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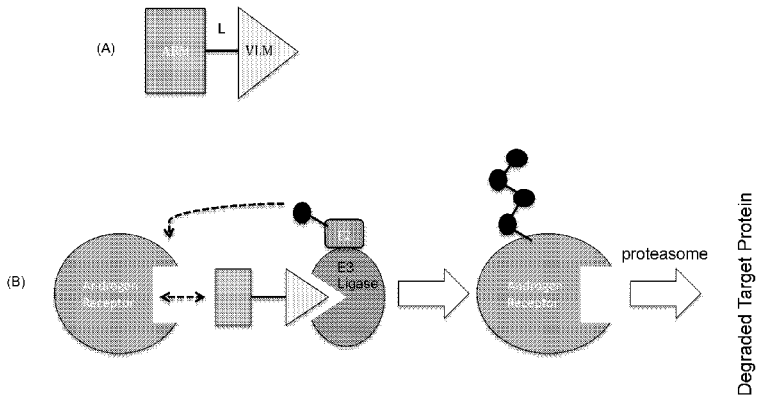
(54) Title: COMPOUNDS AND METHODS FOR THE TARGETED DEGRADATION OF THE ANDROGEN RECEPTOR

FIGURE 1



(57) Abstract: The present invention relates to bifunctional compounds, which find utility to degrade and (inhibit) Androgen Receptor. In particular, the present invention is directed to compounds, which contain on one end a VHL ligand which binds to the ubiquitin ligase and on the other end a moiety which binds Androgen Receptor such that Androgen Receptor is placed in proximity to the ubiquitin ligase to effect degradation (and inhibition) of Androgen Receptor. The present invention exhibits a broad range of pharmacological activities associated with compounds according to the present invention, consistent with the degradation/inhibition of Androgen Receptor.

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COMPOUNDS AND METHODS FOR THE TARGETED DEGRADATION OF ANDROGEN RECEPTOR

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims the benefit of U.S. Provisional Patent Application Serial No. 62/105,210, filed 20 January 2015 and entitled: Compounds and Methods for the Targeted Degradation of the Androgen Receptor, which is incorporated herein by reference in its entirety.

BACKGROUND

[002] 1. Field of the Discovery. The present description relates to bifunctional compounds, which are useful for the modifying the ubiquitination and subsequent degradation of target polypeptides and proteins, in particular, androgen receptor. In certain aspects, the compounds comprise a Von Hippel-Lindau (VHL) binding moiety, which binds to the VHL E3 ubiquitin ligase, a target protein binding moiety, which binds to the target protein (e.g., androgen receptor), and optionally a linker moiety which links the VHL binding moiety and target protein binding moiety.These compounds work in such way that the target protein/polypeptide is placed in proximity to the ubiquitin ligase to effect degradation (and inhibition) of that protein (e.g., androgen receptor).

[003] 2. Background Information. Androgen Receptor (AR) belongs to a nuclear hormone receptor family that is activated by androgens, such as testosterone and dihydrotestosterone (*Pharmacol. Rev.* 2006, 58(4), 782-97; *Vitam. Horm.* 1999, 55:309-52.). In the absence of androgens, AR is bound by Heat Shock Protein 90 (Hsp90) in the cytosol. When an androgen binds AR, its conformation changes to release AR from Hsp90 and to expose the Nuclear Localization Signal (NLS). The latter enables AR to translocate into the nucleus where AR acts as a transcription factor to promote gene expression responsible for male sexual characteristics (*Endocr. Rev.* 1987, 8(1):1-28; *Mol. Endocrinol.* 2002, 16(10), 2181-7). AR deficiency leads to Androgen Insensitivity Syndrome, formerly termed testicular feminization.

[004] While AR is responsible for development of male sexual characteristics, it is also a well-documented oncogene in certain forms cancers including prostate cancers (*Endocr. Rev.* 2004, 25(2), 276-308). A commonly measured target gene of AR activity is the secreted Prostate Specific Antigen (PSA) protein. The current treatment regimen for prostate cancer involves

inhibiting the androgen-AR axis by two methods. The first approach relies on reduction of androgens, while the second strategy aims to inhibit AR function (Nat. Rev. Drug Discovery, 2013, 12,823–824). Despite the development of effective targeted therapies, most patients develop resistance and the disease progresses. An alternative approach for the treatment of prostate cancer involves eliminating the AR protein. Because AR is a critical driver of tumorigenesis in many forms of prostate cancers, its elimination should lead to therapeutically benefical response.

[005] There exists an ongoing need in the art for effective treatments for diseases and conditions that are related to aberrant AR regulation or activity, such as, for example, cancer, prostate cancer, and Kennedy's Disease.

SUMMARY

[006] The present disclosure describes compounds, including compositions comprising the same, which function to recruit endogenous proteins to an E3 ubiquitin ligase, e.g., Von Hippel-Lindau (VHL) E3 ubiquitin ligase, for ubiquitination and subsequent degradation, and methods of using the same. In particular, the present disclosure provides bifunctional or proteolysis targeting chimeric (PROTAC) compounds, which find utility as modulators of targeted ubiquitination and degradation of androgen receptor (AR). In addition, the description provides methods of using an effective amount of the compounds as described herein for the treatment or amelioration of a disease condition including cancer, e.g., prostate cancer, and Kennedy's Disease.

[007] Thus, in one aspect, the disclosure provides compounds which function to recruit endogenous proteins, e.g., AR proteins, to E3 Ubiquitin Ligase for ubiquintination and degradation. In certain embodiments, the compounds have the following general structure:

[008] **ABM – L-ULM (I),**

[009] wherein ABM is an AR binding moiety, ULM is an E3 ligase binding moiety, e.g., a VHL E3 ligase binding moiety (VLM), and L is a bond or a linker moiety which links the ABM and ULM. As such, in certain embodiments, the description provides compounds having the following general structure:

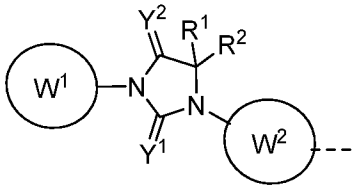
[010] **ABM – L-VLM (II),**

[011] wherein ABM is an AR binding moiety, VLM is a VHL E3 ligase binding moiety and L is a bond or a linker moiety which links the ABM and VLM. In certain embodiments, the VLM comprises a hydroxyl prolyl moiety.

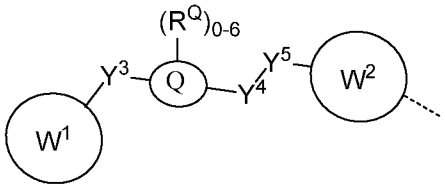
[012] In certain embodiments, the ULM is a moiety specific for an E3 ubiquitin ligase such as, e.g., cereblon, mouse double minute 2 homolog (Mdm2), or inhibitor of apoptosis (IAP), wherein the ULM moiety is coupled to an ABM as described herein.

[013] It will be understood that the general structures are exemplary and the respective moieties can be arranged spatially in any desired order or configuration, e.g., ULM-L-ABM, and VLM-L-ABM respectively.

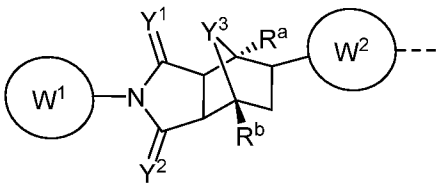
[014] In another aspect, the description provides AR binding moieties (ABM). In an additional embodiment, the description provides compounds having the following general structure: ABM-L, wherein ABM is an AR binding moiety as described herein, and L is a chemical linker moiety, or optionally a bond. In certain embodiments, the ABM and/or L are coupled to a ULM as described herein. In certain embodiments, the ABM is selected from following structures:



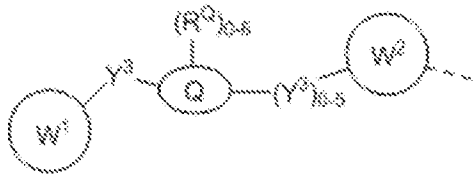
ABM-a ,



ABM-b ,



ABM-c , and



ABM-d .

wherein W^1 is aryl or heteroaryl, independently substituted by 1 or more halo, hydroxyl, nitro, CN, C≡CH, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), C_{1-6} alkoxyl (linear, branched, optionally substituted by 1 or more halo), C_{2-6} alkenyl, C_{2-6} alkynyl;

Y^1, Y^2 are each independently NR^{Y1}, O, S;

Y^3, Y^4, Y^5 are each independently a bond, O, NR^{Y2}, $CR^{Y1}R^{Y2}$, C=O, C=S, SO, SO_2;

Q is a 3-6 membered alicyclic or aromatic ring with 0-4 heteroatoms, optionally substituted with 0-6 R^Q, each R^Q,is independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or 2 R^Q groups taken together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

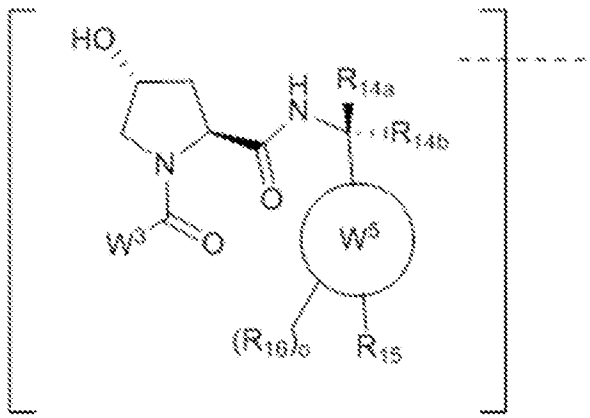
R^1, R^2, R^a, R^b, R^{Y1}, R^{Y2} are each independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or R^1, R^2 together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

W^2 is a bond, C_{1-6} alkyl, C_{1-6} alicyclic, heterocyclic, aryl, or heteroaryl, each optionally substituted by 1, 2 or 3 R^{W2}; and

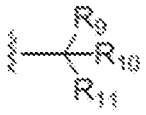
each R^{W2} is independently H, halo, C_{1-6} alkyl (optionally substituted by 1 or more F), OC_{1-3}alkyl (optionally substituted by 1 or more –F), OH, NH_2, $NR^{Y1}R^{Y2}$, CN.

[015] In any of the aspects or embodiments described herein, the ABM can comprise or consist of a structure as set forth herein, in particular in any of the ABMs as provided in Examples 1-593.

[016] In certain embodiments, the ULM (derivatized or configured to be linked or coupled to an ABM via a linker (as indicated by the dashed line)) has the structure,



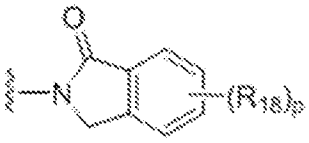
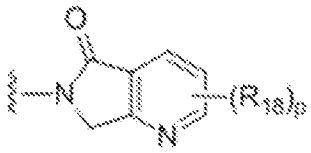
wherein, W^3 is optionally substituted aryl, optionally substituted heteroaryl, or



;

each R_9 and R_{10} is independently hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted hydroxyalkyl, optionally substituted heteroaryl,

or haloalkyl; or R_9, R_{10}, and the carbon atom to which they are attached form an optionally substituted cycloalkyl;

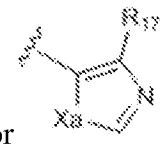
R_{11} is optionally substituted heterocyclic, optionally substituted alkoxy, optionally substituted heteroaryl, optionally substituted aryl,  ,  or  ;

R_{12} is H or optionally substituted alkyl;

R_{13} is H, optionally substituted alkyl, optionally substituted alkylcarbonyl, optionally substituted (cycloalkyl)alkylcarbonyl, optionally substituted aralkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted (heterocyclyl)carbonyl, or optionally substituted aralkyl;

R_{14a}, R_{14b}, is each independently H, haloalkyl, or optionally substituted alkyl;

W^5 is a phenyl or a 5-10 membered heteroaryl,

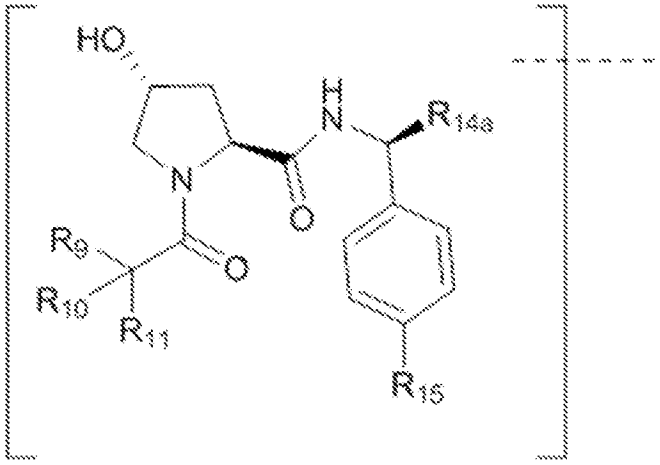
R_{15} is H, halogen, CN, OH, NO_2, N $R_{14a}R_{14b}$, OR_{14a}, $CONR_{14a}R_{14b}$, $NR_{14a}COR_{14b}$, $SO_2NR_{14a}R_{14b}$, NR_{14a} SO_2R_{14b}, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted haloalkoxy; aryl, heteroaryl, cycloalkyl, cycloheteroalkyl each R_{16} is independently halo, optionally substituted alkyl, optionally substituted haloalkyl, hydroxy, or optionally substituted haloalkoxy; or  wherein R_{17} is H, halo, optionally substituted C_{3-6}cycloalkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}alkenyl, and C_{1-6}haloalkyl, and Xa is S or O;

o is 0, 1, 2, 3, or 4;

each R_{18} is independently halo, optionally substituted alkoxy, cyano, optionally substituted alkyl, haloalkyl, haloalkoxy or a linker; and

p is 0, 1, 2, 3, or 4.

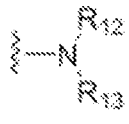
[017] In another embodiments, the ULM has the structure



wherein

R_9 is H;

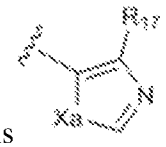
R_{10} is isopropyl, tert-butyl, sec-butyl, cyclopentyl, or cyclohexyl;

R_{11} is  ;

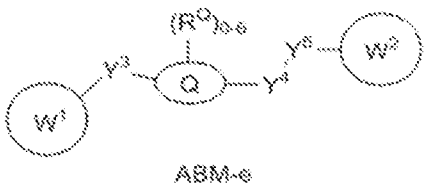
R_{12} is H;

R_{13} is H, optionally substituted alkyl, optionally substituted alkylcarbonyl, optionally substituted (cycloalkyl)alkylcarbonyl, optionally substituted aralkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted (heterocyclyl)carbonyl, or optionally substituted aralkyl;

R_{14a} is H, haloalkyl, or optionally substituted methyl, ethyl, isopropyl, cyclopropyl, or other alkyl; and

R_{15} is  wherein R_{17} is H, halo, optionally substituted C_{3-6}cycloalkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}alkenyl, and C_{1-6}haloalkyl; and Xa is S or O.

[018] In certain embodiments, an androgen receptor binding moiety has a structure of



ASM-e

wherein W^1 is aryl or heteroaryl, independently substituted by 1 or more halo, hydroxyl, nitro, CN, C≡CH, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), C_{1-6} alkoxyl (linear, branched, optionally substituted by 1 or more halo), C_{2-6} alkenyl, C_{2-6} alkynyl;

Y^1, Y^2 are each independently NR^{Y1}, O, S;

Y^3, Y^4, Y^5 are each independently a bond, O, NR^{Y2}, $CR^{Y1}R^{Y2}$, C=O, C=S, SO, SO_2;

Q is a 3-6 membered alicyclic or aromatic ring with 0-4 heteroatoms, optionally substituted with 0-6 R^Q, each R^Q,is independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or 2 R^Q groups taken together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

R^1, R^2, R^a, R^b, R^{Y1}, R^{Y2} are each independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or R^1, R^2 together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

W^2 is a bond, C_{1-6} alkyl, C_{1-6} alicyclic, heterocyclic, aryl, or heteroaryl, each optionally substituted by 1, 2 or 3 R^{W2}; and

each R^{W2} is independently H, halo, C_{1-6} alkyl (optionally substituted by 1 or more F), OC_{1-3}alkyl (optionally substituted by 1 or more –F), OH, NH_2, $NR^{Y1}R^{Y2}$, CN.

[019] In certain additional embodiments, the compounds comprise a plurality of E3 ligase binding moieties and/or a plurality of ABMs.

[020] In certain embodiments, the linker group (L) comprises a chemical structural unit represented by the formula:

$-A_q-$

wherein

q is an integer greater than 1; and

A is independently selected from the group consisting of a bond, $CR^{L1}R^{L2}$, O, S, SO, SO_2, NR^{L3}, SO_2NR^{L3}, $SONR^{L3}$, $CONR^{L3}$, $NR^{L3}CONR^{L4}$, $NR^{L3}SO_2NR^{L4}$, CO, $CR^{L1}=CR^{L2}$, C≡C, $SiR^{L1}R^{L2}$, $P(O)R^{L1}$, $P(O)OR^{L1}$, $NR^{L3}C(=NCN)NR^{L4}$, $NR^{L3}C(=NCN)$, $NR^{L3}C(=CNO_2)NR^{L4}$, C_{3-11}cycloalkyl optionally substituted with 0-6 R^{L1} and/or R^{L2} groups, C_{3-11}heteocyclyl optionally substituted with 0-6 R^{L1} and/or R^{L2} groups, aryl optionally substituted with 0-6 R^{L1} and/or R^{L2} groups, heteroaryl optionally substituted with 0-6 R^{L1} and/or R^{L2} groups;

wherein R^{L1}, R^{L2}, R^{L3}, R^{L4} and R^{L5} are each, independently, selected from the group consisting of H, halo, C_{1-8}alkyl, OC_{1-8}alkyl, SC_{1-8}alkyl, NHC_{1-8}alkyl, $N(C_{1-8}alkyl)_2$, C_{3-11}cycloalkyl, aryl, heteroaryl, C_{3-11}heterocyclyl, OC_{1-8}cycloalkyl, SC_{1-8}cycloalkyl, NHC_{1-8}cycloalkyl, $N(C_{1-8}cycloalkyl)_2$, $N(C_{1-8}cycloalkyl)(C_{1-8}alkyl)$, OH, NH_2, SH, SO_2C_{1-8}alkyl, $P(O)(OC_{1-8}alkyl)(C_{1-8}alkyl)$, $P(O)(OC_{1-8}alkyl)_2$, CC-C_{1-8}alkyl, CCH, $CH=CH(C_{1-8}alkyl)$, $C(C_{1-8}alkyl)=CH(C_{1-8}alkyl)$, $C(C_{1-8}alkyl)=C(C_{1-8}alkyl)_2$, $Si(OH)_3$, $Si(C_{1-8}alkyl)_3$, $Si(OH)(C_{1-8}alkyl)_2$, COC_{1-8}alkyl, CO_2H, halogen, CN, CF_3, CHF_2, CH_2F, NO_2, SF_5, SO_2NHC_{1-8}alkyl, $SO_2N(C_{1-8}alkyl)_2$, $SONHC_{1-8}$alkyl, $SON(C_{1-8}alkyl)_2$, $CONHC_{1-8}$alkyl, $CON(C_{1-8}alkyl)_2$, $N(C_{1-8}alkyl)CONH(C_{1-8}alkyl)$, $N(C_{1-8}alkyl)CON(C_{1-8}alkyl)_2$, $NHCONH(C_{1-8}alkyl)$, $NHCON(C_{1-8}alkyl)_2$, $NHCONH_2$, $N(C_{1-8}alkyl)SO_2NH(C_{1-8}alkyl)$, $N(C_{1-8}alkyl)$ $SO_2N(C_{1-8}alkyl)_2$, NH $SO_2NH(C_{1-8}alkyl)$, NH $SO_2N(C_{1-8}alkyl)_2$, and NH SO_2NH_2; and

wherein when q is greater than 1, R^{L1} or R^{L2} each, independently, can be linked to another A group to form cycloalkyl and/or heterocyclyl moeity that can be further substituted with 0-4 R^{L5} groups.

[021] In certain embodiments, the description provides a bifunctional compound having a structure selected from the group consisting of Examples 1-593, a salt, a polymorph, and a prodrug thereof.

[022] In another aspect, the description provides compositions comprising compounds as described herein, and a pharmaceutically acceptable carrier. In certain embodiments, the compositions are therapeutic or pharmaceutical compositions comprising an effective amount of a compound as described herein and a pharmaceutally acceptable carrier. In certain embodiments, the therapeutic or pharmaceutical compositions comprise an additional biologically active agent, e.g., an agent effective for the treatment of cancer.

[023] In any of the aspects or embodiments described herein, the therapeutic compositions comprising compounds described herein can be in any suitable dosage form, e.g., solid, or liquid, and configured to be delivered by any suitable route, e.g., oral, parenteral, intravenous, intraperitoneal, subcutaneous, intramuscular, etc., and in any desired unit dosage form. For example, in certain embodimetns, the therapeutic composition as described herein is configured to be administered or consumed by a subject one or more times over a descired time period, e.g., day, week, month, etc.

[024] In another aspect, the disclosure provides methods of modulating protein ubiquitination and degradation in a subject, e.g., a cell, a tissue, mammal, or human patient, the method comprising administering an effective amount of a compound as described herein or a composition comprising an effective amount of the same to a subject, wherein the compound or composition comprising the same is effective in modulating protein ubquitination and degration of the protiein in the subject. In certain embodiments, the protein is androgen receptor (AR).

[025] In another aspect, the disclosure provides methods of modulating AR protein ubiquitination and degradation in a subject, e.g., a cell, a tissue, mammal, or human patient, the method comprising administering an effective amount of a compound as described herein or a composition comprising an effective amount of the same to a subject, wherein the compound or composition comprising the same is effective in modulating AR protein ubquitination and degration of the protiein in the subject.

[026] In another aspect, the disclosure provides methods of treating or ameliorating a symptom of a disease related to AR activity in a subject, e.g., a cell, a tissue, mammal, or human patient, the method comprising administering an effective amount of a compound as described herein or a composition comprising an effective amount of the same to a subject in need thereof, wherein the compound or composition comprising the same is effective in treating or ameliorating a symptom of a disease related to AR activity in the subject. In certain embodiments, the disease to be treated is cancer, e.g., prostate cancer, or Kennedy's Disease. In a preferred embodiment, the subject is a human.

[027] In another aspect, the disclosure provides methods for identifying the effects of the degradation of proteins of interest in a biological system using compounds according to the present invention.

[028] In another aspect, the description provides kits comprising compounds or compositions as described herein. The kit may be promoted, distributed, or sold as a unit for performing the methods of the present invention. In addition, the kits of the present invention may preferably contain instructions which describe a suitable use. Such kits can be conveniently used, e.g., in clinical settings, to treat patients exhibiting symptoms of, e.g., cancer or Kennedy's Disease.

[029] Where applicable or not specifically disclaimed, any one of the embodiments described herein are contemplated to be able to combine with any other one or more

embodiments, even though the embodiments are described under different aspects of the invention. As such, the preceding general areas of utility are given by way of example only and are not intended to be limiting on the scope of the present disclosure and appended claims. Additional objects and advantages associated with the compositions, methods, and processes of the present invention will be appreciated by one of ordinary skill in the art in light of the instant claims, description, and examples. For example, the various aspects and embodiments of the invention may be utilized in numerous combinations, all of which are expressly contemplated by the present description. These additional advantages objects and embodiments are expressly included within the scope of the present invention. The publications and other materials used herein to illuminate the background of the invention, and in particular cases, to provide additional details respecting the practice, are incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[030] The accompanying drawings, which are incorporated into and form a part of the specification, illustrate several embodiments of the present invention and, together with the description, serve to explain the principles of the invention. The drawings are only for the purpose of illustrating an embodiment of the invention and are not to be construed as limiting the invention. Further objects, features and advantages of the invention will become apparent from the following detailed description taken in conjunction with the accompanying figures showing illustrative embodiments of the invention, in which:

[031] **Figure 1.** Illustration of general principle for PROTAC function. (A) Exemplary PROTACs comprise an androgen receptor targeting moiety (ABM; *darkly shaded rectangle*), a Von Hippel-Lindau (VHL) E3 ubiquitin ligase binding moiety (VLM; *lightly shaded triangle*), and a linker moiety (L; *black line*) coupling or tethering the ABM to the VLM (as described herein, L can be absent or a bond or a chemical linker moiety). (B) Illustrates the functional use of the PROTACs as described herein. Briefly, the VLM recognizes and binds to Von Hippel-Lindau (VHL) E3 ubiquitin ligase, and the ABM binds and recruits androgen receptor and brings it into close proximity to the Von Hippel-Lindau (VHL) E3 ubiquitin ligase. Typically, the E3 ubiquitin ligase is complexed with an E2 ubiquitin-conjugating protein, and either alone or via the E2 protein catalyzes attachment of ubiquitin (*dark circles*) to a lysine on the target protein via

an isopeptide bond. The poly-ubiquitinated protein (*far right*) is then targeted for degration by the proteosomal machinery of the cell.

[032] **Figure 2. Apoptosis in VCaP cells.** VCaP cells were cultured in Charcoal Stripped Serum containing media supplemented with 0.1 nM R1881 for 48 hrs.

[033] **Figure 3. Anti-proliferation in LNCaP F876L.** LNCaP cells transduced with AR F876L construct were cultured in Charcoal Stripped Serum containing media.

[034] **Figure 4. PSA suppression in LNCaP F876L.** LNCaP cells transduced with AR F876L construct were cultured in Charcoal Stripped Serum containing media supplemented with 0.1 nM R1881 for 7 days.

[035] **Figure 5. Prostate involution in C57B6 mouse model.** 12-week old male C57BL/6 mice were treated with AR PROTAC Example 163 and its inactive epimer analog Compound A which is unable to bind to VHL E3 ligase. Enzalutamide (PO, QD, 30 mpk), Example 163 (IP, QD, 1 and 3 mpk) and Compound A (IP, QD, 1 and 3 mpk) were administered for 10 days, upon which the prostates were isolated and weighed.

[036] **Figure 6. Tumor growth inhibition in VCaP xenograft model.** VCaP cells were implanted into CB17 scid mice subcutaneously. Once the tumors were palpable, the mice were castrated, leading to temporary tumor stasis. Upon regrowth of tumors, the mice were dosed with enzalutamide (PO, QD, 30 mpk) or AR PROTAC Example 163 (IP, QD, at 30, 10 and 3 mpk) as indicated.

[037] **Figure 7. AR degradation of PROTAC is E3 ligase dependent.** (A): AR PROTAC Example 1 was added to LNCaP cells at indicated concentrations for 24 hours in the presence or absence of 10 uM VHL E3 ligase ligand compound B. (B): LNCaP cells were treated with AR PROTAC Example 1 and its inactive epimer analog compound C which is unable to bind to VHL E3 ligase.

DETAILED DESCRIPTION

[038] The following is a detailed description provided to aid those skilled in the art in practicing the present invention. Those of ordinary skill in the art may make modifications and variations in the embodiments described herein without departing from the spirit or scope of the present disclosure. All publications, patent applications, patents, figures and other references mentioned herein are expressly incorporated by reference in their entirety.

[039] The present description relates to the surprising and unexpected discovery that an E3 ubiquitin ligase protein can ubiquitinate a target protein, in particular androgen receptor, once the E3 ubiquitin ligase protein and the target protein are brought into proximity by a chimeric construct (e.g., PROTAC) as described herein, in which a moiety that binds the E3 ubiquitin ligase protein is coupled, e.g., covalently, to a moiety that bind the androgen receptortarget protein. Accordingly, the present description provides compounds, compositions comprising the same, and associated methods of use for ubiquitination and degradation of a chosen target protein, e.g., androgen receptor (See Figure 1).

[040] The present description is related in certain aspects to U.S. Patent Publication 2014/0356322A1, which is incorporated herein by reference in its entirety for all purposes.

[041] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The terminology used in the description is for describing particular embodiments only and is not intended to be limiting of the invention.

[042] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise (such as in the case of a group containing a number of carbon atoms in which case each carbon atom number falling within the range is provided), between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either both of those included limits are also included in the invention.

[043] The following terms are used to describe the present invention. In instances where a term is not specifically defined herein, that term is given an art-recognized meaning by those of ordinary skill applying that term in context to its use in describing the present invention.

[044] The articles "a" and "an" as used herein and in the appended claims are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article unless the context clearly indicates otherwise. By way of example, "an element" means one element or more than one element.

[045] The phrase "and/or," as used herein in the specification and in the claims, should be understood to mean "either or both" of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with "and/or" should be construed in the same fashion, i.e., "one or more" of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the "and/or" clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to "A and/or B", when used in conjunction with open-ended language such as "comprising" can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

[046] As used herein in the specification and in the claims, "or" should be understood to have the same meaning as "and/or" as defined above. For example, when separating items in a list, "or" or "and/or" shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as "only one of' or "exactly one of," or, when used in the claims, "consisting of," will refer to the inclusion of exactly one element of a number or list of elements. In general, the term "or" as used herein shall only be interpreted as indicating exclusive alternatives (i.e., "one or the other but not both") when preceded by terms of exclusivity, such as "either," "one of," "only one of," or "exactly one of."

[047] The term “about” and the like, as used herein, in association with numeric values or ranges, reflects the fact that there is a certain level of variation that is recognized and tolerated in the art due to practical and/or theoretical limitations. For example, minor variation is tolerated due to inherent variances in the manner in which certain devices operate and/or measurements are taken. In accordance with the above, the phrase “about” is normally used to encompass values within the standard deviation or standard error.

[048] In the claims, as well as in the specification above, all transitional phrases such as "comprising," "including," "carrying," "having," "containing," "involving," "holding," "composed of," and the like are to be understood to be open-ended, i.e., to mean including but not limited to. Only the transitional phrases "consisting of' and "consisting essentially of' shall be

closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

[049] As used herein in the specification and in the claims, the phrase "at least one," in reference to a list of one or more elements, should be understood to mean at least one element selected from anyone or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase "at least one" refers, whether related or unrelated to those elements specifically identified. Thus, as a nonlimiting example, "at least one of A and B" (or, equivalently, "at least one of A or B," or, equivalently "at least one of A and/or B") can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

[050] It should also be understood that, in certain methods described herein that include more than one step or act, the order of the steps or acts of the method is not necessarily limited to the order in which the steps or acts of the method are recited unless the context indicates otherwise.

[051] The terms "co-administration" and "co-administering" or “combination therapy” can refer to both concurrent administration (administration of two or more therapeutic agents at the same time) and time varied administration (administration of one or more therapeutic agents at a time different from that of the administration of an additional therapeutic agent or agents), as long as the therapeutic agents are present in the patient to some extent, preferably at effective amounts, at the same time. In certain preferred aspects, one or more of the present compounds described herein, are coadministered in combination with at least one additional bioactive agent, especially including an anticancer agent. In particularly preferred aspects, the co-administration of compounds results in synergistic activity and/or therapy, including anticancer activity.

[052] The term “effective” can mean, but is in no way limited to, that amount/dose of the active pharmaceutical ingredient, which, when used in the context of its intended use,

effectuates or is sufficient to prevent, inhibit the occurrence, ameliorate, delay or treat (alleviate a symptom to some extent, preferably all) the symptoms of a condition, disorder or disease state in a subject in need of such treatment or receiving such treatment. The term effective subsumes all other effective amount or effective concentration terms, e.g., "effective amount/dose," "pharmaceutically effective amount/dose" or "therapeutically effective amount/dose," which are otherwise described or used in the present application.

[053] The effective amount depends on the type and severity of disease, the composition used, the route of administration, the type of mammal being treated, the physical characteristics of the specific mammal under consideration, concurrent medication, and other factors which those skilled in the medical arts will recognize. The exact amount can be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, Pharmaceutical Dosage Forms (vols. 1-3, 1992); Lloyd, The Art, Science and Technology of Pharmaceutical Compounding (1999); Pickar, Dosage Calculations (1999); and Remington: The Science and Practice of Pharmacy, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

[054] The term "pharmacological composition," "therapeutic composition," "therapeutic formulation" or "pharmaceutically acceptable formulation" can mean, but is in no way limited to, a composition or formulation that allows for the effective distribution of an agent provided by the invention, which is in a form suitable for administration to the physical location most suitable for their desired activity, e.g., systemic administration.

[055] The term "pharmaceutically acceptable" or "pharmacologically acceptable" can mean, but is in no way limited to, entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate.

[056] The term "pharmaceutically acceptable carrier" or "pharmacologically acceptable carrier" can mean, but is in no way limited to, any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Suitable carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, a standard reference text in the field, which is incorporated herein by reference. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, finger's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media

and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[057] The term “systemic administration" refers to a route of administration that is, e.g., enteral or parenteral, and results in the systemic distribution of an agent leading to systemic absorption or accumulation of drugs in the blood stream followed by distribution throughout the entire body. Suitable forms, in part, depend upon the use or the route of entry, for example oral, transdermal, or by injection. Such forms should not prevent the composition or formulation from reaching a target cell (i.e., a cell to which the negatively charged polymer is desired to be delivered to). For example, pharmacological compositions injected into the blood stream should be soluble. Other factors are known in the art, and include considerations such as toxicity and forms which prevent the composition or formulation from exerting its effect. Administration routes which lead to systemic absorption include, without limitations: intravenous, subcutaneous, intraperitoneal, inhalation, oral, intrapulmonary and intramuscular. The rate of entry of a drug into the circulation has been shown to be a function of molecular weight or size. The use of a liposome or other drug carrier comprising the compounds of the instant invention can potentially localize the drug, for example, in certain tissue types, such as the tissues of the reticular endothelial system (RES). A liposome formulation which can facilitate the association of drug with the surface of cells, such as, lymphocytes and macrophages is also useful.

[058] The term “local administration" refers to a route of administration in which the agent is delivered to a site that is apposite or proximal, e.g., within about 10 cm, to the site of the lesion or disease.

[059] The term “compound”, as used herein, unless otherwise indicated, refers to any specific chemical compound disclosed herein and includes tautomers, regioisomers, geometric isomers, and where applicable, stereoisomers, including optical isomers (enantiomers) and other steroisomers (diastereomers) thereof, as well as pharmaceutically acceptable salts and derivatives (including prodrug forms) thereof where applicable, in context. Within its use in context, the term compound generally refers to a single compound, but also may include other compounds such as stereoisomers, regioisomers and/or optical isomers (including racemic mixtures) as well as specific enantiomers or enantiomerically enriched mixtures of disclosed compounds. The term

also refers, in context to prodrug forms of compounds which have been modified to facilitate the administration and delivery of compounds to a site of activity. It is noted that in describing the present compounds, numerous substituents and variables associated with same, among others, are described.

[060] It is understood by those of ordinary skill that molecules which are described herein are stable compounds as generally described hereunder. When the bond  is shown, both a double bond and single bond are represented within the context of the compound shown.

[061] As used herein, "derivatives" can mean compositions formed from the native compounds either directly, by modification, or by partial substitution. As used herein, "analogs" can mean compositions that have a structure similar to, but not identical to, the native compound.

[062] The term “Ubiquitin Ligase” refers to a family of proteins that facilitate the transfer of ubiquitin to a specific substrate protein, targeting the substrate protein for degradation. By way of example, Von Hippel-Lindau E3 Ubiquitin Ligase or VCB E3 Ubiquitin Ligase is protein that alone or in combination with an E2 ubiquitin-conjugating enzyme causes the attachment of ubiquitin to a lysine on a target protein, and subsequently targets the specific protein substrates for degradation by the proteasome. Thus, E3 ubiquitin ligase alone or in complex with an E2 ubiquitin conjugating enzyme is responsible for the transfer of ubiquitin to targeted proteins. In general, the ubiquitin ligase is involved in polyubiquitination such that a second ubiquitin is attached to the first; a third is attached to the second, and so forth. Polyubiquitination marks proteins for degradation by the proteasome. However, there are some ubiquitination events that are limited to mono-ubiquitination, in which only a single ubiquitin is added by the ubiquitin ligase to a substrate molecule. Mono-ubiquitinated proteins are not targeted to the proteasome for degradation, but may instead be altered in their cellular location or function, for example, via binding other proteins that have domains capable of binding ubiquitin. Further complicating matters, different lysines on ubiquitin can be targeted by an E3 to make chains. The most common lysine is Lys48 on the ubiquitin chain. This is the lysine used to make polyubiquitin, which is recognized by the proteasome.

[063] The term “subject” is used throughout the specification to describe a cell, tissue, or animal, preferably a mammal, e.g., a human or a domesticated animal, to whom treatment,

including prophylactic treatment, with the compositions according to the present invention is provided. For treatment of those infections, conditions or disease states which are specific for a specific animal such as a human patient, the term patient refers to that specific animal, including a domesticated animal such as a dog or cat or a farm animal such as a horse, cow, sheep, etc. In general, in the present invention, the term patient refers to a human patient unless otherwise stated or implied from the context of the use of the term.

[064] Compounds

[065] In one aspect, the present invention provides compounds useful for regulating protein activity. The composition comprises a ubiquitin pathway protein binding moiety (preferably for an E3 ubiquitin ligase, alone or in complex with an E2 ubiquitin conjugating enzyme which is responsible for the transfer of ubiquitin to targeted proteins) according to a defined chemical structure and a protein targeting moiety which are linked or coupled together, preferably through a linker, wherein the ubiquitin pathway protein binding moiety recognizes an ubiquitin pathway protein and the targeting moiety recognizes a target protein (e.g., androgen receptor). Such compounds may be referred to herein as PROTAC compounds or PROTACs.

[066] In one aspect, the description provides AR binding moieties (ABM). In certain embodiments, the compounds having the following general structure: ABM-L, wherein ABM is an AR binding moiety as described herein, and L is a chemical linker moiety, e.g., a linker as described herein, or optionally a bond. In certain embodiments, the ABM and/or L are coupled to a ULM as described herein below.

[067] In another aspect, the disclosure provides compounds which function to recruit androgen receptor (AR) proteins to E3 Ubiquitin Ligase for ubiquintination and degradation. In certain embodiments, the compounds have the following general structure:

[068] ABM –L–ULM (I),

[069] wherein ULM is an E3 ligase binding moiety, ABM is an AR binding moiety, which binds to an AR protein and L is a bond or a chemical linker moiety which links the ABM and ULM.

[070] In certain embodiments, the ULM is a moiety specific for an E3 ubiquitin ligase such as, e.g., Von Hippel-Lindau E3 ubiquitin ligase (VHL), cereblon, mouse double minute 2 homolog (Mdm2), or inhibitor of apoptosis (IAP), wherein the ULM moiety is coupled to an ABM as described herein.

[071] Without being bound by any particular theory, it is hypothesized that due at least in part to the proximity of AR and the E3 ubiquitin ligase, the AR is ubiquitinated by the ubiquitin ligase and degraded. In certain embodiments, the ABM is chemically linked or coupled directly to the ULM group. In certain additional embodiments, the ABM is chemically linked or coupled to the ULM via a chemical linker moiety. In additional embodiments, the description provides compounds having the following general structure:

[072] **ABM –L–VLM (II),**

[073] wherein ABM is an AR binding moiety and VLM is a Von Hippel-Lindau E3 Ubiquitin Ligase (VHL) binding moiety,and L is a bond or a chemical linker moiety which links the ABM and VLM. The ULM or VLM group and ABM group may be covalently linked to the linker group through any covalent bond which is appropriate and stable to the chemistry of the linker.

[074] In certain embodiments, the ULM or VLM comprises a hydroxyprolyl moiety. The hydroxyl prolyl moiety has been shown to be importantn for binding and recruiting of the VHL protein.

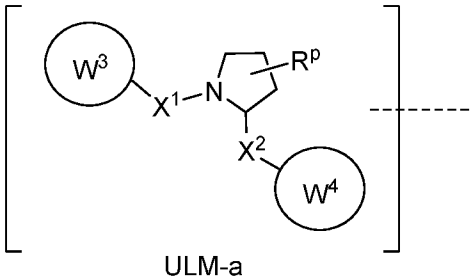
[075] It will be understood that the general structures are exemplary and the respective moieties can be arranged in any desired order or configuration, e.g., ULM-L-ABM, and VLM-L-ABM respectively. In certain additional embodiments, the compounds comprise a plurality of E3 ligase binding moieties and/or a plurality of ABMs.

[076] In certain embodiments, ABM alone, without forming ABM-L-ULM, provides desired properties in regulating protein activity.

[077] In any of the aspects or embodiments of compounds described herein, unless indicated otherwise, the compounds are intended to encompass pharmaceutically acceptable salts, enantiomers, stereoisomers, solvates or polymorphs thereof.

[078] Exemplary ULMs

[079] In certain embodiments of the compounds as described herein, the ULM comprises a chemical structure selected from the group ULM-a:



ULM-a ,

[080] where a dashed line indicates the attachment of at least one ABM, another ULM or VLM (i.e., ULM' or VLM'), or a chemical linker moiety coupling at least one ABM, a ULM' or VLM' to the other end of the linker;

[081] X^1, X^2 are each independently a bond, O, NR^{Y3}, $CR^{Y3}R^{Y4}$, C=O, C=S, SO, SO_2;

[082] R^{Y3}, R^{Y4} are each independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl);

[083] optionally substituted by 1-3 R^P groups in the pyrrolidine moiety, wherein each R^P is independently H, halo, -OH, C_{1-3}alkyl;

[084] W^3 is an optionally substituted –T-$N(R^{1a}R^{1b})$, –T-Aryl, an optionally substituted –T-Heteroaryl, an optionally substituted –T-Heterocycle, an optionally substituted -NR^1-T-Aryl, an optionally substituted -NR^1-T-Heteroaryl or an optionally substituted -NR^1-T-Heterocycle, where T is covalently bonded to X^1;

[085] each R^1 , R^{1a} , R^{1b} is independently H, a C_1-C_6 alkyl group (linear, branched, optionally substituted by 1 or more halo, -OH), $R^{Y3}C=O$, $R^{Y3}C=S$, $R^{Y3}SO$, $R^{Y3}SO_2$, $N(R^{Y3}R^{Y4})C=O$, $N(R^{Y3}R^{Y4})C=S$, $N(R^{Y3}R^{Y4})SO$, $N(R^{Y3}R^{Y4})SO_2$;

[086] T is an optionally substituted –$(CH_2)_n$- group, wherein each one of the methylene groups may be optionally substituted with one or two substituents, preferably selected from halogen, a C_1-C_6 alkyl group (linear, branched, optionally substituted by 1 or more halogen, -OH) or the sidechain of an amino acid as otherwise described herein, preferably methyl, which may be optionally substituted; and n is 0 to 6, often 0, 1, 2, or 3, preferably 0.

[087] Alternatively, T may also be a –$(CH_2O)_n$- group, a –$(OCH_2)_n$- group, a –$(CH_2CH_2O)_n$- group, a –$(OCH_2CH_2)_n$- group, each of which groups is optionally substituted; and

[088] W^4 is an optionally substituted -NR^1-T-Aryl, an optionally substituted -NR^1-T-Heteroaryl group or an optionally substituted -NR^1-T-Heterocycle, where where -NR^1 is covalently bonded to X^2; R^1 is H or CH_3, preferably H, and T is an optionally substituted –$(CH_2)_n$- group, wherein each one of the methylene groups may be optionally substituted with one

or two substituents, preferably selected from halogen, an amino acid sidechain as otherwise described herein or a C_1-C_6 alkyl group (linear, branched, optionally substituted by 1 or more halo, -OH), preferably one or two methyl groups, which may be optionally substituted; and n is 0 to 6, often 0, 1, 2 or 3, preferably 0 or 1.

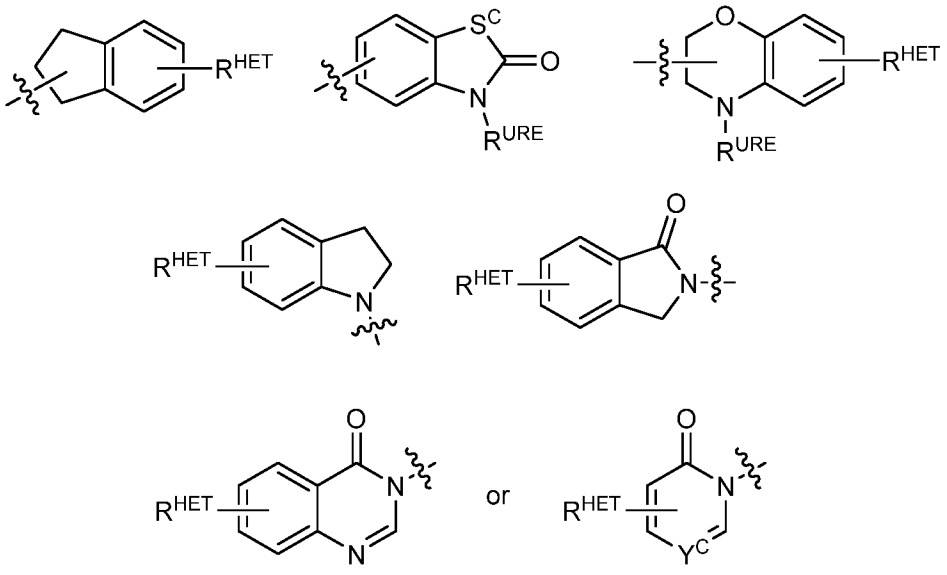
[089] Alternatively, T may also be a $-(CH_2O)_n-$ group, a $-(OCH_2)_n-$ group, a $-(CH_2CH_2O)_n-$ group, a $-(OCH_2CH_2)_n-$ group, all of which groups are optionally substituted.

[090] In any of the embodiments described herein, W^3 and/or W^4 can be attached to a linker moiety as described herein.

[091] In certain embodiments, aryl groups for W^3 include optionally substituted phenyl or naphthyl groups, preferably phenyl groups, wherein the phenyl or naphthyl group is optionally substituted with a linker group to which is attached a ABM group (including a ULM' group) and/or a halogen (preferably F or Cl), an amine, monoalkyl- or dialkyl amine (preferably, dimethylamine), an amido group (preferably a $-(CH_2)_m-NR_1C(O)R_2$ group where m, R_1 and R_2 are the same as for R^1), a halogen (often F or Cl), OH, CH_3, CF_3, OMe, OCF_3, NO_2, ,CN or a $S(O)_2R_S$ group (R_S is a a C_1-C_6 alkyl group, an optionally substituted aryl, heteroaryl or heterocycle group or a $-(CH_2)_mNR_1R_2$ group), each of which may be substituted in ortho-, meta- and/or para- positions of the phenyl ring, preferably para-), or an Aryl (preferably phenyl), heteroaryl or heterocycle. Preferably said substituent phenyl group is an optionally substituted phenyl group (i.e., the substituent phenyl group itself is preferably substituted with at least one of F, Cl, OH, SH, COOH, CH_3, CF_3, OMe, OCF_3, NO_2, CN or a linker group to which is attached a ABM group (including a ULM' group), wherein the substitution occurs in ortho-, meta- and/or para- positions of the phenyl ring, preferably para-), a naphthyl group, which may be optionally substituted including as described above, an optionally substituted heteroaryl (preferably an optionally substituted isoxazole including a methylsubstituted isoxazole, an optionally substituted oxazole including a methylsubstituted oxazole, an optionally substituted thiazole including a methyl substituted thiazole, an optionally substituted pyrrole including a methylsubstituted pyrrole, an optionally substituted imidazole including a methylimidazole, a benzylimidazole or methoxybenzylimidazole, an oximidazole or methyloximidazole, an optionally substituted diazole group, including a methyldiazole group, an optionally substituted triazole group, including a methylsubstituted triazole group, a pyridine group, including a halo- (preferably, F) or methylsubstitutedpyridine group or an oxapyridine group (where the pyridine

group is linked to the phenyl group by an oxygen) or an optionally substituted heterocycle (tetrahydrofuran, tetrahydrothiophene, pyrrolidine, piperidine, morpholine, piperazine, tetrahydroquinoline, oxane or thiane. Each of the aryl, heteroaryl or heterocyclic groups may be optionally substituted with a linker group to which is attached a ABM group (including a ULM' group).

[092] In certain embodiments, heteroaryl groups for W^3 include an optionally substituted quinoline (which may be attached to the pharmacophore or substituted on any carbon atom within the quinoline ring), an optionally substituted indole (including dihydroindole), an optionally substituted indolizine, an optionally substituted azaindolizine (2, 3 or 4-azaindolizine) an optionally substituted benzimidazole, benzodiazole, benzoxofuran, an optionally substituted imidazole, an optionally substituted isoxazole, an optionally substituted oxazole (preferably methyl substituted), an optionally substituted diazole, an optionally substituted triazole, a tetrazole, an optionally substituted benzofuran, an optionally substituted thiophene, an optionally substituted thiazole (preferably methyl and/or thiol substituted), an optionally substituted isothiazole, an optionally substituted triazole (preferably a 1,2,3-triazole substituted with a methyl group, a triisopropylsilyl group, an optionally substituted $-(CH_2)_m-O-C_1-C_6$ alkyl group or an optionally substituted $-(CH_2)_m-C(O)-O-C_1-C_6$ alkyl group), an optionally substituted pyridine (2-, 3, or 4-pyridine) or a group according to the chemical structure:



[093]

[094] where S^c is CHR^{SS}, NR^{URE}, or O;

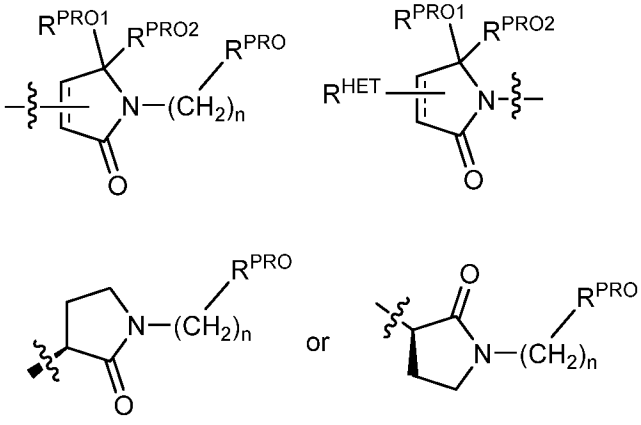
[095] R^{HET} is H, CN, NO_2, halo (preferably Cl or F), optionally substituted C_1-C_6 alkyl (preferably substituted with one or two hydroxyl groups or up to three halo groups (e.g. CF_3), optionally substituted O(C_1-C_6 alkyl) (preferably substituted with one or two hydroxyl groups or up to three halo groups) or an optionally substituted acetylenic group –C≡C-R_a where R_a is H or a C_1-C_6 alkyl group (preferably C_1-C_3 alkyl);

[096] R^{SS} is H, CN, NO_2, halo (preferably F or Cl), optionally substituted C_1-C_6 alkyl (preferably substituted with one or two hydroxyl groups or up to three halo groups), optionally substituted O-(C_1-C_6 alkyl) (preferably substituted with one or two hydroxyl groups or up to three halo groups) or an optionally substituted -C(O)(C_1-C_6 alkyl) (preferably substituted with one or two hydroxyl groups or up to three halo groups);

[097] R^{URE} is H, a C_1-C_6 alkyl (preferably H or C_1-C_3 alkyl) or a –C(O)(C_1-C_6 alkyl), each of which groups is optionally substituted with one or two hydroxyl groups or up to three halogen, preferably fluorine groups, or an optionally substituted heterocycle, for example piperidine, morpholine, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, piperidine, piperazine, each of which is optionally substituted; and

[098] Y^C is N or C-R^{YC}, where R^{YC} is H, OH, CN, NO_2, halo (preferably Cl or F), optionally substituted C_1-C_6 alkyl (preferably substituted with one or two hydroxyl groups or up to three halo groups (e.g. CF_3), optionally substituted O(C_1-C_6 alkyl) (preferably substituted with one or two hydroxyl groups or up to three halo groups) or an optionally substituted acetylenic group –C≡C-R_a where R_a is H or a C_1-C_6 alkyl group (preferably C_1-C_3 alkyl). Each of said heteroaryl groups may be optionally substituted with a linker group to which is attached a ABM group (including a ULM' group).

[099] In additional embodiments, heterocycle groups for W^3 include tetrahydroquinoline, piperidine, piperazine, pyrrollidine, morpholine, tetrahydrofuran, tetrahydrothiophene, oxane and thiane, each of which groups may be optionally substituted or a group according to the chemical structure:



group;

[0100] where R^{PRO} is H, optionally substituted C_1-C_6 alkyl or an optionally substituted aryl (phenyl or napthyl), heteroaryl or heterocyclic group selected from the group consisting of oxazole, isoxazole, thiazole, isothiazole, imidazole, diazole, oximidazole, pyrrole, pyrollidine, furan, dihydrofuran, tetrahydrofuran, thiene, dihydrothiene, tetrahydrothiene, pyridine, piperidine, piperazine, morpholine, quinoline, (each preferably substituted with a C_1-C_3 alkyl group, preferably methyl or a halo group, preferably F or Cl), benzofuran, indole, indolizine, azaindolizine;

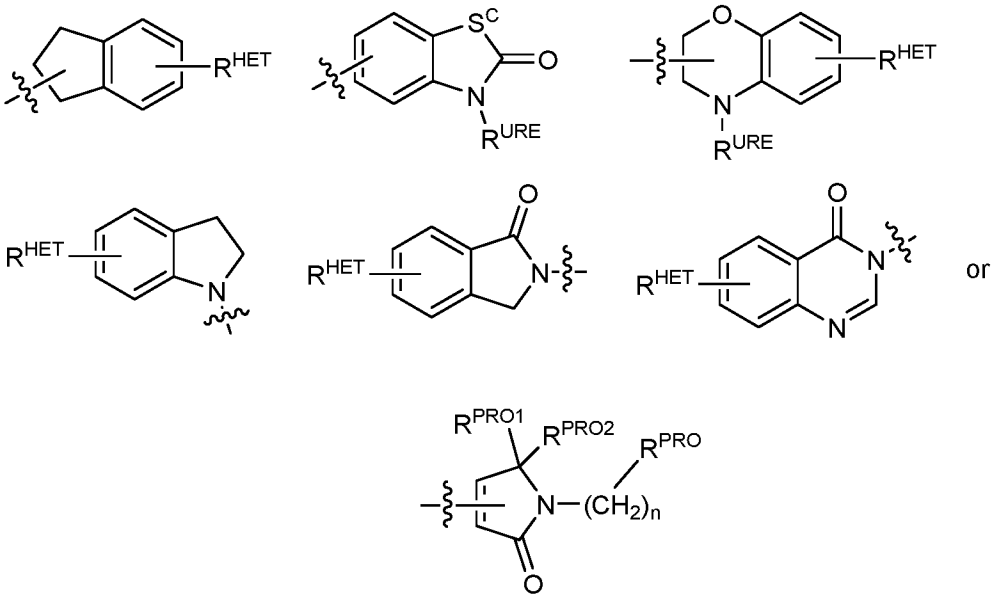
[0101] R^{PRO1} and R^{PRO2} are each independently H, an optionally subsituted C_1-C_3 alkyl group or together form a keto group, and

[0102] each n is 0, 1, 2, 3, 4, 5, or 6 (preferably 0 or 1), wherein each of said Heteocycle groups may be optionally substituted with a linker group to which is attached a ABM group (including a ULM' group) or a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof.

[0103] In certain embodiments, W^3 substituents for use in the present invention also include specifically (and without limitation to the specific compound disclosed) the W^3 substituents which are found in the identified compounds disclosed herein (which includes the specific compounds which are disclosed in the present specification, and the figures which are attached hereto). Each of these W^3 substituents may be used in conjunction with any number of W^4 substituents, which are also disclosed herein.

[0104] In certain embodiments, Aryl groups for W^4 include optionally substituted phenyl or naphthyl groups, preferably phenyl groups, wherein the phenyl group is optionally substituted with a linker group to which is attached an ABMABM group (including a ULM' group), a halogen (preferably F or Cl), an amine, monoalkyl- or dialkyl amine (preferably,

dimethylamine), F, Cl, OH, COOH, C_1-C_6 alkyl, preferably CH_3, CF_3, OMe, OCF_3, NO_2, or CN group (each of which may be substituted in ortho-, meta- and/or para- positions of the phenyl ring, preferably para-), an optionally substituted phenyl group (the phenyl group itself is preferably substituted with a linker group attached to a ABM group, including a ULM' group), and/or at least one of F, Cl, OH, COOH, CH_3, CF_3, OMe, OCF_3, NO_2, or CN group (in ortho-, meta- and/or para- positions of the phenyl ring, preferably para-), a naphthyl group, which may be optionally substituted, an optionally substituted heteroaryl, preferably an optionally substituted isoxazole including a methylsubstituted isoxazole, an optionally substituted oxazole including a methylsubstituted oxazole, an optionally substituted thiazole including a methyl substituted thiazole, an optionally substituted isothiazole including a methyl substituted isothiazole, an optionally substituted pyrrole including a methylsubstituted pyrrole, an optionally substituted imidazole including a methylimidazole, an optionally substituted benzimidazole or methoxybenzylimidazole, an optionally substituted oximidazole or methyloximidazole, an optionally substituted diazole group, including a methyldiazole group, an optionally substituted triazole group, including a methylsubstituted triazole group, an optionally substituted pyridine group, including a halo- (preferably, F) or methylsubstitutedpyridine group or an oxapyridine group (where the pyridine group is linked to the phenyl group by an oxygen), an optionally substituted furan, an optionally substituted benzofuran, an optionally substituted dihydrobenzofuran, an optionally substituted indole, indolizine or azaindolizine (2, 3, or 4-azaindolizine), an optionally substituted quinoline, an optionally substituted group according to the chemical structure:



[0105] where S^c is CHR^{SS}, NR^{URE}, or O;

[0106] R^{HET} is H, CN, NO_2, halo (preferably Cl or F), optionally substituted C_1-C_6 alkyl (preferably substituted with one or two hydroxyl groups or up to three halo groups (e.g. CF_3), optionally substituted O(C_1-C_6 alkyl) (preferably substituted with one or two hydroxyl groups or up to three halo groups) or an optionally substituted acetylenic group –C≡C-R_a where R_a is H or a C_1-C_6 alkyl group (preferably C_1-C_3 alkyl);

[0107] R^{SS} is H, CN, NO_2, halo (preferably F or Cl), optionally substituted C_1-C_6 alkyl (preferably substituted with one or two hydroxyl groups or up to three halo groups), optionally substituted O-(C_1-C_6 alkyl) (preferably substituted with one or two hydroxyl groups or up to three halo groups) or an optionally substituted -C(O)(C_1-C_6 alkyl) (preferably substituted with one or two hydroxyl groups or up to three halo groups);

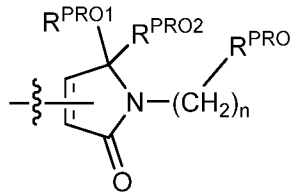
[0108] R^{URE} is H, a C_1-C_6 alkyl (preferably H or C_1-C_3 alkyl) or a –C(O)(C_1-C_6 alkyl) each of which groups is optionally substituted with one or two hydroxyl groups or up to three halogen, preferably fluorine groups, or an optionally substituted phenyl group, an optionally substituted heteroaryl, or an optionally substituted heterocycle, preferably for example piperidine, morpholine, pyrrolidine, tetrahydrofuran);

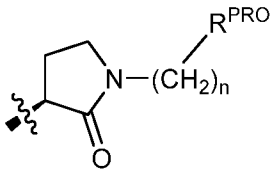
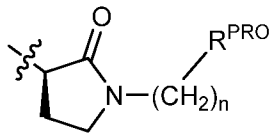
[0109] R^{PRO} is H, optionally substituted C_1-C_6 alkyl or an optionally substituted aryl (phenyl or napthyl), heteroaryl or heterocyclic group selected from the group consisting of oxazole, isoxazole, thiazole, isothiazole, imidazole, diazole, oximidazole, pyrrole, pyrollidine, furan, dihydrofuran, tetrahydrofuran, thiene, dihydrothiene, tetrahydrothiene, pyridine,

piperidine, piperazine, morpholine, quinoline, (each preferably substituted with a C_1-C_3 alkyl group, preferably methyl or a halo group, preferably F or Cl), benzofuran, indole, indolizine, azaindolizine;

[0110] R^{PRO1} and R^{PRO2} are each independently H, an optionally subsituted C_1-C_3 alkyl group or together form a keto group; and

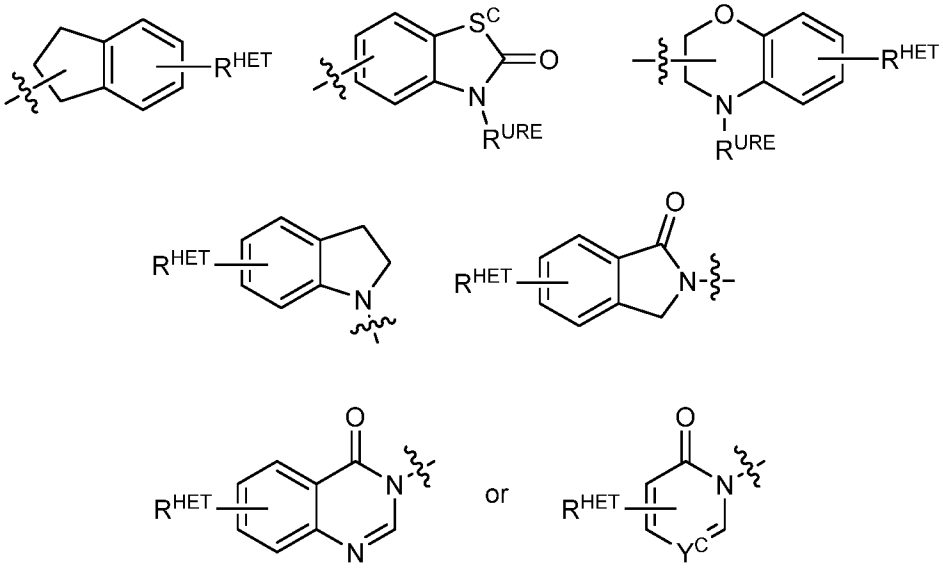
[0111] each n is independently 0, 1, 2, 3, 4, 5, or 6 (preferably 0 or 1), or an optionally substituted heterocycle, preferably tetrahydrofuran, tetrahydrothiene, piperidine, piperazine or morpholine (each of which groups when substituted, are preferably substituted with a methyl or halo (F, Br, Cl), each of which groups may be optionally substituted with a linker group to which is attached a ABM group (including a ULM' group).

[0112] In certain preferred aspects,  is a

[0113]  or  group,

[0114] where R^{PRO} and n are the same as above.

[0115] In certain embodiments, heteroaryl groups for W^4 include an optionally substituted quinoline (which may be attached to the pharmacophore or substituted on any carbon atom within the quinoline ring), an optionally substituted indole, an optionally substituted indolizine, an optionally substituted azaindolizine, an optionally substituted benzofuran, including an optionally substituted benzofuran, an optionally substituted isoxazole, an optionally substituted thiazole, an optionally substituted isothiazole, an optionally substituted thiophene, an optionally substituted pyridine (2-, 3, or 4-pyridine), an optionally substituted imidazole, an optionally substituted pyrrole, an optionally substituted diazole, an optionally substituted triazole, a tetrazole, an optionally substituted oximidazole, or a group according to the chemical structure:



[0116] where S^c is CHR^{SS}, NR^{URE}, or O;

[0117] R^{HET} is H, CN, NO_2, halo (preferably Cl or F), optionally substituted C_1-C_6 alkyl (preferably substituted with one or two hydroxyl groups or up to three halo groups (e.g. CF_3), optionally substituted O(C_1-C_6 alkyl) (preferably substituted with one or two hydroxyl groups or up to three halo groups) or an optionally substituted acetylenic group –C≡C-R_a where R_a is H or a C_1-C_6 alkyl group (preferably C_1-C_3 alkyl);

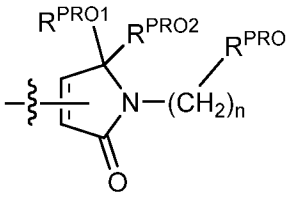
[0118] R^{SS} is H, CN, NO_2, halo (preferably F or Cl), optionally substituted C_1-C_6 alkyl (preferably substituted with one or two hydroxyl groups or up to three halo groups), optionally substituted O-(C_1-C_6 alkyl) (preferably substituted with one or two hydroxyl groups or up to three halo groups) or an optionally substituted -C(O)(C_1-C_6 alkyl) (preferably substituted with one or two hydroxyl groups or up to three halo groups);

[0119] R^{URE} is H, a C_1-C_6 alkyl (preferably H or C_1-C_3 alkyl) or a –C(O)(C_1-C_6 alkyl), each of which groups is optionally substituted with one or two hydroxyl groups or up to three halogen, preferably fluorine groups, or an optionally substituted heterocycle, for example piperidine, morpholine, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, piperidine, piperazine, each of which is optionally substituted, and

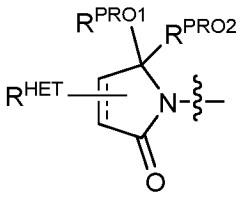
[0120] Y^C is N or C-R^{YC}, where R^{YC} is H, OH, CN, NO_2, halo (preferably Cl or F), optionally substituted C_1-C_6 alkyl (preferably substituted with one or two hydroxyl groups or up to three halo groups (e.g. CF_3), optionally substituted O(C_1-C_6 alkyl) (preferably substituted with one or two hydroxyl groups or up to three halo groups) or an optionally substituted acetylenic

group –C≡C-R_a where R_a is H or a C_1-C_6 alkyl group (preferably C_1-C_3 alkyl), each of which groups may be optionally substituted with a linker group to which is attached a ABM group (including a ULM' group).

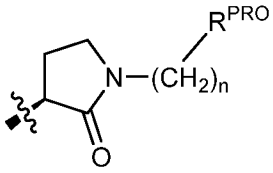
[0121] In certain embodiments, heterocycle groups for W^4 include tetrahydrofuran, tetrahydrothiene, tetrahydroquinoline, piperidine, piperazine, pyrrollidine, morpholine, oxane or thiane, each of which groups may be optionally substituted, or a group according to the chemical structure:



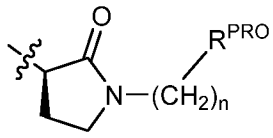
or



preferably, a



or



group,

[0122] where R^{PRO} is H, optionally substituted C_1-C_6 alkyl or an optionally substituted aryl, heteroaryl or heterocyclic group;

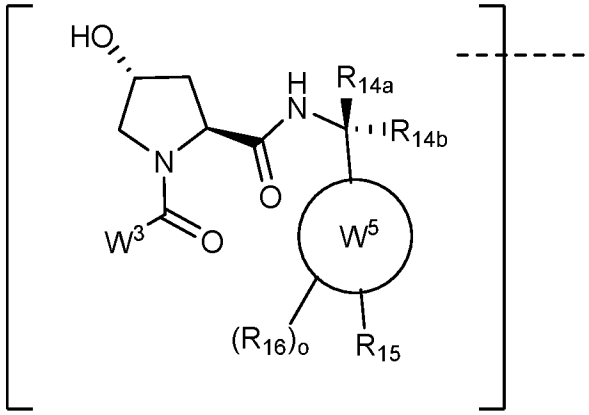
[0123] R^{PRO1} and R^{PRO2} are each independently H, an optionally subsituted C_1-C_3 alkyl group or together form a keto group and

[0124] each n is independently 0, 1, 2, 3, 4, 5, or 6 (often 0 or 1), each of which groups may be optionally substituted with a linker group to which is attached a ABM group (including a ULM' group) In additional embodiments, W^4 substituents for use in the present invention also include specifically (and without limitation to the specific compound disclosed) the W^4 substituents which are found in the identified compounds disclosed herein (which includes the specific compounds which are disclosed in the present specification, and the figures which are attached hereto). Each of these W^4 substituents may be used in conjunction with any number of W^3 substituents which are also disclosed herein.

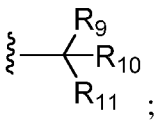
[0125] In certain additional embodiments, ULM-a, is optionally substituted by 1-3 R^P groups in the pyrrolidine moiety. Each R^P is independently H, halo, -OH, C_{1-3}alkyl.

[0126] In any of the embodiments described herein, the W^3, W^4 can independently be covalently coupled to a linker which is attached one or more ABM groups.

[0127] In certain embodiments, ULM is a group (derivatized or configured to be linked or coupled to an ABM via a linker (as indicated by the dashed line) according to the chemical structure:

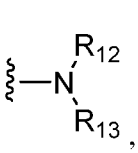


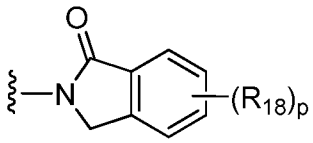
[0128] wherein, W^3 is optionally substituted aryl, optionally substituted heteroaryl, or



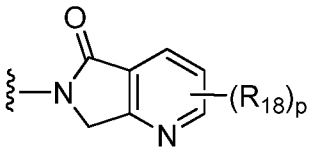
;

[0129] each R_9 and R_{10} is independently hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted hydroxyalkyl, optionally substituted heteroaryl, or haloalkyl; or R_9, R_{10}, and the carbon atom to which they are attached form an optionally substituted cycloalkyl;

[0130] R_{11} is optionally substituted heterocyclic, optionally substituted alkoxy, optionally substituted heteroaryl, optionally substituted aryl, 

, 

or



;

[0131] R_{12} is H or optionally substituted alkyl;

[0132] R_{13} is H, optionally substituted alkyl, optionally substituted alkylcarbonyl, optionally substituted (cycloalkyl)alkylcarbonyl, optionally substituted aralkylcarbonyl,

optionally substituted arylcarbonyl, optionally substituted (heterocyclyl)carbonyl, or optionally substituted aralkyl;

[0133] R_{14a}, R_{14b}, is each independently H, haloalkyl, or optionally substituted alkyl;

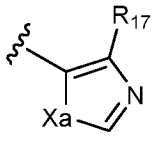
[0134] W^5 is a phenyl or a 5-10 membered heteroaryl,

[0135] R_{15} is H, halogen, CN, OH, NO_2, N $R_{14a}R_{14b}$, OR_{14a}, $CONR_{14a}R_{14b}$, $NR_{14a}COR_{14b}$, $SO_2NR_{14a}R_{14b}$, NR_{14a} SO_2R_{14b}, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted haloalkoxy; aryl, heteroaryl, cycloalkyl, cycloheteroalkyl each R_{16} is independently halo, optionally substituted alkyl, optionally substituted haloalkyl, hydroxy, or optionally substituted haloalkoxy;

[0136] o is 0, 1, 2, 3, or 4;

[0137] each R_{18} is independently halo, optionally substituted alkoxy, cyano, optionally substituted alkyl, haloalkyl, haloalkoxy or a linker; and

[0138] p is 0, 1, 2, 3, or 4.

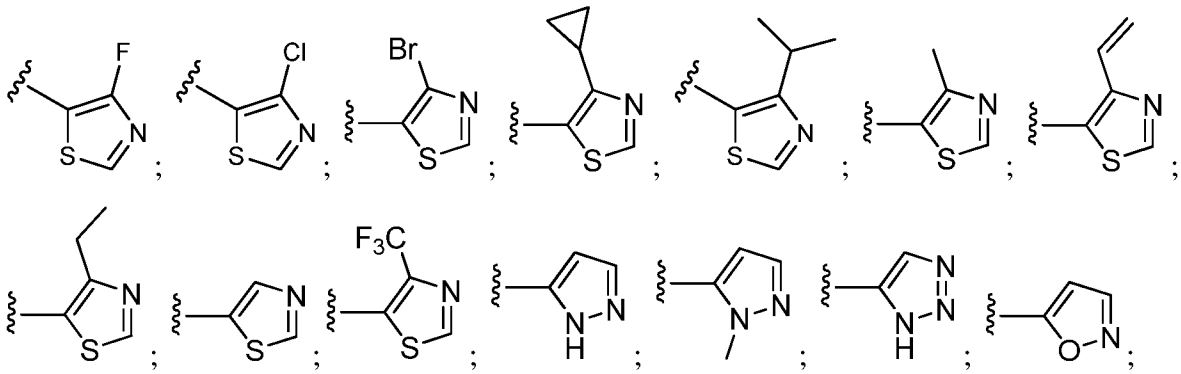
[0139] In certain embodiments, R_{15} is 

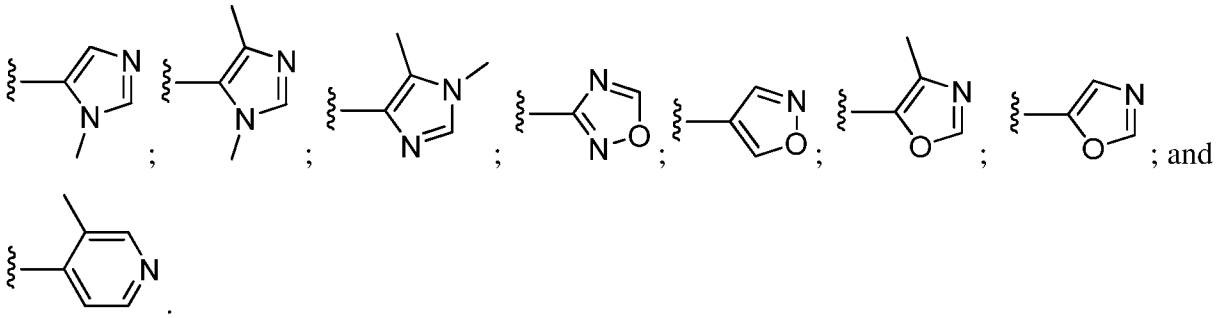
wherein R_{17} is H, halo, optionally substituted C_{3-6}cycloalkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}alkenyl, and C_{1-6}haloalkyl; and

[0140] Xa is S or O.

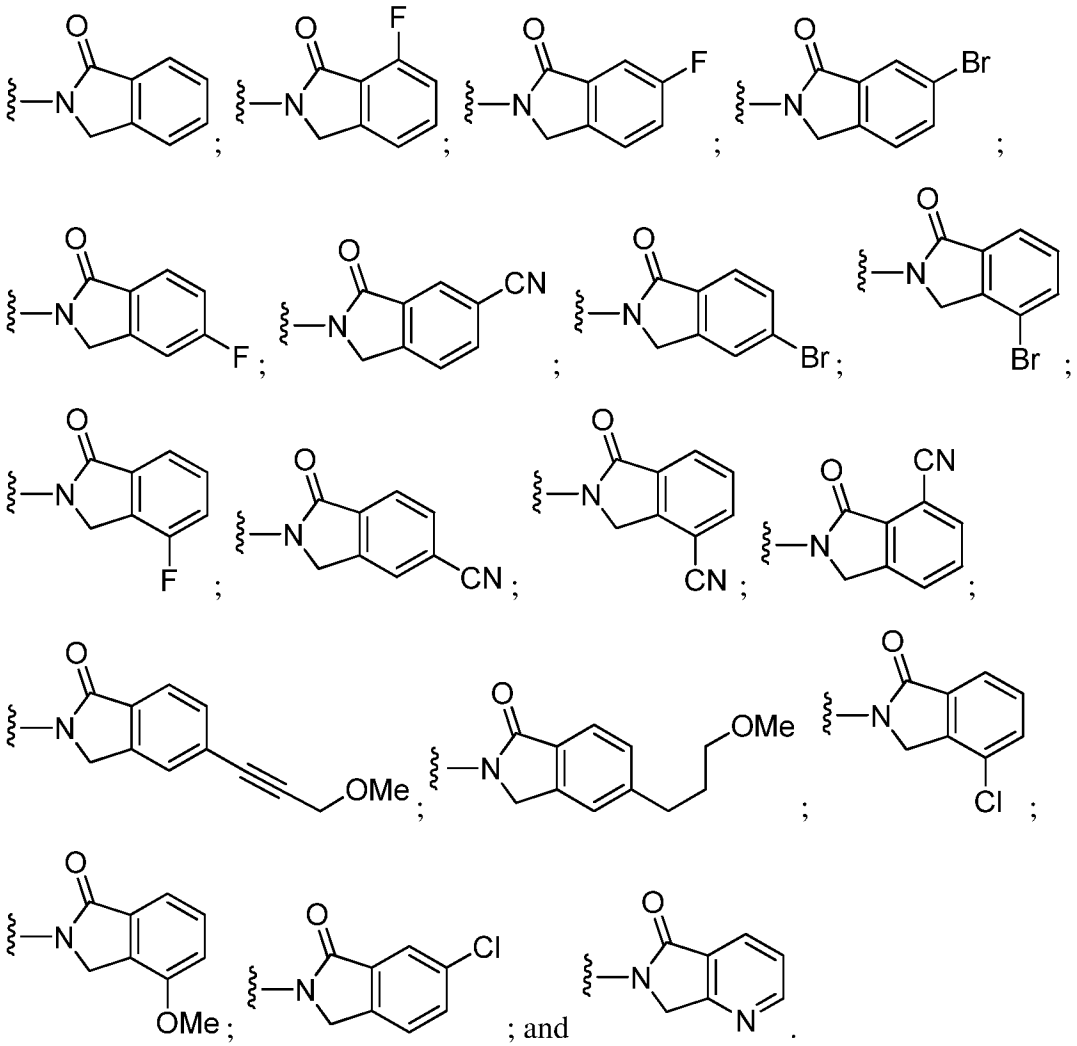
[0141] In certain embodiments, R_{17} is selected from the group methyl, ethyl, isopropyl, and cyclopropyl.

[0142] In certain additional embodiments, R_{15} is selected from the group consisting of:

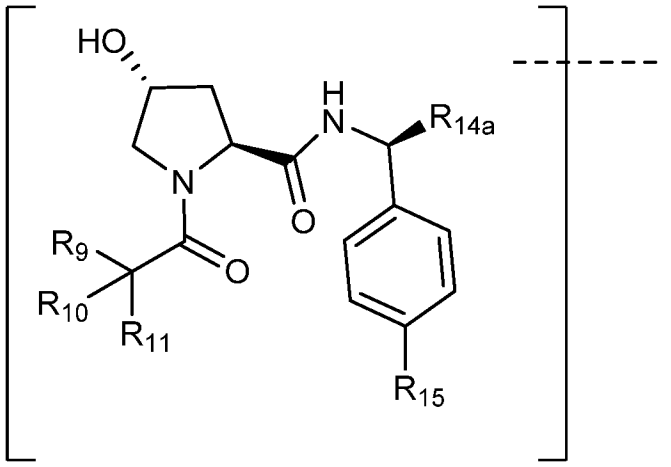




[0143] In certain embodiments, R_{11} is selected from the group consisting of:



[0144] In certain embodiments, the ULM (derivatized or configured to be linked or coupled to an ABM via a linker (as indicated by the dashed line)) has the structure:

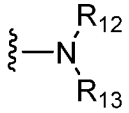


,

[0145] wherein

[0146] R_9 is H;

[0147] R_{10} is isopropyl, tert-butyl, sec-butyl, cyclopentyl, or cyclohexyl;

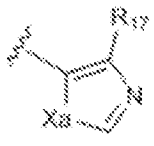
[0148] R_{11} is 

;

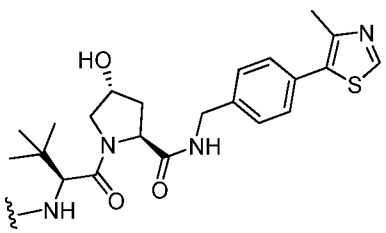
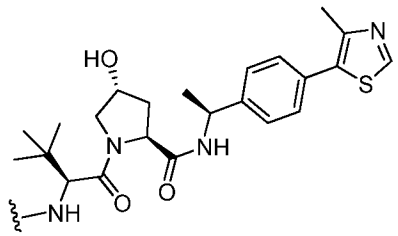
[0149] R_{12} is H;

[0150] R_{13} is H, optionally substituted alkyl, optionally substituted alkylcarbonyl, optionally substituted (cycloalkyl)alkylcarbonyl, optionally substituted aralkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted (heterocyclyl)carbonyl, or optionally substituted aralkyl;

[0151] R14a is H, haloalkyl, or optionally substituted methyl, ethyl, isopropyl, cyclopropyl, or other alkyl; and

[0152] R15 is  wherein R17 is H, halo, optionally substituted C3-6cycloalkyl, optionally substituted C1-6alkyl, optionally substituted C1-6alkenyl, and C1-6haloalkyl; and Xa is S or O.

[0153] In certain embodiments, the ULM or VLM is selected from the group consisting of:


;

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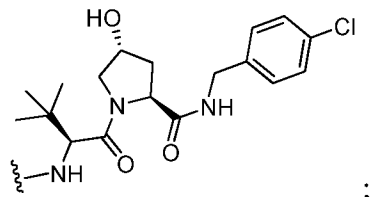
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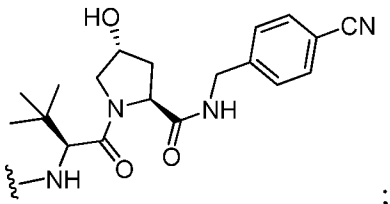
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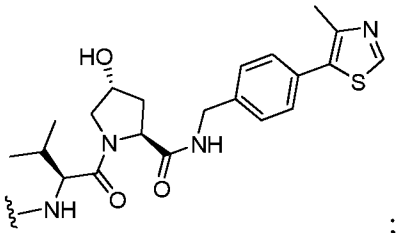
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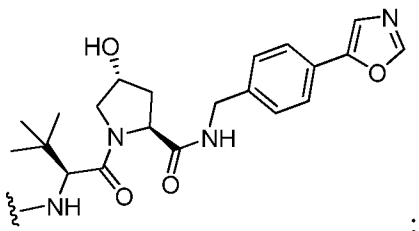
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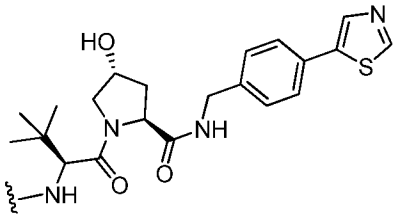
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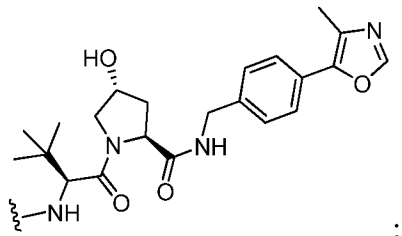
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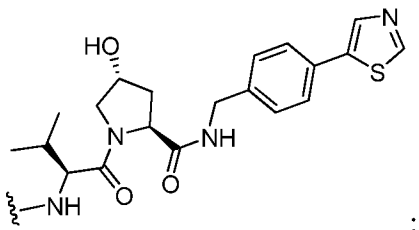
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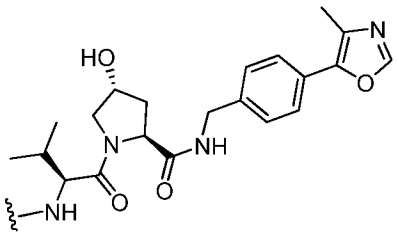
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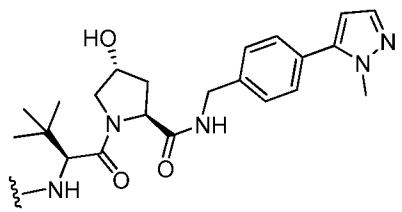
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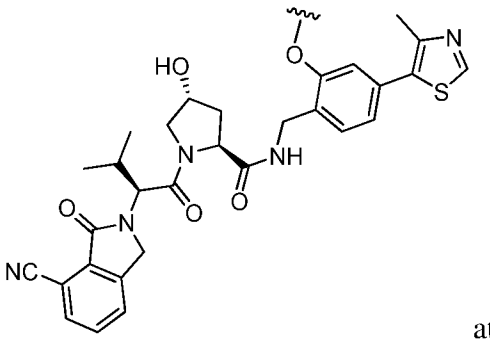

attached to the linker moiety at the position indicated.

[0154] Exemplary Linkers

[0155] In certain embodiments, the compounds as described herein include one or more ABM chemically linked or coupled to one or more ULMs or VLMs via a chemical linker (L). In certain embodiments, the linker group L is a group comprises one or more covalently connected structural units of A (e.g. -$A_{1...}A_q$-), wherein A_1 is coupled to an ABM moiety, and q is an

integer greater than or equal to 0. In certain embodiments, q is an integer greater than or equal to 1.

[0156] In certain embodiments, e. g., where q is greater than 2, A_q is a group which is connected to a ULM or VLM moiety, and A_1 and A_q are connected via structural units of A (number of such structural units of A: q-2).

