.63 – 0.44 (m, 2H)

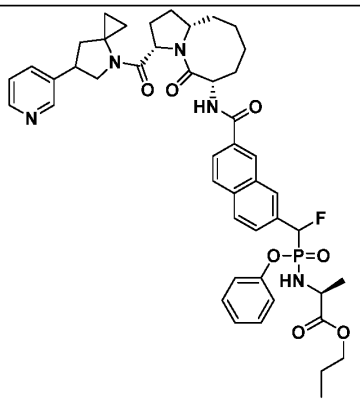
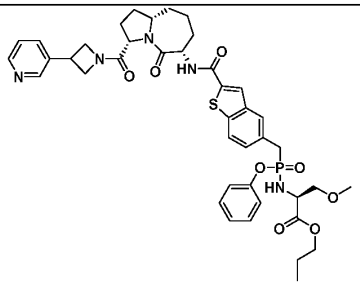
418	cyclopropyl (((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		842.5	^{1}H NMR (400 MHz, DMSO) δ 8.90 – 8.81 (m, 1H), 8.66 (s, 1H), 8.50 (d, J = 4.4 Hz, 1H), 8.30 (s, 1H), 8.14 – 8.03 (m, 2H), 7.94 (d, J = 7.9 Hz, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.50 – 7.42 (m, 1H), 7.41 – 7.32 (m, 2H), 7.24 – 7.11 (m, 3H), 6.28 – 6.08 (m, 2H), 5.00 – 4.89 (m, 1H), 4.56 – 4.47 (m, 1H), 4.30 – 4.20 (m, 1H), 4.19 – 4.11 (m, 1H), 4.06 – 3.91 (m, 1H), 3.88 – 3.64 (m, 3H), 2.27 – 1.52 (m, 16H), 1.16 – 0.88 (m, 3H), 0.73 – 0.37 (m, 6H)
419	propyl ((difluoro(7-(((3S,6S,10aS)-5-oxo-3-((S)-6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		872.4	^{1}H NMR (400 MHz, DMSO) δ 11.49 – 11.31 (m, 1H), 8.70 – 8.62 (m, 2H), 8.32 – 8.26 (m, 1H), 8.17 – 8.10 (m, 1H), 8.10 – 8.04 (m, 2H), 7.83 – 7.74 (m, 1H), 7.41 – 7.32 (m, 2H), 7.31 – 7.24 (m, 1H), 7.23 – 7.16 (m, 2H), 7.15 – 7.10 (m, 1H), 6.89 – 6.78 (m, 1H), 6.27 – 6.21 (m, 1H), 6.20 – 6.13 (m, 1H), 5.06 – 4.95 (m, 1H), 4.58 – 4.49 (m, 1H), 4.35 – 4.15 (m, 2H), 3.95 – 3.79 (m, 3H), 3.65 – 3.51 (m, 1H), 3.25 – 3.20 (m, 1H), 2.20-2.17 (m, 2H), 2.07 – 2.00 (m, 2H), 1.96 – 1.71 (m, 8H), 1.58 –

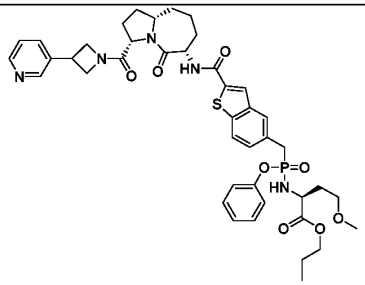
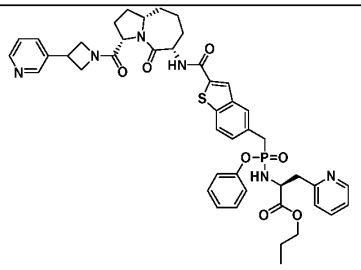
				1.40 (m, 5H), 1.25 – 1.15 (m, 4H), 0.85 – 0.76 (m, 3H), 0.53 – 0.41 (m, 2H)
420	dibutyl 2,2'-((((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(azanediyl))(2S,2'S)-dipropionate		837.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 – 8.55 (m, 2H), 8.12 – 7.73 (m, 5H), 7.69 – 7.37 (m, 3H), 5.10 – 4.58 (m, 4H), 4.56 – 4.42 (m, 1H), 4.24 – 4.18 (m, 1H), 4.12 – 3.91 (m, 8H), 3.35 – 3.22 (m, 2H), 3.17 – 3.06 (m, 1H), 3.05 – 2.90 (m, 1H), 2.34 – 2.20 (m, 2H), 2.12 – 2.02 (m, 4H), 1.99 – 1.91 (m, 2H), 1.87 – 1.73 (m, 2H), 1.63 – 1.53 (m, 4H), 1.43 – 1.29 (m, 10H), 0.93 (t, J = 7.3 Hz, 6H)
421	propyl (((7-(((3S,6S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		819.5	^{1}H NMR (400 MHz, DMSO) δ 8.71 – 8.56 (m, 1H), 8.47 – 8.40 (m, 1H), 7.99 – 7.86 (m, 4H), 7.63 – 7.56 (m, 1H), 7.37 – 7.26 (m, 6H), 7.25 – 7.17 (m, 1H), 7.17 – 7.08 (m, 3H), 5.76 – 5.55 (m, 1H), 5.07 – 4.91 (m, 1H), 4.59 – 4.07 (m, 3H), 3.94 – 3.41 (m, 7H), 2.37 – 2.15 (m, 2H), 2.12 – 1.68 (m, 10H), 1.66 – 1.37 (m, 6H), 1.03 (2d, J = 7.1 Hz, 3H), 0.84 – 0.72 (m, 3H), 0.54 – 0.40 (m, 2H)

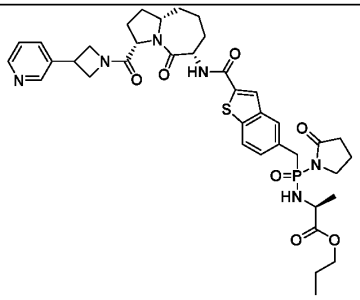
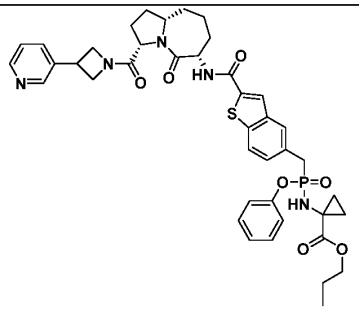
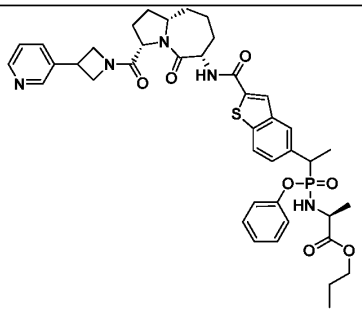
422	ethyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		758.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 – 8.11 (m, 4H), 8.00 – 7.29 (m, 5H), 7.14 – 6.99 (m, 2H), 5.08 – 3.78 (m, 10H), 3.53 – 2.98 (m, 3H), 2.26 – 2.01 (m, 4H), 1.96 – 1.68 (m, 6H), 1.22 – 1.01 (m, 6H)
423	isopropyl (((7-(((3S,6S,10aS)-5-oxo-3-((S)-6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		836.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.26 (m, 1H), 7.98 – 7.71 (m, 5H), 7.57 – 7.49 (m, 1H), 7.42 – 7.35 (m, 1H), 7.32 – 7.27 (m, 2H), 7.18 – 7.10 (m, 3H), 6.66 – 6.45 (m, 2H), 5.36 – 5.22 (m, 1H), 4.98 – 4.86 (m, 1H), 4.64 – 4.31 (m, 3H), 4.00 – 3.86 (m, 1H), 3.59 – 3.42 (m, 4H), 2.25 – 1.64 (m, 16H), 1.27 – 1.15 (m, 9H), 0.59 – 0.44 (m, 2H)
424	isopropyl (((7-(((3S,6S,10aS)-5-oxo-3-((R)-6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		836.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 – 7.27 (m, 8H), 7.23 – 6.84 (m, 4H), 6.46 – 5.90 (m, 2H), 5.32 – 5.12 (m, 1H), 5.03 – 4.81 (m, 1H), 4.55 – 4.47 (m, 1H), 4.39 – 4.26 (m, 1H), 4.11 – 3.78 (m, 3H), 3.65 – 3.46 (m, 2H), 3.35 – 3.21 (m, 1H), 2.43 – 2.28 (m, 1H), 2.04 – 1.79 (m, 6H), 1.76 – 1.57 (m, 4H), 1.45 – 1.30 (m, 6H), 1.22 – 1.16

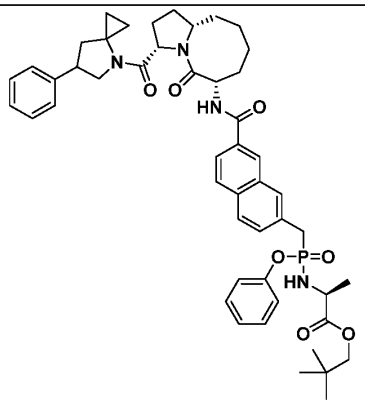
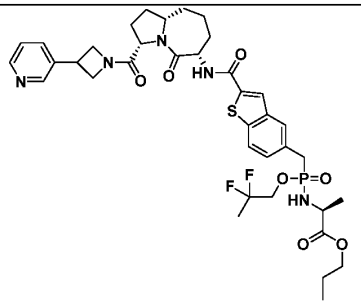
				(m, 6H), 1.14 – 1.08 (m, 2H), 0.60 – 0.42 (m, 2H)
425	propyl ((1-(7-(((3S,6S,10aS)-5-oxo-3-((R)-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)ethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl ((1-(7-(((3S,6S,10aS)-5-oxo-3-((S)-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)ethyl)(phenoxy)phosphoryl)-L-alaninate	 or  Pyrrolidine building block SFC peak 1 was used for synthesis and biological testing	833.7	^{1}H NMR (400 MHz, DMSO) δ 8.58 (d, J = 7.3 Hz, 1H), 8.47 (s, 1H), 7.94 – 7.82 (m, 4H), 7.58 (d, J = 8.6 Hz, 1H), 7.37 – 7.26 (m, 4H), 7.24 – 7.18 (m, 1H), 5.08 – 4.90 (m, 1H), 4.49 (t, J = 8.2 Hz, 1H), 4.33 – 4.21 (m, 1H), 4.12 (t, J = 8.7 Hz, 1H), 3.73 (t, J = 9.9 Hz, 1H), 3.58 – 3.48 (m, 1H), 3.23 – 3.15 (m, 1H), 2.36 – 2.17 (m, 2H), 2.15 – 2.08 (m, 1H), 2.06 – 1.94 (m, 3H), 1.94 – 1.69 (m, 6H), 1.67 – 1.59 (m, 1H), 1.58 – 1.45 (m, 6H), 0.56 – 0.39 (m, 2H)
426	propyl (morpholino((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		765.4	^{1}H NMR (400 MHz, DMSO) δ 8.83 – 8.71 (m, 1H), 8.59 – 8.52 (m, 1H), 8.50 – 8.41 (m, 1H), 8.22 – 8.12 (m, 1H), 7.95 – 7.82 (m, 3H), 7.45 – 7.30 (m, 2H), 5.28 – 5.05 (m, 1H), 4.84 – 4.56 (m, 2H), 4.49 – 4.18 (m, 3H), 4.07 – 3.72

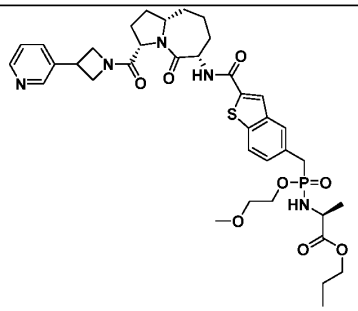
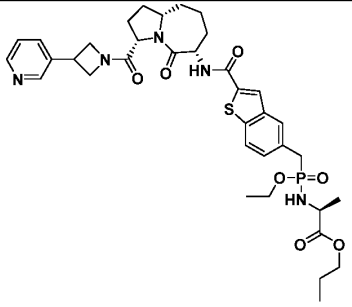
	yl)methyl)phosphoryl)-L-alaninate			(m, 6H), 3.45 – 3.35 (m, 4H), 3.26 – 3.15 (m, 2H), 2.98 – 2.74 (m, 4H), 2.26 – 2.13 (m, 1H), 2.08 – 1.92 (m, 2H), 1.90 – 1.66 (m, 7H), 1.64 – 1.51 (m, 2H), 1.32 – 1.21 (m, 3H), 0.95 – 0.81 (m, 3H)
427	propyl ((fluoro(7-(((3S,6S,10aS)-5-oxo-3-(3-(pyridin-3-yl)pyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		812.4	^{1}H NMR (400 MHz, DMSO) δ 8.61 – 8.44 (m, 2H), 8.38 – 8.27 (m, 1H), 7.95 – 7.78 (m, 4H), 7.68 – 7.37 (m, 3H), 7.32 – 7.28 (m, 1H), 7.27 – 7.24 (m, 2H), 7.20 – 7.07 (m, 3H), 5.26 – 4.93 (m, 1H), 4.69 – 4.51 (m, 1H), 4.45 – 4.14 (m, 2H), 4.08 – 3.63 (m, 5H), 3.60 – 3.15 (m, 5H), 2.49 – 2.29 (m, 2H), 2.18 – 2.00 (m, 6H), 1.88 – 1.63 (m, 6H), 1.60 – 1.46 (m, 2H), 1.20 – 1.08 (m, 3H), 0.92 – 0.78 (m, 3H)
428	propyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(2,2,2-trifluoroethoxy)phosphoryl)-L-alaninate		776.2 [M-H]$^-$	^{1}H NMR (400 MHz, DMSO) δ 8.83-8.53 (m, 3H), 8.22 – 8.09 (m, 2H), 7.97 – 7.90 (m, 1H), 7.87 – 7.81 (m, 1H), 7.69 – 7.50 (m, 1H), 7.42 – 7.34 (m, 1H), 5.62 – 5.48 (m, 1H), 4.84 – 4.61 (m, 2H), 4.48 – 4.26 (m, 5H), 4.06 – 3.83 (m, 5H), 3.80 – 3.65 (m, 1H), 3.43 – 3.29 (m, 2H), 2.26 – 2.16 (m, 1H), 2.08 – 1.92

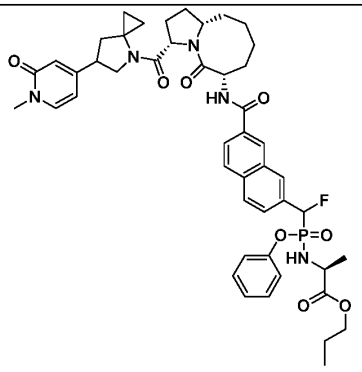
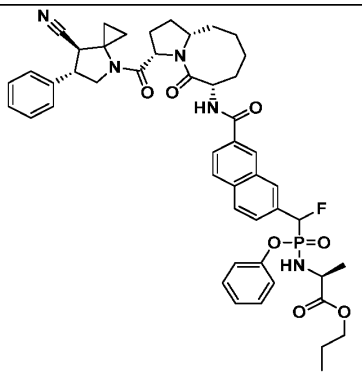
				(m, 2H), 1.91 – 1.64 (m, 7H), 1.62 – 1.48 (m, 2H), 1.30 – 1.08 (m, 3H), 0.91 – 0.80 (m, 3H)
429	propyl ((fluoro(7-(((3S,6S,10aS)-5-oxo-3-(6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		838.5	^{1}H NMR (400 MHz, DMSO) δ 8.72 – 8.64 (m, 1H), 8.64 – 8.50 (m, 2H), 8.49 – 8.38 (m, 1H), 8.23 – 7.98 (m, 4H), 7.83 – 7.69 (m, 2H), 7.38 – 7.28 (m, 3H), 7.23 – 7.09 (m, 3H), 6.38 – 6.11 (m, 2H), 5.09 – 4.95 (m, 1H), 4.75 – 4.06 (m, 3H), 4.00 – 3.46 (m, 5H), 2.42 – 1.36 (m, 18H), 1.21 – 0.95 (m, 3H), 0.83 – 0.72 (m, 3H), 0.58 – 0.34 (m, 2H)
430	propyl O-methyl-N-(((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-serinate		802.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 – 8.53 (m, 2H), 7.96 – 7.61 (m, 5H), 7.54 – 7.31 (m, 2H), 7.29 (d, J = 7.6 Hz, 1H), 7.26 (s, 1H), 7.20 – 7.07 (m, 3H), 5.06 – 4.37 (m, 5H), 4.24 – 4.15 (m, 1H), 4.13 – 3.92 (m, 5H), 3.65 – 3.41 (m, 4H), 3.22 – 3.05 (m, 4H), 2.31 – 2.17 (m, 2H), 2.11 – 1.99 (m, 4H), 1.95 (t, J = 10.1 Hz, 2H), 1.85 – 1.69 (m, 2H), 1.66 – 1.50 (m, 2H), 0.95 – 0.82 (m, 3H)

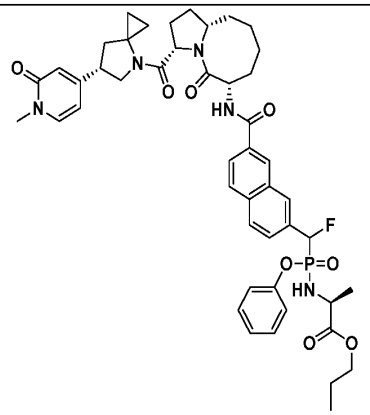
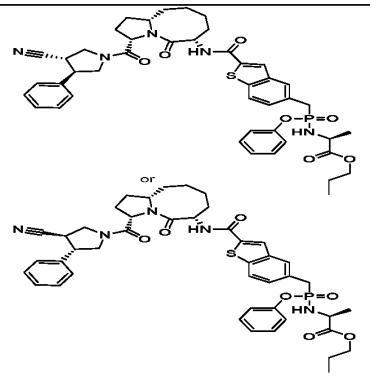
431	propyl O-methyl-N-(((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-homoserinate		816.4	^{1}H NMR (400 MHz, DMSO) δ 8.82 – 8.72 (m, 1H), 8.59 – 8.52 (m, 1H), 8.50 – 8.40 (m, 1H), 8.22 – 8.19 (m, 1H), 7.97 – 7.83 (m, 3H), 7.48 – 7.28 (m, 4H), 7.17 – 7.07 (m, 3H), 5.73 – 5.47 (m, 1H), 4.84 – 4.57 (m, 2H), 4.48 – 4.19 (m, 3H), 4.05 – 3.77 (m, 6H), 3.53 – 3.35 (m, 2H), 3.14 – 2.89 (m, 5H), 2.28 – 2.15 (m, 1H), 2.08 – 1.93 (m, 2H), 1.90 – 1.45 (m, 11H), 0.81 (t, J = 14.0, 6.7 Hz, 3H)
432	propyl (2S)-2-((((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)amino)-3-(pyridin-2-yl)propanoate		849.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 – 8.49 (m, 2H), 8.23 – 8.10 (m, 1H), 8.04 – 7.57 (m, 6H), 7.55 – 7.34 (m, 3H), 7.21 – 7.13 (m, 2H), 7.12 – 7.03 (m, 2H), 7.02 – 6.94 (m, 2H), 4.76 – 4.36 (m, 7H), 4.23 – 4.17 (m, 1H), 4.09 – 3.89 (m, 4H), 3.52 – 3.28 (m, 2H), 3.23 – 3.15 (m, 1H), 3.00 – 2.91 (m, 1H), 2.29 – 2.18 (m, 2H), 2.11 – 2.00 (m, 4H), 1.98 – 1.88 (m, 2H), 1.85 – 1.69 (m, 2H), 1.57 – 1.44 (m, 2H), 0.90 – 0.74 (m, 3H)

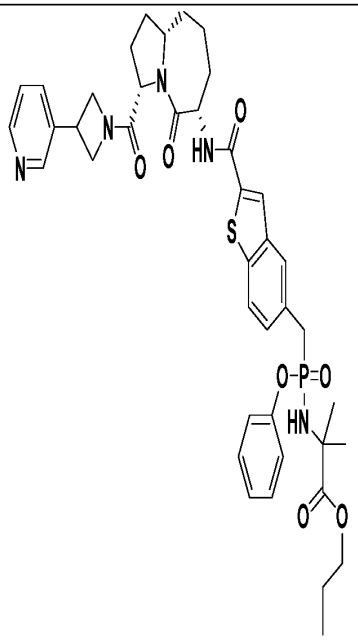
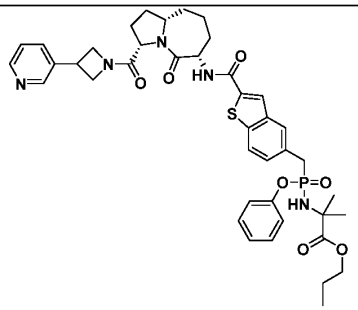
433	propyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(2-oxopyrrolidin-1-yl)phosphoryl)-L-alaninate		763.8	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 – 8.49 (m, 2H), 7.96 – 7.61 (m, 5H), 7.45 – 7.31 (m, 2H), 4.75 – 4.37 (m, 4H), 4.33 – 3.81 (m, 8H), 3.66 – 3.42 (m, 3H), 3.00 – 2.82 (m, 1H), 2.51 – 2.14 (m, 5H), 2.11 – 1.98 (m, 5H), 1.96 – 1.91 (m, 2H), 1.72 – 1.61 (m, 4H), 1.42 – 1.34 (m, 3H), 0.98 – 0.87 (m, 3H)
434	propyl 1-((((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)amino)cyclopropane-1-carboxylate		784	^{1}H NMR (400 MHz, DMSO) δ 8.83 – 8.69 (m, 1H), 8.60 – 8.51 (m, 1H), 8.50 – 8.40 (m, 1H), 8.24 – 8.09 (m, 1H), 8.04 – 7.92 (m, 1H), 7.91 – 7.72 (m, 2H), 7.66 – 7.27 (m, 4H), 7.23 – 7.04 (m, 3H), 6.06 (d, J = 15.8 Hz, 1H), 4.86 – 4.56 (m, 2H), 4.50 – 4.17 (m, 3H), 4.09 – 3.76 (m, 5H), 3.66 – 3.40 (m, 2H), 2.27 – 2.13 (m, 1H), 2.09 – 1.93 (m, 2H), 1.92 – 1.60 (m, 7H), 1.57 – 1.41 (m, 2H), 1.27 – 1.15 (m, 2H), 1.01 – 0.74 (m, 5H)
435	propyl ((1-(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		786.4	^{1}H NMR (400 MHz, DMSO) δ 8.84 – 8.71 (m, 1H), 8.61 – 8.53 (m, 1H), 8.51 – 8.40 (m, 1H), 8.25 – 8.17 (m, 1H), 8.00 – 7.91 (m, 2H), 7.91 – 7.83 (m, 1H), 7.54 – 7.47 (m, 1H), 7.46 – 7.30

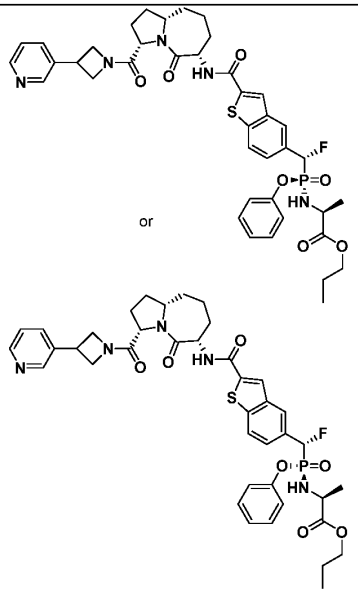
	yl)ethyl)(phenoxy)phosphoryl)-L-alaninate			(m, 2H), 7.30 – 7.04 (m, 3H), 7.01 (t, J = 7.2 Hz, 1H), 5.71 – 5.38 (m, 1H), 4.88 – 4.56 (m, 2H), 4.51 – 4.17 (m, 3H), 4.09 – 3.66 (m, 6H), 3.61 – 3.48 (m, 1H), 2.26 – 2.13 (m, 1H), 2.09 – 1.92 (m, 2H), 1.86 – 1.37 (m, 12H), 1.17 – 0.95 (m, 2H), 0.89 – 0.66 (m, 4H)
436	neopentyl (((7-(((3S,6S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		847.5	^{1}H NMR (400 MHz, DMSO) δ 8.68 – 8.61 (m, 1H), 8.49 – 8.43 (m, 1H), 8.04 – 7.89 (m, 4H), 7.67 – 7.58 (m, 1H), 7.38 – 7.21 (m, 8H), 7.17 – 7.08 (m, 3H), 5.79 – 5.58 (m, 1H), 5.07 – 4.95 (m, 1H), 4.59 – 4.38 (m, 2H), 4.32 – 4.21 (m, 1H), 4.16 – 3.86 (m, 1H), 3.76 – 3.49 (m, 5H), 2.37 – 1.56 (m, 16H), 1.06 (2d, J = 7.1 Hz, 3H), 0.89 – 0.72 (m, 9H), 0.53 – 0.39 (m, 2H)
437	propyl ((2,2-difluoropropoxy)((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)-L-alaninate		774.8	^{1}H NMR (400 MHz, DMSO) δ 8.85 – 8.73 (m, 1H), 8.61 – 8.52 (m, 1H), 8.51 – 8.41 (m, 1H), 8.21 – 8.17 (m, 1H), 7.96 – 7.81 (m, 3H), 7.44 – 7.30 (m, 2H), 5.49 – 5.26 (m, 1H), 4.85 – 4.57 (m, 2H), 4.50 – 4.19 (m, 3H), 4.08 – 3.84 (m, 7H), 3.33 – 3.30 (m, 2H), 2.90 – 2.69 (m, 1H), 2.26 – 2.14

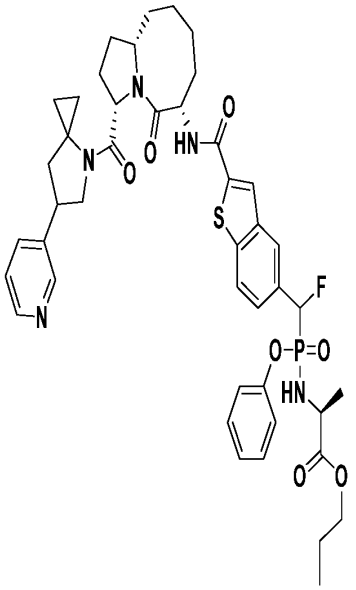
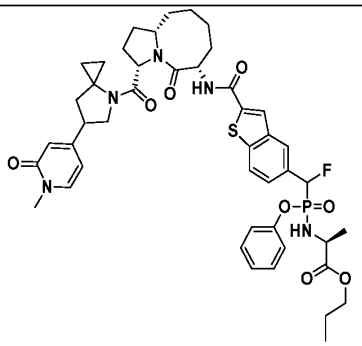
				(m, 1H), 2.08 – 1.93 (m, 2H), 1.89 – 1.65 (m, 7H), 1.62 – 1.59 (m, 1H), 1.57 – 1.56 (m, 1H), 1.29 – 1.12 (m, 3H), 1.10 – 1.09 (m, 3H), 0.91 – 0.81 (m, 3H)
438	propyl ((2-methoxyethoxy)((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)-L-alaninate		754.3	^{1}H NMR (400 MHz, DMSO) δ 8.84 – 8.72 (m, 1H), 8.59 – 8.53 (m, 1H), 8.50 – 8.42 (m, 1H), 8.21 – 8.14 (m, 1H), 7.96 – 7.79 (m, 3H), 7.46 – 7.29 (m, 2H), 5.21 – 5.07 (m, 1H), 4.83 – 4.60 (m, 2H), 4.48 – 4.21 (m, 3H), 4.04 – 3.83 (m, 7H), 3.53 – 3.41 (m, 2H), 3.33 – 3.32 (m, 3H), 3.26 – 3.22 (m, 3H), 2.26 – 2.12 (m, 1H), 2.07 – 1.91 (m, 2H), 1.90 – 1.65 (m, 7H), 1.60 – 1.48 (m, 2H), 1.27 – 1.03 (m, 3H), 0.90 – 0.80 (m, 3H)
439	propyl (ethoxy((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)-L-alaninate		724.4	^{1}H NMR (400 MHz, DMSO) δ 8.82 – 8.70 (m, 1H), 8.59 – 8.53 (m, 1H), 8.50 – 8.41 (m, 1H), 8.21 – 8.16 (m, 1H), 7.96 – 7.79 (m, 3H), 7.44 – 7.30 (m, 2H), 5.17 – 5.02 (m, 1H), 4.84 – 4.56 (m, 2H), 4.48 – 4.18 (m, 3H), 4.05 – 3.63 (m, 8H), 3.27 – 3.15 (m, 2H), 2.28 – 2.11 (m, 1H), 2.12 – 1.90 (m, 2H), 1.91 – 1.45 (m, 9H), 1.31 – 1.02

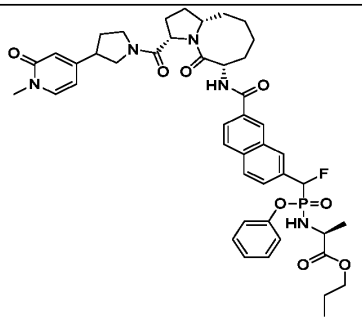
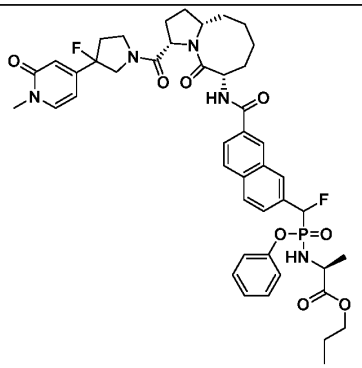
				(m, 6H), 0.94 – 0.78 (m, 3H)
440	propyl ((fluoro(7-(((3S,6S,10aS)-3-(6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		868.5	^{1}H NMR (400 MHz, DMSO) δ 8.75 – 8.61 (m, 1H), 8.55 (s, 1H), 8.13 (s, 1H), 8.08 – 7.97 (m, 3H), 7.81 – 7.69 (m, 1H), 7.68 – 7.50 (m, 1H), 7.42 – 7.25 (m, 2H), 7.24 – 7.08 (m, 3H), 6.49 – 6.05 (m, 4H), 5.13 – 4.87 (m, 1H), 4.83 – 3.52 (m, 8H), 3.40 – 3.32 (m, 3H), 2.37 – 2.12 (m, 1H), 2.11 – 1.58 (m, 12H), 1.60 – 1.33 (m, 6H), 1.22 – 1.06 (m, 2H), 0.86 – 0.68 (m, 3H), 0.55 – 0.37 (m, 2H)
441	propyl ((fluoro(7-(((3S,6S,10aS)-3-((R)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		868.4	^{1}H NMR (400 MHz, DMSO) δ 8.72 – 8.63 (m, 1H), 8.56 (s, 1H), 8.13 (s, 1H), 8.07 – 7.98 (m, 3H), 7.78 – 7.71 (m, 1H), 7.58 (d, J = 7.0 Hz, 1H), 7.39 – 7.30 (m, 2H), 7.22 – 7.11 (m, 3H), 6.39 – 6.11 (m, 4H), 5.08 – 4.96 (m, 1H), 4.49 (t, J = 8.0 Hz, 1H), 4.29 (t, J = 19.1, 9.0 Hz, 1H), 4.06 (t, J = 8.7 Hz, 1H), 3.95 – 3.66 (m, 4H), 3.33 (d, J = 3.9 Hz, 4H), 2.35 – 2.21 (m, 1H), 2.13 – 1.95 (m, 5H), 1.93 – 1.70 (m, 6H), 1.69 – 1.60 (m, 1H), 1.60 – 1.46 (m, 4H), 1.45 – 1.36 (m, 1H), 1.19 – 0.94 (m, 3H),

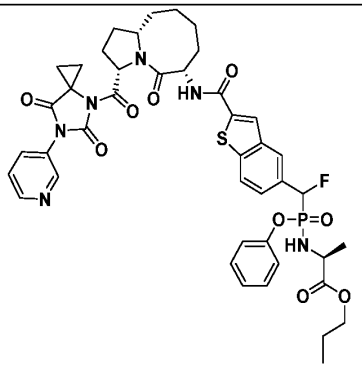
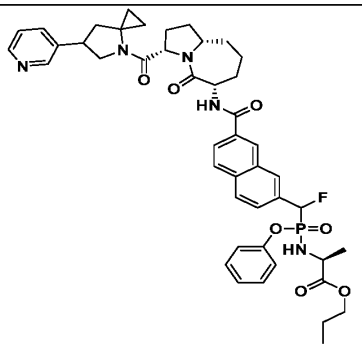
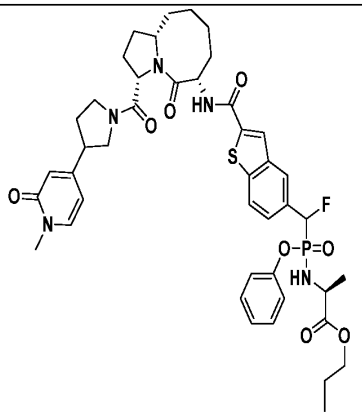
				0.86 – 0.73 (m, 3H), 0.55 – 0.38 (m, 2H)
442	propyl (((7-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		862.3	^{1}H NMR (400 MHz, DMSO) δ 8.79 – 8.65 (m, 1H), 8.57 (s, 1H), 8.13 (s, 1H), 8.08 – 7.95 (m, 3H), 7.76 (d, J = 7.6 Hz, 1H), 7.54 – 7.44 (m, 2H), 7.42 – 7.26 (m, 5H), 7.25 – 7.08 (m, 3H), 6.39 – 6.10 (m, 2H), 5.15 – 4.92 (m, 1H), 4.61 – 4.16 (m, 3H), 4.09 – 3.64 (m, 6H), 2.33 – 1.34 (m, 16H), 1.20 – 1.08 (m, 2H), 0.96 (d, J = 7.1 Hz, 1H), 0.88 – 0.59 (m, 5H)
443	propyl ((fluoro(7-(((3S,6S,10aS)-3-((S)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		868.6	^{1}H NMR (400 MHz, DMSO) δ 8.72 – 8.63 (m, 1H), 8.56 (s, 1H), 8.13 (s, 1H), 8.07 – 7.98 (m, 3H), 7.78 – 7.72 (m, 1H), 7.61 (d, J = 7.0 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.22 – 7.11 (m, 3H), 6.39 – 6.12 (m, 4H), 5.07 – 4.97 (m, 1H), 4.53 (t, J = 8.3 Hz, 1H), 4.37 – 4.22 (m, 2H), 3.98 – 3.68 (m, 3H), 3.58 (t, J = 9.4 Hz, 1H), 3.36 (d, J = 2.5 Hz, 4H), 2.26 – 2.11 (m, 2H), 2.09 – 1.99 (m, 2H), 1.97 – 1.60 (m, 9H), 1.59 – 1.37 (m, 5H), 1.19 – 0.94 (m, 3H), 0.84 – 0.73 (m, 3H), 0.51 – 0.42 (m, 2H)

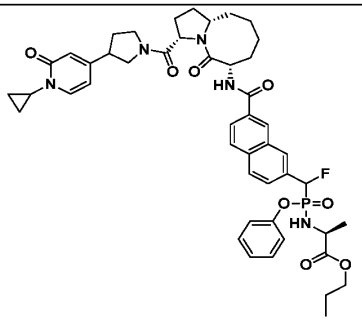
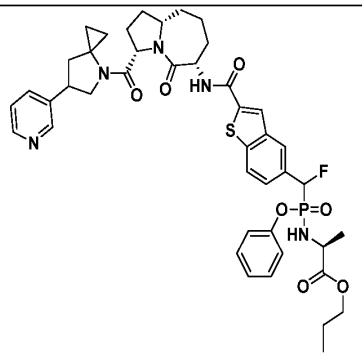
444	propyl (((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	824.5	^{1}H NMR (400 MHz, DMSO) δ 8.85 – 8.72 (m, 1H), 8.22 (d, J = 10.5 Hz, 1H), 7.94 (dd, J = 13.9, 6.0 Hz, 1H), 7.90 – 7.85 (m, 1H), 7.50 – 7.25 (m, 8H), 7.19 – 7.07 (m, 3H), 5.73 – 5.55 (m, 1H), 5.01 – 4.89 (m, 1H), 4.59 – 4.49 (m, 1H), 4.34 – 4.24 (m, 1H), 4.23 – 4.06 (m, 1H), 4.06 – 3.94 (m, 1H), 3.93 – 3.75 (m, 4H), 3.70 – 3.46 (m, 3H), 3.46 – 3.39 (m, 1H), 3.32 – 3.24 (m, 1H), 2.36 – 2.21 (m, 1H), 2.13 -1.38 (m, 13H), 1.16 – 0.96 (m, 3H), 0.86 – 0.76 (m, 3H)
445	propyl 2-methyl-2-((((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)amino)propanoate		786.4	^{1}H NMR (400 MHz, DMSO) δ 8.83 – 8.67 (m, 1H), 8.59 – 8.52 (m, 1H), 8.51 – 8.39 (m, 1H), 8.24 – 8.11 (m, 1H), 7.98 – 7.92 (m, 1H), 7.90 – 7.80 (m, 2H), 7.49 – 7.26 (m, 4H), 7.23 – 7.06 (m, 3H), 5.48 – 5.35 (m, 1H), 4.86 – 4.55 (m, 2H), 4.48 – 4.17 (m, 3H), 4.09 – 3.96 (m, 1H), 3.93 – 3.85 (m, 3H), 3.60 – 3.35 (m, 2H), 2.24 – 2.16 (m, 1H), 2.07 – 1.92 (m, 2H), 1.90 – 1.60

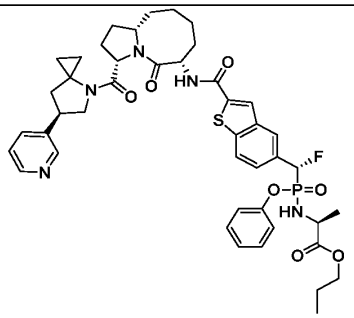
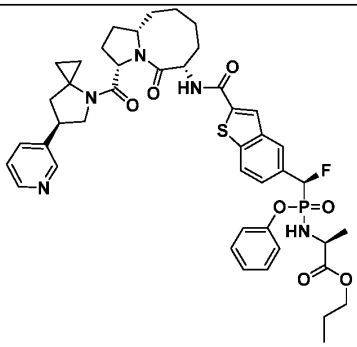
				(m, 7H), 1.54 – 1.41 (m, 2H), 1.25 (s, 6H), 0.89 – 0.77 (m, 3H)
446	propyl ((S)-((R)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate Or propyl ((R)-((R)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 or Linker phosphonamidate building block SFC peak 1 was used for synthesis and biological testing	790.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 – 8.47 (m, 2H), 8.06 – 7.84 (m, 3H), 7.83 – 7.63 (m, 2H), 7.63 – 7.39 (m, 2H), 7.38 – 7.27 (m, 2H), 7.25 (d, J = 8.2 Hz, 1H), 7.22 – 7.02 (m, 2H), 6.08 – 5.86 (m, 1H), 5.08 – 4.49 (m, 4H), 4.48 – 3.83 (m, 7H), 3.72 – 3.50 (m, 1H), 2.34 – 2.15 (m, 3H), 2.08 – 2.02 (m, 3H), 1.98 – 1.67 (m, 4H), 1.67 – 1.54 (m, 2H), 1.28 (d, J = 9.3 Hz, 2H), 1.12 (d, J = 7.1 Hz, 1H), 0.99 – 0.79 (m, 3H)

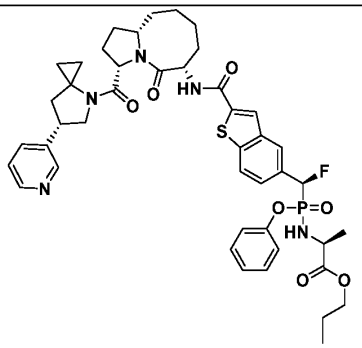
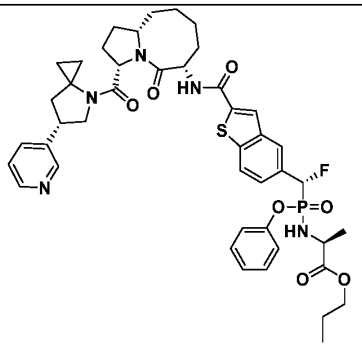
447	propyl ((S)-((R)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate Or propyl ((R)-((R)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 Linker phosphonamidate building block SFC peak 2 was used for synthesis and biological testing	790.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08-8.80 (m, 1H), 8.76 – 8.63 (m, 1H), 8.51 – 8.10 (m, 1H), 8.02 – 7.61 (m, 5H), 7.54 (d, J = 8.4 Hz, 1H), 7.40 – 7.30 (m, 2H), 7.29 – 7.27 (m, 1H), 7.26 – 7.12 (m, 2H), 5.95 (dd, J = 44.6, 6.7 Hz, 1H), 4.79 – 4.66 (m, 2H), 4.51 – 4.45 (m, 2H), 4.24 – 3.92 (m, 7H), 3.83 – 3.64 (m, 1H), 2.37 – 2.12 (m, 2H), 2.09 – 1.99 (m, 3H), 1.98 – 1.66 (m, 4H), 1.65 – 1.28 (m, 3H), 1.14 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H)
448	propyl ((fluoro(2-(((3S,6S,10aS)-5-oxo-3-(6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		844.4	^{1}H NMR (400 MHz, DMSO) δ 8.96 – 8.80 (m, 1H), 8.79 – 8.57 (m, 2H), 8.38 – 8.26 (m, 1H), 8.22 – 8.02 (m, 3H), 7.75 – 7.56 (m, 2H), 7.43 – 7.30 (m, 2H), 7.26 – 7.10 (m, 3H), 6.33 – 6.06 (m, 2H), 5.04 – 4.88 (m, 1H), 4.58 – 4.43 (m, 2H), 4.32 – 4.12 (m, 2H), 4.09 – 3.90 (m, 4H), 2.39 – 1.43 (m, 17H), 1.28 – 1.11 (m, 3H), 1.00 – 0.92 (m, 1H), 0.88 – 0.74

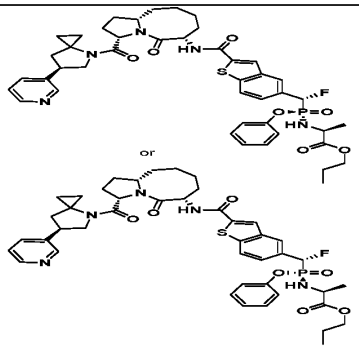
				(m, 3H), 0.56 – 0.38 (m, 2H). (TFA salt)
449	propyl ((fluoro(2-(((3S,6S,10aS)-3-(6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		874.3	^{1}H NMR (400 MHz, DMSO) δ 8.93 – 8.77 (m, 1H), 8.33 – 8.25 (m, 1H), 8.15 – 8.00 (m, 2H), 7.67 – 7.55 (m, 2H), 7.41 – 7.27 (m, 2H), 7.25 – 7.08 (m, 3H), 6.35 – 6.06 (m, 4H), 5.01 – 4.87 (m, 1H), 4.59 – 3.99 (m, 3H), 3.97 – 3.51 (m, 4H), 3.40 – 3.34 (m, 4H), 2.31 – 1.71 (m, 13H), 1.58 – 1.40 (m, 5H), 1.18 – 1.10 (m, 2H), 0.99 – 0.75 (m, 4H), 0.53 – 0.41 (m, 2H)
450	propyl ((fluoro(7-(((3S,6S,10aS)-3-(3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		842.3	^{1}H NMR (400 MHz, DMSO) δ 8.67 – 8.53 (m, 2H), 8.16 – 8.04 (m, 2H), 7.81 – 7.71 (m, 1H), 7.66 – 7.52 (m, 3H), 7.39 – 7.31 (m, 2H), 7.22 – 7.11 (m, 3H), 6.35 – 6.11 (m, 4H), 5.08 – 4.93 (m, 1H), 4.63 – 4.48 (m, 1H), 4.39 – 4.26 (m, 1H), 4.19 – 3.39 (m, 7H), 3.21 – 3.04 (m, 1H), 2.35 – 2.16 (m, 2H), 2.14 – 1.71 (m, 10H), 1.69 – 1.52 (m, 3H), 1.52 – 1.40 (m, 2H), 1.19 – 1.11 (m, 2H), 1.02 – 0.89 (m, 1H), 0.85 – 0.72 (m, 3H)

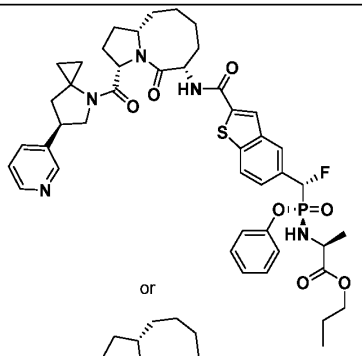
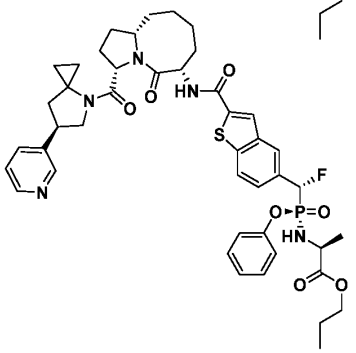
451	propyl ((fluoro(7-(((3S,6S,10aS)-3-(3-fluoro-3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		860.3	^{1}H NMR (400 MHz, DMSO) δ 8.75 – 8.48 (m, 2H), 8.16 – 7.95 (m, 4H), 7.80 – 7.59 (m, 2H), 7.35 (s, 2H), 7.26 – 7.07 (m, 3H), 6.69 – 6.11 (m, 4H), 5.09 – 4.92 (m, 1H), 4.81 – 3.94 (m, 4H), 3.93 – 3.50 (m, 5H), 3.45 – 3.36 (m, 3H), 2.41 – 2.20 (m, 2H), 2.12 – 1.77 (m, 8H), 1.71 – 1.36 (m, 6H), 1.20 – 0.93 (m, 3H), 0.88 – 0.71 (m, 3H)
452	propyl (((2-(((3S,6S,10aS)-3-(5,7-dioxo-6-(pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		873.2	^{1}H NMR (400 MHz, DMSO) δ 9.05 – 8.59 (m, 3H), 8.32 – 7.91 (m, 4H), 7.69 – 7.51 (m, 2H), 7.41 – 7.09 (m, 5H), 6.32 – 6.05 (m, 2H), 5.44 – 5.31 (m, 1H), 5.00 – 4.87 (m, 1H), 4.41 – 4.29 (m, 1H), 4.01 – 3.62 (m, 3H), 2.47 – 2.06 (m, 4H), 1.95 – 1.37 (m, 14H), 1.21 – 0.91 (m, 3H), 0.89 – 0.75 (m, 3H)
453	propyl ((fluoro(7-(((3S,6S,9aS)-5-oxo-3-(6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)naphthalen-2-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		824.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 – 8.47 (m, 2H), 8.45 – 8.33 (m, 1H), 8.09 – 7.60 (m, 7H), 7.40 – 7.27 (m, 3H), 7.26 – 7.14 (m, 2H), 7.11 – 7.06 (m, 1H), 6.19 – 5.85 (m, 1H), 4.77 – 4.46 (m, 2H), 4.12 – 3.53 (m, 7H), 2.39 – 1.92 (m, 14H), 1.84 – 1.74 (m, 2H), 1.64 – 1.41 (m, 2H), 1.35 – 1.21

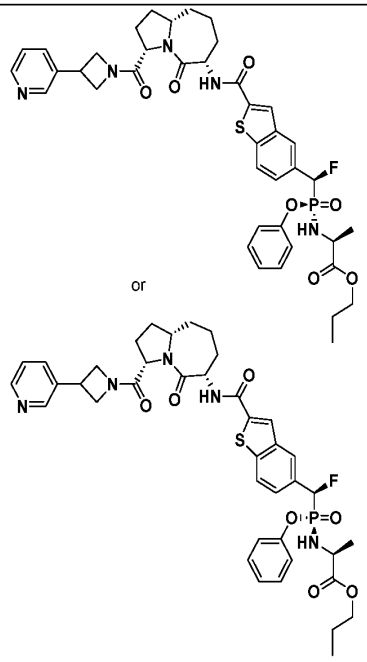
				(m, 2H), 1.11 – 1.03 (m, 1H), 0.94 – 0.76 (m, 3H), 0.58 – 0.53 (m, 1H)
454	propyl ((fluoro(2-(((3S,6S,10aS)-3-(3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		842.3	^{1}H NMR (400 MHz, DMSO) δ 8.67 – 8.52 (m, 2H), 8.16 – 8.12 (m, 1H), 8.08 – 7.97 (m, 3H), 7.78 – 7.72 (m, 1H), 7.64 – 7.60 (m, 1H), 7.39 – 7.31 (m, 2H), 7.22 – 7.12 (m, 3H), 6.38 – 6.12 (m, 4H), 5.08 – 4.93 (m, 1H), 4.63 – 4.48 (m, 1H), 4.38 – 4.10 (m, 1H), 3.97 – 3.47 (m, 6H), 3.44 – 3.35 (m, 3H), 3.21 – 3.04 (m, 1H), 2.35 – 2.16 (m, 2H), 2.14 – 1.71 (m, 10H), 1.69 – 1.52 (m, 3H), 1.52 – 1.40 (m, 2H), 1.19 – 1.11 (m, 2H), 1.02 – 0.89 (m, 1H), 0.85 – 0.72 (m, 3H)
455	propyl (((7-(((3S,6S,10aS)-3-(3-(1-cyclopropyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		868.3	^{1}H NMR (400 MHz, DMSO) δ 8.69 – 8.60 (m, 1H), 8.54 (s, 1H), 8.13 (s, 1H), 8.07 – 7.99 (m, 3H), 7.75 (d, J = 7.9 Hz, 1H), 7.51 – 7.40 (m, 1H), 7.38 – 7.30 (m, 2H), 7.23 – 7.10 (m, 3H), 6.37 – 6.10 (m, 4H), 5.07 – 4.93 (m, 1H), 4.81 – 4.65 (m, 1H), 4.63 – 4.47 (m, 1H), 4.45 – 4.25 (m, 2H), 4.23 – 4.10 (m, 1H), 3.95 – 3.89 (m, 1H), 3.86 – 3.79 (m, 1H), 3.74 – 3.71 (m, 1H),

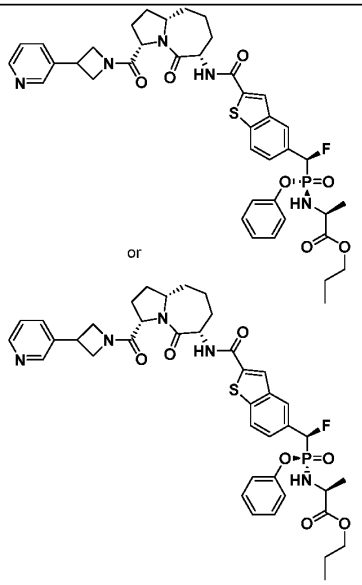
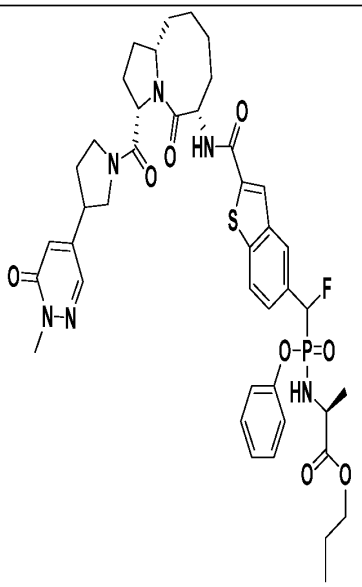
				3.30 – 3.25 (m, 1H), 3.20 – 3.12 (m, 1H), 2.34 – 2.13 (m, 2H), 2.11 – 1.99 (m, 3H), 1.88 – 1.79 (m, 5H), 1.77 – 1.74 (m, 1H), 1.70 – 1.66 (m, 1H), 1.57 – 1.48 (m, 4H), 1.44 – 1.38 (m, 1H), 1.24 – 1.08 (m, 2H), 1.01 – 0.89 (m, 3H), 0.86 – 0.71 (m, 5H)
456	propyl ((fluoro(2-(((3S,6S,9aS)-5-oxo-3-(6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		830.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 – 8.46 (m, 2H), 8.03 – 7.51 (m, 6H), 7.51 – 7.27 (m, 3H), 7.23 – 7.16 (m, 1H), 7.12 – 7.05 (m, 1H), 6.07 – 5.84 (m, 1H), 4.76 – 4.45 (m, 2H), 4.16 – 3.51 (m, 7H), 2.40 – 2.31 (m, 1H), 2.29 – 2.13 (m, 4H), 2.09 – 1.94 (m, 7H), 1.84 – 1.74 (m, 2H), 1.65 – 1.49 (m, 2H), 1.32 – 1.24 (m, 2H), 1.17 – 1.06 (m, 1H), 0.95 – 0.81 (m, 3H), 0.62 – 0.46 (m, 2H)
457	propyl (((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy		844.3	^{1}H NMR (400 MHz, DMSO) δ 8.92 – 8.82 (m, 1H), 8.66 – 8.59 (m, 1H), 8.52 – 8.42 (m, 1H), 8.29 (s, 1H), 8.13 – 8.01 (m, 2H), 7.92 – 7.83 (m, 1H), 7.64 – 7.56 (m, 1H), 7.44 – 7.31 (m, 3H), 7.22 – 7.10 (m, 3H), 6.29 – 6.06 (m, 2H), 5.01 – 4.88 (m, 1H), 4.56 – 4.46 (m, 1H), 4.28 – 4.10 (m, 2H),

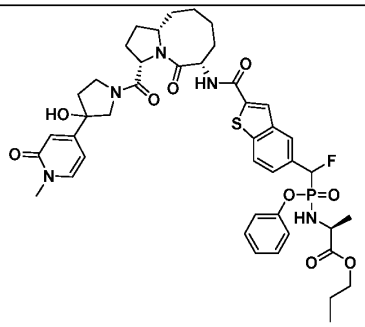
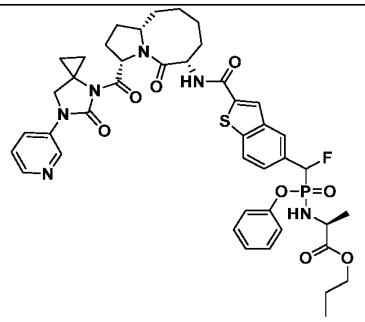
	)phosphoryl)-L-alaninate			3.97 – 3.89 (m, 1H), 3.86 – 3.75 (m, 2H), 3.64 – 3.55 (m, 1H), 2.35 – 1.35 (m, 19H), 1.13 (d, J = 7.1 Hz, 3H), 0.88 – 0.73 (m, 3H), 0.54 – 0.36 (m, 2H)
458	propyl (((S)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		844.5	^{1}H NMR (400 MHz, DMSO) δ 8.92 – 8.80 (m, 1H), 8.62 – 8.53 (m, 1H), 8.48 – 8.38 (m, 1H), 8.32 – 8.24 (m, 1H), 8.14 – 7.99 (m, 2H), 7.84 – 7.75 (m, 1H), 7.65 – 7.54 (m, 1H), 7.39 – 7.30 (m, 3H), 7.24 – 7.09 (m, 3H), 6.31 – 6.05 (m, 2H), 5.05 – 4.84 (m, 1H), 4.59 – 4.40 (m, 1H), 4.29 – 4.07 (m, 2H), 3.96 – 3.79 (m, 3H), 3.71 – 3.55 (m, 1H), 2.29 – 1.45 (m, 19H), 1.17 (d, J = 7.1 Hz, 1H), 0.94 (d, J = 7.1 Hz, 2H), 0.83 – 0.75 (m, 3H), 0.62 – 0.28 (m, 2H)
459	propyl (((S)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((S)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy		844.2	^{1}H NMR (400 MHz, DMSO) δ 8.87 (t, J = 7.0 Hz, 1H), 8.57 (d, J = 1.9 Hz, 1H), 8.45 (dd, J = 4.7, 1.5 Hz, 1H), 8.30 (s, 1H), 8.16 – 8.01 (m, 2H), 7.82 – 7.75 (m, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.41 – 7.30 (m, 3H), 7.23 – 7.08 (m, 3H), 6.32 – 6.19 (m, 1H), 6.19 – 6.07 (m, 1H), 5.00 – 4.90 (m,

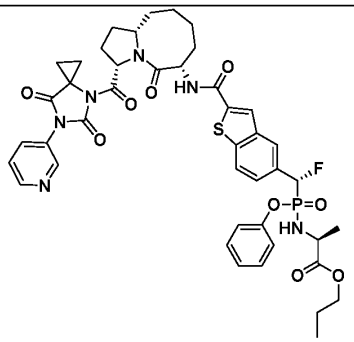
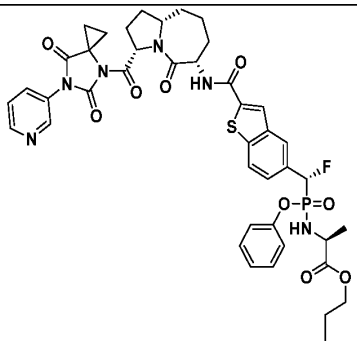
	)phosphoryl)-L-alaninate			1H), 4.54 (t, J = 8.4 Hz, 1H), 4.44 (t, J = 8.6 Hz, 1H), 4.27 – 4.16 (m, 1H), 3.96 – 3.48 (m, 5H), 2.37 – 2.28 (m, 1H), 2.25 – 2.15 (m, 1H), 2.12 – 1.75 (m, 9H), 1.73 – 1.44 (m, 7H), 1.17 (d, J = 7.1 Hz, 1H), 0.94 (d, J = 7.1 Hz, 2H), 0.86 – 0.75 (m, 3H), 0.55 – 0.42 (m, 2H)
460	propyl (((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((S)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		844.3	^{1}H NMR (400 MHz, DMSO) δ 8.93 – 8.80 (m, 1H), 8.57 (d, J = 1.9 Hz, 1H), 8.45 (dd, J = 4.7, 1.5 Hz, 1H), 8.31 (s, 1H), 8.14 – 8.02 (m, 2H), 7.84 – 7.73 (m, 1H), 7.67 – 7.54 (m, 1H), 7.42 – 7.30 (m, 3H), 7.23 – 7.11 (m, 3H), 6.27 – 6.17 (m, 1H), 6.15 – 6.05 (m, 1H), 5.02 – 4.89 (m, 1H), 4.54 (t, J = 8.4 Hz, 1H), 4.45 (t, J = 8.6 Hz, 1H), 4.28 – 4.14 (m, 1H), 4.00 – 3.89 (m, 1H), 3.89 – 3.70 (m, 2H), 3.69 – 3.46 (m, 2H), 2.32 (t, J = 11.3 Hz, 1H), 2.25 – 2.16 (m, 1H), 2.11 – 1.75 (m, 9H), 1.73 – 1.40 (m, 7H), 1.14 (d, J = 6.2 Hz, 3H), 0.88 – 0.73 (m, 3H), 0.56 – 0.42 (m, 2H)

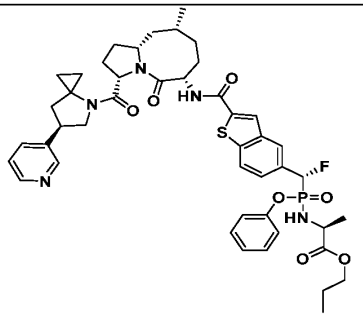
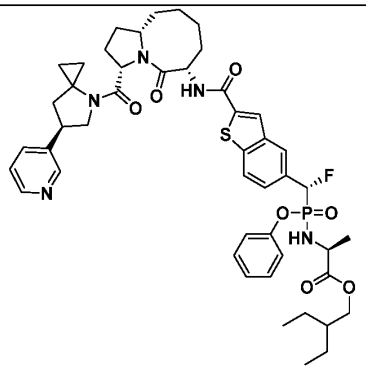
461	propyl ((S)-((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate Or propyl ((R)-((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 or  Linker phosphonamidate building block SFC peak 1 was used for synthesis and biological testing	844.3	^{1}H NMR (400 MHz, DMSO) δ 8.90 – 8.29 (m, 3H), 8.13 – 7.87 (m, 3H), 7.64 – 7.58 (m, 1H), 7.46 – 7.31 (m, 3H), 7.22 – 7.11 (m, 3H), 6.29 – 6.04 (m, 2H), 5.01 – 4.88 (m, 1H), 4.57 – 4.45 (m, 1H), 4.28 – 4.09 (m, 2H), 3.87 – 3.73 (m, 4H), 3.66 – 3.55 (m, 1H), 2.29 – 1.37 (m, 18H), 1.18 – 1.06 (m, 3H), 0.81 – 0.73 (m, 3H), 0.52 – 0.39 (m, 2H)

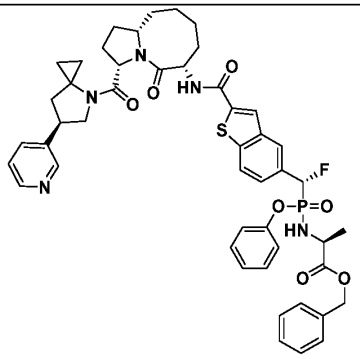
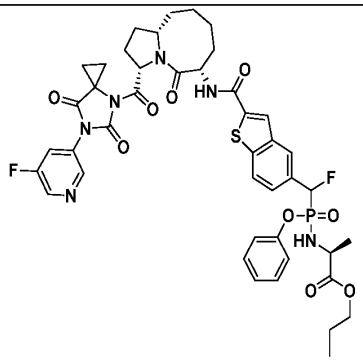
462	propyl ((S)-((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate Or propyl ((R)-((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 Linker phosphonamidate building block SFC peak 2 was used for synthesis and biological testing	844.3	^{1}H NMR (400 MHz, DMSO) δ 8.95 – 7.52 (m, 8H), 7.42 – 7.31 (m, 3H), 7.23 – 7.12 (m, 3H), 6.28 – 6.09 (m, 2H), 5.00 – 4.90 (m, 1H), 4.57 – 4.47 (m, 1H), 4.29 – 4.08 (m, 2H), 3.98 – 3.72 (m, 4H), 3.64 – 3.53 (m, 1H), 2.27 – 1.46 (m, 18H), 1.14 (d, J = 7.1 Hz, 3H), 0.83 (t, J = 7.4 Hz, 3H), 0.52 – 0.34 (m, 2H)

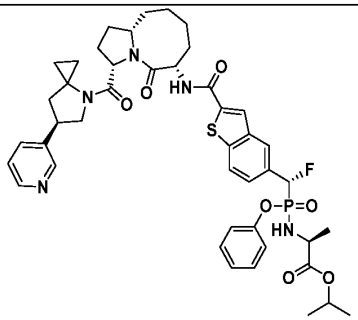
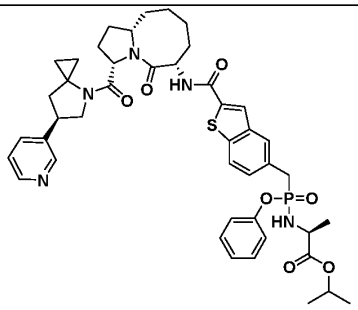
463	propyl ((S)-((S)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate Or propyl ((R)-((S)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 or Linker phosphonamidate building block SFC peak 1 was used for synthesis and biological testing	790.2	^{1}H NMR (400 MHz, DMSO) δ 8.90-8.78 (m, 1H), 8.59-8.52 (m, 1H), 8.50-8.40 (m, 1H), 8.32-8.26 (m, 1H), 8.13-8.04 (m, 1H), 7.90-7.81 (m, 2H), 7.65-7.58 (m, 1H), 7.44-7.30 (m, 3H), 7.24-7.10 (m, 3H), 6.32-6.08 (m, 1H), 4.83-4.57 (m, 2H), 4.47-4.19 (m, 3H), 4.09-3.81 (m, 6H), 3.63-3.57 (m, 1H), 2.09-1.92 (m, 2H), 1.90-1.66 (m, 8H), 1.54-1.42 (m, 2H), 1.20- 0.93 (m, 3H), 0.85-0.77 (m, 3H)
464	propyl ((S)-((S)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate Or propyl ((R)-((S)-fluoro(2-(((3S,6S,9aS)-5-		790.2	^{1}H NMR (400 MHz, DMSO) δ 8.90 – 8.78 (m, 1H), 8.59 – 8.53 (m, 1H), 8.51 – 8.40 (m, 1H), 8.31 – 8.26 (m, 1H), 8.10 – 8.07 (m, 1H), 7.90 – 7.83 (m, 1H), 7.70 – 7.57 (m, 2H), 7.42 – 7.33 (m, 3H), 7.20 – 7.10 (m, 3H), 6.39 – 6.28 (m, 1H), 6.20 – 6.18 (m, 1H), 4.84 – 4.57 (m, 2H), 4.47 – 4.18 (m, 3H), 4.05 – 3.81 (m, 6H), 2.06 – 1.91 (m, 2H), 1.89 – 1.58 (m, 8H), 1.52 – 1.42

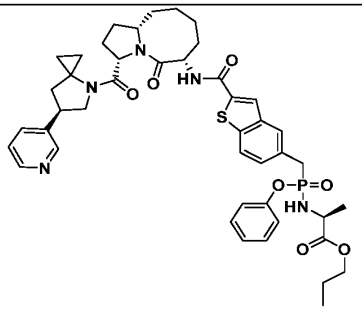
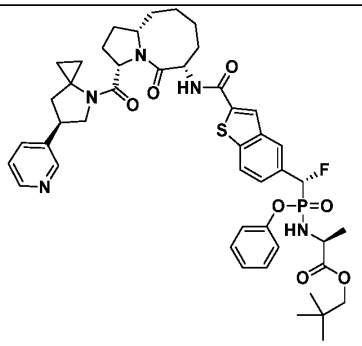
	oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	Linker phosphonamidate building block SFC peak 2 was used for synthesis and biological testing		(m, 2H), 1.18 (d, J = 7.1 Hz, 3H), 0.85 – 0.78 (m, 3H)
465	propyl ((fluoro(2-(((3S,6S,10aS)-3-(3-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		849.2	^{1}H NMR (400 MHz, DMSO) δ 8.88 – 8.77 (m, 1H), 8.33 – 8.27 (m, 1H), 8.14 – 8.03 (m, 2H), 7.96 – 7.87 (m, 1H), 7.65 – 7.57 (m, 1H), 7.40 – 7.31 (m, 2H), 7.23 – 7.09 (m, 3H), 6.83 – 6.75 (m, 1H), 6.28 – 6.08 (m, 1H), 5.02 – 4.88 (m, 1H), 4.61 – 4.49 (m, 1H), 4.33 – 4.14 (m, 1H), 4.00 – 3.39 (m, 9H), 3.25 – 3.06 (m, 1H), 2.53 – 2.52 (m, 1H), 2.29 – 2.21 (m, 1H), 2.12 – 1.39 (m, 15H), 1.19 – 0.92 (m, 3H), 0.87 – 0.74 (m, 3H)
466	propyl ((fluoro(2-(((3S,6S,10aS)-3-(3-hydroxy-3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		864.2	^{1}H NMR (400 MHz, DMSO) δ 8.81 (s, 1H), 8.30 (s, 1H), 8.14 – 8.03 (m, 2H), 7.67 – 7.56 (m, 2H), 7.40 – 7.30 (m, 2H), 7.24 – 7.08 (m, 3H), 6.54 – 6.43 (m, 1H), 6.38 – 6.05 (m, 3H), 5.66 – 5.44 (m, 1H), 5.02 – 4.89 (m, 1H), 4.66 – 4.44 (m, 1H), 4.35 – 4.19 (m, 1H), 4.05 – 3.53 (m, 6H),

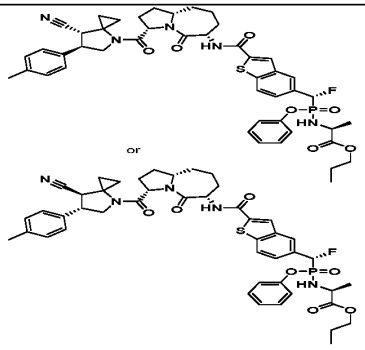
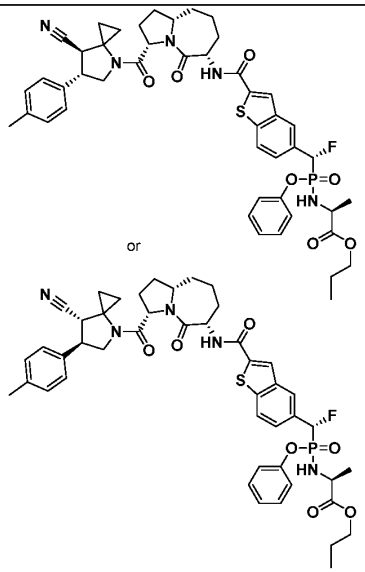
				3.51 – 3.35 (m, 4H), 2.30 – 1.69 (m, 11H), 1.68 – 1.38 (m, 5H), 1.21 – 0.91 (m, 3H), 0.87 – 0.75 (m, 3H)
467	propyl ((fluoro(2-(((3S,6S,10aS)-5-oxo-3-(5-oxo-6-(pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		859.3	^{1}H NMR (400 MHz, DMSO) δ 8.95 – 7.52 (m, 8H), 7.42 – 7.31 (m, 3H), 7.23 – 7.12 (m, 3H), 6.28 – 6.09 (m, 2H), 5.00 – 4.90 (m, 1H), 4.57 – 4.47 (m, 1H), 4.29 – 4.08 (m, 2H), 3.98 – 3.72 (m, 4H), 3.64 – 3.53 (m, 1H), 2.27 – 1.46 (m, 18H), 1.14 (d, J = 7.1 Hz, 3H), 0.83 (t, J = 7.4 Hz, 3H), 0.52 – 0.34 (m, 2H)
468	propyl (((R)-(2-(((3S,6S,10aS)-3-(5,7-dioxo-6-(pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		873.2	^{1}H NMR (400 MHz, DMSO) δ 8.95 – 8.62 (m, 3H), 8.32 – 8.22 (m, 1H), 8.13 – 8.01 (m, 1H), 7.99 – 7.90 (m, 1H), 7.68 – 7.53 (m, 3H), 7.42 – 7.30 (m, 2H), 7.21 – 7.09 (m, 3H), 6.27 – 6.04 (m, 2H), 5.41 – 5.32 (m, 1H), 5.01 – 4.82 (m, 1H), 4.40 – 4.31 (m, 1H), 3.97 – 3.70 (m, 3H), 2.21 – 1.37 (m, 18H), 1.18 – 1.10 (m, 3H), 0.87 – 0.72 (m, 3H)

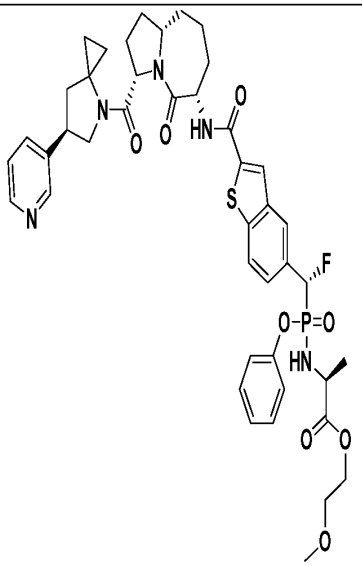
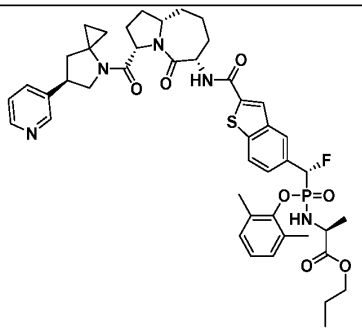
469	propyl (((R)-(2-(((3S,6S,9aS)-3-(5,7-dioxo-6-(pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		859.3	^{1}H NMR (400 MHz, DMSO) δ 8.88 – 8.80 (m, 1H), 8.72 – 8.63 (m, 2H), 8.29 – 8.21 (m, 1H), 8.12 – 8.01 (m, 2H), 7.98 – 7.89 (m, 1H), 7.65 – 7.54 (m, 2H), 7.39 – 7.30 (m, 2H), 7.22 – 7.12 (m, 3H), 6.29 – 6.17 (m, 1H), 6.16 – 6.04 (m, 1H), 5.56 – 5.45 (m, 1H), 4.71 – 4.57 (m, 1H), 4.07 – 3.72 (m, 4H), 2.37 – 2.06 (m, 5H), 2.04 – 1.49 (m, 7H), 1.48 – 1.37 (m, 3H), 1.27 – 1.05 (m, 4H), 0.87 – 0.72 (m, 3H)
470	propyl (((R)-fluoro(2-(((3S,6S,9R,10aR)-9-methyl-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		858.3	^{1}H NMR (400 MHz, DMSO) δ 8.80 – 8.67 (m, 1H), 8.61 – 8.54 (m, 1H), 8.45 – 8.38 (m, 1H), 8.30 – 8.18 (m, 1H), 8.09 – 7.84 (m, 2H), 7.81 – 7.75 (m, 1H), 7.63 – 7.28 (m, 5H), 7.21 – 7.10 (m, 3H), 6.27 – 6.10 (m, 1H), 4.83 – 4.72 (m, 1H), 4.48 (t, J = 8.7 Hz, 1H), 4.34 – 4.26 (m, 1H), 4.14 (t, J = 8.4 Hz, 1H), 3.96 – 3.74 (m, 4H), 3.63 – 3.51 (m, 1H), 2.22 – 2.06 (m, 2H), 2.05 – 1.95 (m, 3H), 1.85 – 1.39 (m, 10H), 1.27 – 1.09 (m, 5H), 0.98 – 0.92 (m, 3H), 0.85 – 0.74 (m, 3H), 0.55 – 0.40 (m, 2H)

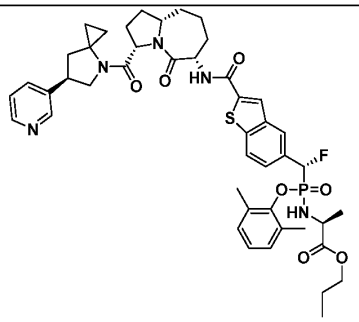
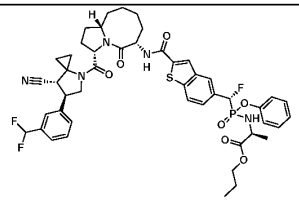
471	2-ethylbutyl (((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		886.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 – 8.59 (m, 1H), 8.50 – 8.40 (m, 1H), 7.95 – 7.84 (m, 2H), 7.82 – 7.62 (m, 3H), 7.59 – 7.51 (m, 1H), 7.27 – 7.20 (m, 3H), 7.14 – 7.03 (m, 3H), 6.05 – 5.86 (m, 1H), 5.22 – 5.05 (m, 1H), 4.60 – 4.47 (m, 1H), 4.35 – 4.23 (m, 1H), 4.19 – 3.90 (m, 5H), 3.85 – 3.69 (m, 1H), 3.65 – 3.48 (m, 1H), 2.39 – 2.31 (m, 1H), 2.28 – 1.94 (m, 9H), 1.91 – 1.70 (m, 4H), 1.69 – 1.55 (m, 2H), 1.53 – 1.43 (m, 1H), 1.36 – 1.26 (m, 7H), 0.93 – 0.82 (m, 6H), 0.56 – 0.44 (m, 2H)
472	benzyl (((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		892.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 – 8.55 (m, 1H), 8.45 – 8.38 (m, 1H), 7.97 – 7.74 (m, 3H), 7.73 – 7.58 (m, 2H), 7.54 – 7.40 (m, 1H), 7.39 – 7.28 (m, 5H), 7.26 – 7.13 (m, 3H), 7.13 – 7.02 (m, 2H), 6.03 – 5.77 (m, 1H), 5.22 – 5.01 (m, 3H), 4.60 – 4.49 (m, 1H), 4.35 – 4.24 (m, 1H), 4.23 – 3.89 (m, 3H), 3.88 – 3.69 (m, 1H), 3.60 – 3.46 (m, 1H), 2.39 – 2.28 (m, 1H), 2.26 – 1.94 (m, 8H), 1.92 – 1.68 (m, 4H), 1.67 – 1.52 (m, 2H), 1.37 – 1.22 (m, 3H), 1.19 – 1.12

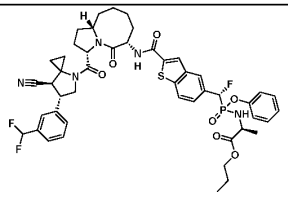
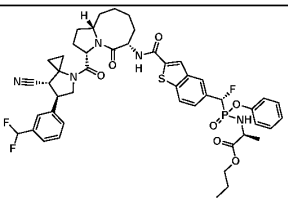
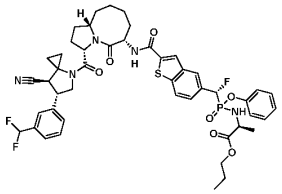
				(m, 1H), 0.55 – 0.41 (m, 2H)
473	propyl ((fluoro(2-(((3S,6S,10aS)-3-(6-(5-fluoropyridin-3-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		891.4	^{1}H NMR (400 MHz, DMSO) δ 8.94 – 7.93 (m, 7H), 7.72 – 7.54 (m, 1H), 7.42 – 7.10 (m, 5H), 6.30 – 6.00 (m, 2H), 5.45 – 5.28 (m, 1H), 4.99 – 4.84 (m, 1H), 4.51 – 4.26 (m, 1H), 3.99 – 3.65 (m, 3H), 2.47 – 2.04 (m, 4H), 1.95 – 1.38 (m, 14H), 1.18 – 1.08 (m, 3H), 0.87 – 0.73 (m, 3H)
474	isopropyl (((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		844.2	^{1}H NMR (400 MHz, DMSO) δ 8.91 – 8.81 (m, 1H), 8.58 (s, 1H), 8.46 – 8.39 (m, 1H), 8.29 (s, 1H), 8.11 – 8.02 (m, 2H), 7.78 (d, J = 7.9 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.40 – 7.28 (m, 3H), 7.21 – 7.10 (m, 3H), 6.27 – 6.03 (m, 2H), 4.99 – 4.90 (m, 1H), 4.88 – 4.69 (m, 1H), 4.51 (t, J = 8.3 Hz, 1H), 4.29 – 4.09 (m, 2H), 3.85 – 3.68 (m, 2H), 3.62 – 3.52 (m, 1H), 2.34 – 1.64 (m, 14H), 1.57 – 1.45 (m, 2H), 1.15 – 1.00 (m, 9H), 0.53 – 0.39 (m, 2H)

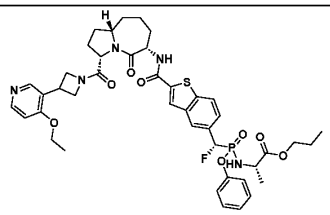
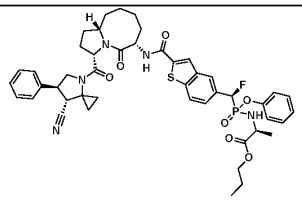
475	isopropyl (((2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		826.2	^{1}H NMR (400 MHz, DMSO) δ 8.84 – 8.79 (m, 1H), 8.58 (s, 1H), 8.44 – 8.40 (m, 1H), 8.21 (s, 1H), 7.95 – 7.86 (m, 2H), 7.79 – 7.75 (m, 1H), 7.66 – 7.54 (m, 2H), 7.45 – 7.40 (m, 1H), 7.35 – 7.28 (m, 3H), 7.17 – 7.09 (m, 3H), 5.69 – 5.50 (m, 1H), 4.98 – 4.88 (m, 1H), 4.84 – 4.73 (m, 1H), 4.56 – 4.45 (m, 1H), 4.28 – 4.08 (m, 2H), 3.85 – 3.68 (m, 2H), 3.62 – 3.40 (m, 3H), 2.34 – 1.48 (m, 16H), 1.12 – 0.96 (m, 9H), 0.53 – 0.37 (m, 2H)
476	propyl (((2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		826.2	^{1}H NMR (400 MHz, DMSO) δ 8.85 – 8.63 (m, 3H), 8.37 – 8.15 (m, 2H), 7.97 – 7.70 (m, 3H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.36 – 7.28 (m, 2H), 7.17 – 7.08 (m, 3H), 5.73 – 5.57 (m, 1H), 4.98 – 4.86 (m, 1H), 4.51 (t, *J* = 8.2 Hz, 1H), 4.28 – 4.11 (m, 2H), 3.94 – 3.64 (m, 5H), 3.52 – 3.33 (m, 2H), 2.34 – 2.14 (m, 3H), 2.05 – 1.71 (m, 9H), 1.68 – 1.41 (m, 6H), 1.10 – 0.97 (m, 3H), 0.84 – 0.77 (m, 3H), 0.55 – 0.38 (m, 2H)

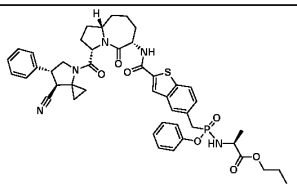
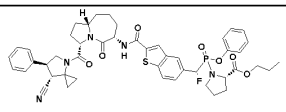
477	neopentyl (((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		873.2	^{1}H NMR (400 MHz, DMSO) δ 8.99 – 7.72 (m, 8H), 7.68 – 7.07 (m, 6H), 6.32 – 6.05 (m, 2H), 4.99 – 4.90 (m, 1H), 4.55 – 4.49 (m, 1H), 4.25 – 4.18 (m, 1H), 3.94 – 3.80 (m, 2H), 3.77 – 3.44 (m, 3H), 3.20 – 3.01 (m, 1H), 2.31 – 1.51 (m, 15H), 1.30 – 1.12 (m, 4H), 1.01 – 0.64 (m, 9H), 0.58 – 0.32 (m, 2H)
478	propyl (((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(p-tolyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((R)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(p-tolyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	868.6	^{1}H NMR (400 MHz, DMSO) δ 8.90 – 8.75 (m, 1H), 8.34 – 8.22 (m, 1H), 8.13 – 8.02 (m, 2H), 7.61 (t, J = 8.0 Hz, 1H), 7.42 – 7.29 (m, 4H), 7.24 – 7.10 (m, 5H), 6.36 – 6.02 (m, 2H), 4.71 – 4.54 (m, 2H), 4.39 – 4.19 (m, 1H), 4.05 – 3.59 (m, 7H), 2.34 – 2.26 (m, 3H), 2.23 – 2.10 (m, 2H), 2.09 – 1.89 (m, 2H), 1.88 – 1.62 (m, 8H), 1.56 – 1.39 (m, 2H), 1.19 – 0.92 (m, 3H), 0.85 – 0.75 (m, 4H), 0.73 – 0.62 (m, 1H)

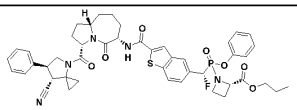
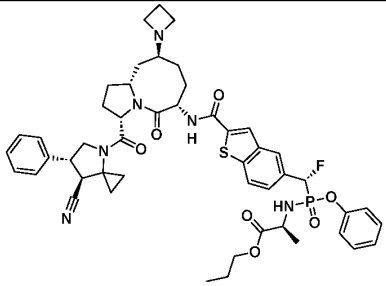
479	propyl (((R)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(p-tolyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(p-tolyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Pyrrolidine building block SFC peak 1 was used for synthesis and biological testing	868.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.92 (m, 1H), 7.91 – 7.84 (m, 1H), 7.83 – 7.79 (m, 1H), 7.69 – 7.63 (m, 1H), 7.62 – 7.52 (m, 1H), 7.39 – 7.32 (m, 1H), 7.31 – 7.27 (m, 2H), 7.26 – 7.25 (m, 1H), 7.25 – 7.17 (m, 3H), 7.15 – 7.04 (m, 2H), 6.07 – 5.83 (m, 1H), 4.72 – 4.56 (m, 2H), 4.14 – 3.96 (m, 5H), 3.94 – 3.87 (m, 1H), 3.75 – 3.51 (m, 2H), 3.40 – 3.35 (m, 1H), 2.54 – 2.44 (m, 1H), 2.36 (s, 3H), 2.29 – 2.16 (m, 2H), 2.13 – 1.88 (m, 6H), 1.87 – 1.76 (m, 2H), 1.65 – 1.55 (m, 3H), 1.34 – 1.23 (m, 2H), 1.14 – 1.05 (m, 2H), 0.94 – 0.87 (m, 3H), 0.77 – 0.67 (m, 1H)
480	2-methoxyethyl (((R)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		846.2	^{1}H NMR (400 MHz, DMSO) δ 8.81 – 8.70 (m, 2H), 8.67 – 8.56 (m, 1H), 8.27 (s, 1H), 8.10 – 8.03 (m, 2H), 7.73 – 7.58 (m, 2H), 7.39 – 7.31 (m, 2H), 7.20 – 7.10 (m, 3H), 6.30 – 6.11 (m, 2H), 4.65 – 4.59 (m, 2H), 4.14 – 4.06 (m, 2H), 4.01 – 3.95 (m, 2H), 3.91 – 3.86 (m, 1H), 3.82 – 3.78 (m, 1H), 3.72 – 3.68 (m, 1H), 3.47 – 3.40 (m, 2H),

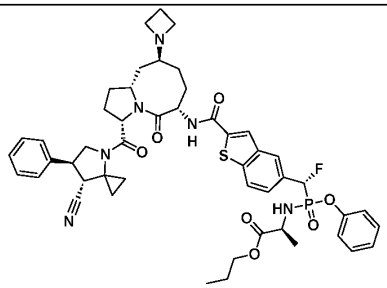
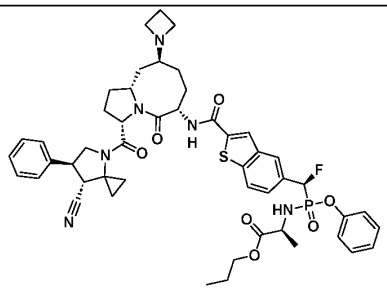
				3.23 – 3.18 (m, 3H), 2.26 – 2.05 (m, 4H), 2.04 – 1.93 (m, 2H), 1.88 – 1.67 (m, 7H), 1.64 – 1.57 (m, 1H), 1.15 (d, J = 7.1 Hz, 3H), 0.56 – 0.37 (m, 2H)
481	propyl ((2,6-dimethylphenoxy)((R)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)-L-alaninate		858.2	^{1}H NMR (400 MHz, DMSO) δ 8.85 – 8.76 (m, 1H), 8.58 (s, 1H), 8.43 (d, J = 4.6 Hz, 1H), 8.27 (s, 1H), 8.12 – 8.03 (m, 2H), 7.79 (d, J = 7.9 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.36 – 7.29 (m, 1H), 7.06 – 6.94 (m, 3H), 6.31 – 6.14 (m, 1H), 5.97 – 5.72 (m, 1H), 4.67 – 4.58 (m, 2H), 4.10 (t, J = 8.5 Hz, 1H), 4.00 – 3.66 (m, 5H), 3.62 – 3.53 (m, 1H), 2.27 – 2.15 (m, 8H), 2.13 – 1.93 (m, 4H), 1.87 – 1.67 (m, 7H), 1.62 – 1.54 (m, 1H), 1.50 – 1.34 (m, 2H), 1.19 – 1.07 (m, 3H), 0.82 – 0.72 (m, 3H), 0.53 – 0.41 (m, 2H)
482	propyl (((R)-(2-(((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(3-(difluoromethyl)phenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-	 Or	918.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (s, 1H), 8.08 (s, 1H), 8.00 - 7.92 (m, 1H), 7.67 - 7.48 (m, 5H), 7.38 - 7.30 (m, 2H), 7.26 - 7.11 (m, 3H), 6.76 (t, *J* = 56.0 Hz, 1H), 6.20 - 5.98 (m, 1H), 5.06 - 4.97 (m, 1H), 4.69 - 4.54 (m, 2H), 4.45 - 4.32 (m,

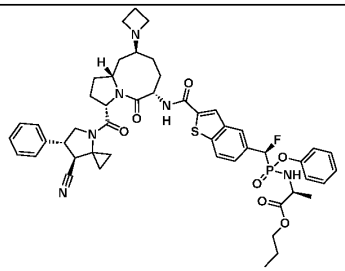
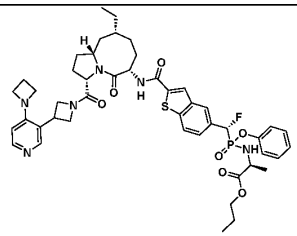
	yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(3-(difluoromethyl)phenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 Pyrrolidine + Core SFC peak 1 was used for synthesis and biological testing		1H), 4.01 - 3.73 (m, 6H), 2.35 - 2.14 (m, 3H), 2.07 - 1.90 (m, 7H), 1.86 - 1.78 (m, 2H), 1.70 - 1.46 (m, 4H), 1.26 - 1.16 (m, 3H), 1.03 - 0.94 (m, 1H), 0.92 - 0.82 (m, 3H), 0.78 - 0.68 (m, 1H)
483	propyl (((R)-(2-(((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(3-(difluoromethyl)phenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate Or propyl (((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(3-(difluoromethyl)phenyl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrro	 Or  Pyrrolidine + Core SFC peak 2 was used for synthesis and biological testing	918.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (s, 1H), 8.08 (s, 1H), 8.01 - 7.97 (m, 1H), 7.70 (s, 1H), 7.67 - 7.59 (m, 2H), 7.51 - 7.47 (m, 2H), 7.37 - 7.31 (m, 2H), 7.25 - 7.13 (m, 3H), 6.76 (t, *J* = 56.2 Hz, 1H), 6.19 - 6.00 (m, 1H), 5.06 - 4.97 (m, 1H), 4.63 - 4.56 (m, 1H), 4.44 - 4.35 (m, 1H), 4.22 - 4.16 (m, 2H), 4.00 - 3.78 (m, 4H), 3.72 - 3.66 (m, 1H), 2.39 - 2.28 (m, 2H), 2.27 - 2.15 (m, 1H), 2.09 - 1.89 (m, 6H), 1.87 - 1.74 (m, 3H), 1.70 - 1.46 (m, 4H), 1.24 -1.19 (m, 3H), 1.01 - 0.93 (m, 1H),

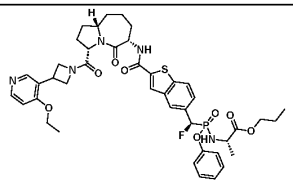
	lo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate			0.92 - 0.82 (m, 3H), 0.73 - 0.62 (m, 1H)
484	propyl (((S)-(2-(((3S,6S,9aS)-3-(3-(4-ethoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		834.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.40 - 8.32 (m, 1H), 8.14 - 8.05 (m, 2H), 8.04 - 7.93 (m, 1H), 7.70 - 7.59 (m, 1H), 7.39 - 7.28 (m, 2H), 7.26 - 7.14 (m, 3H), 7.05 (dd, *J* = 19.0, 5.5 Hz, 1H), 6.19 - 5.99 (m, 1H), 4.80 - 4.71 (m, 1H), 4.70 - 4.62 (m, 1H), 4.62 - 4.57 (m, 1H), 4.49 - 4.31 (m, 2H), 4.25 - 4.16 (m, 3H), 4.15 - 4.03 (m, 2H), 3.99 - 3.95 (m, 1H), 3.94 - 3.85 (m, 1H), 3.85 - 3.75 (m, 1H), 2.37 - 2.26 (m, 1H), 2.17 - 2.04 (m, 2H), 2.03 - 1.81 (m, 7H), 1.60 - 1.51 (m, 2H), 1.45 (td, *J* = 7.0, 1.5 Hz, 3H), 1.23 (dd, *J* = 7.0, 1.8 Hz, 2H), 1.07 (dd, *J* = 7.0, 3.8 Hz, 2H), 0.91 - 0.84 (m, 3H)
485	propyl (((S)-(2-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-		868.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (s, 1H), 8.09 - 8.05 (m, 1H), 7.97 and 7.94 (d, *J* = 8.6 Hz, 1H), 7.67 - 7.59 (m, 1H), 7.44 - 7.28 (m, 7H), 7.24 - 7.14 (m, 3H), 6.13 and 6.02 (dd, *J* = 17.6, 6.4 Hz,

	yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate			1H), 5.07 - 4.96 (m, 1H), 4.68 - 4.51 (m, 2H), 4.44 - 4.32 (m, 1H), 4.02 - 3.68 (m, 6H), 2.36 - 2.13 (m, 3H), 2.08 - 1.86 (m, 7H), 1.85 - 1.74 (m, 2H), 1.70 - 1.47 (m, 4H), 1.23 and 1.06 (d, *J* = 7.1 Hz, 3H), 1.02 - 0.93 (m, 1H), 0.91 - 0.82 (m, 3H), 0.78 - 0.65 (m, 1H)
486	propyl (((2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		836.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (s, 1H), 7.96 - 7.84 (m, 2H), 7.55 - 7.44 (m, 3H), 7.43 - 7.25 (m, 5H), 7.24 - 7.10 (m, 3H), 4.78 - 4.63 (m, 2H), 4.20 - 4.10 (m, 1H), 4.09 - 3.99 (m, 2H), 3.98 - 3.68 (m, 5H), 3.61 - 3.43 (m, 2H), 2.38 - 1.75 (m, 12H), 1.60 - 1.48 (m, 2H), 1.14 (d, *J* = 7.3 Hz, 1.5H), 1.08 (d, *J* = 7.1 Hz, 1.5H), 1.04 - 0.95 (m, 1H), 0.87 (t, *J* = 7.5 Hz, 1.5H), 0.86 (t, *J* = 7.5 Hz, 1.5H), 0.76 - 0.64 (m, 1H).
487	propyl (((S)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		880.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.17 - 7.97 (m, 3H), 7.73 - 7.59 (m, 1H), 7.48 - 7.17 (m, 10H), 6.36 - 6.12 (m, 1H), 4.77 - 4.62 (m, 2H), 4.48 - 4.46 (m, 1H), 4.10 - 3.92 (m, 4H), 3.89 - 3.71 (m, 3H), 3.67 - 3.39 (m, 2H), 3.22 -

	yl)fluoromethyl)(phenoxy)phosphoryl)-L-prolinate			3.08 (m, 1H), 2.37 - 2.22 (m, 2H), 2.17 - 2.06 (m, 2H), 2.02 - 1.76 (m, 11H), 1.66 - 1.54 (m, 2H), 1.06 - 0.98 (m, 1H), 0.94 - 0.87 (m, 3H), 0.80 - 0.70 (m, 1H)
488	propyl (2S)-1-(((S)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)azetidine-2-carboxylate		866.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.21 - 8.00 (m, 3H), 7.76 - 7.64 (m, 1H), 7.47 - 7.20 (m, 10H), 6.43 - 6.25 (m, 1H), 4.74 - 4.71 (m, 2H), 4.58 - 4.54 (m, 1H), 4.47 - 4.44 (m, 1H), 4.18 - 4.10 (m, 2H), 4.07 - 3.88 (m, 2H), 3.87 - 3.71 (m, 3H), 3.51 - 3.42 (m, 1H), 2.66 - 2.56 (m, 1H), 2.38 - 2.23 (m, 3H), 2.17 - 2.05 (m, 2H), 2.02 - 1.79 (m, 8H), 1.71 - 1.61 (m, 2H), 1.05 - 0.98 (m, 1H), 0.95 (t, J = 7.5 Hz, 3H), 0.78 - 0.68 (m, 1H)
489	propyl (((R)-(2-(((3S,6S,9S,10aR)-9-(azetidin-1-yl)-3-((6R,7S)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		923.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 - 8.06 (m, 2H), 8.00 - 7.95 (m, 1H), 7.66 - 7.62 (m, 1H), 7.49 - 7.15 (m, 10H), 6.23 - 5.95 (m, 1H), 4.97 - 4.93 (m, 1H), 4.66 - 4.44 (m, 3H), 4.02 - 3.62 (m, 6H), 3.55 - 3.45 (m, 2H), 2.85 - 2.75 (m, 1H), 2.43 - 2.31 (m, 2H), 2.20 - 1.78 (m, 11H), 1.60 - 1.49 (m, 2H), 1.38 - 1.28 (m, 5H), 1.24 -

				1.19 (m, 2H), 0.90 - 0.84 (m, 3H), 0.75 - 0.65 (m, 1H)
490	propyl (((R)-(2-(((3S,6S,9S,10aR)-9-(azetidin-1-yl)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		923.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 - 8.06 (m, 2H), 8.03 - 7.92 (m, 1H), 7.69 - 7.58 (m, 1H), 7.46 - 7.28 (m, 7H), 7.25 - 7.11 (m, 3H), 6.19 - 5.95 (m, 1H), 4.99 - 4.89 (m, 1H), 4.70 - 4.60 (m, 1H), 4.58 - 4.43 (m, 2H), 4.02 - 3.68 (m, 6H), 3.54 - 3.42 (m, 2H), 2.91 - 2.74 (m, 1H), 2.42 - 2.28 (m, 2H), 2.22 - 1.77 (m, 11H), 1.61 - 1.48 (m, 2H), 1.37 - 1.30 (m, 2H), 1.25 - 1.19 (m, 3H), 1.06 - 0.96 (m, 1H), 0.94 - 0.83 (m, 4H), 0.78 - 0.69 (m, 1H)
491	propyl (((S)-(2-(((3S,6S,9S,10aR)-9-(azetidin-1-yl)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		923.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 - 8.05 (m, 2H), 8.02 - 7.91 (m, 1H), 7.68 - 7.60 (m, 1H), 7.44 - 7.30 (m, 7H), 7.26 - 7.11 (m, 3H), 6.19 - 5.98 (m, 1H), 4.97 - 4.90 (m, 1H), 4.69 - 4.61 (m, 1H), 4.58 - 4.44 (m, 2H), 4.03 - 3.69 (m, 6H), 3.52 - 3.41 (m, 2H), 2.87 - 2.76 (m, 1H), 2.43 - 2.30 (m, 2H), 2.22 - 1.75 (m, 11H), 1.63 - 1.48 (m, 2H), 1.43 - 1.16 (m, 5H), 1.09 - 0.96 (m, 2H), 0.91 -

				0.83 (m, 3H), 0.78 - 0.69 (m, 1H)
492	propyl (((S)-(2-(((3S,6S,9S,10aR)-9-(azetidin-1-yl)-3-((6R,7S)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		923.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.11 - 8.05 (m, 2H), 7.99 - 7.94 (m, 1H), 7.68 - 7.61 (m, 1H), 7.48 - 7.46 (m, 2H), 7.37 - 7.25 (m, 5H), 7.24 - 7.14 (m, 3H), 6.18 - 5.98 (m, 1H), 4.96 - 4.92 (m, 1H), 4.61 - 4.44 (m, 2H), 4.19 - 4.08 (m, 2H), 4.01 - 3.87 (m, 2H), 3.85 - 3.65 (m, 3H), 3.50 - 3.37 (m, 2H), 3.28 - 3.20 (m, 2H), 2.80 - 2.70 (m, 1H), 2.45 - 2.33 (m, 2H), 2.21 - 2.10 (m, 2H), 2.10 - 1.91 (m, 4H), 1.90 - 1.72 (m, 5H), 1.60 - 1.48 (m, 2H), 1.37 - 1.26 (m, 2H), 1.25 - 1.21 (m, 1H), 1.07 - 1.05 (m, 1H), 1.02 - 0.94 (m, 1H), 0.92 - 0.82 (m, 3H), 0.76 - 0.67 (m, 1H)
493	propyl (((R)-(2-(((3S,6S,9R,10aR)-3-(3-(4-(azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-9-ethyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		887.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.28 - 8.21 (m, 1H), 8.13 - 7.84 (m, 4H), 7.67 - 7.57 (m, 1H), 7.39 - 7.29 (m, 2H), 7.27 - 7.10 (m, 3H), 6.42 - 5.97 (m, 2H), 5.05 - 4.94 (m, 1H), 4.74 - 4.59 (m, 1H), 4.54 - 4.14 (m, 4H), 4.07 - 3.80 (m, 8H), 2.33 - 2.18 (m, 4H), 2.12 - 1.78 (m, 6H), 1.69 - 1.47 (m, 5H), 1.44 -

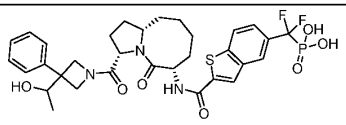
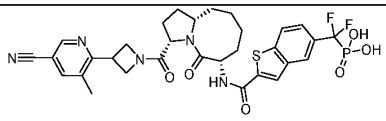
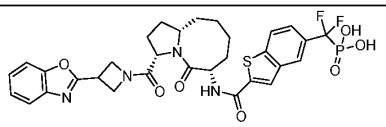
				1.28 (m, 3H), 1.26 - 1.18 (m, 3H), 0.98 - 0.95 (m, 3H), 0.92 - 0.81 (m, 3H)
494	propyl (((R)-(2-(((3S,6S,9aS)-3-(3-(4-ethoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		834.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.38 - 8.27 (m, 2H), 8.14 - 8.05 (m, 2H), 8.02 - 7.95 (m, 1H), 7.69 - 7.61 (m, 1H), 7.38 - 7.30 (m, 2H), 7.25 - 7.14 (m, 3H), 7.09 - 6.99 (m, 1H), 6.20 - 5.97 (m, 1H), 4.84 - 4.80 (m, 1H), 4.79 - 4.71 (m, 1H), 4.69 - 4.55 (m, 2H), 4.49 - 4.30 (m, 1H), 4.27 - 4.15 (m, 3H), 4.15 - 4.03 (m, 2H), 4.01 - 3.95 (m, 1H), 3.94 - 3.78 (m, 2H), 2.37 - 2.26 (m, 1H), 2.19 - 1.76 (m, 9H), 1.61 - 1.47 (m, 2H), 1.44 (td, J = 7.0, 2.4 Hz, 3H), 1.24 - 1.19 (m, 3H), 0.92 - 0.82 (m, 3H)

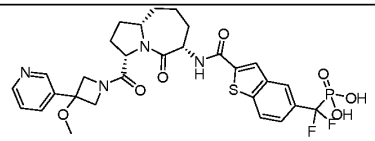
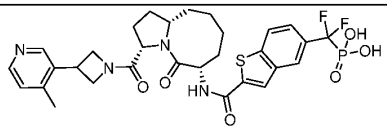
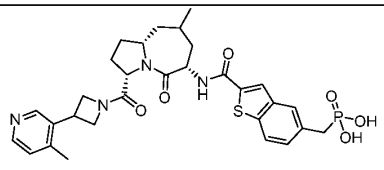
Compounds prepared according to General Scheme 2: Phosphonic Acids

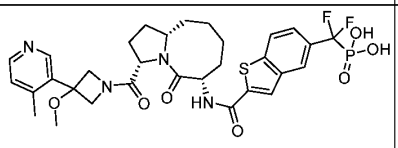
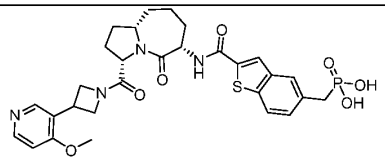
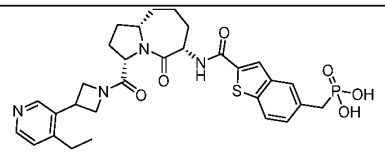
[001570] The following compounds in **Table 109** were prepared according to the representative procedure described above for the synthesis of (difluoro(2-(((3S,6S,10aR,Z)-3-(methyl(phenyl)carbamoyl)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)-1H-indol-5-yl)methyl)phosphonic acid (**30**) utilizing appropriate starting materials and modifications.