[0157] In certain embodiments, e. g., where q is 2, A_q is a group which is connected to A_1 and to a ULM or VLM moiety.

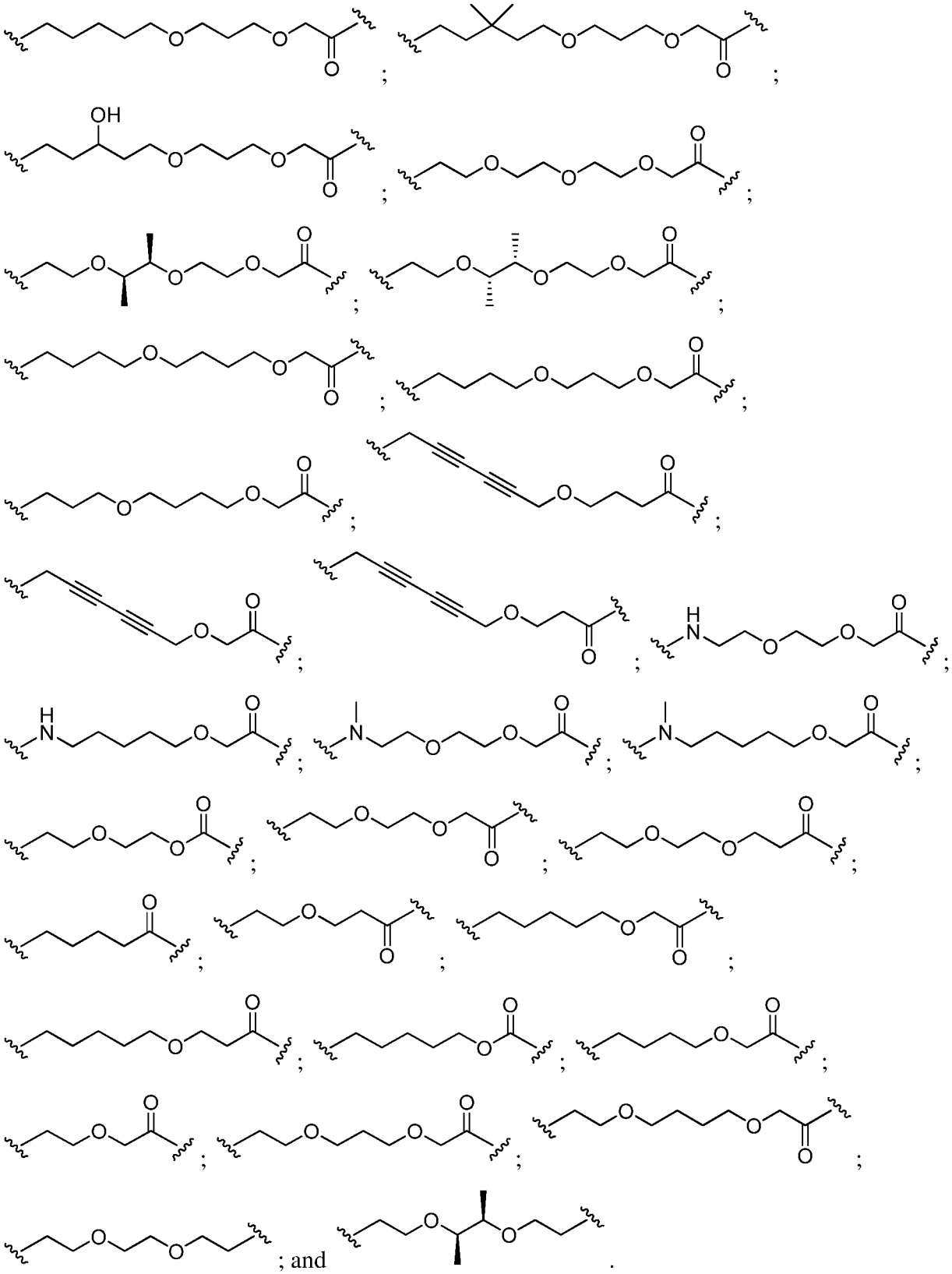
[0158] In certain embodiments, e. g., where q is 1, the structure of the linker group L is –A_1–, and A_1 is a group which is connected to a ULM or VLM moiety and an ABM moiety.

[0159] In additional embodiments, q is an integer from 1 to 100, 1 to 90, 1 to 80, 1 to 70, 1 to 60, 1 to 50, 1 to 40, 1 to 30, 1 to 20, or 1 to 10.

[0160] In certain embodiments, A_1 to A_q are, each independently, a bond, $CR^{L1}R^{L2}$, O, S, SO, SO_2, NR^{L3}, SO_2NR^{L3}, $SONR^{L3}$, $CONR^{L3}$, $NR^{L3}CONR^{L4}$, $NR^{L3}SO_2NR^{L4}$, CO, $CR^{L1}=CR^{L2}$, C≡C, $SiR^{L1}R^{L2}$, $P(O)R^{L1}$, $P(O)OR^{L1}$, $NR^{L3}C(=NCN)NR^{L4}$, $NR^{L3}C(=NCN)$, $NR^{L3}C(=CNO_2)NR^{L4}$, $C_{3\text{-}11}$cycloalkyl optionally substituted with 0-6 R^{L1} and/or R^{L2} groups , $C_{3\text{-}11}$heteocyclyl optionally substituted with 0-6 R^{L1} and/or R^{L2} groups, aryl optionally substituted with 0-6 R^{L1} and/or R^{L2} groups, heteroaryl optionally substituted with 0-6 R^{L1} and/or R^{L2} groups, wherein R^{L1} or $R^{L}{}_2$, each independently, can be linked to other A groups to form cycloalkyl and/or heterocyclyl moeity which can be further substituted with 0-4 R^{L5} groups;

[0161] wherein R^{L1}, R^{L2}, R^{L3}, R^{L4} and R^{L5} are, each independently, H, halo, $C_{1\text{-}8}$alkyl, $OC_{1\text{-}8}$alkyl, $SC_{1\text{-}8}$alkyl, $NHC_{1\text{-}8}$alkyl, $N(C_{1\text{-}8}alkyl)_2$, $C_{3\text{-}11}$cycloalkyl, aryl, heteroaryl, $C_{3\text{-}11}$heterocyclyl, $OC_{1\text{-}8}$cycloalkyl, $SC_{1\text{-}8}$cycloalkyl, $NHC_{1\text{-}8}$cycloalkyl, $N(C_{1\text{-}8}cycloalkyl)_2$, $N(C_{1\text{-}8}cycloalkyl)(C_{1\text{-}8}alkyl)$, OH, NH_2, SH, $SO_2C_{1\text{-}8}$alkyl, $P(O)(OC_{1\text{-}8}alkyl)(C_{1\text{-}8}alkyl)$, $P(O)(OC_{1\text{-}8}alkyl)_2$, CC-$C_{1\text{-}8}$alkyl, CCH, $CH=CH(C_{1\text{-}8}alkyl)$, $C(C_{1\text{-}8}alkyl)=CH(C_{1\text{-}8}alkyl)$, $C(C_{1\text{-}8}alkyl)=C(C_{1\text{-}8}alkyl)_2$, $Si(OH)_3$, $Si(C_{1\text{-}8}alkyl)_3$, $Si(OH)(C_{1\text{-}8}alkyl)_2$, $COC_{1\text{-}8}$alkyl, CO_2H, halogen, CN, CF_3, CHF_2, CH_2F, NO_2, SF_5, $SO_2NHC_{1\text{-}8}$alkyl, $SO_2N(C_{1\text{-}8}alkyl)_2$, $SONHC_{1\text{-}8}$alkyl, $SON(C_{1\text{-}8}alkyl)_2$, $CONHC_{1\text{-}8}$alkyl, $CON(C_{1\text{-}8}alkyl)_2$, $N(C_{1\text{-}8}alkyl)CONH(C_{1\text{-}8}alkyl)$, $N(C_{1\text{-}8}alkyl)CON(C_{1\text{-}8}alkyl)_2$, $NHCONH(C_{1\text{-}8}alkyl)$, $NHCON(C_{1\text{-}8}alkyl)_2$, $NHCONH_2$, $N(C_{1\text{-}8}alkyl)SO_2NH(C_{1\text{-}8}alkyl)$, $N(C_{1\text{-}8}alkyl)\ SO_2N(C_{1\text{-}8}alkyl)_2$, NH $SO_2NH(C_{1\text{-}8}alkyl)$, NH $SO_2N(C_{1\text{-}8}alkyl)_2$, NH SO_2NH_2.

[0162] In certain embodiments, the linker (L) is selected from the group consisting of):



; and .

[0163] In additional embodiments, the linker group is optionally substituted (poly)ethyleneglycol having between 1 and about 100 ethylene glycol units, between about 1 and about 50 ethylene glycol units, between 1 and about 25 ethylene glycol units, between about 1 and 10 ethylene glycol units, between 1 and about 8 ethylene glycol units and 1 and 6 ethylene glycol units, between 2 and 4 ethylene glycol units,or optionally substituted alkyl groups interdispersed with optionally substituted, O, N, S, P or Si atoms. In certain embodiments, the linker is substituted with an aryl, phenyl, benzyl, alkyl, alkylene, or heterocycle group. In certain embodiments, the linker may be asymmetric or symmetrical.

[0164] In certain aspects the description provides a PROTAC compound in which the linker is cleavable in vivo into a functional E3 ligase binding moiety, and target protein binding moiety. In this regard, and without being bound by any particular theory, it is hypothesized that such a configuration can potentiate the beneficial effects of the degradation activity of the intact PROTAC molecule. Thus, in certain embodiments, the linker is configured or "tuned" to have the desired kinetics of cleavage into functional component molecules or active metabolites. In certain embodiments, the enzyme responsible for cleavage of the linker is a liver enzyme, such as, e.g., oxidases, peroxidase, reductases, transferases, dehydrogenases, peroxidases. In certain embodiments, the enzyme is at least one of cytochrome P450 oxidase, e.g., CYP3A4, Flavin-containing monooxygenase, alcohol dehydrogenase, aldehyde dehydrogenase, monoamine oxidase, peroxidase, glutathione S-transferase, cytochrome P450 reductase, sulfotransferase, methyltransferase, N-acetyltransferase, glucuronosyltransferase, transpeptidase, or combination thereof.

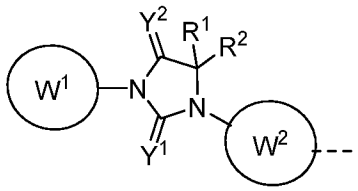
[0165] Exemplary Androgen Binding Moieties (ABMs)

[0166] In another aspect, the description provides AR binding moieties (ABM), which in certain aspects and embodiments are coupled to the ULM.

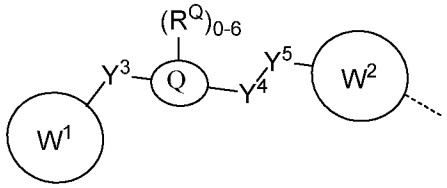
[0167] In any of the compounds described herein, the ABM comprises a chemical moiety that binds to the androgen receptor (AR). Various androgen receptor binding compounds have been described in literature, including various androgen derivatives such as testosterone, dihydrotestosterone, and metribolone (also known as methyltrienolone or R1881), and non-steroidal compounds such as bicalutamide, enzalutamide. Those of ordinary skill in the art would appreciate that these androgen receptor binding compounds could be potentially used as an ABM moiety in a PROTAC compound. Such literature includes, but not limited to, G. F. Allan et. al,

Nuclear Receptor Signaling, 2003, 1, e009; R. H. Bradbury et. al, *Bioorganic & Medicinal Chemistry Letters*, 2011 5442–5445; C. Guo et. al, *Bioorganic & Medicinal Chemistry Letters*, 2012 2572-2578; P. K. Poutiainen et. al, *J. Med. Chem.* 2012, 55, 6316 – 6327 A. Pepe et. al, *J. Med. Chem.* 2013, 56, 8280 – 8297; M. E. Jung et al, *J. Med. Chem.* 2010, 53, 2779–2796, which are incorporated by reference herein.

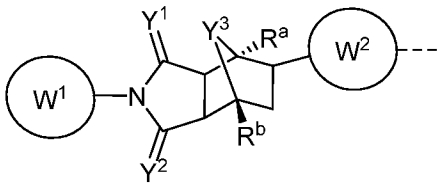
[0168] In certain embodiments, the ABM comprises a structure selected from, but not limited to the structures shown below, where a dashed line indicates the attachment point of linker moiety:



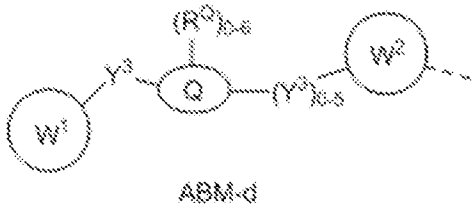
ABM-a ;



ABM-b ;



ABM-c ; and



ABM-d .

[0169] wherein W^1 is aryl or heteroaryl, independently substituted by 1 or more halo, hydroxyl, nitro, CN, C≡CH, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more

halo, C_{1-6} alkoxyl), C_{1-6} alkoxyl (linear, branched, optionally substituted by 1 or more halo), C_{2-6} alkenyl, C_{2-6} alkynyl;

[0170] Y^1, Y^2 are each independently NR^{Y1}, O, S;

[0171] Y^3, Y^4, Y^5 are each independently a bond, O, NR^{Y2}, $CR^{Y1}R^{Y2}$, C=O, C=S, SO, SO_2;

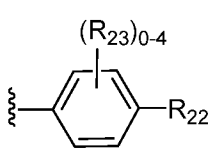
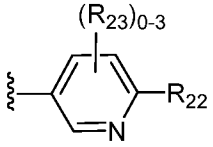
[0172] Q is a 3-6 membered ring with 0-4 heteroatoms, optionally substituted with 0-6 R^Q, each R^Q,is independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or 2 R^Q groups taken together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

[0173] R^1, R^2, R^a, R^b, R^{Y1}, R^{Y2} are each independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or R^1, R^2 together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

[0174] W^2 is a bond, C_{1-6} alkyl, or aryl, or heteroaryl, each optionally substituted by 1, 2 or 3 R^{W2}; and

[0175] each R^{W2} is independently H, halo, C_{1-6} alkyl (optionally substituted by 1 or more F), OC_{1-3}alkyl (optionally substituted by 1 or more –F).

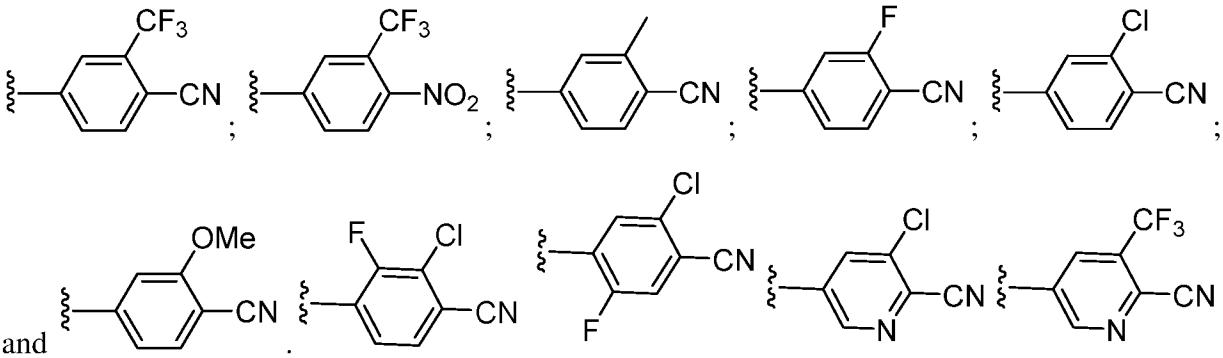
[0176] In any of the embodiments described herein, the W^2 is covalently coupled to one or more ULM or VLM groups, or a linker to which is attached one or more ULM or VLM groups as described herein.

[0177] In certain embodiments, W^1 is  or  ;

[0178] wherein each R_{22} is independently halo, optionally substituted alkyl, haloalkyl, cyano, or nitro; and

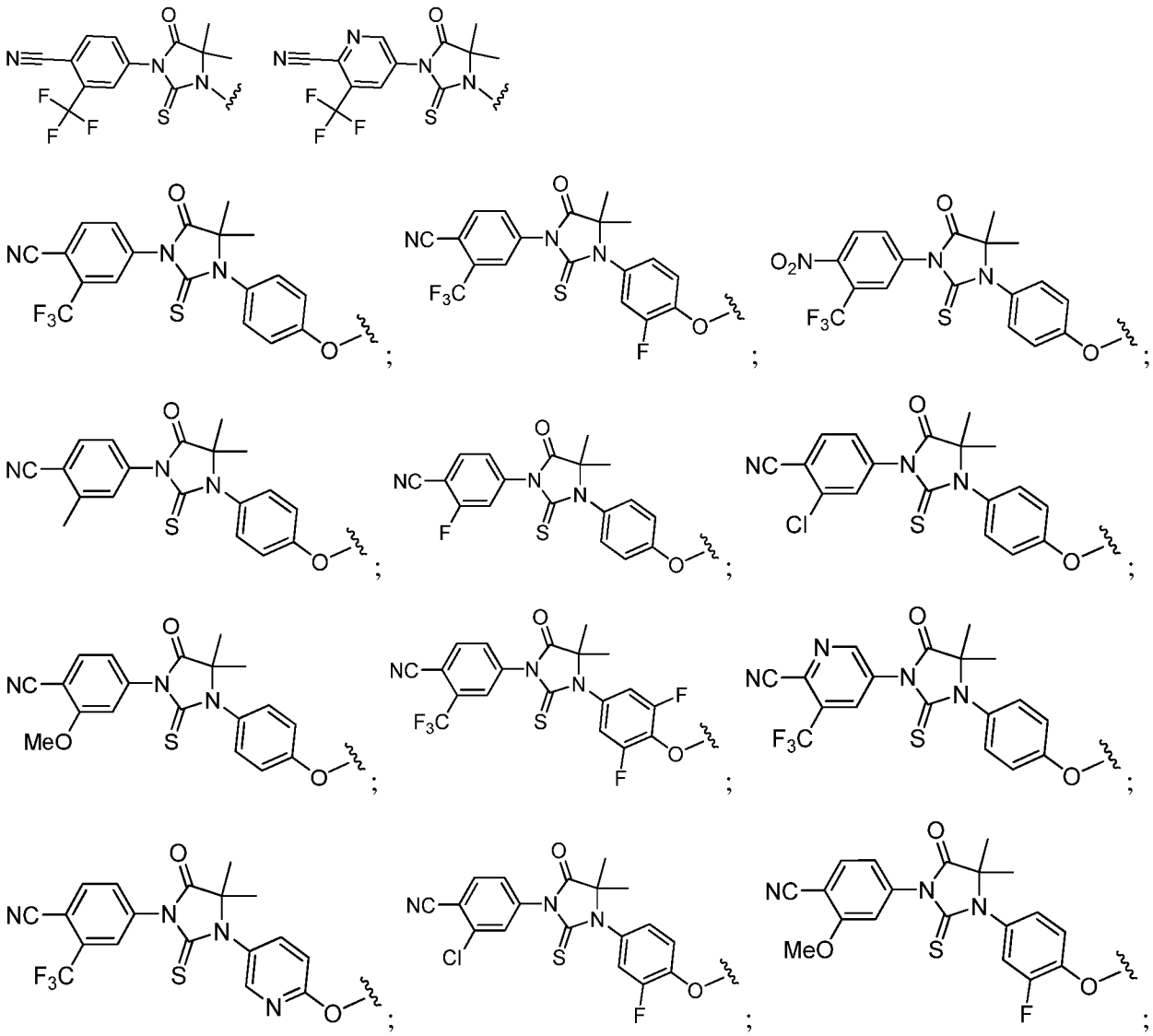
[0179] each R_{23} is independently H, halo, optionally substituted alkyl, haloalkyl, cyano, or nitro.

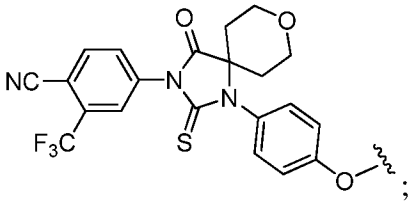
[0180] In certain additional embodiments, W^1 is selected from the group consisting of:



and .

[0181] In certain embodiments, ABM is selected from the group consisting of:

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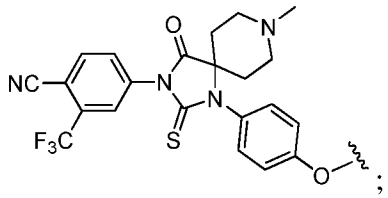
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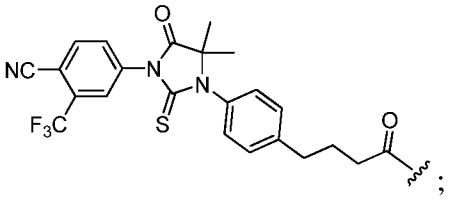
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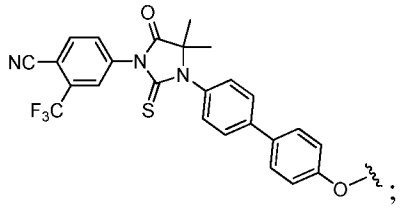
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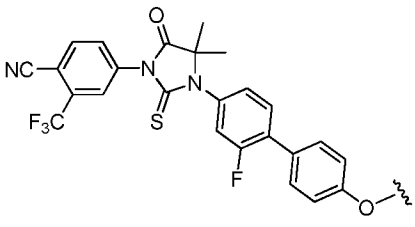
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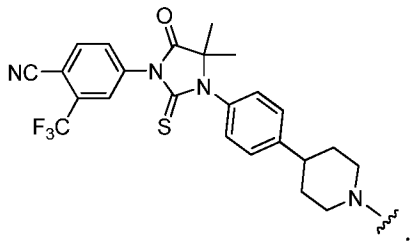
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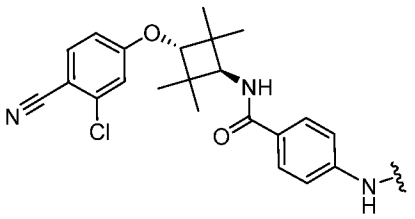

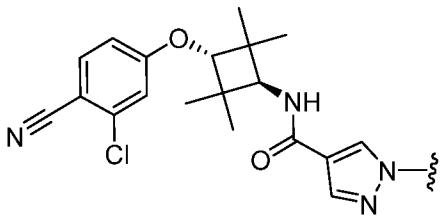

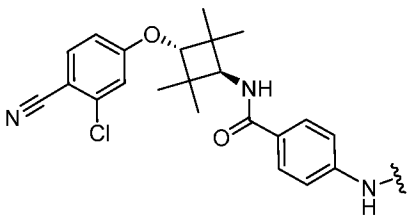

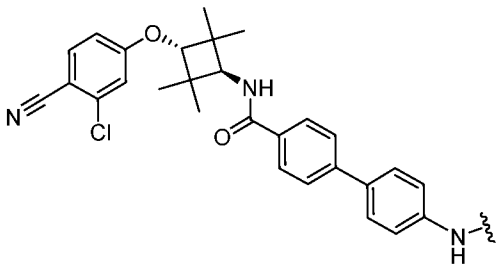

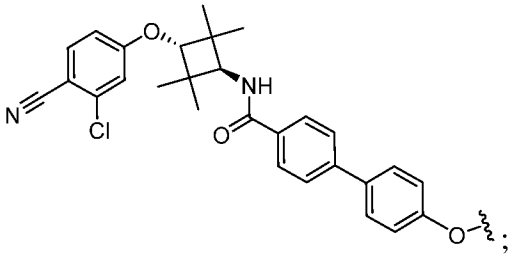
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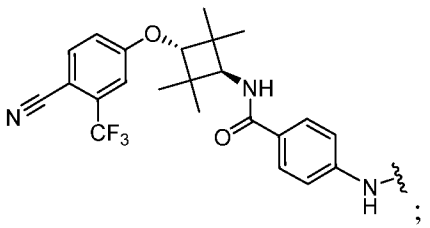
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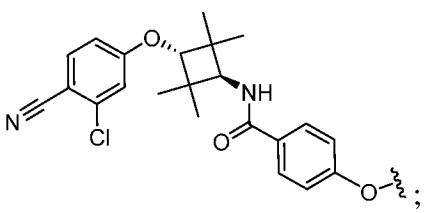
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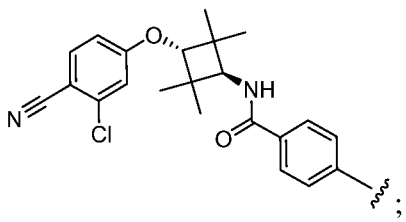
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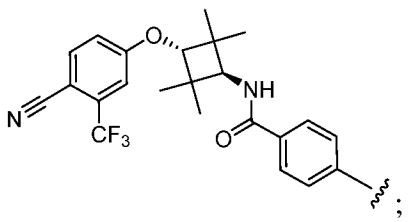
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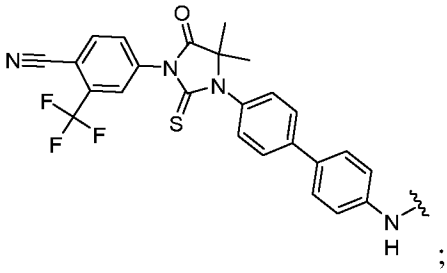
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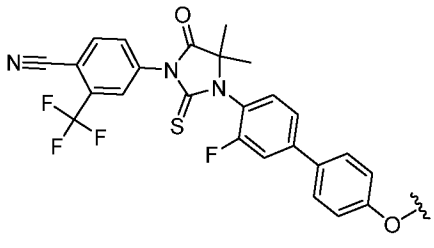
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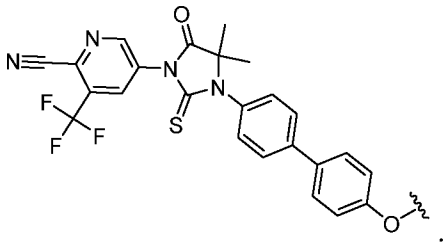
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[0182] In certain embodiments, the ABM comprises the structure:

ABM-b

[0183]

[0184] wherein W^1 is aryl or heteroaryl, independently substituted by 1 or more halo, hydroxyl, nitro, CN, C≡CH, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), C_{1-6} alkoxyl (linear, branched, optionally substituted by 1 or more halo), C_{2-6} alkenyl, C_{2-6} alkynyl;

[0185] Y^3, Y^4, Y^5 are each independently a bond, O, NR^{Y2}, $CR^{Y1}R^{Y2}$, C=O, C=S, SO, SO_2;

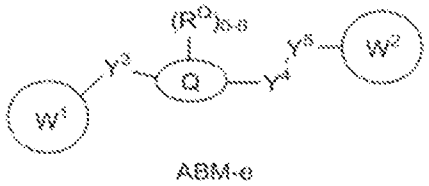
[0186] Q is a 4 membered alicyclic ring with 0-2 heteroatoms, optionally substituted with 0-6 R^Q, each R^Q,is independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or 2 R^Q groups taken together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

[0187] R^{Y1}, R^{Y2} are each independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl);

[0188] W^2 is a bond, C_{1-6} alkyl, C_{1-6} alicyclic, heterocyclic, aryl, or heteroaryl, each optionally substituted by 1, 2 or 3 R^{W2}; and

[0189] each R^{W2} is independently H, halo, C_{1-6} alkyl (optionally substituted by 1 or more F), OC_{1-3}alkyl (optionally substituted by 1 or more –F), OH, NH_2, $NR^{Y1}R^{Y2}$, CN.

[0190] In an additional aspect, the description provides an androgen receptor bindingcompound comprising a structure of:



ABM-e

wherein W^1 is aryl or heteroaryl, independently substituted by 1 or more halo, hydroxyl, nitro, CN, C≡CH, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), C_{1-6} alkoxyl (linear, branched, optionally substituted by 1 or more halo), C_{2-6} alkenyl, C_{2-6} alkynyl;

Y^1, Y^2 are each independently NR^{Y1}, O, S;

Y^3, Y^4, Y^5 are each independently a bond, O, NR^{Y2}, $CR^{Y1}R^{Y2}$, C=O, C=S, SO, SO_2;

Q is a 3-6 membered alicyclic or aromatic ring with 0-4 heteroatoms, optionally substituted with 0-6 R^Q, each R^Q,is independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or 2 R^Q groups taken together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

R^1, R^2, R^a, R^b, R^{Y1}, R^{Y2} are each independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or R^1, R^2 together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

W^2 is a bond, C_{1-6} alkyl, C_{1-6} alicyclic, heterocyclic, aryl, or heteroaryl, each optionally substituted by 1, 2 or 3 R^{W2}; and

each R^{W2} is independently H, halo, C_{1-6} alkyl (optionally substituted by 1 or more F), OC_{1-3}alkyl (optionally substituted by 1 or more –F), OH, NH_2, $NR^{Y1}R^{Y2}$, CN.

[0191] In certain embodimetns, the androgen receptor binding compound of ABM-e is selected from the group consisting of:

trans-2-Chloro-4-[3-amino-2,2,4,4-tetramethylcyclobutoxy]benzonitrile;

cis-2-Chloro-4-[3-amino-2,2,4,4-tetramethylcyclobutoxy]benzonitrile;

trans 6-Amino-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]pyridazine-3-carboxamide;

trans tert-Butyl N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamate;

trans 4-Amino-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide;

trans 5-Amino-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]pyrazine-2-carboxamide;

trans 2-Amino-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]pyrimidine-5-carboxamide;

4-Methoxy-N-[(1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide;

trans 1-(2-Hydroxyethyl)-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]-1H-pyrazole-4-carboxamide;

trans 6-Amino-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]pyridine-3-carboxamide;

trans 4-[(5-Hydroxypentyl)amino]-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide; and

trans tert-Butyl 2-({5-[(4-{[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenyl)aminopentyl}oxy)acetate.

[0192] The term "hydrocarbyl" shall mean a compound which contains carbon and hydrogen and which may be fully saturated, partially unsaturated or aromatic and includes aryl groups, alkyl groups, alkenyl groups and alkynyl groups.

[0193] The term "alkyl" shall mean within its context a linear, branch-chained or cyclic fully saturated hydrocarbon radical or alkyl group, preferably a C_1-C_{10}, more preferably a C_1-C_6, alternatively a C_1-C_3 alkyl group, which may be optionally substituted. Examples of alkyl groups are methyl, ethyl, n-butyl, sec-butyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, isopropyl, 2-methylpropyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclopentylethyl, cyclohexylethyl and cyclohexyl, among others. In certain preferred embodiments, compounds according to the present invention which may be used to covalently bind to dehalogenase enzymes. These compounds generally contain a side chain (often linked through a polyethylene glycol group) which terminates in an alkyl group which has a halogen substituent

(often chlorine or bromine) on its distil end which results in covalent binding of the compound containing such a moiety to the protein.

[0194] The term "Alkenyl" refers to linear, branch-chained or cyclic C_2-C_{10} (preferably C_2-C_6) hydrocarbon radicals containing at least one C=C bond.

[0195] The term "Alkynyl" refers to linear, branch-chained or cyclic C_2-C_{10} (preferably C_2-C_6) hydrocarbon radicals containing at least one C≡C bond.

[0196] The term "alkylene" when used, refers to a $-(CH_2)_n-$ group (n is an integer generally from 0-6), which may be optionally substituted. When substituted, the alkylene group preferably is substituted on one or more of the methylene groups with a C_1-C_6 alkyl group (including a cyclopropyl group or a t-butyl group), more preferably a methyl group, but may also be substituted with one or more halo groups, preferably from 1 to 3 halo groups or one or two hydroxyl groups, O-(C_1-C_6 alkyl) groups or amino acid sidechains as otherwise disclosed herein. In certain embodiments, an alkylene group may be substituted with a urethane or alkoxy group (or other group) which is further substituted with a polyethylene glycol chain (of from 1 to 10, preferably 1 to 6, often 1 to 4 ethylene glycol units) to which is substituted (preferably, but not exclusively on the distal end of the polyethylene glycol chain) an alkyl chain substituted with a single halogen group, preferably a chlorine group. In still other embodiments, the alkylene (often, a methylene) group, may be substituted with an amino acid sidechain group such as a sidechain group of a natural or unnatural amino acid, for example, alanine, β-alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, glutamine, glycine, phenylalanine, histidine, isoleucine, lysine, leucine, methionine, proline, serine, threonine, valine, tryptophan or tyrosine.

[0197] The term "unsubstituted" shall mean substituted only with hydrogen atoms. A range of carbon atoms which includes C_0 means that carbon is absent and is replaced with H. Thus, a range of carbon atoms which is C_0-C_6 includes carbons atoms of 1, 2, 3, 4, 5 and 6 and for C_0, H stands in place of carbon. The term "substituted" or "optionally substituted" shall mean independently (i.e., where more than substituent occurs, each substituent is independent of another substituent) one or more substituents (independently up to five substitutents, preferably up to three substituents, often 1 or 2 substituents on a moiety in a compound according to the present invention and may include substituents which themselves may be further substituted) at a carbon (or nitrogen) position anywhere on a molecule within context, and includes as

substituents hydroxyl, thiol, carboxyl, cyano (C≡N), nitro (NO_2), halogen (preferably, 1, 2 or 3 halogens, especially on an alkyl, especially a methyl group such as a trifluoromethyl), an alkyl group (preferably, C_1-C_{10}, more preferably, C_1-C_6), aryl (especially phenyl and substituted phenyl for example benzyl or benzoyl), alkoxy group (preferably, C_1-C_6 alkyl or aryl, including phenyl and substituted phenyl), thioether (C_1-C_6 alkyl or aryl), acyl (preferably, C_1-C_6 acyl), ester or thioester (preferably, C_1-C_6 alkyl or aryl) including alkylene ester (such that attachment is on the alkylene group, rather than at the ester function which is preferably substituted with a C_1-C_6 alkyl or aryl group), preferably, C_1-C_6 alkyl or aryl, halogen (preferably, F or Cl), amine (including a five- or six-membered cyclic alkylene amine, further including a C_1-C_6 alkyl amine or a C_1-C_6 dialkyl amine which alkyl groups may be substituted with one or two hydroxyl groups) or an optionally substituted –N(C_0-C_6 alkyl)C(O)(O-C_1-C_6 alkyl) group (which may be optionally substituted with a polyethylene glycol chain to which is further bound an alkyl group containing a single halogen, preferably chlorine substituent), hydrazine, amido, which is preferably substituted with one or two C_1-C_6 alkyl groups (including a carboxamide which is optionally substituted with one or two C_1-C_6 alkyl groups), alkanol (preferably, C_1-C_6 alkyl or aryl), or alkanoic acid (preferably, C_1-C_6 alkyl or aryl). Substituents according to the present invention may include, for example –$SiR_1R_2R_3$ groups where each of R_1 and R_2 is as otherwise described herein and R_3 is H or a C_1-C_6 alkyl group, preferably R_1, R_2, R_3 in this context is a C_1-C_3 alkyl group (including an isopropyl or t-butyl group). Each of the above-described groups may be linked directly to the substituted moiety or alternatively, the substituent may be linked to the substituted moiety (preferably in the case of an aryl or heteraryl moiety) through an optionally substituted –$(CH_2)_m$- or alternatively an optionally substituted -$(OCH_2)_m$-, -$(OCH_2CH_2)_m$- or –$(CH_2CH_2O)_m$- group, which may be substituted with any one or more of the above-described substituents. Alkylene groups –$(CH_2)_m$- or –$(CH_2)_n$- groups or other chains such as ethylene glycol chains, as identified above, may be substituted anywhere on the chain. Preferred substitutents on alkylene groups include halogen or C_1-C_6 (preferably C_1-C_3) alkyl groups, which may be optionally substituted with one or two hydroxyl groups, one or two ether groups (O-C_1-C_6 groups), up to three halo groups (preferably F), or a sideshain of an amino acid as otherwise described herein and optionally substituted amide (preferably carboxamide substituted as described above) or urethane groups (often with one or two C_0-C_6 alkyl substitutents, which group(s) may be further substituted). In certain embodiments, the alkylene

group (often a single methylene group) is substituted with one or two optionally substituted C_1-C_6 alkyl groups, preferably C_1-C_4 alkyl group, most often methyl or O-methyl groups or a sidechain of an amino acid as otherwise described herein. In the present invention, a moiety in a molecule may be optionally substituted with up to five substituents, preferably up to three substituents. Most often, in the present invention moieties which are substituted are substituted with one or two substituents.

[0198] The term "substituted" (each substituent being independent of any other substituent) shall also mean within its context of use C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, amido, carboxamido, sulfone, including sulfonamide, keto, carboxy, C_1-C_6 ester (oxyester or carbonylester), C_1-C_6 keto, urethane -O-C(O)-NR_1R_2 or –N(R_1)-C(O)-O-R_1, nitro, cyano and amine (especially including a C_1-C_6 alkylene-NR_1R_2, a mono- or di- C_1-C_6 alkyl substituted amines which may be optionally substituted with one or two hydroxyl groups). Each of these groups contain unless otherwise indicated, within context, between 1 and 6 carbon atoms. In certain embodiments, preferred substituents will include for example, –NH-, -NHC(O)-, -O-, =O, -$(CH_2)_m$- (here, m and n are in context, 1, 2, 3, 4, 5 or 6), -S-, -S(O)-, SO_2- or –NH-C(O)-NH-, -$(CH_2)_n$OH, -$(CH_2)_n$SH, -$(CH_2)_n$COOH, C_1-C_6 alkyl, -$(CH_2)_n$O-(C_1-C_6 alkyl), -$(CH_2)_n$C(O)-(C_1-C_6 alkyl), -$(CH_2)_n$OC(O)-(C_1-C_6 alkyl), -$(CH_2)_n$C(O)O-(C_1-C_6 alkyl), -$(CH_2)_n$NHC(O)-R_1, -$(CH_2)_n$C(O)-NR_1R_2, -$(OCH_2)_n$OH, -$(CH_2O)_n$COOH, C_1-C_6 alkyl, -$(OCH_2)_n$O-(C_1-C_6 alkyl), -$(CH_2O)_n$C(O)-(C_1-C_6 alkyl), -$(OCH_2)_n$NHC(O)-R_1, -$(CH_2O)_n$C(O)-NR_1R_2, -$S(O)_2$-R_S, -S(O)-R_S (R_S is C_1-C_6 alkyl or a –$(CH_2)_m$-NR_1R_2 group), NO_2, CN or halogen (F, Cl, Br, I, preferably F or Cl), depending on the context of the use of the substituent. R_1 and R_2 are each, within context, H or a C_1-C_6 alkyl group (which may be optionally substituted with one or two hydroxyl groups or up to three halogen groups, preferably fluorine). The term "substituted" shall also mean, within the chemical context of the compound defined and substituent used, an optionally substituted aryl or heteroaryl group or an optionally substituted heterocyclic group as otherwise described herein. Alkylene groups may also be substituted as otherwise disclosed herein, preferably with optionally substituted C_1-C_6 alkyl groups (methyl, ethyl or hydroxymethyl or hydroxyethyl is preferred, thus providing a chiral center), a sidechain of an amino acid group as otherwise described herein, an amido group as described hereinabove, or a urethane group O-C(O)-NR_1R_2 group where R_1 and R_2 are as otherwise described herein, although numerous other groups may also be used as substituents. Various optionally substituted moieties may be substituted with 3 or

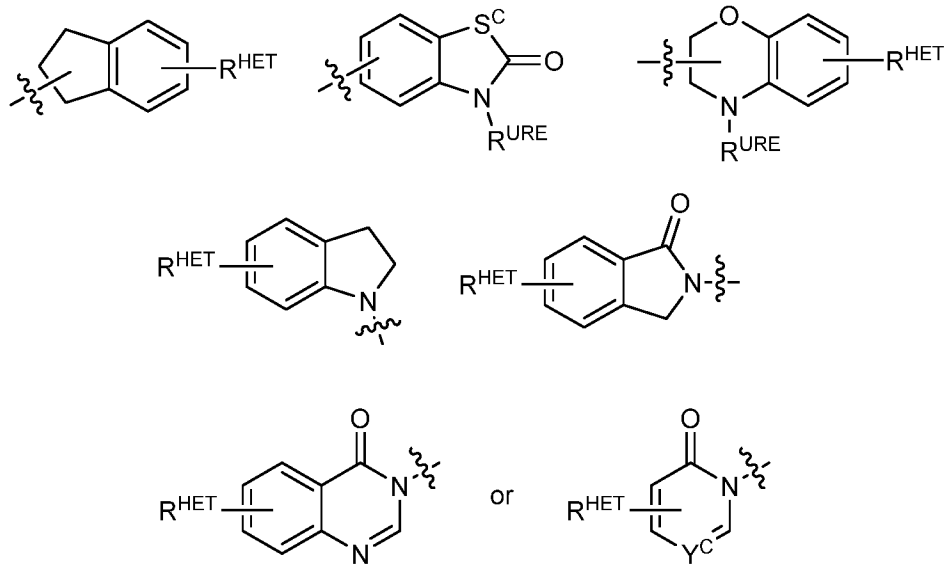
more substituents, preferably no more than 3 substituents and preferably with 1 or 2 substituents. It is noted that in instances where, in a compound at a particular position of the molecule substitution is required (principally, because of valency), but no substitution is indicated, then that substituent is construed or understood to be H, unless the context of the substitution suggests otherwise.

[0199] The term "aryl" or "aromatic", in context, refers to a substituted (as otherwise described herein) or unsubstituted monovalent aromatic radical having a single ring (*e.g.*, benzene, phenyl, benzyl) or condensed rings (e.g., naphthyl, anthracenyl, phenanthrenyl, etc.) and can be bound to the compound according to the present invention at any available stable position on the ring(s) or as otherwise indicated in the chemical structure presented. Other examples of aryl groups, in context, may include heterocyclic aromatic ring systems "heteroaryl" groups having one or more nitrogen, oxygen, or sulfur atoms in the ring (moncyclic) such as imidazole, furyl, pyrrole, furanyl, thiene, thiazole, pyridine, pyrimidine, pyrazine, triazole, oxazole or fused ring systems such as indole, quinoline, indolizine, azaindolizine, benzofurazan, etc., among others, which may be optionally substituted as described above. Among the heteroaryl groups which may be mentioned include nitrogen-containing heteroaryl groups such as pyrrole, pyridine, pyridone, pyridazine, pyrimidine, pyrazine, pyrazole, imidazole, triazole, triazine, tetrazole, indole, isoindole, indolizine, azaindolizine, purine, indazole, quinoline, dihydroquinoline, tetrahydroquinoline, isoquinoline, dihydroisoquinoline, tetrahydroisoquinoline, quinolizine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, imidazopyridine, imidazotriazine, pyrazinopyridazine, acridine, phenanthridine, carbazole, carbazoline, perimidine, phenanthroline, phenacene, oxadiazole, benzimidazole, pyrrolopyridine, pyrrolopyrimidine and pyridopyrimidine; sulfur-containing aromatic heterocycles such as thiophene and benzothiophene; oxygen-containing aromatic heterocycles such as furan, pyran, cyclopentapyran, benzofuran and isobenzofuran; and aromatic heterocycles comprising 2 or more hetero atoms selected from among nitrogen, sulfur and oxygen, such as thiazole, thiadizole, isothiazole, benzoxazole, benzothiazole, benzothiadiazole, phenothiazine, isoxazole, furazan, phenoxazine, pyrazoloxazole, imidazothiazole, thienofuran, furopyrrole, pyridoxazine, furopyridine, furopyrimidine, thienopyrimidine and oxazole, among others, all of which may be optionally substituted.

[0200] The term "substituted aryl" refers to an aromatic carbocyclic group comprised of at least one aromatic ring or of multiple condensed rings at least one of which being aromatic, wherein the ring(s) are substituted with one or more substituents. For example, an aryl group can comprise a substituent(s) selected from: -$(CH_2)_nOH$, -$(CH_2)_n$-O-$(C_1$-$C_6)$alkyl, -$(CH_2)_n$-O-$(CH_2)_n$-$(C_1$-$C_6)$alkyl, -$(CH_2)_n$-C(O)$(C_0$-$C_6)$ alkyl, -$(CH_2)_n$-C(O)O$(C_0$-$C_6)$alkyl, -$(CH_2)_n$-OC(O)$(C_0$-$C_6)$alkyl, amine, mono- or di-$(C_1$-C_6 alkyl) amine wherein the alkyl group on the amine is optionally substituted with 1 or 2 hydroxyl groups or up to three halo (preferably F, Cl) groups, OH, COOH, C_1-C_6 alkyl, preferably CH_3, CF_3, OMe, OCF_3, NO_2, or CN group (each of which may be substituted in ortho-, meta- and/or para- positions of the phenyl ring, preferably para-), an optionally substituted phenyl group (the phenyl group itself is preferably substituted with a linker group attached to a ABM group, including a ULM group), and/or at least one of F, Cl, OH, COOH, CH_3, CF_3, OMe, OCF_3, NO_2, or CN group (in ortho-, meta- and/or para- positions of the phenyl ring, preferably para-), a naphthyl group, which may be optionally substituted, an optionally substituted heteroaryl, preferably an optionally substituted isoxazole including a methylsubstituted isoxazole, an optionally substituted oxazole including a methylsubstituted oxazole, an optionally substituted thiazole including a methyl substituted thiazole, an optionally substituted isothiazole including a methyl substituted isothiazole, an optionally substituted pyrrole including a methylsubstituted pyrrole, an optionally substituted imidazole including a methylimidazole, an optionally substituted benzimidazole or methoxybenzylimidazole, an optionally substituted oximidazole or methyloximidazole, an optionally substituted diazole group, including a methyldiazole group, an optionally substituted triazole group, including a methylsubstituted triazole group, an optionally substituted pyridine group, including a halo- (preferably, F) or methylsubstitutedpyridine group or an oxapyridine group (where the pyridine group is linked to the phenyl group by an oxygen), an optionally substituted furan, an optionally substituted benzofuran, an optionally substituted dihydrobenzofuran, an optionally substituted indole, indolizine or azaindolizine (2, 3, or 4-azaindolizine), an optionally substituted quinoline, and combinations thereof.

[0201] "Carboxyl" denotes the group --C(O)OR, where R is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl , whereas these generic substituents have meanings which are identical with definitions of the corresponding groups defined herein.

[0202] The term "heteroaryl"or "hetaryl" can mean but is in no way limited to an optionally substituted quinoline (which may be attached to the pharmacophore or substituted on any carbon atom within the quinoline ring), an optionally substituted indole (including dihydroindole), an optionally substituted indolizine, an optionally substituted azaindolizine (2, 3 or 4-azaindolizine) an optionally substituted benzimidazole, benzodiazole, benzoxofuran, an optionally substituted imidazole, an optionally substituted isoxazole, an optionally substituted oxazole (preferably methyl substituted), an optionally substituted diazole, an optionally substituted triazole, a tetrazole, an optionally substituted benzofuran, an optionally substituted thiophene, an optionally substituted thiazole (preferably methyl and/or thiol substituted), an optionally substituted isothiazole, an optionally substituted triazole (preferably a 1,2,3-triazole substituted with a methyl group, a triisopropylsilyl group, an optionally substituted -$(CH_2)_m$-O-C_1-C_6 alkyl group or an optionally substituted -$(CH_2)_m$-C(O)-O-C_1-C_6 alkyl group), an optionally substituted pyridine (2-, 3, or 4-pyridine) or a group according to the chemical structure:



[0203] where S^c is CHR^{SS}, NR^{URE}, or O;

[0204] R^{HET} is H, CN, NO_2, halo (preferably Cl or F), optionally substituted C_1-C_6 alkyl (preferably substituted with one or two hydroxyl groups or up to three halo groups (e.g. CF_3), optionally substituted O(C_1-C_6 alkyl) (preferably substituted with one or two hydroxyl groups or up to three halo groups) or an optionally substituted acetylenic group –C≡C-R_a where R_a is H or a C_1-C_6 alkyl group (preferably C_1-C_3 alkyl);

[0205] R^{SS} is H, CN, NO_2, halo (preferably F or Cl), optionally substituted C_1-C_6 alkyl (preferably substituted with one or two hydroxyl groups or up to three halo groups), optionally substituted O-(C_1-C_6 alkyl) (preferably substituted with one or two hydroxyl groups or up to three halo groups) or an optionally substituted -C(O)(C_1-C_6 alkyl) (preferably substituted with one or two hydroxyl groups or up to three halo groups);

[0206] R^{URE} is H, a C_1-C_6 alkyl (preferably H or C_1-C_3 alkyl) or a –C(O)(C_1-C_6 alkyl), each of which groups is optionally substituted with one or two hydroxyl groups or up to three halogen, preferably fluorine groups, or an optionally substituted heterocycle, for example piperidine, morpholine, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, piperidine, piperazine, each of which is optionally substituted, and

[0207] Y^C is N or C-R^{YC}, where R^{YC} is H, OH, CN, NO_2, halo (preferably Cl or F), optionally substituted C_1-C_6 alkyl (preferably substituted with one or two hydroxyl groups or up to three halo groups (e.g. CF_3), optionally substituted O(C_1-C_6 alkyl) (preferably substituted with one or two hydroxyl groups or up to three halo groups) or an optionally substituted acetylenic group –C≡C-R_a where R_a is H or a C_1-C_6 alkyl group (preferably C_1-C_3 alkyl).

[0208] The terms “arylkyl” and “heteroarylalkyl” refer to groups that comprise both aryl or, respectively, heteroaryl as well as alkyl and/or heteroalkyl and/or carbocyclic and/or heterocycloalkyl ring systems according to the above definitions.

[0209] The term "arylalkyl" as used herein refers to an aryl group as defined above appended to an alkyl group defined above. The arylalkyl group is attached to the parent moiety through an alkyl group wherein the alkyl group is one to six carbon atoms. The aryl group in the arylalkyl group may be substituted as defined above.

[0210] The term “heterocycle” refers to a cyclic group which contains at least one heteroatom, i.e., O, N or S, and may be aromatic (heteroaryl) or non-aromatic. Thus, the heteroaryl moieties are subsumed under the definition of heterocycle, depending on the context of its use. Exemplary heterocyclics include: azetidinyl, benzimidazolyl, 1,4- benzodioxanyl, 1,3-benzodioxolyl, benzoxazolyl, benzothiazolyl, benzothienyl, dihydroimidazolyl, dihydropyranyl, dihydrofuranyl, dioxanyl, dioxolanyl, ethyleneurea, 1,3-dioxolane, 1,3-dioxane, 1,4-dioxane, furyl, homopiperidinyl, imidazolyl, imidazolinyl, imidazolidinyl, indolinyl, indolyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, naphthyridinyl, oxazolidinyl, oxazolyl, pyridone, 2-pyrrolidone, pyridine, piperazinyl, , N-

methylpiperazinyl, piperidinyl, phthalimide, succinimide, pyrazinyl, pyrazolinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinolinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydroquinoline, thiazolidinyl, thiazolyl, thienyl, tetrahydrothiophene, oxane, oxetanyl, oxathiolanyl, thiane among others.

[0211] Heterocyclic groups can be optionally substituted with a member selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxy, carboxyalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, —SO-alkyl, —SO-substituted alkyl, —SOaryl, —SO-heteroaryl, —SO2-alkyl, —SO2-substituted alkyl, —SO2-aryl, oxo (=O), and -SO2-heteroaryl. Such heterocyclic groups can have a single ring or multiple condensed rings. Examples of nitrogen heterocycles and heteroaryls include, but are not limited to, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, morpholino, piperidinyl, tetrahydrofuranyl, and the like as well as N-alkoxy-nitrogen containing heterocycles. The term "heterocyclic" also includes bicyclic groups in which any of the heterocyclic rings is fused to a benzene ring or a cyclohexane ring or another heterocyclic ring (for example, indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, and the like).

[0212] The term “cycloalkyl” can mean but is in no way limited to univalent groups derived from monocyclic or polycyclic alkyl groups or cycloalkanes, as defnied herein, e.g., saturated monocyclic hydrocarbon groups having from three to twenty carbon atoms in the ring, including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. The term "substituted cycloalkyl" can mean but is in no way limited to a monocyclic or polycyclic alkyl group and being substituted by one or more substituents, for example, amino, halogen, alkyl, substituted alkyl, carbyloxy, carbylmercapto, aryl, nitro, mercapto or sulfo,

whereas these generic substituent groups have meanings which are identical with definitions of the corresponding groups as defined in this legend.

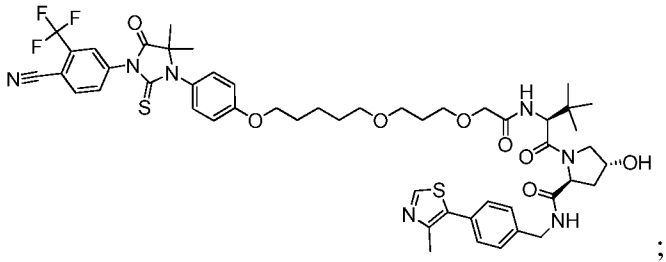
[0213] "Heterocycloalkyl" refers to a monocyclic or polycyclic alkyl group in which at least one ring carbon atom of its cyclic structure being replaced with a heteroatom selected from the group consisting of N, O, S or P. "Substituted heterocycloalkyl" refers to a monocyclic or polycyclic alkyl group in which at least one ring carbon atom of its cyclic structure being replaced with a heteroatom selected from the group consisting of N, O, S or P and the group is containing one or more substituents selected from the group consisting of halogen, alkyl, substituted alkyl, carbyloxy, carbylmercapto, aryl, nitro, mercapto or sulfo, whereas these generic substituent group have meanings which are identical with definitions of the corresponding groups as defined in this legend.

[0214] Exemplary AR-PROTAC Compounds

[0215] As described above, in certain aspects, the description provides bifuctional PROTAC compounds comprising at least one ABM group, a linker, and at least one ULM (or VLM) group as described herein.

[0216] In certain embodiments, the compound is selected from the group consisting of compounds 1-593 (as described in Tables 2-17), and salts and polymorphs thereof.

[0217] In certain embodiments, the compound is selected from the group consisting of: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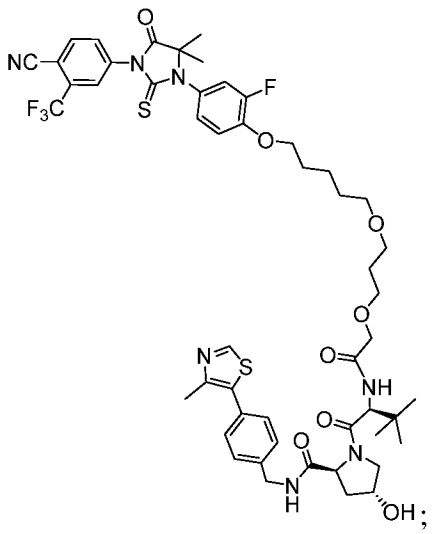
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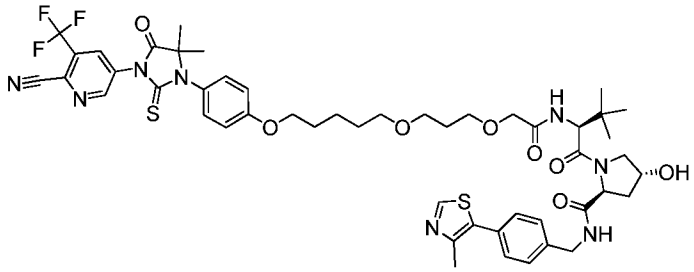
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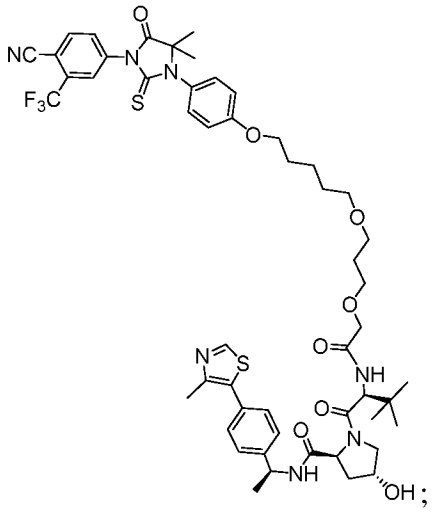
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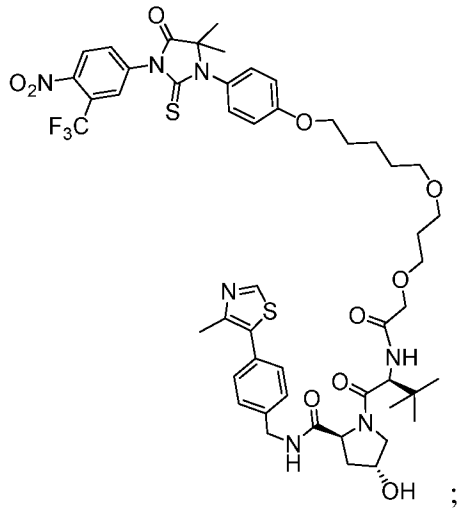
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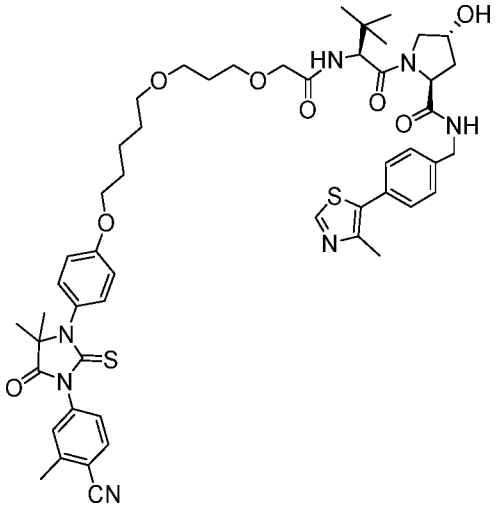
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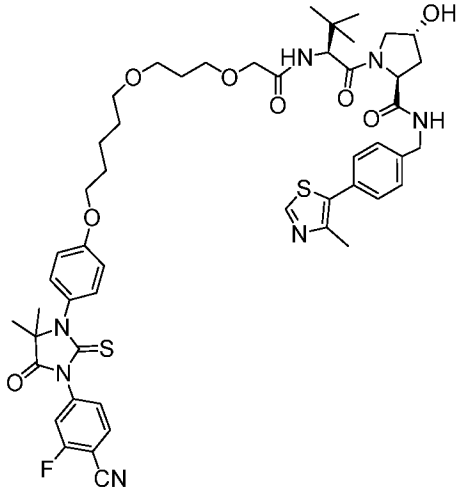
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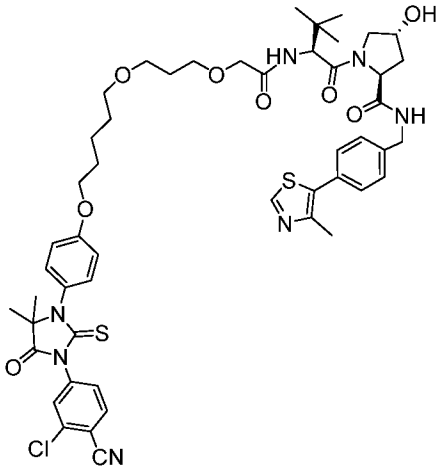
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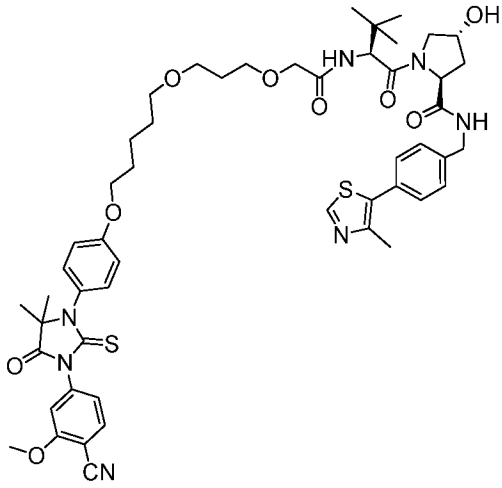
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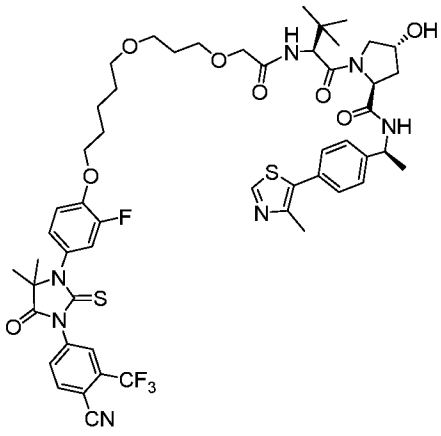
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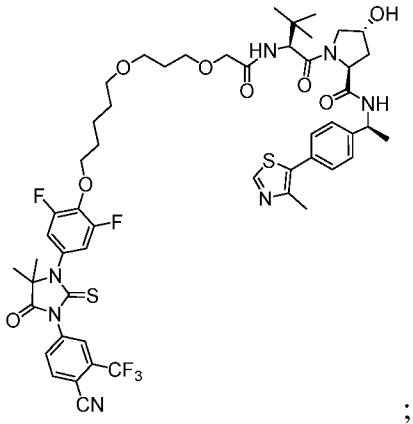
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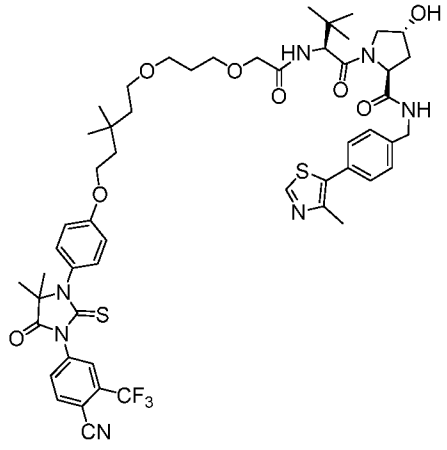
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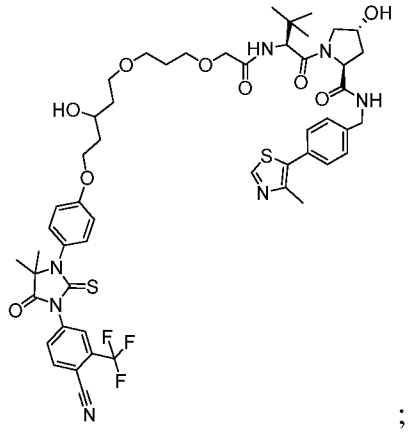
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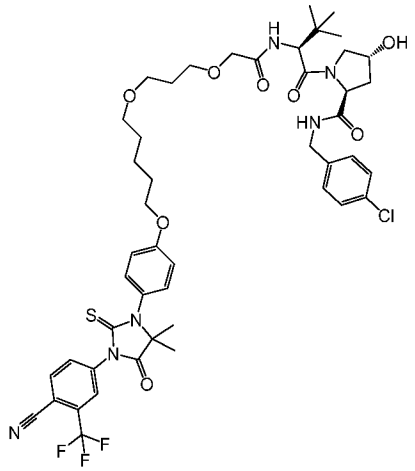
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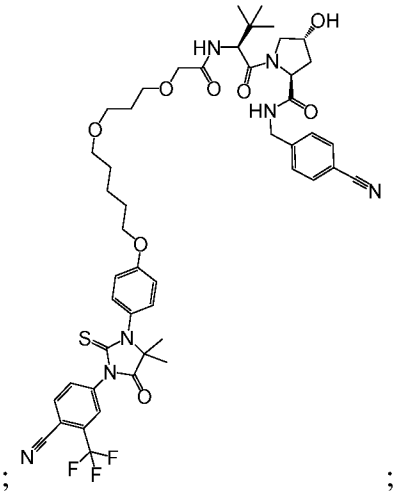
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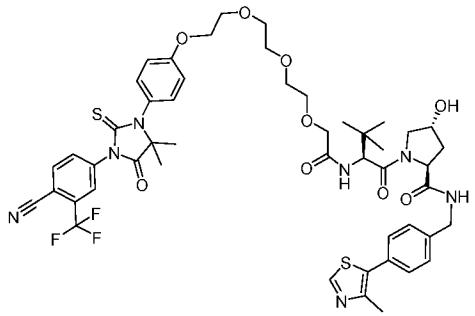
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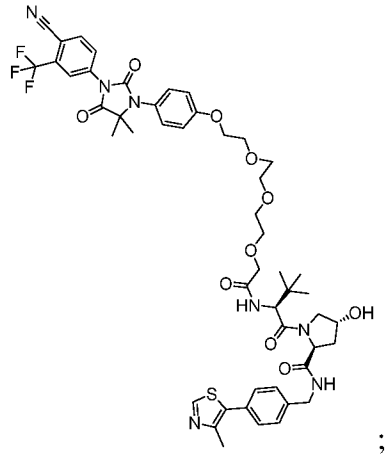
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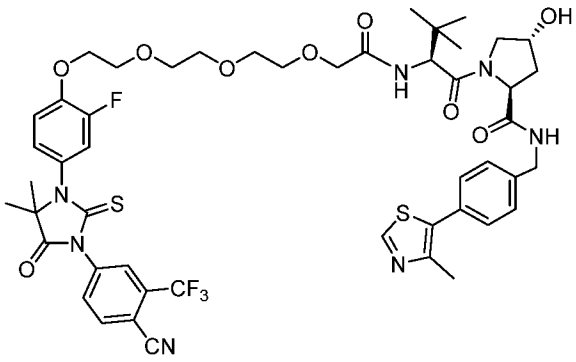
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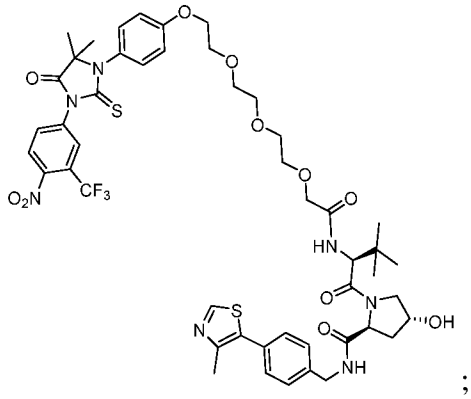
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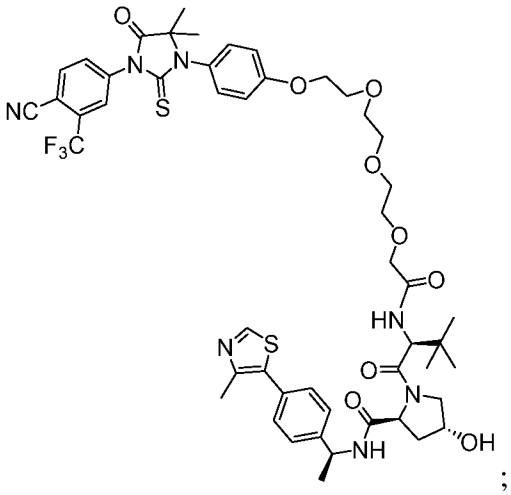
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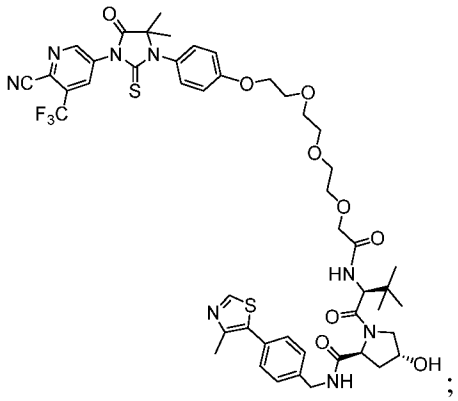
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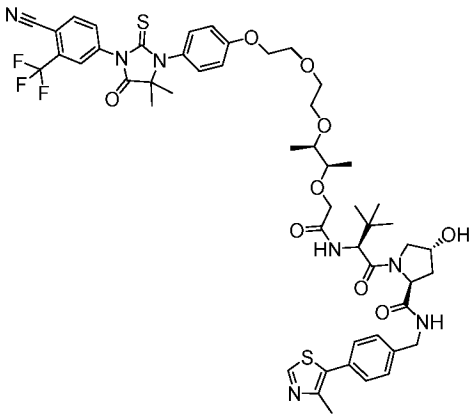
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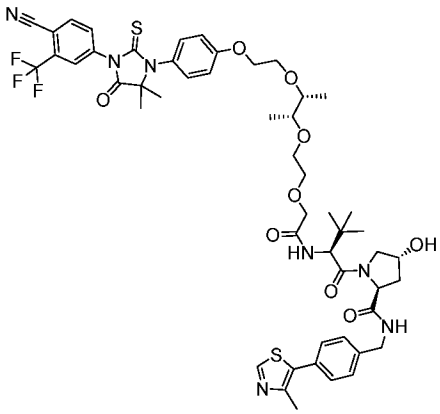
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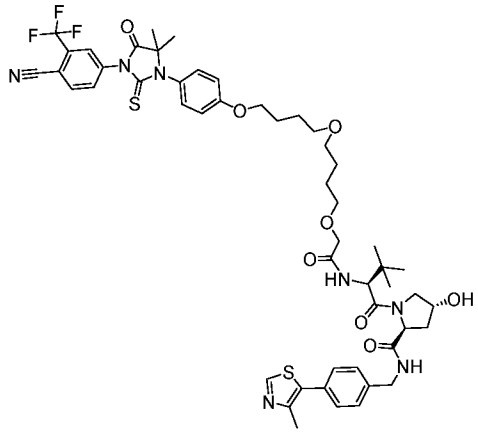
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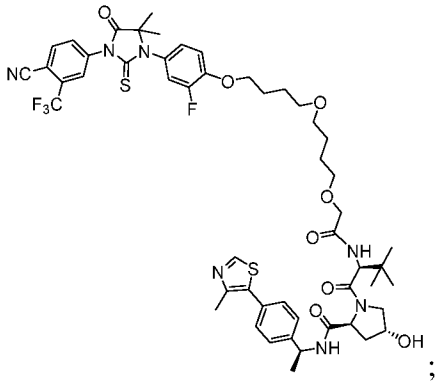
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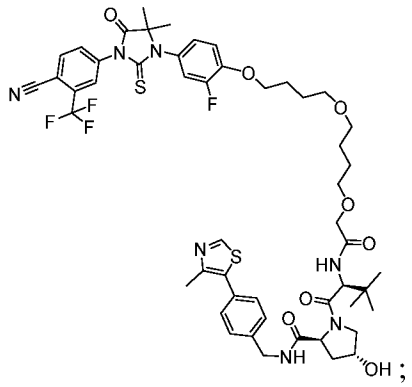
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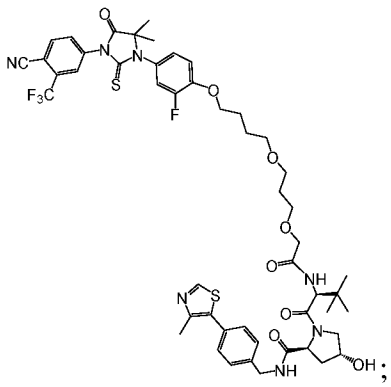
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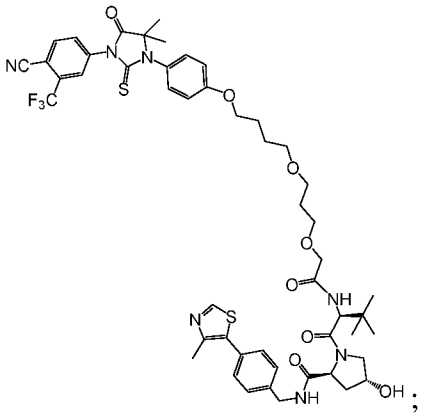
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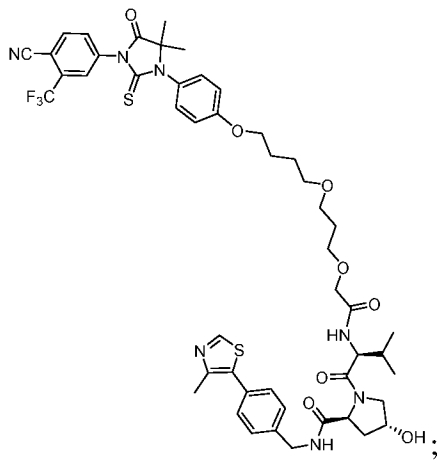
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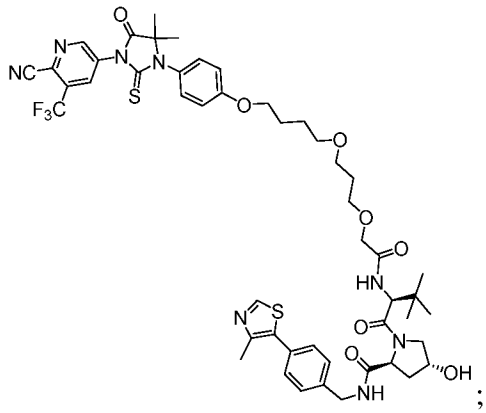
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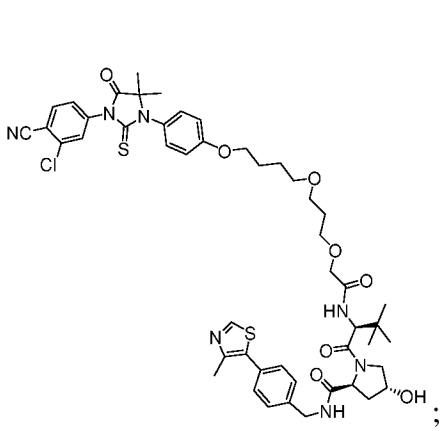

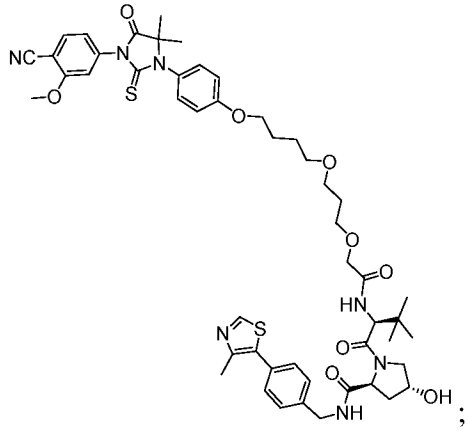

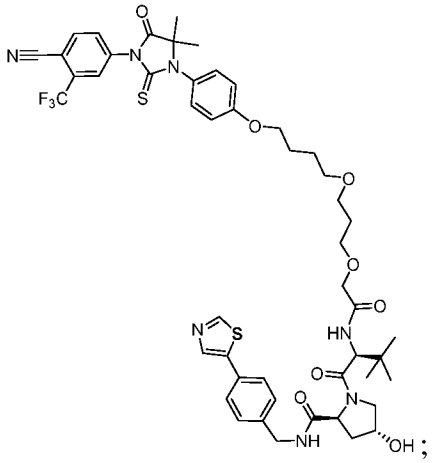

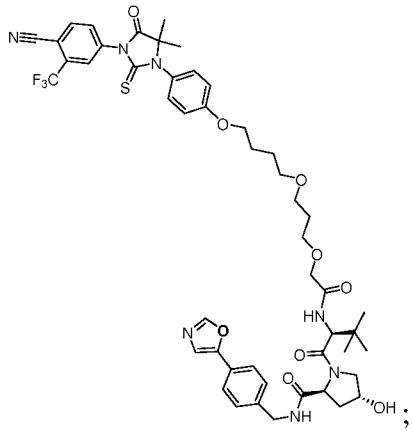

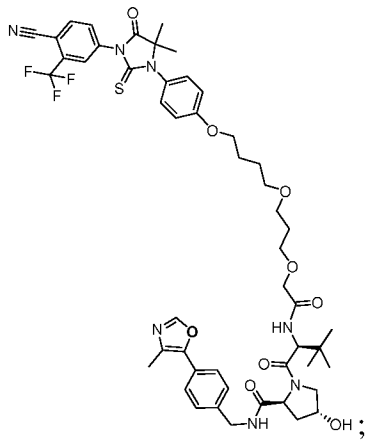

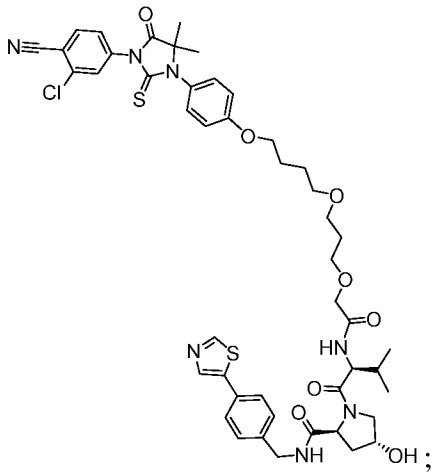

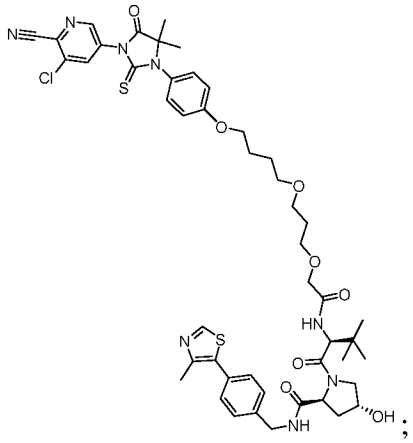

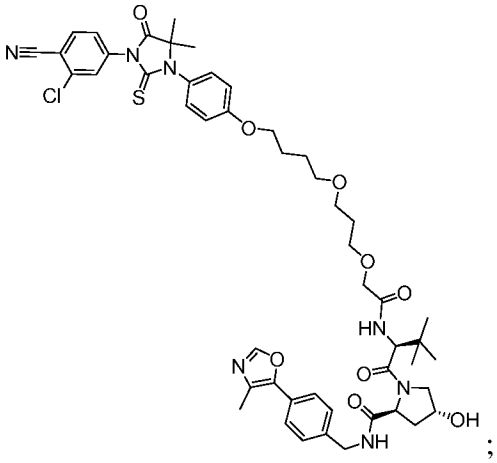

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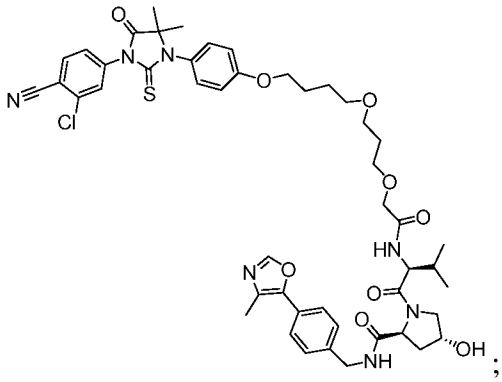

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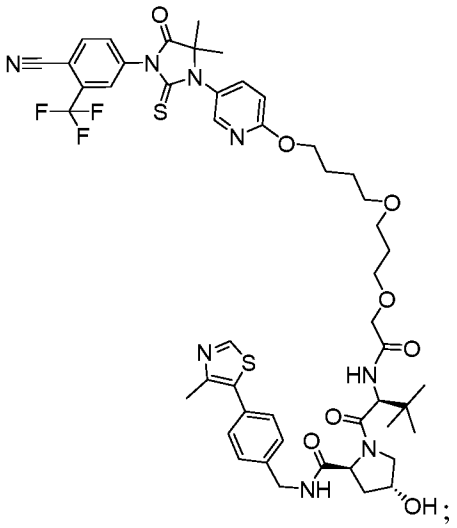

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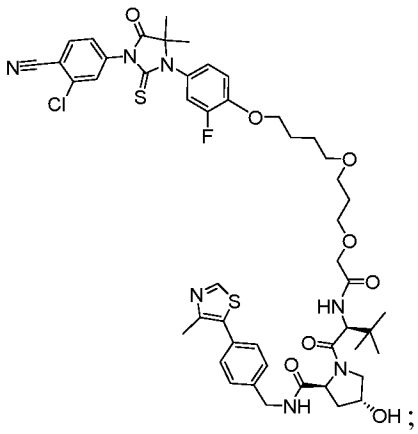

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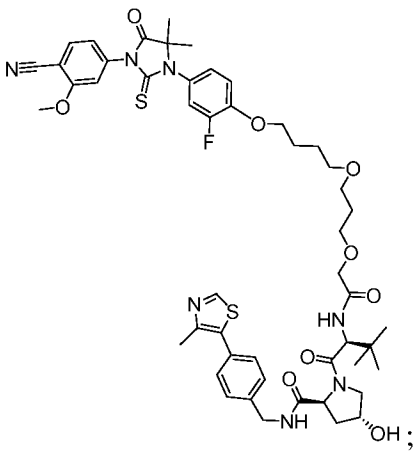

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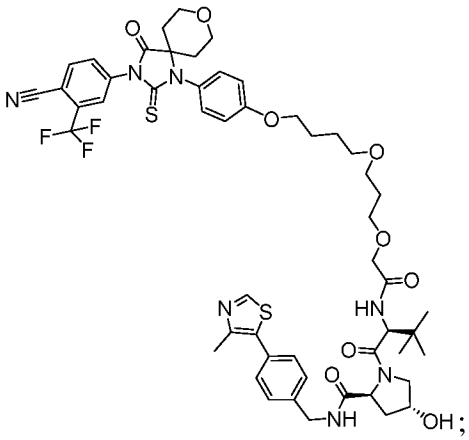

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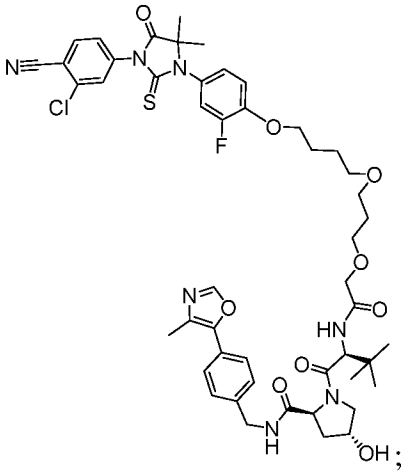