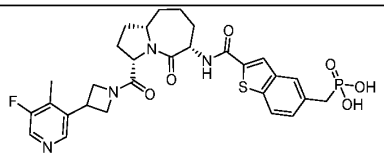
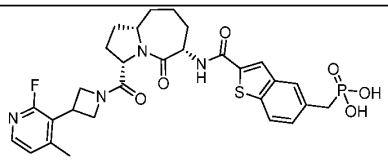
Table 109

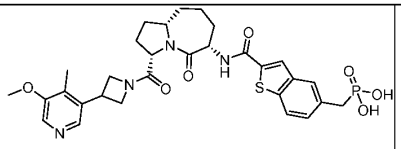
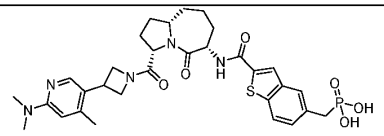
Compound	Name	Structure	LCMS $[M+H]^+$	^{1}H NMR

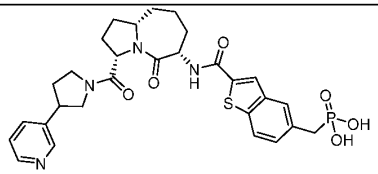
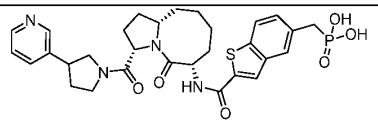
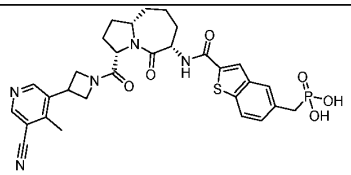
495	(difluoro(2-(((3S,6S,10aS)-3-(3-(1-hydroxyethyl)-3-phenylazetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		676.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 - 8.19 (m, 1H) 7.92 - 8.11 (m, 3H) 7.68 (s, 1H) 7.35 (d, J=8.0 Hz, 1H) 7.27 - 7.30 (m, 1H) 7.19 - 7.22 (m, 1H) 7.13 - 7.16 (m, 1H) 4.94 - 5.06 (m, 1H) 4.33 - 4.60 (m, 4H) 4.22 - 4.30 (m, 1H) 4.14 (s, 1H) 3.94 - 4.04 (m, 1H) 2.18 - 2.32 (m, 2H) 1.91 - 2.07 (m, 6H) 1.83 (m, 2H) 1.60 - 1.71 (m, 2H) 0.91 - 0.95 (m, 3H)
496	((2-(((3S,6S,10aS)-3-(3-(5-cyano-3-methylpyridin-2-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		672.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.79 - 8.62 (m, 1H), 8.25 - 8.19 (m, 1H), 8.06 - 7.92 (m, 2H), 7.90 (d, J = 7.6 Hz, 1H), 7.71 - 7.60 (m, 1H), 5.06 - 4.91 (m, 1H), 4.81 - 4.74 (m, 1H), 4.67 - 4.53 (m, 1H), 4.52 - 4.37 (m, 3H), 4.34 - 4.21 (m, 2H), 2.34 - 2.15 (m, 5H), 2.09 - 1.89 (m, 6H), 1.88 - 1.75 (m, 2H), 1.73 - 1.58 (m, 2H)
497	((2-(((3S,6S,10aS)-3-(3-(benzo[d]oxazol-2-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		673.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.21 - 8.04 (m, 2H), 7.96 - 7.88 (m, 1H), 7.77 - 7.71 (m, 1H), 7.70 - 7.56 (m, 2H), 7.42 - 7.32 (m, 2H), 5.01 (t, J = 8.4 Hz, 1H), 4.75 - 4.69 (m, 1H), 4.62 - 4.55 (m, 1H), 4.50 - 4.38 (m, 3H), 4.32 - 4.19 (m, 2H), 2.32 - 2.20 (m, 2H), 2.07 - 1.92 (m, 6H), 1.89 - 1.78 (m, 2H), 1.73 - 1.58 (m, 2H)

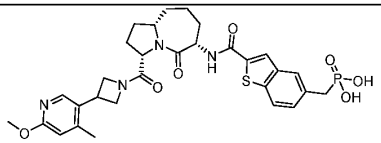
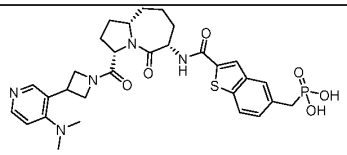
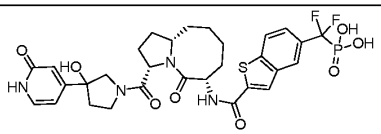
498	(difluoro(2-(((3S,6S,9aS)-3-(3-methoxy-3-(pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		649.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.72 - 8.67 (m, 1H), 8.56 – 8.52 (m, 1H), 8.20 (d, J = 6.0 Hz, 1H), 8.14 - 8.07 (m, 1H), 8.04 - 7.97 (m, 1H), 7.96 - 7.90 (m, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.56 - 7.45 (m, 1H), 4.82 - 4.70 (m, 2H), 4.65 - 4.52 (m, 2H), 4.38 - 4.20 (m, 2H), 4.07 (d, J = 4.4 Hz, 1H), 3.20 - 3.13 (m, 3H), 2.39 - 2.25 (m, 1H), 2.20 (s, 1H), 2.11 - 2.02 (m, 2H), 1.98 – 1.91 (m, 3H), 1.88 - 1.77 (s, 3H)
499	(difluoro(2-(((3S,6S,10aS)-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		647.0	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 - 8.51 (m, 1H), 8.44 - 8.34 (m, 1H), 8.30 (m, 1H), 8.23 - 8.01 (m, 1H), 7.67 - 7.55 (m, 1H), 7.40 - 7.30 (m, 2H), 5.04-4.86 (m, 2H), 4.74 - 4.72 (m, 1H), 4.71 – 4.47 (m, 3H), 4.45-4.44 (m, 1H), 4.42 – 4.17 (m, 1H), 2.47 – 2.27 (m, 3H), 2.25 – 2.23 (m, 2H), 2.05 – 2.03 (m, 6H), 2.02 – 1.99 (m, 2H), 1.98 – 1.68 (m, 2H)
500	((2-(((3S,6S,9aR)-8-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		611.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.79 (s, 1H), 8.62 - 8.44 (m, 1H), 8.05 - 7.91 (m, 1H), 7.89 - 7.74 (m, 3H), 7.47 - 7.37 (m, 1H), 4.80 - 4.71 (m, 2H), 4.69 - 4.58 (m, 1H), 4.58 - 4.51 (m, 1H), 4.49 - 4.39 (m, 1H), 4.38 - 4.26 (m, 1H), 4.20 - 4.04 (m,

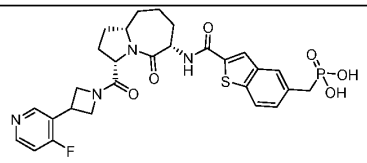
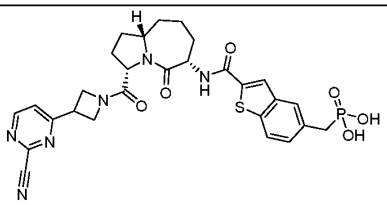
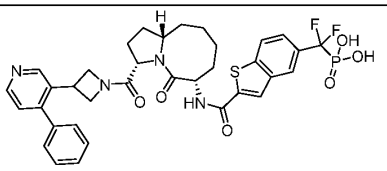
				2H), 3.28 - 3.18 (m, 2H), 2.54 (s, 3H), 2.38 - 2.28 (m, 1H), 2.19 - 1.91 (m, 5H), 1.80 (d, J = 11.2 Hz, 1H), 1.69 - 1.50 (m, 2H), 1.05 (d, J = 6.4 Hz, 3H)
501	(difluoro(2-(((3S,6S,10aS)-3-(3-methoxy-3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		677.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.97 - 8.81 (m, 1H), 8.76 - 8.53 (m, 2H), 8.38 - 8.21 (m, 1H), 8.16 - 8.01 (m, 2H), 7.66 - 7.45 (m, 2H), 5.02 - 4.81 (m, 2H), 4.72 (d, *J* = 5.2 Hz, 1H), 4.58 - 4.38 (m, 2H), 4.37 - 4.06 (m, 4H), 2.93 (d, *J* = 10.4 Hz, 3H), 2.36 (d, *J* = 13.2 Hz, 3H), 2.26 – 2.20 (m, 1H), 1.89 - 1.70 (m, 8H), 1.65 - 1.54 (m, 2H), 1.52 - 1.40 (m, 1H)
502	((2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		613.0	^{1}H NMR (400 MHz, CD$_3$OD) δ 8.52 - 8.37 (m, 2H), 7.99 - 7.87 (m, 1H), 7.81 - 7.70 (m, 2H), 7.51 - 7.36 (m, 2H), 5.03 (d, *J* = 8.4 Hz, 1H), 4.85 - 4.84 (m, 1H), 4.87 - 4.70 (m, 1H), 4.65 - 4.50 (m, 2H), 4.37 - 4.30 (m, 1H), 4.15 - 4.01 (m, 5H), 3.25 - 3.13 (m, 2H), 2.37 - 2.26 (m, 1H), 2.20 - 2.06 (m, 2H), 2.04 - 1.77 (m, 7H)
503	((2-(((3S,6S,9aS)-3-(3-(4-ethylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		611.3	^{1}H NMR (400 MHz, CD$_3$OD) δ 8.61 - 8.44 (m, 1H), 8.29 - 8.10 (m, 1H), 7.95 - 7.62 (m, 3H), 7.47 - 7.23 (m, 2H), 4.96 - 4.91 (m, 1H), 4.73 (d, J = 10.6 Hz, 1H), 4.70 - 4.63 (m, 1H), 4.61 -

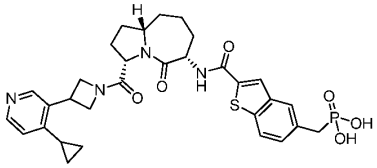
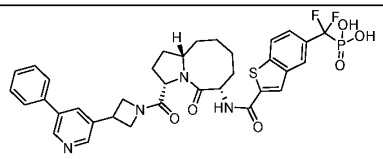
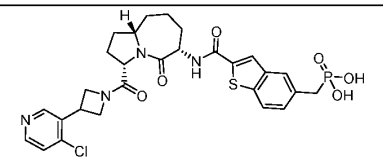
	yl)methyl)phosphonic acid			4.53 (m, 1H), 4.42 - 4.28 (m, 1H), 4.26 - 4.13 (m, 1H), 4.13 - 4.03 (m, 2H), 3.20 - 3.05 (m, 2H), 2.69 - 2.56 (m, 2H), 2.37 - 2.27 (m, 1H), 2.20 - 2.07 (m, 2H), 2.05 - 1.94 (m, 3H), 1.93 - 1.76 (m, 4H), 1.22 - 1.14 (m, 3H)
504	((2-(((3S,6S,9aS)-3-(3-(5-fluoro-4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		615.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.51 - 8.40 (m, 1H), 8.32 - 8.23 (m, 1H), 7.98 (d, J = 11.2 Hz, 1H), 7.86 - 7.73 (m, 2H), 7.44 (t, J = 7.6 Hz, 1H), 4.99 - 4.92 (m, 1H), 4.77 - 4.71 (m, 1H), 4.71 - 4.66 (m, 1H), 4.61 - 4.55 (m, 1H), 4.54 - 4.38 (m, 1H), 4.27 - 4.19 (m, 1H), 4.18 - 4.03 (m, 2H), 3.17 - 3.07 (m, 2H), 2.34 - 2.27 (m, 1H), 2.23 (s, 3H), 2.18 - 2.06 (m, 2H), 2.06 - 1.95 (m, 3H), 1.93 - 1.74 (m, 4H)
505	((2-(((3S,6S,9aS)-3-(3-(2-fluoro-4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		615.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.02 (s, 1H) 7.91 - 7.97 (m, 1H) 7.84 (s, 2H) 7.40 - 7.46 (m, 1H) 7.11 - 7.17 (m, 1H) 4.66 (m, 2H) 4.55 - 4.63 (m, 1H) 4.40 - 4.48 (m, 1H) 4.26 - 4.38 (m, 2H) 4.13 - 4.22 (m, 1H) 4.01 - 4.12 (m, 1H) 3.28 (s, 1H) 3.21 - 3.24 (m, 1H) 2.40 (d, J=4.0 Hz, 3H) 2.31 (s, 1H) 2.14 - 2.20 (m, 1H) 1.82 - 2.08 (m, 8H)

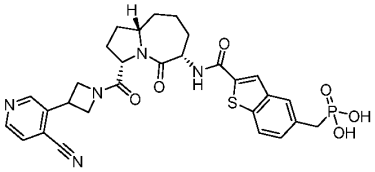
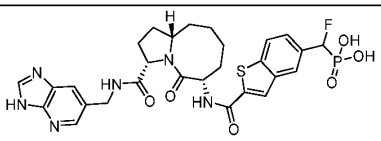
506	((2-(((3S,6S,9aS)-3-(3-(5-methoxy-4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		627.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (s, 1H), 8.34 - 8.24 (m, 1H), 8.01 - 7.91 (m, 1H), 7.85 - 7.76 (m, 2H), 7.46 - 7.37 (m, 1H), 4.78 - 4.71 (m, 2H), 4.67 - 4.57 (m, 1H), 4.56 - 4.50 (m, 1H), 4.48 - 4.38 (m, 1H), 4.37 - 4.28 (m, 1H), 4.18 - 4.12 (m, 1H), 4.11 - 4.06 (m, 1H), 4.04 (s, 1H), 4.00 (s, 2H), 3.26 (d, J = 5.2 Hz, 1H), 3.20 (d, J = 4.8 Hz, 1H), 2.33 (s, 3H), 2.21 - 2.13 (m, 1H), 2.12 - 2.06 (m, 1H), 2.05 - 1.97 (m, 2H), 1.97 - 1.91 (m, 2H), 1.90 - 1.73 (m, 4H)
507	((2-(((3S,6S,9aS)-3-(3-(6-(dimethylamino)-4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		640.1	^{1}H NMR (400 MHz, CD_3OD) 7.69 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.50 (s, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.10 (s, 1H), 6.70 - 6.62 (m, 1H), 4.68 (d, J = 11.2 Hz, 1H), 4.60 (t, J = 8.0 Hz, 1H), 4.42 (d, J = 6.0 Hz, 1H), 4.29 (t, J = 7.6 Hz, 1H), 4.22 - 4.15 (m, 1H), 4.05 (s, 1H), 4.01 - 3.95 (m, 1H), 3.74 - 3.65 (m, 1H), 3.18 - 3.12 (m, 1H), 3.10 (s, 6H), 3.03 (d, J = 2.8 Hz, 1H), 2.34 - 2.26 (m, 1H), 2.16 - 2.05 (m, 3H), 2.05 - 1.95 (m, 3H), 1.89 (s, 3H), 1.83 (d, J = 3.6 Hz, 3H)

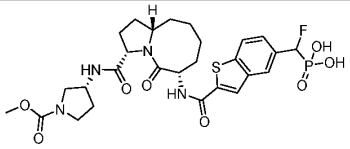
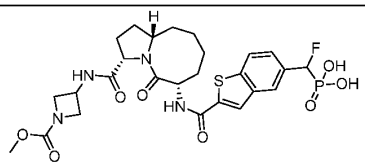
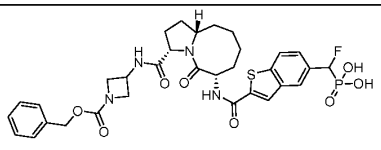
508	((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)pyrrolidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		597.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.47 - 8.30 (m, 1H), 8.23 - 8.09 (m, 1H), 8.04 - 7.75 (m, 3H), 7.74 - 7.55 (m, 1H), 7.53 - 7.32 (m, 2H), 4.85 - 4.73 (m, 2H), 4.23 - 3.95 (m, 2H), 3.92 - 3.57 (m, 2H), 3.55 - 3.36 (m, 2H), 3.22 - 3.08 (m, 2H), 2.35 - 1.85 (m, 12H)
509	((2-(((3S,6S,10aS)-5-oxo-3-(3-(pyridin-3-yl)pyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		611.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 - 8.39 (m, 1H), 8.37 - 8.12 (m, 1H), 8.08 - 7.93 (m, 1H), 7.88 - 7.69 (m, 2H), 7.67 - 7.50 (m, 1H), 7.49 - 7.29 (m, 2H), 5.19 - 5.03 (m, 1H), 4.80 - 4.68 (m, 1H), 4.50 - 4.35 (m, 1H), 4.18 - 3.99 (m, 1H), 3.92 - 3.77 (m, 1H), 3.75 - 3.59 (m, 1H), 3.56 - 3.38 (m, 2H), 3.18 - 2.99 (m, 2H), 2.39 - 1.68 (m, 14H)
510	((2-(((3S,6S,9aS)-3-(3-(5-cyano-4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		622.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.93 - 8.81 (m, 1H), 8.75 (s, 1H), 8.00 (m, 1H), 7.88 (m, 1H), 7.78 (m, 1H), 7.49 (m, 1H), 4.73 (s, 1H), 4.63 - 4.52 (m, 2H), 4.48 - 4.42 (m, 1H), 4.33 - 4.26 (m, 1H), 4.23 - 4.06 (m, 2H), 3.72 (m, 1H), 3.22 (m, 1H), 3.14 - 3.08 (m, 1H), 2.51 (d, J = 2.4 Hz, 3H), 2.36 - 2.29 (m, 1H), 2.14 - 2.04 (m, 2H), 2.03 - 1.96 (m, 2H), 1.92 - 1.85 (m, 2H), 1.38 (m, 3H)

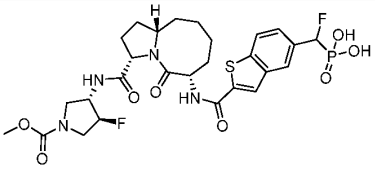
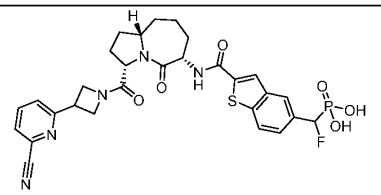
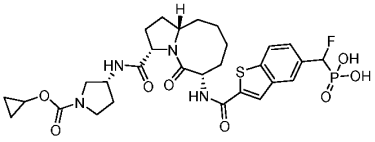
511	((2-(((3S,6S,9aS)-3-(3-(6-methoxy-4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		627.0	^{1}H NMR (400 MHz, CD_3OD) δ 7.99 - 8.03 (m, 1H) 7.85 (d, J=8.00 Hz, 3H) 7.41 - 7.45 (m, 1H) 6.39 - 6.47 (m, 1H) 4.75 (d, J=12.00 Hz, 1H) 4.22 - 4.64 (m, 4H) 3.87 - 4.14 (m, 3H) 3.46 - 3.60 (m, 3H) 3.28 (s, 1H) 3.23 (s, 1H) 2.26 - 2.35 (m, 1H) 2.13 - 2.16 (m, 3H) 2.13 (s, 2H) 1.79 - 2.04 (m, 7H)
512	((2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		626.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (d, J = 4.0 Hz, 1H), 8.14 - 7.93 (m, 2H), 7.87 - 7.78 (m, 2H), 7.46 - 7.39 (m, 1H), 7.13 - 7.01 (m, 1H), 4.78 - 4.66 (m, 2H), 4.60 - 4.47 (m, 2H), 4.46 - 4.34 (m, 1H), 4.34 - 4.25 (m, 1H), 4.15 - 4.00 (m, 2H), 3.27 - 3.23 (m, 1H), 3.20 (d, J = 4.4 Hz, 1H), 3.15 (d, J = 4.4 Hz, 6H), 2.39 - 2.25 (m, 1H), 2.21 - 2.06 (m, 2H), 2.05 - 1.98 (m, 2H), 1.93 (dd, J = 6.6, 12.4 Hz, 2H), 1.89 - 1.74 (m, 3H)
513	(difluoro(2-(((3S,6S,10aS)-3-(3-hydroxy-3-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		679.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (s, 2H), 8.04 - 7.98 (m, 1H), 7.71 - 7.65 (m, 1H), 7.53 - 7.38 (m, 1H), 6.89 - 6.74 (m, 1H), 6.64 (t, J = 5.6 Hz, 1H), 5.08 - 4.98 (m, 1H), 4.46 - 4.40 (m, 1H), 4.21 - 3.99 (m, 1H), 3.95 (s, 2H), 3.69 - 3.46 (m, 2H), 2.34 - 2.23 (m, 2H), 2.14 - 1.93 (m, 8H),

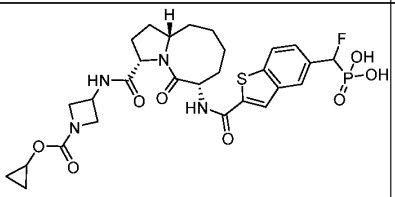
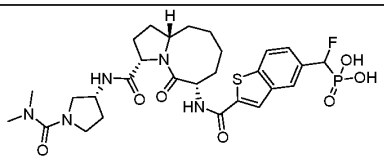
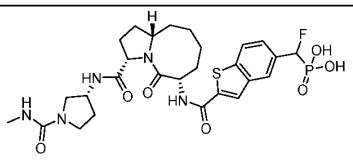
				1.89 - 1.78 (m, 2H), 1.73 - 1.62 (m, 2H)
514	((2-(((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		601.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.90 - 8.71 (m, 1H), 8.65 - 8.58 (m, 1H), 7.99 (d, J = 12.4Hz, 1H), 7.87 - 7.75 (m, 2H), 7.55 - 7.47 (m, 1H), 7.44 - 7.38 (m, 1H), 4.97 - 4.90 (m, 1H), 4.76 - 4.67 (m, 2H), 4.56 (m, 1H), 4.48 - 4.39 (m, 1H), 4.30 - 4.12 (m, 2H), 4.07 (d, J = 5.2Hz, 1H), 3.27 (d, J = 2.4Hz, 1H), 3.22 (d, J = 2.4Hz, 1H), 2.36 - 2.25 (m, 1H), 2.19 - 2.11 (m, 1H), 2.10 - 2.00 (m, 2H), 1.96 (s, 2H), 1.92 - 1.85 (m, 2H), 1.83 (s, 2H)
515	((2-(((3S,6S,9aS)-3-(3-(2-cyanopyrimidin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		608.9	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (dd, J = 5.2, 10.0 Hz, 1H), 8.69 (t, J = 6.4 Hz, 1H), 8.16 (d, J = 11.6 Hz, 1H), 7.97 - 7.84 (m, 2H), 7.78 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H), 4.82 - 4.33 (m, 5H), 4.31 - 3.93 (m, 5H), 3.17 - 2.91 (m, 2H), 2.26 - 2.15 (m, 1H), 2.11 - 1.91 (m, 2H), 1.90 - 1.62 (m, 7H)
516	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-(3-(4-phenylpyridin-3-yl)azetidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		709.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.80 - 8.67 (m, 1H), 8.37 - 8.15 (m, 1H), 8.08 - 7.95 (m, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.89 - 7.75 (m, 1H), 7.74 - 7.58 (m, 2H), 7.58 - 7.52 (m, 2H), 7.47 - 7.42 (m, 1H), 7.35 - 7.30 (m, 1H), 7.26 - 7.16 (m, 1H), 4.98 -

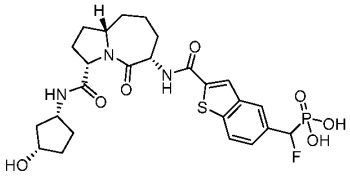
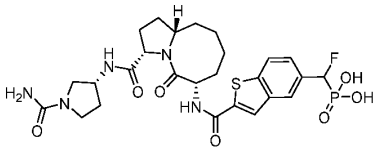
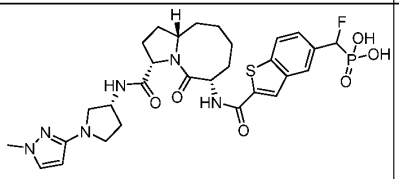
				4.93 (m, 1H), 4.53 - 4.45 (m, 1H), 4.44 - 4.31 (m, 3H), 4.11 - 3.94 (m, 2H), 3.94 - 3.64 (m, 1H), 2.30 - 2.13 (m, 2H), 2.07 - 1.89 (m, 4H), 1.88 - 1.73 (m, 4H), 1.71 - 1.65 (m, 1H), 1.58 (d, J = 2.4 Hz, 1H)
517	((2-(((3S,6S,9aS)-3-(3-(4-cyclopropylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		623.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.72 - 8.61 (m, 1H), 8.55 - 8.38 (m, 1H), 8.03 - 7.92 (m, 1H), 7.89 - 7.76 (m, 2H), 7.50 - 7.32 (m, 2H), 4.86 - 4.66 (m, 3H), 4.61 - 4.46 (m, 3H), 4.28 - 4.18 (m, 1H), 4.09 (s, 1H), 3.28 - 3.16 (m, 2H), 2.38 - 2.26 (m, 1H), 2.21 - 1.95 (m, 6H), 1.95 - 1.80 (m, 4H), 1.50 - 1.37 (m, 2H), 1.19 - 1.05 (m, 2H)
518	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-(3-(5-phenylpyridin-3-yl)azetidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		709.3	^{1}H NMR (400 MHz, CD_3OD) δ 9.01 - 8.92 (m, 1H), 8.91 - 8.82 (m, 1H), 8.79 - 8.67 (m, 1H), 8.15 - 8.03 (m, 1H), 7.96 - 7.86 (m, 1H), 7.84 - 7.74 (m, 3H), 7.72 - 7.65 (m, 1H), 7.63 - 7.54 (m, 1H), 7.50 - 7.36 (m, 2H), 5.09 - 4.92 (m, 2H), 4.79 - 4.73 (m, 1H), 4.51 - 4.37 (m, 3H), 4.24 - 4.11 (m, 2H), 2.31 - 2.18 (m, 2H), 2.13 - 1.96 (m, 5H), 1.94 - 1.77 (m, 3H), 1.75 - 1.60 (m, 2H)
519	((2-(((3S,6S,9aS)-3-(3-(4-chloropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-		616.9	^{1}H NMR (400 MHz, CD_3OD) δ 8.83 - 8.70 (m, 1H), 8.51 – 8.46 (m, 1H), 8.05 - 7.95 (m, 1H), 7.89 - 7.78

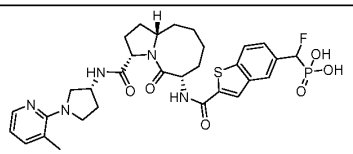
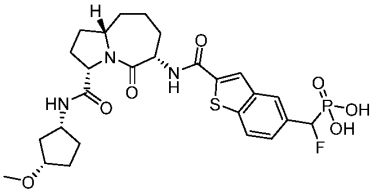
	pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			(m, 2H), 7.71 – 7.69 (m, 1H), 7.47 - 7.38 (m, 1H), 5.02 - 4.90 (m, 1H), 4.78 - 4.68 (m, 2H), 4.61 - 4.53 (m, 1H), 4.52 - 4.42 (m, 1H), 4.34 (t, J = 8.0 Hz, 1H), 4.24 - 4.17 (m, 1H), 4.07 (d, J = 4.0 Hz, 1H), 3.28 - 3.19 (m, 2H), 2.36 - 2.25 (m, 1H), 2.21 - 2.05 (m, 2H), 2.04 - 1.93 (m, 3H), 1.92 - 1.73 (m, 4H)
520	((2-(((3S,6S,9aS)-3-(3-(4-cyanopyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		608.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.89 - 9.15 (m, 1H) 8.69 (m, 1H) 8.02 (d, J=4.00 Hz, 1H) 7.86 (m, 2H) 7.74 (m, 1H) 7.38 - 7.49 (m, 1H) 5.00 (s, 1H) 4.70 - 4.83 (m, 2H) 4.51 - 4.63 (m, 2H) 4.30 - 4.41 (m, 1H) 4.19 - 4.27 (m, 1H) 4.03 - 4.12 (m, 1H) 3.28 (s, 1H) 3.23 (s, 1H) 2.25 - 2.38 (m, 1H) 2.11 - 2.17 (m, 1H) 1.98 - 2.08 (m, 3H) 1.75 - 1.96 (m, 5H)
521	((2-(((3S,6S,10aS)-3-(((3H-imidazo[4,5-b]pyridin-6-yl)methyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		629.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (d, J = 7.2 Hz, 1H), 8.59 (t, J = 5.6 Hz, 1H), 8.45 (s, 1H), 8.37 - 8.21 (m, 2H), 8.13 - 8.03 (m, 1H), 8.03 - 7.89 (m, 2H), 7.61 - 7.50 (m, 1H), 5.91 - 5.73 (m, 1H), 4.99 - 4.90 (m, 1H), 4.55 - 4.49 (m, 1H), 4.40 - 4.32 (m, 2H), 4.31 - 4.26 (m, 1H), 3.90 (s, 1H), 2.20 - 2.10 (m, 1H), 2.09 - 2.02 (m, 1H), 2.02 - 1.95 (m,

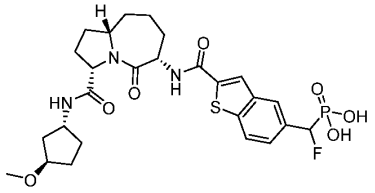
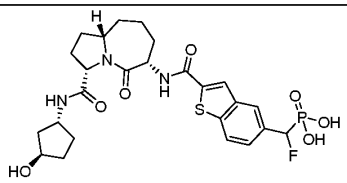
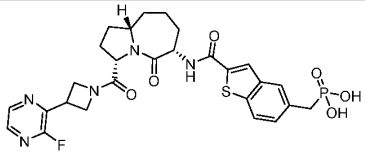
				1H), 1.94 - 1.76 (m, 5H), 1.74 - 1.69 (m, 1H), 1.68 - 1.43 (m, 3H)
522	(fluoro(2-(((3S,6S,10aS)-3-(((R)-1-(methoxycarbonyl)pyrrolidin-3-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		625.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 7.99 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 5.91 - 5.75 (m, 1H), 5.06 - 5.00 (m, 1H), 4.43 - 4.35 (m, 2H), 4.34 - 4.28 (m, 1H), 3.65 (d, J = 2.0 Hz, 3H), 3.63 - 3.59 (m, 1H), 3.51 - 3.40 (m, 2H), 3.27 (d, J = 4.0 Hz, 1H), 2.25 - 2.17 (m, 2H), 2.16 - 2.09 (m, 1H), 2.08 - 2.03 (m, 1H), 2.02 - 1.92 (m, 5H), 1.90 - 1.78 (m, 3H), 1.72 - 1.59 (m, 2H)
523	(fluoro(2-(((3S,6S,10aS)-3-((1-(methoxycarbonyl)azetidin-3-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		611.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (s, 1H), 8.02 (s, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.58 (m, 1H), 5.94 - 5.74 (m, 1H), 5.02 (s, 1H), 4.57 - 4.49 (m, 1H), 4.37 (m, 2H), 4.26 (m, 2H), 3.92 - 3.82 (m, 2H), 3.65 (s, 3H), 2.24 (s, 2H), 2.04 - 1.94 (m, 6H), 1.84 - 1.76 (m, 2H), 1.72 - 1.62 (m, 2H)
524	((2-(((3S,6S,10aS)-3-((1-((benzyloxy)carbonyl)azetidin-3-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		687.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 - 8.05 (m, 1H), 8.02 (s, 1H), 7.97 - 7.91 (m, 1H), 7.62 - 7.56 (m, 1H), 7.38 - 7.26 (m, 5H), 5.92 - 5.69 (m, 1H), 5.08 (s, 2H), 5.05 - 4.99 (m, 1H), 4.60 - 4.48 (m, 1H), 4.43 - 4.33 (m, 2H), 4.32 -

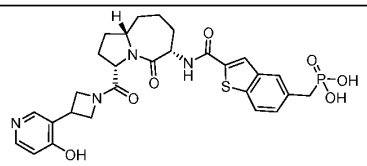
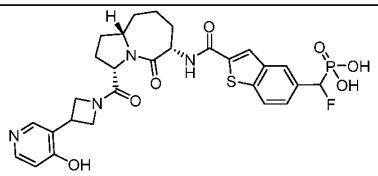
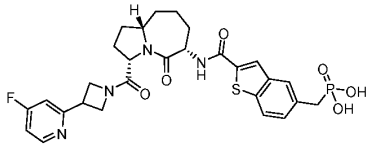
				4.24 (m, 2H), 3.98 - 3.83 (m, 2H), 2.27 - 2.17 (m, 2H), 2.08 - 1.88 (m, 7H), 1.86 - 1.75 (m, 2H), 1.71 - 1.64 (m, 1H)
525	(fluoro(2-(((3S,6S,10aS)-3-(((3S,4S)-4-fluoro-1-(methoxycarbonyl)pyrrolidin-3-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		643.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (s, 1H), 8.01 (s, 1H), 7.94 (d, J=8.00 Hz, 1H), 7.58 (d, J=8.00 Hz, 1H), 5.74 - 5.92 (m, 1H), 5.00 - 5.05 (m, 1H), 4.28 - 4.54 (m, 4H), 3.68 - 3.72 (m, 5H), 3.58 - 3.61 (m, 1H), 3.50 - 3.56 (m, 1H), 2.17 - 2.24 (m, 2H), 2.00 (m, 6H), 1.82 (m, 2H), 1.61 - 1.73 (m, 2H)
526	((2-(((3S,6S,9aS)-3-(3-(6-cyanopyridin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		626.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.08 - 8.01 (m, 2H), 7.97 - 7.85 (m, 2H), 7.79 - 7.73 (m, 1H), 7.64 – 7.60 (m, 2H), 5.76 - 5.60 (m, 1H), 4.77 - 4.64 (m, 2H), 4.61 – 4.58 (m, 1H), 4.50 - 4.26 (m, 2H), 4.19 - 3.99 (m, 3H), 2.37 - 2.26 (m, 1H), 2.14 (d, J = 7.6 Hz, 1H), 2.04 – 1.99 (m, 3H), 1.90 (s, 3H), 1.84 (s, 2H)
527	((2-(((3S,6S,10aS)-3-(((R)-1-(cyclopropoxycarbonyl)pyrrolidin-3-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		651.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (s, 1H), 8.01 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 5.90 - 5.75 (m, 1H), 5.08 - 4.98 (m, 1H), 4.44 - 4.28 (m, 3H), 4.02 - 3.94 (m, 1H), 3.66 - 3.52 (m, 1H), 3.51 - 3.43 (m, 1H), 3.42 - 3.36 (m, 1H), 3.29 - 3.17 (m, 1H), 2.27 - 2.17

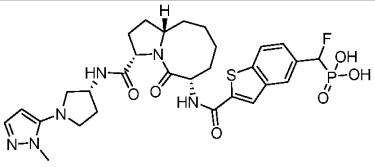
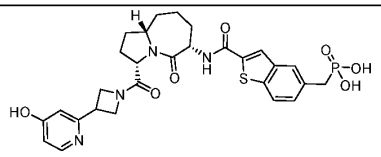
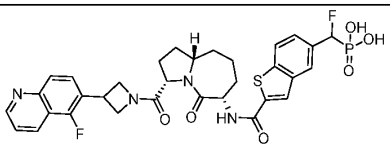
				(m, 2H), 2.12 (dd, J = 6.0, 12.8 Hz, 1H), 2.08 - 1.92 (m, 6H), 1.92 - 1.85 (m, 1H), 1.81 (dd, J = 6.8, 10.4 Hz, 2H), 1.72 - 1.56 (m, 2H), 0.65 (d, J = 3.2 Hz, 4H)
528	((2-(((3S,6S,10aS)-3-((1-(cyclopropoxycarbonyl)azetidin-3-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		637.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (d, J = 6.8 Hz, 1H), 8.69 (d, J = 6.8 Hz, 1H), 8.25 (s, 1H), 8.08 - 7.94 (m, 2H), 7.52 (d, J = 8.4 Hz, 1H), 5.91 - 5.74 (m, 1H), 4.95 - 4.86 (m, 1H), 4.42 - 4.32 (m, 1H), 4.29 - 4.18 (m, 2H), 4.10 (t, J = 8.0 Hz, 2H), 3.93 (s, 1H), 3.69 (dt, J = 5.2, 9.2 Hz, 2H), 2.14 - 1.98 (m, 2H), 1.92 - 1.74 (m, 6H), 1.73 - 1.61 (m, 2H), 1.60 - 1.44 (m, 2H), 0.65 - 0.52 (m, 4H)
529	((2-(((3S,6S,10aS)-3-(((R)-1-(dimethylcarbamoyl)pyrrolidin-3-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		638.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.11 - 8.04 (m, 1H), 8.00 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 5.69 (s, 1H), 5.07 - 4.98 (m, 1H), 4.48 - 4.34 (m, 2H), 4.34 - 4.24 (m, 1H), 3.72 - 3.62 (m, 1H), 3.55 - 3.38 (m, 2H), 3.27 – 3.21 (m, 1H), 2.83 (s, 6H), 2.28 - 2.15 (m, 2H), 2.13 - 1.90 (m, 7H), 1.88 - 1.75 (m, 3H), 1.73 - 1.55 (m, 2H)
530	(fluoro(2-(((3S,6S,10aS)-3-(((R)-1-(methylcarbamoyl)pyrrolidin-3-yl)carbamoyl)-5-		623.9	^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 8.05 - 7.97 (m, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.64 - 7.55 (m, 1H), 5.88 - 5.68

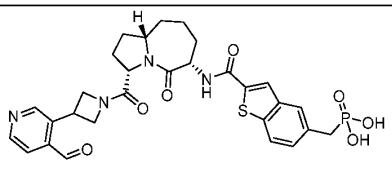
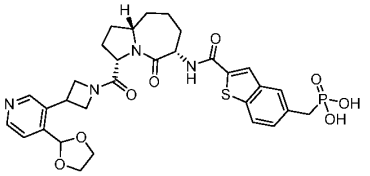
	oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			(m, 1H), 5.09 - 4.95 (m, 1H), 4.46 - 4.29 (m, 3H), 3.64 - 3.53 (m, 1H), 3.50 - 3.35 (m, 3H), 3.24 – 3.21 (m, 1H), 2.70 (s, 3H), 2.25 - 2.09 (m, 3H), 2.09 - 1.86 (m, 7H), 1.86 - 1.73 (m, 2H), 1.73 - 1.55 (m, 2H)
531	(fluoro(2-(((3S,6S,9aS)-3-(((1R,3S)-3-hydroxycyclopentyl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		568.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.07 (s, 1H), 8.03 (s, 1H), 7.97 - 7.93 (m, 1H), 7.61 - 7.57 (m, 1H), 5.87 (d, J = 8.0 Hz, 1H), 4.76 - 4.70 (m, 1H), 4.55 - 4.50 (m, 1H), 4.31 - 4.26 (m, 1H), 4.23 - 4.16 (m, 1H), 4.05 - 3.98 (m, 1H), 2.31 - 2.23 (m, 1H), 2.16 - 1.98 (m, 7H), 1.89 (d, J = 10.4 Hz, 2H), 1.84 - 1.78 (m, 2H), 1.76 - 1.65 (m, 3H), 1.61 - 1.53 (m, 1H)
532	((2-(((3S,6S,10aS)-3-(((R)-1-carbamoylpyrrolidin-3-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		610.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (s, 1H), 8.02 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 6.02 - 5.71 (m, 1H), 5.10 - 5.02 (m, 1H), 4.51 - 4.25 (m, 3H), 3.63 (dd, J = 6.4, 10.8 Hz, 1H), 3.53 - 3.42 (m, 2H), 3.27 (dd, J = 3.6, 10.4 Hz, 1H), 2.33 - 2.14 (m, 3H), 2.09 - 1.76 (m, 9H), 1.74 - 1.55 (m, 2H)
533	(fluoro(2-(((3S,6S,10aS)-3-(((R)-1-(1-methyl-1H-pyrazol-3-yl)pyrrolidin-3-yl)carbamoyl)-5-		647.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (s, 1H), 8.01 (d, J = 6.2 Hz, 2H), 7.85 (d, J = 8.4 Hz, 1H), 7.64 - 7.57 (m, 1H), 7.30 (s,

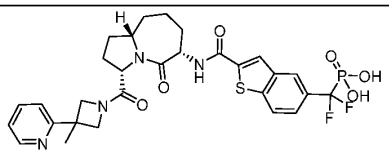
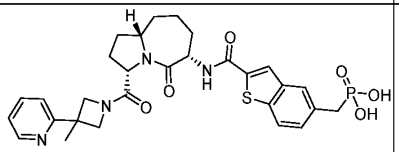
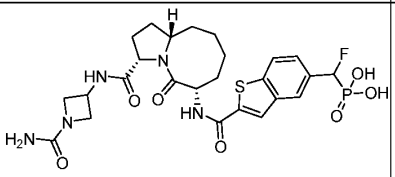
	oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			1H), 5.73 - 5.58 (m, 1H), 5.05 - 5.00 (m, 1H), 4.45 - 4.38 (m, 3H), 3.68 (s, 3H), 3.55 - 3.48 (m, 1H), 3.45 - 3.39 (m, 1H), 3.22 - 3.18 (m, 1H), 3.17 – 3.15 (m, 1H), 2.30 - 2.15 (m, 3H), 2.10-2.04 (m, 1H), 1.99 - 1.91 (m, 6H), 1.84 - 1.77 (m, 2H), 1.68 (d, J = 15.6 Hz, 2H)
534	(fluoro(2-(((3S,6S,10aS)-3-(((R)-1-(3-methylpyridin-2-yl)pyrrolidin-3-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		658.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.02 - 7.9 (m, 2H), 7.7 (d, *J* = 8.0 Hz, 1H), 7.7 - 7.5 (m, 2H), 7.4 (s, 1H), 6.6 - 6.4 (m, 1H), 5.7 - 5.5 (m, 1H), 5.0 - 4.9 (m, 1H), 4.5 (d, *J* = 4.0 Hz, 1H), 4.5 - 4.4 (m, 2H), 4.0 (td, *J* = 4.0, 10.6 Hz, 1H), 4.0 - 3.9 (m, 1H), 3.7 - 3.6 (m, 2H), 2.4 (d, *J* = 4.0 Hz, 3H), 2.3 - 2.2 (m, 3H), 2.1 - 2.02(m, 3H), 2.0 - 1.9 (m, 4H), 1.9 - 1.8 (m, 2H), 1.8 - 1.6 (m, 2H)
535	(fluoro(2-(((3S,6S,9aS)-3-(((1R,3S)-3-methoxycyclopentyl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		582.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (s, 1H), 8.06 - 8.03 (m, 1H), 7.99 - 7.95 (m, 1H), 7.63 - 7.58 (m, 1H), 4.77 - 4.72 (m, 1H), 4.58 - 4.52 (m, 1H), 4.24 - 4.16 (m, 1H), 4.08 - 4.00 (m, 1H), 3.91 - 3.84 (m, 1H), 2.28 (m, 1H), 2.22 - 2.15 (m, 1H), 2.11 - 2.02 (m, 4H), 2.02 - 1.94 (m, 2H), 1.93 - 1.87 (m, 2H), 1.86 - 1.77 (m, 3H), 1.77 - 1.71 (m, 1H), 1.68 - 1.59 (m, 2H)

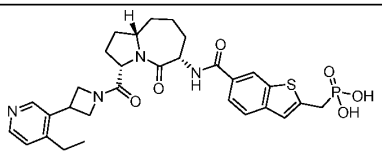
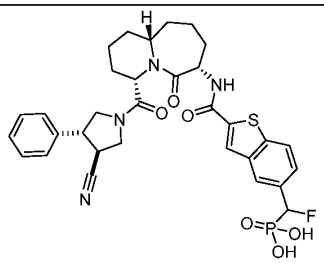
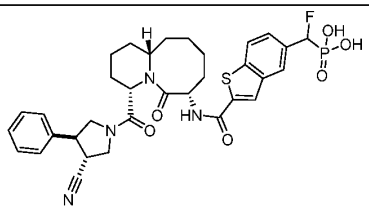
536	(fluoro(2-(((3S,6S,9aS)-3-(((1R,3R)-3-methoxycyclopentyl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		582.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 8.02 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 5.92 - 5.73 (m, 1H), 4.74 (d, J = 11.2 Hz, 1H), 4.48 (m, 1H), 4.23 (m, 1H), 4.07 - 4.00 (m, 1H), 3.91 (m, 1H), 3.26 (s, 3H), 2.27 (m, 1H), 2.10 - 2.04 (m, 4H), 2.02 - 1.92 (m, 4H), 1.91 - 1.81 (m, 5H), 1.68 - 1.64 (m, 1H), 1.55 - 1.48 (m, 1H)
537	(fluoro(2-(((3S,6S,9aS)-3-(((1R,3R)-3-hydroxycyclopentyl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		568.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.07 (s, 1H), 8.02 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 5.90 - 5.73 (m, 1H), 4.74 (d, J = 10.8 Hz, 1H), 4.48 (m, 1H), 4.36 - 4.29 (m, 1H), 4.36 - 4.28 (m, 1H), 4.09 - 3.97 (m, 1H), 2.33 - 2.21 (m, 1H), 2.20 - 2.11 (m, 1H), 2.09 - 1.94 (m, 6H), 1.94 - 1.80 (m, 5H), 1.69 (m, 1H), 1.62 - 1.46 (m, 2H)
538	((2-(((3S,6S,9aS)-3-(3-(3-fluoropyrazin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		601.9	^{1}H NMR (400 MHz, CD_3OD) δ 8.59 - 8.48 (m, 1H), 8.20 - 8.11 (m, 1H), 8.03 - 7.94 (m, 1H), 7.88 - 7.79 (m, 2H), 7.47 - 7.38 (m, 1H), 4.88 (s, 1H), 4.80 - 4.63 (m, 2H), 4.61 - 4.56 (m, 1H), 4.46 - 4.40 (m, 1H), 4.37 - 4.22 (m, 2H), 4.06 (s, 1H), 3.29 - 3.20 (m, 2H), 2.35 - 2.25 (m, 1H), 2.16 -

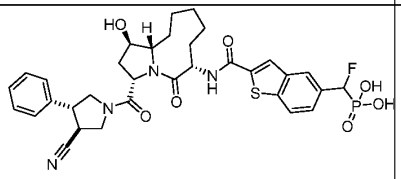
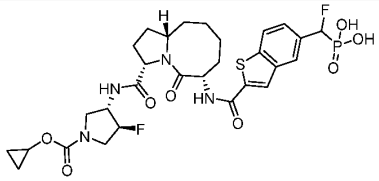
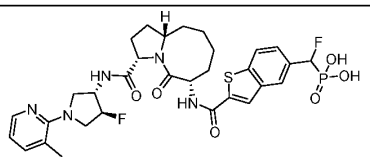
				2.04 (m, 2H), 2.03 - 1.78 (m, 7H)
539	((2-(((3S,6S,9aS)-3-(3-(4-hydroxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		599.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.33 - 8.23 (m, 1H), 8.03 - 7.84 (m, 2H), 7.84 - 7.63 (m, 2H), 7.45 - 7.34 (m, 1H), 7.09 - 6.65 (m, 1H), 4.79 - 4.65 (m, 2H), 4.60 - 4.48 (m, 2H), 4.43 - 4.31 (m, 1H), 4.20 - 3.99 (m, 3H), 3.28 - 3.16 (m, 2H), 2.39 - 2.28 (m, 1H), 2.20 - 2.06 (m, 2H), 2.06 - 1.90 (m, 4H), 1.89 - 1.73 (m, 3H)
540	(fluoro(2-(((3S,6S,9aS)-3-(3-(4-hydroxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		617.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.34 - 8.17 (m, 1H), 8.06 - 7.89 (m, 1H), 7.89 (s, 1H), 7.72 - 7.57 (m, 2H), 7.10 (d, J = 6.8 Hz, 1H), 6.49 (t, J = 7.6 Hz, 1H), 5.88 - 5.63 (m, 1H), 4.80 - 4.68 (m, 2H), 4.61 - 4.52 (m, 1H), 4.49 (t, J = 7.2 Hz, 1H), 4.41 - 4.29 (m, 1H), 4.22 - 4.09 (m, 2H), 4.07 - 3.96 (m, 1H), 2.38 - 2.29 (m, 1H), 2.20 - 2.08 (m, 2H), 2.07 - 1.90 (m, 4H), 1.87 - 1.64 (m, 3H)
541	((2-(((3S,6S,9aS)-3-(3-(4-fluoropyridin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		601.0	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (t, J = 6.8 Hz, 1H), 8.62 (m, 1H), 8.17 (d, J = 14.4 Hz, 1H), 7.91 - 7.89 (m, 1H), 7.78 (d, J = 5.2 Hz, 1H), 7.40 - 7.30 (m, 2H), 7.27 - 7.20 (m, 1H), 4.69 - 4.60 (m, 1H), 4.58 - 4.41 (m, 2H), 4.39 - 4.12 (m, 2H), 4.11 - 3.94 (m, 3H), 3.11 -

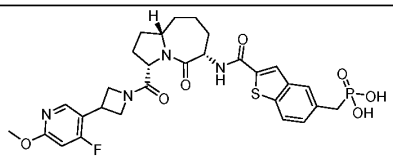
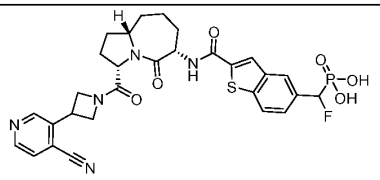
				3.03 (m, 2H), 2.26 - 2.13 (m, 1H), 2.11 - 1.93 (m, 2H), 1.92 - 1.76 (m, 7H)
542	(fluoro(2-(((3S,6S,10aS)-3-(((R)-1-(1-methyl-1H-pyrazol-5-yl)pyrrolidin-3-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		647.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (d, J = 6.8 Hz, 1H), 8.27 (d, J = 7.2 Hz, 1H), 8.25 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.24 (d, J = 2.0 Hz, 1H), 5.93 - 5.74 (m, 1H), 5.67 (d, J = 2.0 Hz, 1H), 4.97 - 4.86 (m, 1H), 4.35 - 4.24 (m, 3H), 3.66 (s, 3H), 3.31 (m, 1H), 3.09 (m, 1H), 2.97 (m, 1H), 2.23 - 2.16 (m, 1H), 2.14 - 2.01 (m, 2H), 1.78 (s, 7H), 1.71 (s, 4H)
543	((2-(((3S,6S,9aS)-3-(3-(4-hydroxypyridin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		599.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.04 - 7.99 (m, 1H), 7.91 - 7.84 (m, 1H), 7.82 - 7.67 (m, 2H), 7.48 - 7.42 (m, 1H), 6.71 - 6.55 (m, 1H), 6.48 - 6.42 (m, 1H), 4.79 - 4.70 (m, 1H), 4.60 - 4.50 (m, 1H), 4.41 (s, 2H), 4.32 - 4.23 (m, 1H), 4.10 - 4.05 (m, 1H), 4.04 - 3.96 (m, 1H), 3.86 - 3.76 (m, 1H), 3.19 - 3.07 (m, 2H), 2.36 - 2.25 (m, 1H), 2.17 - 2.03 (m, 3H), 2.02 - 1.92 (m, 3H), 1.91 - 1.79 (m, 3H)
544	(fluoro(2-(((3S,6S,9aS)-3-(3-(5-fluoroquinolin-6-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-		668.7	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 - 8.94 (m, 1H), 8.79 (m, 1H), 8.50 (m, 1H), 8.31 - 8.23 (m, 1H), 8.07 - 8.02 (m, 1H), 8.00 (s, 1H), 7.96 - 7.90 (m, 2H),

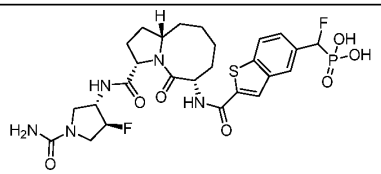
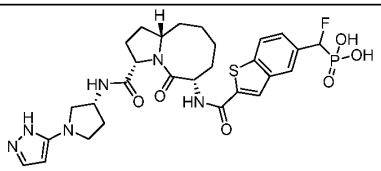
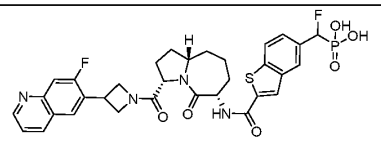
	yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			7.69 - 7.61 (m, 1H), 7.54 (d, J = 8.8 Hz, 1H), 5.92 - 5.77 (m, 1H), 4.74 - 4.64 (m, 2H), 4.49 (m , 2H), 4.41 - 4.35 (m, 2H), 4.06 - 4.02 (m, 2H), 2.26 - 2.19 (m, 1H), 2.06 - 1.96 (m, 2H), 1.89 - 1.81 (m, 3H), 1.79 - 1.67 (m, 4H)
545	((2-(((3S,6S,9aS)-3-(3-(4-formylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		611.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.95 (d, J = 13.2 Hz, 1H), 8.81 (dd, J = 4.8, 8.8 Hz, 1H), 8.75 - 8.67 (m, 1H), 8.22 - 8.12 (m, 1H), 7.95 - 7.86 (m, 1H), 7.83 - 7.75 (m, 2H), 7.42 - 7.30 (m, 1H), 4.71 - 4.26 (m, 6H), 4.09 - 4.00 (m, 2H), 3.14 - 3.06 (m, 2H), 2.24 - 2.14 (m, 1H), 2.09 - 1.91 (m, 2H), 1.90 - 1.75 (m, 4H), 1.75 - 1.59 (m, 3H)
546	((2-(((3S,6S,9aS)-3-(3-(4-(1,3-dioxolan-2-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		655.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 - 8.65 (m, 2H), 8.53 (dd, J = 4.8, 8.8 Hz, 1H), 8.22 - 8.10 (m, 1H), 7.90 (dd, J = 4.8, 8.4 Hz, 1H), 7.81 - 7.76 (m, 1H), 7.43 (t, J = 5.2 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 5.89 (d, J = 2.4 Hz, 1H), 4.79 - 4.54 (m, 2H), 4.50 - 4.43 (m, 1H), 4.34 - 4.22 (m, 2H), 4.22 - 4.10 (m, 1H), 4.06 - 3.93 (m, 6H), 3.12 (s, 1H), 3.06 (s, 1H), 2.25 - 2.15 (m, 1H), 2.09 - 1.93 (m, 2H), 1.89 - 1.82 (m, 2H), 1.81 - 1.74 (m, 2H), 1.74 -

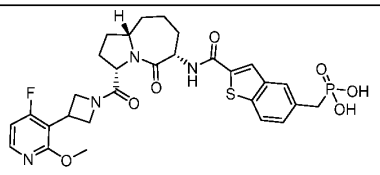
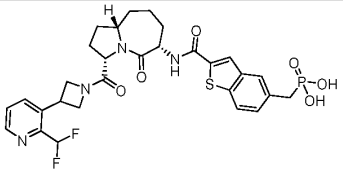
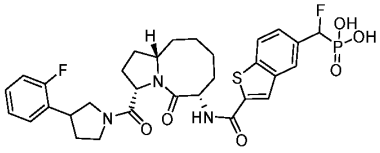
				1.65 (m, 2H), 1.29 - 1.23 (m, 1H)
547	(difluoro(2-(((3S,6S,9aS)-3-(3-methyl-3-(pyridin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		633.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.71 - 8.36 (m, 1H), 8.28 - 8.13 (m, 2H), 8.12 - 8.02 (m, 1H), 8.01 - 7.89 (m, 1H), 7.80 (dd, J = 8.0, 14.8 Hz, 1H), 7.73 - 7.50 (m, 2H), 4.85 - 4.64 (m, 2H), 4.60 - 4.31 (m, 3H), 4.18 - 3.98 (m, 2H), 2.41 - 2.25 (m, 1H), 2.23 - 2.00 (m, 3H), 2.00 - 1.78 (m, 6H), 1.78 - 1.70 (m, 3H)
548	((2-(((3S,6S,9aS)-3-(3-methyl-3-(pyridin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		597.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.69 - 8.56 (m, 1H), 8.19 - 8.08 (m, 1H), 8.07 - 7.94 (m, 1H), 7.91 - 7.81 (m, 2H), 7.78 - 7.65 (m, 1H), 7.60 - 7.51 (m, 1H), 7.49 - 7.39 (m, 1H), 4.88 - 4.66 (m, 2H), 4.64 - 4.31 (m, 3H), 4.17 - 3.98 (m, 2H), 3.31 - 3.18 (m, 2H), 2.42 - 2.26 (m, 1H), 2.24 - 2.01 (m, 3H), 2.01 - 1.80 (m, 6H), 1.77 (d, J = 2.4 Hz, 3H)
549	((2-(((3S,6S,10aS)-3-((1-carbamoylazetidin-3-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		596.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.10 - 8.01 (m, 2H), 7.92 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 5.84 - 5.71 (m, 1H), 5.04 - 5.00 (m, 1H), 4.54 - 4.49 (m, 1H), 4.40 - 4.36 (m, 2H), 4.24 - 4.19 (m, 2H), 3.87 - 3.77 (m, 2H), 2.27 - 2.21 (m, 2H), 2.04 - 1.67 (m, 10H)

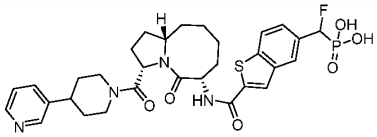
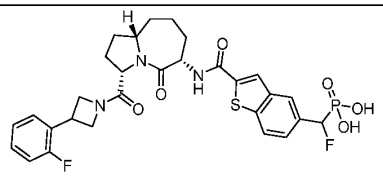
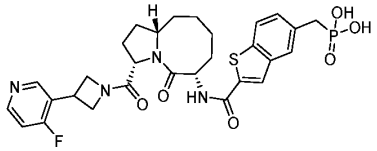
550	((6-(((3S,6S,9aS)-3-(3-(4-ethylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-2-yl)methyl)phosphonic acid		611.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.79 (d, *J* = 10.8 Hz, 1H), 8.57 (dd, *J* = 6.0, 15.6 Hz, 1H), 8.40 - 8.24 (m, 1H), 7.88 - 7.68 (m, 3H), 7.27 (dd, *J* = 3.6, 6.8 Hz, 1H), 4.86 - 4.69 (m, 2H), 4.67 - 4.49 (m, 2H), 4.48 - 4.26 (m, 2H), 4.18 - 4.03 (m, 2H), 3.50 - 3.37 (m, 2H), 2.91 - 2.72 (m, 2H), 2.42 - 2.27 (m, 1H), 2.23 - 1.95 (m, 5H), 1.95 - 1.76 (m, 4H), 1.37 - 1.22 (m, 3H)
551	((2-(((4S,7S,10aS)-4-((*rel-trans*)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-6-oxodecahydropyrido[1,2-a]azepin-7-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		653.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.13 - 8.02 (m, 2H), 7.94 (dd, J = 3.2, 8.4 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.50 - 7.28 (m, 5H), 5.91 - 5.68 (m, 1H), 5.09 (dd, J = 4.4, 9.2 Hz, 1H), 5.01 - 4.97 (m, 1H), 4.18 (d, J = 10.0 Hz, 1H), 4.12 - 3.99 (m, 1H), 3.96 - 3.67 (m, 2H), 3.66 - 3.52 (m, 2H), 3.51 - 3.39 (m, 1H), 2.56 - 2.40 (m, 1H), 2.11 - 2.01 (m, 2H), 2.00 - 1.86 (m, 4H), 1.82 - 1.68 (m, 3H), 1.64 - 1.48 (m, 2H)
552	((2-(((4S,7S,11aS)-4-((*rel-trans*)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-6-oxodecahydro-2H-pyrido[1,2-a]azocin-7-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		667.0	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 - 8.69 (m, 1H), 8.33 - 8.23 (m, 1H), 8.09 - 7.91 (m, 2H), 7.56 - 7.48 (m, 1H), 7.48 - 7.36 (m, 4H), 7.35 - 7.28 (m, 1H), 5.95 - 5.71 (m, 1H), 5.09 - 4.98 (m, 1H), 4.93 - 4.81 (m, 1H), 4.41 - 4.22 (m, 2H), 4.20 -

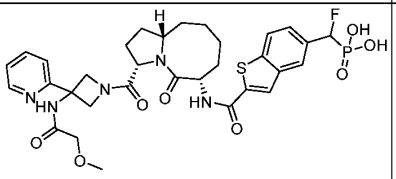
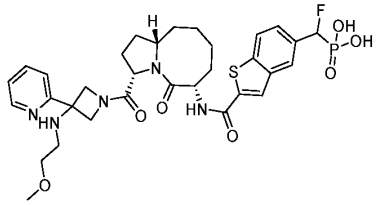
				4.06 (m, 1H), 4.04 - 3.84 (m, 2H), 3.83 - 3.77 (m, 1H), 3.24 (d, J = 10.8 Hz, 1H), 1.95 - 1.73 (m, 6H), 1.73 - 1.55 (m, 4H), 1.55 - 1.40 (m, 3H), 1.39 - 1.27 (m, 1H)
553	((2-(((1R,3S,6S,11aS)-3-((*rel-trans*)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-1-hydroxy-5-oxodecahydro-1H-pyrrolo[1,2-a]azonin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		683.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.12 - 8.07 (m, 1H), 8.02 (s, 1H), 7.97 - 7.88 (m, 1H), 7.62 - 7.56 (m, 1H), 7.46 - 7.27 (m, 5H), 5.91 - 5.71 (m, 1H), 5.19 - 5.10 (m, 1H), 4.92 (s, 1H), 4.24 - 4.12 (m, 3H), 4.11 - 3.74 (m, 2H), 3.73 - 3.39 (m, 3H), 2.30 - 2.18 (m, 1H), 2.16 - 2.02 (m, 3H), 2.02 - 1.89 (m, 2H), 1.88 - 1.72 (m, 3H), 1.70 - 1.50 (m, 3H)
554	((2-(((3S,6S,10aS)-3-(((3S,4S)-1-(cyclopropoxycarbonyl)-4-fluoropyrrolidin-3-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		669.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (s, 1H), 8.01 (s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 5.91 - 5.73 (m, 1H), 5.05 - 5.00 (m, 1H), 4.92 (s, 1H), 4.45 - 4.31 (m, 3H), 4.05 - 4.00 (m, 1H), 3.68 (s, 1H), 3.61 (d, J = 6.0 Hz, 1H), 3.57 - 3.52 (m, 1H), 3.50 - 3.39 (m, 1H), 2.26 - 2.16 (m, 2H), 2.07 - 1.92 (m, 6H), 1.84 – 1.80 (m, 2H), 1.73 - 1.58 (m, 2H), 0.67 (s, 4H)
555	(fluoro(2-(((3S,6S,10aS)-3-(((3S,4S)-4-fluoro-1-(3-methylpyridin-2-yl)pyrrolidin-3-yl)carbamoyl)-5-		676.0	^{1}H NMR (400 MHz, CD_3OD) δ 7.96 - 7.83 (m, 2H), 7.73 (d, J =4.0 Hz, 1H), 7.66 - 7.46 (m, 3H), 6.70 (q, J = 7.2 Hz, 1H), 5.83

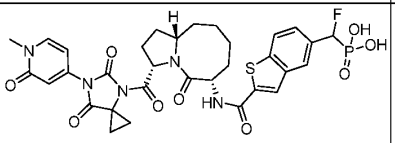
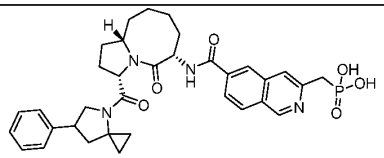
	oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			- 5.65 (m, 1H), 5.32 - 5.14 (m, 1H), 4.97 (d, J = 6.0 Hz, 1H), 4.65 - 4.61 (m, 1H), 4.46 - 4.17 (m, 4H), 4.07 - 3.84 (m, 2H), 2.48 - 2.39 (m, 3H), 2.36 - 2.17 (m, 2H), 2.14 - 1.90 (m, 6H), 1.87 - 1.83 (m, 2H), 1.76 - 1.57 (m, 2H)
556	((2-(((3S,6S,9aS)-3-(3-(4-fluoro-6-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		631.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.30 - 8.10 (m, 1H), 8.02 (d, *J* = 3.2 Hz, 1H), 7.91 - 7.75 (m, 2H), 7.43 (d, *J* = 6.8 Hz, 1H), 6.61 (d, *J* = 11.6 Hz, 1H), 4.75 (d, *J* = 11.2 Hz, 1H), 4.65 (d, *J* = 8.0 Hz, 1H), 4.57 (d, *J* = 3.6 Hz, 1H), 4.48 - 4.34 (m, 2H), 4.17 - 4.03 (m, 3H), 3.96 - 3.83 (m, 3H), 3.28 (d, *J* = 2.4 Hz, 1H), 3.23 (s, 1H), 2.40 - 2.21 (m, 1H), 2.18 - 1.62 (m, 9H)
557	((2-(((3S,6S,9aS)-3-(3-(4-cyanopyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		626.1	^{1}H NMR (400 MHz, CD_3OD) δ 9.18 - 8.87 (m, 1H), 8.69 (d, J = 4.4 Hz, 1H), 8.14 - 8.03 (m, 2H), 7.99 - 7.92 (m, 1H), 7.74 (dd, J = 4.8, 18.8 Hz, 1H), 7.59 (dd, J = 1.6, 8.4 Hz, 1H), 5.94 - 5.72 (m, 1H), 4.80 - 4.74 (m, 2H), 4.68 - 4.44 (m, 3H), 4.41 - 4.31 (m, 1H), 4.23 (dd, J = 6.4, 9.2 Hz, 1H), 4.13 - 4.03 (m, 1H), 2.38 - 2.25 (m, 1H), 2.20 - 1.99 (m, 5H), 1.95 - 1.78 (m, 4H)

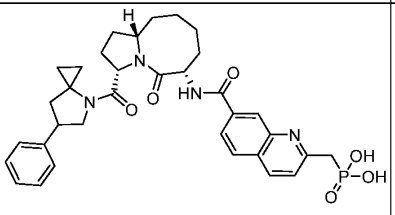
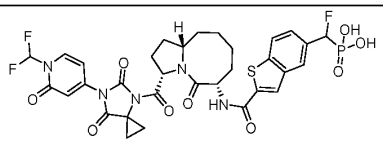
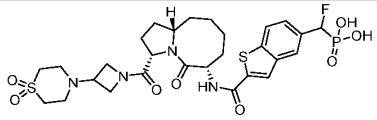
558	((2-(((3S,6S,10aS)-3-(((3S,4S)-1-carbamoyl-4-fluoropyrrolidin-3-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		628.0	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 - 8.79 (m, 1H), 8.38 (d, J = 7.2 Hz, 1H), 8.26 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 7.52 (d, J = 8.4 Hz, 1H), 5.91 (s, 1H), 5.91 - 5.89 (m, 1H), 5.89 - 5.74 (m, 1H), 5.03 - 4.88 (m, 2H), 4.31 - 4.22 (m, 3H), 3.53 (s, 2H), 3.45 (m, 1H), 3.28 - 3.23 (m, 1H), 2.12 - 2.00 (m, 2H), 1.99 - 1.77 (m, 6H), 1.75 - 1.63 (m, 2H), 1.62 - 1.48 (m, 2H)
559	((2-(((3S,6S,10aS)-3-(((R)-1-(1H-pyrazol-5-yl)pyrrolidin-3-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		633.6	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (d, J = 7.2 Hz, 1H), 8.29 - 8.24 (m, 2H), 8.03 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 7.54 - 7.46 (m, 2H), 5.90 - 5.74 (m, 1H), 5.52 (d, J = 2.0 Hz, 1H), 4.96 - 4.89 (m, 1H), 4.29 - 4.23 (m, 2H), 3.42 - 3.39 (m, 1H), 3.33 - 3.28 (m, 1H), 3.17 (d, J = 6.0 Hz, 1H), 3.01 (dd, J = 4.4, 10.0 Hz, 1H), 2.17 - 2.03 (m, 3H), 1.89 - 1.76 (m, 6H), 1.72 - 1.45 (m, 5H)
560	(fluoro(2-(((3S,6S,9aS)-3-(3-(7-fluoroquinolin-6-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		668.9	^{1}H NMR (400 MHz, CD_3OD) δ 8.60 - 8.37 (m, 2H), 8.17 (s, 1H), 7.91 - 7.52 (m, 5H), 7.30 - 7.20 (m, 1H), 5.90 - 5.72 (m, 1H), 5.02 - 4.90 (m, 1H), 4.79 - 4.68 (m, 2H), 4.61 - 4.47 (m, 2H), 4.40 - 4.24 (m, 1H), 4.20 - 4.03 (m, 2H), 2.39 - 2.26 (m, 1H),

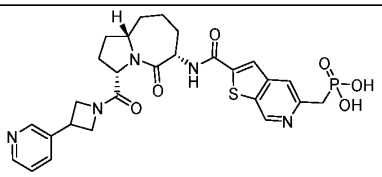
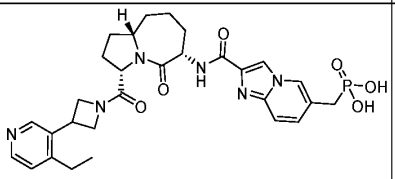
				2.20 - 2.02 (m, 3H), 2.01 - 1.87 (m, 4H), 1.86 - 1.74 (m, 2H)
561	((2-(((3S,6S,9aS)-3-(3-(4-fluoro-2-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		631.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.07 - 7.98 (m, 2H), 7.85 - 7.82 (m, 2H), 7.43 - 7.41 (m, 1H), 6.83 - 6.75 (m, 1H), 4.77 - 4.71 (m, 2H), 4.60 - 4.55 (m, 2H), 4.29 - 4.23 (m, 3H), 4.00 - 3.98 (m, 4H), 3.28 - 3.22 (m, 2H), 2.31 - 2.13 (m, 1H), 2.00 - 1.83 (m, 9H)
562	((2-(((3S,6S,9aS)-3-(3-(2-(difluoromethyl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		632.9	^{1}H NMR (400 MHz, CD_3OD) δ 8.57 - 8.45 (m, 1H), 8.41 (d, J = 4.0 Hz, 1H), 8.02 (s, 1H), 7.89 - 7.81 (m, 2H), 7.67 - 7.52 (m, 1H), 7.47 - 7.40 (m, 1H), 6.95 - 6.81 (m, 1H), 4.96 - 4.90 (m, 1H), 4.75 (d, J = 24.0 Hz, 1H), 4.71 - 4.53 (m, 2H), 4.50 - 4.44 (m, 1H), 4.42 - 4.29 (m, 1H), 4.12 - 4.01 (m, 2H), 3.29 (s, 1H), 3.23 (s, 1H), 2.40 - 2.24 (m, 1H), 2.20 - 2.06 (m, 2H), 2.05 - 1.93 (m, 3H), 1.93 - 1.76 (m, 4H)
563	(fluoro(2-(((3S,6S,10aS)-3-(3-(2-fluorophenyl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		646.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 - 8.06 (m, 1H), 8.00 (s, 1H), 7.95 - 7.88 (m, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.42 - 7.19 (m, 2H), 7.18 - 6.99 (m, 2H), 5.94 - 5.70 (m, 1H), 5.05 (t, J = 8.8 Hz, 1H), 4.77 - 4.67 (m, 1H), 4.44 (m, 1H), 4.12 - 3.94 (m, 1H), 3.93 - 3.81 (m, 1H), 3.80 - 3.71 (m,

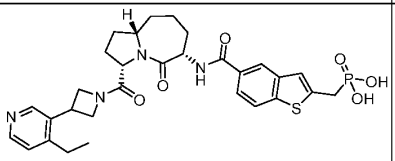
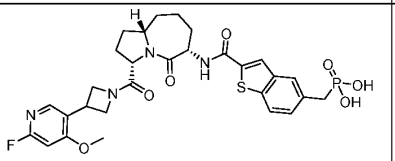
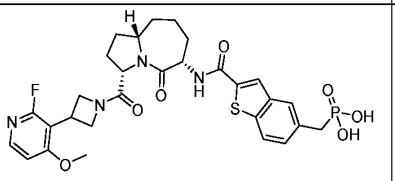
				1H), 3.64 (m, 1H), 3.57 (s, 1H), 2.40 - 2.14 (m, 4H), 2.11 - 1.93 (m, 6H), 1.90 - 1.74 (m, 2H), 1.72 - 1.54 (m, 2H)
564	(fluoro(2-(((3S,6S,10aS)-5-oxo-3-(4-(pyridin-3-yl)piperidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		643.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.62 - 8.44 (m, 2H), 8.41 (d, J = 8.0 Hz, 1H), 8.06 - 7.99 (m, 1H), 7.98 - 7.91 (m, 1H), 7.90 - 7.74 (m, 2H), 7.66 - 7.51 (m, 1H), 5.90 - 5.65 (m, 1H), 5.10 - 4.90 (m, 3H), 4.70 - 4.62 (m, 1H), 4.52 - 4.41 (m, 1H), 4.36 - 4.23 (m, 1H), 3.17 - 3.01 (m, 1H), 2.87 - 2.80 (m, 1H), 2.43 - 2.15 (m, 3H), 2.13 - 1.93 (m, 6H), 1.92 - 1.80 (m, 4H), 1.76 - 1.56 (m, 3H)
565	(fluoro(2-(((3S,6S,9aS)-3-(3-(2-fluorophenyl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		618.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.09 - 7.99 (m, 2H), 7.94 (t, J = 8.0 Hz, 1H), 7.61 - 7.39 (m, 2H), 7.34 - 7.23 (m, 1H), 7.23 - 7.14 (m, 1H), 7.14 - 7.02 (m, 1H), 5.90 - 5.74 (m, 1H), 4.94 - 4.90 (m, 1H), 4.77 - 4.71 (m, 1H), 4.69 - 4.55 (m, 2H), 4.41 - 4.32 (m, 1H), 4.26 - 4.13 (m, 1H), 4.12 - 3.99 (m, 2H), 2.35 - 2.26 (m, 1H), 2.18 - 2.05 (m, 2H), 2.03 - 1.77 (m, 7H)
566	((2-(((3S,6S,10aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-		615.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.78 - 8.58 (m, 1H), 8.54 - 8.42 (m, 1H), 8.08 - 7.99 (m, 1H), 7.85 - 7.77 (m, 2H), 7.44 - 7.38 (m, 1H), 7.31 - 7.19

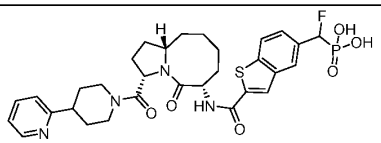
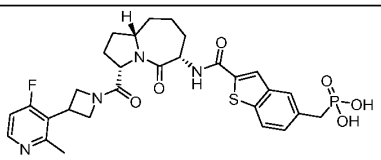
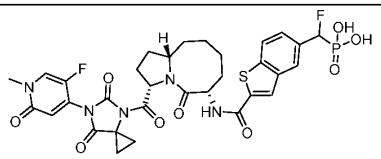
	yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			(m, 1H), 5.06 - 4.99 (m, 1H), 4.99 - 4.89 (m, 1H), 4.76 - 4.66 (m, 1H), 4.52 - 4.46 (m, 1H), 4.45 - 4.36 (m, 2H), 4.20 (q, J = 6.4 Hz, 1H), 4.17 - 4.09 (m, 1H), 3.26 - 3.18 (m, 2H), 2.32 - 2.19 (m, 2H), 2.08 - 1.92 (m, 6H), 1.89 - 1.77 (m, 2H), 1.73 - 1.60 (m, 2H)
567	(fluoro(2-(((3S,6S,10aS)-3-(3-(2-methoxyacetamido)-3-(pyridin-2-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		702.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.65 - 8.46 (m, 1H), 8.10 - 8.03 (m, 1H), 7.99 (d, J = 5.6 Hz, 1H), 7.92 (s, 1H), 7.83 - 7.73 (m, 1H), 7.59 (d, J = 7.2 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.32 (dd, J = 4.4, 7.1 Hz, 1H), 5.90 - 5.71 (m, 1H), 5.02 (dd, J = 5.6, 10.6 Hz, 1H), 4.95 (d, J = 9.2 Hz, 1H), 4.80 - 4.76 (m, 1H), 4.54 - 4.45 (m, 2H), 4.44 - 4.35 (m, 2H), 3.95 (d, J = 12.8 Hz, 2H), 3.47 (s, 3H), 2.35 - 2.21 (m, 2H), 2.10 - 1.94 (m, 6H), 1.90 - 1.78 (m, 2H), 1.73 - 1.59 (m, 2H)
568	(fluoro(2-(((3S,6S,10aS)-3-(3-((2-methoxyethyl)amino)-3-(pyridin-2-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		688.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 - 8.76 (m, 1H), 8.59 (dd, J = 4.8, 11.2 Hz, 1H), 8.31 - 8.18 (m, 1H), 8.00 (t, J = 8.0 Hz, 1H), 7.94 (d, J = 14.4 Hz, 1H), 7.90 - 7.81 (m, 1H), 7.63 (dd, J = 7.6, 16 Hz, 1H), 7.49 (d, J = 6.0 Hz, 1H), 7.40 - 7.31 (m, 1H), 5.77 - 5.61 (m, 1H), 4.93 (dd, J =

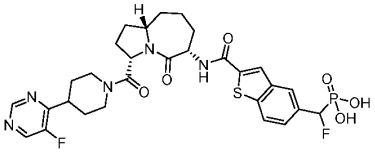
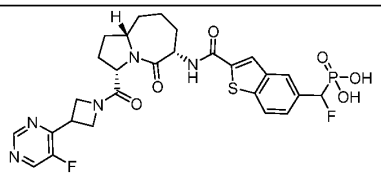
				4.8, 11.0 Hz, 1H), 4.75 - 4.56 (m, 1H), 4.48 (d, J = 7.6 Hz, 1H), 4.35 - 4.18 (m, 4H), 4.04 - 3.95 (m, 2H), 3.35 (d, J = 4.8 Hz, 2H), 3.19 (d, J = 7.6 Hz, 3H), 2.48 - 2.44 (m, 1H), 2.23 - 2.01 (m, 2H), 1.94 - 1.77 (m, 6H), 1.76 - 1.65 (m, 2H), 1.63 - 1.46 (m, 2H)
569	(fluoro(2-(((3S,6S,10aS)-3-(6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		714.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (d, J = 7.2 Hz, 1H), 8.26 (s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.97 (s, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 6.56 (d, J = 2.0 Hz, 1H), 6.42 (dd, J = 2.0, 7.2 Hz, 1H), 5.92 - 5.71 (m, 1H), 5.35 (t, J = 8.4 Hz, 1H), 4.94 (d, J = 6.4 Hz, 1H), 4.41 - 4.30 (m, 1H), 3.44 (s, 3H), 2.42 (d, J = 5.6 Hz, 1H), 2.24 - 2.16 (m, 1H), 2.11 - 2.04 (m, 1H), 1.95 - 1.82 (m, 5H), 1.80 - 1.65 (m, 4H), 1.60 - 1.49 (m, 1H), 1.36 (d, J = 4.4 Hz, 2H), 1.29 - 1.21 (m, 1H)
570	((6-(((3S,6S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)isoquinolin-3-yl)methyl)phosphonic acid		631.2	^{1}H NMR (400 MHz, CD_3OD) δ 9.49 (d, J = 8.0 Hz, 1H), 8.59 - 8.47 (m, 1H), 8.29 - 8.19 (m, 2H), 8.18 - 8.09 (m, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.25 (d, J = 4.4 Hz, 2H), 7.22 - 7.06 (m, 2H), 5.16 - 5.04 (m, 1H), 4.76 - 4.64 (m, 1H), 4.56 - 4.38 (m, 2H), 4.19 - 3.90 (m, 1H),

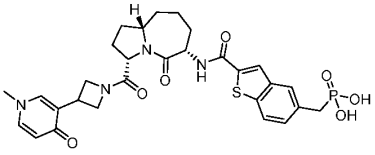
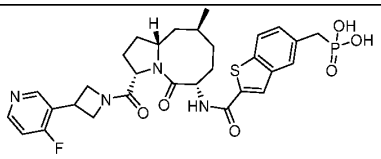
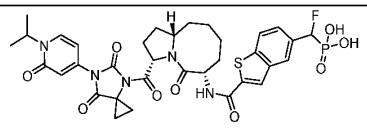
				3.65 - 3.52 (m, 3H), 2.42 - 2.16 (m, 4H), 2.08 - 1.93 (m, 7H), 1.90 - 1.76 (m, 3H), 1.69 - 1.60 (m, 2H), 0.60 - 0.50 (m, 2H)
571	((7-(((3S,6S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)quinolin-2-yl)methyl)phosphonic acid		631.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.75 (d, J = 4.8 Hz, 1H), 8.41 (d, J = 14.8 Hz, 1H), 8.20 - 8.05 (m, 2H), 7.97 (d, J = 8.4 Hz, 1H), 7.42 - 7.03 (m, 5H), 5.10 - 5.05 (m, 1H), 4.75 - 4.68 (m, 2H), 4.56 - 4.39 (m, 2H), 4.16 - 3.93 (m, 1H), 3.75 - 3.51 (m, 2H), 2.43 - 2.18 (m, 4H), 2.17 - 1.96 (m, 7H), 1.90 - 1.75 (m, 3H), 1.71 - 1.59 (m, 2H), 0.66 - 0.44 (m, 2H)
572	((2-(((3S,6S,10aS)-3-(6-(1-(difluoromethyl)-2-oxo-1,2-dihydropyridin-4-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		750.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (d, *J* = 6.8 Hz, 1H), 8.25 (s, 1H), 8.04 - 7.94 (m, 3H), 7.92 - 7.65 (m, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 6.71 (s, 1H), 6.69 - 6.64 (m, 1H), 5.86 - 5.68 (m, 1H), 5.34 (t, *J* = 8.8 Hz, 1H), 4.97 - 4.89 (m, 1H), 4.36 (t, *J* = 8.8 Hz, 1H), 2.47 - 2.41 (m, 1H), 2.36 - 2.32 (m, 1H), 2.23 - 2.15 (m, 1H), 2.10 - 2.05 (m, 1H), 1.94 - 1.83 (m, 5H), 1.80 - 1.66 (m, 4H), 1.60 - 1.51 (m, 1H), 1.42 - 1.34 (m, 2H)
573	((2-(((3S,6S,10aS)-3-(3-(1,1-dioxidothiomorpholino)azetidine-1-carbonyl)-5-		671.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 – 8.81 (m, 1H), 8.31 - 8.11 (m, 1H), 8.02 - 7.77 (m, 2H), 7.52 –

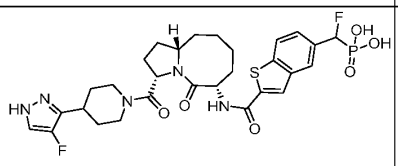
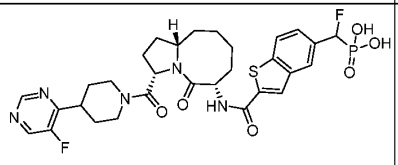
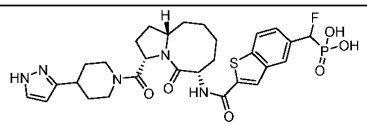
	oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid			7.49 (m, 1H), 7.39 - 7.20 (m, 1H), 5.56 - 5.36 (m, 1H), 4.91 (d, J = 7.2 Hz, 1H), 4.30 - 4.17 (m, 3H), 4.02 - 3.90 (m, 2H), 3.82 - 3.78 (m, 1H), 3.70 (s, 1H), 3.65 - 3.62 (m, 1H), 3.40 (d, J = 6.4 Hz, 1H), 3.13 - 3.07 (m, 3H), 2.81 - 2.72 (m, 3H), 2.19 - 2.09 (m, 1H), 2.09 - 1.97 (m, 1H), 1.97 - 1.68 (m, 7H), 1.68 - 1.41 (m, 3H)
574	((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)thieno[2,3-c]pyridin-5-yl)methyl)phosphonic acid		584.1	^{1}H NMR (400 MHz, CD_3OD) δ 9.40 (s, 1H), 8.83 (s, 1H), 8.74 - 8.50 (m, 2H), 8.26 (d, J = 6.0 Hz, 2H), 7.99 - 7.82 (m, 1H), 4.83 - 4.72 (m, 2H), 4.65 - 4.52 (m, 2H), 4.51 - 4.34 (m, 1H), 4.21 - 4.05 (m, 3H), 3.58 - 3.46 (m, 2H), 2.39 - 2.28 (m, 1H), 2.22 - 2.09 (m, 2H), 2.07 - 2.00 (m, 2H), 2.00 - 1.95 (m, 1H), 1.95 - 1.80 (m, 4H)
575	((2-(((3S,6S,9aS)-3-(3-(4-ethylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)methyl)phosphonic acid		595.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.88 - 9.13 (m, 1H), 8.64 - 8.72 (m, 1H), 8.40 - 8.60 (m, 2H), 7.87 - 7.99 (m, 1H), 7.60 - 7.78 (m, 2H), 4.66 - 4.85 (m, 3H), 4.58 (m, 1H), 4.45 - 4.54 (m, 1H), 4.35 - 4.44 (m, 1H), 4.04 - 4.21 (m, 2H), 3.13 - 3.25 (m, 2H), 2.90 (m, 2H), 2.28 - 2.38 (m, 1H), 2.12 - 2.21 (m, 1H), 1.91 - 2.10 (m, 5H),

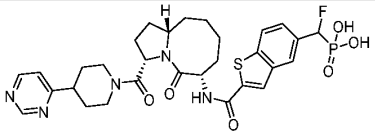
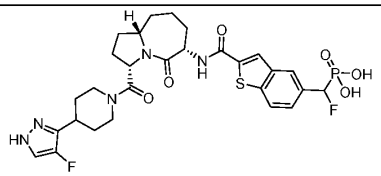
				1.84 (s, 3H), 1.32 (m, 3H)
576	((5-(((3S,6S,9aS)-3-(3-(4-ethylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-2-yl)methyl)phosphonic acid		611.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.82 - 8.67 (m, 1H), 8.50 (t, J = 5.6 Hz, 1H), 8.23 - 8.14 (m, 1H), 7.87 - 7.79 (m, 1H), 7.78 - 7.64 (m, 2H), 7.29 (s, 1H), 4.69 - 4.62 (m, 1H), 4.60 - 4.50 (m, 2H), 4.48 - 4.40 (m, 1H), 4.38 - 4.25 (m, 2H), 4.16 - 4.08 (m, 2H), 3.41 - 3.35 (m, 2H), 2.83 - 2.72 (m, 2H), 2.38 - 2.28 (m, 1H), 2.22 - 2.12 (m, 1H), 2.04 - 1.90 (m, 5H), 1.84 (t, J = 13.2 Hz, 3H), 1.41 - 1.34 (m, 3H)
577	((2-(((3S,6S,9aS)-3-(3-(6-fluoro-4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		630.9	^{1}H NMR (400 MHz, CD_3OD) δ 8.03 - 7.93 (m, 2H), 7.85 (s, 2H), 7.43 (d, J = 8.2 Hz, 1H), 6.73 (d, J = 15.6 Hz, 1H), 4.83 - 4.78 (m, 1H), 4.77 - 4.70 (m, 1H), 4.68 - 4.55 (m, 2H), 4.39 (t, J = 8.2 Hz, 1H), 4.31 (t, J = 9.2 Hz, 1H), 4.18 - 4.10 (m, 2H), 3.97 (d, J = 1.2 Hz, 3H), 3.29 - 3.21 (m, 2H), 2.34 - 2.27 (m, 1H), 1.98 - 1.83 (m, 9H)
578	((2-(((3S,6S,9aS)-3-(3-(2-fluoro-4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		630.9	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 - 7.80 (m, 1H), 7.71 - 7.43 (m, 3H), 7.23 - 7.07 (m, 1H), 6.73 - 6.40 (m, 1H), 4.62 (d, J = 3.2 Hz, 2H), 4.49 (s, 2H), 4.42 - 4.25 (m, 4H), 4.16 - 4.09 (m, 1H), 3.93 (d, J = 14.4 Hz, 1H), 3.81 (s, 1H), 3.73 (s, 1H), 3.15 -

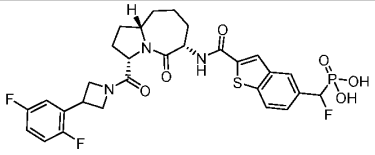
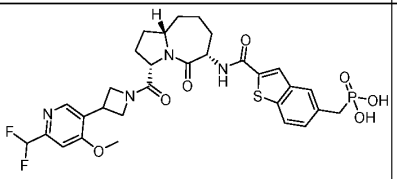
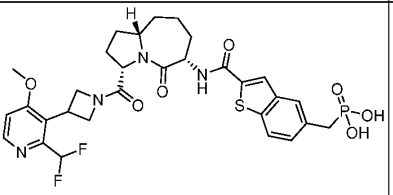
				3.01 (m, 1H), 2.22 (d, J = 7.6 Hz, 1H), 2.10 - 1.79 (m, 6H), 1.78 - 1.62 (m, 2H), 1.36 - 1.21 (m, 1H)
579	(fluoro(2-(((3S,6S,10aS)-5-oxo-3-(4-(pyridin-2-yl)piperidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		643.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.72 - 8.27 (m, 2H), 8.08 - 8.02 (m, 1H), 8.01 - 7.66 (m, 4H), 7.60 - 7.51 (m, 1H), 5.92 - 5.65 (m, 1H), 5.09 - 4.92 (m, 2H), 4.67 (m, 1H), 4.50 - 4.26 (m, 2H), 3.30 - 3.23 (m, 2H), 2.81 (m, 1H), 2.39 - 2.14 (m, 3H), 2.12 - 1.91 (m, 8H), 1.90 - 1.74 (m, 3H), 1.73 - 1.61 (m, 2H)
580	((2-(((3S,6S,9aS)-3-(3-(4-fluoro-2-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		615.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (t, J = 6.6 Hz, 1H), 8.37 - 8.31 (m, 1H), 8.16 (d, J = 7.2 Hz, 1H), 7.90 (dd, J = 3.2, 8.4 Hz, 1H), 7.78 (s, 1H), 7.35 (d, J = 6.8 Hz, 1H), 7.21 - 7.13 (m, 1H), 4.77 - 4.62 (m, 2H), 4.57 - 4.50 (m, 1H), 4.48 - 4.45 (m, 1H), 4.39 - 4.25 (m, 2H), 4.23 - 4.15 (m, 2H), 3.11 (s, 1H), 3.06 (s, 2H), 2.47 (s, 3H), 2.20 (d, J = 6.6 Hz, 1H), 2.03 - 1.94 (m, 2H), 1.84 - 1.66 (m, 7H)
581	(fluoro(2-(((3S,6S,10aS)-3-(6-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrol		731.9	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (d, J = 6.8 Hz, 1H), 8.28 - 8.20 (m, 2H), 8.03 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 7.53 (m, 1H), 6.68 (d, J = 6.8 Hz, 1H), 5.92 - 5.74 (m, 1H), 5.31 (m,

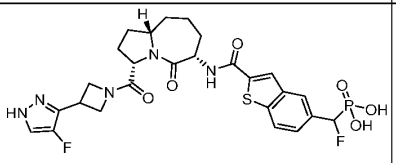
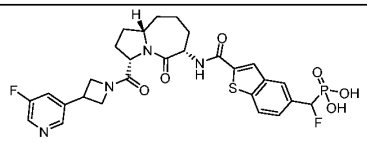
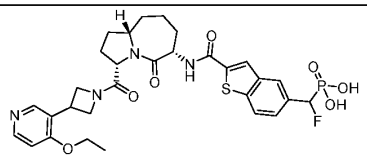
	o[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			1H), 4.93 (m, 1H), 4.37 - 4.32 (m, 1H), 3.43 (s, 3H), 2.36 (m, 2H), 2.22 - 2.14 (m, 1H), 2.09 (m, 1H), 1.95 - 1.82 (m, 5H), 1.80 - 1.69 (m, 3H), 1.66 (s, 1H), 1.61 - 1.52 (m, 1H), 1.45 - 1.36 (m, 2H)
582	(fluoro(2-(((3S,6S,9aS)-3-(4-(5-fluoropyrimidin-4-yl)piperidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		647.9	^{1}H NMR (400 MHz, CD_3OD) δ 8.93 (s, 1H), 8.76 - 8.53 (m, 1H), 8.05 (d, J = 6.0 Hz, 2H), 7.87 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 5.77 - 5.54 (m, 1H), 5.18 - 5.02 (m, 1H), 4.73 (d, J = 9.6 Hz, 1H), 4.61 (t, J = 11.2 Hz, 1H), 4.21 (t, J = 8.0 Hz, 1H), 4.12 - 4.03 (m, 1H), 3.49 - 3.35 (m, 2H), 2.96 - 2.82 (m, 1H), 2.38 - 2.27 (m, 1H), 2.24 - 2.14 (m, 1H), 2.06 - 2.01 (m, 3H), 1.91 (d, J = 3.2 Hz, 7H), 1.86 - 1.76 (m, 2H)
583	(fluoro(2-(((3S,6S,9aS)-3-(3-(5-fluoropyrimidin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		620.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 - 9.06 (m, 1H), 8.82 - 8.75 (m, 2H), 8.24 (d, J = 12.4 Hz, 1H), 8.05 - 7.96 (m, 2H), 7.53 (d, J = 8.4 Hz, 1H), 5.89 - 5.76 (m, 1H), 4.66 - 4.55 (m, 2H), 4.45 (d, J = 4.0 Hz, 1H), 4.30 - 4.14 (m, 3H), 4.07 - 3.98 (m, 2H), 2.22 - 2.16 (m, 1H), 2.02 - 1.93 (m, 2H), 1.85 - 1.72 (m, 7H)

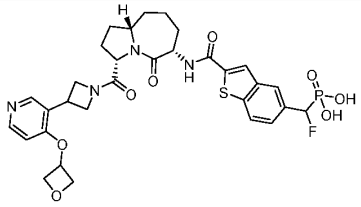
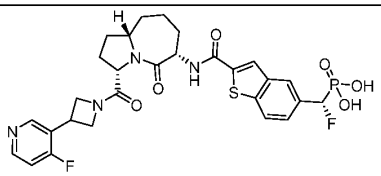
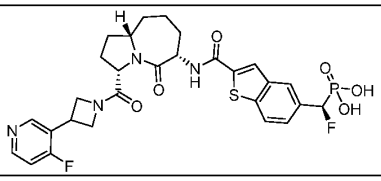
584	((2-(((3S,6S,9aS)-3-(3-(1-methyl-4-oxo-1,4-dihydropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		613.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.47 - 8.26 (m, 1H), 8.06 - 7.50 (m, 4H), 7.47 - 7.32 (m, 1H), 6.70 - 6.29 (m, 1H), 4.84 - 4.68 (m, 2H), 4.61 - 4.54 (m, 1H), 4.52 - 4.30 (m, 2H), 4.20 (s, 1H), 4.14 - 3.98 (m, 3H), 3.84 (d, J = 8.0 Hz, 2H), 3.28 - 3.18 (m, 2H), 2.39 - 2.25 (m, 1H), 2.20 - 2.08 (m, 2H), 2.08 - 1.90 (m, 4H), 1.89 - 1.70 (m, 3H)
585	((2-(((3S,6S,9S,10aR)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-9-methyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		629.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 - 8.53 (m, 3H), 8.18 (d, J = 10.4 Hz, 1H), 7.90 (m, 1H), 7.81 - 7.73 (m, 1H), 7.45 - 7.30 (m, 2H), 4.89 - 4.53 (m, 3H), 4.33 (d, J = 10.4 Hz, 2H), 4.24 (s, 1H), 4.12 - 4.06 (m, 2H), 3.13 - 3.05 (m, 2H), 2.27 - 2.18 (m, 1H), 2.03 - 1.81 (m, 5H), 1.76 - 1.59 (m, 4H), 1.31 - 1.20 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H)
586	(fluoro(2-(((3S,6S,10aS)-3-(6-(1-isopropyl-2-oxo-1,2-dihydropyridin-4-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		742.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.15 - 8.08 (m, 1H), 8.03 - 7.87 (m, 2H), 7.82 (d, J = 7.6 Hz, 1H), 7.60 - 7.52 (m, 1H), 6.84 - 6.62 (m, 2H), 5.90 - 5.70 (m, 1H), 5.61 - 5.50 (m, 1H), 5.20 - 5.05 (m, 2H), 4.53 - 4.42 (m, 1H), 2.63 - 2.53 (m, 1H), 2.43 - 2.23 (m, 3H), 2.10 - 1.93 (m, 5H), 1.92 - 1.76 (m, 3H), 1.76 -

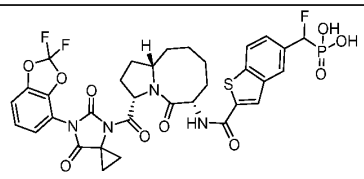
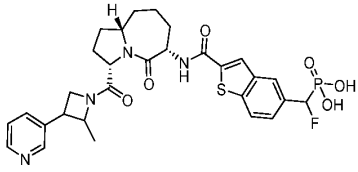
				1.58 (m, 2H), 1.58 - 1.33 (m, 8H)
587	(fluoro(2-(((3S,6S,10aS)-3-(4-(4-fluoro-1H-pyrazol-3-yl)piperidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		650.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (s, 1H), 8.01 (s, 1H), 7.93 (d, J = 8.8 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.48 - 7.39 (m, 1H), 5.91 - 5.75 (m, 1H), 5.08 - 5.02 (m, 1H), 4.99 - 4.91 (m, 3H), 4.53 (d, J = 13.2 Hz, 1H), 4.46 - 4.42 (m, 1H), 4.20 (t, J = 12.8 Hz, 1H), 3.11 - 3.02 (m, 1H), 2.84 (t, J = 12.8 Hz, 1H), 2.35 - 2.17 (m, 3H), 2.06 - 1.94 (m, 7H), 1.87 - 1.74 (m, 3H), 1.67 (d, J = 12.0 Hz, 2H)
588	(fluoro(2-(((3S,6S,10aS)-3-(4-(5-fluoropyrimidin-4-yl)piperidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		662.0	^{1}H NMR (400 MHz, CD_3OD) 8.94 - 8.83 (m, 1H), 8.59 (dd, J = 1.8, 17.6 Hz, 1H), 8.10 (s, 1H), 8.01 (s, 1H), 7.93 (t, J = 7.6 Hz, 1H), 7.62 - 7.52 (m, 1H), 5.95 - 5.69 (m, 1H), 5.06 (d, J = 10.0 Hz, 1H), 5.00 (s, 1H), 4.67 - 4.54 (m, 1H), 4.51 - 4.38 (m, 1H), 4.28 (t, J = 13.2 Hz, 1H), 3.51 - 3.36 (m, 2H), 2.94 - 2.83 (m, 1H), 2.41 - 2.10 (m, 4H), 2.09 - 1.95 (m, 5H), 1.90 (s, 2H), 1.86 (d, J = 4.8 Hz, 3H), 1.68 (d, J = 10.8 Hz, 2H)
589	((2-(((3S,6S,10aS)-3-(4-(1H-pyrazol-3-yl)piperidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo		632.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (s, 1H), 8.00 (s, 1H), 7.96 - 7.90 (m, 1H), 7.68 - 7.63 (m, 1H), 7.58 (d, J = 8.6 Hz, 1H), 6.34 - 6.25 (m,

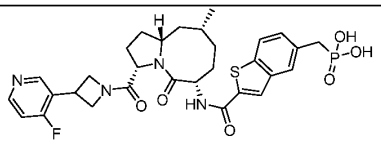
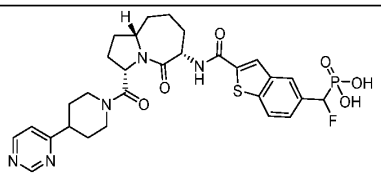
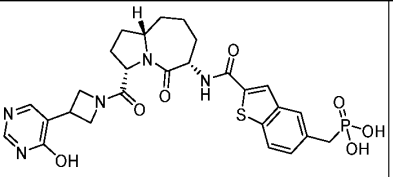
	[b]thiophen-5-yl)fluoromethyl)phosphonic acid			1H), 5.90 - 5.72 (m, 1H), 5.09 - 4.99 (m, 1H), 4.99 - 4.90 (m, 3H), 4.59 - 4.50 (m, 1H), 4.48 - 4.42 (m, 1H), 4.27 - 4.14 (m, 1H), 3.14 - 2.98 (m, 1H), 2.90 - 2.77 (m, 1H), 2.42 - 2.16 (m, 3H), 2.12 - 1.91 (m, 7H), 1.89 - 1.77 (m, 2H), 1.73 - 1.56 (m, 3H)
590	(fluoro(2-(((3S,6S,10aS)-5-oxo-3-(4-(pyrimidin-4-yl)piperidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		644.2	^{1}H NMR (400 MHz, CD_3OD) δ 9.04 (d, J = 19.2 Hz, 1H), 8.73 - 8.56 (m, 1H), 8.10 (s, 1H), 8.01 (d, J = 7.2 Hz, 1H), 7.93 (t, J = 8.8 Hz, 1H), 7.63 - 7.56 (m, 1H), 7.47 (d, J = 5.2 Hz, 1H), 5.92 - 5.71 (m, 1H), 5.10 - 5.03 (m, 2H), 4.70 - 4.57 (m, 1H), 4.54 - 4.40 (m, 1H), 4.36 - 4.21 (m, 1H), 3.52 - 3.34 (m, 2H), 3.05 (tdd, J = 4.0, 7.6, 11.6 Hz, 1H), 2.92 - 2.76 (m, 1H), 2.38 - 2.16 (m, 3H), 2.11 - 1.92 (m, 7H), 1.90 - 1.74 (m, 3H), 1.73 - 1.61 (m, 2H)
591	(fluoro(2-(((3S,6S,9aS)-3-(4-(4-fluoro-1H-pyrazol-3-yl)piperidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		636.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.07 (s, 1H), 8.01 (s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.47 - 7.43 (m, 1H), 5.91 - 5.75 (m, 1H), 5.10 - 5.03 (m, 1H), 4.98 - 4.90 (m, 2H), 4.74 (d, J = 9.6 Hz, 1H), 4.55 - 4.51 (m, 1H), 4.16 - 4.02 (m, 2H), 3.10 - 3.02 (m, 1H), 2.89 - 2.80 (m, 1H), 2.34 -

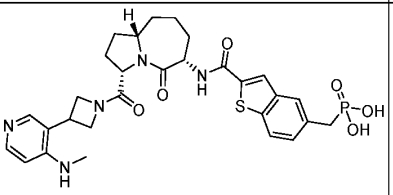
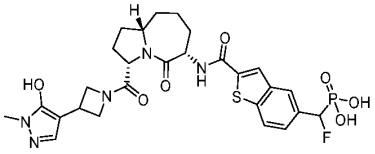
				2.29 (m, 1H), 2.24 - 2.14 (m, 1H), 2.09 - 1.90 (m, 8H), 1.84 - 1.73 (m, 3H)
592	((2-(((3S,6S,9aS)-3-(3-(2,5-difluorophenyl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		636.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.13 - 8.01 (m, 2H), 7.97 - 7.94 (m, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.50 - 7.20 (m, 1H), 7.19 - 6.98 (m, 2H), 5.89 (d, J = 8.0 Hz, 1H), 4.93 - 4.91 (m, 1H), 4.75 (d, J = 11.2 Hz, 1H), 4.70 - 4.54 (m, 2H), 4.42 - 4.32 (m, 1H), 4.25 - 4.12 (m, 1H), 4.10 - 4.05 (m, 2H), 2.39 - 2.25 (m, 1H), 2.20 - 2.11 (m, 1H), 2.11 - 2.03 (m, 2H), 2.03 - 1.98 (m, 1H), 1.98 - 1.88 (m, 3H), 1.88 - 1.78 (m, 2H)
593	((2-(((3S,6S,9aS)-3-(3-(6-(difluoromethyl)-4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		663.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.46 - 8.42 (m, 1H), 8.01 - 7.95 (m, 1H), 7.85 - 7.81 (m, 2H), 7.43 - 7.38 (m, 2H),6.89-6.60 (m, 1H), 4.73 - 4.65 (m, 3H), 4.59 - 4.33 (m, 2H), 4.14 - 4.12 (m, 2H), 4.04 - 4.03 (m, 3H), 3.76 - 3.56 (m, 1H), 3.31 - 3.27 (m, 2H), 2.30 - 2.29 (m, 1H), 2.09 - 2.06 (m, 2H), 1.98 - 1.82 (m, 7H)
594	((2-(((3S,6S,9aS)-3-(3-(2-(difluoromethyl)-4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo		663.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.47 - 8.45 (m, 1H), 8.01 - 7.99 (m, 1H), 7.86 - 7.84 (m, 2H), 7.44 - 7.36 (m, 2H), 7.37-6.85 (m, 1 H), 4.75 - 4.73 (m, 2H), 4.58 - 4.52 (m, 2H), 4.51 - 4.22 (m, 3H), 4.17 - 4.08

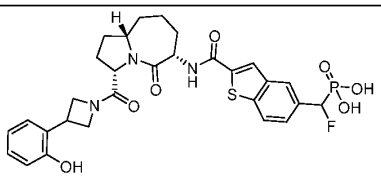
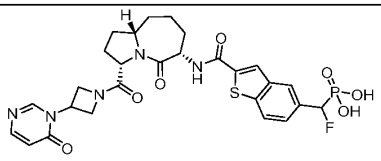
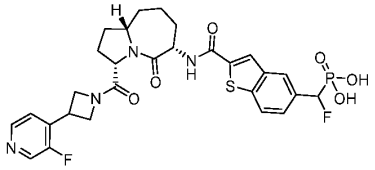
	[b]thiophen-5-yl)methyl)phosphonic acid			(m, 4H), 3.28 - 3.23 (m, 2H), 2.34 - 2.33 (m, 1H), 1.98 - 1.85 (m, 9H)
595	(fluoro(2-(((3S,6S,9aS)-3-(3-(4-fluoro-1H-pyrazol-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		608.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (d, J = 3.6 Hz, 1H), 8.03 (s, 1H), 7.97 - 7.94 (m, 1H), 7.60 - 7.50 (m, 2H), 5.90 - 5.76 (m, 1H), 4.75 (d, J = 10.8 Hz, 2H), 4.64 (d, J = 8.0 Hz, 1H), 4.59 - 4.56 (m, 1H), 4.56 - 4.33 (m, 2H), 4.14 - 4.04 (m, 2H), 2.34 - 2.27 (m, 1H), 2.17 - 2.06 (m, 2H), 2.00 - 1.83 (m, 7H)
596	(fluoro(2-(((3S,6S,9aS)-3-(3-(5-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		619.0	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82-8.76 (m, 1H), 8.50 - 8.42 (m, 2H), 8.25 (d, J = 11.6 Hz, 1H), 8.07 - 7.96 (m, 2H), 7.88 (d, J = 9.8 Hz, 1H), 7.53 (d, J = 8.6 Hz, 1H), 5.92 - 5.75 (m, 1H), 4.80 - 4.60 (m, 2H), 4.47 - 4.38 (m, 2H), 4.31 - 4.22 (m, 2H), 4.00 (s, 1H), 3.90 (s, 1H), 2.22 - 2.16 (m, 1H), 2.08 - 1.93 (m, 2H), 1.90 - 1.80 (m, 3H), 1.79 - 1.59 (m, 4H)
597	((2-(((3S,6S,9aS)-3-(3-(4-ethoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		645.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.36 - 8.21 (m, 2H), 8.00 - 7.88 (m, 1H), 7.84 (t, J = 9.2 Hz, 2H), 7.69 - 7.49 (m, 1H), 7.38 - 7.24 (m, 1H), 5.87 - 5.61 (m, 1H), 4.81 (d, J = 2.8 Hz, 1H), 4.74 (d, J = 11.6 Hz, 1H), 4.68 - 4.57 (m, 1H), 4.54 - 4.47 (m, 1H), 4.45 - 4.36 (m, 1H),

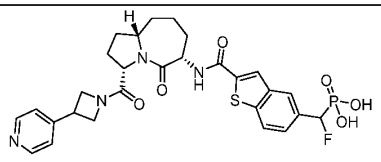
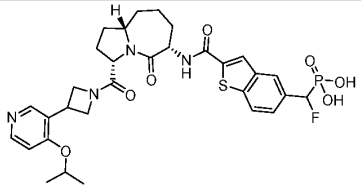
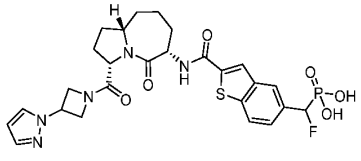
				4.35 - 4.29 (m, 2H), 4.21 - 3.97 (m, 3H), 2.39 - 2.25 (m, 1H), 2.20 - 2.06 (m, 2H), 2.03 - 1.78 (m, 7H), 1.55 - 1.45 (m, 3H)
598	(fluoro(2-(((3S,6S,9aS)-3-(3-(4-(oxetan-3-yloxy)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		673.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 - 8.58 (m, 3H), 8.29 - 8.14 (m, 1H), 8.07 - 7.90 (m, 2H), 7.52 (d, J = 7.6 Hz, 1H), 7.21 - 7.07 (m, 1H), 5.91 - 5.74 (m, 1H), 5.66 - 5.55 (m, 1H), 5.04 - 4.92 (m, 2H), 4.77 (t, J = 9.6 Hz, 1H), 4.68 - 4.59 (m, 3H), 4.49 - 4.36 (m, 2H), 4.31 - 4.09 (m, 3H), 3.99 (s, 1H), 2.27 - 2.11 (m, 1H), 2.08 - 1.93 (m, 2H), 1.90 - 1.75 (m, 4H), 1.74 - 1.51 (m, 3H)
599	((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		619.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (t, J = 7.2 Hz, 1H), 8.68 (dd, J = 2.0, 10.4 Hz, 1H), 8.57 - 8.49 (m, 1H), 8.20 (d, J = 10.0 Hz, 1H), 7.93 - 7.85 (m, 2H), 7.51 (d, J = 8.4 Hz, 1H), 7.36 - 7.28 (m, 1H), 5.54 - 5.35 (m, 1H), 4.82 - 4.57 (m, 2H), 4.54 - 4.35 (m, 2H), 4.34 - 4.22 (m, 1H), 4.16 - 4.02 (m, 2H), 4.00 (d, J = 6.0 Hz, 1H), 2.24 - 2.15 (m, 1H), 2.09 - 1.92 (m, 2H), 1.90 - 1.75 (m, 4H), 1.75 - 1.60 (m, 3H)
600	((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-		619.1	^{1}H NMR (400 MHz, D_2O) δ 8.85 - 8.65 (m, 1H), 8.59 (t, J = 5.6 Hz, 1H), 7.95 - 7.83 (m, 3H), 7.74 -

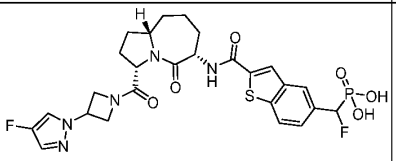
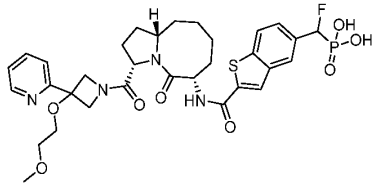
	oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			7.63 (m, 1H), 7.56 – 7.49 (m, 1H), 5.85 - 5.67 (m, 1H), 4.72 - 4.68 (m, 1H), 4.52 (d, J = 16.0 Hz, 1H), 4.49 - 4.39 (m, 2H), 4.36 - 4.20 (m, 2H), 4.20 - 4.10 (m, 1H), 4.09 - 4.02 (m, 1H), 2.32 - 2.22 (m, 1H), 2.17 - 2.09 (m, 1H), 2.07 - 2.02 (m, 1H), 1.98 - 1.89 (m, 2H), 1.88 - 1.74 (m, 4H), 1.72 - 1.65 (m, 1H)
601	((2-(((3S,6S,10aS)-3-(6-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		763.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (s, 1H), 8.03 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.40 - 7.23 (m, 3H), 5.92 - 5.70 (m, 1H), 5.57 (dd, J = 8.0, 9.2 Hz, 1H), 5.05 (dd, J = 4.8, 11.2 Hz, 1H), 4.49 (dd, J = 8.8, 10.2 Hz, 1H), 2.66 - 2.53 (m, 1H), 2.52 - 2.41 (m, 1H), 2.40 - 2.26 (m, 2H), 2.15 - 1.93 (m, 6H), 1.93 - 1.78 (m, 3H), 1.77 - 1.60 (m, 2H), 1.55 - 1.49 (m, 1H)
602	(fluoro(2-(((3S,6S,9aS)-3-(2-methyl-3-(pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		615.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.77 - 8.61 (m, 2H), 8.60 - 8.44 (m, 1H), 8.12 - 7.97 (m, 2H), 7.91 (d, J = 8.0 Hz, 1H), 7.80 - 7.68 (m, 1H), 7.66 - 7.55 (m, 1H), 5.91 - 5.64 (m, 1H), 4.79 - 4.72 (m, 1H), 4.66 (t, J = 8.8 Hz, 1H), 4.60 - 4.35 (m, 3H), 4.17 - 4.05 (m, 1H), 3.64 - 3.59 (m, 1H), 2.42 - 2.25 (m, 1H), 2.23 - 2.04 (m, 3H), 2.01 -

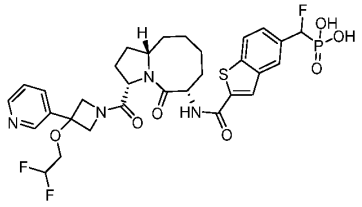
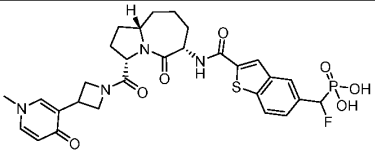
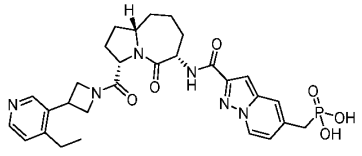
				1.76 (m, 6H), 1.69 - 1.55 (m, 3H)
603	((2-(((3S,6S,9R,10aR)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-9-methyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		629.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 - 8.67 (m, 2H), 8.61 - 8.54 (m, 1H), 8.20 (d, J = 8.8 Hz, 1H), 7.92 - 7.89 (m, 1H), 7.78 (s, 1H), 7.45 - 7.32 (m, 2H), 4.97 - 4.80 (m, 2H), 4.63 - 4.56 (m, 1H), 4.36 - 4.30 (m, 3H), 4.12 (d, J = 7.6 Hz, 2H), 3.13 - 3.04 (m, 2H), 2.22 - 2.13 (m, 1H), 2.10 - 1.97 (m, 2H), 1.88 - 1.64 (m, 6H), 1.51 (d, J = 12.0 Hz, 1H), 1.32 - 1.24 (m, 1H), 0.95 (d, J = 6.0 Hz, 3H)
604	(fluoro(2-(((3S,6S,9aS)-5-oxo-3-(4-(pyrimidin-4-yl)piperidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		630.2	^{1}H NMR (400 MHz, CD_3OD) δ 9.07 (d, J = 8.4 Hz, 1H), 8.67 (dd, J = 5.6, 17.2 Hz, 1H), 8.11 - 7.90 (m, 3H), 7.64 - 7.47 (m, 2H), 5.94 - 5.73 (m, 1H), 5.08 (m, 1H), 4.74 (d, J = 9.6 Hz, 1H), 4.67 - 4.56 (m, 1H), 4.20 (t, J = 13.6 Hz, 1H), 4.08 (d, J = 5.6 Hz, 1H), 3.39 - 3.33 (m, 1H), 3.16 - 3.00 (m, 1H), 2.85 (m, 1H), 2.37 - 2.16 (m, 2H), 2.09 (d, J = 5.2 Hz, 1H), 2.06 - 1.97 (m, 4H), 1.96 - 1.90 (m, 3H), 1.89 - 1.80 (m, 3H), 1.80 - 1.69 (m, 1H)
605	((2-(((3S,6S,9aS)-3-(3-(4-hydroxypyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-		600.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (d, J = 7.6 Hz, 1H), 8.16 (m, 2H), 7.95 (s, 1H), 7.91 (m, 1H), 7.79 (s, 1H), 7.40 - 7.32 (m, 1H), 4.69 - 4.54 (m,

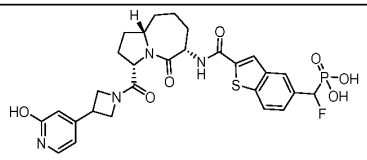
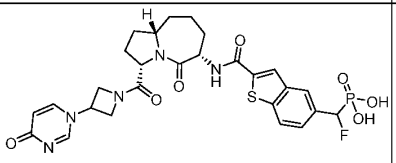
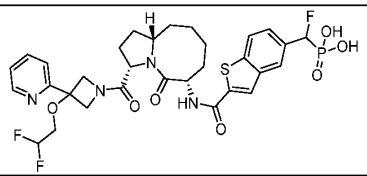
	a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			2H), 4.43 (m, 1H), 4.35 - 4.28 (m, 1H), 4.10 (d, J = 6.8 Hz, 1H), 3.98 - 3.92 (m, 2H), 3.79 - 3.75 (m, 1H), 3.15 - 3.06 (m, 2H), 2.26 - 2.13 (m, 1H), 2.09 - 1.92 (m, 2H), 1.91 - 1.58 (m, 7H)
606	((2-(((3S,6S,9aS)-3-(3-(4-(methylamino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		612.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.22 - 8.09 (m, 2H), 8.03 - 7.94 (m, 1H), 7.88 - 7.82 (m, 2H), 7.45 - 7.41 (m, 1H), 6.95 - 6.89 (m, 1H), 4.75 - 4.67 (m, 2H), 4.63 - 4.56 (m, 1H), 4.55 - 4.51 (m, 1H), 4.45-4.38 (m, 1H), 4.11 - 4.06 (m, 1H), 4.05 - 3.99 (m, 1H), 3.97 - 3.90 (m, 1H), 3.28 (d, J = 3.2 Hz, 1H), 3.22 (d, J = 3.2 Hz, 1H), 3.03 (s, 3H), 2.36 - 2.27 (m, 1H), 2.18 - 2.07 (m, 2H), 2.02 - 1.79 (m, 7H)
607	(fluoro(2-(((3S,6S,9aS)-3-(3-(5-hydroxy-1-methyl-1H-pyrazol-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		620.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (d, J = 4.4 Hz, 1H), 8.04 (s, 1H), 7.96 (d, J = 3.6, 8.8 Hz, 1H), 7.81 - 7.64 (m, 1H), 7.61 (d, J = 8.4 Hz, 1H), 5.94 - 5.74 (m, 1H), 4.78 - 4.74 (m, 1H), 4.62 - 4.50 (m, 2H), 4.47 - 4.35 (m, 1H), 4.34 - 4.25 (m, 1H), 4.08 (s, 1H), 4.03 - 3.92 (m, 1H), 3.79 - 3.70 (m, 1H), 3.53 (d, J = 10.0 Hz, 3H), 2.36 - 2.27 (m, 1H), 2.18 - 2.07 (m, 2H), 2.07 - 1.98 (m, 2H), 1.98 -

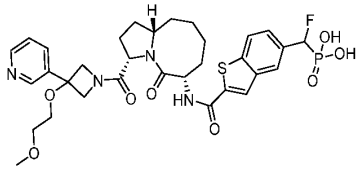
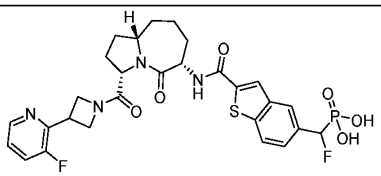
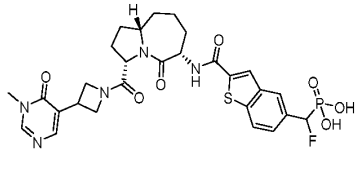
				1.92 (m, 2H), 1.92 - 1.81 (m, 3H)
608	(fluoro(2-(((3S,6S,9aS)-3-(3-(2-hydroxyphenyl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		616.1	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.73 – 8.70 (m, 1H), 8.18 (d, J = 17.6 Hz, 1H), 7.93 - 7.83 (m, 2H), 7.55 - 7.45 (m, 1H), 7.23 – 7.29 (m, 1H), 7.07 – 7.00 (m, 1H), 6.88 - 6.70 (m, 2H), 5.54 - 5.34 (m, 1H), 4.74 - 4.42 (m, 3H), 4.40 - 4.11 (m, 2H), 4.01 – 3.91 (m, 3H), 2.24 - 2.13 (m, 1H), 2.07 - 1.91 (m, 2H), 1.89 - 1.77 (m, 3H), 1.75 - 1.63 (m, 4H)
609	(fluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(6-oxopyrimidin-1(6H)-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		617.8	^{1}H NMR (400 MHz, CD$_3$OD) δ 8.74 - 8.40 (m, 1H), 8.10 (d, J = 6.4 Hz, 1H), 8.03 (s, 1H), 7.97 - 7.94 (m, 2H), 7.59 (d, J = 8.4 Hz, 1H), 6.54 - 6.44 (m, 1H), 5.93 - 5.73 (m, 1H), 5.44 - 5.12 (m, 1H), 4.82 (d, J = 3.6 Hz, 1H), 4.77 - 4.70 (m, 2H), 4.58 - 4.33 (m, 3H), 4.07 (d, J = 6.8 Hz, 1H), 2.37 - 2.25 (m, 1H), 2.20 - 1.99 (m, 4H), 1.98 - 1.75 (m, 5H)
610	(fluoro(2-(((3S,6S,9aS)-3-(3-(3-fluoropyridin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		618.9	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (d, J = 8.0 Hz, 1H), 8.52 (d, J = 10.8 Hz, 1H), 8.43 - 8.38 (m, 1H), 8.25 - 8.23 (m, 1H), 8.04 - 7.97 (m, 2H), 7.59 - 7.48 (m, 2H), 5.89 - 5.76 (m, 1H), 4.65 - 4.62 (m, 1H), 4.43 (d, J = 7.2 Hz, 1H), 4.32 - 4.25 (m, 2H), 4.12 (d, J = 7.6 Hz, 1H), 3.98 (d, J =

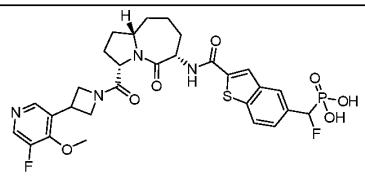
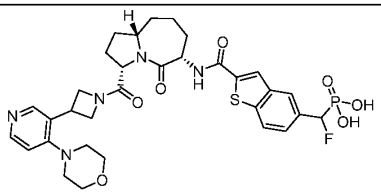
				6.4 Hz, 3H), 2.19 (d, *J* = 3.6 Hz, 1H), 1.97 - 1.94 (m, 2H), 1.85 - 1.80 (m, 3H), 1.77 - 1.72 (m, 4H)
611	(fluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-4-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		601.4	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.80 - 8.67 (m, 1H), 8.56 - 8.53 (m, 1H), 8.51 - 8.46 (m, 1H), 8.20 (d, J = 3.2 Hz, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.52 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 13.2 Hz, 2H), 5.55 - 5.34 (m, 1H), 4.82 - 4.59 (m, 2H), 4.44 - 4.38 (m, 1H), 4.30 - 4.20 (m, 2H), 3.99 (s, 1H), 3.91 - 3.85 (m, 2H), 2.22 - 2.12 (m, 1H), 2.03 - 1.93 (m, 2H), 1.85 - 1.81 (m, 4H), 1.74 - 1.69 (m, 2H), 1.64 (d, J = 9.6 Hz, 1H)
612	(fluoro(2-(((3S,6S,9aS)-3-(3-(4-isopropoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		659.3	^{1}H NMR (400 MHz, CD$_3$OD) δ 8.35 - 8.17 (m, 2H), 8.07 - 7.76 (m, 3H), 7.66 - 7.50 (m, 1H), 7.42 - 7.25 (m, 1H), 5.90 - 5.65 (m, 1H), 5.08 - 5.00 (m, 1H), 4.84 - 4.72 (m, 2H), 4.64 - 4.48 (m, 2H), 4.35 - 4.27 (m, 1H), 4.16 - 3.88 (m, 3H), 2.38 - 2.25 (m, 1H), 2.20 - 2.06 (m, 2H), 2.05 - 1.78 (m, 7H), 1.53 - 1.37 (m, 6H)
613	((2-(((3S,6S,9aS)-3-(3-(1H-pyrazol-1-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo		590.3	^{1}H NMR (400 MHz, CD$_3$OD) 8.15 - 7.98 (m, 2H), 7.93 (d, J = 2.4 Hz, 2H), 7.69 - 7.50 (m, 2H), 6.37 - 6.30 (m, 1H), 5.73 - 5.56 (m, 1H), 5.38 - 5.25 (m, 1H), 4.97 -