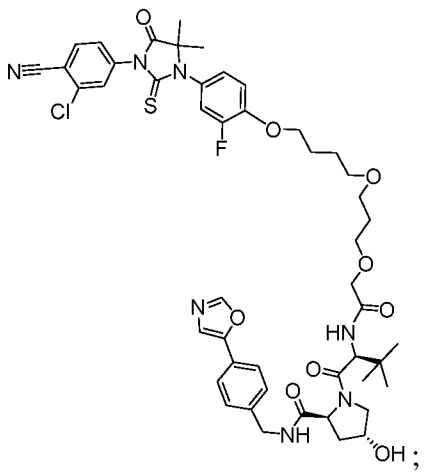

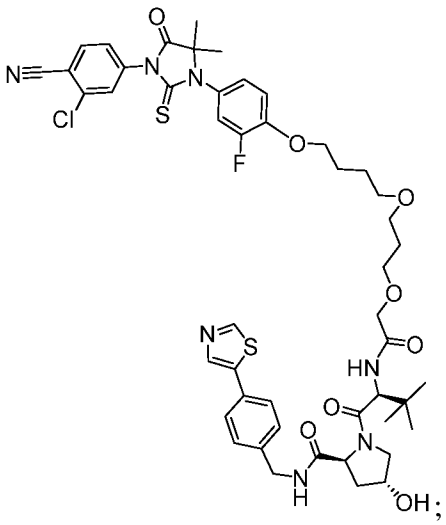

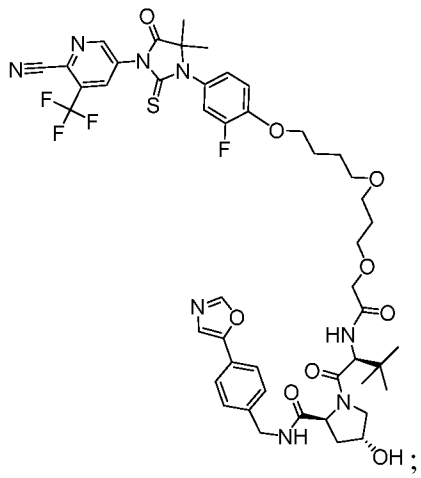

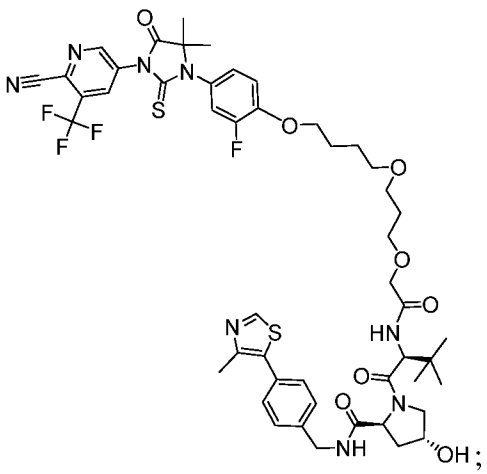

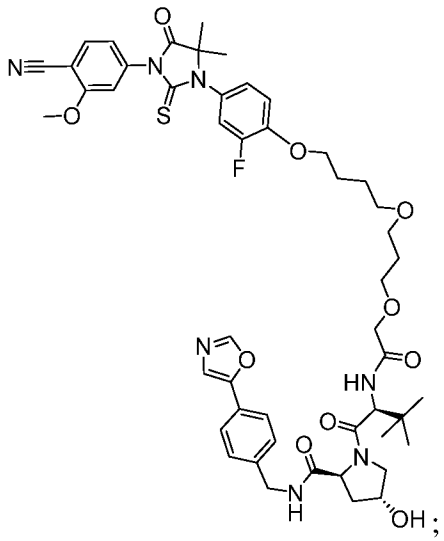

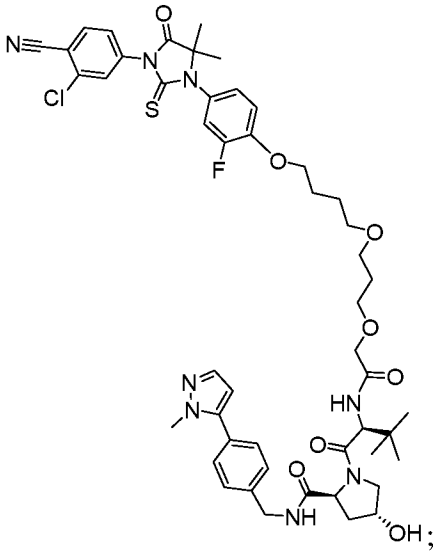

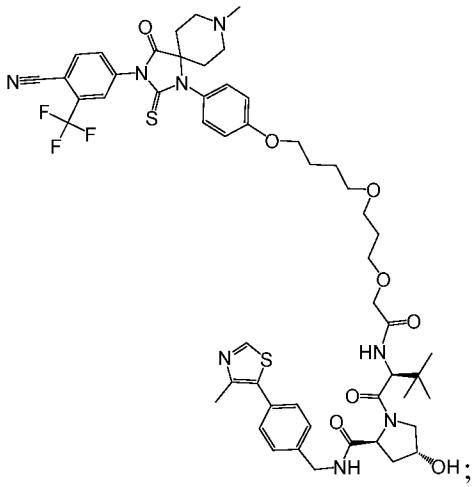

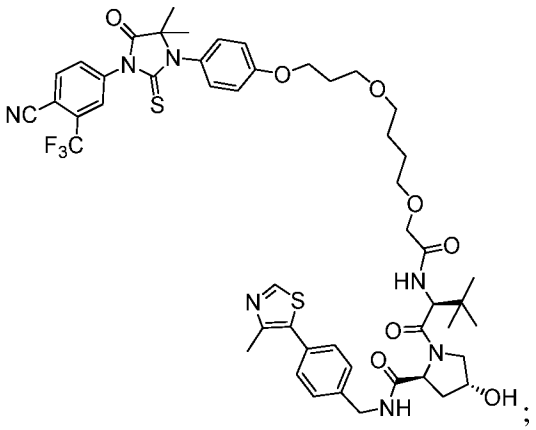

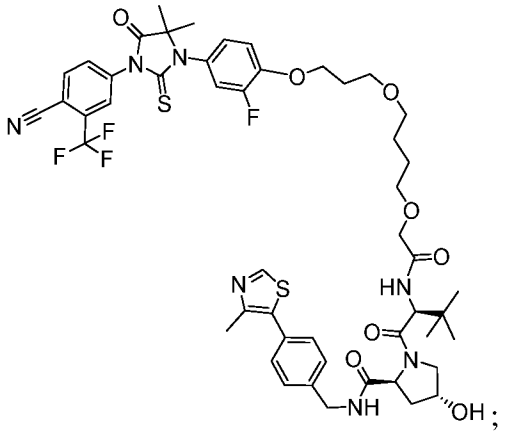

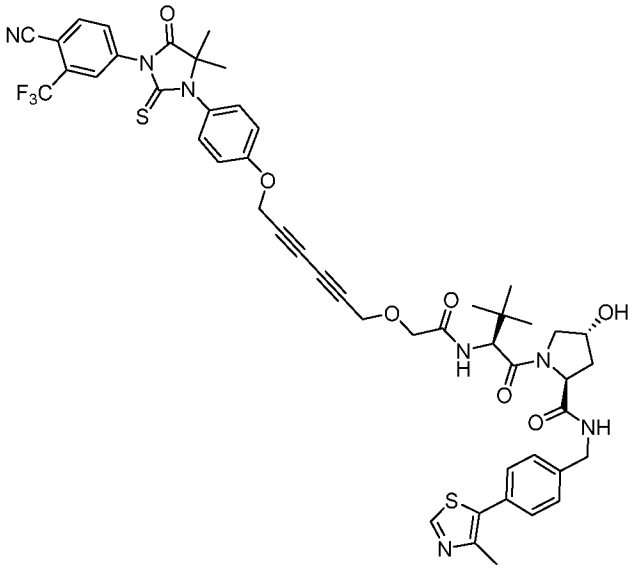

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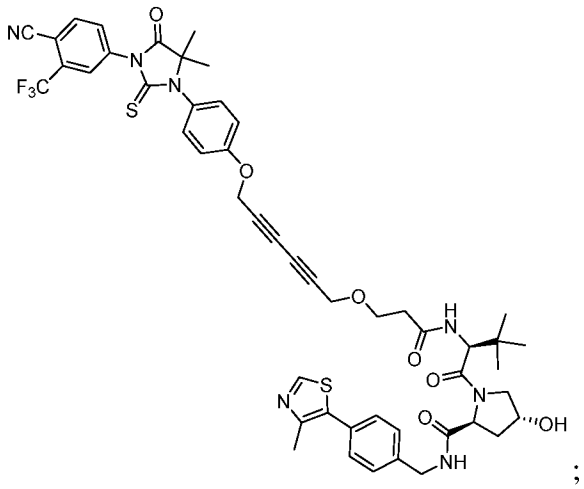

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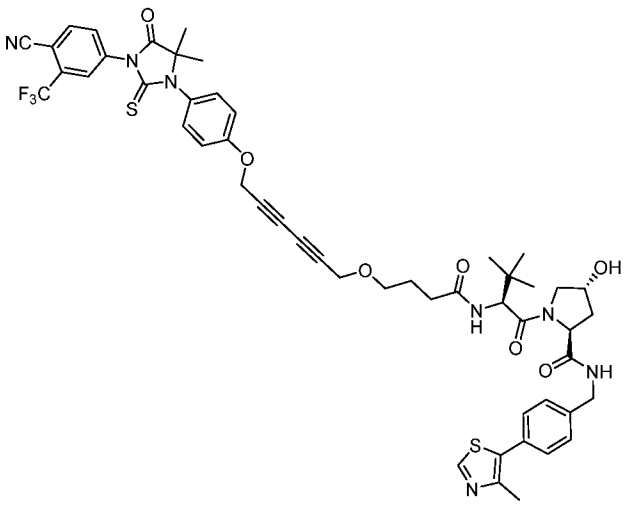
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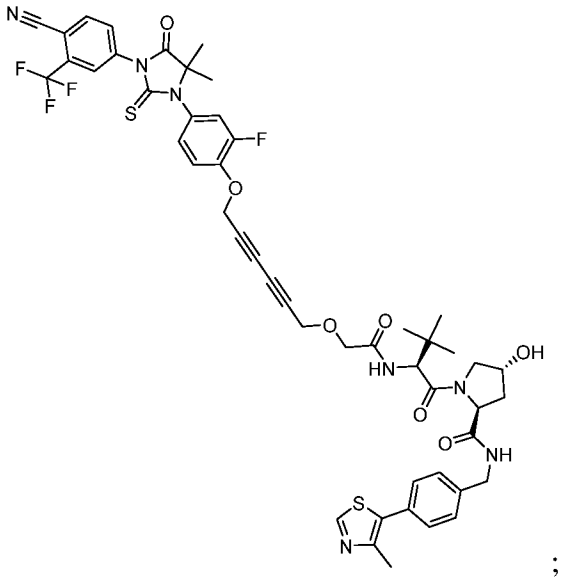
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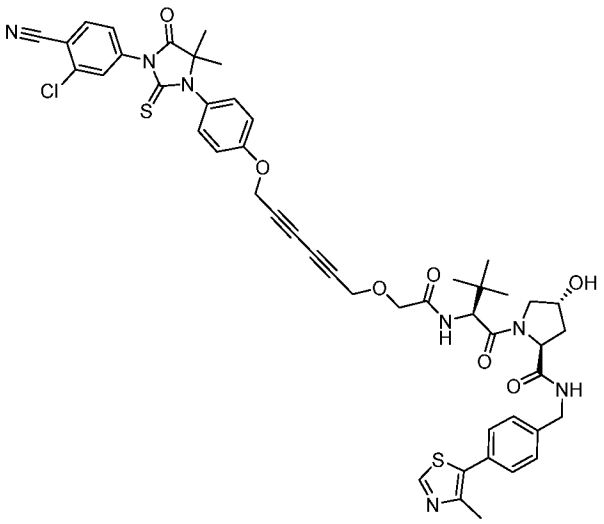
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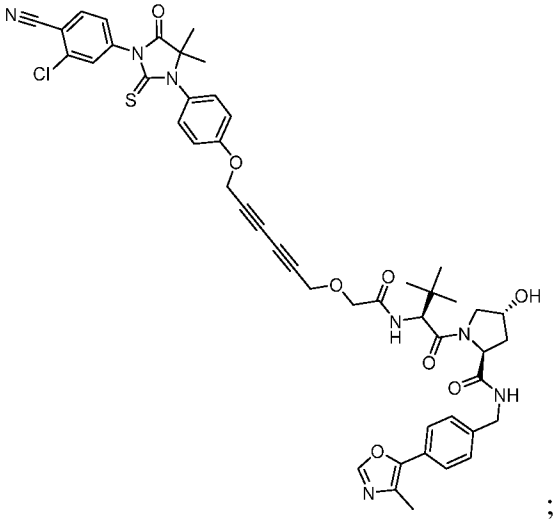
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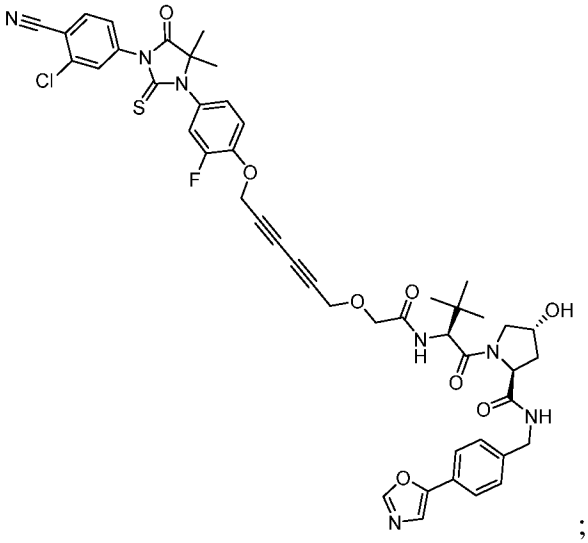
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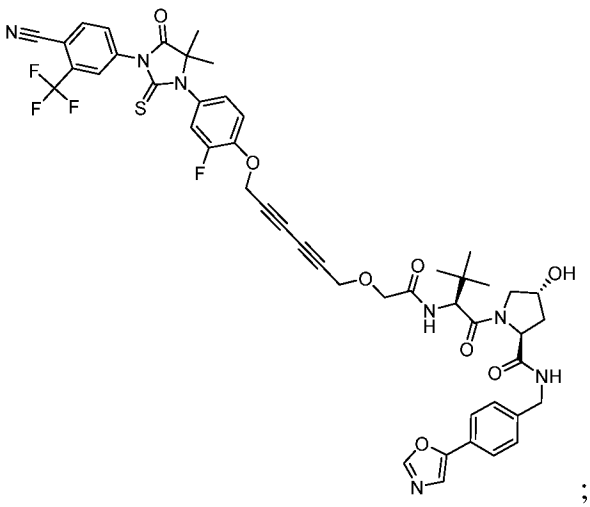
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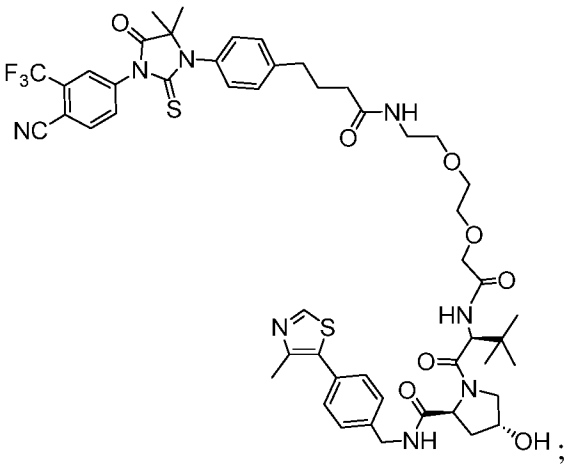
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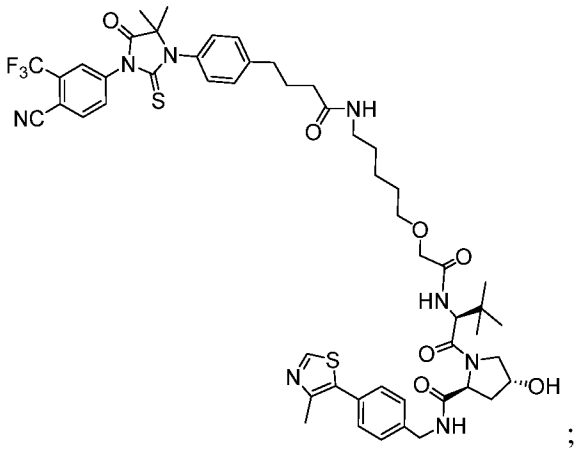
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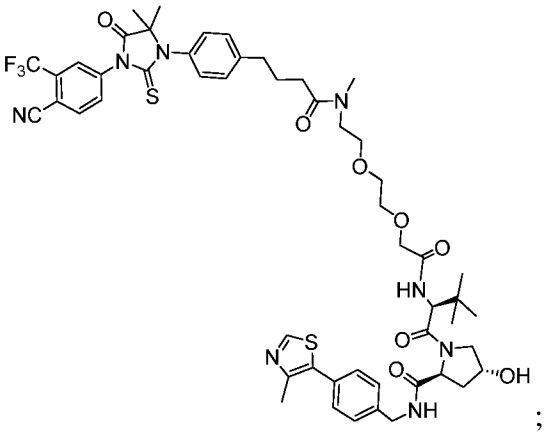
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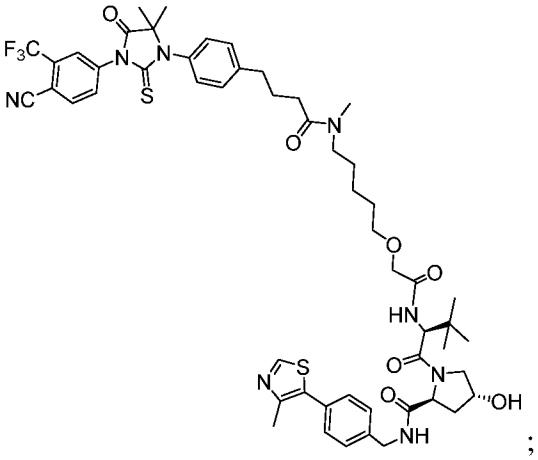
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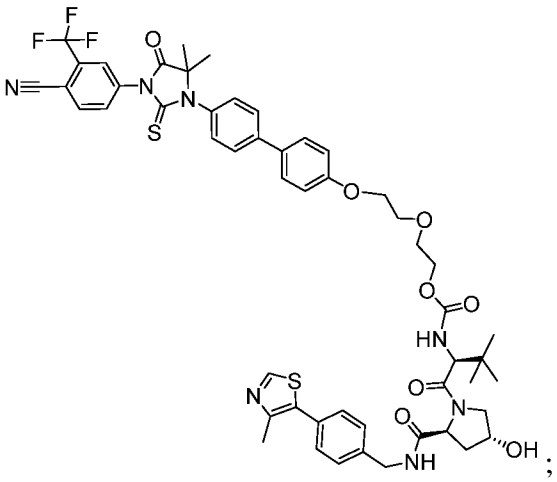
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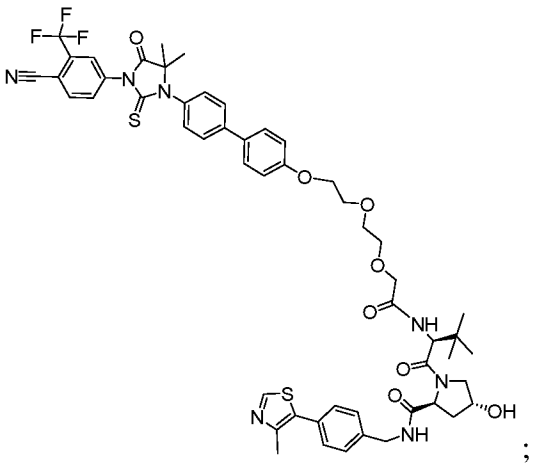
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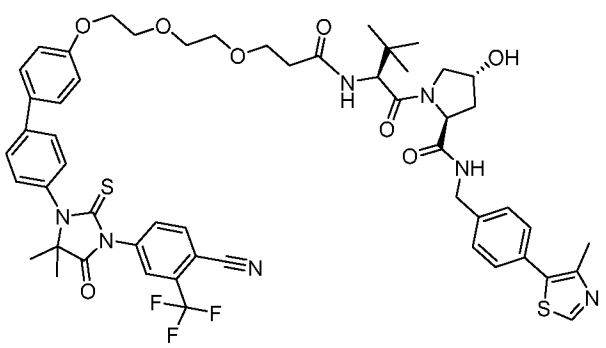
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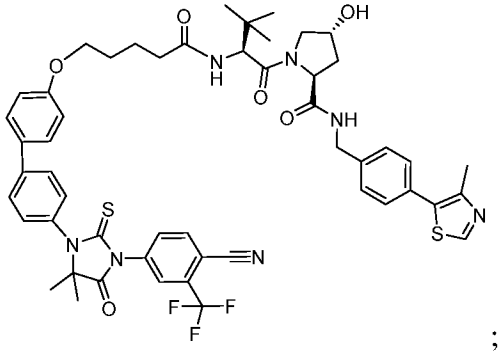
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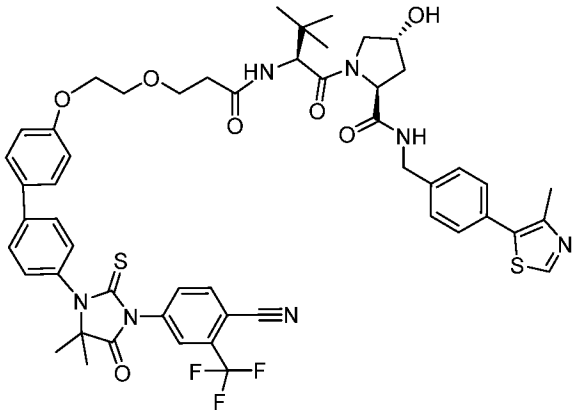
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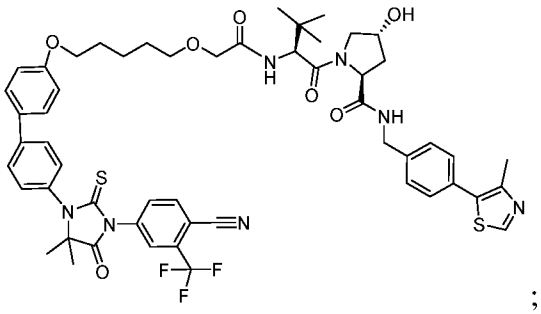
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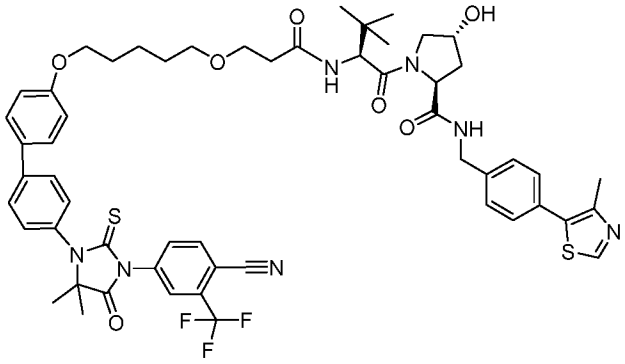
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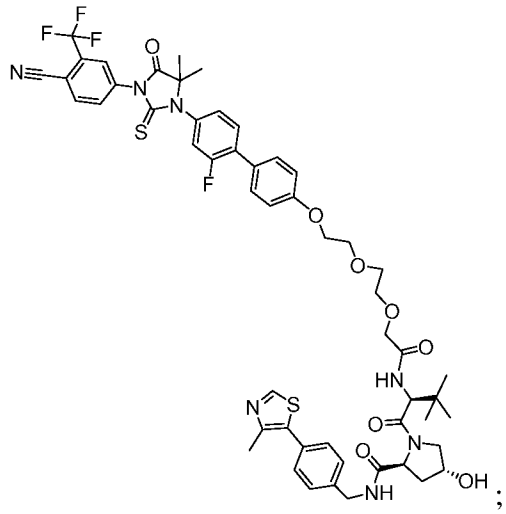
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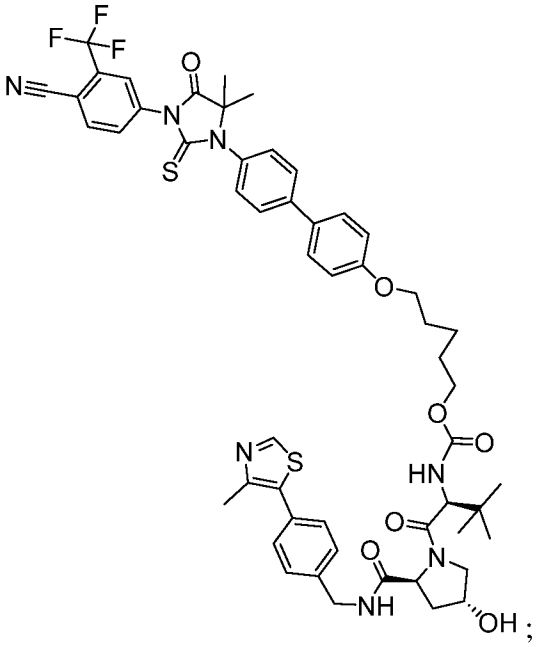

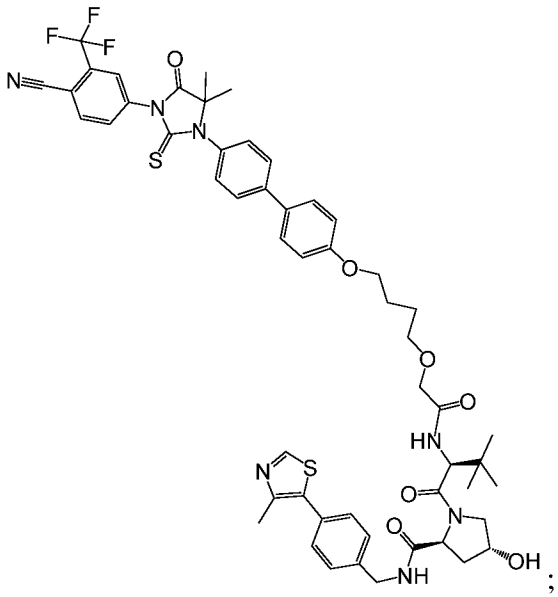

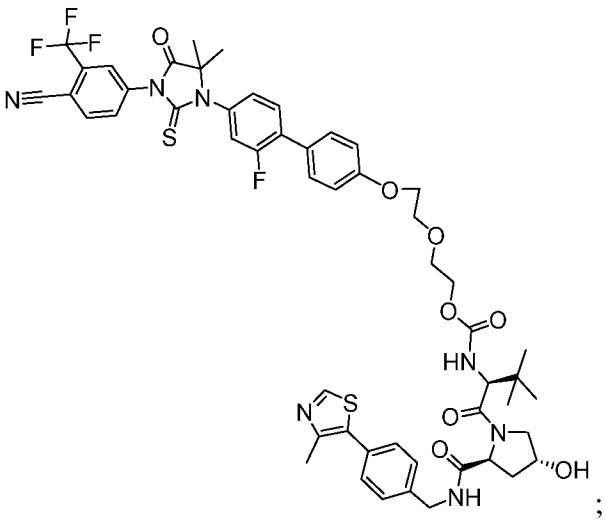

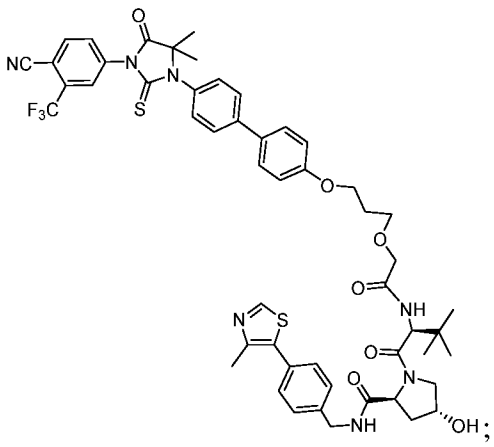

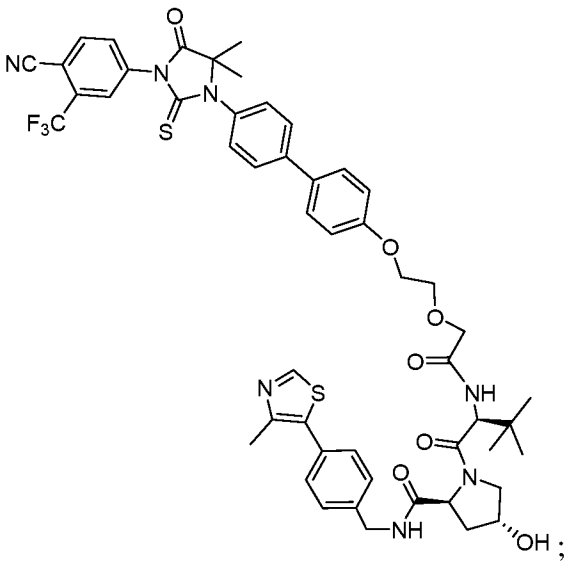

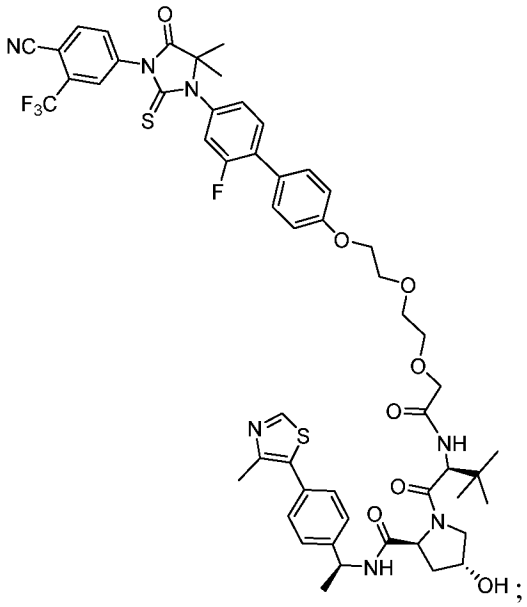

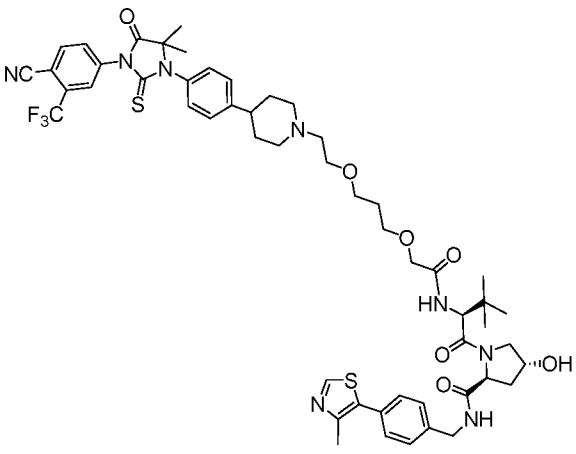

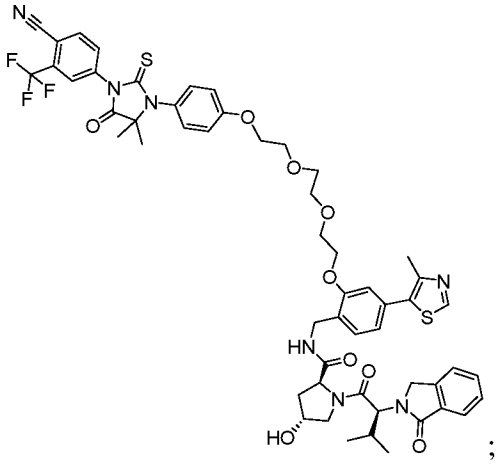

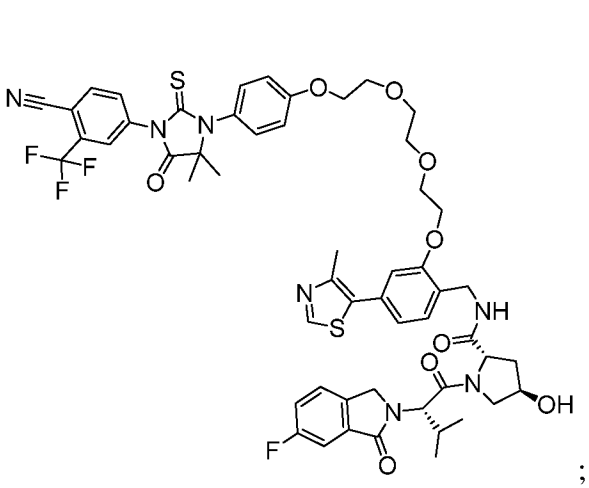
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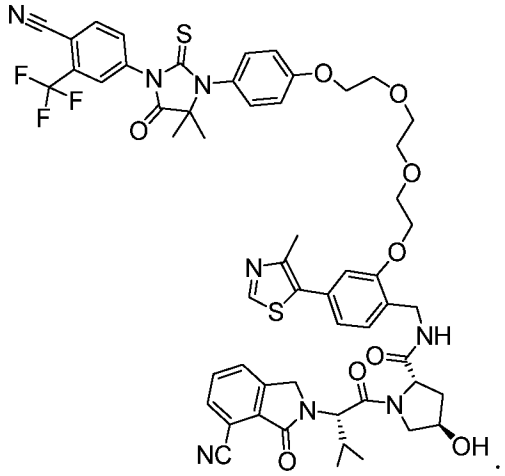
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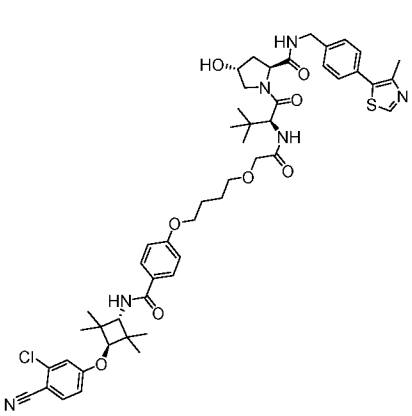
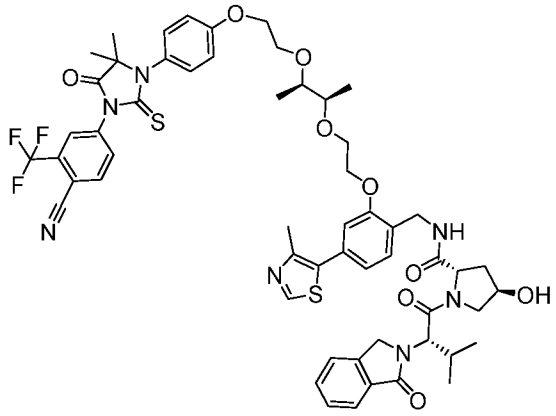



; and .

[0218] In another embodiment, the present invention provides a library of compounds. The library comprises more than one compound wherein each compound has a formula of ABM-L-ULM, wherein ULM is a ubiquitin pathway protein binding moiety (preferably, an E3 ubiquitin ligase moiety as otherwise disclosed herein), e.g., a VLM, and ABM is an AR protein binding moiety, wherein ABM is coupled (preferably, through a linker moiety) to ULM, and wherein the ubiquitin pathway protein binding moiety recognizes an ubiquitin pathway protein, in particular, an E3 ubiquitin ligase.

[0219] The present description includes, where applicable, the compositions comprising the pharmaceutically acceptable salts, in particular, acid or base addition salts of compounds of the present invention.

[0220] The term "pharmaceutically acceptable salt" is used throughout the specification to describe, where applicable, a salt form of one or more of the compounds described herein which are presented to increase the solubility of the compound in the gastic juices of the patient's gastrointestinal tract in order to promote dissolution and the bioavailability of the compounds.

Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic or organic bases and acids, where applicable. Suitable salts include those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium, magnesium and ammonium salts, among numerous other acids and bases well known in the pharmaceutical art. Sodium and potassium salts are particularly preferred as neutralization salts of the phosphates according to the present invention.

[0221] The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds useful in this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3 naphthoate)]salts, among numerous others.

[0222] Pharmaceutically acceptable base addition salts may also be used to produce pharmaceutically acceptable salt forms of the compounds or derivatives according to the present invention. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of the present compounds that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (eg., potassium and sodium) and alkaline earth metal cations (eg, calcium, zinc and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines, among others.

[0223] **Compositions**

[0224] In another aspect, the description provides a composition comprising a compound as described herein, including salts (acid or base), polymorphs, and prodrugs thereof, and a pharmaceutically acceptable carrier. In certain embodiments, the compositions are therapeutic or pharmaceutical compositions comprising an effective amount of a compound as described herein and a pharmaceutally acceptable carrier. In certain embodiments, the composition further comprises at least one of another bioactive agent, an anti-cancer agent, another bifunctional compound as described herein or a combination thereof.

[0225] The amount of compound in a pharmaceutical composition of the instant invention that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host and disease treated, the particular mode of administration. Generally, an amount between 0.1 mg/kg and 1000 mg/kg body weight/day of active ingredients is administered dependent upon potency of the agent. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds that exhibit large therapeutic indices are preferred. While compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects. The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

[0226] The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers and may also be administered in controlled-release formulations. Pharmaceutically acceptable carriers that may be used in these pharmaceutical compositions 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 prolamine 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.

[0227] The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount for the desired indication, without causing serious toxic effects in the patient treated. A preferred dose of the active compound for all of the herein-mentioned conditions is in the range from about 10 ng/kg to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient/patient per day. A typical topical dosage will range from 0.01-5% wt/wt in a suitable carrier.

[0228] The compound is conveniently administered in any suitable unit dosage form, including but not limited to one containing less than 1mg, 1 mg to 3000 mg, preferably 5 to 500 mg of active ingredient per unit dosage form. An oral dosage of about 25-250 mg is often convenient.

[0229] The active ingredient is preferably administered to achieve peak plasma concentrations of the active compound of about 0.00001-30 mM, preferably about 0.1-30 μM. This may be achieved, for example, by the intravenous injection of a solution or formulation of the active ingredient, optionally in saline, or an aqueous medium or administered as a bolus of the active ingredient. Oral administration is also appropriate to generate effective plasma concentrations of active agent.

[0230] The concentration of active compound in the drug composition will depend on absorption, distribution, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

[0231] If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

[0232] In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art.

[0233] Liposomal suspensions may also be pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound are then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

[0234] **Modes of Adminstration**

[0235] In any of the aspects or embodiments described herein, the therapeutic compositions comprising compounds described herein can be in any suitable dosage form configured to be delivered by any suitable route. For example, the compounds can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, including transdermally, in liquid, cream, gel, or solid form, rectally, nasally, buccally, vaginally or via an implanted reservoir or by aerosol form.

[0236] The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously.

[0237] The compounds as described herein may be administered in single or divided doses by the oral, parenteral or topical routes. Administration of the active compound may range

from continuous (intravenous drip) to several oral administrations per day (for example, Q.I.D.) and may include oral, topical, parenteral, intramuscular, intravenous, sub-cutaneous, transdermal (which may include a penetration enhancement agent), buccal, sublingual and suppository administration, among other routes of administration. Enteric coated oral tablets may also be used to enhance bioavailability of the compounds from an oral route of administration. The most effective dosage form will depend upon the pharmacokinetics of the particular agent chosen as well as the severity of disease in the patient.

[0238] Administration of compounds as sprays, mists, or aerosols for intra-nasal, intra-tracheal or pulmonary administration may also be used. Compounds as described herein may be administered in immediate release, intermediate release or sustained or controlled release forms. Sustained or controlled release forms are preferably administered orally, but also in suppository and transdermal or other topical forms. Intramuscular injections in liposomal form may also be used to control or sustain the release of compound at an injection site.

[0239] Sterile injectable forms of the compositions as 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. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1, 3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as Ph. Helv or similar alcohol.

[0240] The pharmaceutical compositions as described herein may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and

dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added. Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound or its prodrug derivative can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials are included as part of the composition.

[0241] The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a dispersing agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or enteric agents.

[0242] The active compound or pharmaceutically acceptable salt thereof can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

[0243] Alternatively, the pharmaceutical compositions as described herein may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient, which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[0244] The pharmaceutical compositions of this invention may also be administered topically. Suitable topical formulations are readily prepared for each of these areas or organs. Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-acceptable transdermal patches may also be used. For topical applications, the pharmaceutical compositions may be

formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. In certain preferred aspects of the invention, the compounds may be coated onto a stent which is to be surgically implanted into a patient in order to inhibit or reduce the likelihood of occlusion occurring in the stent in the patient.

[0245] Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[0246] For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with our without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

[0247] The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[0248] Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0249] It should also be understood that 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 or condition being treated.

[0250] A patient or subject in need of therapy using compounds as described herein can be treated by administering to the patient (subject) an effective amount of the compound including pharmaceutically acceptable salts, solvates or polymorphs, thereof optionally in a pharmaceutically acceptable carrier or diluent, either alone, or in combination with other known agents.

[0251] **Co-administration**

[0252] Disease states of conditions which may be treated using compounds or compositions according to the present description include, but not limited to, for example, cancer (e.g., prostate cancer), and Kennedy's disease. In certain embodiments, the therapeutic or pharmaceutical compositions comprise an effective amount of an additional biologically or bioactive active agent, e.g., an agent effective for the treatment of cancer, that is co-administered.

[0253] The term "coadministration" or "combination therapy" shall mean that at least two compounds or compositions are administered to the patient at the same time, such that effective amounts or concentrations of each of the two or more compounds may be found in the patient at a given point in time. Although compounds according to the present invention may be co-administered to a patient at the same time, the term embraces both administration of two or more agents at the same time or at different times, provided that effective concentrations of all coadministered compounds or compositions are found in the subject at a given time. In certain preferred aspects of the present invention, one or more of the present compounds described above, are coadministered in combination with at least one additional bioactive agent, especially including an anticancer agent. In particularly preferred aspects of the invention, the co-administration of compounds results in synergistic therapeutic, including anticancer therapy.

[0254] In another aspect, the description provides a composition comprising an effective amount of two or more of the PROTAC compounds as described herein, and a pharmaceutically acceptable carrier. In certain embodiments, the composition further comprises an effective or synergistic amount of another bioactive agent that is not a PROTAC compound.

[0255] Pharmaceutical compositions comprising combinations of an effective amount of at least one bifunctional compound according to the present invention, and one or more of the compounds otherwise described herein, all in effective amounts, in combination with a pharmaceutically effective amount of a carrier, additive or excipient, represents a further aspect of the present invention.

[0256] The term "bioactive agent" is used to describe an agent, other than the PROTAC compounds described herein, which is used in combination with the present compounds as an agent with biological activity to assist in effecting an intended therapy, inhibition and/or prevention/prophylaxis for which the present compounds are used. Preferred bioactive agents for use herein include those agents which have pharmacological activity similar to that for which the present compounds are used or administered and include for example, anti-cancer agents.

[0257] The term "additional anti-cancer agent" is used to describe an anti-cancer agent, which may be combined with PROTAC compounds according to the present description to treat cancer. These agents include, for example, everolimus, trabectedin, abraxane, TLK 286, AV-299, DN-101, pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, a FLT-3 inhibitor, an androgen receptor inhibitor, a VEGFR inhibitor, an EGFR TK inhibitor, an aurora kinase inhibitor, a PIK-1 modulator, a Bcl-2 inhibitor, an HDAC inhbitor, a c-MET inhibitor, a PARP inhibitor, a Cdk inhibitor, an EGFR TK inhibitor, an IGFR-TK inhibitor, an anti-HGF antibody, a PI3 kinase inhibitors, an AKT inhibitor, a JAK/STAT inhibitor, a checkpoint-1 or 2 inhibitor, a focal adhesion kinase inhibitor, a Map kinase kinase (mek) inhibitor, a VEGF trap antibody, pemetrexed, erlotinib, dasatanib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab, zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111, 131-I-TM-601, ALT-110, BIO 140, CC 8490, cilengitide, gimatecan, IL13-PE38QQR, INO 1001, IPdR$_1$ KRX-0402, lucanthone, LY317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311, romidepsin, ADS-100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, liposomal doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709, seliciclib; PD0325901, AZD-6244, capecitabine, L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1 H - pyrrolo[2,3- d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate,

camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrazole, exemestane, letrozole, DES(diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11, CHIR-258); 3-[5-(methylsulfonylpiperadinemethyl)- indolylj-quinolone, vatalanib, AG-013736, AVE-0005, the acetate salt of [D- Ser(Bu t) 6 ,Azgly 10] (pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu t)-Leu-Arg-Pro- Azgly-NH_2 acetate [$C_{59}H_{84}N_{18}Oi_4$ -$(C_2H_4O_2)_X$ where x = 1 to 2.4], goserelin acetate, leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714; TAK-165, HKI-272, erlotinib, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-166, GW-572016, Ionafarnib, BMS-214662, tipifarnib; amifostine, NVP-LAQ824, suberoyl analide hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib, KRN951 , aminoglutethimide, arnsacrine, anagrelide, L-asparaginase, Bacillus Calmette-Guerin (BCG) vaccine, adriamycin, bleomycin, buserelin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, diethylstilbestrol, epirubicin, fludarabine, fludrocortisone, fluoxymesterone, flutamide, gleevec, gemcitabine, hydroxyurea, idarubicin, ifosfamide, imatinib, leuprolide, levamisole, lomustine, mechlorethamine, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, octreotide, oxaliplatin, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, teniposide, testosterone, thalidomide, thioguanine, thiotepa, tretinoin, vindesine, 13-cis-retinoic acid, phenylalanine mustard, uracil mustard, estramustine, altretamine, floxuridine, 5-deooxyuridine, cytosine arabinoside, 6-mecaptopurine, deoxycoformycin, calcitriol, valrubicin, mithramycin, vinblastine, vinorelbine, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291 , squalamine, endostatin, SU5416, SU6668, EMD121974, interleukin-12, IM862, angiostatin, vitaxin, droloxifene, idoxyfene, spironolactone, finasteride, cimitidine, trastuzumab, denileukin diftitox,gefitinib, bortezimib, paclitaxel, cremophor-free paclitaxel, docetaxel, epithilone B, BMS- 247550, BMS-310705, droloxifene, 4-hydroxytamoxifen, pipendoxifene, ERA-923, arzoxifene, fulvestrant, acolbifene, lasofoxifene, idoxifene, TSE-424, HMR- 3339, ZK186619, topotecan, PTK787/ZK 222584, VX-745, PD 184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-23573, RAD001, ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684, LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, erythropoietin, granulocyte colony-

stimulating factor, zolendronate, prednisone, cetuximab, granulocyte macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-2a, pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L-asparaginase, lenalidomide, gemtuzumab, hydrocortisone, interleukin-11, dexrazoxane, alemtuzumab, all-transretinoic acid, ketoconazole, interleukin-2, megestrol, immune globulin, nitrogen mustard, methylprednisolone, ibritgumomab tiuxetan, androgens, decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, cortisone, editronate, mitotane, cyclosporine, liposomal daunorubicin, Edwina-asparaginase, strontium 89, casopitant, netupitant, an NK-1 receptor antagonist, palonosetron, aprepitant, diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone, methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, erythropoietin, epoetin alfa, darbepoetin alfa and mixtures thereof.

[0258] **Methods of Treatment**

[0259] In another aspect, the disclosure provides methods of modulating protein ubiquitination and degradation in a subject, e.g., a cell, a tissue, mammal, or human patient, the method comprising administering an effective amount of a PROTAC compound as described herein or a composition comprising an effective amount of the same to a subject, wherein the compound or composition comprising the same is effective in modulating protein ubquitination and degration of the protiein in the subject. In certain embodiments, the protein is androgen receptor (AR).

[0260] In certain embodiments, the description provides a method for regulating protein activity of the androgen receptor in a patient in need comprising administering to said patient an amount of a compound as described herein to a patient.

[0261] In still additional embodiments, the description provides a method of treating a disease state or condition in a patient wherein dysregulated protein activity is responsible for said disease state or condition, said method comprising administering to said patient an effective amount of a compound as described herein to said patient in order to regulate said protein activity in said patient. In certain embodiments, the protein is AR.

[0262] The terms “treat”, “treating”, and “treatment”, etc., as used herein, refer to any action providing a benefit to a patient for which the present compounds may be administered, including the treatment of any disease state or condition which is modulated through the protein

to which the present compounds bind. Disease states or conditions, including cancer, which may be treated using compounds according to the present invention are set forth hereinabove.

[0263] In another aspect, the disclosure provides methods of modulating AR protein ubiquitination and degradation in a subject, e.g., a cell, a tissue, mammal, or human patient, the method comprising administering an effective amount of a compound as described herein or a composition comprising an effective amount of the same to a subject, wherein the compound or composition comprising the same is effective in modulating AR protein ubquitination and degration of the protiein in the subject.

[0264] In another aspect, the disclosure provides methods of treating or ameliorating a symptom of a disease related to AR activity in a subject, e.g., a cell, a tissue, mammal, or human patient, the method comprising administering an effective amount of a compound as described herein or a composition comprising an effective amount of the same to a subject in need thereof, wherein the compound or composition comprising the same is effective in treating or ameliorating a symptom of a disease related to AR activity in the subject.

[0265] In another aspect, the description provides a composition, e.g., therapeutic composition, comprising a pharmaceutically acceptable carrier and an effective amount of at least one compound as described herein for treating a disease or disorder in a subject, the method comprising administering the composition to a subject in need thereof, wherein the compound is effective in treating or ameliorating at least one symptom of the disease or disorder. In certain embodiments, the composition comprises at least one compound from the examples in Tables 2-17.

[0266] In another aspect, the description provides the use of a compound as described herein in the preparation or manufacture of a medicament for use in treating a disease or disorder in a subject. In certain embodiments, the medicament comprises an effective amount of a compound as described herein and a pharmaceutically acceptable carrier. In additional embodiments, the medicament comprises an effective amount of at least one compound from the examples in Tables 2-17.

[0267] In certain embodiments, the disease or disorder is asthma, multiple sclerosis, cancer, prostate cancer, Kenney's disease, ciliopathies, cleft palate, diabetes, heart disease, hypertension, inflammatory bowel disease, mental retardation, mood disorder, obesity, refractive error, infertility, Angelman syndrome, Canavan disease, Coeliac disease, Charcot–Marie–Tooth

disease, Cystic fibrosis, Duchenne muscular dystrophy, Haemochromatosis, Haemophilia, Klinefelter's syndrome, Neurofibromatosis, Phenylketonuria, Polycystic kidney disease, (PKD1) or 4 (PKD2) Prader–Willi syndrome, Sickle-cell disease, Tay–Sachs disease, Turner syndrome. The method according to claim 48 wherein said cancer is squamous-cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinomas, and renal cell carcinomas, cancer of the bladder, bowel, breast, cervix, colon, esophagus, head, kidney, liver, lung, neck, ovary, pancreas, prostate, and stomach; leukemias; benign and malignant lymphomas, particularly Burkitt's lymphoma and Non-Hodgkin's lymphoma; benign and malignant melanomas; myeloproliferative diseases; sarcomas, including Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma, synovial sarcoma, gliomas, astrocytomas, oligodendrogliomas, ependymomas, gliobastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors, meningiomas, meningeal sarcomas, neurofibromas, and Schwannomas; bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, esophageal cancer, pancreatic cancer, stomach cancer, liver cancer, colon cancer, melanoma; carcinosarcoma, Hodgkin's disease, Wilms' tumor or teratocarcinomas. In certain embodiments, the disease to be treated is cancer, e.g., prostate cancer, or Kennedy's Disease. In a preferred embodiment, the subject is a human.

[0268] In another aspect, the disclosure provides methods of treating or ameliorating a symptom of a disease related to AR activity in a subject, e.g., a cell, a tissue, mammal, or human patient, the method comprising administering an effective amount of a compound as described herein or a composition comprising an effective amount of the same and an effective or synergistic amounf of another bioactive agent to a subject in need thereof, wherein the composition comprising the same is effective in treating or ameliorating a symptom of a disease related to AR activity in the subject. In certain embodiments, the disease to be treated is cancer, e.g., prostate cancer, or Kennedy's Disease. In a preferred embodiment, the subject is a human. In certain additional embodiments, the additional bioactive agent is an anti-cancer agent.

[0269] In alternative aspects, the present invention relates to a method for treating a disease state by degrading a protein or polypeptide through which a disease state or condition is modulated comprising administering to said patient or subject an effective amount of at least one compound as described hereinabove, optionally in combination with an additional bioactive

agent. The method according to the present invention may be used to treat a large number of disease states or conditions including cancer, by virtue of the administration of effective amounts of at least one compound described herein.

[0270] In another aspect, the disclosure provides methods for identifying the effects of the degradation of proteins of interest in a biological system using compounds according to the present invention.

[0271] **Kits**

[0272] In another aspect, the description provides kits comprising compounds or compositions as described herein. The kit may be promoted, distributed, or sold as a unit for performing the methods of the present invention. In addition, the kits of the present invention may preferably contain instructions which describe a suitable use. Such kits can be conveniently used, e.g., in clinical settings, to treat patients exhibiting symptoms of, e.g., cancer or Kennedy's Disease.

[0273] **EXAMPLES**

[0274] **General Chemistry – Analysis and Synthesis**

[0275] Unless otherwise noted, all materials/reagents were obtained from commercial suppliers and used without further purification. Reactions were monitored by LC-MS and/or thin layer chromatography (TLC) on silica gel 60 F_{254} (0.2mm) pre-coated aluminum foil or glass-backed and visualized using UV light. Flash chromatography (alternatively called "ISCO chromatography") was performed using an ISCO CombiFiash RF 75 PSI or equivalent with RediSep normal-phase silica gel cartridges. Preparative TLC was performed on Whatman LK6F Silica Gel 60A size 20x20 cm plates with a thickness of 1000 μm or equivalent.

[0276] ^{1}HNMR (300 or 400 MHz) and ^{13}CNMR (100.6 MHz) spectra were recorded on Bruker spectrometers at rt with TMS or the residual solvent peak as the internal standard. The line positions or multiples are given in (δ) and the coupling constants *(J)* are given as absolute values in Hertz (Hz). The multiplicities in ^{1}HNMR spectra are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br or broad (broadened).

[0277] Preparative HPLC purifications were performed on a Waters® UV-Directed Purification System equipped with 2545 Binary Gradient Module, 2767 Sample Manager and 2489 UV/Visible Detector, controlled by MassLynx V4.1 software. All purification work was completed using the following columns: Atlantis Prep T3 OBD Column, SunFire Prep C18 OBD

Column and XBridge Prep Phenyl OBD Column. The mobile phases were water (with 0.1%TFA or 0.01% NH_4HCO_3) and acetonitrile; all reagents used were of HPLC grade. The flow rate was 30ml/min. After the columns, a 1:1000 LC packings flow splitter allowed transfer of a small portion of the eluent into the UV detector. The electrospray source was set at 3.0 kV capillary voltage, 30 V conevoltage, 110°C source temperature, 350°C desolvation temperature, 600L/h desolvation gas flow, and 60L/h cone gas flow. For the analyzer, the multiplier was set at 550 for preparative tune method.

[0278] Analytical LC-MS data was collected on a Shimadzu LCMS-2020 with a mobile phase of 0.05% TFA in Acetonitrile (A) and 0.05% TFA in HPLC grade water (B); 0.1% FA in Acetonitrile (A) and 0.1% FA in HPLC grade water (B); Acetonitrile (A) and 5 mM ammonium bicarbonate in HPLC grade water (B).

[0279] Shimadzu LCMS-2020 equipped with LC-20AD or 30AD pumps, SPD-M20A PDA and Alltech 3300 ELSD. The system uses the following conditions for 2.0 min, 2.6 min, 3 min, 3.6 min, 5 min or 5.6 min run time.

[0280] 2.0 minute run: Kinetex XB-C 18 100A column, 2.6 μm, 3.0x 50 mm. The flow rate is 1.5 mL/min, the run time is 2.0 min, and the gradient profiles are 0.01 min 10% A, 1.10 min 100% A, 1.60 min 100% A, 1.70 min 10% A, 2.00 min 10% A.

[0281] 2.6 minute run: Shim-pack VP-ODS column, 2.2 μm, 3.0x 50 mm. The flow rate is 1.5 mL/min, the run time is 2.6 min, and the gradient profiles are 0.01 min 5% A, 1.20 min 100% A, 2.20 min 100% A, 2.30 min 5% A, 2.60 min 5% A.

[0282] 3.0 minute run: ACE UltraCore Super C18 column, 2.5 μm, 3.0x 50 mm. The flow rate is 1.5 mL/min, the run time is 3.0 min, and the gradient profiles are 0.01 min 10% A, 2.00 min 95% A, 2.60 min 95% A, 2.70 min 10% A, 3.00 min 10% A.

[0283] 3.6 minute run: Shim-pack VP-ODS column, 2.2 μm, 3.0x 50 mm. The flow rate is 1.5 mL/min, the run time is 3.6 min, and the gradient profiles are 0.01 min 5% A, 2.20 min 100% A, 3.20 min 100% A, 3.30 min 5% A, 3.60 min 5% A.

[0284] 5.0 minute run: ACE UltraCore Super C18 column, 2.5 μm, 3.0x 50 mm. The flow rate is 1.5 mL/min, the run time is 5.0 min, and the gradient profiles are 0.01 min 10% A, 4.00 min 60% A, 4.70 min 60% A, 4.80 min 10% A, 5.00 min 10% A.

[0285] 5.6 minute run: Shim-pack VP-ODS column, 2.2 µm, 3.0x 50 mm. The flow rate is 1.5 mL/min, the run time is 5.6 min, and the gradient profiles are 0.01 min 5% A, 3.00 min 50% A, 5.00 min 50% A, 5.20 min 5% A, 5.60 min 5% A

[0286] Alternatively, analytical LC-MS data was collected on Agilent infinity 1260 LC, Agilent 6230 TOF mass spectrometer. The analysis is conducted on a Poroshell 120 EC C18 column (50mm x 3.0mm internal diameter 2.7µm packing diameter) at 45°C.

[0287] The solvents employed are:

[0288] A = 0.1% v/v solution of formic acid in water.

[0289] B = 0.1% v/v solution of formic acid in acetonitrile.

[0290] The gradient employed are as follows:

[0291] **Table 1. Exemplary Column Gradients.**

Time (minutes)	Flow Rate (mL/min)	% A	% B
0	1	95	5
0.5	1	95	5
3.0	1	1	99
4.0	1	1	99
4.1	1	95	5
4.5	1	95	5

[0292]

[0293] The UV detection is an averaged signal from wavelength of 210nm to 350nm and mass spectra are recorded on a mass spectrometer using positive mode electrospray ionization.

[0294] Unless otherwise noted, all compounds were prepared with LC-MS purity >95%.

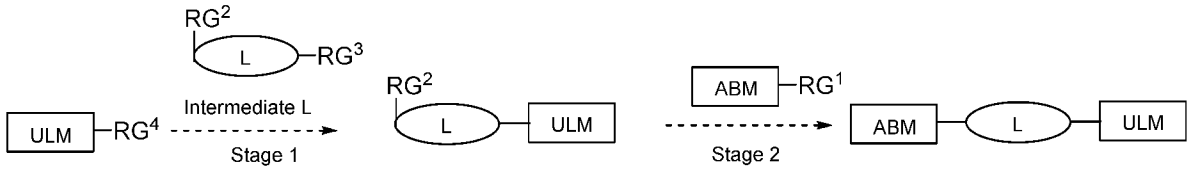
[0295] **Chemical Synthesis**

[0296] A PROTAC of ABM-L-ULM, or their pharmaceutically acceptable salts, polymorphic forms, prodrugs, solvate forms and isotope containing derivatives thereof, may be prepared by the general approaches described below (scheme 3-4), together with synthetic methods known in the art of organic chemistry, or modifications and derivatizations that are familiar to those of ordinary skill in the art.

[0297] Scheme 3:

Scheme 3

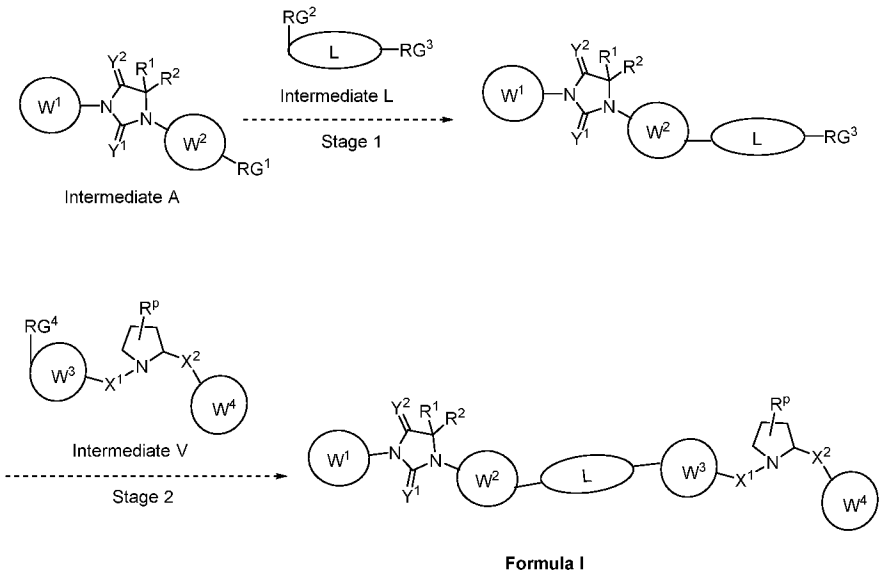
[0298] Scheme 4:



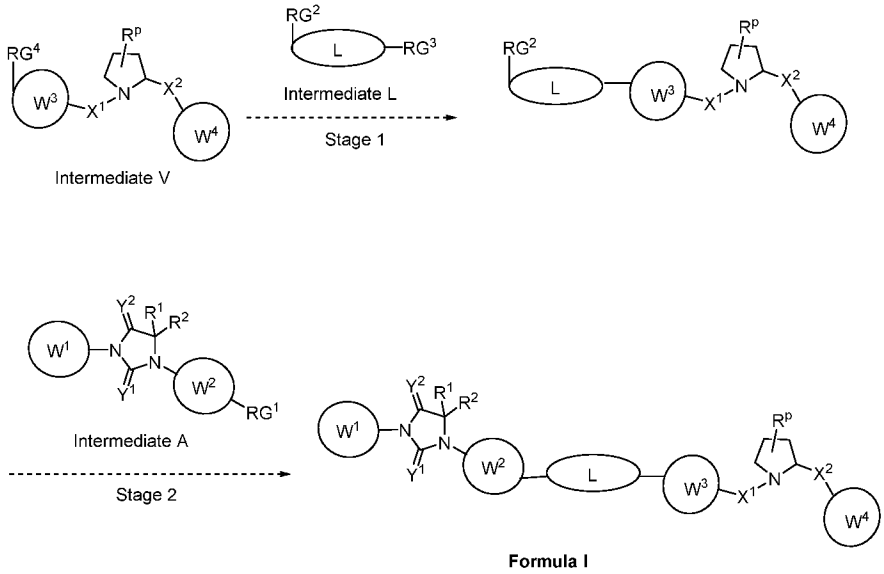
Scheme 4

[0299] More specifically, The compounds of the Formula I, or their pharmaceutically acceptable salts, may be prepared by the general approaches described below (scheme 5-6), together with synthetic methods known in the art of organic chemistry, or modifications and derivatizations that are familiar to those of ordinary skill in the art.

[0300] Scheme 5:



Scheme 5



Scheme 6

[0301] Scheme 6:

[0302] In schemes 3-6, L, ABM, ULM groups, W^1, W^2, W^3, W^4, X^1, X^2, Y^1, Y^2, R^1, R^2, and R^P are as define above. RG^1, RG^2, RG^3 and RG^4 are moieties with suitable reacting groups that would be necessary to enable the synthetic chemistry to connect intermediate A, intermediate L and intermediate V together into PROTAC compounds of Formula I via covalent bond formation chemistries. These chemistries, depends on specific reacting groups, include but not limited to, amide formation, ester formation, carbamate formation, urea formation, ether formation, amine formation and various C-C, C=C bond formation. The stage 1 and stage 2 transformations in scheme 5 and scheme 6 may involve 1 or multiple synthetic steps. These are routine methods known in the art such as those methods disclosed in standard reference books such as the *Compendium of Organic Synthetic Methods*, Vol. I-VI (Wiley-lnterscience); or the *Comprehensive Organic Transformations*, by R.C. Larock (Wiley-lnterscience). Unless otherwise indicated, the substituents in the schemes are defined as above. Isolation and purification of the products is accomplished by standard procedures, which are known to a chemist of ordinary skill.

[0303] In certain examples, for the chemistry described in schemes 3-6, RG^1 is a moiety with a suitable nucleophile such as -OH and RG^2 is a moiety with a suitable leaving group such as halogen, -OMs, or –OTs. In a typical procedure, a RG^1 containing intermediate is reacted with a RG^2 containing intermediate in a suitable solvent. Suitable solvents include, but are not limited

to, water, ethers such as THF, glyme, and the like; chlorinated solvents such as DCM, 1,2-dichloroethane (DCE) or CHCI3 and the like, toluene, benzene and the like, DMF, DMSO, MeCN. If desired, mixtures of these solvents are used. A base may be added to the reaction to facilitate the reaction. Suitable bases include, but are not limited to, Cs_2CO_3, K_2CO_3, and the like. The above process may be carried out at temperatures between about -78 °C and about 150 °C. Preferably, the reaction is carried out between about 20 °C and about 120 °C.

[0304] In another example, chemistry described in in schemes 3-6, RG^3 is a moiety contains a –COOH group and RG^4 is a moiety contains a suitable amine group. In a typical procedure, a RG^3 containing intermediate is reacted with a RG^4 containing intermediate in a suitable solvent in the presence of a suitable amide coupling reagent. Suitable solvents include, but are not limited to, water, ethers such as THF, glyme, and the like; chlorinated solvents such as DCM, 1,2-dichloroethane (DCE) or $CHCl_3$ and the like, toluene, benzene and the like, DMF, DMSO, MeCN. If desired, mixtures of these solvents are used. In this case, the preferred solvents are DMF or DCM. A suitable amide coupling reagent include, but are not limited to, DCC, EDC, HATU, HBTU, PyBOP and the like. A base is often added to the reaction. Suitable bases include, but are not limited to, TEA, DIPEA, and the like. The above process may be carried out at temperatures between about -78 °C and about 150 °C. Preferably, the reaction is carried out between about 0 °C and about 100 °C.

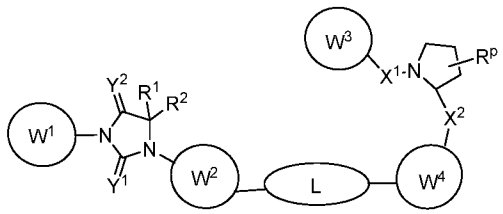
[0305] Although not explicitly shown in schemes 3-6, a chemist of ordinary skill would realize that during any of the synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This can be achieved by means of conventional protecting groups, such as those described in T.W. Greene, Protective Groups in Organic Chemistry, John Wiley & Sons (1981); T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons (1991), and T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1999, which are hereby incorporated by reference in their entireties.

[0306] When a general or exemplary synthetic procedure is referred to, one skilled in the art can readily determine the appropriate reagents, if not indicated, extrapolating from the general or exemplary procedures. Some of the general procedures are given as examples for preparing specific compounds. One skilled in the art can readily adapt such procedures to the synthesis of other compounds. Representation of an unsubstituted position in structures shown or

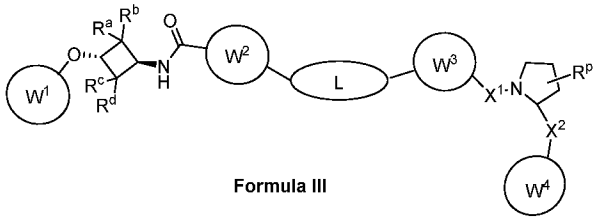
referred to in the general procedures is for convenience and does not preclude substitution as described elsewhere herein. For specific groups that can be present, either as R groups in the general procedures or as optional substituents not shown, refer to the descriptions in the remainder of this document, including the claims, summary and detailed description.

[0307] The process to produce compounds of the present invention is preferably carried out at about atmospheric pressure although higher or lower pressures can be used if desired. Substantially equimolar amounts of reactants are preferably used although higher or lower amounts can also be used.

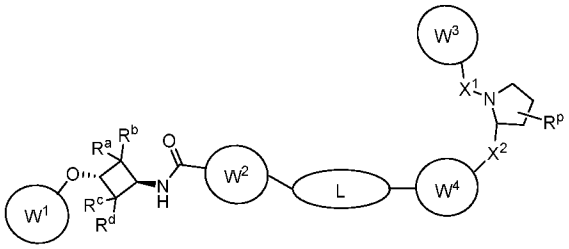
[0308] The compounds of Formulae II-IV (below), or their pharmaceutically acceptable salts, may be prepared by the methods similar to chemistry illustrated above for synthesis of compounds of Formula I (scheme 3-6), together with synthetic methods known in the art of organic chemistry, or modifications and derivatizations that are familiar to those of ordinary skill in the art:



Formula II ;



Formula III ; and



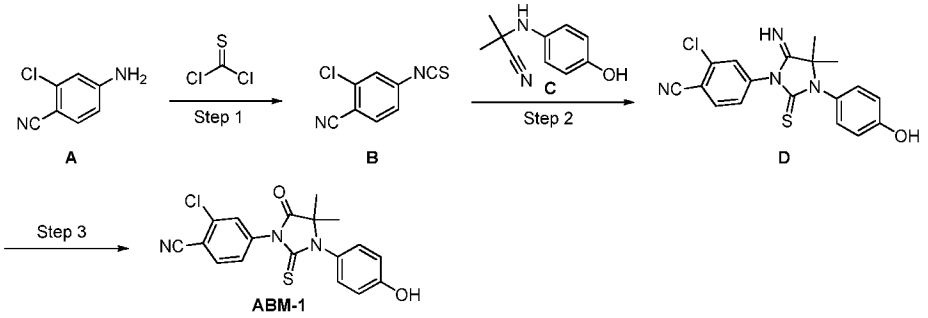
Formula IV .

[0309] For compounds of Formulae II-IV, L, ABM, ULM groups, W^1, W^2, W^3, W^4, X^1, X^2, Y^1, Y^2, R^1, R^2, R^P, R^a, R^b, R^c and R^d are as define above.

[0310] In certain embodiments, ABM compounds are active without forming bifunctional compounds of formular II-IV.

[0311] **Synthesis of ABM Moieties**

[0312] **ABM-1: 2-chloro-4-(3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)benzonitrile**



[0313]

[0314] Step 1: Synthesis of 2-chloro-4-isothiocyanatobenzonitrile (**B**).

[0315] To a stirred solution of 4-amino-2-chlorobenzonitrile (**A**, 1 g, 6.55 mmol) in dichloromethane (9 mL) was added sodium bicarbonate (2.21 g, 26.31 mmol) and water (9 mL). The resulting mixture was cooled to 0 °C, to which thiophosgene (817 mg, 7.11 mmol) was added in drop wise in 30 min at 0 °C. The resulting mixture was then warmed up to rt and stirred at rt for 1 h. The reaction mixture was diluted with dichloromethane (200 mL), washed with brine (50 mL x 2), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue. The residue was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v: v = 1: 30)) to give desired product (yield: 71%) ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.0 Hz, 1H), 7.38 (s, 1H), 7.28 (m, 1H);

[0316] Step 2: Synthesis of 2-chloro-4-[3-(4-hydroxyphenyl)-5-imino-4, 4-dimethyl-2-sulfanylideneimidazolidin-1-yl]benzonitrile (**D**).

[0317] To a stirred solution of 2-chloro-4-isothiocyanatobenzonitrile (**B**, 399 mg, 2.05 mmol) in toluene (5 mL) was added 2-[(4-hydroxyphenyl)amino]-2-methylpropanenitrile (**C**, 300 mg, 1.70 mmol) and 4-dimethylaminopyridine (312 mg, 2.55 mmol). The resulting solution was then heated in an oil bath to 100 °C and stirred at the same temperature for 16h. LC-MS indicated formation of the desired product. The reaction mixture was concentrated under vacuum to give a crude reside which was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v: v =1:1)) to give desired product (yield: 48%) as a brown solid. LC-MS (ES$^+$): m/z 370.95 [MH$^+$], t_R =0.74 min (2.0 minute run);

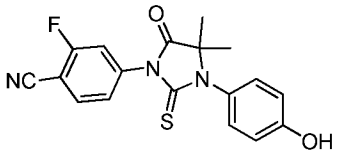
[0318] Step 3: Synthesis of 2-chloro-4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo- 2-sulfanylideneimidazolidin-1-yl]benzonitrile (**ABM-1**).

[0319] To a stirred solution of 2-chloro-4-[3-(4-hydroxyphenyl)-5-imino-4, 4-dimethyl-2-sulfanylideneimidazolidin-1-yl]benzonitrile (**D**, 300 mg, 0.81 mmol) in methanol (6 mL) was added aqueous hydrogen chloride (2N, 3.0 mL). The resulting solution was then heated in an oil

bath to 100 °C and stirred at the same temperature for 2h. The reaction mixture was diluted with water (30 mL), extracted with ethyl acetate (60 mL x 3), washed with water (50 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to give titled product (yield: 93%) as a yellow solid, which was used for the next step without any further purifications. LC-MS (ES^+): *m/z* 372.00 [MH^+], t_R =0.97 min (2.0 minute run).

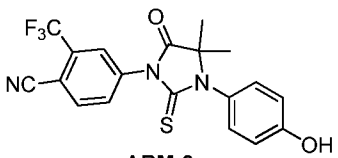
[0320] Unless otherwise noted, the following intermediates and their analogs (for examples, but not limited to, analogs with substitutions such as halogens) were synthesized according to similar procedures described above for the synthesis of **ABM-1**, by utilizing corresponding starting materials and reagents.

[0321] **ABM-2: 2-fluoro-4-(3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)benzonitrile:**



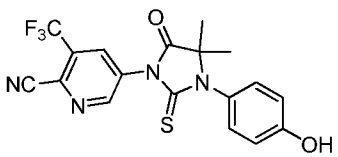
[0322] **ABM-2** .

[0323] **ABM-3: 4-(3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile:**



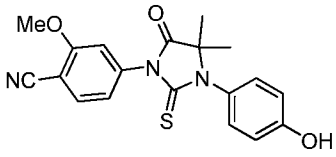
[0324] **ABM-3** .

[0325] **ABM-4: 5-(3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-3-(trifluoromethyl)picolinonitrile:**



[0326] **ABM-4** .

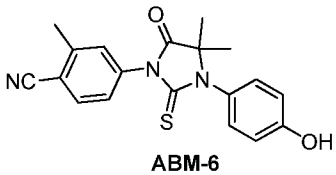
[0327] **ABM-5: 4-(3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-methoxybenzonitrile:**



ABM-5

[0328] .

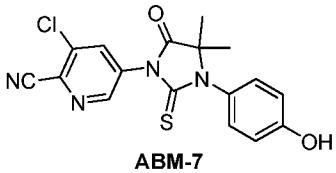
[0329] **ABM-6: 4-(3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-methylbenzonitrile:**



ABM-6

[0330] .

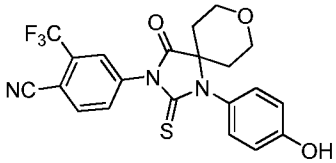
[0331] **ABM-7: 3-chloro-5-(3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)picolinonitrile:**



ABM-7

[0332] .

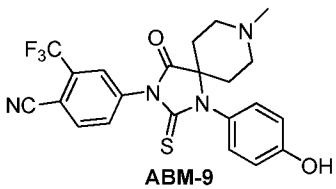
[0333] **ABM-8: 4-(1-(4-hydroxyphenyl)-4-oxo-2-thioxo-8-oxa-1,3-diazaspiro[4.5]decan-3-yl)-2-(trifluoromethyl)benzonitrile:**



ABM-8

[0334] .

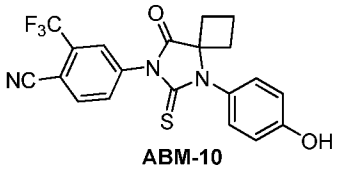
[0335] **ABM-9: 4-(1-(4-hydroxyphenyl)-8-methyl-4-oxo-2-thioxo-1,3,8-triazaspiro[4.5]decan-3-yl)-2-(trifluoromethyl)benzonitrile:**



ABM-9

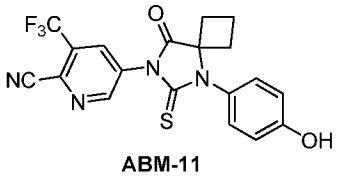
[0336] .

[0337] **ABM-10: 4-(5-(4-hydroxyphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-7-yl)-2-(trifluoromethyl)benzonitrile**

[0338] 

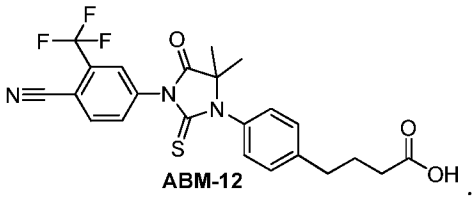
ABM-10.

[0339] **ABM-11: 5-(5-(4-hydroxyphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-7-yl)-3-(trifluoromethyl)picolinonitrile:**

[0340] 

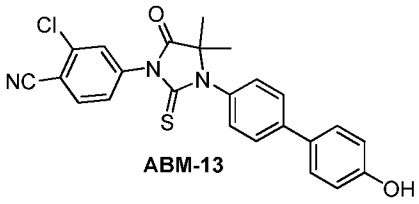
ABM-11.

[0341] **ABM-12: 4-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenyl)butanoic acid:**

[0342] 

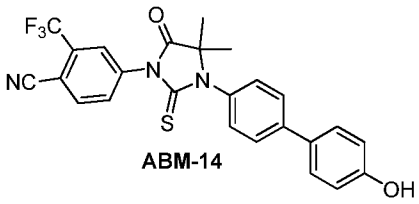
ABM-12.

[0343] **ABM-13: 2-chloro-4-(3-(4'-hydroxybiphenyl-4-yl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)benzonitrile:**

[0344] 

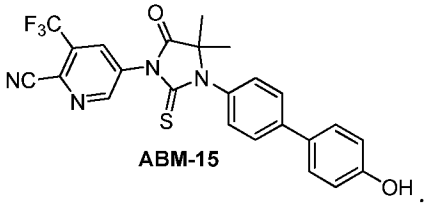
ABM-13.

[0345] **ABM-14: 4-(3-(4'-hydroxybiphenyl-4-yl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile:**

[0346] 

ABM-14.

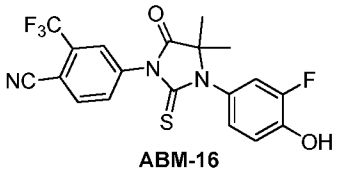
[0347] **ABM-15: 5-(3-(4'-hydroxybiphenyl-4-yl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-3-(trifluoromethyl)picolinonitrile:**



ABM-15

[0348]

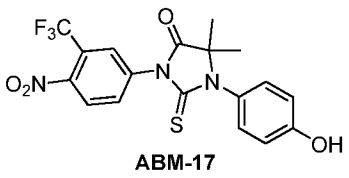
[0349] **ABM-16: 4-(3-(3-fluoro-4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile:**



ABM-16

[0350]

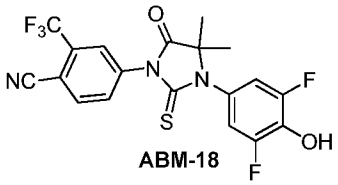
[0351] **ABM-17: 1-(4-hydroxyphenyl)-5,5-dimethyl-3-(4-nitro-3-(trifluoromethyl)phenyl)-2-thioxoimidazolidin-4-one:**



ABM-17

[0352]

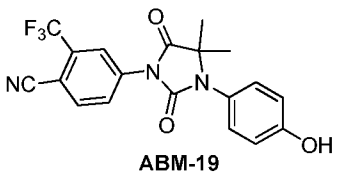
[0353] **ABM-18: 4-(3-(3,5-difluoro-4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile:**



ABM-18

[0354]

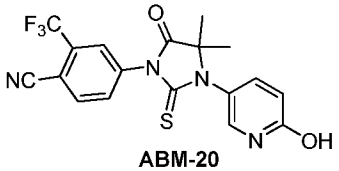
[0355] **ABM-19: 4-(3-(4-hydroxyphenyl)-4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile:**



ABM-19

[0356]

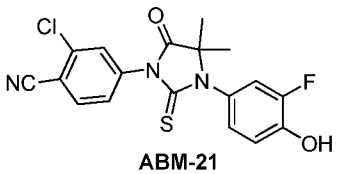
[0357] **ABM-20: 4-(3-(6-hydroxypyridin-3-yl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile:**



ABM-20

[0358]

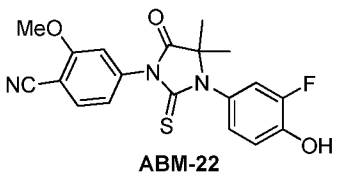
[0359] **ABM-21: 2-chloro-4-(3-(3-fluoro-4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)benzonitrile:**



ABM-21

[0360]

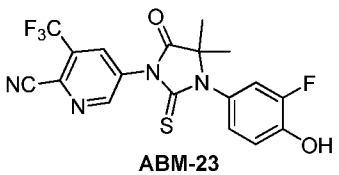
[0361] **ABM-22: 4-(3-(3-fluoro-4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-methoxybenzonitrile:**



ABM-22

[0362]

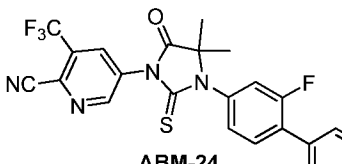
[0363] **ABM-23: 5-(3-(3-fluoro-4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-3-(trifluoromethyl)picolinonitrile:**



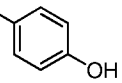
ABM-23

[0364]

[0365] **ABM-24: 5-(3-(2-fluoro-4'-hydroxybiphenyl-4-yl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-3-(trifluoromethyl)picolinonitrile:**

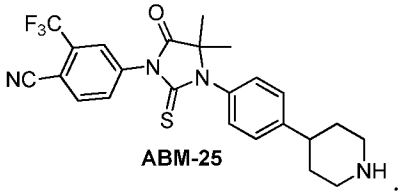


ABM-24



[0366]

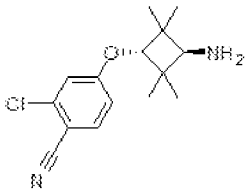
[0367] **ABM-25: 4-(4,4-dimethyl-5-oxo-3-(4-(piperidin-4-yl)phenyl)-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile:**



ABM-25

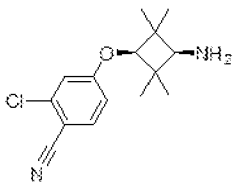
[0368]

[0369] **ABM-26: trans-2-Chloro-4-[3-amino-2,2,4,4-tetramethylcyclobutoxy]benzonitrile**.



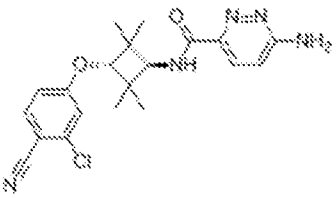
[0370]

[0371] **ABM-27: cis-2-Chloro-4-[3-amino-2,2,4,4-tetramethylcyclobutoxy]benzonitrile**



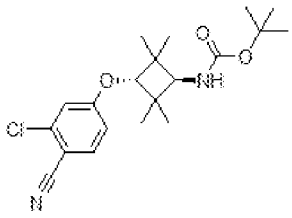
[0372]

[0373] **ABM-28: trans 6-Amino-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]pyridazine-3-carboxamide**



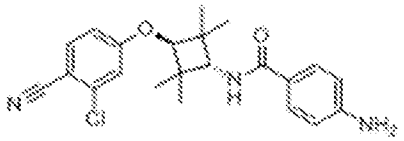
[0374]

[0375] **ABM-29: trans tert-Butyl N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamate**.



[0376]

[0377] **ABM-30: trans 4-Amino-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide**

[0378] 

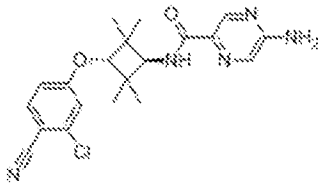
[0379] Step 1: Synthesis of *tert*-butyl (4-((*trans*-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)carbamate.

[0380] A suspension of 4-((*tert*-butoxycarbonyl)amino)benzoic acid (1.50 g, 6.34 mmol) in methylene dichloride (40 mL) was charged with *N*,*N*-diisopropylethylamine (3.30 mL, 19.0 mmol), followed by 4-(*trans*-3-amino-2,2,4,4-tetramethylcyclobutoxy)-2-chlorobenzonitrile hydrochloride (2.0 g, 6.34 mmol). The mixture was stirred for several minutes and then charged with HATU (2.41 g, 6.34 mmol). The reaction mixture was allowed to stir at room temperature for 2 h. The mixture was diluted with methylene dichloride (40 mL), washed with aqueous 1N HCl (2 x), saturated aqueous sodium bicarbonate (2 x), brine, and dried over anhydrous Na_2SO_4. The crude product was used in next step;

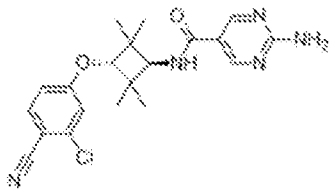
[0381] Step 2: synthesis of trans 4-Amino-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide.

[0382] 4M HCl in Dioxane (1.38 mL, 40.0 mmol) was added to a pre-mixed solution of *tert*-butyl (4-((*trans*-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)carbamate (2.00 g, 4.01 mmol) in MeOH (2 mL) and left to stir at rt for 1 h till completion. The reaction mixture was concentrated in vacuo to a solid, which was dissolved with 5% MeOH in DCM. The organic layer was washed with sodium bicarbonate (2 x), filtered through a Biotage Universal Phase Separator and then concentrated in vacuo to a solid. The crude product was recrystallized from EtOH/Heptanes to afford the desired product as a white solid, 1.2 g, 75% yield. ^{1}H NMR (400 MHz, METHANOL-d4) δ 7.72 (d, J = 8.80 Hz, 1H), 7.61 (d, J = 8.61 Hz, 2H), 7.13 (d, J = 2.35 Hz, 1H), 6.98 (dd, J = 2.45, 8.71 Hz, 1H), 6.69 (d, J = 8.61 Hz, 2H), 4.28 (s, 1H), 4.12 (s, 1H), 1.27 (s, 6H), 1.22 (s, 6H). LC-MS (ES+): *m/z* 398.16/400.15 [MH^+].

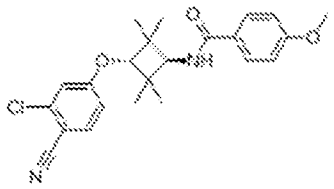
[0383] **ABM-31: trans 5-Amino-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]pyrazine-2-carboxamide**

[0384] 

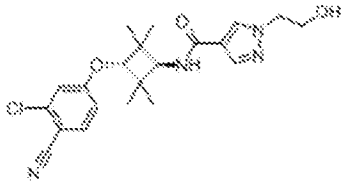
[0385] **ABM-32: trans 2-Amino-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]pyrimidine-5-carboxamid**

[0386] 

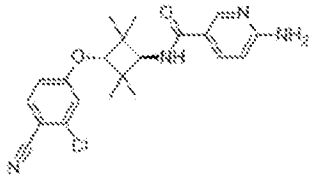
[0387] **ABM-33: 4-Methoxy-N-[(1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide**

[0388] 

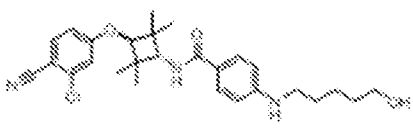
[0389] **ABM-34: trans 1-(2-Hydroxyethyl)-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]-1H-pyrazole-4-carboxamide**

[0390] 

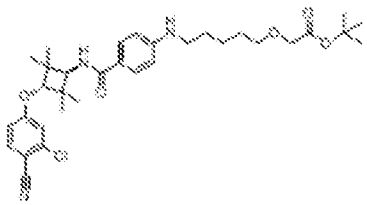
[0391] **ABM-35: trans 6-Amino-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]pyridine-3-carboxamide**.

[0392] 

[0393] **ABM-36: trans 4-[(5-Hydroxypentyl)amino]-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide**

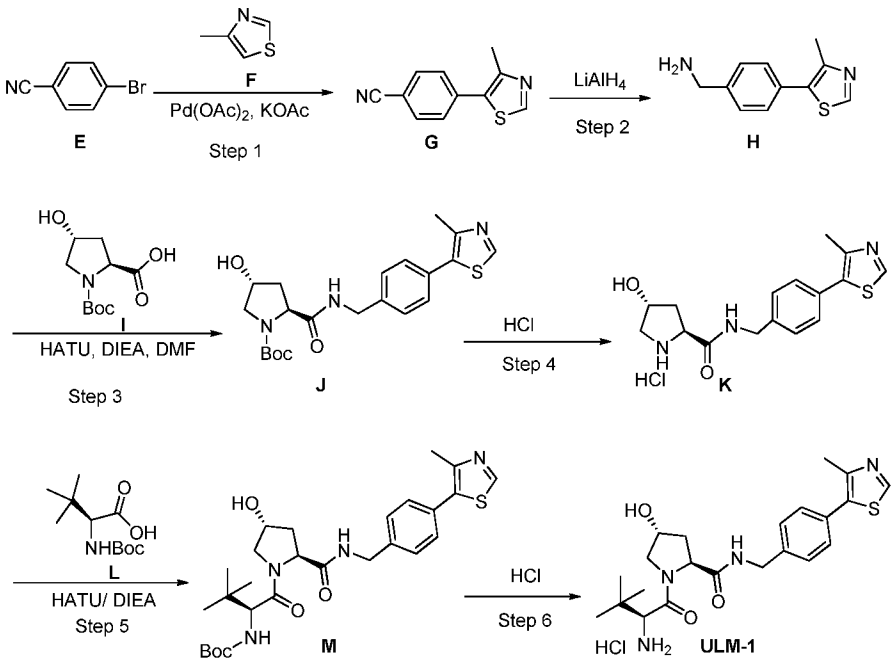
[0394] 

[0395] **ABM-37: trans tert-Butyl 2-({5-[(4-{[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenyl)aminopentyl}oxy)acetate**

[0396] 

[0397] **Synthesis of ULM Moieties**

[0398] **ULM-1: (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**

[0399] 

[0400] Step 1: Synthesis of 4-(4-methyl-1,3-thiazol-5-yl)benzonitrile (**G**)

[0401] To a stirred solution of 4-bromobenzonitrile (**E**, 20 g, 109.88 mmol) in DMA (250 mL) under a nitrogen atmosphere was added 4-methyl-1,3-thiazole (**F**, 21.88 g, 220.67 mmol), palladium (II) acetate (743 mg, 3.31 mmol) and potassium acetate (21.66 g, 220.71 mmol) at rt. The resulting solution was heated to 150 ^{o}C and stirred at this temperature for 5 h, LC-MS indicated formation of the desired product. The reaction was cooled to rt, diluted with 1 L of water and extracted with ethyl acetate (300 mL x 3). The organic layers were combined, washed with saturated aqueous solution of sodium chloride (200 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified

by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether, v: v = 1:5) to give the **G** (yield: 91%) as a white solid.

[0402] Step 2: Synthesis of [4-(4-methyl-1,3-thiazol-5-yl)phenyl]methanamine (**H**)

[0403] To a stirred solution of 4-(4-methyl-1,3-thiazol-5-yl)benzonitrile (**G**, 35.0 g, 174.8 mmol) in tetrahydrofuran (1000 mL) was added $LiAlH_4$ (20.0 g, 526.3 mmol) in portions at 0°C in 10 min under a nitrogen atmosphere. The resulting solution was then stirred at 60 °C for 3h. LC-MS indicated formation of the desired product. The reaction was then cooled to 0°C, quenched by the addition water (20 mL, added slowly), aq. solution of NaOH(15%, 20 mL) and water (60 mL). The resulting mixture was then extracted with ethyl acetate (300 mL x 2). The organic layers were combined, washed with saturated aqueous solution of sodium chloride (100 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel chromatography (eluent: dichloromethane/methanol (v:v = 10:1)) to give **H** (yield: 56%) as a yellow oil.

[0404] Step 1: synthesis of tert-butyl (2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidine-1-carboxylate (**J**)

[0405] To a stirred solution of (2S,4R)-1-[(tert-butoxy)carbonyl]-4-hydroxypyrrolidine-2-carboxylic acid (**I**, 2.7 g, 11.7 mmol) in N,N-dimethylformamide (20 mL) was added DIEA (2.52 g, 19.50 mmol), HATU (4.47 g, 11.76 mmol) and [4-(4-methyl-1,3-thiazol-5-yl)phenyl]methanamine (**H**, 2.0 g, 9.79 mmol) at rt. The resulting mixture was stirred at rt overnight, LC-MS indicated formation of the desired product. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (50 mL x 3). The organic layers were combined, washed with saturated aqueous solution of sodium chloride (50 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel chromatography (eluent: dichloromethane/methanol (v:v = 20:1)) to give **J** (yield: 56%) as a yellow solid.

[0406] Step 2: Synthesis of (2S,4R)-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide hydrochloride (**K**)

[0407] To a stirred solution of tert-butyl (2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidine-1-carboxylate (**J**, 45 g, 107.78 mmol), was added a solution of hydrogen chloride in dioxane (4N, 300 mL) . The resulting solution was

stirred at 20 °C for 2 h. The solids were collected by filtration to give **K** (yield: 98%) as a yellow solid, which was used for the next step without any further purification.

[0408] Step 3: Synthesis of tert-butyl N-[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate (**M**)

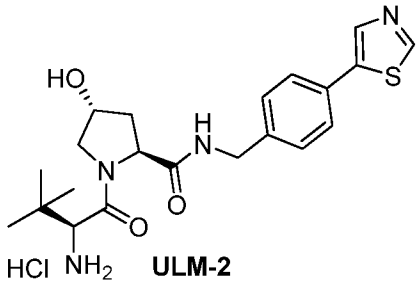
[0409] To a stirred solution of (2S)-2-{[(tert-butoxy)carbonyl]amino}-3,3-dimethylbutanoic acid (**L**, 15.7 g, 68.0 mmol) in N,N-dimethylformamide (500 mL) was added DIEA (29.2 g, 225.9 mmol), HATU (25.9 g, 68.1 mmol) and (2S,4R)-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} pyrrolidine-2-carboxamide hydrochloride (**K**, 20.0 g, 56.5 mmol) at rt.

[0410] The resulting solution was stirred at rt for 16h, LC-MS indicated formation of the desired product. The reaction mixture was diluted by water (200 mL) and extracted with ethyl acetate (200 mL x 3). The organic layers were combined, washed with saturated aqueous solution of sodium chloride (50 mL x 2), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v = 2:1)) to give **M** (yield: 51%) as a yellow solid.

[0411] Step 4: Synthesis of (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide hydrochloride (**ULM-1**)

[0412] To a stirred solution of tert-butyl N-[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate (**M**, 12 g, 22.61 mmol) in dioxane (20 mL) was added a solution of hydrogen chloride in dioxane (4N, 80 mL) at rt. The resulting solution was stirred at rt for 2 h, LC-MS indicated formation of the desired product. Precipitated solids were collected by filtration to give **ULM-1** (yield: 48%) as a yellow solid. ^{1}HNMR (400 MHz, CD_3OD): δ 9.84-9.82 (s, 1H), 7.58-7.54 (m, 4H), 4.71-4.41 (m, 4H), 4.13-4.08 (m, 1H), 3.86-3.71 (m, 2H), 3.36 (s, 1H), 2.60-2.58 (s, 3H), 2.35-2.07 (m, 2H), 1.19-1.12(m, 9H). LC-MS (ES^+): m/z 431.11 [MH^+], t_R = 0.73 min (2.0 minute run).

[0413] **ULM-2: (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(thiazol-5-yl)benzyl)pyrrolidine-2-carboxamide:**

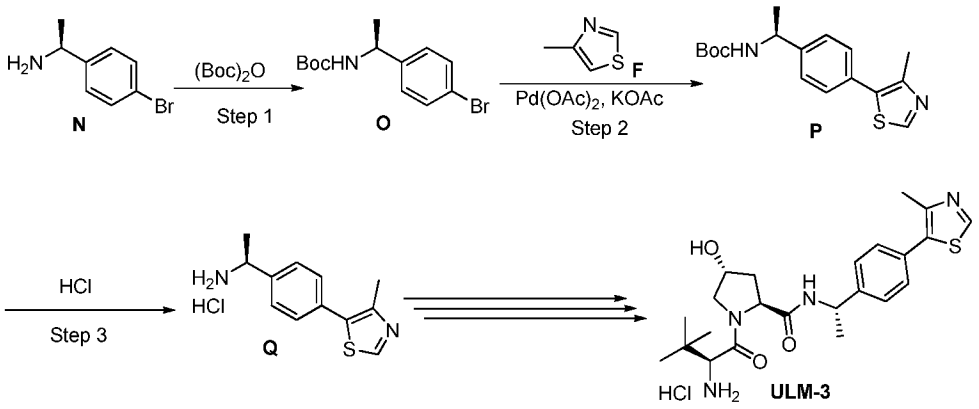


ULM-2

[0414]

[0415] **ULM-2** was synthesized according to similar procedure described above for the synthesis of **ULM-1**, utilizing 4-bromobenzonitrile and 1,3-thiazole as starting materials. LC-MS (ES^+): *m/z* 417.10 [MH^+], t_R = 0.51 min (2.0 minute run).

[0416] **ULM-3: (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide:**



[0417]

[0418] Step 1: Synthesis of tert-butyl N-[(1S)-1-(4-bromophenyl)ethyl]carbamate (**O**)

[0419] To a stirred mixture of (1S)-1-(4-bromophenyl)ethan-1-amine (**N**, 10.0 g, 49.98 mmol) in dichloromethane (100 mL) was added Et_3N (10.0 g, 99.01 mmol) and $(Boc)_2O$ (13.0 g, 59.63 mmol). The resulting mixture was stirred at rt for 2 h. The bulk of solvent was then removed under reduced pressure to give a crude residue, which was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether, v: v = 1:10) to give **O** (yield: 99%) as a white solid.

[0420] Step 2: Synthesis of tert-butyl N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]carbamate (**P**)

[0421] To a stirred solution of tert-butyl N-[(1S)-1-(4-bromophenyl)ethyl]carbamate (**O**, 15.0 g, 49.97 mmol) in DMA (100 mL), under an atmosphere of nitrogen, was added 4-methyl-1,3-thiazole (9.9 g, 99.84 mmol), potassium acetate (9.8 g, 99.86 mmol) and $Pd(OAc)_2$ (112.5 mg, 0.50 mmol) at rt. The resulting mixture was then stirred at 120°C for 2h. The reaction

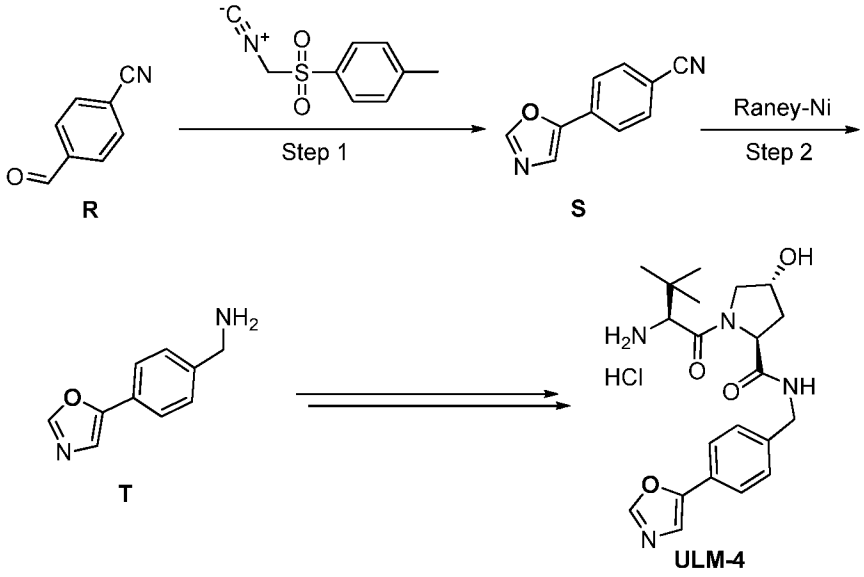
mixture was then cooled to rt, diluted by water (120mL), and extracted with ethyl acetate (200 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether, v: v = 1:5) to give **P** (yield: 47%) as a white solid. LC-MS (ES^+): *m/z* 319.13 [MH^+], t_R = 0.97 min (2.0 minute run).

[0422] Step 3. Synthesis of (1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethan-1-amine hydrochloride (**Q**)

[0423] To a stirred solution of tert-butyl N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]carbamate (**P**, 7.5 g, 23.55 mmol) in methanol (20 mL) was bubbled in hydrogen chloride (gas) at rt for 2 h. Then the resulting mixture was concentrated under vacuum to give **Q** (yield: 86%) as a white solid, which was used in the next step without any further purifications.

[0424] Intermediate **Q** was converted to **ULM-3** in a similar manner as described for the conversion of **H** to **ULM-1**. ^1H NMR (300MHz, DMSO): δ 8.99 (s, 1 H), 8.57-8.55 (d, *J* = 7.8 Hz, 1 H), 8.01 (br. s, 3 H), 7.46-7.43 (d, *J* = 8.4 Hz, 2 H), 7.39-7.37 (d, *J* = 8.4 Hz, 2 H), 4.98-4.90 (m, 1 H), 4.57-4.51 (m, 1 H), 4.34 (br. s, 1 H), 3.94-3.92 (m, 1 H), 3.69-3.66 (m, 1 H), 3.53-3.49 (m, 1 H), 2.52 (s, 3 H), 2.10-2.07 (m, 1 H), 1.83-1.81 (m, 1 H), 1.40-1.30 (m, 3 H), 1.03 (s, 9 H). LC-MS (ES^+): *m/z* 445.05 [MH^+], t_R = 0.53 min (2.0 minute run).

[0425] **ULM-4: (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(oxazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride:**



[0426]

[0427] Step 1: 1. Synthesis of 4-(1,3-oxazol-5-yl)benzonitrile (**S**)

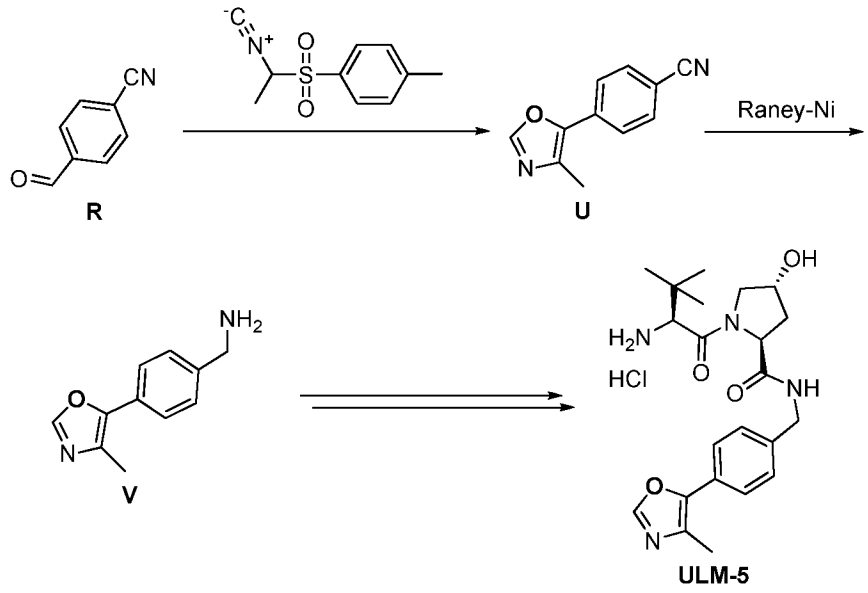
[0428] To a stirred solution of 4-formylbenzonitrile (**R**, 1.0 g, 7.63 mmol) in methanol (40 mL) was added [[(4-methylbenzene)sulfonyl]methyl](methyliumylidyne)azanuide (1.6 g, 8.40 mmol) and potassium carbonate (1.4 g, 9.91 mmol), the resulting mixture was stirred at rt for 1.5 h. The bulk of solvent was then removed under reduced pressure. The residue was diluted with saturated aqueous sodium bicarbonate (20 mL) and was extracted with dichloromethane (30 mL x 3). The organic layers were combined, washed with brine (30 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to give a crude product, which was purified by re-crystallization using dichloromethane and hexane to give **S** (1.0 g) as a white solid. ^{1}H NMR (400 MHz, DMSO) δ 8.56 (s, 1H), 7.97-7.83 (m, 5H); LC-MS (ES$^+$): *m/z* 170.95 [MH$^+$], t_R = 0.79 min (2.0 minute run).

[0429] Step 2. Synthesis of [4-(1,3-oxazol-5-yl)phenyl]methanamine (**T**)

[0430] To a stirred solution of 4-(1,3-oxazol-5-yl)benzonitrile (**S**, 900.0 mg, 5.29 mmol) in methanol (15 mL) was added Raney-Ni (900 mg) and aq. ammonium hydroxide (3.0 mL). Hydrogen gas was then introduced into the reaction mixture via a balloon. The resulting mixture was stirred at rt for 16 h. The solids were then removed by filtration and the solution was concentrated under vacuum to give **T** (yield: 81%) as brown oil, which was used in the next step without any further purifications. LC-MS (ES$^+$): m/z 175.90 [MH$^+$], t_R = 0.26 min (2.0 minute run).

[0431] Intermediate **T** was converted to **ULM-4** in a similar manner as described for the conversion of **H** to **ULM-1**. LC-MS (ES$^+$): m/z 400.96 [MH$^+$], t_R = 0.66 min (2.0 minute run).

[0432] **ULM-5: (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methyloxazol-5-yl)benzyl)pyrrolidine-2-carboxamide:**

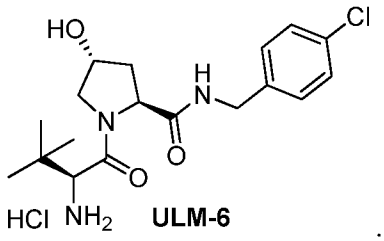


[0433]

[0434] [4-(4-methyl-1,3-oxazol-5-yl)phenyl]methanamine (**V**) was synthesized according to similar procedure described above for the synthesis of [4-(1,3-oxazol-5-yl)phenyl]methanamine (**T**).

[0435] Intermediate **V** was converted to **ULM-5** in a similar manner as described for the conversion of **H** to **ULM-1**. LC-MS (ES^+): m/z 415.10 [MH^+], t_R = 1.17 min (2.6 minute run).

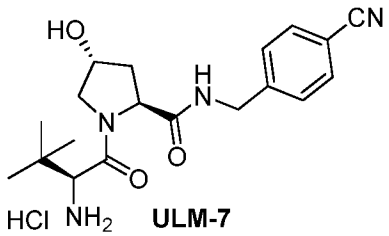
[0436] **ULM-6: (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-N-(4-chlorobenzyl)-4-hydroxypyrrolidine-2-carboxamide hydrochloride:**



[0437] **ULM-6**

[0438] **ULM-6** was synthesized according to similar procedure described above for the synthesis of **ULM-1**, utilizing 4-chlorobenzonitrile as the starting material.

[0439] **ULM-7: (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-N-(4-cyanobenzyl)-4-hydroxypyrrolidine-2-carboxamide hydrochloride:**

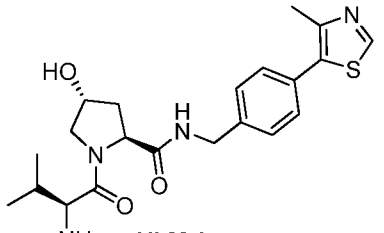


[0440] **ULM-7**

[0441] **ULM-7** was synthesized according to similar procedure described above for the synthesis of **ULM-1**, utilizing 4-cyanobenzonitrile as the starting material.

[0442] **ULM-8: (2S,4R)-1-((S)-2-amino-3-methylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride:**

[0443]

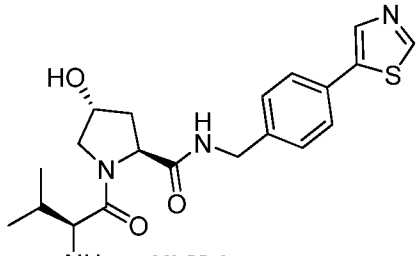


ULM-8

[0444] **ULM-8** was synthesized according to similar procedure described above for the synthesis of **ULM-1**, utilizing (S)-2-(tert-butoxycarbonylamino)-3-methylbutanoic acid and 4-methyl-1,3-thiazole (**F**) as starting materials.

[0445] **ULM-9: (2S,4R)-1-((S)-2-amino-3-methylbutanoyl)-4-hydroxy-N-(4-(thiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride:**

[0446]

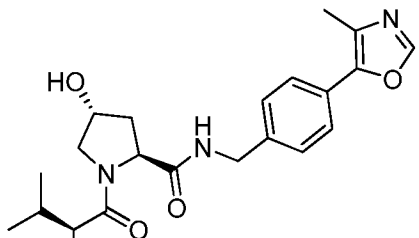


ULM-9

[0447] **ULM-9** was synthesized according to similar procedure described above for the synthesis of **ULM-1**, utilizing (S)-2-(tert-butoxycarbonylamino)-3-methylbutanoic acid and 1,3-thiazole as starting materials.

[0448] **ULM-10: (2S,4R)-1-((S)-2-amino-3-methylbutanoyl)-4-hydroxy-N-(4-(4-methyloxazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride:**

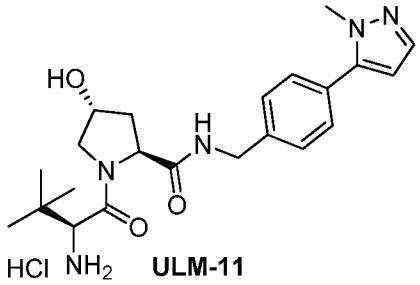
[0449]



ULM-10

[0450] **ULM-10** was synthesized according to similar procedure described above for the synthesis of **ULM-5**, utilizing (S)-2-(tert-butoxycarbonylamino)-3-methylbutanoic acid as starting material.

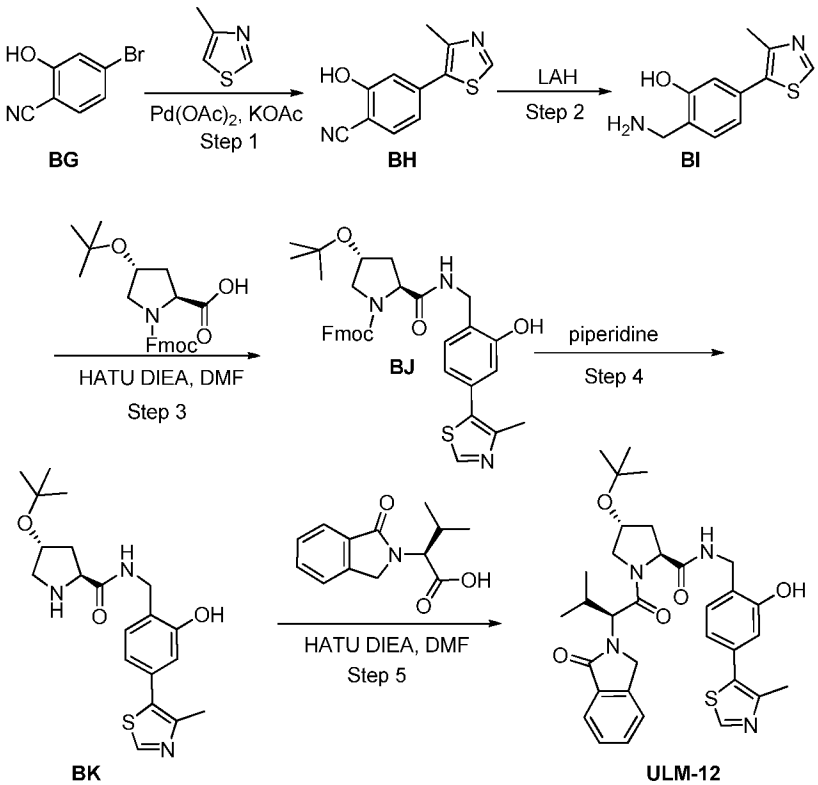
[0451] **ULM-11: (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(1-methyl-1H-pyrazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride:**

[0452] 

ULM-11

[0453] **ULM-11** was synthesized according to similar procedure described above for the synthesis of **ULM-1**, utilizing 1-methylpyrazole as the starting material.

[0454] **ULM-12: (2S,4R)-4-tert-butoxy-N-(2-hydroxy-4-(4-methylthiazol-5-yl)benzyl)-1-((S)-3-methyl-2-(1-oxoisoindolin-2-yl)butanoyl)pyrrolidine-2-carboxamide:**

[0455] 

BG **BH** **BI** **BJ** **BK** **ULM-12**

[0456] Step 1: Synthesis of 2-hydroxy-4-(4-methyl-1,3-thiazol-5-yl)benzonitrile (**BH**)

[0457] To a stirred solution of 4-bromo-2-hydroxybenzonitrile (**BG**, 28 g, 141.40 mmol) in DMA (300 mL) was added 4-methyl-1,3-thiazole (28.1 g, 283.40 mmol), potassium acetate (28 g, 285.31 mmol) and palladium (II) acetate (940 mg, 4.19 mol) at rt under an atmosphere of nitrogen. The resulting mixture was then heated to 150 °C and stirred at this temperature for 2.5 h, LC-MS indicated formation of the desired product. The reaction was then cooled to rt, diluted by water (1000 mL) and then extracted with ethyl acetate (500 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude residue, which was purified by a flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v : v = 1 : 1) to give **BH** (yield: 78%) as a yellow solid. LC-MS (ES^+): *m/z* 216.95 [MH^+], t_R = 1.25 min (2.6 minute run).

[0458] Step 1: 2-(aminomethyl)-5-(4-methyl-1,3-thiazol-5-yl)phenol (**BI**)

[0459] To a stirred solution of 2-hydroxy-4-(4-methyl-1,3-thiazol-5-yl)benzonitrile (**BH**, 15.6 g, 72.14 mmol) in tetrahydrofuran (400 mL) under an atmosphere of nitrogen was added $LiAlH_4$ (11 g, 289.86 mmol) in several portions at 10 °C. The resulting mixture was then heated to reflux for 3 h, LC-MS indicated formation of the desired product. The reaction was then cooled to 0 °C, quenched by the water (10 mL, added slowly and drop wise), 15% NaOH (aq.) (30 mL) and water (10 mL). The solids precipitated were removed by filtration, the solution phase was concentrated under reduced pressure followed by high vacuum pump to give **BI** (yield: 65%). LC-MS (ES^+): *m/z* 220.85 [MH^+], t_R = 1.02 min (2.6 minute run).

[0460] Step 3. Synthesis of 9H-fluoren-9-ylmethyl (2S,4R)-4-(tert-butoxy)-2-({[2-hydroxy-4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidine-1-carboxylate (**BJ**)

[0461] To a stirred solution of (2S,4R)-4-(tert-butoxy)-1-[(9H-fluoren-9-ylmethoxy)carbonyl]pyrrolidine-2-carboxylic acid (**BI**, 18.6 g) in N,N-dimethylformamide (250 mL) was added DIEA (7.9 g, 61.24 mmol), HATU (17.3 g, 45.53 mmol) and 2-(aminomethyl)-5-(4-methyl-1,3-thiazol-5-yl)phenol (20 g, 90.79 mmol) at rt. The resulting mixture was stirred overnight at rt, and LC-MS indicated formation of the desired product. The reaction mixture was diluted by water (200 mL) and then extracted with ethyl acetate (300 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel chromatography (eluent: dichloromethane/methanol (v: v = 25:1)) to give **BJ** (yield: 31%) as a yellow oil. LC-MS (ES^+): *m/z* 611.20 [MH^+], t_R = 1.12 min (2.0 minute run).

[0462] Step 4: Synthesis of (2S,4R)-4-(tert-butoxy)-N-{[2-hydroxy-4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**BK**)

[0463] To a stirred solution of 9H-fluoren-9-ylmethyl (2S,4R)-4-(tert-butoxy)-2-({[2-hydroxy-4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidine-1-carboxylate (**BJ**, 17.2 g, 28.12 mmol) in dichloromethane (270 mL) was added piperidine (30 mL, 280.00 mmol) at rt. The resulting solution was stirred at rt for 3 h, and LC-MS indicated formation of the desired product. The reaction mixture was concentrated under vacuum to give a crude residue, which was then diluted by dichloromethane (300 mL), washed with water (300 mL x 2), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel chromatography (eluent: dichloromethane/methanol (v: v = 20:1)) to give **BK** (yield: 71%) as a yellow oil. LC-MS (ES^+): *m/z* 389.95 [MH^+], t_R = 0.88 min (2.0 minute run).

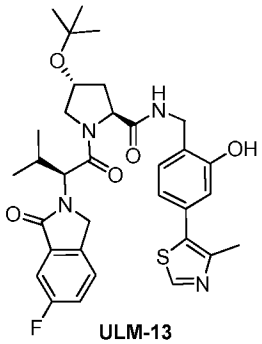
[0464] Step 5: Synthesis of (2S,4R)-4-(tert-butoxy)-N-{[2-hydroxy-4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}-1-[(2S)-3-methyl-2-(1-oxo-2,3-dihydro-1H-isoindol-2-yl)butanoyl]pyrrolidine-2-carboxamide **ULM-12**)

[0465] To a stirred solution of (2S)-3-methyl-2-(1-oxo-2,3-dihydro-1H-isoindol-2-yl)butanoic acid (3.6 g, 15.43 mmol) in N,N-dimethylformamide (50 mL) was added DIEA (2.7 g, 20.93 mmol), HATU (5.89 g, 15.49 mmol) and (2S,4R)-4-(tert-butoxy)-N-{[2-hydroxy-4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**BK**, 4.0 g, 10.27 mmol) at rt. The resulting solution was stirred overnight at rt, and LC-MS indicated formation of the desired product. The reaction was diluted by the water (100 mL) and extracted with dichloromethane (100 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude residue, which was purified by a flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v = 2:1)) to give **ULM-12** (yield: 43%) as a yellow solid. ^1H NMR (400 MHz, CD_3OD) δ 8.88 (s, 1 H), 7.83-7.81 (d, *J* = 7.6 Hz, 1 H), 7.66-7.63 (m, 2 H), 7.61-7.59 (m, 1 H), 7.36-7.34 (d, *J* = 8.0 Hz, 1 H), 6.94-6.87 (d, *J* = 6.4 Hz, 1 H), 4.88 (s, 1 H), 4.56-4.39 (m, 6 H), 3.88-3.81 (m, 2 H), 2.51 (s, 3 H), 2.47-2.45 (m, 1 H), 2.15-2.13 (m, 2 H), 1.16-1.14 (d, *J* = 6.4 Hz, 3 H) 1.02 (s, 9 H), 0.89-0.86 (d, *J* = 6.4 Hz, 3 H); LC-MS (ES^+): *m/z* 605.40 [MH^+], t_R = 1.91 min (3.6 minute run).

[0466] Unless otherwise noted, the following intermediates and their analogs (for examples, but not limited to, analogs with substitutions such as halogens) were synthesized

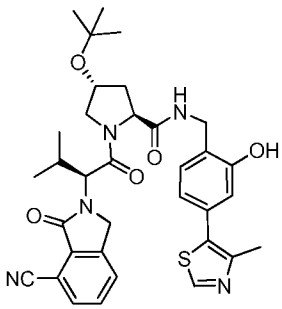
according to similar procedures described above for the synthesis of **ULM-12**, by utilizing corresponding starting materials and reagents.

[0467] **ULM-13: (2S,4R)-4-tert-butoxy-1-((S)-2-(6-fluoro-1-oxoisoindolin-2-yl)-3-methylbutanoyl)-N-(2-hydroxy-4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide:**



[0468] **ULM-13** .

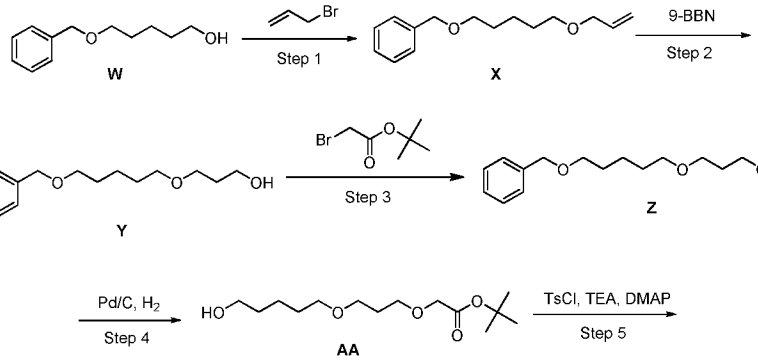
[0469] **ULM-14: (2S,4R)-4-tert-butoxy-1-((S)-2-(7-cyano-1-oxoisoindolin-2-yl)-3-methylbutanoyl)-N-(2-hydroxy-4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide:**



[0470] **ULM-14** .

[0471] **Synthesis of Linker Chemistry, L**

[0472] **L-1: 2-(3-(5-(tosyloxy)pentyloxy)propoxy)acetic acid**



[0473] .

[0474] Step 1: Synthesis of ({[5-(prop-2-en-1-yloxy)pentyl]oxy}methyl)benzene

[0475] To a stirred solution of 5-(benzyloxy)pentan-1-ol (**W**, 4.0 g, 20.59 mmol) in N,N-dimethylformamide (50 mL) was added sodium hydride (1.24 g, 51.67 mmol) in portions at 0 °C under an atmosphere of nitrogen. The resulting mixture was then stirred at rt for 1 h. To this mixture was added 3-bromoprop-1-ene (3.71 g, 30.67 mmol), the reaction mixture was stirred overnight at 60 °C in an oil bath. LC-MS indicated formation of the desired product. The reaction mixture was cooled to 0 °C and then quenched by water (100 mL), the resulting mixture was extracted with ethyl acetate (200 mL x 2). The organic layers were combined, washed with saturated aqueous solution of sodium chloride (60 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue. The residue was purified by a flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v = 1:40)) to give 4.57 g of **X**. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.36(s, 4 H), 7.32 (m, 1 H), 5.98 (m, 1 H), 5.33 (m, 1H), 5.21 (m, 1H), 4.53 (s, 2H), 3.99 (m, 2H), 3.53 (m, 4H), 1.72 (m, 4H), 1.52 (m, 2H). LC-MS (ES^+): m/z 235.00 [MH^+], t_R = 1.18 min (2.0 minute run).

[0476] Step 2: Synthesis of 3-{[5-(benzyloxy)pentyl]oxy}propan-1-ol (**Y**)

[0477] To a 250-mL round-bottom flask with 9-BBN (0.5 M in THF, 77 mL) was added a solution of ({[5-(prop-2-en-1-yloxy)pentyl]oxy}methyl)benzene (**X**, 3.0 g, 12.80 mmol) in anhydrous tetrahydrofuran (20 mL) with stirring at 0 °C under an atmosphere of nitrogen. The resulting solution was stirred overnight at rt. LC-MS indicated formation of the desired product. Methanol (15 mL, with 30% sodium hydroxide and 30% H_2O_2) was added to the reaction and the resulting mixture was stirred at rt for 2 h. This mixture was then extracted with ethyl acetate (20 mL x 3). The organic layers were combined, washed with saturated aqueous solution of sodium chloride (100 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue. The residue was purified by a flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v: v = 1:1)) to provide 1.96 g of **Y** as light yellow oil. ^{1}H NMR (300MHz, $CDCl_3$): δ7.34 (m, 5H), 4.49 (s, 2H), 3.75 (m, 2H), 3.59 (m, 2H), 3.49 (m, 4H), 2.65 (bs, 1 H), 1.84 (m, 2H), 1.68 (m, 4H), 1.50 (m, 2H). LC-MS (ES^+): m/z 253.17 [MH^+], t_R = 1.44 min (2.6 minute run).

[0478] Step 3: Synthesis of tert-butyl 2-(3-{[5-(benzyloxy)pentyl]oxy}propoxy)acetate (**Z**)

[0479] To a stirred solution of 3-{[5-(benzyloxy)pentyl]oxy}propan-1-ol (**Y**, 3.7 g, 14.66 mmol) in dichloromethane (30 mL) was added a solution of NaOH in water (37%, 30 mL)

followed by tert-butyl 2-bromoacetate (11.39 g, 58.39 mmol) and TBACl (4.17 g). The resulting mixture was stirred at rt overnight. LC-MS indicated formation of the desired product. The reaction mixture was then extracted with ethyl acetate (50 mL x 3). The organic layers were combined, washed with saturated aqueous solution of sodium chloride (60 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue. The residue was purified by a flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v = 1:2) to give 3.2g of **Z** as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$): δ7.34(s, 4 H), 7.29 (m, 1 H), 4.50 (s, 4H), 4.3 (m, 2H), 3.51 (m, 4H), 3.42 (m, 2H), 1.98 (m, 2H), 1.67 (m, 4H), 1.48 (s, 9H), 1.46 (m, 2H). LC-MS (ES^+): m/z 367.25 [MH^+], t_R = 1.28 min (2.0 minute run).

[0480] Step 4: Synthesis of tert-butyl 2-[3-[(5-hydroxypentyl)oxy]propoxy]acetate (**AA**)

[0481] To a stirred solution of tert-butyl 2-(3-{[5-(benzyloxy)pentyl]oxy}propoxy)acetate (**Z**, 3.2 g, 8.73 mmol) in methanol (30 mL) was added AcOH (1.5 mL), palladium on carbon (1.5 g) under an atmosphere of nitrogen. Hydrogen was then introduced to the reaction mixture via a hydrogen balloon, and the reaction was stirred at rt for 3h. The solid material was removed by filtration, the solution was concentrated under vacuum to provide 2.3 g of **AA** as light yellow oil, which was used for the next step without any further purifications. LC-MS (ES^+): m/z 277.10 [MH^+], t_R = 0.86 min (2.0 minute run).

[0482] Step 5: Synthesis of tert-butyl 2-[3-({5-[(4-methylbenzenesulfonyl)oxy]pentyl}oxy)propoxy]acetate (**AB**)

[0483] To a stirred solution of tert-butyl 2-[3-[(5-hydroxypentyl)oxy]propoxy]acetate (**AA**, 2.3 g, 8.32 mmol) in dichloromethane (30 mL) was added 4-methylbenzene-1-sulfonyl chloride (3.17 g, 16.63 mmol), triethylamine (2.52 g, 24.90 mmol) and 4-dimethylaminopyridine (203 mg, 1.66 mmol) at rt. The resulting mixture was stirred overnight at rt. The resulting mixture was concentrated under reduced pressure to give a crude residue, which was purified by a flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v = 1:2) to give 2.6 g of **AB** as a yellow oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.77 (d, J = 8.1 Hz, 2 H), 7.36 (d, J = 8.1 Hz, 2 H), 4.51 (s, 2H), 4.31 (m, 2H), 4.13 (m, 2H), 3.52 (m, 4H), 2.05 (s, 3H), 1.97 (m, 2H), 1.69 (m, 4H), 1.48 (s, 9H), 1.46 (m, 2H). LC-MS (ES^+): m/z 431.20 [MH^+], t_R = 1.21 min (2.0 minute run).

[0484] Step 1: Synthesis of 2-[3-({5-[(4-methylbenzenesulfonyl)oxy]pentyl}oxy)propoxy]acetic acid (**L-1**)

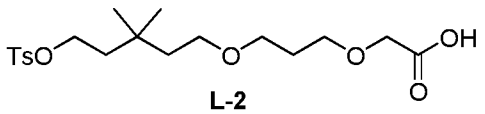
[0485] To a stirred solution of tert-butyl 2-[3-({5-[(4-methylbenzenesulfonyl)oxy]pentyl}oxy)propoxy]acetate (**AB**, 1.3 g, 3.02 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (10 mL) at rt. The resulting solution was stirred at rt for 3 h. The reaction mixture was then concentrated under vacuum to give 1.5 g (crude) of **L-1**, which was used for next step without any further purification. LC-MS (ES^+): *m/z* 375.34 [MH^+], t_R = 1.39 min (2.6 minute run).

[0486]

[0487] The following Linkers (**L**) were prepared in a similar manner as for the preparation of **L-1**.

[0488]

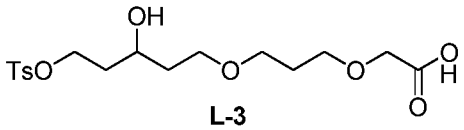
[0489] **L-2: 2-(3-(3,3-dimethyl-5-(tosyloxy)pentyloxy)propoxy)acetic acid**

[0490] 

L-2

[0491]

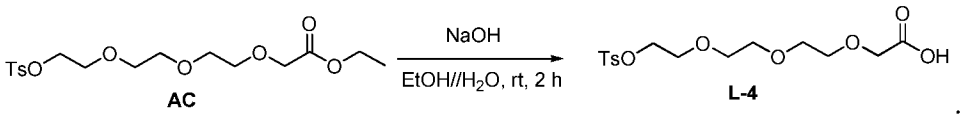
[0492] **L-3: 2-(3-(3-hydroxy-5-(tosyloxy)pentyloxy)propoxy)acetic acid**

[0493] 

L-3

[0494]

[0495] **L-4: 2-(2-(2-(2-(tosyloxy)ethoxy)ethoxy)ethoxy)acetic acid**

[0496] 

AC **L-4**

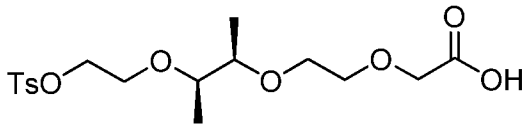
[0497] To a stirred solution of ethyl 2-[2-(2-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}ethoxy)ethoxy]acetate (**AC**, 2 g, 5.12 mmol, 1.00 equiv) in methanol (20 mL) was added a solution of NaOH (500 mg, 12.50 mmol) in water (4 mL), and the resulting mixture was stirred at rt for 2 h. Aqueous hydrogen chloride (1 M) was then added to the reaction mixture to adjust pH to ~5. Solids precipitated were collected by filtration to give **L-4** (yield: 98%). Mass (ES+): m/z 363, [MH+].

[0498]

[0499] The following Linkers (**L**) were prepared in a similar manner as for the preparation of **L-4**.

[0500]

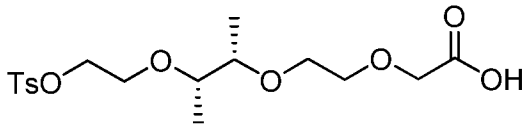
[0501] L-5: 2-(2-((2R,3R)-3-(2-(tosyloxy)ethoxy)butan-2-yloxy)ethoxy)acetic acid

[0502] 

L-5

[0503]

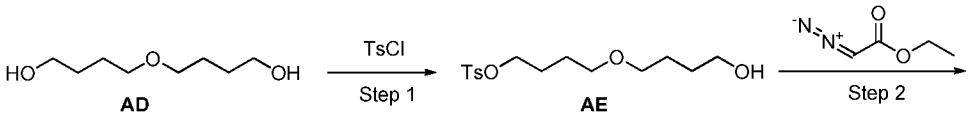
[0504] L-6: 2-(2-((2S,3S)-3-(2-(tosyloxy)ethoxy)butan-2-yloxy)ethoxy)acetic acid

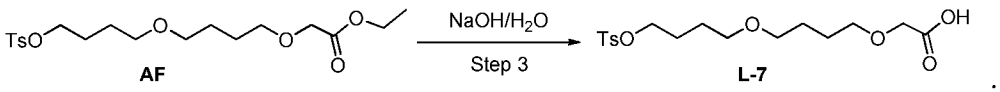
[0505] 

L-6

[0506]

[0507] L-7: 2-(4-(4-(tosyloxy)butoxy)butoxy)acetic acid



[0508] 

[0509] Step 1: Synthesis of 4-{4-[(4-methylbenzenesulfonyl)oxy]butoxy}butan-1-ol (**AE**)

[0510] To a stirred solution of 4-(4-hydroxybutoxy)butan-1-ol (**AD**, 2 g, 12.33 mmol) in dichloromethane (20 mL) was added Ag_2O (4.25 g, 18.49 mmol), KI (409 mg, 2.46 mmol) and TsCl (2.345 g, 12.30 mmol). The resulting mixture was stirred at rt for 12 h. The inorganic salt formed was removed by filtration and the organic solution was concentrated under reduced pressure to give a crude residue. The residue was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v = 1:1)) to give **AE** (yield: 28%) as a colorless oil.

[0511] Step 2: Synthesis of ethyl 2-(4-{4-[(4-methylbenzenesulfonyl)oxy]butoxy}butoxy)acetate (**AF**)

[0512] To a stirred solution of 4-{4-[(4-methylbenzenesulfonyl)oxy]butoxy}butan-1-ol (**AE**, 1.1 g, 3.48 mmol) in dichloromethane (10 mL) was slowly added $BF_3.Et_2O$ (49.4 mg, 0.35 mmol)

followed by ethyl 2-diazoacetate (794 mg, 6.96 mmol) at 0 °C. The resulting mixture was stirred overnight at rt. The reaction was then quenched by water (2.0 mL). The resulting mixture was extracted with dichloromethane (50mL x 3), the organic layers were combined, dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue. The residue was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v: v = 1:4) to give **AF** (yield: 93 as light yellow oil. Mass (ES^+): *m/z* 403.10 [MH^+].

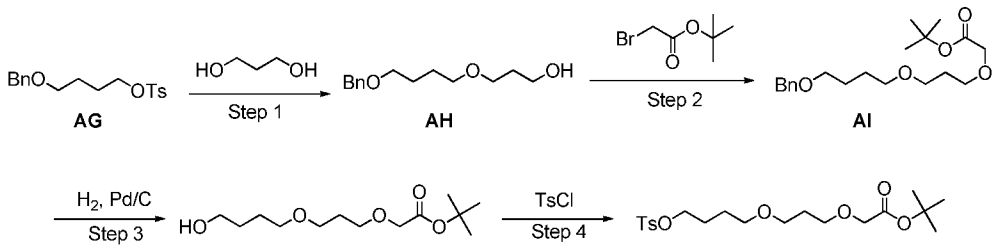
[0513] Step 3: Synthesis of 2-(4-{4-[(4-methylbenzenesulfonyl)oxy]butoxy}butoxy)acetic acid (**L-7**)

[0514] To a stirred solution of ethyl 2-(4-{4-[(4-methylbenzenesulfonyl)oxy]butoxy}butoxy)acetate (**AF**, 1.3 g, 3.23 mmol) in methanol (25mL) was added a solution of NaOH (388 mg, 9.70 mmol) in water (6 mL) at rt. The resulting solution was stirred at rt for 4 h. The bulk of organic solvent was removed under reduced pressure, to the resulting mixture was added aqueous hydrogen chloride (1.0 M) to adjust the pH = ~5. The solution was then extracted with ethyl acetate (250 mL x 3), the organic layers were combined and dried over anhydrous sodium sulfate, concentrated under reduced pressure to give **I-7** (yield: 93%) as light yellow oil. Mass (ES^+): *m/z* 375.05 [MH^+].

[0515]

[0516] L-8: tert-butyl 2-(3-(4-(tosyloxy)butoxy)propoxy)acetate

[0517]



[0518] Step 1. Synthesis of 3-[4-(benzyloxy)butoxy]propan-1-ol (**AH**)

[0519] To a stirred solution of propane-1, 3-diol (1.52 g, 19.98 mmol) in N, N-dimethylformamide (20 mL) was added sodium hydride (840 mg, 35.00 mmol) at rt, the resulting mixture was stirred at rt for 30min. Then to the mixture was added 4-(benzyloxy) butyl 4-methylbenzene-1-sulfonate (**AG**, 6.68 g, 19.97 mmol) and the reaction was stirred overnight at 50 °C. TLC indicated formation of the desired product, at this time the reaction was allowed to cool down to rt. Water (10 mL) was added slowly to quench the reaction; the resulting mixture was then extracted with ethyl acetate (80 mL x 2). The organic layers were combined, washed

with saturated aqueous solution of sodium chloride (20 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v = 1:2)) to give **AH** (yield: 67%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 4.52 (m, 2H), 3.80 (m, 2H), 3.61 (m, 2H), 3.49-3.46 (m, 4H), 2.04 (m, 2H), 1.82 (m, 2H), 1.68 (m, 2H); Mass (ES^+): *m/z* 239.05 [MH^+].

[0520] Step 2. Synthesis of tert-butyl 2-[3-[4-(benzyloxy)butoxy]propoxy]acetate (**AI**).

[0521] To a stirred solution of 3-[4-(benzyloxy)butoxy]propan-1-ol (**AH**, 2.38 g, 9.99 mmol) in dichloromethane (15 mL) was added tert-butyl 2-bromoacetate (7.76 g, 39.78 mmol), TBAC (2.78 g, 10.00 mmol) followed by aqueous sodium hydroxide (37 %, 15 mL). The resulting mixture was stirred overnight at rt. The reaction mixture was then extracted with dichloromethane (100 mL x 3), the organic layers were combined, washed with saturated aqueous solution of sodium chloride (20 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue. The residue was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v = 1: 5)) to give **AI** (yield 57%) as a yellow oil. Mass (ES^+): *m/z* 353.10 [MH^+].

[0522] Step 3. Synthesis of tert-butyl 2-[3-(4-hydroxybutoxy)propoxy]acetate (**AJ**)

[0523] To a stirred mixture of tert-butyl 2-[3-[4-(benzyloxy)butoxy]propoxy]acetate (**AI**, 1 g, 2.84 mmol), palladium on carbon (10%, 200 mg) in methanol (20 mL) was added acetic acid (0.05 mL) under a nitrogen atmosphere. Hydrogen was then introduced to the reaction mixture via a balloon, the reaction was then stirred overnight at rt. The insoluble solids were removed by filtration and the solution phase was concentrated under reduced pressure to give the desired product (yield: 94%) as a yellow oil. Mass (ES^+): *m/z* 263.05 [MH^+].

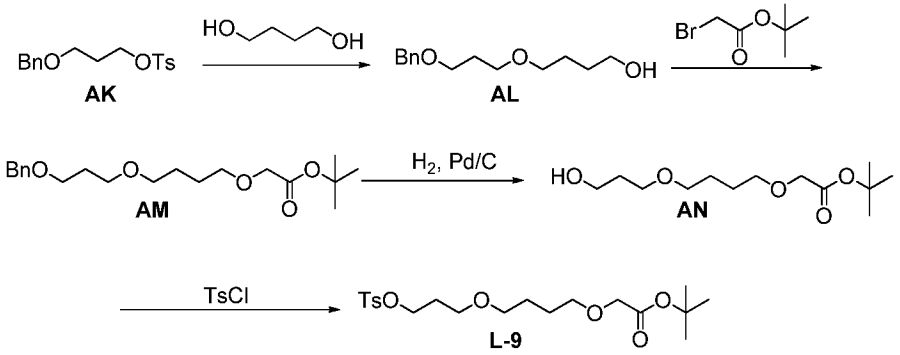
[0524] Step 4. Synthesis of tert-butyl 2-(3-{4-[(4-methylbenzenesulfonyl)oxy]butoxy}propoxy)acetate (**L-8**)

[0525] To a stirred solution of tert-butyl 2-[3-(4-hydroxybutoxy)propoxy]acetate (**AJ**, 700 mg, 2.67 mmol) in dichloromethane (10 mL) was added 4-methylbenzene-1-sulfonyl chloride (558.4 mg, 2.93 mmol), TEA (539.5 mg, 5.33 mmol) and 4-dimethylaminopyridine (32.6 mg, 0.27 mmol). The resulting mixture was stirred overnight at rt. The bulk of solvent was removed under

reduced pressure to give a crude residue, which was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v= 1: 2)) to give titled product (yield: 52%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ7.79 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.05 (m, 2H), 3.95 (s, 2H), 3.59 (m, 2H), 3.48 (m, 2H), 3.38 (m, 2H), 2.46 (s, 3H), 1.82 (m, 2H), 1.70 (m, 2H), 1.57 (m, 2H), 1.50 (s, 9H); Mass (ES^+): *m/z* 417.05 [MH^+].

[0526]

[0527] L-9: tert-butyl 2-(4-(3-(tosyloxy)propoxy)butoxy)acetate

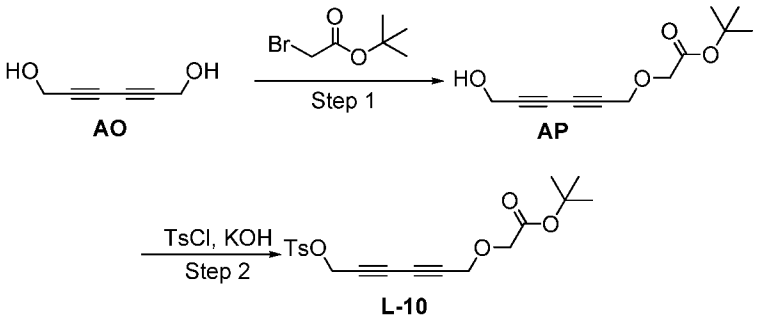


[0528]

[0529] L-9 was prepared in a similar manner as that used to prepare **L-8**, except that **AK** was used in place of **AG**. Mass (ES^+): *m/z* 439.15 [MNa^+].

[0530]

[0531] L-10: tert-butyl 2-(6-(tosyloxy)hexa-2,4-diynyloxy)acetate



[0532]

[0533] Step1: Synthesis of tert-butyl 2-[(6-hydroxyhexa-2,4-diyn-1-yl)oxy]acetate (**AP**)

[0534] To a stirred solution of hexa-2, 4-diyne-1, 6-diol (**AO**, 100 mg, 0.91 mmol) in N, N-dimethylformamide (5 mL) was added sodium hydride (32 mg, 1.33 mmol) at 0 °C. The resulting mixture was then warmed up to rt and stirred at rt for 30 min. The reaction mixture was cooled to 0 °C followed by addition of tert-butyl 2-bromoacetate (176 mg, 0.90 mmol), and the resulting mixture was stirred at 0 °C for 2h. LC-MS indicated formation of the desired product. The reaction was then quenched by water (10 mL, added slowly) at 0 °C, and was extracted with

ethyl acetate (20 x 2 mL). The organic layers were combined, dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v = 1:2)) to give **AP** (yield: 49%) as a yellow oil.

[0535] Step 2. Synthesis of tert-butyl 2-({6-[(4-methylbenzenesulfonyl)oxy]hexa-2,4-diyn-1-yl}oxy)acetate (**L-10**)

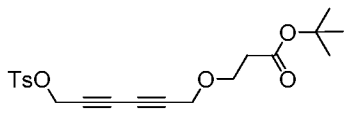
[0536] To a stirred solution of tert-butyl 2-[(6-hydroxyhexa-2, 4-diyn-1-yl) oxy] acetate (**AP**, 50 mg, 0.22 mmol) in ether (2 mL) was added 4-toluenesulfonyl chloride (51 mg, 0.27 mmol) at 0 ^{o}C, followed by potassium hydroxide (125 mg, 2.23 mmol) in several batches at 0 ^{o}C. The resulting mixture was stirred at 0 ^{o}C for 4 h. LC-MS indicated formation of the desired product. Water (10 mL) was added to the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL x 2). The organic layers were combined, dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v = 1:2)) to give **L-10** (yield: 71%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, *J* = 6.0 Hz, 2H), 7.39 (d, *J* = 6.0 Hz, 2H), 4.79 (s, 2H), 4.37 (s, 2H), 4.05 (s, 2H), 2.48 (s, 3H), 1.51 (s, 9H); LC-MS (ES^+): *m/z* 401.05 [MNa^+], t_R = 1.71 min (2.6 minute run).

[0537]

[0538] The following Linkers (**L**) were prepared in a similar manner as for the preparation of **L-10**.

[0539]

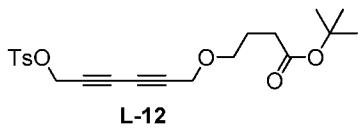
[0540] L-11: tert-butyl 3-(6-(tosyloxy)hexa-2,4-diynyloxy)propanoate



[0541] **L-11** .

[0542]

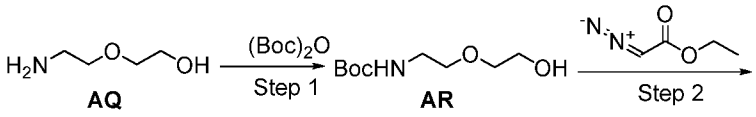
[0543] L-12: tert-butyl 4-(6-(tosyloxy)hexa-2,4-diynyloxy)butanoate



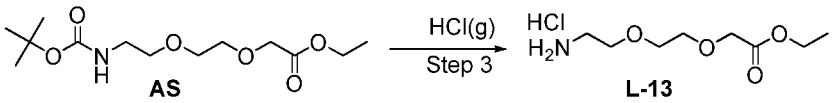
[0544] **L-12** .

[0545]

[0546] L-13: ethyl 2-(2-(2-aminoethoxy)ethoxy)acetate hydrochloride



[0547]



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[0548] Step 1: Synthesis of tert-butyl N-[2-(2-hydroxyethoxy)ethyl]carbamate (**AR**)

[0549] To a stirred solution of 2-(2-aminoethoxy)ethan-1-ol (**AQ**, 5.25 g, 49.94 mmol) in tetrahydrofuran (100 mL) was added aqueous solution of sodium bicarbonate (20% (w/w), 40 ml) and $(Boc)_2O$ (11.4 g, 52.23 mmol, added in several batches) at 0 °C. The resulting mixture was then warmed up slowly to rt and stirred at rt for 5h. The bulk of organic solvent was removed under reduced pressure and the resulting residue was diluted with water (300 mL), extracted with of ethyl acetate (100 mL x 3). The organic layers were combined, washed with saturated aqueous solution of sodium chloride (20 mL x 2), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give **AR** (yield: 98%) as colorless oil.

[0550] Step 2: Synthesis of ethyl 2-[2-(2-{[(tert-butoxy)carbonyl]amino}ethoxy)ethoxy]acetate (**AS**)

[0551] To a stirred solution of tert-butyl N-[2-(2-hydroxyethoxy)ethyl]carbamate (**AR**, 4.0 g, 19.49 mmol) in dichloromethane (30 mL) was added 1-diazo-3-methoxypropan-2-one (3.34 g, 29.27 mmol) and BF_3-Et_2O (0.2 mL) at rt. The resulting solution was stirred at rt for 2 h. Water (20 mL) was added to the reaction mixture, organic layer was separated and washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude residue. The residue was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v: v = 1:2)) to give **AS** (yield: 18%) as yellow solid. ^1H NMR (400MHz, $CDCl_3$): δ 4.25-4.22 (q, J = 7.2 Hz, 2 H), 4.14 (s, 2 H), 3.74 (b, 2 H), 3.72 (b, 1 H), 3.67-3.32 (m, 4 H), 1.414 (s, 9 H), 1.31 (t, J = 7.2 Hz, 3 H).

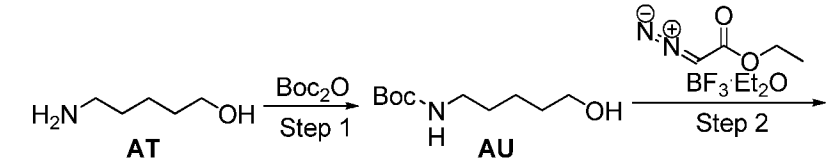
[0552] Step 3: Synthesis of ethyl 2-[2-(2-aminoethoxy)ethoxy]acetate hydrochloride (**L-13**)

[0553] To a stirred solution of ethyl 2-[2-(2-{[(tert-butoxy)carbonyl]amino}ethoxy)ethoxy]acetate (**AS**, 500 mg, 1.72 mmol) in 1,4-dioxane (10 mL) was introduced hydrogen chloride (gas) via bubbling at rt for 2h. The solvent was then removed

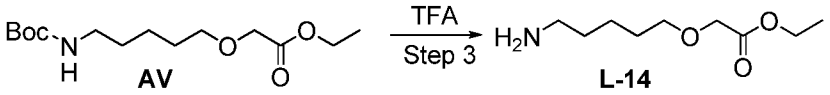
under vacuum to give **L-13** (yield: 99%). LC-MS (ES^+): *m/z* 192.00 [MH^+], t_R = 0.41 min (2.0 minute run).

[0554]

[0555] L-14: ethyl 2-(5-aminopentyloxy)acetate



[0556]



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[0557] Step 1: Synthesis of tert-butyl 5-hydroxypentylcarbamate (**AU**)

[0558] To a stirred solution of 5-aminopentan-1-ol (**AT**, 3.1 g, 30.05 mmol) in dichloromethane (30 mL) was added di-tert-butyl dicarbonate (6.56 g, 30.06 mmol) at 0 °C. The resulting mixture was then stirred at rt for 4h. The solvent was removed under reduced pressure to give a crude residue which was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v= 1: 2)) to give **AU** (yield: 98%) as a colorless oil. LC-MS (ES^+): *m/z* 204.00 [MH^+], t_R =1.29 min (2.6 minute run).

[0559] Step 2: Synthesis of ethyl 2-[(5-{[(tert-butoxy)carbonyl]amino}pentyl)oxy]acetate (**AV**)

[0560] To a stirred solution of tert-butyl N-(5-hydroxypentyl)carbamate (**AU**, 1.5 g, 7.38 mmol) in dichloromethane (10 mL) was added $BF_3{\cdot}Et_2O$ (0.1 mL) at 0 °C. To this mixture was then added a solution of ethyl 2-diazoacetate (850 mg, 7.45 mmol) in dichloromethane (2 mL) at 0 °C. The resulting mixture was allowed to warm up to rt and stirred at rt for 2 h. Saturated aqueous sodium bicarbonate (30 mL) was added to the reaction, the resulting mixture was extracted with ethyl acetate (150 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v= 1: 7)) to give **AV** (yield: 15%) as a colorless oil. LC-MS (ES^+): *m/z* 290.05 [MH^+], t_R =1.55 min (2.6 minute run).

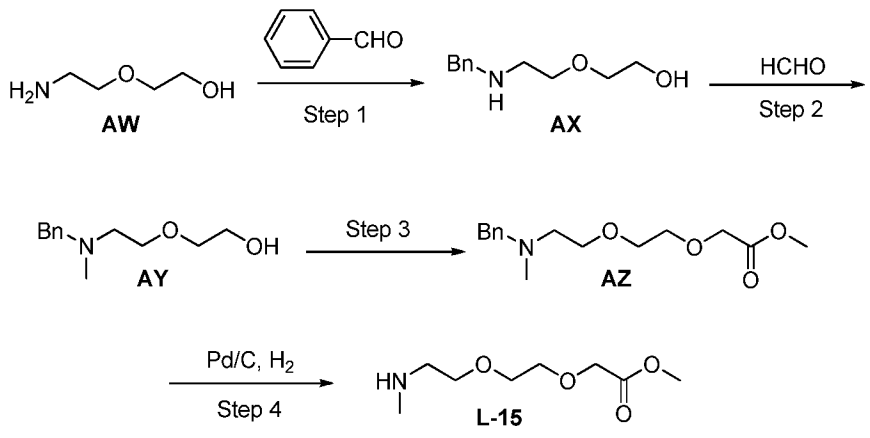
[0561] Step 3: Synthesis of ethyl 2-(5-aminopentyloxy)acetate (**L-14**)

[0562] To a stirred solution of ethyl ethyl 2-[(5-{[(tert-butoxy)carbonyl]amino}pentyl)oxy]acetate (**AV**, 400 mg, 1.38 mmol) in dichloromethane (5

mL) was added trifluoroacetic acid (5 mL) at rt. The resulting solution was stirred at rt for 2 h. The reaction mixture was then concentrated under vacuum to give **L-14** (yield: 84%) as a yellow oil. LC-MS (ES^+): *m/z* 190.00 [MH^+], t_R =1.01 min (2.6 minute run).

[0563]

[0564] L-15: methyl 2-(2-(2-(methylamino)ethoxy)ethoxy)acetate



[0565]

[0566] Step 1: Synthesis of 2-[2-(benzylamino)ethoxy]ethan-1-ol (**AX**)

[0567] To a stirred solution of 2-(2-aminoethoxy)ethan-1-ol (**AW**, 5.0 g) and benzaldehyde (5.0 g) in THF (50 mL) was added sodium triacetoxyborohydride (15.8 g, 74.5 mmol) at 0 °C. The resulting solution was then stirred at rt for 4 h. Water (50 mL) was added to the reaction and the resulting mixture was extracted with ethyl acetate (50 mL x 2). The organic layers were combined, dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel chromatography (eluent: dichloromethane/methanol (v:v = 3:1) to give **AX** (yield: 85%) as a white solid. LC-MS (ES^+): *m/z* 195.95[MH^+], t_R = 0.22 min (2.0 minute run).

[0568] Step 2: Synthesis of 2-{2-[benzyl(methyl)amino]ethoxy}ethan-1-ol (**AY**)

[0569] To a stirred solution of of 2-[2-(benzylamino)ethoxy]ethan-1-ol (**AX**, 10.0 g) in methanol (200 mL) was added formaldehyde (38% in water) (4.9 mL) and triacetoxyborohydride (17.0 g) at rt. The resulting solution was stirred at rt for 2 h. Saturated aq. sodium bicarbonate (100 mL) was added to the reaction, and bulk of organic solvent was then removed under reduced pressure. The resulting mixture was extracted with ethyl acetate (200 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate and then concentrated under reduced pressure followed by high vacuum pump to give **AY** (yield: 33%) as a yellow oil. LC-MS (ES^+): *m/z* 210.00 [MH^+], t_R = 0.43 min (2.0 minute run).

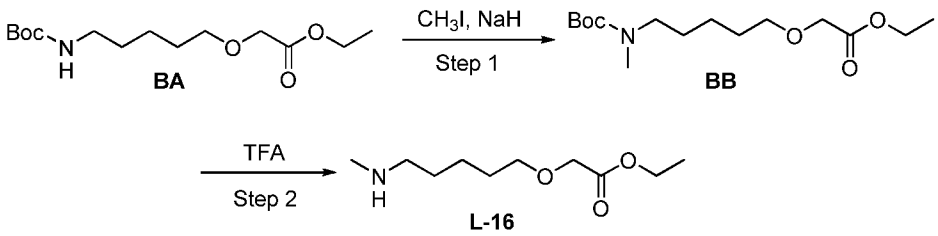
[0570] Step 3: Synthesis of methyl 2-(2-{2-[benzyl(methyl)amino]ethoxy}ethoxy)acetate (**AZ**)

[0571] To a stirred solution of 2-{2-[benzyl(methyl)amino]ethoxy}ethan-1-ol (**AY**, 2 g) in dichloromethane (20 mL) was added a solution of sodium hydroxide (37%) in water (20 mL) followed by tert-butyl 2-bromoacetate (7.76 g) and TBAC (2.78 g) at rt. The resulting mixture was stirred at rt for 15 h. The aqueous layer was separated, and to which aq. hydrogen chloride (4N) was added to adjust the pH to ~3 before it was concentrated under reduced pressure to give a crude residue. Methanol (20 mL) was then added to this residue and insoluble salts were filtered out. The solution was concentrated under vacuum to give 2-(2-[2-[benzyl(methyl)amino]ethoxy]ethoxy)acetic acid (yield: 78%) as a yellow oil. To a stirred solution of 2-(2-{2-[benzyl(methyl)amino]ethoxy}ethoxy)acetic acid (2 g, 7.48 mmol, 1.00 equiv) prepare above in methanol (50 mL) was slowly added sulfuric acid (2 mL) at rt. The resulting solution was stirred at 70 ^{o}C in an oil bath for 3h. The bulk of solvent was removed under reduced pressure to give a residue, which was diluted with H_2O (30 mL). Sodium carbonate was then added to the mixture to adjust the pH to ~8. The mixture was then extracted with ethyl acetate (50 mL x 2), the organic layers were combined, dried over anhydrous sodium sulfate and then concentrated under reduced pressure followed by high vacuum pump to give **AZ** (yield: 29%) as a yellow oil. LC-MS (ES^+): *m/z* 281.95 [MH^+], t_R = 0.30 min (2.0 minute run).

[0572] Step 4: Synthesis of methyl 2-{2-[2-(methylamino)ethoxy]ethoxy}acetate (**L-15**)

[0573] To a stirred mixture of methyl 2-(2-{2-[benzyl(methyl)amino]ethoxy}ethoxy)acetate (**AZ**, 600 mg, 2.13 mmol) and palladium on carbon (300 mg) in methanol (30 mL) under a nitrogen atmosphere was charged with hydrogen gas via a balloon. The resulting mixture was stirred at rt for 15 h. The solid material was removed by filtration and the solution was concentrated under vacuum to give **L-15** (400 mg) as yellow oil, which was used for next step without any further purifications. LC-MS (ES^+): *m/z* 191.95 [MH^+], t_R = 0.31 min (2.0 minute run).

[0574] **L-16: ethyl 2-(5-(methylamino)pentyloxy)acetate**



[0575]

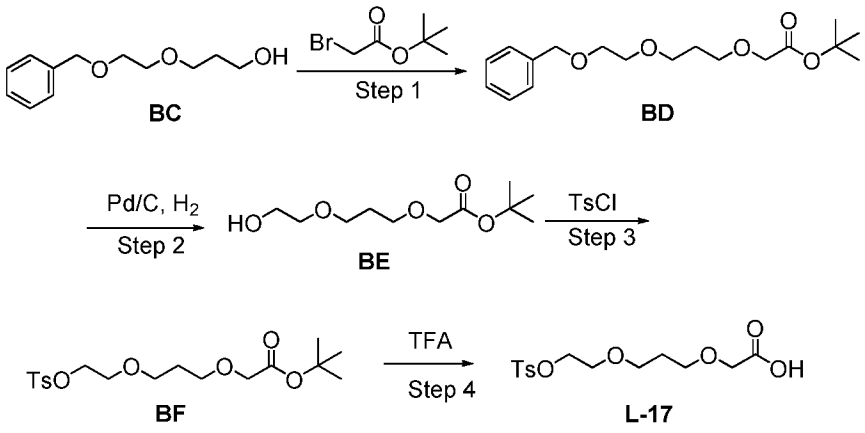
[0576] Step 1: Synthesis of ethyl 2-[(5-{[(tert-butoxy)carbonyl](methyl)amino}pentyl)oxy]acetate (**BB**)

[0577] To a stirred solution of ethyl 2-[(5-{[(tert-butoxy)carbonyl]amino}pentyl)oxy]acetate (**BA**, 1.1 g, 3.8 mmol) in N,N-dimethylformamide (10 mL) was added CH_3I (0.71 mL, 11.4 mmol) at 0 °C, followed by sodium hydride (304 mg, 7.60 mmol, 60% in mineral oil) in several portions at 0 °C. The resulting mixture was stirred at rt for 16 h. Water (1.0 mL) was added and the resulting mixture was extracted with ethyl acetate (50 mL x 2). The organic layers were combined, washed with saturated aqueous solution of sodium chloride (100 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue which was purified by a flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v: v = 1: 10)) to give **BB** (yield: 21%) as a yellow oil. LC-MS (ES^+): m/z 326.20 [MNa^+], t_R = 1.55 min (2.6 minute run).

[0578] Step 2: Synthesis of ethyl 2-{[5-(methylamino)pentyl]oxy}acetate (**L-16**)

[0579] To a stirred solution of ethyl 2-[(5-{[(tert-butoxy)carbonyl](methyl)amino}pentyl)oxy]acetate (**BB**, 240 mg, 0.79 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (0.5 mL). The resulting solution was stirred at rt for 16 h. The solvents were removed under recued pressure followed by high vacuum pump to give **L-16** (yield: 99%) as a yellow oil. LC-MS (ES^+): m/z 204.20 [MH^+], t_R = 0.56 min (2.0 minute run).

[0580] L-17: 2-(3-(2-(tosyloxy)ethoxy)propoxy)acetic acid



[0581]

[0582] Step 1: Synthesis of tert-butyl 2-{3-[2-(benzyloxy)ethoxy]propoxy}acetate (**BD**)

[0583] To a stirred solution of 3-[2-(benzyloxy)ethoxy]propan-1-ol (**BC**, 1.8 g, 8.56 mmol) and tert-butyl 2-bromoacetate (6.6 g, 33.84 mmol, 4.00 equiv) in dichloromethane (40 mL) was added TBAC (2.4 g) and aq. Solution of sodium hydroxide (37%, 40 mL). The resulting mixture was stirred at rt overnight. LC-MS indicated formation of the desired product. The reaction mixture was then extracted with ethyl acetate (150 x 3 mL), the organic layers combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude residue, which was purified by a flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v : v = 1 : 2) to give **BD** (yield: 90%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.27 (m, 5H), 4.57 (s, 2H), 3.94 (s, 2H), 3.63-3.57 (m, 8H), 1.96-1.87 (m, 2H), 1.47 (s, 9H); LC-MS (ES^+): *m/z* 347.10 [MNa^+], t_R = 1.72 min (2.6 minute run).

[0584] Step 2: Synthesis of tert-butyl 2-[3-(2-hydroxyethoxy)propoxy]acetate (**BE**)

[0585] To a stirred mixture of tert-butyl 2-{3-[2-(benzyloxy)ethoxy]propoxy}acetate (**BD**, 2.5 g, 7.71 mmol) and palladium on carbon (2.0 g) in methanol (20 mL) under a nitrogen atmosphere was introduced hydrogen gas via a balloon. The resulting mixture was stirred overnight at rt under hydrogen gas atmosphere. LC-MS indicated completion of the reaction. The solids were removed by filtration, the solution was concentrated under vacuum to give **BE** (yield: 99%) as a colorless oil. LC-MS (ES^+): m/z 257.10 [MNa^+], t_R = 1.21 min (2.6 minute run).

[0586] Step 3: Synthesis of tert-butyl 2-(3-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}propoxy)acetate (**BF**)

[0587] To a stirred solution of tert-butyl 2-[3-(2-hydroxyethoxy)propoxy]acetate (**BE**, 1.8 g, 7.68 mmol) in dichloromethane (50 mL) was added 4-toluenesulfonyl chloride (2.2 g, 11.54 mmol), triethylamine (2.33 g, 23.03 mmol) and 4-dimethylaminopyridine (95 mg, 0.78 mmol).

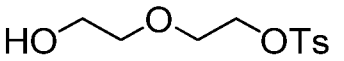
The resulting mixture was stirred overnight at rt. LC-MS indicated formation of the desired product. The reaction mixture was concentrated under reduced pressure to give a crude residue, which was purified by a flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v : v = 1 : 2) to give **BF** (yield: 80%) as a yellow oil.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 4.15 (t, J = 3.6 Hz, 2H), 3.93 (s, 2H), 3.61 (t, J = 3.6 Hz, 2H), 3.55-3.49 (m, 4H), 2.45 (s, 3H), 1.85-1.78 (m, 2H), 1.48 (s, 9H); LC-MS (ES$^+$): *m/z* 411.00 [MNa$^+$], t_R = 1.12 min (2.0 minute run).

[0588] Step 4: Synthesis of 2-(3-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}propoxy)acetic acid (**L-17**)

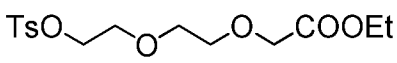
[0589] To a stirred solution of tert-butyl 2-(3-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}propoxy)acetate (**BF**, 400 mg, 1.03 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL) at rt. The resulting solution was stirred at rt for 1 h. LC-MS indicated completion of the reaction. The reaction mixture was concentrated under reduced pressure to give **L-17** (350 mg) as a yellow oil, which was used for next step without further purifications. LC-MS (ES$^+$): *m/z* 332.90 [MH$^+$], t_R = 0.81 min (2.0 minute run).

[0590] Unless otherwise noted, the following intermediates and their analogs (for examples, but not limited to, analogs with substitutions such as halogens) were synthesized according to similar procedures described above for the synthesis of **L-17**, by utilizing corresponding starting materials and reagents.

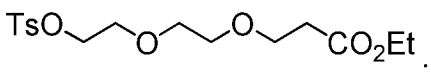
[0591] L-18: 2-(2-hydroxyethoxy)ethyl 4-methylbenzenesulfonate

[0592] 

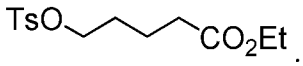
[0593] L-19: ethyl 2-(2-(2-(tosyloxy)ethoxy)ethoxy)acetate

[0594] 

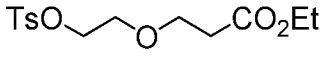
[0595] L-20: ethyl 3-(2-(2-(tosyloxy)ethoxy)ethoxy)propanoate

[0596] 

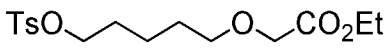
[0597] L-21: ethyl 5-(tosyloxy)pentanoate

[0598] 

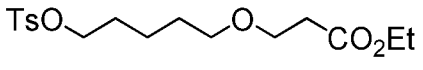
[0599] **L-22: ethyl 3-(2-(tosyloxy)ethoxy)propanoate**

[0600] 

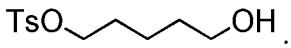
[0601] **L-23: ethyl 2-(5-(tosyloxy)pentyloxy)acetate**

[0602] 

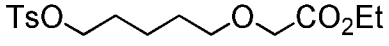
[0603] **L-24: ethyl 3-(5-(tosyloxy)pentyloxy)propanoate**

[0604] 

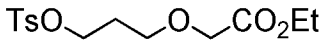
[0605] **L-25: 5-hydroxypentyl 4-methylbenzenesulfonate**

[0606] 

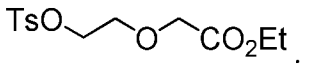
[0607] **L-26: ethyl 2-(5-(tosyloxy)pentyloxy)acetate**

[0608] 

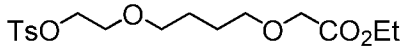
[0609] **L-27: ethyl 2-(3-(tosyloxy)propoxy)acetate**

[0610] 

[0611] **L-28: ethyl 2-(2-(tosyloxy)ethoxy)acetate**

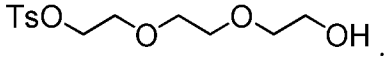
[0612] 

[0613] **L-29: ethyl 2-(4-(2-(tosyloxy)ethoxy)butoxy)acetate**

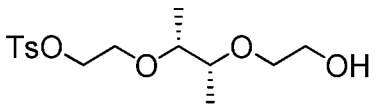


[0614] **L-29**

[0615] **L-30: 2-(2-(2-hydroxyethoxy)ethoxy)ethyl 4-methylbenzenesulfonate**

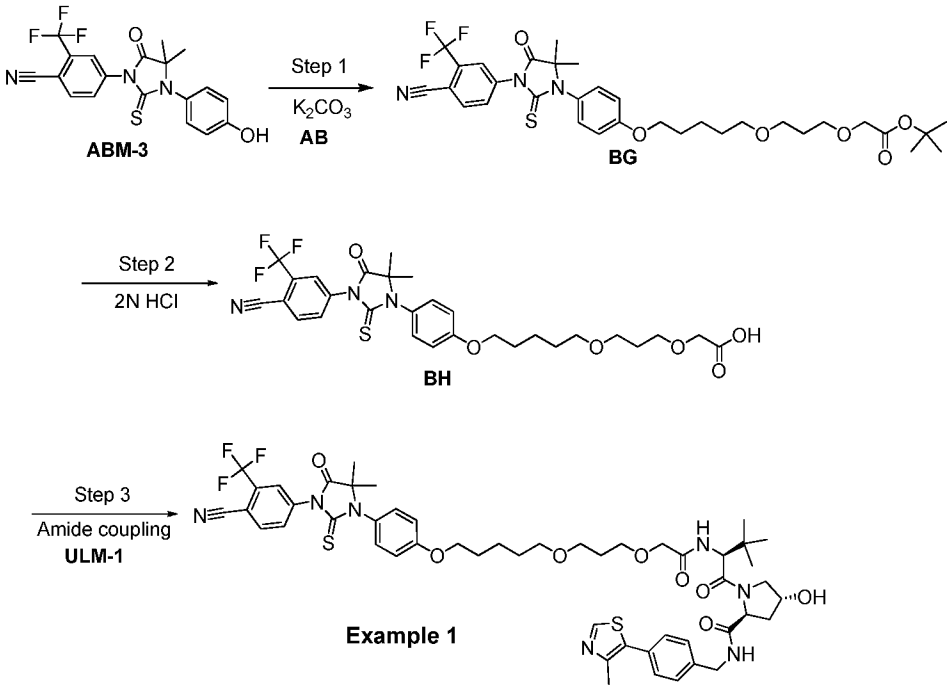
[0616] 

[0617] **L-31: 2-((2R,3R)-3-(2-hydroxyethoxy)butan-2-yloxy)ethyl 4-methylbenzenesulfonate**

[0618] 

[0619] **Synthesis of Examples**

[0620] **Example 1: (2S,4R)-1-((S)-2-(2-(3-(5-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)pentyloxy)propoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**



[0621]

[0622] Step 1: Synthesis of tert-butyl 2-(3-{[5-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)pentyl]oxy}propoxy)acetate (**BG**)

[0623] To a stirred solution of tert-butyl 2-[3-[(5-[[(4-methylbenzene)sulfonyl]oxy]pentyl)oxy]propoxy]acetate (**AB**, 150 mg, 0.35 mmol) in acetonitrile (10 mL) was added 4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-sulfanylideneimidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile (**ABM-3**, 141 mg, 0.35 mmol) and potassium carbonate (144 mg, 1.04 mmol). The resulting mixture was stirred overnight at 80 °C in an oil bath. LC-MS indicated formation of the desired product. The reaction mixture was then extracted with ethyl acetate (20 mL x 2). The organic layers were combined, washed with

saturated aqueous solution of sodium chloride (20 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether, v: v = 1:1) to give 0.22 g of **BG** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 2H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 2H), 4.50 (s, 2H), 4.30 (t, *J* = 6.4 Hz, 2H), 4.02 (t, *J* = 6.4 Hz, 2H), 3.53 (m, 2H), 3.44 (m, 2H), 1.96-1.80 (m, 4H), 1.69-1.53 (m, 2H), 1.49 (s, 6H), 1.48 (s, 9H), 1.44-1.22 (m, 2H); Mass (ES^+): *m/z* 686.35 [MNa^+].