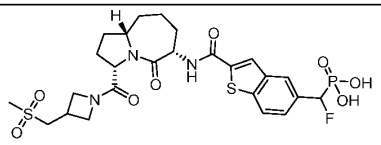
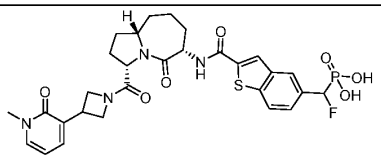
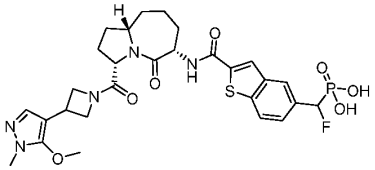
	[b]thiophen-5-yl)fluoromethyl)phosphonic acid			4.93 (m, 1H), 4.74 (d, J = 11.2 Hz, 1H), 4.63 - 4.53 (m, 2H), 4.53 - 4.40 (m, 1H), 4.38 - 4.24 (m, 1H), 4.07 (d, J = 6.1 Hz, 1H), 2.19 - 2.07 (m, 2H), 2.07 - 2.00 (m, 2H), 1.99 - 1.90 (m, 2H), 1.90 - 1.76 (m, 4H)
614	(fluoro(2-(((3S,6S,9aS)-3-(3-(4-fluoro-1H-pyrazol-1-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		608.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 8.03 (s, 1H), 7.98 - 7.93 (m, 1H), 7.85 - 7.67 (m, 1H), 7.62 - 7.54 (m, 1H), 7.54 - 7.42 (m, 1H), 5.91 - 5.75 (m, 1H), 5.22 - 5.14 (m, 1H), 4.94 - 4.90 (m, 1H), 4.83 - 4.67 (m, 2H), 4.55 (m, 1H), 4.51 - 4.38 (m, 1H), 4.35 - 4.23 (m, 1H), 4.11 - 4.02 (m, 1H), 2.36 - 2.24 (m, 1H), 2.08 (m, 2H), 2.05 - 1.99 (m, 2H), 1.98 - 1.90 (m, 2H), 1.90 - 1.79 (m, 3H)
615	(fluoro(2-(((3S,6S,10aS)-3-(3-(2-methoxyethoxy)-3-(pyridin-2-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		689.1	^{1}H NMR (400 MHz, D_2O) δ 8.73 - 8.55 (m, 1H), 8.34 - 8.21 (m, 1H), 8.20 - 8.03 (m, 1H), 8.02 - 7.81 (m, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.69 - 7.60 (m, 2H), 7.51 - 7.38 (m, 1H), 5.81 - 5.62 (m, 1H), 4.97 - 4.93 (m, 1H), 4.80 - 4.79 (m, 2H), 4.54 - 4.45 (m, 2H), 4.44 - 4.28 (m, 2H), 3.64 - 3.35 (m, 4H), 3.31 - 3.09 (m, 3H), 2.36 - 2.12 (m, 2H), 2.02 - 1.73 (m, 7H), 1.71 - 1.58 (m, 2H), 1.58 - 1.45 (m, 1H)

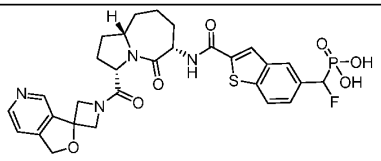
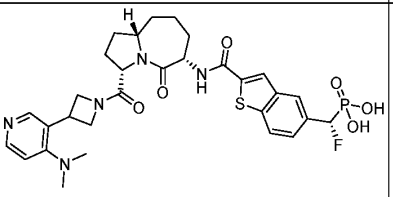
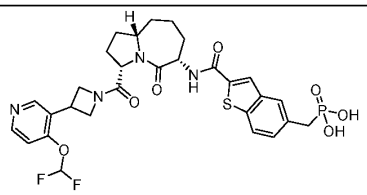
616	((2-(((3S,6S,10aS)-3-(3-(2,2-difluoroethoxy)-3-(pyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		695.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.90 - 8.80 (m, 1H), 8.73 - 8.61 (m, 1H), 8.49 - 8.36 (m, 1H), 8.07 - 7.95 (m, 2H), 7.94 - 7.77 (m, 2H), 7.61 - 7.53 (m, 1H), 6.17 - 5.95 (m, 1H), 5.90 - 5.70 (m, 1H), 5.05 - 4.94 (m, 2H), 4.70 - 4.59 (m, 1H), 4.52 - 4.23 (m, 4H), 3.70 - 3.56 (m, 2H), 2.36 - 2.16 (m, 2H), 2.13 - 1.76 (m, 8H), 1.74 - 1.56 (m, 2H)
617	(fluoro(2-(((3S,6S,9aS)-3-(3-(1-methyl-4-oxo-1,4-dihydropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		631.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (s, 1H), 7.84 - 7.80 (m, 1H), 7.61 - 7.46 (m, 2H), 7.45 - 7.36 (m, 1H), 6.02 (s, 1H), 5.86 - 5.74 (m, 1H), 5.73 - 5.59 (m, 1H), 4.78 - 4.70 (m, 1H), 4.61 - 4.42 (m, 2H), 4.25 (m, 2H), 4.22 - 4.08 (m, 2H), 4.01 - 3.90 (m, 1H), 3.74 (s, 3H), 2.40 - 2.30 (m, 1H), 2.22 - 2.13 (m, 2H), 2.05 - 2.00 (m, 2H), 2.00 - 1.91 (m, 2H), 1.89 - 1.79 (m, 2H), 1.75 - 1.60 (m, 1H)
618	((2-(((3S,6S,9aS)-3-(3-(4-ethylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)pyrazolo[1,5-a]pyridin-5-yl)methyl)phosphonic acid		595.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.97 - 8.82 (m, 1H), 8.65 (d, J = 6.0 Hz, 1H), 8.51 - 8.41 (m, 1H), 7.91 (d, J = 6.0 Hz, 1H), 7.56 (d, J = 2.0 Hz, 1H), 7.01 - 6.89 (m, 2H), 4.83 - 4.71 (m, 2H), 4.69 - 4.55 (m, 2H), 4.51 - 4.34 (m, 2H), 4.22 - 4.04 (m, 2H), 3.23 - 3.12 (m, 2H),

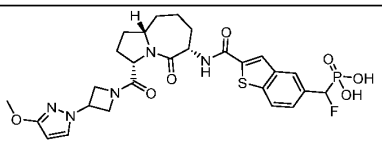
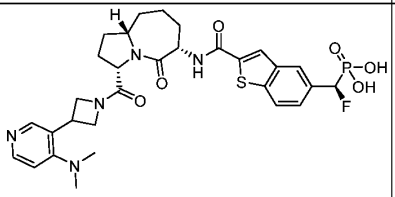
				2.93 - 2.82 (m, 2H), 2.37 - 2.26 (m, 1H), 2.22 - 2.08 (m, 2H), 2.08 - 2.00 (m, 2H), 2.00 - 1.92 (m, 2H), 1.90 - 1.79 (m, 2H), 1.77 - 1.67 (m, 1H), 1.39 - 1.30 (m, 3H)
619	(fluoro(2-(((3S,6S,9aS)-3-(3-(2-hydroxypyridin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		617.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 - 8.60 (m, 1H), 8.31 - 8.15 (m, 1H), 8.06 - 7.90 (m, 1H), 7.53 - 7.41 (m, 1H), 7.35 - 7.11 (m, 3H), 6.40 - 6.16 (m, 1H), 5.70 - 5.38 (m, 1H), 4.74 - 4.61 (m, 1H), 4.50 - 4.30 (m, 2H), 4.22 - 4.09 (m, 1H), 4.02 - 3.95 (m, 1H), 3.79 - 3.65 (m, 3H), 2.23 - 2.12 (m, 1H), 2.03 - 1.89 (m, 3H), 1.87 - 1.64 (m, 6H)
620	(fluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(4-oxopyrimidin-1(4H)-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		618.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.81 (d, J = 10.0 Hz, 1H), 8.60 - 8.48 (m, 1H), 8.11 - 8.05 (m, 1H), 8.05 - 7.99 (m, 1H), 7.98 - 7.91 (m, 1H), 7.60 (t, J = 8.4 Hz, 1H), 7.13 - 7.01 (m, 1H), 5.94 - 5.74 (m, 1H), 5.64 - 5.49 (m, 1H), 4.80 - 4.72 (m, 2H), 4.62 - 4.48 (m, 2H), 4.46 - 4.32 (m, 1H), 4.16 - 4.01 (m, 2H), 2.39 - 2.26 (m, 1H), 2.19 - 2.08 (m, 2H), 2.05 - 1.91 (m, 4H), 1.90 - 1.79 (m, 3H)
621	((2-(((3S,6S,10aS)-3-(3-(2,2-difluoroethoxy)-3-(pyridin-2-yl)azetidine-1-		695.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.70 - 8.50 (m, 1H), 8.11 - 7.82 (m, 4H), 7.69 (d, J = 8.4, 1H), 7.61 - 7.52

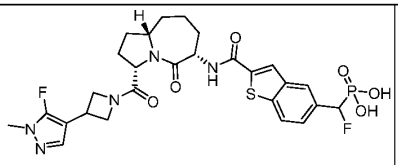
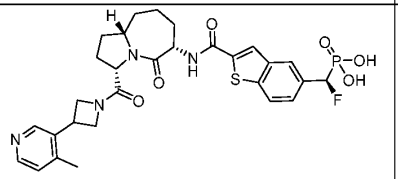
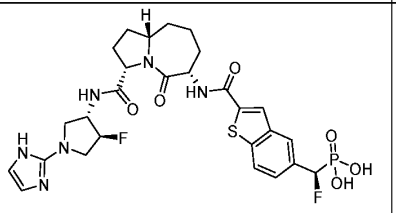
	carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid			(m, 1H), 7.46 (d, J = 5.2, 1H), 6.14 - 5.91 (m, 1H), 5.90 - 5.73 (m, 1H), 5.08 - 4.92 (m, 2H), 4.86 - 4.72 (m, 1H), 4.64 - 4.55 (m, 1H), 4.54 - 4.47 (m, 1H), 4.41 (d, J = 13.2 Hz, 1H), 4.37 - 4.20 (m, 1H), 3.68 - 3.45 (m, 2H), 2.38 - 2.17 (m, 2H), 2.14 - 1.91 (m, 5H), 1.91 - 1.75 (m, 3H), 1.74 - 1.54 (m, 2H)
622	(fluoro(2-(((3S,6S,10aS)-3-(3-(2-methoxyethoxy)-3-(pyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		689.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.96 - 8.82 (m, 1H), 8.69 - 8.35 (m, 2H), 8.10 - 7.96 (m, 2H), 7.93 - 7.75 (m, 2H), 7.63 - 7.53 (m, 1H), 5.87 - 5.66 (m, 1H), 5.06 - 4.95 (m, 1H), 4.70 - 4.60 (m, 1H), 4.59 - 4.38 (m, 3H), 4.38 - 4.15 (m, 2H), 3.62 - 3.45 (m, 4H), 3.37 (s, 3H), 2.37 - 2.17 (m, 2H), 2.11 - 1.78 (m, 8H), 1.75 - 1.56 (m, 2H)
623	(fluoro(2-(((3S,6S,9aS)-3-(3-(3-fluoropyridin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		619.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.51 - 8.35 (m, 1H), 8.16 - 7.86 (m, 3H), 7.65 - 7.48 (m, 2H), 7.45 - 7.29 (m, 1H), 5.95 - 5.74 (m, 1H), 4.80 - 4.70 (m, 2H), 4.67 - 4.51 (m, 2H), 4.46 - 4.19 (m, 3H), 4.13 - 4.00 (m, 1H), 2.38 - 2.25 (m, 1H), 2.20 - 1.73 (m, 9H)
624	(fluoro(2-(((3S,6S,9aS)-3-(3-(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)azetidine-1-		632.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 8.08 - 8.01 (m, 2H), 7.94 - 7.80 (m, 2H), 7.68 - 7.58 (m, 1H), 5.75 - 5.59 (m,

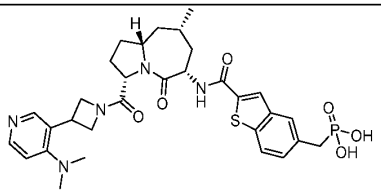
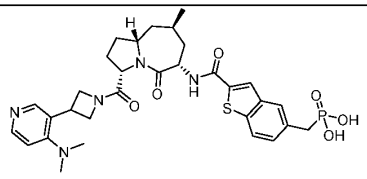
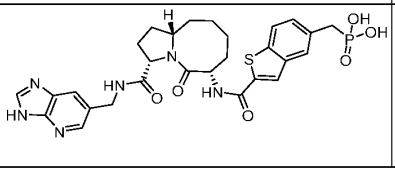
	carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			1H), 4.75 - 4.70 (m, 2H), 4.58 (d, J = 7.4 Hz, 1H), 4.44 - 4.43 (m, 1H), 4.48 - 4.41 (m, 1H), 4.18 - 4.04 (m, 2H), 3.96 - 3.84 (m, 1H), 3.52 (d, J = 13.2 Hz, 3H), 2.33 - 2.24 (m, 1H), 2.10 - 1.99 (m, 3H), 1.98 - 1.86 (m, 4H), 1.83 (dd, J = 0.8, 10.2 Hz, 2H)
625	(fluoro(2-(((3S,6S,9aS)-3-(3-(5-fluoro-4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		649.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.53 - 8.44 (m, 1H), 8.36 - 8.26 (m, 1H), 8.07 - 8.00 (m, 1H), 8.00 - 7.94 (m, 1H), 7.94 - 7.89 (m, 1H), 7.63 - 7.53 (m, 1H), 5.89 - 5.71 (m, 1H), 4.74 (d, J = 8.8 Hz, 2H), 4.64 (d, J = 7.6 Hz, 2H), 4.56 - 4.52 (m, 1H), 4.35 - 4.30 (m, 3H), 4.20 - 4.00 (m, 3H), 2.35 - 2.27 (m, 1H), 2.14 - 2.06 (m, 2H), 2.04 - 1.99 (m, 1H), 1.97 - 1.88 (m, 3H), 1.87 - 1.78 (m, 3H)
626	(fluoro(2-(((3S,6S,9aS)-3-(3-(4-morpholinopyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		686.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.36 - 8.14 (m, 1H), 8.14 - 7.94 (m, 1H), 7.92 - 7.83 (m, 1H), 7.82 - 7.69 (m, 2H), 7.61 - 7.43 (m, 1H), 7.26 - 6.88 (m, 1H), 5.86 - 5.63 (m, 1H), 4.81 - 4.67 (m, 2H), 4.59 - 4.47 (m, 2H), 4.43 - 4.25 (m, 1H), 4.18 - 4.00 (m, 3H), 3.78 (d, J = 2.8 Hz, 4H), 3.35 (s, 1H), 3.22 (s, 3H), 2.36 - 2.30 (m, 1H), 2.21 - 2.08 (m, 2H), 2.06 - 1.79 (m, 7H)

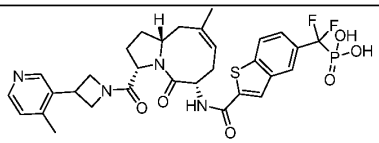
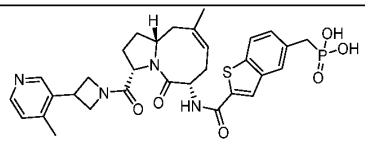
627	(fluoro(2-(((3S,6S,9aS)-3-(3-((methylsulfonyl)methyl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		616.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 8.03 (s, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 5.94 - 5.60 (m, 1H), 4.76 - 4.66 (m, 1H), 4.56 - 4.13 (m, 4H), 4.13 - 3.99 (m, 1H), 3.98 - 3.81 (m, 1H), 3.61 - 3.49 (m, 2H), 3.29 - 3.19 (m, 1H), 3.31-2.97 (m, 3H), 2.35 - 2.22 (m, 1H), 2.12 - 1.77 (m, 9H)
628	(fluoro(2-(((3S,6S,9aS)-3-(3-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		631.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.10 - 7.97 (m, 2H), 7.90 - 7.83 (m, 1H), 7.68 - 7.45 (m, 3H), 6.42 - 6.33 (m, 1H), 5.78 - 5.50 (m, 1H), 4.80 - 4.69 (m, 2H), 4.61 - 4.50 (m, 2H), 4.40 - 4.30 (m, 1H), 4.14 - 3.92 (m, 3H), 3.58 - 3.53 (m, 3H), 2.34 - 2.23 (m, 1H), 2.13 - 1.78 (m, 9H)
629	(fluoro(2-(((3S,6S,9aS)-3-(3-(5-methoxy-1-methyl-1H-pyrazol-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		634.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.08 - 8.07 (m, 1H), 8.03 (s, 1H), 7.96 - 7.93 (m, 1H), 7.64 - 7.49 (m, 2H), 5.91 - 5.75 (m, 1H), 4.88 - 4.80 (m, 1H), 4.73 - 4.75 (m, 1H), 4.65 - 4.52 (m, 2H), 4.52 - 4.37 (m, 1H), 4.35 - 4.20 (m, 1H), 4.11 - 4.03 (m, 1H), 3.98 – 3.95 (m, 1H), 3.94 - 3.91 (m, 3H), 3.65 - 3.63 (m, 3H), 2.36 - 2.25 (m, 1H), 2.17 - 2.05 (m, 2H), 2.04 - 1.81 (m, 7H)

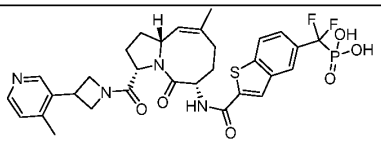
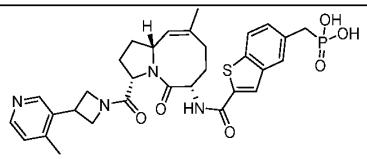
630	(fluoro(2-(((3S,6S,9aS)-5-oxo-3-(1'H-spiro[azetidine-3,3'-furo[3,4-c]pyridine]-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		629.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 - 8.75 (m, 2H), 8.73 - 8.53 (m, 1H), 8.37 - 8.19 (m, 1H), 8.12 - 7.91 (m, 2H), 7.70 - 7.44 (m, 2H), 5.94 - 5.74 (m, 1H), 5.22 - 5.08 (m, 2H), 4.77 - 4.64 (m, 2H), 4.56 - 4.44 (m, 2H), 4.30 - 4.15 (m, 3H), 4.06 - 3.95 (m, 2H), 2.36 - 2.14 (m, 1H), 2.12 - 1.61 (m, 9H)
631	((S)-(2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		644.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.27 - 8.14 (m, 1H), 8.08 - 7.80 (m, 4H), 7.64 - 7.51 (m, 1H), 7.07 - 6.82 (m, 1H), 5.85 - 5.67 (m, 1H), 4.79 - 4.66 (m, 2H), 4.59 - 4.47 (m, 2H), 4.44 - 4.21 (m, 2H), 4.15 - 3.98 (m, 2H), 3.14 - 3.05 (m, 6H), 2.38 - 2.25 (m, 1H), 2.18 - 2.06 (m, 2H), 2.04 - 1.92 (m, 3H), 1.92 - 1.75 (m, 4H)
632	((2-(((3S,6S,9aS)-3-(3-(4-(difluoromethoxy)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		648.6	^{1}H NMR (400 MHz, CD_3OD) δ 8.80 - 8.67 (m, 1H), 8.66 - 8.54 (m, 1H), 7.97 (d, J = 10.4 Hz, 1H), 7.89 - 7.73 (m, 2H), 7.63 - 7.48 (m, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.37 - 7.11 (m, 1H), 4.92 (s, 1H), 4.78 - 4.64 (m, 2H), 4.58-4.51 (m, 1H), 4.48 - 4.37 (m, 1H), 4.27 - 4.13 (m, 2H), 4.07 (d, J = 4.4 Hz, 1H), 3.29 - 3.17 (m, 2H), 2.39 - 2.24 (m, 1H), 2.20 - 2.05 (m, 2H), 2.04 - 1.96 (m, 2H), 1.95-

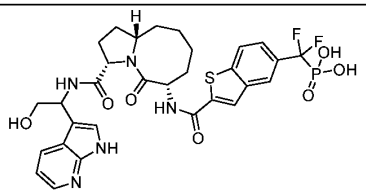
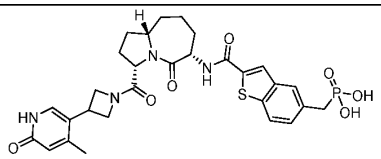
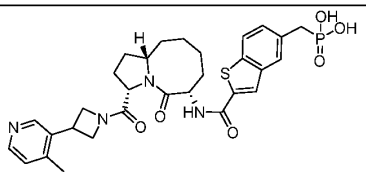
				1.90 (m, 2H), 1.89 - 1.77 (m, 3H)
633	(fluoro(2-(((3S,6S,9aS)-3-(3-(3-methoxy-1H-pyrazol-1-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		620.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.11 - 8.01 (m, 2H), 7.88 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 6.8 Hz, 1H), 7.55 - 7.35 (m, 1H), 5.81 - 5.57 (m, 1H), 5.17 - 5.05 (m, 1H), 4.74 (d, J = 10.8 Hz, 1H), 4.66 - 4.52 (m, 2H), 4.49 - 4.40 (m, 1H), 4.40 - 4.30 (m, 1H), 4.30 - 4.20 (m, 1H), 4.07 (d, J = 5.2 Hz, 1H), 3.92 (s, 1H), 3.87 (s, 1H), 3.83 (s, 1H), 2.36 - 2.26 (m, 1H), 2.16 - 2.10 (m, 1H), 2.09 - 2.03 (m, 2H), 2.02 (s, 1H), 1.97 - 1.90 (m, 2H), 1.89 - 1.80 (m, 3H)
634	((R)-(2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		644.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.22 - 8.09 (m, 1H), 8.06 - 7.97 (m, 1H), 7.94 (s, 1H), 7.89 - 7.85 (m, 1H), 7.79 (m, 1H), 7.60 - 7.49 (m, 1H), 6.81 (m, 1H), 5.86 - 5.65 (m, 1H), 4.73 (s, 1H), 4.66 (s, 1H), 4.57 - 4.50 (m, 1H), 4.46 (s, 1H), 4.39 (s, 1H), 4.26 - 4.18 (m, 1H), 4.08 (s, 1H), 4.02 - 3.96 (m, 1H), 3.09 - 3.02 (m, 6H), 2.36 - 2.26 (m, 1H), 2.15 (m, 1H), 2.09 (m, 1H), 2.02 - 1.96 (m, 2H), 1.95 - 1.90 (m, 2H), 1.88 - 1.81 (m, 3H)

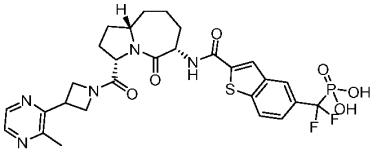
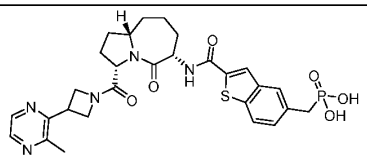
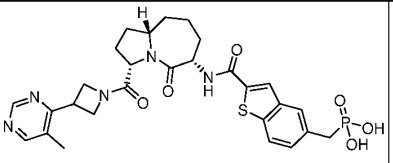
635	(fluoro(2-(((3S,6S,9aS)-3-(3-(5-fluoro-1-methyl-1H-pyrazol-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		622.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.11 - 7.99 (m, 2H), 7.95 (d, J = 8.4 Hz, 1H), 7.64 - 7.43 (m, 2H), 5.92 - 5.75 (m, 1H), 4.82 - 4.72 (m, 2H), 4.62 - 4.45 (m, 2H), 4.43 - 4.27 (m, 1H), 4.10 - 3.92 (m, 2H), 3.85 - 3.75 (m, 1H), 3.70 (d, J = 11.1 Hz, 3H), 2.36 - 2.23 (m, 1H), 2.15 - 1.79 (m, 9H)
636	((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		615.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.71 - 8.47 (m, 1H), 8.41 - 8.16 (m, 1H), 8.03 - 7.60 (m, 4H), 7.55 (d, J = 8.0 Hz, 1H), 5.88 - 5.67 (m, 1H), 4.74 (d, J = 11.2 Hz, 2H), 4.63 - 4.48 (m, 2H), 4.46 - 4.29 (m, 1H), 4.27 - 3.98 (m, 3H), 2.50 - 2.37 (m, 3H), 2.36 - 2.26 (m, 1H), 2.21 - 2.06 (m, 2H), 2.05 - 1.93 (m, 3H), 1.92 - 1.76 (m, 4H)
637	((R)-fluoro(2-(((3S,6S,9aS)-3-(((3S,4S)-4-fluoro-1-(1H-imidazol-2-yl)pyrrolidin-3-yl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		637.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.00 (s, 2H), 7.89 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 6.88 (s, 2H), 5.82 - 5.68 (m, 1H), 5.29 - 5.16 (m, 1H), 4.70 (d, J = 11.6 Hz, 1H), 4.62 - 4.58 (m, 1H), 4.43 - 4.40 (m, 1H), 4.07 - 4.05 (m, 1H), 3.94 - 3.72 (m, 3H), 3.61 (d, J = 10.4 Hz, 1H), 2.31 - 2.27 (m, 1H), 2.13 - 2.07 (m, 3H), 2.04 - 1.79 (m, 6H)

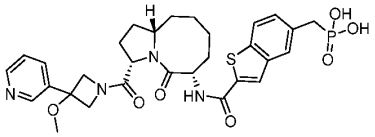
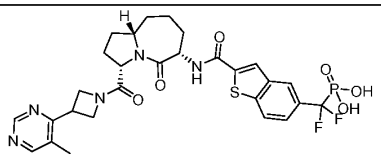
638	((2-(((3S,6S,8R,9aR)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		640.3	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.73 - 8.60 (m, 1H), 8.26 - 8.21 (m, 1H), 8.14 (d, *J* = 17.2 Hz, 1H), 7.90 (d, *J* = 3.6 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.39 - 7.32 (m, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 4.77 (t, *J* = 8.0 Hz, 1H), 4.69 - 4.58 (m, 2H), 4.46 - 4.34 (m, 2H), 4.30 - 4.20 (m, 3H), 4.01 - 3.94 (m, 2H), 3.12 (s, 2H), 3.07 (d, *J* = 4.0 Hz, 6H), 2.27 - 2.15 (m, 1H), 2.07 - 1.90 (m, 2H), 1.87 - 1.75 (m, 3H), 1.69 (d, *J* = 13.2 Hz, 1H), 1.55 - 1.34 (m, 2H), 0.95 (d, *J* = 4.8 Hz, 3H)
639	((2-(((3S,6S,8S,9aR)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		640.1	^{1}H NMR (400 MHz, CD$_3$OD) *δ* 8.23 - 8.12 (m, 1H), 8.00 - 7.93 (m, 1H), 7.81 - 7.67 (m, 3H), 7.35 - 7.33 (m, 1H), 7.03 - 6.83 (m, 1H), 5.00 - 4.97 (m, 1H), 4.67 (t, *J* = 8.8 Hz, 1H), 4.50 - 4.47 (m, 2H), 4.38 (t, *J* = 8.8 Hz, 1H), 4.29 - 4.25 (m, 2H), 4.02 - 3.98 (m, 1H), 3.31 - 3.13 (m, 2H), 3.08 - 3.04 (m, 6H), 2.32 - 2.29 (m, 2H), 2.21 - 2.10 (m, 1H), 2.05 - 1.99 (m, 3H), 1.93 - 1.87 (m, 1H), 1.82 - 1.78 (m, 1H), 1.62 - 1.58 (m, 1H), 1.23 - 1.21 (m, 3H)
640	((2-(((3S,6S,10aS)-3-(((3H-imidazo[4,5-b]pyridin-6-yl)methyl)carbamoy		611.0	^{1}H NMR (400 MHz, CD$_3$OD) δ 8.84 (s, 1H), 8.58 (s, 1H), 8.28 (s, 1H), 7.99 (s, 1H), 7.92 - 7.77 (m,

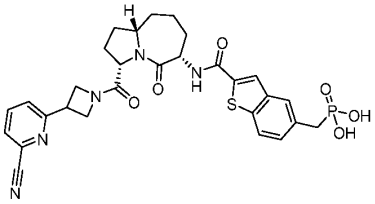
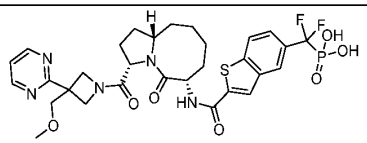
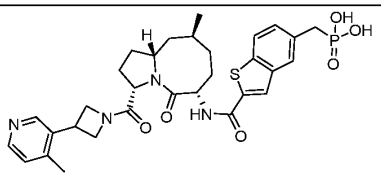
	l)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			2H), 7.44 (d, J = 8.4 Hz, 1H), 5.05 - 4.99 (m, 1H), 4.75 (s, 1H), 4.57 - 4.38 (m, 3H), 3.29 (s, 1H), 3.24 (s, 1H), 2.35 - 2.20 (m, 2H), 2.15 - 2.07 (m, 1H), 2.05 - 1.90 (m, 5H), 1.87 – 1.83 (m, 1H), 1.80 - 1.57 (m, 3H)
641	(difluoro(2-(((3S,6S,10aR,Z)-9-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		659.1	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.94 - 8.85 (m, 1H), 8.36 - 8.27 (m, 1H), 8.16 - 8.00 (m, 2H), 7.98 - 7.91 (m, 1H), 7.62 - 7.50 (m, 1H), 7.33 - 7.16 (m, 1H), 5.58 - 5.50 (m, 1H), 5.03 - 4.95 (m, 1H), 4.62 (t, J = 8.0 Hz, 1H), 4.47 - 4.39 (m, 1H), 4.37 - 4.32 (m, 1H), 4.30 - 4.24 (m, 1H), 4.18 (t, J = 8.4 Hz, 1H), 4.09 - 3.95 (m, 2H), 2.81 - 2.65 (m, 1H), 2.60 - 2.50 (m, 3H), 2.40 - 2.24 (m, 2H), 2.23 (s, 1H), 2.09 (s, 3H), 1.98 - 1.89 (m, 1H), 1.82 (s, 3H)
642	((2-(((3S,6S,10aR,Z)-9-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		623.2	^{1}H NMR (400 MHz, CD$_3$OD) δ 8.39 (s, 1H), 8.09 - 8.02 (m, 1H), 7.87 - 7.78 (m, 1H), 7.73 - 7.60 (m, 2H), 7.44 - 7.27 (m, 2H), 5.62 (t, J = 6.4 Hz, 1H), 5.12 - 5.01 (m, 1H), 4.75 - 4.51 (m, 2H), 4.48 - 4.42 (m, 1H), 4.42 - 4.37 (m, 1H), 4.36 - 4.20 (m, 1H), 4.19 - 4.01 (m, 2H), 3.19 - 3.08 (m, 2H), 2.83 - 2.64 (m, 2H), 2.56 - 2.38 (m, 2H), 2.27 (d, J =

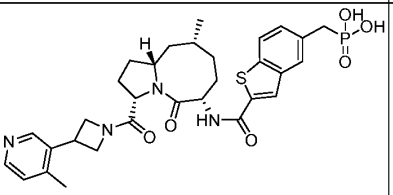
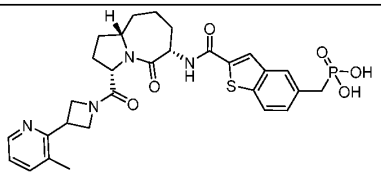
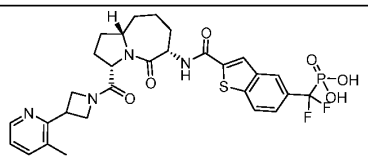
				9.6 Hz, 3H), 2.22 - 2.08 (m, 3H), 2.03 - 1.95 (m, 1H), 1.91 (d, J = 12.0 Hz, 3H)
643	(difluoro(2-(((3S,6S,10aR,Z)-9-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		658.9	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (dd, J = 7.2, 16.0 Hz, 1H), 8.61 - 8.46 (m, 1H), 8.37 - 8.24 (m, 2H), 8.14 - 8.01 (m, 2H), 7.62 - 7.55 (m, 1H), 7.27 - 7.20 (m, 1H), 5.33 (s, 1H), 4.86 - 4.79 (m, 1H), 4.58 (s, 1H), 4.56 - 4.43 (m, 2H), 4.38 - 4.18 (m, 2H), 4.14 - 4.07 (m, 1H), 4.05 - 3.97 (m, 1H), 2.47 - 2.40 (m, 1H), 2.35 - 2.24 (m, 1H), 2.21 (d, J = 1.6 Hz, 3H), 2.07 - 1.88 (m, 3H), 1.84 (td, J = 5.6, 11.6 Hz, 2H), 1.77 (s, 3H), 1.68 - 1.60 (m, 1H)
644	((2-(((3S,6S,10aR,Z)-9-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		623.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.53 - 8.38 (m, 1H), 8.12 - 7.97 (m, 1H), 7.82 (s, 1H), 7.77 - 7.64 (m, 2H), 7.42 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 5.6 Hz, 1H), 5.41 (s, 1H), 5.01 - 4.88 (m, 2H), 4.77 - 4.52 (m, 4H), 4.24 - 4.17 (m, 1H), 4.13 - 4.06 (m, 1H), 3.22 - 3.10 (m, 2H), 2.32 (s, 1H), 2.29 (s, 3H), 2.19 - 2.10 (m, 2H), 2.10 - 2.01 (m, 2H), 2.01 - 1.89 (m, 2H), 1.85 (s, 3H), 1.82 (s, 1H)

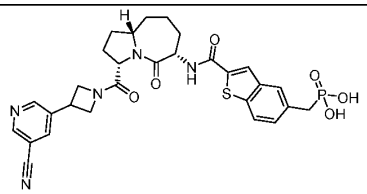
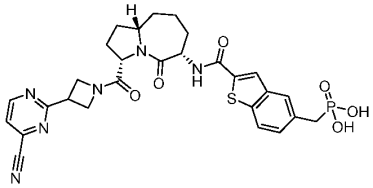
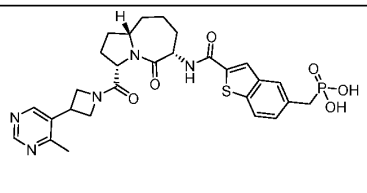
645	(difluoro(2-(((3S,6S,10aS)-3-((2-hydroxy-1-(1H-pyrrolo[2,3-b]pyridin-3-yl)ethyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		676.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.74 - 8.50 (m, 1H), 8.20 (d, *J* = 5.6 Hz, 1H), 8.13 - 8.03 (m, 1H), 7.96 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.71 - 7.63 (m, 2H), 7.42 - 7.29 (m, 1H), 5.35 - 5.25 (m, 1H), 5.02 - 4.94 (m, 1H), 4.54 - 4.45 (m, 1H), 4.44 - 4.36 (m, 1H), 3.92 (d, *J* = 6.0 Hz, 2H), 2.33 - 2.09 (m, 3H), 1.99 - 1.81 (m, 6H), 1.76 - 1.56 (m, 3H)
646	((2-(((3S,6S,9aS)-3-(3-(4-methyl-6-oxo-1,6-dihydropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		613.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (d, J=8.00 Hz, 1H) 8.17 (d, J=8.00 Hz, 1H) 7.82 - 7.97 (m, 1H) 7.78 (s, 1H) 7.19 (s, 2H) 6.21 (d, J=4.00 Hz, 1H) 4.64 (s, 2H) 4.40 - 4.49 (m, 2H) 4.25 - 4.34 (m, 2H) 4.16 (s, 1H) 3.83 (s, 1H) 3.06 - 3.13 (m, 2H) 2.15 - 2.23 (m, 1H) 1.93 - 2.04 (m, 5H) 1.66 - 1.87 (m, 7H)
647	((2-(((3S,6S,10aS)-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		611.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.76 - 8.66 (m, 1H), 8.49 - 8.37 (m, 1H), 7.96 (s, 1H), 7.82 - 7.66 (m, 3H), 7.43 - 7.32 (m, 1H), 5.03 - 4.93 (m, 1H), 4.79 - 4.53 (m, 2H), 4.52 - 4.39 (m, 3H), 4.30 - 4.22 (m, 1H), 4.21 - 4.08 (m, 1H), 3.26 - 3.14 (m, 2H), 2.46 (s, 3H), 2.35 - 2.16 (m, 2H), 2.12 - 1.83 (m, 8H), 1.75 - 1.54 (m, 2H)

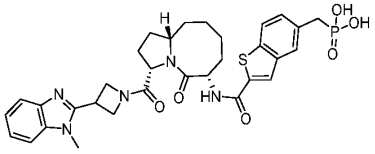
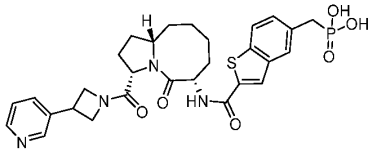
648	(difluoro(2-(((3S,6S,9aS)-3-(3-(3-methylpyrazin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		634.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (d, *J* = 2.4 Hz, 1H), 8.36 - 8.27 (m, 1H), 8.23 - 8.05 (m, 2H), 7.93 (d, *J* = 9.6 Hz, 1H), 7.78 - 7.70 (m, 1H), 4.80 - 4.69 (m, 2H), 4.67 - 4.50 (m, 2H), 4.47 - 4.39 (m, 1H), 4.33 - 4.22 (m, 2H), 4.09 - 4.02 (m, 1H), 2.50 (d, *J* = 8.8 Hz, 3H), 2.35 - 2.25 (m, 1H), 2.16 - 2.05 (m, 2H), 2.03 - 1.79 (m, 7H)
649	((2-(((3S,6S,9aS)-3-(3-(3-methylpyrazin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		598.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.50 - 8.43 (m, 1H), 8.37 - 8.31 (m, 1H), 7.97 (d, *J* = 16.8 Hz, 1H), 7.86 (d, *J* = 12.0 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.50 - 7.44 (m, 1H), 4.89 - 4.83 (m, 1H), 4.74 (d, *J* = 10.8 Hz, 1H), 4.60 (d, *J* = 4.4 Hz, 1H), 4.57 - 4.53 (m, 1H), 4.46 - 4.41 (m, 1H), 4.32 (d, *J* = 7.6 Hz, 1H), 4.23 (d, *J* = 8.8 Hz, 1H), 4.09 - 3.80 (m, 2H), 3.11 (d, *J* = 4.0 Hz, 1H), 3.06 (d, *J* = 4.0 Hz, 1H), 2.50 (d, *J* = 7.6 Hz, 3H), 2.29 (d, *J* = 6.4 Hz, 1H), 2.11 - 2.02 (m, 2H), 1.97 - 1.81 (m, 6H)
650	((2-(((3S,6S,9aS)-3-(3-(5-methylpyrimidin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		598.3	^{1}H NMR (400 MHz, CD_3OD) δ 9.02 (d, *J* = 12.0 Hz, 1H), 8.57 - 8.50 (m, 1H), 8.00 (d, *J* = 19.2 Hz, 1H), 7.87 - 7.81 (m, 2H), 7.46 - 7.39 (m, 1H), 4.84 - 4.81 (m, 1H), 4.76 - 4.71 (m, 1H), 4.67 - 4.54 (m, 2H), 4.48 -

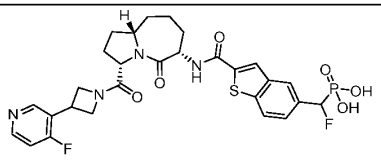
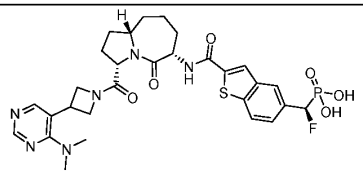
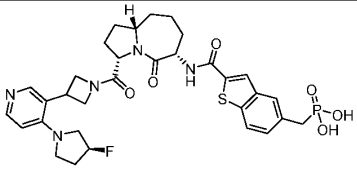
	yl)methyl)phosphonic acid			4.39 (m, 1H), 4.34 - 4.21 (m, 2H), 4.10 - 4.03 (m, 1H), 3.28 (d, *J* = 4.4 Hz, 1H), 3.23 (d, *J* = 4.4 Hz, 1H), 2.36 - 2.29 (m, 1H), 2.27 (d, *J* = 6.0 Hz, 3H), 2.16 - 2.05 (m, 2H), 2.02 - 1.81 (m, 7H)
651	((2-(((3S,6S,10aS)-3-(3-methoxy-3-(pyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		627.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.92 - 8.84 (m, 1H), 8.76 - 8.63 (m, 1H), 8.57 - 8.42 (m, 1H), 8.07 - 7.96 (m, 1H), 7.92 - 7.74 (m, 3H), 7.45 - 7.36 (m, 1H), 4.99 (d, J = 7.6 Hz, 2H), 4.68 - 4.53 (m, 1H), 4.52 - 4.39 (m, 2H), 4.34 - 4.17 (m, 2H), 3.28 - 3.18 (m, 5H), 2.37 - 2.19 (m, 2H), 2.07 - 1.91 (m, 6H), 1.89 - 1.75 (m, 2H), 1.74 - 1.58 (m,2H)
652	(difluoro(2-(((3S,6S,9aS)-3-(3-(5-methylpyrimidin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		634.0	^{1}H NMR (400 MHz, CD_3OD) δ 9.04 - 8.94 (m, 1H), 8.57 - 8.45 (m, 1H), 8.24 - 8.15 (m, 1H), 8.13 - 8.05 (m, 1H), 7.97 - 7.87 (m, 1H), 7.80 - 7.71 (m, 1H), 4.89 - 4.83 (m, 1H), 4.76 - 4.73 (m, 1H), 4.64 - 4.54 (m, 2H), 4.49 - 4.40 (m, 1H), 4.33 - 4.20 (m, 2H), 4.10 - 4.01 (m, 1H), 2.31 (d, *J* = 4.8 Hz, 1H), 2.29 - 2.24 (m, 3H), 2.16 - 2.05 (m, 2H), 2.03 - 1.80 (m, 7H)

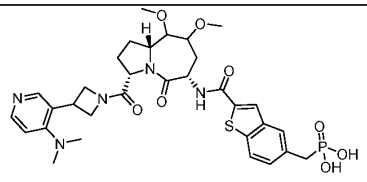
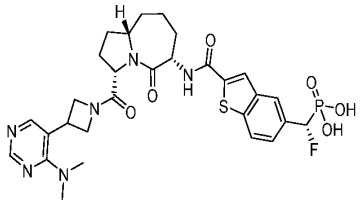
653	((2-(((3S,6S,9aS)-3-(3-(6-cyanopyridin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		608.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.03 - 7.90 (m, 2H), 7.86 (d, *J* = 7.2 Hz, 1H), 7.82 - 7.57 (m, 3H), 7.51 - 7.42 (m, 1H), 4.72 - 4.69 (m, 1H), 4.61 – 4.58 (m, 1H), 4.44 (s, 3H), 4.14 (d, *J* = 6.0 Hz, 3H), 3.18 - 3.09 (m, 2H), 2.35 - 2.27 (m, 1H), 2.18 - 2.06 (m, 2H), 2.04 (s, 2H), 2.01 - 1.94 (m, 2H), 1.93 - 1.86 (m, 2H), 1.84 (s, 1H)
654	(difluoro(2-(((3S,6S,10aS)-3-(3-(methoxymethyl)-3-(pyrimidin-2-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		678.4	^{1}H NMR (400 MHz, ACETONITRILE-d_3) δ 8.07 (s, 2H), 8.00 - 7.92 (m, 2H), 7.75 (s, 1H), 7.57 (d, J = 8.4 Hz, 1H), 5.71 - 5.60 (m, 4H), 5.01 (q, J = 7.6 Hz, 1H), 4.93 - 4.84 (m, 1H), 4.23 (d, J = 4.8 Hz, 1H), 3.79 - 3.43 (m, 8H), 2.39 - 2.30 (m, 2H), 2.10 (d, J = 7.6 Hz, 2H), 1.92 - 1.82 (m, 2H), 1.67 (m, 1H), 1.52 - 1.40 (m, 1H), 1.31 (s, 1H), 1.15 (s, 18H), 0.93 - 0.84 (m, 1H), 0.80 (m, 1H), 0.01 (m, 1H)
655	((2-(((3S,6S,9S,10aR)-9-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		625.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.75 (d, J = 12.0 Hz, 1H), 8.56 - 8.36 (m, 1H), 8.02 - 7.92 (m, 1H), 7.85 - 7.66 (m, 3H), 7.39 (dd, J = 7.6, 17.6 Hz, 1H), 4.84 - 4.70 (m, 2H), 4.67 - 4.52 (m, 1H), 4.49 - 4.37 (m, 3H), 4.32 - 4.21 (m, 1H), 4.19 - 4.10 (m, 1H), 3.25 (s, 1H), 3.19 (s, 1H), 2.52 -

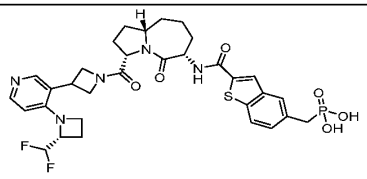
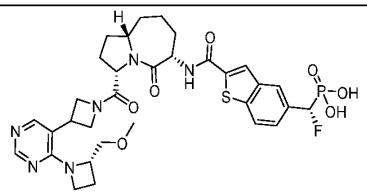
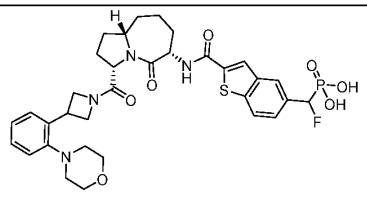
				2.40 (m, 3H), 2.37 - 2.27 (m, 1H), 2.23 - 2.06 (m, 3H), 2.00 - 1.91 (m, 2H), 1.90 - 1.81 (m, 2H), 1.80 - 1.68 (m, 2H), 1.42 - 1.32 (m, 1H), 1.05 (d, J = 6.4 Hz, 3H)
656	((2-(((3S,6S,9R,10aR)-9-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		625.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.83 - 8.69 (m, 1H), 8.50 - 8.36 (m, 1H), 7.99 (s, 1H), 7.85 - 7.67 (m, 3H), 7.47 - 7.31 (m, 1H), 4.72 (s, 1H), 4.65 - 4.55 (m, 1H), 4.54 – 4.53 (m, 1H), 4.51 - 4.43 (m, 3H), 4.42 - 4.34 (m, 1H), 4.28-4.25 (m, 1H), 4.13 (dd, J = 6.4, 10.0 Hz, 1H), 3.27 - 3.15 (m, 2H), 2.47 (s, 3H), 2.29 - 2.21 (m, 2H), 2.09 - 1.99 (m, 3H), 1.93 - 1.79 (m, 3H), 1.63 (m, 1H), 1.52 - 1.41 (m, 1H), 1.06 (s, 3H)
657	((2-(((3S,6S,9aS)-3-(3-(3-methylpyridin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		597.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.46 - 8.29 (m, 1H), 8.05 - 7.90 (m, 1H), 7.88 - 7.74 (m, 2H), 7.68 - 7.58 (m, 1H), 7.48 - 7.37 (m, 1H), 7.28 - 7.17 (m, 1H), 4.85 - 4.69 (m, 2H), 4.68 - 4.50 (m, 2H), 4.46 - 4.16 (m, 3H), 4.06 (d, J = 5.2 Hz, 1H), 3.28 - 3.17 (m, 2H), 2.37 - 2.22 (m, 4H), 2.20 - 1.73 (m, 10H)
658	(difluoro(2-(((3S,6S,9aS)-3-(3-(3-methylpyridin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-		633.0	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (dd, J = 7.2, 12.8 Hz, 1H), 8.42 (dd, J = 4.0, 14.0 Hz, 1H), 8.30 (d, J = 19.6 Hz, 1H), 8.19

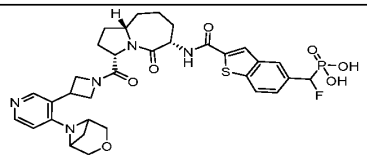
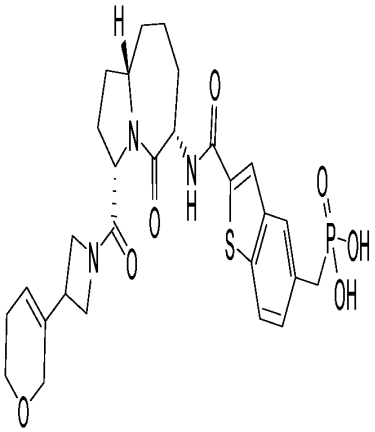
	pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			- 7.99 (m, 2H), 7.70 - 7.53 (m, 2H), 7.29 - 7.13 (m, 1H), 4.73 - 4.41 (m, 4H), 4.30 - 4.06 (m, 4H), 2.21 (d, J = 3.0 Hz, 3H), 2.09 - 1.60 (m, 10H)
659	((2-(((3S,6S,9aS)-3-(3-(5-cyanopyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		607.9	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.86 (dd, J = 2.0, 10.4 Hz, 1H), 8.70 (dd, J = 7.6, 10.4 Hz, 1H), 8.50 - 8.34 (m, 1H), 8.17 (d, J = 12.8 Hz, 1H), 7.90 (dd, J = 5.6, 8.0 Hz, 1H), 7.79 (s, 1H), 7.36 (dd, J = 1.2, 8.4 Hz, 1H), 4.82 - 4.59 (m, 2H), 4.48 - 4.24 (m, 3H), 4.06 - 3.90 (m, 3H), 3.15 - 3.04 (m, 2H), 2.25 - 2.15 (m, 1H), 2.09 - 1.93 (m, 2H), 1.92 - 1.77 (m, 4H), 1.73 (s, 2H), 1.70 - 1.60 (m, 1H)
660	((2-(((3S,6S,9aS)-3-(3-(4-cyanopyrimidin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		609.0	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.16 (m, 1H) 8.69 (m, 1H) 8.16 (d, J=16.0 Hz, 1H) 8.04 (m, 1H) 7.90 (m, 1H) 7.78 (m, 1H) 7.36 (m, 1H) 4.77 (m, 1H) 4.56 - 4.65 (m, 2H) 4.40 - 4.49 (m, 2H) 4.21 - 4.30 (m, 2H) 4.11 - 4.17 (m, 1H) 3.98 - 4.05 (m, 2H) 3.06 - 3.14 (m, 2H) 2.16 - 2.24 (m, 1H) 1.95 - 2.06 (m, 2H) 1.69 - 1.87 (m, 7H)
661	((2-(((3S,6S,9aS)-3-(3-(4-methylpyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-		597.9	^{1}H NMR (400 MHz, CD_3OD) δ 8.96 - 8.90 (m, 1H), 8.89 - 8.73 (m, 1H), 8.03 - 7.95 (m, 1H), 7.87 - 7.79 (m, 2H), 7.47 - 7.38

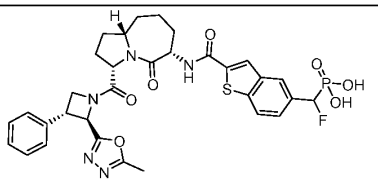
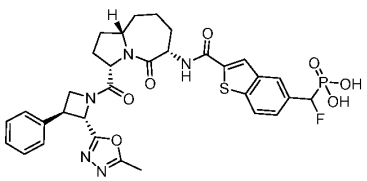
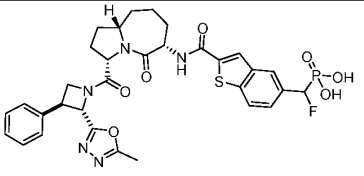
	pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			(m, 1H), 4.95 - 4.90 (m, 1H), 4.76 - 4.64 (m, 2H), 4.60 - 4.53 (m, 1H), 4.51 - 4.37 (m, 1H), 4.24 - 4.11 (m, 2H), 4.10 - 4.02 (m, 1H), 3.29 - 3.20 (m, 2H), 2.52 - 2.45 (m, 3H), 2.35 - 2.25 (m, 1H), 2.19 - 2.04 (m, 2H), 2.03 - 1.72 (m, 7H)
662	((2-(((3S,6S,10aS)-3-(3-(1-methyl-1H-benzo[d]imidazol-2-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		650.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 - 8.70 (m, 1H), 8.26 - 8.07 (m, 1H), 7.84 - 7.64 (m, 2H), 7.63 – 7.58 (m, 1H), 7.51 – 7.46 (m, 1H), 7.30 (d, *J* = 6.0 Hz, 1H), 7.25 - 7.11 (m, 2H), 4.92 (d, *J* = 7.6 Hz, 1H), 4.79 - 4.47 (m, 2H), 4.39 - 4.13 (m, 5H), 3.66 (d, *J* = 1.6 Hz, 3H), 2.92 - 2.79 (m, 2H), 2.35 - 1.41 (m, 12H)
663	((2-(((3S,6S,10aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		597.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.83 - 8.68 (m, 1H), 8.66 - 8.58 (m, 1H), 8.55 - 8.37 (m, 1H), 8.04 (s, 1H), 7.91 - 7.73 (m, 3H), 7.42 (d, *J* = 8.4 Hz, 1H), 5.04 - 5.00 (m, 1H), 4.73 (s, 1H), 4.65 (d, *J* = 5.6 Hz, 1H), 4.56 - 4.43 (m, 3H), 4.15 - 4.01 (m, 2H), 3.28 - 3.20 (m, 2H), 2.30 - 2.26 (m, 1H), 2.07 - 2.01 (m, 3H), 1.88 - 1.80 (m, 2H), 1.72 - 1.61 (m, 2H), 1.42 - 1.24 (m, 4H)

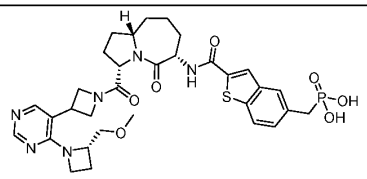
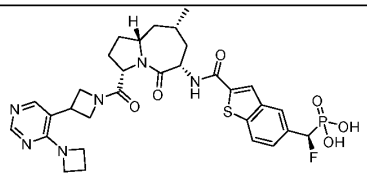
664	(fluoro(2-(((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		619.0	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 - 8.68 (m, 1H), 8.60 - 8.31 (m, 1H), 8.29 - 8.14 (m, 1H), 8.09 - 7.94 (m, 2H), 7.59 - 7.46 (m, 1H), 7.41 - 7.01 (m, 1H), 5.92 - 5.75 (m, 1H), 4.69 - 4.63 (m, 1H), 4.59 - 4.47 (m, 1H), 4.45 – 4.42 (m, 1H), 4.32 – 4.25 (m, 1H), 4.22 - 4.11 (m, 1H), 4.09 - 3.96 (m, 3H), 2.26 - 2.12 (m, 1H), 2.11 - 1.92 (m, 2H), 1.92 - 1.75 (m, 4H), 1.73 (s, 3H)
665	((R)-(2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		645.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.35 - 8.24 (m, 1H), 8.20 - 8.12 (m, 1H), 8.07 - 7.97 (m, 1H), 7.93 (d, J = 9.6 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.64 - 7.54 (m, 1H), 5.84 - 5.66 (m, 1H), 4.77 - 4.61 (m, 2H), 4.56 - 4.44 (m, 2H), 4.36 (s, 1H), 4.25 - 4.14 (m, 1H), 4.12 - 3.94 (m, 2H), 3.30 (s, 2H), 3.24 (s, 4H), 2.34 - 2.26 (m, 1H), 2.20 - 2.06 (m, 2H), 2.06 - 1.96 (m, 2H), 1.96 - 1.89 (m, 2H), 1.89 - 1.74 (m, 3H)
666	((2-(((3S,6S,9aS)-3-(3-(4-((S)-3-fluoropyrrolidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		670.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 8.08 - 7.93 (m, 2H), 7.87 - 7.79 (m, 2H), 7.47 - 7.40 (m, 1H), 6.92 (s, 1H), 5.50 - 5.33 (m, 1H), 4.81 - 4.61 (m, 2H), 4.61 - 4.49 (m, 2H), 4.48 - 4.45 (m, 1H), 4.45 - 4.39 (m, 1H),

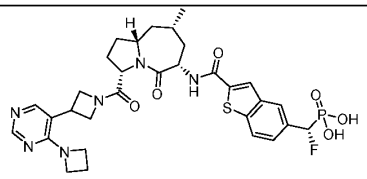
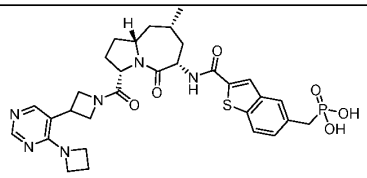
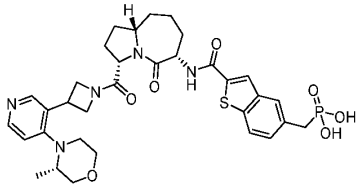
	yl)methyl)phosphonic acid			4.21 - 4.06 (m, 2H), 4.0 (s, 2H), 3.80 (s, 2H), 3.30 - 3.20 (m, 2H), 2.46 - 2.37 (m, 1H), 2.36 - 2.30 (m, 1H), 2.28 - 2.08 (m, 3H), 2.08 - 1.93 (m, 4H), 1.92 (s, 3H)
667	((S)-(2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		645.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (d, J = 8.4 Hz, 1H), 8.32 - 8.19 (m, 1H), 8.07 - 7.96 (m, 2H), 7.93 - 7.86 (m, 1H), 7.66 - 7.55 (m, 1H), 5.88 - 5.65 (m, 1H), 4.73 (d, J = 11.2 Hz, 1H), 4.66 (t, J = 8.8 Hz, 1H), 4.57 - 4.48 (m, 2H), 4.42 - 4.33 (m, 1H), 4.29 - 4.22 (m, 1H), 4.12 - 3.99 (m, 2H), 3.28 (d, J = 3.6 Hz, 6H), 2.36 - 2.25 (m, 1H), 2.16 - 2.06 (m, 2H), 2.05 - 1.94 (m, 3H), 1.94 - 1.86 (m, 2H), 1.85 (s, 2H)
668	((2-(((3S,6S,9aS)-3-(3-(4-((R)-2-(difluoromethyl)azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		688.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.50 - 8.34 (m, 1H), 8.20 - 7.94 (m, 2H), 7.89 - 7.75 (m, 2H), 7.52 - 7.33 (m, 1H), 7.02 - 6.82 (m, 1H), 6.43 - 6.03 (m, 1H), 4.69 - 4.64 (m, 2H), 4.56 - 4.49 (m, 2H), 4.42 - 4.33 (m, 2H), 4.28 - 4.26 (m, 1H), 4.16 - 4.06 (m, 3H), 4.01 - 3.97 (m, 1H), 3.29 - 3.26 (m, 2H), 2.71 - 2.64 (m, 1H), 2.47 - 2.42 (m, 1H), 2.33 - 2.28 (m, 1H), 2.12 - 2.06 (m, 2H), 1.99 - 1.93 (m, 3H), 1.89 - 1.78 (m, 4H)

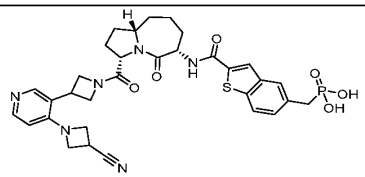
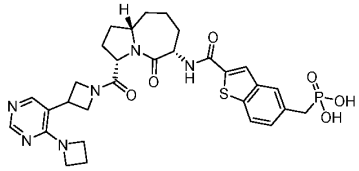
669	((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-((S)-2-(methoxymethyl)azetidin-1-yl)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		701.5	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.72 (dd, J = 7.6, 16.4 Hz, 1H), 8.62 (d, J = 18.2 Hz, 1H), 8.43 - 8.27 (m, 1H), 8.23 (d, J = 12.0 Hz, 1H), 8.07 - 8.01 (m, 1H), 7.98 (s, 1H), 7.53 (d, J = 8.8 Hz, 1H), 5.96 - 5.71 (m, 1H), 4.81 - 4.72 (m, 1H), 4.65 (t, J = 8.8 Hz, 2H), 4.53 - 4.40 (m, 3H), 4.26 - 4.13 (m, 3H), 4.00 - 3.93 (m, 3H), 3.76 (d, J = 5.2 Hz, 1H), 3.59 (d, J = 7.6 Hz, 1H), 3.29 (d, J = 3.6 Hz, 3H), 2.45 - 2.37 (m, 1H), 2.33 - 2.16 (m, 2H), 2.07 - 1.92 (m, 2H), 1.90 - 1.62 (m, 7H)
670	(fluoro(2-(((3S,6S,9aS)-3-(3-(2-morpholinophenyl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		685.1	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.65 - 8.41 (m, 1H), 8.21 (d, J = 7.2 Hz, 1H), 8.10 - 7.91 (m, 3H), 7.71 - 7.51 (m, 3H), 5.92 - 5.71 (m, 1H), 4.73 - 4.51 (m, 2H), 4.42 - 4.25 (m, 1H), 4.24 - 4.11 (m, 2H), 4.11 - 4.03 (m, 2H), 4.03 - 3.92 (m, 2H), 3.91 - 3.83 (m, 1H), 3.75 - 3.65 (m, 2H), 3.63 - 3.56 (m, 2H), 3.53 - 3.47 (m, 2H), 2.23 - 2.10 (m, 1H), 2.08 - 1.87 (m, 3H), 1.87 - 1.53 (m, 6H)
671	((2-(((3S,6S,9aS)-3-(3-(4-(3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-		698.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.82 - 8.54 (m, 1H), 8.23 - 8.07 (m, 2H), 7.95 - 7.84 (m, 2H), 7.54 - 7.42 (m, 1H), 6.71 - 6.51 (m, 1H), 5.56-

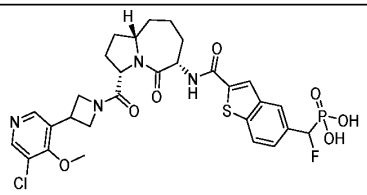
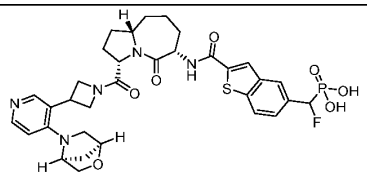
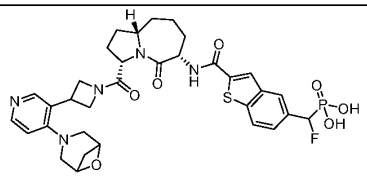
	pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid			5.44 (m, 1H), 4.68 - 4.61 (m, 1H), 4.53 - 4.38 (m, 4H), 4.28 - 4.20 (m, 1H), 4.18 - 4.10 (m, 1H), 4.03 - 3.90 (m, 5H), 3.70 (d, J = 6.2 Hz, 2H), 2.23 - 2.17 (m, 1H), 2.02 - 1.94 (m, 2H), 1.88 - 1.63 (m, 9H)
672	((2-(((3S,6S,9aS)-3-(3-(5,6-dihydro-2H-pyran-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		588.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.01 (s, 1H), 7.85 (d, J = 4.8 Hz, 2H), 7.43 (d, J = 8.4 Hz, 1H), 5.83 (s, 1H), 4.73 (d, J = 10.8 Hz, 1H), 4.64 - 4.49 (m, 2H), 4.44 - 4.32 (m, 1H), 4.20 - 4.13 (m, 1H), 4.07 (t, J = 9.6 Hz, 4H), 3.96 - 3.84 (m, 1H), 3.74 (td, J = 5.6, 8.0 Hz, 2H), 3.28 (s, 1H), 3.24 - 3.21 (m, 1H), 2.34 - 2.25 (m, 1H), 2.17 (td, J = 1.6, 2.8 Hz, 2H), 2.12 - 2.04 (m, 2H), 2.01 (d, J = 12.0 Hz, 1H), 1.97 - 1.86 (m, 4H), 1.83 (d, J = 11.2 Hz, 2H)
673	(fluoro(2-(((3S,6S,9aS)-3-((2R,3R)-2-(5-methyl-1,3,4-oxadiazol-2-yl)-3-phenylazetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid Or (fluoro(2-(((3S,6S,9aS)-3-((2S,3S)-2-(5-	 HPLC Peak 1 of LHS BB used for synthesis and biological testing	682.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.12 - 8.05 (m, 2H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 4.0 Hz, 1H), 7.39 - 7.34 (m, 3H), 5.92 - 5.76 (m, 1H), 5.46 - 5.45 (m, 1H), 4.81 - 4.61 (m, 3H), 4.48 - 4.40 (m, 1H), 4.17 - 4.04 (m, 2H), 2.58 - 2.48 (m, 3H), 2.35 - 2.14 (m, 2H), 2.12 - 2.06 (m, 1H), 2.01 - 2.00 (m,

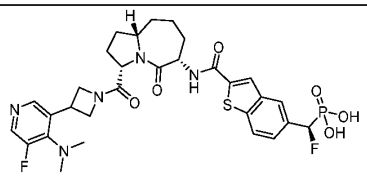
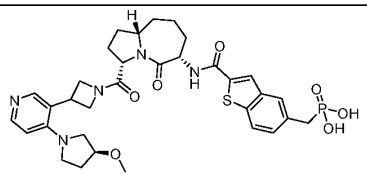
	methyl-1,3,4-oxadiazol-2-yl)-3-phenylazetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			1H), 1.95 - 1.79 (m, 6H)
674	(fluoro(2-(((3S,6S,9aS)-3-((2R,3R)-2-(5-methyl-1,3,4-oxadiazol-2-yl)-3-phenylazetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid Or (fluoro(2-(((3S,6S,9aS)-3-((2S,3S)-2-(5-methyl-1,3,4-oxadiazol-2-yl)-3-phenylazetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid	 or  HPLC Peak 2 of LHS BB used for synthesis and biological testing	682.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.10 - 8.04 (m, 2H), 8.00 - 7.94 (m, 1H), 7.61 - 7.59 (m, 1H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.37 - 7.29 (m, 3H), 5.90 - 5.76 (m, 1H), 5.40 (d, *J* = 6.4 Hz, 1H), 4.85 - 4.72 (m, 3H), 4.66 - 4.64 (m, 1H), 4.17 - 4.01 (m, 2H), 2.57 - 2.56 (m, 3H), 2.33 - 2.28 (m, 1H), 2.22 - 2.19 (m, 1H), 2.17 - 2.05 (m, 1H), 2.02 - 1.99 (m, 1H), 1.87 - 1.86 (m, 6H)
675	((2-(((3S,6S,9aS)-3-(3-(4-((S)-2-(methoxymethyl)azetidin-1-yl)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-		683.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.30 - 8.17 (m, 1H), 8.04 (d, J = 14.4 Hz, 1H), 7.94 (d, J = 4.0 Hz, 1H), 7.78 (d, J = 5.2 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.47 - 7.39 (m, 1H), 4.72 (t, J = 8.8 Hz, 2H), 4.65 - 4.57

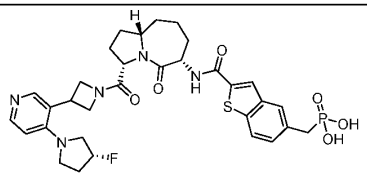
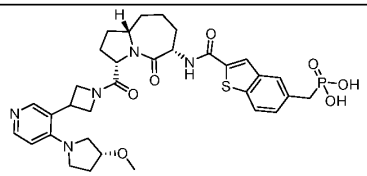
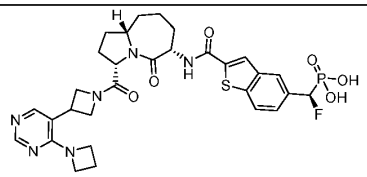
	yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			(m, 1H), 4.57 - 4.48 (m, 2H), 4.42 - 4.26 (m, 1H), 4.25 - 4.16 (m, 1H), 4.09 - 4.03 (m, 2H), 4.02 - 3.88 (m, 2H), 3.86 - 3.83 (m, 1H), 3.60 - 3.54 (m, 1H), 3.36 (d, J = 12.0 Hz, 3H), 3.17 - 3.03 (m, 2H), 2.56 - 2.42 (m, 1H), 2.42 - 2.24 (m, 2H), 2.16 - 2.04 (m, 2H), 2.01 - 1.78 (m, 7H)
676	((R)-(2-(((3S,6S,8R,9aR)-3-(3-(4-(azetidin-1-yl)pyrimidin-5-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		671.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.36 - 8.02 (m, 2H), 7.99 (d, *J* = 6.8 Hz, 2H), 7.87 (t, *J* = 10.0 Hz, 1H), 7.56 (t, *J* = 8.4 Hz, 1H), 5.83 - 5.69 (m, 1H), 4.75 (d, *J* = 11.2 Hz, 2H), 4.55 - 4.43 (m, 6H), 4.29 - 4.14 (m, 1H), 4.08 - 4.04 (m, 3H), 2.47 - 2.43 (m, 2H), 2.35 - 2.25 (m, 1H), 2.15 - 2.03 (m, 2H), 1.97 - 1.91 (m, 3H), 1.80 (d, *J* = 13.6 Hz, 1H), 1.63 - 1.60 (m, 2H), 1.05 (d, *J* = 4.0 Hz, 3H)
677	((S)-(2-(((3S,6S,8R,9aR)-3-(3-(4-(azetidin-1-yl)pyrimidin-5-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		671.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.40 - 8.18 (m, 1H), 8.08 - 7.94 (m, 3H), 7.89 (d, J = 8.4 Hz, 1H), 7.61 (t, J = 9.2 Hz, 1H), 5.85 - 5.68 (m, 1H), 4.79 - 4.71 (m, 2H), 4.61 - 4.42 (m, 6H), 4.31 - 4.19 (m, 1H), 4.14 - 3.97 (m, 3H), 2.53 - 2.41 (m, 2H), 2.35 - 2.27 (m, 1H), 2.14 - 2.02 (m, 2H), 1.99 - 1.94 (m, 2H), 1.83 - 1.76 (m, 1H), 1.68 - 1.53 (m, 2H), 1.34 -

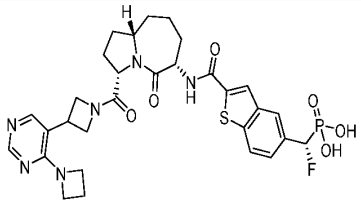
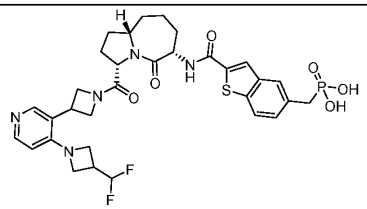
				1.27 (m, 1H), 1.08 - 1.03 (m, 3H)
678	((2-(((3S,6S,8R,9aR)-3-(3-(4-(azetidin-1-yl)pyrimidin-5-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		653.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (d, J = 2.0 Hz, 1H), 8.22 (d, J = 17.6 Hz, 1H), 7.99 (d, J = 6.4 Hz, 1H), 7.86 - 7.81 (m, 2H), 7.45 - 7.40 (m, 1H), 4.78 - 4.72 (m, 1H), 4.62 - 4.49 (m, 6H), 4.45 - 4.34 (m, 1H), 4.30 (t, J = 8.4 Hz, 1H), 4.14 - 4.02 (m, 3H), 3.27 - 3.19 (m, 2H), 2.55 - 2.43 (m, 2H), 2.32 (td, J = 6.8, 13.2 Hz, 1H), 2.16 - 2.03 (m, 2H), 1.99 - 1.93 (m, 2H), 1.80 (dd, J = 2.8, 14.8 Hz, 1H), 1.67 - 1.52 (m, 2H), 1.37 - 1.27 (m, 1H), 1.05 (d, J = 6.8 Hz, 3H)
679	((2-(((3S,6S,9aS)-3-(3-(4-((S)-3-methylmorpholino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		682.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.38 - 8.10 (m, 1H), 8.08 - 7.84 (m, 1H), 7.83 - 7.51 (m, 3H), 7.50 - 7.25 (m, 1H), 7.15 - 6.70 (m, 1H), 4.79 - 4.66 (m, 3H), 4.57 - 4.28 (m, 3H), 4.25 - 3.98 (m, 3H), 3.96 - 3.46 (m, 4H), 3.23 - 2.94 (m, 3H), 2.92 - 2.52 (m, 1H), 2.40 - 2.23 (m, 1H), 2.20 - 2.06 (m, 2H), 2.05 - 1.73 (m, 7H), 1.24 - 0.94 (m, 3H)
680	((2-(((3S,6S,9aS)-3-(3-(4-(3-cyanoazetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-		663.3	^{1}H NMR (400 MHz, CD_3OD) 8.23 (d, *J* = 6.8 Hz, 1H), 8.02 - 7.88 (m, 2H), 7.83 - 7.72 (m, 2H), 7.40 (t, *J* = 7.2 Hz, 1H), 6.48 - 6.42 (m, 1H), 4.85 - 4.68 (m, 2H), 4.67 -

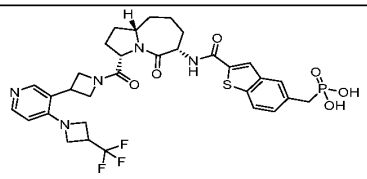
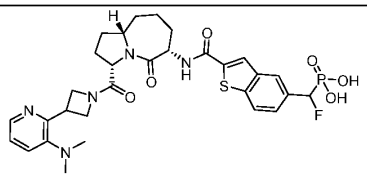
	a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			4.56 (m, 3H), 4.56 - 4.40 (m, 3H), 4.39 - 4.24 (m, 1H), 4.18 - 3.96 (m, 3H), 3.94 - 3.80 (m, 1H), 3.29 - 3.15 (m, 2H), 2.39 - 2.22 (m, 1H), 2.20 - 2.05 (m, 2H), 2.05 - 2.01 (m, 1H), 2.01 - 1.89 (m, 3H), 1.89 - 1.72 (m, 3H)
681	((2-(((3S,6S,9aS)-3-(3-(4-(azetidin-1-yl)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		639.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.46 - 8.42 (m, 1H), 8.20 (d, J = 12.8 Hz, 1H), 7.98 (d, J = 4.8 Hz, 1H), 7.86 - 7.79 (m, 2H), 7.45 - 7.39 (m, 1H), 4.73 (d, J = 10.8 Hz, 1H), 4.63 - 4.46 (m, 7H), 4.33 - 4.26 (m, 1H), 4.12 - 4.02 (m, 3H), 3.26 - 3.18 (m, 2H), 2.54 - 2.43 (m, 2H), 2.35 - 2.27 (m, 1H), 2.15 - 2.06 (m, 2H), 2.04 - 1.90 (m, 4H), 1.88 - 1.78 (m, 3H)
682	((2-(((3S,6S,9aS)-3-(3-(5-chloro-4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		665.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 - 8.67 (m, 1H), 8.54 (t, J = 6.4 Hz, 2H), 8.18 (d, J = 13.6 Hz, 1H), 7.94 - 7.85 (m, 2H), 7.58 - 7.47 (m, 1H), 7.34 - 7.02 (m, 2H), 5.54 - 5.29 (m, 1H), 4.83 - 4.58 (m, 2H), 4.48 - 4.44 (m, 1H), 4.36 - 4.19 (m, 2H), 4.16 - 4.08 (m, 1H), 4.04 - 3.96 (m, 2H), 3.91 (d, J = 3.6 Hz, 3H), 2.25 - 2.15 (m, 1H), 2.06 - 1.93 (m, 2H), 1.89 - 1.76 (m, 4H), 1.76 - 1.66 (m, 3H)

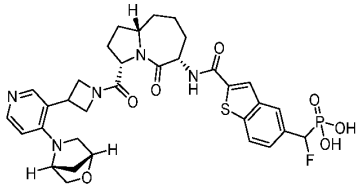
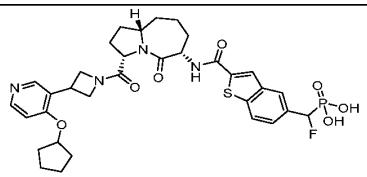
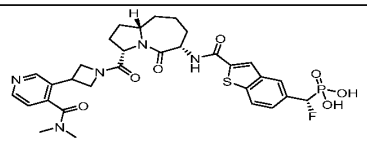
683	((2-(((3S,6S,9aS)-3-(3-(4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		698.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 8.09 - 7.98 (m, 3H), 7.97 (d, J = 1.6 Hz, 1H), 7.64 - 7.56 (m, 1H), 7.02 - 6.95 (m, 1H), 5.91 - 5.70 (m, 1H), 4.78 - 4.68 (m, 3H), 4.62 - 4.33 (m, 4H), 4.29 - 3.99 (m, 3H), 3.87 (s, 3H), 3.42 (d, J = 9.6 Hz, 1H), 2.36 - 2.26 (m, 1H), 2.17 - 2.06 (m, 4H), 2.06 - 1.91 (m, 4H), 1.90 - 1.77 (m, 3H)
684	((2-(((3S,6S,9aS)-3-(3-(4-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		698.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.38 - 8.35 (m, 1H), 8.17 - 7.97 (m, 3H), 7.95 - 7.88 (m, 1H), 7.64 - 7.52 (m, 1H), 7.29 - 7.14 (m, 1H), 5.89 - 5.69 (m, 1H), 4.76 - 4.63 (m, 4H), 4.62 - 4.44 (m, 3H), 4.42 - 4.33 (m, 1H), 4.15 - 4.02 (m, 2H), 3.93 - 3.76 (m, 4H), 2.36 - 2.26 (m, 1H), 2.17 - 2.06 (m, 2H), 2.06 - 1.95 (m, 4H), 1.92 (d, J = 14.4 Hz, 2H), 1.83 (s, 3H)
685	((R)-(2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)-5-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		662.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.32 - 8.21 (m, 1H), 8.11 - 8.05 (m, 1H), 8.05 - 7.99 (m, 1H), 7.91 - 7.82 (m, 2H), 7.62 - 7.53 (m, 1H), 5.85 - 5.64 (m, 1H), 4.76 - 4.68 (m, 2H), 4.59 - 4.48 (m, 2H), 4.46 - 4.36 (m, 1H), 4.32 - 4.20 (m, 1H), 4.11 - 4.00 (m, 2H), 3.14 - 3.01 (m, 6H), 2.37 - 2.24 (m, 1H), 2.18 - 2.07

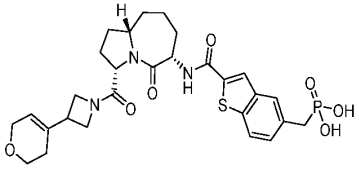
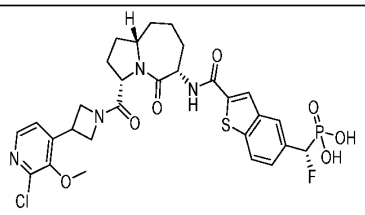
				(m, 2H), 2.06 - 1.98 (m, 2H), 1.97 - 1.90 (m, 2H), 1.87 (d, J = 10.4 Hz, 2H), 1.83 - 1.78 (m, 1H)
686	((2-(((3S,6S,9aS)-3-(3-(4-((S)-3-methoxypyrrolidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		682.4	^{1}H NMR (400 MHz, CD_3OD) δ = 8.32 (d, J = 2.4 Hz, 1H), 8.01 - 7.89 (m, 2H), 7.86 - 7.79 (m, 2H), 7.44 (t, J = 8.4 Hz, 1H), 6.91 - 6.77 (m, 1H), 4.79 - 4.72 (m, 1H), 4.69 - 4.57 (m, 1H), 4.56 - 4.33 (m, 4H), 4.17 - 4.05 (m, 3H), 3.88 - 3.75 (m, 2H), 3.64 - 3.58 (m, 1H), 3.56 - 3.49 (m, 1H), 3.36 (d, J = 11.2 Hz, 3H), 3.28 - 3.20 (m, 2H), 2.36 - 2.22 (m, 2H), 2.17 - 2.09 (m, 2H), 2.07 - 1.96 (m, 4H), 1.94 - 1.79 (m, 4H)
687	((2-(((3S,6S,9aS)-3-(3-(4-((R)-3-fluoropyrrolidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		670.2	^{1}H NMR (400 MHz, CD_3OD) δ = 8.38 (s, 1H), 8.15 - 7.93 (m, 2H), 7.90 - 7.78 (m, 2H), 7.49 - 7.40 (m, 1H), 7.03 - 6.90 (m, 1H), 5.56 - 5.33 (m, 1H), 4.81 - 4.69 (m, 2H), 4.67 - 4.53 (m, 2H), 4.52 - 4.45 (m, 1H), 4.38 - 4.28 (m, 1H), 4.19 - 4.06 (m, 2H), 4.05 - 3.87 (m, 2H), 3.87 - 3.73 (m, 2H), 3.29 - 3.21 (m, 2H), 2.50 - 2.38 (m, 1H), 2.36 - 2.29 (m, 1H), 2.24 - 2.06 (m, 3H), 2.06 - 1.90 (m, 4H), 1.90 - 1.76 (m, 3H)

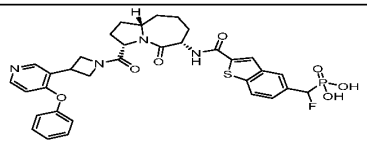
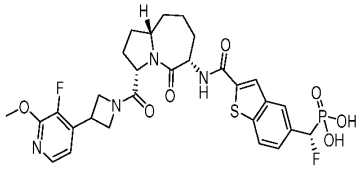
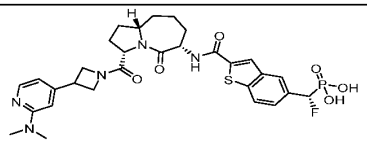
688	((2-(((3S,6S,9aS)-3-(3-(4-((R)-3-methoxypyrrolidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		682.2	^{1}H NMR (400 MHz, CD_3OD) δ 7.91 - 7.89 (m, 1H), 7.84 - 7.78 (m, 1H), 7.67 - 7.62 (m, 2H), 7.43 - 7.38 (m, 2H), 6.44 – 6.43 (m, 1H), 4.74 - 4.28 (m, 2H), 4.07-4.06 (m, 2H), 4.05 - 4.04 (m, 1H), 3.50 - 3.36 (m, 4H), 3.33 - 3.32 (m, 1H), 3.31 - 3.30 (m, 3H), 3.29 – 3.27(m, 3H), 3.26 - 3.15 (m, 2H), 2.31 - 2.10 (m, 1H), 2.04 – 2.01 (m, 4H), 1.97 – 1.91 (m, 4H), 1.89 – 1.88 (m, 3H)
689	((R)-(2-(((3S,6S,9aS)-3-(3-(4-(azetidin-1-yl)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		657.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.43 - 8.35 (m, 1H), 8.22 - 8.11 (m, 1H), 8.03 (d, J = 7.6 Hz, 1H), 8.00 (s, 1H), 7.91 (dd, J = 3.6, 8.4 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 5.87 - 5.71 (m, 1H), 4.82 - 4.70 (m, 2H), 4.62 - 4.47 (m, 5H), 4.45 - 4.37 (m, 1H), 4.32 - 4.23 (m, 1H), 4.12 - 3.99 (m, 3H), 2.54 - 2.42 (m, 2H), 2.35 - 2.26 (m, 1H), 2.15 - 2.00 (m, 3H), 1.98 - 1.78 (m, 6H)
690	((S)-(2-(((3S,6S,9aS)-3-(3-(4-(azetidin-1-yl)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		657.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.45 - 8.35 (m, 1H), 8.23 - 8.11 (m, 1H), 8.03 (d, J = 4.8 Hz, 1H), 7.99 (d, J = 6.8 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.60 (t, J = 8.8 Hz, 1H), 5.86 - 5.71 (m, 1H), 4.83 - 4.70 (m, 2H), 4.62 - 4.46 (m, 5H), 4.40 (t, J = 9.2 Hz, 1H), 4.32 - 4.23

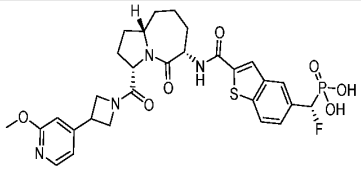
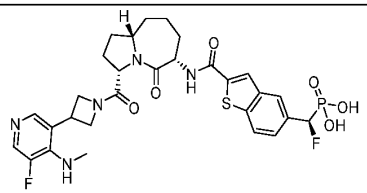
				(m, 1H), 4.11 - 4.00 (m, 3H), 2.54 - 2.41 (m, 2H), 2.35 - 2.26 (m, 1H), 2.14 - 2.00 (m, 3H), 1.99 - 1.78 (m, 6H)
691	((2-(((3S,6S,9aS)-3-(3-(4-(3-(difluoromethyl)azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		688.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.36 - 8.24 (m, 1H), 8.03 - 7.93 (m, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 1H), 6.57 (t, J = 7.2 Hz, 1H), 6.39 - 6.03 (m, 1H), 4.76 – 4.72 (m, 1H), 4.66 - 4.56 (m, 2H), 4.55 – 4.52 (m, 3H), 4.48 - 4.25 (m, 4H), 4.23 - 4.14 (m, 1H), 4.12 - 4.04 (m, 2H), 3.26 (s, 1H), 3.21 (s, 1H), 2.38 - 2.25 (m, 1H), 2.21 - 2.06 (m, 2H), 2.06 - 2.00 (m, 1H), 2.00 - 1.96 (m, 1H), 1.94 (d, J = 5.4 Hz, 1H), 1.90 (d, J = 10.4 Hz, 1H), 1.87 - 1.76 (m, 3H)
692	((2-(((3S,6S,9aS)-5-oxo-3-(3-(4-(3-(trifluoromethyl)azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		706.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (d, J = 15.6 Hz, 1H), 8.05 (dd, J = 7.6, 10.4 Hz, 1H), 8.02 - 7.97 (m, 1H), 7.88 - 7.81 (m, 2H), 7.49 - 7.38 (m, 1H), 6.67 - 6.59 (m, 1H), 4.77 - 4.70 (m, 1H), 4.69 - 4.59 (m, 3H), 4.59 - 4.49 (m, 3H), 4.42 (d, J = 9.6 Hz, 1H), 4.33 (q, J = 8.8 Hz, 1H), 4.20 - 4.13 (m, 1H), 4.10 (td, J = 3.6, 9.6 Hz, 2H), 3.78 - 3.66 (m, 1H), 3.26 (s, 1H), 3.21 (s, 1H), 2.39 - 2.25 (m, 1H), 2.20 - 2.12 (m, 1H), 2.11 -

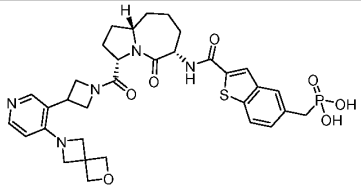
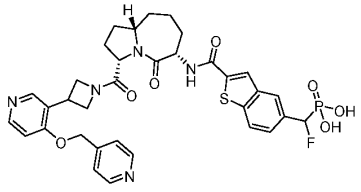
				1.99 (m, 3H), 1.99 - 1.91 (m, 2H), 1.89 (s, 1H), 1.85 (d, J = 6.8 Hz, 2H)
693	((2-(((3S,6S,9aS)-3-(3-(3-(dimethylamino)pyridin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		644.6	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.56 - 8.45 (m, 1H), 8.29 - 8.20 (m, 1H), 8.10 (d, *J* = 12.4 Hz, 1H), 7.95 - 7.85 (m, 2H), 7.58 - 7.49 (m, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 5.89 - 5.46 (m, 1H), 4.56 - 4.47 (m, 1H), 4.32 (s, 1H), 3.89 (d, *J* = 3.6 Hz, 1H), 3.76 - 3.70 (m, 1H), 3.56 (s, 2H), 3.40 (s, 1H), 3.37 (s, 1H), 2.41 (s, 6H), 2.13 - 2.03 (m, 1H), 1.95 - 1.75 (m, 4H), 1.71 - 1.67 (m, 1H), 1.67 - 1.56 (m, 4H)
694	((2-(((3S,6S,9aS)-3-(3-(4-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		698.2	^{1}H NMR (400 MHz, DMSO-d_6) 8.71 - 8.64 (m, 1H), 8.42 (s, 1H), 8.23 - 8.08 (m, 2H), 8.01 - 7.95 (m, 2H), 7.59 - 7.46 (m, 1H), 7.14 - 6.92 (m, 1H), 5.89 - 5.60 (m, 1H), 4.82 (s, 1H), 4.69 - 4.58 (m, 3H), 4.52 - 4.39 (m, 2H), 4.32 - 4.26 (m, 1H), 4.21 (d, J = 7.6 Hz, 1H), 4.14 (d, J = 7.2 Hz, 1H), 3.99 (d, J = 4.8 Hz, 2H), 3.92 (s, 1H), 3.80 (d, J = 8.8 Hz, 3H), 3.33 (d, J = 9.6 Hz, 1H), 2.32 - 2.14 (m, 1H), 2.10 - 1.92 (m, 4H), 1.92 - 1.52 (m, 7H)

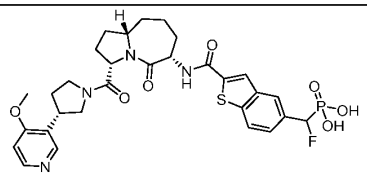
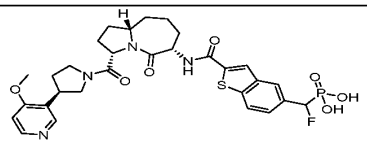
695	((2-(((3S,6S,9aS)-3-(3-(4-(cyclopentyloxy)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		685.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 - 8.62 (m, 1H), 8.60 - 8.42 (m, 2H), 8.27 - 8.12 (m, 1H), 8.08 - 7.92 (m, 2H), 7.58 - 7.48 (m, 1H), 7.41 - 7.28 (m, 1H), 5.92 - 5.71 (m, 1H), 5.13 (d, J = 16.8 Hz, 1H), 4.72 - 4.53 (m, 2H), 4.46 - 4.30 (m, 2H), 4.21 - 4.13 (m, 1H), 4.08 - 3.96 (m, 3H), 2.27 - 2.10 (m, 1H), 2.05 - 1.89 (m, 4H), 1.88 - 1.54 (m, 13H)
696	((S)-(2-(((3S,6S,9aS)-3-(3-(4-(dimethylcarbamoyl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		672.2	^{1}H NMR (400 MHz, CD_3OD) δ 9.11 - 8.84 (m, 1H), 8.74 - 8.53 (m, 1H), 8.07 (d, J = 7.6 Hz, 1H), 8.02 (s, 1H), 7.96 - 7.90 (m, 1H), 7.67 - 7.52 (m, 2H), 6.02 - 5.52 (m, 1H), 4.77 - 4.71 (m, 1H), 4.70 - 4.61 (m, 1H), 4.57 - 4.52 (m, 1H), 4.52 - 4.25 (m, 2H), 4.19 - 4.12 (m, 1H), 4.08-4.06 (m, 2H), 3.17 - 3.08 (m, 3H), 2.86 (s, 3H), 2.37 - 2.25 (m, 1H), 2.19 - 2.06 (m, 2H), 2.05 (s, 2H), 1.98 - 1.90 (m, 2H), 1.90 - 1.77 (m, 3H)
697	((2-(((3S,6S,9aS)-3-(3-(3,6-dihydro-2H-pyran-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		588.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.01 (d, J = 2.4 Hz, 1H), 7.85 (d, J = 5.2 Hz, 2H), 7.43 (d, J = 8.4 Hz, 1H), 5.66 (s, 1H), 4.77 - 4.70 (m, 1H), 4.62 - 4.52 (m, 1H), 4.46 - 4.28 (m, 1H), 4.22 - 4.12 (m, 3H), 4.11 - 4.01 (m, 2H), 3.97 - 3.85 (m, 1H),

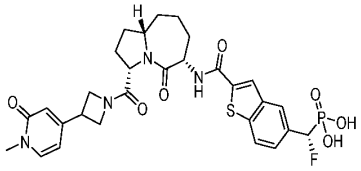
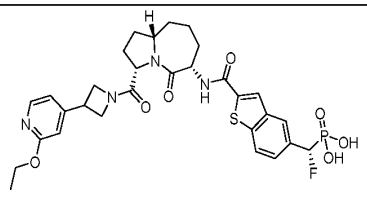
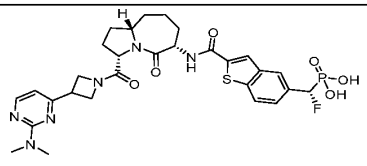
				3.85 - 3.75 (m, 2H), 3.34 (d, J = 8.8 Hz, 1H), 3.28 (s, 1H), 3.23 (s, 1H), 2.33 - 2.25 (m, 1H), 2.19 - 1.98 (m, 5H), 1.96 - 1.75 (m, 6H)
698	((S)-(2-(((3S,6S,9aS)-3-(3-(2-chloro-3-methoxypyridin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		665.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.16-8.10 (m, 1H), 8.11 - 8.06 (m, 1H), 8.03 (s, 1H), 7.98 - 7.92 (m, 1H), 7.63 - 7.59 (m, 1H), 7.58 (s, 1H), 5.95 - 5.70 (m, 1H), 4.78 - 4.66 (m, 2H), 4.62 - 4.46 (m, 2H), 4.44 - 4.24 (m, 2H), 4.11 - 4.01 (m, 2H), 3.86 (s, 3H), 2.40 - 2.22 (m, 1H), 2.20 - 2.05 (m, 2H), 2.03-1.96 (m, 2H), 1.96 - 1.90 (m, 2H), 1.89 (s, 3H)
699	(fluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(4-phenoxypyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		693.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 - 8.66 (m, 2H), 8.51 - 8.41 (m, 1H), 8.23 (d, J = 13.6 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.97 (s, 1H), 7.55 - 7.48 (m, 3H), 7.38 - 7.30 (m, 1H), 7.24 (t, J = 8.8 Hz, 2H), 6.80 (dd, J = 6.0, 16.8 Hz, 1H), 5.90 - 5.75 (m, 1H), 4.78 (t, J = 8.0 Hz, 1H), 4.67 - 4.59 (m, 2H), 4.54 - 4.47 (m, 1H), 4.45 (dd, J = 4.0, 7.6 Hz, 1H), 4.30 - 4.25 (m, 1H), 4.23 - 4.17 (m, 2H), 4.01 - 3.95 (m, 2H), 2.23 - 2.11 (m, 1H), 2.08 - 2.00 (m, 1H), 1.96 - 1.93 (m, 1H), 1.88 - 1.80 (m, 2H), 1.78 - 1.63 (m, 5H)

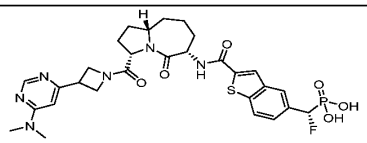
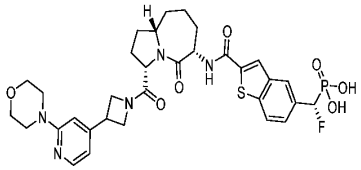
700	((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(3-fluoro-2-methoxypyridin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		649.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (d, J = 8.0 Hz, 1H), 8.06 - 8.02 (m, 1H), 7.99 - 7.94 (m, 1H), 7.93-7.89 (m, 1H), 7.63 - 7.52 (m, 1H), 7.25 - 6.99 (m, 1H), 5.96 - 5.71 (m, 1H), 4.98 - 4.88 (m, 1H), 4.75 (d, J = 8.0 Hz, 1H), 4.72 - 4.64 (m, 1H), 4.60 - 4.54 (m, 1H), 4.43 - 4.32 (m, 1H), 4.28 - 4.14 (m, 1H), 4.11-4.05 (m, 2H), 3.98 (d, J = 8.8 Hz, 3H), 2.37 - 2.26 (m, 1H), 2.20 - 2.06 (m, 2H), 2.05 - 1.94 (m, 3H), 1.93 - 1.86 (m, 2H), 1.85 - 1.74 (m, 2H)
701	((S)-(2-(((3S,6S,9aS)-3-(3-(2-(dimethylamino)pyridin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		644.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 - 8.66 (m, 1H), 8.30 - 8.22 (m, 1H), 8.04 (dd, J = 5.6, 8.4 Hz, 1H), 8.00 - 7.84 (m, 2H), 7.58 - 7.47 (m, 1H), 7.10 - 6.88 (m, 1H), 5.95 - 5.72 (m, 1H), 4.73 - 4.54 (m, 2H), 4.49 - 4.35 (m, 2H), 4.29 - 4.21 (m, 1H), 4.04 - 3.92 (m, 3H), 3.90 - 3.83 (m, 2H), 3.22 - 3.04 (m, 6H), 2.29 - 2.14 (m, 1H), 2.10 - 1.94 (m, 2H), 1.92 - 1.78 (m, 4H), 1.75 - 1.62 (m, 3H)
702	((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(2-methoxypyridin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-		631.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 - 8.76 (m, 1H), 8.26 (d, J = 4.8 Hz, 1H), 8.16 – 8.10 (m, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.99 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.01

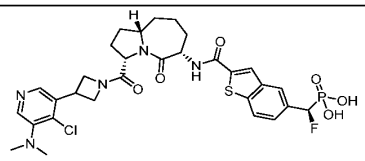
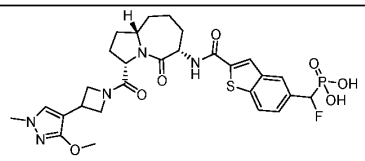
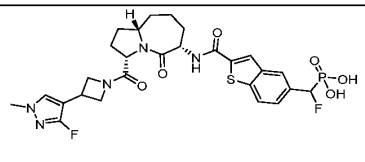
	yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			(t, J = 5.6 Hz, 1H), 6.82 (d, J = 2.0 Hz, 1H), 5.92 - 5.78 (m, 1H), 4.81 - 4.63 (m, 2H), 4.57 (t, J = 8.4 Hz, 1H), 4.47 - 4.33 (m, 2H), 4.28 - 4.19 (m, 1H), 4.05 - 3.96 (m, 1H), 3.92 - 3.71 (m, 5H), 2.26 - 2.13 (m, 1H), 2.08 - 1.92 (m, 2H), 1.90 - 1.64 (m, 7H)
703	((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(5-fluoro-4-(methylamino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		648.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.28 - 8.20 (m, 1H), 8.15 - 8.08 (m, 1H), 8.06 - 7.96 (m, 2H), 7.95 - 7.89 (m, 1H), 7.63 - 7.54 (m, 1H), 5.88 - 5.67 (m, 1H), 4.79 - 4.66 (m, 2H), 4.61 - 4.48 (m, 2H), 4.41 (t, J = 9.2 Hz, 1H), 4.14 - 4.00 (m, 2H), 3.97 - 3.83 (m, 1H), 3.26 (dd, J = 2.4, 7.2 Hz, 3H), 2.37 - 2.26 (m, 1H), 2.19 - 2.06 (m, 2H), 2.05 - 1.90 (m, 4H), 1.89 - 1.76 (m, 3H)
704	((2-(((3S,6S,9aS)-3-(3-(4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		680.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 - 8.58 (m, 1H), 8.12 - 8.00 (m, 2H), 7.82 - 7.66 (m, 2H), 7.32 - 7.21 (m, 1H), 6.36 (d, J = 6.0 Hz, 1H), 4.72 - 4.65 (m, 4H), 4.64 - 4.60 (m, 1H), 4.59 - 4.52 (m, 1H), 4.49 - 4.42 (m, 1H), 4.41 - 4.34 (m, 1H), 4.25 (d, J = 3.6 Hz, 1H), 4.19 (s, 2H), 4.15 (d, J = 5.4 Hz, 1H), 4.03 - 3.95 (m, 2H), 3.94 - 3.85 (m, 2H), 2.95 - 2.87 (m, 2H), 2.22 -

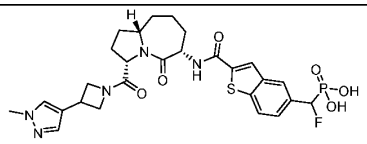
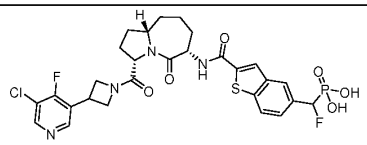
				2.16 (m, 1H), 2.04 - 1.93 (m, 2H), 1.89 - 1.78 (m, 4H), 1.70 (d, *J* = 10.4 Hz, 3H)
705	(fluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(4-(pyridin-4-ylmethoxy)pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		708.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (dd, J = 7.6, 12.4 Hz, 1H), 8.57 (dd, J = 5.2, 9.6 Hz, 2H), 8.35 (d, J = 6.0 Hz, 2H), 8.42 (d, J = 9.6 Hz, 1H), 8.03 - 7.92 (m, 2H), 7.55 - 7.39 (m, 3H), 7.20 - 7.02 (m, 1H), 5.88 - 5.66 (m, 1H), 5.31 (s, 2H), 4.72 (t, J = 8.4 Hz, 1H), 4.67 - 4.60 (m, 1H), 4.59 - 4.50 (m, 1H), 4.46 - 4.34 (m, 2H), 4.28 - 4.21 (m, 1H), 4.10 (s, 1H), 3.98 - 3.95 (m, 1H), 2.24 - 2.09 (m, 1H), 2.04 - 2.01 (m, 1H), 1.90 - 1.79 (m, 3H), 1.78 - 1.66 (m, 4H), 1.65 - 1.56 (m, 1H)
706	(fluoro(2-(((3S,6S,9aS)-3-((S)-3-(4-methoxypyridin-3-yl)pyrrolidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		645.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (t, J = 7.6 Hz, 1H), 8.61 (dd, J = 6.0, 10.0 Hz, 1H), 8.45 (d, J = 11.2 Hz, 1H), 8.27 - 8.19 (m, 1H), 8.02 (dd, J = 5.2, 8.4 Hz, 1H), 7.96 (s, 1H), 7.55 - 7.48 (m, 1H), 7.40 (dd, J = 6.4, 10.0 Hz, 1H), 5.91 - 5.71 (m, 1H), 4.66 (d, J = 8.8 Hz, 2H), 4.03 (d, J = 5.2 Hz, 3H), 4.01 - 3.97 (m, 1H), 3.91 - 3.87 (m, 1H), 3.71 (s, 1H), 3.68 (s, 1H), 3.55 (dd, J = 4.0, 7.6 Hz, 1H), 3.46 (d, J = 14.4 Hz, 1H), 3.33 (dd, J = 4.0, 8.0 Hz, 1H), 3.22 (dd,

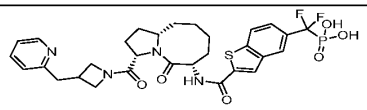
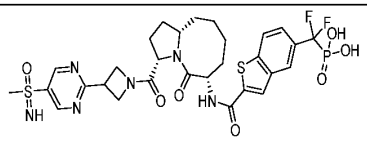
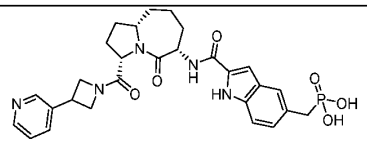
				J = 9.6, 10.8 Hz, 1H), 2.36 - 2.25 (m, 1H), 2.25 - 2.15 (m, 2H), 2.13 - 2.04 (m, 1H), 2.02 - 1.88 (m, 2H), 1.86 - 1.76 (m, 4H), 1.72 (d, J = 13.6 Hz, 2H)
707	(fluoro(2-(((3S,6S,9aS)-3-((R)-3-(4-methoxypyridin-3-yl)pyrrolidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		645.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 - 8.66 (m, 1H), 8.65 - 8.61 (m, 1H), 8.51 - 8.40 (m, 1H), 8.22 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.97 (s, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.47 - 7.40 (m, 1H), 5.91 - 5.74 (m, 1H), 4.73 - 4.59 (m, 2H), 4.17 - 4.08 (m, 1H), 4.04 (d, J = 12.0 Hz, 3H), 4.00 (d, J = 7.2 Hz, 1H), 3.89 - 3.81 (m, 1H), 3.81 - 3.74 (m, 1H), 3.59 (s, 1H), 3.47 (d, J = 9.6 Hz, 1H), 3.34 (d, J = 9.6 Hz, 1H), 2.33 - 2.12 (m, 3H), 2.08 - 1.94 (m, 2H), 1.91 - 1.67 (m, 7H)
708	((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		631.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.13 - 8.02 (m, 2H), 7.88 (d, *J* = 8.00 Hz, 1H), 7.69 - 7.51 (m, 2H), 6.67 - 6.41 (m, 2H), 5.76 - 5.57 (m, 1H), 4.74 (m, 1H), 4.64 - 4.49 (m, 2H), 4.48 - 4.15 (m, 2H), 4.11 - 3.90 (m, 2H), 3.86 - 3.74 (m, 1H), 3.58 - 3.46 (m, 3H), 2.35 - 2.24 (m, 1H), 2.17 - 2.06 (m, 2H), 1.98 (s, 2H), 1.96 - 1.90 (m, 2H), 1.90 - 1.77 (m, 3H)

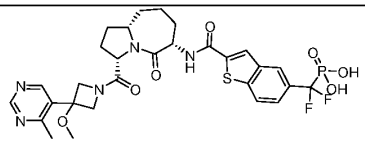
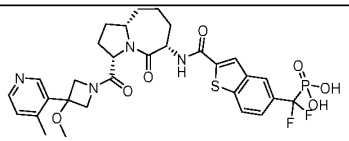
709	((S)-(2-(((3S,6S,9aS)-3-(3-(2-ethoxypyridin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		645.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.16 - 8.01 (m, 3H), 7.96 (d, J = 2.8, 8.6 Hz, 1H), 7.65 - 7.55 (m, 1H), 7.38 - 7.27 (m, 1H), 7.18 - 7.08 (m, 1H), 5.92 - 5.74 (m, 1H), 4.78 - 4.73 (m, 1H), 4.72 - 4.55 (m, 2H), 4.55 - 4.44 (m, 1H), 4.43 - 4.28 (m, 3H), 4.13 - 3.94 (m, 3H), 2.37 - 2.26 (m, 1H), 2.19 - 2.06 (m, 2H), 2.05 - 1.94 (m, 3H), 1.94 - 1.76 (m, 4H), 1.46 - 1.29 (m, 3H)
710	((S)-(2-(((3S,6S,9aS)-3-(3-(2-(dimethylamino)pyrimidin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		645.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.13 - 7.98 (m, 3H), 7.94 - 7.89 (m, 1H), 7.65 - 7.56 (m, 1H), 6.88 - 6.59 (m, 1H), 5.89 - 5.70 (m, 1H), 4.82 - 4.76 (m, 1H), 4.72 (d, J = 12.0 Hz, 1H), 4.60 - 4.53 (m, 1H), 4.52 - 4.38 (m, 1H), 4.38 - 4.27 (m, 1H), 4.23 - 4.11 (m, 1H), 4.10 - 4.03 (m, 1H), 4.01 - 3.87 (m, 1H), 3.27 - 3.11 (m, 6H), 2.34 - 2.25 (m, 1H), 2.17 - 2.06 (m, 2H), 2.04 - 1.96 (m, 2H), 1.95 - 1.87 (m, 3H), 1.86 - 1.76 (m, 2H)
711	((S)-(2-(((3S,6S,9aS)-3-(3-(6-(dimethylamino)pyrimidin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo		645	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, J = 4.2 Hz, 1H), 8.52 - 8.43 (m, 1H), 8.24 (d, J = 6.8 Hz, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.97 (s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 6.65 - 6.57 (m, 1H), 5.86 - 5.66 (m, 1H), 4.64 (t, J = 8.4

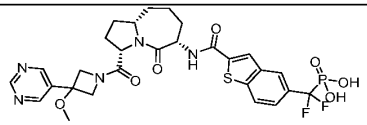
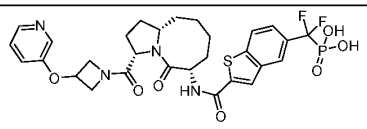
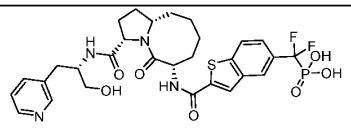
	[b]thiophen-5-yl)fluoromethyl)phosphonic acid			Hz, 1H), 4.53 - 4.47 (m, 1H), 4.44 (d, J = 7.3 Hz, 1H), 4.34 - 4.26 (m, 1H), 4.19 - 4.09 (m, 2H), 4.01 - 3.96 (m, 2H), 3.83 - 3.77 (m, 2H), 3.05 (s, 3H), 2.98 (s, 3H), 2.23 - 2.14 (m, 1H), 2.04 - 1.92 (m, 2H), 1.89 - 1.76 (m, 4H), 1.75 - 1.64 (m, 3H)
712	((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(2-morpholinopyridin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		686.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (s, 1H), 8.06 - 8.01 (m, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.70 - 7.58 (m, 2H), 7.32 (d, J = 6.4 Hz, 1H), 7.18 - 7.11 (m, 1H), 5.92 - 5.70 (m, 1H), 4.82 - 4.55 (m, 3H), 4.54 - 4.30 (m, 2H), 4.12 - 3.91 (m, 3H), 3.87 - 3.71 (m, 4H), 3.68 - 3.55 (m, 4H), 2.37 - 2.24 (m, 1H), 2.17 - 2.07 (m, 2H), 2.06 - 1.88 (m, 5H), 1.87 - 1.76 (m, 2H)
713	((R)-(2-(((3S,6S,9aS)-3-(3-(4-chloro-5-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		678.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (t, J = 6.8 Hz, 1H), 8.42 - 8.31 (m, 2H), 8.25 (d, J = 20.0 Hz, 1H), 8.07 - 7.94 (m, 2H), 7.53 (dd, J = 4.0, 8.4 Hz, 1H), 5.91 - 5.76 (m, 1H), 4.81 (t, J = 8.8 Hz, 1H), 4.66 (t, J = 8.4 Hz, 1H), 4.48 - 4.41 (m, 2H), 4.31 (s, 1H), 4.24 - 4.12 (m, 2H), 4.10 - 4.05 (m, 1H), 2.80 (s, 3H), 2.78 (s, 3H), 2.24 - 2.13 (m, 1H), 2.09 - 1.91 (m, 2H), 1.83 (d, J = 11.2 Hz, 2H), 1.80

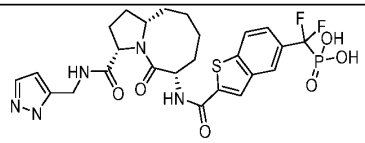
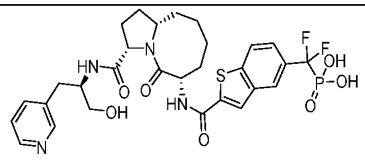
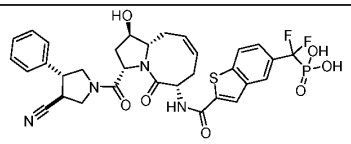
				(d, J = 6.0 Hz, 2H), 1.75 - 1.62 (m, 3H)
714	(fluoro(2-(((3S,6S,9aS)-3-(3-(3-methoxy-1-methyl-1H-pyrazol-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		634.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (d, J = 2.4 Hz, 1H), 8.05 - 8.00 (m, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.49 - 7.33 (m, 1H), 5.92 - 5.74 (m, 1H), 4.73 (s, 1H), 4.60 - 4.47 (m, 2H), 4.46 - 4.30 (m, 1H), 4.29 - 4.19 (m, 1H), 4.10 - 4.01 (m, 1H), 3.99 - 3.91 (m, 1H), 3.86 (d, J = 11.6 Hz, 3H), 3.79 - 3.71 (m, 1H), 3.70 - 3.62 (m, 3H), 2.36 - 2.25 (m, 1H), 2.16 - 2.05 (m, 2H), 2.04 - 1.98 (m, 1H), 1.98 - 1.86 (m, 4H), 1.85 - 1.76 (m, 2H)
715	(fluoro(2-(((3S,6S,9aS)-3-(3-(3-fluoro-1-methyl-1H-pyrazol-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		622.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 - 8.67 (m, 1H), 8.26 (d, J = 2.8 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 3.6 Hz, 1H), 7.76 - 7.66 (m, 1H), 7.53 (d, J = 8.4 Hz, 1H), 5.97 - 5.69 (m, 1H), 4.73 - 4.60 (m, 1H), 4.53 - 4.37 (m, 1H), 4.25 - 4.15 (m, 1H), 4.10 - 4.05 (m, 1H), 4.03 - 3.94 (m, 2H), 3.68 (s, 3H), 3.61 (d, J = 2.0 Hz, 2H), 2.26 - 2.11 (m, 1H), 2.06 - 1.92 (m, 2H), 1.92 - 1.74 (m, 4H), 1.71 - 1.69 (m, 2H), 1.65 (s, 1H)
716	(fluoro(2-(((3S,6S,9aS)-3-(3-(1-methyl-1H-pyrazol-4-yl)azetidine-1-		604.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (d, J = 7.6 Hz, 1H), 8.24 (s, 1H), 8.15 (t, J = 5.6 Hz, 1H), 8.03 (d,