[0624] Step 2: synthesis of 2-(3-[[5-(4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenoxy)pentyl]oxy]propoxy)acetic acid (**BH**)

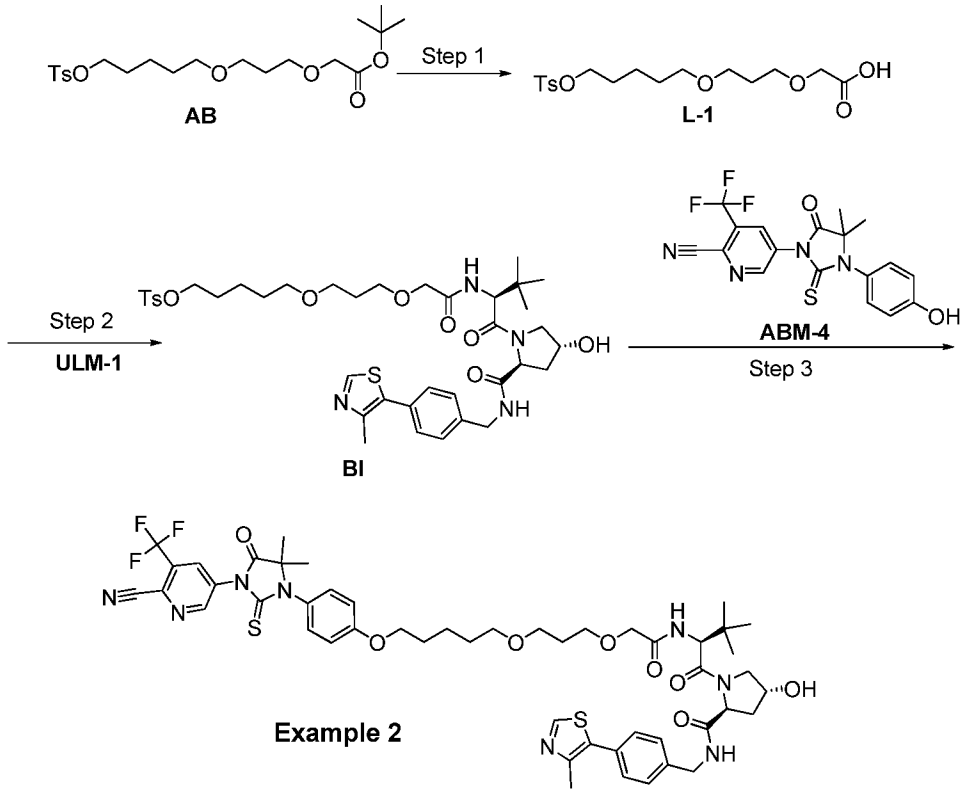
[0625] To a stirred solution of tert-butyl 2-(3-{[5-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)pentyl]oxy}propoxy)acetate (**BG**, 220 mg, 0.33 mmol) in dioxane (4.0 mL) was added hydrogen chloride (2N in water, 1.0 mL). The resulting mixture was stirred at 80 °C for 2h. LC-MS indicated formation of the desired product. The resulting mixture was concentrated under reduced pressure to provide 200 mg of **BH** as light yellow oil. Mass (ES^+): m/z 608.25 [MH^+].

[0626] Step 3: Synthesis of Example 1:

[0627] To a stirred solution of 2-(3-[[5-(4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenoxy)pentyl]oxy]propoxy)acetic acid (**BH**, 160 mg, 0.26 mmol) in N,N-dimethylformamide (5 mL) was added (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide hydrochloride (**ULM-1**, 182 mg, 0.39 mmol), DIPEA (151 mg, 1.17 mmol), EDCI (101 mg, 0.53 mmol) and HOBt (70 mg, 0.52 mmol). The resulting mixture was stirred at rt for 5 h and LC-MS indicated formation of the desired product. Water (20 mL) was added to the reaction, the resulting mixture was extracted with ethyl acetate (20 mL x 2). The organic layers were combined, washed with saturated aqueous solution of sodium chloride (20 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue. The residue was purified by Prep-HPLC to give 60 mg of **Example 1** as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 8.88 (s, 1H), 8.16 (d, *J* = 8.0 Hz, 2H), 8.00 (s, 1H), 7.49-7.42 (m, 4H), 7.28 (d, *J* = 8.8 Hz, 2H), 7.06 (m, 2H), 4.87 (s, 1H), 4.59 (m, 3H), 4.37 (m, 1H), 4.05 (m, 4H), 3.88 (m, 2H), 3.65 (m, 2H), 3.58 (m, 2H), 3.50 (m, 2H), 2.48 (s, 3H), 2.25 (m, 1H), 2.10 (m, 1H),

1.90 (m, 2H), 1.80 (m, 2H), 1.66 (m, 2H), 1.56 (s, 8H), 1.04 (s, 9H); LC-MS (ES^+): *m/z* 1020.20 [MH^+], t_R = 2.28 min (3.6 minute run).

[0628] Example 2: (2S,4R)-1-((S)-2-(2-(3-(5-(4-(3-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)pentyloxy)propoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide:



[0629] Step 1: Synthesis of 2-[3-({5-[(4-methylbenzenesulfonyl)oxy]pentyl}oxy)propoxy]acetic acid (**L-1**)

[0630] To a stirred solution of tert-butyl 2-[3-({5-[(4-methylbenzenesulfonyl)oxy]pentyl}oxy)propoxy]acetate (**AB**, 1.3 g, 3.02 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (10 mL) at rt. The resulting solution was stirred at rt for 3 h. The reaction mixture was then concentrated under vacuum to give 1.5 g (crude) of **L-1**, which was used for next step without any further purification. LC-MS (ES^+): *m/z* 375.34 [MH^+], t_R = 1.39 min (2.6 minute run).

[0631] Step 2: Synthesis of (2S,4R)-1-[(2S)-3,3-dimethyl-2-{2-[3-({5-[(4-methylbenzenesulfonyl)oxy]pentyl}oxy)propoxy]acetamido}butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**BI**)

[0632] To a stirred solution 2-[3-({5-[(4-methylbenzenesulfonyl)oxy]pentyl}oxy)propoxy]acetic acid (**L-1**, 1.5 g, 4.01 mmol) in N,N-dimethylformamide (20 mL) was added HATU (1.36 g, 3.58 mmol), DIEA (0.7 mL) and (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**ULM-1**, 1.3 g, 3.02 mmol) at rt. The resulting mixture was stirred for 2h at rt. It was then diluted with water (100 mL) and extracted with ethyl acetate (100 mL x 3). The organic layers were combined, washed with saturated aqueous solution of sodium chloride (60 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel chromatography (eluent: dichloromethane/methanol (v: v = 10:1)) to give 0.5 g of **BI**. LC-MS (ES^+): *m/z* 787.34 [MH^+], t_R = 1.87 min (3.0 minute run).

[0633] Step 3: Synthesis of (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{3-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)pentyl]oxy}propoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Example 2**)

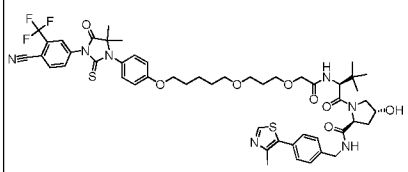
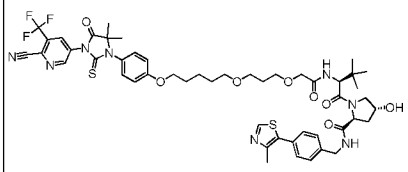
[0634] To a stirred solution of 5-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-sulfanylideneimidazolidin-1-yl]-3-(trifluoromethyl)pyridine-2-carbonitrile (**ABM-4**, 52 mg, 0.13 mmol), (2S,4R)-1-[(2S)-3,3-dimethyl-2-{2-[3-({5-[(4-methylbenzenesulfonyl)oxy]pentyl}oxy)propoxy]acetamido}butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**BI**, 100 mg, 0.13 mmol) in N,N-dimethylformamide (10 mL) was added potassium carbonate (34 mg, 0.25 mmol) under an atmosphere of nitrogen. The resulting solution was stirred for 2 h at 80°C. The resulting mixture was concentrated under vacuum to give a crude residue, which was purified by Prep-HPLC to give 38.1 mg of Example 2 as a white solid. ^{1}H NMR (300 MHz, CD_3OD): δ 9.12 (s, 1H), 8.83(s, 1H), 8.63 (s, 1H), 7.44-7.39 (m, 4H), 7.00 (d, *J* = 9.0 Hz, 2H), 7.20 (d, *J* = 9.0 Hz, 2H), 4.80-4.26 (m, 5H), 4.06-3.65 (m, 6H), 3.62-3.35 (m, 6H), 2.43 (s, 3H) , 2.21-2.01 (m, 2H), 1.85-

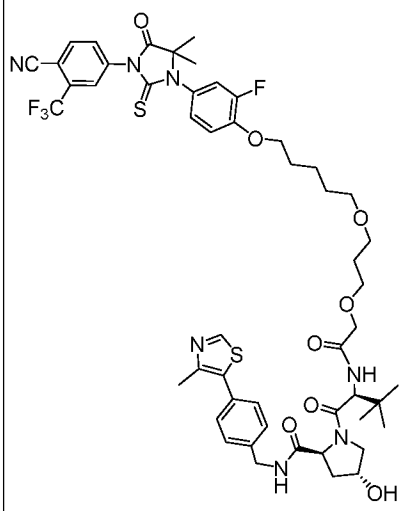
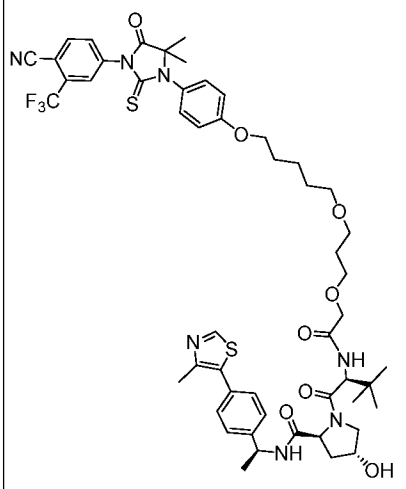
1.65 (m, 4H), 1.60-1.42 (m, 10H), 1.00 (s, 9H): LC-MS (ES^+): *m/z* 1021.12 [MH^+], t_R = 2.36 min (3.6 minute run).

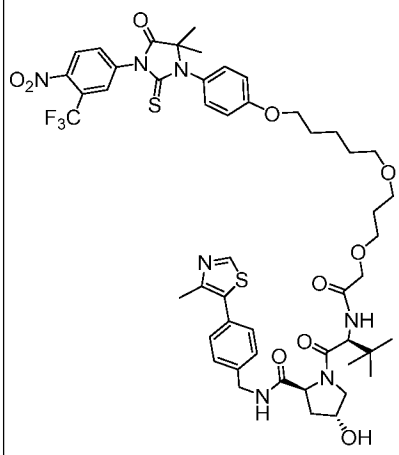
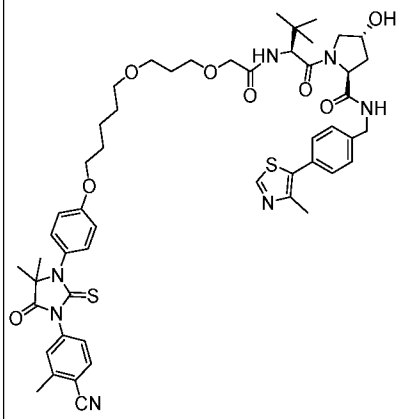
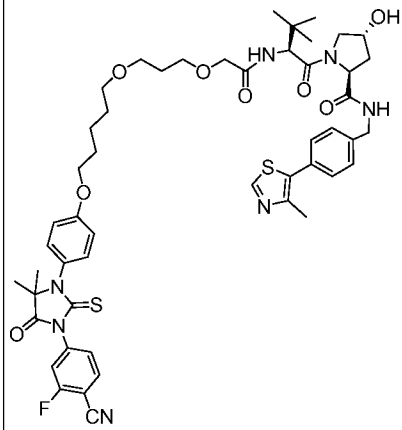
[0635] Unless otherwise noted, the following examples were synthesized according to analogous procedures described above for synthesis of examples 1 and 2, utilizing corresponding reagents, intermediates, and starting materials.

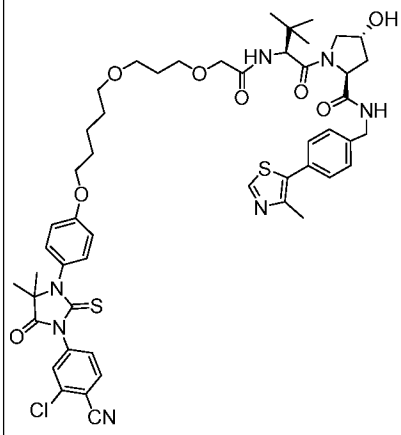
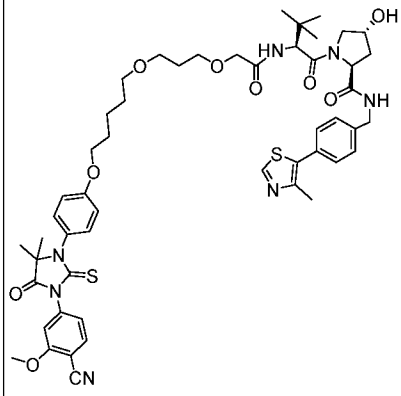
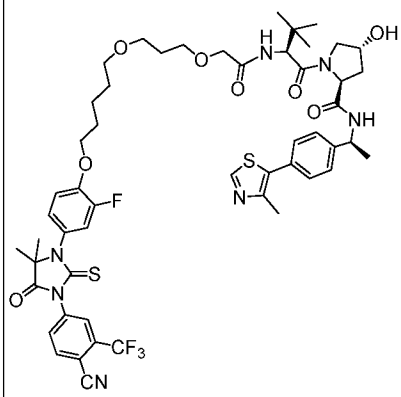
[0636] When referring to the specific exemplary compounds presented herein, the specification uses the terms "example #." For example, compound 1 (Table 2) is also referred to as Example 1.

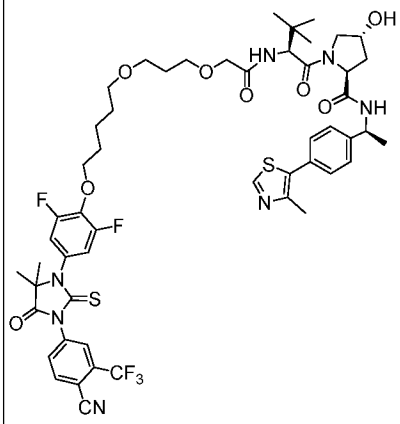
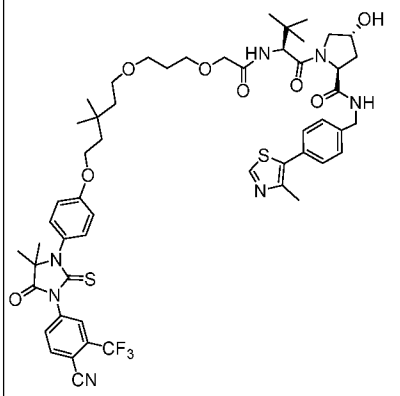
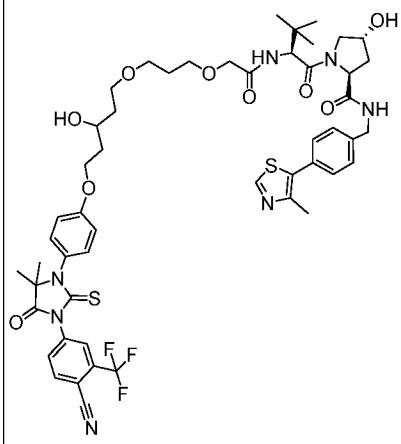
[0637] Table 2. Exemplary Compounds.

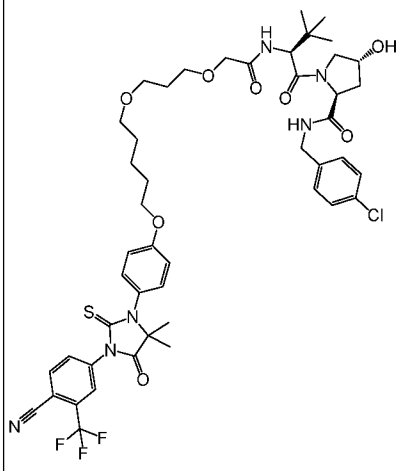
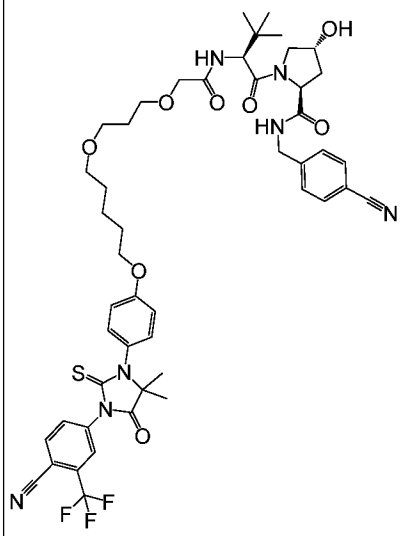
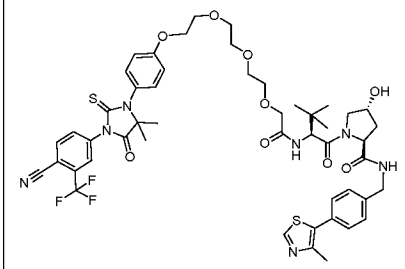
Ex #	Structure	Compound name and Analytical data
1		(2S,4R)-1-((S)-2-(2-(3-(5-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)pentyloxy)propoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide 1H NMR (400 MHz, CDCl3): δ 7.96 (s, 2H), 7.86 (d, J = 8.6 Hz, 1H), 7.19 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.6 Hz, 2H), 4.50 (s, 2H), 4.30 (t, J = 6.4 Hz, 2H), 4.02 (t, J = 6.4 Hz, 2H), 3.53 (m, 2H), 3.44 (m, 2H), 1.96-1.80 (m, 4H), 1.69-1.53 (m, 2H), 1.49 (s, 6H), 1.48 (s, 9H), 1.44-1.22 (m, 2H); Mass (ES+): m/z 686.35 [MNa+]
2		(2S,4R)-1-((S)-2-(2-(3-(5-(4-(3-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)pentyloxy)propoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide 1H NMR (300 MHz, CD3OD): δ 9.12 (s, 1H), 8.83(s, 1H), 8.63 (s, 1H), 7.44-7.39 (m, 4H), 7.00 (d, J = 9.0 Hz, 2H), 7.20 (d, J = 9.0 Hz, 2H), 4.80-4.26 (m, 5H), 4.06-3.65 (m, 6H), 3.62-3.35 (m, 6H), 2.43 (s, 3H) , 2.21-2.01 (m, 2H), 1.85-1.65 (m, 4H), 1.60-1.42 (m, 10H), 1.00 (s, 9H): LC-MS (ES+): m/z 1021.12 [MH+], tR = 2.36 min (3.6 minute run).

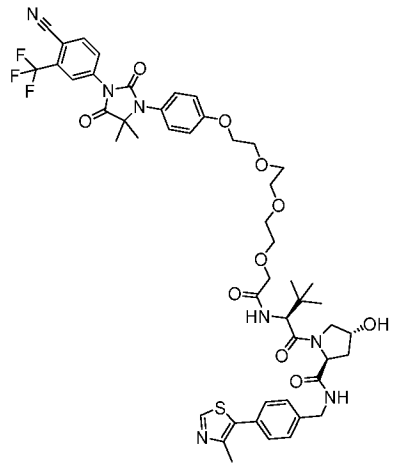
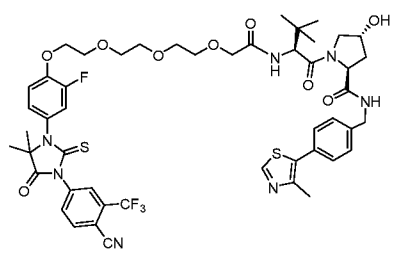
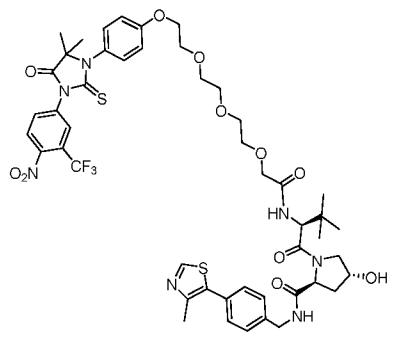
Ex #	Structure	Compound name and Analytical data
3		Prepared from **ABM-16**, **L-1**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluorophenoxy)pentyl]oxy}propoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD) : δ 8.84 (s, 1H), 8.13-8.09 (m, 2H), 8.01-7.93 (m, 1H), 7.51-7.31 (m, 4H), 7.21-7.01 (m, 3H), 4.70-4.41 (m, 4H), 4.35-4.22 (m, 1H), 4.15-4.03 (m, 2H), 3.95-3.90 (m, 2 H), 3.90-3.73 (m, 2H), 3.61-3.56 (m, 2 H), 3.56-3.51 (m, 2 H), 3.50-3.42 (m, 2 H), 2.45 (s, 3H), 2.21-2.10 (m, 1 H), 2.10-2.12 (m, 1H), 1.92-1.70 (m, 4H), 1.63-1.50 (m, 3 H), 3.50-1.45(m, 7H), 1.04 (s, 9H); LC-MS (ES^+): *m/z* 1038.31 [MH^+], t_R = 2.35 min (3.6 minute run)
4		Prepared from **ABM-3**, **L-1**, and **ULM-3** (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)pentyl]oxy}propoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD):δ8.88 (s, 1H), 8.58 (d, *J* = 7.5 Hz, 1H), 8.16 (m, 2H), 8.00 (m, 1H), 7.53 (d, *J* = 9.3 Hz, 1H), 7.42 (m, 4H), 7.26 (m, 2H), 7.05 (m, 2H), 5.01 (m, 1H), 4.72 (d, *J* = 9.3 Hz, 1H), 4.58 (m, 1H), 4.44 (s, 1H), 4.04 (m, 4H), 3.83-3.49 (m, 8H), 2.48 (s, 3H), 2.20 (m, 1H), 1.83 (m, 5H), 1.50 (m, 13H), 1.03 (s, 9H); LC-MS (ES^+): *m/z* 518.20 [M+2] /2, t_R = 3.67 min, (5.6 minute run)

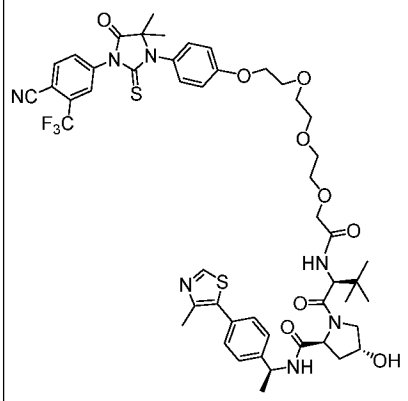
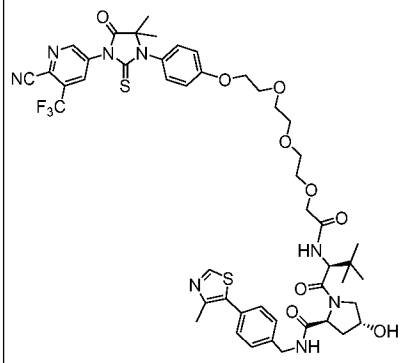
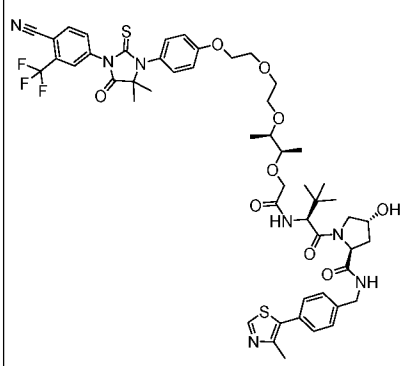
Ex #	Structure	Compound name and Analytical data
5		Prepared from **ABM-17**, **L-1**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{5,5-dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl]-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)pentyl]oxy}propoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD) : δ 8.82 (s, 1H), 8.15-8.13 (m, 2H), 8.01-7.93 (m, 1H), 7.51-7.31 (m, 4H), 7.22-7.22 (m, 2H), 7.22-7.05 (m, 2H), 4.71 (s, 1 H), 4.60-4.35 (m, 3 H), 4.32-4.24 (m, 1H), 4.120-3.95 (m, 4H), 3.93-3.75 (m, 2H), 3.62- 3.52 (m, 2 H), 3.51-3.41 (m, 2 H), 3.40--3.35 (m, 2H), 2.45 (s, 3H), 2.24-2.10 (m, 1H), 2.09-2.01 (m, 1H), 1.90-1.72 (m, 4H), 1.65-1.52 (m, 3 H), 1.51-1.34(m, 7H), 1.00 (s, 9H); LC-MS (ES^+): *m/z* 1040.32 [MH^+], t_R = 2.52 min (3.6 minute run)
6		Prepared from **ABM-6**, **L-1**, and **ULM-1** (2S,4R)-1-[(2S)-2-(2-{3-[(5-{4-[3-(4-cyano-3-methylphenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenoxy}pentyl)oxy]propoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamid ^{1}H NMR (400 MHz, CD_3OD):δ8.88 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.53 (m, 6H),7.28 (d, *J* = 9.2 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 4.71 (s, 1H), 4.59 (m, 3H), 4.39 (d, *J* = 15.6 Hz, 1H), 4.05 (m, 4H), 3.88 (m, 2H), 3.68 (m, 4H), 3.52 (m, 2H), 2.61 (s, 3H), 2.50 (s, 3H), 2.25 (m, 1H), 2.10 (m, 1H), 1.93 (m, 4H), 1.68 (m, 10H), 1.06 (s, 9H); LC-MS (ES^+): *m/z* 483.95 [M+2] /2, t_R =2.28 min (3.60 minute run).
7		Prepared from **ABM-2**, **L-1**, and **ULM-1** (2S,4R)-1-[(2S)-2-(2-{3-[(5-{4-[3-(4-cyano-3-fluorophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenoxy}pentyl)oxy]propoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD3OD): δ 8.87 (s, 1H), 7.91 (t, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.54-7.41 (m, 5H), 7.26 (d, *J* = 8.7, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 4.70 (s, 1H), 4.61-4.4.51 (m, 3H), 4.37-4.32 (m, 1H), 4.04-3.98 (m, 4H), 3.98-3.81 (m, 2H), 3.67-3.63 (m, 2H), 3.57 (t, *J* = 6.6 Hz, 2H), 3.57 (t, *J* = 6.6Hz, 1H), 2.48 (s, 3H), 2.23-2.09 (m, 2H), 1.92-1.79 (m, 4H), 1.67-1.53 (m, 10H), 1.03 (s, 9H); LC-MS (ES^+): *m/z* 970.55 [MH^+], t_R = 1.55 min (3.6 minute run)

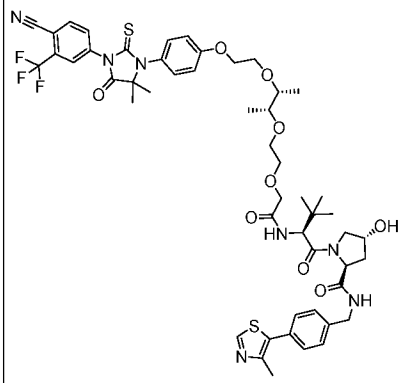
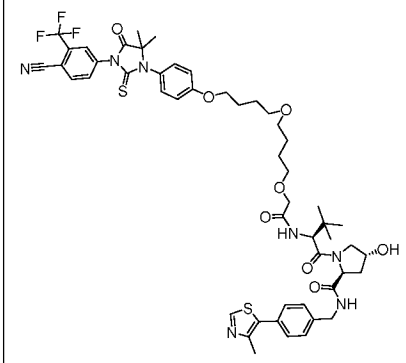
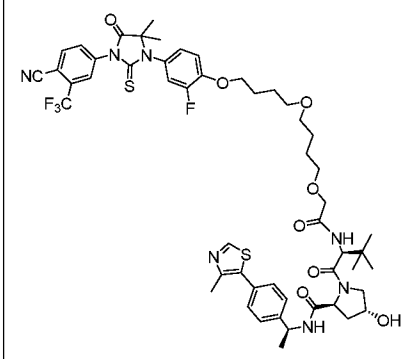
Ex #	Structure	Compound name and Analytical data
8		Prepared from **ABM-1**, **L-1**, and **ULM-1** 2S,4R)-1-[(2S)-2-(2-{3-[(5-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenoxy}pentyl)oxy]propoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD):δ9.00 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.87 (s, 1H),7.66 (d, J = 10.4 Hz,1H), 7.50 (m, 4H), 7.29 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 4.71 (s, 1H), 4.62 (m, 3H), 4.39 (d, J = 15.6 Hz, 1H), 4.05 (m, 4H), 3.89 (m, 2H), 3.68 (m, 4H), 3.52 (m, 2H), 2.50 (s, 3H), 2.25 (m, 1H), 2.10 (m, 1H), 1.93(m, 4H), 1.68 (m, 2H), 1.59 (m, 8H), 1.05 (s, 9H); LC-MS (ES^+): m/z 986.25 [MH^+] , t_R =3.44 min. (5.00 minute run)
9		Prepared from **ABM-5**, **L-1**, and **ULM-1** (2S,4R)-1-[(2S)-2-(2-{3-[(5-{4-[3-(4-cyano-3-methoxyphenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenoxy}pentyl)oxy]propoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.88 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.49-7.42 (m, 4H), 7.37 (d, J = 1.6 Hz, 1H), 7.18-7.16 (m, 3H), 7.06-7.04 (m, 2H), 4.71 (s, 1H), 4.62-4.54 (m, 3H), 4.39 (d, J = 15.6 Hz, 1H), 4.05-4.00 (m, 7H), 3.91-3.80 (m, 2H), 3.72-3.49 (m, 6H), 2.50 (s, 3H), 2.27-2.07 (m, 2H), 1.93-1.81 (m, 4H), 1.66-1.56 (m, 10H), 1.06 (s, 9H); LC-MS (ES^+): m/z 982.55 [MH^+], t_R = 2.67 min (5.0 minute run)
10		Prepared from **ABM-16**, **L-1**, and **ULM-3** (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluorophenoxy)pentyl]oxy}propoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, DMSO) δ 8.98 (s, 1H), 8.44-8.40 (m, 2H), 8.27 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.45-7.28 (m, 7H), 7.17 (d, J = 8.7 Hz, 1H), 5.12 (d, J = 3.3 Hz, 1H), 4.92-4.88 (m, 1H), 4.52-4.45 (m, 2H), 4.28 (s, 1H), 4.12 (t, J = 6.6 Hz, 2H), 3.92 (s, 2H), 3.58-3.38 (m, 8H), 2.45 (s, 3H), 2.08-2.02 (m, 1H), 1.83-1.74 (m, 5H), 1.61-1.46 (m, 11H), 1.38 (d, J = 6.9 Hz, 2H), 0.93 (s, 9H); LC-MS (ES^+): m/z 1052.40 [MH^+], t_R = 1.79 min

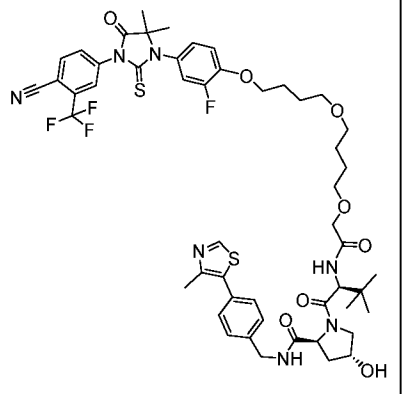
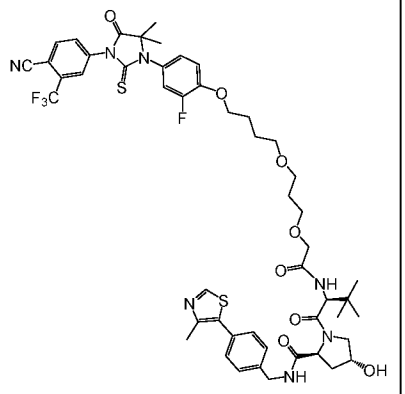
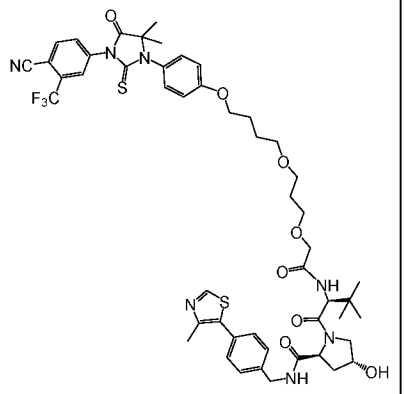
Ex #	Structure	Compound name and Analytical data
11		Prepared from **ABM-18**, **L-1**, and **ULM-3** (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2,6-difluorophenoxy)pentyl]oxy}propoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO) δ 8.98 (s, 1H), 8.45-8.39 (m, 2H), 8.26 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.44-7.28 (m, 7H), 5.12 (d, *J* = 3.6 Hz, 1H), 4.92-4.88 (m, 1H), 4.55 (d, *J* = 9.6 Hz, 1H), 4.44 (t, *J* = 8.0 Hz, 1H), 4.28 (s, 1H), 4.20 (t, *J* = 6.8 Hz, 2H), 3.91 (s, 2H), 3.57-3.37 (m, 8H), 2.45 (s, 3H), 2.08-2.02 (m, 1H), 1.80-1.71 (m, 5H), 1.61-1.46 (m, 10H), 1.38 (d, *J* = 6.8 Hz, 3H), 0.93 (s, 9H); Mass (ES$^+$): *m/z* 1070.50 [MH$^+$]
12		Prepared from **ABM-3**, **L-2**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)-3,3-dimethylpentyl]oxy}propoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.88 (s, 1H), 8.15 (m, 2H), 8.01 (m, 1H), 7.49 (m, 4H), 7.30 (d, *J* = 9.2 Hz, 2H), 7.06 (d, *J* =8.8 Hz, 2H), 4.71 (s, 1H), 4.61 (m, 3H), 4.39 (m, 1H), 4.13 (m, 2H), 3.98 (m, 2H), 3.88 (m, 1H), 3.84 (m, 1H), 3.66 (m, 2H), 3.59 (m, 4H), 2.49 (s, 3H), 2.28 (m, 1H), 2.14 (m, 1H), 1.91 (m, 2H), 1.81 (m, 2H), 1.64 (m, 2H), 1.56 (s, 6H), 1.05 (m, 15H); LC-MS (ES$^+$): *m/z* 1048.55 [MH$^+$], t_R = 1.86 min (3.0 minute run).
13		Prepared from **ABM-3**, **L-3**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)-3-hydroxypentyl]oxy}propoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.86 (s, 1H), 8.16-8.13 (d, *J* = 7.8 Hz, 2H), 8.00-7.96 (d, *J* = 9.9 Hz, 1H), 7.78-7.40 (m, 4H), 7.29-7.26 (d, *J* = 9.9 Hz, 2H), 7.07-7.04 (d, *J* = 8.7 Hz , 2H) , 4.70-4.33 (m, 5H), 4.19-4.13 (m, 2H), 4.04-3.81 (m, 5H), 3.65-3.56 (m, 6H), 2.47 (s, 3H), 2.23-1.70 (m, 8H), 1.54 (s, 6H), 1.02 (d, *J* = 6.0 Hz, 9H). LC-MS (ES$^+$): *m/z* 1036.35 [MH$^+$], t_R = 1.51 min (3.0 minute run).

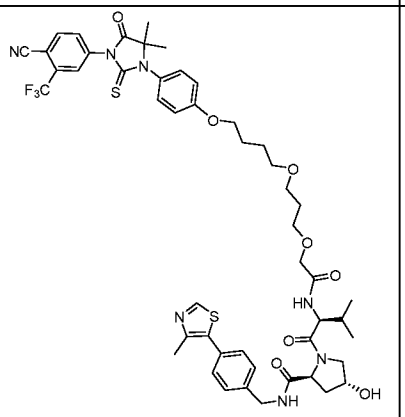
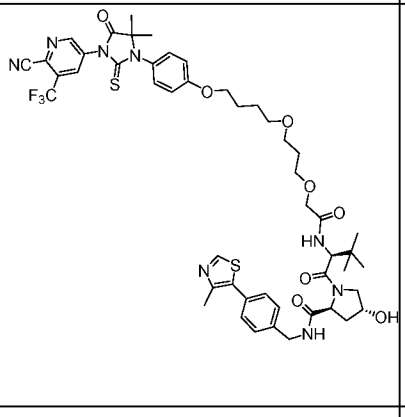
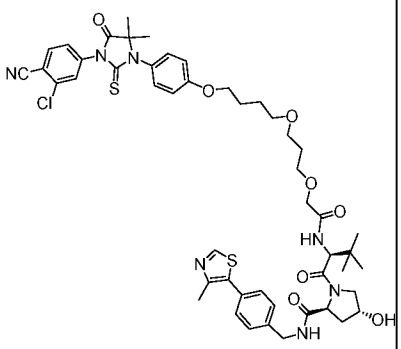
Ex #	Structure	Compound name and Analytical data
14		Prepared from **ABM-3**, **L-1**, and **ULM-6** (2S,4R)-N-[(4-chlorophenyl)methyl]-1-[(2S)-2-[2-(3-{[5-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)pentyl]oxy}propoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxypyrrolidine-2-carboxamide NMR (400 MHz, CD_3OD) δ 8.13-8.17 (m, 2H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.32-7.36 (m, 2H), 7.25-7.31 (m, 4H), 7.05 (d, *J* = 9.0 Hz, 2H), 4.51-4.57 (m, 2H), 4.47 (d, *J* = 16.0 Hz, 2H), 4.27 (d, *J* = 14.9 Hz, 2H), 4.04 (t, *J* = 6.5 Hz, 1H), 3.99 (d, *J* = 3.5 Hz, 2H), 3.64-3.68 (m, 2H), 3.56-3.61 (m, 2H), 3.50 (t, *J* = 6.3 Hz, 2H), 2.17-2.24 (m, 1H), 2.07 (dd, *J* = 3.9, 13.3 Hz, 1H), 1.89-1.92 (m, 2H), 1.81-1.86 (m, 1H), 1.64-1.70 (m, 1H), 1.57-1.61 (m, 1H), 1.30 (br. s., 6H), 0.99-1.07 (m, 9H), 0.91 (t, *J* = 6.8 Hz, 4H). LC-MS (ES^+): *m/z* 957.35 [MH^+]
15		Prepared from **ABM-3**, **L-1**, and **ULM-7** (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)pentyl]oxy}propoxy)acetamido]-3,3-dimethylbutanoyl]-N-[(4-cyanophenyl)methyl]-4-hydroxypyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.11-8.17 (m, 2H), 7.98 (d, *J* = 8.6 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 9.0 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 4.68 (s, 1H), 4.58 (d, *J* = 16.0 Hz, 2H), 4.54 (d, *J* = 9.4 Hz, 1H), 4.48 (br. s., 1H), 4.03 (t, *J* = 6.3 Hz, 2H), 3.97 (d, *J* = 2.7 Hz, 1H), 3.84-3.88 (m, 1H), 3.78 (dd, *J* = 3.5, 11.0 Hz, 1H), 3.61-3.66 (m, 2H), 3.55-3.60 (m, 2H), 3.49 (t, *J* = 6.3 Hz, 2H), 1.88-1.92 (m, 1H), 1.80-1.85 (m, 2H), 1.63-1.68 (m, 2H), 1.55-1.59 (m, 2H), 1.25-1.33 (m, 6H), 1.00 (br. s., 9H), 0.89 (t, *J* = 6.8 Hz, 4H). LC-MS (ES^+): *m/z* 949.38 [MH^+].
16		Prepared from **ABM-3**, **L-4**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-(2-{2-[2-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)ethoxy]ethoxy}ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.89 (s, 1 H), 8.18-8.15 (d, *J* = 8.4 Hz, 2 H), 8.01-7.99 (m, 1 H), 7.49-7.42 (m, 4 H), 7.31-7.28 (d, *J* = 10.0 Hz, 2 H), 7.10-7.07 (m, 2 H), 4.72(s, 1 H), 4.61-4.52(m, 3 H), 4.38-4.34(m, 1 H), 4.19-4.17(m, 2 H), 4.10-4.05(m, 2 H), 3.91-3.80 (m, 4 H), 3.77-3.72 (m, 8 H), 2.49 (s, 3 H), 2.24-2.05 (m, 2 H), 1.54 (s, 6 H), 1.06 (s, 9 H); LC-MS (ES^+): *m/z* 1008.50 [MH^+], t_R = 1.49 min (3.0 minute run).

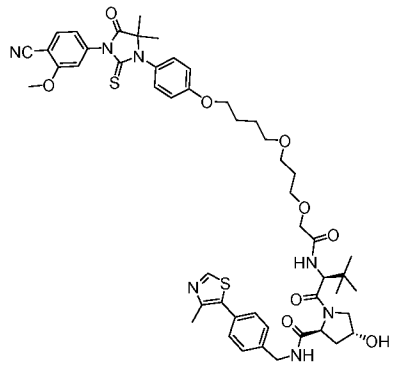
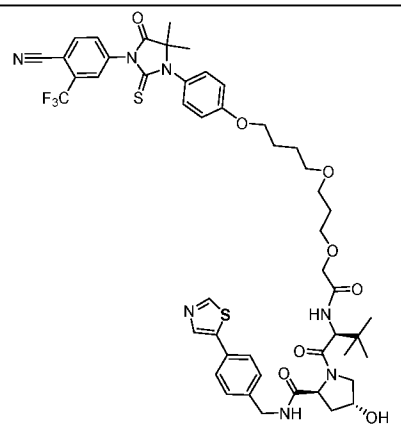
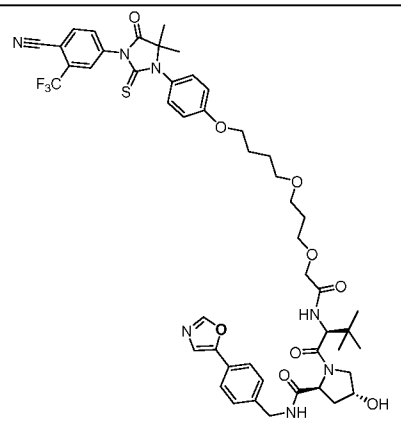
Ex #	Structure	Compound name and Analytical data
17		Prepared from **ABM-19**, **L-4**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-(2-{2-[2-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl}phenoxy)ethoxy]ethoxy}ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.84 - 8.89 (m, 1 H), 8.67 (t, *J* = 5.67 Hz, 1 H), 8.25 (s, 1 H), 8.08 - 8.15 (m, 2 H), 7.67 (d, *J* = 9.00 Hz, 1 H), 7.43 (q, *J* = 8.22 Hz, 4 H), 7.30 (d, *J* = 8.22 Hz, 2 H), 7.00 - 7.08 (m, 2 H), 4.70 (d, *J* = 9.78 Hz, 1 H), 4.45 - 4.61 (m, 3 H), 4.35 (dd, *J* = 15.85, 4.89 Hz, 1 H), 4.12 - 4.17 (m, 2 H), 4.04 (d, *J* = 3.91 Hz, 2 H), 3.77 - 3.90 (m, 4 H), 3.67 - 3.75 (m, 8 H), 2.47 (d, *J* = 0.78 Hz, 3 H), 2.22 (dd, *J* = 12.91, 8.61 Hz, 1 H), 2.03 - 2.12 (m, 1 H), 1.46 - 1.55 (m, 6 H), 0.98 - 1.10 (m, 9 H); Mass (ES^+): *m/z* 992.38 [MH^+]
18		Prepared from **ABM-16**, **L-4**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-(2-{2-[2-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluorophenoxy)ethoxy]ethoxy}ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.89 (s, 1H), 8.18-8.16 (d, *J* = 7.2Hz, 2H), 8.01-7.99 (d, *J* = 8.4 Hz, 1H), 7.49-744 (m, 4H), 7.28-7.21 (m, 2H), 7.16-7.14 (m, 1H), 4.71 (s, 1H), 4.61-4.53 (m, 3H), 4.35-4.31(m, 1H), 4.28-4.26 (m, 2H), 4.10-4.06 (m, 2H), 3.94-3.81 (m, 3H), 3.81-3.80 (m, 1H), 3.80-3.75 (m, 8H), 2.49 (s, 3H), 2.26-2.24 (m, 1H), 2.11-2.09 (m, 1H), 1.57 (s, 6H), 1.03 (s, 9H); LC-MS (ES^+): *m/z* 1026.34 [MH^+], t_R =2.73 min (5.6 minute run).
19		Prepared from **ABM-17**, **L-4**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-(2-{2-[2-(4-{5,5-dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl]-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)ethoxy]ethoxy}ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (400MHz, CD_3OD): δ 8.89 (s, 1H), 8.19-8.16 (m, 2H), 8.05-8.02 (m, 1H), 7.49-7.42 (m, 4H), 7.31-7.29 (d, *J* = 8.8Hz, 2H), 7.09-7.07 (d, *J* = 8.8Hz, 2H), 4.71(s, 1H), 4.61-4.52 (m, 3H), 4.38-4.34 (m, 1H), 4.23-4.17 (m, 2H), 4.06-4.01 (m, 2H), 3.91-3.80 (m, 4H), 3.78-3.68 (m ,8H), 2.49 (s, 3H), 2.27-2.22 (m, 1H), 2.13-2.07 (m, 1H), 1.56 (s, 6H), 1.06 (s, 9H) ; LC-MS (ES^+): *m/z* 1028.50 [MH^+], t_R = 2.62 min (5.0 minute run).

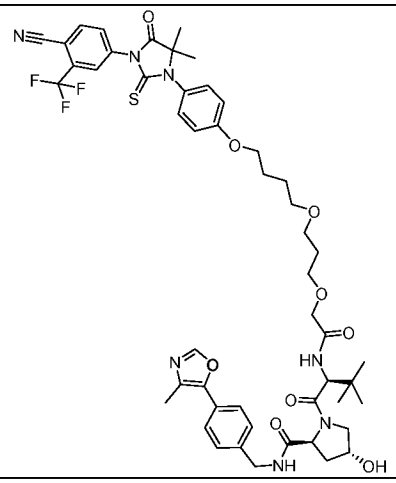
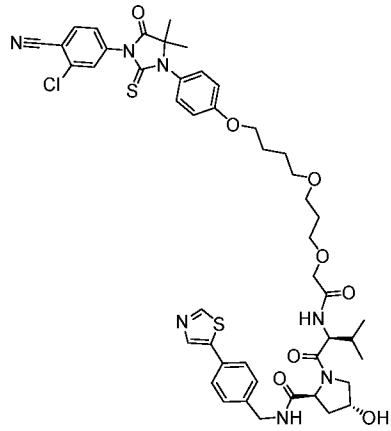
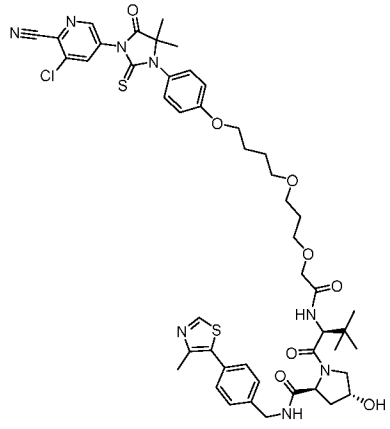
Ex #	Structure	Compound name and Analytical data
20		Prepared from **ABM-3**, **L-4**, and **ULM-3** (2S,4R)-1-[(2S)-2-[2-(2-{2-[2-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)ethoxy]ethoxy}ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (300MHz, CD_3OD): δ 8.90 (s, 1H), 8.16-8.13 (d, *J* = 8.1 Hz, 2H), 8.00-7.97 (d, *J* = 8.1 Hz, 1H), 7.45-7.35 (m, 4H), 7.30-7.27 (d, *J* = 9.0 Hz, 2H), 7.11-7.08 (d, *J* = 9.0 Hz, 2H), 5.03-5.00(m, 1H), 4.69 (s, 1H), 4.60-4.57(m, 1H), 4.54-4.43 (m, 1H), 4.23-4.22 (m, 2H), 4.12-4.10 (m, 2H), 3.99-3.88 (m, 3H), 3.83-3.71 (m, 9H), 2.54 (s, 3H), 2.24-2.04 (m, 1H), 2.00-1.94 (m, 1H), 1.57 (s, 9H), 1.03 (s, 9H). LC-MS (ES^+): *m/z* 1022.56 [MH^+], t_R =2.07 min (3.6 minute run).
21		Prepared from **ABM-4**, **L-4**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-(2-{2-[2-(4-{3-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)ethoxy]ethoxy}ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 9.12 (s, 1H), 8.83(s, 1H), 8.63 (s, 1H), 7.70-7.50 (m, 1 H), 7.47-7.30 (m, 4 H), 7.22 (d, *J* = 9 Hz, 2 H), 7.02 (d, *J* = 9 Hz, 2 H), 4.80-4.26 (m, 5H), 4.25-4.06 (m, 4H), 3.92-3.78 (m, 3 H), 3.75-3.60 (m, 8H), 2.43 (s, 3H) , 2.20-2.10 (m, 1 H), 2.10-2.01 (m, 1 H), 1.52 (s, 6H), 1.00 (s, 9H); LC-MS (ES^+): *m/z* 1009.12 [MH^+], t_R = 2.16 min (3.6 minute run).
22		Prepared from **ABM-3**, **L-5**, and **ULM-1** (2S,4R)-1-[(2S)-2-(2-{[(2R,3R)-3-{2-[2-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)ethoxy]ethoxy}butan-2-yl]oxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.81 - 8.94 (m, 1 H), 8.17 (d, *J* = 7.43 Hz, 2 H), 8.01 (d, *J* = 8.61 Hz, 1 H), 7.73 - 7.89 (m, 1 H), 7.37 - 7.57 (m, 3 H), 7.21 - 7.36 (m, 2 H), 7.01 - 7.17 (m, 2 H), 5.48 - 5.54 (m, 1 H), 3.36 - 4.88 (m, 20 H), 3.20 - 3.29 (m, 2 H), 2.43 - 2.52 (m, 2 H), 2.16 - 2.30 (m, 1 H), 2.03 - 2.16 (m, 1 H), 1.52 - 1.59 (m, 3 H), 1.39 (d, *J* = 4.30 Hz, 9 H), 1.11 - 1.21 (m, 3 H), 1.06 (s, 3 H); Mass (ES^+): *m/z* 1036.47 [MH^+]

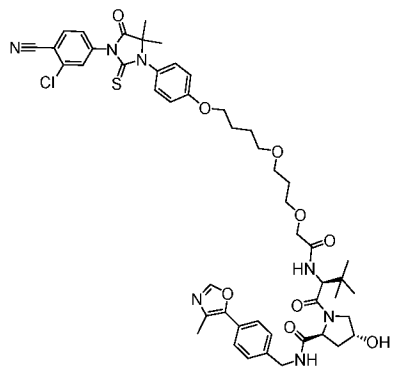
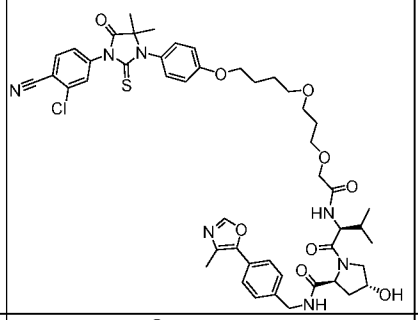
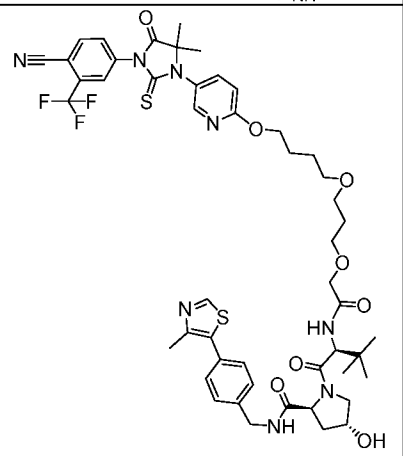
Ex #	Structure	Compound name and Analytical data
23		Prepared from **ABM-3**, **L-6**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-(2-{[(2R,3R)-3-[2-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)ethoxy]butan-2-yl]oxy}ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.86 (s, 1 H), 8.12 - 8.17 (m, 2 H), 7.98 (dd, *J* = 8.22, 1.96 Hz, 1 H), 7.39 - 7.48 (m, 4 H), 7.24 - 7.30 (m, 2 H), 7.03 - 7.08 (m, 2 H), 4.70 (s, 1 H), 4.58 - 4.63 (m, 2 H), 4.55 (d, *J* = 15.65 Hz, 2 H), 4.50 (br. s., 1 H), 4.15 (d, *J* = 4.30 Hz, 2 H), 4.02 (d, *J* = 7.83 Hz, 1 H), 3.88 - 3.94 (m, 2 H), 3.71 - 3.75 (m, 2 H), 3.63 - 3.68 (m, 2 H), 3.56 - 3.61 (m, 1 H), 3.47 - 3.52 (m, 1 H), 2.44 - 2.50 (m, 3 H), 2.19 - 2.25 (m, 1 H), 2.06 - 2.11 (m, 1 H), 1.53 (s, 6 H), 1.35 (d, *J* = 6.65 Hz, 3 H), 1.11 (d, *J* = 6.26 Hz, 6 H), 1.01 - 1.07 (m, 9 H); Mass (ES^+): *m/z* 1036.47
24		Prepared from **ABM-3**, **L-7**, and **ULM-1** (2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)butoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400MHz, CD_3OD): δ 8.90 (s, 1H), 8.17-8.15 (d, *J* = 8.4Hz, 2H), 8.01-8.01 (d, *J* = 1.6Hz, 1H), 7.49-7.42 (m, 4H), 7.30-7.27 (d, *J* = 11.6Hz, 2H), 7.06-7.04 (d, *J* = 8.8Hz, 2H), 4.71 (s, 1H), 4.61-4.54 (m, 3H), 4.38-4.34 (m, 1H), 4.07-4.04 (m, 2H), 3.40-3.95 (m, 2H), 3.91-3.83 (m, 2H), 3.61-3.58 (m, 2H), 3.52-3.50 (m, 4H), 2.50 (s, 3H), 2.05-2.14(m, 1H), 2.20-2.30 (m, 1H), 1.89-1.86 (m, 2H), 1.79-1.723 (m, 6H), 1.56 (s, 6H), 1.06 (s, 9H); LC-MS (ES^+): *m/z* 1020.30 [MH^+], t_R = 4.06 min (5.6 minute run).
25		Prepared from **ABM-16**, **L-7**, and **ULM-3** (2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluorophenoxy)butoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.88 (s, 1H), 8.17-8.14 (d, *J* = 7.5 Hz, 2H), 8.00-7.97 (d, *J* = 8.4 Hz, 1H), 7.46-7.39 (m, 4H), 7.27-7.12 (m, 3H), 5.01-4.86 (m, 1H), 4.69 (s, 1H), 4.60-4.55 (t, *J* = 7.5 Hz, 1H), 4.44 (m, 1H), 4.19-4.17 (t, *J* = 6.0 Hz, 2H), 3.98-3.97 (d, *J*= 2.7 Hz, 2H), 3.87-3.76 (m, 2H), 3.61-3.49 (m, 6H), 2.48 (s, 3H), 2.17 (m, 1H), 2.00-1.89 (m, 3H), 1.84-1.75 (m, 2H), 1.74-1.71 (m, 4H), 1.58 (s, 6H), 1.52-1.49 (m, 3H), 1.04 (s, 9H); Mass (ES^+): *m/z* 1052.20 [MH^+]

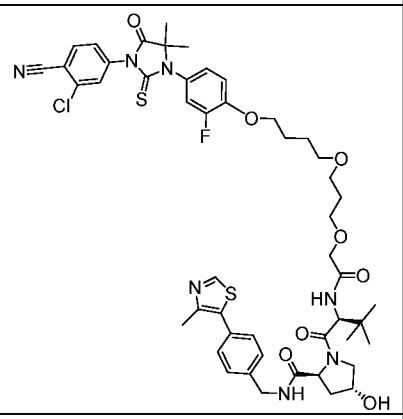
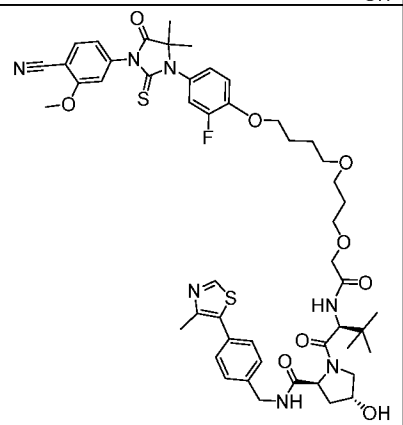
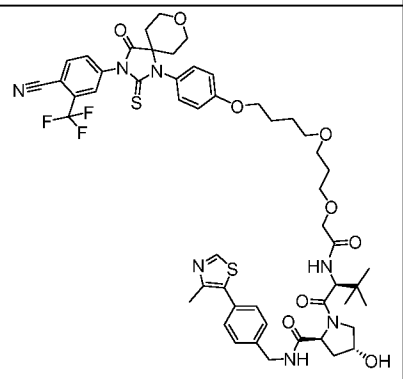
Ex #	Structure	Compound name and Analytical data
26		Prepared from **ABM-16**, **L-7**, and **ULM-3** (2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluorophenoxy)butoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.88 (s, 1 H), 8.17-8.15 (m, 2 H), 8.00-7.99 (d, J = 6.4 Hz, 1 H), 7.49-7.42 (m, 4 H), 7.23-7.13(m, 3 H), 4.71 (s, 1 H), 4.61-4.52 (m, 3 H), 4.38-4.34 (m, 1 H), 4.00-3.83 (m, 3 H), 3.61-3.49 (m, 6 H), 2.49 (s, 3 H), 2.30-2.10 (m, 2 H), 1.92-1.89(m, 2 H), 1.79-1.73 (m, 6 H), 1.72 (s, 6 H), 1.05(s, 9 H); LC-MS (ES^+): *m/z* 1038.50[MH^+], t_R = 3.05 min (5.0 minute run).
27		Prepared from **ABM-16**, **L-8**, and **ULM-1** (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluorophenoxy)butoxy]propoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ8.87 (s, 1H), 8.10 (d, J = 8.6 Hz, 2H), 7.93 (m, 1H), 7.37 (m, 4H), 7.11 (m, 3H), 4.83-4.48 (m, 5H), 4.12 (m, 2H), 3.94 (m, 2H) , 3.78 (m, 2H), 3.50 (m, 6H), 2.44 (s, 3H), 2.05 (m, 2H), 1.73 (m, 6H), 1.52 (s, 6H), 1.00 (s, 9H); LC-MS (ES^+): *m/z* 1024.10 [MH^+], t_R = 2.79 min (5.6 minute run).
28		Prepared from **ABM-3**, **L-8**, and **ULM-1** (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)butoxy]propoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD) δ 8.88 (s, 1H), 8.14 (m, 2H), 7.97 (m, 1H), 7.49-7.41 (m, 4H), 7.26 (m, 2H), 7.02 (m, 2H), 4.70 (s, 1H), 4.61-4.52 (m, 3H), 4.38-4.33 (m, 1H), 4.03 (t, J = 6.3 Hz, 2H), 3.98 (s, 2H), 3.86-3.82 (m, 2H), 3.68-3.51 (m, 6H), 2.48 (s, 3H), 2.23-2.09 (m, 2H), 1.93-1.73 (m, 6H), 1.55 (s, 6H), 1.02 (s, 9H); LC-MS (ES^+): *m/z* 1006.50 [MH^+], t_R = 2.81 min (5.6 minute run).

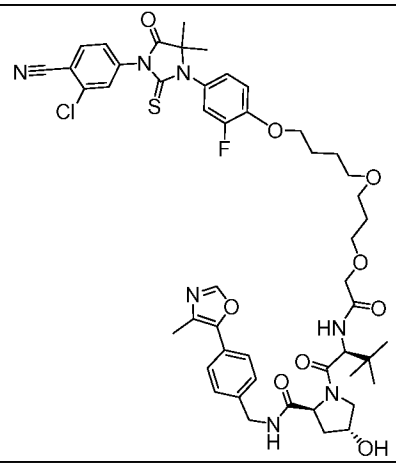
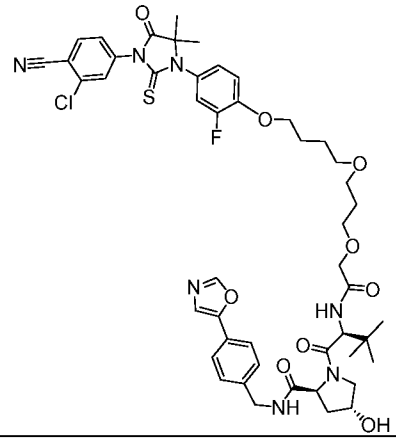
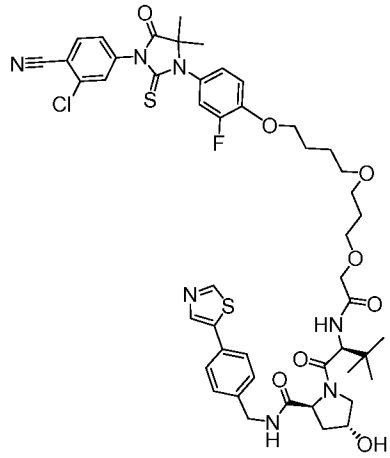
Ex #	Structure	Compound name and Analytical data
29		Prepared from **ABM-3**, **L-8**, and **ULM-8** (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)butoxy]propoxy}acetamido)-3-methylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.88 (s, 1H), 8.17 (d, *J* = 8.8 Hz, 2H), 8.01 (m, 1H), 7.47 (m, 4H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 4.66 (m, 1H), 4.61 (m, 1H), 4.54 (m, 2H), 4.42 (m, 1H), 4.08 (m, 2H), 4.01 (m, 2H), 3.85 (m, 2H), 3.67 (m, 2H), 3.61 (m, 2H), 3.56 (m, 2H), 2.50 (s, 3H), 2.25 (m, 1H), 2.16 (m, 2H), 1.93 (m, 4H), 1.78 (m, 2H), 1.56 (s, 6H), 1.03 (m, 3H), 0.96 (m, 3H); LC-MS (ES^+): *m/z* 992.55 [MH^+], t_R = 3.39 min (5.6 minute run).
30		Prepared from **ABM-4**, **L-8**, and **ULM-1** (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)butoxy]propoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD) δ 9.15-9.10 (m, 1H), 8.80 (s, 1H), 8.66-8.62 (m, 1H), 7.45-7.36 (m, 4H), 7.25-7.18 (m, 2H), 7.02-6.92 (m, 2H), 4.70-4.62 (m, 1H), 4.60-4.44 (m, 3H), 4.35-4.26 (m, 1H), 4.10-3.90 (m, 4H), 3.89-3.69 (m, 2H), 3.65-3.40 (m, 6H), 2.44 (s, 4H), 2.20-2.01 (m, 2H), 1.88-1.60 (m, 6H), 1.52 (s, 6H), 1.00 (s, 9H); LC-MS (ES^+): *m/z* 1007.30 [MH^+], t_R =1.71 min (3.0 minute run).
31		Prepared from **ABM-1**, **L-8**, and **ULM-1** (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenoxy}butoxy)propoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD) δ 8.87 (s, 1H), 7.97(d, *J* = 8.4 Hz, 1H), 7.87 (s, 1H), 7.66 (m, 1H), 7.49 (m, 4H), 7.28 (m, 2H), 7.05 (m, 2H), 4.71 (s, 1H), 4.59 (m, 3H), 4.38 (m, 1H), 4.07 (m, 4H), 3.987 (m, 2H), 3.68 (m, 6H), 2.48 (s, 3H), 2.27 (m, 2H), 1.93 (m, 6H), 1.54 (s, 6H),1.03 (s, 9H). LC-MS (ES^+): m/z 486.40 [$M/2H^+$], t_R = 2.21 min (3.6 minute run).

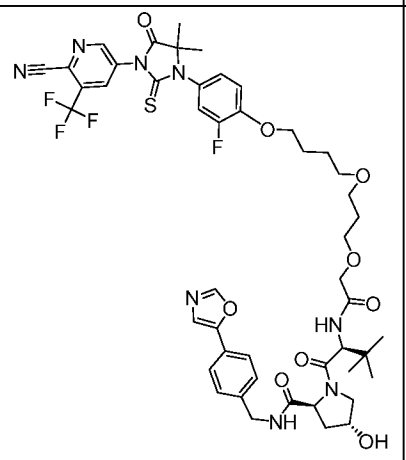
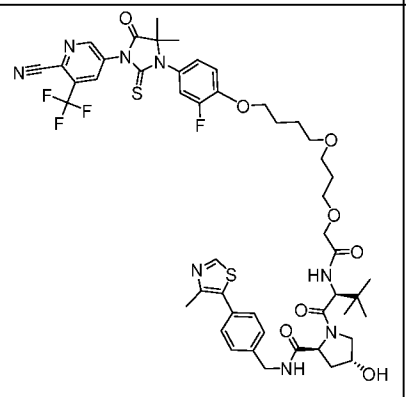
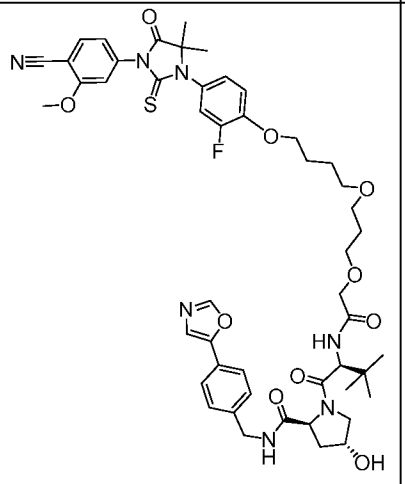
Ex #	Structure	Compound name and Analytical data
32		Prepared from **ABM-5**, **L-8**, and **ULM-1** (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(4-cyano-3-methoxyphenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenoxy}butoxy)propoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.89 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.49-7.42 (m, 4H), 7.37 (s, 1H), 7.27 (d, *J* = 8.8 Hz, 2H), 7.18-7.15 (m, 1H), 7.06-7.04 (m, 2H), 4.88 (s, 1H), 4.59-4.46 (m, 3H), 4.38-4.35 (m, 1H), 4.07-4.00 (m, 2H), 3.99-3.87 (m, 5H), 3.88-3.76 (m, 2H), 3.68-3.60 (m, 2H), 3.59-3.55 (m, 2H), 3.54-3.53 (m, 2H), 2.49 (s, 3H), 2.28-2.19 (m, 1H), 2.14-2.05 (m, 1H), 1.93-1.86 (m, 4H), 1.80-1.78 (m, 2H), 1.54 (s, 6H), 1.04 (s, 9H); LC-MS (ES^+): *m/z* 968.35 [MH^+], t_R = 2.57 min (5.6 minute run).
33		Prepared from **ABM-3**, **L-8**, and **ULM-2** (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)butoxy]propoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.94 (s, 1H), 8.16 (d, *J* = 8.8 Hz, 3H), 8.00 (d, *J* = 1.6 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 4.71 (s, 1H), 4.61-4.51 (m, 3H), 4.37-4.33 (m, 1H), 4.07-4.03 (m, 2H), 4.01-3.96 (m, 2H), 3.88-3.82 (m, 1H), 3.81-3.77 (m, 1H), 3.69-3.3.62 (m, 2H), 3.61-3.55 (m, 2H), 3.54-3.53 (m, 2H), 2.28-2.19 (m, 1H), 2.14-2.05 (m, 1H), 1.96-1.84 (m, 4H), 1.80-1.74 (m, 2H), 1.56 (s, 6H), 1.06 (s, 9H); LC-MS (ES^+): *m/z* 496.85 [$MH/2^+$], t_R = 1.60 min (3.0 minute run).
34		Prepared from **ABM-3**, **L-8**, and **ULM-4** (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)butoxy]propoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 8.17 (d, *J* = 8.0 Hz, 2H), 8.01 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.49-7.45 (m, 3H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 4.72 (s, 1H), 4.61-4.51 (m, 3H), 4.37 (m, 1H), 4.08-3.83 (m, 6H), 3.69-3.54 (m, 6H), 2.15-2.05 (m, 2H), 1.93-1.76 (m, 6H), 1.56 (s, 6H), 1.03 (s, 9H); LC-MS (ES^+): *m/z* 976.45 [MH^+], t_R = 1.69 min (3.0 minute run).

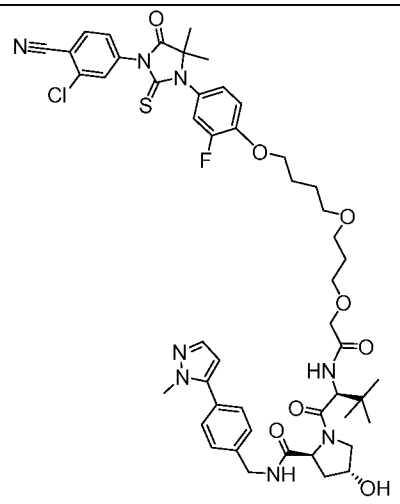
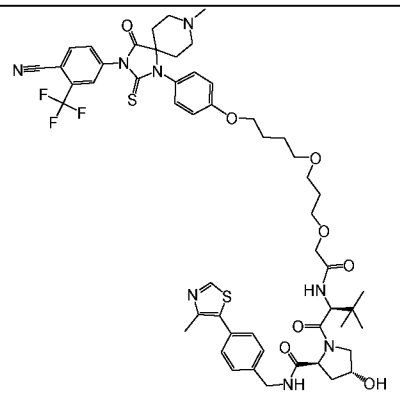
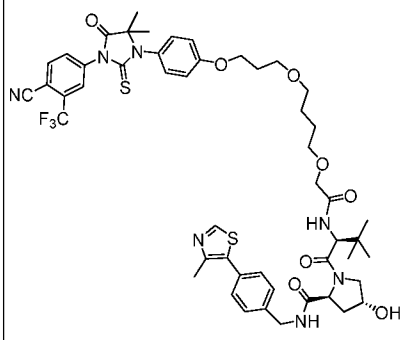
Ex #	Structure	Compound name and Analytical data
35		Prepared from **ABM-3**, **L-8**, and **ULM-5** (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)butoxy]propoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.16-8.14 (d, *J* = 8.8 Hz, 3 H), 7.98-7.98 (d, *J* = 2.0 Hz, 1 H), 7.61-7.59 (d, *J* = 8.4 Hz, 2 H), 7.49-7.47 (d, *J* = 8.4 Hz, 2 H), 7.29-7.27 (d, *J* = 8.8 Hz, 2 H), 7.05-7.03 (d, *J* = 8.8 Hz, 2 H), 4.71-4.52 (m, 4 H), 4.37-4.34 (m, 1 H), 4.07-3.99 (m, 4 H), 3.87-3.82 (m, 2 H), 3.68-3.53 (m, 6 H), 2.41 (s, 3 H), 2.21-2.00 (m, 2 H), 1.93-1.76 (m, 6 H), 1.55 (s, 6 H), 1.05 (s, 9 H); LC-MS (ES^+): *m/z* 990.60 [MH^+], t_R = 3.50 min (5.6 minute run).
36		Prepared from **ABM-1**, **L-8**, and **ULM-9** (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenoxy}butoxy)propoxy]acetamido}-3-methylbutanoyl]-4-hydroxy-N-{[4-(1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.89 (s, 1H), 8.12 (s, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.82 (s, 1H), 7.62-7.56 (m, 3H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.00 (s, 2H), 4.61-4.52 (m, 1H), 4.51-4.40 (m, 2H), 4.39-4.36 (m, 1H), 4.03-3.95 (m, 4H), 3.78-3.74 (m, 2H), 3.63-3.27 (m, 7H), 2.23-1.98 (m, 3H), 1.89-1.71 (m, 6H), 1.50 (s, 6H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); LC-MS (ES^+): *m/z* 944.25 [MH^+], t_R = 1.51 min (3.0 minute run).
37		Prepared from **ABM-1**, **L-8**, and **ULM-1** (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(5-chloro-6-cyanopyridin-3-yl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenoxy}butoxy)propoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.87-8.86(m, 2 H), 8.44 (s, 1 H), 7.49-7.42 (m, 4 H), 7.29-7.27 (d, *J* = 8.8 Hz, 2 H), 7.06-7.04 (d, *J* = 8.8 Hz, 2 H), 4.72 (s, 1 H), 4.59-4.52 (m, 3 H), 4.39-4.35 (m, 1 H), 4.08-3.99 (m, 4 H), 3.96-3.83 (m, 2 H), 3.68-3.59 (m, 6 H), 2.50 (s, 3 H), 2.15-2.05 (m, 2 H), 1.92-1.88 (m, 6 H), 1.56 (s, 6 H), 1.04 (s, 9 H); LC-MS (ES^+): *m/z* 973.30 [MH^+], t_R = 1.58 min (3.0 minute run).

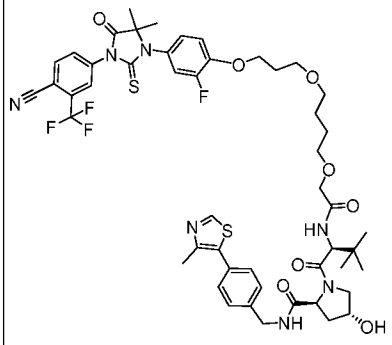
Ex #	Structure	Compound name and Analytical data
38		Prepared from **ABM-1**, **L-8**, and **ULM-5** (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenoxy}butoxy)propoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (s, 1 H), 7.97-7.95 (d, *J* = 8.4 Hz, 1 H), 7.87 (s, 1 H), 7.66-7.59 (m, 3 H), 7.49-7.47 (d, *J* = 8.4 Hz, 2 H), 7.28-7.26 (d, *J* = 9.2 Hz, 2 H), 7.05-7.03 (d, *J* = 8.8 Hz, 2 H), 4.71 (s, 1 H), 4.57-4.52 (m, 3 H), 4.38-4.34 (m, 1 H), 4.07-3.99 (m, 4 H), 3.87-3.80 (m, 2 H), 3.67-3.53 (m, 6 H), 2.42 (s, 1 H), 2.20-2.00 (m, 2 H), 1.93-1.77 (m, 6 H), 1.54 (s, 6 H), 1.06 (s, 9 H); LC-MS (ES^+): *m/z* 956.30 [MH^+], t_R = 1.56 min (3.0 minute run).
39		Prepared from **ABM-1**, **L-8**, and **ULM-10** (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenoxy}butoxy)propoxy]acetamido}-3-methylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (s, 1 H), 7.97-7.95 (d, *J* = 8.4 Hz, 1 H), 7.87 (s, 1 H), 7.66-7.60 (m, 3 H), 7.48-7.45 (d, *J* = 8.4 Hz, 2 H), 7.28-7.26 (d, *J* = 9.2 Hz, 2 H), 7.06-7.03 (d, *J* = 9.2 Hz, 2 H), 4.66-4.41 (m, 5 H), 4.07-3.99 (m, 4 H), 3.85-3.83 (m, 2 H), 3.66-3.53 (m, 6 H), 2.41 (s, 3 H), 2.25-2.00 (m, 3 H), 1.93-1.77 (m, 6 H), 1.53 (s, 6 H), 1.03-1.02 (d, *J*=6.8 Hz, 3 H), 0.95-0.93(d, *J*=6.8 Hz, 3 H); LC-MS (ES^+): *m/z* 942.30 [MH^+], t_R = 1.50 min (3.0 minute run).
40		Prepared from **ABM-20**, **L-8**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-(3-{4-[(5-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}pyridin-2-yl)oxy]butoxy}propoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD):δ8.81 (s, 1 H), 8.16-8.03 (m, 3 H), 8.00-7.90 (m, 1 H), 7.70-7.60 (m, 1 H), 7.51-7.30 (m, 4H), 6.91-6.80 (m, 1 H), 4.67 (s, 1 H), 4.60-4.40 (m, 4 H), 4.32-4.21 (m, 3 H), 3.89-3.70 (m, 4 H), 3.65-3.40 (m, 6 H), 2.41 (s, 3 H), 2.23-2.01 (m, 2 H), 1.90-1.62 (m, 6 H), 1.55 (s, 6 H), 1.02 (s, 9 H); LC-MS (ES^+): *m/z*, 1007.35 [MH^+], t_R =1.58 min (3.0 minute run).

Ex #	Structure	Compound name and Analytical data
41		Prepared from **ABM-21**, **L-8**, and **ULM-1** (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]-2-fluorophenoxy}butoxy)propoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.88 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.88 (s, 1H), 7.66-7.64 (m, 1H), 7.48-7.39 (m, 4H), 7.22-7.19 (m, 2H), 7.14 (s, 1H), 4.71 (s, 1H), 4.59-4.47 (m, 3H), 4.36 (d, *J* = 15.6 Hz, 1H), 4.14 (t, *J* = 6.4 Hz, 2H), 4.00 (d, *J* = 3.6 Hz, 2H), 3.87-3.78 (m, 2H), 3.67-3.54 (m, 6H), 2.45 (s, 3H), 2.26-2.21 (m, 1H), 2.13-2.04 (m, 1H), 1.93-1.89 (m, 4H), 1.83-1.74 (m, 2H), 1.55 (s, 6H), 1.04 (s, 9H); LC-MS (ES^+): *m/z* 990.35 [MH^+], t_R = 1.59 min (3.0 minute run).
42		Prepared from **ABM-22**, **L-8**, and **ULM-1** (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(4-cyano-3-methoxyphenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]-2-fluorophenoxy}butoxy)propoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.98 (s, 1 H), 7.77-7.75 (d, *J* = 8.4 Hz, 2 H), 7.49-7.42 (m, 4 H), 7.36-7(s, 1 H), 7.21-7.14 (m, 4 H), 4.71 (s, 1 H), 4.59-4.52 (m, 3 H), 4.39-4.35(m, 1 H), 4.16-4.13 (m, 2 H), 4.00-3.98 (m, 5 H), 3.99-3.83 (m, 2 H), 3.68-3.66 (m, 2 H), 2.50 (s, 3 H), 2.30-2.10 (m, 2 H), 1.93-1.89 (m, 4 H), 1.80-1.76 (m, 2 H), 1.55 (s, 6 H), 1.03 (s, 9 H); LC-MS (ES^+): *m/z* 986.45 [MH^+], t_R = 1.65 min (3.0 minute run).
43		Prepared from **ABM-8**, **L-8**, and **ULM-1** (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-4-oxo-2-sulfanylidene-8-oxa-1,3-diazaspiro[4.5]decan-1-yl}phenoxy)butoxy]propoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.98-8.83 (s, 1 H), 8.18-8.16 (d, *J* = 8.4 Hz, 2 H), 8.01-7.99 (m, 1 H), 7.49-7.42(m, 4 H), 7.42-7.24 (d, *J* = 8.4 Hz, 2 H), 7.08-7.06 (d, *J* = 8.4 Hz, 2 H), 4.80 (s, 1 H), 4.72 (s, 1 H), 4.59-4.34(m, 3 H), 4.20-4.08 (m, 6 H), 3.99-3.87 (m, 4 H), 3.67-3.56 (m, 6 H), 2.49 (s, 3 H), 2.21-1.87 (m, 12 H), 1.05 (s, 9 H); LC-MS (ES^+): *m/z* 1048.45 [MH^+], t_R = 1.73 min (3.0 minute run).

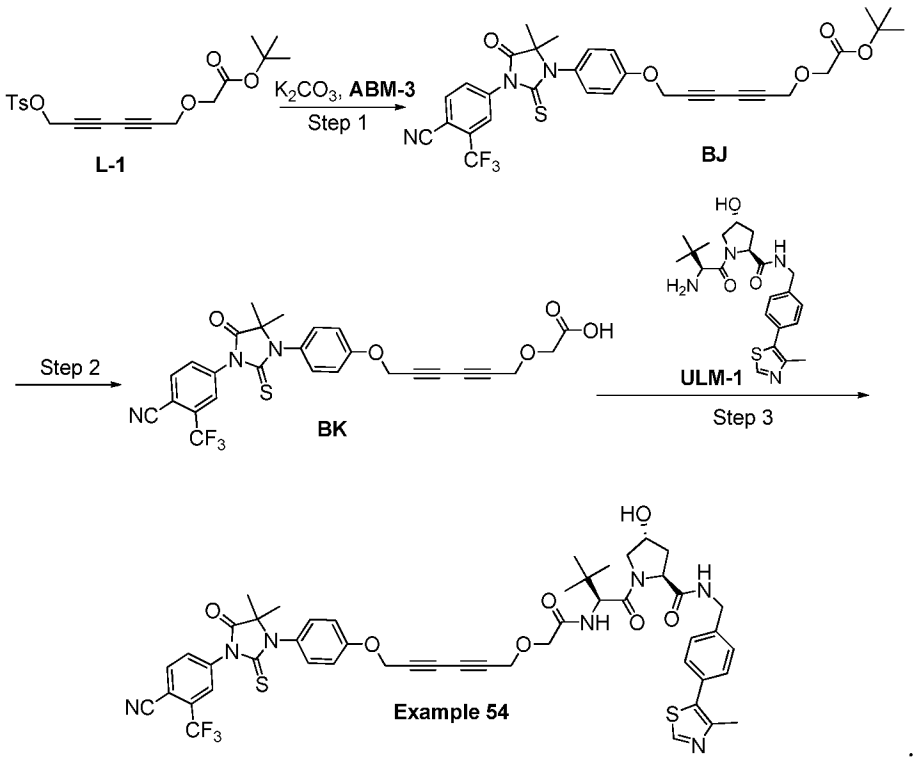
Ex #	Structure	Compound name and Analytical data
44		Prepared from **ABM-21**, **L-8**, and **ULM-5** (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]-2-fluorophenoxy}butoxy)propoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.15 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.87 (s, 1H), 7.66-7.60 (m, 3H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.24-7.14 (m, 3H), 4.71 (s, 1H), 4.61-4.52 (m, 3H), 4.38-4.33 (m, 1H), 4.14 (m, 2H), 4.00 (d, *J* = 4.0 Hz, 3H), 3.88-3.82 (m, 2H), 3.68-3.54 (m, 6H), 2.42 (s, 3H), 2.27-2.18 (m, 1H), 2.13-2.04 (m, 1H), 1.93-1.89 (m, 4H), 1.88-1.80 (m, 2H), 1.55 (s, 6H), 1.06 (s, 9H); LC-MS (ES^+): *m/z* 974.25 [MH^+], t_R = 1.57 min (3.0 minute run).
45		Prepared from **ABM-21**, **L-8**, and **ULM-4** (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]-2-fluorophenoxy}butoxy)propoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.24 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.87 (s, 1H), 7.70-7.7.64 (m, 3H), 7.49-7.40 (m, 3H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 4.71 (s, 1H), 4.60-4.51 (m, 3H), 4.38-4.34 (m, 1H), 4.18-4.11 (m, 2H), 4.00-3.96 (m, 2H), 3.92-3.76 (m, 2H), 3.68-3.55 (m, 6H), 2.27-2.21 (m, 1H), 2.18-2.06 (m, 1H), 1.95-1.86 (m, 4H), 1.83-1.72 (m, 2H), 1.55 (s, 6H), 1.06 (s, 9H); LC-MS (ES^+): *m/z* 960.30 [MH^+], t_R = 1.54 min (3.0 minute run).
46		Prepared from **ABM-21**, **L-8**, and **ULM-2** (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]-2-fluorophenoxy}butoxy)propoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.94 (s, 1H), 8.15 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.87 (s, 1H), 7.66-7.61 (m, 3H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.19-7.12 (m, 3H), 4.71 (s, 1H), 4.60-4.51 (m, 3H), 4.38-4.34 (m, 1H), 4.17-4.11 (m, 2H), 3.99-3.94 (m, 2H), 3.88-3.75 (m, 2H), 3.71-3.55 (m, 6H), 2.37-2.20 (m, 1H), 2.13-2.06 (m, 1H), 1.94-1.89 (m, 4H), 1.80-1.77 (m, 2H), 1.55 (s, 6H), 1.03 (s, 9H); LC-MS (ES^+): *m/z* 976.25 [MH^+], t_R = 1.57 min (3.0 minute run).