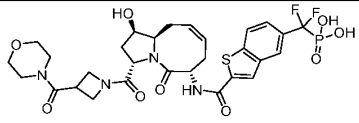
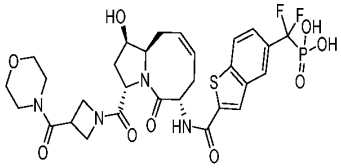
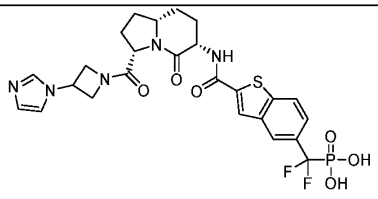
	carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			J = 8.4 Hz, 1H), 7.97 (s, 1H), 7.76 (s, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.45 (s, 1H), 6.25 (d, J = 11.6 Hz, 1H), 5.91 - 5.75 (m, 1H), 5.40 - 5.31 (m, 1H), 4.63 (t, J = 8.4 Hz, 1H), 4.43 (dd, J = 3.6, 8.0 Hz, 1H), 4.03 - 3.91 (m, 2H), 3.88 (t, J = 5.6 Hz, 2H), 3.82 (s, 3H), 2.23 - 2.12 (m, 1H), 2.01 - 1.90 (m, 2H), 1.89 - 1.80 (m, 2H), 1.78 - 1.65 (m, 5H)
717	((2-(((3S,6S,9aS)-3-(3-(5-chloro-4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		653.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.71 - 8.63 (m, 2H), 8.19 (d, J = 10.8 Hz, 1H), 7.92 - 7.85 (m, 2H), 7.58 - 7.48 (m, 1H), 5.57 - 5.27 (m, 2H), 4.79 (t, J = 8.8 Hz, 1H), 4.62 (d, J = 4.8 Hz, 1H), 4.60 - 4.50 (m, 1H), 4.44 (dd, J = 4.4, 7.6 Hz, 1H), 4.42 - 4.36 (m, 1H), 4.31 - 4.24 (m, 1H), 4.16 - 4.11 (m, 1H), 4.07 (d, J = 8.0 Hz, 1H), 4.02 - 3.96 (m, 1H), 2.24 - 2.15 (m, 1H), 2.08 - 1.92 (m, 2H), 1.90 - 1.76 (m, 4H), 1.72 (s, 3H)
718	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-(3-(pyridin-2-ylmethyl)azetidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		646.9	^{1}H NMR (400 MHz, CD_3OD) δ 8.66 - 8.55 (m, 1H), 8.47 - 8.32 (m, 1H), 8.16 - 8.06 (m, 2H), 7.97 - 7.63 (m, 4H), 5.00 – 4.96 (m, 1H), 4.47 - 4.24 (m, 3H), 4.24 - 3.97 (m, 1H), 3.88 - 3.70 (m, 1H), 3.38 - 3.31 (m, 3H), 3.17 - 3.08 (m, 1H), 2.28 - 2.14

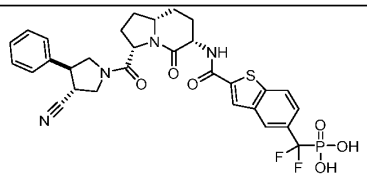
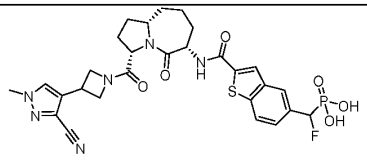
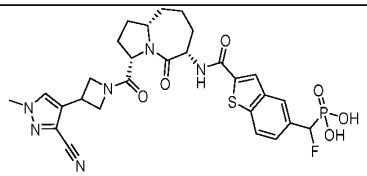
				(m, 2H), 2.07 - 1.88 (m, 6H), 1.88 - 1.75 (m, 2H), 1.73 - 1.55 (m, 2H)
719	(difluoro(2-(((3S,6S,10aS)-3-(3-(5-(S-methylsulfonimidoyl)pyrimidin-2-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		711.2	^{1}H NMR (400 MHz, CD_3OD) δ 9.25 (s, 1H), 9.18 (d, J = 4.4 Hz, 1H), 8.20 - 8.14 (m, 1H), 8.14 - 8.01 (m, 1H), 7.96 - 7.84 (m, 1H), 7.77 - 7.70 (m, 1H), 5.07 - 4.92 (m, 2H), 4.73 - 4.54 (m, 1H), 4.53 - 4.44 (m, 2H), 4.44 - 4.37 (m, 1H), 4.36 - 4.22 (m, 2H), 3.28 - 3.20 (m, 3H), 2.33 - 2.17 (m, 2H), 2.09 - 1.90 (m, 6H), 1.89 - 1.76 (m, 2H), 1.73 - 1.57 (m, 2H)
720	((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)-1H-indol-5-yl)methyl)phosphonic acid		566.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.71 - 8.60 (m, 2H), 8.59 - 8.46 (m, 1H), 7.92 - 7.72 (m, 1H), 7.56 (s, 1H), 7.40 - 7.33 (m, 1H), 7.25 - 7.18 (m, 1H), 7.10 (s, 1H), 4.79 (d, J = 10.4 Hz, 1H), 4.70 (t, J = 8.4 Hz, 1H), 4.61 - 4.47 (m, 2H), 4.46 - 4.25 (m, 1H), 4.15 - 3.99 (m, 3H), 3.23 - 3.15 (m, 2H), 2.37 - 2.27 (m, 1H), 2.21 - 2.07 (m, 2H), 2.06 - 1.92 (m, 4H), 1.90 - 1.77 (m, 3H)
721	(difluoro(2-(((3S,6S,9aS)-3-(3-methoxy-3-(4-methylpyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-		664.1	^{1}H NMR (400 MHz, CD_3OD) δ 9.03 - 8.94 (m, 1H), 8.76 (m, 1H), 8.17 - 8.13 (m, 1H), 8.13 - 8.03 (m, 1H), 8.02 - 7.95 (m, 1H), 7.68 (m, 1H), 5.04 - 4.98 (m, 1H), 4.81 (m, 1H), 4.79 -

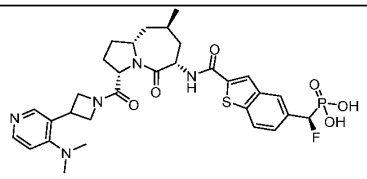
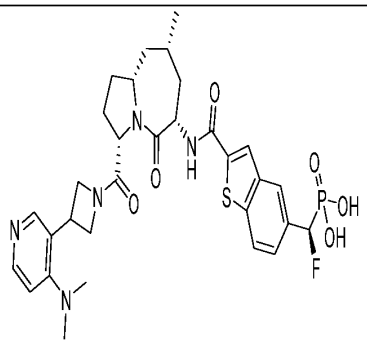
	yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			4.69 (m, 1H), 4.65 - 4.56 (m, 1H), 4.55 - 4.44 (m, 1H), 4.36 - 4.23 (m, 1H), 4.07 (m, 1H), 3.08 - 3.02 (m, 3H), 2.52 (m, 3H), 2.38 - 2.26 (m, 1H), 2.23 - 2.13 (m, 1H), 2.12 - 2.02 (m, 2H), 2.02 - 1.81 (m, 6H)
722	(difluoro(2-(((3S,6S,9aS)-3-(3-methoxy-3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		663.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.64 - 8.57 (m, 1H), 8.40 - 8.34 (m, 1H), 8.22 (d, J = 5.6 Hz, 1H), 8.06 (s, 1H), 7.98 (s, 1H), 7.90 - 7.86 (m, 1H), 7.86 - 7.75 (m, 1H), 5.00 (d, J = 9.6 Hz, 1H), 4.72 (d, J = 10.4 Hz, 1H), 4.62 (d, J = 10.0 Hz, 1H), 4.56 - 4.44 (m, 2H), 4.35 - 4.24 (m, 1H), 4.09 (s, 1H), 3.04 - 2.94 (m, 3H), 2.61 - 2.48 (m, 3H), 2.38 - 2.27 (m, 1H), 2.22 - 2.14 (m, 1H), 2.12 - 2.06 (m, 1H), 2.05 - 1.95 (m, 3H), 1.93 - 1.75 (m, 4H)
723	(difluoro(2-(((3S,6S,9aS)-3-(3-methoxy-3-(pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		650.1	^{1}H NMR (400 MHz, CD_3OD) δ 9.17 (s, 1H), 9.00 (s, 1H), 8.95 (s, 1H), 8.22 (s, 1H), 8.14 - 8.09 (m, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 4.93 - 4.89 (m, 1H), 4.78 - 4.71 (m, 1H), 4.63 - 4.55 (m, 2H), 4.39 - 4.24 (m, 2H), 4.07 (d, J = 5.2 Hz, 1H), 3.26 - 3.21 (m, 3H), 2.38 - 2.25 (m, 1H), 2.16 - 1.93 (m, 6H), 1.87 - 1.76 (m, 3H)

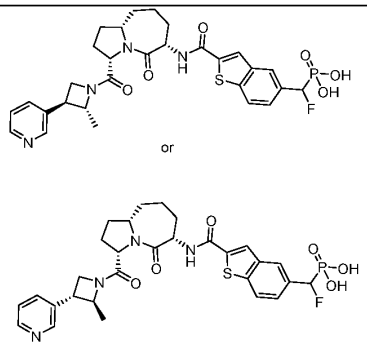
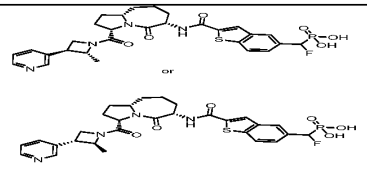
724	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-(3-(pyridin-3-yloxy)azetidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		649.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.25 - 8.05 (m, 4H), 7.98 - 7.86 (m, 1H), 7.80 - 7.68 (m, 1H), 7.43 - 7.26 (m, 2H), 5.15 (d, J = 4.0 Hz, 1H), 5.00 (m, 2H), 4.76 - 4.56 (m, 1H), 4.55 - 4.35 (m, 3H), 4.12 - 3.91 (m, 1H), 2.35 - 2.15 (m, 2H), 1.94 (s, 6H), 1.89 - 1.75 (m, 2H), 1.74 - 1.57 (m, 2H)
725	(difluoro(2-(((3S,6S,10aS)-3-(((S)-1-hydroxy-3-(pyridin-3-yl)propan-2-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		651.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.63 (d, J = 1.6 Hz, 1H), 8.51 (d, J = 4.4 Hz, 1H), 8.19 - 8.07 (m, 3H), 7.98 (s, 1H), 7.79 - 7.68 (m, 2H), 5.11 (t, J = 8.8 Hz, 1H), 4.41 - 4.27 (m, 2H), 4.15 - 4.05 (m, 1H), 3.57 (d, J = 5.6 Hz, 2H), 3.09 (m, 1H), 2.84 (m, 1H), 2.24 - 2.09 (m, 2H), 2.04 - 1.83 (m, 5H), 1.81 - 1.74 (m, 1H), 1.73 - 1.51 (m, 4H)
726	((2-(((3S,6S,10aS)-3-(((2l2-pyrazol-3-yl)methyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		596.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89 (d, *J* = 6.8 Hz, 1H), 8.41 - 8.29 (m, 2H), 8.16 - 8.06 (m, 2H), 7.62 - 7.48 (m, 2H), 7.01 - 6.89 (m, 1H), 6.17 (d, *J* = 2.0 Hz, 1H), 4.99 - 4.89 (m, 1H), 4.38 - 4.32 (m, 1H), 4.31 - 4.21 (m, 3H), 2.16 - 2.01 (m, 2H), 2.01 - 1.95 (m, 1H), 1.95 - 1.75 (m, 5H), 1.75 - 1.63 (m, 2H), 1.62 - 1.47 (m, 2H)

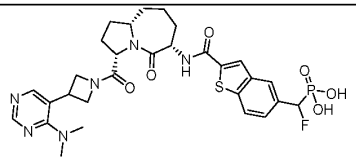
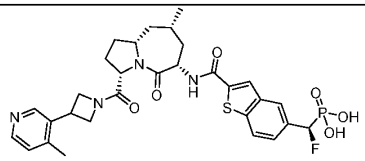
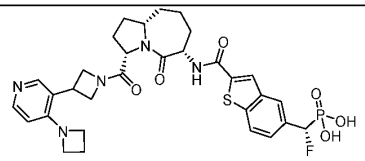
727	(difluoro(2-(((3S,6S,10aS)-3-(((R)-1-hydroxy-3-(pyridin-3-yl)propan-2-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		651.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (d, J=8.0 Hz, 1 H) 8.47 (s, 2H) 8.31 (s, 1H) 8.13 (d, J=8.0 Hz, 1H) 8.06 (s, 1H) 7.89 (d, J=8.0 Hz, 1H) 7.73 - 7.79 (m, 1H) 7.58 (d, J=8.0Hz, 1H) 7.41 - 7.46 (m, 1H) 4.86 - 4.92 (m, 1H) 4.20 (m, 2H) 3.90 - 3.99 (m, 2H) 3.48 (s, 1H) 2.98 (m, 2H) 1.76 - 1.94 (m, 6H) 1.55 - 1.65 (m, 3H) 1.41 - 1.51 (m, 3H) 1.24 (m, 1H)
728	(difluoro(2-(((3S,6S,8aS)-5-oxo-3-(3-(pyridin-2-yl)azetidine-1-carbonyl)octahydroindolizin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		605.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.62 - 8.47 (m, 1H), 8.21 (s, 1H), 8.08 (d, J = 5.6 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 7.2 Hz, 2H), 7.55 - 7.35 (m, 1H), 7.34 - 7.24 (m, 1H), 4.85 - 4.72 (m, 2H), 4.67 (d, J = 7.6 Hz, 1H), 4.48 (d, J = 8.4 Hz, 1H), 4.44 - 4.36 (m, 1H), 4.25 - 4.03 (m, 2H), 3.76 (s, 1H), 2.26 - 2.09 (m, 4H), 2.04 - 1.97 (m, 1H), 1.93 - 1.78 (m, 2H), 1.32 (d, J = 6.4 Hz, 1H)
729	((2-(((1R,3S,6S,10aS,Z)-3-((*rel-trans*)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-1-hydroxy-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-		685.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.26 - 8.09 (m, 2H), 8.06 - 7.95 (m, 1H), 7.75 - 7.64 (m, 1H), 7.49 - 7.26 (m, 5H), 5.87 (d, *J* = 4.4 Hz, 2H), 5.22 - 5.14 (m, 1H), 4.85 - 4.77 (m, 1H), 4.33 - 4.26 (m, 1H), 4.24 - 3.93 (m, 3H), 3.91 - 3.74 (m, 1H), 3.70 - 3.56 (m, 1H), 3.52 (s,

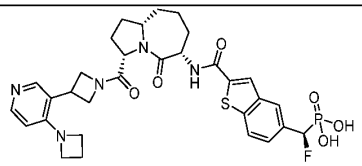
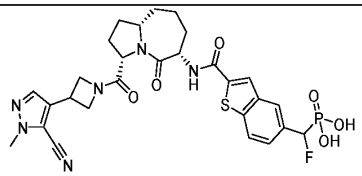
	yl)difluoromethyl)phosphonic acid			1H), 2.86 - 2.55 (m, 4H), 2.28 - 2.08 (m, 2H)
730	(difluoro(2-(((1R,3S,6S,10aR,Z)-1-hydroxy-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		683.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (s, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.90 - 7.83 (m, 2H), 5.90 - 5.62 (m, 2H), 5.10 - 4.94 (m, 2H), 4.78 - 4.57 (m, 3H), 4.45 - 4.32 (m, 2H), 4.25 - 4.00 (m, 2H), 3.85 - 3.75 (m, 1H), 3.68 - 3.57 (m, 6H), 3.39 - 3.36 (m, 1H), 3.06 - 2.94 (m, 1H), 2.67 - 2.57 (m, 1H), 2.51 - 2.31 (m, 2H), 2.22 - 2.12 (m, 1H), 2.05 - 1.94 (m, 1H)
731	(difluoro(2-(((3S,6S,8aS)-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxooctahydroindolizin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		641.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.17 - 8.07 (m, 2H), 8.03 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 4.78 - 4.59 (m, 2H), 4.48 - 4.40 (m, 2H), 4.28 - 4.04 (m, 2H), 3.85 - 3.71 (m, 2H), 3.69 - 3.54 (m, 6H), 3.42 - 3.32 (m, 2H), 2.31 - 2.09 (m, 4H), 2.03 - 1.93 (m, 2H), 1.91 - 1.74 (m, 2H)
732	((2-(((3S,6S,8aS)-3-(3-(1H-imidazol-1-yl)azetidine-1-carbonyl)-5-oxooctahydroindolizin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		594.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.22 - 8.17 (m, 1H), 8.12 - 8.06 (m, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.84 - 7.61 (m, 2H), 7.32 - 7.21 (m, 1H), 5.38 - 5.28 (m, 1H), 4.86 - 4.77 (m, 3H), 4.65 - 4.51 (m, 1H), 4.50 - 4.45 (m, 1H), 4.28 - 4.17 (m, 1H), 3.85 - 3.75 (m, 1H), 2.36 - 2.13 (m, 4H), 2.12 - 1.98

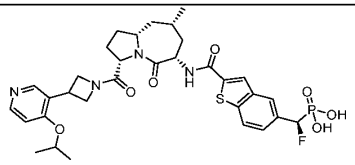
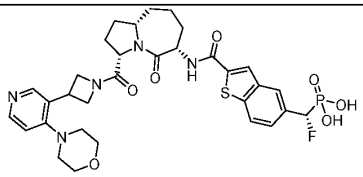
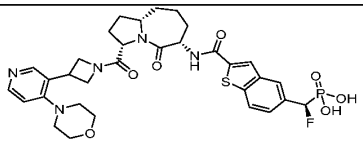
				(m, 2H), 1.97 - 1.78 (m, 2H)
733	((2-(((3S,6S,8aS)-3-((*rel-trans*)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxooctahydroindolizin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		643.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (d, J = 7.2 Hz, 1H), 8.12 - 8.08 (m, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.49 - 7.37 (m, 4H), 7.36 - 7.28 (m, 1H), 4.82 - 4.75 (m, 1H), 4.74 - 4.62 (m, 1H), 4.49 - 4.12 (m, 1H), 4.13 - 3.95 (m, 1H), 3.90 - 3.75 (m, 2H), 3.74 - 3.39 (m, 3H), 2.36 - 2.11 (m, 4H), 2.09 - 1.96 (m, 2H), 1.92 - 1.78 (m, 2H)
734	((2-(((3S,6S,9aS)-3-(3-(3-cyano-1-methyl-1H-pyrazol-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		629.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (d, J = 6.0 Hz, 1H), 8.07 - 7.81 (m, 3H), 7.62 - 7.57 (m, 1H), 5.90 - 5.75 (m, 1H), 4.78 - 4.73 (m, 1H), 4.69 (t, J = 8.4 Hz, 1H), 4.60 - 4.46 (m, 2H), 4.42 - 4.25 (m, 1H), 4.13 - 4.04 (m, 1H), 4.03 - 3.92 (m, 4H), 3.85 (d, J = 2.4 Hz, 1H), 2.37 - 2.25 (m, 1H), 2.13 - 2.06 (m, 2H), 2.06 - 1.99 (m, 2H), 1.98 - 1.88 (m, 3H), 1.88 - 1.81 (m, 2H)
735	((R)-(2-(((3S,6S,8S,9aR)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		658.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.16 - 7.92 (m, 3H), 7.83 - 7.51 (m, 3H), 6.94 - 6.70 (m, 1H), 5.82 - 5.77 (m, 1H), 5.01 - 4.98 (m, 2H), 4.64 - 4.40 (m, 3H), 4.29 - 4.19 (m, 2H), 3.96 - 3.95 (m, 1H), 3.05 - 2.98 (m, 6H), 2.33 - 2.27 (m, 3H), 2.04 - 1.82 (m, 5H), 1.62 - 1.60

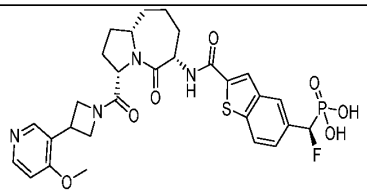
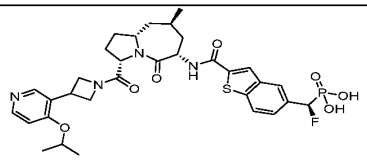
	yl)fluoromethyl)phosphonic acid			(m, 1H), 1.24 - 1.21 (m, 3H).
736	((R)-(2-(((3S,6S,8R,9aR)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		658.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.22 - 8.15 (m, 1H), 8.02 - 7.95 (m, 2H), 7.86 - 7.78 (m, 1H), 7.58 - 7.57 (m, 1H), 7.47 - 7.35 (m, 1H), 7.00 - 6.86 (m, 1H), 5.77 - 5.63 (m, 1H), 4.78 - 4.73 (m, 1H), 4.70 - 4.67 (m, 1H), 4.53 - 4.49 (m, 2H), 4.43 - 4.37 (m, 1H), 4.27 - 4.22 (m, 1H), 4.09 - 4.08 (m, 2H), 3.13 - 3.05 (m, 6H), 2.37 - 2.28 (m, 1H), 2.09 - 2.05 (m, 2H), 1.97 - 1.94 (m, 3H), 1.82 - 1.77 (m, 1H), 1.70- 1.67 (m, 2H), 1.05 (d, *J* = 6.0 Hz, 3H)
737	(fluoro(2-(((3S,6S,9aS)-3-((2R,3S)-2-methyl-3-(pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid Or (fluoro(2-(((3S,6S,9aS)-3-((2S,3R)-2-methyl-3-(pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-	 Azetidine BB SFC peak 2 was used for synthesis and biological testing	615.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.76 (d, J = 8.0 Hz, 1H), 8.71 (s, 1H), 8.48 (d, J = 6.0 Hz, 1H), 8.06 - 7.98 (m, 2H), 7.93 (d, J = 8.8 Hz, 1H), 7.88 (t, J = 7.6 Hz, 1H), 7.69 - 7.53 (m, 1H), 5.96 - 5.70 (m, 1H), 4.87 - 4.78 (m, 1H), 4.71 (d, J = 11.2 Hz, 1H), 4.58 - 4.47 (m, 1H), 4.45 - 4.33 (m, 1H), 4.11 (d, J = 2.0 Hz, 1H), 4.01 - 3.92 (m, 1H), 3.66 - 3.64 (m, 1H), 2.46 - 2.29 (m, 1H), 2.25 - 1.99 (m, 5H), 1.98 - 1.78 (m, 4H), 1.70 (d, J = 6.1 Hz, 3H)

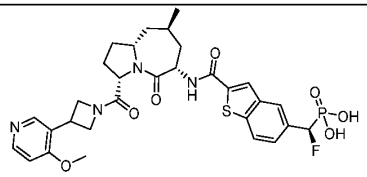
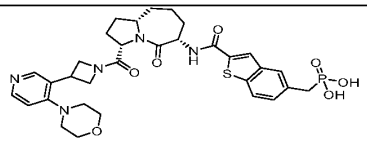
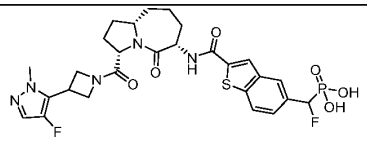
	yl)methyl)phosphonic acid			
738	(fluoro(2-(((3S,6S,9aS)-3-((2R,3S)-2-methyl-3-(pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid Or (fluoro(2-(((3S,6S,9aS)-3-((2S,3R)-2-methyl-3-(pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid	 Azetidine BB SFC peak 1 was used for synthesis and biological testing	615.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.69 (d, J = 8.0 Hz, 1H), 8.60 (d, J = 2.8 Hz, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.01 (s, 2H), 7.90 (d, J = 8.4 Hz, 1H), 7.77 (dd, J = 5.6, 8.0 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 5.92 - 5.65 (m, 1H), 4.75 (d, J = 11.2 Hz, 1H), 4.71 - 4.63 (m, 1H), 4.53 (dd, J = 6.4, 8.8 Hz, 1H), 4.47 (t, J = 6.8 Hz, 1H), 4.41 (t, J = 6.0 Hz, 1H), 4.10 (d, J = 6.0 Hz, 1H), 3.58 (q, J = 6.4 Hz, 1H), 2.42 - 2.29 (m, 1H), 2.25 - 2.09 (m, 2H), 2.09 - 1.97 (m, 3H), 1.94 - 1.75 (m, 4H), 1.58 (d, J = 6.3 Hz, 3H)
739	((2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		645.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.41 - 8.27 (m, 1H), 8.18 (d, *J* = 11.6 Hz, 1H), 8.05 - 7.93 (m, 2H), 7.91 - 7.84 (m, 1H), 7.66 - 7.50 (m, 1H), 5.88 - 5.64 (m, 1H), 4.73 (d, *J* = 10.4 Hz, 1H), 4.65 (t, *J* = 8.8 Hz, 1H), 4.57 - 4.46 (m, 2H), 4.42 - 4.31 (m, 1H), 4.26 - 4.19 (m, 1H), 4.07 (d, *J* = 9.6 Hz, 1H), 4.05 - 3.96 (m, 1H), 3.25 (s, 6H), 2.37 - 2.24 (m, 1H), 2.18 - 2.07 (m, 2H), 2.05 - 1.94 (m, 3H), 1.92 - 1.85 (m, 2H), 1.84 - 1.74 (m, 2H)

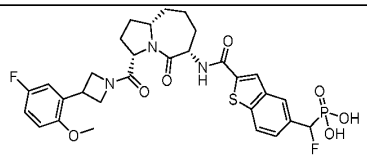
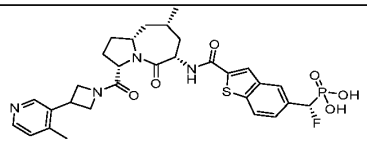
740	((R)-fluoro(2-(((3S,6S,8R,9aR)-8-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		629.3	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.82 - 8.62 (m, 2H), 8.61 - 8.49 (m, 1H), 8.23 (d, *J* = 19.6 Hz, 1H), 8.07 - 7.92 (m, 2H), 7.69 - 7.47 (m, 2H), 5.92 - 5.74 (m, 1H), 4.88 - 4.58 (m, 3H), 4.53 - 4.42 (m, 2H), 4.38 - 4.24 (m, 2H), 4.21 - 4.16 (m, 1H), 4.07 - 4.01 (m, 2H), 2.35 (d, *J* = 8.8 Hz, 3H), 2.27 - 2.16 (m, 1H), 2.09 - 1.92 (m, 2H), 1.89 - 1.76 (m, 3H), 1.70 (d, *J* = 12.8 Hz, 1H), 1.58 - 1.35 (m, 2H), 1.01 - 0.90 (m, 3H)
741	((S)-(2-(((3S,6S,9aS)-3-(3-(4-(azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		656.2	^{1}H NMR (400 MHz, CD$_3$OD) δ 8.22 - 8.08 (m, 1H), 8.06 - 8.00 (m, 1H), 7.98 (d, *J* = 12.4 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.87 - 7.78 (m, 1H), 7.60 (t, *J* = 8.4 Hz, 1H), 6.45 - 6.31 (m, 1H), 5.86 - 5.63 (m, 1H), 4.73 (d, *J* = 4.0 Hz, 2H), 4.62 - 4.56 (m, 3H), 4.54 - 4.51 (m, 2H), 4.46 - 4.40 (m, 3H), 4.32 (d, *J* = 8.4 Hz, 1H), 4.24 (d, *J* = 6.0 Hz, 1H), 4.12 - 4.03 (m, 2H), 2.52 - 2.43 (m, 1H), 2.36 - 2.25 (m, 1H), 2.18 - 2.06 (m, 2H), 2.05 - 1.89 (m, 4H), 1.85 - 1.79 (m, 2H)
742	((R)-(2-(((3S,6S,9aS)-3-(3-(4-(azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-		656.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.78 - 8.63 (m, 1H), 8.35 - 8.20 (m, 1H), 8.19 - 8.08 (m, 1H), 8.08 - 7.97 (m, 1H), 7.96 - 7.87 (m, 1H), 7.57 -

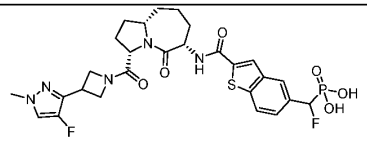
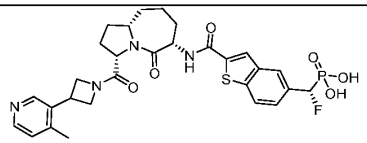
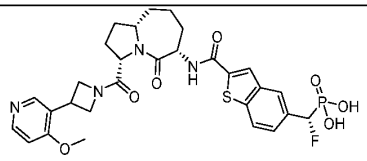
	pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid			7.40 (m, 1H), 6.53 - 6.27 (m, 1H), 5.88 - 5.61 (m, 1H), 4.73 - 4.59 (m, 2H), 4.53 (t, *J* = 8.4 Hz, 1H), 4.46 - 4.41 (m, 1H), 4.41 - 4.24 (m, 5H), 4.23 - 4.08 (m, 2H), 4.07 - 3.93 (m, 3H), 2.41 - 2.28 (m, 2H), 2.25 - 2.14 (m, 1H), 2.08 - 1.92 (m, 2H), 1.90 - 1.77 (m, 3H), 1.75 - 1.66 (m, 2H)
743	((2-(((3S,6S,9aS)-3-(3-(5-cyano-1-methyl-1H-pyrazol-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		629.3	^{1}H NMR (400 MHz, $CDCl_3$) 8.16 - 7.65 (m, 2H), 7.64 - 7.32 (m, 3H), 6.07 - 5.53 (m, 1H), 4.94 - 4.61 (m, 1H), 4.59 - 4.23 (m, 3H), 4.20 - 4.06 (m, 2H), 4.00 (s, 3H), 3.92 (d, *J* = 4.0 Hz, 2H), 2.36 - 2.18 (m, 1H), 2.13 - 1.91 (m, 4H), 1.90 - 1.51 (m, 5H)
744	((1R)-fluoro(2-(((3S,6S,8R,9aR)-3-(3-(4-isopropoxypyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)-2,3-dihydrobenzo[b]thiophen-5-yl)methyl)phosphonic acid		673.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.23 - 8.18 (m, 2H), 7.98 - 7.97 (m, 1H), 7.86 - 7.82 (m, 2H), 7.56 - 7.54 (m, 1H), 7.36 - 7.33 (m, 1H), 5.90 - 5.77 (m, 1H), 4.78 - 4.76 (m, 1H), 4.61 - 4.50 (m, 3H), 4.30 - 4.24 (m, 2H), 4.10 - 3.98 (m, 3H), 2.33 - 2.31 (m, 1H), 2.15 - 2.00 (m, 3H), 1.98 - 1.92 (m, 2H), 1.82 - 1.75 (m, 1H), 1.64 - 1.61 (m, 2H), 1.51 - 1.42 (m, 6H), 1.06 - 1.04 (m, 3H)

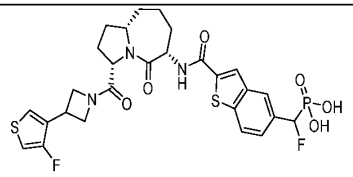
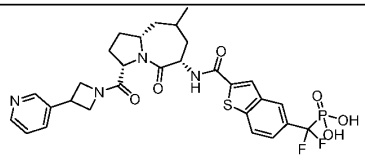
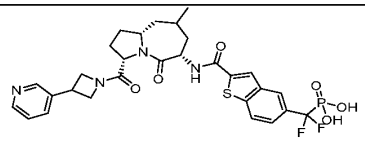
745	((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-morpholinopyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		686.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.36 - 8.16 (m, 1H), 8.16 - 8.00 (m, 1H), 7.98 - 7.89 (m, 1H), 7.88 - 7.81 (m, 1H), 7.80 - 7.72 (m, 1H), 7.64 - 7.41 (m, 1H), 7.26 - 6.85 (m, 1H), 5.89 - 5.58 (m, 1H), 4.81 - 4.76 (m, 1H), 4.75 - 4.68 (m, 1H), 4.61 - 4.45 (m, 2H), 4.43 - 4.26 (m, 1H), 4.17 - 4.01 (m, 3H), 3.88 - 3.66 (m, 4H), 3.31 - 3.11 (m, 4H), 2.39 - 2.25 (m, 1H), 2.20 - 2.06 (m, 2H), 2.03 - 1.76 (m, 7H)
746	((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-morpholinopyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		686.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.37 - 8.12 (m, 1H), 8.12 - 7.98 (m, 1H), 7.97 - 7.84 (m, 1H), 7.84 - 7.75 (m, 1H), 7.72 - 7.52 (m, 1H), 7.58 - 7.47 (m, 1H), 7.22 - 6.85 (m, 1H), 5.91 - 5.55 (m, 1H), 4.84 - 4.78 (m, 1H), 4.73 - 4.65 (m, 1H), 4.59 - 4.44 (m, 2H), 4.42 - 4.25 (m, 1H), 4.16 - 3.98 (m, 3H), 3.76 - 3.75 (m, 4H), 3.30 - 3.13 (m, 4H), 2.37 - 2.26 (m, 1H), 2.22 - 2.07 (m, 2H), 2.06 - 1.75 (m, 7H)
747	((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		631.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.36 - 8.23 (m, 2H), 8.01 - 7.92 (m, 1H), 7.91 - 7.77 (m, 2H), 7.55 (d, J = 7.6 Hz, 1H), 7.41 - 7.22 (m, 1H), 5.86 - 5.65 (m, 1H), 4.84 - 4.70 (m, 2H), 4.65 - 4.55 (m, 1H), 4.53 -

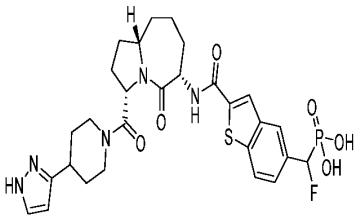
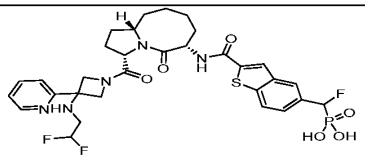
	yl)methyl)phosphonic acid			4.46 (m, 1H), 4.34 - 4.24 (m, 1H), 4.18 - 3.97 (m, 6H), 2.37 - 2.25 (m, 1H), 2.17 - 2.05 (m, 2H), 2.03 - 1.80 (m, 7H)
748	((R)-fluoro(2-(((3S,6S,8S,9aR)-3-(3-(4-isopropoxypyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		673.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 - 8.65 (m, 1H), 8.54 - 8.41 (m, 2H), 8.29 - 8.17 (m, 1H), 8.07 - 7.93 (m, 2H), 7.57 - 7.49 (m, 1H), 7.36 - 7.22 (m, 1H), 5.92 - 5.72 (m, 1H), 4.97 - 4.82 (m, 2H), 4.73 - 4.53 (m, 1H), 4.44 - 4.29 (m, 2H), 4.23 - 4.13 (m, 2H), 4.10 - 3.92 (m, 3H), 2.27 - 1.97 (m, 4H), 1.92 - 1.74 (m, 4H), 1.71 - 1.61 (m, 1H), 1.53 - 1.43 (m, 1H), 1.35 - 1.29 (m, 6H), 1.12 (t, J = 6.4 Hz, 3H)
749	((R)-fluoro(2-(((3S,6S,8S,9aR)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		645.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 - 8.72 (m, 1H), 8.43 - 8.35 (m, 2H), 8.24 - 8.18 (m, 1H), 8.03 - 7.94 (m, 2H), 7.52 (t, J = 9.6 Hz, 1H), 7.22 - 7.09 (m, 1H), 5.86 - 5.72 (m, 1H), 4.87 - 4.74 (m, 1H), 4.71 - 4.53 (m, 1H), 4.43 - 4.37 (m, 2H), 4.21 - 4.15 (m, 2H), 4.02 - 3.96 (m, 2H), 3.91 - 3.89 (m, 3H), 2.19 - 2.09 (m, 2H), 2.07 - 2.03 (m, 1H), 1.91 - 1.88 (m, 2H), 1.81 - 1.79 (m, 1H), 1.70 - 1.62 (m, 1H), 1.49 - 1.45 (m, 1H), 1.27 - 1.23 (m, 1H), 1.13 - 1.09 (m, 3H)

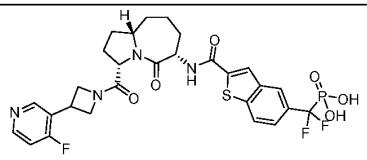
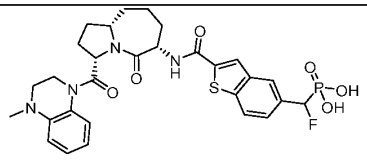
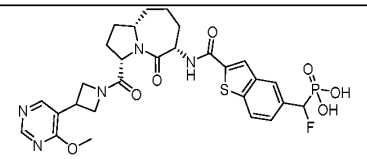
750	((2-(((3S,6S,9aS)-3-(3-(4-morpholinopyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		668.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.49 - 8.30 (m, 1H), 8.29 - 8.02 (m, 1H), 8.01 - 7.88 (m, 1H), 7.87 - 7.77 (m, 1H), 7.76 - 7.70 (m, 1H), 7.46 - 7.34 (m, 1H), 7.33 - 7.10 (m, 1H), 5.00 - 4.93 (m, 1H), 4.92 - 4.87 (m, 2H), 4.79 - 4.68 (m, 2H), 4.54 (t, J = 6.8 Hz, 2H), 4.47 - 4.31 (m, 1H), 4.24 - 4.14 (m, 1H), 4.14 - 4.02 (m, 2H), 3.82 (d, J = 4.0 Hz, 4H), 3.38 (d, J = 4.0 Hz, 1H), 3.27 - 3.14 (m, 2H), 2.39 - 2.26 (m, 1H), 2.23 - 1.75 (m, 9H)
751	(fluoro(2-(((3S,6S,9aS)-3-(3-(4-fluoro-1-methyl-1H-pyrazol-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		622.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (m, 2H), 7.94 (s, 1H), 7.63 - 7.55 (m, 1H), 7.35 (m, 1H), 5.91 - 5.73 (m, 1H), 4.95 - 4.92 (m, 1H), 4.77 - 4.66 (m, 2H), 4.61 - 4.53 (m, 1H), 4.46 (s, 1H), 4.31 (s, 1H), 4.19 (m, 1H), 4.12 - 4.02 (m, 1H), 3.73 (d, J = 7.8 Hz, 3H), 2.35 - 2.26 (m, 1H), 2.17 - 2.11 (m, 1H), 2.10 - 2.01 (m, 2H), 2.00 - 1.93 (m, 2H), 1.92 - 1.87 (m, 2H), 1.86 - 1.78 (m, 2H)
752	(fluoro(2-(((3S,6S,9aS)-3-(3-(5-fluoro-2-methoxyphenyl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)-2,3-dihydrobenzo[b]thio		648.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.13 - 8.01 (m, 2H), 7.97 - 7.94 (m, 1H), 7.60 - 7.57 (m, 1H), 7.21 - 7.05 (m, 1H), 7.01 - 6.90 (m, 2H), 5.93 - 5.76 (m, 1H), 4.77 - 4.74 (m, 2H), 4.64 - 4.53 (m, 2H), 4.40 - 4.39

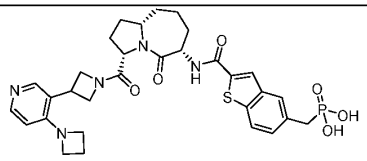
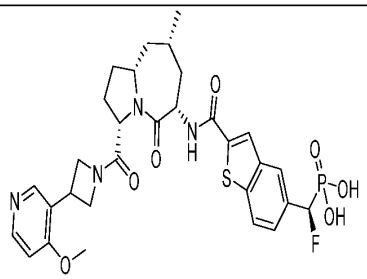
	phen-5-yl)methyl)phosphonic acid			(m, 1H), 4.18 - 4.02 (m, 3H), 3.82 (s, 3H), 2.36 - 2.26 (m, 1H), 2.18 - 2.05 (m, 2H), 2.03 - 2.01(m, 1H), 1.99 - 1.78 (m, 6H)
753	((S)-fluoro(2-(((3S,6S,8R,9aR)-8-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		629.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 - 8.60 (m, 2H), 8.57 - 8.46 (m, 1H), 8.23 (d, *J* = 19.6 Hz, 1H), 8.07 - 7.91 (m, 2H), 7.62 - 7.48 (m, 2H), 5.94 - 5.69 (m, 1H), 4.87 - 4.75 (m, 1H), 4.71 - 4.59 (m, 2H), 4.52 - 4.42 (m, 2H), 4.39 - 4.24 (m, 2H), 4.17 (d, *J* = 7.6 Hz, 1H), 4.09 - 4.00 (m, 2H), 2.33 (d, *J* = 8.0 Hz, 3H), 2.26 - 2.15 (m, 1H), 2.08 - 1.92 (m, 2H), 1.89 - 1.75 (m, 3H), 1.70 (d, *J* = 11.2 Hz, 1H), 1.56 - 1.35 (m, 2H), 1.03 - 0.88 (m, 3H)
754	(fluoro(2-(((3S,6S,9aS)-3-(3-(4-fluoro-1-methyl-1H-pyrazol-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		622.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.07 (d, J = 8.0 Hz, 1H), 8.04 - 7.98 (m, 1H), 7.98 - 7.90 (m, 1H), 7.55 (m, 2H), 5.91 - 5.76 (m, 1H), 4.78 - 4.71 (m, 1H), 4.65 - 4.55 (m, 2H), 4.43 - 4.35 (m, 1H), 4.34 - 4.23 (m, 1H), 4.12 - 4.02 (m, 2H), 3.97 (m, 1H), 3.82 - 3.74 (m, 3H), 2.36 - 2.22 (m, 1H), 2.12 (m, 1H), 2.09 - 2.03 (m, 1H), 2.02 - 1.93 (m, 3H), 1.92 - 1.87 (m, 2H), 1.86 - 1.78 (m, 2H)

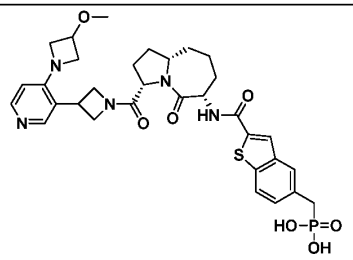
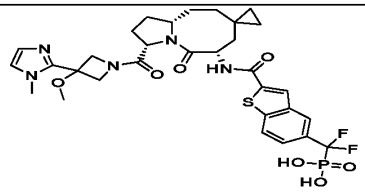
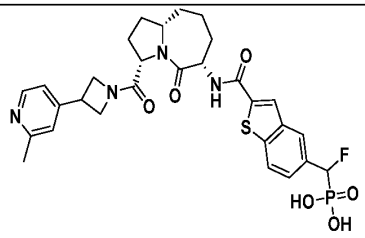
755	((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		615.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.64 (d, J = 5.6 Hz, 1H), 8.42 - 8.27 (m, 1H), 8.03 - 7.49 (m, 5H), 5.89 - 5.68 (m, 1H), 4.74 (d, J = 10.4 Hz, 2H), 4.66 - 4.50 (m, 2H), 4.46 - 4.22 (m, 2H), 4.16 - 4.02 (m, 2H), 2.53 - 2.40 (m, 3H), 2.36 - 2.27 (m, 1H), 2.18 - 1.81 (m, 9H)
756	((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		631.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.36 - 8.28 (m, 2H), 8.06 - 7.98 (m, 2H), 7.85 (t, *J* = 9.6 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.13 - 7.05 (m, 1H), 5.73 - 5.57 (m, 1H), 4.77 - 4.65 (m, 2H), 4.64 - 4.59 (m, 1H), 4.59 - 4.53 (m, 1H), 4.44 - 4.35 (m, 1H), 4.22 - 4.11 (m, 1H), 4.10 - 4.01 (m, 2H), 3.97 (d, *J* = 6.0 Hz, 3H), 2.37 - 2.25 (m, 1H), 2.19 - 2.05 (m, 2H), 2.04 - 1.99 (m, 1H), 1.99 - 1.90 (m, 3H), 1.90 - 1.78 (m, 3H)
757	(fluoro(2-(((3S,6S,9aS)-3-(3-(4-fluorothiophen-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		624.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.09 - 8.08 (m, 1H), 8.04 (s, 1H), 7.97 - 7.94(m, 1H), 7.60 -7.58 (m, 1H), 7.13 - 6.62 (m, 2H), 5.93 - 5.73 (m, 1H), 4.76 - 4.74 (m, 1H), 4.62 - 4.48 (m, 2H), 4.45 - 4.17 (m, 2H), 4.10 - 3.82 (m, 3H), 2.37 - 2.24 (m, 1H), 2.16 - 2.06 (m, 2H), 2.05 - 1.99 (m, 1H), 1.99 - 1.88 (m, 4H), 1.87 - 1.81 (m, 2H)

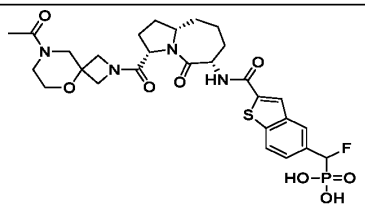
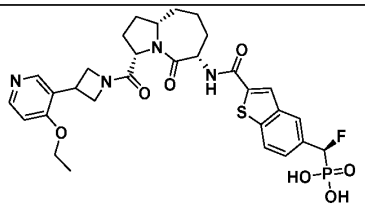
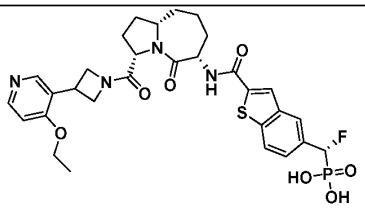
758	((2-(((1R,3S,6S,10aR,Z)-3-((*rel-trans*)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-1-hydroxy-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		685.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (d, J = 10.0 Hz, 1H), 8.11 - 8.06 (m, 1H), 7.95 (m, 1H), 7.78 - 7.70 (m, 1H), 7.48 - 7.31 (m, 5H), 5.89 - 5.68 (m, 2H), 5.12 - 4.96 (m, 2H), 4.76 - 4.63 (m, 2H), 4.49 - 4.31 (m, 1H), 4.24 - 3.94 (m, 2H), 3.89 - 3.76 (m, 1H), 3.71 - 3.51 (m, 2H), 3.08 - 2.93 (m, 1H), 2.68 - 2.58 (m, 1H), 2.54 - 2.35 (m, 2H), 2.29 - 2.16 (m, 1H), 2.11 - 2.01 (m, 1H)
759	(difluoro(2-(((3S,6S,9aR)-8-methyl-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		633.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.61 - 8.54 (m, 2H), 8.50 - 8.44 (m, 1H), 8.37 - 8.31 (m, 1H), 8.19 (d, J = 3.8 Hz, 1H), 8.13 - 8.07 (m, 2H), 7.94 (d, J = 8.5 Hz, 1H), 7.74 (d, J = 8.6 Hz, 1H), 7.61 - 7.54 (m, 1H), 4.78 - 4.66 (m, 3H), 4.65 - 4.38 (m, 4H), 4.33 - 4.24 (m, 1H), 4.09 - 4.00 (m, 3H), 2.38 - 2.25 (m, 2H), 2.00 - 1.90 (m, 3H), 1.80 (d, J = 14.4 Hz, 1H), 1.68 - 1.57 (m, 2H), 1.25 - 1.21 (m, 1H), 1.10 - 1.00 (m, 3H)
760	((2-(((3S,6S,9aS)-3-(4-(1H-pyrazol-3-yl)piperidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		618.1	^{1}H NMR (400 MHz, DMSO-d6) δ 8.70 (m, 1H), 8.23 (m, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.97 (m, 1H), 7.53 (d, J = 8.6 Hz, 1H), 7.49 (d, J = 4.6 Hz, 1H), 6.07 (d, J = 17.4 Hz, 1H), 5.77 (d, J = 8.0 Hz, 1H),

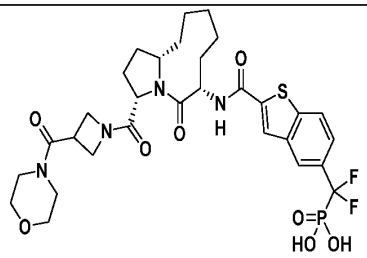
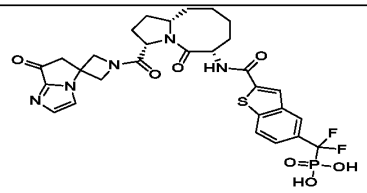
	yl)fluoromethyl)phosphonic acid			5.00 - 4.91 (m, 1H), 4.66 - 4.60 (m, 1H), 4.36 (d, J = 11.8 Hz, 1H), 3.62 (m, 1H), 3.23 - 3.12 (m, 1H), 2.95 - 2.83 (m, 1H), 2.71 (t, J = 12.0 Hz, 1H), 2.27 - 2.16 (m, 1H), 2.13 - 2.02 (m, 1H), 2.01 - 1.82 (m, 4H), 1.81 - 1.66 (m, 4H), 1.65 - 1.36 (m, 2H), 1.28 - 1.22 (m, 2H)
761	((2-(((3S,6S,10aS)-3-(3-((2,2-difluoroethyl)amino)-3-(pyridin-2-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		694.4	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.85 - 8.74 (m, 1H), 8.57 (dd, *J* = 4.0, 15.6 Hz, 1H), 8.29 - 8.18 (m, 1H), 8.02 - 7.80 (m, 3H), 7.64 - 7.53 (m, 1H), 7.52 - 7.43 (m, 1H), 7.35 - 7.30 (m, 1H), 6.08 - 5.64 (m, 2H), 4.98 - 4.88 (m, 1H), 4.71 (d, *J* = 8.8 Hz, 1H), 4.53 (d, *J* = 8.4 Hz, 1H), 4.42 (d, *J* = 8.8 Hz, 1H), 4.39 - 4.31 (m, 1H), 4.30 - 4.17 (m, 3H), 4.06 - 3.90 (m, 1H), 3.89 - 3.80 (m, 1H), 2.22 - 2.02 (m, 2H), 1.91 - 1.72 (m, 7H), 1.65 - 1.48 (m, 3H)
762	(difluoro(2-(((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		637.1	1H NMR (400 MHz, DMSO-d6) δ 8.79 (t, J = 7.2 Hz, 1H), 8.68 (dd, J = 3.6, 10.4 Hz, 1H), 8.57 - 8.48 (m, 1H), 8.25 (d, J = 9.6 Hz, 1H), 8.05 - 8.01 (m, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.65 - 7.60 (m, 1H), 7.33 (dt, J = 5.6, 11.2 Hz, 1H), 4.70 - 4.57 (m, 2H), 4.55 - 4.40 (m, 2H), 4.37 - 4.30 (m,

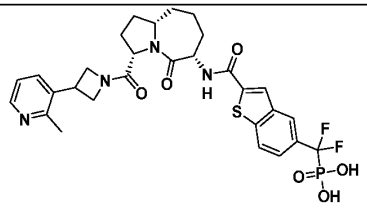
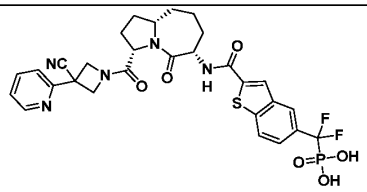
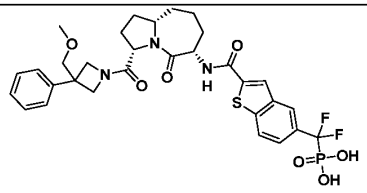
				1H), 4.29 - 4.22 (m, 1H), 4.16 - 4.04 (m, 2H), 4.02 - 3.94 (m, 2H), 2.22 - 2.15 (m, 1H), 2.08 - 2.00 (m, 1H), 2.00 - 1.91 (m, 2H), 1.83 - 1.79 (m, 2H), 1.75 - 1.66 (m, 4H)
763	(fluoro(2-(((3S,6S,9aS)-3-(4-methyl-1,2,3,4-tetrahydroquinoxaline-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		615.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.09 - 8.00 (m, 2H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.34 - 7.24 (m, 1H), 7.14 - 7.04 (m, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.63 (t, *J* = 7.4 Hz, 1H), 5.91 - 5.72 (m, 1H), 5.27 - 5.16 (m, 1H), 4.75 - 4.67 (m, 1H), 4.05 (d, *J* = 1.8, 4.0 Hz, 1H), 3.92 - 3.72 (m, 2H), 3.48 - 3.37 (m, 2H), 2.97 (s, 3H), 2.31 - 2.18 (m, 1H), 2.08 - 1.79 (m, 9H)
764	(fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		632.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 - 8.73 (m, 1H), 8.72 - 8.52 (m, 1H), 8.28 - 8.16 (m, 1H), 8.09 - 8.01 (m, 1H), 8.01 - 7.93 (m, 1H), 7.61 - 7.48 (m, 1H), 5.91 - 5.74 (m, 1H), 4.72 - 4.61 (m, 2H), 4.55 - 4.49 (m, 1H), 4.46 - 4.43 (m, 1H), 4.35 - 4.29 (m, 1H), 4.20-4.14 (m, 2H), 4.05-4.01 (m, 1H), 3.95 (s, 3H), 2.27 - 1.92 (m, 4H), 1.89 - 1.68 (m, 6H)
765	((2-(((3S,6S,9aS)-3-(3-(4-(azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-		638.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 - 8.58 (m, 1H), 8.37 - 8.09 (m, 2H), 8.08 - 7.87 (m, 1H), 7.86 -

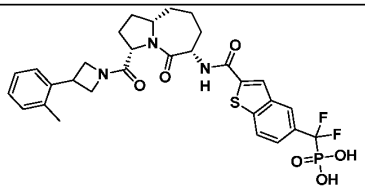
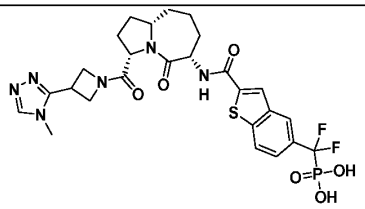
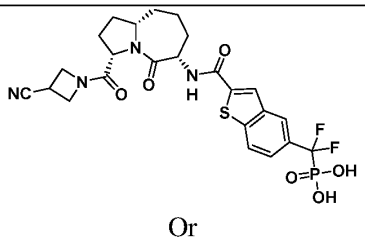
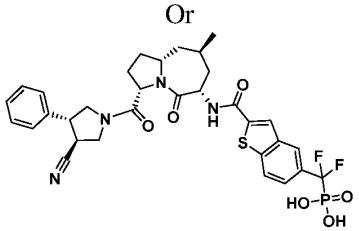
	oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			7.74 (m, 1H), 7.45 - 7.28 (m, 1H), 6.56 - 6.31 (m, 1H), 4.73 - 4.58 (m, 2H), 4.57 - 4.49 (m, 1H), 4.47 - 4.27 (m, 6H), 4.26 - 4.10 (m, 2H), 4.07 - 3.96 (m, 3H), 3.12 - 3.02 (m, 2H), 2.43 - 2.29 (m, 2H), 2.26 - 2.15 (m, 1H), 2.06 - 1.91 (m, 2H), 1.89 - 1.77 (m, 3H), 1.75 - 1.61 (m, 2H)
766	((R)-fluoro(2-(((3S,6S,8R,9aR)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		645.1	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.80 - 8.50 (m, 3H), 8.28 - 8.18 (m, 1H), 8.06 - 7.92 (m, 2H), 7.58 - 7.36 (m, 2H), 5.92 - 5.72 (m, 1H), 4.76 - 4.61 (m, 2H), 4.55 (t, *J* = 8.4 Hz, 1H), 4.49 - 4.40 (m, 2H), 4.36 - 4.29 (m, 1H), 4.26 - 4.14 (m, 2H), 4.02 (s, 5H), 2.27 - 2.15 (m, 1H), 2.08 - 1.93 (m, 2H), 1.81 (t, *J* = 9.2 Hz, 3H), 1.70 (d, *J* = 12.8 Hz, 1H), 1.56 - 1.36 (m, 2H), 0.96 (d, *J* = 6.0 Hz, 3H)
767	((2-(((3S,6S,9aS)-3-(3-(4-(3-methoxyazetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		688.1	^{1}H NMR (400 MHz, CD$_3$OD) δ 8.08 - 7.33 (m, 6H), 6.28 - 6.07 (m, 1H), 4.80 - 4.67 (m, 2H), 4.67 - 4.17 (m, 6H), 4.16 - 3.95 (m, 5H), 3.36 (s, 1.5H), 3.28 (s, 1.5H), 3.18 - 2.96 (m, 2H), 2.36 - 2.22 (m, 1H), 2.18 - 1.75 (m, 9H)

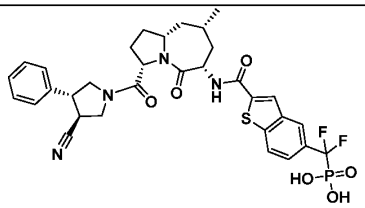
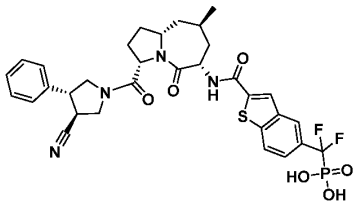
768	(difluoro(2-(((3'S,6'S,10a'S)-3'-(3-methoxy-3-(1-methyl-1H-imidazol-2-yl)azetidine-1-carbonyl)-5'-oxooctahydro-5'H-spiro[cyclopropane-1,8'-pyrrolo[1,2-a]azocin]-6'-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		692.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 - 8.66 (m, 1H), 8.29 - 8.17 (m, 1H), 8.05 - 7.93 (m, 2H), 7.65 - 7.58 (m, 1H), 7.22 (dd, J = 9.8, 1.0 Hz, 1H), 6.86 (s, 1H), 4.97 - 4.84 (m, 1.5H), 4.78 - 4.68 (m, 1H), 4.51 - 4.26 (m, 3.5H), 4.11 - 3.98 (m, 1H), 3.56 (d, J = 5.9 Hz, 3H), 2.91 (d, J = 7.6 Hz, 3H), 2.25 - 2.15 (m, 0.5H), 2.14 - 1.99 (m, 1.5H), 1.98 - 1.65 (m, 5H), 1.62 - 1.43 (m, 3H), 0.53 - 0.29 (m, 4H)
769	(fluoro(2-(((3S,6S,9aS)-3-(3-(2-methylpyridin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		615.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.21 - 7.95 (m, 3H), 7.85 - 7.24 (m, 4H), 5.86 - 5.60 (m, 1H), 5.00 - 4.92 (m, 1H), 4.78 - 4.66 (m, 2H), 4.56 - 4.34 (m, 2H), 4.25 - 3.92 (m, 3H), 2.60 - 2.46 (m, 3H), 2.38 - 2.25 (m, 1H), 2.23 - 1.75 (m, 9H)
770	((2-(((3S,6S,9aS)-3-(8-acetyl-5-oxa-2,8-diazaspiro[3.5]nonane-2-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		637.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.13 - 8.00 (m, 2H), 7.97 - 7.91 (m, 1H), 7.64 - 7.56 (m, 1H), 5.89 - 5.68 (m, 1H), 4.77 - 4.71 (m, 1H), 4.61 - 4.31 (m, 2H), 4.19 - 4.01 (m, 2H), 4.00 - 3.76 (m, 3H), 3.75 - 3.65 (m, 2H), 3.65 - 3.47 (m, 2H), 2.36 - 2.24 (m, 1H), 2.18 - 2.02 (m, 5H), 2.02 - 1.90 (m, 3H), 1.89 - 1.75 (m, 3H), 1.39 - 1.35 (m, 2H)

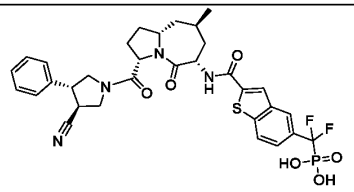
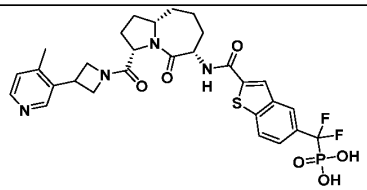
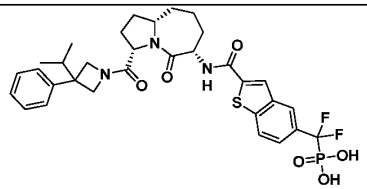
771	((S)-(2-(((3S,6S,9aS)-3-(3-(4-ethoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		645.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.18 - 8.08 (m, 1H), 8.06 - 7.99 (m, 1H), 7.96 - 7.91 (m, 0.5H), 7.90 - 7.83 (m, 1H), 7.83 - 7.78 (m,1H), 7.78 - 7.73 (m, 0.5H), 7.71 - 7.65 (m, 0.5H), 7.58 - 7.52 (m, 0.5H), 7.14 - 7.02 (m, 1H), 5.79 - 5.59 (m, 1H), 4.63 - 4.44 (m, 3H), 4.38 - 4.02 (m, 6H), 4.02 - 3.83 (m, 1H), 2.39 - 2.23 (m, 1H), 2.20 - 1.72 (m, 9H), 1.52 - 1.40 (m, 3H).
772	((R)-(2-(((3S,6S,9aS)-3-(3-(4-ethoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		645.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.26 - 8.13 (m, 2H), 8.05 - 7.97 (m, 1H), 7.93 - 7.89 (m, 0.5H), 7.89 - 7.76 (m, 1.5H), 7.63 - 7.54 (m, 1H), 7.14 - 6.99 (m, 1H), 5.76 - 5.56 (m, 1H), 4.65 - 4.59 (m, 1H), 4.56 - 4.49 (m, 1H), 4.40 - 4.12 (m, 6H), 4.11 - 3.96 (m, 2H), 2.39 - 2.22 (m, 1H), 2.20 - 1.75 (m, 9H), 1.50 - 1.40 (m, 3H)
773	(difluoro(2-(((3S,6S,11aS)-3-(3-(morpholine-4-carbonyl)azetidine-1-carbonyl)-5-oxodecahydro-1H-pyrrolo[1,2-a]azonin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		682.68	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (dd, J = 17.9, 6.4 Hz, 1H), 8.32 (s, 1H), 8.11 (d, J = 8.2 Hz, 1H), 8.04 (s, 1H), 7.57 (d, J = 8.5 Hz, 1H), 5.05 – 4.94 (m, 1H), 4.53 (dt, J = 35.3, 8.1 Hz, 2H), 4.30 (q, J = 6.9, 5.8 Hz, 2H), 4.21 (s, 2H), 4.08 (t, J = 9.5 Hz, 1H), 3.45 (s, 4H), 3.26 (t, J = 5.0 Hz, 3H), 3.06 (dd, J = 7.6,

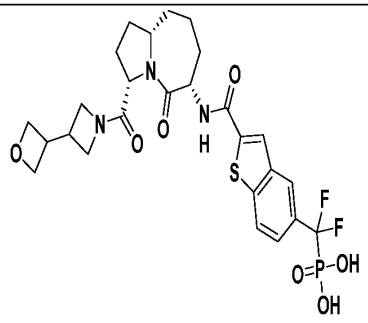
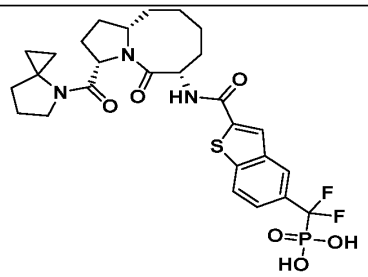
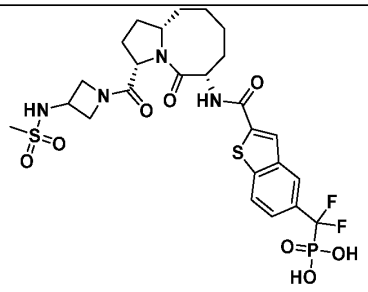
				5.1 Hz, 2H), 2.15 – 2.02 (m, 2H), 2.02 – 1.92 (m, 2H), 1.75 (q, *J* = 14.3, 12.6 Hz, 5H), 1.69 – 1.58 (m, 2H), 1.49 (s, 2H), 1.40 (d, *J* = 14.9 Hz, 1H)
774	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-(7'-oxo-6',7'-dihydrospiro[azetidine-3,5'-pyrrolo[1,2-a]imidazole]-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		661.62	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.98 – 8.87 (m, 1H), 8.33 – 8.27 (m, 1H), 8.16 – 7.95 (m, 3H), 7.56 (dd, *J* = 9.0, 5.2 Hz, 2H), 4.97 – 4.89 (m, 1H), 4.82 (dd, *J* = 40.6, 9.9 Hz, 1H), 4.58 (dd, *J* = 51.4, 10.0 Hz, 1H), 4.40 – 4.17 (m, 4H), 3.03 (d, *J* = 7.4 Hz, 1H), 2.26 – 2.01 (m, 3H), 1.85 (q, *J* = 12.4 Hz, 5H), 1.78 – 1.64 (m, 3H), 1.61 (s, 1H), 1.52 (d, *J* = 10.0 Hz, 1H)
775	(difluoro(2-(((3S,6S,9aS)-3-(3-(2-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		632.62	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.74 (dd, *J* = 15.0, 7.7 Hz, 1H), 8.29 (s, 1H), 8.24 (d, *J* = 15.1 Hz, 1H), 8.07 (dd, *J* = 8.7, 3.6 Hz, 1H), 8.03 (s, 1H), 7.98 – 7.84 (m, 1H), 7.61 – 7.50 (m, 1H), 7.30 (d, *J* = 30.7 Hz, 1H), 4.81 – 4.50 (m, 3H), 4.47 – 4.38 (m, 2H), 4.28 – 4.21 (m, 1H), 4.09 – 4.04 (m, 1H), 2.38 (d, *J* = 6.4 Hz, 3H), 2.18 (d, *J* = 9.6 Hz, 1H), 1.98 (dd, *J* = 39.2, 10.0 Hz, 2H), 1.89 – 1.63 (m, 8H)

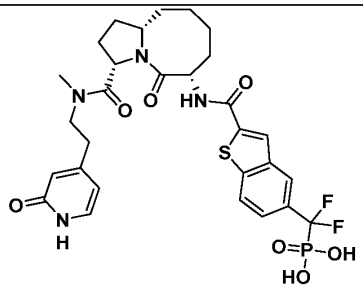
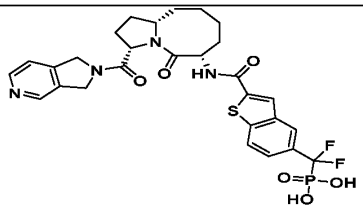
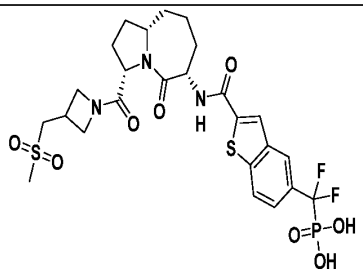
776	((2-(((3S,6S,9aS)-3-(3-cyano-3-(pyridin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		643.6	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.83 (dd, J = 64.2, 7.7 Hz, 1H), 8.65 (dd, J = 31.9, 4.8 Hz, 1H), 8.32 – 8.24 (m, 1H), 8.11 (dd, J = 8.5, 5.1 Hz, 1H), 8.06 (d, J = 15.1 Hz, 1H), 7.98 – 7.86 (m, 1H), 7.71 (t, J = 7.3 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.44 (ddd, J = 30.3, 7.6, 4.8 Hz, 1H), 5.04 – 4.73 (m, 2H), 4.66 (dt, J = 21.8, 9.8 Hz, 1H), 4.48 (dd, J = 16.5, 10.0 Hz, 1H), 4.45 – 4.35 (m, 2H), 4.34 (s, 1H), 4.00 (s, 1H), 2.19 (dt, J = 13.6, 7.2 Hz, 1H), 2.09 – 1.99 (m, 1H), 1.94 (s, 1H), 1.87 – 1.75 (m, 4H), 1.75 – 1.50 (m, 4H)
777	(difluoro(2-(((3S,6S,9aS)-3-(3-(methoxymethyl)-3-phenylazetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		661.66	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, J = 33.4 Hz, 1H), 8.17 – 7.99 (m, 2H), 7.57 (t, J = 7.7 Hz, 1H), 7.34 (q, J = 8.4 Hz, 2H), 7.29 – 7.19 (m, 3H), 4.62 (d, J = 13.2 Hz, 1H), 4.53 – 4.41 (m, 2H), 4.34 (dd, J = 11.8, 8.5 Hz, 1H), 4.15 – 3.85 (m, 4H), 3.19 (s, 3H), 2.27 – 2.11 (m, 1H), 1.98 (d, J = 31.6 Hz, 2H), 1.88 – 1.50 (m, 7H)
778	(difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(o-tolyl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo		631.63	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.77 (d, J = 7.6 Hz, 1H), 8.28 (d, J = 20.9 Hz, 1H), 8.12 – 8.03 (m, 2H), 7.60 – 7.19 (m, 2H), 7.17 – 6.87 (m, 3H), 4.79 – 4.55 (m, 2H),

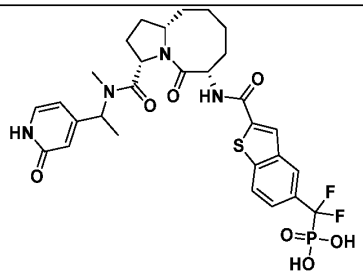
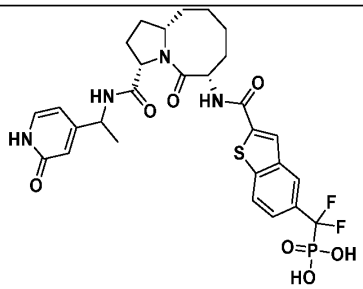
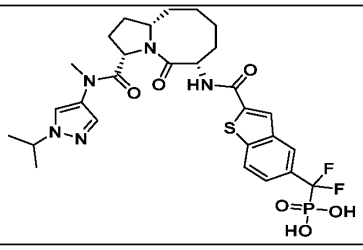
	[b]thiophen-5-yl)methyl)phosphonic acid			4.44 (dd, *J* = 7.9, 4.8 Hz, 1H), 4.38 – 4.22 (m, 2H), 4.19 (d, *J* = 8.9 Hz, 1H), 4.05 (q, *J* = 8.3 Hz, 2H), 2.23 (s, 1H), 2.16 (s, 3H), 1.98 (d, *J* = 40.8 Hz, 2H), 1.88 – 1.59 (m, 7H)
779	(difluoro(2-(((3S,6S,9aS)-3-(3-(4-methyl-4H-1,2,4-triazol-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		622.58	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.78 (dd, *J* = 15.8, 7.7 Hz, 1H), 8.45 – 8.37 (m, 1H), 8.28 (d, *J* = 13.8 Hz, 1H), 8.12 – 8.02 (m, 2H), 7.61 – 7.51 (m, 1H), 4.80 – 4.51 (m, 3H), 4.42 (td, *J* = 8.3, 3.8 Hz, 2H), 4.30 – 4.14 (m, 2H), 4.06 (dp, *J* = 13.2, 6.4, 5.2 Hz, 2H), 3.97 (s, 1H), 2.23 – 2.13 (m, 1H), 2.02 – 1.90 (m, 2H), 1.85 – 1.63 (m, 7H), 1.23 – 1.10 (m, 1H)
780	((2-(((3S,6S,9aS)-3-(3-cyanoazetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		566.52	
781	((2-(((3S,6S,8R,9aR)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid Or	 Or 	670.67	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.75 (dd, *J* = 13.6, 7.6 Hz, 1H), 8.28 (d, *J* = 11.6 Hz, 1H), 8.11 (dd, *J* = 8.6, 4.5 Hz, 1H), 8.06 (s, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.38 (td, *J* = 7.6, 5.7 Hz, 2H), 7.31 (q, *J* = 7.0 Hz, 1H), 4.65 (ddt, *J* = 13.3, 8.3, 4.6 Hz, 2H), 4.19 – 3.87 (m,

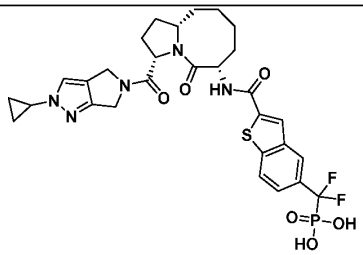
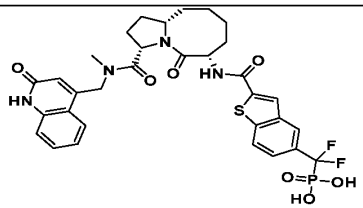
	((2-(((3S,6S,8S,9aR)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid			6H), 3.27 (t, *J* = 11.0 Hz, 1H), 2.21 (td, *J* = 12.0, 11.4, 4.5 Hz, 1H), 2.07 (qd, *J* = 8.4, 3.6 Hz, 1H), 1.96 (s, 1H), 1.80 (qt, *J* = 18.3, 6.0 Hz, 3H), 1.69 (d, *J* = 12.8 Hz, 1H), 1.56 (qd, *J* = 11.5, 6.3 Hz, 1H), 1.44 (qd, *J* = 12.0, 4.5 Hz, 1H), 0.95 (dd, *J* = 6.6, 4.3 Hz, 3H)
782	((2-(((3S,6S,8S,9aR)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid Or ((2-(((3S,6S,8R,9aR)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid	 Or 	670.67	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.73 (dd, *J* = 14.9, 7.7 Hz, 1H), 8.27 (d, *J* = 12.9 Hz, 1H), 8.10 (dd, *J* = 8.5, 5.9 Hz, 1H), 8.05 (s, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.37 (q, *J* = 7.5 Hz, 2H), 7.31 (q, *J* = 7.7 Hz, 1H), 4.89 – 4.81 (m, 1H), 4.59 (ddd, *J* = 12.2, 8.1, 4.7 Hz, 1H), 4.17 (q, *J* = 8.8 Hz, 2H), 4.06 (t, *J* = 8.9 Hz, 1H), 3.97 (dd, *J* = 11.4, 8.0 Hz, 1H), 3.91 (dd, *J* = 11.8, 8.2 Hz, 1H), 3.85 (t, *J* = 10.0 Hz, 1H), 3.08 – 3.05 (m, 1H), 2.25 (s, 1H), 2.21 – 2.14 (m, 1H), 2.09 (t, *J* = 10.3 Hz, 1H), 1.97 – 1.88 (m, 2H), 1.84 (dt, *J* = 12.4, 6.1 Hz, 1H), 1.78 – 1.72 (m, 1H), 1.67 (d, *J* = 14.9 Hz, 1H), 1.52 – 1.45 (m, 1H), 1.11 (d, *J* = 7.0 Hz, 3H)

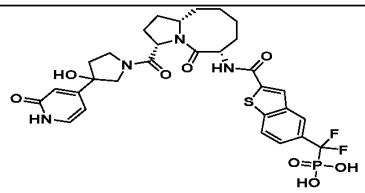
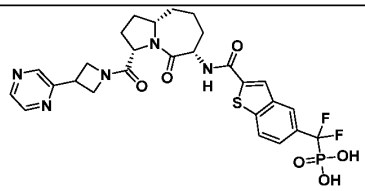
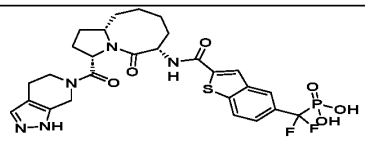
783	(difluoro(2-(((3S,6S,9aS)-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		632.62	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 – 8.59 (m, 1H), 8.43 – 8.11 (m, 3H), 8.11 – 7.95 (m, 2H), 7.55 (dd, J = 17.2, 8.6 Hz, 1H), 7.28 (dd, J = 37.3, 5.1 Hz, 1H), 4.84 – 4.60 (m, 2H), 4.48 – 4.24 (m, 3H), 4.10 – 3.96 (m, 4H), 3.89 (d, J = 2.7 Hz, 1H), 2.20 (d, J = 36.4 Hz, 3H), 1.98 (q, J = 10.1, 5.8 Hz, 2H), 1.88 – 1.65 (m, 6H)
784	(difluoro(2-(((3S,6S,9aS)-3-(3-isopropyl-3-phenylazetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		659.69	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.86 – 8.16 (m, 1H), 8.16 – 7.97 (m, 3H), 7.61 – 7.08 (m, 5H), 6.92 (d, J = 8.9 Hz, 1H), 4.61 (s, 1H), 4.54 – 4.29 (m, 3H), 4.05 – 3.92 (m, 3H), 3.15 (s, 1H), 1.92 (s, 4H), 1.74 (d, J = 49.7 Hz, 6H), 0.71 (dd, J = 19.1, 7.1 Hz, 6H)
785	(difluoro(2-(((3S,6S,9aS)-3-(3-(oxetan-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		597.57	

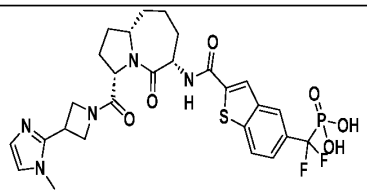
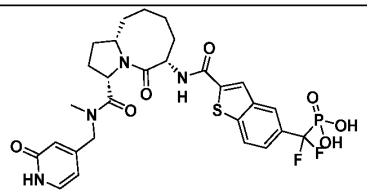
786	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-(4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		595.6	
787	(difluoro(2-(((3S,6S,10aS)-3-(3-(methylsulfonamido)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		648.63	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.83 (dd, J = 10.4, 7.0 Hz, 1H), 8.30 (d, J = 1.8 Hz, 1H), 8.12 (d, J = 8.5 Hz, 1H), 8.06 (s, 1H), 7.86 (dd, J = 25.6, 7.0 Hz, 1H), 7.57 (d, J = 9.0 Hz, 1H), 4.95 – 4.88 (m, 1H), 4.53 (dt, J = 128.7, 7.8 Hz, 1H), 4.22 (dd, J = 12.3, 5.6 Hz, 3H), 4.07 – 4.00 (m, 2H), 2.89 (d, J = 8.0 Hz, 3H), 2.12 (dd, J = 12.0, 7.2 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.90 – 1.77 (m, 7H), 1.72 (dd, J = 12.0, 5.5 Hz, 1H), 1.62 (s, 1H), 1.55 (d, J = 12.9 Hz, 1H), 1.49 (s, 1H).
788	(difluoro(2-(((3S,6S,10aS)-3-(methyl(2-(2-oxo-1,2-dihydropyridin-4-yl)ethyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		650.63	^{1}H NMR (600 MHz, DMSO-d_6) δ 11.48 (s, 1H), 8.83 (dd, J = 11.7, 7.2 Hz, 1H), 8.30 (t, J = 3.6 Hz, 1H), 8.25 – 8.10 (m, 3H), 8.05 (s, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.26 (d, J = 6.7 Hz, 1H), 6.23 – 6.10 (m, 2H), 4.99 – 4.91 (m, 1H), 4.72 – 4.66 (m, 1H), 3.02 (d, J = 4.3 Hz, 3H), 2.75 (d, J = 2.5 Hz, 2H), 2.73

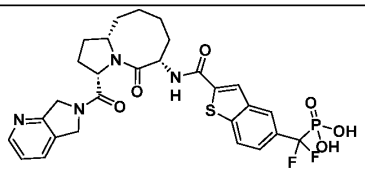
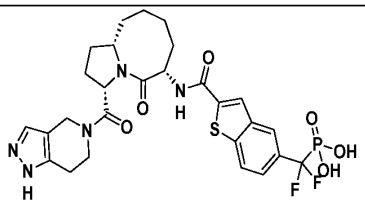
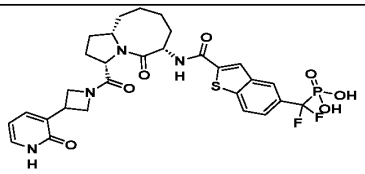
				(d, *J* = 8.0 Hz, 1H), 2.12 – 1.98 (m, 4H), 1.87 (d, *J* = 14.7 Hz, 2H), 1.82 (d, *J* = 14.5 Hz, 2H), 1.70 (d, *J* = 13.5 Hz, 1H), 1.62 (d, *J* = 14.3 Hz, 1H), 1.53 (d, *J* = 14.4 Hz, 2H)
789	((2-(((3S,6S,10aS)-3-(2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-2-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		618.59	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 – 8.15 (m, 2H), 8.11 (d, *J* = 8.8 Hz, 2H), 7.98 (d, *J* = 38.7 Hz, 1H), 7.52 (dd, *J* = 18.9, 7.5 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 5.26 – 4.76 (m, 3H), 4.72 (d, *J* = 18.0 Hz, 1H), 4.66 – 4.29 (m, 3H), 2.93 (d, *J* = 105.2 Hz, 2H), 2.41 (s, 2H), 2.09 (s, 1H), 1.98 – 1.79 (m, 5H), 1.62 (t, *J* = 26.5 Hz, 2H)
790	(difluoro(2-(((3S,6S,9aS)-3-(3-((methylsulfonyl)methyl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		633.62	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.75 (dd, *J* = 7.6, 4.0 Hz, 1H), 8.28 (s, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 8.06 (s, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 4.63 (s, 1H), 4.52 – 4.14 (m, 4H), 4.04 – 3.96 (m, 3H), 3.17 – 3.04 (m, 2H), 2.95 (s, 3H), 2.16 (s, 1H), 1.96 (d, *J* = 11.6 Hz, 2H), 1.84 (d, *J* = 13.2 Hz, 1H), 1.80 – 1.60 (m, 6H)
791	(difluoro(2-(((3S,6S,10aS)-3-(methyl(1-(2-oxo-1,2-dihydropyridin-4-yl)ethyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo		650.63	

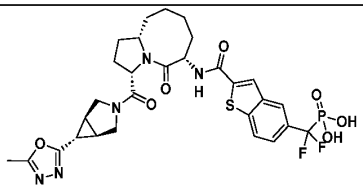
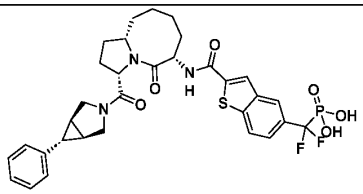
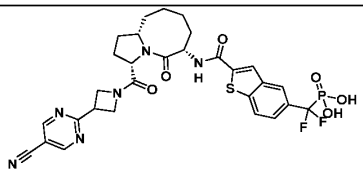
	[b]thiophen-5-yl)methyl)phosphonic acid			
792	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-((1-(2-oxo-1,2-dihydropyridin-4-yl)ethyl)carbamoyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		636.61	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.87 (dd, J = 56.1, 7.0 Hz, 1H), 8.39 – 8.35 (m, 1H), 8.31 (d, J = 6.5 Hz, 1H), 8.22 – 8.04 (m, 3H), 7.57 (d, J = 8.7 Hz, 1H), 7.27 (dd, J = 21.7, 6.8 Hz, 1H), 6.28 – 6.16 (m, 1H), 6.15 – 6.08 (m, 1H), 4.91 (td, J = 12.1, 6.3 Hz, 1H), 4.67 – 4.62 (m, 1H), 4.35 (dd, J = 16.1, 7.9 Hz, 1H), 4.25 (d, J = 7.7 Hz, 1H), 2.12 (t, J = 9.6 Hz, 1H), 2.04 (dd, J = 14.0, 6.8 Hz, 1H), 1.86 – 1.80 (m, 3H), 1.79 – 1.74 (m, 2H), 1.70 (dd, J = 12.2, 7.5 Hz, 2H), 1.63 – 1.58 (m, 1H), 1.57 – 1.53 (m, 1H), 1.48 (d, J = 11.6 Hz, 1H), 1.26 (dd, J = 7.1, 2.5 Hz, 3H)
793	(difluoro(2-(((3S,6S,10aS)-3-((1-isopropyl-1H-pyrazol-4-yl)(methyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		637.64	
794	((2-(((3S,6S,10aS)-3-(2-cyclopropyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)-5-oxodecahydropyrrol		647.63	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (s, 1H), 8.28 (s, 1H), 8.10 (d, J = 8.6 Hz, 1H), 8.05 (s, 1H), 7.58 (d, J = 8.2 Hz, 2H), 4.96 (dd, J =

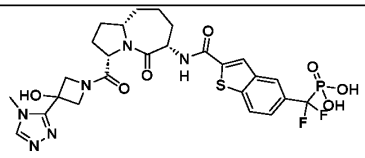
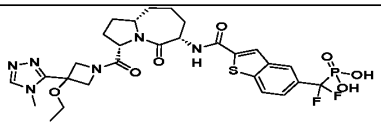
	o[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid			15.6, 7.1 Hz, 1H), 4.87 – 4.78 (m, 1H), 4.60 (t, *J* = 9.5 Hz, 2H), 4.35 (dq, *J* = 28.2, 12.6 Hz, 4H), 2.29 (d, *J* = 10.4 Hz, 1H), 2.09 (s, 1H), 1.98 – 1.73 (m, 7H), 1.68 – 1.47 (m, 3H), 1.01 (s, 2H), 0.93 (d, *J* = 7.1 Hz, 2H)
795	(difluoro(2-(((3S,6S,10aS)-3-(methyl((2-oxo-1,2-dihydroquinolin-4-yl)methyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		686.67	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.95 – 8.90 (m, 1H), 8.33 (s, 1H), 8.11 (d, *J* = 9.0 Hz, 1H), 8.05 (s, 2H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 6.25 (d, *J* = 6.1 Hz, 1H), 4.96 (s, 1H), 4.93 – 4.87 (m, 1H), 4.75 (s, 2H), 4.32 (s, 1H), 3.13 (s, 3H), 2.10 (d, *J* = 8.1 Hz, 2H), 1.87 (s, 4H), 1.79 (q, *J* = 9.2, 8.5 Hz, 4H), 1.58 (s, 2H)
796	(difluoro(2-(((3S,6S,9aS)-3-(3-methoxy-3-(4-methyl-4H-1,2,4-triazol-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		652.61	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (dd, *J* = 21.1, 7.6 Hz, 1H), 8.62 (s, 1H), 8.30 (d, *J* = 23.3 Hz, 1H), 8.13 (t, *J* = 8.3 Hz, 1H), 8.08 (d, *J* = 7.2 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 1H), 4.90 – 4.80 (m, 1H), 4.66 (q, *J* = 9.9 Hz, 2H), 4.51 (d, *J* = 8.6 Hz, 1H), 4.45 (d, *J* = 5.6 Hz, 1H), 4.12 (t, *J* = 9.2 Hz, 1H), 3.99 (s, 1H), 3.59 (s, 3H), 2.98 (d, *J* = 11.3 Hz, 3H), 2.25 – 2.14 (m, 1H), 2.08 – 1.89 (m, 2H), 1.86 –

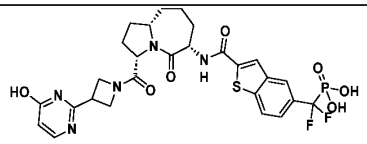
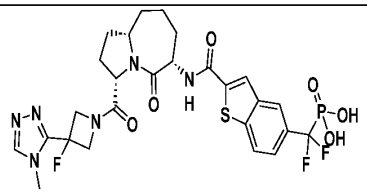
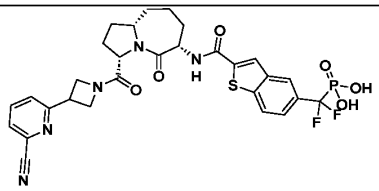
				1.64 (m, 6H), 1.29 – 1.07 (m, 1H)
797	(difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyrazin-2-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		619.58	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.77 (d, J = 7.6 Hz, 1H), 8.69 – 8.60 (m, 2H), 8.53 (dd, J = 16.1, 2.5 Hz, 1H), 8.29 (d, J = 14.1 Hz, 1H), 8.10 (dd, J = 8.5, 4.7 Hz, 1H), 8.06 (d, J = 6.3 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 4.69 (dt, J = 52.3, 9.2 Hz, 1H), 4.58 – 4.41 (m, 2H), 4.33 – 4.21 (m, 1H), 4.18 – 4.03 (m, 2H), 3.96 (s, 1H), 3.06 (p, J = 6.9 Hz, 1H), 2.19 (dd, J = 12.5, 6.0 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.94 (s, 1H), 1.85 – 1.65 (m, 7H)
798	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-(4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-6-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		621.6	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.76 (d, J = 7.4 Hz, 1H), 8.24 (s, 1H), 8.06 – 7.94 (m, 2H), 7.57 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 14.1 Hz, 1H), 7.17 (s, 1H), 4.91 (tt, J = 25.5, 7.0 Hz, 2H), 4.74 (dd, J = 15.8, 7.0 Hz, 1H), 4.41 – 4.23 (m, 2H), 3.91 – 3.67 (m, 2H), 3.63 (p, J = 4.8 Hz, 1H), 2.79 (dd, J = 14.9, 8.2 Hz, 1H), 2.29 – 2.18 (m, 1H), 2.13 – 2.04 (m, 2H), 1.94 – 1.66 (m, 6H), 1.61 (s, 1H), 1.54 (d, J = 16.7 Hz, 1H), 1.52 – 1.42 (m, 1H)
799	(difluoro(2-(((3S,6S,9aS)-3-(3-(1-methyl-1H-imidazol-2-yl)azetidine-1-carbonyl)-5-		621.6	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (d, J = 7.6 Hz, 1H), 8.23 (d, J = 26.3 Hz, 1H), 8.03 (t, J = 11.4 Hz, 2H), 7.57 (t, J = 7.7

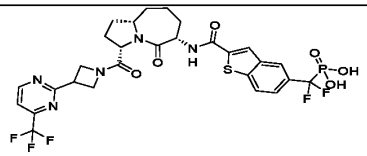
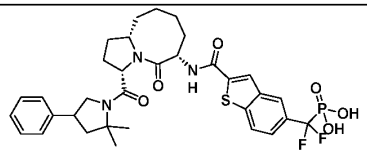
	oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			Hz, 1H), 7.28 (d, *J* = 36.5 Hz, 1H), 7.09 (d, *J* = 55.5 Hz, 1H), 4.77 – 4.53 (m, 2H), 4.51 – 4.37 (m, 2H), 4.24 – 4.12 (m, 2H), 4.08 (dd, *J* = 16.9, 8.1 Hz, 1H), 3.98 (s, 1H), 3.59 (s, 3H), 2.18 (s, 1H), 2.07 – 1.92 (m, 2H), 1.89 – 1.64 (m, 7H)
800	(difluoro(2-(((3S,6S,10aS)-3-(methyl((2-oxo-1,2-dihydropyridin-4-yl)methyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		636.61	^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 11.41 (s, 1H), 8.89 (dd, *J* = 24.7, 7.1 Hz, 1H), 8.31 (d, *J* = 8.3 Hz, 1H), 8.09 (t, *J* = 7.0 Hz, 1H), 8.04 (s, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.32 – 7.23 (m, 1H), 6.18 – 5.98 (m, 2H), 4.96 (dt, *J* = 12.1, 5.6 Hz, 1H), 4.80 (t, *J* = 8.4 Hz, 1H), 4.47 (d, *J* = 15.7 Hz, 1H), 4.17 (d, *J* = 16.0 Hz, 1H), 3.02 (s, 3H), 2.76 (s, 1H), 2.08 (d, *J* = 18.3 Hz, 2H), 1.93 – 1.68 (m, 6H), 1.67 – 1.42 (m, 4H)
801	((2-(((3S,6S,10aS)-3-(6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-6-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		618.59	^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.80 (t, *J* = 7.5 Hz, 1H), 8.44 (dd, *J* = 9.4, 4.9 Hz, 1H), 8.27 (s, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 8.02 (s, 1H), 7.76 (dd, *J* = 24.7, 7.8 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.30 (t, *J* = 6.7 Hz, 1H), 4.99 – 4.89 (m, 2H), 4.74 – 4.55 (m, 4H), 4.29 (t, *J* = 9.9 Hz, 1H), 2.31 (s, 1H), 2.09 (s, 1H), 1.94 – 1.87 (m, 4H), 1.79 (d, *J* = 12.9 Hz,

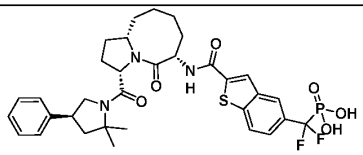
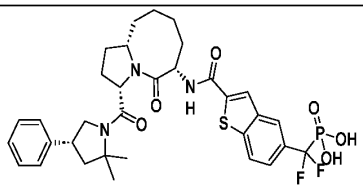
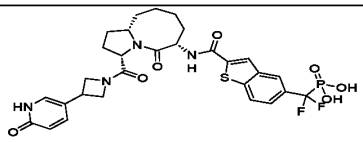
				3H), 1.64 (s, 1H), 1.59 (d, J = 15.1 Hz, 1H), 1.52 (d, J = 11.2 Hz, 1H)
802	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-(4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine-5-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		621.6	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.27 (s, 1H), 8.12 – 8.02 (m, 3H), 7.59 (dd, J = 39.0, 8.6 Hz, 2H), 7.37 (d, J = 12.2 Hz, 1H), 4.98 – 4.89 (m, 2H), 4.70 (t, J = 14.4 Hz, 1H), 4.26 (s, 2H), 3.94 (d, J = 14.8 Hz, 1H), 2.25 (s, 1H), 2.07 (s, 2H), 1.88 (d, J = 14.9 Hz, 1H), 1.75 (d, J = 20.6 Hz, 4H), 1.56 (t, J = 16.6 Hz, 4H), 1.23 (t, J = 6.8 Hz, 2H)
803	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-(3-(2-oxo-1,2-dihydropyridin-3-yl)azetidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		648.62	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.83 (d, J = 7.8 Hz, 1H), 8.30 (d, J = 10.8 Hz, 1H), 8.14 (d, J = 17.3 Hz, 1H), 8.09 (d, J = 9.8 Hz, 2H), 8.04 (s, 1H), 7.56 (d, J = 8.9 Hz, 1H), 7.41 (dd, J = 28.8, 6.7 Hz, 1H), 7.26 (dd, J = 14.8, 6.3 Hz, 1H), 4.92 (s, 1H), 4.28 (d, J = 9.2 Hz, 2H), 4.24 (s, 2H), 4.15 (d, J = 7.2 Hz, 1H), 2.13 (s, 1H), 2.01 (s, 1H), 1.82 (s, 4H), 1.69 (d, J = 11.4 Hz, 2H), 1.56 (s, 1H), 1.48 (s, 1H), 1.13 (t, J = 7.3 Hz, 4H)
804	(difluoro(2-(((3S,6S,10aS)-3-((1R,5S,6S)-6-(5-methyl-1,3,4-oxadiazol-2-yl)-3-azabicyclo[3.1.0]hexane-3-carbonyl)-5-oxodecahydropyrrol		663.63	

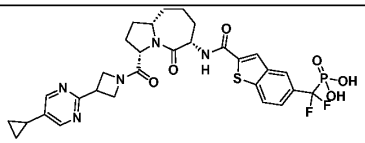
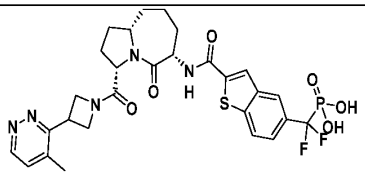
	o[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			
805	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-((1R,5S,6R)-6-phenyl-3-azabicyclo[3.1.0]hexane-3-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		657.67	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (t, J = 9.3 Hz, 1H), 8.32 (d, J = 3.5 Hz, 1H), 8.12 (d, J = 8.3 Hz, 1H), 8.06 (s, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.29 – 7.19 (m, 2H), 7.14 (d, J = 5.8 Hz, 1H), 7.07 (dd, J = 13.4, 7.7 Hz, 2H), 4.95 (s, 1H), 4.52 (dd, J = 17.9, 9.2 Hz, 1H), 4.27 (s, 1H), 4.04 (d, J = 10.3 Hz, 1H), 3.90 – 3.78 (m, 2H), 3.67 (dd, J = 20.5, 11.6 Hz, 2H), 3.40 (td, J = 12.9, 12.0, 7.0 Hz, 2H), 2.29 – 2.16 (m, 1H), 2.08 (d, J = 5.5 Hz, 1H), 1.99 (d, J = 5.9 Hz, 2H), 1.92 – 1.74 (m, 6H), 1.66 – 1.53 (m, 2H)
806	((2-(((3S,6S,10aS)-3-(3-(5-cyanopyrimidin-2-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		658.62	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 (d, J = 11.8 Hz, 1H), 8.87 (s, 1H), 8.32 (d, J = 11.6 Hz, 1H), 8.13 (d, J = 9.0 Hz, 1H), 8.06 (s, 1H), 7.58 (d, J = 8.9 Hz, 1H), 5.15 – 4.38 (m, 3H), 4.37 – 3.95 (m, 5H), 2.03 (s, 2H), 1.84 (s, 7H), 1.57 (d, J = 16.0 Hz, 3H)
807	(difluoro(2-(((3S,6S,9aS)-3-(3-hydroxy-3-(4-methyl-4H-1,2,4-triazol-3-yl)azetidine-1-carbonyl)-5-		638.58	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.77 (d, J = 7.6 Hz, 1H), 8.46 (d, J = 13.6 Hz, 1H), 8.27 (d, J = 21.9 Hz, 1H), 8.11 (t, J = 9.1 Hz, 1H), 8.06 (d, J =

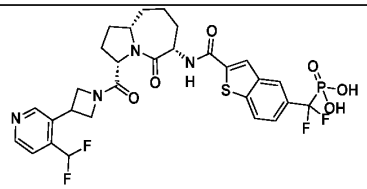
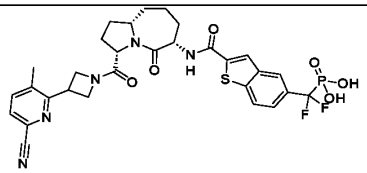
	oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			9.9 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 14.7 Hz, 1H), 4.89 (dd, *J* = 27.9, 9.1 Hz, 1H), 4.63 (q, *J* = 9.6 Hz, 1H), 4.53 (dd, *J* = 23.5, 9.6 Hz, 1H), 4.48 – 4.31 (m, 2H), 4.00 (dd, *J* = 25.7, 9.9 Hz, 2H), 3.61 (d, *J* = 3.0 Hz, 3H), 2.23 – 2.09 (m, 1H), 2.06 – 1.86 (m, 2H), 1.87 – 1.53 (m, 7H)
808	((2-(((3S,6S,9aS)-3-(3-ethoxy-3-(4-methyl-4H-1,2,4-triazol-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		666.64	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (dd, *J* = 19.0, 7.2 Hz, 1H), 8.54 (d, *J* = 12.9 Hz, 1H), 8.28 (dd, *J* = 22.0, 3.2 Hz, 1H), 8.16 – 8.09 (m, 1H), 8.07 (s, 1H), 7.57 (s, 1H), 4.85 (dd, *J* = 28.4, 9.2 Hz, 1H), 4.63 (d, *J* = 10.9 Hz, 1H), 4.50 (d, *J* = 9.3 Hz, 1H), 4.46 – 4.41 (m, 1H), 4.12 (d, *J* = 9.6 Hz, 1H), 3.98 (s, 1H), 3.58 (t, *J* = 2.3 Hz, 3H), 3.19 – 3.03 (m, 2H), 2.18 (s, 1H), 2.06 – 1.91 (m, 2H), 1.71 (s, 8H), 1.13 – 1.01 (m, 3H)
809	(difluoro(2-(((3S,6S,9aS)-3-(3-(4-hydroxypyrimidin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		635.58	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.76 (d, *J* = 7.8 Hz, 1H), 8.29 (d, *J* = 13.2 Hz, 1H), 8.11 (dt, *J* = 10.9, 5.4 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.91 (dd, *J* = 13.1, 6.9 Hz, 1H), 7.60 – 7.55 (m, 1H), 6.20 (dd, *J* = 14.9, 6.5 Hz, 1H), 4.62 (dt, *J* = 22.3, 9.6 Hz, 2H), 4.42 – 4.34 (m, 2H), 4.10 – 3.99 (m, 2H), 3.10 – 3.02 (m, 2H),

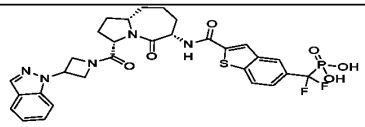
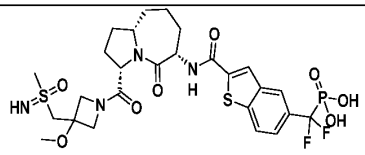
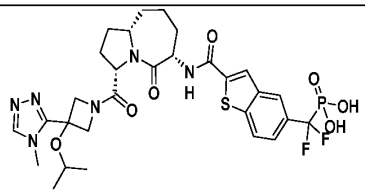
				2.18 (dd, *J* = 13.3, 6.1 Hz, 1H), 2.01 – 1.91 (m, 2H), 1.85 – 1.62 (m, 7H), 1.15 (t, *J* = 7.3 Hz, 2H)
810	(difluoro(2-(((3S,6S,9aS)-3-(3-fluoro-3-(4-methyl-4H-1,2,4-triazol-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		640.57	
811	((2-(((3S,6S,9aS)-3-(3-(6-cyanopyridin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		643.6	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.77 (t, *J* = 7.9 Hz, 1H), 8.28 (d, *J* = 19.8 Hz, 1H), 8.14 – 8.04 (m, 2H), 8.01 (dt, *J* = 12.7, 7.8 Hz, 1H), 7.92 (dd, *J* = 15.2, 7.6 Hz, 1H), 7.72 (dd, *J* = 11.0, 8.0 Hz, 1H), 7.57 (dd, *J* = 8.9, 4.2 Hz, 1H), 4.73 (t, *J* = 8.7 Hz, 1H), 4.64 (d, *J* = 10.9 Hz, 1H), 4.55 (t, *J* = 8.5 Hz, 1H), 4.44 (dt, *J* = 9.0, 4.9 Hz, 1H), 4.32 (dd, *J* = 8.5, 5.7 Hz, 1H), 4.22 (dt, *J* = 35.0, 9.1 Hz, 1H), 4.16 – 4.01 (m, 2H), 3.98 – 3.93 (m, 1H), 3.11 – 3.06 (m, 1H), 2.21 – 2.16 (m, 1H), 2.06 – 1.92 (m, 2H), 1.85 – 1.65 (m, 5H)
812	(difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(4-(trifluoromethyl)pyrimidin-2-yl)azetidine-1-carbonyl)octahydro-		687.58	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.20 (dd, *J* = 8.3, 5.0 Hz, 1H), 8.76 (dd, *J* = 26.3, 7.5 Hz, 1H), 8.28 (d, *J* = 24.8 Hz, 1H), 8.11 (dd, *J* = 8.5,

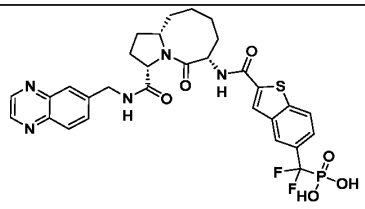
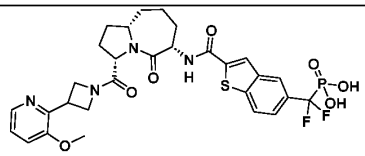
	1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			5.5 Hz, 1H), 8.05 (d, *J* = 14.0 Hz, 1H), 7.92 (dd, *J* = 16.0, 5.1 Hz, 1H), 7.61 – 7.54 (m, 1H), 4.80 – 4.57 (m, 3H), 4.46 – 4.43 (m, 1H), 4.30 (t, *J* = 9.5 Hz, 1H), 4.25 (t, *J* = 7.7 Hz, 1H), 2.23 – 2.16 (m, 1H), 2.00 (ddd, *J* = 36.9, 19.0, 10.1 Hz, 3H), 1.85 – 1.68 (m, 8H)
813	((2-(((3S,6S,10aS)-3-(2,2-dimethyl-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		673.71	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.90 (d, *J* = 7.3 Hz, 1H), 8.32 (d, *J* = 2.7 Hz, 1H), 8.14 – 8.09 (m, 1H), 8.05 (s, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.36 – 7.26 (m, 4H), 7.25 – 7.13 (m, 1H), 5.02 – 4.91 (m, 1H), 4.60 – 3.96 (m, 2H), 3.61 – 3.36 (m, 2H), 2.23 (d, *J* = 34.6 Hz, 2H), 2.14 – 2.01 (m, 3H), 1.88 (d, *J* = 12.0 Hz, 4H), 1.84 – 1.69 (m, 4H), 1.63 (s, 2H), 1.49 (d, *J* = 3.6 Hz, 3H), 1.40 (s, 3H)
814	((2-(((3S,6S,10aS)-3-((S)-2,2-dimethyl-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		673.71	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.91 (d, *J* = 7.3 Hz, 1H), 8.32 (s, 1H), 8.14 – 8.10 (m, 1H), 8.05 (s, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.34 – 7.27 (m, 4H), 7.21 (dd, *J* = 8.1, 4.7 Hz, 1H), 5.06 – 4.88 (m, 1H), 4.44 (t, *J* = 8.3 Hz, 1H), 4.24 (t, *J* = 9.7 Hz, 1H), 4.00 (t, *J* = 8.4 Hz, 1H), 3.55 (d, *J* = 10.1 Hz, 1H), 3.46 (dt, *J* = 13.0, 7.0 Hz, 1H), 2.28 (s, 1H), 2.13 – 2.02 (m, 2H), 2.01 –

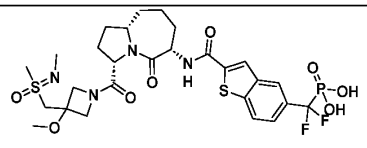
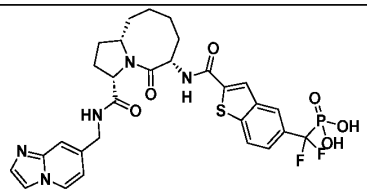
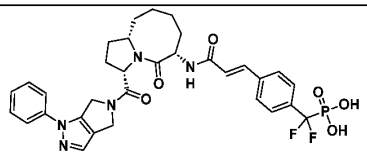
				1.68 (m, 8H), 1.69 – 1.51 (m, 3H), 1.48 (s, 3H), 1.40 (s, 3H)
815	((2-(((3S,6S,10aS)-3-((R)-2,2-dimethyl-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		673.71	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (d, J = 7.3 Hz, 1H), 8.33 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.05 (s, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.36 – 7.26 (m, 4H), 7.22 (d, J = 7.0 Hz, 1H), 5.03 – 4.93 (m, 1H), 4.56 (t, J = 8.5 Hz, 1H), 4.34 (s, 1H), 4.23 (s, 1H), 3.41 (d, J = 6.8 Hz, 2H), 2.20 (d, J = 10.2 Hz, 1H), 2.11 – 1.98 (m, 3H), 1.92 (q, J = 11.5 Hz, 4H), 1.75 (dq, J = 26.8, 9.1, 7.2 Hz, 4H), 1.64 (s, 2H), 1.49 (s, 3H), 1.39 (s, 3H)
816	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-(3-(6-oxo-1,6-dihydropyridin-3-yl)azetidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		648.62	
817	((2-(((3S,6S,9aS)-3-(3-(5-cyclopropylpyrimidin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		659.65	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.78 (dd, J = 13.8, 7.6 Hz, 1H), 8.55 (d, J = 13.5 Hz, 2H), 8.29 (d, J = 16.2 Hz, 1H), 8.14 – 8.02 (m, 2H), 7.57 (d, J = 8.7 Hz, 1H), 4.71 (t, J = 8.4 Hz, 1H), 4.63 (q, J = 11.3, 10.7 Hz, 1H), 4.54 – 4.47 (m, 1H), 4.43 (q, J = 4.3 Hz, 1H), 4.36 (dd, J = 8.5, 5.0 Hz, 1H),

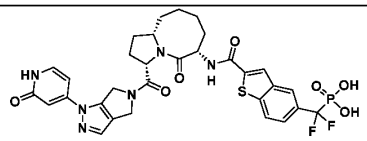
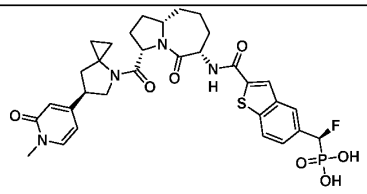
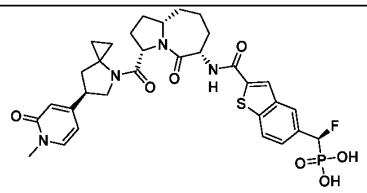
				4.24 (d, J = 5.9 Hz, 1H), 4.15 (d, J = 11.7 Hz, 1H), 4.07 (q, J = 5.0, 3.8 Hz, 1H), 3.98 (p, J = 7.3, 6.5 Hz, 2H), 3.07 (dd, J = 7.3, 4.8 Hz, 1H), 2.17 (dt, J = 13.1, 6.6 Hz, 1H), 2.01 – 1.89 (m, 2H), 1.84 – 1.66 (m, 5H), 0.99 (ddt, J = 14.9, 8.5, 3.2 Hz, 2H), 0.81 (ddt, J = 9.6, 6.7, 4.5 Hz, 2H)
818	(difluoro(2-(((3S,6S,9aS)-3-(3-(4-methylpyridazin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		633.61	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.01 (dd, J = 11.2, 5.1 Hz, 1H), 8.78 (t, J = 7.1 Hz, 1H), 8.28 (d, J = 27.0 Hz, 1H), 8.12 (dd, J = 11.8, 8.9 Hz, 1H), 8.06 (d, J = 13.9 Hz, 1H), 7.54 (dt, J = 18.8, 6.9 Hz, 2H), 4.73 (dt, J = 28.9, 7.3 Hz, 1H), 4.62 (dd, J = 16.6, 10.1 Hz, 2H), 4.46 (dd, J = 8.6, 4.1 Hz, 1H), 4.35 – 4.32 (m, 1H), 3.07 (dd, J = 7.4, 4.7 Hz, 1H), 2.22 (s, 3H), 2.21 – 2.03 (m, 2H), 1.98 (d, J = 44.7 Hz, 2H), 1.76 (t, J = 26.5 Hz, 8H)
819	((2-(((3S,6S,9aS)-3-(3-(4-(difluoromethyl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		668.6	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.96 (d, J = 18.6 Hz, 1H), 8.82 (dd, J = 28.9, 7.6 Hz, 1H), 8.66 (dd, J = 14.2, 5.1 Hz, 1H), 8.29 (d, J = 8.9 Hz, 1H), 8.12 (dd, J = 9.0, 4.7 Hz, 1H), 8.08 (d, J = 5.3 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.20 (td, J = 54.1, 4.0 Hz, 1H), 4.80 – 4.46 (m, 4H), 4.43 (dd, J = 8.1, 4.7 Hz, 1H), 4.40 –

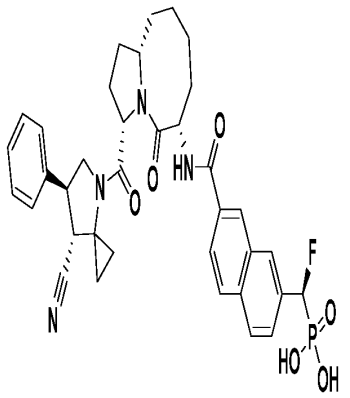
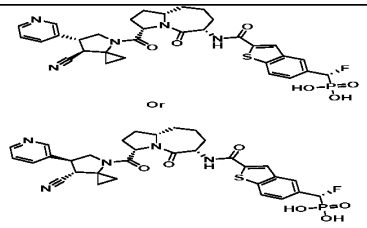
				4.26 (m, 2H), 2.24 – 2.08 (m, 1H), 2.08 – 1.98 (m, 1H), 1.94 (s, 1H), 1.92 – 1.55 (m, 8H)
820	((2-(((3S,6S,9aS)-3-(3-(6-cyano-3-methylpyridin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		657.63	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.76 (dd, J = 14.7, 7.5 Hz, 1H), 8.27 (d, J = 28.6 Hz, 1H), 8.10 (t, J = 9.4 Hz, 1H), 8.05 (d, J = 12.7 Hz, 1H), 7.90 – 7.76 (m, 2H), 7.56 (t, J = 7.7 Hz, 1H), 4.71 (t, J = 8.3 Hz, 1H), 4.64 (q, J = 9.9 Hz, 1H), 4.58 – 4.40 (m, 3H), 4.22 (dp, J = 19.1, 7.1, 6.5 Hz, 2H), 2.27 (d, J = 2.1 Hz, 3H), 2.22 – 2.13 (m, 1H), 2.01 (ddd, J = 14.6, 7.6, 3.8 Hz, 1H), 1.93 (s, 1H), 1.91 – 1.50 (m, 7H)
821	((2-(((3S,6S,9aS)-3-(3-(1H-indazol-1-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		657.63	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.82 (dd, J = 20.7, 7.6 Hz, 1H), 8.31 (d, J = 3.9 Hz, 1H), 8.20 (d, J = 22.3 Hz, 1H), 8.12 (d, J = 8.9 Hz, 1H), 8.07 (s, 1H), 7.81 – 7.67 (m, 2H), 7.57 (d, J = 8.6 Hz, 1H), 7.38 (q, J = 8.2 Hz, 1H), 7.14 (dt, J = 16.0, 7.5 Hz, 1H), 5.74 (hept, J = 6.1, 4.9 Hz, 1H), 4.84 (dt, J = 76.4, 7.7 Hz, 1H), 4.73 – 4.60 (m, 2H), 4.59 – 4.40 (m, 3H), 2.19 (dd, J = 13.1, 7.1 Hz, 1H), 2.04 (tt, J = 8.1, 4.5 Hz, 1H), 1.95 (s, 1H), 1.90 – 1.77 (m, 4H), 1.72 (s, 4H)