Ex #	Structure	Compound name and Analytical data
47		Prepared from **ABM-23**, **L-8**, and **ULM-4** (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluorophenoxy)butoxy]propoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD) δ 9.16 (s, 1 H), 8.67 (s, 1 H), 8.23 (s, 1 H), 7.69-7.66 (d, *J* = 8.1 Hz, 2 H), 7.48-7.43 (m, 3 H), 7.22-7.15 (m, 3 H), 4.70 (s, 1 H), 4.60-4.49 (m, 3 H), 4.36-4.31 (m, 1 H), 4.16-4.12 (m, 2 H), 3.99 (m, 2 H), 3.86-3.81 (m, 2 H), 3.67-3.53 (m, 6 H), 2.22-2.08 (m, 2 H), 1.95-1.75 (m, 6 H), 1.57(s, 6 H), 1.04 (s, 9 H); LC-MS (ES^+): *m/z* 995.10 [MH^+], t_R = 2.26 min (3.6 minute run).
48		Prepared from **ABM-23**, **L-8**, and **ULM-1** (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluorophenoxy)butoxy]propoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD) δ 9.16 (s, 1 H), 8.87 (s, 1 H), 8.67(s, 1 H), 7.48-7.40 (m, 4 H), 7.24-7.12 (m, 3 H), 4.70 (s, 1 H), 4.62-4.46 (m, 3 H),4.38-4.32 (m, 1 H), 4.15-4.09 (m, 2 H), 3.99 (s, 2 H), 3.90-3.78 (m, 2 H), 3.67-3.52 (m, 6 H), 2.47 (s, 3 H), 2.27-2.17 (m, 1 H), 2.16-2.06 (m, 1 H), 1.94-1.83 (m, 4 H), 1.82-1.71 (m, 2 H), 1.57(s, 6 H), 1.04 (s, 9 H); LC-MS (ES^+): *m/z* 1025.30 [MH^+], t_R = 2.27 min, (3.6 minute run)
49		Prepared from **ABM-22**, **L-8**, and **ULM-4** (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(4-cyano-3-methoxyphenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]-2-fluorophenoxy}butoxy)propoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.70(d, *J* = 8.4 Hz, 2H), 7.50 (m, 3H), 7.36 (m, 1H), 7.24 (m, 4H), 4.71 (s, 1H), 4.60 (m, 3H), 4.37 (m, 1H), 4.16 (m, 2H), 4.01 (m, 5H), 3.88 (m, 1H),3.83 (m, 1H), 3.69 (m, 6H), 2.28 (m, 1H), 2.14 (m, 1H), 1.94 (m, 4H), 1.81 (m, 2H), 1.56 (s, 6H), 1.06 (m, 9H); LC-MS (ES^+): *m/z* 956.45 [MH^+], t_R = 2.17 min (3.6 minute run).

Ex #	Structure	Compound name and Analytical data
50		Prepared from **ABM-21**, **L-8**, and **ULM-11** (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]-2-fluorophenoxy}butoxy)propoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1-methyl-1H-pyrazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD) δ 7.96-7.93 (d, *J* = 8.1 Hz, 1 H), 7.86 (s, 1 H), 7.65-7.61(d, *J* = 9.6 Hz, 1 H), 7.50-7.41 (m, 5 H), 7.23-7.10 (m, 3 H), 6.34 (s, 1 H), 4.71 (s, 1 H), 4.61-4.46 (m, 3 H), 4.41-4.34 (m, 1 H), 4.18-4.09 (m, 2 H), 3.98 (s, 2 H), 3.90-3.79 (m, 5 H), 3.66-3.51 (m, 6 H), 2.28-2.16 (m, 1 H), 2.14-2.01 (m, 1 H), 1.93-1.83 (m, 4 H), 1.81-1.72 (m, 2 H), 1.54 (s, 6 H), 1.04 (s, 9 H); LC-MS (ES^+): *m/z* 973.35 [MH^+], t_R = 1.55 min, (3 minute run)
51		Prepared from **ABM-9**, **L-8**, and **ULM-1** (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-8-methyl-4-oxo-2-sulfanylidene-1,3,8-triazaspiro[4.5]decan-1-yl}phenoxy)butoxy]propoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD):δ8.81 (s, 1 H), 8.16-8.03 (m, 2 H), 8.00-7.90 (m, 1 H), 7.50-7.30 (m, 4 H), 7.23-7.15 (m, 2H), 7.05-6.90 (m, 2 H), 4.67 (s, 1 H), 4.60-4.30 (m, 4 H), 4.12-3.91 (m, 4 H), 3.80-3.70 (m, 2 H), 3.65-3.40 (m, 6 H), 2.80-2.61 (m, 4 H), 2.41 (s, 3 H), 2.25-2.11 (m, 6 H), 2.10-1.60 (m, 9 H), 1.02 (s, 9 H); LC-MS (ES^+): *m/z*, 531.35 $[M/2+H]^+$, t_R =1.86 min (3.6 minute run).
52		Prepared from **ABM-3**, **L-9**, and **ULM-1** (2S,4R)-1-[(2S)-2-(2-{4-[3-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)propoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD) δ 8.83 (s, 1H), 8.12-8.10 (m, 2H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.44-7.37 (m, 4H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 4.66-4.29 (m, 5H), 4.09-3.78 (m, 6H), 3.60-3.47 (m, 6H), 2.44 (s, 3H), 2.19-1.97 (m, 4H), 1.70-1.63 (m, 4H), 1.50 (s, 6H), 1.00 (s, 9H); LC-MS (ES^+): *m/z* 1006.30 [M H^+], t_R = 1.71 min (3.0 minute run).

Ex #	Structure	Compound name and Analytical data
53		Prepared from **ABM-16**, **L-9**, and **ULM-1** (2S,4R)-1-[(2S)-2-(2-{4-[3-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluorophenoxy)propoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.98 (s, 1 H), 8.17-8.15 (d, J = 8.4 Hz, 2 H), 8.01-7.99 (m, 1 H), 7.49-7.42 (m, 4 H), 7.42-7.20 (m, 3 H), 4.80 (s, 1 H), 4.71-4.70 (d, J = 2.8 Hz, 1 H), 4.59-4.51 (m, 4 H), 4.38-4.20 (m, 4 H), 3.99-3.87 (m, 2 H), 3.65-3.52 (m, 6 H), 2.50 (s, 3 H), 2.10-2.05 (m, 4 H), 1.72 (m, 4 H), 1.56 (s, 6 H), 1.03 (s, 9 H); LC-MS (ES^+): *m/z* 1025.50 [MH^+], t_R = 3.50 min (5.6 minute run).

[0638] Example 54: (2S,4R)-1-((S)-2-(2-(6-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)hexa-2,4-diynyloxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide:



[0639] Step 1: Synthesis of tert-butyl 2-{[6-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)hexa-2,4-diyn-1-yl]oxy}acetate (**BJ**)

[0640] This material was synthesized according to a similar procedure described in reaction step 1 for the synthesis of **Example 1**. LC-MS (ES^+): *m/z* 634.05 [MNa^+], t_R = 1.26 min (2.0 minute run).

[0641] Step 2: Synthesis of 2-{[6-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)hexa-2,4-diyn-1-yl]oxy}acetic acid (**BK**)

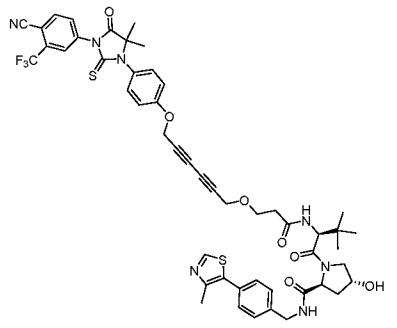
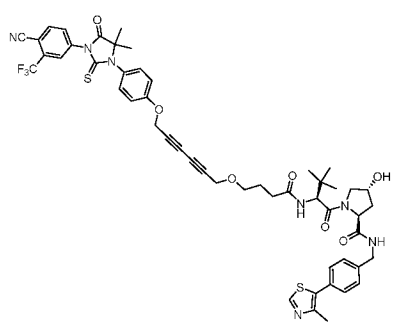
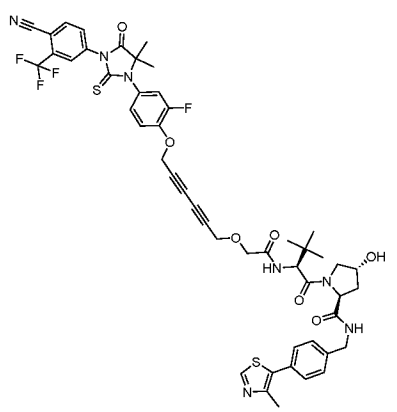
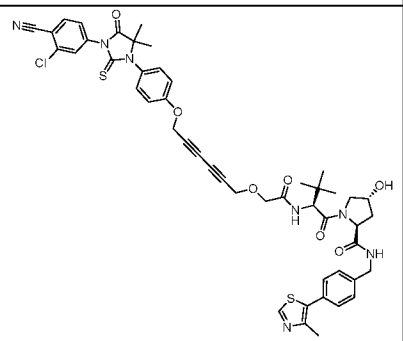
[0642] This material was synthesized according to a similar procedure described in reaction step 2 for the synthesis of example 1. LC-MS (ES^+): *m/z* 556.10 [MH^+], t_R = 1.54 min (2.6 minute run).

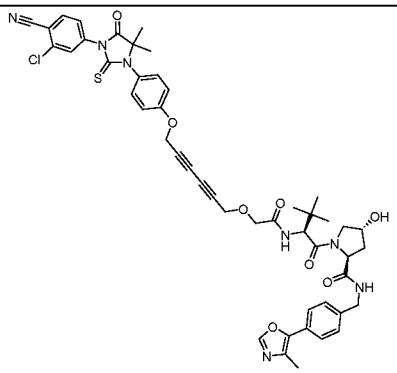
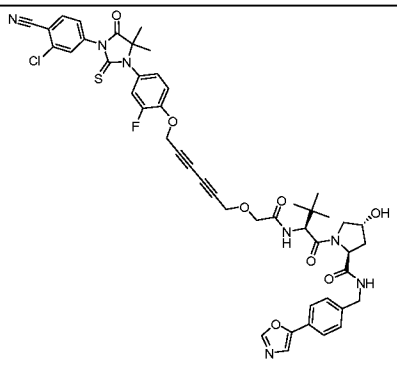
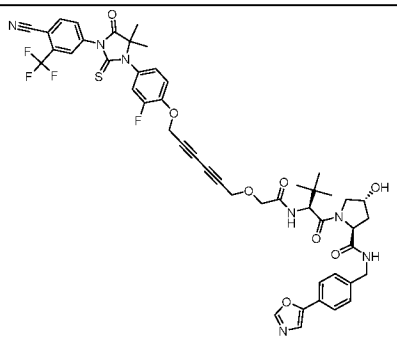
[0643] Step 3: Synthesis of (2S,4R)-1-[(2S)-2-(2-{[6-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)hexa-2,4-diyn-1-yl]oxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Example 54**)

[0644] This material was synthesized according to a similar procedure described in reaction step 3 for the synthesis of **Example 1**. ^1H NMR (400 MHz, CD_3OD): δ 8.88 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 8.00 (d, *J* = 1.6 Hz, 1H), 7.49-7.43 (m, 4H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.8 Hz, 2H), 4.93 (s, 2H), 4.71 (s, 1H), 4.60-4.34 (m, 6H), 4.08 (s, 2H), 3.90-3.80 (m, 2H), 2.49 (s, 3H), 2.25-2.22 (m, 1H), 2.13-2.05 (m, 1H), 1.56 (s, 6H), 1.03 (s, 9H); LC-MS (ES^+): *m/z* 968.45 [MH^+], t_R = 1.67 min (3.0 minute run).

[0645] Table 3. Exemplary Compounds.

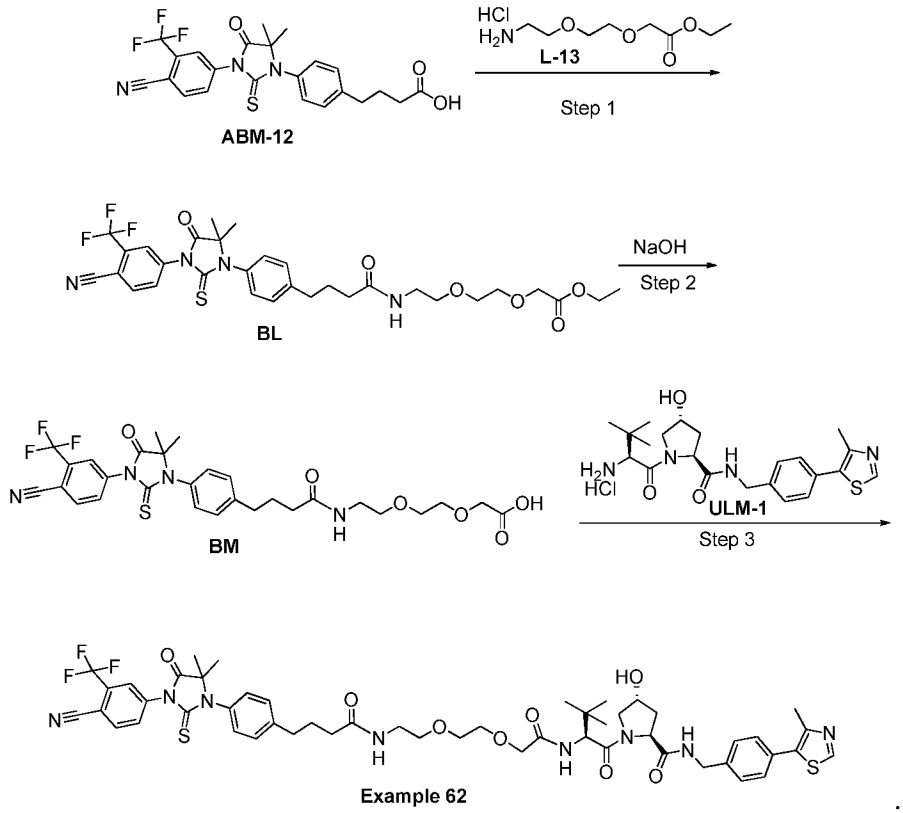
Ex #	Structure	Compound name and Analytical data

Ex #	Structure	Compound name and Analytical data
55		Prepared from **ABM-3**, **L-11**, and **ULM-1** (2S,4R)-1-[(2S)-2-(3-{[6-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)hexa-2,4-diyn-1-yl]oxy}propanamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.88 (s, 1H), 8.16 (d, *J* = 8.8 Hz, 2H), 7.99 (d, *J* = 1.6 Hz, 1H), 7.49-7.42 (m, 4H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.8 Hz, 2H), 4.93 (s, 2H), 4.66 (s, 1H), 4.60-4.38 (m, 3H), 4.38-4.27 (m, 3H), 3.92-3.80 (m, 4H), 2.63-2.59 (m, 1H), 2.58-2.49 (m, 4H), 2.26-2.18 (m, 1H), 2.13-2.05 (m, 1H), 1.56 (s, 6H), 1.03 (s, 9H); LC-MS (ES^+): *m/z* 982.40 [MH^+], t_R = 3.35 min (5.6 minute run).
56		Prepared from **ABM-3**, **L-12**, and **ULM-1** (2S,4R)-1-[(2S)-2-(4-{[6-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)hexa-2,4-diyn-1-yl]oxy}butanamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.88 (s, 1H), 8.16 (d, *J* = 8.8 Hz, 2H), 7.99 (d, *J* = 1.6 Hz, 1H), 7.49-7.42 (m, 4H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.8 Hz, 2H), 4.93 (s, 2H), 4.63 (s, 1H), 4.59-4.51 (m, 3H), 4.38-4.27 (d, *J* = 12.4 Hz, 1H), 4.25 (s, 2H), 3.93-3.79 (m, 2H), 3.53 (t, *J* = 6.0 Hz, 2H), 2.50 (s, 3H), 2.49-2.33 (m, 2H), 2.26-2.18 (m, 1H), 2.13-2.05 (m, 1H), 1.90-1.86 (m, 2H), 1.57 (s, 6H), 1.02 (s, 9H); LC-MS (ES^+): *m/z* 996.40 [MH^+], t_R = 3.41 min (5.6 minute run).
57		Prepared from **ABM-16**, **L-10**, and **ULM-1** (2S,4R)-1-[(2S)-2-(2-{[6-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluorophenoxy)hexa-2,4-diyn-1-yl]oxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.88 (s, 1H), 8.16 (d, *J* = 8.0 Hz, 2H), 8.00 (d, *J* = 1.2 Hz, 1H), 7.49-7.43 (m, 4H), 7.36-7.29 (m, 2H), 7.19 (d, *J* = 8.0 Hz, 1H), 5.03 (s, 2H), 4.71 (s, 1H), 4.61-4.42 (m, 3H), 4.41-4.33 (m, 3H), 4.09 (s, 2H), 3.90-3.80 (m, 2H), 2.49 (s, 3H), 2.27-2.15 (m, 1H), 2.12-2.06 (m, 1H), 1.56 (s, 6H), 1.03 (s, 9H); LC-MS (ES^+): *m/z* 986.30 [MH^+], t_R = 1.58 min (3.0 minute run).
58		Prepared from **ABM-1**, **L-10**, and **ULM-1** (2S,4R)-1-[(2S)-2-{2-[(6-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenoxy}hexa-2,4-diyn-1-yl)oxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.88 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.87 (s, 1H), 7.66-7.64 (m, 1H), 7.49-7.43 (m, 4H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.14 (d, *J* = 9.2 Hz, 1H), 4.94 (s, 2H), 4.71 (s, 1H), 4.61-4.42 (m, 3H), 4.41-4.29 (m, 3H), 4.09 (s, 2H), 3.92-3.86 (m, 1H), 3.82-3.77 (m, 1H), 2.49 (s, 3H), 2.27-2.18 (m, 1H), 2.12-2.06 (m, 1H), 1.52 (s, 6H),

Ex #	Structure	Compound name and Analytical data
		1.01 (s, 9H); LC-MS (ES^+): *m/z* 934.20 [MH^+], t_R = 1.54 min (3.0 minute run).
59		Prepared from **ABM-1**, **L-10**, and **ULM-5** (2S,4R)-1-[(2S)-2-{2-[(6-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenoxy}hexa-2,4-diyn-1-yl)oxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.15 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.87 (s, 1H), 7.66-7.58 (m, 3H), 7.49-7.47 (m, 2H), 7.35-7.31 (m, 2H), 7.14 (d, *J* = 8.8 Hz, 2H), 4.94 (s, 2H), 4.71 (s, 1H), 4.63-4.57 (m, 3H), 4.41-4.28 (m, 3H), 4.09 (s, 2H), 3.90-3.86 (m, 1H), 3.82-3.77 (m, 1H), 2.42 (s, 3H), 2.27-2.20 (m, 1H), 2.12-2.02 (m, 1H), 1.55 (s, 6H), 1.03 (s, 9H); LC-MS (ES^+): *m/z* 918.25 [MH^+], t_R = 1.51 min (3.0 minute run).
60		Prepared from **ABM-21**, **L-10**, and **ULM-4** (2S,4R)-1-[(2S)-2-{2-[(6-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]-2-fluorophenoxy}hexa-2,4-diyn-1-yl)oxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.23 (s, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.86 (s, 1H), 7.70-7.63 (m, 3H), 7.49-7.43 (m, 3H), 7.36-7.21 (m, 2H), 7.18-7.12 (m, 1H), 5.12 (s, 2H), 4.71 (s, 1H), 4.61-4.47 (m, 3H), 4.44-4.29 (m, 3H), 4.09 (s, 2H), 3.89-3.79 (m, 2H), 2.22-2.18 (m, 1H), 2.12-2.06 (m, 1H), 1.55 (s, 6H), 1.02 (s, 9H); LC-MS (ES^+): *m/z* 922.15 [MH^+], t_R = 2.53 min (5.0 minute run).
61		Prepared from **ABM-16**, **L-10**, and **ULM-4** (2S,4R)-1-[(2S)-2-(2-{[6-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluorophenoxy)hexa-2,4-diyn-1-yl]oxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.23 (s, 1H), 8.15 (d, *J* = 7.5 Hz, 2H), 7.98 (d, *J* = 9.0 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 2H), 7.49-7.40 (m, 3H), 7.36-7.21 (m, 2H), 7.18-7.12 (m, 1H), 5.02 (s, 2H), 4.71 (s, 1H), 4.59-4.47 (m, 3H), 4.44-4.29 (m, 3H), 4.09 (s, 2H), 3.89-3.74 (m, 2H), 2.22-2.18 (m, 1H), 2.12-2.01 (m, 1H), 1.57 (s, 6H), 1.04 (s, 9H); LC-MS (ES^+): *m/z* 956.20 [MH^+], t_R = 2.60 min (5.0 minute run).

[0646]

[0647] Example 62: (2S,4R)-1-((S)-2-tert-butyl-16-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenyl)-4,13-dioxo-6,9-dioxa-3,12-diazahexadecane)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide:



[0648] Step 1: Synthesis of ethyl 2-(2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)butanamido]ethoxy}ethoxy)acetate (**BL**)

[0649] To a stirred solution of 4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)butanoic acid (**ABM-12**, 417 mg, 0.88 mmol) in N,N-dimethylformamide (10 mL) was added HATU (669 mg, 1.76 mmol), DIEA (454 mg, 3.51 mmol) and ethyl 2-[2-(2-aminoethoxy)ethoxy]acetate hydrochloride (**L-13**, 400 mg, 1.76 mmol) at 0 °C . The resulting solution was stirred at 0 °C for 30 min, and then it was warmed up to rt and stirred at rt for 15 h. A mixture of water/ice (1: 1, 50 mL) was added to the reaction, the resulting mixture was extracted with ethyl acetate (100 mL x 3). The organic layers were combined,

washed with saturated aqueous solution of sodium chloride (20 mL x 2), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v = 1:1) to give **BL** (yield: 35%) as a yellow solid. LC-MS (ES^+): *m/z* 649.15[MH^+], t_R = 1.05 min (2.0 minute run).

[0650] Step 2: Synthesis of 2-(2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)butanamido]ethoxy}ethoxy)acetic acid (**BM**)

[0651] To a stirred solution of ethyl 2-(2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)butanamido]ethoxy}ethoxy)acetate (**BL**, 200 mg, 0.31 mmol) in methanol (10 mL) was added a solution of NaOH (123 mg, 3.08 mmol) in water (10 mL) at rt. The resulting solution was then heated to 50 °C and stirred at this temperature for 2h. The bulk of organic solvent was removed under reduced pressure. To the remaining residue was added aqueous hydrogen chloride (1 M) to adjust the pH to ~3. The resulting mixture was extracted with ethyl acetate (50 mL x 2), the organic layers were combined, washed with saturated aqueous solution of sodium chloride (20 mL x 2), dried over anhydrous sodium sulfate and then concentrated under reduced pressure followed by high vacuum pump to give **BM** (yield: 78%) as a yellow solid. LC-MS (ES^+): *m/z* 621.20 [MH^+], t_R = 0.96 min (2.0 minute run).

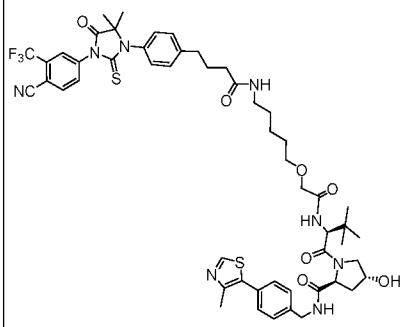
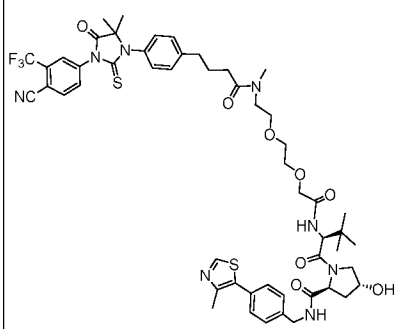
[0652] Step 3: Synthesis of (2S,4R)-1-[(2S)-2-[2-(2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)butanamido]ethoxy}ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Example 62**)

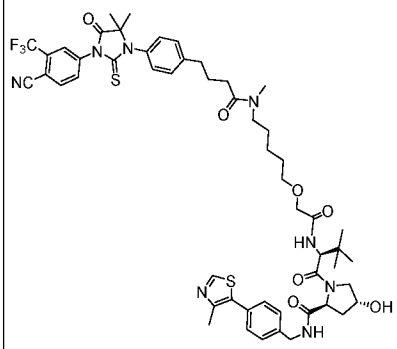
[0653] To a stirred solution of 2-(2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)butanamido]ethoxy}ethoxy)acetic acid (**BM**, 200 mg, 0.32 mmol) in N,N-dimethylformamide (20 mL) was added HATU (245 mg, 0.64 mmol), DIEA (166 mg, 1.28 mmol) and (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide hydrochloride (**ULM-1**, 226 mg, 0.48 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 30 min, and then it was warmed up to rt and stirred at rt for 15 h. A mixture of water/ice (1: 1, 50 mL) was added to the reaction, the resulting mixture was extracted with ethyl acetate (100 mL

x 3). The organic layers were combined, washed with saturated aqueous solution of sodium chloride (50 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by Prep-HPLC to give **Example 62** (yield: 6%) as a yellow solid. ^{1}H NMR (400MHz, CD_3OD): δ 8.89 (s, 1H), 8.18-8.16 (d, J = 8.4 Hz, 2H), 8.01-7.99 (d, J = 8.0 Hz, 1H), 7.47-7.41(m, 4H), 7.38-7.36 (d, J = 8.4 Hz, 2H), 7.30-7.28 (d, J = 8.4 Hz, 2H), 4.87 (s, 1H), 4.78-4.60 (m, 3H), 4.39-4.35 (d, J = 15.2 Hz, 1H), 4.04-3.98 (m, 2H), 3.98-3.85 (m, 2H), 3.72-3.60 (m, 7H), 3.50-3.49(m, 1H), 2.71-2.69 (m, 2H), 2.49 (s, 3H), 2.45-2.28 (m, 3H), 2.25-2.10 (m, 1H), 2.10-1.95 (m, 2H), 1.58 (s, 6H), 1.09 (s, 9H); LC-MS (ES$^+$): m/z 1033.50 [MH$^+$], t_R = 3.06 min (5.6 minute run).

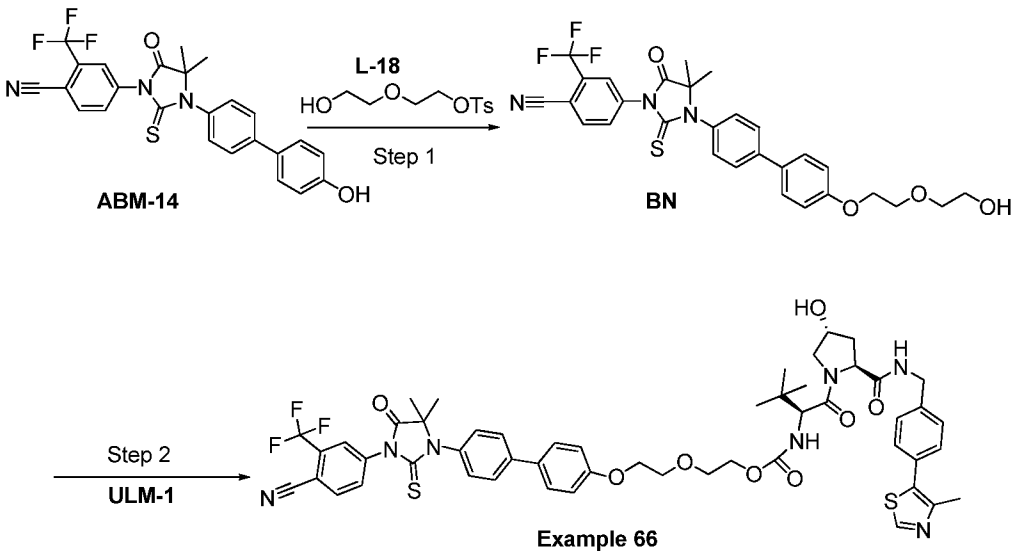
[0654] Examples 63-65 were synthesized according to similar procedure described for synthesis of example 62, by using corresponding starting materials and intermediates.

[0655] Table 4. Exemplary Compounds.

Ex #	Structure	Compound name and Analytical data
63		Prepared from **ABM-12**, **L-14**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-({5-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)butanamido]pentyl}oxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO):δ8.98 (s, 1H), 8.60 (m, 1H), 8.40 (d, J = 8.0 Hz, 1H), 8.30 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.79 (m, 1H), 7.40 (m, 4H), 7.36 (m, 3H), 7.29 (d, J = 8.0 Hz, 2H), 5.16 (m, 1H), 4.57 (d, J = 9.2 Hz, 1H), 4.45 (m, 4H), 3.92 (m, 2H), 3.66 (m, 2H), 3.48 (m, 2H), 3.07 (m, 2H), 2.64 (m, 2H), 2.51 (m, 3H), 2.14 (m, 3H), 1.90 (m, 3H), 1.57 (m, 2H), 1.50 (s, 6H), 1.44 (m, 2H),1.36 (m, 2H), 0.94 (s, 9H); LC-MS (ES$^+$): m/z 516.65 [M+2] /2, t_R = 2.55 min. (5.0 minute run).
64		Prepared from **ABM-12**, **L-15**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-(2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)-N-methylbutanamido]ethoxy}ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD) δ 8.87 (s, 1H), 8.17-8.14 (d, J = 8.4 Hz, 2H), 8.01-7.98(d, J = 8.7 Hz, 1H), 7.47-7.31 (m, 6H), 7.28-7.13 (d, J = 8.1 Hz, 2H), 4.71 (s, 1H), 4.61-4.51 (m, 3H), 4.38-4.33(d, J =15.2 Hz, 1H), 4.04-4.02 (m, 2H), 3.86-3.81(m, 2H), 3.69-3.60 (m, 7H), 3.59-3.52 (m, 1H), 3.10 (s, 2H), 2.97 (s, 1H), 2.75-2.73 (m, 2H), 2.46 (s, 3H), 2.46-2.41 (m, 2H), 2.38-2.23 (m, 1H), 2.21-2.09 (m, 1H), 1.99-1.91 (m, 2H), 1.55 (s, 6H),

Ex #	Structure	Compound name and Analytical data
		1.02 (s, 9H); LC-MS (ES^+): *m/z* 1047.80 [MH^+], t_R = 2.09 min (3.6 minute run).
65		Prepared from **ABM-12**, **L-16**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-({5-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)-N-methylbutanamido]pentyl}oxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO) δ 8.98 (s, 1H), 8.60 (s, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 8.30 (s, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.46-7.27 (m, 9H), 5.15 (s, 1H), 4.57-4.55 (m, 1H), 4.47-4.23 (m, 4H), 3.92-3.85 (m, 2H), 3.68-3.59 (m, 2H), 3.47 (s, 2H), 3.29-3.20 (m, 2H), 2.91-2.64 (m, 5H), 2.44 (s, 3H), 2.33-2.30 (m, 2H), 2.09-2.03 (m, 1H), 1.95-1.81 (m, 3H), 1.59-1.46 (m, 10H), 1.30-1.24 (m, 2H), 0.94 (s, 9H); Mass (ES^+): *m/z* 1045.40 [MH^+]

[0656] Example 66: 2-(2-(4'-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)biphenyl-4-yloxy)ethoxy)ethyl (S)-1-((2S,4R)-4-hydroxy-2-(4-(4-methylthiazol-5-yl)benzylcarbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-ylcarbamate:



[0657] Step 1: Synthesis of 4-[3-(4-{4-[2-(2-hydroxyethoxy)ethoxy]phenyl}phenyl)-4,4-dimethyl-5-oxo-2-sulfanylideneimidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile (**BN**)

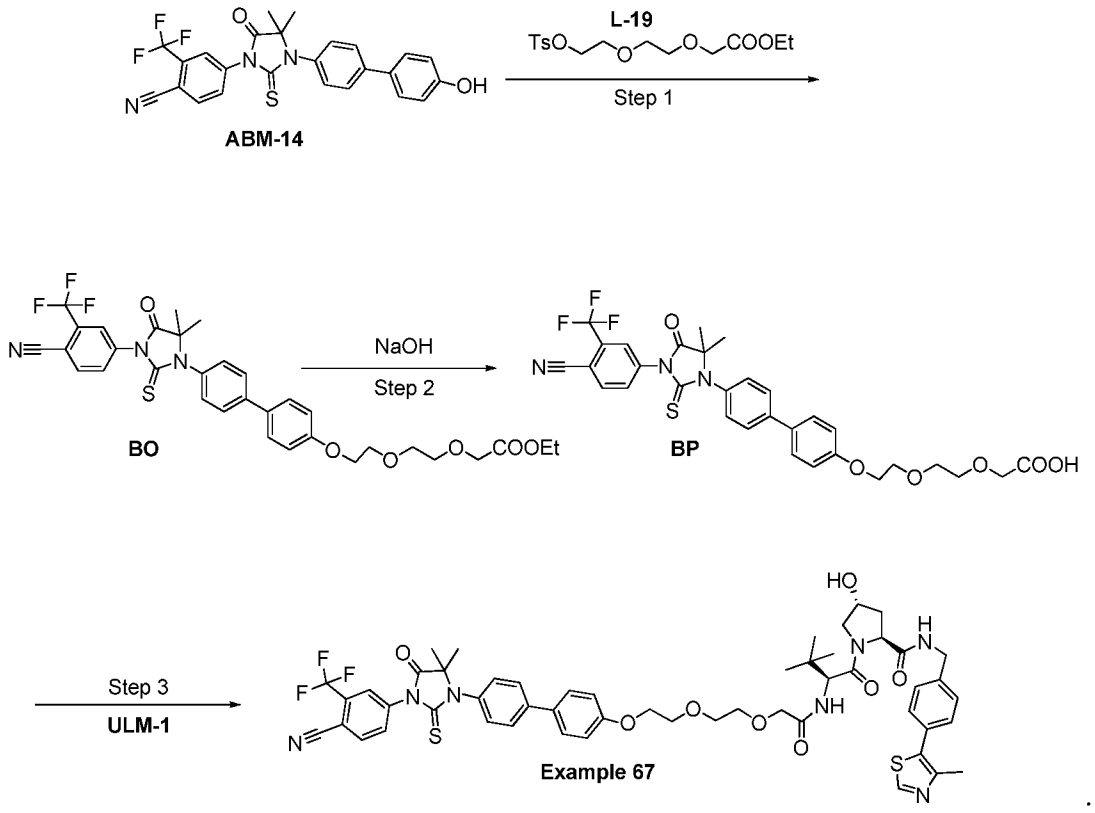
[0658] To a stirred solution of 4-{3-[4-(4-hydroxyphenyl)phenyl]-4,4-dimethyl-5-oxo-2-sulfanylideneimidazolidin-1-yl}-2-(trifluoromethyl)benzonitrile (**ABM-14**, 610.5 mg, 1.27 mmol) in N,N-dimethylformamide (10 mL) was added K_2CO_3 (318.46 mg, 2.29 mmol) and 2-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}ethan-1-ol (**L-18**, 300 mg, 1.15 mmol) at rt. The resulting mixture was then stirred at 80 °C for 2 hours in an oil bath, LC-MS indicated formation of the desired product. The reaction mixture was cooled down to rt, water (20mL) was added and the resulting mixture was extracted with ethyl acetate (100 mL x 2). The organic layers were combined, washed with saturated aqueous solution of sodium chloride (20 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue which was purified by a flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v = 7:3) to give **BN** (yield: 66%) as a light yellow oil. LC-MS (ES^+): m/z 570, [MH^+], t_R = 1.60 min (2.0 minute run).

[0659] Step 2: synthesis of 2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]ethoxy}ethyl N-[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate (**Example 66**)

[0660] To a stirred solution of 4-[3-(4-{4-[2-(2-hydroxyethoxy)ethoxy]phenyl}phenyl)-4,4-dimethyl-5-oxo-2-sulfanylideneimidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile (200 mg, 0.35 mmol) in dichloromethane (10 mL) was added triethylamine (106.5 mg, 1.05 mmol), followed by triphosgene (36.5 mg, 0.12 mmol) which was added slowly in 30 min at 0 °C. To this mixture was then added (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide hydrochloride (**ULM-1**, 196.9 mg, 0.42 mmol) at 0 °C. The resulting mixture was then warmed up to rt and stirred at rt for 2 hours. Water (20mL) was added to the reaction and the resulting mixture was extracted with dichloromethane (50 mL x 3). The organic layers were combined, washed with saturated aqueous solution of sodium chloride (20 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by Prep-HPLC to give **Example 66** (yield: 6%) as a white solid. ^{1}H-NMR (400MHz, CD_3OD): δ 8.88 (s, 1 H), 8.20-

8.17 (m, 2 H), 8.04-8.02 (d, J = 8.0 Hz, 1 H), 7.77-7.72 (m, 2 H), 7.65-7.59 (m, 2 H), 7.48-7.42 (m, 6 H), 7.08-7.06 (d, J = 8.4 Hz, 2 H), 4.61-4.53 (m, 1 H), 4.47-4.44 (s, 1 H), 4.38-4.34 (m, 2 H), 4.25-4.20 (m, 4 H), 3.92-3.90 (m, 3 H), 3.82-3.79 (m, 3 H), 2.48 (s, 3 H), 2.26-2.21 (m, 1 H), 2.13-1.09 (m, 1 H), 1.61 (s, 6 H), 1.30 (s, 1 H), 1.04 (s, 9 H); LC-MS (ES^+): m/z 1026.40 [MH^+], t_R = 2.23 min (3.0 minute run).

[0661] Example 67: (2S,4R)-1-((S)-2-(2-(2-(2-(4'-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)biphenyl-4-yloxy)ethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide:



[0662] Step 1: Synthesis of ethyl 2-(2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]ethoxy}ethoxy)acetate (**BO**)

[0663] To a stirred solution of 4-{3-[4-(4-hydroxyphenyl)phenyl]-4,4-dimethyl-5-oxo-2-sulfanylideneimidazolidin-1-yl}-2-(trifluoromethyl)benzonitrile (**ABM-14**, 300 mg, 0.62 mmol) in N,N-dimethylformamide (10 mL) was added K_2CO_3 (172 mg, 1.24 mmol) and ethyl 2-(2-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}ethoxy)acetate (**L-19**, 237.4 mg, 0.69 mmol). The

resulting mixture was stirred at 80 °C in an oil bath for 2 hours. The reaction was cooled down to rt, water (50mL) was added and the resulting mixture was extracted with ethyl acetate (100 mL x 2). The organic layers were combined, washed with saturated aqueous solution of sodium chloride (30 mL x 3), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by a flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v = 3:7)) to give **BO** (yield: 48%) as light yellow oil. LC-MS (ES^+): m/z 656, [MH^+], t_R = 1.19 min (2.0 minute run).

[0664] Step 2: Synthesis of 2-(2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]ethoxy}ethoxy)acetic acid (**BP**)

[0665] To a stirred solution of ethyl 2-(2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]ethoxy}ethoxy)acetate (**BO**, 198 mg, 0.30 mmol) in ethanol (5 mL) was added a solution of sodium hydroxide (36.3 mg, 0.91 mmol) in water (2 mL) at rt. The resulting solution was stirred overnight at rt, the bulk of organic solvent was then removed under reduced pressure. To the remaining aqueous residue was added hydrogen chloride in water (1N) to adjust the pH to ~5.0, and the resulting mixture was extracted with ethyl acetate (250 mL x 2). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure followed by high vacuum pump to give **BP** (yield: 99%) as a light yellow oil. LC-MS (ES^+): m/z 628, [MH^+], t_R = 1.08 min (2.0 minute run).

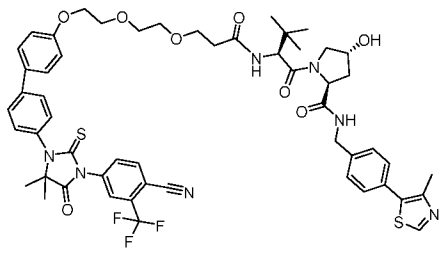
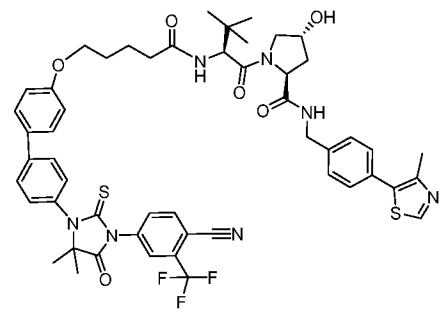
[0666] Step 3: Synthesis of (2S,4R)-1-[(2S)-2-[2-(2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]ethoxy}ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Example 67**)

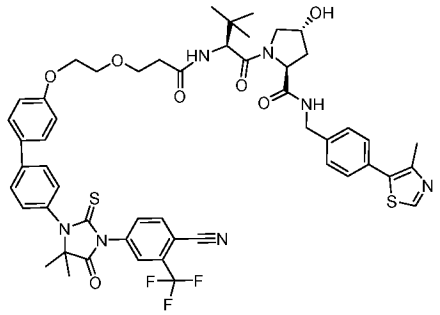
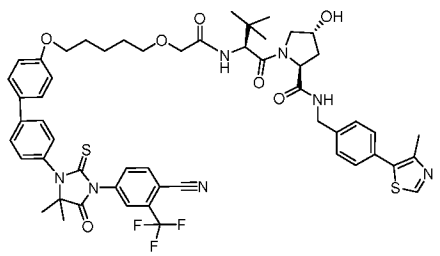
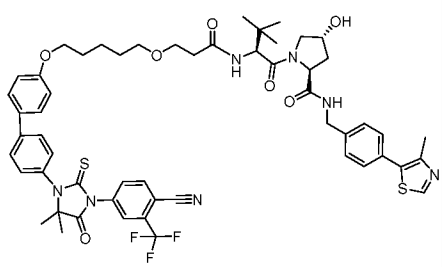
[0667] To a stirred solution of 2-(2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]ethoxy}ethoxy)acetic acid (**BP**, 190 mg, 0.30 mmol) in N,N-dimethylformamide (10 mL) was added HATU (149.7 mg, 0.39 mmol), DIEA (156.4 mg, 1.21 mmol) and (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide hydrochloride (**ULM-1**, 183.9 mg, 0.39 mmol). The resulting solution was stirred at rt for 2 hours. Water (50mL) was added and the resulting mixture was extracted with ethyl acetate (100 mL x 2). The organic layers were combined, washed with saturated aqueous solution of sodium

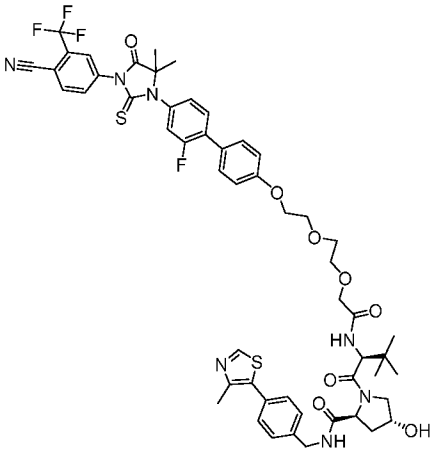
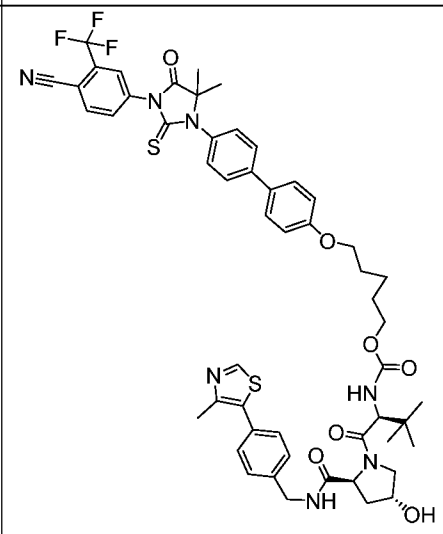
chloride (25 mL x 3), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified Prep-HPLC to give **Example 67** (yield: 17%) as a white solid. ^{1}H-NMR (400MHz, CD_3OD): δ 8.82 (s, 1 H), 8.19-8.16 (d, J = 9.0 Hz, 2 H), 8.02-8.00 (d, J = 8.1 Hz, 1 H), 7.72-7.69 (d, J = 8.1 Hz, 2 H), 7.61-7.55 (m, 2 H), 7.46-7.37 (m, 6 H),7.08-7.01 (m, 2 H), 4.71(s, 1 H), 4.61-4.51 (m, 1 H), 4.47 (s, 2 H), 4.38-4.31 (m, 1 H), 4.23-4.20 (m, 2 H), 4.01(s, 2 H), 3.96-3.78 (m, 4 H), 3.63 (s, 4 H), 2.43 (s, 3H), 2.27-2.20 (m,1 H), 2.13-2.04 (m, 1 H), 1.61 (s, 6 H), 1.04 (s, 9 H); LC-MS (ES$^+$): *m/z* 1040.10 [MH$^+$], t_R = 2.26 min (3.0 minute run).

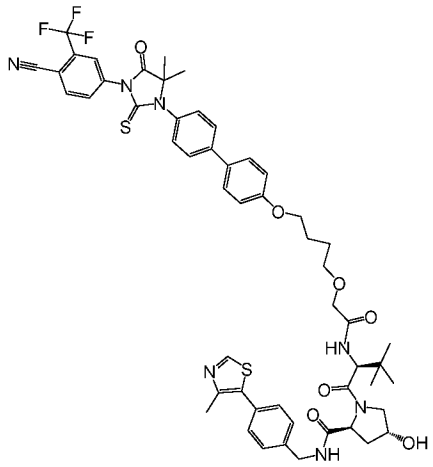
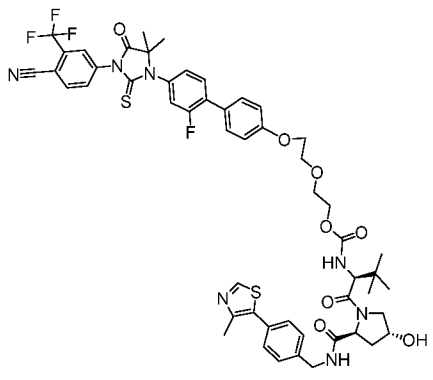
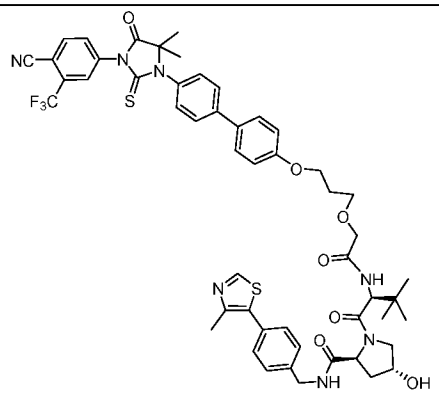
[0668] Examples 74 and 76 were synthesized according to similar procedure described for synthesis of Example 66, by using corresponding starting materials and intermediates. Examples 68-73, 75, 77-79 were synthesized according to similar procedure described for synthesis of Example 67, by using corresponding starting materials and intermediates.

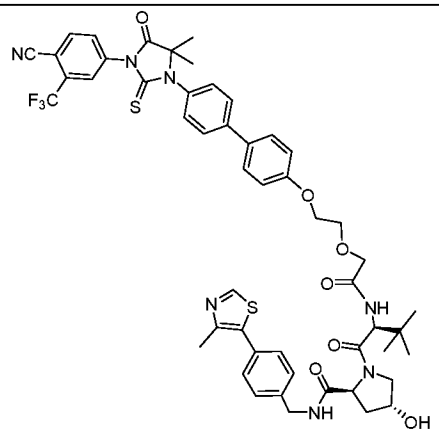
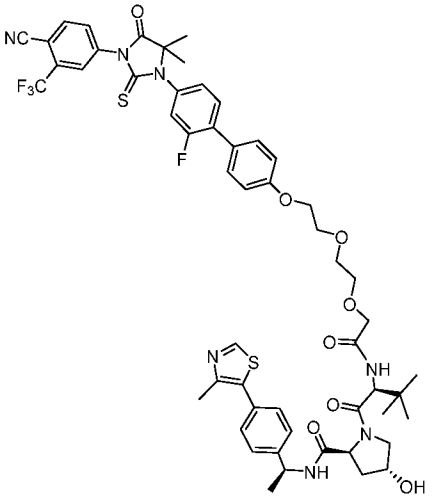
[0669] Table 5. Exemplary Compounds.

Ex #	Structure	Compound name and Analytical data
68		Prepared from **ABM-14**, **L-20**, and **ULM-1** (2S,4R)-1-[(2S)-2-[3-(2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]ethoxy}ethoxy)propanamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.87 (s, 1H), 8.21-8.17 (m, 2H), 8.04 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H), 7.49-7.41 (m, 6H), 7.07 (d, J = 8.8 Hz, 2H), 4.67 (s, 1H), 4.61-4.51 (m, 3H), 4.37-4.33 (m, 1H), 4.20-4.18 (m, 2H), 3.92-3.66 (m, 10H), 2.62-2.45 (m, 5H), 2.26-2.17 (m, 1H), 2.14-2.05 (m, 1H), 1.61 (s, 6H),1.05 (s, 9H); LC-MS (ES$^+$): *m/z* 1054.50 [MH$^+$], t_R = 2.20 min (3.6 minute run).
69		Prepared from **ABM-14**, **L-21**, and **ULM-1** (2S,4R)-1-[(2S)-2-{5-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]pentanamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.90 (s, 1H), 8.20-8.18 (d, J = 8.4 Hz, 2H), 8.04-8.02 (d, J = 7.6 Hz, 1H), 7.77-7.74 (d, J = 8.4 Hz, 2H), 7.63-7.61 (d, J = 8.4 Hz, 2H), 7.50-7.48 (m, 2H), 7.50-7.41 (m, 4H), 7.06-7.04 (d, J = 8.8Hz, 2H), 4.67(s, 1H), 4.61-4.52 (m, 3H), 4.39-4.35 (m, 1H), 4.08-4.07 (m, 2H), 3.95-3.93 (m, 1H), 3.85-3.81 (m, 1H), 2.48 (s, 3H), 2.41-2.37 (m, 2H), 2.23-2.21 (m, 1H), 2.14-2.10 (m, 1H), 1.86-1.85 (m, 4H), 1.62 (s, 6H), 1.06 (s, 9H); LC-MS (ES$^+$):

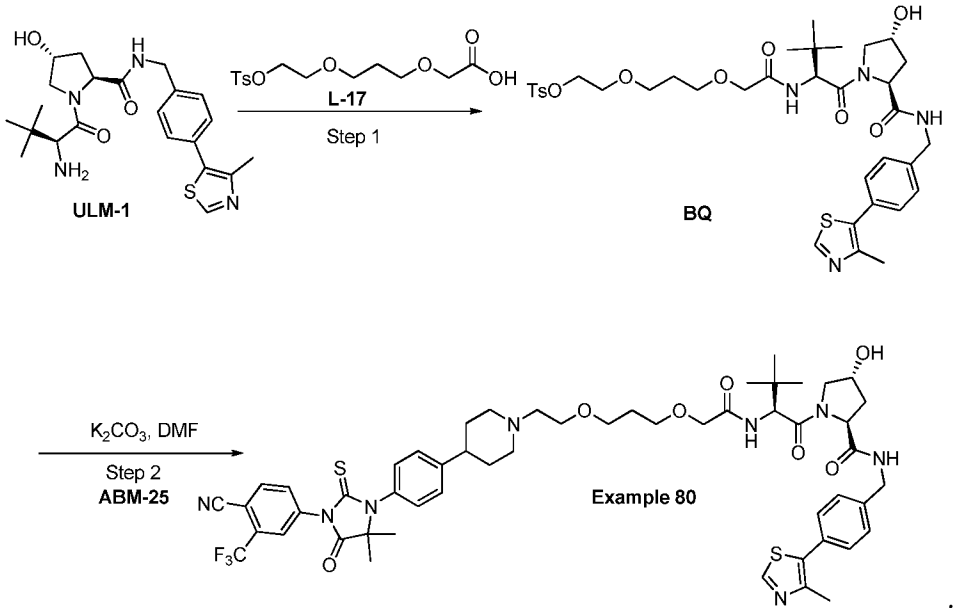
Ex #	Structure	Compound name and Analytical data
		m/z 994.40 [MH^+], t_R = 1.71 min (3.0 minute run).
70		Prepared from **ABM-14**, **L-22**, and **ULM-1** (2S,4R)-1-[(2S)-2-(3-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]ethoxy}propanamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.85 (s, 1H), 8.21-8.17 (m, 2H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.49-7.39 (m, 6H), 7.08 (d, *J* = 8.8 Hz, 2H), 4.68 (s, 1H), 4.59-4.51 (m, 3H), 4.37 (s, 1H), 4.23-4.20 (m, 2H), 3.93-3.80 (m, 6H), 2.63-2.45 (m, 2H), 2.45 (s, 3H), 2.23-2.06 (m, 2H), 1.62 (s, 6H), 1.05 (s, 9H); LC-MS (ES^+): *m/z* 1010.30 [MH^+], t_R = 1.68 min (3.0 minute run).
71		Prepared from **ABM-14**, **L-23**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-({5-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]pentyl}oxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.84 (s, 1 H), 8.19-8.17 (d, *J* = 8.4 Hz, 2H), 8.04-8.02 (d, *J* = 8.4 Hz, 1H), 7.73-7.71 (d, *J* = 8.4 Hz, 2H), 7.59-7.57 (d, *J* = 8.4 Hz, 2H), 7.49-7.38 (m, 6H), 7.02-7.00 (d, *J* = 8.4 Hz, 2H), 4.72 (s, 1H), 4.59-4.46 (m, 3H), 4.37-4.33 (d, *J* = 10.6 Hz, 1H), 4.08-4.06 (m, 2H), 4.05-4.00 (m, 2H), 3.98-3.83 (m, 2H), 3.64-3.61 (m, 2H), 2.49 (s, 3H), 2.29-2.21 (m, 1H), 2.11-2.01 (m, 1H), 1.90-1.86 (m, 2H), 1.78-1.75 (m, 2H), 1.66-1.62 (m, 2H), 1.61(s, 6H), 1.06 (s, 9H) LC-MS (ES^+): *m/z* 1038.38 [MH^+], t_R = 1.68 min (3.0 minute run).
72		Prepared from **ABM-14**, **L-24**, and **ULM-1** (2S,4R)-1-[(2S)-2-[3-({5-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]pentyl}oxy)propanamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.84 (s, 1 H), 8.19-8.17 (d, *J* = 8.4 Hz, 2H), 8.04-8.02 (d, *J* = 8.4 Hz, 1H), 7.73-7.71 (d, *J* = 8.4 Hz, 2H), 7.59-7.57 (d, *J* = 8.4 Hz, 2H), 7.49-7.38 (m, 6H), 7.02-7.00 (d, *J* = 8.4 Hz, 2H), 4.72 (s, 1H),

Ex #	Structure	Compound name and Analytical data
		4.59-4.46 (m, 3H), 4.37-4.33 (d, J = 10.6 Hz, 1H), 4.08-4.06 (m, 2H), 4.05-4.00 (m, 2H), 3.98-3.83 (m, 2H), 3.64-3.61 (m, 2H), 2.49 (s, 3H), 2.29-2.21 (m, 1H), 2.11-2.01 (m, 1H), 1.90-1.86 (m, 2H), 1.78-1.75 (m, 2H), 1.66-1.62 (m, 2H), 1.61(s, 6H), 1.06 (s, 9H); LC-MS (ES^+): m/z 1052.39 [MH^+], t_R = 1.81 min (3.0 minute run).
73		Prepared from **ABM-24**, **L-29**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-(2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluorophenyl)phenoxy]ethoxy}ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.89 (s, 1H), 8.20-8.18 (d, J = 8.4 Hz, 2H), 8.04-8.02 (d, J = 8.4 Hz, 1H), 7.62 -7.59 (m, 1H), 7.59-7.57 (m, 2H), 7.49-7.40(m, 2H), 7.40-7.30 (m, 2H), 7.30-7.10 (m, 2H), 7.08-7.06 (d, J = 8.4 Hz, 2H), 4.72 (s, 1H), 4.62-4.60 (m, 3H), 4.37-4.34 (d, J = 15.2 Hz, 1H), 4.25-4.23 (m, 2H), 4.13-4.09 (m, 2H), 3.97-3.92 (m, 4H), 3.89-3.79(m, 4H), 2.46(s, 3H), 2.24-2.22(m, 1H), 2.14-2.12(m, 1H), 1.63 (s, 6H), 1.06 (s, 9H); LC-MS (ES^+): m/z 1058.35 [MH^+], t_R = 1.47 min (4.6 minute run).
74		Prepared from **ABM-14**, **L-25**, and **ULM-1** 5-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]pentyl N-[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate ^{1}H NMR (300 MHz, CD_3OD): δ 8.87 (s, 1H), 8.18-8.15 (d, J = 10.2 Hz, 2H), 8.02-8.00 (d, J = 8.1 Hz, 1H), 7.75-7.73 (d, J = 8.4 Hz, 2H), 7.63-7.60 (d, J = 8.4 Hz, 2H), 7.47-7.40 (m, 6H), 7.04-7.01 (d, J = 8.7 Hz, 2H) , 4.61-4.51 (m, 3H), 4.37-4.32 (m, 2H), 4.16-4.02 (m, 4H), 3.92-3.78 (m, 2H), 2.47 (s, 3H), 2.26-2.11 (m, 1H), 2.10-2.07 (m, 1H), 1.86-1.80 (m, 2H), 1.76-1.64 (m, 2H), 1.60 (m, 8H), 1.03 (s, 9H) ; LC-MS (ES^+): m/z 1023.82 [MH^+], t_R = 2.36 min (3.6 minute run)

Ex #	Structure	Compound name and Analytical data
75		Prepared from **ABM-14**, **L-26**, and **ULM-1** (2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.83 (s, 1H), 8.19-8.17 (d, *J* = 8.4 Hz, 2H), 8.04-8.02 (d, *J* = 9.6 Hz, 1H), 7.75-7.72 (d, *J* = 8.4 Hz, 2H), 7.60-7.58 (d, *J* = 8.4Hz, 2H), 7.59-7.39 (m, 6H), 7.04-7.02 (d, *J* = 8.8 Hz, 2H) , 4.88 (s, 1H), 4.71-4.41 (m, 3H), 4.37-4.32 (d, *J* = 15.2Hz, 1H), 4.11-4.09 (m, 2H), 4.08-4.01(m, 2H), 3.98-3.90 (m, 1H), 3.90-3.83 (m, 1H), 3.69-3.66 (m, 2H), 2.44 (s, 3H), 2.25-2.23 (m, 1H), 2.12-2.10 (m,1H), 1.98-1.90 (m, 2H), 1.90-1.84 (m, 2H), 1.60 (s, 6H), 1.03 (s, 9H); LC-MS (ES^+): m/z 1024.10 [MH^+], t_R = 2.33 min (4.6 minute run)
76		Prepared from **ABM-24**, **L-18**, and **ULM-1** 2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluorophenyl)phenoxy]ethoxy}ethyl N-[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate ^{1}H NMR (400 MHz, CD_3OD): δ 8.88 (s, 1H), 8.20-8.18 (d, *J* = 9.6 Hz, 2H), 8.04-8.02 (d, *J* = 8.4 Hz, 1H), 7.69-7.63 (m, 1H), 7.58-7.56 (d, *J* = 8.0 Hz, 2H), 7.48-7.42 (m, 4H), 7.34-7.30 (m, 2H), 7.10-7.08 (d, *J* = 8.8 Hz, 2H), 4.61-4.57 (m, 3H), 4.53-4.47 (m, 2H), 4.38-4.21 (m, 4H), 3.93-3.90 (m, 3H), 3.84-3.78 (m, 3H), 2.48 (s, 3 H), 2.26-2.17 (m, 1H), 2.11-2.07 (m, 1H), 1.63 (s, 6H), 1.02 (s, 9H) ; LC-MS (ES^+): *m/z* 1044.33 [MH^+], t_R = 2.21 min. (3.6 minute run).
77		Prepared from **ABM-14**, **L-27**, and **ULM-1** (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]propoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.83 (s, 1H), 8.19-8.16 (d, *J* = 9.0 Hz, 2H), 8.03-8.01 (d, *J* = 8.1 Hz, 1H), 7.75-7.72 (d, *J* = 8.7 Hz, 2H), 7.72-7.69 (d, *J* = 8.7Hz, 2H), 7.63-7.36 (m, 6H), 7.08-7.05 (d, *J* = 8.7 Hz, 2H), 4.72 (s, 1H), 4.62-4.51 (m, 3H), 4.36-4.31 (d, *J* = 15.3Hz, 1H), 4.22-4.19 (m, 2H), 4.04-3.98 (m, 2H), 3.91-3.76 (m, 4H), 2.43 (s, 3H), 2.21-2.10 (m, 4H), 1.60 (s, 6H), 1.02 (s, 9H); Mass (ES^+): m/z 1010.30 [MH^+]

Ex #	Structure	Compound name and Analytical data
78		Prepared from **ABM-14**, **L-28**, and **ULM-1** (2S,4R)-1-[(2S)-2-(2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]ethoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.79 (s, 1H), 8.71-8.69 (m, 1H), 8.19-8.16 (d, *J* = 9.0 Hz, 2H), 8.03-8.01 (d, *J* = 8.4 Hz, 1H), 7.77-7.75 (d, *J* = 4.8 Hz, 1H), 7.77-7.75 (d, *J* = 4.8 Hz, 1H), 7.72-7.64 (m, 4H), 7.55-7.45 (m, 4H), 7.17-7.14 (d, *J* = 8.7 Hz, 2H), 4.78-4.75 (d, *J* = 6.6 Hz, 1H), 4.75-4.62 (m, 2H), 4.55-4.52 (m, 1H), 4.28-4.26 (m, 3H), 4.14 (s, 2H), 3.98-3.95 (m, 2H), 3.88-3.84 (m, 2H), 2.38 (s, 3H), 2.29-2.11(m, 1H), 2.11-2.01(m, 1H), 1.60 (s, 6H), 1.04 (s, 9H); LC-MS (ES^+): m/z 996.33 [MH^+], t_R = 2.92 min (5.0 minute run).
79		Prepared from **ABM-24**, **L-19**, and **ULM-3** (2S,4R)-1-[(2S)-2-[2-(2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluorophenyl)phenoxy]ethoxy}ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.76 (s, 1H), 8.08-8.06 (d, *J* = 9.6Hz, 2H), 7.91-7.89 (d, *J* = 7.2 Hz, 1H), 7.56-7.53 (m, 1H), 7.45-7.42 (d, *J* = 9.2 Hz, 2H), 7.33-7.29 (m, 4H), 7.22-7.20 (m, 2H), 6.99-6.97 (d, *J* = 8.8 Hz, 2H), 4.95-4.93 (m, 1H), 4.60 (s, 1H), 4.50-4.47 (m, 1H), 4.45-4.34 (m, 1H), 4.16-4.14 (m, 2H), 3.98-3.97 (m, 2H), 3.83-3.81 (m, 2H), 3.77-3.74 (m, 1H), 3.67-3.63 (m, 5H), 2.36 (s, 3H), 2.12-2.10 (m, 1H), 1.89-1.85 (m, 1H), 1.51 (s, 6H), 1.37-1.36 (m, 3H) , 0.93 (s, 9H); LC-MS (ES^+): m/z 1072.4 [MH^+], t_R = 1.46 min (4.6 minute run).

[0670] Example 80: (2S,4R)-1-((S)-2-(2-(3-(2-(4-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenyl)piperidin-1-yl)ethoxy)propoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide:



[0671] Step 1: synthesis of (2S,4R)-1-[(2S)-3,3-dimethyl-2-[2-(3-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}propoxy)acetamido]butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**BQ**)

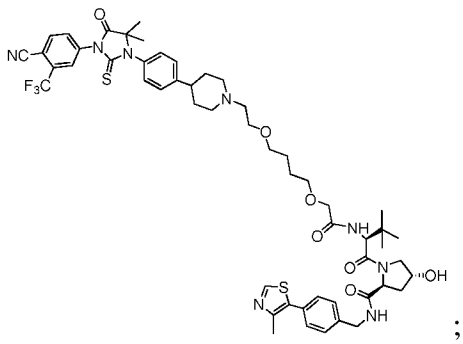
[0672] To a stirred solution of 2-(3-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}propoxy)acetic acid (**L-17**, 300 mg, 0.90 mmol) in N,N-dimethylformamide (5 mL) was added EDCI (350 mg, 1.83 mmol), HOBt (240 mg, 1.78 mmol) and DIEA (350 mg, 2.71 mmol) at rt. The resulting solution was stirred at rt for 10 min. Then to the solution was added (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**ULM-1**, 390 mg, 0.91 mmol), and the resulting solution was stirred at rt for 1 h. Water (30mL) was added and the resulting mixture was extracted with ethyl acetate (30 mL x 3). The organic layers were combined, washed with saturated aqueous solution of sodium chloride (30 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by a flash silica gel chromatography (eluent: dichloromethane/methanol (v:v = 10:1) to give **BQ** (yield: 64%) as a yellow solid. LC-MS (ES^+): m/z 745.35 [MH^+], t_R = 0.96 min (2.0 minute run).

[0673] Step 2: Synthesis of (2S,4R)-1-[(2S)-2-[2-(3-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)piperidin-1-yl]ethoxy}propoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Exampl 80**)

[0674] To a stirred solution of 4-{4,4-dimethyl-5-oxo-3-[4-(piperidin-4-yl)phenyl]-2-sulfanylideneimidazolidin-1-yl}-2-(trifluoromethyl)benzonitrile (**ABM-25**, 150 mg, 0.32 mmol), (2S,4R)-1-[(2S)-3,3-dimethyl-2-[2-(3-{2-[(4-methylbenzenesulfonyl) oxy]ethoxy}propoxy)acetamido]butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**BQ**, 236 mg, 0.32 mmol) in N,N-dimethylformamide (5 mL) was added potassium carbonate (131 mg, 0.95 mmol). The resulting mixture was stirred at 60 °C overnight. The reaction mixture was cooled to rt, water (20mL) was added and the resulting mixture was extracted with ethyl acetate (30 mL x 3). The organic layers were combined, washed with saturated aqueous solution of sodium chloride (20 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by Prep-HPLC to give **Example 80** (yield: 7%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD): δ 8.91 (s, 1H), 8.15 (d, J = 4.5 Hz, 2H), 8.02 (d, J = 4.5 Hz, 1H), 7.40 (m, 7H), 4.45 (d, J = 12.0 Hz, 1H), 4.45 (m, 4H), 4.02 (d, J = 3.9 Hz, 2H), 3.70 (m, 10H), 3.38 (m, 2H), 3.11 (m, 3H), 2.48 (s, 3H), 2.26 (m, 8H), 1.54 (s, 6H), 1.03 (s, 9H); LC-MS (ES^+): *m/z* 1045.35 [MH^+], t_R = 2.74 min (5.6 minute run).

[0675] **Example 81** was synthesized according to similar procedure described for synthesis of **Example 80**, by using corresponding starting materials and intermediates.

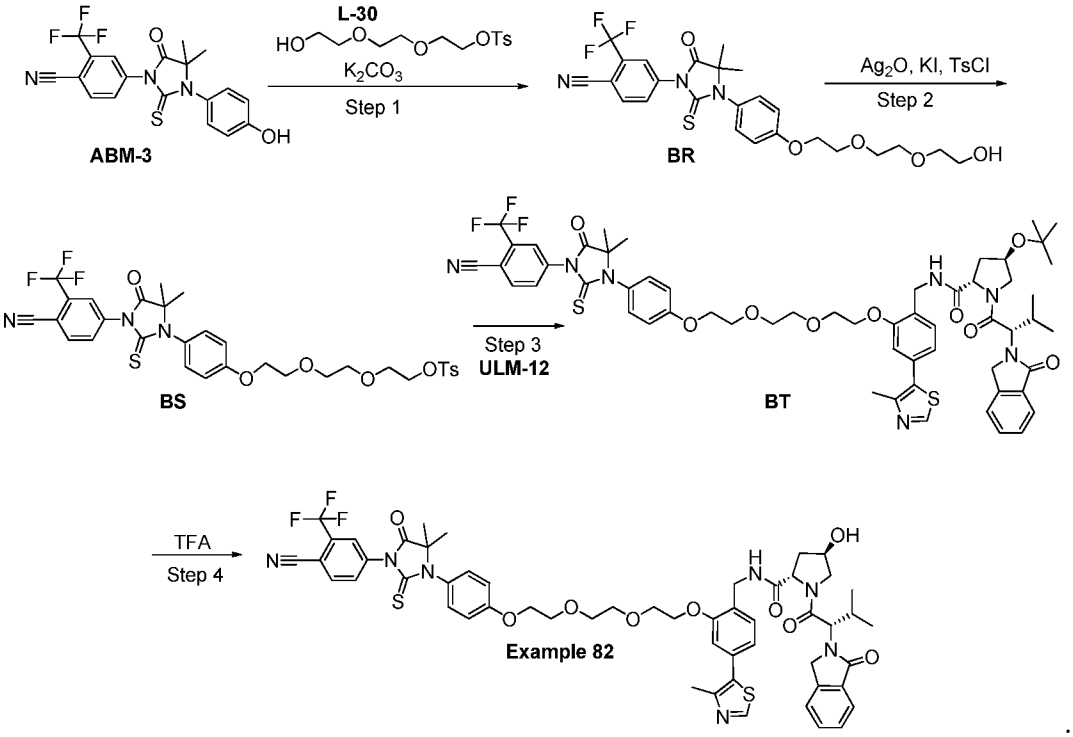
[0676] **Example 81: (2S,4R)-1-((S)-2-(2-(4-(2-(4-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenyl)piperidin-1-yl)ethoxy)butoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide**

[0677]  ;

[0678] ^{1}H NMR (300 MHz, DMSO): δ 8.98 (s, 1H), 8.63-8.61 (m, 1H), 8.40-8.37 (m, 1H), 8.37-8.34 (m, 1H), 8.11-8.01(m, 1H), 7.44-7.40 (m, 3H), 7.37-7.32 (m, 6H), 4.57-4.54 (d, J = 9.6

Hz, 1H), 4.47-4.45 (m, 2H), 4.45-4.44 (m, 2H), 4.39-4.37 (m, 1H), 3.92 (s, 2H), 3.71-3.65 (m, 2H), 3.58-3.47 (m, 5H), 3.45-3.40 (m, 4H), 2.99-2.95 (m, 2H), 2.51 (s, 3H), 2.12-2.02 (m, 3H), 1.93-1.90 (m, 1H), 1.90-1.79 (m, 3H), 1.77-1.71 (m, 5H), 1.67-1.61 (m, 6H), 0.94 (s, 9H); Mass (ES^+): *m/z* 1059.44 [MH^+].

[0679] Example 82: (2S,4R)-N-(2-(2-(2-(2-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)ethoxy)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-4-hydroxy-1-((S)-3-methyl-2-(1-oxoisoindolin-2-yl)butanoyl)pyrrolidine-2-carboxamide:



[0680] Step 1: Synthesis of 4-[3-(4-{2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}phenyl)-4,4-dimethyl-5-oxo-2-sulfanylideneimidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile (**BR**)

[0681] To a stirred solution of 4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-sulfanylideneimidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile (**ABM-3**, 405 mg, 1.00 mmol) in CH_3CN (20 mL) was added potassium carbonate (276 mg, 1.98 mmol) and 2-(2-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}ethoxy)ethan-1-ol (**L-30**, 456 mg, 1.50 mmol) at rt. The resulting mixture was then heated to 80 °C and stirred at this temperature overnight. LC-MS indicated formation of the desired product. The reaction mixture was cooled to rt, concentrated

under vacuum to give a crude residue, which was purified by a flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v = 1:1)) to give **BR** (yield: 91%) of as a brown oil.

[0682] Step 2: Synthesis of 2-{2-[2-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)ethoxy]ethoxy}ethyl 4-methylbenzene-1-sulfonate (**BS**)

[0683] To a stirred solution of 4-[3-(4-{2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}phenyl)-4,4-dimethyl-5-oxo-2-sulfanylideneimidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile (**BR**, 490 mg, 0.91 mmol) in dichloromethane (10 mL) was added tosyl chloride (190 mg, 1.00 mmol), potassium iodide (30.2 mg) and silver oxide (314 mg) at rt. The resulting mixture was then stirred at 30°C for 6h, LC-MS indicated formation of the desired product. The inorganic salts were removed from the reaction by filtration, the solution phase was concentrated under vacuum to give a crude residue, which was purified by a flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v = 1:3)) to give **BS** (yield: 60%) of as a light yellow solid.

[0684] Step 3: Synthesis of (2S,4R)-4-(tert-butoxy)-N-{[2-(2-{2-[2-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)ethoxy]ethoxy}ethoxy)-4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}-1-[(2S)-3-methyl-2-(1-oxo-2,3-dihydro-1H-isoindol-2-yl)butanoyl]pyrrolidine-2-carboxamide (**BT**)

[0685] To a stirred solution of 2-{2-[2-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)ethoxy]ethoxy}ethyl 4-methylbenzene-1-sulfonate (**BS**, 207 mg, 0.30 mmol) and (2S,4R)-4-(tert-butoxy)-N-{[2-hydroxy-4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}-1-[(2S)-3-methyl-2-(1-oxo-2,3-dihydro-1H-isoindol-2-yl)butanoyl]pyrrolidine-2-carboxamide (**ULM-12**, 181 mg, 0.30 mmol) in N,N-dimethylformamide (2 mL) was added potassium carbonate (83 mg, 0.60 mmol) at rt. The resulting mixture was then heated to 80 °C and stirred at the same temperature overnight, and LC-MS indicated formation of the desired product. The reaction was then cooled to rt, diluted by water (10 mL) and then extracted with ethyl acetate (20 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude residue, which was purified by a flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v = 1 : 1) to give **BT** (yield: 54%) as a white solid.

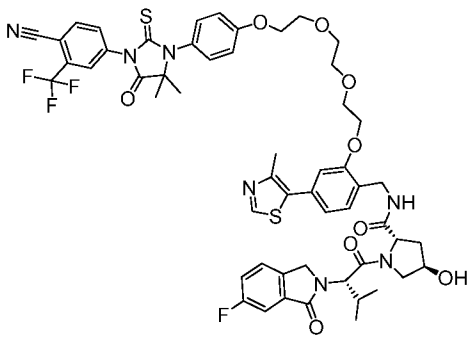
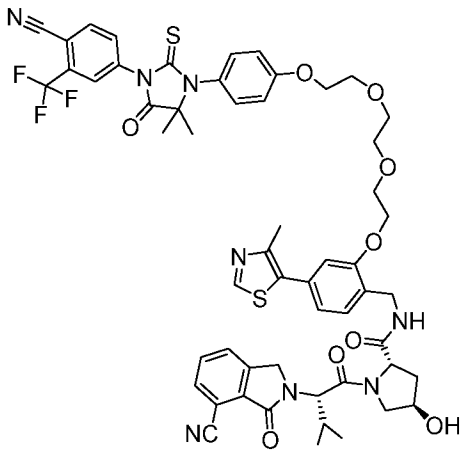
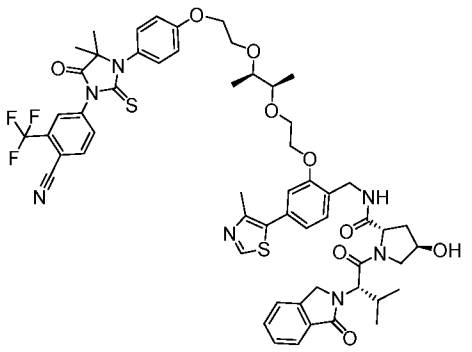
[0686] Step 4: Synthesis of (2S,4R)-N-{[2-(2-{2-[2-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)ethoxy]ethoxy}ethoxy)-4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}-4-hydroxy-1-[(2S)-3-methyl-2-(1-oxo-2,3-dihydro-1H-isoindol-2-yl)butanoyl]pyrrolidine-2-carboxamide (**Example 82**)

[0687] To a stirred solution of (2S,4R)-4-(tert-butoxy)-N-{[2-(2-{2-[2-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)ethoxy]ethoxy}ethoxy)-4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}-1-[(2S)-3-methyl-2-(1-oxo-2,3-dihydro-1H-isoindol-2-yl)butanoyl]pyrrolidine-2-carboxamide (**BT**, 180 mg, 0.16 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (0.5 mL) at rt. The resulting solution was stirred rt for 6 h, LC-MS indicated formation of the desired product. Saturated aq. solution of sodium bicarbonate was added to the reaction to neutralize the trifluoroacetic acid. Organic layer was separated, the aqueous layer was extracted with of dichloromethane (10 mL x 2). The organic layers combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude residue, which was purified by Pre-HPLC to give **Example 82** (yield: 31%) as a white solid. ^{1}H NMR (400MHz, CD_3OD): δ 8.90 (s, 1 H), 8.40-8.38 (d, *J* = 8.0Hz, 2 H), 8.29 (s, 1 H), 8.09-8.07 (d, *J* = 8.4 Hz, 1 H), 7.72-7.70 (d, *J* = 7.6Hz, 1 H), 7.62-7.61 (d, *J* = 4.0Hz, 2 H), 7.50-7.40(m, 1H), 7.35-7.33 (d, *J* = 7.6Hz, 1H), 7.27-7.25 (d, *J* =8.8Hz, 2 H), 7.10-7.06 (m, 3H), 7.05-7.00 (m, 1H), 5.09 (s, 1H), 4.72-4.69 (d, *J* =10.8 Hz, 1H), 4.61 -4.41 (m, 2H), 4.41 -4.31 (m, 2H), 4.31 -4.21 (m, 2H), 4.21 -4.11 (m, 2H), 4.11 -4.01 (m, 2H), 3.82-3.71 (m, 5H), 3.69-3.61 (m, 5H), 2.51 (m, 3H), 2.47-2.25 (m, 1 H), 2.10-2.00 (m, 1H), 2.00-1.95 (m, 1H), 1.48 (s, 6 H), 0.97- 0.96 (d, *J* = 6.4Hz, 3H), 0.74-0.72 (d, *J* = 6.4Hz, 3H); LC-MS (ES$^+$): *m/z* 1068.20 [MH$^+$], t_R = 1.59 min (3.0 minute run).

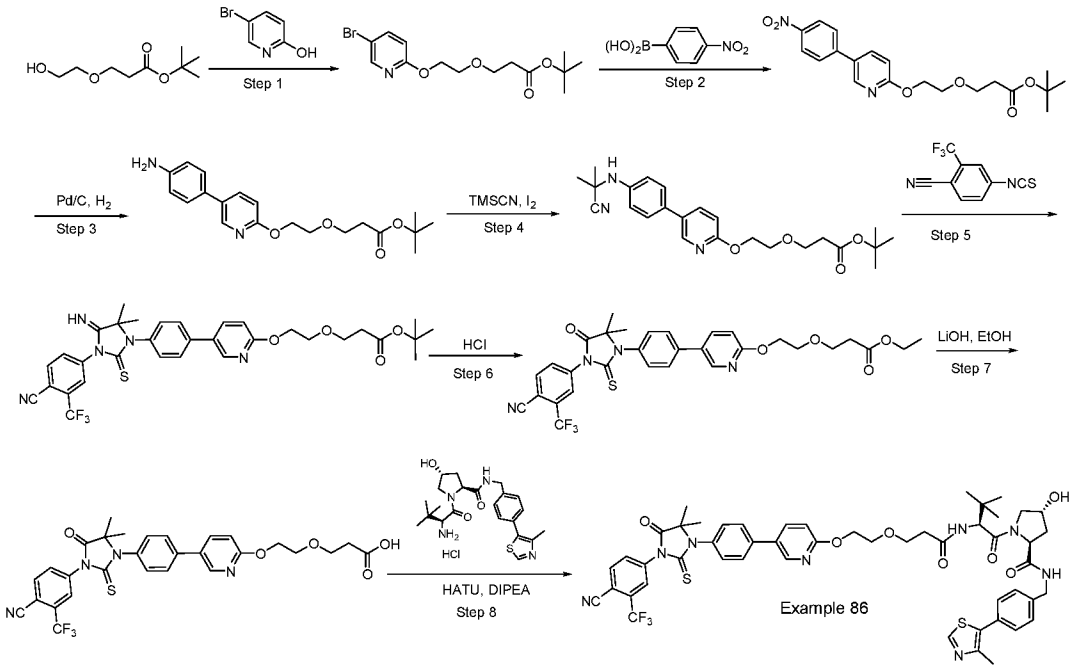
[0688] Examples 83-85 were synthesized according to similar procedure described for synthesis of Example 82, by using corresponding starting materials and intermediates.

[0689] Table 6. Exemplary Compounds.

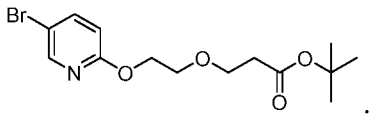
Ex #	Structure	Compound name and Analytical data

Ex #	Structure	Compound name and Analytical data
83		Prepared from **ABM-3**, **L-30**, and **ULM-13** (2S,4R)-N-{[2-(2-{2-[2-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)ethoxy]ethoxy}ethoxy)-4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}-1-[(2S)-2-(6-fluoro-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-3-methylbutanoyl]-4-hydroxypyrrolidine-2-carboxamide ^{1}H NMR (400MHz, CD_3OD): δ 8.89 (s, 1H), 8.17-8.15 (d, *J* = 8.0 Hz, 2H), 8.00-7.98 (d, *J*=8.4 Hz, 1H), 7.60-7.56 (m, 1H), 7.49-7.37 (m, 3H), 7.28-7.26 (d, *J*=8.8 Hz, 2H), 7.08-7.05 (m, 4H), 4.90-7.83 (m, 1H), 4.59-4.46 (m, 6H), 4.26-4.25 (m, 2H), 417-4.15 (m, 2H), 3.98-3.86 (m, 6H), 3.79-3.77 (m, 4 H), 2.51 (s, 3H), 2.50-2.49 (m, 1H), 2.25-2.15 (m, 1H), 2.01-2.00 (m, 1H), 1.54 (s, 6 H), 1.07-1.06 (d, *J* = 6.8Hz, 3H), 0.85-0.83 (d, *J* = 6.8Hz, 3H); LC-MS (ES^+): *m/z* 1086.60 [MH^+], t_R = 2.24 min (3.6 minute run).
84		Prepared from **ABM-3**, **L-30**, and **ULM-14** (2S,4R)-1-[(2S)-2-(7-cyano-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-3-methylbutanoyl]-N-{[2-(2-{2-[2-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)ethoxy]ethoxy}ethoxy)-4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}-4-hydroxypyrrolidine-2-carboxamide H NMR (400MHz, CD_3OD): δ 8.89 (s, 1H), 8.17-8.15 (d, *J* =7.2Hz, 2H), 8.01-7.98 (d, *J* =8.4Hz, 1H), 7.98-7.76 (m, 3H), 7.44-7.42 (m, 1H), 7.29-7.25 (m, 2H), 7.08-7.04 (m, 4H), 4.87-7.85 (m, 1H), 4.69-4.41 (m, 6H), 4.25-4.23 (m, 2H), 4.22-4.16 (m, 2H), 4.10-4.00 (m, 1H), 3.94-3.87 (m, 5H), 3.79-3.77 (m, 4H), 2.51 (s, 3H), 2.50-2.49 (m, 1H), 2.23-2.13 (m, 1H), 2.05-2.00 (m, 1H), 1.54 (s, 6H), 1.10-1.07 (d, *J* = 6.8Hz, 3H), 0.88-0.86 (d, *J* = 6.8Hz, 3H); LC-MS (ES^+): *m/z* 1093.00 [MH^+], t_R = 2.22 min (3.6 minute run).
85		Prepared from **ABM-3**, **L-31**, and **ULM-12** (2S,4R)-N-{[2-(2-{[(2R,3R)-3-[2-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)ethoxy]butan-2-yl]oxy}ethoxy)-4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}-4-hydroxy-1-[(2S)-3-methyl-2-(1-oxo-2,3-dihydro-1H-isoindol-2-yl)butanoyl]pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 0.82 (d, *J* = 6.65 Hz, 3 H), 1.05 (d, *J* = 6.65 Hz, 3 H), 1.15 (t, *J* = 5.48 Hz, 6 H), 1.44 - 1.56 (m, 6 H), 1.98 - 2.10 (m, 2 H), 2.14 - 2.24 (m, 1 H), 2.37 - 2.52 (m, 4 H), 3.52 - 3.62 (m, 2 H), 3.89 (td, *J* = 10.76, 4.70 Hz, 3 H), 3.93 - 4.01 (m, 3 H), 4.09 (br. s., 2 H), 4.16 - 4.24 (m, 2 H), 4.44 - 4.67 (m, 6 H), 4.84 (d, *J* = 10.96 Hz, 1 H), 6.95 - 7.08 (m, 4 H), 7.19 - 7.30 (m, 2 H), 7.43 (d, *J* = 7.43 Hz, 1 H), 7.46 - 7.51 (m, 1 H), 7.52 - 7.63 (m, 2 H), 7.78 (d, *J* = 7.43 Hz, 1 H), 7.97 (d, *J* = 7.83 Hz, 1 H), 8.08 - 8.17 (m, 2 H), 8.43 (t, *J* = 5.87 Hz, 1 H), 8.87 (s, 1 H); Mass (ES^+): *m/z* 1096.37 [MH^+]

[0690] Synthesis of example 86.