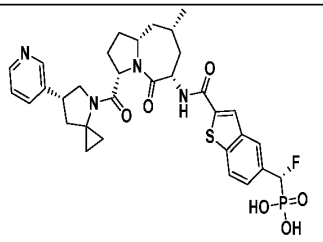
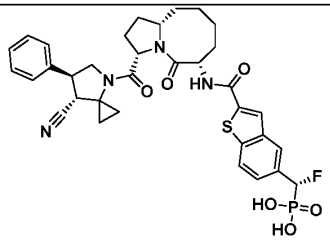
822	(difluoro(2-(((3S,6S,9aS)-3-(3-methoxy-3-((S-methylsulfonimidoyl)methyl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		662.66	
823	(difluoro(2-(((3S,6S,9aS)-3-(3-isopropoxy-3-(4-methyl-4H-1,2,4-triazol-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		680.66	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.79 (dd, J = 32.7, 7.7 Hz, 1H), 8.53 (d, J = 16.2 Hz, 1H), 8.26 (d, J = 27.6 Hz, 1H), 8.14 – 8.02 (m, 2H), 7.57 (t, J = 7.5 Hz, 1H), 4.89 (dd, J = 27.3, 9.3 Hz, 1H), 4.64 (d, J = 13.2 Hz, 1H), 4.56 (dd, J = 28.5, 10.0 Hz, 1H), 4.49 – 4.40 (m, 2H), 4.07 (dd, J = 10.3, 5.3 Hz, 1H), 3.97 (s, 1H), 3.57 (d, J = 3.6 Hz, 3H), 3.40 (d, J = 5.6 Hz, 1H), 3.11 – 3.02 (m, 1H), 2.16 (dt, J = 13.5, 7.2 Hz, 1H), 2.07 – 1.92 (m, 2H), 1.86 – 1.66 (m, 6H), 0.97 – 0.80 (m, 6H)
824	((2-(((3S,6S,9aS)-3-(3-(4-cyanopyrimidin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		644.59	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.14 (dd, J = 11.9, 5.0 Hz, 1H), 8.76 (dd, J = 17.9, 7.8 Hz, 1H), 8.28 (d, J = 20.3 Hz, 1H), 8.13 – 7.99 (m, 3H), 7.59 – 7.53 (m, 1H), 4.63 (h, J = 8.7, 7.7 Hz, 1H), 4.55 (q, J = 8.6, 8.1 Hz, 1H), 4.43 (ddd, J = 14.5, 8.3, 4.7 Hz, 1H), 4.21 (t, J = 3.9 Hz, 1H),

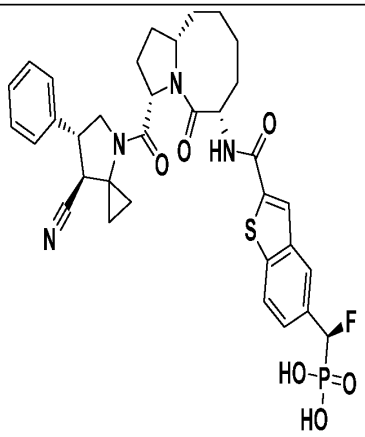
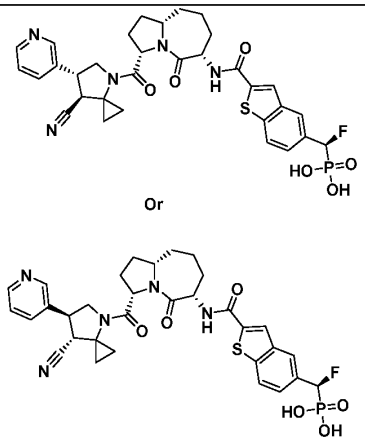
				4.13 (ddd, *J* = 13.8, 9.4, 3.5 Hz, 1H), 4.04 – 3.91 (m, 2H), 3.09 – 3.00 (m, 1H), 2.18 (dt, *J* = 14.0, 7.0 Hz, 1H), 2.06 – 1.91 (m, 2H), 1.87 – 1.66 (m, 7H)
825	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-((quinoxalin-6-ylmethyl)carbamoyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		648.62	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 – 8.87 (m, 3H), 8.71 (t, *J* = 6.0 Hz, 1H), 8.31 (s, 1H), 8.11 (d, *J* = 8.6 Hz, 1H), 8.07 – 8.01 (m, 2H), 7.95 (s, 1H), 7.77 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 4.93 (dt, *J* = 12.4, 6.2 Hz, 1H), 4.59 (dd, *J* = 16.0, 6.0 Hz, 1H), 4.52 (dd, *J* = 16.0, 5.4 Hz, 1H), 4.41 (t, *J* = 8.6 Hz, 1H), 4.29 (dd, *J* = 11.9, 7.5 Hz, 1H), 3.09 – 3.00 (m, 1H), 2.19 (dt, *J* = 12.4, 7.6 Hz, 1H), 2.13 – 2.01 (m, 1H), 1.94 – 1.78 (m, 5H), 1.72 (dd, *J* = 11.9, 6.7 Hz, 1H), 1.59 (q, *J* = 15.7, 13.0 Hz, 2H), 1.53 – 1.44 (m, 1H)
826	(difluoro(2-(((3S,6S,9aS)-3-(3-(3-methoxypyridin-2-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		676.69	^{1}H NMR (600 MHz, DMSO-d_6) δ 8.33 – 8.02 (m, 5H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.41 (dd, *J* = 16.0, 8.4 Hz, 1H), 7.30 (ddd, *J* = 18.3, 8.3, 4.7 Hz, 1H), 4.67 – 4.59 (m, 1H), 4.53 – 4.40 (m, 2H), 4.36 (dt, *J* = 8.0, 4.1 Hz, 1H), 4.20 – 4.03 (m, 3H), 3.96 (t, *J* = 7.5 Hz, 1H), 3.80 (s, 3H), 2.16 (dt, *J* = 13.0, 6.5 Hz, 1H),

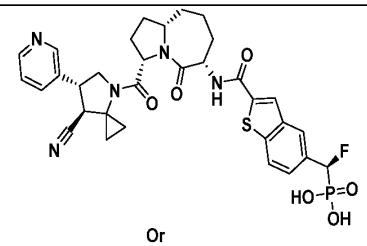
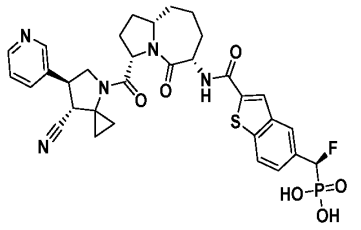
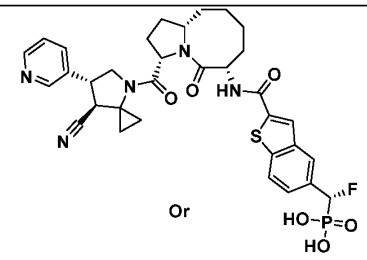
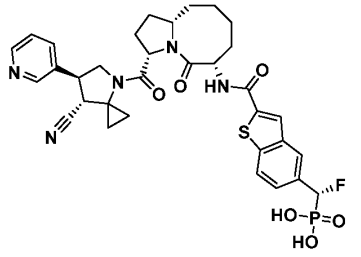
				2.06 – 1.91 (m, 2H), 1.87 – 1.62 (m, 7H)
827	((2-(((3S,6S,9aS)-3-(3-((N,S-dimethylsulfonimidoyl)methyl)-3-methoxyazetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		645.62	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.77 (dt, J = 12.6, 6.4 Hz, 1H), 8.26 (d, J = 15.3 Hz, 1H), 8.14 – 8.02 (m, 2H), 7.56 (d, J = 8.6 Hz, 1H), 4.68 – 4.56 (m, 1H), 4.44 – 4.30 (m, 2H), 3.95 (dt, J = 32.0, 14.2 Hz, 4H), 3.78 – 3.72 (m, 2H), 3.34 – 3.28 (m, 3H), 2.98 (d, J = 13.7 Hz, 3H), 2.60 (d, J = 31.2 Hz, 3H), 2.17 (d, J = 11.7 Hz, 1H), 2.02 – 1.90 (m, 2H), 1.85 – 1.64 (m, 6H)
828	(difluoro(2-(((3S,6S,10aS)-3-((imidazo[1,2-a]pyridin-7-ylmethyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		653.62	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 – 8.77 (m, 2H), 8.30 (d, J = 9.8 Hz, 1H), 8.25 (s, 1H), 8.08 (dd, J = 16.1, 9.8 Hz, 3H), 7.73 (d, J = 14.8 Hz, 1H), 7.58 (t, J = 11.8 Hz, 2H), 7.37 (d, J = 7.1 Hz, 1H), 4.92 (s, 1H), 4.60 – 4.52 (m, 1H), 4.46 (s, 1H), 4.40 (t, J = 8.8 Hz, 1H), 4.30 (s, 1H), 2.21 (s, 1H), 2.09 (s, 1H), 1.80 (t, J = 31.4 Hz, 6H), 1.55 (d, J = 40.3 Hz, 4H)
829	(difluoro(4-((E)-3-oxo-3-(((3S,6S,10aS)-5-oxo-3-(1-phenyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)amino)prop-1-en-1-		700.65	

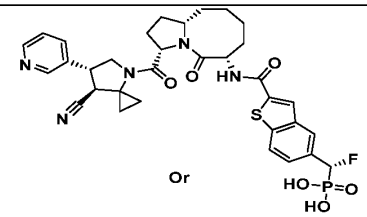
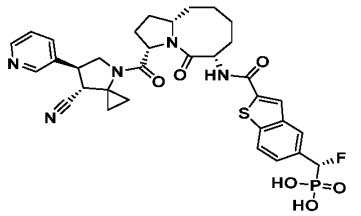
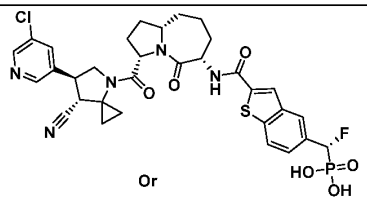
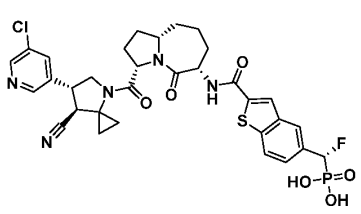
	yl)phenyl)methyl)phosphonic acid			
830	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-(1-(2-oxo-1,2-dihydropyridin-4-yl)-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		648.62	
831	((S)-fluoro(2-(((3S,6S,9aS)-3-((R)-6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		671.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.81-8.68 (m, 1H), 8.23 (s, 1H), 8.09-7.93 (m, 2H), 7.67-7.59 (m, 1H), 7.56-7.46 (m, 1H), 6.33 (s, 1H), 6.29-6.23 (m, 1H), 5.91-5.65 (m, 1H), 4.69-4.57 (m, 2H), 4.24-4.17 (m, 1H), 3.96-3.91 (m, 1H), 3.56-3.53 (m, 1H), 3.37 (s, 3H), 2.24-2.13 (m, 2H), 2.07-1.91 (m, 4H), 1.87-1.50 (m, 9H), 0.58-0.36 (m, 2H)
832	((S)-(7-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)fluoromethyl)phosphonic acid		673.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.77-8.63 (m, 1H), 8.56 (s, 1H), 8.08-7.93 (m, 4H), 7.70-7.63 (m, 1H), 7.54-7.28 (m, 5H), 6.01-5.85 (m, 1H), 5.05-4.98 (m, 1H), 4.55-4.44 (m, 2H), 4.31-4.24 (m, 1H), 4.07-3.98 (m, 1H), 3.77-3.67 (m, 2H), 2.25-1.49 (m, 14H), 0.88-0.61 (m, 2H)

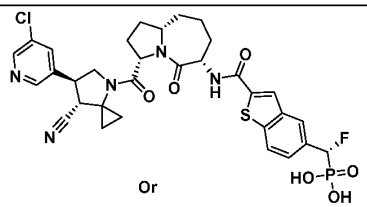
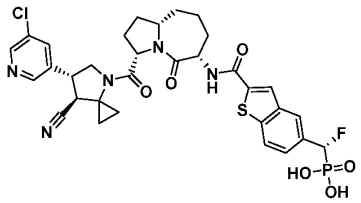
833	((R)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 SFC Pyrrolidine + core peak 1 was used for synthesis and biological testing	666.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (d, J = 7.6 Hz, 1H), 8.70 (s, 1H), 8.52 (d, J = 4.4 Hz, 1H), 8.24 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.99-7.86 (m, 2H), 7.53 (d, J = 8.5 Hz, 1H), 7.46-7.33 (m, 1H), 5.82 (dd, J = 44.4, 8.0 Hz, 1H), 4.68-4.56 (m, 2H), 4.20-4.11 (m, 1H), 4.00-3.86 (m, 4H), 2.26-1.91 (m, 4H), 1.89-1.64 (m, 8H), 0.84-0.58 (m, 2H)
834	((R)-fluoro(2-(((3S,6S,8R,9aR)-8-methyl-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		655.0	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (d, J = 7.4 Hz, 1H), 8.59 (s, 1H), 8.45 (d, J = 4.3 Hz, 1H), 8.25 (s, 1H), 8.07-7.93 (m, 2H), 7.87-7.78 (m, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.41-7.33 (m, 1H), 5.81 (dd, J = 44.6, 7.4 Hz, 1H), 4.67-4.61 (m, 2H), 4.13-4.07 (m, 1H), 4.01-3.94 (m, 1H), 3.77-3.70 (m, 1H), 3.63-3.55 (m, 1H), 2.22-1.90 (m, 6H), 1.83-1.40 (m, 7H), 0.97 (d, J = 6.3 Hz, 3H), 0.61-0.35 (m, 2H)

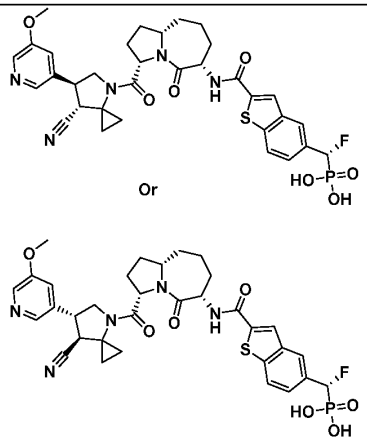
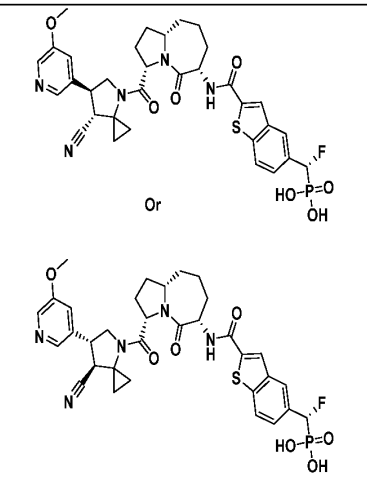
835	((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		679.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (d, J = 6.9 Hz, 1H), 8.28 (s, 1H), 8.06-7.90 (m, 2H), 7.56-7.44 (m, 3H), 7.42-7.29 (m, 3H), 5.91-5.70 (m, 1H), 5.01-4.88 (m, 1H), 4.57-4.39 (m, 2H), 4.29-4.14 (m, 1H), 4.03 (d, J = 9.1 Hz, 1H), 3.79-3.63 (m, 2H), 2.30-2.14 (m, 2H), 2.08-1.95 (m, 1H), 1.94-1.63 (m, 9H), 1.60-1.45 (m, 2H), 0.87-0.74 (m, 1H), 0.73-0.59 (m, 1H)
836	((S)-(2-(((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		679.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (d, J = 6.7 Hz, 1H), 8.27 (s, 1H), 8.06-7.90 (m, 2H), 7.58-7.42 (m, 3H), 7.40-7.27 (m, 3H), 5.81 (dd, J = 44.4, 7.8 Hz, 1H), 5.00-4.89 (m, 1H), 4.54-4.42 (m, 1H), 4.31-4.12 (m, 2H), 3.94-3.75 (m, 3H), 2.35-2.21 (m, 1H), 2.20-2.08 (m, 1H), 2.06-1.97 (m, 1H), 1.96-1.71 (m, 8H), 1.68-1.60 (m, 1H), 1.59-1.42 (m, 2H), 0.87-0.76 (m, 1H), 0.71-0.58 (m, 1H)

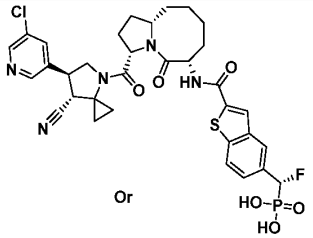
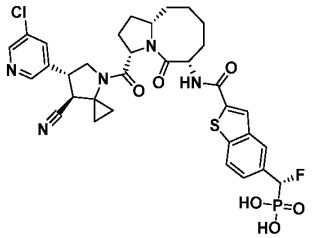
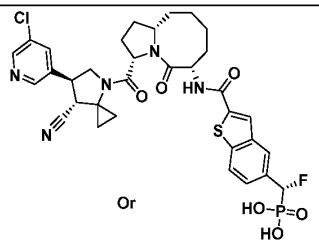
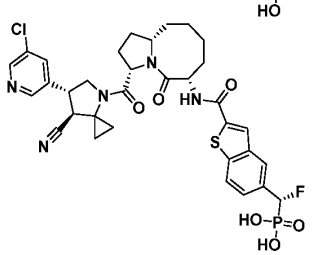
837	((S)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((S)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 SFC Pyrrolidine + core peak 2 was used for synthesis and biological testing	666.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (d, J = 7.7 Hz, 1H), 8.72 (d, J = 1.9 Hz, 1H), 8.54 (dd, J = 4.8, 1.5 Hz, 1H), 8.23 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.99-7.90 (m, 2H), 7.56-7.33 (m, 2H), 5.79 (dd, J = 44.4, 8.0 Hz, 1H), 4.70-4.56 (m, 2H), 4.36 (t, J = 8.5 Hz, 1H), 4.11-4.02 (m, 1H), 4.00-3.92 (m, 1H), 3.89-3.73 (m, 2H), 2.25-2.10 (m, 2H), 2.09-1.90 (m, 2H), 1.88-1.55 (m, 8H), 0.90-0.58 (m, 2H)
838	((S)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((S)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-	 SFC Pyrrolidine + core peak 1 was used for synthesis and biological testing	666.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 1H), 8.77 (d, J = 7.6 Hz, 1H), 8.67 (d, J = 4.9 Hz, 1H), 8.29-8.22 (m, 2H), 8.04 (d, J = 8.4 Hz, 1H), 7.99 (s, 1H), 7.71-7.64 (m, 1H), 7.54 (d, J = 8.5 Hz, 1H), 5.84 (dd, J = 44.3, 8.0 Hz, 1H), 4.67-4.63 (m, 2H), 4.21-4.17 (m, 1H), 4.05-3.96 (m, 4H), 2.26-1.93 (m, 4H), 1.90-1.66 (m, 8H), 0.83-0.61 (m, 2H)

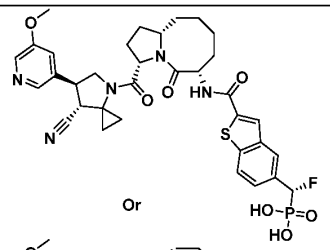
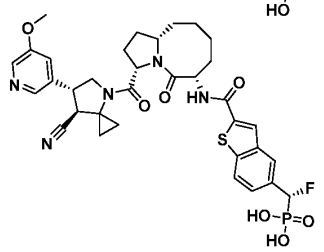
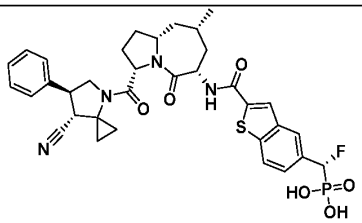
	a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid			
839	((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((R)-(2-(((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 Or  SFC Pyrrolidine + core peak 1 was used for synthesis and biological testing	680.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92-8.76 (m, 2H), 8.72-8.60 (m, 1H), 8.30-8.11 (m, 2H), 8.03 (d, J = 8.2 Hz, 1H), 7.97 (s, 1H), 7.74-7.59 (m, 1H), 7.53 (d, J = 8.5 Hz, 1H), 5.84 (dd, J = 44.4, 7.7 Hz, 1H), 4.99-4.89 (m, 1H), 4.63-4.44 (m, 2H), 4.30-4.18 (m, 1H), 4.14-4.03 (m, 1H), 3.98-3.74 (m, 2H), 2.30-2.14 (m, 2H), 2.09-1.97 (m, 1H), 1.93-1.49 (m, 11H), 0.86-0.77 (m, 1H), 0.75-0.61 (m, 1H)
840	((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((R)-(2-(((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-	 Or 	680.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92-8.76 (m, 2H), 8.72-8.60 (m, 1H), 8.30-8.11 (m, 2H), 8.03 (d, J = 8.2 Hz, 1H), 7.97 (s, 1H), 7.74-7.59 (m, 1H), 7.53 (d, J = 8.5 Hz, 1H), 5.84 (dd, J = 44.4, 7.7 Hz, 1H), 4.99-4.89 (m, 1H), 4.63-4.44 (m, 2H), 4.30-4.18 (m, 1H), 4.14-4.03 (m, 1H), 3.98-3.74 (m, 2H), 2.30-2.14 (m, 2H), 2.09-1.97 (m, 1H), 1.93-1.49 (m, 11H),

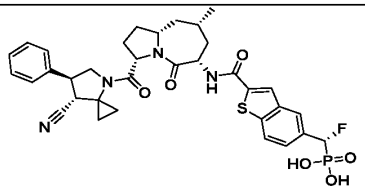
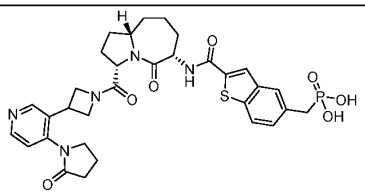
	oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	SFC Pyrrolidine + core peak 2 was used for synthesis and biological testing		0.86-0.77 (m, 1H), 0.75-0.61 (m, 1H)
841	((R)-(2-(((3S,6S,9aS)-3-((6S,7R)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 Or  SFC Pyrrolidine + core peak 2 was used for synthesis and biological testing	700	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (d, J = 7.7 Hz, 1H), 8.69 (d, J = 1.4 Hz, 1H), 8.62 (d, J = 2.2 Hz, 1H), 8.25 (s, 1H), 8.20-8.14 (m, 1H), 8.06-7.96 (m, 2H), 7.53 (d, J = 8.5 Hz, 1H), 5.84 (dd, J = 44.3, 8.0 Hz, 1H), 4.66-4.59 (m, 2H), 4.39-4.31 (m, 1H), 4.13 (d, J = 10.3 Hz, 1H), 3.98-3.87 (m, 2H), 3.83-3.76 (m, 1H), 2.26-2.13 (m, 2H), 2.11-1.93 (m, 2H), 1.86-1.66 (m, 8H), 0.89-0.78 (m, 1H), 0.76-0.63 (m, 1H)
842	((R)-(2-(((3S,6S,9aS)-3-((6S,7R)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or	 Or 	700.3	^{1}H NMR (400 MHz, DMSO) δ 8.77 (d, J = 7.0 Hz, 1H), 8.71-8.65 (m, 1H), 8.62-8.55 (m, 1H), 8.27-8.16 (m, 2H), 8.04 (d, J = 8.4 Hz, 1H), 7.99 (s, 1H), 7.54 (d, J = 8.2 Hz, 1H), 5.84 (dd, J = 44.3, 7.7 Hz, 1H), 4.67-4.57 (m, 2H), 4.02-3.93 (m, 5H), 2.23-2.07 (m, 2H), 2.05-1.93 (m, 2H),

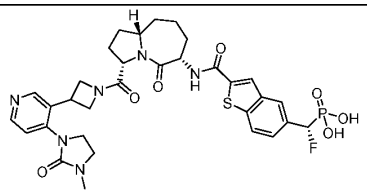
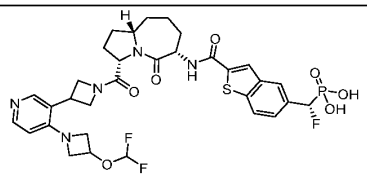
	((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	SFC Pyrrolidine + core peak 1 was used for synthesis and biological testing		1.90-1.67 (m, 8H), 0.82-0.57 (m, 2H)
843	((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((R)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 Or  SFC Pyrrolidine + core peak 2 was used for synthesis and biological testing	696.1	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.80 (d, J = 7.7 Hz, 1H), 8.40-8.32 (m, 2H), 8.25 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.98 (s, 1H), 7.75 (s, 1H), 7.53 (d, J = 8.5 Hz, 1H), 5.84 (dd, J = 44.3, 8.0 Hz, 1H), 4.66-4.60 (m, 2H), 4.38-4.33 (m, 1H), 4.14 (d, J = 10.2 Hz, 1H), 3.99-3.94 (m, 1H), 3.91-3.83 (m, 4H), 3.78 (t, J = 9.6 Hz, 1H), 2.24-2.15 (m, 2H), 2.08-1.90 (m, 2H), 1.89-1.65 (m, 8H), 0.87-0.81 (m, 1H), 0.75-0.68 (m, 1H)

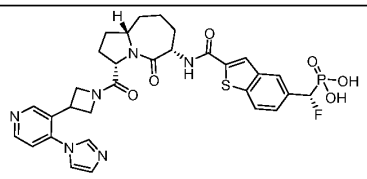
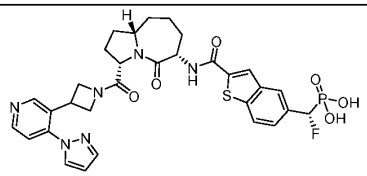
844	((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((R)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 SFC Pyrrolidine + core peak 1 was used for synthesis and biological testing	696	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, J = 7.5 Hz, 1H), 8.40-8.28 (m, 2H), 8.23 (s, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.98 (s, 1H), 7.83-7.70 (m, 1H), 7.54 (d, J = 8.5 Hz, 1H), 5.91-5.77 (m, 1H), 4.64-4.59 (m, 2H), 4.17-4.13 (m, 1H), 4.01-3.94 (m, 4H), 3.85-3.82 (m, 3H), 2.23-1.95 (m, 4H), 1.88-1.68 (m, 8H), 0.82-0.73 (m, 1H), 0.70-0.62 (m, 1H)
845	((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((R)-(2-(((3S,6S,10aS)-3-((6R,7S)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-	 SFC Pyrrolidine + core peak 2 was used for synthesis and biological testing	714.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (d, J = 7.2 Hz, 1H), 8.67 (s, 1H), 8.61 (d, J = 2.2 Hz, 1H), 8.27 (s, 1H), 8.16 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.97 (s, 1H), 7.53 (d, J = 8.5 Hz, 1H), 5.84 (dd, J = 44.3, 8.0 Hz, 1H), 4.98-4.91 (m, 1H), 4.53-4.46 (m, 2H), 4.27-4.20 (m, 1H), 4.15-4.10 (m, 1H), 3.90-3.81 (m, 2H), 2.29-2.18 (m, 2H), 2.07-1.97 (m, 1H), 1.92-1.49 (m, 11H), 0.85-0.78 (m, 1H), 0.73-0.63 (m, 1H)

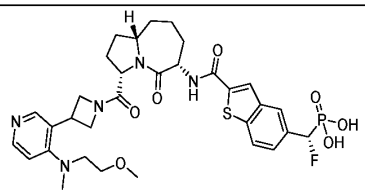
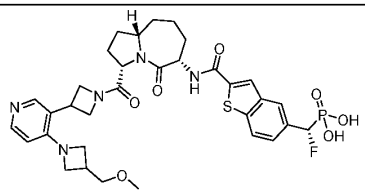
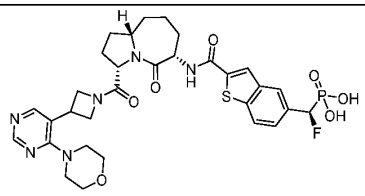
	oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid			
846	((R)-(2-(((3S,6S,10aS)-3-((6S,7R)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((R)-(2-(((3S,6S,10aS)-3-((6R,7S)-6-(5-chloropyridin-3-yl)-7-cyano-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 Or  SFC Pyrrolidine + core peak 1 was used for synthesis and biological testing	714.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (d, J = 6.2 Hz, 1H), 8.72-8.65 (m, 1H), 8.61-8.55 (m, 1H), 8.30-8.23 (m, 1H), 8.20-8.12 (m, 1H), 8.03 (d, J = 8.3 Hz, 1H), 7.98 (s, 1H), 7.54 (d, J = 8.2 Hz, 1H), 5.84 (dd, J = 44.4, 7.6 Hz, 1H), 4.97-4.91 (m, 1H), 4.49-4.45 (m, 1H), 4.28-4.19 (m, 2H), 4.11-4.05 (m, 1H), 3.99-3.89 (m, 2H), 2.34-2.25 (m, 1H), 2.08-1.72 (m, 11H), 1.67-1.52 (m, 2H), 0.81-0.58 (m, 2H)
847	((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((R)-(2-(((3S,6S,9aS)-3-	 Or 	710	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91-8.79 (m, 1H), 8.33-8.17 (m, 3H), 8.05-7.91 (m, 2H), 7.60-7.47 (m, 2H), 5.87-5.66 (m, 1H), 5.00-4.89 (m, 1H), 4.55-4.44 (m, 2H), 4.26-4.19 (m, 1H), 4.15-4.08 (m, 1H), 3.83 (s, 3H), 3.81-3.77 (m, 2H), 2.29-2.17 (m, 2H), 2.13-1.91 (m, 2H), 1.90-1.44 (m, 10H), 0.88-0.61 (m, 2H)

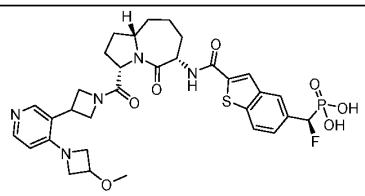
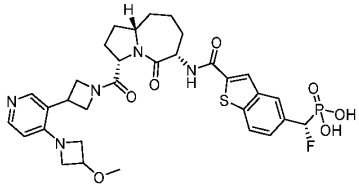
	((6S,7R)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	SFC Pyrrolidine + core peak 2 was used for synthesis and biological testing		
848	((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((R)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-(5-methoxypyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 Or  SFC Pyrrolidine + core peak 1 was used for synthesis and biological testing	710	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (d, J = 7.0 Hz, 1H), 8.31-8.23 (m, 2H), 8.21 (d, J = 2.7 Hz, 1H), 8.05-8.00 (m, 1H), 7.99-7.96 (m, 1H), 7.58-7.50 (m, 2H), 5.90-5.73 (m, 1H), 4.96-4.88 (m, 1H), 4.54-4.48 (m, 1H), 4.28-4.23 (m, 1H), 4.21-4.16 (m, 1H), 4.07-4.02 (m, 1H), 3.90-3.86 (m, 2H), 3.81 (s, 3H), 2.36-2.23 (m, 1H), 2.07-1.97 (m, 2H), 1.96-1.50 (m, 11H), 0.79-0.71 (m, 1H), 0.67-0.58 (m, 1H)
849	((R)-(2-(((3S,6S,8R,9aR)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-		679.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (d, J = 7.1 Hz, 1H), 8.21 (s, 1H), 7.98-7.86 (m, 2H), 7.51-7.29 (m, 6H), 5.49 (dd, J = 45.4, 8.0 Hz, 1H), 4.73-4.58 (m, 2H), 4.39-4.28 (m, 1H),

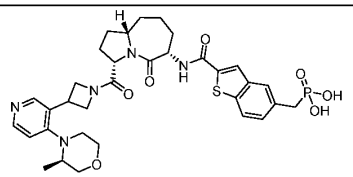
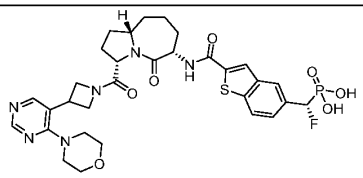
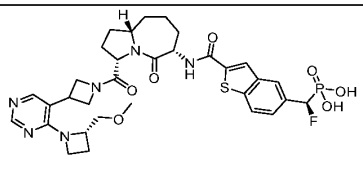
	a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid			4.05-3.91 (m, 2H), 3.79-3.65 (m, 2H), 2.29-2.12 (m, 2H), 2.11-1.89 (m, 2H), 1.80 (d, J = 12.5 Hz, 2H), 1.68 (d, J = 10.4 Hz, 3H), 1.58-1.35 (m, 2H), 0.96 (d, J = 5.2 Hz, 3H), 0.88-0.52 (m, 2H)
850	((2-(((3S,6S,9aS)-5-oxo-3-(3-(4-(2-oxopyrrolidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		666.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.94 - 8.88 (m, 1H), 8.63 - 8.41 (m, 1H), 8.04 - 7.94 (m, 1H), 7.85 - 7.76 (m, 2H), 7.69 - 7.60 (m, 1H), 7.42 - 7.39 (m, 1H), 4.89 - 4.74 (m, 1H), 4.74 - 4.59 (m, 1H), 4.59 - 4.45 (m, 2H), 4.41 - 4.29 (m, 1H), 4.19 - 4.08 (m, 2H), 4.06 - 4.01 (m, 1H), 4.01 - 3.91 (m, 2H), 3.30 - 3.19 (m, 2H), 2.68 - 2.57 (m, 2H), 2.38 - 2.24 (m, 3H), 2.22 - 2.08 (m, 2H), 2.07 - 1.99 (m, 2H), 1.99 - 1.93 (m, 2H), 1.92 – 1.90 (m, 1H), 1.87 - 1.84 (m, 2H)
851	((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-(3-methyl-2-oxoimidazolidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		699.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.80 - 8.68 (m, 1 H) 8.33 - 8.15 (m, 1 H) 7.96 (s, 1 H) 7.93 (d, J = 11.2 Hz, 1 H) 7.84 (d, J = 7.2 Hz, 1 H) 7.68 - 7.53 (m, 1 H) 7.52 - 7.51 (m, 1 H) 5.87 - 5.73 (m, 1 H) 4.78 (d, J = 10.8 Hz, 1 H) 4.67 (t, J = 8.4 Hz, 1 H) 4.60 - 4.45 (m, 2 H) 4.39 - 4.22 (m, 2 H) 4.10 (d, J = 7.6 Hz, 1 H) 4.02 - 4.01 (m, 1 H) 4.00 – 3.86 (m, 2 H) 3.70 -

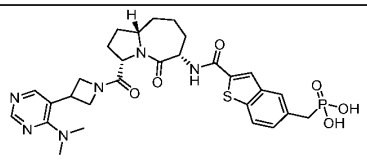
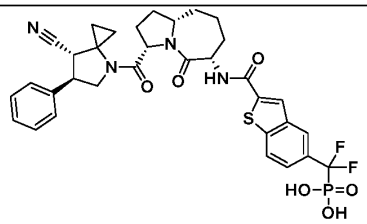
				3.60 (m, 2 H) 2.94 - 2.89 (m, 3 H) 2.36 - 2.16 (s, 1 H) 2.11 - 2.09 (m, 2 H) 2.08 - 2.00 (m, 2 H) 1.93 - 1.91 (s, 2 H) 1.90 - 1.85 (m, 3 H)
852	((S)-(2-(((3S,6S,9aS)-3-(3-(4-(3-(difluoromethoxy)azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		722.6	^{1}H NMR (400 MHz, CD_3OD) δ 8.32 - 8.13 (m, 1 H) 8.03 (s, 1 H) 7.98 (s, 1 H) 7.97 - 7.89 (m, 1 H) 7.88 - 7.71 (m, 1 H) 7.61 - 7.54 (m, 1 H) 6.76 - 6.33 (m, 2 H) 5.87 - 5.71 (m, 1 H) 5.22 - 5.11 (m, 1 H) 4.81 - 4.72 (m, 3 H) 4.67 - 4.52 (m, 3 H) 4.51 - 4.29 (m, 3 H) 4.19 - 4.08 (m, 3 H) 2.36 - 2.12 (m, 2 H) 2.10 – 1.95 (m, 4 H) 1.94 – 1.93 (m, 4 H)
853	((S)-(2-(((3S,6S,9aS)-3-(3-(4-(1H-imidazol-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		667.3	^{1}H NMR (400 MHz, CD_3OD, 300 K) 9.16 - 9.10 (m, 1H), 9.00 (s, 1H), 8.77 (d, J = 5.2 Hz, 1H), 8.71 (s, 1H), 8.04 – 7.95 (m, 2H), 7.93 (d, J = 3.2 Hz, 1H), 7.92 - 7.83 (m, 1H), 7.75 - 7.73 (m, 1H), 7.61 - 7.59 (m, 1H), 7.53 (d, J = 5.2 Hz, 1H), 5.87 - 5.79 (m, 1H), 4.79 - 4.76 (m, 1H), 4.64 (d, J = 6.4 Hz, 1H), 4.55 (s, 1H), 4.50 (d, J = 2.8 Hz, 1H), 4.38 - 4.33 (m, 1H), 4.26 - 4.24 (m, 1H), 4.11 – 4.09 (m, 1H), 4.04 - 3.99 (m, 1H), 2.32 – 2.31 (m, 1H), 2.12 - 2.09 (m, 2H), 2.01 – 2.00 (m, 2H), 1.99 – 1.98 (m, 2H), 1.93 - 1.92

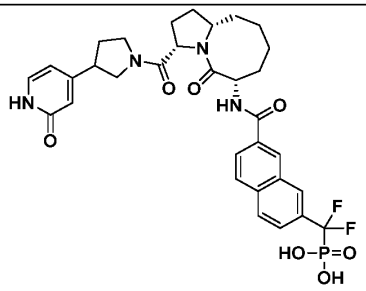
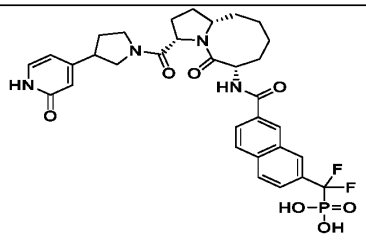
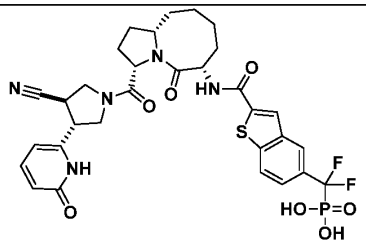
				(m, 1H), 1.84 – 1.83 (m, 2H)
854	((S)-(2-(((3S,6S,9aS)-3-(3-(4-(1H-pyrazol-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		667.2	^{1}H NMR (400 MHz, CD_3OD, 300 K) δ 9.29 (d, J = 2.0 Hz, 1H), 8.87 (d, J = 6.8 Hz, 1H), 8.81 (d, J = 5.6 Hz, 1H), 8.74 - 8.58 (m, 1H), 8.10 (d, J = 6.0 Hz, 1H), 8.05 (s, 1H), 8.00 - 7.94 (m, 2H), 7.62 - 7.60 (m, 1H), 7.24 - 7.20 (m, 1H), 5.88 - 5.74 (m, 1H), 5.32-5.01 (m, 1H), 4.79 - 4.76 (m, 1H), 4.73 - 4.65 (m, 1H), 4.49 - 4.43 (m, 1H), 4.13 - 4.04 (m, 1H), 3.80 - 3.68 (m, 1H), 3.56 - 3.52 (m, 1H), 3.30 - 3.15 (m, 1H), 2.32 - 2.28 (m, 1H), 2.17 - 2.10 (m, 2H), 2.08-2.05 (m, 1H), 1.99 - 1.94 (m, 2H), 1.92 - 1.86 (m, 2H), 1.85 - 1.81 (m, 2H)
855	((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-((2-methoxyethyl)(methyl)amino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		688.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.24 - 8.19 (m, 1H), 8.12 - 8.01 (m, 1H), 8.01 - 7.94 (m, 1H), 7.94 - 7.86 (m, 1H), 7.86 - 7.80 (m, 1H), 7.64 - 7.52 (m, 1H), 7.19 - 7.01 (m, 1H), 5.86 - 5.70 (m, 1H), 4.77 (d, J = 10.4 Hz, 1H), 4.69 (t, J = 8.8 Hz, 1H), 4.60 - 4.47 (m, 2H), 4.43 - 4.21 (m, 2H), 4.20 - 4.11 (m, 1H), 4.06 - 3.98 (m, 1H), 3.66 - 3.57 (m, 4H), 3.29 - 3.24 (m, 3H), 3.15 - 3.08 (m, 3H), 2.39 - 2.27 (m, 1H), 2.24 - 2.09 (m, 2H), 2.09 -

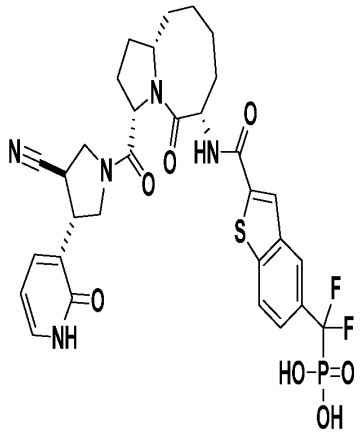
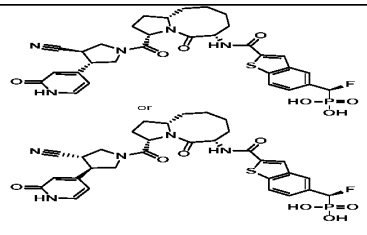
				1.99 (m, 2H), 1.99 - 1.96 (m, 2H), 1.94 - 1.92 (s, 3H)
856	((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-(3-(methoxymethyl)azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		700.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.20 - 8.08 (m, 1 H) 8.04 – 7.98 (m, 2 H) 7.91 - 7.68 (m, 2 H) 7.61 - 7.57 (m, 1 H) 6.41 - 6.31 (m, 1 H) 5.86 - 5.74 (m, 1 H) 4.89 - 4.76 (m, 2 H) 4.56 - 4.54 (m, 3 H) 4.32 (t, *J*=8.4 Hz, 1 H) 4.12 - 4.07 (m, 5 H) 3.62 - 3.59 (m, 2 H) 3.42 - 3.35 (m, 3 H) 3.11 - 2.99 (m, 1 H) 2.36 - 2.21(m, 1 H) 2.20 - 2.09 (m, 2 H) 2.02 – 1.96 (m, 4 H) 1.94 - 1.85 (m, 4 H)
857	((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-morpholinopyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		687.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.53 - 8.22 (m, 1H), 8.17 (d, J = 19.2 Hz, 1H), 8.07 - 7.96 (m, 1H), 7.85 (s, 1H), 7.82 (d, J = 12.0 Hz, 1H), 7.59 - 7.52 (m, 1H), 5.86 - 5.65 (m, 1H), 4.74 (d, J = 10.8 Hz, 1H), 4.67 - 4.59 (m, 1H), 4.55 - 4.43 (m, 2H), 4.39 - 4.23 (m, 1H), 4.15 - 3.97 (m, 3H), 3.83 - 3.67 (m, 8H), 2.37 - 2.24 (m, 1H), 2.19 - 2.06 (m, 2H), 2.04 - 1.95 (m, 2H), 1.94 - 1.86 (m, 2H), 1.86 - 1.71 (m, 3H)
858	((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-(3-methoxyazetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-		686.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.22 - 8.16 (m, 1H), 8.04 - 7.99 (m, 2H), 7.92 - 7.84 (m, 2H), 7.58 (d, J = 8.4 Hz, 1H), 6.45 (d, J = 7.2 Hz, 1H), 5.88 - 5.72 (m, 1H), 4.87 -

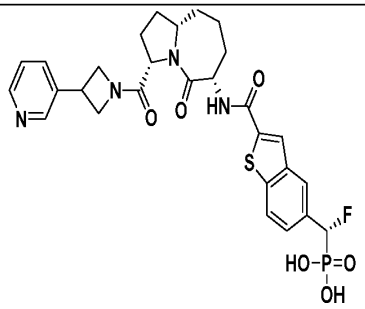
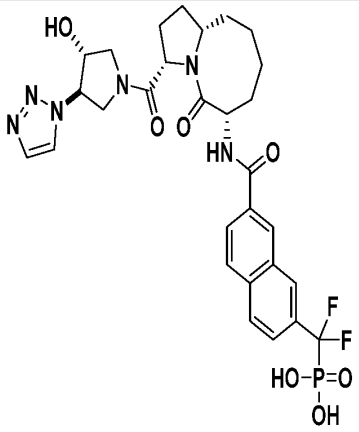
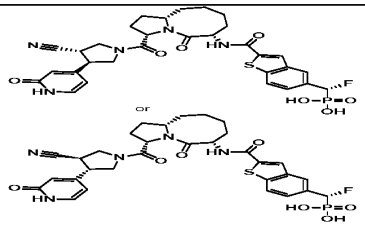
	pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			4.80 (m, 1H), 4.79 - 4.74 (m, 1H), 4.65 - 4.60 (m, 1H), 4.60 - 4.51 (m, 3H), 4.48 - 4.38 (m, 1H), 4.37 - 4.32 (m, 1H), 4.31 - 4.21 (m, 2H), 4.10 (t, J = 7.6 Hz, 3H), 3.36 (d, J = 18.4 Hz, 3H), 2.37 - 2.29 (m, 1H), 2.19 - 2.09 (m, 2H), 2.07 - 1.85 (m, 7H)
859	((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-(3-methoxyazetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		686.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.21 - 8.14 (m, 1H), 8.00 - 7.92 (m, 2H), 7.91 - 7.88 (m, 2H), 7.61- 7.59 (m, 1H), 6.44 (d, J = 6.8 Hz, 1H), 5.89 - 5.72 (m, 1H), 4.87 - 4.83 (m, 1H), 4.75 (d, J = 9.6 Hz, 1H), 4.66 - 4.60 (m, 1H), 4.59 - 4.54 (m, 2H), 4.52 (s, 1H), 4.42 - 4.35 (m, 1H), 4.35 - 4.17 (m, 3H), 4.16 - 4.04 (m, 3H), 3.36 (d, J = 19.2 Hz, 3H), 2.37 - 2.28 (m, 1H), 2.18 - 2.08 (m, 2H), 2.07 - 1.83 (m, 7H)
860	((2-(((3S,6S,9aS)-3-(3-(4-((R)-3-methylmorpholino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		682.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (s, 1H), 8.01 (s, 1H), 7.93 (s, 1H), 7.86 - 7.77 (m, 1H), 7.74 - 7.68 (m, 1H), 7.44 - 7.34 (m, 1H), 7.16 (d, J = 7.2 Hz, 1H), 4.80 - 4.67 (m, 2H), 4.60 - 4.48 (m, 2H), 4.44 - 4.29 (m, 1H), 4.22 - 4.01 (m, 3H), 4.00 - 3.92 (m, 1H), 3.85 - 3.75 (m, 1H), 3.75 - 3.63 (m, 3H), 3.62 - 3.53 (m, 1H), 3.28 - 3.11 (m, 3H), 2.40 - 2.24 (m, 1H), 2.10 (s,

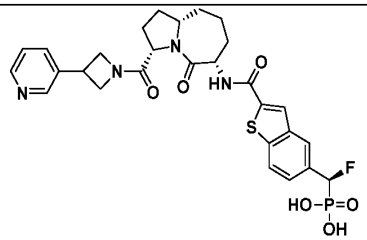
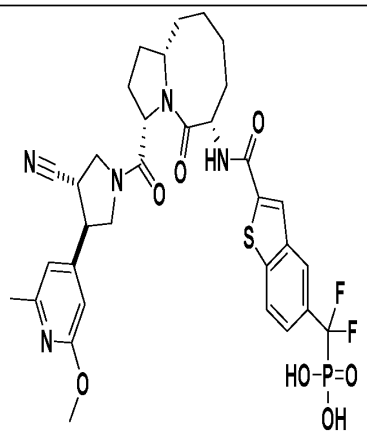
				2H), 2.06 - 1.96 (m, 2H), 1.96 - 1.88 (m, 2H), 1.83 (s, 3H), 1.27-1.20 (m, 3H)
861	((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-morpholinopyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		687.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.58 - 8.49 (m, 1H), 8.47 - 8.37 (m, 1H), 8.08 - 7.98 (m, 2H), 7.86 (d, J = 8.4, 12.5 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 5.73 - 5.56 (m, 1H), 4.77 - 4.65 (m, 2H), 4.65 - 4.46 (m, 2H), 4.44 - 4.32 (m, 1H), 4.20 - 4.02 (m, 3H), 3.76 (t, J = 4.4 Hz, 4H), 3.45 - 3.35 (m, 4H), 2.37 - 2.24 (m, 1H), 2.19 - 2.04 (m, 2H), 2.04 - 1.89 (m, 4H), 1.89 - 1.73 (m, 3H)
862	((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-((S)-2-(methoxymethyl)azetidin-1-yl)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		701.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.34 - 8.10 (m, 1H), 8.09 - 7.92 (m, 3H), 7.83 (t, J = 8.4 Hz, 1H), 7.63 - 7.46 (m, 1H), 5.84 - 5.60 (m, 1H), 4.81 - 4.65 (m, 3H), 4.63 - 4.45 (m, 3H), 4.43 - 4.20 (m, 2H), 4.13 - 3.91 (m, 4H), 3.57 - 3.51 (m, 1H), 3.36 (d, J = 14.0 Hz, 3H), 2.60 - 2.51 (m, 1H), 2.45 - 2.26 (m, 2H), 2.17 - 2.01 (m, 3H), 1.98 - 1.74 (m, 6H)
863	((2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo		627.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.43 - 8.28 (m, 1H), 8.19 (s, 1H), 7.96 (d, J = 14.0 Hz, 1H), 7.83 - 7.71 (m, 2H), 7.46 - 7.33 (m, 1H), 4.77 - 4.60 (m, 2H), 4.57 - 4.42 (m, 2H), 4.40 - 4.16 (m, 2H), 4.13 - 3.95 (m,

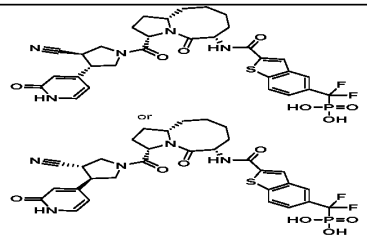
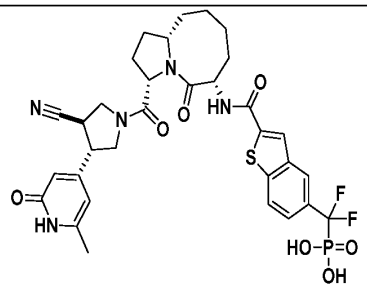
	[b]thiophen-5-yl)methyl)phosphonic acid			2H), 3.24 (s, 6H), 3.20 - 3.11 (m, 2H), 2.39 - 2.24 (m, 1H), 2.21 - 2.06 (m, 2H), 2.05 - 1.79 (m, 7H)
864	((6-fluoro-2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)-1H-indol-5-yl)methyl)phosphonic acid		584	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.48 (s, 1H), 8.56 (d, J = 8.9 Hz, 1H), 8.51-8.36 (m, 2H), 7.91-7.81 (m, 1H), 7.64-7.52 (m, 1H), 7.45-7.31 (m, 1H), 7.22-7.14 (m, 1H), 7.11 (d, J = 10.4 Hz, 1H), 4.85-4.61 (m, 2H), 4.45-4.38 (m, 1H), 4.35-4.18 (m, 2H), 4.07-4.00 (m, 1H), 3.96-3.89 (m, 2H), 3.04-2.98 (m, 2H), 2.23-2.13 (m, 1H), 2.07-1.94 (m, 2H), 1.87-1.66 (m, 7H)
865	((2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		683.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89-8.79 (m, 1H), 8.34-8.26 (m, 1H), 8.17-8.04 (m, 2H), 7.64-7.56 (m, 1H), 7.54-7.47 (m, 2H), 7.45-7.37 (m, 2H), 7.37-7.30 (m, 1H), 4.69-4.59 (m, 2H), 4.36-4.33 (m, 1H), 4.02-3.96 (m, 2H), 3.79-3.67 (m, 2H), 2.27-2.14 (m, 2H), 2.07-1.92 (m, 2H), 1.89-1.66 (m, 8H), 0.90-0.78 (m, 1H), 0.76-0.63 (m, 1H)

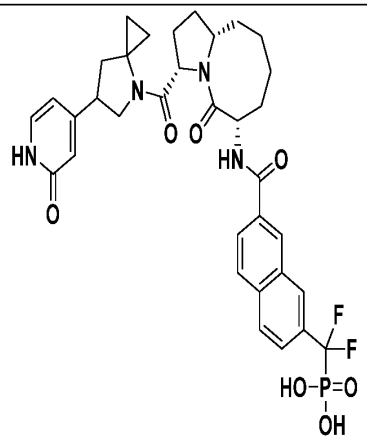
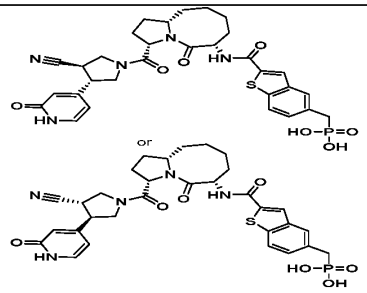
866	(difluoro(7-(((3S,6S,10aS)-5-oxo-3-(3-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		657.4	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.72-8.58 (m, 2H), 8.20 (s, 1H), 8.13-7.98 (m, 3H), 7.72 (d, J = 8.6 Hz, 1H), 7.38-7.26 (m, 1H), 6.25-6.15 (m, 2H), 5.04-5.00 (m, 1H), 4.57 (m, 1H), 4.32 (m, 1H), 3.83 (m, 2H), 3.52-3.07 (m, 3H), 2.28-1.48 (m, 14H)
867	((2-(((3S,6S,10aS)-3-((*rel*-trans)-3-cyano-4-(6-oxo-1,6-dihydropyridin-2-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		688	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.89-8.79 (m, 1H), 8.35-8.28 (m, 1H), 8.17-8.10 (m, 1H), 8.07 (s, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.52-7.42 (m, 1H), 6.46-6.30 (m, 2H), 5.00-4.89 (m, 1H), 4.59-4.50 (m, 1H), 4.36-4.26 (m, 2H), 3.92-3.83 (m, 2H), 3.64-3.50 (m, 3H), 2.32-2.17 (m, 1H), 2.13-1.72 (m, 9H), 1.66-1.54 (m, 2H)
868	((2-(((3S,6S,10aS)-3-((*rel*-trans)-3-cyano-4-(2-oxo-1,2-dihydropyridin-3-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		688.3	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 11.84 (s, 1H), 8.96-8.77 (m, 1H), 8.38-8.27 (m, 1H), 8.18-8.01 (m, 2H), 7.62-7.32 (m, 3H), 6.29-6.13 (m, 1H), 5.01-4.92 (m, 1H), 4.58-4.51 (m, 1H), 4.35-4.24 (m, 2H), 4.04-3.73 (m, 5H), 2.27-1.52 (m, 12H)

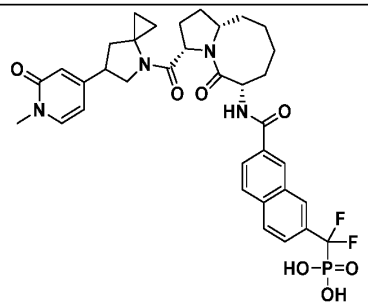
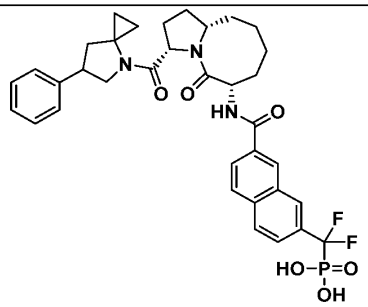
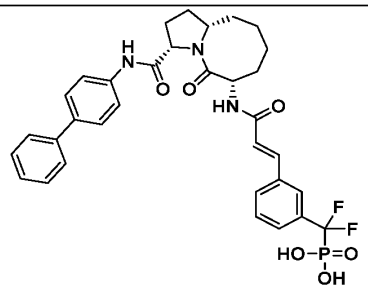
869	((S)-(2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((S)-(2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 Pyrrolidine building block SFC peak 1 was used for synthesis and biological testing	670	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (m, 1H), 8.27 (s, 1H), 8.03 (dd, J = 8.4, 3.0 Hz, 1H), 7.97 (s, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.39 (d, J = 6.8 Hz, 1H), 6.37 (d, J = 10.7 Hz, 1H), 6.29-6.22 (m, 1H), 5.89-5.72 (m, 1H), 5.00-4.90 (m, 1H), 4.56 (m, 1H), 4.33-4.23 (m, 2H), 3.96-3.91 (m, 1H), 3.82-3.78 (m, 1H), 3.68-3.65 (m, 1H), 3.51-3.46 (m, 1H), 3.33-3.18 (m, 1H), 2.35-2.18 (m, 1H), 2.05 (m, 1H), 2.01-1.70 (m, 7H), 1.70-1.44 (m, 3H)
870	((R)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		601.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 – 8.75 (m, 1H), 8.63 – 8.44 (m, 2H), 8.27 (s, 1H), 8.17 (s, 1H), 8.00 – 7.96 (m, 1H), 7.93 – 7.84 (m, 1H), 7.58 – 7.53 (m, 1H), 7.46 – 7.34 (m, 1H), 5.89 – 5.76 (m, 1H), 4.73 – 4.57 (m, 2H), 4.48 – 4.36 (m, 2H), 4.35 – 4.19 (m, 2H), 4.04 – 3.94 (m, 2H), 2.24 – 2.15 (m, 1H), 2.03 – 1.72 (m, 9H)

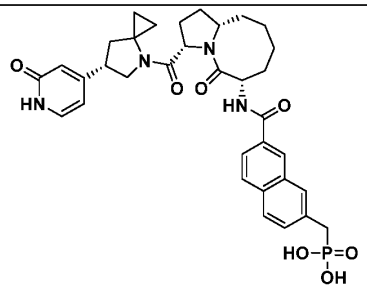
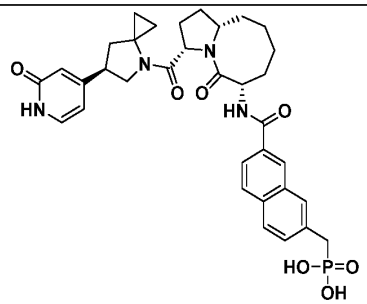
871	(difluoro(7-(((3S,6S,10aS)-3-((*rel*-trans)-3-hydroxy-4-(1H-1,2,3-triazol-1-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		647.0	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.76 – 8.61 (m, 2H), 8.25 – 7.99 (m, 6H), 7.80 – 7.68 (m, 2H), 5.15 – 4.94 (m, 2H), 4.63 – 4.54 (m, 1H), 4.41 – 4.29 (m, 2H), 3.96 – 3.56 (m, 4H), 2.19 – 1.63 (m, 12H)
872	((R)-(2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid Or ((R)-(2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid	 Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	670.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.83 – 8.75 (m, 1H), 8.26 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.96 (s, 1H), 7.55 – 7.47 (m, 1H), 7.39 (d, *J* = 6.7 Hz, 1H), 6.40 – 6.32 (m, 1H), 6.28 – 6.20 (m, 1H), 5.77 (dd, *J* = 44.6, 7.7 Hz, 1H), 4.99 – 4.90 (m, 1H), 4.56 (t, *J* = 8.1 Hz, 1H), 4.35 – 4.25 (m, 2H), 3.83 – 3.58 (m, 4H), 3.24 – 3.08 (m, 1H), 2.32 – 2.17 (m, 1H), 2.06 – 1.73 (m, 8H), 1.69 – 1.49 (m, 3H)
873	((S)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(802yridine-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		601.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.85 – 8.74 (m, 1H), 8.62 – 8.50 (m, 1H), 8.50 – 8.42 (m, 1H), 8.26 (s, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 8.01 – 7.96 (m, 1H), 7.90 – 7.83 (m, 1H), 7.57 – 7.47 (m, 1H), 7.44 – 7.33

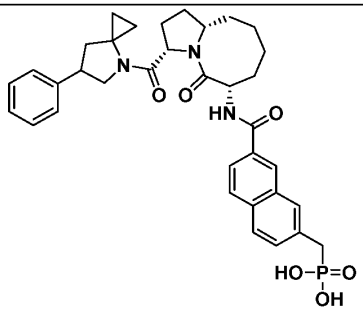
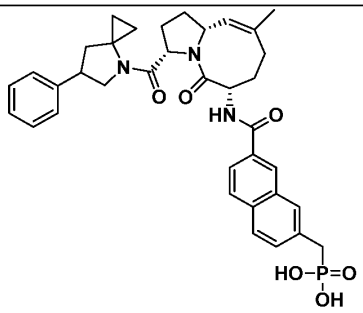
	yl)methyl)phosphonic acid			(m, 1H), 5.92 – 5.71 (m, 1H), 4.83 – 4.59 (m, 2H), 4.46 – 4.40 (m, 1H), 4.35 – 4.17 (m, 2H), 4.04 – 3.98 (m, 1H), 3.94 – 3.86 (m, 2H), 2.20 (d, *J* = 6.6 Hz, 1H), 2.09 – 1.93 (m, 2H), 1.89 – 1.66 (m, 7H)
874	((2-(((3S,6S,10aS)-3-((*rel*-trans)-3-cyano-4-(2-methoxy-6-methylpyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		716.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.07 – 8.51 (m, 1H), 8.41 – 8.25 (m, 1H), 8.21 – 8.10 (m, 1H), 8.08 (s, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 6.99 – 6.79 (m, 1H), 6.75 – 6.49 (m, 1H), 5.02 – 4.88 (m, 1H), 4.63 – 4.47 (m, 1H), 4.38 – 4.24 (m, 1H), 4.23 – 4.08 (m, 1H), 4.06 – 3.91 (m, 1H), 3.87 – 3.77 (m, 3H), 3.75 – 3.62 (m, 1H), 3.62 – 3.55 (m, 1H), 3.55 – 3.46 (m, 1H), 3.45 – 3.11 (m, 1H), 2.45 – 2.31 (m, 3H), 2.32 – 2.16 (m, 1H), 2.16 – 2.00 (m, 1H), 2.00 – 1.71 (m, 7H), 1.71 – 1.40 (m, 3H) (TFA salt)
875	((2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid Or ((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(2-oxo-1,2-		688.0	H NMR (400 MHz, DMSO-d$_6$) δ 8.92 – 8.81 (m, 1H), 8.32 (s, 1H), 8.18 – 8.10 (m, 1H), 8.07 (s, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.39 (d, *J* = 6.7 Hz, 1H), 6.42 – 6.19 (m, 2H), 5.01 – 4.88 (m, 1H), 4.62 – 4.50 (m, 1H), 4.37 – 4.20 (m, 2H), 4.01 – 3.76 (m, 2H), 3.72 – 3.59 (m, 1H), 3.55 – 3.44 (m, 1H), 3.25 – 3.02 (m, 1H), 2.35 – 2.16

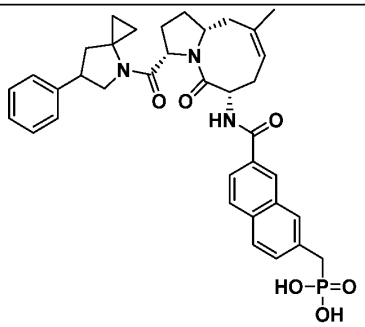
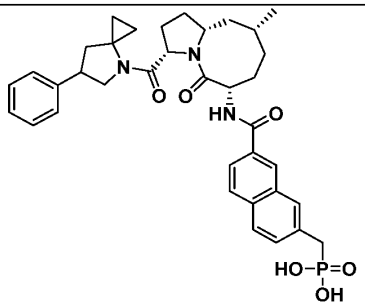
	dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid	Pyrrolidine building block SFC peak 1 was used for synthesis and biological testing		(m, 1H), 2.14 – 1.99 (m, 1H), 1.97 – 1.69 (m, 7H), 1.69 – 1.41 (m, 3H) (free base)
876	((2-(((3S,6S,10aS)-3-((*rel*-trans)-3-cyano-4-(6-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		702.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.00 – 8.70 (m, 1H), 8.36 – 8.22 (m, 1H), 8.08 – 7.94 (m, 2H), 7.59 (d, *J* = 8.5 Hz, 1H), 6.23 – 6.13 (m, 1H), 6.11 – 5.91 (m, 1H), 5.07 – 4.84 (m, 1H), 4.63 – 4.43 (m, 1H), 4.37 – 4.27 (m, 1H), 4.24 – 4.11 (m, 1H), 4.09 – 3.98 (m, 1H), 3.96 – 3.85 (m, 1H), 3.85 – 3.76 (m, 1H), 3.31 – 3.14 (m, 2H), 2.34 – 2.22 (m, 1H), 2.18 – 2.11 (m, 3H), 2.10 – 2.01 (m, 1H), 1.95 – 1.71 (m, 7H), 1.71 – 1.48 (m, 3H). (free base)
877	(difluoro(7-(((3S,6S,10aS)-5-oxo-3-(6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		683.3	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.77 – 8.51 (m, 2H), 8.26 – 8.11 (m, 1H), 8.07 – 7.89 (m, 3H), 7.73 (s, 1H), 7.31 – 7.16 (m, 1H), 6.30 – 6.05 (m, 2H), 5.13 – 4.91 (m, 1H), 4.60 – 4.17 (m, 3H), 4.09 – 3.98 (m, 1H), 3.75 – 3.70 (m, 1H), 3.15 – 3.09 (m, 1H), 2.29 – 2.19 (m, 1H), 2.10 – 1.99 (m, 3H), 1.97 – 1.68 (m, 8H), 1.65 – 1.48 (m, 4H), 0.58 – 0.34 (m, 2H)

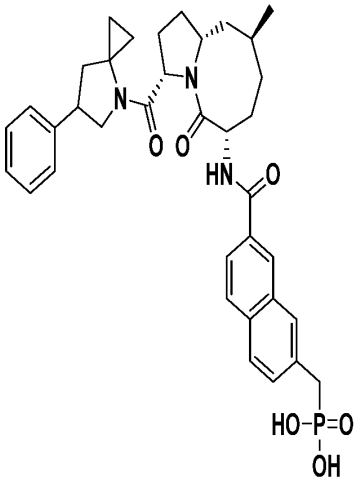
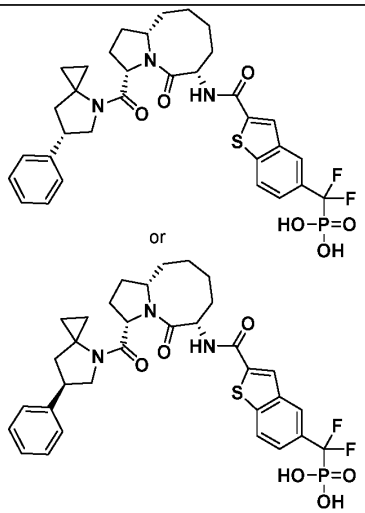
878	((2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid Or ((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid	 Pyrrolidine building block SFC peak 1 was used for synthesis and biological testing	652.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 – 8.71 (m, 1H), 8.23 – 8.15 (m, 1H), 7.94 – 7.87 (m, 1H), 7.81 – 7.76 (m, 1H), 7.41 – 7.33 (m, 2H), 6.40 – 6.32 (m, 1H), 6.28 – 6.22 (m, 1H), 4.97 – 4.90 (m, 1H), 4.59 – 4.52 (m, 1H), 4.33 – 4.24 (m, 2H), 3.91 – 3.75 (m, 2H), 3.63 – 3.50 (m, 2H), 3.27 – 3.14 (m, 1H), 3.13 – 3.05 (m, 2H), 2.32 – 2.17 (m, 1H), 2.11 – 1.99 (m, 1H), 1.97 – 1.70 (m, 7H), 1.66 – 1.48 (m, 3H)
879	(difluoro(7-(((3S,6S,10aS)-3-(6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		695.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 – 8.53 (m, 2H), 8.27 – 8.11 (m, 1H), 8.10 – 7.93 (m, 3H), 7.80 – 7.65 (m, 1H), 7.66 – 7.49 (m, 1H), 6.31 (s, 1H), 6.27 – 6.10 (m, 1H), 5.09 – 4.93 (m, 1H), 4.58 – 4.44 (m, 1H), 4.32 – 4.03 (m, 2H), 3.73 – 3.53 (m, 1H), 3.41 – 3.24 (m, 4H), 2.40 – 2.10 (m, 2H), 2.10 – 1.67 (m, 11H), 1.66 – 1.37 (m, 4H), 0.46 (s, 2H)

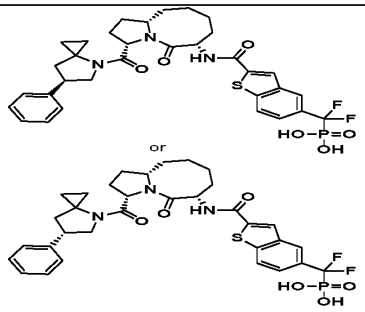
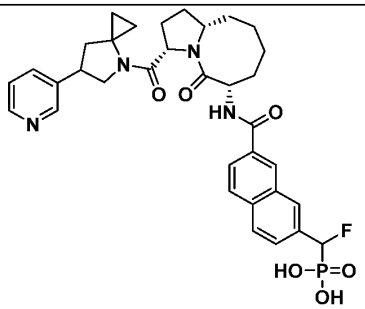
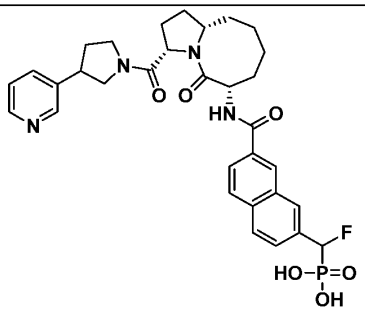
880	(difluoro(7-(((3S,6S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		666.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 – 8.42 (m, 2H), 8.26 – 7.97 (m, 4H), 7.89 – 7.68 (m, 1H), 7.40 – 7.11 (m, 5H), 5.07 – 4.96 (m, 1H), 4.58 – 4.38 (m, 2H), 4.33 – 4.22 (m, 1H), 4.16 – 3.69 (m, 1H), 3.61 – 3.42 (m, 2H), 2.37 – 1.43 (m, 16H), 0.91 – 0.41 (m, 2H)
881	((3-((E)-3-(((3S,6S,10aS)-3-([1,1'-biphenyl]-4-ylcarbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)amino)-3-oxoprop-1-en-1-yl)phenyl)difluoromethyl)phosphonic acid		636.2 $[M-H]^-$	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 – 9.96 (m, 1H), 8.39 – 8.31 (m, 1H), 7.75 – 7.68 (m, 2H), 7.68 – 7.59 (m, 6H), 7.59 – 7.48 (m, 2H), 7.48 – 7.40 (m, 3H), 7.36 – 7.29 (m, 1H), 6.86 (d, J = 15.8 Hz, 1H), 5.00 – 4.81 (m, 1H), 4.55 – 4.40 (m, 1H), 4.37 – 4.21 (m, 1H), 3.68 – 3.53 (m, 1H), 3.20 – 3.05 (m, 1H), 2.29 – 2.18 (m, 1H), 2.17 – 2.04 (m, 1H), 2.02 – 1.83 (m, 4H), 1.82 – 1.71 (m, 2H), 1.71 – 1.58 (m, 3H), 1.57 – 1.39 (m, 1H)
882	((7-(((3S,6S,10aS)-5-oxo-3-((S)-6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		647.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (d, J = 7.3 Hz, 1H), 8.45 (s, 1H), 7.90 (M, 4H), 7.52 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 6.8 Hz, 1H), 6.25 (s, 1H), 6.19 (d, J = 6.6 Hz, 1H), 5.06 – 4.95 (m, 1H), 4.56 – 4.49 (m, 1H), 4.40 – 4.17 (m, 3H), 3.60 – 3.59 (m, 1H), 3.19 – 3.15 (m, 2H), 2.25 – 2.13 (m, 2H), 2.07 – 2.00 (m, 2H), 1.97 – 1.85 (m,

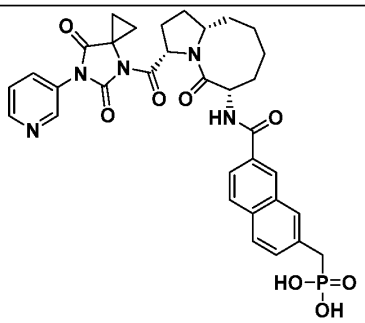
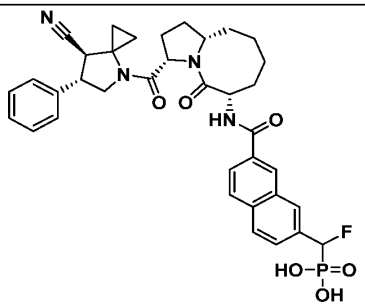
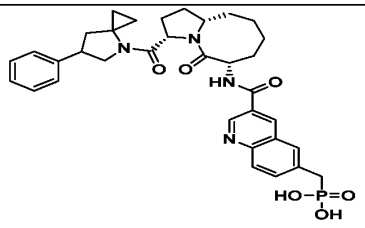
				4H), 1.84 – 1.78 (m, 2H), 1.76 – 1.66 (m, 2H), 1.64 – 1.47 (m, 4H), 0.52 – 0.41 (m, 2H)
883	((7-(((3S,6S,10aS)-5-oxo-3-((R)-6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		647.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (d, J = 7.3 Hz, 1H), 8.44 (s, 1H), 8.00 – 7.79 (m, 4H), 7.52 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 6.7 Hz, 1H), 6.26 (s, 1H), 6.21 – 6.16 (m, 1H), 5.06 – 4.94 (m, 1H), 4.53 – 4.44 (m, 1H), 4.31 – 4.23 (m, 1H), 4.09 – 4.02 (m, 1H), 3.74 – 3.68 (m, 2H), 3.18 – 3.14 (m, 2H), 2.36 – 2.18 (m, 2H), 2.12 – 1.96 (m, 5H), 1.92 – 1.81 (m, 3H), 1.78 – 1.69 (m, 2H), 1.66 – 1.60 (m, 1H), 1.58 – 1.48 (m, 3H), 0.53 – 0.40 (m, 2H)
884	((7-(((3S,6S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		630.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 – 8.41 (m, 2H), 7.96 – 7.80 (m, 4H), 7.55 – 7.48 (m, 1H), 7.37 – 7.17 (m, 5H), 5.06 – 4.94 (m, 1H), 4.58 – 4.39 (m, 1H), 4.31 – 4.23 (m, 1H), 4.16 – 3.69 (m, 1H), 3.59-3.47 (m, 2H), 3.16 (d, J = 21.4 Hz, 2H), 2.36 – 2.16 (m, 2H), 2.13 – 1.70 (m, 10H), 1.68 – 1.46 (m, 4H), 0.55 – 0.39 (m, 2H)

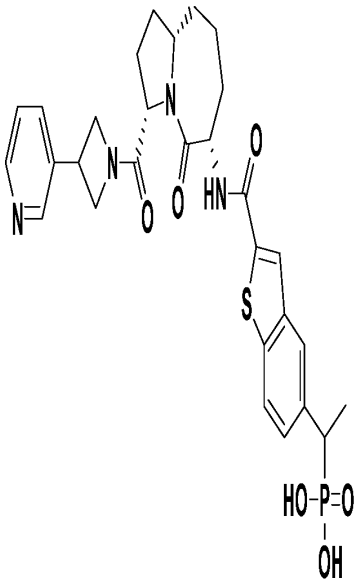
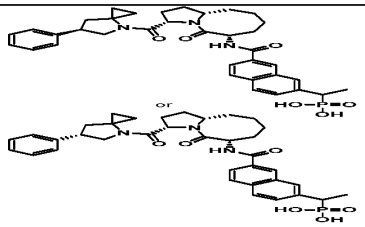
885	((7-(((3S,6S,10aR,Z)-9-methyl-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		642.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 – 8.60 (m, 1H), 8.44 (s, 1H), 8.01 – 7.78 (m, 4H), 7.56 – 7.46 (m, 1H), 7.39 – 7.28 (m, 4H), 7.26 – 7.13 (m, 1H), 5.34 (s, 1H), 4.98 – 4.82 (m, 1H), 4.77 – 4.65 (m, 1H), 4.60 – 4.49 (m, 1H), 4.40 – 4.31 (m, 0.6 H), 3.72 – 3.67 (m, 0.4 H), 3.58 – 3.45 (m, 2H), 3.15 (d, J = 21.5 Hz, 2H), 2.38 – 2.18 (m, 2H), 2.13 – 1.82 (m, 8H), 1.81 – 1.73 (m, 3H), 1.66 – 1.45 (m, 2H), 0.59 – 0.35 (m, 2H)
886	((7-(((3S,6S,10aR,Z)-9-methyl-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		642.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, J = 7.5 Hz, 1H), 8.45 (s, 1H), 8.00 – 7.77 (m, 4H), 7.52 (d, J = 8.5 Hz, 1H), 7.42 – 7.15 (m, 5H), 5.64 (t, J = 7.1 Hz, 1H), 5.03 – 4.81 (m, 1H), 4.60 – 4.49 (m, 1H), 4.44 – 4.35 (m, 1H), 4.32 – 4.19 (m, 1H), 3.79 – 3.64 (m, 2H), 3.15 (d, J = 21.4 Hz, 2H) , 2.67 – 2.54 (m, 2H), 2.46 – 2.38 (m, 1H), 2.36 – 2.26 (m, 2H), 2.22 – 2.11 (m, 3H), 2.09 – 1.90 (m, 2H), 1.81 (s, 3H), 1.78 – 1.68 (m, 1H), 1.62 – 1.52 (m, 1H), 0.64 – 0.37 (m, 2H)

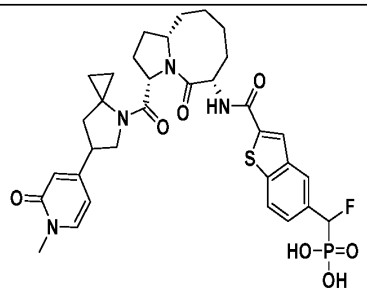
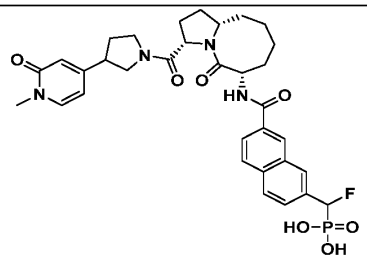
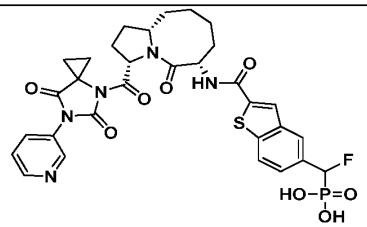
887	((7-(((3S,6S,9R,10aR)-9-methyl-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		644.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 – 8.35 (m, 1H), 8.50 – 8.36 (m, 1H), 8.06 – 7.74 (m, 4H), 7.55 – 7.46 (m, 1H), 7.42 – 7.10 (m, 5H), 5.76 (s, 1H), 5.21 – 4.93 (m, 1H), 4.66 – 4.45 (m, 1H), 4.38 – 4.22 (m, 1H), 4.14-4.10 (m, 0.5H), 3.73-3.71 (m, 0.5H), 3.62 – 3.48 (m, 1H), 3.11 (d, J = 21.4 Hz, 2H), 2.37 – 1.67 (m, 12H), 1.61 – 1.43 (m, 2H), 1.36 – 1.17 (m, 1H), 0.97 (d, J = 6.1 Hz, 3H), 0.58 – 0.39 (m, 2H)
888	((7-(((3S,6S,9S,10aR)-9-methyl-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		644.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 – 8.45 (m, 1H), 8.44 – 8.36 (m, 1H), 7.94 – 7.73 (m, 4H), 7.51 (d, J = 8.4 Hz, 1H), 7.36 – 7.16 (m, 5H), 5.76 (s, 1H), 4.89 – 4.75 (m, 1H), 4.57 – 4.42 (m, 1H), 4.36 – 4.27 (m, 0.5 H), 4.15 – 4.08 (m, 0.5 H), 3.76 – 3.70 (m, 1H), 3.59 – 3.53 (m, 1H), 3.11 (d, J = 21.4 Hz, 2H), 2.36 – 2.21 (m, 2H), 2.12 – 1.93 (m, 5H), 1.84 – 1.49 (m, 7H), 1.25 – 1.17 (m, 1H), 0.96 (d, J = 6.8 Hz, 3H), 0.55 – 0.38 (m, 2H)

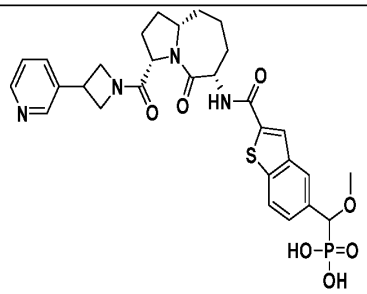
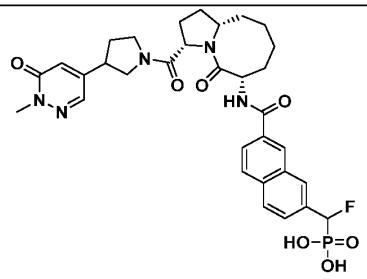
889	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid Or (difluoro(2-(((3S,6S,10aS)-5-oxo-3-((S)-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid	 Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	672.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (d, J = 7.3 Hz, 1H), 8.32 (s, 1H), 8.12 (d, J = 8.6 Hz, 1H), 8.06 (s, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.37 – 7.27 (m, 4H), 7.26 – 7.20 (m, 1H), 5.02 – 4.91 (m, 1H), 4.58 – 4.49 (m, 1H), 4.47 – 4.39 (m, 1H), 4.26 – 4.19 (m, 1H), 3.89 – 3.79 (m, 2H), 2.28 – 1.55 (m, 16H), 0.52 – 0.43 (m, 2H)
890	(difluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid Or (difluoro(2-(((3S,6S,10aS)-5-oxo-3-((S)-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-	 Pyrrolidine building block SFC peak 1 was used for synthesis and biological testing	672.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (d, J = 7.1 Hz, 1H), 8.31 (s, 1H), 8.11 (d, J = 8.5 Hz, 1H), 8.05 (s, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.38 – 7.27 (m, 4H), 7.25 – 7.18 (m, 1H), 5.02 – 4.90 (m, 1H), 4.56 – 4.45 (m, 1H), 4.30 – 4.19 (m, 1H), 4.16 – 4.08 (m, 1H), 3.80 – 3.69 (m, 1H), 3.56 – 3.50 (m, 1H), 2.27 – 1.55 (m, 16H), 0.53 – 0.40 (m, 2H)

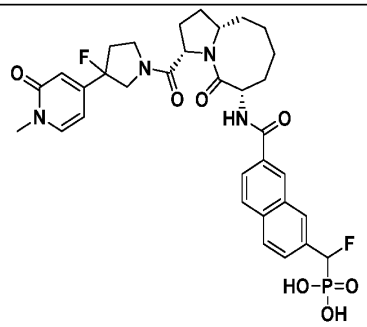
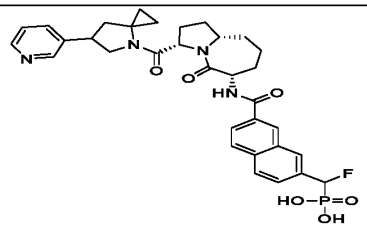
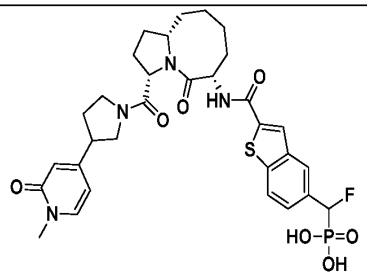
	a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			
891	(fluoro(7-(((3S,6S,10aS)-5-oxo-3-(6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		649.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 – 8.37 (m, 4H), 8.21 – 7.92 (m, 4H), 7.86 – 7.75 (m, 1H), 7.72 – 7.58 (m, 1H), 7.45 – 7.25 (m, 1H), 6.04 – 5.73 (m, 1H), 5.09 – 4.91 (m, 1H), 4.61 – 4.04 (m, 3H), 3.88 – 3.41 (m, 2H), 2.36 – 1.73 (m, 12H), 1.69 – 1.46 (m, 4H), 0.56 – 0.37 (m, 2H)
892	(fluoro(7-(((3S,6S,10aS)-5-oxo-3-(3-(pyridin-3-yl)pyrrolidine-1-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		623.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 – 8.57 (m, 1H), 8.56 – 8.47 (m, 2H), 8.46 – 8.38 (m, 1H), 8.01 – 7.87 (m, 4H), 7.76 – 7.68 (m, 1H), 7.66 – 7.56 (m, 1H), 7.38 – 7.27 (m, 1H), 5.79 – 5.58 (m, 1H), 5.07 – 4.95 (m, 1H), 4.64 – 4.51 (m, 1H), 4.37 – 4.29 (m, 1H), 4.01 – 3.88 (m, 1H), 3.61 – 3.45 (m, 3H), 3.13 – 3.03 (m, 1H), 2.39 – 2.19 (m, 2H), 2.10 – 1.72 (m, 9H), 1.69 – 1.46 (m, 3H)
893	((7-(((3S,6S,10aS)-3-(5,7-dioxo-6-(pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		660.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 – 8.39 (m, 4H), 7.98 – 7.79 (m, 5H), 7.62 – 7.47 (m, 2H), 5.38 (t, J = 8.6 Hz, 1H), 5.03 – 4.92 (m, 1H), 4.45 – 4.34 (m, 1H), 3.20 – 3.07 (m, 2H), 2.46 – 2.31 (m, 2H), 2.26 – 2.04 (m, 2H), 1.98 –

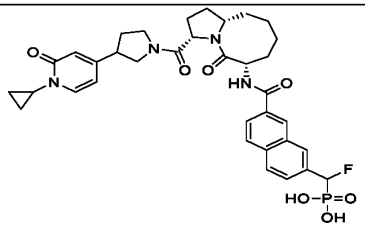
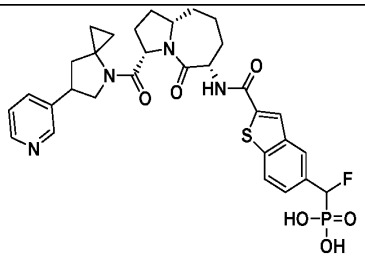
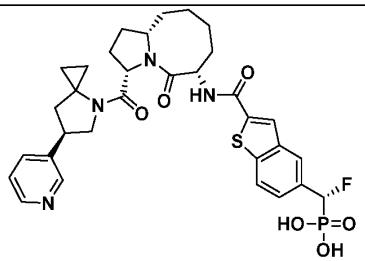
				1.52 (m, 10H), 1.45 – 1.34 (m, 2H)
894	((7-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)fluoromethyl)phosphonic acid		673.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.75 – 8.63 (m, 1H), 8.59 – 8.49 (m, 1H), 8.10 – 7.91 (m, 4H), 7.73 – 7.62 (m, 1H), 7.62 – 7.42 (m, 2H), 7.40 – 7.30 (m, 2H), 5.92 (dd, J = 44.4, 8.5 Hz, 1H), 5.10 – 4.90 (m, 1H), 4.56 – 4.47 (m, 1H), 4.32 – 4.19 (m, 1H), 4.08 – 3.97 (m, 1H), 3.90 – 3.69 (m, 2H), 3.27 – 3.00 (m, 1H), 2.30 – 1.48 (m, 12H), 1.31 – 1.21 (m, 2H), 0.90 – 0.76 (m, 1H), 0.75 – 0.55 (m, 1H) (TFA salt)
895	((3-(((3S,6S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)quinolin-6-yl)methyl)phosphonic acid		631.3	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.26 – 9.16 (m, 1H), 8.87 (t, J = 7.3 Hz, 1H), 8.83 – 8.77 (m, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.37 – 7.26 (m, 4H), 7.25 – 7.18 (m, 1H), 5.10 – 4.96 (m, 1H), 4.60 – 4.47 (m, 1H), 4.46 – 4.09 (m, 2H), 3.74 – 3.57 (m, 1H), 3.53 – 3.44 (m, 1H), 3.18 (d, J = 21.5 Hz, 2H), 2.36 – 2.16 (m, 2H), 2.14 – 1.42 (m, 14H), 0.54 – 0.40 (m, 2H)
896	(1-(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		597.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.78 – 8.68 (m, 1H), 8.59 – 8.53 (m, 1H), 8.50 – 8.41 (m, 1H), 8.18 (s, 1H), 7.93 – 7.78 (m, 3H), 7.45 – 7.32 (m, 2H), 4.81 – 4.60 (m,

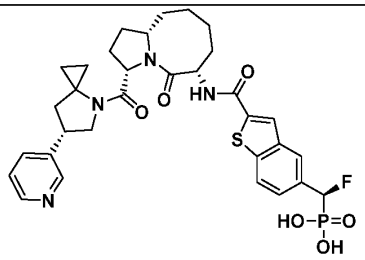
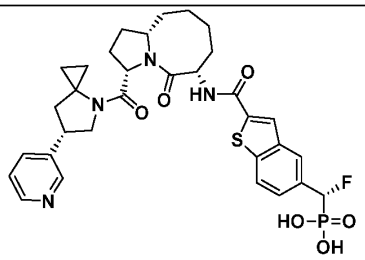
	yl)ethyl)phosphonic acid			2H), 4.49 – 4.36 (m, 2H), 4.34 – 4.20 (m, 2H), 4.02 – 3.98 (m, 1H), 3.94 – 3.90 (m, 1H), 3.19 – 3.09 (m, 1H), 2.25 – 2.14 (m, 1H), 2.08 – 1.94 (m, 2H), 1.88 – 1.64 (m, 7H), 1.53 – 1.44 (m, 3H)
897	(1-(7-(((3S,6S,10aS)-5-oxo-3-((R)-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)ethyl)phosphonic acid Or (1-(7-(((3S,6S,10aS)-5-oxo-3-((S)-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)ethyl)phosphonic acid	 Pyrrolidine building block SFC peak 1 was used for synthesis and biological testing	644.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, *J* = 7.3 Hz, 1H), 8.47 (s, 1H), 7.94 – 7.82 (m, 4H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.37 – 7.26 (m, 4H), 7.24 – 7.18 (m, 1H), 5.08 – 4.90 (m, 1H), 4.49 (t, *J* = 8.2 Hz, 1H), 4.33 – 4.21 (m, 1H), 4.12 (t, *J* = 8.7 Hz, 1H), 3.73 (t, *J* = 9.9 Hz, 1H), 3.58 – 3.48 (m, 1H), 3.23 – 3.15 (m, 1H), 2.36 – 2.17 (m, 2H), 2.15 – 2.08 (m, 1H), 2.06 – 1.94 (m, 3H), 1.94 – 1.69 (m, 6H), 1.67 – 1.59 (m, 1H), 1.58 – 1.45 (m, 6H), 0.56 – 0.39 (m, 2H)
898	(fluoro(2-(((3S,6S,10aS)-3-(6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		685.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (d, J = 7.3 Hz, 1H), 8.27 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.97 (s, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 8.6 Hz, 1H), 6.32 (s, 1H), 6.26 – 6.16 (m, 1H), 5.83 (dd, J = 44.3, 8.0 Hz, 1H), 5.00 – 4.85 (m, 1H), 4.59 – 4.44 (m, 1H),

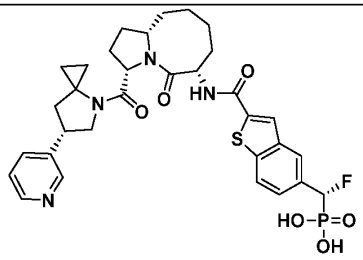
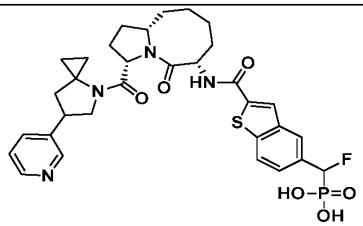
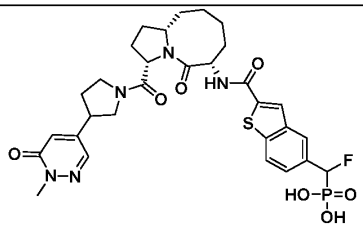
				4.38 – 4.14 (m, 2H), 4.10 – 4.00 (m, 1H), 3.74 – 3.68 (m, 0.5H), 3.59 – 3.55 (m, 0.5H), 3.37 – 3.34 (m, 3H), 2.31 – 2.10 (m, 2H), 2.10 – 1.97 (m, 3H), 1.96 – 1.67 (m, 7H), 1.66 – 1.41 (m, 4H), 0.57 – 0.37 (m, 2H).
899	(fluoro(7-(((3S,6S,10aS)-3-(3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		651.2 $[M-H]^-$	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 – 8.41 (m, 2H), 8.17 – 7.85 (m, 4H), 7.71 – 7.47 (m, 2H), 6.33 – 6.10 (m, 2H), 5.95 – 5.75 (m, 1H), 5.07 – 4.94 (m, 1H), 4.64 – 4.49 (m, 1H), 4.39 – 4.27 (m, 1H), 4.20 – 3.87 (m, 1H), 3.85 – 3.39 (m, 3H), 3.36 – 3.06 (m, 4H), 2.35 – 1.47 (m, 14H)
900	((2-(((3S,6S,10aS)-3-(5,7-dioxo-6-(pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		684.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 – 8.60 (m, 3H), 8.30 – 8.19 (m, 1H), 8.07 – 7.88 (m, 3H), 7.63 – 7.46 (m, 2H), 5.88 – 5.69 (m, 1H), 5.44 – 5.31 (m, 1H), 4.98 – 4.86 (m, 1H), 4.40 – 4.30 (m, 1H), 2.45 – 2.32 (m, 2H), 2.24 – 2.06 (m, 2H), 1.96 – 1.53 (m, 10H), 1.44 – 1.32 (m, 2H)
901	(methoxy(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		680.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 – 8.64 (m, 1H), 8.56 (s, 1H), 8.47 (d, J = 13.3 Hz, 1H), 8.23 (s, 1H), 7.97 (d, J = 8.1 Hz, 1H), 7.92 – 7.81 (m, 2H), 7.46 (d, J = 8.0 Hz, 1H), 7.43 – 7.30 (m, 1H), 4.87 – 4.54 (m, 2H), 4.52 – 4.19 (m, 4H), 4.04 – 3.84

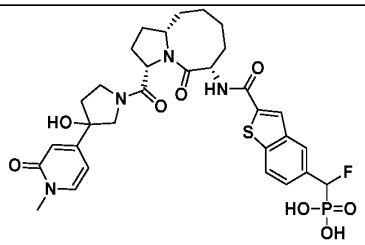
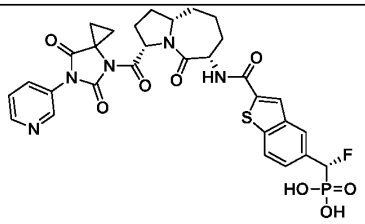
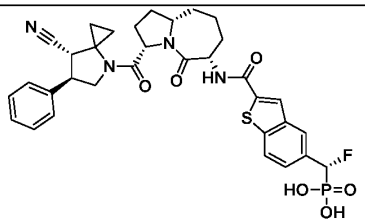
				(m, 3H), 3.28 (s, 3H), 2.25 – 2.11 (m, 1H), 2.10 – 1.91 (m, 2H), 1.91 – 1.61 (m, 7H).
902	(fluoro(7-(((3S,6S,10aS)-3-(3-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		654.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 – 8.42 (m, 2H), 8.21 – 7.76 (m, 5H), 7.71 – 7.51 (m, 1H), 6.86 – 6.69 (m, 1H), 5.93 – 5.62 (m, 1H), 5.09 – 4.91 (m, 1H), 4.63 – 4.50 (m, 1H), 4.39 – 4.30 (m, 1H), 3.98 – 3.90 (m, 1H), 3.77 – 3.71 (m, 1H), 3.61 (s, 3H), 3.54 – 3.51 (m, 1H), 3.37 – 3.32 (m, 1H), 2.33 – 2.16 (m, 2H), 2.11 – 1.98 (m, 2H), 1.95 – 1.72 (m, 6H), 1.71 – 1.13 (m, 5H)
903	(fluoro(7-(((3S,6S,10aS)-3-(3-fluoro-3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		671.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 – 8.42 (m, 2H), 8.15 – 7.86 (m, 4H), 7.80 – 7.57 (m, 2H), 6.53 – 6.22 (m, 2H), 5.86 – 5.66 (m, 1H), 5.02 (s, 1H), 4.63 – 4.50 (m, 1H), 4.36 – 4.31 (m, 1H), 4.16 – 4.09 (m, 1H), 3.92 – 3.87 (m, 1H), 3.72 – 3.65 (m, 1H), 3.59 – 3.50 (m, 1H), 3.42 – 3.36 (m, 3H), 2.40 – 2.22 (m, 2H), 2.12 – 1.77 (m, 8H), 1.74 – 1.44 (m, 4H)

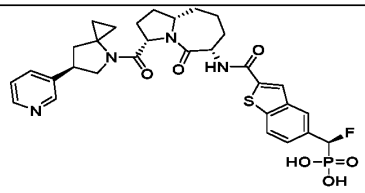
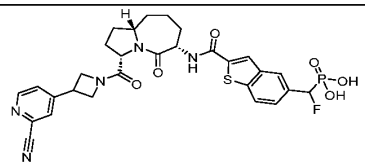
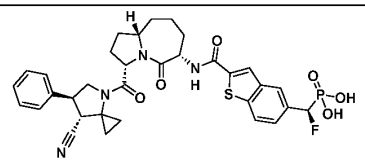
904	(fluoro(7-(((3S,6S,9aS)-5-oxo-3-(6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphonic acid		635.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 – 8.39 (m, 4H), 8.17 – 7.91 (m, 4H), 7.88 – 7.78 (m, 1H), 7.70 – 7.61 (m, 1H), 7.43 – 7.30 (m, 1H), 5.94 – 5.79 (m, 1H), 4.69 – 4.66 (m, 1H), 4.36 – 4.27 (m, 1H), 4.11 – 3.93 (m, 2H), 3.78 – 3.54 (m, 2H), 2.44 – 1.22 (m, 14H), 0.92 – 0.43 (m, 2H)
905	(fluoro(2-(((3S,6S,10aS)-3-(3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		659.1	
906	((7-(((3S,6S,10aS)-3-(3-(1-cyclopropyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)fluoromethyl)phosphonic acid		679.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 – 8.58 (m, 1H), 8.55 (s, 1H), 8.08 – 7.93 (m, 4H), 7.67 (d, J = 8.3 Hz, 1H), 7.48 – 7.40 (m, 1H), 6.24 (dd, J = 44.4, 8.4 Hz, 1H), 6.18 – 6.11 (m, 1H), 5.86 (d, J = 8.2 Hz, 1H), 5.07 – 4.96 (m, 1H), 4.63 – 4.50 (m, 1H), 4.39 – 4.27 (m, 1H), 4.17 – 3.77 (m, 1H), 3.76 – 3.36 (m, 2H), 3.35 – 3.21 (m, 2H), 3.21 – 3.03 (m, 1H), 2.34 – 1.74 (m, 11H), 1.68 – 1.47 (m, 3H), 1.01 – 0.87 (m, 2H), 0.83 – 0.71 (m, 2H)

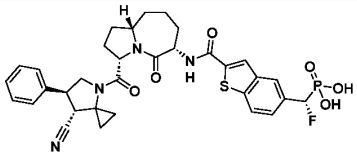
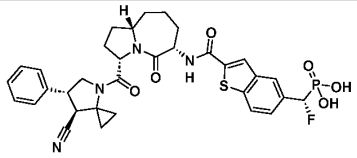
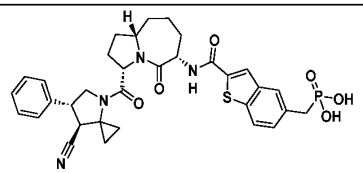
907	(fluoro(2-(((3S,6S,9aS)-5-oxo-3-(6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		641.3	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.80 – 8.70 (m, 1H), 8.64 – 8.40 (m, 2H), 8.26 – 8.13 (m, 1H), 8.07 – 7.91 (m, 2H), 7.88 – 7.76 (m, 1H), 7.57 – 7.47 (m, 1H), 7.42 – 7.30 (m, 1H), 5.79 (dd, J = 44.0, 7.6 Hz, 1H), 4.67 – 4.62 (m, 1H), 4.36 – 4.28 (m, 1H), 4.10 – 3.94 (m, 2H), 3.76 – 3.58 (m, 2H), 2.41 – 1.50 (m, 14H), 0.56 – 0.40 (m, 2H)
908	((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		655.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.93 – 8.75 (m, 1H), 8.61 – 8.53 (m, 1H), 8.47 – 8.40 (m, 1H), 8.26 (s, 1H), 8.07 – 7.91 (m, 2H), 7.84 – 7.76 (m, 1H), 7.56 – 7.47 (m, 1H), 7.43 – 7.30 (m, 1H), 5.89 – 5.70 (m, 1H), 5.00 – 4.88 (m, 1H), 4.57 – 4.49 (m, 1H), 4.25 – 4.12 (m, 1H), 3.85 – 3.77 (m, 1H), 3.62 – 3.53 (m, 1H), 2.34 – 1.45 (m, 17H), 0.55 – 0.39 (m, 2H)
909	((S)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((S)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		655.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.83 (d, J = 7.3 Hz, 1H), 8.57 (d, J = 1.9 Hz, 1H), 8.45 (dd, J = 4.7, 1.4 Hz, 1H), 8.27 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.97 (s, 1H), 7.85 – 7.77 (m, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.37 (dd, J = 7.9, 4.8 Hz, 1H), 5.92 – 5.69 (m, 1H), 5.02 – 4.87 (m, 1H), 4.54 (t, J = 8.4 Hz, 1H), 4.45

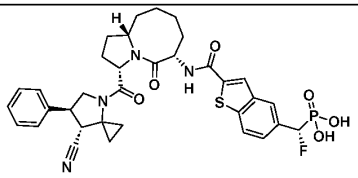
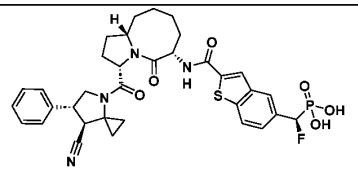
				(t, J = 8.6 Hz, 1H), 4.27 – 4.18 (m, 1H), 3.66 – 3.59 (m, 1H), 3.58 – 3.48 (m, 1H), 2.37 – 2.27 (m, 1H), 2.24 – 2.15 (m, 1H), 2.13 – 1.40 (m, 14H), 0.56 – 0.41 (m, 2H)
910	((S)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		655.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.83 – 8.22 (m, 3H), 8.26 (s, 1H), 8.03 – 7.93 (m, 2H), 7.84 – 7.77 (m, 1H), 7.54 – 7.30 (m, 2H), 5.87 – 5.72 (m, 1H), 4.98 – 4.91 (m, 1H), 4.54 – 4.49 (m, 1H), 4.26 – 4.12 (m, 1H), 3.84 – 3.79 (m, 1H), 3.63 – 3.53 (m, 1H), 2.34 – 2.09 (m, 3H), 2.06 – 1.48 (m, 14H), 0.55 – 0.38 (m, 2H)
911	((R)-fluoro(2-(((3S,6S,10aS)-5-oxo-3-((S)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		655.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.83 (d, J = 7.3 Hz, 1H), 8.59 (d, J = 2.0 Hz, 1H), 8.48 (dd, J = 4.8, 1.5 Hz, 1H), 8.28 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.99 – 7.94 (m, 1H), 7.90 – 7.81 (m, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.41 (dd, J = 7.8, 4.8 Hz, 1H), 5.83 (dd, J = 44.3, 8.0 Hz, 1H), 5.01 – 4.89 (m, 1H), 4.57 – 4.50 (m, 1H), 4.49 – 4.42 (m, 1H), 4.27 – 4.20 (m, 1H), 3.67 – 3.59 (m, 1H), 3.58 – 3.50 (m, 1H), 2.37 – 2.27 (m, 1H), 2.25 – 2.15 (m, 1H), 2.13 – 1.43 (m, 14H), 0.57 – 0.42 (m, 2H)

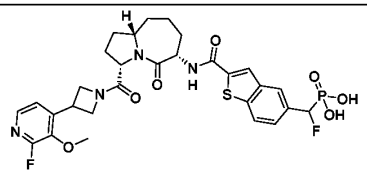
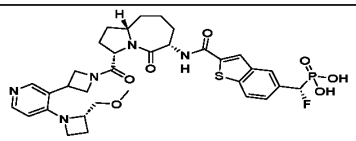
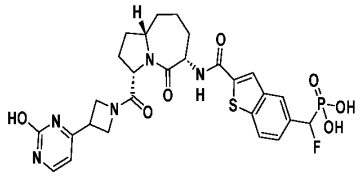
912	(fluoro(2-(((3S,6S,10aS)-5-oxo-3-(6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		655.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 – 8.79 (m, 1H), 8.69 – 8.60 (m, 1H), 8.58 – 8.49 (m, 1H), 8.32 – 8.24 (m, 1H), 8.09 – 7.94 (m, 3H), 7.60 – 7.47 (m, 2H), 5.92 – 5.76 (m, 1H), 5.00 – 4.87 (m, 1H), 4.58 – 4.42 (m, 2H), 4.26 – 4.18 (m, 1H), 3.67 – 3.60 (m, 2H), 2.35 – 2.30 (m, 1H), 2.24 – 2.17 (m, 1H), 2.11 – 2.05 (m, 1H), 2.04 – 1.96 (m, 2H), 1.94 – 1.73 (m, 6H), 1.70 – 1.46 (m, 5H), 0.58 – 0.41 (m, 2H)
913	(fluoro(2-(((3S,6S,10aS)-3-(3-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		660.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 – 8.20 (m, 2H), 8.15 – 7.41 (m, 4H), 6.91 – 6.62 (m, 1H), 6.00 – 5.66 (m, 1H), 5.01 – 4.88 (m, 1H), 4.61 – 4.49 (m, 1H), 4.34 – 4.20 (m, 1H), 3.98 – 3.88 (m, 1H), 3.76 – 3.68 (m, 1H), 3.63 – 3.58 (m, 3H), 3.53 – 3.46 (m, 1H), 3.35 – 3.28 (m, 1H), 3.24 – 3.11 (m, 1H), 2.40 – 1.45 (m, 14H)
914	(fluoro(2-(((3S,6S,10aS)-3-(3-hydroxy-3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		675.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 – 8.66 (m, 1H), 8.30 – 8.19 (m, 1H), 8.07 – 7.87 (m, 2H), 7.66 – 7.45 (m, 2H), 6.55 – 6.43 (m, 1H), 6.36 – 6.22 (m, 1H), 5.87 – 5.69 (m, 1H), 5.68 – 5.39 (m, 1H), 4.99 – 4.89 (m, 1H), 4.65 – 4.45 (m, 1H), 4.31 – 4.22 (m, 1H), 4.03 – 3.97 (m, 1H), 3.86 –

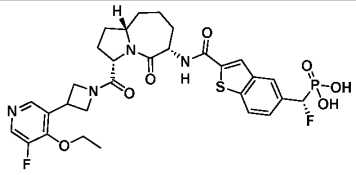
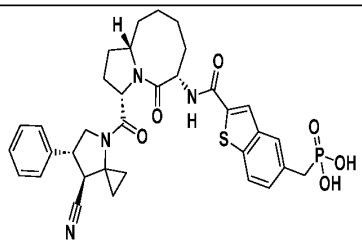
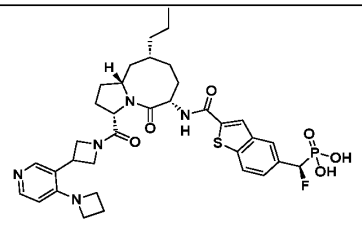
				3.81 (m, 1H), 3.74 – 3.69 (m, 1H), 3.59 – 3.54 (m, 1H), 3.39 – 3.34 (m, 3H), 2.28 – 1.71 (m, 11H), 1.69 – 1.46 (m, 3H)
915	((R)-(2-(((3S,6S,9aS)-3-(5,7-dioxo-6-(pyridin-3-yl)-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		670.1	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.81 – 8.61 (m, 3H), 8.22 (s, 1H), 8.07 – 7.92 (m, 3H), 7.66 – 7.49 (m, 2H), 5.92 – 5.74 (m, 1H), 5.53 – 5.48 (m, 1H), 4.67 – 4.60 (m, 1H), 4.07 – 3.99 (m, 1H), 2.33 – 1.55 (m, 12H), 1.44 – 1.34 (m, 2H)
916	((R)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		665.3	^{1}H NMR (400 MHz, DMSO) δ 8.77 (d, J = 7.6 Hz, 1H), 8.24 (s, 1H), 8.07 – 7.94 (m, 2H), 7.56 – 7.46 (m, 3H), 7.43 – 7.27 (m, 3H), 5.83 (dd, J = 44.3, 8.0 Hz, 1H), 4.65 – 4.59 (m, 2H), 4.17 – 4.10 (m, 1H), 3.99 – 3.90 (m, 2H), 3.86 – 3.76 (m, 2H), 2.26 – 2.01 (m, 3H), 2.00 – 1.91 (m, 1H), 1.90 – 1.60 (m, 8H), 0.89 – 0.57 (m, 2H)
917	((S)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-((R)-6-(pyridin-3-yl)-4-azaspiro[2.4]heptane-4-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		641.2	^{1}H NMR (400 MHz, DMSO) δ 8.76 (d, J = 7.5 Hz, 1H), 8.58 (s, 1H), 8.44 (d, J = 4.4 Hz, 1H), 8.24 (s, 1H), 8.04 – 7.93 (m, 2H), 7.85 – 7.76 (m, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.39 – 7.31 (m, 1H), 5.88 – 5.67 (m, 1H), 4.65 – 4.59 (m, 2H), 4.12 – 4.07 (m, 1H), 3.98 – 3.93 (m, 1H), 3.75 – 3.70 (m, 1H), 3.61 – 3.56 (m,

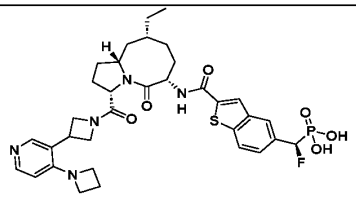
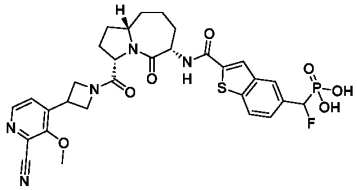
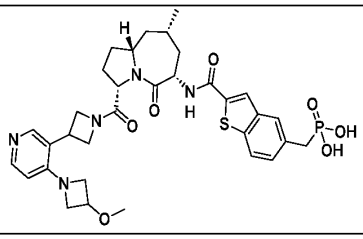
				1H), 2.24 – 1.55 (m, 14H), 0.57 – 0.35 (m, 2H)
918	((2-(((3S,6S,9aS)-3-(3-(2-cyanopyridin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		626.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.66 (dd, J = 15.7, 5.1 Hz, 1H), 8.14 - 8.06 (m, 2H), 8.05 (br. s., 1H), 7.98 - 7.93 (m, 1H), 7.80 - 7.68 (m, 1H), 7.60 (d, J = 8.6 Hz, 1H), 5.91 - 5.74 (m, 1H), 4.99 - 4.90 (m, 1H), 4.78 - 4.68 (m, 1H), 4.64 - 4.47 (m, 2H), 4.46 - 4.29 (m, 1H), 4.13 - 3.97 (m, 3H), 2.39 - 2.25 (m, 1H), 2.20 - 2.05 (m, 2H), 2.03 - 1.77 (m, 7H)
919	((R)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		665.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 8.06 - 8.02 (m, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.48 - 7.37 (m, 4H), 7.36 - 7.30 (m, 1H), 5.82 (dd, *J* = 44.7, 7.6 Hz, 1H), 4.77 - 4.69 (m, 2H), 4.49 - 4.42 (m, 1H), 4.08 - 3.97 (m, 1H), 3.89 - 3.71 (m, 3H), 2.39 - 2.23 (m, 2H), 2.17 - 1.76 (m, 10H), 1.04 - 0.96 (m, 1H), 0.79 - 0.71 (m, 1H)
920	((S)-(2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		665.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 8.05 - 8.02 (m, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.48 - 7.37 (m, 4H), 7.36 - 7.30 (m, 1H), 5.82 (dd, *J* = 44.7, 8.1 Hz, 1H), 4.78 - 4.68 (m, 2H), 4.50 - 4.39 (m, 1H), 4.08 - 3.96 (m,

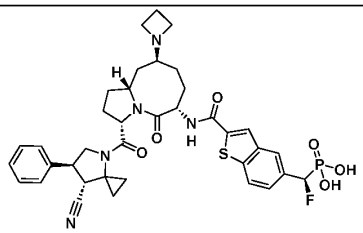
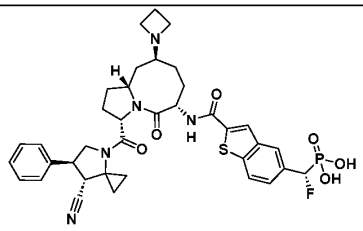
	yl)fluoromethyl)phosphonic acid			1H), 3.89 - 3.71 (m, 3H), 2.38 - 2.22 (m, 2H), 2.18 - 1.73 (m, 10H), 1.07 - 0.96 (m, 1H), 0.80 - 0.69 (m, 1H)
921	((S)-(2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		665.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.10 - 8.01 (m, 2H), 7.97 - 7.91 (m, 1H), 7.63 - 7.57 (m, 1H), 7.51 - 7.45 (m, 2H), 7.43 - 7.28 (m, 3H), 5.89 - 5.71 (m, 1H), 4.76 - 4.64 (m, 2H), 4.19 - 4.11 (m, 1H), 4.10 - 4.00 (m, 2H), 3.84 - 3.68 (m, 2H), 2.38 - 2.24 (m, 2H), 2.24 - 2.13 (m, 1H), 2.12 - 1.99 (m, 2H), 1.98 - 1.89 (m, 2H), 1.89 - 1.77 (m, 4H), 1.41 - 1.33 (m, 1H), 1.04 - 0.94 (m, 1H), 0.76 - 0.64 (m, 1H).
922	((2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		647.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.01 (s, 1H), 7.90 - 7.80 (m, 2H), 7.53 - 7.28 (m, 6H), 4.76 - 4.64 (m, 2H), 4.19 - 4.11 (m, 1H), 4.10 - 3.99 (m, 2H), 3.85 - 3.69 (m, 2H), 3.29 - 3.20 (m, 2H), 2.39 - 2.24 (m, 2H), 2.24 - 2.13 (m, 1H), 2.12 - 1.75 (m, 9H), 1.05 - 0.94 (m, 1H), 0.76 - 0.64 (m, 1H).
923	((S)-(2-(((3S,6S,10aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo		679.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (s, 1H), 8.04 - 7.97 (m, 1H), 7.92 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 8.6 Hz, 1H), 7.44 - 7.28 (m, 5H), 5.81 (dd, J = 44.7, 7.3 Hz, 1H), 5.07 - 4.97 (m,

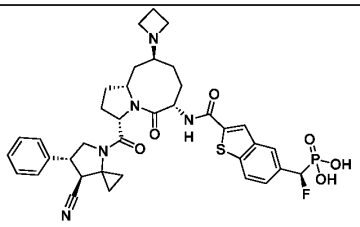
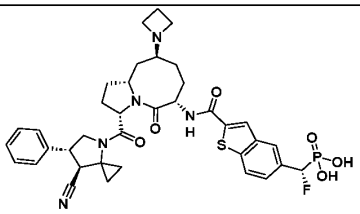
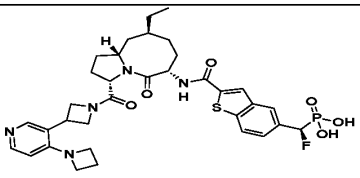
	[b]thiophen-5-yl)fluoromethyl)phosphonic acid			1H), 4.68 - 4.52 (m, 2H), 4.45 - 4.32 (m, 1H), 3.86 - 3.69 (m, 3H), 2.37 - 2.13 (m, 3H), 2.05 - 1.78 (m, 9H), 1.69 - 1.54 (m, 2H), 1.04 - 0.94 (m, 1H), 0.77 - 0.68 (m, 1H)
924	((R)-(2-(((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		679.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (s, 1H), 8.02 (s, 1H), 7.96 - 7.88 (m, 1H), 7.62 - 7.56 (m, 1H), 7.54 - 7.26 (m, 5H), 5.86 (d, *J* = 5.9 Hz, 0.5H), 5.75 (d, *J* = 5.9 Hz, 0.5H), 5.10 - 4.95 (m, 1H), 4.64 - 4.54 (m, 1H), 4.47 - 4.35 (m, 1H), 4.22 - 4.07 (m, 2H), 3.85 - 3.65 (m, 2H), 2.43 - 2.29 (m, 2H), 2.28 - 2.15 (m, 1H), 2.12 - 1.89 (m, 6H), 1.87 - 1.74 (m, 3H), 1.72 - 1.55 (m, 2H), 1.05 - 0.91 (m, 1H), 0.76 - 0.61 (m, 1H).
925	(fluoro(2-(((3S,6S,9aS)-3-(3-(2-fluoro-3-methoxypyridin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		649.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (d, *J* = 10.5 Hz, 1H), 7.88 - 7.85 (m, 1H), 7.70 - 7.61 (m, 1H), 7.44 (d, *J* = 5.4 Hz, 1H), 7.33 (d, *J* = 5.1 Hz, 1H), 5.74 - 5.55 (m, 1H), 4.95 - 4.92 (m, 1H), 4.77 - 4.71 (m, 1H), 4.67 (s, 1H), 4.61 - 4.56 (m, 1H), 4.51 - 4.45 (m, 1H), 4.42 - 4.31 (m, 1H), 4.30 - 4.22 (m, 1H), 4.13 - 4.04 (m, 2H), 3.96 (d, *J* = 2.7 Hz, 3H), 2.36 - 2.26 (m, 1H), 2.18 - 1.79 (m, 9H)

926	((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-((S)-2-(methoxymethyl)azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		700.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (s, 1H), 8.11 - 8.03 (m, 2H), 7.84 - 7.78 (m, 1H), 7.75 - 7.68 (m, 1H), 6.76 (dd, *J* = 5.7, 4.0 Hz, 1H), 5.68 - 5.54 (m, 1H), 4.76 - 4.71 (m, 1H), 4.67 - 4.55 (m, 2H), 4.52 - 4.44 (m, 2H), 4.34 - 4.13 (m, 3H), 4.10 - 4.02 (m, 2H), 3.74 - 3.66 (m, 1H), 3.59 (t, *J* = 4.6 Hz, 2H), 3.36 - 3.33 (m, 3H), 2.42 - 2.16 (m, 4H), 2.16 - 1.76 (m, 9H)
927	(fluoro(2-(((3S,6S,9aS)-3-(3-(2-hydroxypyrimidin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		618.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.17 - 7.87 (m, 4H), 7.72 - 7.54 (m, 1H), 6.87 - 6.51 (m, 1H), 5.87 - 5.61 (m, 1H), 4.70 - 4.61 (m, 0.5H), 4.60 - 4.51 (m, 1H), 4.50 - 4.30 (m, 1H), 4.27 - 4.19 (m, 0.5H), 4.17 - 4.04 (m, 1.5H), 3.77 - 3.64 (m, 0.5H), 3.24 - 3.11 (m, 1H), 2.77 - 2.65 (m, 1H), 2.40 - 2.26 (m, 1H), 2.21 - 2.05 (m, 1H), 2.04 - 1.91 (m, 1H), 1.88 - 1.78 (m, 2H), 1.62 - 1.41 (m, 1H), 1.41 - 1.34 (m, 4H), 1.32 - 1.17 (m, 2H)
928	((S)-(2-(((3S,6S,9aS)-3-(3-(4-ethoxy-5-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		663.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.68 - 8.53 (m, 1H), 8.17 - 8.04 (m, 3H), 7.89 - 7.82 (m, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 5.75 - 5.54 (m, 1H), 4.77 - 4.72 (m, 1H), 4.66 - 4.45 (m, 3H), 4.42 - 4.21 (m, 1H), 4.13 - 3.84 (m, 5H), 2.35 -

	yl)fluoromethyl)phosphonic acid			2.25 (m, 1H), 2.13 - 1.80 (m, 9H), 1.45 (t, *J* = 7.2 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 2H)
929	((2-(((3S,6S,10aS)-3-((6R,7S)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		661.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.03 (s, 1H), 7.89 - 7.76 (m, 2H), 7.53 - 7.25 (m, 6H), 5.05 - 4.95 (m, 1H), 4.62 - 4.54 (m, 1H), 4.45 - 4.34 (m, 1H), 4.21 - 4.04 (m, 2H), 3.82 - 3.72 (m, 1H), 3.71 - 3.64 (m, 1H), 3.28 - 3.18 (m, 2H), 2.44 - 2.29 (m, 2H), 2.27 - 2.14 (m, 1H), 2.11 - 1.88 (m, 6H), 1.87 - 1.73 (m, 3H), 1.70 - 1.55 (m, 2H), 1.02 - 0.92 (m, 1H), 0.75 - 0.61 (m, 1H)
930	((R)-(2-(((3S,6S,9R,10aR)-3-(3-(4-(azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxo-9-propyldecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		712.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 - 7.48 (m, 6H), 6.34 - 6.05 (m, 1H), 5.78 - 5.52 (m, 1H), 5.04 - 5.03 (m, 1H), 4.79 - 4.41 (m, 3H), 4.38 - 4.14 (m, 5H), 4.11 - 3.96 (m, 2H), 2.49 - 2.30 (m, 2H), 2.28 - 2.15 (m, 2H), 2.09 - 1.79 (m, 6H), 1.70 - 1.38 (m, 5H), 1.34 - 1.27 (m, 3H), 0.98 - 0.89 (m, 3H)
931	((R)-(2-(((3S,6S,9R,10aR)-3-(3-(4-(azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-9-ethyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		698.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.10 - 7.39 (m, 6H), 6.26 - 6.01 (m, 1H), 5.76 - 5.54 (m, 1H), 5.07 - 4.96 (m, 1H), 4.77 - 4.42 (m, 3H), 4.34 - 4.13 (m, 5H), 4.11 - 3.98 (m, 2H), 2.47 - 2.16 (m, 4H), 2.10 - 1.79 (m, 6H), 1.67 - 1.49 (m, 3H), 1.45 - 1.37

				(m, 2H), 1.34 - 1.28 (m, 1H), 0.99 - 0.94 (m, 3H)
932	((2-(((3S,6S,9aS)-3-(3-(2-cyano-3-methoxypyridin-4-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		656.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.49 - 8.33 (m, 1H), 8.10 - 8.00 (m, 2H), 7.98 - 7.90 (m, 1H), 7.85 - 7.67 (m, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 5.94 - 5.70 (m, 1H), 4.96 - 4.89 (m, 1H), 4.78 - 4.71 (m, 1H), 4.71 - 4.65 (m, 1H), 4.62 - 4.51 (m, 2H), 4.51 - 4.31 (m, 1H), 4.30 - 4.19 (m, 1H), 4.10 (d, *J* = 1.7 Hz, 3H), 4.08 - 4.03 (m, 1H), 2.38 - 2.25 (m, 1H), 2.20 - 2.05 (m, 2H), 2.04 - 1.75 (m, 7H)
933	((2-(((3S,6S,8R,9aR)-3-(3-(4-(3-methoxyazetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		682.4	^{1}H NMR (400 MHz, CD_3OD) δ 7.93 - 7.83 (m, 1H), 7.81 - 7.67 (m, 3H), 7.53 - 7.39 (m, 2H), 6.33 - 6.14 (m, 1H), 4.80 - 4.67 (m, 2H), 4.63 - 4.44 (m, 3H), 4.43 - 4.25 (m, 2H), 4.22 - 4.15 (m, 1H), 4.14 - 4.01 (m, 3H), 3.54 - 3.41 (m, 1H), 3.39 - 3.34 (m, 2H), 3.16 - 3.02 (m, 2H), 2.40 - 2.24 (m, 1H), 2.17 - 2.00 (m, 3H), 1.99 - 1.88 (m, 2H), 1.84 - 1.72 (m, 1H), 1.70 - 1.45 (m, 2H), 1.38 - 1.25 (m, 2H), 1.05 (t, *J* = 6.8 Hz, 3H)
934	((R)-(2-(((3S,6S,9S,10aR)-9-(azetidin-1-yl)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-		734.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (s, 1H), 7.98 - 7.92 (m, 2H), 7.78 - 7.76 (m, 1H), 7.41 - 7.26 (m, 5H), 5.81 - 5.62 (m, 1H), 4.55 - 4.37 (m,

	oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid			2H), 3.99 - 3.76 (m, 4H), 3.71 - 3.51 (m, 3H), 3.13 - 3.03 (m, 1H), 2.36 - 2.03 (m, 5H), 1.88 - 1.67 (m, 4H), 1.65 - 1.49 (m, 2H), 1.43 - 1.37 (m, 1H), 1.34 - 1.29 (m, 2H), 1.00 - 0.87 (m, 1H), 0.73 - 0.51 (m, 2H), 0.36 - 0.22 (m, 1H)
935	((S)-(2-(((3S,6S,9S,10aR)-9-(azetidin-1-yl)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		734.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.19 - 8.10 (m, 2H), 7.92 - 7.90 (m, 1H), 7.52 - 7.50 (m, 1H), 7.41 - 7.26 (m, 5H), 5.79 - 5.60 (m, 1H), 4.64 - 4.47 (m, 1H), 4.44 - 4.26 (m, 1H), 4.05 - 3.78 (m, 4H), 3.72 - 3.53 (m, 3H), 3.15 - 3.08 (m, 1H), 2.36 - 2.20 (m, 4H), 2.13 - 2.00 (m, 1H), 1.85 - 1.68 (m, 4H), 1.67 - 1.49 (m, 3H), 1.35 - 1.21 (m, 2H), 0.95 - 0.90 (m, 1H), 0.73 - 0.64 (m, 1H), 0.52 - 0.48 (m, 1H), 0.40 - 0.28 (m, 1H)
936	((R)-(2-(((3S,6S,9S,10aR)-9-(azetidin-1-yl)-3-((6R,7S)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		734.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.19 - 8.10 (m, 1H), 8.00 - 7.94 (m, 2H), 7.80 - 7.74 (m, 1H), 7.44 - 7.24 (m, 5H), 5.80 - 5.61 (m, 1H), 4.47 (t, J = 8.4 Hz, 1H), 4.11 - 3.96 (m, 3H), 3.88 - 3.78 (m, 1H), 3.76 - 3.60 (m, 4H), 3.18 - 3.12 (m, 1H), 2.43 - 2.25 (m, 4H), 2.16 - 2.06 (m, 1H), 1.88 - 1.82 (m, 1H), 1.79 - 1.69 (m, 3H), 1.65 - 1.55 (m, 2H), 1.46 -

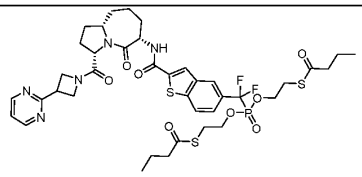
				1.38 (m, 1H), 1.35 - 1.28 (m, 2H), 0.97 - 0.90 (m, 1H), 0.72 - 0.53 (m, 2H), 0.43 - 0.33 (m, 1H)
937	((S)-(2-(((3S,6S,9S,10aR)-9-(azetidin-1-yl)-3-((6R,7S)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		734.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.22 - 8.11 (m, 2H), 7.92 - 7.90 (m, 1H), 7.53 - 7.51 (m, 1H), 7.45 - 7.24 (m, 5H), 5.79 - 5.58 (m, 1H), 4.48 - 4.43 (m, 1H), 4.11 - 3.96 (m, 3H), 3.85 - 3.75 (m, 1H), 3.75 - 3.52 (m, 4H), 3.14 - 3.04 (m, 1H), 2.41 - 2.18 (m, 4H), 2.15 - 2.03 (m, 1H), 1.88 - 1.53 (m, 6H), 1.47 - 1.43 (m, 1H), 1.35 - 1.28 (m, 2H), 0.96 - 0.91 (m, 1H), 0.69 - 0.48 (m, 2H), 0.42 - 0.32 (m, 1H)
938	((R)-(2-(((3S,6S,9S,10aR)-3-(3-(4-(azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-9-ethyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphonic acid		698.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.55 - 8.23 (m, 1H), 8.10 - 7.98 (m, 3H), 7.83 - 7.68 (m, 2H), 6.41 - 6.35 (m, 1H), 5.71 - 5.50 (m, 1H), 4.94 - 4.78 (m, 1H), 4.72 - 4.58 (m, 1H), 4.52 - 4.39 (m, 2H), 4.36 - 4.26 (m, 1H), 4.18 - 3.98 (m, 6H), 2.42 - 1.88 (m, 7H), 1.87 - 1.45 (m, 5H), 1.44 - 1.27 (m, 3H), 1.07 - 1.03 (m, 1H), 0.98 - 0.89 (m, 3H)
939	(fluoro(2-(((3S,6S,9aS)-3-(3-(4-isopropylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-		643.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.52 - 8.42 (m, 1H), 8.25 - 8.13 (m, 1H), 8.01 - 7.92 (m, 1H), 7.88 - 7.79 (m, 1H), 7.79 - 7.71 (m, 1H), 7.64 - 7.46 (m, 2H), 5.83 - 5.59

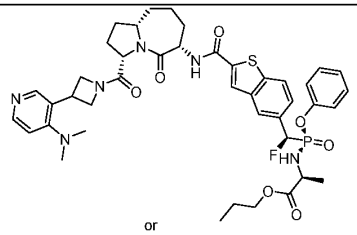
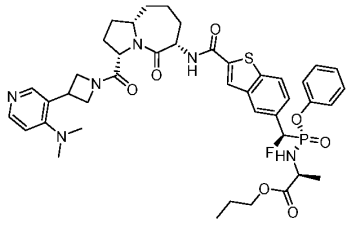
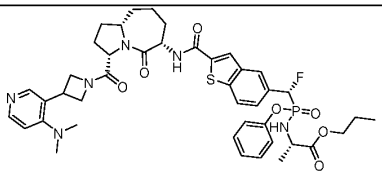
	yl)carbamoyl)benzo [b]thiophen-5-yl)methyl)phosphon ic acid			(m, 1H), 4.95 - 4.90 (m, 1H), 4.78 - 4.67 (m, 1H), 4.64 - 4.50 (m, 2H), 4.46 - 4.36 (m, 1H), 4.33 - 4.17 (m, 1H), 4.15 - 3.97 (m, 2H), 3.09 - 2.93 (m, 1H), 2.39 - 2.26 (m, 1H), 2.22 - 2.07 (m, 2H), 2.07 - 1.79 (m, 7H), 1.26 - 1.13 (m, 6H)

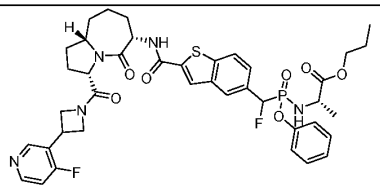
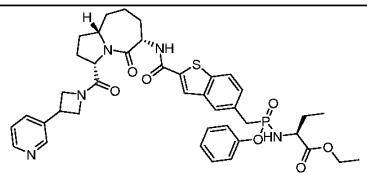
Compounds prepared according to General Scheme 2: Phosphonate Esters

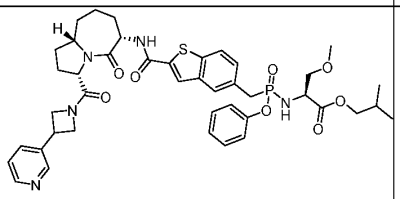
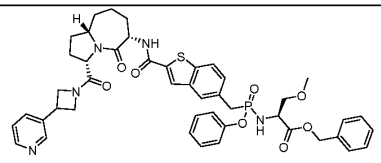
[001571] The following compounds in Table **110** were prepared according to the representative procedure described above for the synthesis of S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-hydroxy-2,2-dimethylpropanethioate) trifluoroacetate (199) utilizing the appropriate starting materials and modifications.