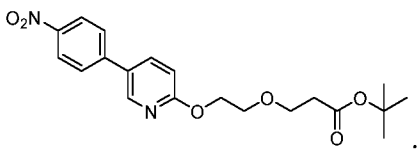


[0691] Step 1: Synthesis of tert-butyl 3-{2-[(5-bromopyridin-2-yl)oxy]ethoxy}propanoate:



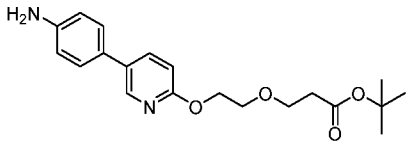
[0692] To a stirred solution of 5-bromopyridin-2-ol (3.0 g, 17.24 mmol), tert-butyl 3-(2-hydroxyethoxy)propanoate (3.3 g, 17.19 mmol) and triphenylphosphine (6.8 g, 25.81 mmol) in tetrahydrofuran (120.0 mL) was added diethyl diazene-1,2-dicarboxylate (4.49 g, 25.78 mmol) dropwise at 0 °C under an atmosphere of nitrogen. The resulting solution was stirred overnight at rt. The reaction mixture was concentrated under reduced pressure to give a crude residue, which was purified by silica gel flash chromatography (eluent: ethyl acetate/petroleum ether, v/v =1/3) to provide the titled product (yield: 50%) as colorless oil.

[0693] Step 2: Synthesis of tert-butyl 3-(2-{[5-(4-nitrophenyl)pyridin-2-yl]oxy}ethoxy)propanoate:



[0694] To a stirred mixture of tert-butyl 3-{2-[(5-bromopyridin-2-yl)oxy]ethoxy}propanoate (3.0 g, 8.67 mmol) and (4-nitrophenyl)boronic acid (1.5 g, 8.87 mmol) in a mixed solvent of dioxane (90.0 mL) and water (9.0 mL) was added potassium carbonate (2.4 g, 17.36 mmol) and $Pd(PPh_3)_4$ (450.0 mg, 0.39 mmol) under an atmosphere of nitrogen. The resulting mixture was stirred for 12 h at 100 °C. The bulk of solvent was removed under reduced pressure, and the resulting aqueous residue was extracted with ethyl acetate (100 mL x 2). The organic layers were combined, washed with brine (70 mL x 2), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluent: ethyl acetate/petroleum ether, v/v =1/5) to provide the titled product (yield: 83%) a yellow solid. Mass (ES^+): *m/z* 389.00 [MH^+].

[0695] Step 3: Synthesis of tert-butyl 3-(2-{[5-(4-aminophenyl)pyridin-2-yl]oxy}ethoxy)propanoate:



[0696] To a stirred solution of tert-butyl 3-(2-{[5-(4-nitrophenyl)pyridin-2-yl]oxy}ethoxy)propanoate (2.8 g, 7.21 mmol) in ethanol (200.0 mL) under an atmosphere of nitrogen was added palladium on carbon (1.5 g) at rt. The reaction mixture was then charge with hydrogen gas and stirred at rt for 12h. The solids were removed by filtration and the solution phase was concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluent: ethyl acetate/petroleum ether, v/v=1/3) to provide the titled product (yield: 89%) a yellow oil. LC-MS (ES^+): *m/z* 358.97 [MH^+].

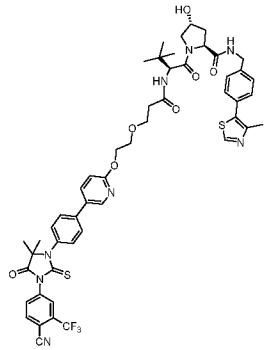
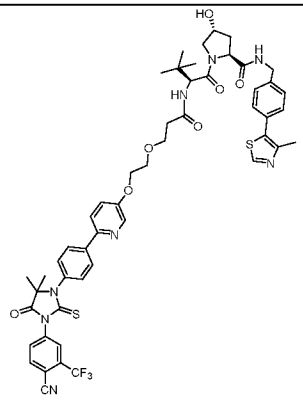
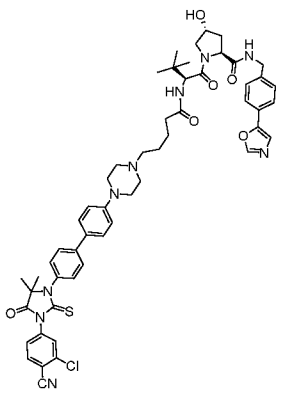
[0697] Example 86 was synthesized from tert-butyl 3-(2-{[5-(4-aminophenyl)pyridin-2-yl]oxy}ethoxy)propanoate, according to chemistry highlighted above (steps 4-8), utilizing similar procedures described for the similar chemistry carried out for the synthesis of examples 67, 75, 103, by using corresponding starting materials and intermediates.

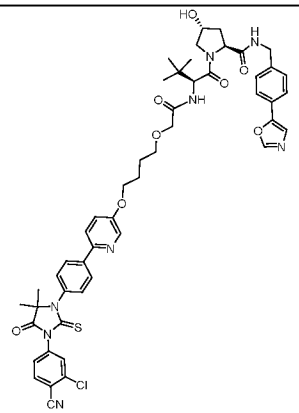
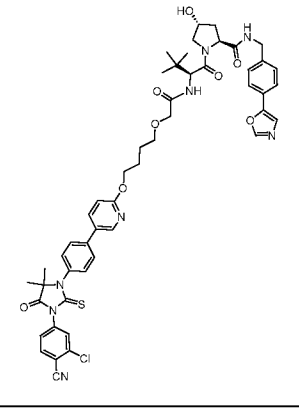
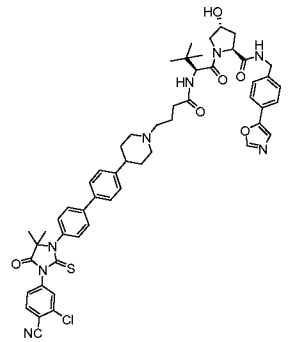
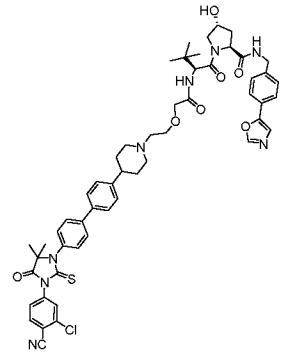
[0698] Example 90 was synthesized according to similar procedures described for the synthesis of examples 86, by using corresponding starting materials and intermediates.

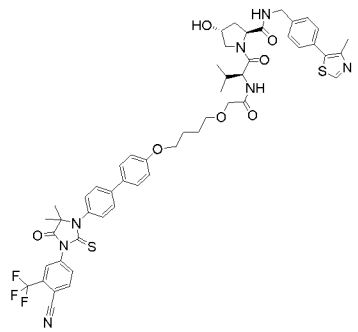
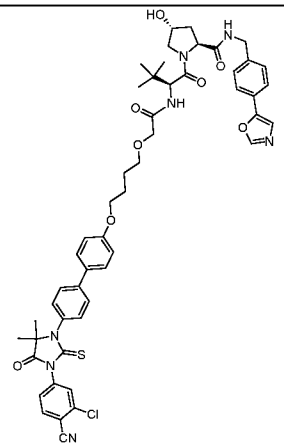
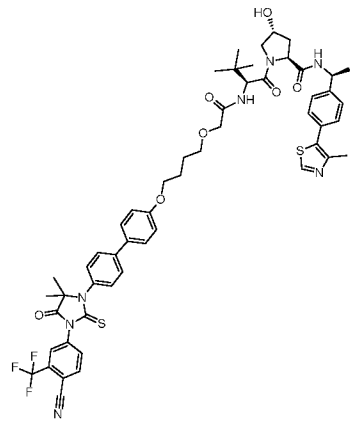
[0699] Examples 88, 91-92 were synthesized according to similar procedures described for the synthesis of examples 80, 75, 103, by using corresponding starting materials and intermediates.

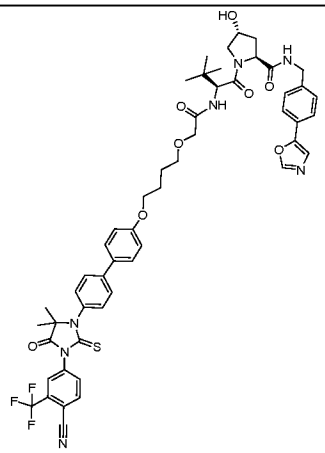
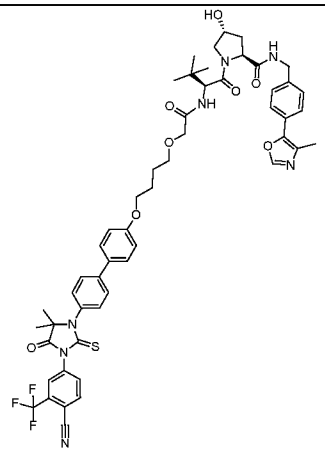
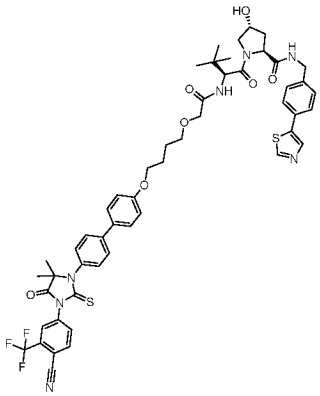
[0700] Examples 87, 89, 93-102, 104-134, 136-142, 146-149 were synthesized according to similar procedures described for the synthesis of examples 75, by using corresponding starting materials and intermediates.

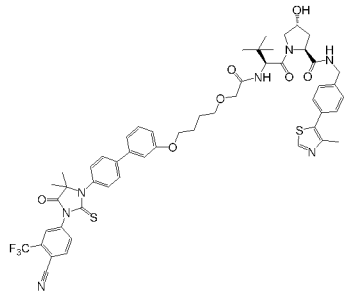
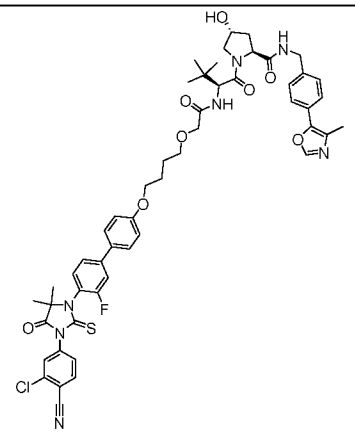
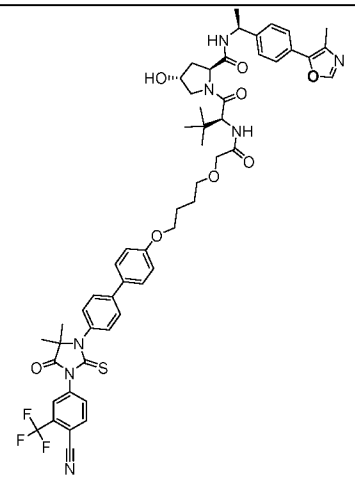
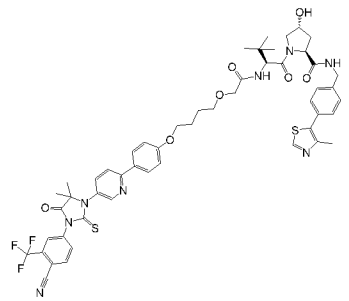
[0701] Table 7. Exemplary Compounds.

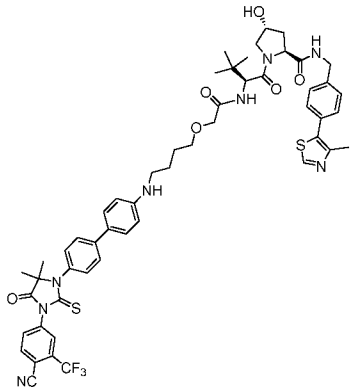
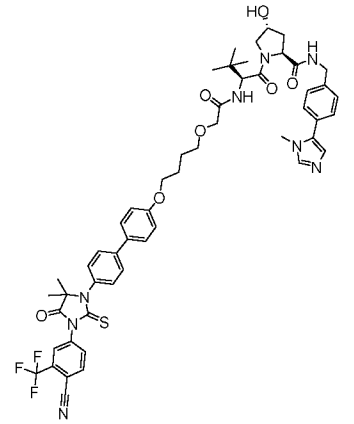
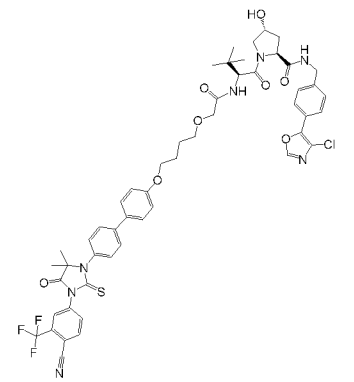
Ex #	Structure	Compound name and Analytical data
86		(2S,4R)-1-[(2S)-2-[3-(2-{[5-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)pyridin-2-yl]oxy}ethoxy)propanamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD):δ8.80 (s, 1 H), 8.36-8.30 (m, 1 H), 8.17-8.10 (m, 2 H), 7.96-7.88 (m, 2 H), 7.71-7.65 (m, 2H), 7.46-7.26 (m, 6 H), 6.88-6.80 (m, 1 H), 4.64-4.35 (m, 6 H), 4.30-4.21 (m, 1 H), 3.89-3.65 (m, 8 H), 3.60-3.35 (m, 5 H), 2.23-1.98 (m, 2 H), 1.55 (s, 6 H), 1.02 (s, 9 H); LC-MS (ES^+): *m/z* 1011.20 [MH^+]
87		(2S,4R)-1-[(2S)-2-[3-(2-{[6-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)pyridin-3-yl]oxy}ethoxy)propanamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD):δ8.80 (s, 1 H), 8.36-8.30 (m, 1 H), 8.17-8.10 (m, 2 H), 8.07-7.92 (m, 3 H), 7.81-7.75 (m, 1H), 7.46-7.26 (m, 7 H), 4.61 (s, 1 H), 4.54-4.50 (m, 1 H), 4.49-4.40 (m, 2H), 4.33-4.28 (m, 1 H), 4.26-4.15 (m, 2 H), 3.89-3.65 (m, 6 H), 2.64-2.40 (m, 2 H), 2.38 (s, 3 H), 2.20-2.10 (m, 1 H), 1.19-1.95 (m, 1 H), 1.55 (s, 6 H), 1.01 (s, 9 H); LC-MS (ES^+): *m/z* 1011.20 [MH^+]
88		(2S,4R)-1-[(2S)-2-{5-[4-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}phenyl)piperazin-1-yl]pentanamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO): δ 8.51-8.58 (m, 1H), 8.42 (s, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.05 (s, 1H), 7.87 (d, J = 9.3 Hz, 1H), 7.73-7.79 (m, 3H), 7.60-7.65 (m, 5H), 7.38-7.44 (m, 4H), 7.05 (d, J = 9.0 Hz, 2H), 5.13 (m, 1H), 4.58 (d, J = 9.3 Hz, 1H), 4.36-4.45 (m, 3H), 4.23 (m, 1H), 3.68 (m, 2H), 3.31 (s, 2H), 3.21 (m, 4H), 2.53 (s, 2H), 2.27-2.34 (m, 3H), 2.17-2.19 (m, 1H), 2.07 (m, 1H), 1.89 (m, 1H), 1.52 (m, 10H), 0.96 (s, 9H); LC-MS (ES^+): *m/z* 998.30 [MH^+]

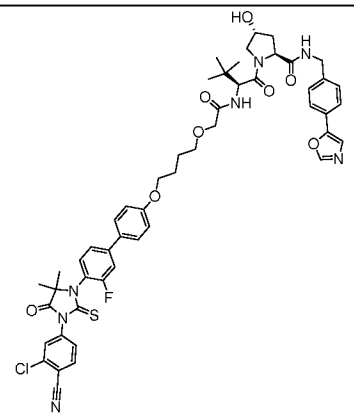
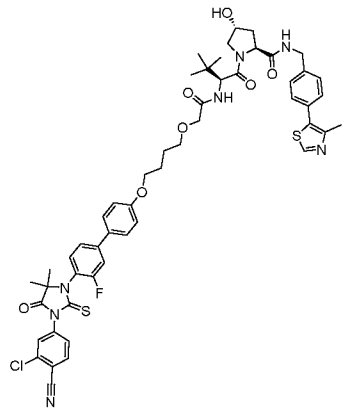
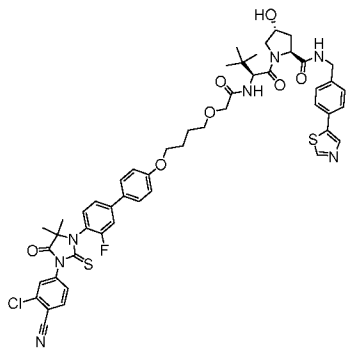
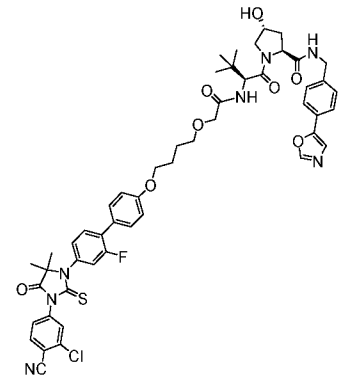
89		(2S,4R)-1-[(2S)-2-(2-{4-[(6-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}pyridin-3-yl)oxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD):δ8.38 (s, 1 H), 8.21 (s, 1 H), 8.10-7.95 (m, 3 H), 7.90 (s, 1 H), 7.89-7.80 (m, 1 H), 7.71-7.60 (m, 3 H), 7.55-7.40 (m, 6 H), 4.70 (m, 1 H), 4.63-4.45 (m, 3 H), 4.40-4.30 (m, 1 H), 4.22-4.13 (m, 2 H), 4.10-3.92 (m, 2 H), 3.90-3.79 (m, 2 H), 3.70 -3.60 (m, 2 H), 2.30-2.21 (m, 1 H), 2.14-2.00 (m, 1 H), 2.00-1.90 (m, 2 H), 1.90-1.80 (m, 2H), 1.58 (s, 6 H), 1.01 (s, 9 H); LC-MS (ES^+): *m/z*, 961.20 [MH^+]
90		(2S,4R)-1-[(2S)-2-(2-{4-[(5-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}pyridin-2-yl)oxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD):δ8.42 (s, 1 H), 8.21 (s, 1 H), 8.00-7.95 (m, 2 H), 7.90 (s, 1 H), 7.79-7.71 (m, 2 H), 7.70-7.61 (m, 3 H), 7.55-7.40 (m, 5 H), 6.90 (d, *J* = 6.6 Hz, 1 H), 4.70 (m, 1 H), 4.63-4.45 (m, 3 H), 4.42-4.30 (m, 3 H), 4.10-3.96 (m, 2 H), 3.90-3.85 (m, 1 H), 3.84-3.76 (m, 1 H), 3.70 -3.60 (m, 2 H), 2.30-2.21 (m, 1 H), 2.14-2.00 (m, 1 H), 2.00-1.90 (m, 2 H), 1.90-1.80 (m, 2H), 1.58 (s, 6 H), 1.01 (s, 9 H); LC-MS (ES^+): *m/z*, 961.20 [MH^+]
91		(2S,4R)-1-[(2S)-2-{4-[4-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}phenyl)piperidin-1-yl]butanamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.91 (s, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.69-7.63 (m, 5H), 7.49-7.45 (m, 5H), 7.39 (d, *J* = 8.4 Hz, 2H), 4.67 (s, 1H), 4.60-4.52 (m, 3H), 4.38 (d, *J* = 15.6 Hz, 1H), 3.95-3.91 (m, 1H), 3.88-3.81 (m, 1H), 3.17-3.15 (m, 2H), 2.66-2.61 (m, 1H), 2.54-2.45 (m, 2H), 2.38-2.31 (m, 2H), 2.29-2.15 (m, 3H), 2.13-2.06 (m, 1H), 1.88-1.85 (m, 6H), 1.61 (s, 6H), 1.08 (s, 9H); LC-MS (ES^+): *m/z* 983.45 [MH^+]
92		(2S,4R)-1-[(2S)-2-(2-{2-[4-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}phenyl)piperidin-1-yl]ethoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.91 (s, 1H), 7.77-7.73 (m, 2H), 7.69-7.52 (m, 5H), 7.45-7.43 (m, 5H), 7.36 (d, *J* = 8.4 Hz, 2H), 4.73 (s, 1H), 4.61-4.49 (m, 3H), 4.36-4.32 (m, 1H), 4.13-4.01 (m, 2H), 3.91-3.77 (m, 4H), 3.21-3.12 (m, 2H), 2.78 (t, *J* = 5.2 Hz, 2H), 2.68-2.61 (m, 1H), 2.37-2.30 (m, 2H), 2.28-2.19 (m, 1H), 2.14-2.05 (m, 1H), 1.92-1.88 (m, 4H), 1.60 (s, 6H), 1.08 (s, 9H); LC-MS (ES^+): *m/z* 999.65 [MH^+]

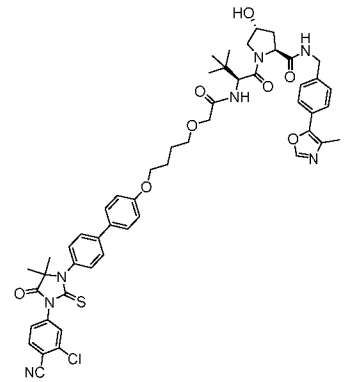
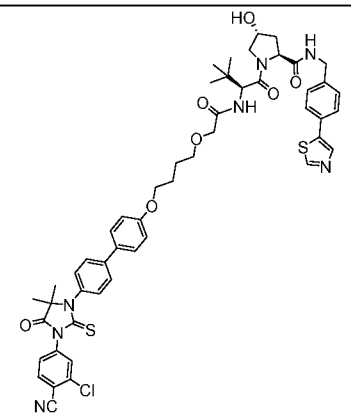
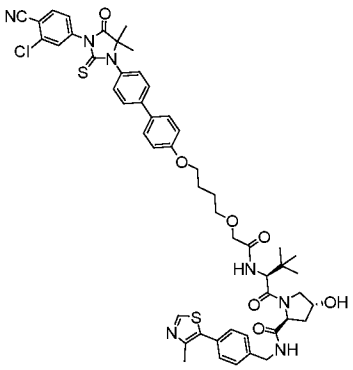
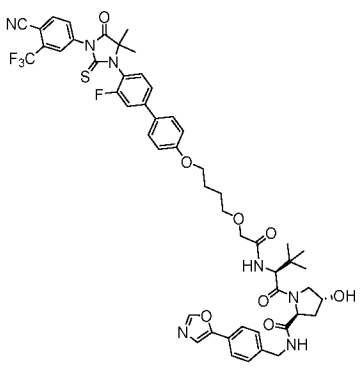
93		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3-methylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.83 (s, 1 H,) 8.67 (t, *J* = 6.06 Hz, 1 H), 8.18 (d, *J* = 1.96 Hz, 1 H), 8.15 (d, *J* = 8.22 Hz, 1 H), 8.00 (dd, *J* = 8.22, 1.96 Hz, 1 H), 7.69 - 7.74 (m, 2 H), 7.64 (d, *J* = 9.00 Hz, 1 H), 7.54 - 7.60 (m, 2 H), 7.37 - 7.46 (m, 6 H), 6.96 - 7.02 (m, 2 H), 4.63 - 4.69 (m, 1H), 4.55 - 4.61 (m, 1 H), 4.48 - 4.55 (m, 2 H), 4.34 - 4.41 (m, 1 H), 4.04 - 4.10 (m, 2 H), 3.98 - 4.03 (m, 2 H), 3.83 - 3.88 (m, 1 H), 3.77 - 3.82 (m, 1 H), 3.64 (t, *J* = 6.26 Hz, 2 H), 2.42 - 2.47 (m, 3 H), 2.25 (dd, *J* = 13.30, 7.83 Hz, 1 H), 2.14 (dd, *J* = 13.30, 6.65 Hz, 1 H), 2.07 (ddd, *J* = 13.30, 9.00, 4.30 Hz, 1H), 1.89 - 1.97 (m, 2 H), 1.81 - 1.89 (m, 2 H), 1.59 (s, 6 H), 1.01 (d, *J* = 6.65 Hz, 3 H), 0.91 (d, *J* = 6.26 Hz, 3 H); LC-MS (ES^+): *m/z* 1010.36 [MH^+]
94		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD):δ8.14 (s, 1 H), 8.00-7.91 (m, 1 H), 7.90-7.80 (m, 1 H), 7.71-7.60 (m, 5 H), 7.59-7.51 (m, 2 H), 7.45-7.30 (m, 5 H), 7.05-6.94 (m, 2 H), 4.67 (s, 1 H), 4.55-4.50 (m, 1 H), 4.49-4.40 (m, 2 H), 4.31-3.25 (m, 1 H), 4.10-4.00 (m, 2 H), 3.99-3.96 (m, 2 H), 3.90 -3.70 (m, 2 H), 3.65-3.55 (m, 2 H), 2.22-2.13 (m, 1 H), 2.14-2.00 (m, 1 H), 2.00-1.72 (m, 4 H), 1.56 (s, 6 H), 1.01 (s, 9 H); LC-MS (ES^+): *m/z*, 960.30 [MH^+]
95		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.86 (s, 1H), 8.18-8.15 (d, *J* = 9.0 Hz, 2H), 8.03-7.99 (m, 1H), 7.76-7.71 (d, *J* = 14.4 Hz, 2H), 7.64-7.59 (d, *J* = 15.3 Hz, 2H), 7.45-7.39 (m, 6H), 7.07-7.04 (d, *J* = 8.7 Hz, 2H) , 5.01-4.99 (m, 1H), 4.70 (s, 1H), 4.61-4.55 (m, 1H), 4.45 (s, 1H), 4.13-4.08 (m, 2H), 4.03-3.96 (m, 2H), 3.84-3.80 (m, 1H), 3.78-3.76 (m, 1H), 3.68-3.64 (m, 2H), 2.47 (s, 3H), 2.22-2.15 (m, 1H) ,1.99-1.85 (m, 5H), 1.60 (s, 6H), 1.51-1.48 (d, *J* = 6.9Hz, 3H), 1.05 (s, 9H) ; LC-MS (ES^+): m/z 1038.50 [MH^+]

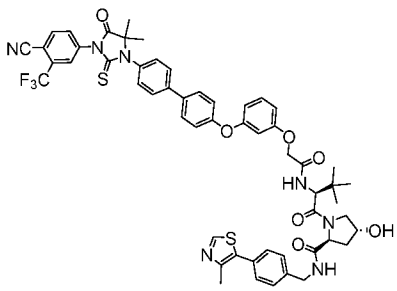
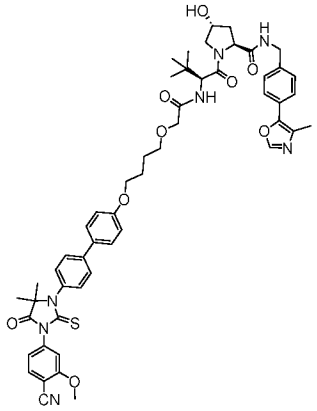
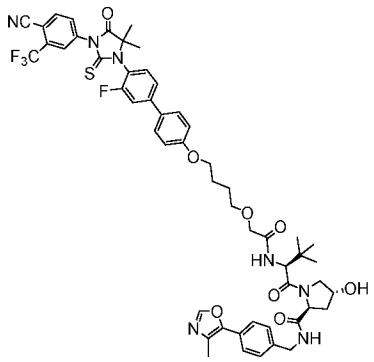
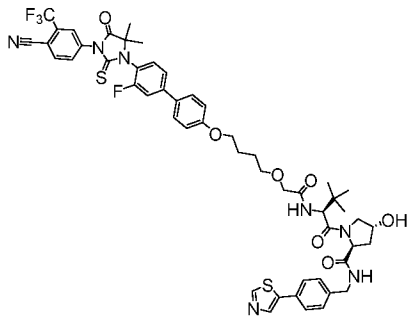
96		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.23-8.15 (m, 3H) , 8.03-7.99 (d, *J* = 9.9 Hz, 1H), 7.73-7.65 (m , 4H), 7.60-7.57 (d, *J* = 8.7Hz, 2H), 7.46-7.41 (m, 5H), 7.05-7.00 (d, *J* =12.6 Hz, 2H) , 4.71 (s, 1H), 4.61-4.50 (m, 3H), 4.36-4.31 (d, *J* =15.6 Hz, 1H), 4.10-4.08 (m, 4H), 4.03-3.82(m, 2H), 3.68-3.64 (t, *J*= 7.3Hz, 2H), 2.22-2.10 (m, 1H), 2.10-2.02 (m, 1H), 1.98-1.85 (m, 4H), 1.60 (s, 6H), 1.05 (s, 9H) ; LC-MS (ES^+): m/z 994.65 [MH^+]
97		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.18-8.15 (d, *J*= 9.3 Hz, 2H), 8.08 (s, 1H), 8.03-7.99 (d, *J* = 9.9 Hz,1H), 7.73-7.70 (d, *J*=8.4 Hz, 2H), 7.61-7.56 (m, 4H), 7.49-7.41 (m, 4H), 7.02-7.00 (d, *J*=8.7 Hz, 2H) , 4.71(s, 1H), 4.61-4.52 (m, 3H), 4.37-4.11 (d, *J* = 15.6 Hz, 2H), 4.11-4.07 (m, 4H), 3.96-3.82 (m, 2H), 3.68-3.64 (t, *J*=6.0 Hz, 2H), 2.36 (s, 3H), 2.23-2.14 (m, 1H), 2.14-2.09 (m, 1H), 1.98-1.84 (m, 4H), 1.60 (s, 6H), 1.05 (s, 9H) ; LC-MS (ES^+): m/z 1008.20 [MH^+]
98		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.89(s, 1H), 8.18-8.15 (d, *J*= 9.0 Hz, 2H), 8.10 (s, 1H), 8.03-7.99 (d, *J*=12.0 Hz, 1H), 7.73-7.70 (d, *J*=8.4 Hz, 2H), 7.62-7.56 (m, 4H), 7.44-7.41(m, 4H), 7.05-7.00 (d, *J*=14.1 Hz, 2H) , 4.71 (s, 1H), 4.61-4.51 (m, 3H), 4.35-4.30 (m, 1H), 4.12-4.08 (m, 2H), 4.08-4.03 (m, 2H), 3.95-3.82 (m, 2H), 3.68-3.64 (t, *J*=6.0 Hz, 2H), 2.22-2.20 (m, 1H), 2.13-2.08(m, 1H), 1.98-1.84 (m, 4H), 1.60 (s, 6H), 1.04 (s, 9H) ; LC-MS (ES^+): m/z 1010.30 [MH^+]

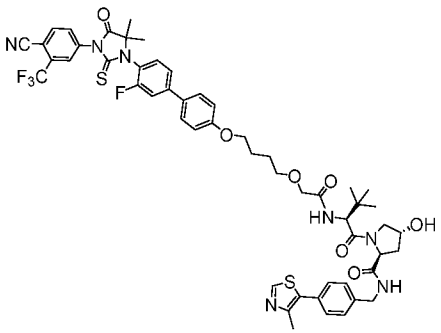
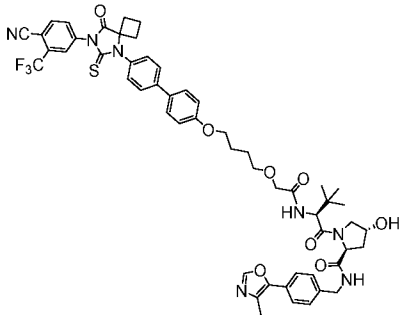
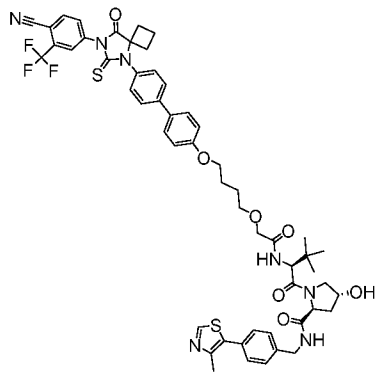
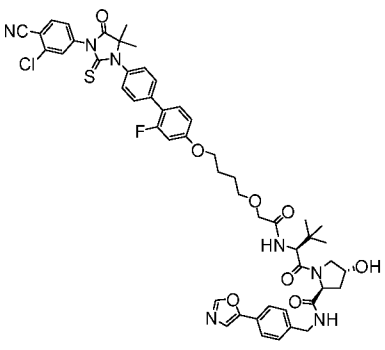
99		(2S,4R)-1-[(2S)-2-(2-{4-[3-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.82 (s, 1H), 8.20 (d, *J* = 5.4 Hz, 2H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 5.4 Hz, 2H), 7.52 (m, 4H), 7.44 (m, 3H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 1H), 4.71 (s, 1H), 4.56 (m, 3H), 4.34 (m, 1H), 4.12 (m, 2H), 4.00 (m, 2H), 3.84 (m, 1H), 3.72 (m, 1H), 3.67 (m, 2H), 2.45 (s, 3H), 2.24 (m, 1H), 2.10 (m, 1H), 1.90 (m, 4H), 1.61 (s, 6H), 1.03 (s, 9H); LC-MS (ES^+): *m/z* 1024.35 [MH^+]
100		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]-3-fluorophenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO) δ 8.61 (s, 1H), 8.29 (s, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 8.08 (s, 1H), 7.78-7.64 (m, 5H), 7.53-7.42 (m, 6H), 7.04 (m, *J* = 8.8 Hz, 2H), 5.16 (s, 1H), 4.58 (d, *J* = 9.6 Hz, 1H), 4.57-4.27 (m, 4H), 4.20 (t, *J* = 6.8 Hz, 2H), 3.91 (s, 2H), 3.68-3.53 (m, 4H), 2.33 (s, 3H), 2.07 (s, 1H), 1.90-1.72 (m, 5H), 1.60 (s, 3H), 1.48 (s, 3H), 0.95 (s, 9H); LC-MS (ES^+): *m/z* 992.30 [MH^+]
101		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-oxazol-5-l)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.19-8.14 (m, 3H), 8.03-8.01 (d, *J*=8.4 Hz, 1H), 7.77-7.73 (d, *J*=16.0 Hz, 2H), 7.64-7.60 (m, 4H), 7.45-7.42 (m, 4H), 7.07-7.05 (d, *J*=8.4 Hz, 2H) , 5.01-5.00 (m, 1H), 4.71(s, 1H), 4.61-4.56 (m, 1H), 4.45 (s, 1H), 4.13-4.10 (m, 2H), 4.07-4.01 (m, 2H), 3.88-3.85 (m, 1H), 3.78-3.75 (m, 1H), 3.69-3.66 (t, *J*= 12.0Hz, 2H), 2.40 (s, 3H), 2.21-2.19 (m, 1H) ,2.00-1.86 (m, 5H), 1.61 (s, 6H), 1.51-1.49 (d, *J*= 7.2 Hz, 3H), 1.06 (s, 9H) ; LC-MS (ES^+): m/z 1022.45 [MH^+]
102		(2S,4R)-1-[(2S)-2-(2-{4-[4-(5-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}pyridin-2-yl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.96 (s, 1H), 8.62 (m, 2H), 8.42 (d, J = 8.4 Hz, 1H), 8.33 (s, 1H), 8.12 (m, 4H), 7.89 (m, 1H), 7.44 (m, 5H), 7.07 (d, J = 8.8 Hz, 2H), 5.17 (m, 1H), 4.59 (d, J = 9.6 Hz, 1H), 4.41-4.48 (m, 1H), 4.38 (m, 2H), 4.29 (m, 1H), 4.07-4.10 (m, 2H), 3.97 (m, 2H), 3.55-3.67 (m, 4H), 2.45 (s, 3H), 2.08 (m, 1H), 1.81-1.91 (m, 3H), 1.72-1.77 (m, 2H), 1.58 (s, 6H), 0.95

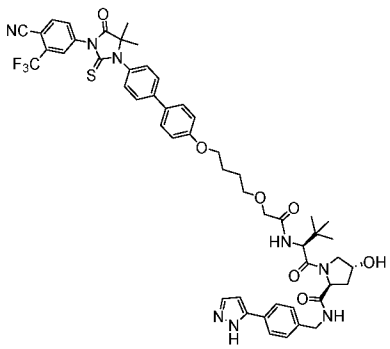
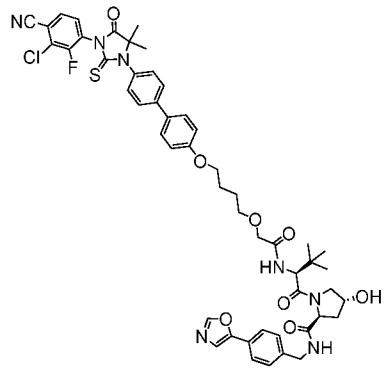
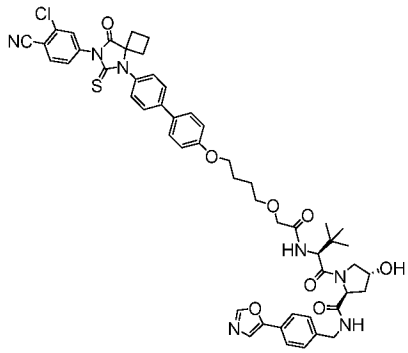
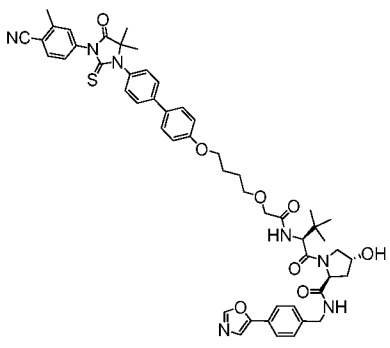
		(s, 9H); LC-MS (ES^+): *m/z* 1025.55 [MH^+]
103		(2S,4R)-1-[(2S)-2-[2-(4-{[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenyl]amino}butoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^1H NMR (300 MHz, CD_3OD) δ 8.71 (s, 1H), 8.18-8.15 (d, *J* = 8.4 Hz, 2H), 8.03-8.00 (d, *J* = 7.8 Hz, 1H), 7.68-7.66 (d, *J* = 8.4 Hz, 2H), 7.47-7.35 (m, 8H), 6.74-6.71 (d, *J* = 8.7 Hz, 2H), 4.72 (s, 1H), 4.62-4.50 (m, 3H), 4.37-4.32 (d, *J* = 15.2 Hz, 1H), 4.00-3.98 (m, 2H), 3.94-3.79 (m, 2H), 3.64-3.61 (m, 2H), 3.21-3.11 (m, 2H), 2.48 (s, 3H), 2.28-2.21 (m, 1H), 2.09-2.05 (m, 1H), 1.93-1.89 (m, 4H), 1.59 (s, 6H), 1.01 (s, 9H); LC-MS (ES^+): *m/z* 1023.30 [MH^+]
104		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1-methyl-1H-imidazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^1H NMR (300 MHz, CD_3OD): δ 8.18-8.15 (d, *J*= 9.0 Hz, 2H), 8.02-7.99 (d, *J* = 10.2 Hz, 1H), 7.73-7.70 (d, *J*=8.4 Hz, 2H), 7.59-7.56 (d, *J*=8.7 Hz, 2H), 7.50-7.39 (m, 7H), 7.03-7.00 (d, *J*=8.7 Hz, 2H), 6.30 (s, 1H), 4.71 (s, 1H), 4.62-4.50 (m, 3H), 4.39-4.33 (d, *J*= 15.2 Hz, 1H), 4.11-4.08 (m, 2H), 4.08-4.00 (m, 2H), 3.87-3.80 (m, 5H), 3.68-3.64 (t, *J*=6.0 Hz, 2H), 2.25-2.15 (m, 1H), 2.10-2.00 (m, 1H), 1.97-1.84 (m, 4H), 1.60 (s, 6H), 1.04 (s, 9H) ; LC-MS (ES^+): m/z 1007.50 [MH^+]
105		(2S,4R)-N-{[4-(4-chloro-1,3-oxazol-5-yl)phenyl]methyl}-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxypyrrolidine-2-carboxamide ^1H NMR (400 MHz, CD_3OD): δ 8.63-8.66 (m, 1H), 8.53 (s, 1H), 8.41 (d, J = 8.4 Hz, 1H), 8.32 (s, 1H), 8.12 (d, J =8.8 Hz, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.75 (d, J =8.4 Hz, 2H), 7.67 (d, J =8.4 Hz, 2H), 7.50 (m, 5H), 7.04 (d, J =8.8 Hz, 2H), 5.17 (m, 1H), 4.59 (d, J = 8.4 Hz, 1H), 4.48 (m, 2H), 4.39 (m, 1H), 4.32 (m, 1H), 4.08 (m, 2H), 3.97 (m, 2H), 3.55-3.67 (m, 4H), 2.06-2.08 (m, 1H), 1.81-1.91 (m, 3H), 1.72-1.77 (m, 2H), 1.55 (s, 6H), 0.95 (s, 9H); LC-MS (ES^+): *m/z* 1028.50 [MH^+]

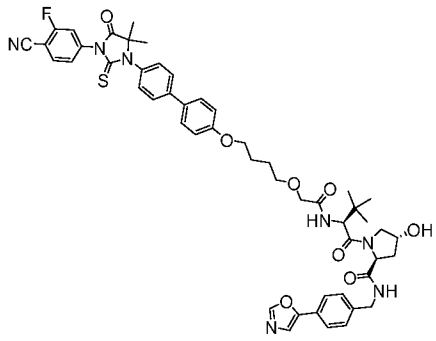
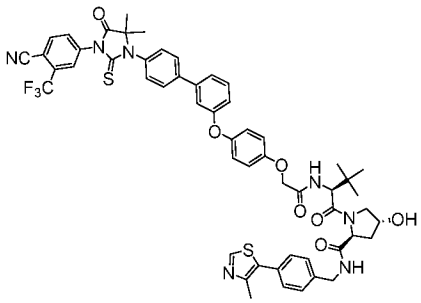
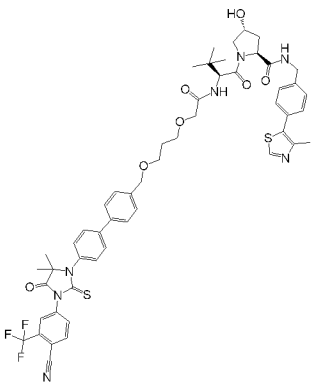
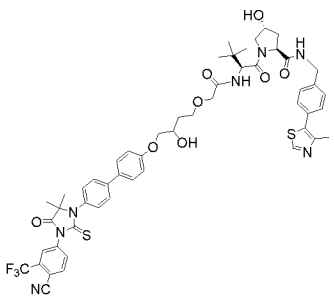
106		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]-3-fluorophenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.90 (s, 1H), 7.70-7.44 (m, 11H), 7.05 (d, *J* = 8.8 Hz, 2H), 4.72 (s, 1H), 4.61-4.52 (m, 3H), 4.37-4.33 (m, 1H), 4.14-4.02 (m, 4H), 3.98-3.84 (m, 2H), 3.67 (t, *J* = 6.4 Hz, 2H), 2.24-2.22 (m, 1H), 2.12-2.09 (m, 1H), 1.99-1.86 (m, 4H), 1.66 (s, 3H), 1.54 (s, 3H), 1.06 (s, 9H); LC-MS (ES^+): *m/z* 978.25 [MH^+]
107		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]-3-fluorophenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO) δ 8.96 (s, 1H), 8.61 (m, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.19 (s, 1H), 7.78-7.64 (m, 5H), 7.70-7.37 (m, 6H), 7.03 (m, *J* = 8.8 Hz, 2H), 5.16 (s, 1H), 4.57 (d, *J* = 9.6 Hz, 1H), 4.57-4.27 (m, 4H), 4.08 (t, *J* = 6.8 Hz, 2H), 3.96 (s, 2H), 3.66-3.55 (m, 4H), 2.43 (s, 3H), 2.16 (m, 1H), 1.92-1.75 (m, 5H), 1.60 (s, 3H), 1.48 (s, 3H), 0.93 (s, 9H); LC-MS (ES^+): *m/z* 1008.50 [MH^+]
108		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]-3-fluorophenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO) δ 9.04 (s, 1H), 8.61-8.56 (m, 1H), 8.27 (s, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 8.08 (s, 1H), 7.78-7.36 (m, 11H), 7.06 (d, *J* = 8.4 Hz, 2H), 5.16 (s, 1H), 4.58-4.56 (m, 1H), 4.47-4.22 (m, 4H), 4.09-4.06 (m, 2H), 3.96 (s, 2H), 3.66-3.55 (m, 4H), 2.07-2.04 (m, 1H), 1.89-1.72 (m, 5H), 1.60 (s, 3H), 1.48 (s, 3H), 0.95 (s, 9H); LC-MS (ES^+): *m/z* 994.50 [MH^+]
109		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]-2-fluorophenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.23 (s, 1H), 8.19-7.99 (d, *J* = 5.9 Hz, 1H), 7.96 (s, 1H), 7.78-7.61 (m, 4H), 7.58-7.51 (m, 2H), 7.47-7.46 (m, 2H), 7.46-7.41 (m, 3H), 7.31-7.29 (m, 2H), 7.05-7.02 (d, *J* = 8.7Hz, 1H), 4.71(s, 1H), 4.61-4.51 (m, 3H), 4.36-4.31 (d, *J* = 15.2 Hz, 1H), 4.13-4.11 (m, 2H), 4.09-4.01 (m, 2H), 3.96-3.79 (m, 2H), 3.69-3.65 (t, *J* = 6.0 Hz, 2H), 2.23-2.20 (m, 1H), 2.13-2.09 (m, 1H), 1.96-1.87 (m, 4H), 1.60(s, 6H), 1.03 (s, 9H) ; LC-MS (ES^+): m/z 978.25 [MH^+]

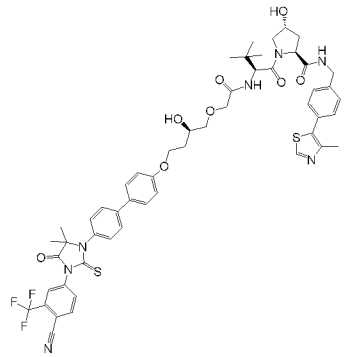
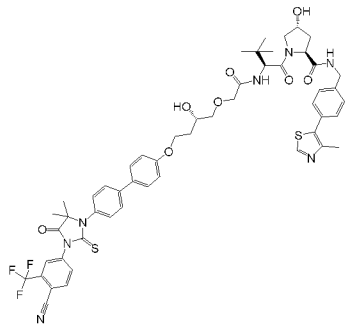
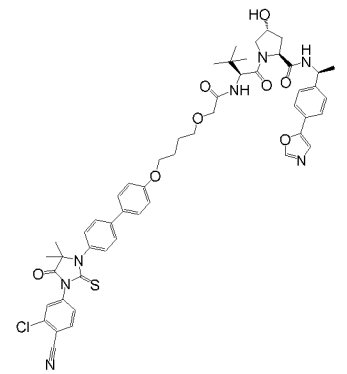
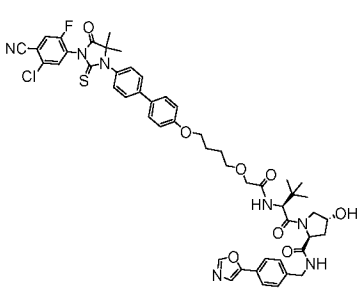
110		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.08 (s, 1H), 7.77-7.72 (m, 3H), 7.69-7.56 (m, 4H), 7.48-7.39 (m, 5H), 7.19-7.17 (d, *J* = 6.3Hz, 1H), 7.02-6.99 (d, *J* = 9.0 Hz, 2H), 4.71 (s, 1H), 4.61-4.52 (m, 3H), 4.36-4.31 (m, 1H), 4.11-4.08 (m, 2H), 4.03-4.01 (m, 5H), 3.95-3.82 (m, 2H), 3.68-3.64 (m, 2H), 2.36 (s, 3H), 2.22-2.09 (m, 1H), 2.09-2.01(m, 1H), 1.95-1.84 (m, 4H), 1.58 (s, 6H), 1.04 (s, 9H); LC-MS (ES^+): m/z 974.30 [MH^+]
111		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.89 (s, 1H), 8.10 (s, 1H), 7.98-7.95 (d, *J* = 8.4 Hz, 1H), 7.89-7.88 (d, *J* = 1.8 Hz, 1H), 7.72-7.56 (m, 7H), 7.44-7.39 (m, 4H), 7.03-7.00 (d, *J* = 8.7 Hz, 2H) , 4.70 (s, 1H), 4.61-4.50 (m, 3H), 4.35-4.30 (d, *J* = 15.2 Hz, 1H), 4.12-4.03 (m, 2H), 4.01-3.95 (m, 2H), 3.86-3.82 (m, 2H), 3.68-3.64 (m, 2H), 2.22-2.18 (m, 1H), 2.12-2.08 (m, 1H), 1.98-1.85 (m, 4H), 1.58 (s, 6H), 1.04 (s, 9H) ; LC-MS (ES^+): m/z 976.20 [MH^+]
112		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.81 (s, 1H), 7.98-7.95 (d, *J*=8.4 Hz, 1H), 7.89-7.88 (d, *J*=1.8 Hz, 1H), 7.73-7.64 (m, 3H), 7.58-7.56 (d, *J*=8.7 Hz, 2H), 7.48-7.38 (m, 6H), 7.02-6.99(d, *J* = 8.7Hz, 2H), 4.71 (s, 1H), 4.62-4.51 (m, 3H), 4.36-4.31 (m, 1H), 4.11-4.07 (m, 2H), 4.02-4.00 (d, *J*=5.4 Hz, 2H), 3.87-3.82 (m, 2H), 3.68-3.64 (t, *J*=6.0 Hz, 2H), 2.44 (s, 3H), 2.23-2.10 (m, 1H), 2.09-2.00 (m, 1H), 1.97-1.84 (m, 4H), 1.58(s, 6H), 1.04 (s, 9H) ; LC-MS (ES^+): m/z 990.30 [MH^+]
113		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-3-fluorophenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, DMSO) δ 8.62-8.56 (m, 1H), 8.41 (s, 1H), 8.39 (s, 1H), 8.35 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.76-7.63 (m, 7H), 7.51-7.38 (m, 4H), 7.06 (d, *J* = 8.7 Hz, 2H), 5.15 (d, *J* = 3.3 Hz, 1H), 4.58-4.26 (m, 5H), 4.09-4.05 (m, 2H), 3.96 (s, 2H), 3.66-3.56 (m, 4H), 2.12-2.04 (m, 1H), 1.93-1.73 (m, 5H), 1.60 (s, 3H), 1.50 (s, 3H), 0.95 (s, 9H); LC-MS (ES^+): *m/z* 1012.30 [MH^+]

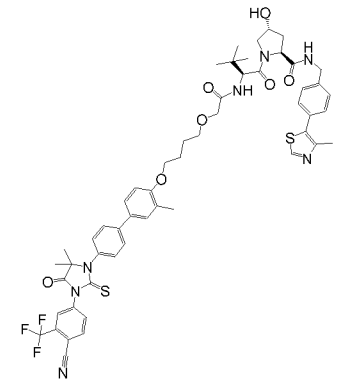
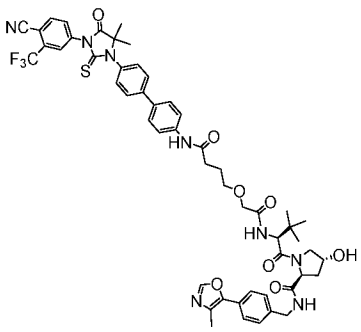
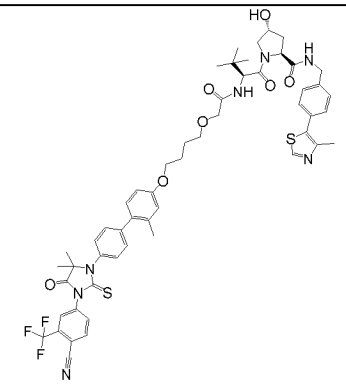
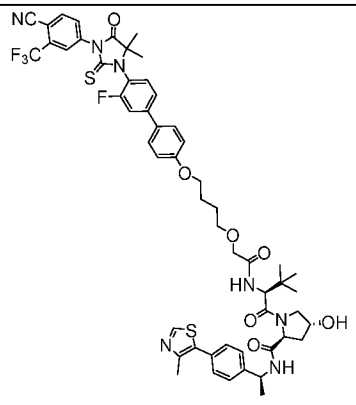
114		(2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]phenoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD):δ8.81 (s, 1 H), 8.14-8.05 (m, 2 H), 8.00-7.95 (m, 1 H), 7.75-7.69 (m, 2 H), 7.65-7.59 (m, 2 H), 7.44-7.20 (m, 7 H), 7.10-7.00 (m, 2 H), 6.80-6.78 (m, 1 H), 6.75-6.55 (m, 2 H), 4.68 (s, 1 H), 4.60-4.40 (m, 5 H), 4.30-4.20 (m, 1 H), 3.90-3.65 (m, 2 H), 2.40 (s, 3 H), 2.25-2.21 (m, 1 H), 2.14-2.00 (m, 1 H), 1.55 (s, 6 H), 0.99 (s, 9 H); LC-MS (ES^+): *m/z*, 1044.30 [MH^+]
115		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(4-cyano-3-methoxyphenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.08 (s, 1H), 7.76-7.69 (m, 3H), 7.60-7.55 (d, *J*=15.9 Hz, 4H), 7.48-7.37 (m, 5H), 7.19-7.16 (d, *J*=9.9 Hz, 1H), 7.02-6.99 (d, *J*= 8.7 Hz, 2H), 4.71(s, 1H), 4.61-4.51 (m, 3H), 4.36-4.31 (m, 1H), 4.10-4.00 (m, 7H), 3.98-3.82 (m, 2H), 3.67-3.63 (t, *J*= 6.0 Hz, 2H), 2.35 (s, 3H), 2.22-2.12 (m, 1H), 2.12-2.09 (m, 1H), 1.97-1.84 (m, 4H), 1.58 (s, 6H), 1.04 (s, 9H) ; LC-MS (ES^+): m/z 971.45 [MH^+]
116		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-3-fluorophenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO) δ 8.66-8.61 (m, 1H), 8.42 (d, *J* = 8.0 Hz, 1H), 8.35 (s, 1H), 8.29 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.76-7.64 (m, 4H), 7.53-7.40 (m, 6H), 7.05 (d, *J* = 8.8 Hz, 2H), 5.16 (s, 1H), 4.58-4.27 (m, 5H), 4.09-4.06 (m, 2H), 3.96 (s, 2H), 3.66-3.55 (m, 4H), 2.33 (s, 3H), 2.07-2.02 (m, 1H), 1.94-1.73 (m, 5H), 1.61 (s, 3H), 1.50 (s, 3H), 0.95 (s, 9H); LC-MS (ES^+): *m/z* 1026.30 [MH^+]
117		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-3-fluorophenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO) δ 9.04 (s, 1H), 8.60 (s, 1H), 8.42-8.35 (m, 2H), 8.27 (s, 1H), 8.14 (d, *J* = 8.0 Hz, 2H), 7.75-7.67 (m, 3H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.59 (m, *J* = 8.4 Hz, 2H), 7.48 (t, *J* = 8.4 Hz, 1H), 7.41-7.36 (m, 3H), 7.05 (d, *J* = 8.8 Hz, 2H), 5.19 (s, 1H), 4.57 (d, *J* = 9.2 Hz, 1H), 4.58-4.44 (m, 1H),4.42-4.34(m, 2H), 4.35-4.33(m, 1H), 4.08 (s, 2H), 3.96 (s, 2H), 3.66-3.55 (m, 4H), 2.10-2.02 (m, 1H), 1.89-1.72 (m, 5H), 1.61 (s, 3H), 1.50 (s, 3H), 0.95 (s, 9H); LC-MS (ES^+): *m/z* 1028.30 [MH^+],

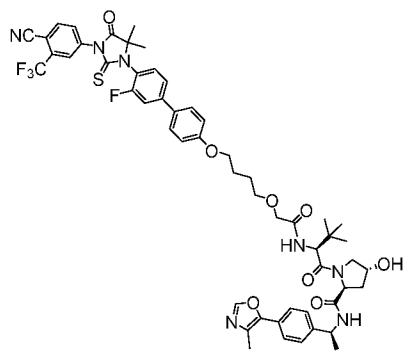
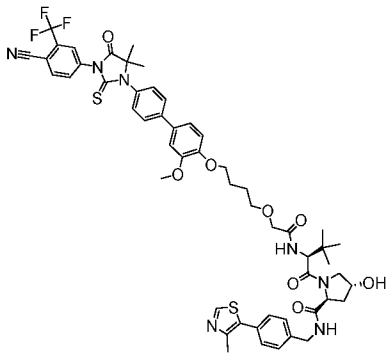
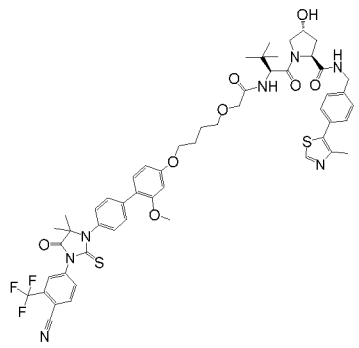
118		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-3-fluorophenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO) δ 8.96 (s, 1H), 8.61 (s, 1H), 8.42-8.35 (m, 2H), 8.15 (d, *J* = 1.6 Hz, 2H), 7.76-7.64 (m, 4H), 7.51-7.39(m, 6H), 7.04 (d, *J* = 8.8 Hz, 2H), 5.17 (s, 1H), 4.57 (d, *J* = 9.6 Hz, 1H), 4.56-4.38 (m, 3H), 4.36-4.27(m, 1H), 4.08 (s, 2H), 3.96 (s, 2H), 3.66-3.55 (m, 4H), 2.45(s, 3H), 2.10-2.02 (m, 1H), 1.93-1.84 (m, 1H),1.84-1.82(m, 2H),1.75-1.73(m, 2H), 1.61 (s, 3H), 1.50 (s, 3H), 0.94 (s, 9H); LC-MS (ES$^+$): *m/z* 1042.25 [MH$^+$]
119		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{7-[4-cyano-3-(trifluoromethyl)phenyl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ8.17-8.15 (d, *J* = 8.1 Hz, 2H), 8.09 (s, 1H), 8.02-8.00 (d, *J* = 8.7 Hz, 1H), 7.78-7.75 (d, *J* = 8.4 Hz, 2H), 7.62-7.57 (m, 4H), 7.49-7.43 (m, 4H), 7.04-7.01 (d, *J* = 8.7Hz, 2H), 4.71 (s, 1H), 4.62-4.53 (m, 3H), 4.37-4.32(d, *J* = 15.3 Hz, 1H), 4.12-4.11 (m, 2H), 4.09-4.01(m, 2H), 3.96-3.82 (m, 2H), 3.69-3.65 (m, 2H), 2.80-2.55 (m, 4H), 2.41 (s, 3H), 2.23-2.21 (m, 1H), 2.15-2.10 (m, 2H), 1.98-1.88 (m, 4H), 1.70-1.66 (m, 1H), 1.03 (s, 9H); LC-MS (ES$^+$): m/z 1020.35 [MH$^+$]
120		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{7-[4-cyano-3-(trifluoromethyl)phenyl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.82 (s, 1H), 8.17-8.15 (d, *J* = 7.8 Hz, 2H), 8.02-8.00 (d, *J*=8.1 Hz, 1H), 7.78-7.75 (d, *J* = 8.4 Hz, 2H), 7.61-7.59 (d, *J* = 8.4 Hz, 2H), 7.48-7.42 (m, 6H), 7.04-7.01 (d, *J* = 8.7 Hz, 2H), 4.71 (s, 1H), 4.62-4.51 (m, 3H), 4.47-4.32(d, *J* = 15.9 Hz, 1H), 4.12-4.10 (m, 2H), 4.08-4.01(m, 2H), 3.96-3.82 (m, 2H), 3.69-3.65 (m, 2H), 2.80-2.55 (m, 4H), 2.48 (s, 3H), 2.23-2.21 (m, 1H), 2.14-2.10 (m, 1H), 1.98-1.89 (m, 4H), 1.70-1.66 (m, 1H), 1.03 (s, 9H); LC-MS (ES$^+$): m/z 1036.25 [MH$^+$]
121		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}-3-fluorophenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD):δ8.14 (s, 1 H), 8.00-7.91 (m, 1 H), 7.90-7.80 (m, 1 H), 7.71-7.58 (m, 5 H), 7.50-7.41 (m, 6 H), 6.90-6.71 (m, 2 H), 4.67 (s, 1 H), 4.58-4.41 (m, 3 H), 4.30-4.22 (m, 1 H), 4.12-4.01 (m, 2 H), 3.99-3.94 (m, 2 H), 3.90 -3.70 (m, 2 H), 3.65-3.55 (m, 2 H), 2.22-2.13 (m, 1 H), 2.14-2.00 (m, 1 H), 2.00-1.72 (m, 4 H), 1.56 (s, 6 H), 1.01 (s, 9 H); LC-MS (ES$^+$): *m/z*, 978.30 [MH$^+$]

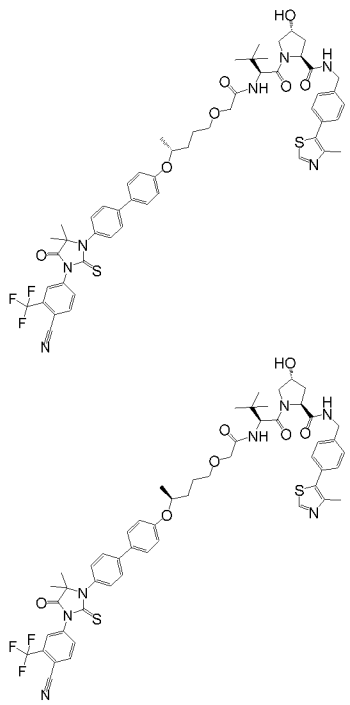
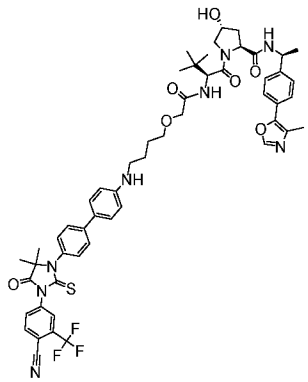
122		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1H-pyrazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): 8.25-8.15 (m, 2H), 8.05-8.00 (s, 1 H), 7.78-7.70 (m, 4 H), 7.70-7.58 (m, 3 H), 7.48-7.39 (m, 4 H), 7.08-7.00 (m, 2 H), 6.69-6.60, (s, 1 H), 4.95-4.85 (s, 1 H), 4.65-4.58 (s, 1 H), 4.55-4.49 (m, 2 H), 4.40-4.30 (s, 1 H),4.15-4.08(m,2 H),4.05-4.00(m,2 H),3.90-3.85 (s, 1 H), 3.82--3.75 (s, 1 H), 3.70-3.60 (m, 2 H), 2.28-2.20 (s, 1 H), 2.15-2.05 (s, 1 H), 1.98-1.89 (m, 4 H), 1.63-1.59 (m, 6 H)1.10-1.00(m,9 H); LC-MS (ES$^+$): *m/z* 993.35 [MH$^+$]
123		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(3-chloro-4-cyano-2-fluorophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.21 (s, 1H), 7.88-7.87 (d, *J* = 1.6Hz, 1H), 7.86-7.73 (m, 3H), 7.69-7.67 (d, *J* = 8.4 Hz, 2H), 7.61-7.59 (d, *J* = 8.4 Hz, 2H), 7.48-7.43 (m, 5H), 7.05-7.02 (d, *J* = 8.8 Hz, 2H), 4.88 (s, 1H), 4.73-4.59 (m, 3H), 4.52-4.37 (d, *J* = 15.2 Hz, 1H), 4.08-4.02 (m, 2H), 3.98-3.82 (m, 2H), 3.89-3.88(m, 1H), 3.84-3.83(m, 1H), 3.69-3.66 (t, *J* = 6.0 Hz, 2H), 2.23-2.20 (m, 1H), 2.13-2.04 (m, 1H), 1.97-1.88 (m, 4H), 1.62 (s, 6H), 1.04 (s, 9H); LC-MS (ES$^+$): *m/z* 978.26[MH$^+$]
124		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[7-(3-chloro-4-cyanophenyl)-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl]phenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.18 (s, 1H), 7.99-7.96 (d, *J* = 8.4Hz, 1H), 7.89 (s, 1H), 7.79-7.77 (d, *J* = 8.4Hz, 2H), 7.67-7.61 (m, 5H), 7.48-7.43 (m, 5H), 7.06-7.04 (d, *J* = 8.8 Hz, 2H), 4.88 (s, 1H), 4.73-4.59 (m, 3H), 4.52-4.37 (d, *J* = 15.2 Hz, 1H), 4.14-4.11 (m, 2H), 4.05-4.02 (m, 2H), 3.99-3.83 (m, 2H), 3.70-3.67(t, *J* = 6.0 Hz, 2H), 2.66-2.62 (m, 4H), 2.13-2.00 (m, 3H), 1.98-1.88 (m, 4H), 1.80-1.70 (m, 1H), 1.04 (s, 9H); LC-MS (ES$^+$): *m/z* 972.25[MH$^+$]
125		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(4-cyano-3-methylphenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO) δ 8.60 (t, *J* = 6.0 Hz, 1H), 8.40 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.67-7.63 (m, 6H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.44-7.39 (m, 5H), 7.05 (d, *J* = 8.8 Hz, 2H), 5.16 (s, 1H), 4.58-4.56 (m, 1H), 4.47-4.26 (m, 4H), 4.08-4.05 (m, 2H), 3.97 (s, 2H), 3.66-3.57 (m, 4H), 2.56 (s, 3H), 2.06-2.02 (m, 1H), 1.93-1.72 (m, 5H), 1.52 (s, 6H), 0.93 (s, 9H); LC-MS (ES$^+$): *m/z* 940.30 [MH$^+$]

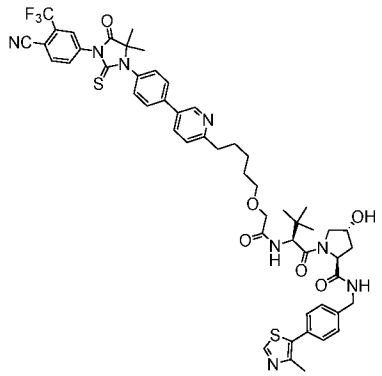
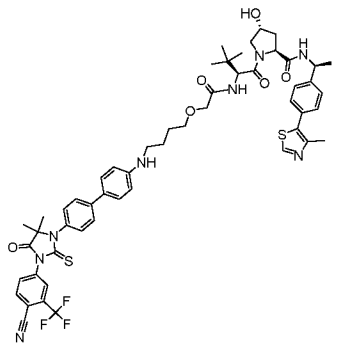
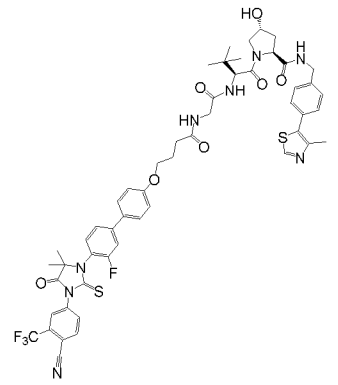
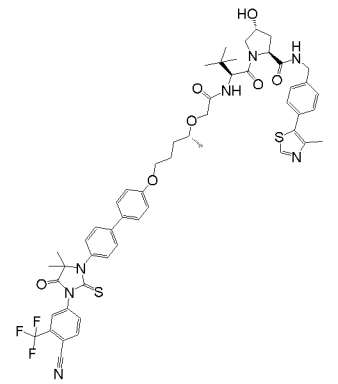
126		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(4-cyano-3-fluorophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO) δ 8.60 (t, *J* = 6.0 Hz, 1H), 8.40 (s, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.85-7.78 (m, 3H), 7.67-7.63 (m, 6H), 7.43-7.39 (m, 5H), 7.05 (d, *J* = 8.8 Hz, 2H), 5.16 (s, 1H), 4.58-4.56 (m, 1H), 4.47-4.26 (m, 4H), 4.08-4.05 (m, 2H), 3.97 (s, 2H), 3.66-3.55 (m, 4H), 2.06-2.02 (m, 1H), 1.93-1.72 (m, 5H), 1.53 (s, 6H), 0.95 (s, 9H); LC-MS (ES$^+$): *m/z* 944.50 [MH$^+$]
127		(2S,4R)-1-[(2S)-2-(2-{4-[3-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]phenoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD):δ8.81 (s, 1 H), 8.14-8.05 (m, 2 H), 8.00-7.95 (m, 1 H), 7.75-7.69 (m, 2 H), 7.55-7.32 (m, 8 H), 7.20-7.15 (m, 1 H), 7.10-7.00 (m, 4 H), 6.99-6.85 (m, 1 H), 4.68 (s, 1 H), 4.65-4.60 (m, 2 H), 4.63-4.55 (m, 1 H), 4.50-4.40 (m, 2 H), 4.30-4.20 (m, 1 H), 3.90-3.80 (m, 1H), 3.75-3.65 (m, 1 H), 2.40 (s, 3 H), 2.25-2.21 (m, 1 H), 2.14-2.00 (m, 1 H), 1.55 (s, 6 H), 0.99 (s, 9 H); LC-MS (ES$^+$): *m/z*, 1044.30 [MH$^+$]
128		(2S,4R)-1-[(2S)-2-[2-(3-{[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenyl]methoxy}propoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.85 (s, 1H), 8.20 (m, 2H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.48 (m, 6H), 7.39 (m, 2H), 4.71 (s, 1H), 4.61 (m, 5H), 4.34 (m, 1H), 4.01 (m, 2H), 3.84 (m, 2H), 3.72 (m, 4H), 2.45 (s, 3H), 2.25 (m, 1H), 2.12 (m, 1H), 1.97 (m, 2H), 1.62 (s, 6H), 1.02 (s, 9H); LC-MS (ES$^+$): *m/z* 1024.20 [MH$^+$]
129		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]-3-hydroxybutoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.82 (s, 1H), 8.20 (m, 2H), 8.03 (m, 1H), 7.74 (m, 2H), 7.60 (m, 2H), 7.48 (m, 6H), 7.07 (m, 2H), 4.74 (m, 1H), 4.60-4.53 (m, 3H), 4.37 (m, 1H), 4.21 (m, 1H), 4.08 (m, 4H), 3.92-3.88 (m, 1H), 3.83-3.75 (m, 3H), 2.49 (s, 3H), 2.26 (m, 1H), 2.14 (m, 2H), 1.87 (m, 1H), 1.62 (s, 6H), 1.03 (s, 9H); LC-MS (ES$^+$): *m/z* 1040.25 [MH$^+$]

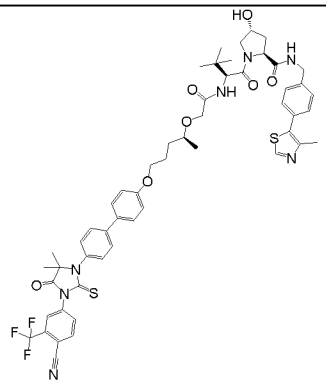
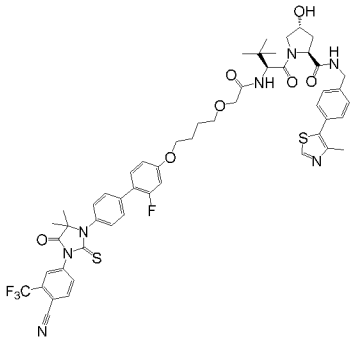
130		(2S,4R)-1-[(2S)-2-{2-[(2R)-4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]-2-hydroxybutoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.81 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 2H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.71 (s, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.44 (m, 6H), 7.02 (d, *J* = 8.8 Hz, 2H), 4.71 (s, 1H), 4.56 (m, 3H), 4.33 (m, 1H), 4.17 (m, 2H), 4.05 (m, 3H), 3.75 (m, 2H), 3.65 (m, 2H), 2.44 (s, 3H), 2.22 (m, 1H), 2.08 (m, 2H), 1.90 (m, 1H), 1.60 (s, 6H), 1.05 (s, 9H); LC-MS (ES^+): m/z 1040.20 [MH^+]
131		(2S,4R)-1-[(2S)-2-{2-[(2S)-4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]-2-hydroxybutoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.84 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 2H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.71 (s, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.44 (m, 6H), 7.02 (d, *J* = 8.8 Hz, 2H), 4.71 (s, 1H), 4.56 (m, 3H), 4.33 (m, 1H), 4.17 (m, 2H), 4.05 (m, 3H), 3.90 (m, 1H), 3.83 (m, 1H), 3.60 (m, 2H), 2.44 (s, 3H), 2.22 (m, 1H), 2.08 (m, 2H), 1.90 (m, 1H), 1.60 (s, 6H), 1.05 (s, 9H); LC-MS (ES^+): m/z 1040.20 [MH^+],
132		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(1,3-oxazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.22 (s, 1H), 7.97-7.95(d, *J* = 8.4 Hz, 1H), 7.89-7.88 (d, *J*=1.8Hz, 1H), 7.75-7.58 (m, 7H), 7.47(s, 1H), 7.43-7.38 (m, 4H), 7.06-7.01 (d, *J*=14.1 Hz, 2H) ,5.00 (m, 1H), 4.69 (s, 1H), 4.61-4.55(m, 1H), 4.44 (s, 1H), 4.13-4.09 (t, *J*=6.0 Hz, 2H), 4.02-4.00 (d, *J*=6.0 Hz, 2H), 3.87-3.76 (m, 2H), 3.68-3.64 (m, 2H), 2.19-2.16(m, 1H) ,2.03-1.84 (m, 5H), 1.58 (s, 6H), 1.49-1.47(d, *J*=6.9 Hz, 3H) 1.04 (s, 9H); LC-MS (ES^+): m/z 974.20, 976.20 [MH^+]
133		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(5-chloro-4-cyano-2-fluorophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD) δ 8.23 (s, 1H), 8.18-7.94 (m, 2H), 7.74-7.65 (m, 6H), 7.50-7.40 (m, 5H), 7.04-7.01 (d, *J* = 8.7Hz, 2H), 4.71 (s, 1H), 4.60-4.56 (m, 3H), 4.53-4.34 (d, *J* = 15.2Hz, 1H), 4.12-4.08 (m, 2H), 4.08-4.01 (m, 2H), 3.96-3.82 (m, 2H), 3.69-3.65 (m, 2H), 2.23-2.20 (m, 1H), 2.13-2.04 (m, 1H), 1.98-1.85 (m, 4H), 1.59 (s, 6H), 1.05 (s, 9H); LC-MS (ES^+): *m/z* 978.26[MH^+]

134		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)-2-methylphenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO): δ 8.96 (s, 1H), 8.61 (m, 1H), 8.42 (d, J = 7.6 Hz, 1H), 8.33 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 10.4 Hz, 7H), 7.19 (d, J = 8.0 Hz, 1H), 6.83-6.89 (m, 2H), 5.17 (m, 1H), 4.59 (d, J = 9.6 Hz, 1H), 4.40-4.48 (m, 1H), 4.37-4.38 (m, 2H), 4.25-4.29 (m, 1H), 4.02-4.05 (m, 2H), 3.97 (s, 2H), 3.55-3.69 (m, 4H), 2.45 (s, 3H), 2.25 (s, 3H), 2.05-2.10 (m, 1H), 1.91-1.93 (m, 1H), 1.81-1.84 (m, 2H), 1.72-1.75 (m, 2H), 1.55 (s, 6H), 0.95 (s, 9H); LC-MS (ES$^+$): *m/z* 1038.35 [MH$^+$]
135		(2S,4R)-1-[(2S)-2-[2-(3-{[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenyl]carbamoyl}propoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.19-8.16 (d, *J* = 12.4Hz, 2H), 8.13 (s, 1H), 8.04-8.01(d, *J* = 10.8Hz, 1H), 7.78-7.75 (d, *J* = 11.2Hz, 2H), 7.75-7.60 (m, 6H), 7.57-7.44 (m, 4H), 4.87 (s, 1H), 4.73-4.57 (m, 3H), 4.52-4.37 (d, *J* = 15.2 Hz, 1H), 4.10-4.05 (m, 2H), 3.96-3.83 (m, 2H), 3.70-3.66 (m, 2H), 2.59-2.54 (t, *J* = 9.6 Hz, 2H), 2.36 (s, 3H), 2.24-2.22 (m, 1H), 2.17-2.04 (m, 3H), 1.05 (s, 6H), 1.03 (s, 9H); LC-MS (ES$^+$): *m/z* 1021.25[MH$^+$]
136		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)-3-methylphenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.80 (s, 1H), 8.15-8.18 (m, 2H), 7.99-8.02 (m, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.38-7.47 (m, 8H), 6.98 (d, J = 8.8 Hz, 1H), 4.70 (s, 1H), 4.50-4.60 (m, 3H), 4.31-4.34 (m, 1H), 3.96-4.11 (m, 4H), 3.81-3.87 (m, 2H), 3.65-3.68 (m, 2H), 2.43 (s, 3H), 2.26 (m, 4H), 2.09 (m, 1H), 1.87-1.98 (m, 4H), 1.59 (s, 6H), 1.04 (s, 9H); LC-MS (ES$^+$): *m/z* 1038.40 [MH$^+$]
137		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-3-fluorophenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO) δ 8.99 (s, 1H), 8.46-8.40 (m, 2H), 8.36 (s, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.78-7.67 (m, 4H), 7.45-7.35 (m, 6H), 7.09 (d, *J* = 8.8 Hz, 2H), 5.15 (s, 1H), 4.93-4.89 (m, 1H), 4.57 (d, *J* = 9.6 Hz, 1H), 4.46-4.39 (m, 1H), 4.30 (s, 1H), 4.11-4.08 (m, 2H), 3.96 (s, 2H), 3.60-3.56 (m, 4H), 2.46 (s, 3H), 2.07-2.03 (m, 1H), 1.84-1.74 (m, 5H), 1.62 (s, 3H), 1.50 (s, 3H), 1.38

		(d, *J* = 6.8 Hz, 3H), 0.95 (s, 9H); LC-MS (ES^+): *m/z* 1056.30 [MH^+]
138		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-3-fluorophenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-oxazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO) δ 8.46-8.40 (m, 2H), 8.36 (s, 1H), 8.31 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.78-7.67 (m, 4H), 7.57-7.48 (m, 3H), 7.40-7.35 (m, 3H), 7.09 (d, *J* = 8.4 Hz, 2H), 5.15 (s, 1H), 4.93-4.89 (m, 1H), 4.57 (d, *J* = 9.2 Hz, 1H), 4.46-4.40 (m, 1H), 4.28 (s, 1H), 4.11-4.07 (m, 2H), 3.96 (s, 2H), 3.59-3.56 (m, 4H), 2.35 (s, 3H), 2.07-2.03 (m, 1H), 1.84-1.73 (m, 5H), 1.62 (s, 3H), 1.51 (s, 3H), 1.39 (d, *J* = 6.4 Hz, 3H), 0.95 (s, 9H); LC-MS (ES^+): *m/z* 1040.25 [MH^+]
139		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)-2-methoxyphenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO) δ 8.96 (s, 1H), 8.61 (s, 1H), 8.41 (d, *J* = 8.4 Hz, 1H), 8.33 (s, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.45-7.40 (m, 7H), 7.30-7.23 (m, 2H), 7.06 (d, *J* = 8.4 Hz, 1H), 5.17 (s, 1H), 4.57 (d, *J* = 9.2 Hz, 1H), 4.46-4.36 (m, 3H), 4.30-4.28 (m, 1H), 4.06-4.03 (m, 2H), 3.96 (s, 2H), 3.86 (s, 3H), 3.67-3.56 (m, 4H), 2.44 (s, 3H), 2.08 (s, 1H), 1.85-1.75 (m, 5H), 1.55 (s, 6H), 0.95 (s, 9H); LC-MS (ES^+): *m/z* 1054.25 [MH^+]
140		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)-3-methoxyphenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO) δ 8.96 (s, 1H), 8.61 (s, 1H), 8.41 (d, *J* = 8.4 Hz, 1H), 8.33 (s, 1H), 8.12 (d, *J* = 1.6 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.43-7.37 (m, 7H), 7.28 (d, *J* = 8.4 Hz, 1H), 6.68-6.61 (m, 2H), 5.17 (s, 1H), 4.57 (d, *J* = 9.6 Hz, 1H), 4.46-4.36 (m, 3H), 4.30-4.28 (m, 1H), 4.06-4.03 (m, 2H), 3.96 (s, 2H), 3.86 (s, 3H), 3.67-3.56 (m, 4H), 2.44 (s, 3H), 2.08 (s, 1H), 1.85-1.75 (m, 5H), 1.56 (s, 6H), 0.95 (s, 9H); LC-MS (ES^+): *m/z* 1054.25 [MH^+]

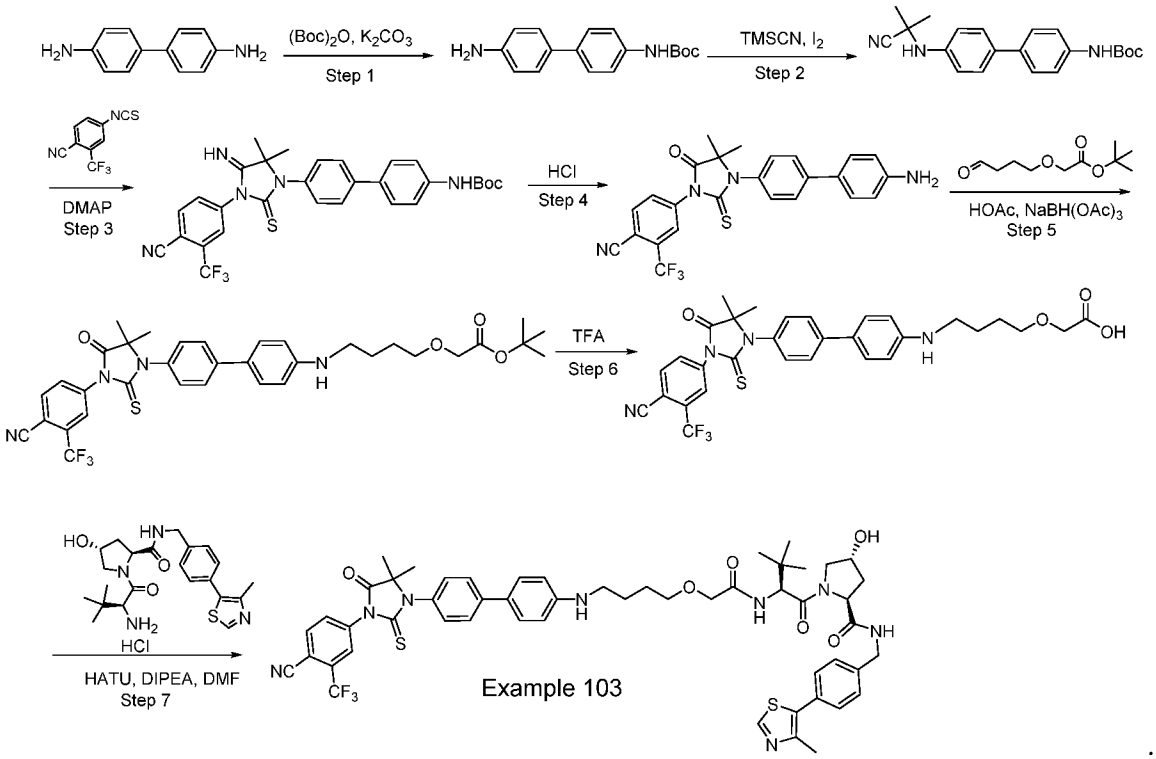
141, 142		(2S,4R)-1-[(2S)-2-(2-{[(4S)-4-[4-(4-{3-[4-cyano-3-trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]pentyl]oxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (2S,4R)-1-[(2S)-2-(2-{[(4R)-4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]pentyl]oxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.84 (s, 1H), 8.19-8.17 (d, *J* = 8.0Hz, 2H), 8.04-8.02 (d, *J* = 8.4Hz, 1H), 7.75-7.73 (d, *J* = 8.4Hz, 2H), 7.60-7.58 (d, *J* = 8.4Hz, 2H), 7.49-7.41 (m, 6H), 7.03-7.01 (d, *J* = 8.8Hz, 2H), 4.87 (s, 1H), 4.73-4.58 (m, 4H), 4.50-4.39 (d, *J* = 15.2 Hz, 1H), 4.02-4.00 (m, 2H), 3.91-3.88 (m, 1H), 3.84-3.83 (m, 1H), 3.64-3.62 (m, 2H), 2.46 (s, 3H), 2.25-2.23 (m, 1H), 2.13-2.11 (m, 1H), 1.86-1.78 (m, 4H), 1.62(s, 6H), 1.37-1.34 (m, 3H), 1.12 (s, 9H); LC-MS (ES^+): *m/z* 1038.15[MH^+] ^{1}H NMR (400 MHz, CD_3OD) δ 8.84 (s, 1H), 8.19-8.17 (d, *J* = 8.0Hz, 2H), 8.04-8.02 (d, *J* = 8.4Hz, 1H), 7.75-7.73 (d, *J* = 8.4Hz, 2H), 7.60-7.58 (d, *J* = 8.4Hz, 2H), 7.49-7.41 (m, 6H), 7.03-7.01 (d, *J* = 8.8Hz, 2H), 4.87 (s, 1H), 4.73-4.58 (m, 4H), 4.50-4.39 (d, *J* = 15.2 Hz, 1H), 4.02-4.00 (m, 2H), 3.91-3.88 (m, 1H), 3.84-3.83 (m, 1H), 3.64-3.62 (m, 2H), 2.46 (s, 3H), 2.25-2.23 (m, 1H), 2.13-2.11 (m, 1H), 1.86-1.78 (m, 4H), 1.62(s, 6H), 1.37-1.34 (m, 3H), 1.12 (s, 9H); LC-MS (ES^+): *m/z* 1038.15[MH^+]
143		(2S,4R)-1-[(2S)-2-[2-(4-{[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenyl]amino}butoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-oxazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.20-8.17 (m, 3H), 8.03-8.01 (d, *J* = 8.1Hz, 1H), 7.73-7.71 (d, *J* = 8.4Hz, 2H), 7.70-7.67 (d, *J* = 8.4Hz, 2H), 7.63-7.61 (d, *J* = 8.4Hz, 2H), 7.52-7.40 (m, 4H), 6.78-6.76 (d, *J* = 8.4Hz, 2H), 5.02-5.00 (m, 1H), 4.87 (s, 1H), 4.62-4.60 (m, 1H), 4.58-4.56 (m, 1H), 4.07-4.00 (m, 2H), 3.88-3.85 (m, 1H), 3.78-3.77 (m, 1H), 3.65-3.63 (m, 2H), 3.23-3.22 (m, 2H), 2.41 (s, 3H), 2.24-2.22 (m, 1H), 1.97-1.96 (m, 1H), 1.80-1.70 (m, 4H), 1.61 (s, 6H), 1.49-1.48 (d, *J* = 4.4Hz, 3H), 1.04 (s, 9H); LC-MS (ES^+): *m/z* 1021.25[MH^+]

144		(2S,4R)-1-[(2S)-2-[2-({5-[5-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)pyridin-2-yl]pentyl}oxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 9.01 (s, 1 H), 8.89 (s, 1 H), 8.72-8.70 (m, 1 H), 8.21-8.18 (m, 2 H), 8.04-7.96 (m, 4 H), 7.65-7.47 (m, 2 H),7.46-7.38 (m, 4 H), 4.73(s, 1 H), 4.63-4.50 (m, 3 H), 4.41-4.37 (m, 1 H), 4.05-3.99 (m, 2 H), 3.89-3.85 (m, 1 H), 3.85-3.84m (m, 1 H), 3.63-3.60 (m, 2 H), 3.14-3.10(m, 2 H), 2.45 (s, 3 H), 2.30-2.28 (m, 1 H), 2.15-2.03 (m, 1 H),1.94-1.93 (m, 2 H), 1.78-1.76 (m, 2 H), 1.63-1.59 (m, 8 H), 1.01 (s, 9 H); LC-MS (ES^+): *m/z* 1023.45[MH^+]
145		(2S,4R)-1-[(2S)-2-[2-(4-{[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenyl]amino}butoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD) δ 8.95 (s, 1H), 8.19-8.16 (d, *J* = 8.7Hz, 2H), 8.03-8.00(d, *J* = 8.1Hz, 1H), 7.87-7.82 (m, 4H), 7.53-7.37 (m, 8H), 5.01-4.99 (m, 1H), 4.87 (s, 1H), 4.70-4.68 (m, 1H), 4.56-4.54 (m, 1H), 4.08-4.05 (m, 2H), 3.83-3.80 (m, 2H), 3.70-3.59 (m, 2H), 3.52-3.47 (m, 2H), 2.48 (s, 3H), 2.24-2.22 (m, 1H), 1.98-1.89 (m, 5H), 1.61 (s, 6H), 1.61-1.60 (m, 1H), 1.56-1.54 (m, 2H), 1.03 (s, 9H); LC-MS (ES^+): *m/z* 1037.10[MH^+]
146		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-3-fluorophenyl)phenoxy]butanamido}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD3OD) δ 8.87 (s, 1H), 8.19 (m, 2H), 8.05 (m, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.59 (m, 2H), 7.49 (m, 3H), 7.41 (m, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 4.88 (s, 1H), 4.66 (m, 3H), 4.38 (m, 1H), 4.11 (m, 2H), 3.92 (m, 3H), 3.80 (m,1H), 2.54 (m, 2H), 2.47 (s, 3H), 2.23-2.09 (m, 4H), 1.68 (s, 3H), 1.57 (s, 3H), 1.05 (s, 9H); LC-MS (ES^+): *m/z* 1055.10 [MH^+]
147, 148		(2S,4R)-1-[(2S)-2-(2-{[(2S)-5-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]pentan-2-yl]oxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (2S,4R)-1-[(2S)-2-(2-{[(2R)-5-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]pentan-2-yl]oxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.88 (s, 1H) , 8.18-8.15 (m, 2H), 8.02-8.00 (d,

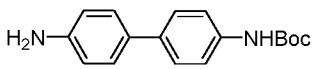
		*J* = 8.4 Hz, 1H), 7.72-7.70 (d, *J* = 8.8 Hz, 2H), 7.58-7.55 (d, *J* = 8.8 Hz, 2H), 7.47-7.38 (m , 6H), 7.01-6.99 (d, *J* = 4.8 Hz, 2H), 4.86 (s, 1H), 4.58-4.50 (m, 3H), 4.35-4.31 (m, 1H), 4.09-4.05 (m, 3H), 3.86-3.81 (m, 3H), 3.71-3.61 (m, 1H), 2.47 (s, 3H), 2.37-2.23 (m, 1H), 2.11-2.09 (m, 1H), 2.02-1.87 (m, 2H), 1.84-1.68 (m, 2H), 1.59 (s, 6H), 1.26 (s, 3H), 1.02 (s, 9H); LC-MS (ES^+): m/z 1038.10 [MH^+] ^{1}H NMR (400 MHz, CD_3OD): δ 8.88 (s, 1H) , 8.18-8.15 (m, 2H), 8.02-8.00 (d, *J* = 8.4 Hz, 1H), 7.72-7.70 (d, *J* = 8.8 Hz, 2H), 7.58-7.55 (d, *J* = 8.8 Hz, 2H), 7.47-7.38 (m , 6H), 7.01-6.99 (d, *J* = 4.8 Hz, 2H), 4.87 (s, 1H), 4.70-4.50 (m, 3H), 4.36-4.32 (m, 1H), 4.09-4.00 (m, 4H), 3.86-3.81 (m, 3H), 2.47 (s, 3H), 2.37-2.23 (m, 1H), 2.11-2.09 (m, 1H), 2.00-1.85 (m, 2H), 1.84-1.68 (m, 2H), 1.58 (s, 6H), 1.23 (s, 3H),1.01 (s, 9H); LC-MS (ES^+): m/z 1038.10 [MH^+]
149		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)-3-fluorophenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): 8.80 (s, 1H),8.18-8.12 (m,2 H), 8.00-7.95 (s, 1 H), 7.65-7.60 (m, 2 H), 7.45-7.35 (m, 7 H), 6.88-6.72 (m, 2 H), 4.65 (s, 1 H), 4.61-4.52 (s, 1 H), 4.50-4.35 (m, 2 H), 4.32-4.22 (s, 1 H), 4.18-4.02 (m, 2 H), 4.00-3.94 (m, 2 H),3.95-3.75 (m, 2 H), 3.74-3.55 (m, 2 H),2.40 (m, 3 H), 2.28-2.15 (s, 1 H), 2.14-2.01 (s, 1 H),2.00-1.72 (m, 4 H),1.68-1.48 (m, 6 H), 1.00(m, 9 H); LC-MS (ES^+): *m/z* 1042.05 [MH^+]

[0702] Examples 135, 143-145 were synthesized according to similar procedures described for the synthesis of examples 103, by using corresponding starting materials and intermediates.