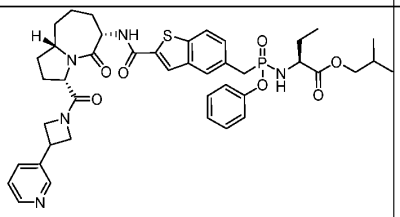
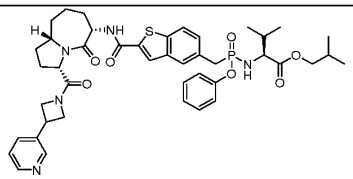
Table 110

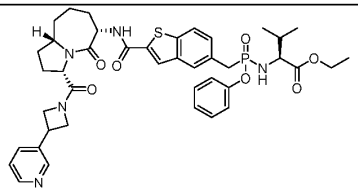
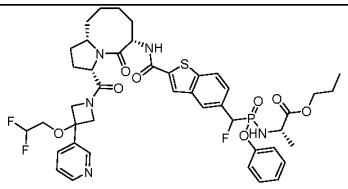
Compound	Name	Structure	LCMS $[M+H]^+$	NMR
940	S,S'-((((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyrimidin-2-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) dibutanethioate		880.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 - 8.73 (m, 2H), 8.18 - 8.09 (m, 1H), 8.03 - 7.95 (m, 1H), 7.92 - 7.84 (m, 1H), 7.79 - 7.68 (m, 2H), 7.28 - 7.22 (m, 1H), 4.97 - 4.84 (m, 1H), 4.73 - 4.55 (m, 4H), 4.32 - 4.18 (m, 6H), 3.98 - 3.91 (m, 1H), 3.19 - 3.02 (m, 4H), 2.36 - 2.28 (m, 5H), 2.23 (d, J = 8.0 Hz, 1H), 2.06 (d, J = 4.0 Hz, 4H), 2.01 - 1.92 (m, 2H), 1.88 - 1.72 (m, 3H), 1.66 (d, J = 7.2 Hz, 3H), 0.99 - 0.93 (m, 6H)

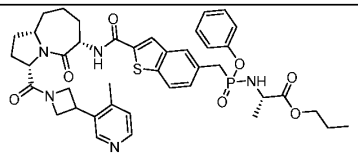
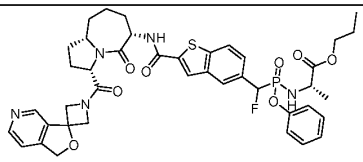
941	propyl ((R)-((R)-(2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate or propyl ((S)-((R)-(2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 or  HPLC peak 2 was used for biological testing	833.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 - 8.53 (m, 1H), 8.27 (d, J = 1.2 Hz, 1H), 8.12 - 7.79 (m, 3H), 7.68 - 7.32 (m, 2H), 7.30 - 7.27 (m, 1H), 7.27 - 7.15 (m, 2H), 7.14 - 7.04 (m, 2H), 6.92 - 6.79 (m, 1H), 6.08 - 5.85 (m, 1H), 5.09 - 4.89 (m, 1H), 4.85 - 4.59 (m, 2H), 4.57 - 4.32 (m, 2H), 4.20 - 4.10 (m, 1H), 4.09 - 3.91 (m, 5H), 3.60 (s, 1H), 3.16 - 2.98 (m, 6H), 2.27 (d, J = 6.0 Hz, 1H), 2.19 (d, J = 14.0 Hz, 1H), 2.12 - 1.95 (m, 5H), 1.89 - 1.82 (m, 2H), 1.72 - 1.68 (m, 1H), 1.65 - 1.55 (m, 2H), 1.33 - 1.25 (m, 2H), 1.19 - 1.10 (m, 1H), 0.90 (q, J = 8.0 Hz, 3H)
942	propyl (((R)-(2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		833.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 - 8.54 (m, 1H), 8.40 - 8.22 (m, 2H), 8.13 - 7.78 (m, 3H), 7.65 - 7.51 (m, 1H), 7.29 (s, 1H), 7.25 (s, 1H), 7.16 - 7.02 (m, 3H), 6.95 - 6.79 (m, 1H), 6.07 - 5.88 (m, 1H), 5.09 - 4.95 (m, 1H), 4.85 - 4.61 (m, 2H), 4.55 - 4.32 (m, 2H), 4.20 - 4.11 (m, 1H), 4.09 - 3.92 (m, 5H), 3.71 - 3.53 (m, 1H), 3.13 (s, 3H), 3.06 (s, 3H),

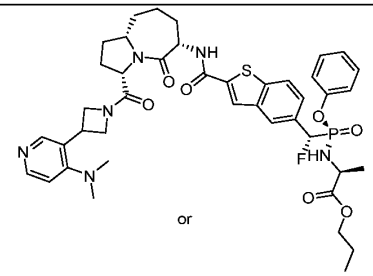
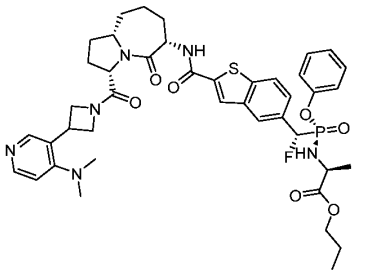
				2.31 - 2.27 (m, 1H), 2.23 - 2.13 (m, 2H), 2.10 - 2.02 (m, 3H), 2.00 - 1.91 (m, 2H), 1.88 - 1.82 (m, 2H), 1.65 - 1.56 (m, 2H), 1.29 (t, J = 7.6 Hz, 3H), 0.90 (q, J = 7.2 Hz, 3H)
943	propyl ((fluoro(2-(((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		808.7	^{1}H NMR (400 MHz, CD_3OD) δ 0.80 - 0.94 (m, 3H) 1.03 - 1.10 (m, 1H) 1.16 - 1.27 (m, 3H) 1.46 - 1.60 (m, 2H) 1.78 - 1.92 (m, 4H) 1.93 - 2.00 (m, 2H) 2.06 - 2.19 (m, 2H) 2.26 - 2.36 (m, 1H) 3.72 - 3.94 (m, 2H) 3.95 - 3.99 (m, 1H) 4.03 - 4.25 (m, 4H) 4.38 - 4.52 (m, 2H) 4.55 - 4.60 (m, 1H) 4.69 - 4.80 (m, 3H) 5.98 - 6.21 (m, 1H) 7.12 - 7.39 (m, 6H) 7.55 - 7.69 (m, 1H) 7.94 - 8.03 (m, 1H) 8.07 - 8.13 (m, 2H) 8.44 - 8.56 (m, 1H) 8.58 - 8.79 (m, 1H)
944	ethyl (2S)-2-((((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)amino)butanoate		772.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50–8.52 (m, 1 H) 8.48 (s, 1 H) 7.83 (d, J = 41 Hz, 1 H) 7.62-7.73 (m, 4 H) 7.31-7.35 (m, 1 H) 7.20 (s, 3 H) 7.02-7.17 (m, 3H) 4.91 (t, J = 8.8 Hz, 1 H) 4.52-4.60 (m, 4 H) 4.27 (t, J = 4.0 Hz, 1 H) 3.92-3.97 (m, 1 H) 3.79-3.85 (m, 5 H) 3.60-3.81 (m, 1 H) 3.31-3.39 (m, 2 H) 3.10-3.23 (m, 1 H) 2.10-2.17 (m, 3 H) 1.87-

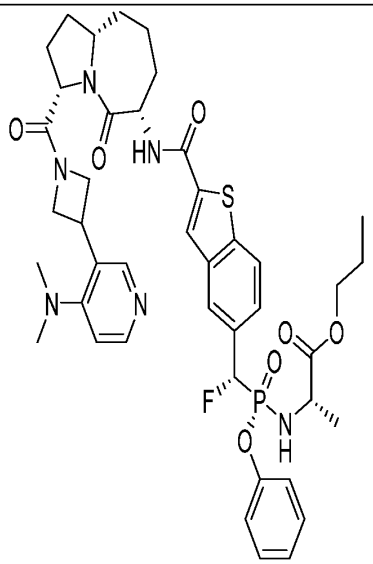
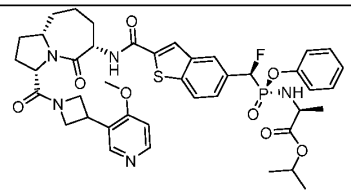
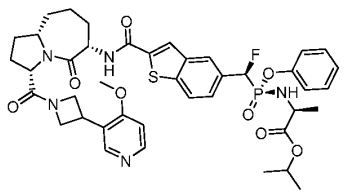
				1.94 (m, 2H) 1.82-1.84 (m, 3 H) 1.16-1.44 (m, 3 H) 1.04-1.14 (m, 3 H) 0.64-0.66 (m, 1 H) 0.53-0.63 (m, 1 H)
945	isobutyl O-methyl-N-(((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-serinate		816.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1 H) 8.55-8.56 (m, 1 H) 7.83-7.95 (m, 1 H) 7.79-7.82 (m, 2 H) 7.63-7.77 (m, 2 H) 7.43-7.61 (m, 2 H) 7.28-7.43 (m, 1 H) 7.10-7.17 (m, 3 H) 5.01-5.03 (m, 1 H) 4.64-4.69 (m, 1 H) 4.55-4.63 (m, 1 H) 4.51-4.53 (m, 1 H) 4.49-4.50 (m, 1 H) 4.20-4.22(m, 1 H) 4.01-4.03 (m, 1 H) 3.95-3.97 (m, 3 H) 3.84-3.94 (m, 2H) 3.77-3.79 (m, 1 H) 3.48-3.54 (m, 3 H) 3.20-3.43 (m, 2 H) 3.07-3.20 (m, 1 H) 2.07-2.08 (m, 2 H) 2.05-2.07 (m, 4 H) 1.95-1.97 (m, 2 H) 1.92-1.94 (m, 1 H) 1.77-1.85 (m, 3 H) 0.89-0.91 (m, 3 H) 0.84-0.88 (m, 3 H)
946	benzyl O-methyl-N-(((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy		850.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.7.4 (s, 1 H) 8.58-8.59 (m, 2 H) 8.04-8.05 (m, 1 H) 7.91-8.03 (m, 3 H) 7.47-7.49 (m, 1 H) 7.29-7.32 (m, 7 H) 7.14-7.28 (m, 3H) 4.89-5.04 (m, 3 H) 4.77-4.86 (m, 2 H) 4.73-4.76 (m, 2 H) 4.53-4.55 (m, 1 H) 4.05-4.09 (m, 5 H) 3.51-3.52 (m, 3 H)

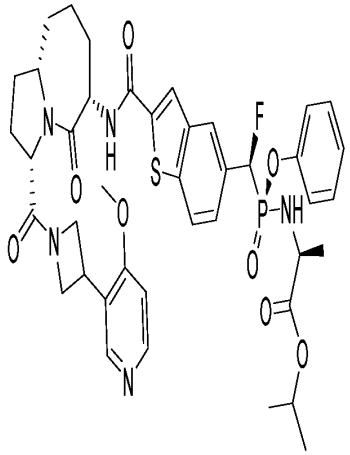
	)phosphoryl)-L-serinate			3.30-3.31 (m, 1 H) 3.11-3.12 (m, 4 H) 2.01-2.14 (m, 1 H) 1.83-1.99 (m, 6 H)
947	isobutyl (2S)-2-((((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)amino)butanoate		800.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.55–8.57 (m, 1 H) 8.47-8.54 (m, 1 H) 8.07-8.09 (m, 1 H) 7.89-8.06 (m, 3 H) 7.49-7.51 (m, 2 H) 7.29-7.33 (m, 2 H) 7.15-7.19 (m, 3 H) 4.78-4.87 (m, 2 H) 4.60-4.76 (m, 2 H) 4.07-4.59 (m, 1 H) 4.03-4.07 (m, 3 H) 3.3.73-4.06 (m, 3 H) 3.51-3.72 (m, 2 H) 1.84-2.14 (m, 11 H) 1.46-1.48 (m, 2 H) 0.81-0.87 (m, 7 H) 0.68-0.69 (m, 3 H)
948	isobutyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-valinate		814.4	^{1}H NMR (400 MHz, CD_3OD) δ8.51–8.62 (m, 1 H) 8.47-8.49 (m, 1 H) 8.24 (d, J = 8.0 Hz, 1 H) 8.04-8.21 (m, 1 H) 7.87-7.89 (m, 2 H) 7.48-7.52 (m, 2 H) 7.27-7.48 (m, 2H) 7.12-7.21 (m, 3 H) 4.77-4.83 (m, 3 H) 4.56-4.58 (m, 2 H) 4.46-4.49 (m, 1 H) 4.04-4.08 (m, 3 H) 3.58-3.69 (m, 2 H) 3.52-3.57 (m, 3 H) 2.14-2.32 (m, 1 H) 1.78-2.02 (m, 9 H) 0.86-0.87 (m, 3 H) 0.84-0.85 (m, 3 H) 0.67-0.80 (m, 6 H)

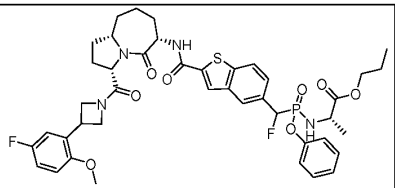
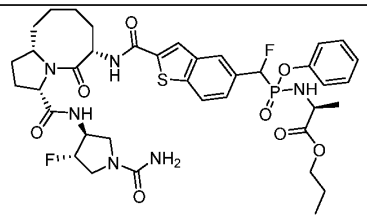
949	ethyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-valinate		786.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.63 (d, J = 10.4 Hz, 1 H) 8.49-8.61 (m, 1 H) 8.05-8.26 (m, 1 H) 8.04-8.05 (m, 1 H) 7.88-7.90 (m, 2 H) 7.51-7.54 (m, 1 H) 7.49-7.56 (m, 1 H) 7.30-7.32 (m, 2 H) 7.13-7.19 (m, 3 H) 4.75-4.77 (m, 2 H) 4.56-4.59 (m, 2 H) 4.07-4.43 (m, 1 H) 4.02-4.05 (m, 3 H) 3.95-3.97 (m, 2 H) 3.58-3.95 (m, 1 H) 3.56-3.58 (m, 1 H) 3.53-3.56 (m, 1 H) 2.02-2.14 (m, 1 H) 1.82-2.01 (m, 10 H) 1.08-1.15 (m, 3 H) 0.66-0.73 (m, 6 H)
950	propyl (((2-(((3S,6S,10aS)-3-(3-(2,2-difluoroethoxy)-3-(pyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		884.6	^{1}H NMR (400 MHz, CD_3OD) δ 8.89 - 8.78 (m, 1H), 8.72 - 8.61 (m, 1H), 8.34 - 8.22 (m, 1H), 8.16 - 8.03 (m, 2H), 8.02 - 7.90 (m, 1H), 7.79 - 7.58 (m, 2H), 7.51 - 7.27 (m, 3H), 7.22 - 7.16 (m, 2H), 6.21 - 6.05 (m, 1H), 6.03 - 5.80 (m, 1H), 5.02 - 4.98 (m, 1H), 4.68 - 4.61 (m, 1H), 4.58 - 4.17 (m, 5H), 4.00 - 3.87 (m, 2H), 3.87 - 3.75 (m, 1H), 3.67 - 3.55 (m, 2H), 2.35 - 2.19 (m, 2H), 2.15 - 2.05 (m, 1H), 2.05 - 1.87 (m, 6H), 1.81 - 1.72 (m, 1H), 1.73 - 1.61 (m, 2H), 1.59 - 1.47 (m, 2H), 1.33 - 1.17 (m, 2H), 1.07 -

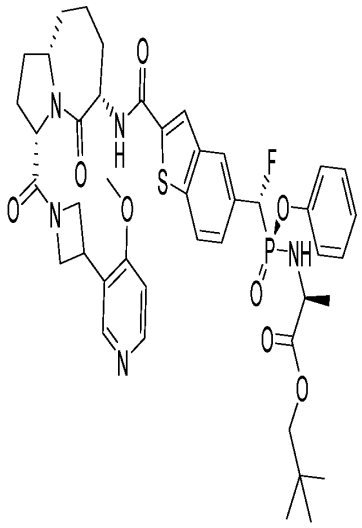
				1.05 (m, 1H), 0.92 - 0.80 (m, 3H)
951	propyl (((2-(((3S,6S,9aS)-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		786.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 - 8.89 (m, 1H), 8.71 - 8.56 (m, 1H), 8.16 - 7.92 (m, 1H), 7.86 - 7.77 (m, 2H), 7.65 - 7.53 (m, 1H), 7.48 - 7.35 (m, 1H), 7.34 - 7.27 (m, 2H), 7.18 - 7.08 (m, 3H), 5.13 - 5.01 (m, 1H), 4.84 - 4.77 (m, 1H), 4.75 - 4.69 (m, 2H), 4.50 - 4.39 (m, 2H), 4.29 - 4.06 (m, 2H), 4.05 - 3.90 (m, 5H), 3.51 - 3.41 (m, 2H), 2.50 (s, 3H), 2.35 - 2.24 (m, 1H), 2.24 - 2.14 (m, 1H), 2.11 - 1.98 (m, 4H), 1.95 - 1.75 (m, 4H), 1.62 - 1.50 (m, 2H), 1.21 - 1.12 (m, 3H), 0.91 - 0.83 (m, 3H)
952	propyl ((fluoro(2-(((3S,6S,9aS)-5-oxo-3-(1'H-spiro[azetidine-3,3'-furo[3,4-c]pyridine]-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		818.0	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 - 8.77 (m, 2H), 8.72 - 8.52 (m, 1H), 8.39 - 8.27 (m, 1H), 8.20 - 8.03 (m, 2H), 7.73 - 7.10 (m, 7H), 6.30 - 6.05 (m, 2H), 5.33 - 5.09 (m, 2H), 4.84 - 4.64 (m, 2H), 4.59 - 4.43 (m, 2H), 4.28 - 4.15 (m, 2H), 4.05 - 3.99 (m, 1H), 3.96 - 3.88 (m, 2H), 3.80 - 3.75 (m, 1H), 2.26 - 2.15 (m, 1H), 2.12 - 1.92 (m, 3H), 1.91 - 1.65 (m, 6H), 1.56 - 1.38 (m, 2H), 1.31 - 1.10 (m, 3H), 0.98 - 0.76 (m, 3H)

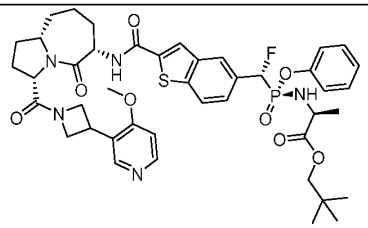
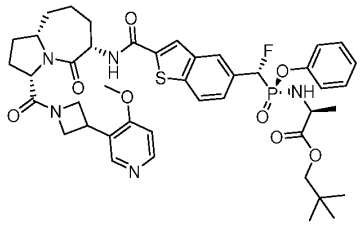
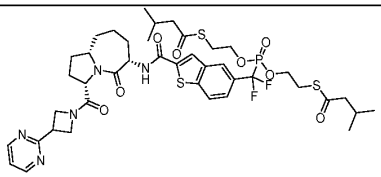
953	propyl (((S)-(2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate or propyl (((S)-(2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 or  CFTE-27A, SFC Peak 1 was used for synthesis and biological testing	833.7	^{1}H NMR (400 MHz, CD_3OD) δ 8.40 - 8.33 (m, 1H), 8.17 - 8.04 (m, 3H), 8.00 - 7.93 (m, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.40 - 7.30 (m, 2H), 7.24 - 7.15 (m, 3H), 7.14 - 7.08 (m, 1H), 6.20 - 6.03 (m, 1H), 4.77 - 4.69 (m, 2H), 4.58 - 4.50 (m, 2H), 4.49 - 4.40 (m, 1H), 4.37 - 4.30 (m, 1H), 4.13 - 4.02 (m, 2H), 4.02 - 3.83 (m, 3H), 3.16 (s, 6H), 2.35 – 2.28 (m, 1H), 2.19 - 2.06 (m, 2H), 2.06 - 1.98 (m, 2H), 1.98 - 1.90 (m, 2H), 1.88 (s, 1H), 1.87 - 1.79 (m, 2H), 1.59 – 1.50 (m, 2H), 1.23 (d, J = 7.2 Hz, 3H), 0.92 - 0.83 (m, 3H)

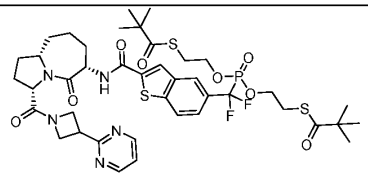
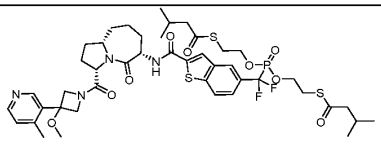
954	propyl (((S)-(2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate or propyl (((S)-(2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate	 CFTE-27B, SFC Peak 2 was used for synthesis and biological testing	833.7	^{1}H NMR (400 MHz, CD_3OD) δ 8.42 – 8.31 (m, 1H), 8.18 – 8.05 (m, 3H), 8.03 – 7.95 (m, 1H), 7.69 – 7.60 (m, 1H), 7.41 – 7.30 (m, 2H), 7.25 – 7.15 (m, 3H), 7.14 – 7.08 (m, 1H), 6.20 – 5.99 (m, 1H), 4.78 – 4.68 (m, 2H), 4.59 – 4.50 (m, 2H), 4.49 – 4.40 (m, 1H), 4.36 – 4.29 (m, 1H), 4.14 – 4.02 (m, 2H), 3.99 – 3.95 (m, 2H), 3.86 – 3.76 (m, 1H), 3.16 (s, 6H), 2.35 – 2.28 (m, 1H), 2.08 (d, J = 2.4 Hz, 2H), 2.03 – 1.98 (m, 2H), 1.98 – 1.90 (m, 2H), 1.88 (s, 1H), 1.86 – 1.79 (m, 2H), 1.63 – 1.50 (m, 2H), 1.14 – 1.02 (m, 3H), 0.90 – 0.84 (m, 3H)
955	isopropyl ((S)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or	 or 	820.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 2H), 8.13 - 8.02 (m, 1H), 7.98 (s, 1H), 7.88 - 7.63 (m, 2H), 7.55 (t, J = 7.6 Hz, 1H), 7.38 - 7.32 (m, 2H), 7.26 - 7.17 (m, 3H), 6.04 - 5.89 (m, 1H), 5.05 - 4.87 (m, 2H), 4.81 - 4.59 (m, 2H), 4.54 (t, J = 5.6 Hz, 1H), 4.43 - 4.34 (m, 1H), 4.15 (s, 3H), 4.11 - 4.02 (m, 1H), 4.01 - 3.91 (m, 1H), 3.83 - 3.73 (m, 2H),

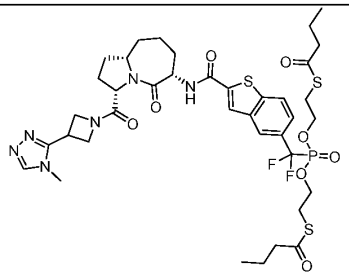
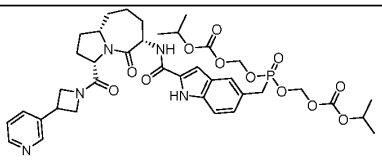
	isopropyl ((R)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	Less polar linker building block used for synthesis and biological testing		3.72 - 3.64 (m, 1H), 2.34 - 2.25 (m, 1H), 2.24 - 2.09 (m, 2H), 2.07 - 1.98 (m, 3H), 1.96 - 1.68 (m, 4H), 1.26 (dd, J = 3.2, 6.4 Hz, 3H), 1.17 (d, J = 6.4 Hz, 3H), 1.11 (dd, J = 6.4, 9.6 Hz, 3H)
956	isopropyl ((S)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or isopropyl ((R)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 More polar linker building block used for synthesis and biological testing	820.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 - 8.70 (m, 2H), 8.09 - 7.94 (m, 2H), 7.90 - 7.79 (m, 1H), 7.70 - 7.54 (m, 1H), 7.27 - 7.16 (m, 3H), 7.14 - 7.05 (m, 3H), 6.04 - 5.89 (m, 1H), 5.03 - 4.97 (m, 1H), 4.91 (dd, J = 6.0, 8.8 Hz, 1H), 4.77 (dd, J = 7.6, 10.0 Hz, 1H), 4.73 - 4.58 (m, 2H), 4.53 (t, J = 5.6 Hz, 1H), 4.41 - 4.34 (m, 1H), 4.21 - 4.13 (m, 1H), 4.12 - 4.08 (m, 3H), 4.08 - 4.02 (m, 1H), 4.00 - 3.91 (m, 1H), 3.84 - 3.65 (m, 1H), 2.33 - 2.24 (m, 1H), 2.12 (dd, J = 6.0, 13.2 Hz, 2H), 2.07 - 1.97 (m, 3H), 1.95 - 1.67 (m, 4H), 1.27 (d, J = 7.1 Hz, 3H), 1.25 - 1.19 (m, 6H)

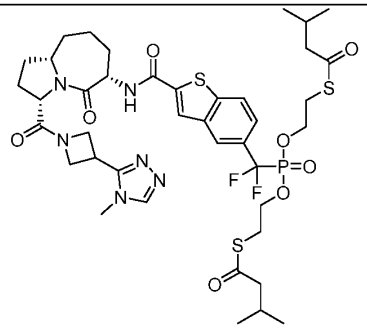
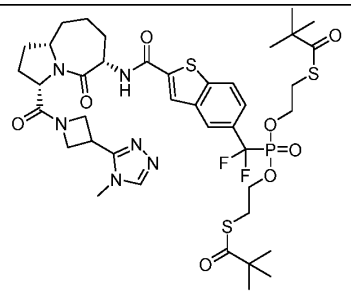
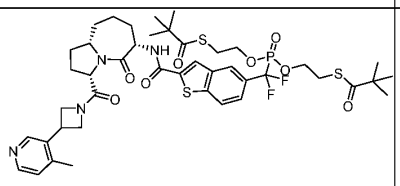
957	propyl ((fluoro(2-(((3S,6S,9aS)-3-(3-(5-fluoro-2-methoxyphenyl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		837.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.82 (s, 1H), 7.74 (d, J = 4.8 Hz, 1H), 7.61 - 7.53 (m, 1H), 7.38 - 7.28 (m, 1H), 7.24 (s, 1H), 7.22 - 7.16 (m, 1H), 7.10 (s, 1H), 7.09 - 7.06 (m, 1H), 6.98 - 6.93 (m, 1H), 6.82 – 6.78 (m, 1H), 6.13 - 5.83 (m, 1H), 4.93 - 4.81 (m, 1H), 4.69 (d, J = 4.4 Hz, 1H), 4.53 (d, J = 11.2 Hz, 2H), 4.50 - 4.32 (m, 1H), 4.27 - 4.18 (m, 1H), 4.18 - 4.09 (m, 2H), 4.08 - 3.90 (m, 3H), 3.82 (d, J = 4.8 Hz, 3H), 3.77 - 3.60 (m, 1H), 2.34 - 2.13 (m, 2H), 2.11 - 2.02 (m, 3H), 2.01 (s, 3H), 1.85 - 1.68 (m, 2H), 1.67 - 1.48 (m, 2H), 1.33 - 1.09 (m, 3H), 0.97 - 0.80 (m, 3H)
958	propyl (((2-(((3S,6S,10aS)-3-(((3S,4S)-1-carbamoyl-4-fluoropyrrolidin-3-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		817.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.13 - 8.05 (m, 2H), 8.02 - 7.93 (m, 1H), 7.68 - 7.61 (m, 1H), 7.38 - 7.28 (m, 2H), 7.24 - 7.11 (m, 3H), 6.18 - 5.98 (m, 1H), 5.08 - 5.01 (m, 1H), 4.94 (s, 1H), 4.47 - 4.33 (m, 3H), 4.00 - 3.94 (m, 1H), 3.94 - 3.87 (m, 1H), 3.84 – 3.81 (m, 1H), 3.74 - 3.64 (m, 2H), 3.61 - 3.55 (m, 1H), 3.47 (d, J = 10.8 Hz, 1H), 2.25 - 2.15 (m, 2H), 2.07 - 1.91

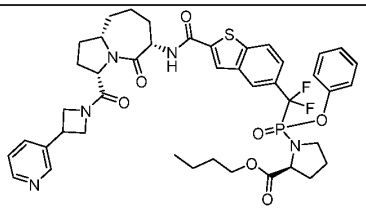
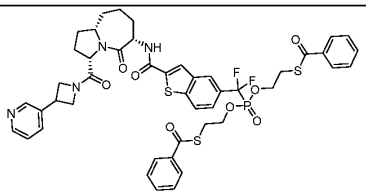
				(m, 6H), 1.82 (d, J = 4.0 Hz, 2H), 1.72 - 1.60 (m, 2H), 1.60 - 1.47 (m, 2H), 1.24 - 1.18 (m, 2H), 1.06 (d, J = 7.2 Hz, 1H), 0.91 - 0.82 (m, 3H)
959	neopentyl ((R)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or neopentyl ((S)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 Less polar linker building block used for synthesis and biological testing	848.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 - 8.67 (m, 2H), 8.06 - 7.94 (m, 2H), 7.91 - 7.79 (m, 1H), 7.68 - 7.51 (m, 1H), 7.41 - 7.31 (m, 2H), 7.29 (s, 1H), 7.25 (s, 1H), 7.23 - 7.14 (m, 2H), 6.03 - 5.85 (m, 1H), 5.04 - 4.85 (m, 1H), 4.80 - 4.52 (m, 3H), 4.42 - 4.32 (m, 1H), 4.23 - 4.02 (m, 6H), 3.95 (d, J = 8.0 Hz, 1H), 3.88 - 3.72 (m, 3H), 2.34 - 2.24 (m, 1H), 2.23 - 1.98 (m, 5H), 1.95 - 1.69 (m, 4H), 1.16 (dd, J = 7.2, 10.8 Hz, 3H), 0.90 (s, 9H)

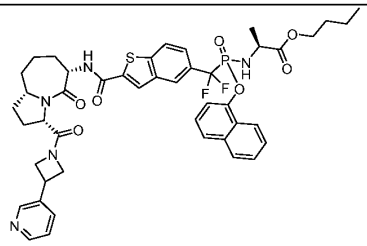
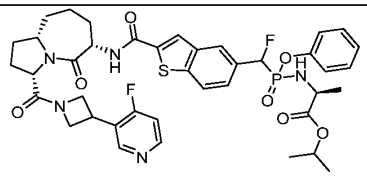
960	neopentyl ((R)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or neopentyl ((S)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 or  More polar linker building block used for synthesis and biological testing	848.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 - 8.66 (m, 2H), 8.07 - 7.94 (m, 2H), 7.91 - 7.81 (m, 1H), 7.70 - 7.56 (m, 1H), 7.29 (s, 1H), 7.25 (s, 2H), 7.17 - 7.06 (m, 3H), 6.09 - 5.91 (m, 1H), 5.05 - 4.88 (m, 1H), 4.80 - 4.51 (m, 3H), 4.43 - 4.33 (m, 1H), 4.21 - 4.04 (m, 5H), 4.00 - 3.92 (m, 1H), 3.90 - 3.57 (m, 4H), 2.34 - 2.25 (m, 1H), 2.22 - 1.97 (m, 5H), 1.96 - 1.68 (m, 4H), 1.31 (d, J = 6.8 Hz, 3H), 0.95 - 0.87 (m, 9H)
961	S,S'-((((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyrimidin-2-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methylbutanethioate)		908.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 - 8.73 (m, 2H), 8.15 - 8.07 (m, 1H), 8.00 - 7.93 (m, 1H), 7.89 - 7.83 (m, 1H), 7.75 (d, J = 5.5 Hz, 1H), 7.71 - 7.66 (m, 1H), 7.26 - 7.22 (m, 1H), 4.93 - 4.85 (m, 1H), 4.71 - 4.64 (m, 1H), 4.63 - 4.56 (m, 2H), 4.55 - 4.39 (m, 1H), 4.31 - 4.14 (m, 6H), 3.97 - 3.88 (m, 1H), 3.18 - 2.97 (m, 4H), 2.36 - 2.21 (m, 2H), 2.19

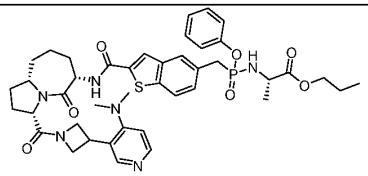
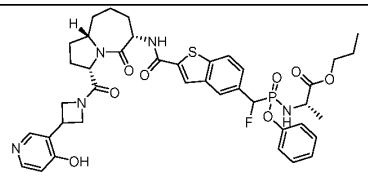
				(d, J = 7.0 Hz, 4H), 2.14 - 2.01 (m, 6H), 2.00 - 1.90 (m, 2H), 1.85 - 1.74 (m, 2H), 0.95 (d, J = 6.6 Hz, 12H)
962	S,S'-((((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyrimidin-2-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2,2-dimethylpropanethioate)		908.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 - 8.74 (m, 2H), 8.12 - 8.06 (m, 1H), 7.99 - 7.92 (m, 1H), 7.91 - 7.81 (m, 1H), 7.75 - 7.63 (m, 2H), 7.26 - 7.21 (m, 1H), 4.96 - 4.83 (m, 1H), 4.73 - 4.52 (m, 4H), 4.33 - 4.09 (m, 6H), 4.02 - 3.86 (m, 1H), 3.19 - 3.08 (m, 4H), 2.34 - 2.18 (m, 2H), 2.09 - 2.01 (m, 4H), 2.00 - 1.91 (m, 2H), 1.84 - 1.76 (m, 2H), 1.23 (s, 18H)
963	S,S'-((((difluoro(2-(((3S,6S,9aS)-3-(3-methoxy-3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methylbutanethioate)		951.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 5.6 Hz, 1H), 8.21 - 8.12 (m, 1H), 8.01 - 7.85 (m, 2H), 7.72 - 7.65 (m, 1H), 7.41 - 7.33 (m, 1H), 7.32 - 7.28 (m, 1H), 5.39 - 5.17 (m, 1H), 4.73 - 4.66 (m, 1H), 4.64 - 4.55 (m, 1H), 4.53 - 4.43 (m, 2H), 4.27 - 4.17 (m, 4H), 4.16 - 4.10 (m, 1H), 3.98 - 3.91 (m, 1H), 3.73 - 3.64 (m, 1H), 3.15 - 3.10 (m, 2H), 3.06 - 3.03 (m, 3H), 2.47 - 2.39 (m, 3H), 2.19 (d, J = 7.2 Hz, 6H), 2.04 - 2.01 (m, 2H), 1.87 - 1.83 (m, 2H), 1.55 - 1.49 (m, 4H), 1.45 (d, J = 7.2 Hz,

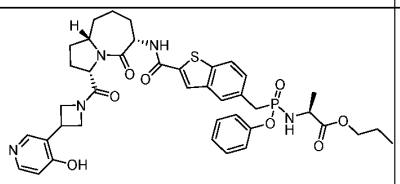
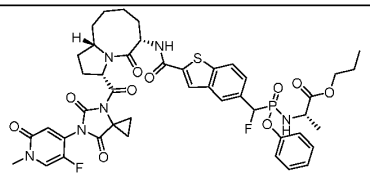
				3H), 0.95 (d, J = 6.4 Hz, 12H)
964	S,S'-((((difluoro(2-(((3S,6S,9aS)-3-(3-(4-methyl-4H-1,2,4-triazol-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) dibutanethioate		883.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 - 8.17 (m, 1H), 8.17 - 8.10 (m, 1H), 8.00 - 7.92 (m, 1H), 7.89 - 7.75 (m, 1H), 7.73 - 7.65 (m, 2H), 5.01 - 4.92 (m, 1H), 4.89 - 4.83 (m, 1H), 4.72 - 4.53 (m, 3H), 4.28 - 4.16 (m, 5H), 4.08 - 3.88 (m, 2H), 3.74 - 3.60 (m, 3H), 3.18 - 2.98 (m, 4H), 2.29 (t, J = 7.2 Hz, 4H), 2.21 (d, J = 12.4 Hz, 1H), 2.04 (s, 3H), 1.92 (m, 2H), 1.84 (m, 5H), 1.68 - 1.59 (m, 4H), 0.94 (t, J = 7.2 Hz, 6H)
965	diisopropyl (((((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)-1H-indol-5-yl)methyl)phosphoryl)bis(oxy))bis(methylene)) bis(carbonate)		798.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 - 8.80 (m, 1H), 8.64 - 8.57 (m, 1H), 8.04 - 7.83 (m, 1H), 7.76 - 7.62 (m, 1H), 7.61 - 7.55 (m, 1H), 7.53 - 7.49 (m, 1H), 7.43 - 7.33 (m, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.05 - 6.89 (m, 1H), 5.66 - 5.54 (m, 4H), 4.91 (t, J = 6.0 Hz, 2H), 4.81 - 4.57 (m, 3H), 4.55 - 4.41 (m, 1H), 4.27 - 3.83 (m, 4H), 3.42 - 3.33 (m, 2H), 2.31 - 2.14 (m, 2H), 2.11 - 2.01 (m, 4H), 1.99 - 1.91 (m, 2H), 1.87 - 1.78 (m, 2H), 1.31 (d, J = 6.0 Hz, 12H)

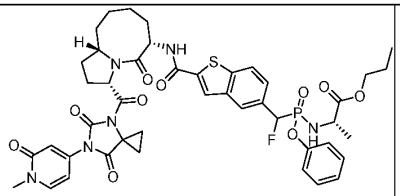
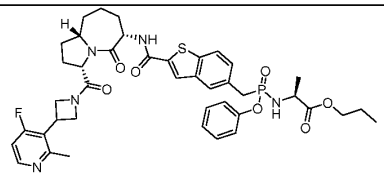
966	S,S'-((((difluoro(2-(((3S,6S,9aS)-3-(3-(4-methyl-4H-1,2,4-triazol-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methylbutanethioate)		911.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.18 - 8.10 (m, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.89 - 7.80 (m, 1H), 7.75 - 7.63 (m, 2H), 5.09 - 4.95 (m, 1H), 4.94 - 4.82 (m, 1H), 4.71 - 4.64 (m, 1H), 4.62 - 4.51 (m, 2H), 4.29 - 4.17 (m, 5H), 4.09 - 3.86 (m, 2H), 3.75 - 3.63 (m, 3H), 3.17 - 2.99 (m, 4H), 2.29 - 2.22 (m, 1H), 2.19 (d, J = 7.2 Hz, 4H), 2.13 - 2.08 (m, 2H), 2.06 - 2.01 (m, 5H), 1.96 - 1.89 (m, 2H), 1.87 - 1.80 (m, 1H), 1.76 - 1.66 (m, 1H), 0.95 (d, J = 6.4 Hz, 12H)
967	S,S'-((((difluoro(2-(((3S,6S,9aS)-3-(3-(4-methyl-4H-1,2,4-triazol-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2,2-dimethylpropanethioate)		911.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 - 8.09 (m, 2H), 8.01 - 7.93 (m, 1H), 7.87 (s, 1H), 7.80 - 7.67 (m, 2H), 5.10 - 4.77 (m, 2H), 4.72 - 4.52 (m, 3H), 4.28 - 4.12 (m, 5H), 4.05 - 3.88 (m, 2H), 3.74 - 3.62 (m, 3H), 3.20 - 2.97 (m, 4H), 2.31 - 2.15 (m, 2H), 2.11 - 2.05 (m, 2H), 2.00 - 1.89 (m, 4H), 1.87 - 1.62 (m, 2H), 1.19 (s, 18H)
968	S,S'-((((difluoro(2-(((3S,6S,9aS)-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-		921.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 - 9.02 (m, 1H) 8.44 (m, 1H) 8.20 (s, 1H) 7.95 (s, 1H) 7.69 (m, 1H) 7.29 - 7.34 (m, 1H) 7.17 (d, J = 4.0 Hz,

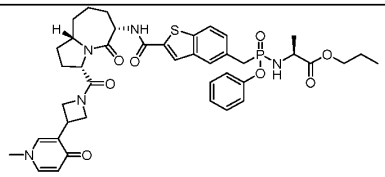
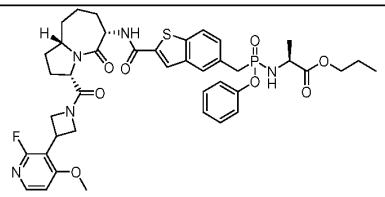
	a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2,2-dimethylpropanethioate)			1H) 5.00 (s, 1H) 4.61 - 4.80 (m, 2H) 4.53 - 4.60 (m, 1H) 4.29 - 4.47 (m, 1H), 4.12 - 4.24 (m, 6H) 3.94 (s, 1H) 2.99 - 3.15 (m, 4H), 2.30 (s, 3H) 2.12 - 2.21 (m, 2H) 2.00 (s, 5H) 1.82 - 1.91 (m, 3H) 1.17 - 1.19 (m, 18H)
969	butyl ((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-prolinate		848.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 - 8.54 (m, 2H), 8.16 (d, J = 9.2 Hz, 1H), 7.67 (s, 5H), 7.46 - 7.34 (m, 1H), 7.24 (t, J = 7.6 Hz, 3H), 7.09 (d, J = 8.4 Hz, 2H), 4.73 - 4.41 (m, 5H), 4.21 (dd, J = 6.4, 8.8 Hz, 1H), 4.13 - 4.05 (m, 1H), 4.02 - 3.87 (m, 4H), 3.52 - 3.28 (m, 2H), 2.31 - 2.11 (m, 3H), 2.10 - 2.00 (m, 5H), 2.00 - 1.91 (m, 3H), 1.83 (d, J = 10.0 Hz, 1H), 1.76 (s, 1H), 1.57 - 1.46 (m, 2H), 1.37 - 1.24 (m, 3H), 0.88 (t, J = 7.6 Hz, 3H)
970	S,S'-((((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) dibenzothioate		947.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 - 8.85 (m, 1H), 8.83 - 8.69 (m, 1H), 8.46 (d, J = 7.2 Hz, 1H), 8.17 (s, 1H), 8.02 (m, 4H), 7.99 - 7.90 (m, 3H), 7.88 - 7.83 (m, 1H), 7.74 - 7.68 (m, 1H), 7.60 - 7.54 (m, 2H), 7.44 (t, J = 7.6 Hz, 4H), 4.88 - 4.67 (m, 3H), 4.55 - 4.41 (m, 6H), 4.20 - 4.14 (m, 1H), 4.04 - 3.92 (m, 2H), 3.28 - 3.20 (m,

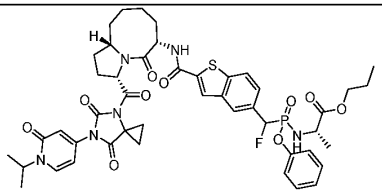
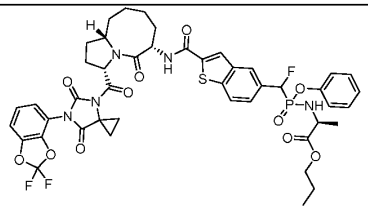
				4H), 2.34 - 2.26 (m, 1H), 2.23 - 2.12 (m, 2H), 2.09 - 2.03 (m, 3H), 1.98 - 1.81 (m, 4H)
971	butyl ((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(naphthalen-1-yloxy)phosphoryl)-L-alaninate		872.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 - 8.85 (m, 1H), 8.76 - 8.45 (m, 2H), 8.23 - 8.18 (m, 1H), 7.95 - 7.90 (m, 2H), 7.87 - 7.75 (m, 4H), 7.66 - 7.60 (m, 1H), 7.53 - 7.39 (m, 3H), 7.36 - 7.29 (m, 1H), 4.86 - 4.66 (m, 3H), 4.56 - 4.45 (m, 1H), 4.30 - 4.12 (m, 2H), 4.11 - 4.01 (m, 3H), 4.00 - 3.89 (m, 3H), 2.35 - 2.25 (m, 1H), 2.20 - 2.03 (m, 5H), 1.95 - 1.67 (m, 4H), 1.56 - 1.43 (m, 2H), 1.34 - 1.25 (m, 5H), 0.93 - 0.85 (m, 3H)
972	isopropyl ((fluoro(2-(((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		808.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 - 8.51 (m, 2H), 8.03 - 7.93 (m, 1H), 7.91 - 7.79 (m, 2H), 7.73 - 7.64 (m, 1H), 7.63 - 7.51 (m, 1H), 7.40 - 7.28 (m, 1H), 7.26 - 7.22 (m, 1H), 7.22 - 7.04 (m, 3H), 6.08 - 5.84 (m, 1H), 5.06 - 4.73 (m, 2H), 4.72 - 4.53 (m, 3H), 4.47 - 4.18 (m, 2H), 4.17 - 4.07 (m, 1H), 3.93 (s, 1H), 3.67 - 3.51 (m, 1H), 2.33 - 2.15 (m, 2H), 2.12 - 2.00 (m, 4H), 1.95 (t, J = 9.2 Hz, 2H), 1.86 - 1.79 (m, 1H), 1.76 - 1.69 (m, 1H), 1.32 - 1.24 (m, 3H), 1.24 - 1.15 (m,

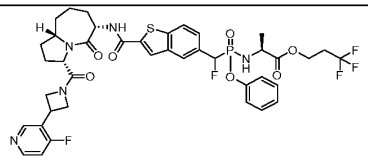
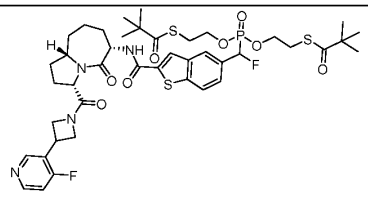
				5H), 1.12 - 1.07 (m, 1H)
973	propyl (((2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		815.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.48 - 8.33 (m, 1H), 8.22 - 8.12 (m, 1H), 8.06 - 7.98 (m, 1H), 7.94 - 7.82 (m, 2H), 7.53 - 7.44 (m, 1H), 7.34 – 7.29 (m, 2H), 7.19 – 7.14 (m, 3H), 7.03 - 6.92 (m, 1H), 4.94 (s, 1H), 4.76 - 4.70 (m, 1H), 4.62 - 4.50 (m, 2H), 4.47 - 4.31 (m, 1H), 4.30 - 4.21 (m, 1H), 4.07 (d, J = 7.6 Hz, 2H), 3.96 - 3.80 (m, 3H), 3.60 - 3.45 (m, 2H), 2.95 - 2.85 (m, 6H), 2.38 - 2.24 (m, 1H), 2.19 - 2.03 (m, 3H), 2.02 - 1.87 (m, 3H), 1.84 (d, J = 12.8 Hz, 3H), 1.59 - 1.48 (m, 2H), 1.19 - 1.05 (m, 3H), 0.94 - 0.82 (m, 3H)
974	propyl ((fluoro(2-(((3S,6S,9aS)-3-(3-(4-hydroxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		806.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 - 8.18 (m, 1H), 8.09 - 7.88 (m, 1H), 7.86 - 7.54 (m, 4H), 7.53 - 7.32 (m, 1H), 7.27 (s, 1H), 7.26 - 7.22 (m, 1H), 7.20 - 7.01 (m, 3H), 6.19 - 5.89 (m, 1H), 4.91 - 4.67 (m, 2H), 4.66 - 4.48 (m, 2H), 4.46 - 4.30 (m, 2H), 4.30 - 4.23 (m, 1H), 4.14 - 3.97 (m, 4H), 3.96 - 3.88 (m, 1H), 2.27 (d, J = 8.8 Hz, 1H), 2.15 - 1.96 (m, 5H), 1.95 - 1.83 (m, 2H), 1.66 (s, 2H), 1.65 - 1.51 (m, 2H),

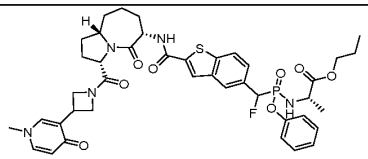
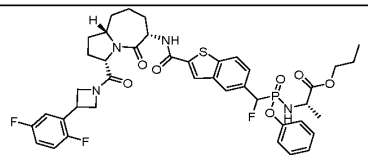
				1.38 - 1.19 (m, 3H), 0.99 - 0.82 (m, 3H)
975	propyl (((2-(((3S,6S,9aS)-3-(3-(4-hydroxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		788.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 - 8.31 (m, 1H), 7.77 - 7.63 (m, 1H), 7.62 - 7.39 (m, 3H), 7.39 - 7.27 (m, 3H), 7.26 - 7.17 (m, 2H), 7.17 - 7.04 (m, 2H), 4.76 - 4.66 (m, 2H), 4.56 (t, J = 7.6 Hz, 1H), 4.42 - 4.32 (m, 2H), 4.32 - 4.24 (m, 1H), 4.19 - 4.00 (m, 3H), 3.99 - 3.87 (m, 3H), 3.65 - 3.37 (m, 2H), 2.33 - 2.21 (m, 1H), 2.19 - 1.95 (m, 6H), 1.92 - 1.76 (m, 2H), 1.74 - 1.61 (m, 2H), 1.61 - 1.50 (m, 1H), 1.29 (d, J = 7.2 Hz, 1H), 1.21 - 1.13 (m, 2H), 0.97 - 0.83 (m, 3H)
976	propyl ((fluoro(2-(((3S,6S,10aS)-3-(6-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		921.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 - 7.91 (m, 1H), 7.89 - 7.83 (m, 1H), 7.77 (s, 1H), 7.64 - 7.51 (m, 1H), 7.44 - 7.32 (m, 2H), 7.23 - 7.17 (m, 3H), 7.15 - 7.02 (m, 2H), 6.78 - 6.63 (m, 1H), 6.06 - 5.83 (m, 1H), 5.52 - 5.42 (m, 1H), 5.17 - 5.07 (m, 1H), 4.40 - 4.30 (m, 1H), 4.16 - 3.93 (m, 3H), 3.57 (s, 3H), 2.65 - 2.53 (m, 1H), 2.52 - 2.39 (m, 2H), 2.30 - 2.16 (m, 2H), 2.04 - 1.83 (m, 6H), 1.63 - 1.57 (m, 4H), 1.35 - 1.24 (m, 5H), 0.96 - 0.81 (m, 4H)

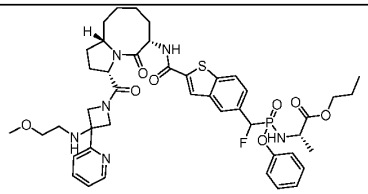
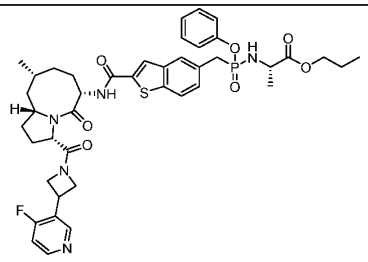
977	propyl ((fluoro(2-(((3S,6S,10aS)-3-(6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		903.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 12.4 Hz, 1H), 7.90 - 7.83 (m, 1H), 7.80 (d, J = 2.8 Hz, 1H), 7.63 - 7.51 (m, 1H), 7.45 (d, J = 7.2 Hz, 1H), 7.40 - 7.30 (m, 2H), 7.27 - 7.22 (m, 2H), 7.20 - 6.98 (m, 3H), 6.60 (d, J = 4.0 Hz, 1H), 6.13 - 5.83 (m, 1H), 5.47 (t, J = 7.2 Hz, 1H), 5.14 (d, J = 6.0 Hz, 1H), 4.44 - 4.30 (m, 1H), 4.18 - 3.84 (m, 3H), 3.79 - 3.66 (m, 1H), 3.63 (s, 3H), 2.66 - 2.57 (m, 1H), 2.53 - 2.35 (m, 2H), 2.33 - 2.12 (m, 2H), 2.07 - 1.91 (m, 3H), 1.90 - 1.67 (m, 6H), 1.65 -1.58 (m, 2H), 1.57 - 1.48 (m, 2H), 1.36 - 1.11 (m, 3H), 0.97 - 0.81 (m, 3H)
978	propyl (((2-(((3S,6S,9aS)-3-(3-(4-fluoro-2-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		804.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 - 8.68 (m, 1H), 8.40 - 8.27 (m, 1H), 8.19 (d, J = 7.8 Hz, 1H), 7.98 - 7.86 (m, 2H), 7.44 (d, J = 8.6 Hz, 1H), 7.35 - 7.29 (m, 2H), 7.20 - 7.10 (m, 4H), 5.75 - 5.55 (m, 1H), 4.77 - 4.54 (m, 2H), 4.48 - 4.43 (m, 1H), 4.46 (d, J = 4.6 Hz, 1H), 4.50 - 4.14 (m, 2H), 4.07 - 3.95 (m, 2H), 3.90 - 3.73 (m, 3H), 3.49 - 3.39 (m, 2H), 2.47 (s, 3H), 2.05 - 1.94 (m, 2H), 1.89 - 1.64 (m, 8H), 1.52 - 1.44 (m, 2H),

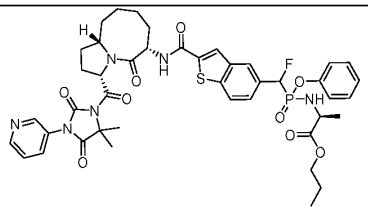
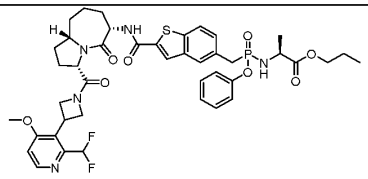
				1.08 - 0.95 (m, 3H), 0.83 - 0.78 (m, 3H)
979	propyl (((2-(((3S,6S,9aS)-3-(3-(1-methyl-4-oxo-1,4-dihydropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		802.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 - 7.81 (m, 1H), 7.81 - 7.70 (m, 4H), 7.66 (s, 1H), 7.46 - 7.35 (m, 1H), 7.31 - 7.28 (m, 1H), 7.18 - 7.08 (m, 4H), 4.75 - 4.57 (m, 3H), 4.52 - 4.41 (m, 2H), 4.40 - 4.29 (m, 1H), 4.11 - 4.02 (m, 2H), 4.01 - 3.94 (m, 4H), 3.89 (d, J = 7.2 Hz, 2H), 3.51 - 3.40 (m, 2H), 2.25 (d, J = 7.2 Hz, 1H), 2.14 - 1.96 (m, 5H), 1.91 (t, J = 9.2 Hz, 2H), 1.79 (s, 2H), 1.62 - 1.51 (m, 2H), 1.47 - 1.37 (m, 1H), 1.22 - 1.14 (m, 3H), 0.91 - 0.83 (m, 3H)
980	propyl (((2-(((3S,6S,9aS)-3-(3-(2-fluoro-4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		819.9	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 5.2 Hz, 1H), 7.90 - 7.76 (m, 3H), 7.74 - 7.65 (m, 1H), 7.45 - 7.41 (m, 1H), 7.31 (s, 1H), 7.22 - 7.10 (m, 3H), 6.86 - 6.76 (m, 1H), 4.87 - 4.76 (m, 1H), 4.74 - 4.66 (m, 1H), 4.62 (d, J = 4.0 Hz, 1H), 4.55 - 4.43 (m, 2H), 4.37 - 4.18 (m, 2H), 4.11 - 3.90 (m, 7H), 3.53 - 3.42 (m, 2H), 2.34 - 2.19 (m, 3H), 1.94 (d, J = 1.2 Hz, 5H), 1.87 - 1.71 (m, 2H), 1.59 (d, J = 7.3, 14.4 Hz, 2H), 1.17 (dd, J = 7.2, 10.9 Hz, 3H), 0.96 - 0.83 (m, 3H)

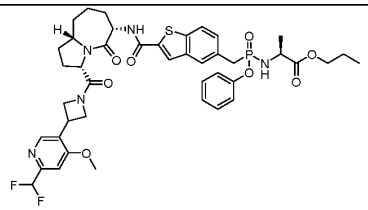
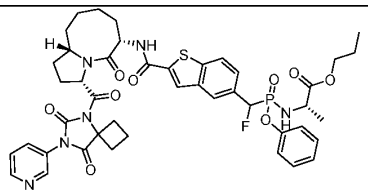
981	propyl ((fluoro(2-(((3S,6S,10aS)-3-(6-(1-isopropyl-2-oxo-1,2-dihydropyridin-4-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		931.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 - 7.90 (m, 1H), 7.89 - 7.82 (m, 1H), 7.81 - 7.77 (m, 1H), 7.61 - 7.52 (m, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.39 - 7.29 (m, 2H), 7.26 - 7.17 (m, 2H), 7.13 - 7.03 (m, 1H), 6.96 (s, 1H), 6.65 - 6.59 (m, 1H), 6.08 - 5.87 (m, 1H), 5.51 - 5.44 (m, 1H), 5.33 - 5.24 (m, 1H), 5.19 - 5.10 (m, 1H), 4.41 - 4.33 (m, 1H), 4.16 - 4.06 (m, 1H), 4.06 - 3.95 (m, 2H), 2.66 - 2.57 (m, 1H), 2.51 - 2.44 (m, 1H), 2.42 - 2.35 (m, 1H), 2.33 - 2.13 (m, 2H), 2.03 - 1.90 (m, 3H), 1.90 - 1.81 (m, 2H), 1.81 - 1.73 (m, 2H), 1.72 - 1.60 (m, 3H), 1.60 - 1.48 (m, 3H), 1.40 (d, J = 6.8 Hz, 6H), 1.32 - 1.25 (m, 2H), 1.12 (d, J = 7.2 Hz, 1H), 1.01 - 0.77 (m, 3H)
982	propyl (((2-(((3S,6S,10aS)-3-(6-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-5,7-dioxo-4,6-diazaspiro[2.4]heptane-4-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		952.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.59 (d, J = 4.4 Hz, 1H), 7.90 - 7.74 (m, 3H), 7.70 (d, J = 2.6 Hz, 1H), 7.55 - 7.41 (m, 2H), 7.30 - 7.24 (m, 1H), 7.15 - 7.06 (m, 2H), 7.06 - 6.94 (m, 2H), 6.00 - 5.76 (m, 1H), 5.46 - 5.35 (m, 1H), 5.34 - 5.19 (m, 1H), 5.14 - 5.01 (m, 1H), 4.37 - 4.23 (m, 1H), 4.01 - 3.87 (m, 2H), 3.59 - 3.40 (m, 1H), 3.23 -

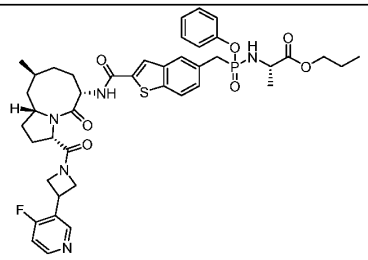
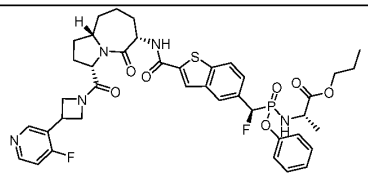
				3.08 (m, 2H), 2.66 - 2.48 (m, 3H), 2.28 - 2.09 (m, 5H), 1.83 - 1.73 (m, 3H), 1.22 - 1.18 (m, 8H), 0.86 - 0.76 (m, 6H)
983	3,3,3-trifluoropropyl ((fluoro(2-(((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		862.4	^{1}H NMR (400 MHz, $CDCl_{34}$) δ 8.79 - 8.52 (m, 2H), 8.03 - 7.94 (m, 1H), 7.92 - 7.79 (m, 2H), 7.68 (d, J = 1.2 Hz, 1H), 7.63 - 7.52 (m, 1H), 7.40 - 7.32 (m, 1H), 7.25 - 7.19 (m, 1H), 7.16 - 7.00 (m, 3H), 6.08 - 5.85 (m, 1H), 5.04 - 4.73 (m, 1H), 4.71 - 4.53 (m, 3H), 4.39 - 4.28 (m, 2H), 4.26 - 4.07 (m, 3H), 4.00 - 3.86 (m, 1H), 3.58 - 3.42 (m, 1H), 2.50 - 2.35 (m, 2H), 2.32 - 2.16 (m, 2H), 2.08 - 2.03 (m, 3H), 2.00 - 1.91 (m, 2H), 1.82 (dd, J = 3.6, 5.6 Hz, 1H), 1.73 (dt, J = 2.4, 5.2 Hz, 1H), 1.44 (d, J = 6.8 Hz, 1H), 1.29 (dd, J = 7.2, 12.4 Hz, 3H)
984	S,S'-((((fluoro(2-(((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2,2-		907.3	^{1}H NMR (400 MHz, CDCl3) δ 8.79 - 8.58 (m, 1H), 8.58 - 8.52 (m, 1H), 7.95 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.86 (s, 1H), 7.69 (dd, J = 6.0, 11.2 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.07 (dd, J = 5.6, 10.0 Hz, 1H), 5.93 - 5.76 (m, 1H), 5.04 - 4.72 (m, 1H), 4.71 - 4.54 (m, 3H), 4.46 - 4.19 (m, 2H), 4.18 - 4.11 (m, 3H), 4.10 - 4.03 (m,

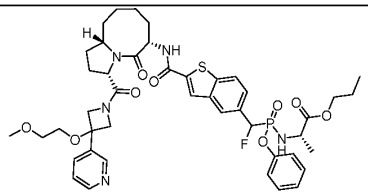
	dimethylpropanethioate)			2H), 3.93 (d, J = 3.9 Hz, 1H), 3.16 - 3.01 (m, 4H), 2.32 - 2.15 (m, 2H), 2.11 - 2.06 (m, 1H), 2.00 (s, 2H), 1.99 - 1.86 (m, 3H), 1.82 (d, J = 5.6 Hz, 1H), 1.72 (d, J = 10.4 Hz, 1H), 1.28 - 1.19 (m, 18H)
985	propyl ((fluoro(2-(((3S,6S,9aS)-3-(3-(1-methyl-4-oxo-1,4-dihydropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		820.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.41 - 8.21 (m, 1H), 8.15 - 8.05 (m, 2H), 8.05 - 7.94 (m, 1H), 7.71 - 7.59 (m, 1H), 7.41 - 7.30 (m, 2H), 7.24 - 7.15 (m, 3H), 7.15 - 7.04 (m, 1H), 6.20 - 6.01 (m, 1H), 4.78 - 4.66 (m, 2H), 4.65 - 4.51 (m, 2H), 4.46 - 4.37 (m, 1H), 4.23 - 4.03 (m, 5H), 4.02 - 3.95 (m, 3H), 3.94 - 3.79 (m, 2H), 2.37 - 2.27 (m, 1H), 2.18 - 2.06 (m, 2H), 2.04 - 1.94 (m, 3H), 1.93 - 1.78 (m, 4H), 1.61 - 1.48 (m, 2H), 1.26 - 1.20 (m, 2H), 1.13 - 1.05 (m, 1H), 0.93 - 0.80 (m, 3H)
986	propyl (((2-(((3S,6S,9aS)-3-(3-(2,5-difluorophenyl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(ph		825.2	^{1}H NMR (400 MHz, CDCl3) δ 7.98 (d, J = 7.6 Hz, 1H), 7.93 - 7.85 (m, 1H), 7.85 - 7.81 (m, 1H), 7.79 - 7.66 (m, 1H), 7.65 - 7.55 (m, 1H), 7.54 - 7.41 (m, 1H), 7.40 - 7.32 (m, 1H), 7.16 - 6.95 (m, 5H), 6.09 - 5.87 (m, 1H), 4.77 - 4.65 (m, 2H), 4.64 - 4.55 (m, 2H), 4.31 - 3.90 (m, 8H), 3.72 -

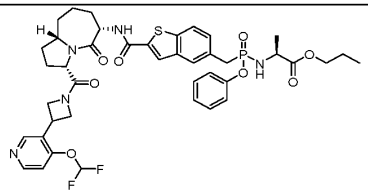
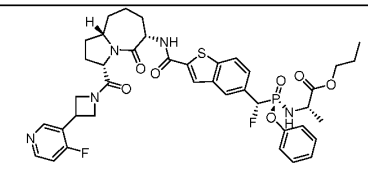
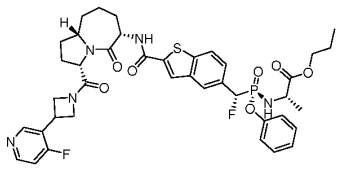
	enoxy)phosphoryl)-L-alaninate			3.54 (m, 1H), 2.32 - 2.18 (m, 3H), 1.96 (t, J = 10.2 Hz, 2H), 1.83 (d, J = 8.8 Hz, 1H), 1.78 - 1.70 (m, 1H), 1.70 - 1.60 (m, 2H), 1.59 - 1.49 (m, 1H), 1.33 - 1.25 (m, 3H), 1.14 - 1.11 (m, 1H), 0.97 - 0.89 (m, 3H), 0.89 - 0.82 (m, 1H)
987	propyl ((fluoro(2-(((3S,6S,10aS)-3-(3-((2-methoxyethyl)amino)-3-(pyridin-2-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		877.8	^{1}H NMR (400 MHz, CD_3OD) δ 8.72 - 8.62 (m, 1H), 8.16 - 8.06 (m, 2H), 8.06 - 7.81 (m, 3H), 7.69 - 7.61 (m, 1H), 7.54 - 7.41 (m, 1H), 7.38 - 7.30 (m, 2H), 7.24 - 7.14 (m, 3H), 6.19 - 6.00 (m, 1H), 5.12 - 4.96 (m, 2H), 4.82 - 4.75 (m, 1H), 4.59 - 4.39 (m, 4H), 3.98 (t, J = 3.8, 6.6 Hz, 1H), 3.94 - 3.76 (m, 2H), 3.68 - 3.63 (m, 1H), 3.61 - 3.56 (m, 1H), 3.44 - 3.33 (m, 3H), 3.19 - 3.04 (m, 2H), 2.35 - 2.21 (m, 2H), 2.16 - 1.78 (m, 8H), 1.77 - 1.61 (m, 2H), 1.60 - 1.47 (m, 2H), 1.26 - 1.19 (m, 2H), 1.07 (d, J = 2.6, 7.1 Hz, 1H), 0.92 - 0.82 (m, 3H)
988	propyl (((2-(((3S,6S,9R,10aR)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-9-methyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-		818.7	^{1}H NMR (400 MHz, CDCl3) δ 9.70 - 9.66 (m, 1H), 8.82 - 8.58 (m, 1H), 8.05 - 7.70 (m, 4H), 7.49 - 7.30 (m, 2H), 7.29 (s, 1H), 7.27 - 7.20 (m, 1H), 7.19 - 7.07 (m, 3H), 5.29 - 5.16 (m, 1H), 5.10 - 4.96 (m, 1H),

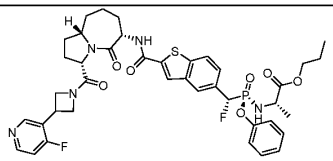
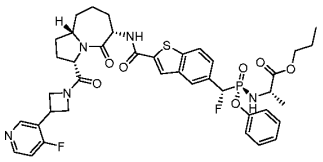
	yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate			4.74 - 4.61 (m, 1H), 4.51 - 4.30 (m, 3H), 4.25 - 4.11 (m, 2H), 4.05 - 3.91 (m, 3H), 3.50 - 3.40 (m, 2H), 2.26 - 2.12 (m, 3H), 2.07 - 2.02 (m, 1H), 2.01 - 1.91 (m, 2H), 1.90 - 1.70 (m, 3H), 1.65 - 1.42 (m, 4H), 1.23 - 1.11 (m, 3H), 1.04 (d, J = 6.4 Hz, 3H), 0.93 - 0.82 (m, 3H)
989	propyl (((2-(((3S,6S,10aS)-3-(5,5-dimethyl-2,4-dioxo-3-(pyridin-3-yl)imidazolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		875.4	^{1}H NMR (400 MHz, CDCl3) δ 8.85 - 8.60 (m, 2H), 7.99 - 7.91 (m, 1H), 7.88 - 7.81 (m, 2H), 7.79 - 7.75 (m, 1H), 7.63 - 7.51 (m, 1H), 7.47 (d, J = 3.2 Hz, 1H), 7.38 - 7.31 (m, 1H), 7.26 - 7.15 (m, 3H), 7.14 - 7.00 (m, 2H), 6.06 - 5.85 (m, 1H), 5.56 - 5.45 (m, 1H), 5.20 - 5.07 (m, 1H), 4.42 - 4.32 (m, 1H), 4.21 - 3.76 (m, 3H), 3.65 - 3.47 (m, 1H), 2.60 - 2.55(m, 1H), 2.32 - 2.17 (m, 2H), 2.08 - 1.91 (m, 4H), 1.86 (d, J = 5.4 Hz, 7H), 1.83 - 1.67 (m, 5H), 1.56 - 1.48 (m, 1H), 1.34 - 1.21 (m, 3H), 0.96 - 0.81 (m, 3H)
990	propyl (((2-(((3S,6S,9aS)-3-(3-(2-(difluoromethyl)-4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-		851.9	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 - 8.47 (m, 1H), 7.81 - 7.74 (m, 3H), 7.70 - 7.65 (m, 1H), 7.45 - 7.38 (m, 1H), 7.31 - 7.27 (m, 2H), 7.15 - 7.09 (m, 4H), 6.78-6.65 (m, 1H), 4.85 - 4.77 (m, 1H), 4.66 - 4.58

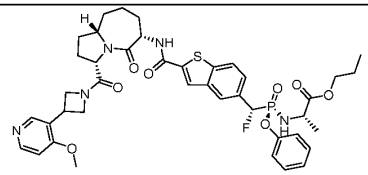
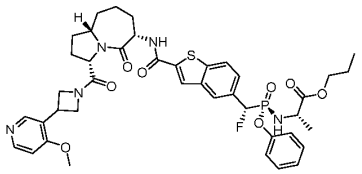
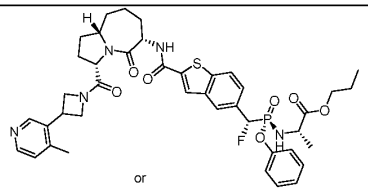
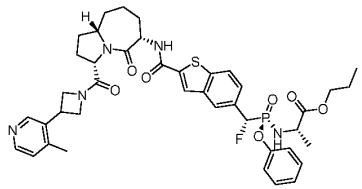
	a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate			(m, 2H), 4.52 - 4.51 (m, 2H), 4.46 - 4.41 (m, 1H), 4.25 - 4.18 (m, 3H), 4.00 (s, 1H), 3.97 - 3.92 (m, 3H), 3.50 - 3.42 (m, 4H), 2.29 - 2.20 (m, 2H), 2.07 - 1.95 (m, 6H), 1.84 - 1.70 (m, 2H), 1.56 (d, J = 7.6 Hz, 2H), 1.17 - 1.13 (m, 3H), 0.89 - 0.84 (m, 3H)
991	propyl (((2-(((3S,6S,9aS)-3-(3-(6-(difluoromethyl)-4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		851.9	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 - 8.43 (m, 1H), 7.81 - 7.76 (m, 3H), 7.73 - 7.66 (m, 1H), 7.46 - 7.39 (m, 1H), 7.30 - 7.28 (m, 1H), 7.26 - 7.25 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.15 - 7.11 (m, 3H), 4.92 - 4.68 (m, 2H), 4.57 - 4.55 (m, 2H), 4.34 - 4.29 (m, 1H), 4.26 - 4.11 (m, 1H), 4.01 (d, *J* = 23.2 Hz, 3H), 3.95 - 3.92 (m, 3H), 3.48 - 3.41 (m, 3H), 3.21 - 3.07 (m, 2H), 2.26 - 2.16 (m, 2H), 2.03 – 2.00 (m, 4H), 1.92 - 1.89 (m, 2H), 1.82 - 1.69 (m, 2H), 1.57 - 1.55 (m, 2H), 1.17 - 1.12 (m, 3H), 0.88 - 0.85 (m, 3H)
992	propyl (((2-(((3S,6S,10aS)-3-(6,8-dioxo-7-(pyridin-3-yl)-5,7-diazaspiro[3.4]octane-5-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-		887.4	^{1}H NMR (400 MHz, CDCl3) δ 8.72 (s, 1H), 8.59 (d, J = 4.4 Hz, 1H), 7.90 - 7.74 (m, 3H), 7.70 (d, J = 2.6 Hz, 1H), 7.55 - 7.41 (m, 2H), 7.30 - 7.24 (m, 1H), 7.15 - 7.06 (m, 2H), 7.06 - 6.94 (m, 2H), 6.00 - 5.76 (m, 1H), 5.46 -

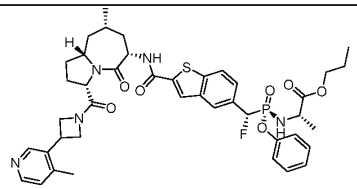
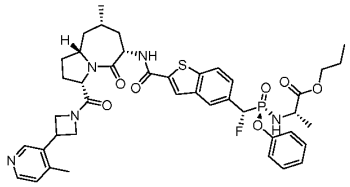
	yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate			5.35 (m, 1H), 5.34 - 5.19 (m, 1H), 5.14 - 5.01 (m, 1H), 4.37 - 4.23 (m, 1H), 4.01 - 3.87 (m, 2H), 3.59 - 3.40 (m, 1H), 3.23 - 3.08 (m, 2H), 2.66 - 2.48 (m, 3H), 2.28 - 2.09 (m, 5H), 1.83 - 1.73 (m, 3H), 1.22 - 1.18 (m, 8H), 0.86 - 0.76 (m, 6H)
993	propyl (((2-(((3S,6S,9S,10aR)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-9-methyl-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		818.3	^{1}H NMR (400 MHz, CDCl3) δ 8.75 - 8.59 (m, 1H), 7.92 - 7.71 (m, 4H), 7.56 - 7.37 (m, 2H), 7.29 (s, 1H), 7.24 - 7.19 (m, 1H), 7.17 - 7.10 (m, 3H), 4.98 - 4.83 (m, 2H), 4.73 - 4.66 (m, 1H), 4.49 - 4.42 (m, 1H), 4.39 - 4.32 (m, 2H), 4.26 - 4.14 (m, 2H), 4.00 - 3.91 (m, 3H), 3.41 (s, 2H), 2.26 - 2.14 (m, 3H), 2.08 - 1.92 (m, 3H), 1.89 - 1.80 (m, 2H), 1.76 - 1.62 (m, 3H), 1.61 - 1.52 (m, 2H), 1.34 - 1.28 (m, 1H), 1.20 - 1.13 (m, 3H), 1.04 (d, J = 6.8 Hz, 3H), 0.92 - 0.83 (m, 3H)
994	propyl (((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy		808.2	^{1}H NMR (400 MHz, CDCl3) δ 9.15 - 8.76 (m, 1H), 8.75 - 8.63 (m, 1H), 8.02 - 7.94 (m, 1H), 7.93 - 7.88 (m, 1H), 7.88 - 7.81 (m, 1H), 7.70 - 7.60 (m, 1H), 7.59 - 7.50 (m, 1H), 7.39 - 7.28 (m, 2H), 7.27 - 7.17 (m, 2H), 7.15 - 7.04 (m, 2H), 6.08 - 5.87 (m, 1H), 4.90 (d, J = 6.4 Hz, 1H), 4.79 -

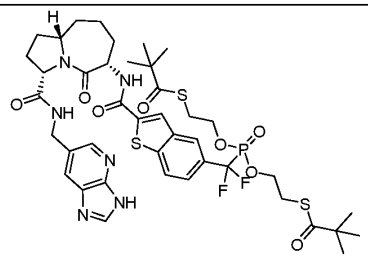
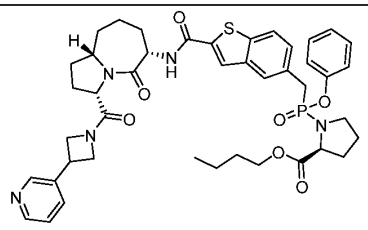
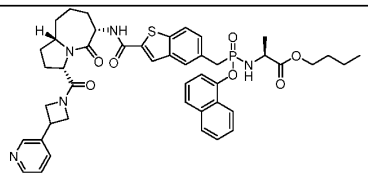
	)phosphoryl)-L-alaninate			4.76 (m, 1H), 4.70 (d, J = 8.8 Hz, 1H), 4.58 - 4.43 (m, 2H), 4.29 - 4.11 (m, 2H), 4.10 - 4.02 (m, 2H), 4.01 - 3.92 (m, 2H), 3.84 - 3.58 (m, 1H), 2.34 - 2.24 (m, 1H), 2.23 - 2.08 (m, 2H), 2.07 - 2.00 (m, 3H), 1.97 - 1.80 (m, 3H), 1.79 - 1.68 (m, 1H), 1.66 - 1.57 (m, 2H), 1.30 (dd, J = 3.6, 7.2 Hz, 2H), 1.14 (d, J = 7.2 Hz, 1H), 0.94 - 0.87 (m, 3H)
995	propyl ((fluoro(2-(((3S,6S,10aS)-3-(3-(2-methoxyethoxy)-3-(pyridin-3-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		878.3	^{1}H NMR (400 MHz, CD_3OD) δ 9.01 - 8.92 (m, 1H), 8.79 - 8.68 (m, 1H), 8.66 - 8.48 (m, 1H), 8.16 - 8.03 (m, 2H), 8.02 - 7.79 (m, 2H), 7.70 - 7.57 (m, 1H), 7.41 - 7.27 (m, 2H), 7.25 - 7.12 (m, 3H), 6.19 - 5.95 (m, 1H), 5.07 - 4.95 (m, 1H), 4.73 - 4.64 (m, 1H), 4.62 - 4.40 (m, 3H), 4.39 - 4.17 (m, 2H), 4.03 - 3.78 (m, 3H), 3.63 - 3.46 (m, 4H), 3.41 - 3.32 (m, 3H), 2.36 - 2.18 (m, 2H), 2.13 - 1.92 (m, 6H), 1.90 - 1.75 (m, 2H), 1.83 - 1.62 (m, 2H), 1.60 - 1.47 (m, 2H), 1.25 - 1.15 (m, 2H), 1.10 - 1.02 (m, 1H), 0.92 - 0.76 (m, 3H)

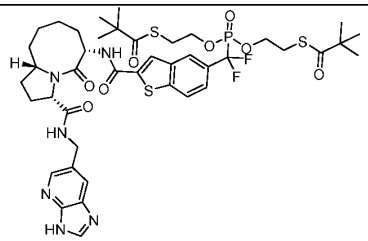
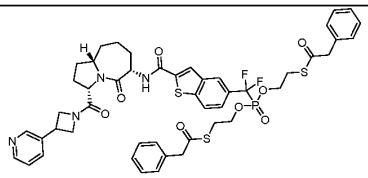
996	propyl (((2-(((3S,6S,9aS)-3-(3-(4-(difluoromethoxy)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		837.9	^{1}H NMR (400 MHz, CD_3OD) 8.68 - 8.52 (m, 1H), 8.51 - 8.41 (m, 1H), 8.03 (d, J = 12.0 Hz, 1H), 7.96 - 7.80 (m, 2H), 7.55 - 7.44 (m, 1H), 7.40 - 7.28 (m, 2H), 7.27 - 7.17 (m, 3H), 7.16 (s, 1H), 7.14 (s, 1H), 4.77 - 4.72 (m, 1H), 4.71 - 4.66 (m, 1H), 4.62 - 4.54 (m, 1H), 4.51 - 4.30 (m, 2H), 4.27 - 4.13 (m, 2H), 4.06 (d, J = 3.8 Hz, 1H), 3.98 - 3.75 (m, 3H), 3.59 - 3.44 (m, 2H), 2.38 - 2.24 (m, 1H), 2.17 - 2.04 (m, 2H), 2.03 - 1.93 (m, 3H), 1.93 - 1.77 (m, 4H), 1.60 - 1.46 (m, 2H), 1.17 - 1.01 (m, 3H), 0.96 - 0.78 (m, 3H)
997	propyl ((R)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or propyl ((S)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-	 or  CFTE-27A, SFC peak 1 was used for synthesis and biological testing	808.3	^{1}H NMR (400 MHz, CDCl3) δ 9.12 - 8.53 (m, 2H), 7.97 (s, 1H), 7.95 - 7.77 (m, 3H), 7.58 (t, J = 8.0 Hz, 1H), 7.26 - 7.19 (m, 2H), 7.14 - 7.06 (m, 3H), 6.04 - 5.88 (m, 1H), 5.10 - 4.83 (m, 1H), 4.79 - 4.61 (m, 2H), 4.60 - 4.51 (m, 1H), 4.49 - 4.22 (m, 2H), 4.22 - 4.01 (m, 4H), 4.00 - 3.91 (m, 1H), 3.74 - 3.59 (m, 1H), 2.11 - 1.99 (m, 5H), 1.98 - 1.72 (m, 5H), 1.68 – 1.58 (m, 2H), 1.31 (d, J = 6.8 Hz, 3H), 0.94 – 0.89 (m, 3H)

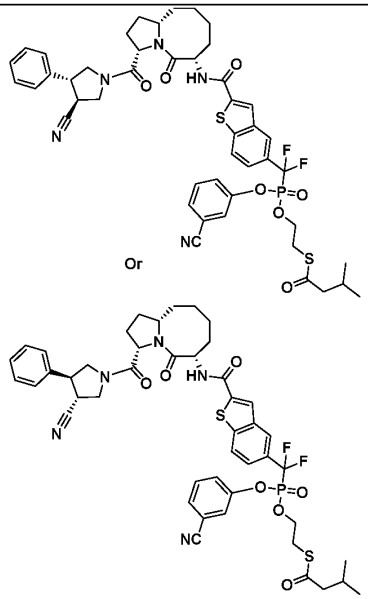
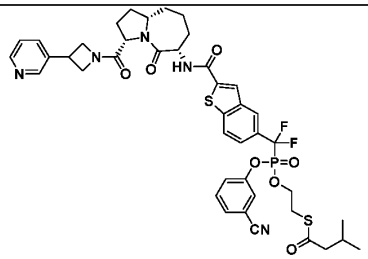
	oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate			
998	propyl ((R)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or propyl ((S)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 or  CFTE-27B, SFC peak 2 was used for synthesis and biological testing	808.3	^{1}H NMR (400 MHz, CDCl3) δ 9.17 - 8.61 (m, 2H), 7.97 (s, 1H), 7.92 - 7.81 (m, 2H), 7.58 (t, J = 8.8 Hz, 1H), 7.33 – 7.29 (m, 1H), 7.27 - 7.22 (m, 2H), 7.12 (d, J = 7.6 Hz, 1H), 7.08 (d, J = 7.2 Hz, 2H), 6.08 - 5.84 (m, 1H), 5.10 - 4.86 (m, 1H), 4.80 - 4.60 (m, 2H), 4.59 - 4.50 (m, 1H), 4.49 - 4.35 (m, 1H), 4.30 - 4.11 (m, 3H), 4.07 – 4.03 (m, 2H), 3.97 (d, J = 6.4 Hz, 1H), 3.79 - 3.63 (m, 1H), 2.34 - 2.08 (m, 3H), 2.08 - 1.99 (m, 3H), 1.98 - 1.70 (m, 4H), 1.68 - 1.56 (m, 2H), 1.30 (d, J = 7.2 Hz, 3H), 0.94 – 0.89 (m, 3H)

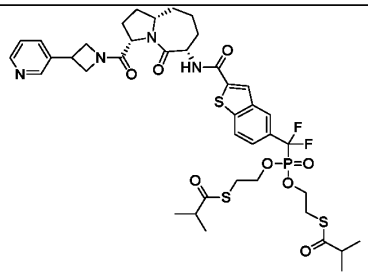
999	propyl ((R)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or propyl ((S)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 or  CFTE-27B, SFC peak 2 was used for synthesis and biological testing	820.2	^{1}H NMR (400 MHz, CDCl3) 8.95 - 8.66 (m, 2H), 8.08 - 7.92 (m, 2H), 7.92 - 7.62 (m, 2H), 7.61 - 7.54 (m, 1H), 7.26 - 7.18 (m, 2H), 7.17 - 7.06 (m, 3H), 6.05 - 5.88 (m, 1H), 4.94 - 4.84 (m, 1H), 4.80 - 4.67 (m, 1H), 4.66 - 4.57 (m, 1H), 4.56 - 4.49 (m, 1H), 4.42 - 4.33 (m, 1H), 4.21 - 4.11 (m, 2H), 4.09 (d, *J* = 3.6 Hz, 3H), 4.06 - 4.02 (m, 2H), 4.01 - 3.91 (m, 1H), 3.91 - 3.68 (m, 1H), 2.34 - 2.23 (m, 1H), 2.22 - 2.08 (m, 2H), 2.03 - 1.99 (m, 3H), 1.95 - 1.69 (m, 4H), 1.68 - 1.56 (m, 2H), 1.28 (d, *J* = 7.2 Hz, 3H), 0.97 - 0.87 (m, 3H)
1000	propyl ((S)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or	 or 	804.3	^{1}H (400 MHz, CDCl3) δ 9.34 - 8.86 (m, 1H), 8.74 - 8.55 (m, 1H), 8.28 - 8.02 (m, 1H), 7.96 (s, 1H), 7.91 - 7.79 (m, 1H), 7.62 - 7.50 (m, 2H), 7.27 - 7.20 (m, 2H), 7.17 - 7.04 (m, 3H), 6.07 - 5.84 (m, 1H), 5.13 - 5.04 (m, 1H), 4.83 (d, J = 9.2 Hz, 1H), 4.76 - 4.70 (m, 1H), 4.56 - 4.42 (m, 2H), 4.24 - 4.07 (m, 2H), 4.05 - 3.93 (m, 3H), 3.87 - 3.58 (m,

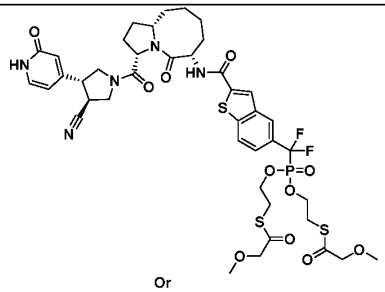
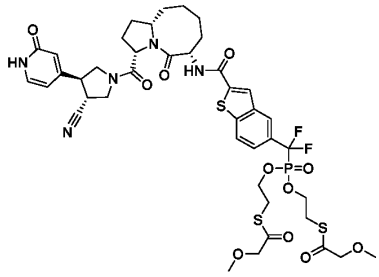
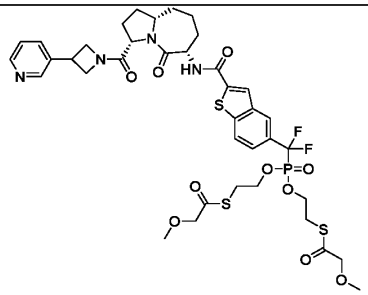
	propyl ((R)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	CFTE-27B, SFC peak 2 was used for synthesis and biological testing		1H), 2.49 (s, 3H), 2.36 - 2.15 (m, 2H), 2.14 - 1.96 (m, 4H), 1.85 (d, J = 3.6 Hz, 3H), 1.65 – 1.59 (m, 2H), 1.46 – 1.39 (m, 1H), 1.33 - 1.25 (m, 3H), 0.97 - 0.86 (m, 3H)
1001	propyl ((S)-((S)-fluoro(2-(((3S,6S,8R,9aR)-8-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or propyl ((R)-((S)-fluoro(2-(((3S,6S,8R,9aR)-8-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy	 or  CFTE-27B, SFC peak 2 was used for synthesis and biological testing	818.2	^{1}H NMR (400 MHz, CDCl3) δ 9.31 - 8.88 (m, 1H), 8.76 - 8.56 (m, 1H), 8.24 (d, *J* = 7.6 Hz, 1H), 8.03 (s, 1H), 7.96 (s, 1H), 7.89 - 7.81 (m, 1H), 7.66 - 7.54 (m, 2H), 7.27 - 7.21 (m, 2H), 7.15 - 7.04 (m, 3H), 6.03 - 5.90 (m, 1H), 5.15 - 5.05 (m, 1H), 4.88 - 4.67 (m, 2H), 4.54 (t, *J* = 4.4 Hz, 1H), 4.50 - 4.40 (m, 1H), 4.24 - 3.96 (m, 6H), 3.82 - 3.65 (m, 1H), 2.50 (s, 3H), 2.35 - 2.18 (m, 2H), 2.14 - 1.98 (m, 4H), 1.81 (t, *J* = 12.8 Hz, 1H), 1.70 - 1.58 (m, 3H), 1.57 - 1.42 (m, 1H), 1.34 - 1.26 (m, 3H), 1.07 - 0.99 (m, 3H), 0.96 - 0.86 (m, 3H)

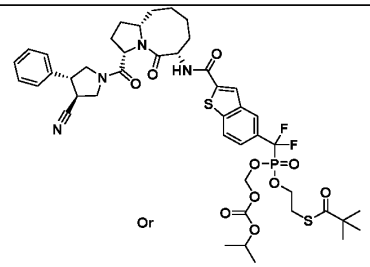
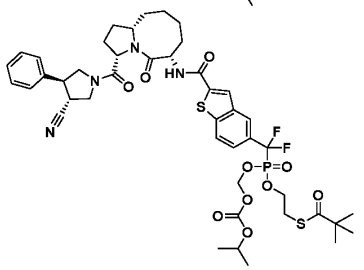
	)phosphoryl)-L-alaninate			
1002	S,S'-(((((2-(((3S,6S,9aS)-3-(((3H-imidazo[4,5-b]pyridin-6-yl)methyl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2,2-dimethylpropanethioate)		921.5	^{1}H NMR (400 MHz, CDCl3) δ 8.32 (s, 1H), 8.22 (s, 1H), 8.18 - 8.09 (m, 1H), 8.02 - 7.92 (m, 2H), 7.89 (s, 1H), 7.77 (s, 1H), 7.68 (d, J = 8.8 Hz, 1H), 4.82 - 4.64 (m, 3H), 4.49 – 4.44 (m, 1H), 4.29 - 4.15 (m, 4H), 3.95 - 3.85 (m, 1H), 3.20 - 2.99 (m, 4H), 2.40 - 2.15 (m, 4H), 2.05 - 1.97 (m, 2H), 1.91 (d, J = 11.6 Hz, 2H), 1.61 - 1.47 (m, 2H), 1.19 (d, J = 2.4 Hz, 18H)
1003	butyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-prolinate		812.0	^{1}H NMR (400 MHz, CDCl3) δ 8.64 - 8.55 (m, 2H), 7.98 - 7.70 (m, 4H), 7.69 - 7.28 (m, 5H), 7.24 (s, 1H), 7.19 - 7.07 (m, 2H), 4.73 - 4.61 (m, 2H), 4.59 - 4.47 (m, 1H), 4.25 - 4.18 (m, 1H), 4.17 - 4.03 (m, 3H), 4.01 - 3.89 (m, 2H), 3.67 - 3.41 (m, 2H), 3.38 - 2.74 (m, 2H), 2.30 - 2.19 (m, 2H), 1.96 (t, J = 10.4 Hz, 2H), 1.91 - 1.79 (m, 4H), 1.76 - 1.68 (m, 2H), 1.66 - 1.49 (m, 6H), 1.47 - 1.23 (m, 4H), 0.93 (m, 3H)
1004	butyl ((naphthalen-1-yloxy)((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-		836.1	^{1}H NMR (400 MHz, CDCl3) δ 8.92 (s, 1H), 8.67 (s, 1H), 8.48 - 8.09 (m, 1H), 7.95 - 7.68 (m, 6H), 7.64 - 7.58 (m, 1H), 7.54 - 7.40 (m, 3H), 7.39 - 7.28 (m, 2H),

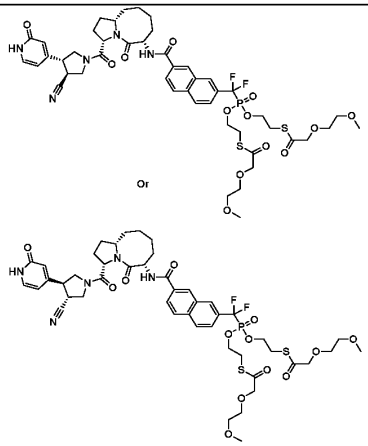
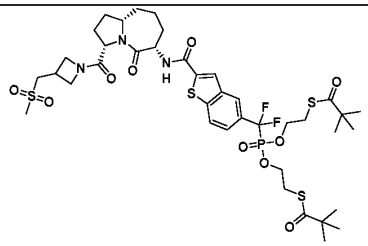
	a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)-L-alaninate			4.81 - 4.66 (m, 3H), 4.56 - 4.45 (m, 2H), 4.26 - 4.11 (m, 2H), 3.97 - 3.89 (m, 3H), 3.67 - 3.53 (m, 3H), 2.34 - 2.14 (m, 2H), 2.13 - 2.00 (m, 4H), 1.99 - 1.72 (m, 4H), 1.54 - 1.40 (m, 2H), 1.34 - 1.21 (m, 2H), 1.20 - 1.14 (m, 2H), 1.07 - 0.99 (m, 1H), 0.92 - 0.83 (m, 3H)
1005	S,S'-(((((2-(((3S,6S,10aS)-3-(((3H-imidazo[4,5-b]pyridin-6-yl)methyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2,2-dimethylpropanethioate)		935.5	^{1}H NMR (400 MHz, CDCl3) δ 8.34 (s, 1H), 8.28 (s, 1H), 8.03 (s, 1H), 7.95 (s, 1H), 7.90 (d, *J* = 8.8 Hz, 1H), 7.83 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 5.24 - 5.11 (m, 1H), 4.82 - 4.80 (m, 1H), 4.58 (t, *J* = 8.4 Hz, 1H), 4.41 - 4.33 (m, 1H), 4.30 - 4.08 (m, 5H), 3.18 - 3.04 (m, 4H), 2.42 - 2.30 (m, 1H), 2.28 - 2.14 (m, 2H), 2.12 - 1.98 (m, 2H), 1.98 - 1.90 (m, 2H), 1.75 - 1.49 (m, 5H), 1.20 (d, *J* = 11.6 Hz, 18H)
1006	S,S'-((((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2-phenylethanethioate)		975.1	^{1}H NMR (400 MHz, CDCl3) δ 8.50 - 8.71 (m, 2H) 8.11 (d, J=8.00 Hz, 1H) 7.82 - 7.94 (m, 2H) 7.62 - 7.73 (m, 2H) 7.24 - 7.38 (m, 11H) 4.52 - 5.04 (m, 4H) 4.14 - 4.46 (m, 6H) 3.89 - 4.08 (m, 2H) 3.58 - 3.69 (m, 4H) 2.89 - 3.18 (m, 4H) 2.15 - 2.31 (m, 2H) 1.90 - 2.12 (m, 6H) 1.71 - 1.84 (m, 2H)

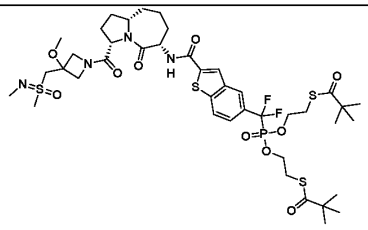
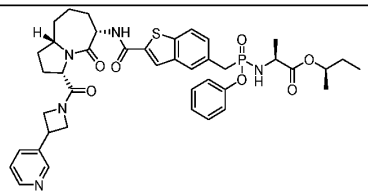
1007	S-(2-((((2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(3-cyanophenoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate Or S-(2-((((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(3-cyanophenoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate	 Or Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	916.1	^{1}H NMR (400 MHz, ACETONITRILE-d_3) δ 8.19 - 8.12 (m, 1H), 8.08 - 7.95 (m, 2H), 7.82 - 7.75 (m, 0.6H), 7.73 - 7.67 (m, 0.4H), 7.67 - 7.61 (m, 1H), 7.60 - 7.55 (m, 1H), 7.54 - 7.43 (m, 3H), 7.43 - 7.28 (m, 5H), 5.09 - 4.99 (m, 1H), 4.64 - 4.55 (m, 1H), 4.41 - 4.21 (m, 4H), 4.10 - 4.02 (m, 0.6H), 4.02 - 3.94 (m, 0.4H), 3.82 - 3.75 (m, 0.4H), 3.74 - 3.32 (m, 3.6H), 3.17 - 3.09 (m, 2H), 2.42 - 2.36 (m, 2H), 2.35 - 2.17 (m, 2H), 2.12 - 1.97 (m, 5H), 1.90 - 1.52 (m, 6H), 0.88 (d, J = 6.6 Hz, 6H).
1008	S-(2-(((3-cyanophenoxy)(difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo		864.1	^{1}H NMR (400 MHz, ACETONITRILE-d_3) δ 8.61 - 8.54 (m, 1H), 8.50 - 8.45 (m, 1H), 8.24 - 8.17 (m, 1H), 8.11 - 8.05 (m, 1H), 8.04 - 7.99 (m, 1H), 7.92 - 7.87 (m, 0.5H), 7.86 - 7.76 (m, 1.5H), 7.70 -

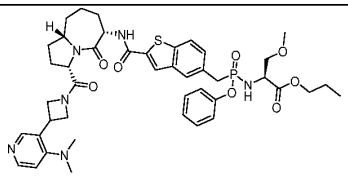
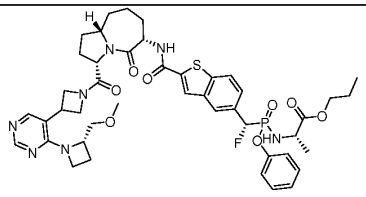
	[b]thiophen-5-yl)methyl)phosphoryl)oxy)ethyl) 3-methylbutanethioate			7.64 (m, 1H), 7.61 - 7.55 (m, 1H), 7.55 - 7.44 (m, 3H), 7.40 - 7.33 (m, 1H), 4.83 - 4.75 (m, 0.5H), 4.68 - 4.58 (m, 1.5H), 4.58 - 4.49 (m, 1H), 4.49 - 4.43 (m, 0.5H), 4.40 - 4.24 (m, 3H), 4.23 - 4.16 (m, 0.5H), 4.02 - 3.87 (m, 3H), 3.16 - 3.09 (m, 2H), 2.41 - 2.35 (m, 2H), 2.10 - 1.99 (m, 5H), 1.91 - 1.74 (m, 5H), 1.69 - 1.54 (m, 1H), 0.91 - 0.85 (m, 6H).
1009	S,S'-((((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2-methylpropanethioate)		879.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.62 - 8.53 (m, 1H), 8.45 (dd, *J* = 11.7, 4.4 Hz, 1H), 8.21 - 8.19 (m, 2H), 8.14 - 7.94 (m, 2H), 7.69 - 7.63 (m, 1H), 7.52 - 7.39 (m, 1H), 4.99 - 4.88 (m, 1H), 4.80 - 4.68 (m, 1H), 4.63 - 4.47 (m, 2H), 4.45 - 4.15 (m, 5H), 4.13 - 3.96 (m, 3H), 3.22 - 3.10 (m, 4H), 2.80 - 2.65 (m, 2H), 2.38 - 2.25 (m, 1H), 2.21 - 1.79 (m, 9H), 1.18 - 1.11 (m, 12H).

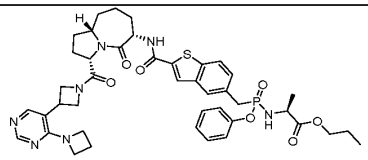
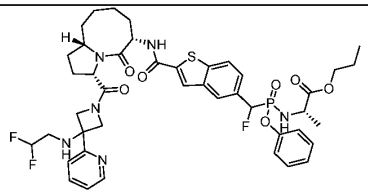
1010	S,S'-(((((2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2-methoxyethanethioate) Or S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2-methoxyethanethioate)	 Or  Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	952.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.23 - 8.18 (m, 1H), 8.18 - 8.13 (m, 1H), 8.12 - 8.05 (m, 1H), 7.69 - 7.61 (m, 1H), 7.45 (dd, *J* = 18.3, 6.8 Hz, 1H), 6.65 - 6.56 (m, 1H), 6.53 - 6.43 (m, 1H), 5.09 - 4.99 (m, 1H), 4.67 - 4.58 (m, 1H), 4.49 - 4.39 (m, 1H), 4.35 - 4.13 (m, 5H), 4.13 - 4.05 (m, 5H), 3.96 - 3.86 (m, 1H), 3.79 - 3.48 (m, 3H), 3.47 - 3.35 (m, 6H), 3.26 - 3.12 (m, 4H), 2.41 - 2.18 (m, 2H), 2.13 - 1.92 (m, 6H), 1.92 - 1.75 (m, 2H), 1.75 - 1.58 (m, 2H).
1011	S,S'-((((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphor		883.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.60 - 8.52 (m, 1H), 8.49 - 8.41 (m, 1H), 8.23 - 8.16 (m, 2H), 8.13 - 7.92 (m, 2H), 7.70 - 7.61 (m, 1H), 7.52 - 7.39 (m, 1H), 5.00 - 4.91 and 4.74 - 4.67 (m, 1H), 4.81 - 4.75

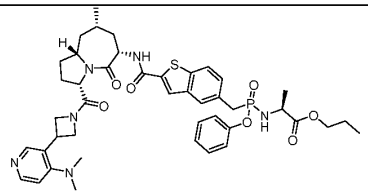
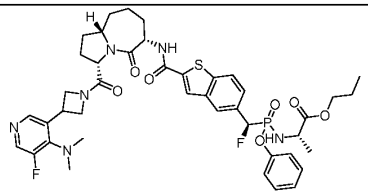
	yl)bis(oxy))bis(ethane-2,1-diyl)) bis(2-methoxyethanethioate)			(m, 1H), 4.64 - 4.50 (m, 2H), 4.45 - 4.17 (m, 5H), 4.13 - 3.99 (m, 7H), 3.50 - 3.38 (m, 6H), 3.27 - 3.12 (m, 4H), 2.39 - 2.25 (m, 1H), 2.22 - 1.78 (m, 9H).
1012	S-(2-((((2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)((isopropoxycarbonyl)oxy)methoxy)phosphoryl)oxy)ethyl) 2,2-dimethylpropanethioate Or S-(2-((((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-phenylpyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)((isopropoxycarbonyl)oxy)methoxy)phosphoryl)oxy)ethyl) 2,2-dimethylpropanethioate	 Or  Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	931.1	^{1}H NMR (400 MHz, ACETONITRILE-d_3) δ 8.17 - 8.09 (m, 1H), 8.08 - 8.01 (m, 1H), 7.99 (s, 1H), 7.74 - 7.55 (m, 2H), 7.45 - 7.21 (m, 5H), 5.72 - 5.49 (m, 2H), 5.11 - 4.96 (m, 1H), 4.94 - 4.77 (m, 1H), 4.59 (t, J = 8.4 Hz, 1H), 4.44 - 4.23 (m, 2H), 4.22 - 3.92 (m, 3H), 3.85 - 3.30 (m, 4H), 3.07 (t, J = 6.5 Hz, 2H), 2.38 - 2.19 (m, 1H), 2.13 - 1.95 (m, 5H), 1.92 - 1.85 (m, 1H), 1.83 - 1.56 (m, 5H), 1.27 (d, J = 6.1 Hz, 6H), 1.16 (s, 9H).

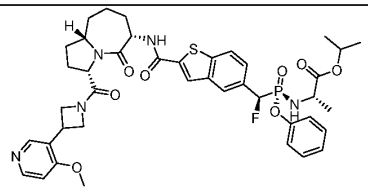
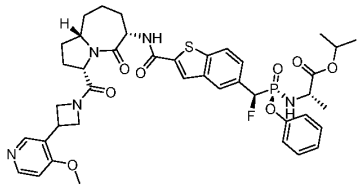
1013	S,S'-(((((7-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2-(2-methoxyethoxy)ethanethioate) Or S,S'-(((((7-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2-(2-methoxyethoxy)ethanethioate)	 Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	1034.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1H), 8.29 (br. s., 1H), 8.10 (d, *J* = 8.3 Hz, 1H), 8.06 (d, *J* = 2.4 Hz, 2H), 7.77 (d, *J* = 9.0 Hz, 1H),7.46 (t, *J* = 7.6 Hz, 1H), 6.58 (d, *J* = 9.5 Hz, 1H), 6.51 - 6.43 (m, 1H), 5.14 - 5.06 (m, 1H), 4.73 - 4.65 (m, 1H), 4.57 - 4.51 (m, 0.5H), 4.51 - 4.45 (m, 1H), 4.35 - 4.21 (m, 4H), 4.19 (s, 4H), 4.08 - 4.02 (m, 0.5H), 3.97 - 3.91 (m, 0.5H), 3.89 - 3.82 (m, 0.5H), 3.75 - 3.63 (m, 6H), 3.62 - 3.51 (m, 6H), 3.35 (s, 6H), 3.26 - 3.13 (m, 4H), 2.41 - 2.19 (m, 2H), 2.13 - 1.94 (m, 6H), 1.93 - 1.76 (m, 2H), 1.76 - 1.60 (m, 2H).
1014	S,S'-((((difluoro(2-(((3S,6S,9aS)-3-(3-((methylsulfonyl)methyl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		922.08	^{1}H NMR (400 MHz, CDCl3) δ 8.08 (s, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.84 (s, 1H), 7.63 (d, *J* = 8.6 Hz, 2H), 4.63 (s, 1H), 4.43 (d, *J* = 9.4 Hz, 2H), 4.17 (dt, *J* = 19.8, 6.9 Hz, 4H), 4.02 – 3.78 (m, 2H),

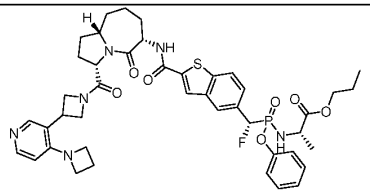
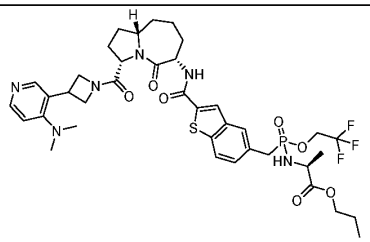
	yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2,2-dimethylpropanethioate)			3.50 – 3.26 (m, 3H), 3.08 (q, *J* = 6.2 Hz, 3H), 2.95 (d, *J* = 7.4 Hz, 3H), 2.28 – 2.13 (m, 2H), 1.94 (d, *J* = 33.2 Hz, 5H), 1.78 (s, 1H), 1.64 (d, *J* = 12.4 Hz, 6H), 1.20 (s, 18H).
1015	S,S'-(((((2-(((3S,6S,9aS)-3-(3-((N,S-dimethylsulfonimidoyl)methyl)-3-methoxyazetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy)) bis(ethane-2,1-diyl)) bis(2,2-dimethylpropanethioate)		965.15	^{1}H NMR (400 MHz, CDCl3) δ 8.08 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.89 – 7.78 (m, 1H), 7.68 – 7.52 (m, 2H), 4.93 – 4.57 (m, 2H), 4.44 (t, *J* = 19.6 Hz, 2H), 4.16 (d, *J* = 24.1 Hz, 4H), 4.06 – 3.79 (m, 2H), 3.58 – 3.46 (m, 3H), 3.09 (s, 7H), 2.95 – 2.76 (m, 3H), 2.28 – 2.12 (m, 2H), 2.01 (s, 4H), 1.90 (s, 2H), 1.77 (s, 5H), 1.20 (q, *J* = 3.5 Hz, 18H).
1016	(R)-sec-butyl (((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		786.3	^{1}H NMR (400 MHz, CDCl3) δ 9.01 - 8.80 (m, 1H), 8.78 - 8.66 (m, 1H), 8.49 (d, J = 7.2 Hz, 1H), 7.89 - 7.76 (m, 4H), 7.75 - 7.61 (m, 1H), 7.49 - 7.38 (m, 1H), 7.32 - 7.28 (m, 1H), 7.17 - 7.09 (m, 3H), 4.74 (s, 3H), 4.57 - 4.44 (m, 2H), 4.28 - 4.14 (m, 1H), 3.97 (m, 3H), 3.57 - 3.17 (m, 3H), 2.36 - 2.23 (m, 1H), 2.23 - 2.14 (m, 1H),, 2.12 - 1.99 (m, 4H), 1.97 - 1.86 (m, 2H), 1.86 - 1.66 (m, 2H), 1.57 - 1.43 (m, 2H),

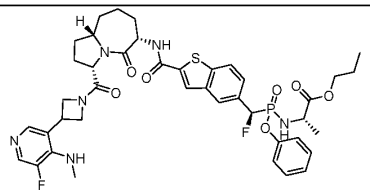
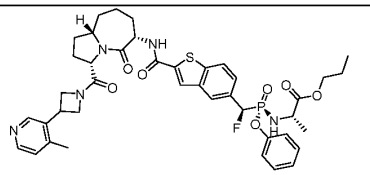
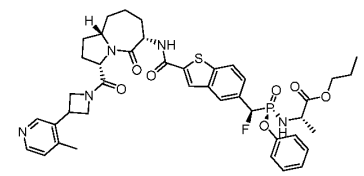
				1.22 - 1.16 (m, 2H), 1.16 - 1.06 (m, 4H), 0.88 - 0.79 (m, 3H)
1017	propyl N-(((2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-O-methyl-L-serinate		845.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.40 - 8.33 (m, 1H), 8.16 - 8.06 (m, 1H), 8.05 - 7.98 (m, 1H), 7.94 - 7.84 (m, 2H), 7.53 - 7.46 (m, 1H), 7.36 - 7.28 (m, 2H), 7.21 - 7.14 (m, 3H), 7.10 (dd, J = 7.2, 18.4 Hz, 1H), 4.78 - 4.67 (m, 2H), 4.58 - 4.49 (m, 2H), 4.49 - 4.40 (m, 1H), 4.37 - 4.29 (m, 1H), 4.12 - 4.04 (m, 2H), 4.02 - 3.89 (m, 3H), 3.61 (s, 1H), 3.58 - 3.49 (m, 2H), 3.39 - 3.33 (m, 1H), 3.17 - 3.14 (m, 9H), 2.37 - 2.26 (m, 1H), 2.20 - 2.06 (m, 2H), 2.04 - 1.90 (m, 4H), 1.89 - 1.78 (m, 3H), 1.62 - 1.48 (m, 2H), 0.92 - 0.80 (m, 3H)
1018	propyl (((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-((S)-2-(methoxymethyl)azetidin-1-yl)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		890.3	^{1}H NMR (400 MHz, CDCl3) δ 8.64 - 8.51 (m, 1H), 8.46 - 8.30 (m, 1H), 8.10 - 7.78 (m, 3H), 7.65 - 7.52 (m, 1H), 7.39 - 7.29 (m, 1H), 7.27 - 7.03 (m, 4H), 6.03-5.89 (m, 1H), 5.08 - 4.63 (m, 4H), 4.60 - 4.42 (m, 3H), 4.35 - 4.20 (m, 2H), 4.15 - 4.10 (m, 1H), 4.03 (t, J = 6.4 Hz, 1H), 3.98 - 3.90 (m, 2H), 3.88 - 3.77 (m, 1H), 3.76 - 3.65 (m, 1H), 3.49 (t, J = 10.8 Hz, 1H), 3.45 - 3.27 (m, 3H), 2.65 - 2.42 (m, 2H),

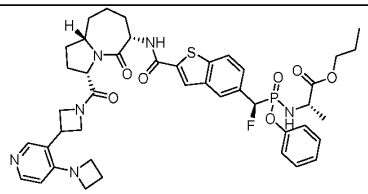
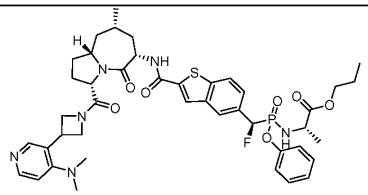
				2.31 - 2.12 (m, 2H), 2.04 (d, J = 4.8 Hz, 2H), 1.99 - 1.87 (m, 2H), 1.82 (s, 2H), 1.66 - 1.58 (m, 1H), 1.57 - 1.46 (m, 1H), 1.43 (d, J = 6.9 Hz, 2H), 1.38 (d, J = 6.4 Hz, 1H), 1.30 - 1.25 (m, 2H), 1.02 - 0.72 (m, 3H)
1019	propyl (((2-(((3S,6S,9aS)-3-(3-(4-(azetidin-1-yl)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		828.6	^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (dd, J = 0.8, 20.0 Hz, 1H), 8.26 (d, J = 4.4 Hz, 1H), 8.04 - 8.01 (m, 1H), 7.93 - 7.86 (m, 2H), 7.52 - 7.44 (m, 1H), 7.35 - 7.29 (m, 2H), 7.20 - 7.12 (m, 3H), 4.81 (s, 1H), 4.74 (dd, J = 3.2, 10.8 Hz, 1H), 4.61 - 4.51 (m, 5H), 4.41 - 4.27 (m, 2H), 4.11 - 4.04 (m, 3H), 3.97 - 3.90 (m, 2H), 3.89 - 3.82 (m, 1H), 3.58 - 3.47 (m, 2H), 2.54 - 2.45 (m, 2H), 2.35 - 2.27 (m, 1H), 2.18 - 2.07 (m, 2H), 2.05 - 1.83 (m, 7H), 1.58 - 1.50 (m, 2H), 1.15 - 1.07 (m, 3H), 0.90 - 0.83 (m, 3H)
1020	propyl (((2-(((3S,6S,10aS)-3-(3-((2,2-difluoroethyl)amino)-3-(pyridin-2-yl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(ph		883.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.68 - 8.57 (m, 1H), 8.18 - 7.91 (m, 4H), 7.80 (d, J = 7.4 Hz, 1H), 7.71 - 7.59 (m, 1H), 7.52 - 7.41 (m, 1H), 7.40 - 7.29 (m, 2H), 7.27 - 7.13 (m, 3H), 6.20 - 5.75 (m, 2H), 5.06 - 4.94 (m, 2H), 4.73 (s, 1H), 4.50 - 4.14 (m, 4H), 4.01 -

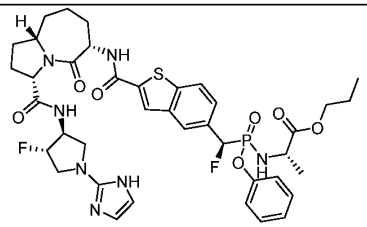
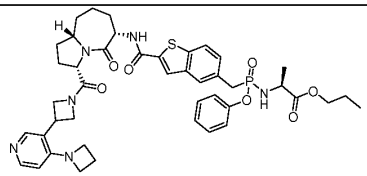
	enoxy)phosphoryl)-L-alaninate			3.76 (m, 3H), 3.05 - 2.86 (m, 2H), 2.35 - 2.18 (m, 2H), 2.11 - 1.78 (m, 8H), 1.72 - 1.47 (m, 4H), 1.29 - 1.18 (m, 2H), 1.06 (d, J = 7.2 Hz, 1H), 0.95 - 0.81 (m, 3H)
1021	propyl (((2-(((3S,6S,8R,9aR)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		829.5	^{1}H NMR (400 MHz, CDCl3) δ 8.68 - 8.28 (m, 2H), 7.96 - 7.63 (m, 4H), 7.51 - 7.37 (m, 1H), 7.33 - 7.27 (m, 2H), 7.20 - 7.08 (m, 3H), 6.89 - 6.82 (m, 1H), 5.05 - 4.79 (m, 1H), 4.77 - 4.54 (m, 3H), 4.48 - 4.26 (m, 1H), 4.24 - 4.08 (m, 2H), 4.02 - 3.90 (m, 4H), 3.50 - 3.38 (m, 2H), 3.35 - 3.08 (m, 1H), 2.93 - 2.83 (m, 6H), 2.33 - 2.25 (m, 1H), 2.18 - 1.99 (m, 5H), 1.82 - 1.65 (m, 2H), 1.63 - 1.47 (m, 3H), 1.20 - 1.12 (m, 3H), 1.05 - 0.99 (m, 3H), 0.95 - 0.85 (m, 3H)
1022	propyl (((R)-(2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)-5-fluoropyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		851.5	^{1}H NMR (400 MHz, CDCl3) δ 8.83 - 8.50 (m, 1H), 8.47 - 8.33 (m, 1H), 8.04 - 7.79 (m, 3H), 7.67 - 7.59 (m, 1H), 7.59 - 7.46 (m, 1H), 7.39 - 7.29 (m, 1H), 7.25 - 7.17 (m, 1H), 7.15 - 7.04 (m, 2H), 6.08 - 5.85 (m, 1H), 5.11 - 4.92 (m, 1H), 4.86 - 4.63 (m, 2H), 4.53 (t, J = 5.6 Hz, 1H), 4.48 - 4.28 (m, 1H), 4.21 - 4.09 (m, 1H), 4.08 - 4.03 (m, 2H), 4.02 - 3.97 (m, 2H), 3.65 -

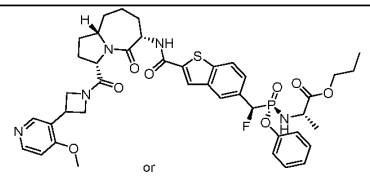
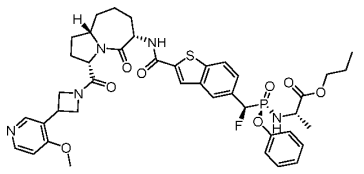
				3.53 (m, 2H), 3.12 - 3.05 (m, 6H), 2.35 - 2.25 (m, 1H), 2.24 - 2.15 (m, 1H), 2.13 - 1.97 (m, 4H), 1.96 - 1.90 (m, 1H), 1.85 (d, J = 6.4 Hz, 2H), 1.81 - 1.66 (m, 1H), 1.66 - 1.55 (m, 2H), 1.31 - 1.12 (m, 3H), 0.95 - 0.87 (m, 3H)
1023	isopropyl ((S)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or isopropyl ((R)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 or  Less polar linker building block was used in synthesis and biological testing	820.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.61 (m, 2H), 8.12 - 8.04 (m, 2H), 7.97 (m, 1H), 7.67 - 7.54 (m, 2H), 7.33 (m, 2H), 7.24 - 7.15 (m, 3H), 6.19 - 5.96 (m, 1H), 4.95 - 4.90 (m, 1H), 4.78 - 4.71 (m, 1H), 4.65 (m, 1H), 4.56 (m, 1H), 4.46 - 4.34 (m, 1H), 4.22 - 4.14 (m, 5H), 4.13 - 4.05 (m, 2H), 3.88 - 3.79 (m, 1H), 2.38 - 2.23 (m, 1H), 2.08 (m, 2H), 2.06 - 2.02 (m, 1H), 2.00 - 1.97 (m, 1H), 1.90 (s, 2H), 1.88 - 1.79 (m, 3H), 1.24 - 1.21 (m, 3H), 1.17 (t, *J* = 8.00 Hz, 6H)

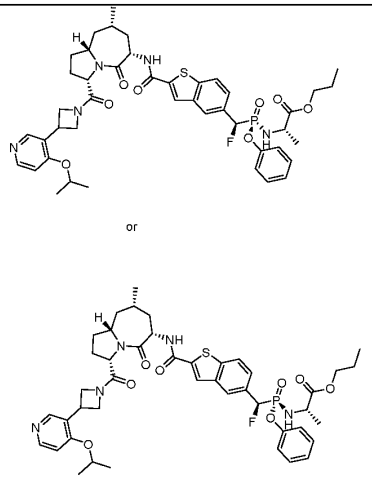
1024	propyl (((S)-(2-(((3S,6S,9aS)-3-(3-(4-(azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		845.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.32 - 8.21 (m, 1H), 8.15 - 8.06 (m, 2H), 8.04 - 7.93 (m, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.40 - 7.29 (m, 2H), 7.26 - 7.13 (m, 3H), 6.57 - 6.46 (m, 1H), 6.19 - 5.97 (m, 1H), 4.78 - 4.72 (m, 1H), 4.66 - 4.52 (m, 3H), 4.51 - 4.41 (m, 3H), 4.41 - 4.29 (m, 2H), 4.23 - 4.14 (m, 1H), 4.13 - 4.04 (m, 2H), 3.97 (t, J = 6.8 Hz, 2H), 3.87 - 3.74 (m, 1H), 2.58 - 2.43 (m, 2H), 2.38 - 2.26 (m, 1H), 2.20 - 2.07 (m, 2H), 2.06 - 1.97 (m, 2H), 1.97 – 1.94 (m, 2H), 1.90 - 1.78 (m, 3H), 1.61 – 1.52 (m, 2H), 1.09 – 1.07 (m, 3H), 0.88 (t, J = 7.2 Hz, 3H)
1025	propyl (((2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(2,2,2-trifluoroethoxy)phosphoryl)-L-alaninate		821.3	^{1}H NMR (400 MHz, CDCl3) δ 8.76 - 8.49 (m, 1H), 8.31 - 8.22 (m, 1H), 7.92 (d, J = 4.0 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.76 - 7.61 (m, 1H), 7.41 - 7.29 (m, 1H), 6.94 - 6.84 (m, 1H), 4.92 - 4.79 (m, 1H), 4.77 - 4.60 (m, 2H), 4.52 (d, J = 5.2 Hz, 1H), 4.47 - 4.33 (m, 2H), 4.29 - 4.24 (m, 1H), 4.22 (s, 1H), 4.11 - 4.05 (m, 1H), 4.04 - 3.87 (m, 4H), 3.54 - 3.42 (m, 1H), 3.40 - 3.24 (m, 2H), 3.14 (s, 3H), 3.09 (s, 3H), 2.35 - 2.24 (m, 1H),

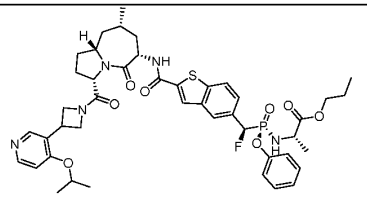
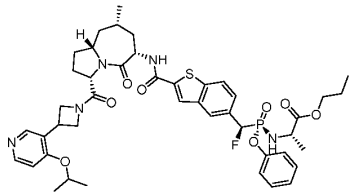
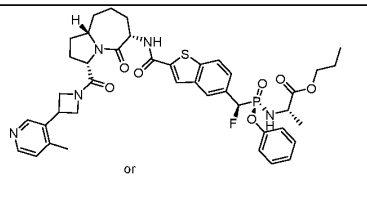
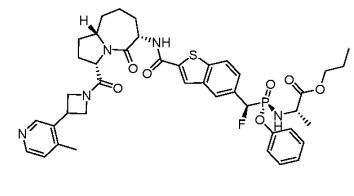
				2.22 - 2.14 (m, 1H), 2.13 - 2.05 (m, 2H), 2.04 - 1.98 (m, 2H), 1.95 - 1.74 (m, 4H), 1.67 - 1.58 (m, 2H), 1.37 - 1.24 (m, 3H), 0.91 (m, 3H)
1026	propyl (((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(5-fluoro-4-(methylamino)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		837.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.41 - 8.28 (m, 1H), 8.18 (d, J = 8.4 Hz, 1H), 8.12 - 8.04 (m, 2H), 8.02 - 7.95 (m, 1H), 7.71 - 7.61 (m, 1H), 7.39 - 7.29 (m, 2H), 7.23 - 7.13 (m, 3H), 6.19 - 6.01 (m, 1H), 5.00 - 4.90 (m, 1H), 4.80 - 4.67 (m, 2H), 4.63 - 4.48 (m, 2H), 4.46 - 4.28 (m, 1H), 4.13 - 4.00 (m, 2H), 3.98 - 3.86 (m, 2H), 3.85 - 3.79 (m, 1H), 3.29 (d, J = 7.2 Hz, 3H), 2.38 - 2.25 (m, 1H), 2.18 - 2.05 (m, 2H), 2.03 - 1.75 (m, 7H), 1.62 - 1.45 (m, 2H), 1.29 - 1.18 (m, 3H), 0.97 - 0.80 (m, 3H)
1027	propyl ((S)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 or 	804.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.86 - 8.80 (m, 1H), 8.62 - 8.52 (m, 1H), 8.15 - 8.05 (m, 2H), 8.00 (d, J = 4.4, 8.3 Hz, 1H), 7.89 - 7.79 (m, 1H), 7.67 - 7.61 (m, 1H), 7.40 - 7.30 (m, 2H), 7.26 - 7.16 (m, 3H), 6.10 (s, 1H), 4.79 - 4.72 (m, 2H), 4.71 - 4.63 (m, 1H), 4.61 - 4.48 (m, 2H), 4.47 - 4.31 (m, 2H), 4.21 - 4.07 (m, 2H), 4.00 - 3.96 (m, 1H),

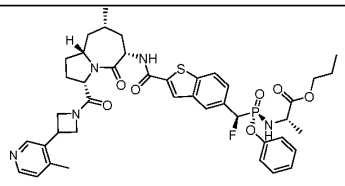
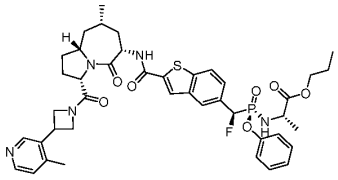
	or propyl ((R)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	CFTE-28A, SFC peak 2 was used in synthesis and biological testing		3.92 - 3.82 (m, 1H), 2.59 - 2.51 (m, 3H), 2.38 - 2.26 (m, 1H), 2.22 - 2.09 (m, 2H), 2.08 - 2.00 (m, 2H), 2.00 - 1.93 (m, 2H), 1.92 - 1.85 (m, 2H), 1.85 - 1.79 (m, 1H), 1.63 - 1.53 (m, 2H), 1.28 - 1.20 (m, 3H), 0.95 - 0.85 (m, 3H)
1028	propyl (((R)-(2-(((3S,6S,9aS)-3-(3-(4-(azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		845.2	^{1}H NMR (400 MHz, CDCl3) δ 8.68 - 8.39 (m, 1H), 7.89 - 7.80 (m, 2H), 8.15 - 7.78 (m, 2H), 7.67 - 7.56 (m, 1H), 7.26 (s, 2H), 7.17 - 7.01 (m, 3H), 6.32 - 6.10 (m, 1H), 6.08 - 5.90 (m, 1H), 5.05 - 4.86 (m, 1H), 4.83 - 4.65 (m, 1H), 4.59 - 4.46 (m, 2H), 4.45 - 4.19 (m, 5H), 4.11 - 4.00 (m, 3H), 4.00 - 3.92 (m, 2H), 3.84 (s, 1H), 2.54 (td, J = 8.1, 16.7 Hz, 2H), 2.33 - 2.14 (m, 2H), 2.04 (s, 3H), 2.00 - 1.88 (m, 2H), 1.87 - 1.66 (m, 3H), 1.63 - 1.55 (m, 2H), 1.33 - 1.29 (m, 3H), 0.95 - 0.84 (m, 3H)
1029	propyl (((R)-(2-(((3S,6S,8R,9aR)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-		847.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 - 8.56 (m, 1H), 8.30 - 7.98 (m, 3H), 7.88 - 7.58 (m, 3H), 7.23 (s, 1H), 7.10 - 7.05 (m, 3H), 6.90 - 6.82 (m, 1H), 6.05 - 5.91 (m, 1H),

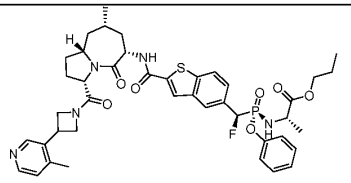
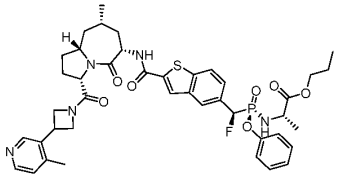
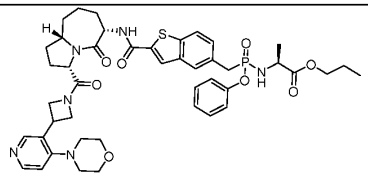
	oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate			5.03 - 4.94 (m, 1H), 4.83 - 4.68 (m, 2H), 4.52 (t, *J* = 4.8 Hz, 1H), 4.43 - 4.34 (m, 1H), 4.04 - 3.95 (m, 6H), 3.69 - 3.57 (m, 1H), 3.12 (s, 3H), 3.06 (s, 3H), 2.30 - 2.28 (m, 1H), 2.10 - 2.01 (m, 5H), 1.63 - 1.57 (m, 5H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 3.6 Hz, 3H), 0.90 (q, *J* = 6.8 Hz, 3H)
1030	propyl (((R)-fluoro(2-(((3S,6S,9aS)-3-(((3S,4S)-4-fluoro-1-(1H-imidazol-2-yl)pyrrolidin-3-yl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		826.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.09 - 8.05 (m, 2H), 8.01 - 7.96 (m, 1H), 7.67 - 7.62 (m, 1H), 7.36 - 7.31 (m, 2H), 7.22 - 7.15 (m, 3H), 6.95 (s, 2H), 6.19 - 5.99 (m, 1H), 5.33 - 5.14 (m, 1H), 4.72 (d, J = 11.2 Hz, 1H), 4.63 - 4.59 (m, 1H), 4.45 - 4.42 (m, 1H), 4.11 - 4.04 (m, 1H), 3.99 - 3.73 (m, 6H), 3.64 (d, J = 10.8 Hz, 1H), 2.34 - 2.23 (m, 1H), 2.15 - 1.82 (m, 9H), 1.60 - 1.48 (m, 2H), 1.25 - 1.19 (m, 3H), 0.91 - 0.83 (m, 3H)
1031	propyl (((2-(((3S,6S,9aS)-3-(3-(4-(azetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy		827.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.26 (d, *J* = 9.2 Hz, 1H), 8.04 - 8.00 (m, 1H), 7.96 (d, *J* = 7.2 Hz, 1H), 7.92 - 7.84 (m, 2H), 7.53 - 7.46 (m, 1H), 7.35 - 7.28 (m, 2H), 7.20 - 7.13 (m, 3H), 6.51 (dd, *J* = 7.2, 10.8 Hz, 1H), 4.95 - 4.91 (m, 1H), 4.74 (d, *J* = 11.2 Hz, 1H),

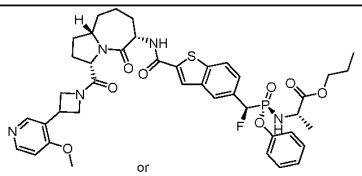
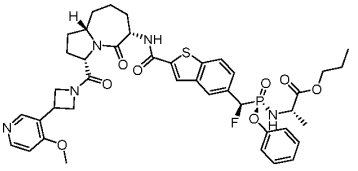
	)phosphoryl)-L-alaninate			4.62 - 4.52 (m, 3H), 4.49 - 4.37 (m, 3H), 4.35 - 4.30 (m, 1H), 4.21 - 4.14 (m, 1H), 4.10 - 4.05 (m, 2H), 3.95 - 3.90 (m, 2H), 3.89 - 3.81 (m, 1H), 3.57 - 3.46 (m, 2H), 2.56 - 2.46 (m, 2H), 2.34 - 2.27 (m, 1H), 2.15 - 2.06 (m, 2H), 2.01 - 1.82 (m, 7H), 1.58 - 1.50 (m, 2H), 1.14 (d, *J* = 7.2 Hz, 2H), 1.09 (dd, *J* = 4.8, 7.2 Hz, 1H), 0.89 - 0.84 (m, 3H)
1032	propyl ((S)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or propyl ((R)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy	 or  CFTE-28B, SFC peak 1 was used for synthesis and biological testing	820.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.72 - 8.60 (m, 2H), 8.13 - 8.03 (m, 2H), 8.01 - 7.95 (m, 1H), 7.69 - 7.55 (m, 2H), 7.39 - 7.30 (m, 2H), 7.22 - 7.13 (m, 3H), 6.19 - 6.02 (m, 1H), 4.78 - 4.71 (m, 1H), 4.66 (d, J = 7.2 Hz, 1H), 4.60 - 4.51 (m, 1H), 4.49 - 4.41 (m, 1H), 4.40 - 4.32 (m, 1H), 4.23 - 4.14 (m, 5H), 4.09 (d, J = 4.0 Hz, 1H), 3.97 - 3.88 (m, 1H), 3.86 - 3.77 (m, 2H), 2.38 - 2.26 (m, 1H), 2.20 - 2.06 (m, 2H), 2.05 - 1.96 (m, 2H), 1.95 - 1.89 (m, 2H), 1.88 - 1.77 (m, 3H), 1.57 - 1.45 (m, 2H), 1.21 (d, J = 7.2 Hz, 3H), 0.90 - 0.80 (m, 3H)

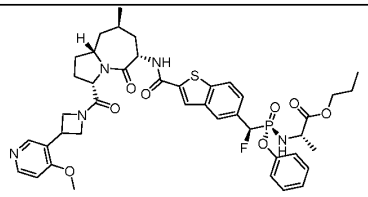
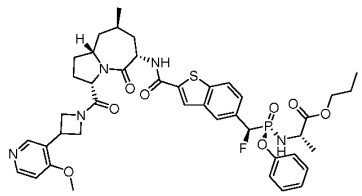
	)phosphoryl)-L-alaninate			
1033	propyl ((R)-((R)-fluoro(2-(((3S,6S,8R,9aR)-3-(3-(4-isopropoxypyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or propyl ((S)-((R)-fluoro(2-(((3S,6S,8R,9aR)-3-(3-(4-isopropoxypyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 or CFTE-28B, SFC peak 1 was used for synthesis and biological testing	862.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 - 8.63 (m, 2H), 8.05 - 7.77 (m, 4H), 7.73 - 7.51 (m, 2H), 7.26 - 7.24 (m, 1H), 7.19 - 7.05 (m, 4H), 6.07 - 5.92 (m, 1H), 5.01 - 4.81 (m, 2H), 4.79 - 4.68 (m, 1H), 4.67 - 4.50 (m, 2H), 4.45 - 4.35 (m, 1H), 4.19 - 3.93 (m, 6H), 3.75 - 3.56 (m, 1H), 2.35 - 2.23 (m, 1H), 2.17 - 1.97 (m, 5H), 1.83 - 1.73 (m, 1H), 1.71 - 1.56 (m, 3H), 1.54 - 1.43 (m, 7H), 1.33 - 1.26 (m, 3H), 1.02 (t, *J* = 6.0 Hz, 3H), 0.95 – 0.86 (m, 3H)

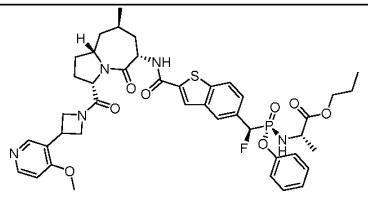
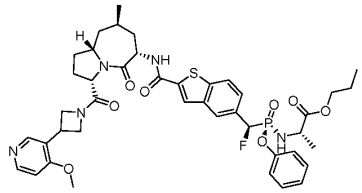
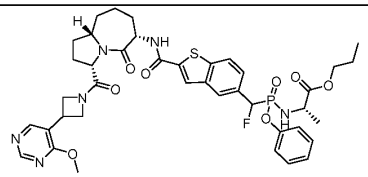
1034	propyl ((R)-((R)-fluoro(2-(((3S,6S,8R,9aR)-3-(3-(4-isopropoxypyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or propyl ((S)-((R)-fluoro(2-(((3S,6S,8R,9aR)-3-(3-(4-isopropoxypyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 or  CFTE-28A, SFC peak 2 was used for synthesis and biological testing	862.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 - 8.57 (m, 2H), 8.09 - 7.77 (m, 4H), 7.70 - 7.46 (m, 2H), 7.39 – 7.31 (m, 2H), 7.23 - 7.08 (m, 2H), 6.04 - 5.84 (m, 1H), 5.01 - 4.82 (m, 2H), 4.79 - 4.69 (m, 1H), 4.66 - 4.52 (m, 2H), 4.44 - 4.34 (m, 1H), 4.16 - 3.95 (m, 6H), 3.80 - 3.65 (m, 1H), 2.35 - 2.24 (m, 1H), 2.17 - 1.97 (m, 5H), 1.82 - 1.73 (m, 1H), 1.71 - 1.57 (m, 3H), 1.48 (s, 6H), 1.45 - 1.38 (m, 1H), 1.13 (t, *J* = 6.8 Hz, 3H), 1.02 (t, *J* = 5.6 Hz, 3H), 0.95 - 0.83 (m, 3H)
1035	propyl ((R)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy	 or 	804.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.87 - 8.80 (m, 1H), 8.64 - 8.53 (m, 1H), 8.14 - 8.04 (m, 2H), 7.98 (d, J = 5.2, 8.3 Hz, 1H), 7.90 - 7.82 (m, 1H), 7.70 - 7.62 (m, 1H), 7.40 - 7.13 (m, 5H), 6.21 - 6.02 (m, 1H), 5.01 (d, J = 8.8 Hz, 1H), 4.79 - 4.71 (m, 2H), 4.70 - 4.62

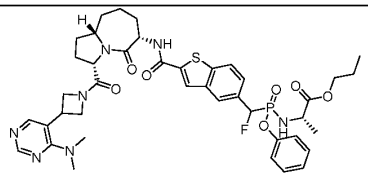
	)phosphoryl)-L-alaninate or propyl ((S)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	CFTE-28B, SFC peak 1 was used for synthesis and biological testing		(m, 1H), 4.61 - 4.52 (m, 2H), 4.50 - 4.41 (m, 1H), 4.40 - 4.31 (m, 1H), 4.17 (d, J = 6.8, 9.8 Hz, 1H), 4.14 - 4.06 (m, 1H), 3.88 - 3.79 (m, 2H), 2.60 - 2.52 (m, 3H), 2.37 - 2.28 (m, 1H), 2.22 - 2.14 (m, 1H), 2.14 - 2.06 (m, 2H), 2.02 (td, J = 5.8, 11.9 Hz, 2H), 1.97 - 1.91 (m, 2H), 1.90 - 1.85 (m, 2H), 1.84 - 1.79 (m, 2H), 1.57 - 1.46 (m, 2H), 1.21 (d, J = 7.1 Hz, 3H), 0.95 - 0.81 (m, 3H)
1036	propyl ((S)-((R)-fluoro(2-(((3S,6S,8R,9aR)-8-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or propyl ((R)-((R)-fluoro(2-(((3S,6S,8R,9aR)-8-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo	 or  CFTE-28B, SFC peak 1 was used for synthesis and biological testing	818.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 - 8.91 (m, 1H), 8.69 - 8.57 (m, 1H), 8.19 (d, *J* = 7.2 Hz, 1H), 8.00 (d, *J* = 6.0 Hz, 2H), 7.90 - 7.81 (m, 1H), 7.65 - 7.54 (m, 2H), 7.28 (s, 1H), 7.24 (s, 1H), 7.17 - 7.03 (m, 3H), 6.12 - 5.88 (m, 1H), 5.08 (d, *J* = 4.8 Hz, 1H), 4.82 (d, *J* = 7.6 Hz, 1H), 4.75 - 4.70 (m, 1H), 4.54 (t, *J* = 5.6 Hz, 1H), 4.47 (d, *J* = 8.8 Hz, 1H), 4.26 - 3.96 (m, 6H), 3.71 - 3.56 (m, 1H), 2.51 (d, *J* = 2.9 Hz, 3H), 2.36 - 2.26 (m, 1H), 2.22 - 1.98 (m, 5H), 1.85 - 1.76 (m, 1H), 1.71 - 1.45 (m, 4H), 1.32 - 1.26 (m, 3H), 1.02 (t, *J* = 5.6 Hz, 3H), 0.95 - 0.87 (m, 3H)

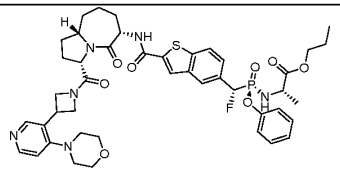
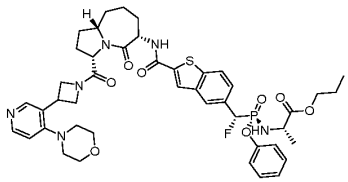
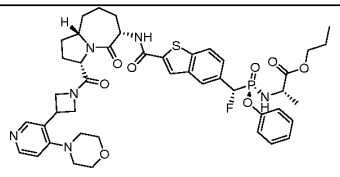
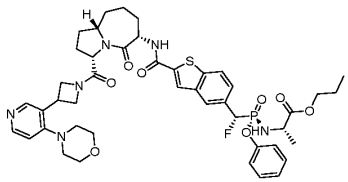
	[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate			
1037	propyl ((S)-((R)-fluoro(2-(((3S,6S,8R,9aR)-8-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or propyl ((R)-((R)-fluoro(2-(((3S,6S,8R,9aR)-8-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 or  CFTE-28A, SFC peak 2 was used for synthesis and biological testing	818.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 - 8.91 (m, 1H), 8.70 - 8.58 (m, 1H), 8.19 (d, *J* = 7.2 Hz, 1H), 8.06 - 7.92 (m, 2H), 7.89 - 7.82 (m, 1H), 7.67 - 7.48 (m, 3H), 7.38 - 7.31 (m, 2H), 7.25 - 7.16 (m, 2H), 6.02 - 5.86 (m, 1H), 5.12 - 5.04 (m, 1H), 4.82 (d, *J* = 8.0 Hz, 1H), 4.75 - 4.71 (m, 1H), 4.56 - 4.53 (m, 1H), 4.47 - 4.43 (m, 1H), 4.29 - 4.20 (m, 1H), 4.09 - 3.98 (m, 5H), 3.81 - 3.67 (m, 1H), 2.51 (s, 3H), 2.35 - 2.26 (m, 1H), 2.22 - 2.11 (m, 1H), 2.09 - 1.96 (m, 4H), 1.84 - 1.76 (m, 1H), 1.73 - 1.58 (m, 3H), 1.56 - 1.42 (m, 1H), 1.17 - 1.11 (m, 3H), 1.05 - 0.99 (m, 3H), 0.93 - 0.87 (m, 3H)
1038	propyl (((2-(((3S,6S,9aS)-3-(3-(4-morpholinopyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-		857.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 - 8.47 (m, 1H), 8.36 - 8.23 (m, 1H), 8.07 - 7.96 (m, 1H), 7.95 - 7.82 (m, 2H), 7.53 - 7.44 (m, 1H), 7.39 - 7.27 (m, 3H), 7.18 – 7.14 (m, 3H), 4.78 - 4.70 (m, 2H), 4.61 -

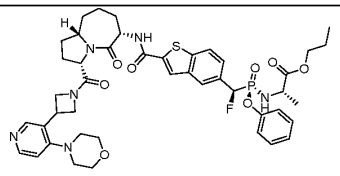
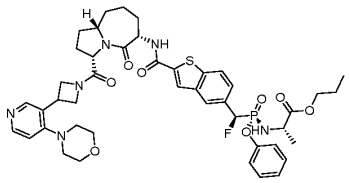
	yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate			4.51 (m, 2H), 4.49 - 4.34 (m, 1H), 4.27 – 4.18 (m, 1H), 4.15 - 4.04 (m, 2H), 3.96 - 3.89 (m, 2H), 3.88 (d, J = 3.6 Hz, 1H), 3.84 (d, J = 4.4 Hz, 4H), 3.59 - 3.45 (m, 2H), 3.41 (d, J = 4.8 Hz, 4H), 2.38 - 2.25 (m, 1H), 2.20 - 2.05 (m, 2H), 2.04 - 1.91 (m, 4H), 1.89 - 1.78 (m, 3H), 1.57 – 1.50 (m, 2H), 1.16 - 1.06 (m, 3H), 0.90 - 0.83 (m, 3H)
1039	propyl ((S)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or propyl ((R)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy	 or  CFTE-28A, SFC peak 2 was used synthesis and biological testing	820.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 - 8.70 (m, 1H), 8.70 - 8.64 (m, 1H), 8.10 - 7.98 (m, 1H), 7.96 (s, 1H), 7.92 - 7.82 (m, 1H), 7.82 - 7.69 (m, 1H), 7.56 - 7.47 (m, 1H), 7.39 - 7.31 (m, 2H), 7.26 - 7.08 (m, 3H), 6.05 - 5.85 (m, 1H), 5.02 - 4.94 (m, 1H), 4.86 - 4.78 (m, 1H), 4.77 - 4.72 (m, 1H), 4.71 - 4.62 (m, 1H), 4.61 - 4.56 (m, 1H), 4.55 - 4.48 (m, 1H), 4.41 - 4.30 (m, 1H), 4.22 - 4.13 (m, 1H), 4.09 (d, J = 18.1 Hz, 3H), 4.05 - 3.99 (m, 4H), 3.99 - 3.90 (m, 1H), 2.34 - 2.22 (m, 1H), 2.21 - 2.09 (m, 1H), 2.09 - 1.97 (m, 4H), 1.94 - 1.78 (m, 3H), 1.77 - 1.67 (m, 1H), 1.66 - 1.56 (m, 2H), 1.22 - 1.07 (m, 3H), 0.99 - 0.81 (m, 3H)

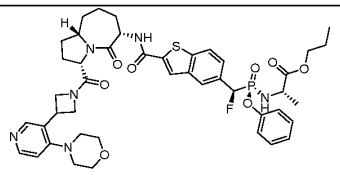
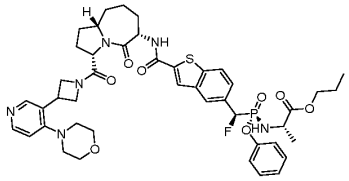
	)phosphoryl)-L-alaninate			
1040	propyl ((S)-((R)-fluoro(2-(((3S,6S,8S,9aR)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or propyl ((R)-((R)-fluoro(2-(((3S,6S,8S,9aR)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 or  CFTE-28B, SFC peak 1 was used for synthesis and biological testing	834.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 - 8.59 (m, 2H), 7.98 (s, 1H), 7.89 - 7.78 (m, 2H), 7.62 - 7.56 (m, 1H), 7.28 (d, *J* = 2.8 Hz, 1H), 7.24 - 7.23 (m, 2H), 7.13 - 7.04 (m, 3H), 6.05 - 5.91 (m, 1H), 4.98 - 4.85 (m, 3H), 4.61 - 4.59 (m, 1H), 4.49 - 4.45 (m, 1H), 4.38 - 4.36 (m, 1H), 4.15 (d, *J* = 6.0 Hz, 2H), 4.10 (s, 1H), 4.05 - 4.00 (m, 5H), 3.80 - 3.62 (m, 1H), 2.28 - 2.23 (m, 2H), 2.03 - 1.92 (m, 6H), 1.61 - 1.58 (m, 3H), 1.30 - 1.23 (m, 6H), 0.89 (t, *J* = 3.2 Hz, 3H)

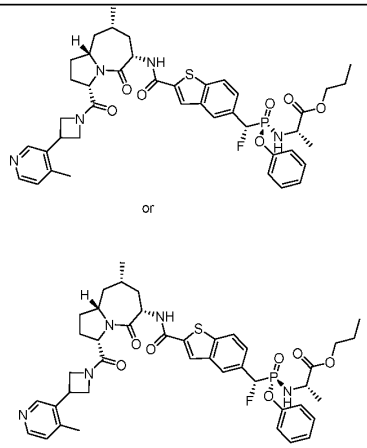
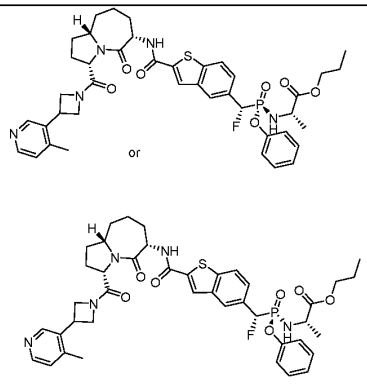
1041	propyl ((S)-((R)-fluoro(2-(((3S,6S,8S,9aR)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or propyl ((R)-((R)-fluoro(2-(((3S,6S,8S,9aR)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 or  CFTE-28A, SFC peak 2 was used synthesis and biological testing	834.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 - 8.64 (m, 2H), 7.99 - 7.90 (m, 2H), 7.80 - 7.78 (m, 1H), 7.64 - 7.51 (m, 1H), 7.35 - 7.31 (m, 2H), 7.24 - 7.23 (m, 2H), 7.19 - 7.18 (m, 2H), 5.99 - 5.85 (m, 1H), 4.97 - 4.85 (m, 2H), 4.60 - 4.58 (m, 1H), 4.49 - 4.45 (m, 1H), 4.34 (t, *J* = 9.6 Hz, 1H), 4.16 - 4.14 (m, 2H), 4.08 - 4.02 (m, 7H), 3.93 - 3.73 (m, 1H), 2.30 - 2.24 (m, 2H), 2.06 - 2.01 (m, 6H), 1.61 - 1.58 (m, 3H), 1.30 - 1.23 (m, 3H), 1.14 (d, *J* = 7.6 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H)
1042	propyl ((fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy		821.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 - 8.75 (m, 1H), 8.73 - 8.65 (m, 1H), 8.52 (d, *J* = 6.2 Hz, 1H), 8.32 - 8.19 (m, 1H), 8.14 - 7.99 (m, 2H), 7.65 - 7.56 (m, 1H), 7.42 - 7.29 (m, 2H), 7.27 - 7.07 (m, 3H), 6.27 - 6.17 (m, 1H), 6.15 - 6.05 (m, 1H), 4.56 - 4.50 (m, 2H),

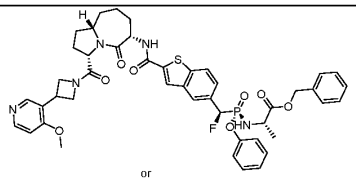
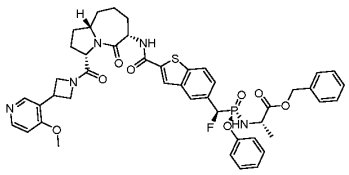
	)phosphoryl)-L-alaninate			4.67 (d, *J* = 9.1 Hz, 2H), 4.48 - 4.29 (m, 1H), 4.07 - 3.97 (m, 2H), 3.95 (s, 3H), 3.93 - 3.86 (m, 2H), 3.72 - 3.70 (m, 1H), 3.86 - 3.58 (m, 1H), 2.23 - 2.14 (m, 1H), 2.05 - 1.93 (m, 2H), 1.87 - 1.66 (m, 7H), 1.52 - 1.37 (m, 2H), 1.18 - 1.11 (m, 2H), 0.98 - 0.90 (m, 1H), 0.86 - 0.74 (m, 3H)
1043	propyl (((2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		834.4	^{1}H NMR (400 MHz, CD_3OD) 8.63 - 8.49 (m, 1H), 8.40 - 8.28 (m, 1H), 8.17 - 8.04 (m, 2H), 8.04 - 7.93 (m, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.40 - 7.28 (m, 2H), 7.26 - 7.11 (m, 3H), 6.20 - 5.98 (m, 1H), 4.74 (d, *J* = 10.8 Hz, 1H), 4.67 (t, *J* = 8.8 Hz, 1H), 4.59 - 4.49 (m, 2H), 4.48 - 4.36 (m, 1H), 4.35 - 4.26 (m, 1H), 4.13 - 4.02 (m, 2H), 4.01 - 3.95 (m, 1H), 3.93 - 3.76 (m, 2H), 3.32 (s, 6H), 2.36 - 2.25 (m, 1H), 2.17 - 2.06 (m, 2H), 2.05 - 1.97 (m, 2H), 1.97 - 1.90 (m, 2H), 1.89 - 1.79 (m, 3H), 1.62 - 1.47 (m, 2H), 1.27 - 1.19 (m, 2H), 1.09 – 1.06 (m, 1H), 0.93 - 0.82 (m, 3H)

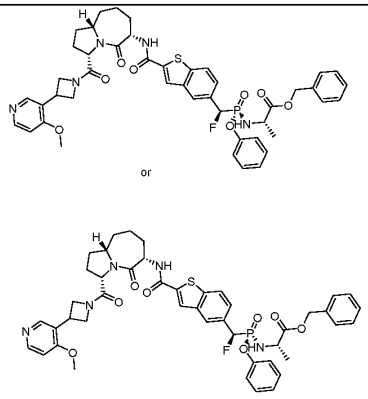
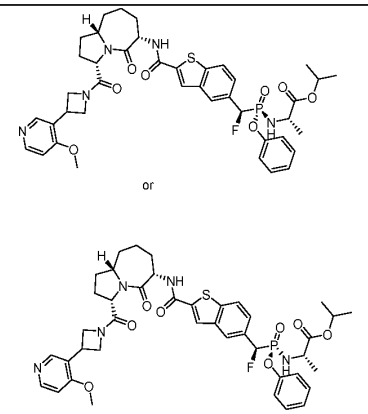
1044	propyl ((R)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-morpholinopyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or propyl ((S)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-morpholinopyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 or  CFTE-27B, SFC peak 2 was used synthesis and biological testing	875.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 - 8.48 (m, 1H), 8.36 - 8.24 (m, 1H), 8.14 - 8.05 (m, 2H), 8.03 - 7.96 (m, 1H), 7.70 - 7.61 (m, 1H), 7.39 - 7.28 (m, 3H), 7.25 - 7.15 (m, 3H), 6.17 - 5.97 (m, 1H), 4.79 - 4.71 (m, 2H), 4.61 - 4.50 (m, 2H), 4.49 - 4.34 (m, 1H), 4.29 - 4.16 (m, 1H), 4.15 - 4.05 (m, 2H), 4.01 - 3.93 (m, 2H), 3.84 (d, J = 4.8 Hz, 4H), 3.82 - 3.76 (m, 1H), 3.41 (s, 4H), 2.39 - 2.26 (m, 1H), 2.20 - 2.06 (m, 2H), 2.05 - 1.90 (m, 4H), 1.90 - 1.78 (m, 3H), 1.61 – 1.52 (m, 2H), 1.09 – 1.07 (m, 3H), 0.91 – 0.86 (m, 3H)
1045	propyl ((R)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-morpholinopyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy	 or 	875.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 - 8.48 (m, 1H), 8.36 - 8.23 (m, 1H), 8.14 - 8.03 (m, 2H), 8.01 - 7.92 (m, 1H), 7.68 - 7.60 (m, 1H), 7.42 - 7.28 (m, 3H), 7.25 - 7.14 (m, 3H), 6.20 - 6.01 (m, 1H), 4.78 - 4.70 (m, 2H), 4.60 - 4.50 (m, 2H), 4.49 - 4.34 (m, 1H), 4.30 - 4.17 (m, 1H), 4.15 - 4.05 (m, 2H), 4.01 -

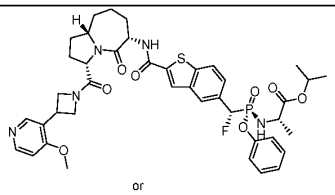
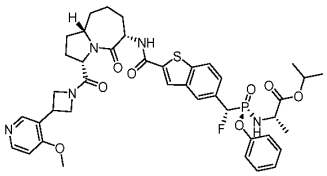
	)phosphoryl)-L-alaninate or propyl ((S)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-morpholinopyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	CFTE-27A, SFC peak 1 was used synthesis and biological testing		3.87 (m, 3H), 3.87 - 3.78 (m, 4H), 3.41 (s, 4H), 2.39 - 2.26 (m, 1H), 2.19 - 2.07 (m, 2H), 2.04 - 1.90 (m, 4H), 1.90 - 1.78 (m, 3H), 1.62 - 1.48 (m, 2H), 1.23 (d, J = 7.2 Hz, 3H), 0.93 - 0.82 (m, 3H)
1046	propyl ((R)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-morpholinopyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or propyl ((S)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-morpholinopyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-	 or  CFTE-28B, SFC peak1 was used for synthesis and biological testing	875.5	1H NMR (400 MHz, $CDCl_3$) δ 9.03 - 8.70 (m, 1H), 8.49 - 8.30 (m, 1H), 8.07 - 7.79 (m, 3H), 7.64 - 7.55 (m, 1H), 7.29 (s, 1H), 7.25 (s, 1H), 7.15 - 7.06 (m, 3H), 7.02 - 6.95 (m 1H), 6.07 - 5.90 (m, 1H), 5.12 - 4.95 (m, 1H), 4.86 - 4.61 (m, 2H), 4.55 - 4.48 (m, 1H), 4.46 - 4.34 (m, 1H), 4.18 - 4.06 (m, 2H), 4.05 - 3.93 (m, 4H), 3.92 - 3.82 (m, 4H), 3.66 - 3.57 (m, 1H), 3.30 - 3.24 (m, 1H), 3.20 - 3.15 (m, 2H), 2.34 - 2.26 (m, 1H), 2.25 - 2.16 (m, 1H), 2.12 - 1.97 (m, 4H), 1.95 - 1.71 (m, 4H), 1.65 - 1.55 (m, 2H), 1.33 - 1.25 (m, 3H), 0.90 (q, J = 7.2 Hz, 3H)

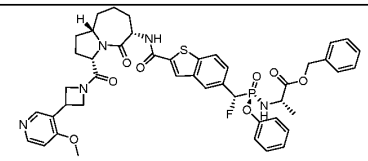
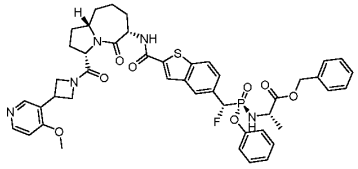
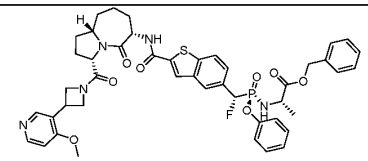
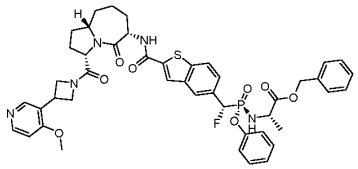
	yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate			
1047	propyl ((R)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-morpholinopyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or propyl ((S)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-morpholinopyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 or  CFTE-28A, SFC peak 2 was used for synthesis and biological testing	875.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 - 8.68 (m, 1H), 8.53 - 8.27 (m, 1H), 8.06 - 7.78 (m, 3H), 7.67 - 7.49 (m, 1H), 7.40 - 7.31 (m, 2H), 7.28 (s, 1H), 7.25 (s, 1H), 7.19 (q, J = 7.0 Hz, 1H), 7.10 - 7.01 (m, 1H), 6.03 - 5.85 (m, 1H), 5.11 - 4.93 (m, 1H), 4.84 - 4.64 (m, 2H), 4.55 - 4.49 (m, 1H), 4.42 - 4.34 (m, 1H), 4.16 - 4.10 (m, 1H), 4.09 - 4.02 (m, 3H), 4.01 - 3.95 (m, 1H), 3.92 - 3.85 (m, 4H), 3.77 - 3.77 (m, 1H), 3.33 - 3.06 (m, 4H), 2.34 - 2.24 (m, 1H), 2.23 - 2.13 (m, 1H), 2.12 - 1.96 (m, 4H), 1.94 - 1.69 (m, 4H), 1.68 - 1.55 (m, 2H), 1.15 (dd, J = 7.2, 14.8 Hz, 3H), 0.90 (dt, J = 4.0, 7.2 Hz, 3H)

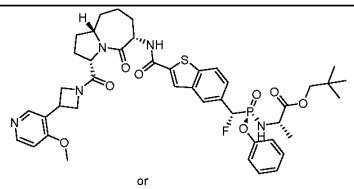
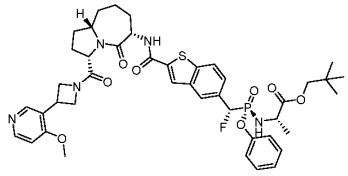
1048	propyl ((R)-((S)-fluoro(2-(((3S,6S,8R,9aR)-8-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or propyl ((S)-((S)-fluoro(2-(((3S,6S,8R,9aR)-8-methyl-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 CFTE-27A, SFC peak 1 was used for synthesis and biological testing	818.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 - 8.91 (m, 1H), 8.71 - 8.59 (m, 1H), 8.22 (d, *J* = 7.6 Hz, 1H), 8.02 (s, 1H), 7.96 (s, 1H), 7.87 - 7.80 (m, 1H), 7.67 - 7.51 (m, 3H), 7.39 - 7.30 (m, 2H), 7.24 (s, 1H), 7.22 - 7.16 (m, 1H), 6.05 - 5.88 (m, 1H), 5.11 - 5.08 (m, 1H), 4.85 - 4.71 (m, 2H), 4.56 - 4.42 (m, 2H), 4.27 - 4.02 (m, 2H), 4.00 - 3.87 (m, 3H), 3.85 - 3.64 (m, 2H), 2.51 (s, 3H), 2.36 - 2.17 (m, 2H), 2.14 - 1.99 (m, 4H), 1.80 (t, *J* = 12.4 Hz, 1H), 1.73 - 1.60 (m, 1H), 1.58 - 1.45 (m, 3H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.05 - 0.99 (m, 3H), 0.86 (t, *J* = 7.6 Hz, 3H)
1049	propyl ((S)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy		804.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 - 8.86 (m, 1H), 8.74 - 8.54 (m, 1H), 8.27 - 8.01 (m, 1H), 7.96 (s, 1H), 7.88 - 7.79 (m, 1H), 7.67 - 7.52 (m, 2H), 7.40 - 7.29 (m, 2H), 7.27 - 7.12 (m, 3H), 6.04 - 5.89 (m, 1H), 5.15 - 5.04 (m, 1H), 4.85 - 4.66 (m, 2H), 4.57 - 4.51 (m, 1H), 4.50 - 4.39 (m, 1H), 4.12 - 3.83 (m, 5H),

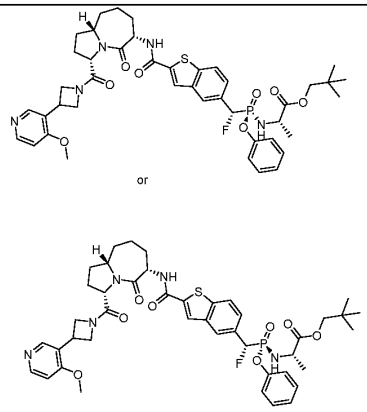
	)phosphoryl)-L-alaninate or propyl ((R)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methylpyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	CFTE-27A, SFC peak 1 was used for synthesis and biological testing		3.79 - 3.63 (m, 1H), 2.50 (s, 3H), 2.36 - 2.15 (m, 2H), 2.12 - 1.70 (m, 8H), 1.53 (q, J = 7.2 Hz, 2H), 1.33 - 1.22 (m, 3H), 0.92 - 0.79 (m, 3H)
1050	benzyl ((S)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or benzyl ((R)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy	 or  More polar linker building block was used synthesis and biological testing	868.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.72 - 8.57 (m, 2H), 8.14 - 7.97 (m, 2H), 7.95 - 7.86 (m, 1H), 7.66 - 7.53 (m, 2H), 7.37 - 7.24 (m, 7H), 7.21 - 7.12 (m, 3H), 6.12 - 5.92 (m, 1H), 5.07 - 4.99 (m, 1H), 4.97 - 4.90 (m, 2H), 4.77 - 4.71 (m, 1H), 4.66 (d, J = 8.0 Hz, 1H), 4.55 (t, J = 4.8 Hz, 1H), 4.48 - 4.38 (m, 1H), 4.37 - 4.30 (m, 1H), 4.18 (s, 3H), 4.17 - 4.13 (m, 1H), 4.09 (d, J = 5.6 Hz, 1H), 3.89 (d, J = 7.2 Hz, 1H), 2.38 - 2.25 (m, 1H), 2.20 - 2.05 (m, 2H), 2.04 - 1.90 (m, 4H), 1.89 - 1.77 (m, 3H), 1.22 (d, J = 7.2 Hz, 3H)

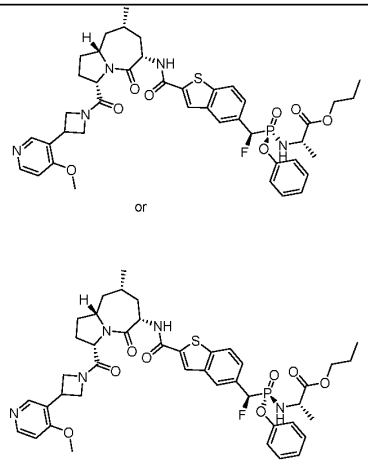
	)phosphoryl)-L-alaninate			
1051	benzyl ((S)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or benzyl ((R)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 or Less polar linker building block was used in synthesis and biological testing	868.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 - 8.65 (m, 1H), 8.07 - 7.89 (m, 2H), 7.87 - 7.77 (m, 1H), 7.55 - 7.45 (m, 1H), 7.38 - 7.29 (m, 6H), 7.28 - 7.27 (m, 1H), 7.27 - 7.25 (m, 2H), 7.25 - 7.22 (m, 1H), 7.19 (d, J = 6.8 Hz, 1H), 7.16 (d, J = 7.2 Hz, 1H), 6.04 - 5.83 (m, 1H), 5.13 (s, 2H), 5.01 (t, J = 9.6 Hz, 1H), 4.80 - 4.67 (m, 1H), 4.67 - 4.59 (m, 1H), 4.54 (s, 1H), 4.42 - 4.34 (m, 1H), 4.26 - 4.17 (m, 1H), 4.16 - 4.10 (m, 3H), 4.08 - 4.03 (m, 1H), 4.00 - 3.92 (m, 1H), 3.88 - 3.75 (m, 1H), 2.32 - 2.25 (m, 1H), 2.23 - 2.10 (m, 2H), 2.03 (dd, J = 6.8, 12.0 Hz, 3H), 1.96 - 1.81 (m, 3H), 1.79 - 1.67 (m, 1H), 1.15 (t, J = 7.2 Hz, 3H)
1052	isopropyl ((S)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy	 or 	820.7	^{1}H NMR (400 MHz, CD_3OD) δ 8.61 (m, 2H), 8.12 - 8.02 (m, 2H), 7.95 (m, 1H), 7.56 (m, 2H), 7.36 - 7.28 (m, 2H), 7.16 (m, 3H), 6.25 - 5.98 (m, 1H), 4.95 - 4.87 (m, 1H), 4.77 - 4.70 (m, 1H), 4.64 (s, 1H), 4.58 - 4.52 (m, 1H), 4.45 - 4.35 (m, 1H), 4.18 (s, 6H), 4.10 - 4.03 (m, 1H), 3.86 -

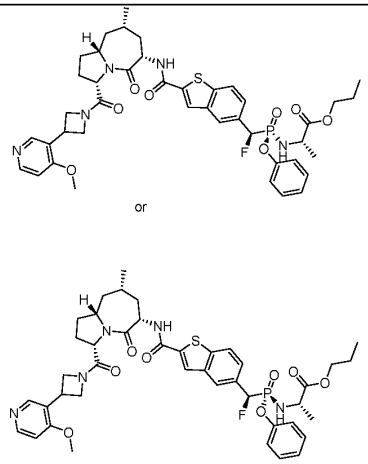
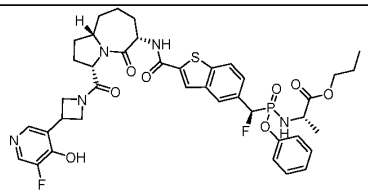
	)phosphoryl)-L-alaninate or isopropyl ((R)-((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	More polar linker building block was used in synthesis and biological testing		3.75 (m, 1H), 2.36 - 2.25 (m, 1H), 2.16 - 2.05 (m, 2H), 2.04 - 1.94 (m, 3H), 1.94 - 1.87 (m, 2H), 1.84 (m, 2H), 1.23 - 1.15 (m, 6H), 1.12 - 1.06 (m, 3H)
1053	isopropyl ((S)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or isopropyl ((R)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy	 or  Less polar linker building block was used in synthesis and biological testing	820.4	^{1}H NMR (400 MHz, CD_3OD) 8.73 - 8.52 (m, 2H), 8.13 - 8.02 (m, 2H), 8.01 - 7.91 (m, 1H), 7.68 - 7.54 (m, 2H), 7.42 - 7.27 (m, 2H), 7.18 (d, *J* = 7.6 Hz, 3H), 6.22 - 5.98 (m, 1H), 4.78 - 4.71 (m, 1H), 4.68 - 4.62 (m, 1H), 4.56 – 4.53 (m, 1H), 4.50 - 4.41 (m, 1H), 4.40 - 4.25 (m, 1H), 4.19 (s, 5H), 4.08 (d, *J* = 3.6 Hz, 1H), 4.01 - 3.84 (m, 3H), 2.39 - 2.25 (m, 1H), 2.21 - 2.06 (m, 2H), 2.02 – 1.98 (m, 1H), 1.96 – 1.91 (m, 2H), 1.90 - 1.79 (m, 3H), 1.62 - 1.46 (m, 2H), 1.38 – 1.36 (m, 1H), 1.24 (d, *J* = 7.2 Hz, 3H), 0.94 - 0.81 (m, 3H)

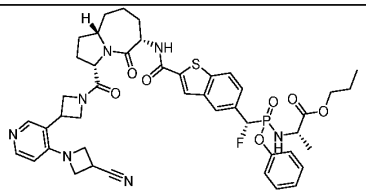
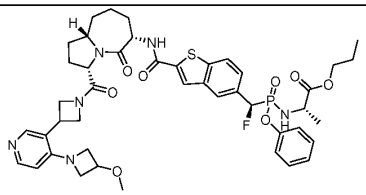
	)phosphoryl)-L-alaninate			
1054	benzyl ((R)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or benzyl ((S)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 or  More polar linker building block was used in synthesis and biological testing	868.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 - 8.67 (m, 2H), 8.13 - 7.93 (m, 2H), 7.89 - 7.79 (m, 1H), 7.60 - 7.52 (m, 1H), 7.41 - 7.27 (m, 6H), 7.22 (t, J = 7.2 Hz, 2H), 7.17 - 7.05 (m, 3H), 6.02 - 5.85 (m, 1H), 5.19 - 5.05 (m, 2H), 5.04 - 4.90 (m, 1H), 4.83 - 4.70 (m, 1H), 4.68 - 4.58 (m, 1H), 4.54 (t, J = 5.2 Hz, 1H), 4.43 - 4.33 (m, 1H), 4.25 - 4.18 (m, 1H), 4.11 (d, J = 3.0 Hz, 3H), 4.08 - 4.02 (m, 1H), 3.96 (s, 1H), 3.76 - 3.64 (m, 1H), 2.34 - 2.22 (m, 1H), 2.20 - 1.97 (m, 5H), 1.95 - 1.66 (m, 4H), 1.31 (d, J = 7.2 Hz, 3H)
1055	benzyl ((R)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy	 or 	868.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 - 8.38 (m, 2H), 8.06 - 7.89 (m, 2H), 7.84 - 7.61 (m, 2H), 7.51 (t, J = 8.0 Hz, 1H), 7.43 - 7.27 (m, 5H), 7.24 (d, J = 7.6 Hz, 4H), 7.02 - 6.98 (m, 1H), 6.07 - 5.84 (m, 1H), 5.11 - 4.97 (m, 2H), 4.96 - 4.82 (m, 1H), 4.79 - 4.64 (m, 1H), 4.62 - 4.47 (m, 2H),

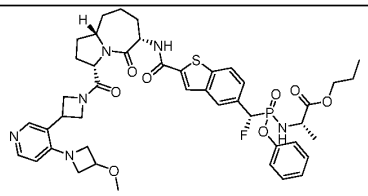
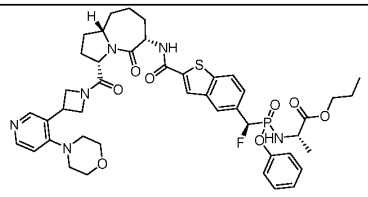
	)phosphoryl)-L-alaninate or benzyl ((S)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	Less polar linker building block was used in synthesis and biological testing		4.42 - 4.27 (m, 1H), 4.22 - 4.11 (m, 1H), 4.05 - 3.97 (m, 3H), 3.97 - 3.83 (m, 2H), 3.80 - 3.63 (m, 1H), 2.33 - 2.21 (m, 1H), 2.21 - 1.98 (m, 5H), 1.98 - 1.60 (m, 4H), 1.28 – 1.26 (m, 3H)
1056	neopentyl ((R)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or neopentyl ((S)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy	 or  More polar linker building block was used in synthesis and biological testing	848.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.71 - 8.57 (m, 2H), 8.13 - 8.05 (m, 2H), 8.03 - 7.97 (m, 1H), 7.68 - 7.58 (m, 2H), 7.35 - 7.28 (m, 2H), 7.24 - 7.13 (m, 3H), 6.15 - 6.00 (m, 1H), 4.78 - 4.71 (m, 2H), 4.66 (d, J = 6.4 Hz, 1H), 4.55 (dt, J = 4.8, 8.0 Hz, 1H), 4.46 - 4.34 (m, 1H), 4.20 (d, J = 2.8 Hz, 3H), 4.19 - 4.14 (m, 2H), 4.13 - 4.04 (m, 1H), 3.90 - 3.81 (m, 1H), 3.80 - 3.70 (m, 2H), 2.37 - 2.25 (m, 1H), 2.18 - 2.06 (m, 2H), 2.05 - 1.91 (m, 4H), 1.90 - 1.79 (m, 3H), 1.11 (dd, J = 4.0, 7.2 Hz, 3H), 0.89 (s, 9H)

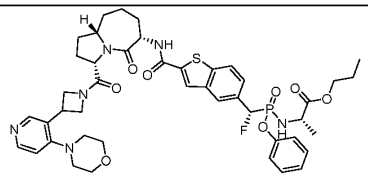
	)phosphoryl)-L-alaninate			
1057	neopentyl ((R)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or neopentyl ((S)-((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 or Less polar linker building block was used in synthesis and biological testing	848.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.71 - 8.58 (m, 2H), 8.15 - 8.04 (m, 2H), 8.02 - 7.92 (m, 1H), 7.67 - 7.57 (m, 2H), 7.39 - 7.31 (m, 2H), 7.26 - 7.13 (m, 3H), 6.19 - 6.03 (m, 1H), 4.90 (s, 1H), 4.78 - 4.72 (m, 1H), 4.65 (d, J = 6.4 Hz, 1H), 4.56 (dt, J = 4.8, 8.4 Hz, 1H), 4.46 - 4.33 (m, 1H), 4.23 - 4.15 (m, 5H), 4.08 (d, J = 4.8 Hz, 1H), 3.93 - 3.85 (m, 1H), 3.80 - 3.73 (m, 1H), 3.62 - 3.54 (m, 1H), 2.37 - 2.26 (m, 1H), 2.19 - 2.05 (m, 2H), 2.04 - 1.90 (m, 4H), 1.89 - 1.78 (m, 3H), 1.25 (d, J = 7.2 Hz, 3H), 0.86 (d, J = 2.4 Hz, 9H)

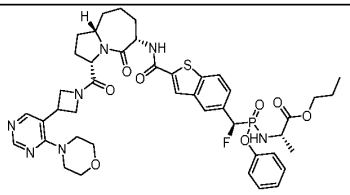
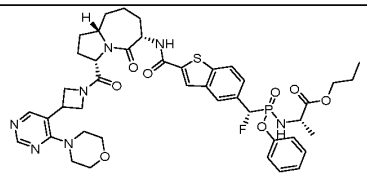
1058	propyl ((R)-((R)-fluoro(2-(((3S,6S,8R,9aR)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or propyl ((S)-((R)-fluoro(2-(((3S,6S,8R,9aR)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 CFTE-28B, SFC peak 1 was used in synthesis and biological testing	834.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 - 8.67 (m, 2H), 8.02 - 7.80 (m, 3H), 7.68 - 7.56 (m, 1H), 7.30 - 7.25 (m, 3H), 7.25 - 7.20 (m, 1H), 7.19 - 7.05 (m, 3H), 6.10 - 5.88 (m, 1H), 5.02 - 4.89 (m, 1H), 4.79 - 4.68 (m, 1H), 4.64 - 4.58 (m, 1H), 4.55 (t, *J* = 5.6 Hz, 1H), 4.41 - 4.34 (m, 1H), 4.23 - 4.15 (m, 1H), 4.14 - 4.09 (m, 3H), 4.07 - 3.93 (m, 4H), 3.73 - 3.55 (m, 1H), 2.35 - 2.24 (m, 1H), 2.19 - 1.92 (m, 5H), 1.84 - 1.71 (m, 1H), 1.71 - 1.42 (m, 4H), 1.36 - 1.23 (m, 3H), 1.07 - 0.98 (m, 3H), 0.96 - 0.83 (m, 3H)

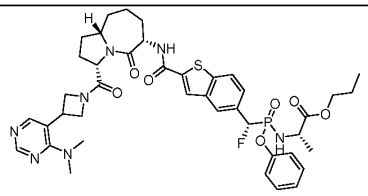
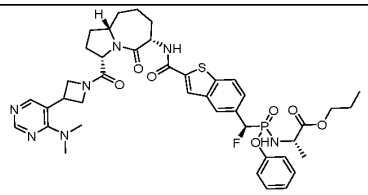
1059	propyl ((R)-((R)-fluoro(2-(((3S,6S,8R,9aR)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate or propyl ((S)-((R)-fluoro(2-(((3S,6S,8R,9aR)-3-(3-(4-methoxypyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate	 or CFTE-28A, SFC peak 2 was used in synthesis and biological testing	834.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 - 8.67 (m, 2H), 8.02 - 7.81 (m, 3H), 7.68 - 7.51 (m, 1H), 7.40 - 7.31 (m, 2H), 7.29 - 7.25 (m, 3H), 7.23 - 7.15 (m, 2H), 6.03 - 5.86 (m, 1H), 5.02 - 4.89 (m, 1H), 4.79 - 4.69 (m, 1H), 4.65 - 4.58 (m, 1H), 4.55 (t, *J* = 5.6 Hz, 1H), 4.41 - 4.34 (m, 1H), 4.23 - 4.16 (m, 1H), 4.14 - 4.03 (m, 6H), 4.00 - 3.92 (m, 1H), 3.84 - 3.65 (m, 1H), 2.35 - 2.23 (m, 1H), 2.18 - 1.91 (m, 5H), 1.84 - 1.73 (m, 1H), 1.71 - 1.43 (m, 4H), 1.20 - 1.09 (m, 3H), 1.06 - 0.98 (m, 3H), 0.94 – 0.84 (m, 3H)
1060	propyl (((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(5-fluoro-4-hydroxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		824.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.13 - 8.04 (m, 2H), 8.02 - 7.93 (m, 2H), 7.91 - 7.77 (m, 1H), 7.68 - 7.61 (m, 1H), 7.37 - 7.29 (m, 2H), 7.22 - 7.13 (m, 3H), 6.19 - 6.01 (m, 1H), 4.79 - 4.72 (m, 2H), 4.66 - 4.52 (m, 2H), 4.51 - 4.41 (m, 1H), 4.39 - 4.31 (m, 1H), 4.10 -

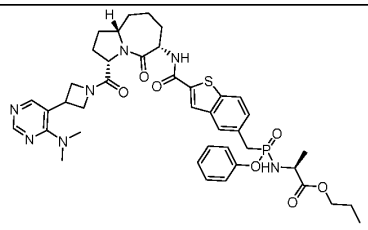
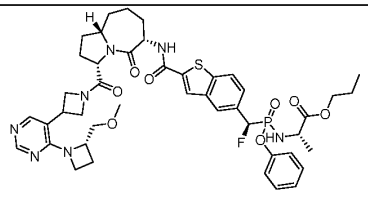
	yl)methyl)(phenoxy)phosphoryl)-L-alaninate			3.98 (m, 2H), 3.95 - 3.87 (m, 1H), 3.86 - 3.78 (m, 2H), 2.35 - 2.25 (m, 1H), 2.18 - 2.05 (m, 2H), 2.04 - 1.87 (m, 5H), 1.87 - 1.77 (m, 2H), 1.55 - 1.44 (m, 2H), 1.21 (d, J = 7.2 Hz, 3H), 0.90 - 0.81 (m, 3H)
1061	propyl (((S)-(2-(((3S,6S,9aS)-3-(3-(4-(3-cyanoazetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		870.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.46 - 8.37 (m, 1H), 8.19 - 8.07 (m, 3H), 8.05 - 7.96 (m, 1H), 7.71 - 7.63 (m, 1H), 7.40 - 7.30 (m, 2H), 7.30 - 7.12 (m, 3H), 6.70 - 6.60 (m, 1H), 6.22 - 6.00 (m, 1H), 4.75 (t, J = 12.0 Hz, 3H), 4.70 - 4.64 (m, 2H), 4.64 - 4.59 (m, 1H), 4.59 - 4.54 (m, 1H), 4.54 - 4.18 (m, 2H), 4.17 - 4.06 (m, 3H), 4.02 - 3.92 (m, 3H), 3.91 – 3.90 (m, 1H), 2.39 - 2.28 (m, 1H), 2.21 - 2.08 (m, 2H), 2.08 - 1.93 (m, 4H), 1.92 - 1.82 (m, 3H), 1.64 - 1.51 (m, 2H), 1.25 (d, J = 7.2 Hz, 1H), 1.13 - 1.07 (m, 2H), 0.94 - 0.85 (m, 3H)
1062	propyl (((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-(3-methoxyazetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-		875.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (d, J = 8.8 Hz, 1H), 8.15 - 7.92 (m, 4H), 7.69 - 7.61 (m, 1H), 7.38 - 7.28 (m, 2H), 7.24 - 7.12 (m, 3H), 6.58 (dd, J = 7.2, 12.0 Hz, 1H), 6.19 - 5.99 (m, 1H), 4.87 (s, 1H), 4.74 (d, J = 11.2 Hz, 1H), 4.66 - 4.51 (m,

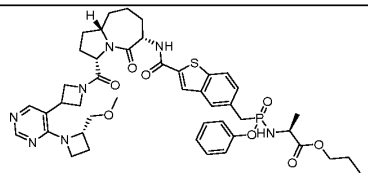
	yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate			4H), 4.44 - 4.30 (m, 3H), 4.30 - 4.24 (m, 1H), 4.22 - 4.15 (m, 1H), 4.09 (d, J = 6.8 Hz, 2H), 3.98 (t, J = 6.8 Hz, 1H), 3.94 - 3.79 (m, 2H), 3.37 (s, 3H), 2.38 - 2.24 (m, 1H), 2.21 - 2.06 (m, 2H), 2.05 - 1.80 (m, 7H), 1.61 - 1.46 (m, 2H), 1.27 - 1.19 (m, 3H), 0.94 - 0.80 (m, 3H)
1063	propyl (((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-(3-methoxyazetidin-1-yl)pyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		875.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (d, J = 8.4 Hz, 1H), 8.15 - 7.99 (m, 4H), 7.70 - 7.60 (m, 1H), 7.42 - 7.29 (m, 2H), 7.27 - 7.12 (m, 3H), 6.58 (dd, J = 6.8, 11.6 Hz, 1H), 6.20 – 6.02 (m, 1H), 4.87 - 4.85 (m, 1H), 4.75 (d, J = 11.2 Hz, 1H), 4.66 - 4.51 (m, 4H), 4.44 - 4.30 (m, 3H), 4.28 (d, J = 1.2 Hz, 1H), 4.23 - 4.15 (m, 1H), 4.09 (d, J = 6.4 Hz, 2H), 4.01 - 3.76 (m, 3H), 3.35 (d, J = 19.2 Hz, 3H), 2.38 - 2.25 (m, 1H), 2.21 - 2.07 (m, 2H), 2.05 - 1.90 (m, 4H), 1.89 - 1.79 (m, 3H), 1.64 - 1.47 (m, 2H), 1.26 - 1.05 (m, 3H), 0.95 - 0.86 (m, 3H)
1064	propyl (((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-morpholinopyridin-3-yl)azetidine-1-carbonyl)-5-		875.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 - 8.67 (m, 1H), 8.50 - 8.28 (m, 2H), 8.11 - 7.98 (m, 1H), 7.98 - 7.80 (m, 2H), 7.67 - 7.57 (m, 1H), 7.56 - 7.27 (m, 2H), 7.26 - 7.08

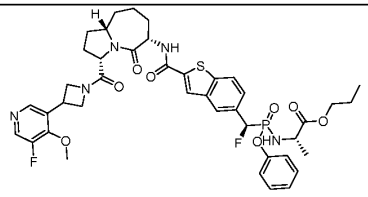
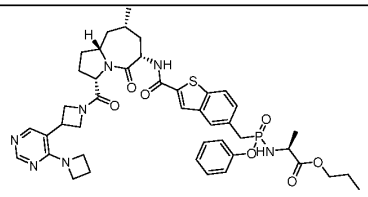
	oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate			(m, 3H), 7.08 - 6.98 (m, 1H), 6.06 - 5.88 (m, 1H), 5.11 - 4.93 (m, 1H), 4.86 - 4.64 (m, 2H), 4.54 - 4.36 (m, 2H), 4.15 - 3.92 (m, 6H), 3.91 - 3.86 (m, 4H), 3.79 - 3.57 (m, 1H), 3.35 - 3.14 (m, 4H), 2.35 - 2.25 (m, 1H), 2.24 - 2.14 (m, 1H), 2.14 - 1.97 (m, 4H), 1.96 - 1.68 (m, 4H), 1.66 - 1.55 (m, 2H), 1.35 - 1.11 (m, 3H), 0.95 - 0.86 (m, 3H)
1065	propyl (((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-morpholinopyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		875.6	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 - 8.47 (m, 1H), 8.28 (d, J = 6.0 Hz, 1H), 8.13 - 8.09 (m, 1H), 8.07 (d, J = 3.2 Hz, 1H), 8.03 - 7.93 (m, 1H), 7.69 - 7.60 (m, 1H), 7.39 - 7.30 (m, 2H), 7.29 - 7.14 (m, 4H), 6.21 - 5.99 (m, 1H), 4.78 - 4.71 (m, 2H), 4.65 - 4.51 (m, 2H), 4.49 - 4.35 (m, 1H), 4.29 - 4.20 (m, 1H), 4.16 - 4.05 (m, 2H), 4.02 - 3.87 (m, 3H), 3.87 - 3.79 (m, 4H), 3.23 (s, 4H), 2.39 - 2.26 (m, 1H), 2.21 - 2.04 (m, 3H), 2.04 - 2.00 (m, 1H), 1.99 - 1.96 (m, 1H), 1.95 - 1.88 (m, 2H), 1.87 - 1.79 (m, 2H), 1.61 - 1.49 (m, 2H), 1.26 - 1.04 (m, 3H), 0.92 - 0.83 (m, 3H)

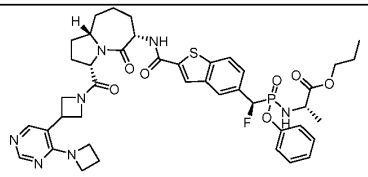
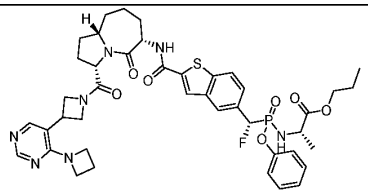
1066	propyl (((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-morpholinopyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		876.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.65 - 8.53 (m, 1H), 8.39 (d, *J* = 6.8 Hz, 1H), 8.13 - 8.03 (m, 2H), 8.01 - 7.92 (m, 1H), 7.69 - 7.58 (m, 1H), 7.39 - 7.29 (m, 2H), 7.26 - 7.12 (m, 3H), 6.23 - 5.97 (m, 1H), 4.78 - 4.70 (m, 1H), 4.59 - 4.44 (m, 2H), 4.43 - 4.28 (m, 1H), 4.20 - 4.12 (m, 1H), 4.12 - 4.02 (m, 2H), 4.01 - 3.95 (m, 1H), 3.95 - 3.87 (m, 1H), 3.85 (d, *J* = 7.2 Hz, 1H), 3.83 - 3.76 (m, 2H), 3.76 (s, 4H), 3.73 - 3.61 (m, 3H), 2.37 - 2.24 (m, 1H), 2.20 - 2.05 (m, 2H), 2.04 - 1.89 (m, 4H), 1.88 - 1.73 (m, 3H), 1.64 - 1.44 (m, 2H), 1.27 - 1.17 (m, 3H), 0.94 - 0.79 (m, 3H)
1067	propyl (((S)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-morpholinopyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		876.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.69 - 8.54 (m, 1H), 8.38 (d, J = 9.2 Hz, 1H), 8.15 - 8.04 (m, 2H), 8.03 - 7.93 (m, 1H), 7.70 - 7.60 (m, 1H), 7.41 - 7.29 (m, 2H), 7.26 - 7.14 (m, 3H), 6.19 - 5.99 (m, 1H), 4.78 - 4.65 (m, 2H), 4.59 - 4.44 (m, 2H), 4.42 - 4.30 (m, 1H), 4.25 - 4.13 (m, 1H), 4.12 - 4.01 (m, 2H), 4.00 - 3.93 (m, 2H), 3.93 - 3.87 (m, 1H), 3.87 - 3.80 (m, 4H), 3.76 (s, 4H), 2.37 - 2.25 (m, 1H), 2.19 - 2.06 (m, 2H), 2.03 -

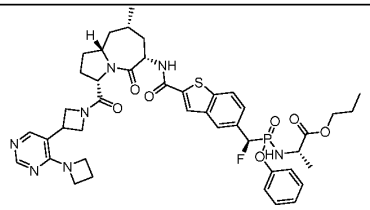
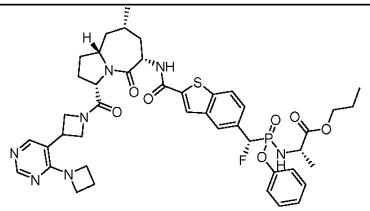
				1.89 (m, 4H), 1.88 - 1.77 (m, 3H), 1.60 - 1.50 (m, 2H), 1.23 (d, J = 7.1 Hz, 1H), 1.08 (d, J = 7.2 Hz, 2H), 0.91 - 0.84 (m, 3H)
1068	propyl (((S)-(2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		834.6	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 - 8.59 (m, 1H), 8.52 - 8.20 (m, 1H), 8.04 - 7.90 (m, 1H), 7.88 - 7.79 (m, 1H), 7.63 - 7.54 (m, 1H), 7.41 - 7.31 (m, 1H), 7.29 - 7.27 (m, 1H), 7.27 - 7.25 (m, 1H), 7.25 - 7.20 (m, 1H), 7.19 - 7.05 (m, 2H), 6.09 - 5.84 (m, 1H), 5.06 - 4.98 (m, 1H), 4.84 (d, J = 6.4 Hz, 1H), 4.73 - 4.55 (m, 2H), 4.53 - 4.46 (m, 1H), 4.41 - 4.32 (m, 1H), 4.17 - 4.10 (m, 1H), 4.06 - 4.02 (m, 1H), 4.00 - 3.92 (m, 2H), 3.88 - 3.76 (m, 1H), 3.75 - 3.63 (m, 1H), 3.36 - 3.18 (m, 6H), 2.34 - 2.13 (m, 2H), 2.11 - 1.89 (m, 5H), 1.73 - 1.57 (m, 2H), 1.56 - 1.45 (m, 2H), 1.42 (d, J = 6.8 Hz, 1H), 1.31 - 1.25 (m, 3H), 0.96 - 0.81 (m, 3H)
1069	propyl (((R)-(2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-		834.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.48 - 8.30 (m, 2H), 8.14 - 8.07 (m, 2H), 8.05 - 7.95 (m, 1H), 7.71 - 7.62 (m, 1H), 7.39 - 7.30 (m, 2H), 7.26 - 7.15 (m, 3H), 6.20 - 6.01 (m, 1H), 4.81 - 4.66 (m, 2H), 4.65 - 4.46 (m, 2H), 4.45 -

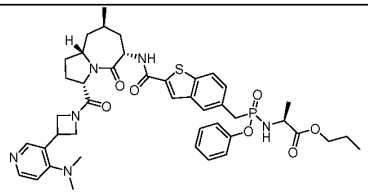
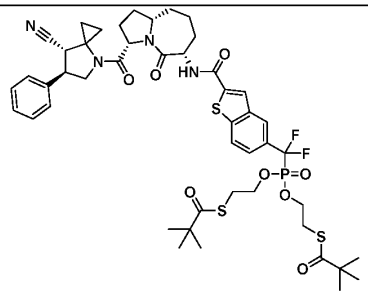
	yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate			4.32 (m, 1H), 4.27 - 4.15 (m, 1H), 4.03 (s, 2H), 4.02 - 3.97 (m, 1H), 3.96 - 3.80 (m, 2H), 3.04 (d, J = 2.0 Hz, 6H), 2.38 - 2.25 (m, 1H), 2.18 - 2.06 (m, 2H), 2.05 - 1.92 (m, 4H), 1.90 - 1.78 (m, 3H), 1.64 - 1.47 (m, 2H), 1.27 - 1.17 (m, 3H), 0.93 - 0.83 (m, 3H)
1070	propyl (((2-(((3S,6S,9aS)-3-(3-(4-(dimethylamino)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		816.6	^{1}H NMR (400 MHz, CD_3OD) δ 8.49 - 8.24 (m, 2H), 8.03 (d, J = 9.2 Hz, 1H), 7.94 - 7.83 (m, 2H), 7.53 - 7.44 (m, 1H), 7.36 - 7.26 (m, 2H), 7.16 (dd, J = 8.0, 15.2 Hz, 3H), 4.86 - 4.63 (m, 2H), 4.62 - 4.43 (m, 2H), 4.42 - 4.28 (m, 1H), 4.25 - 4.14 (m, 1H), 4.12 - 3.99 (m, 2H), 3.98 - 3.78 (m, 3H), 3.62 - 3.43 (m, 2H), 3.02 (d, J = 1.6 Hz, 6H), 2.38 - 2.20 (m, 1H), 2.18 - 1.99 (m, 3H), 1.98 - 1.76 (m, 6H), 1.62 - 1.46 (m, 2H), 1.21 - 1.02 (m, 3H), 1.00 - 0.86 (m, 3H)
1071	propyl (((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(4-((S)-2-(methoxymethyl)azetidin-1-yl)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-		890.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (d, *J* = 18 Hz, 1H), 8.29 (s, 1H), 8.14 - 8.04 (m, 2H), 8.02 - 7.94 (m, 1H), 7.69 - 7.60 (m, 1H), 7.37 - 7.27 (m, 2H), 7.24 - 7.13 (m, 3H), 6.24 - 5.97 (m, 1H), 4.90-4.89 (m, 1H), 4.83 (s, 1H), 4.78 - 4.71 (m, 1H), 4.62 - 4.50 (m, 3H),

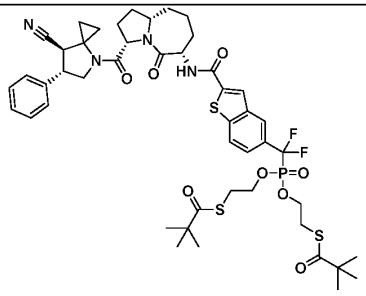
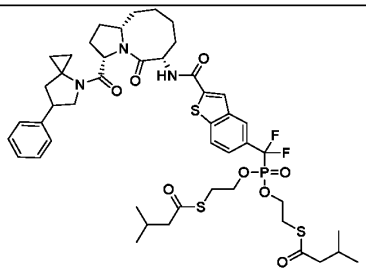
	yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate			4.45 - 4.37 (m, 1H), 4.33 (s, 1H), 4.13 - 4.02 (m, 3H), 4.01 - 3.95 (m, 2H), 3.94 - 3.79 (m, 2H), 3.62 - 3.56 (m, 1H), 3.38 (d, *J* = 5.6 Hz, 3H), 2.63 - 2.50 (m, 1H), 2.49 - 2.36 (m, 1H), 2.36 - 2.25 (m, 1H), 2.20 - 2.06 (m, 2H), 2.04 (s, 3H), 1.92 - 1.76 (m, 4H), 1.62 - 1.48 (m, 2H), 1.29 (s, 3H), 0.93 - 0.82 (m, 3H)
1072	propyl (((2-(((3S,6S,9aS)-3-(3-(4-((S)-2-(methoxymethyl)azetidin-1-yl)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		872.7	^{1}H NMR (400 MHz, CD_3OD) δ 8.58 - 8.50 (m, 1H), 8.30 (s, 1H), 8.07 - 8.01 (m, 1H), 7.95 - 7.86 (m, 2H), 7.53 - 7.46 (m, 1H), 7.37 - 7.29 (m, 2H), 7.21 - 7.13 (m, 3H), 4.94 (d, J = 3.2 Hz, 1H), 4.74 (d, J = 11.2 Hz, 1H), 4.64 - 4.57 (m, 2H), 4.56 - 4.51 (m, 1H), 4.51 - 4.25 (m, 3H), 4.14 - 3.99 (m, 4H), 3.98 - 3.81 (m, 3H), 3.63 - 3.55 (m, 2H), 3.54 - 3.46 (m, 1H), 3.41 - 3.38 (m, 3H), 2.65 - 2.53 (m, 1H), 2.51 - 2.38 (m, 1H), 2.37 - 2.25 (m, 1H), 2.17 - 2.05 (m, 2H), 2.04 - 1.90 (m, 4H), 1.89 - 1.77 (m, 3H), 1.62 - 1.48 (m, 2H), 1.20 - 1.06 (m, 3H), 0.94 - 0.81 (m, 3H)

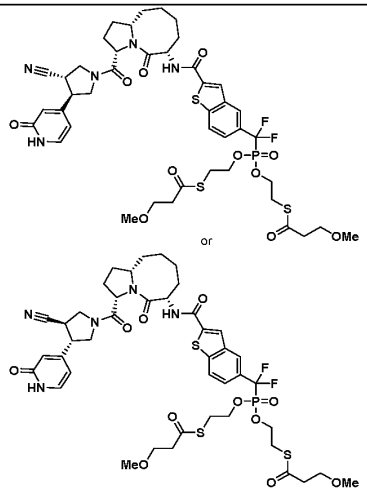
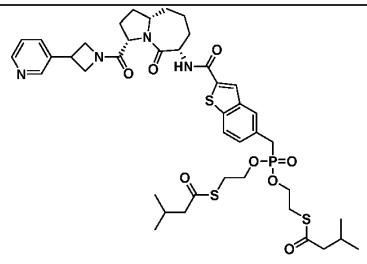
1073	propyl (((R)-fluoro(2-(((3S,6S,9aS)-3-(3-(5-fluoro-4-methoxypyridin-3-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		838.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.42 - 8.35 (m, 1H), 8.31 - 8.23 (m, 1H), 8.10 (d, J = 13.6 Hz, 2H), 8.03 - 7.94 (m, 1H), 7.71 - 7.61 (m, 1H), 7.37 - 7.29 (m, 2H), 7.25 - 7.12 (m, 3H), 6.18 - 5.99 (m, 1H), 4.79 - 4.71 (m, 1H), 4.68 - 4.61 (m, 1H), 4.61 - 4.55 (m, 1H), 4.47 - 4.31 (m, 2H), 4.26 - 4.19 (m, 3H), 4.18 - 4.03 (m, 3H), 4.01 - 3.95 (m, 1H), 3.94 - 3.87 (m, 1H), 3.84 - 3.77 (m, 1H), 2.37 - 2.26 (m, 1H), 2.18 - 2.06 (m, 2H), 2.04 - 1.88 (m, 5H), 1.87 - 1.77 (m, 2H), 1.62 - 1.46 (m, 2H), 1.26 - 1.18 (m, 3H), 0.92 - 0.81 (m, 3H)
1074	propyl (((2-(((3S,6S,8R,9aR)-3-(3-(4-(azetidin-1-yl)pyrimidin-5-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		842.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 - 8.48 (m, 1H), 8.26 (d, *J* = 4.0 Hz, 1H), 8.06 - 8.00 (m, 1H), 7.93 - 7.85 (m, 2H), 7.52 - 7.46 (m, 1H), 7.35 - 7.28 (m, 2H), 7.16 (t, *J* = 9.2 Hz, 3H), 4.86 - 4.80 (m, 1H), 4.74 (d, J = 11.2 Hz, 1H), 4.61 - 4.50 (m, 5H), 4.39 - 4.25 (m, 2H), 4.14 - 4.03 (m, 3H), 3.97 - 3.81 (m, 3H), 3.59 - 3.45 (m, 2H), 2.55 - 2.43 (m, 2H), 2.36 - 2.28 (m, 1H), 2.18 - 2.04 (m, 2H), 2.00 - 1.90 (m, 3H), 1.79 (d, J = 12.0 Hz, 1H), 1.67 - 1.48 (m, 4H), 1.16 -

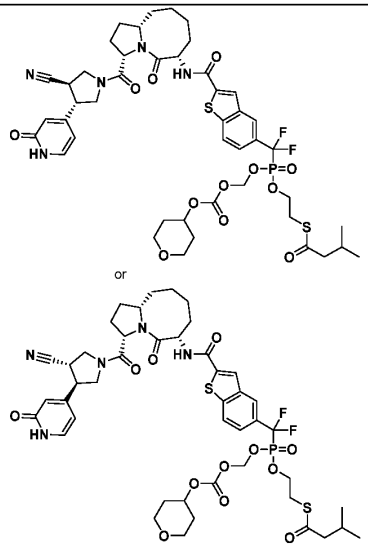
				1.03 (m, 6H), 0.90 - 0.83 (m, 3H)
1075	propyl (((R)-(2-(((3S,6S,9aS)-3-(3-(4-(azetidin-1-yl)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		846.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 - 8.47 (m, 1H), 8.26 (d, J = 4.4 Hz, 1H), 8.13 - 8.05 (m, 2H), 7.98 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.38 - 7.29 (m, 2H), 7.23 - 7.13 (m, 3H), 6.19 - 6.02 (m, 1H), 4.95 - 4.88 (m, 1H), 4.74 (d, J = 10.6 Hz, 1H), 4.60 - 4.50 (m, 5H), 4.41 - 4.26 (m, 2H), 4.12 - 4.04 (m, 3H), 4.00 - 3.89 (m, 1H), 3.86 - 3.80 (m, 2H), 2.56 - 2.44 (m, 2H), 2.35 - 2.27 (m, 1H), 2.18 - 2.07 (m, 2H), 2.06 - 1.90 (m, 4H), 1.89 - 1.80 (m, 3H), 1.60 - 1.48 (m, 2H), 1.26 - 1.19 (m, 3H), 0.91 - 0.83 (m, 3H)
1076	propyl (((S)-(2-(((3S,6S,9aS)-3-(3-(4-(azetidin-1-yl)pyrimidin-5-yl)azetidine-1-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		846.6	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 - 8.49 (m, 1H), 8.39 - 8.33 (m, 1H), 8.07 - 7.79 (m, 3H), 7.68 - 7.53 (m, 2H), 7.27 - 7.23 (m, 2H), 7.08 - 7.07 (m, 3H), 6.01 - 5.89 (m, 1H), 4.89 - 4.76 (m, 2H), 4.67 - 4.45 (m, 6H), 4.18 - 4.16 (m, 2H), 4.04 - 3.69 (m, 5H), 2.47 - 2.46 (m, 2H), 2.24 - 2.12 (m, 2H), 2.10 - 1.98 (m, 5H), 1.94 - 1.80 (m, 3H), 1.62 - 1.59 (m, 2H), 1.27 - 1.24 (m, 3H), 0.90 - 0.83 (m, 3H)

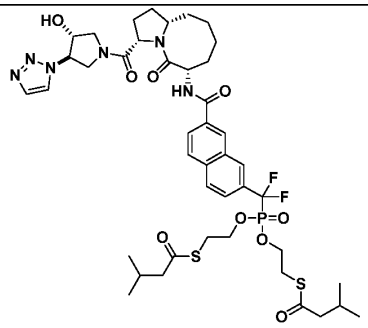
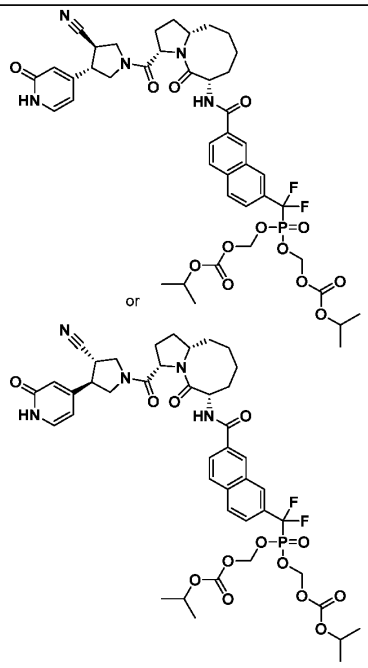
1077	propyl (((R)-(2-(((3S,6S,8R,9aR)-3-(3-(4-(azetidin-1-yl)pyrimidin-5-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		860.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.49 - 8.57 (m, 1H), 8.27 (s, 1H), 8.08 - 8.16 (m, 2H), 8.00 (d, J=8.40 Hz, 1H), 7.68 (d, J=8.00 Hz, 1H), 7.33 - 7.44 (m, 2H), 7.12 - 7.27 (m, 3H), 6.03 - 6.23 (m, 1H), 4.85 (s, 1H), 4.77 (d, J=11.20 Hz, 1H), 4.50 - 4.66 (m, 5H), 4.27 - 4.44 (m, 2H), 4.05 - 4.16 (m, 3H), 3.82 - 4.02 (m, 3H), 2.44 - 2.58 (m, 2H), 2.34 (m, 1H), 2.06 - 2.22 (m, 2H), 1.89 - 2.03 (m, 3H), 1.82 (d, J=13.20 Hz, 1H), 1.49 - 1.71 (m, 4H), 1.21 - 1.28 (m, 3H), 1.07 (d, J=6.40 Hz, 3H), 0.85 - 0.93 (m, 3H)
1078	propyl (((S)-(2-(((3S,6S,8R,9aR)-3-(3-(4-(azetidin-1-yl)pyrimidin-5-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)(phenoxy)phosphoryl)-L-alaninate		860.7	^{1}H NMR (400 MHz, CD_3OD) δ 8.47 - 8.58 (m, 1H), 8.26 (s, 1H), 8.08 - 8.15 (m, 2H), 8.01 (d, J=8.40 Hz, 1H), 7.61 - 7.72 (m, 1H), 7.30 - 7.39 (m, 2H), 7.12 - 7.25 (m, 3H), 6.01 - 6.16 (m, 1H), 4.80 - 4.84 (m, 1H), 4.76 (d, J=11.60 Hz, 1H), 4.50 - 4.63 (m, 5H), 4.26 - 4.42 (m, 2H), 4.04 - 4.13 (m, 3H), 3.95 - 4.01 (m, 2H), 3.77 - 3.85 (m, 1H), 2.45 - 2.54 (m, 2H), 2.27 - 2.38 (m, 1H), 2.04 - 2.19 (m, 2H), 1.89 - 2.01 (m, 3H), 1.80 (d, J=11.60 Hz, 1H), 1.52 - 1.65 (m, 4H), 1.02 - 1.12 (m,

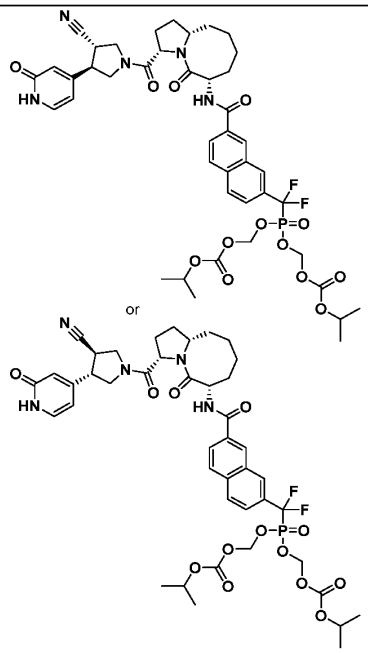
				6H), 0.88 (t, J=7.20 Hz, 3H)
1079	propyl (((2-(((3S,6S,8S,9aR)-3-(3-(4-(dimethylamino)pyridin-3-yl)azetidine-1-carbonyl)-8-methyl-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(phenoxy)phosphoryl)-L-alaninate		829.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.40 - 8.30 (m, 1H), 8.17 - 8.06 (m, 1H), 8.03 (d, J = 18.8 Hz, 1H), 7.94 - 7.83 (m, 2H), 7.49 (t, J = 7.2 Hz, 1H), 7.37 - 7.27 (m, 2H), 7.16 (t, J = 9.2 Hz, 3H), 7.13 - 7.03 (m, 1H), 4.99 - 4.94 (m, 1H), 4.71 (t, J = 8.8 Hz, 1H), 4.57 - 4.46 (m, 2H), 4.46 - 4.39 (m, 1H), 4.35 - 4.26 (m, 2H), 4.12 - 4.01 (m, 1H), 3.97 - 3.90 (m, 2H), 3.89 - 3.80 (m, 1H), 3.60 - 3.54 (m, 1H), 3.53 - 3.45 (m, 1H), 3.15 (s, 6H), 2.36 - 2.24 (m, 2H), 2.24 - 2.09 (m, 1H), 2.07 - 2.00 (m, 2H), 1.98 - 1.89 (m, 1H), 1.88 - 1.78 (m, 1H), 1.64 - 1.57 (m, 1H), 1.56 - 1.50 (m, 2H), 1.39 – 1.36 (m, 1H), 1.24 – 1.22 (m, 3H), 1.17 - 1.06 (m, 3H), 0.87 (t, J = 7.2 Hz, 3H)
1080	S,S'-(((((2-(((3S,6S,9aS)-3-((6R,7S)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))		971.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-8.08 (m, 1H), 7.97-7.92 (m, 1H), 7.87-7.85 (m, 1H), 7.70-7.63 (m, 2H), 7.45-7.34 (m, 5H), 4.71-4.59 (m, 2H), 4.28-4.04 (m, 6H), 3.95-3.87 (m, 1H), 3.79-3.70 (m, 1H), 3.44-3.35 (m, 1H), 3.17-3.06 (m, 4H), 2.54-2.43 (m, 1H), 2.32-2.17

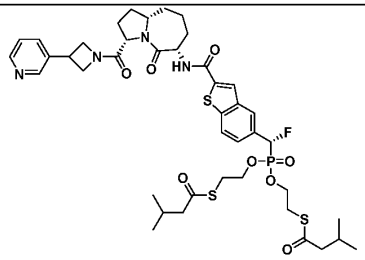
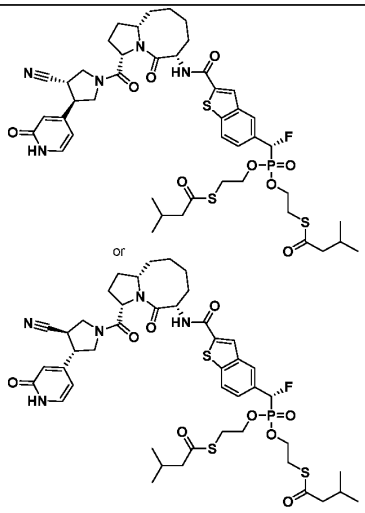
	bis(ethane-2,1-diyl)) bis(2,2-dimethylpropanethioate)			(m, 2H), 2.13-1.76 (m, 9H), 1.27-1.17 (m, 18H), 1.10-1.02 (m, 1H), 0.80-0.66 (m, 1H)
1081	S,S'-(((((2-(((3S,6S,9aS)-3-((6S,7R)-7-cyano-6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy)) bis(ethane-2,1-diyl)) bis(2,2-dimethylpropanethioate)		971.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-8.07 (m, 1H), 7.97-7.91 (m, 1H), 7.88-7.85 (m, 1H), 7.69-7.62 (m, 2H), 7.44-7.33 (m, 5H), 4.75-4.45 (m, 3H), 4.27-4.11 (m, 4H), 3.96-3.78 (m, 2H), 3.67 (d, J = 9.5 Hz, 1H), 3.56-3.48 (m, 1H), 3.16-3.06 (m, 4H), 2.48-2.33 (m, 1H), 2.28-2.16 (m, 2H), 2.09-1.87 (m, 7H), 1.84-1.72 (m, 2H), 1.24-1.19 (m, 18H), 1.18-1.10 (m, 1H), 0.83-0.67 (m, 1H)
1082	S,S'-((((difluoro(2-(((3S,6S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methylbutanethioate)		960.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-7.96 (m, 1H), 7.93-7.80 (m, 2H), 7.64-7.56 (m, 1H), 7.27-7.17 (m, 5H), 5.33-5.02 (m, 1H), 4.73-4.51 (m, 1H), 4.38-4.08 (m, 5H), 4.05-3.91 (m, 1H), 3.72-3.48 (m, 2H), 3.27-3.05 (m, 4H), 2.47-2.41 (m, 4H), 2.23-1.62 (m, 18H), 0.95 (d, J = 6.4 Hz, 12H), 0.62-0.49 (m, 2H)

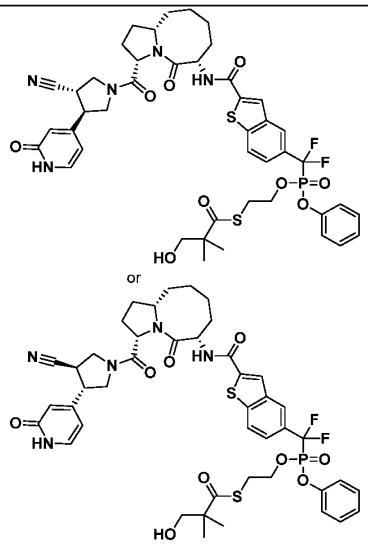
1083	S,S'-(((((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methoxypropanethioate) Or S,S'-(((((2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methoxypropanethioate)	 Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	980	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.61 (s, 1H), 8.97-8.85 (m, 1H), 8.39-8.29 (m, 1H), 8.25-8.19 (m, 1H), 8.16 (s, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.43-7.34 (m, 1H), 6.43-6.33 (m, 1H), 6.30-6.19 (m, 1H), 4.96 (s, 1H), 4.62-4.49 (m, 1H), 4.37-4.10 (m, 6H), 3.60-3.53 (m, 5H), 3.20 (s, 6H), 3.15 (t, J = 6.3 Hz, 4H), 2.82 (t, J = 5.9 Hz, 4H), 2.28-1.51 (m, 12H)
1084	S,S'-(((((2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphor		871	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.80-8.64 (m, 1H), 8.42-8.00 (m, 1H), 7.88-7.72 (m, 4H), 7.66-7.59 (m, 1H), 7.40-7.34 (m, 1H), 4.81-4.45 (m, 4H), 4.27-4.13 (m, 1H), 4.10-3.82 (m,

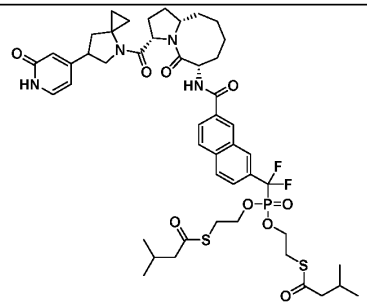
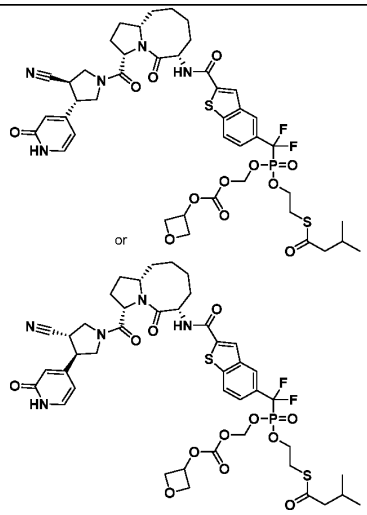
	yl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methylbutanethioate)			11H), 3.31 (d, J = 21.6 Hz, 2H), 3.17-2.99 (m, 4H), 2.33-1.83 (m, 12H), 0.94 (d, J = 6.6 Hz, 12H)
1085	S-(2-((((2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(((((tetrahydro-2H-pyran-4-yl)oxy)carbonyl)oxy)methoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate Or S-(2-((((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(((((tetrahydro-2H-pyran-4-yl)oxy)carbonyl)oxy)methoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate	 or Pyrrolidine building block SFC peak 1 was used for synthesis and biological testing	990.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 8.04 (s, 1H), 7.95 – 7.81 (m, 2H), 7.66 – 7.58 (m, 1H), 7.45 – 7.39 (m, 1H), 6.65 – 6.53 (m, 1H), 6.33 – 6.22 (m, 1H), 5.75 – 5.60 (m, 2H), 5.17 – 5.08 (m, 1H), 4.90 – 4.80 (m, 1H), 4.62 – 4.46 (m, 2H), 4.39 – 4.18 (m, 3H), 4.02 – 3.87 (m, 3H), 3.84 – 3.77 (m, 1H), 3.57 – 3.47 (m, 3H), 3.39 – 3.24 (m, 1H), 3.21 – 3.04 (m, 3H), 2.41 (d, J = 7.1 Hz, 2H), 2.28 – 2.03 (m, 7H), 2.00 – 1.82 (m, 6H), 1.79 – 1.70 (m, 3H), 0.96 – 0.91 (m, 6H)

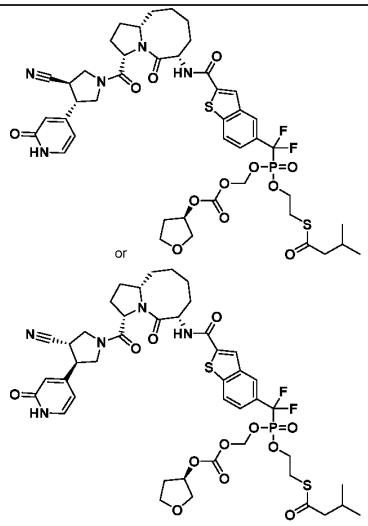
1086	S,S'-((((difluoro(7-(((3S,6S,10aS)-3-((*rel*-trans)-3-hydroxy-4-(1H-1,2,3-triazol-1-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methylbutanethioate)		934.9	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 – 8.62 (m, 2H), 8.31 – 8.26 (m, 1H), 8.22 – 8.08 (m, 4H), 7.79 – 7.68 (m, 2H), 5.15 – 4.91 (m, 2H), 4.67 – 4.43 (m, 2H), 4.43 – 4.28 (m, 2H), 4.25 – 4.10 (m, 5H), 4.08 – 3.88 (m, 2H), 3.85 – 3.76 (m, 2H), 3.61 – 3.41 (m, 3H), 3.20 – 3.11 (m, 4H), 2.47 – 2.39 (m, 4H), 2.25 – 1.54 (m, 14H), 0.90 – 0.85 (m, 12H)
1087	((((7-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) diisopropyl bis(carbonate) Or ((((7-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)napht	 Pyrrolidine building block SFC peak 1 was used for synthesis and biological testing	914.0	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 – 8.39 (m, 1H), 8.33 – 8.18 (m, 1H), 8.09 – 7.68 (m, 6H), 7.48 – 7.37 (m, 1H), 6.69 – 6.54 (m, 1H), 6.31 – 6.21 (m, 1H), 5.78 – 5.64 (m, 4H), 5.23 – 5.10 (m, 1H), 4.95 – 4.88 (m, 2H), 4.60 – 4.47 (m, 2H), 4.41 – 4.30 (m, 1H), 3.97 – 3.80 (m, 2H), 3.67 – 3.46 (m, 2H), 3.36 – 3.18 (m, 1H), 2.25 – 2.13 (m, 4H), 2.07 – 1.90 (m, 4H), 1.82 – 1.63 (m, 4H), 1.29 (d, *J* = 6.2 Hz, 12H)

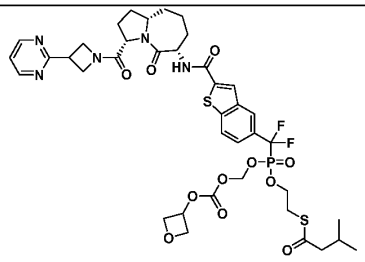
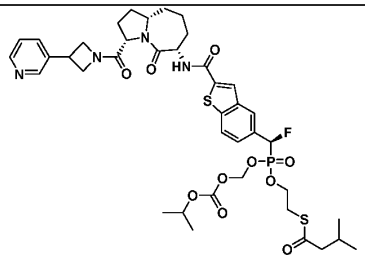
	halen-2-yl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) diisopropyl bis(carbonate)			
1088	((((7-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) diisopropyl bis(carbonate) Or ((((7-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) diisopropyl bis(carbonate)	 Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	914.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 – 8.42 (m, 1H), 8.30 – 8.20 (m, 1H), 8.08 – 7.86 (m, 4H), 7.77 – 7.68 (m, 1H), 7.47 – 7.30 (m, 1H), 6.77 – 6.51 (m, 1H), 6.31 – 6.19 (m, 1H), 5.79 – 5.63 (m, 4H), 5.24 – 5.10 (m, 1H), 4.96 – 4.84 (m, 2H), 4.60 – 4.49 (m, 1H), 4.41 – 4.15 (m, 3H), 4.11 – 3.92 (m, 1H), 3.78 – 3.57 (m, 2H), 3.19 – 3.08 (m, 1H), 2.32 – 1.60 (m, 14H), 1.32 – 1.26 (m, 12H)

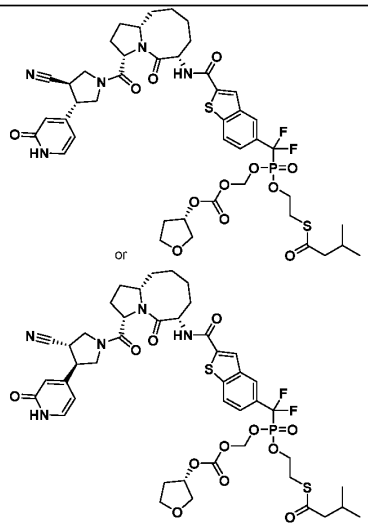
1089	S,S'-(((((R)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methylbutanethioate)		889.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.02 – 7.87 (m, 3H), 7.86 – 7.79 (m, 1H), 7.76 – 7.66 (m, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.51 – 7.33 (m, 1H), 5.84 (dd, J = 44.4, 7.4 Hz, 1H), 4.75 – 4.37 (m, 4H), 4.25 – 3.84 (m, 8H), 3.16 – 3.03 (m, 4H), 2.47 – 2.37 (m, 4H), 2.34 – 1.72 (m, 13H), 0.94 (d, J = 6.6 Hz, 12H)
1090	S,S'-(((((R)-(2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methylbutanethioate) Or S,S'-(((((R)-(2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)fluoromethyl)ph	 Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	958.0	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.82 (m, 3H), 7.56 – 7.36 (m, 2H), 6.65 – 6.55 (m, 1H), 6.31 – 6.23 (m, 1H), 5.92 – 5.75 (m, 1H), 5.16 – 5.07 (m, 1H), 4.62 – 4.47 (m, 2H), 4.41 – 4.27 (m, 1H), 4.18 – 3.64 (m, 7H), 3.57 – 3.31 (m, 2H), 3.16 – 3.04 (m, 4H), 2.47 – 2.38 (m, 4H), 2.22 – 1.63 (m, 14H), 0.99 – 0.88 (m, 12H)

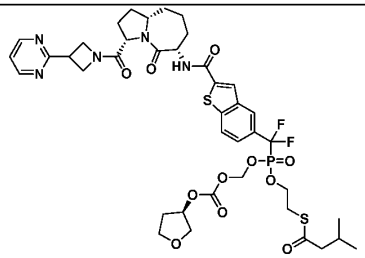
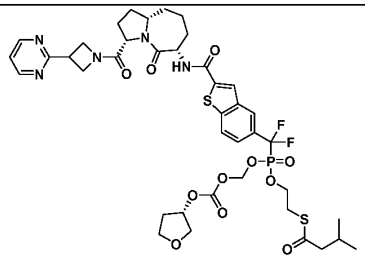
	osphoryl)bis(oxy))bis(ethane-2,1-diyl))bis(3-methylbutanethioate)			
1091	S-(2-((((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(phenoxy)phosphoryl)oxy)ethyl) 3-hydroxy-2,2-dimethylpropanethioate Or S-(2-((((2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(phenoxy)phosphoryl)oxy)ethyl) 3-hydroxy-2,2-dimethylpropanethioate	 or Pyrrolidine building block SFC peak 2 was used for synthesis and biological testing	924.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.62 (s, 1H), 8.99 – 8.88 (m, 1H), 8.39 – 8.30 (m, 1H), 8.26 – 8.17 (m, 2H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.46 – 7.34 (m, 3H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.42 – 6.33 (m, 1H), 6.31 – 6.16 (m, 1H), 5.00 – 4.86 (m, 2H), 4.61 – 4.50 (m, 1H), 4.35 – 4.07 (m, 4H), 4.02 – 3.41 (m, 5H), 3.26 – 3.15 (m, 1H), 3.10 (t, *J* = 6.3 Hz, 2H), 2.33 – 2.19 (m, 1H), 2.09 – 1.77 (m, 8H), 1.68 – 1.45 (m, 3H), 1.07 (s, 6H)

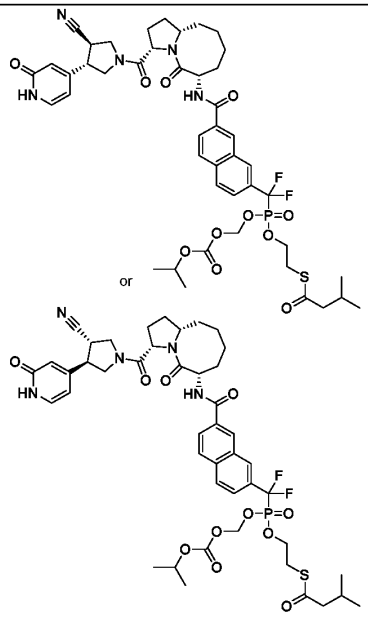
1092	S,S'-((((difluoro(7-(((3S,6S,10aS)-5-oxo-3-(6-(2-oxo-1,2-dihydropyridin-4-yl)-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methylbutanethioate)		971.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 – 8.39 (m, 1H), 8.19 (d, *J* = 10.2 Hz, 1H), 8.06 – 7.84 (m, 3H), 7.78 – 7.67 (m, 1H), 7.64 – 7.54 (m, 1H), 7.41 – 7.30 (m, 1H), 6.75 – 6.46 (m, 1H), 6.46 – 6.19 (m, 1H), 5.28 – 5.09 (m, 1H), 4.58 – 4.32 (m, 2H), 4.30 – 4.13 (m, 4H), 4.13 – 3.86 (m, 1H), 3.67 – 3.35 (m, 2H), 3.21 – 3.08 (m, 4H), 2.47 – 2.36 (m, 4H), 2.27 – 1.88 (m, 13H), 1.88 – 1.76 (m, 2H), 1.72 – 1.58 (m, 2H), 1.36 – 1.26 (m, 1H), 1.02 – 0.83 (m, 12H), 0.62 – 0.35 (m, 2H)
1093	S-(2-((((2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(((oxetan-3-yloxy)carbonyl)oxy)methoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate Or S-(2-((((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(2-oxo-1,2-	 or Pyrrolidine building block SFC peak 1 was used for synthesis and biological testing	962.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 11.62 (s, 1H), 9.00 – 8.86 (m, 1H), 8.38 – 8.30 (m, 1H), 8.25 – 8.18 (m, 1H), 8.14 (s, 1H), 7.57 (d, J = 8.6 Hz, -106.65 (d, J = 121.2 Hz).), 7.39 (d, J = 6.6 Hz, 1H), 6.39 – 6.34 (m, 1H), 6.28 – 6.21 (m, 1H), 5.70 (d, J = 13.1 Hz, 2H), 5.43 – 5.33 (m, 1H), 5.00 – 4.89 (m, 1H), 4.80 (t, J = 7.0 Hz, 2H), 4.51 (dd, J = 39.1, 7.5 Hz, 3H), 4.33 – 4.15 (m, 4H), 3.95 – 3.44 (m, 5H), 3.13 (t, J = 6.2 Hz, 2H), 2.43 (d, J = 7.1 Hz, 2H), 2.32 – 2.18 (m, 1H), 2.05 – 1.95 (m, 2H), 1.92 – 1.67 (m, 7H), 1.66 –

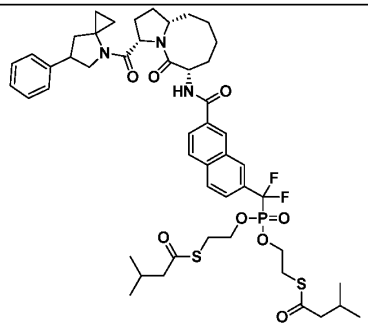
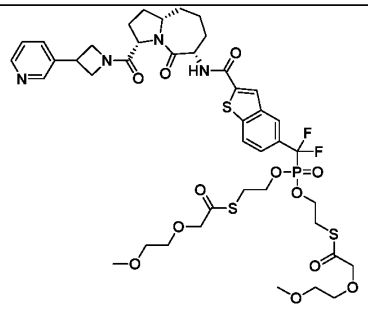
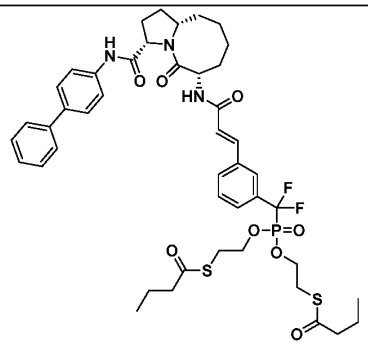
	dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(((oxetan-3-yloxy)carbonyl)oxy)methoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate			1.46 (m, 3H), 0.89 – 0.83 (m, 6H)
1094	S-(2-((((2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(((((R)-tetrahydrofuran-3-yl)oxy)carbonyl)oxy)methoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate Or S-(2-((((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-	 Pyrrolidine building block SFC peak 1 was used for synthesis and biological testing	975.9	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 7.79 (m, 2H), 7.66 – 7.56 (m, 1H), 7.50 – 7.36 (m, 1H), 6.70 – 6.51 (m, 1H), 6.41 – 6.24 (m, 1H), 5.76 – 5.57 (m, 1H), 5.31 – 5.20 (m, 1H), 5.17 – 5.02 (m, 1H), 4.57 – 4.43 (m, 1H), 4.39 – 4.18 (m, 3H), 4.13 – 3.82 (m, 6H), 3.80 – 3.30 (m, 3H), 3.25 – 3.07 (m, 3H), 2.42 (d, *J* = 7.1 Hz, 2H), 2.27 – 2.06 (m, 9H), 2.01 – 1.90 (m, 2H), 1.83 – 1.75 (m, 1H), 1.70 – 1.60 (m, 2H), 1.46 – 1.37 (m, 1H), 0.98 – 0.90 (m, 6H) (TFA salt)

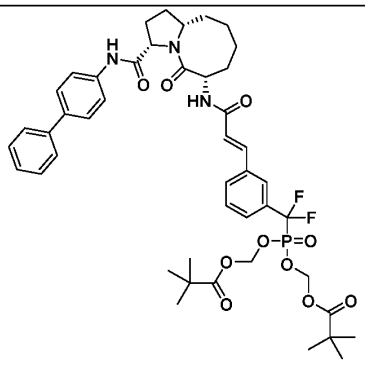
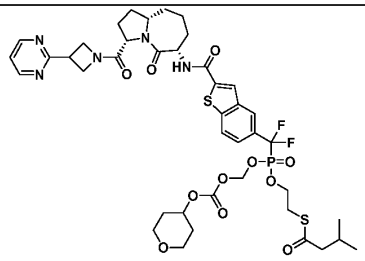
	yl)difluoromethyl)(((((R)-tetrahydrofuran-3-yl)oxy)carbonyl)oxy)methoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate			
1095	S-(2-(((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyrimidin-2-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)((((oxetan-3-yloxy)carbonyl)oxy)methoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate		894.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 – 8.78 (m, 3H), 8.33 (d, J = 16.2 Hz, 1H), 8.26 – 8.19 (m, 1H), 8.14 (d, J = 10.9 Hz, 1H), 7.64 – 7.55 (m, 1H), 7.47 – 7.37 (m, 1H), 5.70 (d, J = 13.1 Hz, 2H), 5.43 – 5.35 (m, 1H), 4.84 – 4.40 (m, 8H), 4.31 – 3.94 (m, 6H), 3.13 (t, J = 6.0 Hz, 2H), 2.46 – 2.40 (m, 2H), 2.26 – 2.14 (m, 1H), 2.07 – 1.92 (m, 3H), 1.89 – 1.63 (m, 7H), 0.90 – 0.81 (m, 6H)
1096	S-(2-((((S)-fluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(((isopropoxycarbonyl)oxy)methoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate		861.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 – 8.53 (m, 2H), 8.00 – 7.94 (m, 1H), 7.90 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 13.0 Hz, 1H), 7.77 – 7.70 (m, 1H), 7.70 – 7.62 (m, 1H), 7.53 (d, J = 8.7 Hz, 1H), 7.45 – 7.30 (m, 1H), 5.96 – 5.76 (m, 1H), 5.69 – 5.58 (m, 2H), 5.04 – 4.90 (m, 1H), 4.71 – 4.37 (m, 4H), 4.23 – 4.06 (m, 3H), 3.99 – 3.87 (m, 2H), 3.09 (q, J = 6.6 Hz, 2H), 2.43 – 2.36 (m, 2H), 2.31 – 2.17 (m, 2H), 2.09 – 2.02 (m, 4H), 1.97 – 1.90

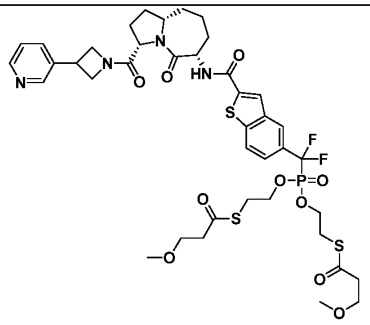
				(m, 2H), 1.86 – 1.68 (m, 4H), 1.32 (d, J = 6.2 Hz, 6H), 0.97 – 0.89 (m, 6H)
1097	S-(2-((((2-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(((((S)-tetrahydrofuran-3-yl)oxy)carbonyl)oxy)methoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate Or S-(2-((((2-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)(((((S)-tetrahydrofuran-3-yl)oxy)carbonyl)oxy)methoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate	 Pyrrolidine building block SFC peak 1 was used for synthesis and biological testing	976.0	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 7.86 (m, 3H), 7.84 – 7.30 (m, 3H), 6.61 – 6.47 (m, 1H), 6.24 – 6.16 (m, 1H), 5.75 – 5.59 (m, 2H), 5.30 – 5.06 (m, 2H), 4.63 – 4.47 (m, 2H), 4.38 – 4.16 (m, 3H), 4.13 – 3.57 (m, 7H), 3.54 – 3.04 (m, 4H), 2.45 – 2.38 (m, 2H), 2.26 – 2.09 (m, 7H), 1.95 – 1.83 (m, 6H), 1.71 – 1.60 (m, 2H), δ 1.01 – 0.86 (m, 6H)

1098	S-(2-(((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyrimidin-2-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)((((((R)-tetrahydrofuran-3-yl)oxy)carbonyl)oxy)methoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate		908.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 2H), 8.12 – 8.02 (m, 1H), 7.98 – 7.80 (m, 2H), 7.79 – 7.59 (m, 2H), 7.26 – 7.18 (m, 1H), 5.75 – 5.60 (m, 2H), 5.32 – 5.20 (m, 1H), 4.96 – 4.82 (m, 1H), 4.74 – 4.12 (m, 8H), 4.00 – 3.79 (m, 5H), 3.18 – 3.03 (m, 2H), 2.42 (d, J = 7.1 Hz, 2H), 2.29 – 2.03 (m, 8H), 1.98 – 1.72 (m, 5H), 0.94 (d, J = 6.6 Hz, 6H)
1099	S-(2-(((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyrimidin-2-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)((((((S)-tetrahydrofuran-3-yl)oxy)carbonyl)oxy)methoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate		908.0	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 – 8.68 (m, 2H), 8.12 – 8.03 (m, 1H), 7.99 – 7.83 (m, 2H), 7.82 – 7.73 (m, 1H), 7.68 – 7.58 (m, 1H), 7.30 – 7.27 (m, 1H), 5.76 – 5.58 (m, 2H), 5.31 – 5.21 (m, 1H), 4.96 – 4.83 (m, 1H), 4.72 – 4.14 (m, 8H), 4.00 – 3.83 (m, 5H), 3.18 – 3.05 (m, 2H), 2.46 – 2.37 (m, 2H), 2.30 – 1.99 (m, 9H), 1.98 – 1.69 (m, 4H), 1.01 – 0.86 (m, 6H) (TFA salt)

1100	S-(2-((((7-(((3S,6S,10aS)-3-((3R,4S)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)((isopropoxycarbonyl)oxy)methoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate Or S-(2-((((7-(((3S,6S,10aS)-3-((3S,4R)-3-cyano-4-(2-oxo-1,2-dihydropyridin-4-yl)pyrrolidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)difluoromethyl)((isopropoxycarbonyl)oxy)methoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate	 Pyrrolidine building block SFC peak 1 was used for synthesis and biological testing	942.3	^{1}H NMR (400 MHz, CDCl3) δ 8.63 – 8.39 (m, 1H), 8.35 – 8.16 (m, 1H), 8.09 – 7.63 (m, 5H), 7.51 – 7.37 (m, 1H), 6.75 – 6.61 (m, 1H), 6.38 – 6.28 (m, 1H), 5.75 – 5.56 (m, 2H), 5.21 – 5.08 (m, 1H), 4.96 – 4.86 (m, 1H), 4.65 – 4.42 (m, 2H), 4.38 – 4.29 (m, 1H), 4.29 – 4.09 (m, 2H), 3.98 – 3.43 (m, 4H), 3.36 – 3.05 (m, 3H), 2.42 – 2.36 (m, 2H), 2.26 – 1.61 (m, 13H), 1.30 (d, J = 6.2 Hz, 6H), 0.92 (d, J = 6.6 Hz, 6H)

1101	S,S'-((((difluoro(7-(((3S,6S,10aS)-5-oxo-3-(6-phenyl-4-azaspiro[2.4]heptane-4-carbonyl)decahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)naphthalen-2-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methylbutanethioate)		954.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 – 8.31 (m, 1H), 8.09 (s, 1H), 7.91 – 7.79 (m, 3H), 7.65 (d, J = 8.7 Hz, 1H), 7.54 – 7.46 (m, 1H), 7.24 – 7.12 (m, 5H), 5.16 – 5.05 (m, 1H), 4.54 – 4.17 (m, 3H), 4.18 – 4.05 (m, 4H), 3.72 – 3.55 (m, 1H), 3.54 – 3.40 (m, 1H), 3.13 – 2.96 (m, 4H), 2.37 – 2.28 (m, 5H), 2.18 – 1.48 (m, 17H), 0.84 (d, J = 6.7 Hz, 12H), 0.53 – 0.37 (m, 2H)
1102	S,S'-((((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(2-(2-methoxyethoxy)ethanethioate)		971.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 – 8.52 (m, 2H), 8.19 – 7.85 (m, 4H), 7.83 – 7.61 (m, 2H), 7.57 – 7.35 (m, 1H), 5.10 – 4.51 (m, 4H), 4.49 – 3.86 (m, 12H), 3.80 – 3.70 (m, 4H), 3.65 – 3.55 (m, 4H), 3.39 (s, 6H), 3.25 – 3.08 (m, 4H), 2.36 – 1.67 (m, 10H).
1103	S,S'-(((((3-((E)-3-(((3S,6S,10aS)-3-([1,1'-biphenyl]-4-ylcarbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)amino)-3-oxoprop-1-en-1-yl)phenyl)difluoromethyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) dibutanethioate		898.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 8.37 (d, J = 7.2 Hz, 1H), 7.79 – 7.67 (m, 4H), 7.67 – 7.55 (m, 6H), 7.51 – 7.38 (m, 3H), 7.37 – 7.27 (m, 1H), 6.91 (d, J = 15.8 Hz, 1H), 5.01 – 4.85 (m, 1H), 4.48 (t, J = 8.5 Hz, 1H), 4.38 – 4.25 (m, 1H), 4.24 – 4.05 (m, 4H), 3.21 – 3.04 (m, 4H), 2.57 (t, J = 7.3

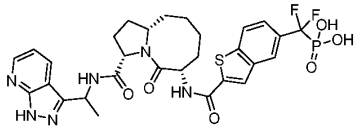
				Hz, 4H), 2.30 – 2.19 (m, 1H), 2.17 – 2.04 (m, 1H), 2.04 – 1.72 (m, 6H), 1.71 – 1.50 (m, 8H), 0.88 (t, J = 7.4 Hz, 6H)
1104	((((3-((E)-3-(((3S,6S,10aS)-3-([1,1'-biphenyl]-4-ylcarbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)amino)-3-oxoprop-1-en-1-yl)phenyl)difluoromethyl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)		866.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 – 10.14 (m, 1H), 8.42 – 8.25 (m, 1H), 7.75 – 7.67 (m, 4H), 7.67 – 7.60 (m, 4H), 7.59 – 7.52 (m, 2H), 7.49 – 7.38 (m, 3H), 7.37 – 7.27 (m, 1H), 6.97 – 6.76 (m, 1H), 5.81 – 5.58 (m, 4H), 4.98 – 4.85 (m, 1H), 4.54 – 4.39 (m, 1H), 4.37 – 4.23 (m, 1H), 2.30 – 2.18 (m, 1H), 2.17 – 2.04 (m, 1H), 2.03 – 1.83 (m, 4H), 1.83 – 1.71 (m, 2H), 1.71 – 1.57 (m, 3H), 1.57 – 1.46 (m, 1H), 1.15 (d, J = 6.5 Hz, 18H).
1105	S-(2-(((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyrimidin-2-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)(((((tetrahydro-2H-pyran-4-yl)oxy)carbonyl)oxy)methoxy)phosphoryl)oxy)ethyl) 3-methylbutanethioate		922.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 – 8.72 (m, 2H), 8.11 – 8.04 (m, 1H), 7.97 – 7.89 (m, 1H), 7.88 – 7.81 (m, 1H), 7.80 – 7.73 (m, 1H), 7.66 – 7.60 (m, 1H), 7.26 – 7.22 (m, 1H), 5.75 – 5.62 (m, 2H), 4.95 – 4.79 (m, 2H), 4.69 – 4.55 (m, 3H), 4.29 – 4.18 (m, 3H), 3.98 – 3.88 (m, 3H), 3.60 – 3.48 (m, 2H), 3.17 – 3.06 (m, 2H), 2.42 (d, J = 7.1 Hz, 2H), 2.32 – 2.08 (m, 4H), 2.07 – 1.91 (m, 8H), 1.82 – 1.69 (m, 4H), 1.56 –

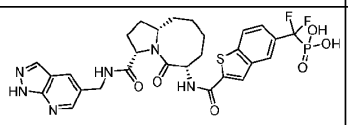
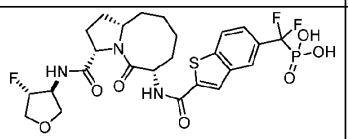
				1.40 (m, 1H), 0.97 – 0.92 (m, 6H)
1106	S,S'-((((difluoro(2-(((3S,6S,9aS)-5-oxo-3-(3-(pyridin-3-yl)azetidine-1-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) bis(3-methoxypropanethioate)		911.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.65 – 8.36 (m, 2H), 8.25 – 7.92 (m, 4H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.54 – 7.38 (m, 1H), 5.01 – 4.40 (m, 5H), 4.36 – 4.18 (m, 4H), 4.15 – 3.96 (m, 3H), 3.72 – 3.57 (m, 4H), 3.32 – 3.29 (m, 6H), 3.25 – 3.12 (m, 4H), 2.87 – 2.77 (m, 4H), 2.40 – 2.26 (m, 1H), 2.22 – 1.78 (m, 9H).

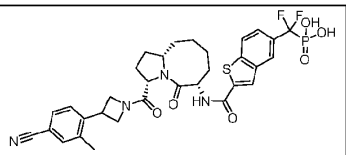
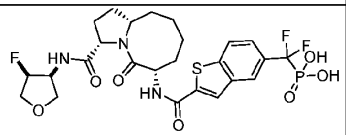
General Scheme 3: Acids Table

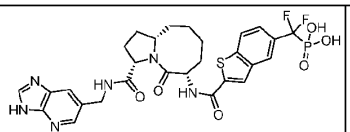
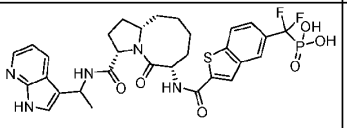
[001572] The following compounds in Table **111** were prepared according to the representative procedure described above for the synthesis of (Difluoro(2-(((3S,6S,9aS)-3-(methyl(phenyl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid (111) utilizing the appropriate starting materials and modifications.

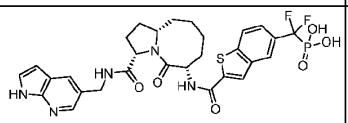
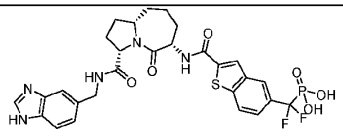
Table 111

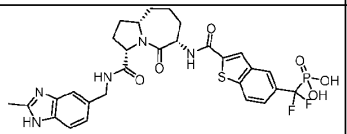
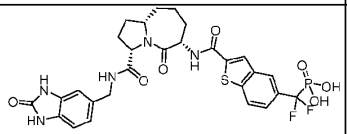
Compound	Name	Structure	LCMS $[M+H]^+$	NMR
1107	((2-(((3S,6S,10aS)-3-((1-(1H-pyrazolo[3,4-b]pyridin-3-yl)ethyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromet		661.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.55 - 8.27 (m, 2H), 8.21 - 8.06 (m, 2H), 7.97 - 7.88 (m, 1H), 7.78 - 7.68 (m, 1H), 7.23 - 7.12 (m, 1H), 5.55 - 5.47 (m, 1H), 5.04 (d, J = 1.6 Hz, 1H), 4.52 - 4.36 (m, 2H), 2.26 - 2.12 (m,

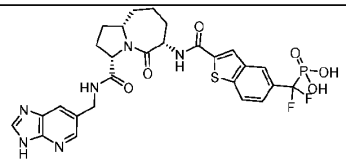
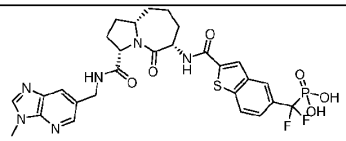
	hyl)phosphonic acid			2H), 2.08 - 1.87 (m, 6H), 1.86 - 1.73 (m, 2H), 1.73 - 1.57 (m, 5H)
1108	((2-(((3S,6S,10aS)-3-(((1H-pyrazolo[3,4-b]pyridin-5-yl)methyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		647.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.53 - 8.56 (m, 1H), 8.24 (d, J=2.00 Hz, 1H), 8.17 (s, 1H), 8.13 (s, 1H), 8.10 (s, 1H), 7.93 - 7.98 (m, 1H), 7.69 - 7.74 (m, 1H), 5.06 (m, 1H), 4.60 - 4.69 (m, 1H), 4.46 (m, 3H), 2.18 - 2.28 (m, 2H), 1.98 (s, 4H) 1.75 - 1.89 (m, 2H) 1.66 (s, 2H), 1.30 (s, 2H)
1109	(difluoro(2-(((3S,6S,10aS)-3-(((*rel-trans*)-4-fluorotetrahydrofuran-3-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		604.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.18 (s, 1H), 8.13 (m, 1H), 7.93 (m, 1H), 7.74 (d, J = 8.8 Hz, 1H), 5.17 - 4.95 (m, 2H), 4.45 - 4.31 (m, 3H), 4.12 - 4.05 (m, 1H), 4.04 - 3.86 (m, 2H), 3.77 - 3.69 (m, 1H), 2.27 - 2.16 (m, 2H), 2.08 - 1.92 (m, 6H), 1.87 - 1.77 (m, 2H), 1.73 - 1.60 (m, 2H)

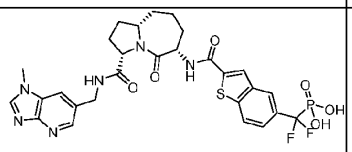
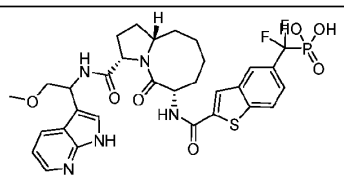
1110	((2-(((3S,6S,10aS)-3-(3-(4-cyano-2-methylphenyl)azetidine-1-carbonyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		671.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.23 - 8.05 (m, 2H), 7.94 – 7.88 (m, 1H), 7.73 (t, J = 7.2 Hz, 1H), 7.66 - 7.55 (m, 2H), 7.55 - 7.46 (m, 1H), 5.06 - 4.90 (m, 2H), 4.69 - 4.64 (m, 1H), 4.53 - 4.47 (m, 1H), 4.46 - 4.39 (m, 1H), 4.39 - 4.26 (m, 1H), 4.26 - 4.17 (m, 1H), 4.12 - 4.00 (m, 1H), 2.33 - 2.18 (m, 5H), 2.09 - 1.91 (m, 6H), 1.89 - 1.75 (m, 2H), 1.74 - 1.57 (m, 2H)
1111	(difluoro(2-(((3S,6S,10aS)-3-(((*rel-trans*)-4-fluorotetrahydrofuran-3-yl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		604.0	^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (s, 1H), 8.12 (s, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 5.11 - 5.01 (m, 2H), 4.60 - 4.36 (m, 3H), 4.15 - 4.03 (m, 2H), 4.03 - 3.95 (m, 1H), 3.70 - 3.52 (m, 1H), 2.31 - 2.17 (m, 2H), 2.11 - 1.91 (m, 6H), 1.87 - 1.77 (m, 2H), 1.74 - 1.58 (m, 2H)

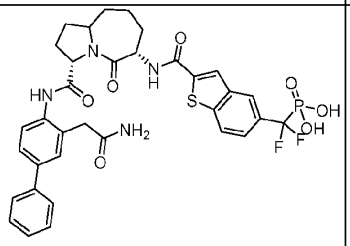
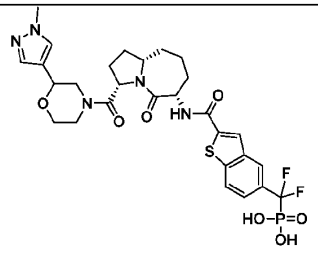
1112	((2-(((3S,6S,10aS)-3-(((3H-imidazo[4,5-b]pyridin-6-yl)methyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		647.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.48 - 8.38 (m, 2H), 8.18 - 8.09 (m, 2H), 8.04 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 5.01 (d, J = 10.4 Hz, 1H), 4.67 (d, J = 15.2 Hz, 1H), 4.52 - 4.44 (m, 2H), 4.43 – 4.38 (m, 1H), 2.32 - 2.17 (m, 2H), 2.13 - 2.05 (m, 1H), 2.02 - 1.91 (m, 5H), 1.85 - 1.79 (m, 1H), 1.75 (d, J = 10.0 Hz, 1H), 1.70 - 1.53 (m, 2H)
1113	((2-(((3S,6S,10aS)-3-((1-(1H-pyrrolo[2,3-b]pyridin-3-yl)ethyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		660.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.46 (d, J = 8.4 Hz, 1H), 8.33 (d, J = 7.2 Hz, 1H), 8.14 (s, 1H), 8.04 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.45 (s, 1H), 7.18 - 7.10 (m, 1H), 5.37 - 5.27 (m, 1H), 5.01 (s, 1H), 4.48 - 4.36 (m, 2H), 2.29 - 2.16 (m, 2H), 2.15 - 2.05 (m, 1H), 2.05 - 1.86 (m, 5H), 1.85 - 1.61

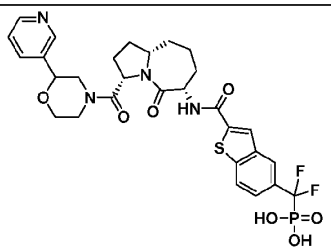
				(m, 4H), 1.59 (d, J = 6.8 Hz, 3H)
1114	((2-(((3S,6S,10aS)-3-(((1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)carbamoyl)-5-oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		646.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.21 - 8.13 (m, 2H), 8.08 (s, 1H), 8.01 (d, J = 2.0 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 3.6 Hz, 1H), 6.47 (d, J = 3.2 Hz, 1H), 5.08 - 5.00 (m, 1H), 4.58 - 4.51 (m, 1H), 4.50 - 4.43 (m, 2H), 4.43 - 4.32 (m, 1H), 2.30 - 2.17 (m, 2H), 2.14 - 2.05 (m, 1H), 2.04 - 1.90 (m, 5H), 1.85 - 1.73 (m, 2H), 1.71 - 1.56 (m, 2H)
1115	((2-(((3S,6S,9aS)-3-(((1H-benzo[d]imidazol-5-yl)methyl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		632.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.62 (s, 1H), 8.14 (s, 1H), 7.96 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.75 - 7.70 (m, 1H), 7.65 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 4.74 (d, *J* = 10.4 Hz, 1H), 4.70 - 4.56 (m, 2H), 4.44 (d, *J* = 15.2 Hz, 1H), 4.12 - 4.02 (m,

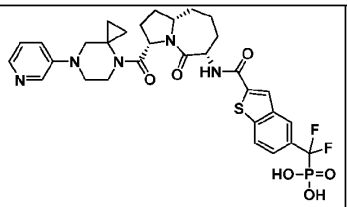
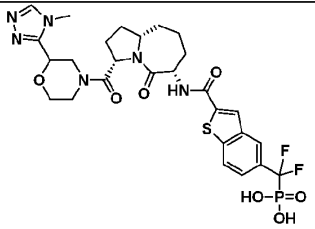
				1H), 2.36 - 2.25 (m, 1H), 2.22 - 2.11 (m, 1H), 2.10 - 1.98 (m, 3H), 1.96 - 1.76 (m, 5H)
1116	(difluoro(2-(((3S,6S,9aS)-3-(((2-methyl-1H-benzo[d]imidazol-5-yl)methyl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		646.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (s, 1H), 7.90 - 7.85 (m, 2H), 7.72 (d, J = 8.4 Hz, 1H), 7.51 (s, 1H), 7.42 - 7.37 (m, 1H), 7.30 (d, J = 8.4 Hz, 1H), 4.73 (d, J = 10.4 Hz, 1H), 4.65 - 4.56 (m, 2H), 4.42 (d, J = 15.2 Hz, 1H), 4.11 - 4.02 (m, 1H), 2.59 (s, 3H), 2.36 - 2.26 (m, 1H), 2.21 - 2.12 (m, 1H), 2.11 - 1.99 (m, 3H), 1.95 - 1.80 (m, 5H)
1117	(difluoro(2-(((3S,6S,9aS)-5-oxo-3-(((2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)carbamoyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-		648.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (s, 1H) 8.09 (s, 1H) 7.92 (s, 1H) 7.72 - 7.78 (m, 1H) 7.03 (s, 1H) 6.96 - 7.00 (m, 2H) 4.74 (m, 1H) 4.61 (m, 1H) 4.43 - 4.49 (m, 1H) 4.36 (s, 1H) 4.00 - 4.08 (m, 1H) 2.23 - 2.35 (m, 1H) 2.04 (s,

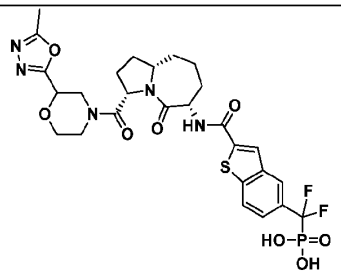
	yl)methyl)phosphonic acid			4H) 1.86 (m, 5H)
1118	((2-(((3S,6S,9aS)-3-(((3H-imidazo[4,5-b]pyridin-6-yl)methyl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		633.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (d, J = 7.2 Hz, 1H), 8.51 (t, J = 5.6 Hz, 1H), 8.38 (s, 1H), 8.28 (s, 1H), 8.23 (s, 1H), 8.05 (s, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.87 (s, 1H), 7.62 (d, J = 8.4 Hz, 1H), 4.62 (d, J = 7.2 Hz, 1H), 4.50 – 4.45 (m, 2H), 4.42 - 4.32 (m, 1H), 3.96 (d, J = 6.4 Hz, 1H), 2.25 - 2.13 (m, 1H), 2.02 - 1.91 (m, 2H), 1.90 - 1.81 (m, 2H), 1.73 (s, 5H)
1119	(difluoro(2-(((3S,6S,9aS)-3-(((3-methyl-3H-imidazo[4,5-b]pyridin-6-yl)methyl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		647.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (d, J = 7.2 Hz, 1H), 8.53 (t, J = 6.0 Hz, 1H), 8.41 (s, 1H), 8.30 (d, J = 1.6 Hz, 1H), 8.25 (s, 1H), 8.05 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 1.6 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.39 - 7.17 (m, 2H), 4.64 (t, J = 8.4 Hz, 1H),

				4.53 - 4.44 (m, 2H), 4.42 - 4.34 (m, 1H), 4.00 - 3.93 (m, 1H), 3.82 (s, 3H), 2.23 - 2.15 (m, 1H), 2.05 - 1.92 (m, 2H), 1.91 - 1.81 (m, 2H), 1.80 - 1.66 (m, 5H)
1120	(difluoro(2-(((3S,6S,9aS)-3-(((1-methyl-1H-imidazo[4,5-b]pyridin-6-yl)methyl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		647.1	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, J = 7.2 Hz, 1H), 8.57 (t, J = 6.0 Hz, 1H), 8.44 (s, 1H), 8.36 (s, 1H), 8.29 (s, 1H), 8.15 - 8.08 (m, 2H), 8.04 (s, 1H), 7.59 (d, J = 8.4 Hz, 1H), 4.69 - 4.53 (m, 3H), 4.48 (m, 1H), 4.39 - 4.33 (m, 1H), 4.00 (d, J = 4.8 Hz, 1H), 3.79 (s, 3H), 2.24 - 2.16 (m, 1H), 2.07 - 1.94 (m, 2H), 1.91 - 1.84 (m, 2H), 1.77 (s, 1H), 1.76 - 1.70 (m, 4H)
1121	(difluoro(2-(((3S,6S,10aS)-3-((2-methoxy-1-(1H-pyrrolo[2,3-b]pyridin-3-yl)ethyl)carbamoyl)-5-		690.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.50 - 8.20 (m, 1H), 8.19 - 8.07 (m, 2H), 7.98 (s, 2H), 7.73 - 7.62 (m, 1H), 7.52 - 7.44 (m, 1H), 7.38 - 7.23 (m,

	oxodecahydropyrrolo[1,2-a]azocin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid			1H), 5.44 (d, J = 5.6 Hz, 1H), 5.00 - 4.94 (m, 1H), 4.50 - 4.37 (m, 2H), 3.94 - 3.75 (m, 2H), 3.43 - 3.38 (m, 3H), 2.31 - 2.09 (m, 3H), 2.07 - 1.87 (m, 6H), 1.82 - 1.62 (m, 3H)
1122	((2-(((3S,6S)-3-((3-(2-amino-2-oxoethyl)-[1,1'-biphenyl]-4-yl)carbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid		711.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.21 - 8.13 (m, 2H), 8.04 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.67 - 7.60 (m, 4H), 7.59 - 7.55 (m, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.38 - 7.31 (m, 1H), 4.86 - 4.80 (m, 1H), 4.78 (dd, J = 4.8, 7.6 Hz, 1H), 4.19 - 4.02 (m, 1H), 3.77 - 3.59 (m, 2H), 2.45 - 2.32 (m, 1H), 2.30 - 2.21 (m, 2H), 2.15 - 2.08 (m, 1H), 2.07 - 1.90 (m, 5H), 1.89 - 1.80 (m, 1H).
1123			652.0	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82-8.67 (m, 1H), 8.29 (d, J = 6.1 Hz, 1H), 8.13 (d, J = 7.7 Hz, 1H), 8.07 (s, 1H), 7.80-7.65

				(m, 1H), 7.61-7.55 (m, 1H), 7.46-7.38 (m, 1H), 5.07-4.89 (m, 1H), 4.68-4.59 (m, 1H), 4.45-4.19 (m, 2H), 4.12-3.82 (m, 4H), 3.82-3.75 (m, 3H), 3.62-3.44 (m, 2H), 3.32-3.25 (m, 1H), 2.88-2.75 (m, 1H), 2.26-1.62 (m, 10H)
1124	(difluoro(2-(((3S,6S,9aS)-5-oxo-3-(2-(pyridin-3-yl)morpholine-4-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		649	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83-8.69 (m, 1H), 8.67-8.59 (m, 1H), 8.58-8.51 (m, 1H), 8.33-8.25 (m, 1H), 8.17-8.10 (m, 1H), 8.09-8.04 (m, 1H), 7.90-7.80 (m, 1H), 7.61-7.55 (m, 1H), 7.46-7.40 (m, 1H), 5.17-4.89 (m, 1H), 4.69-4.57 (m, 1H), 4.54-4.34 (m, 1H), 4.28-4.12 (m, 1H), 4.05-3.98 (m, 2H), 3.64-3.55 (m, 1H), 3.38-3.31 (m, 1H), 3.21-3.13 (m, 1H), 2.85-2.66 (m, 1H), 2.30-1.94 (m, 3H), 1.93-1.60 (m, 7H)

1125	(difluoro(2-(((3S,6S,9aS)-5-oxo-3-(7-(pyridin-3-yl)-4,7-diazaspiro[2.5]octane-4-carbonyl)octahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		674	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 6.8 Hz, 1H), 8.25 (s, 1H), 8.10-8.03 (m, 1H), 8.00-7.75 (m, 3H), 7.73-7.63 (m, 1H), 7.56-7.41 (m, 2H), 5.10 (s, 1H), 4.69-4.65 (m, 1H), 4.09-4.02 (m, 2H), 3.80-3.74 (m, 1H), 3.62-3.56 (m, 1H), 3.15-3.10 (m, 1H), 2.28-2.13 (m, 2H), 2.04-1.64 (m, 10H), 1.30-1.18 (m, 2H), 0.97-0.79 (m, 2H)
1126	(difluoro(2-(((3S,6S,9aS)-3-(2-(4-methyl-4H-1,2,4-triazol-3-yl)morpholine-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		653	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85-8.62 (m, 2H), 8.30 (s, 1H), 8.14 (d, J = 8.5 Hz, 1H), 8.08 (s, 1H), 7.59 (d, J = 8.5 Hz, 1H), 5.09-4.88 (m, 1H), 4.85-4.60 (m, 2H), 4.58-3.77 (m, 4H), 3.75-3.56 (m, 4H), 3.49-3.24 (m, 1H), 3.21-2.74 (m, 1H), 2.27-1.62 (m, 10H)

1127	(difluoro(2-(((3S,6S,9aS)-3-(2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholine-4-carbonyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)carbamoyl)benzo[b]thiophen-5-yl)methyl)phosphonic acid		654	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83-8.68 (m, 1H), 8.30 (s, 1H), 8.17-8.05 (m, 2H), 7.59 (d, J = 8.3 Hz, 1H), 5.09-4.77 (m, 2H), 4.75-4.58 (m, 1H), 4.50-4.16 (m, 1H), 4.06-3.85 (m, 3H), 3.79-3.02 (m, 3H), 2.48 (s, 3H), 2.28-2.16 (m, 1H), 2.12-1.68 (m, 9H)

Biochemical and Cellular Assays

STAT3 Fluorescence Polarization (FP) Assay

[001573] An FP assay was developed to determine IC_{50} values for test substances. Recombinant STAT3 protein (STAT3(G127-I722)) at 25 nM was combined with a fluorescently labeled, phosphotyrosine peptide probe (5-FAM-GpYLPQTV-NH_2) at 2 nM in FP buffer (10 mM HEPES pH 7.4, 50 mM NaCl, 1 mM EDTA, 0.05% Tween 20, 2 mM DTT). 50 µL of STAT3-probe mixture was added to serial diluted compounds in black, 96-well plates (Greiner BioOne 655076) to a final concentration of 1% DMSO. Reaction components were mixed, and FP was measured after 45-minute incubation at room temperature using a Tecan Spark multimode plate reader. FP signal (mP) was plotted against the log concentration of the test substances and IC_{50} values were calculated by nonlinear regression analysis using GraphPad Prism software. Results are shown in **Table 112**. For STAT3 FP assay, A = ≤100 nM; B = >100–1000 nM; C = >1–10 µM; and D = >10 µM.

STAT6 Fluorescence Polarization (FP) Assay

[001574] An FP assay was developed to determine IC_{50} values for test substances. Recombinant STAT6 protein (STAT6(W123-T658)) at 250 nM was combined with a fluorescently labeled, phosphotyrosine peptide probe (5-FAM-ApYKPFQDLI-NH_2) at 2 nM in FP buffer (10 mM HEPES pH 7.4, 50 mM NaCl, 1 mM EDTA, 0.05% Tween 20, 2 mM

DTT). 50 µL of STAT6-probe mixture was added to serial diluted compounds in black, 96-well plates (Greiner BioOne 655076) to a final concentration of 1% DMSO. Reaction components were mixed, and FP was measured after 45-minute incubation at room temperature using a Tecan Spark multimode plate reader. FP signal (mP) was plotted against the log concentration of the test substances and IC_{50} values were calculated by nonlinear regression analysis using GraphPad Prism software. Results are shown in **Table 112**. For STAT6 FP assay, A = ≤300 nM; B = >300–3000 nM; C = >3–30 µM; and D = >30 µM.

Table 112

Cmp#	STAT3	STAT6
1	D	B
2	B	C
3	B	C
4	B	C
5	B	C
6	B	C
7	B	C
8	B	C
9	B	C
10	B	C
11	B	C
12	C	A
13	A	C
14	B	A
15	A	B
16	A	B
17	A	C
18	C	A
19	C	A
20	B	C
21	C	A
22	C	A
23	C	B
24	B	A
25	A	B
26	A	B
27	C	A
28	C	A
29	B	C
30	C	B
31	B	B
32	A	C
33	A	B
34	B	C
35	D	C

Cmp#	STAT3	STAT6
63	B	A
64	A	B
65	B	B
66	A	C
67	A	B
68	B	C
69	B	B
70	B	C
71	B	B
72	B	B
73	B	C
74	C	A
75	C	A
76	C	A
77	B	C
78	B	D
79	B	A
80	B	A
81	A	B
82	B	A
83	B	A
84	B	B
85	A	C
86	B	A
87	B	B
88	C	B
89	C	A
90	D	B
91	C	A
92	B	B
93	B	C
94	B	C
95	B	A
96	B	A
97	B	B

36	A	B
37	B	B
38	A	B
39	B	B
40	B	C
41	A	A
42	B	A
43	A	B
44	C	B
45	A	B
46	A	C
47	C	B
48	C	C
49	B	C
50	B	B
51	A	B
52	C	B
53	A	B
54	A	B
55	B	B
56	B	C
57	B	B
58	B	B
59	B	B
60	A	C
61	B	B
62	D	D

98	B	C
99	B	B
100	C	A
101	B	B
102	B	B
103	A	C
104	B	B
105	B	A
106	C	A
107	B	A
108	A	B
109	A	C
110	A	C
111	C	B
113	B	C
114	A	C
115	A	C
116	B	B
117	A	C
118A	B	C
118B	B	B
119	B	C
120	B	B
121	B	B
122	A	C
123	A	C
124	A	C

Table 113

Cmp#	**STAT3**	**STAT6**
203	B	B
205	A	C
206	A	C
207	A	C
208	C	C
209	A	B
210	A	C
211	A	C
212	C	A
213	A	C
214	B	C
215	C	C
216	B	C
217	C	C
218	B	A
219	C	C

220	C	C
221	A	C
222	B	B
223	B	B
224	C	A
225	C	A
226	C	A
227	B	B
228	C	B
229	C	A
230	C	A
231	C	A
232	C	B
233	A	C
234	C	A
235	C	A
236	A	C

237	C	A
238	C	A
239	C	A
240	C	A
241	A	C
244	C	B
245	A	C
246	A	C
247	A	C
495	B	C
496	A	B
497	B	B
498	A	B
499	A	B
500	B	C
501	B	C
502	B	C
503	B	C
504	C	C
505	C	C
506	C	C
507	C	C
508	C	C
509	C	C
510	C	C
511	C	C
512	A	C
513	B	B
514	A	C
515	C	C
516	A	B
517	B	C
518	B	C
519	C	C
520	C	C
521	A	C
522	C	B
523	C	C
524	B	B
525	C	B
526	A	C
527	C	B
528	C	B
529	B	C

530	B	C
531	C	C
532	A	C
533	C	B
534	B	C
535	C	C
536	C	C
537	C	C
538	C	C
539	A	C
540	A	B
541	C	C
542	C	C
543	C	C
544	C	C
545	C	C
546	C	C
547	A	B
548	C	C
549	A	C
550	B	C
551	C	A
552	C	A
553	C	B
554	C	B
555	B	C
556	C	C
557	C	C
558	A	B
559	C	B
560	C	C
561	C	C
562	B	C
563	C	B
564	B	C
565	B	C
566	A	C
567	B	C
568	A	C
569	C	B
570	C	C
571	C	C
572	C	B
573	B	C

574	C	C
575	C	C
576	B	C
577	C	C
578	C	C
579	B	C
580	C	C
581	C	B
582	C	C
583	B	C
584	C	C
585	A	C
586	C	B
587	C	C
588	C	C
589	C	C
590	C	C
591	C	C
592	B	C
593	C	C
594	C	C
595	B	C
596	B	C
597	A	C
598	A	C
599	A	B
600	A	B
601	C	A
602	A	C
603	A	C
604	B	C
605	A	C
606	A	C
607	A	B
608	A	B
609	B	C
610	B	C
611	B	C
612	A	C
613	B	C
614	B	C
615	A	C
616	A	C
617	B	C

618	C	C
619	B	C
620	B	B
621	A	C
622	A	C
623	B	C
624	C	C
625	B	C
626	A	C
627	A	C
628	A	C
629	B	C
630	B	C
631	A	C
632	C	C
633	B	C
634	A	B
635	B	C
636	A	C
637	A	B
638	A	C
639	A	C
640	B	C
641	A	B
642	B	C
643	A	B
644	B	C
645	B	C
646	C	C
647	B	C
648	A	C
649	C	C
650	C	C
651	C	C
652	B	B
653	B	C
654	B	C
655	B	C
656	B	C
657	C	C
658	B	B
659	C	C
660	C	C
661	C	C

662	C	C
663	B	C
664	A	B
665	A	C
666	A	C
667	A	C
668	A	C
669	A	C
670	B	C
671	A	B
672	C	C
673	B	C
674	B	C
675	A	C
676	A	C
677	A	C
678	A	C
679	A	C
680	A	C
681	A	C
682	B	C
683	A	C
684	A	C
685	A	C
686	A	C
687	A	C
688	A	C
689	A	B
690	A	C
691	A	C
692	A	C
693	C	C
694	A	B
695	A	C
696	C	C
697	C	C
698	B	C
699	A	C
700	B	C
701	B	C
702	B	C
703	A	C
704	A	C
705	A	C

706	A	B
707	A	B
708	B	C
709	B	C
710	B	C
711	C	C
712	C	C
713	B	C
714	B	C
715	B	C
716	C	C
717	A	C
718	A	B
719	B	C
720	C	C
721	B	C
722	B	C
723	B	C
724	A	B
725	B	C
726	B	C
727	C	C
728	B	C
729	B	A
730	C	C
731	C	C
732	C	C
733	C	B
734	B	B
735	A	C
736	A	C
737	A	C
738	A	B
739	A	C
740	A	C
741	A	B
742	A	B
743	C	C
744	A	C
745	A	C
746	A	C
747	A	C
748	A	C
749	A	C

750	A	C
751	B	C
752	B	C
753	A	C
754	C	C
755	A	C
756	A	C
757	B	C
758	C	B
759	D	B
760	C	C
761	A	C
762	A	B
763	C	C
764	B	C
765	A	C
766	A	C
767	A	C
768	B	C
769	A	C
770	C	C
771	A	C
772	A	C
773	B	D
774	A	C
775	A	B
776	A	B
777	A	B
778	A	B
779	A	C
780	B	B
781	B	A
782	B	B
783	D	D
784	B	C
785	B	C
786	C	B
787	A	B
788	C	B
789	B	B
790	A	C
791	B	B
792	B	B
793	C	C

794	B	C
795	B	B
796	B	C
513	B	B
797	B	C
798	C	B
799	A	B
800	C	B
801	B	C
802	C	B
803	A	B
804	B	B
805	B	C
806	A	C
807	B	B
808	B	C
809	A	C
810	B	B
811	A	B
812	B	C
813	C	B
814	C	B
815	C	B
816	B	C
817	C	C
818	B	C
819	B	B
820	B	C
821	B	B
822	B	C
823	B	C
824	A	B
825	B	B
826	B	B
827	B	C
828	A	B
829	C	B
830	B	B
831	C	B
832	C	A
833	C	A
834	B	A
835	C	A
836	C	A

837	C	A
838	C	A
839	C	A
840	C	A
841	C	B
842	C	B
843	C	B
844	C	B
845	C	A
846	C	B
847	C	B
848	C	B
849	C	A
850	C	C
851	B	C
852	A	B
853	C	C
854	C	C
855	A	C
856	A	B
857	A	C
858	A	B
859	A	B
860	B	C
861	A	C
862	A	C
863	A	C
864	D	C
865	C	A
866	B	A
867	B	A
870	A	C
871	C	B
872	B	A
873	A	C
874	C	B
875	B	A
876	C	B
877	C	A
878	C	B
879	C	A
880	C	A
882	C	B
883	C	B

884	C	B
885	C	B
886	C	B
887	C	B
888	C	B
889	C	A
890	C	A
891	C	A
892	C	B
893	C	B
894	C	A
895	C	B
896	B	C
897	C	C
898	C	A
899	C	B
900	C	A
901	C	C
902	C	C
903	C	B
904	C	B
905	B	B
906	C	B
907	C	A
908	C	A
909	C	A
910	C	A
911	C	A
912	C	A
913	C	B
914	B	B
915	C	A
916	C	A
917	C	A
918	A	C
919	C	A
920	C	A
921	C	A
922	C	B
923	C	A
924	C	A
925	A	C
926	A	C
927	A	C

928	C	C
929	C	A
930	B	C
931	A	B
932	A	C
933	A	C
934	C	A
935	C	A
936	C	A
937	C	A
938	A	B
939	A	C
1107	B	B
1108	B	C
1109	B	B
1110	A	B
1111	C	C

1112	A	B
1113	B	B
1114	B	B
1115	A	B
1116	B	C
1117	B	B
1118	A	B
1119	B	B
1120	B	B
1121	C	C
1122	B	C
1123	C	B
1124	B	A
1125	A	B
1126	B	B
1127	B	B

MSD-pSTAT-PBMC Assay

[001575] Materials:

[001576] Cryopreserved Peripheral Blood Mononuclear Cells (PBMC) are from AllCells. Recombinant Human IL-4 and IL-6 are from Peprotech. Mouse monoclonal anti-STAT3 antibody, rabbit monoclonal anti-pY705-STAT3 antibody, rabbit monoclonal Anti-pY641-STAT6 antibody, and lysis buffer are from Cell Signaling Technology (CST). Mouse monoclonal anti-STAT6 antibody is from BioLegend. Assay plates, blocker, and anti-rabbit secondary antibody are from Meso Scale Discovery (MSD).

[001577] Assay Method:

[001578] Cyropreserved PBMCs were thawed out and allowed to recover overnight in IMDM +10% heat-inactivated FBS prior to plating 50,000 (STAT3) or 25,000 (STAT6) cells per well in 96-well U-bottom tissue culture plates. Cells were treated with compound for 3hrs, then stimulated with 10ng/mL IL-6 (STAT3) or 1 ng/mL IL-4 (STAT6) for 10min. Cells were then spun down and washed with ice-cold PBS prior to lysing the cell pellet with 1x lysis buffer (CST) with 1x HALT protease and phosphatase inhibitor cocktail (Thermo). Lysates were transferred to and incubated overnight at 4 °C with shaking in QuickPlex 96-well high bind assay plates (MSD) pre-coated overnight with 30 µL per well of 0.6 µg/mL mouse monoclonal anti-STAT3 antibody (STAT3) or 2 µg/mL mouse monoclonal anti-STAT6 antibody (STAT6) in 1x PBS, and pre-blocked for 1 hour with 3% Blocker-A (MSD). Captured protein in the assay plates were then washed and probed with 25 µL per well of

0.25 µg/ml rabbit monoclonal anti-pY705-STAT3 antibody (STAT3) or 0.18 µg/ml rabbit monoclonal Anti-pY641-STAT6 antibody (STAT6) in 1% Blocker-A for 1 hour at room temperature with shaking, then washed and probed with 25ul per well of 1ug/ml Sulfo-TAG Labeled Goat Anti-Rabbit Antibody (MSD) in 1% Blocker-A for 1 hour at room temperature with shaking. Assay plates were then washed and 150 µL of 1x Read Buffer-T (MSD) was added to each well prior to reading on an SQ120 MSD Plate Reader. Assay signal from each sample was subtracted by the signal from unstimulated control wells and normalized to DMSO control wells. IC_{50} values were calculated using Graph Pad Prism Dose-Response Nonlinear Regression with variable slope. Results are shown in **Table 114**. For both pSTAT3 and pSTAT6 A = ≤100 nM; B = >100–1000 nM; C = >1000–3000 nM; D = >3 µM; and NT = Not Tested.

Table 1114

Cmp#	pSTAT3	pSTAT6	Cmp#	pSTAT3	pSTAT6
125	D	C	**164**	B	B
126	B	A	**165**	C	B
127	C	B	**166**	B	A
128	D	B	**167**	D	B
129	D	B	**168**	B	A
130	A	D	**169**	B	A
131	B	A	**170**	B	A
132	A	D	**171**	D	D
133	D	B	**172**	A	C
134	D	B	**173**	B	D
135	D	B	**174**	A	B
136	A	C	**175**	A	B
137	D	B	**176**	A	C
138	D	B	**177**	A	C
139	B	A	**178**	B	D
140	A	C	**179**	A	C
141	B	B	**180**	A	D
142	B	A	**181**	A	D
143	B	A	**182**	A	C
144	C	B	**183**	B	A
145	A	A	**184**	B	A
146	C	A	**185**	B	A
147	B	A	**186**	A	D
148	D	B	**187**	A	C
149	D	D	**188**	A	B
150	B	D	**189**	A	D
151	B	B	**190**	A	A

152	C	B
153	D	D
154	B	B
155	B	A
156	B	A
157	B	B
158	A	D
159	D	D
160	A	A
161	A	D
162	B	B
163	D	A

191	A	B
192	B	C
193	A	A
194	B	A
195	B	D
196	B	D
197	D	D
198	D	D
199	D	D
200	C	D
201	B	D
202	D	C

Table 115

Cmp #	**STAT3**	**STAT6**
248	D	NT
249	A	B
250	A	NT
251	A	NT
252	C	B
253	D	B
254	B	NT
255	A	D
256	A	NT
257	A	NT
258	A	NT
259	A	NT
260	C	NT
261	A	NT
262	A	D
263	A	D
264	B	NT
265	B	NT
266	A	NT
267	A	NT
268	B	NT
269	NT	A
270	NT	B
271	B	NT
272	A	NT
273	B	NT
274	A	NT
275	D	NT
276	B	NT

277	A	NT
278	B	NT
279	A	NT
280	A	D
281	A	NT
282	A	NT
283	A	NT
284	A	D
285	D	NT
286	A	NT
287	A	NT
288	B	NT
289	A	NT
290	B	NT
291	A	NT
292	A	D
293	A	NT
294	C	NT
295	C	NT
296	A	NT
297	B	NT
298	B	NT
299	NT	B
300	A	NT
301	A	NT
302	A	C
303	NT	B
304	A	D
305	NT	B
306	C	NT

307	D	NT
308	D	NT
309	D	NT
310	B	NT
311	D	NT
312	NT	D
313	C	NT
314	NT	D
315	D	A
316	NT	A
317	NT	A
318	NT	D
319	NT	C
320	A	B
321	NT	A
322	NT	A
323	D	NT
324	A	D
325	D	A
326	D	A
327	NT	D
328	NT	B
329	NT	D
330	NT	D
331	NT	C
332	NT	D
333	NT	D
334	NT	A
335	NT	A
336	NT	A
337	D	A
338	NT	A
339	NT	A
340	NT	A
341	NT	A
342	NT	A
343	D	A
344	NT	A
345	NT	A
346	NT	A
347	NT	A
348	NT	A
349	NT	A
350	NT	A

351	NT	A
352	NT	A
353	NT	A
354	D	A
355	NT	A
356	NT	B
357	NT	A
358	NT	A
359	NT	A
360	NT	A
361	NT	A
362	NT	A
363	NT	A
364	NT	A
365	NT	A
366	NT	B
367	NT	B
368	NT	D
369	NT	C
370	NT	A
371	NT	C
372	NT	D
373	NT	D
374	NT	A
375	NT	A
376	NT	A
377	NT	A
378	NT	A
379	NT	A
380	D	A
381	D	A
382	D	A
384	NT	A
385	NT	A
386	NT	A
387	NT	A
388	D	A
389	B	NT
390	B	NT
391	C	NT
392	B	NT
393	B	NT
394	A	NT
395	B	NT

396	D	C
397	D	D
398	D	NT
399	C	NT
400	B	NT
401	D	NT
402	D	C
403	D	B
404	D	C
405	D	C
406	D	C
407	D	C
408	D	B
409	D	C
410	D	D
411	NT	A
412	NT	B
413	NT	B
414	NT	B
415	A	C
416	NT	D
417	NT	A
418	NT	A
419	D	B
420	B	NT
421	D	B
422	A	NT
423	NT	B
424	NT	B
425	NT	D
426	D	NT
427	NT	A
428	A	NT
429	NT	A
430	B	NT
431	B	NT
432	B	NT
433	C	NT
434	B	NT
435	B	NT
436	NT	D
437	B	NT
438	C	NT
439	B	NT

440	NT	A
441	NT	A
442	NT	A
443	NT	B
444	NT	B
445	A	NT
446	A	NT
447	A	NT
448	NT	A
449	NT	B
450	NT	B
451	NT	B
452	NT	A
453	NT	B
454	NT	D
455	NT	D
456	NT	A
457	D	A
458	NT	A
459	NT	A
460	NT	A
461	NT	A
462	NT	A
463	A	NT
464	A	NT
465	NT	D
466	NT	D
467	NT	D
468	NT	A
469	NT	B
470	NT	A
471	NT	A
472	NT	A
473	NT	D
474	NT	A
475	NT	B
476	NT	A
477	NT	A
478	NT	A
479	NT	A
480	NT	A
481	NT	A
482	NT	A
483	NT	A

484	A	NT
485	D	A
486	NT	A
487	NT	C
488	NT	C
489	NT	B
490	NT	B
491	NT	A
492	NT	A
493	A	NT
494	A	NT
940	A	B
941	A	C
942	B	D
943	A	D
944	B	NT
945	B	NT
946	B	NT
947	A	NT
948	C	NT
949	C	NT
950	A	NT
951	A	NT
952	B	NT
953	A	NT
954	A	D
955	A	NT
956	A	NT
957	D	NT
958	C	NT
959	A	NT
960	B	NT
961	A	C
962	A	D
963	B	NT
964	B	NT
965	B	NT
966	A	NT
967	A	NT
968	A	NT
969	D	NT
970	A	NT
971	C	NT
972	A	NT

973	A	D
324	A	D
974	B	NT
975	A	NT
976	NT	D
977	NT	B
978	B	NT
979	D	NT
980	C	NT
981	NT	D
982	NT	D
983	A	NT
984	A	D
985	D	NT
986	C	NT
987	B	NT
988	A	NT
989	NT	D
990	D	NT
991	D	NT
992	NT	B
993	A	NT
994	B	NT
995	A	NT
996	B	NT
997	A	NT
998	A	NT
999	A	NT
1000	A	NT
1001	A	NT
1002	A	NT
1003	C	NT
1004	B	NT
1005	A	NT
1006	A	NT
1007	D	B
1008	B	D
1009	A	B
1010	C	B
1011	A	B
1012	NT	A
1013	NT	B
1014	A	B
1015	A	NT

1016	B	NT
1017	A	NT
1018	A	NT
1019	A	NT
1020	A	NT
1021	A	NT
1022	A	NT
1023	B	NT
1024	B	NT
1025	A	NT
1026	A	NT
1027	A	NT
1028	B	NT
1029	A	NT
1030	D	NT
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1032	A	NT
1033	A	NT
1034	A	NT
1035	A	NT
1036	A	NT
1037	A	NT
1038	A	NT
1039	A	NT
1040	A	NT
1041	A	NT
1042	B	NT
1043	A	NT
1044	A	NT
1045	A	D
1046	B	NT
1047	B	NT
1048	A	NT
1049	A	NT
1050	B	NT
1051	B	NT
1052	B	NT
1053	A	NT
1054	A	NT
1055	A	D
1056	A	NT
1057	A	NT
1058	A	NT
1059	A	NT

1060	B	NT
1061	B	NT
1062	B	NT
1063	A	NT
1064	A	NT
1065	A	NT
1066	B	NT
1067	B	NT
1068	A	NT
1069	A	NT
1070	A	NT
1071	A	NT
1072	A	NT
1073	B	NT
1074	A	NT
1075	A	NT
1076	A	NT
1077	A	NT
1078	A	NT
1079	A	NT
1080	NT	A
1081	NT	A
1082	D	B
1083	C	B
1084	B	NT
1085	B	A
1086	A	B
1087	B	A
1088	C	A
1089	A	B
1090	C	B
1091	D	D
1092	B	A
1093	D	B
1094	C	B
1095	A	NT
1096	A	NT
1097	C	B
1098	A	NT
1099	A	NT
1100	B	A
1101	D	A
1102	A	NT
1105	A	NT

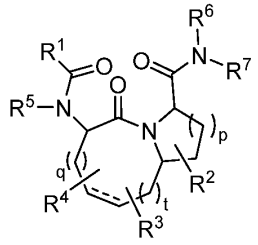
1106	A	B

[001579] While we have described a number of embodiments, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

[001580] The contents of all references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated herein in their entireties by reference. Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art.

Listing of Claims:

1. A compound having the structural Formula **I**:



(**I**);

or a pharmaceutically acceptable salt thereof, wherein:

q is 0 or 1 and t is 0, 1, or 2, provided that at least one of q or t is 1;

p is 1 or 2;

the dotted line represents a single or double bond;

R^1 is selected from an 8- to 10-membered fused bicyclic heteroaryl substituted with –$CR^{1a}R^{2a}P(O)OR^{1b}OR^{2b}$ or –$CR^{1a}R^{2a}P(O)[OR^{1b}][NH(AA)C(O)OR^T]$, an 8- to 10-membered fused bicyclic heterocyclyl substituted with –$CR^{1a}R^{2a}P(O)OR^{1b}OR^{2b}$ or –$CR^{1a}R^{2a}P(O)[OR^{1b}][NH(AA)C(O)OR^T]$, an aryl substituted with $CR^{1a}R^{2a}P(O)OR^{1b}OR^{2b}$ or –$CR^{1a}R^{2a}P(O)[OR^{1b}][NH(AA)C(O)OR^T]$, a -($C_1$-$C_4$)alkyl(aryl) wherein said aryl portion of -(C_1-C_4)alkyl(aryl) is substituted with –$CR^{1a}R^{2a}P(O)OR^{1b}OR^{2b}$ or –$CR^{1a}R^{2a}P(O)[OR^{1b}][NH(AA)C(O)OR^T]$, and a -($C_2$-$C_4$)alkenyl(aryl) wherein said aryl portion of -(C_2-C_4)alkenyl(aryl) is substituted with –$CR^{1a}R^{2a}P(O)OR^{1b}OR^{2b}$ or –$CR^{1a}R^{2a}P(O)[OR^{1b}][NH(AA)C(O)OR^T]$;

R^{1a} and R^{2a} are each absent or are independently selected from hydrogen, cyano, (C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl and fluoro; or R^{1a} and R^{2a} taken together with the carbon they are attached form oxo;

R^{1b} and R^{2b} are each absent or are independently selected from hydrogen, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, -[(C_1-C_4)alkyl]-OC(O)-[(C_1-C_4)alkyl], -[(C_1-C_4)alkyl]-C(O)O-[(C_1-C_4)alkyl], -[(C_1-C_4)alkyl]-O-[(C_1-C_{20})alkyl], -[(C_1-C_4)alkyl]-OC(O)-[halo(C_1-C_4)alkyl], [(C_1-C_4)alkyl]-OC(O)O-[5- to 7-membered heterocyclyl], [(C_1-C_4)alkyl]-OC(O)-[5- to 7-membered heterocyclyl], -[(C_1-C_4)alkyl]-OC(O)-[(C_1-C_4)alkyl]-OH, -[(C_1-C_4)alkyl]-OC(O)-[(C_1-C_4)alkyl]-O-[(C_1-C_4)alkyl], -[(C_1-C_4)alkyl]-OC(O)O-[(C_1-C_4)alkyl], -[(C_1-C_4)alkyl]-OC(O)O-[halo(C_1-C_4)alkyl], -[(C_1-C_4)alkyl]-OC(O)O-[(C_1-C_4)alkyl]-OH, -[(C_1-C_4)alkyl]-OC(O)O-[(C_1-C_4)alkyl]-O-[(C_1-C_4)alkyl], -[(C_1-C_4)alkyl]-SC(O)-[(C_1-C_4)alkyl], -[(C_1-C_4)alkyl]-SC(O)-[halo(C_1-C_4)alkyl], -[(C_1-C_4)alkyl]-SC(O)-[(C_1-C_4)alkyl]-OH, -[(C_1-

C_4)alkyl]-SC(O)-[(C_1-C_4)alkyl]-O-[(C_1-C_4)alkyl], -[(C_1-C_4)alkyl]-OC(O)NH(C_1-C_4)alkyl], -[(C_1-C_4)alkyl]-OC(O)N[(C_1-C_4)alkyl]$_2$, 5- to 6- membered heteroaryl, and aryl, wherein said 5- to 6- membered heteroaryl and aryl are each optionally and independently substituted with, as valency permits, 1 to 2 groups selected from halo, cyano, and (C_1-C_4)alkyl and wherein said 5- to 7-membered heterocyclyl of [(C_1-C_4)alkyl]-OC(O)O-[5- to 7-membered heterocyclyl] and [(C_1-C_4)alkyl]-OC(O)-[5- to 7-membered heterocyclyl] are each optionally and independently substituted with, as valency permits 1 to 2 groups selected from C(O)OR^h;

R^2 is selected from hydrogen, halo, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, hydroxy(C_1-C_4)alkyl, cyano, and hydroxyl;

R^3 and R^4 are each independently selected from hydrogen, halo, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, -(C_1-C_4)alkylphenyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, -(C_1-C_4)alkyl(C_1-C_4)alkoxy, hydroxyl, cyano, -NR^{a}R^b, phenyl, (C_3-C_6)cycloalkyl, 5- to 6-membered heteroaryl, and 4- to 6-membered heterocyclyl, wherein said phenyl, (C_3-C_6)cycloalkyl, 5- to 6-membered heteroaryl, and 4- to 6-membered heterocyclyl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^S;

or R^3 and R^4 are taken together on the same carbon atom to form a (C_3-C_6)cycloalkyl or a 4- to 6-membered heterocyclyl each optionally substituted with, as valency permits, 1 to 3 groups selected from halo, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, and halo(C_1-C_4)alkoxy;

R^5 and R^6 are each independently selected from hydrogen and (C_1-C_4)alkyl;

R^7 is selected from (C_1-C_4)alkyl, phenyl, 4- to 9-membered monocyclic or bicyclic heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl, wherein said (C_1-C_4)alkyl is optionally substituted with, as valency permits, 1 to 3 groups selected from R^Y and said phenyl, 4- to 9-membered monocyclic or bicyclic heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^Z; or

R^6 and R^7 together with the nitrogen atom to which they are attached form a 4- to 14-membered monocyclic or bicyclic heterocyclyl or a 5- to 12-membered monocyclic or bicyclic heteroaryl, each of which being optionally substituted with, as valency permits, 1 to 3 groups selected from R^Q;

AA is the residue of an alpha or beta natural or non-natural amino acid;

R^T is selected from (C_1-C_4)alkyl, benzyl, and phenyl, wherein said phenyl is optionally substituted with 1 or 2 groups selected from halo, (C_1-C_4)alkyl, and halo(C_1-C_4)alkyl;

R^Q is selected from halo, $(C_2$-$C_4)$alkenyl, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, cyano, phenyl, hydroxyl, 4- to 6-membered heterocyclyl, 5- to 10-membered monocyclic or bicyclic heteroaryl, $(C_3$-$C_6)$cycloalkyl, oxo, imino, -O(phenyl), $-C(O)R^g$, $-C(O)OR^e$, $-NHC(O)R^e$, $-C(O)NR^cR^d$, $-NR^aR^b$, $-S(O)R^eR^f$, $-S(O)_2R^f$, $-S(O)$=NH$(C_1$-$C_4)$alkyl, $-S(O)NR^eR^f$, and $-S(O)_2NR^eR^f$, wherein said $(C_2$-$C_4)$alkenyl and $(C_1$-$C_4)$alkyl are each optionally and independently substituted with, as valency permits, 1 to 3 groups selected from R^M, and wherein said phenyl, 5- to 10- membered monocyclic or bicyclic heteroaryl, $(C_3$-$C_6)$cycloalkyl, and 4- to 6-membered heterocyclyl are each optionally and independently substituted with, as valency permits, 1 to 3 groups selected from R^F;

R^Y is selected from halo, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, cyano, $-C(O)R^g$, $-C(O)OR^e$, $-NHC(O)R^e$, $-NR^aR^b$, $-S(O)R^eR^f$, $-S(O)_2R^f$, $-S(O)NR^eR^f$, $-S(O)$=NH$(C_1$-$C_4)$alkyl, $-S(O)_2NR^eR^f$, hydroxyl, phenyl, 4- to 6-membered heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl, wherein said phenyl, 4- to 6-membered heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^X;

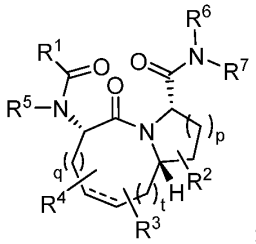
R^J and R^M are each independently selected from halo, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, cyano, $-C(O)R^g$, $-C(O)OR^e$, $-NHC(O)R^e$, $-C(O)NR^cR^d$, $-NR^aR^b$, $-S(O)R^eR^f$, $-S(O)_2R^f$, $-S(O)NR^eR^f$, $-S(O)$=NH$(C_1$-$C_4)$alkyl, $-S(O)_2NR^eR^f$, hydroxyl, phenyl, 4- to 6-membered heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl, wherein said phenyl, 4- to 6-membered heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^X;

R^F, R^S, R^X, and R^Z are each independently selected from halo, cyano, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, -$(C_1$-$C_4)$alkyl$(C_1$-$C_4)$alkoxy, hydroxy$(C_1$-$C_4)$alkyl, -$(C_1$-$C_4)$alkylphenyl, $(C_2$-$C_4)$alkenyl, halo$(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, halo$(C_2$-$C_4)$alkynyl, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, hydroxyl, oxo, imino, phenyl, $-S(O)R^eR^f$, $-S(O)_2R^f$, $-S(O)$=NH$(C_1$-$C_4)$alkyl, $-S(O)NR^eR^f$, and $-S(O)_2NR^eR^f$, $-C(O)OR^e$, $-NR^cC(O)R^e$, $-C(O)R^g$, $-C(O)NR^cR^d$, and $-NR^aR^b$, wherein said phenyl and said phenyl for the group -$(C_1$-$C_4)$alkylphenyl are each optionally and independently substituted with, as valency permits 1 to 3 groups selected from halo, cyano, $(C_1$-$C_{10})$alkyl, $(C_2$-$C_{10})$alkenyl, $(C_2$-$C_{10})$alkynyl, halo$(C_1$-$C_{10})$alkyl, $(C_1$-$C_{10})$alkoxy, and halo$(C_1$-$C_{10})$alkoxy, wherein said $(C_1$-$C_{10})$alkyl, $(C_2$-$C_{10})$alkenyl and $(C_2$-$C_{10})$alkynyl are each optionally substituted with, as valency permits a 5-to 10-membered monocyclic or bicyclic heteroaryl or a 4-to 10-membered monocyclic or bicyclic heterocyclyl each of said 5-to 10-membered monocyclic and bicyclic heteroaryl or a 4-to 10-membered

monocyclic or bicyclic heterocyclyl being optionally substituted with oxo or a 5- to 7-membered heterocyclyl that is optionally substituted with 1 to 2 oxo; and

R^a, R^b, R^c, R^d, R^e, R^f, R^g, and R^h are each independently selected from, as valency permits, hydrogen, (C_1-C_4)alkyl, phenyl, (C_3-C_6)cycloalkyl, 4- to 6-membered heterocyclyl and 5- to 6-membered heteroaryl, wherein said (C_1-C_4)alkyl is optionally substituted with, as valency permits, 1 to 3 groups selected from R^J, and said phenyl, (C_3-C_6)cycloalkyl, 4- to 6-membered heterocyclyl, and 5- to 6-membered heteroaryl are each independentlsy optionally substituted with, as valency permits, 1 to 3 groups selected from halo, cyano, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, hydroxyl, phenyl, and benzyl.

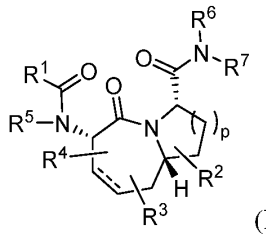
2. The compound of Claim 1, wherein the compound is of the structural Formula **II**:



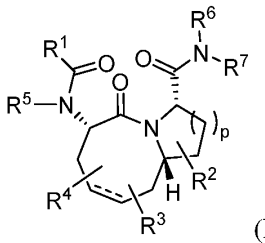
;

or a pharmaceutically acceptable salt thereof.

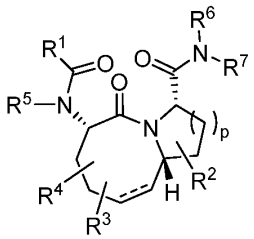
3. The compound of Claim 1 or 2, wherein the compound is of the structural **III**, **IV**, **V**, or **VII**:



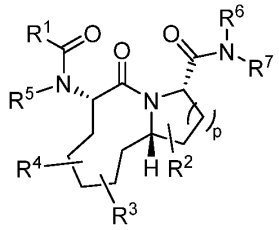
(**III**),



(**IV**),

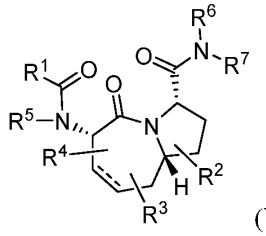
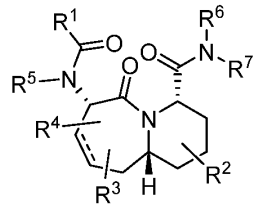
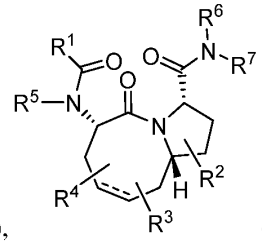
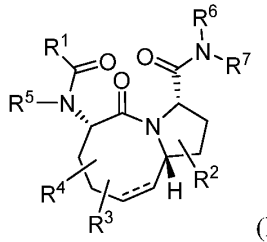
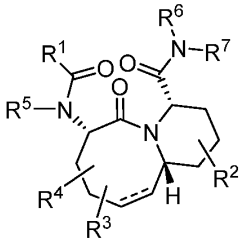
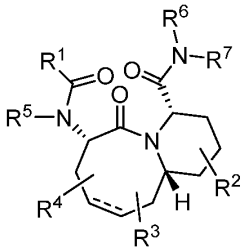
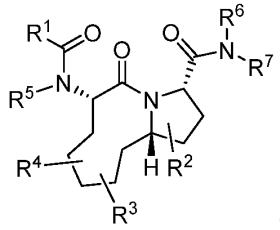


(**V**), or

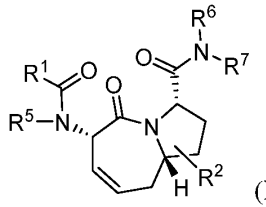
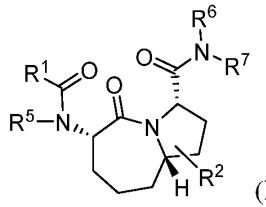
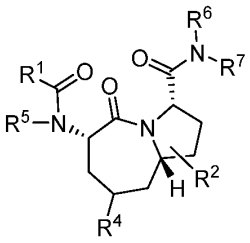
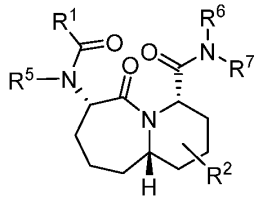
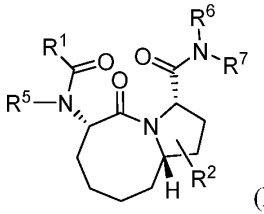
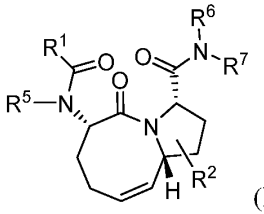


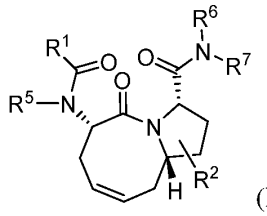
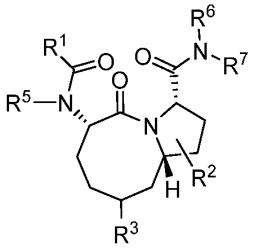
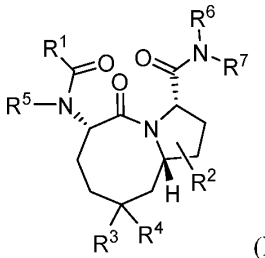
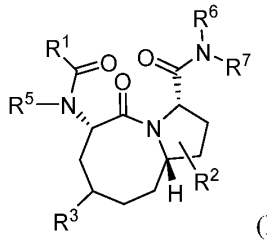
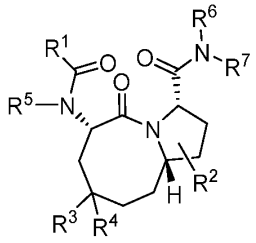
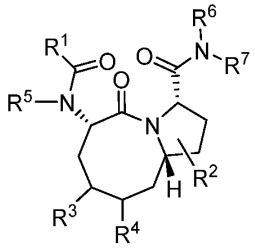
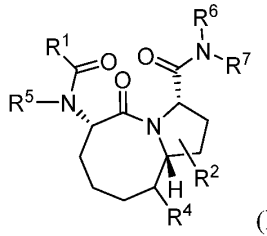
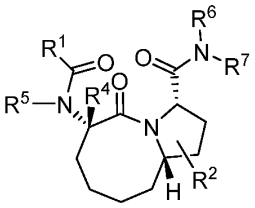
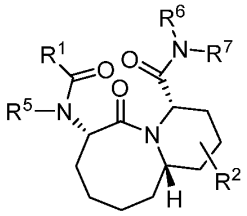
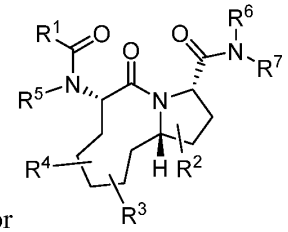
(**VII**); or a pharmaceutically acceptable salt thereof.

4. The compound of any one of Claims 1 to 3, wherein the compound is of the structural **VIII**, **VIII'**, **IX**, **X**, **XI, XII**, or **XIII**:

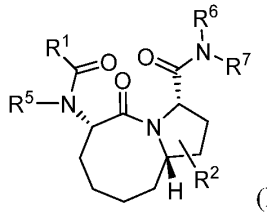
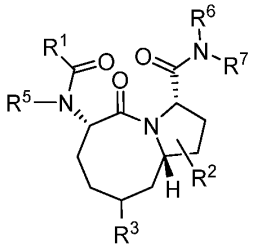
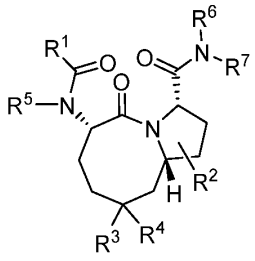
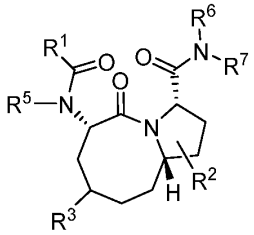
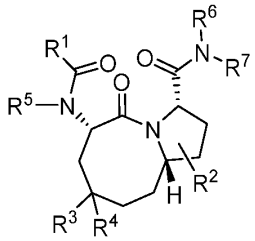
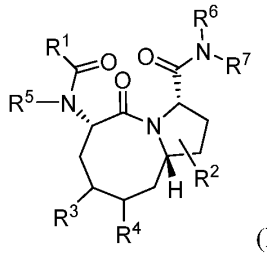
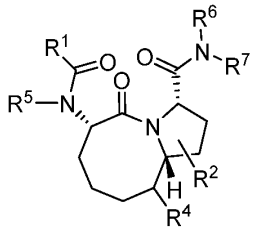
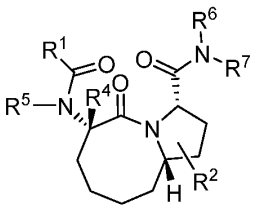

(**VIII**),

(**VIII'**),

(**IX**),

(**X**),

(**XI**),

(**XII**), or

(**XIII**); or a pharmaceutically acceptable salt thereof.

5. The compound of any one of Claims 1 to 4, wherein the compound is of the structural **XIV**, **XV**, **XVI**, **XVI'**, **XVII, XVIII**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, or **XXVIII**:


(**XIV**),

(**XV**),

(**XVI**),

(**XVI'**),

(**XVII**),

(**XVIII**),


(**XX**),

(**XXI**),

(**XXII**),

(**XXIII**),

(**XXIV**),

(**XXV**),

(**XXVI**),

(**XXVII**),


(**XXVIII**), or (**XXIX**); or a pharmaceutically acceptable salt thereof.

6. The compound of any one of Claims 1 to 5, wherein the compound is of the structural Formula **XXX**, **XXXI**, **XXXII, XXXIII XXXIV**, **XXXV**, **XXXVI**, or **XXVII**:


(**XXX**),

(**XXXI**),

(**XXXII**),

(**XXXIII**),

(**XXXIV**),

(**XXXV**),

(**XXXVI**), or

(**XXXVII**); or a pharmaceutically acceptable salt thereof.

7. The compound of any one of Claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from hydrogen, (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylphenyl, and 4- to 6-membered heterocyclyl; or R^3 and R^4 are taken together on the same carbon atom to form a (C_3-C_6)cycloalkyl.

8. The compound of any one of Claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from hydrogen (C_1-C_4)alkyl, and hydroxyl; or R^3 and R^4 are taken together on the same carbon atom to form a (C_3-C_6)cycloalkyl.

9. The compound of any one of Claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from hydrogen, (C_1-C_2)alkyl, hydroxyl, (C_1-C_2)alkoxy, benzyl, and azetidinyl; or R^3 and R^4 are taken together on the same carbon atom to form a cyclopropyl.

10. The compound of any one of Claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are hydrogen.

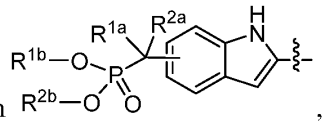
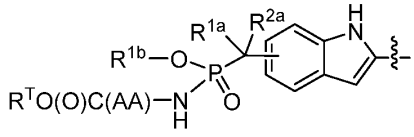
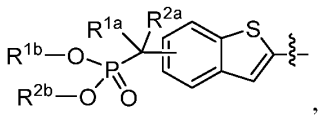
11. The compound of any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from hydrogen and hydroxyl.

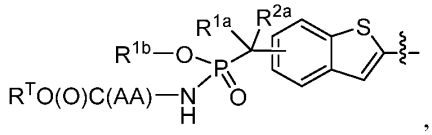
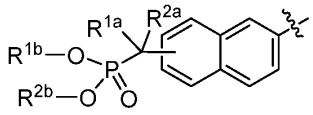
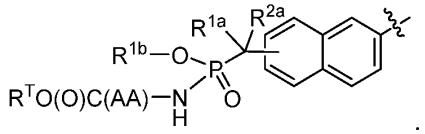
12. The compound of any one of Claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen.

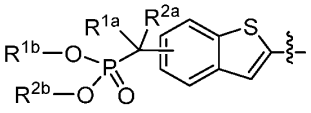
13. The compound of any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen.

14. The compound of any one of Claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from 8- to 10-membered fused bicyclic heteroaryl and aryl, each of which are substituted with $–CR^{1a}R^{2a}P(O)OR^{1b}OR^{2b}$ or $–CR^{1a}R^{2a}P(O)[OR^{1b}][NH(AA)C(O)OR^{T}]$.

15. The compound of any one of Claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein, R^1 is selected from benzothiophenyl, indolyl, and naphthalenyl, each of which are substituted with $–CR^{1a}R^{2a}P(O)OR^{1b}OR^{2b}$ or $–CR^{1a}R^{2a}P(O)[OR^{1b}][NH(AA)C(O)OR^{T}]$.

16. The compound of any one of Claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein, R^1 is selected from  ,  ,  ,



, and

.

17. The compound of any one of Claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein, R^1 is  .

18. The compound of any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is hydrogen and R^{2a} is fluoro or R^{1a} is fluoro and R^{2a} is fluoro.

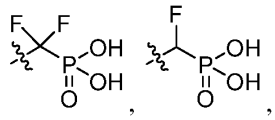
19. The compound of any one of Claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein R^{1a} and R^{2a} are fluoro.

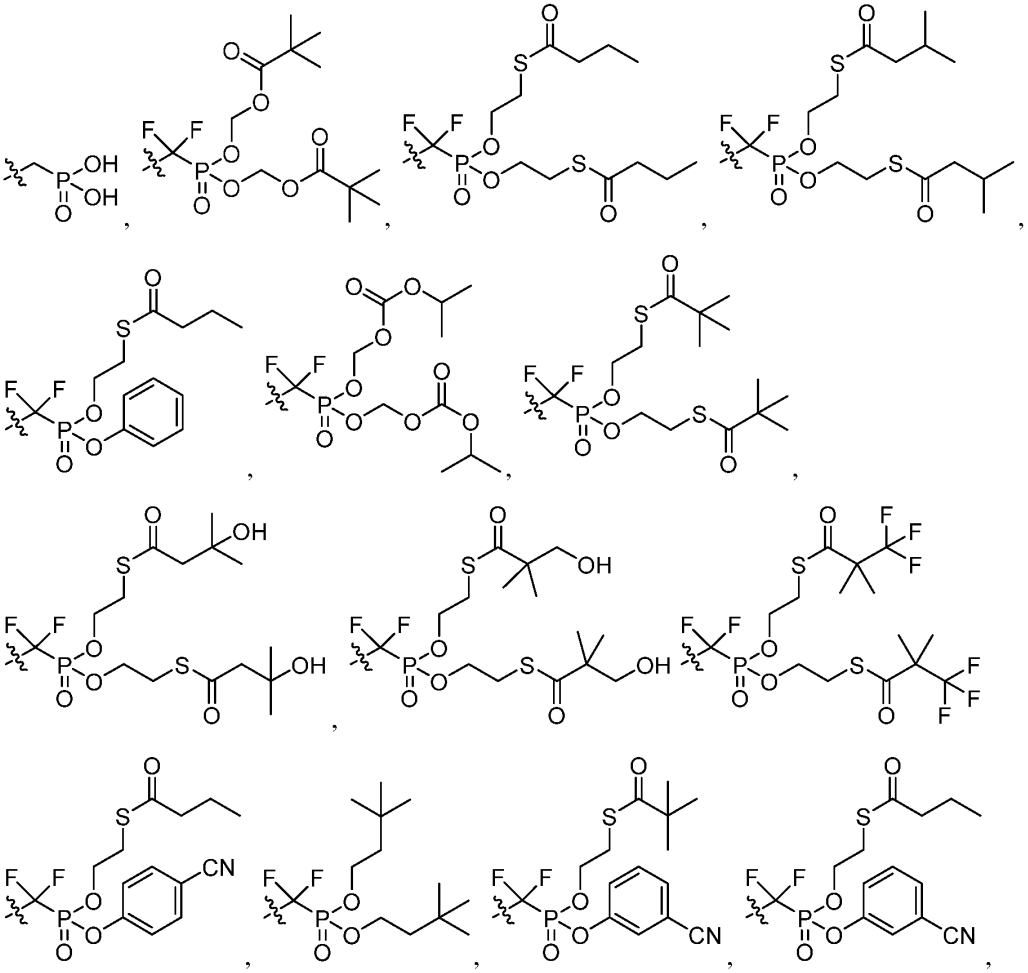
20. The compound of any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein R^{1b} and R^{2b} are each independently selected from hydrogen, (C_1-C_4)alkyl, -[(C_1-C_4)alkyl]-OC(O)-[(C_1-C_4)alkyl], -[(C_1-C_4)alkyl]-OC(O)O-[(C_1-C_4)alkyl], -[(C_1-C_4)alkyl]-SC(O)-[(C_1-C_4)alkyl], -[(C_1-C_4)alkyl]-SC(O)-[halo(C_1-C_4)alkyl], -[(C_1-C_4)alkyl]-SC(O)-[(C_1-C_4)alkyl]-OH, phenyl, pyridinyl, and naphthalenyl, wherein said phenyl, pyridinyl, and naphthalenyl are each optionally and independently substituted with cyano.

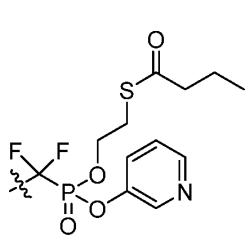
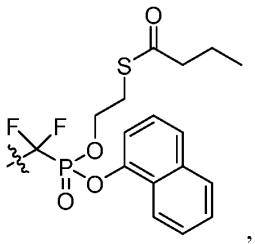
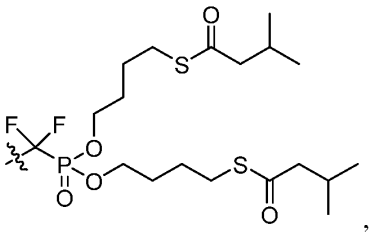
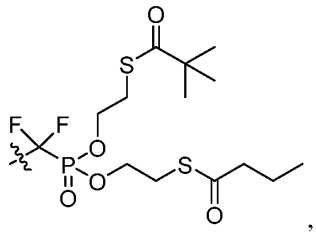
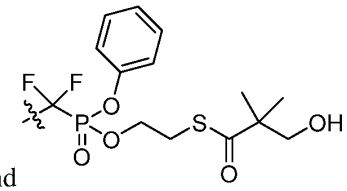
21. The compound of any one of Claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein R^{1b} and R^{2b} are each -[(C_1-C_4)alkyl]-OC(O)-[(C_1-C_4)alkyl].

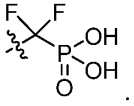
22. The compound of any one of Claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein R^{1b} and R^{2b} are hydrogen.

23. The compound of any one of Claims 1 to 17 and 20, or a pharmaceutically acceptable salt thereof, wherein $-CR^{1a}R^{2a}P(O)OR^{1b}OR^{2b}$ is selected from






,

,

,

, and

.

24. The compound of any one of Claims 1 to 17 and 20, or a pharmaceutically acceptable salt thereof, wherein $-CR^{1a}R^{2a}P(O)OR^{1b}OR^{2b}$ is  .

25. The compound of any one of Claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein -NH[AA]C(O)OR^T is $-NHC(R')(R)C(O)R^T$ or $-NHC(R')(R)CH_2C(O)R^T$, wherein R' is hydrogen, $(C_1\text{-}C_3)$alkyl, or $(C_1\text{-}C_3)$alkyl$(C_1\text{-}C_3)$alkoxy and R is selected from hydrogen, methyl, isopropyl, $-CH_2CH(CH_3)_2$, $-(CH_2)_2SCH_3$, $-CH(CH_3)(CH_2CH_3)$, CH_2OH, $-CH(OH)(CH_3)$, CH_2SH, $-CH_2C(O)NH_2$, $-(CH_2)_2C(O)NH_2$, benzyl, p-hydroxybenzyl, $-CH_2$(indolyl), $-(CH_2)_4NH_2$, $-(CH_2)_3NHC(=NH_2)NH_2$, $-CH_2$(imidazolyl), $-(CH_2)COOH$, and $-(CH_2)_2COOH$; or R taken together with the nitrogen atom of $-NHC(R')(R)C(O)R^T$ or $-NHC(R')(R)CH_2C(O)R^T$ forms a pyrrolidinyl ring.

26. The compound of any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from $(C_1\text{-}C_4)$alkyl, phenyl, 5- or 6-membered monocyclic heterocyclyl, 9- or 10-membered fused bicyclic heterocyclyl, 5- or 6-membered monocyclic heteroaryl, and 9- or 10-membered fused bicyclic heteroaryl, wherein said $(C_1\text{-}C_4)$alkyl is optionally substituted with, as valency permits, 1 to 3 groups selected from R^Y and said phenyl, 5- or 6-membered monocyclic heterocyclyl, 9- or 10-membered fused bicyclic heterocyclyl, 5- or 6-membered monocyclic heteroaryl, and 9- or 10-membered fused

bicyclic heteroaryl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^Z.

27. The compound of any one of Claims 1 to 26, or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from (C_1-C_4)alkyl, phenyl, pyrrolidinyl, thiochromanyl, dihydrobenzo[b]thiophenyl, pyridinyl, indazolyl, cinnolinyl, and quinolinyl, wherein said (C_1-C_4)alkyl is optionally substituted with, as valency permits, 1 to 3 groups selected from R^Y and said phenyl, pyrrolidinyl, thiochromanyl, dihydrobenzo[b]thiophenyl, pyridinyl, indazolyl, cinnolinyl, and quinolinyl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^Z.

28. The compound of any one of Claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein R^Y is selected from halo, hydroxyl, phenyl, 4- to 6-membered heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl, wherein said phenyl, 4- to 6-membered heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^X.

29. The compound of any one of Claims 1 to 28, or a pharmaceutically acceptable salt thereof, wherein R^Y is selected from halo, hydroxyl, 4- to 6-membered heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl, wherein said 4- to 6-membered heterocyclyl, and 5- to 10-membered monocyclic or bicyclic heteroaryl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^X.

30. The compound of any one of Claims 1 to 29, or a pharmaceutically acceptable salt thereof, wherein R^Y is selected from hydroxyl, phenyl, imidazolyl, 1,2-dihydropyridinyl, pyridinyl, and pyrazolo[3,4-b]pyridinyl, wherein said phenyl, imidazolyl, 1,2-dihydropyridinyl, pyridinyl, and pyrazolo[3,4-b]pyridinyl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^X.

31. The compound of any one of Claims 1 to 30, or a pharmaceutically acceptable salt thereof, wherein R^Y is selected from hydroxyl, imidazolyl, 1,2-dihydropyridinyl, pyridinyl, and pyrazolo[3,4-b]pyridinyl, wherein said phenyl, imidazolyl, 1,2-dihydropyridinyl, pyridinyl, and pyrazolo[3,4-b]pyridinyl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^X.

32. The compound of any one of Claims 1 to 31, or a pharmaceutically acceptable salt thereof, wherein R^Z is selected from phenyl, -C(O)(C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkyl, halo, cyano, and (C_1-C_4)alkoxy.

33. The compound of any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 together with the nitrogen atom to which they are attached form 4- to 6-membered monocyclic heterocyclyl, 7- to 13-membered spiro bicyclic heterocyclyl, or 9- to 10-membered fused bicyclic heterocyclyl, each of which being optionally substituted with, as valency permits, 1 to 3 groups selected from R^Q.

34. The compound of any one of Claims 1 to 25 and 33, or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 together with the nitrogen atom to which they are attached form pyrrolidinyl, azetidinyl, piperazinyl, 5-oxa-2,6-diazaspiro[3.4]oct-6-enyl, 6-thia-2,7-diazaspiro[3.4]octanyl, 2-thia-6-azaspiro[3.3]heptanyl, 4-azaspiro[2.4]heptanyl, spiro[indoline-3,3'-pyrrolidinyl], or 1,2,3,4,5,6-hexahydro-2,6-naphthyridinyl, each of which being optionally substituted with, as valency permits, 1 to 3 groups selected from R^Q.

35. The compound of any one of Claims 1 to 25, 33, and 34, or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 together with the nitrogen atom to which they are attached form pyrrolidinyl or azetidinyl, each of which being optionally substituted with, as valency permits, 1 to 3 groups selected from R^Q.

36. The compound of any one of Claims 1 to 35, or a pharmaceutically acceptable salt thereof, wherein R^Q is selected from halo, (C_2-C_4)alkenyl, (C_1-C_4)alkyl, cyano, phenyl, hydroxyl, 4- to 6-membered heterocyclyl, 5- to 10-membered monocyclic or bicyclic heteroaryl, (C_3-C_6)cycloalkyl, oxo, imino, -O(phenyl), -C(O)R^g, -NHC(O)R^e, -S(O)=NH(C_1-C_4)alkyl, and -$S(O)_2NR^eR^f$, wherein said (C_2-C_4)alkenyl and (C_1-C_4)alkyl are each optionally and independently substituted with, as valency permits, 1 to 3 groups selected from R^M, and wherein said phenyl, 4- to 6-membered heterocyclyl, 5- to 10-membered monocyclic or bicyclic heteroaryl, and (C_3-C_6)cycloalkyl are each optionally and independently substituted with, as valency permits, 1 to 3 groups selected from R^F.

37. The compound of any one of Claims 1 to 36, or a pharmaceutically acceptable salt thereof, wherein R^Q is selected from halo, $(C_2$-$C_4)$alkenyl, $(C_1$-$C_4)$alkyl, cyano, phenyl, hydroxyl, morpholinyl, dihydropyridinyl, tetrahydro-2H-thiopyranyl, pyridinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, triazolyl, indazolyl, benzoimidazolyl, pyrazolo[3,4-b]pyridinyl, cyclohexyl, cyclopropyl, oxo, imino, -O(phenyl), $-C(O)R^g$, $-NHC(O)R^e$, $-S(O)=NH(C_1$-$C_4)$alkyl, and $-S(O)_2NR^eR^f$, wherein said $(C_2$-$C_4)$alkenyl and $(C_1$-$C_4)$alkyl are each optionally and independently substituted with, as valency permits, 1 to 3 groups selected from R^M, and wherein said phenyl, morpholinyl, dihydropyridinyl, tetrahydro-2H-thiopyranyl, pyridinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, triazolyl, indazolyl, benzoimidazolyl, pyrazolo[3,4-b]pyridinyl, cyclohexyl, and cyclopropyl are each optionally and independently substituted with, as valency permits, 1 to 3 groups selected from R^F.

38. The compound of any one of Claims 1 to 37, or a pharmaceutically acceptable salt thereof, wherein R^M is selected from 4- to 6-membered heterocyclyl, 5- to 6-membered monocyclic heteroaryl, $-S(O)=NH(C_1$-$C_4)$alkyl, cyano, and phenyl, wherein said 4- to 6-membered heterocyclyl, 5- to 6-membered monocyclic heteroaryl, and phenyl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^X.

39. The compound of any one of Claims 1 to 38, or a pharmaceutically acceptable salt thereof, wherein R^M is selected from tetrahydropyranyl, pyrazolyl, $-S(O)=NH(C_1$-$C_4)$alkyl, cyano, and phenyl, wherein said tetrahydropyranyl, pyrazolyl, and phenyl are each optionally substituted with, as valency permits, 1 to 3 groups selected from R^X.

40. The compound of any one of Claims 1 to 39, or a pharmaceutically acceptable salt thereof, wherein R^X is selected from $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, and oxo.

41. The compound of any one of Claims 1 to 40, or a pharmaceutically acceptable salt thereof, wherein R^F is selected from halo, $(C_1$-$C_4)$alkyl, hydroxy$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_2$-$C_4)$alkynyl, cyano, oxo, and imino.

42. The compound of any one of Claims 1 to 41, or a pharmaceutically acceptable salt thereof, wherein R^g is selected from $(C_1$-$C_4)$alkyl, morpholinyl, imidazolyl, benzyl, and cyclopropyl.

43. The compound of any one of Claims 1 to 42, or a pharmaceutically acceptable salt thereof, wherein R^e and R^f are each independently selected from $(C_1$-$C_4)$alkyl and halo$(C_1$-$C_4)$alkyl.

44. The compound of any one of Claims 1 to 43, or a pharmaceutically acceptable salt thereof, wherein R^c and R^d are each independently selected from hydrogen and $(C_1$-$C_4)$alkyl.

45. The compound of Claim 1, wherein the compound is selected from any one of Compounds 1 to 1127, or a pharmaceutically acceptable salt thereof.

46. A pharmaceutically acceptable composition comprising the compound of any one of Claims 1 to 45, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

47. A method of treating a condition responsive to the modulation of STAT3 or STAT6 in a subject comprising administering to the subject a therapeutically effective amount of the compound of any one of Claims 1 to 45 or a pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable composition of Claim 46.