[0703] Synthesis of example 103:

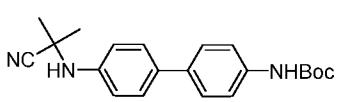


[0704] Step 1: Synthesis of tert-butyl N-[4-(4-aminophenyl)phenyl]carbamate:



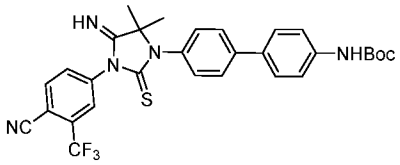
[0705] To a stirred solution of 4-(4-aminophenyl)aniline (15.0 g, 81.42 mmol) in a mixed solvent of N,N-dimethylformamide / tetrahydrofuran /water (v/v/v = 100/300/50 mL) was added potassium carbonate (9.5 g, 68.74 mmol) and di-tert-butyl dicarbonate (13.67 g, 62.63 mmol) at rt. The resulting mixtire was stirred for 5h at rt. The reaction was then diluted by water (500 mL) and extracted with ethyl acetate (200 mL x 3). The organic layers were combined, washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluent: ethyl acetate/petroleum ether, v:v = 1:2) to provide the titled product (yield: 97%) as a yellow solid.

[0706] Step 2: Synthesis of tert-butyl N-(4-{4-[(1-cyano-1-methylethyl)amino]phenyl}phenyl)carbamate:



[0707] To a stirred solution of tert-butyl N-[4-(4-aminophenyl)phenyl]carbamate (7.0 g, 24.62 mmol) in acetone (100 mL) under an atmosphere of nitrogen was added trimethylsilanecarbonitrile (4.9 g, 49.49 mmol) drop wise at 0 °C, followed by addition of iodine (630.0 mg, 2.48 mmol) in several batches at 0 °C. The resulting mixture was stirred for 15h at rt. The reaction was then quenched by the addition of water (100 mL), and the resulting solution was extracted with ethyl acetate (100 mL x 2). The organic layers were combined, washed with brine (70 mL x 2), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluent: ethyl acetate/petroleum ether, v:v = 1:3) to provide the titled product (yield: 87%) as a yellow solid. Mass (ES^+): *m/z* 352.20 [MH^+].

[0708] Step 3: Synthesis of tert-butyl N-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-4-imino-5,5-dimethyl-2-sulfanylideneimidazolidin-1-yl}phenyl)phenyl]carbamate:



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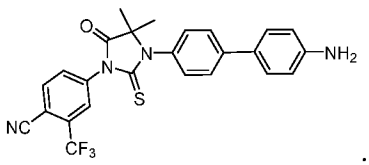
[0709] To a stirred solution of tert-butyl N-(4-{4-[(1-cyano-1-methylethyl)amino]phenyl}phenyl)carbamate (3.1 g, 8.82 mmol) in toluene (40.0 mL) was added 4-dimethylaminopyridine (1.6 g, 13.10 mmol) and 4-isothiocyanato-2-(trifluoromethyl)benzonitrile (2.0 g, 8.76 mmol) at rt under an atmosphere of nitrogen. The resulting solution was stirred for 12h at 100°C in an oil bath. The reaction mixture was then concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluent: ethyl acetate/petroleum ether, v:v = 1:1) to provide the titled product (yield: 36%) as a yellow solid. Mass (ES^+): *m/z* 580.30 [MH^+].

[0710] Step 4: Synthesis of 4-{3-[4-(4-aminophenyl)phenyl]-4,4-dimethyl-5-oxo-2-sulfanylideneimidazolidin-1-yl}-2-(trifluoromethyl)benzonitrile:



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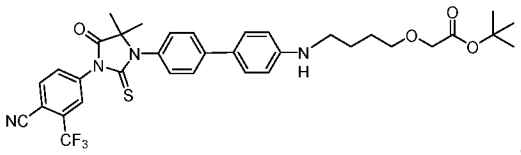
[0711] To a stirred solution of tert-butyl N-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-4-imino-5,5-dimethyl-2-sulfanylideneimidazolidin-1-yl}phenyl)phenyl]carbamate (2.0 g) in methanol (20 mL) was added hydrogen chloride (3 N solution in water, 5 mL) at rt. The resulting solution was stirred for 2 h at 70°C in an oil bath. The reaction mixture was then concentrated under reduced pressure to remove the bulk of methanol. To the resulting aqueous mixture was added sodium bicarbonate (sat. aqueous solution) to adjust the pH to ~ 8, and the resulting mixture was extracted with ethyl acetate (80 mL x 3). The organic layers were combined, washed with brine (30 mL x 2), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluent: ethyl acetate/petroleum ether, v:v = 1:2) to provide the titled product (yield: 45%) as a yellow solid. Mass (ES^+): *m/z* 481.15 [MH^+].

[0712] Step 5: Synthesis of tert-butyl 2-(4-{[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenyl]amino}butoxy)acetate:



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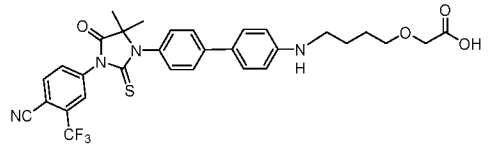
[0713] To a stirred solution of 4-{3-[4-(4-aminophenyl)phenyl]-4,4-dimethyl-5-oxo-2-sulfanylideneimidazolidin-1-yl}-2-(trifluoromethyl)benzonitrile (200.0 mg, 0.42 mmol) in dichloromethane (10 mL) was added acetic acid (0.01 mL) and tert-butyl 2-(4-oxobutoxy)acetate (93.0 mg, 0.46 mmol) at rt. The resulting mixture was stirred for 10 min at rt, then to the mixture was added sodium triacetoxyborohydride (124.0 mg, 0.59 mmol). The resulting mixture was stirred overnight at rt. The reaction mixture was diluted by water (30 mL), extracted with dichloromethane (20 mL x 3). The organic layers were combined, washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluent: ethyl acetate/petroleum ether, v:v = 1:2) to provide the titled product (yield: 36%). Mass (ES^+): *m/z* 667.20[MH^+].

[0714] Step 6: Synthesis of 2-(4-{[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenyl]amino}butoxy)acetic acid:



[0715] To a stirred solution of tert-butyl 2-(4-{[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenyl]amino}butoxy)acetate (100.0 mg, 0.15 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (2.0 mL) at rt. The resulting solution was stirred for 2h at rt. The reaction mixture was then concentrated under reduced pressure to give a crude material (yield: 99% based on crude) which was used for next step reaction without any further purification. Mass (ES^+): *m/z* 611.10[MH^+]

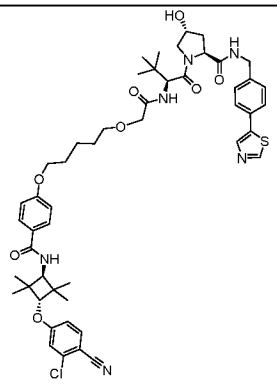
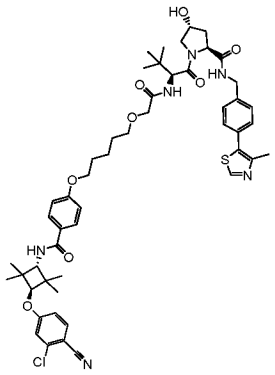
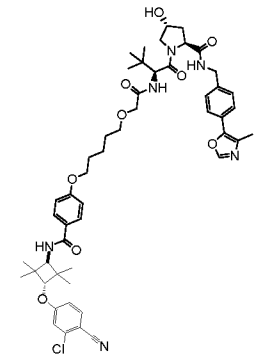
[0716] Step 7: Synthesis of example 103.

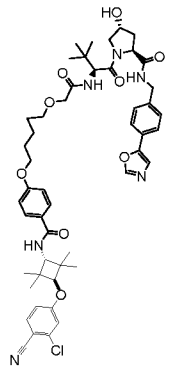
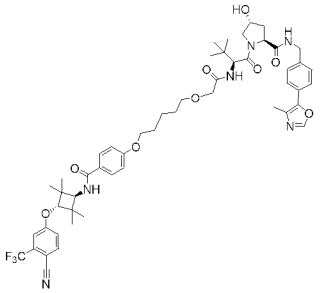
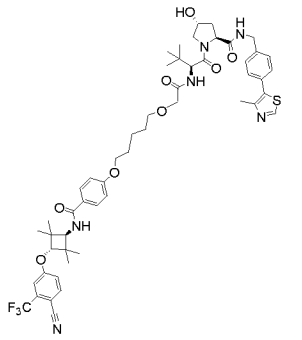
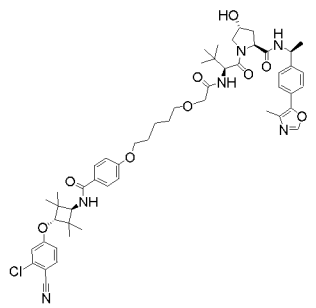
[0717] This compound was synthesized from 2-(4-{[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenyl]amino}butoxy)acetic acid and (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide hydrochloride, according to similar procedures in the last step (amide coupling) described for the synthesis of example 75.

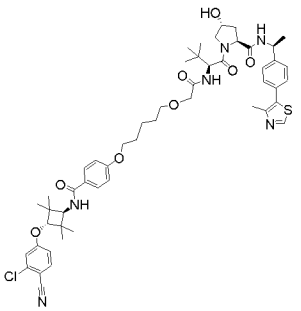
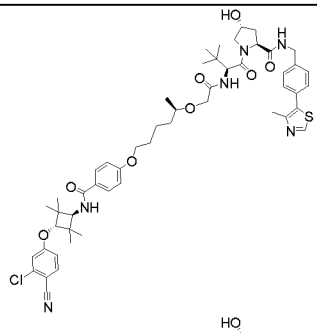
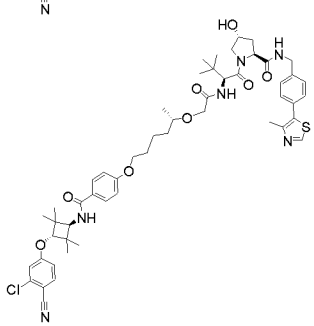
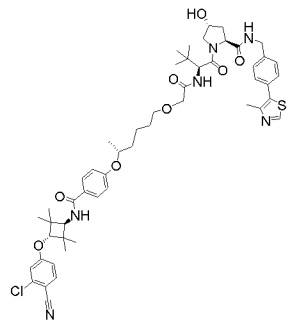
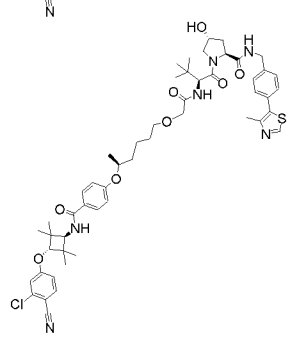
[0718] Synthesis of tert-butyl 2-(4-oxobutoxy) acetate:

[0719] To a stirred solution of tert-butyl 2-(4-hydroxybutoxy)acetate (1.0 g, 4.90 mmol) in dichloromethane (10 mL) was added (1,1,1-triacetoxy)-1,1-dihydro-1,2-benziodoxol-3(1H)-one (2.7 g, 6.37 mmol) at rt. The resulting mixture was stirred for 12h at rt. The reaction mixture was then diluted with water (20 mL), extracted with ethyl acetate (20 mL x 3). The organic layers were combined, washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluent: ethyl acetate/petroleum ether, v/v = 1:2) to provide the titled product (yield: 50%) as colorless oil. ^1H NMR (300 MHz, CD_3OD) δ 9.68 (s, 1H), 3.95 (s, 2H), 3.48-3.45 (m, 2H), 2.51-2.50 (m, 2H), 1.81-1.63 (m, 2H), 1.42 (s, 9H).

[0720] Table 8. Exemplary Compounds.

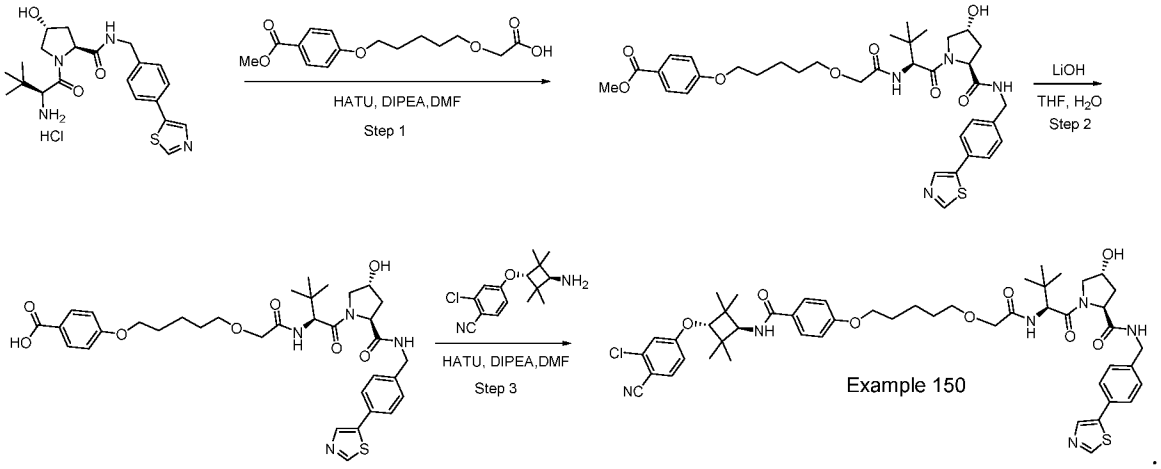
Ex #	Structure	Compound name and Analytical data
150		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{[5-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)pentyl]oxy}acetamido)butanoyl]-4-hydroxy-N-{[4-(1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (s, 9H), 1.22 (s, 6H), 1.27 (s, 6H), 1.56-1.58 (m, 2H), 1.68-1.70 (m, 2H), 1.83-1.86 (m, 2H), 2.11-2.12 (m, 1H), 2.54 (br, 1H), 3.52-3.63 (m, 3H), 3.91-4.16 (m, 7H), 4.28-4.54 (m, 5H), 4.70-4.71 (m, 1H), 6.19 (d, *J* = 6.8 Hz, 1H), 6.80-6.97 (m, 4H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 6.8 Hz, 2H), 7.48-7.58 (m, 3H), 7.72-7.74 (m, 2H), 8.03-8.10 (m, 2H), 8.78 (br, 1H); LC-MS: (ES^+): m/z 941.20 [$M+H^+$]
151		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{[5-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)pentyl]oxy}acetamido)butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.72 (d, J = 9.0 Hz, 2H), 7.57 (d, J = 8.6 Hz, 1H), 7.31-7.38 (m, 4H), 7.20 (d, J = 9.0 Hz, 1H), 6.97 (d, J = 2.3 Hz, 1H), 6.92 (d, J = 8.6 Hz, 1H), 6.81 (dd, J = 2.5, 8.8 Hz, 1H), 6.19 (d, J = 8.2 Hz, 1H), 4.72 (t, J = 7.8 Hz, 1H), 4.47-4.58 (m, 3H), 4.31-4.41 (m, 1H), 3.87-4.18 (m, 7H), 3.73 (s, 1H), 3.58 (br. s., 2H), 3.54 (t, J = 6.5 Hz, 2H), 3.48 (s, 1H), 2.46-2.55 (m, 3H), 2.08-2.17 (m, 1H), 1.80-1.88 (m, 2H), 1.65-1.74 (m, 2H), 1.53-1.61 (m, 2H), 1.46 (s, 1H), 1.26 (br. s., 6H), 1.22 (s, 6H), 0.95 (s, 9H). LC-MS (ES^+): *m/z* 955.42 [MH^+]
152		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{[5-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)pentyl]oxy}acetamido)butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.72 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.6 Hz, 1H), 7.52 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 3H), 7.20 (d, J = 8.6 Hz, 1H), 6.97 (d, J = 2.7 Hz, 1H), 6.92 (d, J = 8.6 Hz, 2H), 6.81 (dd, J = 2.3, 8.6 Hz, 1H), 6.20 (d, J = 7.8 Hz, 1H), 4.70 (t, J = 7.8 Hz, 1H), 4.48-4.56 (m, 3H), 4.34 (dd, J = 5.3, 15.1 Hz, 1H), 4.12-4.16 (m, 1H), 4.04-4.09 (m, 2H), 4.01 (t, J = 6.3 Hz, 2H), 3.85-3.97 (m, 2H), 3.63 (dd, J = 3.3, 11.2 Hz, 1H), 3.53 (t, J = 6.5 Hz, 2H), 2.49 (ddd, J = 4.7, 8.0, 13.1 Hz, 2H), 2.41 (s, 3H), 2.12 (dd, J = 8.2, 13.3 Hz, 1H), 1.80-1.86 (m, 2H), 1.65-1.72 (m, 2H), 1.53-1.60 (m, 2H), 1.26-1.28 (m, 6H), 1.22 (s, 6H), 0.96 (s, 9H). LC-MS (ES^+): *m/z* 940.44 [MH^+],

153		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{[5-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)pentyl]oxy}acetamido)butanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.72 (d, J = 9.0 Hz, 2H), 7.54-7.57 (m, 2H), 7.34 (s, 3H), 7.21 (d, J = 8.6 Hz, 1H), 6.96 (d, J = 2.3 Hz, 1H), 6.92 (d, J = 9.0 Hz, 2H), 6.81 (dd, J = 2.5, 8.8 Hz, 1H), 6.21 (d, J = 7.8 Hz, 1H), 4.69 (t, J = 8.0 Hz, 1H), 4.48-4.55 (m, 3H), 4.32 (dd, J = 5.3, 15.1 Hz, 1H), 4.15 (d, J = 7.8 Hz, 1H), 3.98-4.08 (m, 4H), 3.84-3.97 (m, 2H), 3.63 (dd, J = 3.5, 11.3 Hz, 1H), 3.53 (t, J = 6.3 Hz, 2H), 2.40-2.57 (m, 4H), 2.11 (dd, J = 8.0, 13.5 Hz, 1H), 1.79-1.88 (m, 2H), 1.64-1.73 (m, 2H), 1.51-1.60 (m, 2H), 1.27 (s, 6H), 1.22 (s, 6H), 0.96 (s, 9H). LC-MS (ES^+): *m/z* 926.42 [MH^+]
154		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{[5-(4-{[trans--3-[4-cyano-3-(trifluoromethyl)phenoxy]-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)pentyl]oxy}acetamido)butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.10 (s, 1 H),7.90-7.83 (m, 1 H), 7.80-7.71 (m, 2 H), 7.60-7.52 (m, 2 H), 7.49-7.541 (m, 2 H), 7.32 (s, 1 H), 7.23-7.19 (m, 1 H), 7.00-6.89 (m, 2 H), 4.67 (s, 1 H), 4.60-4.40 (m, 3 H), 4.35-4.25 (m, 2 H), 4.15-4.10 (m, 1 H), 1.09-3.98 (m, 2 H), 3.97-3.90 (m, 2 H), 3.85-3.70 (m, 2 H), 3.63-3.49 (m, 2 H), 2.40 (s, 3 H), 2.25-2.10 (m, 1 H), 2.09-2.00 (m, 1 H), 1.89-1.79 (m, 2 H),1.80-1.45(m, 4H), 1.33-1.14 (m, 12 H), 1.01 (s, 9 H); LC-MS (ES^+): *m/z*, 973.35 [MH^+]
155		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{[5-(4-{[trans-3-[4-cyano-3-(trifluoromethyl)phenoxy]-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)pentyl]oxy}acetamido)butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.84 (s, 1 H), 7.90-7.84 (m, 1 H), 7.80-7.70 (m, 2 H), 7.45-7.32 (m, 4 H), 7.26-7.22 (m, 1 H), 7.28-7.20 (m, 1 H), 7.00-6.89 (m, 2 H), 4.67 (s, 1 H),4.60-4.50 (m, 1 H), 4.46-4.40 (m, 1 H), 4.27-4.20 (m, 2 H), 4.13 (s, 1 H), 4.15-4.00 (m, 2 H), 3.99-3.95 (m, 2 H), 3.90-3.80 (m, 2 H), 3.59-3.51 (m, 2 H), 2.40 (s, 3 H), 2.25-2.10 (m, 1 H),2.11-2.00 (m, 1 H), 1.85-1.75 (m, 2 H), 1.70-1.50 (m, 4 H), 1.33-1.14 (m, 12 H), 1.01 (s, 9 H); LC-MS (ES^+): *m/z*, 989.30 [MH^+]
156		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{[5-(4-{[trans--3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)pentyl]oxy}acetamido)butanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-oxazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.14 (s, 1 H),7.85-7.80 (m, 2 H), 7.78-7.72 (m, 1 H), 7.65-7.55 (m, 2 H), 7.47-7.40 (m, 2 H), 7.15-7.10 (m, 1 H), 7.15-6.95 (m, 3 H), 5.03-4.94 (m, 1 H), 4.67 (s, 1 H),4.60-4.50 (m, 1 H), 4.46-4.40 (m, 1 H), 4.27-4.25 (m, 1 H), 4.15-4.00 (m, 3 H), 3.99-3.95 (m, 2 H), 3.90-3.80 (m, 1 H), 3.79-3.80 (m, 1 H), 3.63-3.49 (m, 2 H), 2.40 (s, 3 H), 2.25-2.10 (m, 1 H), 2.09-1.80 (m, 3 H), 1.79-1.50 (m, 4 H), 1.48-1.46 (m, 3 H), 1.33-1.14 (m, 12 H), 1.01 (s, 9 H); LC-MS (ES^+): *m/z*, 953.35 [MH^+]

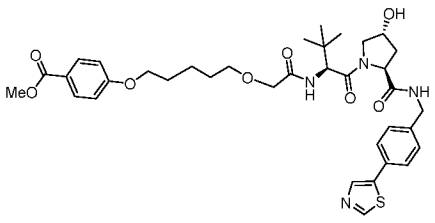
157		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{[5-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)pentyl]oxy}acetamido)butanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.90 (s, 1 H), 7.85-7.00 (m, 3 H), 7.50-7.39 (m, 4 H), 7.15-7.10 (s, 1 H), 7.05-6.95 (m, 3 H), 5.05-4.98 (m, 1 H),4.70 (s, 1 H), 4.65-4.52 (m, 1 H), 4.48-4.40 (m, 1 H), 4.30 (s, 1 H), 4.15-4.10 (m, 3 H), 4.00 (m, 2 H), 4.02-3.70(m, 2 H),3.70-3.58 (m, 2 H), 2.50 (m, 3 H), 2.45-2.35 (m, 1 H), 2.28-2.15 (m, 1 H),2.08-1.82 (m, 4 H),1.80-1.45 (m, 7 H), 1.39-1.20 (m, 12 H),1.10-1.00 (m, 9 H); LC-MS (ES$^+$): *m/z* 969.50 [MH$^+$]
158, 159	 	(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{[(2R)-6-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)hexan-2-yl]oxy}acetamido)butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{[(2S)-6-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)hexan-2-yl]oxy}acetamido)butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide
160, 161	 	(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{[(5S)-5-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)hexyl]oxy}acetamido)butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{[(5R)-5-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)hexyl]oxy}acetamido)butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.88 (s, 1H), 7.75-7.67 (m, 3 H), 7.44-7.36 (m, 4 H), 7.09 (s, 1 H), 6.96-6.91 (m, 3 H), 4.84 (s, 1 H), 4.66-4.47 (m, 4 H), 4.36-4.31 (m, 1 H), 4.26 (s, 1 H), 4.24 (s, 1 H), 4.10 (s, 1 H), 3.93-3.91 (m, 2 H), 3.83-5.78 (m, 2 H), 3.55-3.51 (m, 2 H), 2.43 (s, 3 H), 2.12-2.10 (m, 1 H), 2.09-1.95 (m, 1 H), 1.67-1.62 (m, 6 H), 1.30-1.28 (m, 9 H), 1.18 (s, 6 H), 1.00 (s, 9 H); LC-MS (ES$^+$): *m/z* 969.10 [MH$^+$] ^{1}H NMR (300 MHz, CD_3OD): δ 8.88 (s, 1H), 7.75-7.67 (m, 3 H), 7.44-7.36 (m, 4 H), 7.10 (s, 1 H), 6.96-6.91 (m, 3 H), 4.66 (s, 1 H), 4.58-4.48 (m, 4 H), 4.35-4.03 (m, 1 H), 4.24 (s, 1 H), 4.10 (s, 1 H), 3.92-3.86 (m, 2 H), 3.83-5.55 (m, 2 H), 3.53-3.51 (m,

		2 H), 2.43 (s, 3 H), 2.20-2.10 (m, 1 H), 2.09-2.01 (m, 1 H), 1.67-1.62 (m, 6 H), 1.30 (s, 9 H), 1.19 (s, 6 H),1.00 (s, 9 H); LC-MS (ES^+): *m/z* 969.15 [MH^+]

[0721] Synthesis of example 150:



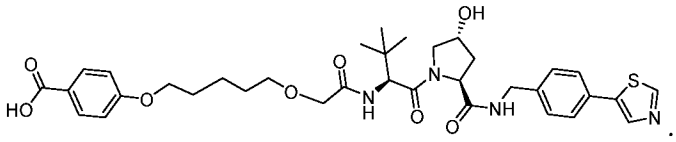
[0722] Step 1: Synthesis of methyl 4-{[5-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)pentyl]oxy}benzoate:



[0723] To a stirred solution of 2-({5-[4-(methoxycarbonyl)phenoxy]pentyl}oxy)acetic acid (200 mg), (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide hydrogen chloride salt (149 mg, 0.32 mmol), N-ethyl-N-isopropylpropan-2-amine (185 mg, 1.44 mmol) in anhydrous N,N-dimethylformamide (5

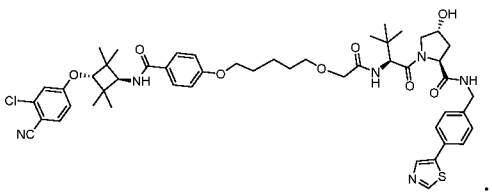
mL) was added HATU (2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (203 mg, 0.54 mmol) at 0 °C. The resulting mixture was allowed to warm up to rt and stirred at rt for 20 min. TLC and LC-MS showed formation of the desired product. The mixture was partitioned between ethyl acetate (100 mL) and water (50 mL). The organic layer was collected, washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluent 2% methanol in methylene dichloride) to afford the titled product (yield 25%, 2 steps) as a white solid. Mass: (ES^+): m/z 695.30 [$M+H^+$].

[0724] Step 2: Synthesis of 4-{[5-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)pentyl]oxy}benzoic acid:



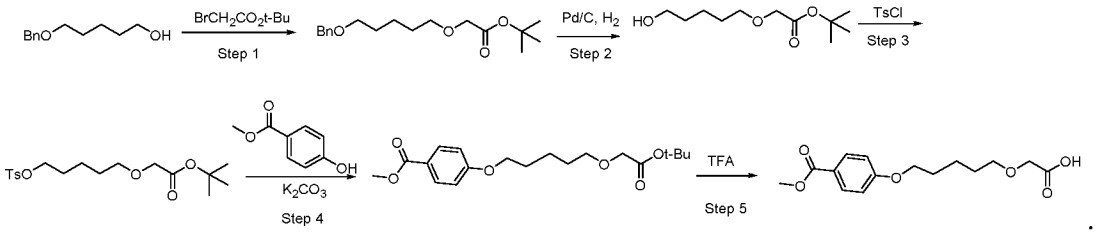
[0725] To a stirred solution of methyl 4-{[5-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)pentyl]oxy}benzoate (150 mg, 0.22 mmol) in a mixed solvents of tetrahydrofuran (4 mL)-water (2 mL)-methanol (1 ml) was added lithium hydroxide monohydrate (36 mg, 0.86 mmol) at rt. The resulting mixture was stirred at 35°C overnight. TLC and LC-MS showed formation of the desired product. The reaction mixture was acidified with aqueous HCl (3N) to pH =3-4 and extracted with methylene dichloride (50 mL × 2). The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated to afford the titled product (110 mg, crude) as a white solid which was used for next step without further purification. Mass: (ES^+): m/z 681.20 [$M+H^+$].

[0726] Step 3: Synthesis of exmaple 150:

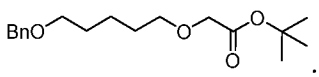


[0727] To a stirred mixture of 4-{[5-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)pentyl]oxy}benzoic acid (110 mg, 0.16 mmol), 2-chloro-4-[trans-3-amino-2,2,4,4-tetramethylcyclobutoxy]benzonitrile hydrogen chloride salt (50 mg, 0.16 mmol), N-ethyl-N-isopropylpropan-2-amine (77 mg, 0.64 mmol) in anhydrous N,N-dimethylformamide (4 mL) was added HATU ((2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate)) (68 mg, 0.18 mmol) at 0 °C. The resulting mixture was allowed to warm up to rt and stirred at rt for 20 min. TLC and LC-MS showed formation of the desired product. The reaction mixture was partitioned between ethyl acetate (100 mL) and water (40 mL). The organic phase was separated, washed with brine (50mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by preparative TLC (eluent: 5% methanol in methylene dichloride) to afford the titled product (yield 25%, 2 steps) as a white solid.

[0728] Synthesis of 2-({5-[4-(methoxycarbonyl)phenoxy]pentyl}oxy)acetic acid



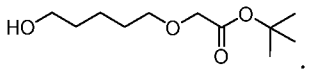
[0729] Step 1: Synthesis of tert-butyl 2-{[5-(benzyloxy)pentyl]oxy}acetate:



[0730] To a stirred mixture of 5-(benzyloxy)pentan-1-ol (10 g, 51.5 mmol), tert-butyl 2-bromoacetate (40.2 g, 206 mmol) and tetrabutyl ammonium chloride (14.2 g, 51.5 mmol) in methylene dichloride (60 mL) was added sodium hydroxide (40 ml, 35% in water) at rt, and the resulting mixture was stirred at rt for 16 h. The reaction mixture was then partitioned between methylene dichloride (200 mL) and water (100 mL). The organic layer was collected and washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluent: 5% ethyl acetate in hexane) to afford tert-butyl 2-{[5-(benzyloxy)pentyl]oxy}acetate (yield

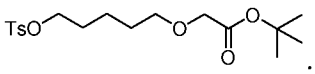
31.6%) as light yellow oil. LC-MS: (ES^+): m/z 331.10 [$M+Na^+$], ^1H NMR (400 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.63-1.67 (m, 6H), 3.46-3.53 (m, 4H), 4.10 (s, 2H), 4.50 (s, 2H), 7.28-7.34 (m, 5H).

[0731] Step 2: Synthesis of tert-butyl 2-[(5-hydroxypentyl)oxy]acetate:



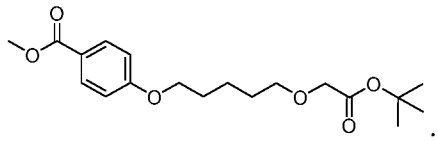
[0732] To a stirred solution of tert-butyl 2-{[5-(benzyloxy)pentyl]oxy}acetate (5 g, 16.2 mmol) in ethanol (100 ml) under a nitrogen atmosphere was added palladium on carbon (10%, 600 mg) at rt. The resulting mixture was stirred at 50°C overnight under hydrogen atmosphere (hydrogen balloon). TLC showed formation of desired product. Palladium on carbon was removed through filtration and washed with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure to afford tert-butyl 2-[(5-hydroxypentyl)oxy]acetate (2.5 g, crude) as colorless oil which was used in next step without further purification.

[0733] Step 3: Synthesis of tert-butyl 2-({5-[(4-methylbenzenesulfonyl)oxy]pentyl}oxy)acetate:

[0734] 

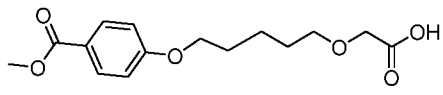
[0735] To a stirred solution of tert-butyl 2-[(5-hydroxypentyl)oxy]acetate (2.5 g, crude) and triethylamine (3.5 g, 34.5 mmol) in anhydrous methylene dichloride (50 mL) was added a solution of 4-toluenesulfonyl chloride (2.7 g, 13.8 mmol) in anhydrous methylene dichloride (8 mL) drop wise at 0 °C. The reaction mixture was allowed to warm up to rt and stirred at rt overnight. TLC showed formation of desired product. The mixture was quenched with aqueous solution of potassium carbonate (1N, 50 mL) at rt and extracted with ethyl acetate (50 mL × 3). The organic layers were combined, washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluent: 1% methanol in methylene dichloride) to afford tert-butyl 2-({5-[(4-methylbenzenesulfonyl)oxy]pentyl}oxy)acetate (yield 35.1%) as colorless oil. Mass: (ES^+): m/z 395.10 [MNa^+].

[0736] Step 4: Synthesis of methyl 4-({5-[2-(tert-butoxy)-2-oxoethoxy]pentyl}oxy)benzoate:

[0737]  .

[0738] To a stirred mixture of tert-butyl 2-({5-[(4-methylbenzenesulfonyl)oxy]pentyl}oxy)acetate (1.0g, 2.7 mmol) and potassium carbonate (266 mg, 1.6 mmol) in acetonitrile (15 mL) was added methyl 4-hydroxybenzoate (500 mg, 3.29 mmol) at rt. The resulting mixture was refluxed overnight. TLC showed formation of desired product. The reaction mixture was cooled to rt, and partitioned between ethyl acetate (150 mL) and water (50 mL). The organic layer was washed with washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluent 10% ethyl acetate in hexane) to afford methyl 4-({5-[2-(tert-butoxy)-2-oxoethoxy]pentyl}oxy)benzoate (yield 33%) as colorless oil. Mass (ES^+): m/z 353.10 [$M+Na^+$]; ^1H NMR (400 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.55-1.61 (m, 2H), 1.68-1.72 (m, 2H), 1.80-1.87 (m, 2H), 3.55 (t, J = 6.4 Hz, 2H), 3.88 (s, 3H), 3.96 (s, 2H), 4.02 (t, J = 6.4 Hz, 2H), 6.89 (d, J = 9.2 Hz, 2H), 7.97 (d, J = 9.2 Hz, 2H).

[0739] Step 5: Synthesis of 2-({5-[4-(methoxycarbonyl)phenoxy]pentyl}oxy)acetic acid:

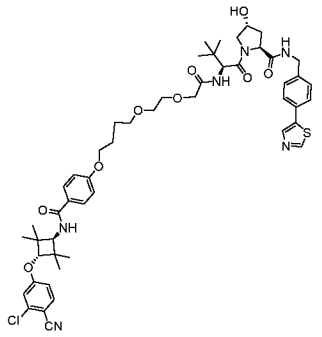
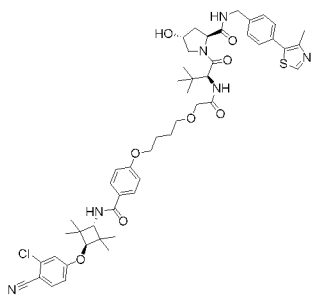
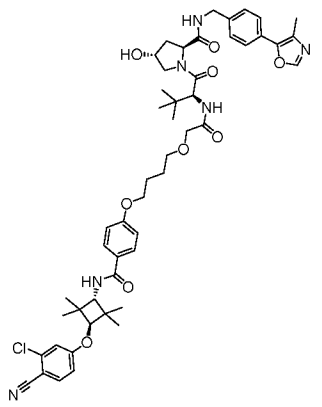
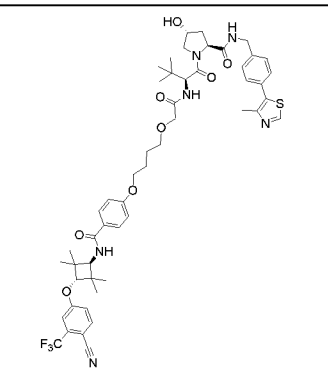
[0740]  .

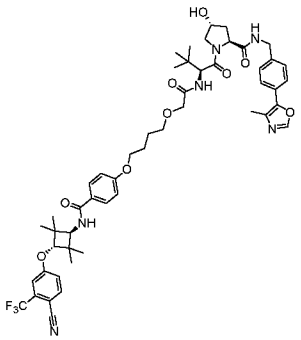
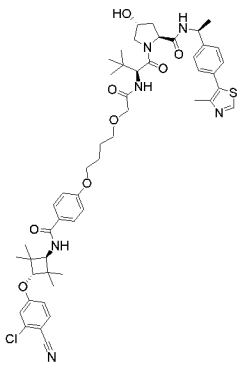
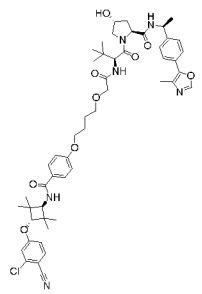
[0741] To a stirred solution of methyl 4-({5-[2-(tert-butoxy)-2-oxoethoxy]pentyl}oxy)benzoate (300 mg, 0.85 mmol) in DCM (4 mL) was added and TFA (2 ml) at rt, the resulting solution was stirred at room temperature for 1 h. TLC showed formation of the desired product. The solvent was evaporated to afford 2-({5-[4-(methoxycarbonyl)phenoxy]pentyl}oxy)acetic acid (200 mg, crude) as yellow oil which was used in next step without further purification.

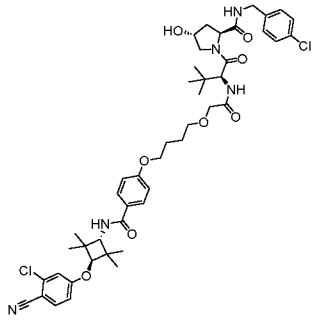
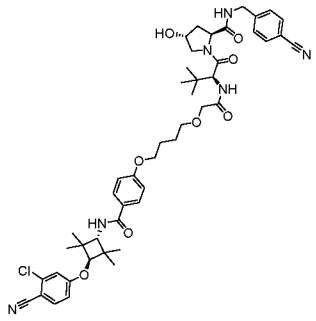
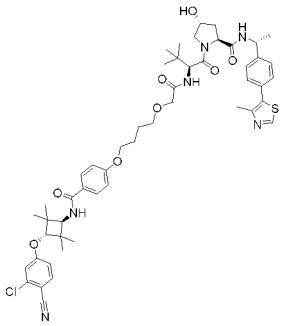
[0742] Examples 151-157 were synthesized according to similar procedure described for synthesis of example 150, by using corresponding starting materials and intermediates.

[0743] **Table 9. Exemplary Compounds.**

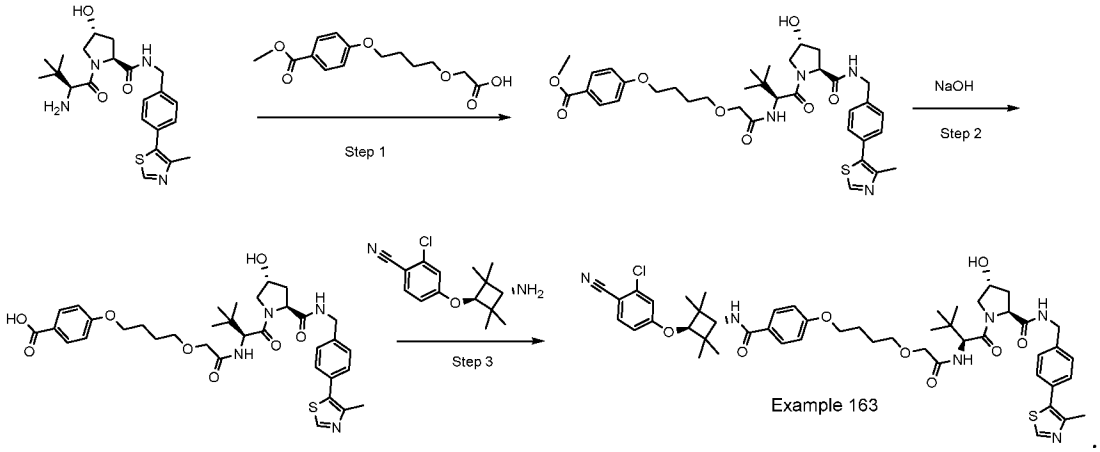
Ex #	Structure	Compound name and Analytical data

162		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{2-[4-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)butoxy]ethoxy}acetamido)butanoyl]-4-hydroxy-N-{[4-(1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (s, 9H), 1.22 (s, 6H), 1.27 (s, 6H), 1.74-1.80 (m, 4H), 2.09-2.14 (m, 1H), 2.53-2.60 (m, 1H), 3.54-3.69 (m, 8H), 3.99-4.05 (m, 5H), 4.12-4.16 (m, 2H), 4.28-4.33 (m, 1H), 4.46-4.58 (m, 3H), 4.72 (t, J = 8.0 Hz, 1H), 6.20 (d, J = 8.0Hz, 1H), 6.79-6.97 (m, 4H), 7.26-7.33 (m, 3H), 7.49 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 8.03 (s, 1H), 8.78 (s, 1H). LC-MS: (ES$^+$): m/z 971.20 [M+H$^+$]
163		(2S,4R)-1-[(2S)-3,3-dimethyl-2-{2-[4-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)butoxy]acetamido}butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.85 (s, 1 H), 7.75 - 7.81 (m, 2 H), 7.72 (d, *J* = 9.00 Hz, 1 H), 7.44 - 7.50 (m, 2 H), 7.38 - 7.43 (m, 2 H), 7.13 (d, *J* = 2.35 Hz, 1 H), 6.94 - 7.02 (m, 3 H), 4.70 (s, 1 H), 4.54 - 4.61 (m, 2 H), 4.48 - 4.54 (m, 2 H), 4.36 (d, *J* = 15.65 Hz, 1 H), 4.28 (s, 1 H), 4.14 (s, 1 H), 4.10 (t, *J* = 6.06 Hz, 2 H), 4.01 (d, *J* = 7.43 Hz, 2 H), 3.85 - 3.90 (m, 1 H), 3.77 - 3.84 (m, 1 H), 3.64 (t, *J* = 6.26 Hz, 2 H), 2.45 (s, 3 H), 2.24 (dd, *J* = 13.30, 7.43 Hz, 1 H), 2.09 (ddd, *J* = 13.21, 9.10, 4.30 Hz, 1 H), 1.89 - 1.98 (m, 2 H), 1.80 - 1.88 (m, 2 H), 1.28 (s, 6 H), 1.22 (s, 6 H), 0.99 - 1.06 (m, 9 H); LC-MS (ES$^+$): *m/z* 941.41 [MH$^+$]
164		(2S,4R)-1-[(2S)-3,3-dimethyl-2-{2-[4-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)butoxy]acetamido}butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.12 (s, 1 H), 7.75 - 7.81 (m, 2 H), 7.72 (d, *J* = 9.00 Hz, 1 H), 7.56 - 7.64 (m, 2 H), 7.47 (d, *J* = 8.61 Hz, 2 H), 7.13 (d, *J* = 2.35 Hz, 1 H), 6.95 - 7.03 (m, 3 H), 4.70 (s, 1 H), 4.56 - 4.61 (m, 1 H), 4.55 (s, 1 H), 4.46 - 4.53 (m, 2 H), 4.35 (d, *J* = 15.65 Hz, 1 H), 4.28 (s, 1 H), 4.12 - 4.15 (m, 1 H), 4.06 - 4.12 (m, 2 H), 3.98 - 4.03 (m, 2 H), 3.85 - 3.92 (m, 1 H), 3.78 - 3.84 (m, 1 H), 3.65 (t, *J* = 6.06 Hz, 2 H), 2.38 (s, 3 H), 2.19 - 2.28 (m, 1 H), 2.08 (ddd, *J* = 13.30, 9.19, 4.50 Hz, 1 H), 1.91 - 1.98 (m, 2 H), 1.82 - 1.89 (m, 2 H), 1.28 (s, 6 H), 1.22 (s, 6 H), 1.04 (s, 9 H); LC-MS (ES$^+$): *m/z* 925.43 [MH$^+$]
165		(2S,4R)-1-[(2S)-3,3-dimethyl-2-{2-[4-(4-{[trans-3-[4-cyano-3-(trifluoromethyl)phenoxy]-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)butoxy]acetamido}butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.88 (s, 1H), 7.75-7.67 (m, 3 H), 7.44-7.36 (m, 4 H), 7.09 (s, 1 H), 6.96-6.91 (m, 3 H), 4.84 (s, 1 H), 4.66-4.47 (m, 4 H), 4.36-4.31 (m, 1 H), 4.26 (s, 1 H), 4.24 (s, 1 H), 4.10 (s, 1 H), 3.93-3.91 (m, 2 H), 3.83-5.78 (m, 2 H), 3.55-3.51 (m, 2 H), 2.43 (s, 3 H), 2.12-2.10 (m, 1 H), 2.09-1.95 (m, 1 H), 1.67-1.62 (m, 6 H), 1.30-1.28 (m, 9 H), 1.18 (s, 6 H), 1.00 (s, 9 H); LC-MS (ES$^+$): *m/z* 969.10

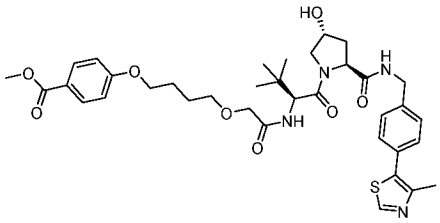
		[MH+]
166		(2S,4R)-1-[(2S)-3,3-dimethyl-2-{2-[4-(4-{[trans-3-[4-cyano-3-(trifluoromethyl)phenoxy]-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)butoxy]acetamido}butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD):8.09 (s, 1H),7.89 (d, 1 H), 7.80-7.70 (m, 2 H), 7.69-7.50 (m, 2 H), 7.49-7.40 (m, 2 H),7.32 (s, 1 H), 7.28-7.08 (m, 1 H), 7.00-6.82 (m, 2 H), 4.72 (s, 1 H), 4.60-4.40 (m, 3 H), 4.39-4.20 (m, 2 H), 4.19-4.00 (m, 3 H), 3.99-3.95 (m, 2 H),3.92-3.70 (m, 2 H),3.69-3.53 (m, 2 H), 2.40-2.32 (m, 3 H), 2.30-2.18 (m, 1 H),2.15-2.01 (m, 1 H), 2.00-1.60 (m, 4 H),1.35-1.28 (m, 6 H),1.25-1.15 (m, 6 H),1.03-1.00(m, 9 H); LC-MS (ES+): *m/z* 959.60 [MH+].
167		(2S,4R)-1-[(2S)-3,3-dimethyl-2-{2-[4-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)butoxy]acetamido}butanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): 8.82 (s, 1H),7.81-7.75 (m,2 H), 7.74-7.62 (s, 1 H), 7.61-7.53 (m, 2 H), 7.49-7.35 (m, 2 H), 7.19-7.10 (s, 1 H), 7.08-6.80 (m, 3 H), 5.08-4.91 (m, 1 H), 4.65 (s, 1 H), 4.60-4.59 (m, 1 H), 4.45-4.36 (m, 1 H),4.22 (s, 1 H), 4.11-4.05 (m, 3 H),4.01-3.96 (m, 2 H), 3.95-3.70 (m, 2 H), 3.69-3.45 (m, 2 H), 2.40-2.35 (m, 3 H), 2.21-2.04 (s, 1 H),2.00-1.70 (m, 4 H),1.60-1.40 (m, 3 H), 1.21-1.12 (m, 12 H), 1.00-0.95(m, 9 H); LC-MS (ES+): *m/z* 478.45 [(M/2)H+]
168		(2S,4R)-1-[(2S)-3,3-dimethyl-2-{2-[4-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)butoxy]acetamido}butanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-oxazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): 8.82 (s, 1H),7.81-7.75 (m,2 H), 7.74-7.62 (s, 1 H), 7.61-7.53 (m, 2 H), 7.49-7.35 (m, 2 H), 7.19-7.10 (s, 1 H), 7.08-6.80 (m, 3 H), 5.08-4.91 (m, 1 H), 4.65 (s, 1 H), 4.60-4.59 (m, 1 H), 4.45-4.36 (m, 1 H),4.22 (s, 1 H), 4.11-4.05 (m, 3 H),4.01-3.96 (m, 2 H), 3.95-3.70 (m, 2 H), 3.69-3.45 (m, 2 H), 2.40-2.35 (m, 3 H), 2.21-2.04 (s, 1 H),2.00-1.70 (m, 4 H),1.60-1.40 (m, 3 H), 1.21-1.12 (m, 12 H), 1.00-0.95(m, 9 H); LC-MS (ES+): *m/z* 478.45 [MH+]

169		(2S,4R)-N-[(4-chlorophenyl)methyl]-1-[(2S)-3,3-dimethyl-2-{2-[4-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)butoxy]acetamido}butanoyl]-4-hydroxypyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.80 (d, *J* = 8.61 Hz, 2 H), 7.72 (d, *J* = 9.00 Hz, 1 H), 7.24 - 7.37 (m, 4 H), 7.13 (d, *J* = 2.35 Hz, 1 H), 6.94 - 7.04 (m, 3 H), 4.69 (s, 1 H), 4.54 (dd, *J* = 8.80, 7.63 Hz, 1 H), 4.43 - 4.51 (m, 2 H), 4.24 - 4.32 (m, 2 H), 4.08 - 4.16 (m, 3 H), 3.95 - 4.06 (m, 2 H), 3.84 - 3.90 (m, 1 H), 3.76 - 3.83 (m, 1 H), 3.65 (t, *J* = 6.26 Hz, 2 H), 2.21 (dd, *J* = 13.11, 7.63 Hz, 1 H), 2.06 (ddd, *J* = 13.30, 9.19, 4.50 Hz, 1 H), 1.90 - 1.98 (m, 2 H), 1.80 - 1.89 (m, 2 H), 1.28 (s, 6 H), 1.22 (s, 6 H), 0.95 - 1.15 (m, 9 H); LC-MS (ES^+): *m/z* 878.28[MH^+]
170		(2S,4R)-N-[(4-cyanophenyl)methyl]-1-[(2S)-3,3-dimethyl-2-{2-[4-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)butoxy]acetamido}butanoyl]-4-hydroxypyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.80 (d, *J* = 8.61 Hz, 2 H), 7.72 (d, *J* = 8.61 Hz, 1 H), 7.64 (d, *J* = 8.22 Hz, 2 H), 7.54 (d, *J* = 8.22 Hz, 2 H), 7.13 (d, *J* = 2.35 Hz, 1 H), 6.94 - 7.05 (m, 3 H), 4.69 (s, 1 H), 4.49 - 4.62 (m, 4 H), 4.34 (d, *J* = 16.04 Hz, 1 H), 4.29 (s, 1 H), 4.08 - 4.17 (m, 3 H), 3.95 - 4.06 (m, 2 H), 3.85 - 3.91 (m, 1 H), 3.80 (dd, *J* = 11.15, 3.72 Hz, 1 H), 3.65 (t, *J* = 6.06 Hz, 2 H), 2.23 (dd, *J* = 13.11, 7.63 Hz, 1 H), 2.06 (ddd, *J* = 13.11, 9.19, 4.30 Hz, 1 H), 1.90 - 1.99 (m, 2 H), 1.81 - 1.90 (m, 2 H), 1.28 (s, 6 H), 1.22 (s, 6 H), 0.92 - 1.18 (m, 9 H); LC-MS (ES^+): *m/z* 869.32 [MH^+]
171		(2S,4R)-1-[(2S)-3,3-dimethyl-2-{2-[4-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)butoxy]acetamido}butanoyl]-4-hydroxy-N-[(1R)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.85(s, 1H), 7.79 (m, 3H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.42(d, *J* = 8.0 Hz, 2H), 7.15 (s, 1H), 7.01 (m, 3H), 5.00 (m, 1H), 4.69 (m, 2H), 4.53 (s, 1H), 4.30 (s, 1H), 4.16 (s, 1H), 4.13 (m, 2H), 4.01 (s, 2H), 3.91-3.85 (m, 1H), 3.85-3.78 (m, 1H),3.65 (m, 2H), 2.46 (s, 3H), 2.30-2.19 (m, 1H), 2.18-2.05 (m, 1H),1.99-1.92 (m, 2H), 1.89-1.82 (m, 2H),1.53 (m, 3H), 1.30 (s, 6H), 1.24 (s, 6H), 0.92 (s, 9H); Mass (ES^+): *m/z* 955.45 [MH^+]

[0744] Synthesis of example 163:

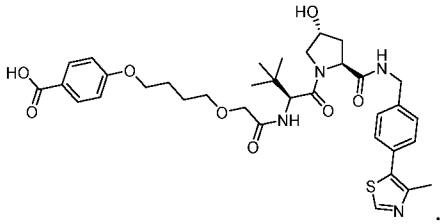


[0745] Step 1: synthesis of methyl 4-[4-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)butoxy]benzoate



[0746] To a stirred solution of 2-{4-[4-(methoxycarbonyl)phenoxy]butoxy}acetic acid (22.0 mg, 77.9 µmol) and (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide hydrochloride (36.3 mg, 77.9 µmol) in methylene chloride (2.0 mL) was added O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate (25.0 mg, 77.9 µmol) and diisopropylethylamine (40.5 µL, 233 µmol) at rt. The reaction mixture was stirred at rt for 30 minutes, LC-MS indicated formation of the desired product. The reaction mixture was concentrated under reduced pressure. The crude material was purified by flash silica gel chromatography on a Teledyne Combiflash ISCO (gradient eluent: Heptane/Acetone (v:v = 100:0 to 0:100)) to give the titled product (yield: 78%) as a white solid. LC-MS (ES^+): *m/z* 695.3138 [MH^+].

[0747] Step 2: Synthesis of 4-[4-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)butoxy]benzoic acid:

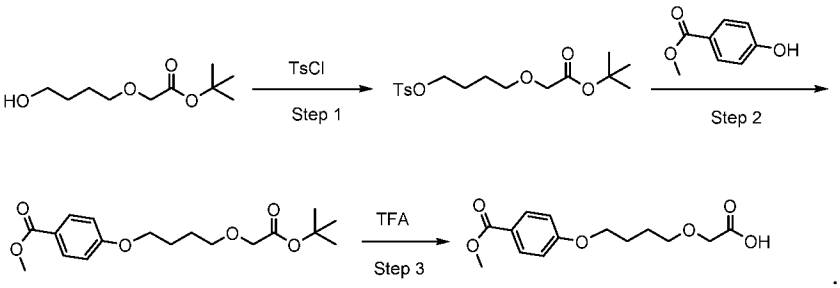


[0748] To a stirred solution of methyl 4-[4-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)butoxy]benzoate (42.4 mg, 61.0 µmol) in methanol (2.0 mL) was added 1 M NaOH in water (0.5 mL, 12.5 mmol) at rt. The reaction mixture was stirred at rt for 16 hours. LC-MS indicated formation of the desired product. The reaction mixture was quenched with 1.0 M aqueous HCl and then concentrated under reduced pressure to remove the methanol. The aqueous residue was extracted with EtOAc (15 mL x 2). The organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the titled product (yield: 82%) as a white solid. The material was used in next step without any further purification. Mass (ES^+): *m/z* 681.2986 [MH^+].

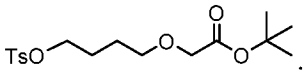
[0749] Step 3: Synthesis of example 163:

[0750] To a stirred solution of 2-chloro-4-[trans-3-amino-2,2,4,4-tetramethylcyclobutoxy]benzonitrile (13.9 mg, 50.2 µmol) and 4-[4-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)butoxy]benzoic acid (34.2 mg, 50.2 µmol) in methylene chloride (2.0 mL) was added O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (16.1 mg, 50.2 µmol) and diisopropylethylamine (26.0 µL, 150 µmol) at rt. The reaction mixture was stirred at rt for 1.5 hours. LC-MS indicated formation of the desired product. The reaction mixture was quenched with water (5 mL) and extracted with DCM (15 mL x 3). The organic layers were combined, washed with aqueous $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude material, which was purified by flash silica gel chromatography on a Teledyne Combiflash ISCO (eluent: DCM/MeOH (v:v = 90:10)) to give the titled product (yield: 39%) as an off white solid.

[0751] Synthesis of 2-{4-[4-(methoxycarbonyl)phenoxy]butoxy}acetic acid:



[0752] Step 1: synthesis of tert-butyl 2-{4-[(4-methylbenzenesulfonyl)oxy]butoxy}acetate:



[0753] This material was synthesized from tert-butyl 2-(4-hydroxybutoxy)acetate and 4-toluenesulfonyl chloride according to similar procedures described above for the synthesis of tert-butyl 2-({5-[(4-methylbenzenesulfonyl)oxy]pentyl}oxy)acetate.

[0754] Step 2: synthesis of methyl 4-{4-[2-(tert-butoxy)-2-oxoethoxy]butoxy}benzoate.

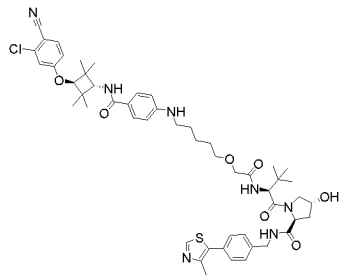
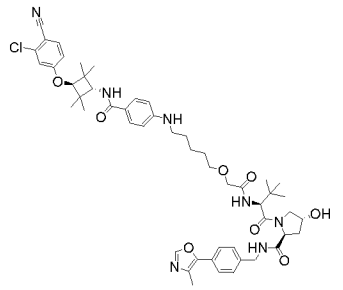
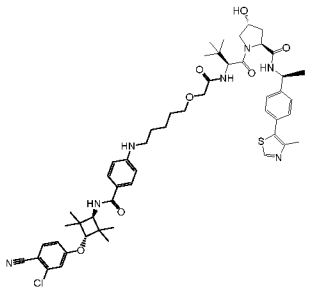
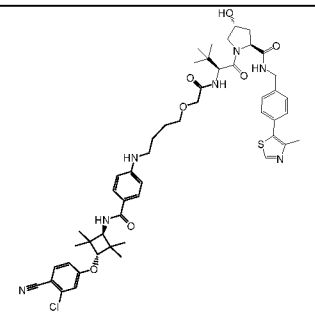
[0755] To a stirred mixture of methyl 4-hydroxybenzoate (27.99 mg, 184.0 µmol) and tert-butyl 2-{4-[(4-methylbenzenesulfonyl)oxy]butoxy}acetate in acetonitrile (2.0 mL) was added potassium carbonate (34.67 mg, 250.9 µmol) at rt. The reaction mixture was then stirred at 80 °C for 16 hours. LC-MS indicated formation of the desired product. The reaction mixture was concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel chromatography on a Teledyne Combiflash ISCO (gradient eluent: heptane/acetone (v:v = 100:0 to 50:50)) to give the titled product (yield: 94%) as a clear oil. Mass (ES^+): m/z 361.16 [M+Na].

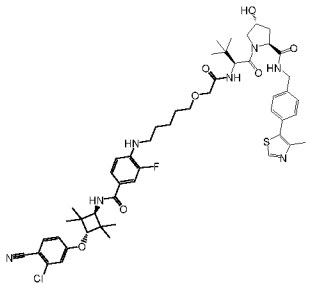
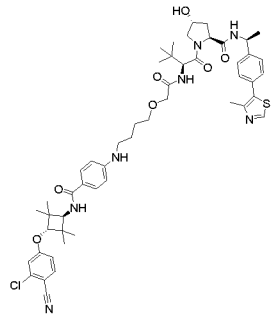
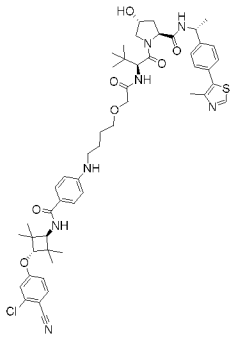
[0756] Step 3: Synthesis of Synthesis of 2-{4-[4-(methoxycarbonyl)phenoxy]butoxy}acetic acid:

[0757] To a stirred solution of methyl 4-{4-[2-(tert-butoxy)-2-oxoethoxy]butoxy}benzoate (53.1 mg, 156 µmol) in dichloromethane (1.0 mL) was added trifluoroacetic acid (1.0 mL, 12.9 mmol) at rt. The reaction mixture was then stirred at rt for 30 minutes. LC-MS indicated formation of the desired product. The reaction mixture was concentrated under reduced pressure to give the titled product (yield: 99% based on crude material) as an off white solid. The crude material was then used in next step without any further purification. Mass (ES^+): *m/z* 305.10.

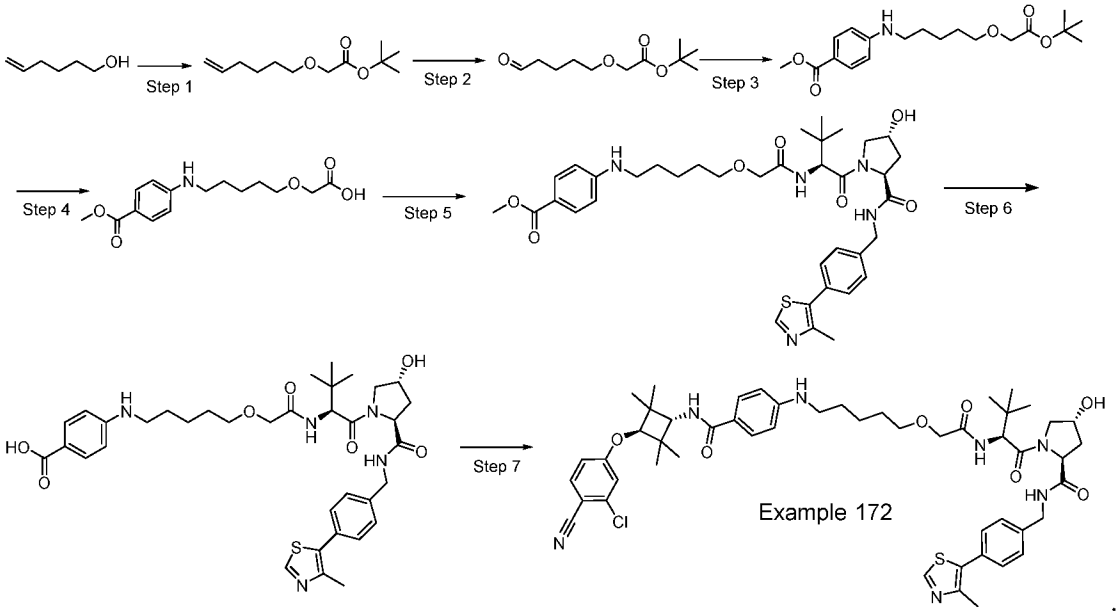
[0758] Examples 162, 164-171 were synthesized according to similar procedure described for synthesis of example 163, by using corresponding starting materials and intermediates.

[0759] Table 10. Exemplary Compounds.

Ex#	Structure	Compound name and Analytical data
172		(2S,4R)-1-[(2S)-3,3-dimethyl-2-[2-({5-[(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenyl)amino]pentyl}oxy)acetamido]butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.63 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.6 Hz, 1H), 7.35 (q, J = 8.5 Hz, 4H), 6.97 (d, J = 2.3 Hz, 1H), 6.81 (dd, J = 2.5, 8.8 Hz, 1H), 6.60 (d, J = 9.0 Hz, 2H), 6.07-6.12 (m, 1H), 4.74 (s, 1H), 4.50-4.59 (m, 3H), 4.37 (d, J = 5.1 Hz, 1H), 4.11-4.17 (m, 2H), 3.64 (dd, J = 3.5, 11.3 Hz, 1H), 3.53 (d, J = 7.0 Hz, 2H), 3.19 (t, J = 7.0 Hz, 2H), 2.55-2.61 (m, 1H), 2.52 (s, 3H), 2.10-2.19 (m, 2H), 1.65-1.71 (m, 4H), 1.50-1.53 (m, 2H), 1.24-1.33 (m, 9H), 1.22 (s, 6H), 0.96 (s, 9H), 0.86-0.91 (m, 3H). LC-MS (ES^+): *m/z* 955.43 [MH^+]
173		(2S,4R)-1-[(2S)-3,3-dimethyl-2-[2-({5-[(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenyl)amino]pentyl}oxy)acetamido]butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.63 (d, J = 8.6 Hz, 2H), 7.53 (d, J = 8.6 Hz, 2H), 7.35 (s, 2H), 7.18-7.21 (m, 1H), 6.97 (d, J = 2.3 Hz, 1H), 6.81 (dd, J = 2.3, 8.6 Hz, 1H), 6.59 (d, J = 8.6 Hz, 2H), 6.08-6.12 (m, 1H), 4.73 (t, J = 8.0 Hz, 1H), 4.49-4.60 (m, 3H), 4.32-4.39 (m, 1H), 4.11-4.17 (m, 2H), 3.63 (dd, J = 3.5, 11.3 Hz, 1H), 3.49-3.57 (m, 2H), 3.18 (t, J = 6.8 Hz, 2H), 2.53-2.61 (m, 1H), 2.42 (s, 3H), 2.08-2.18 (m, 2H), 1.68 (td, J = 7.2, 14.5 Hz, 4H), 1.50-1.53 (m, 2H), 1.26 (d, J = 0.8 Hz, 9H), 1.22 (s, 6H), 0.96 (s, 9H), 0.86-0.91 (m, 3H). LC-MS (ES^+): m/z 939.46 [MH^+]
174		(2S,4R)-1-[(2S)-3,3-dimethyl-2-[2-({5-[(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenyl)amino]pentyl}oxy)acetamido]butanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD):δ8.88 (s, 1 H), 7.80-7.65 (m, 3 H), 7.50-7.33 (m, 4 H), 7.16 (s, 1H), 7.03-6.93 (m, 1 H), 6.54-6.43 (m, 2 H), 5.02 – 4.95 (m, 1 H), 4.67 (s, 1 H), 4.65-4.50 (m, 1 H), 4.46-4.40 (m, 1 H), 4.29-4.25 (m, 1 H), 4.20-4.15 (m, 1 H), 4.04-3.90 (m, 2 H), 3.89-3.85 (m, 1 H), 3.80-3.73 (m, 1 H), 3.66-3.52 (m, 2H), 3.20-3.10 (m, 2 H), 2.40 (s, 3 H), 2.25-1.95 (m, 1 H), 2.02 – 1.90 (m, 1 H), 1.80-1.68 (m, 4 H), 1.65-1.50 (m, 2 H), 1.49-1.43 (m, 2H), 1.30-1.23 (m, 6 H), 1.22-1.15 (m, 6 H), 1.01 (s, 9 H); LC-MS (ES^+): *m/z*, 968.40 [MH^+]
175		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{4-[(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenyl)amino]butoxy}acetamido)butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD):δ8.88 (s, 1 H), 7.750-7.65 (m, 3 H), 7.50-7.33 (m, 4 H), 7.10-7.05 (m, 1H), 6.99-6.90 (m, 1 H), 6.54-6.43 (m, 2 H), 4.67 (s, 1 H), 4.60-4.50 (m, 3 H), 4.48-4.45 (m, 1 H), 4.21 (s, 1 H), 4.13-4.05 (m, 1 H), 3.98-3.90 (m, 2 H), 3.88-3.70 (m, 2 H), 3.66-3.48 (m, 2 H), 3.20-3.03 (m, 2 H), 2.40 (s, 3 H), 2.25-2.12 (m, 1 H), 2.09 – 1.99 (m, 1 H), 1.80-1.68 (m, 4 H), 1.30-1.10 (m, 12 H), 1.01 (s, 9 H); LC-MS

		(ES+): *m/z*, 940.15 [MH+]
176		(2S,4R)-1-[(2S)-2-[2-({5-[(2-fluoro-4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenyl)amino]pentyl}oxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ8.86 (s, 1 H), 7.80-7.70 (m, 1 H), 7.60-7.55 (m, 1 H), 7.50-7.37 (m, 4H), 7.14 (s, 1 H), 7.00-6.93 (m, 1 H), 6.80-6.65 (m, 1 H), 4.70 (s, 1 H), 4.65-4.50 (m, 3 H), 4.40-4.30 (m, 1 H), 4.29-4.25 (m, 1 H), 4.20-4.15 (m, 1 H), 4.04-3.90 (m, 2 H), 3.89-3.85 (m, 1 H), 3.80-3.73 (m, 1 H), 3.70-3.65 (m, 1 H), 3.60-3.52 (m, 2H), 3.30-3.15 (m, 2 H), 2.40 (s, 3 H), 2.25-1.95 (m, 1 H), 2.02 – 1.90 (m, 1 H), 1.80-1.68 (m, 4 H), 1.65-1.50 (m, 2 H), 1.30-1.23 (m, 6 H), 1.22-1.15 (m, 6 H), 1.01 (s, 9 H); LC-MS (ES+): *m/z*, 972.10 [MH+]
177		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{4-[(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenyl)amino]butoxy}acetamido)butanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD3OD) δ 8.86 (s, 1H), 7.72-7.64 (m, 3H), 7.44 (s, 4H), 7.12 (s, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 2H), 5.00 (d, *J* = 6.8 Hz, 1H), 4.69 (s, 1H), 4.62-4.58 (m, 1H), 4.44 (s, 1H), 4.28 (s, 1H), 4.12 (s, 1H), 4.00-3.93 (m, 2H), 3.87-3.75 (m, 2H), 3.65-3.59 (m, 2H),3.21 (s, 2H), 2.47 (s, 3H), 2.27-2.15 (m, 1H), 1.95 (m, 1H), 1.76 (s, 4H), 1.58-1.49 (m, 3H), 1.26 (d, *J* = 9.6 Hz, 12H), 1.02(s, 9H); Mass (ES+): *m/z* 955.20 [MH+]
178		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{4-[(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenyl)amino]butoxy}acetamido)butanoyl]-4-hydroxy-N-[(1R)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO) δ 8.96 (s, 1H), 8.49 (d, *J* = 7.6 Hz, 1H), 7.90 (d, *J* = 8.8 Hz, 1H), 7. 63 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.42-7.21 (m, 4H), 7.20 (s, 1H), 7.00 (d, *J* = 8.8 Hz, 1H), 6.55 (d, *J* = 8.8 Hz, 2H), 6.19 (s, 1H), 5.16 (s, 1H), 4.89 (s, 1H), 4.56-4.47 (m, 2H), 4.36-4.40 (m, 2H), 4.03 (d, *J* = 9.2 Hz, 1H), 3.94 (s, 2H), 3.67-3.57 (m, 2H), 3.56-3.50 (m, 2H),3.07 (s, 2H), 2.44 (s, 3H), 2.08-2.01 (m, 1H), 1.98-1.92 (m, 1H), 1.64 (m, 4H), 1.38 (d, *J* = 6.8 Hz, 3H), 1.20 (s, 6H), 1.11 (s, 6H), 0.91 (s, 9H); Mass (ES+): *m/z* 954.15 [MH+].

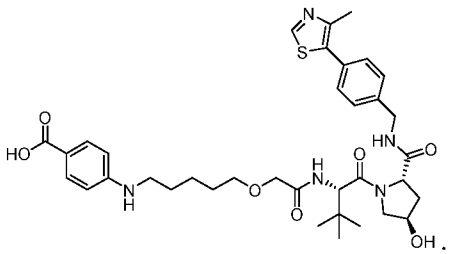
[0760] Synthesis of example 172:



[0761] Step 7: Synthesis of example 172:

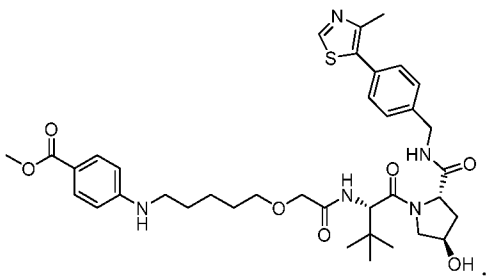
[0762] TBTU (21.5 mg, 0.067 mmol) was added to a solution of 4-{[5-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)pentyl]amino}benzoic acid (31 mg, 0.044 mmol), 2-chloro-4-[trans-3-amino-2,2,4,4-tetramethylcyclobutoxy]benzonitrile (12.4 mg, 0.044 mmol) in DMF (3.0 mL) and DIPEA (15.4 µL, 0.089 mmol) at rt. The resulting reaction mixture was stirred at rt for 1hr. LC-MS indicated formation of the desired product. The reaction mixture was diluted with EtOAc (30 mL), washed with water (15 mL x 2), brine (15 mL x 1), filtered through a Biotage universal phase separator and then concentrated under reduced pressure to give a crude residue, which was purified by silica gel chromatography on a Teledyne Combiflash ISCO system eluting with MeOH/DCM (v/v = 0:100 to 10:90) to yield the desired title product (yield: 41%).

[0763] Step 6: Synthesis of 4-{[5-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)pentyl]amino}benzoic acid:



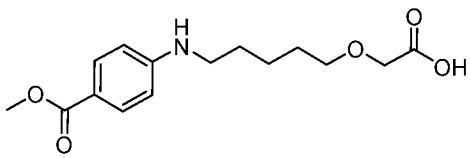
[0764] Lithium hydroxide (9.0 mg, 0.38 mmol) was added to a solution of methyl 4-{[5-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)pentyl]amino}benzoate (96 mg, 0.14 mmol) in a mixed solvent of THF/water/methanol (v/v/v = 1/1/1, 2.00 mL) at rt. The resulting mixture was stirred at rt overnight. Aqueous HCl (1 N) was added to the reaction mixture to adjust pH to ~3. The resulting mixture was diluted with EtOAc (30 mL), washed with brine (15 mL x 2), dried over sodium sulfate, filtered through a Biotage Universal Phase Separator and then concentrated under reduced pressure to give a crude product, which was used for next step without any further purification. LC-MS (ES^+): *m/z* 694.33[MH^+].

[0765] Step 5: Synthesis of methyl 4-{[5-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)pentyl]amino}benzoate.



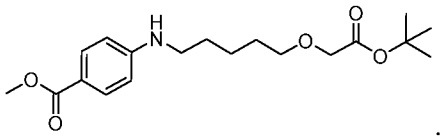
[0766] TBTU (81.5 mg, 0.25 mmol) was added to a solution of 2-[(5-{[4-(methoxycarbonyl)phenyl]amino}pentyl)oxy]acetic acid (50.0 mg, 0.17 mmol), (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (72.8 mg, 0.17 mmol) in DMF (3.0 mL) and DIPEA (59 µL, 0.34mmol) at rt. The resulting mixture was stirred at rt for 1h. The reaction mixture was diluted with EtOAc (30 mL), washed with water (15 mL x 2), brine (15 mL x 1), dried over sodium sulfate, filtered through a Biotage universal phase separator and then concentrated under reduced pressure to give a crude residue, which was purified by silica gel chromatography on a Teledyne Combiflash ISCO system eluting with MeOH/DCM (v/v = 0:100 to 10:90) to yield the titled product (yield: 51%, 2 steps). LC-MS (ES^+): *m/z* 708.35 [MH^+].

[0767] Step 4: Synthesis of 2-[(5-{[4-(methoxycarbonyl)phenyl]amino}pentyl)oxy]acetic acid:



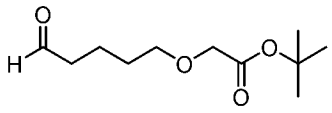
[0768] Trifluoroacetic acid (2.63 mL, 34.5 mmol) was added to a solution of methyl 4-{[5-(2-methoxy-2-oxoethoxy)pentyl]amino}benzoate (270 mg, 0.7682 mmol) in DCM (3.00 ml) at rt. The resulting mixture was stirred at 45 °C for 2h. The reaction mixture was then concentrated under reduced pressure to give a crude product, which was used for next step without any further purification. LC-MS (ES^+): *m/z* 296.15 [MH^+].

[0769] Step 3: Synthesis of methyl 4-({5-[2-(tert-butoxy)-2-oxoethoxy]pentyl}amino)benzoate:



[0770] To a solution of tert-butyl 2-[(5-oxopentyl)oxy]acetate (269 mg, 1.24 mmol) and methyl 4-aminobenzoate (187 mg, 1.24 mmol) in dichloroethane (5.00 mL) was added acetic acid (199 µL, 2.48 mmol) and sodium triacetoxyborohydride (394 mg, 1.86 mmol) at rt. The reaction mixture was stirred at rt for 18h. NaOH (1N solution in water) was then added to neutralize the acetic acid, the resulting reaction mixture was extracted with DCM (100 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude residue, which was purified by silica gel chromatography on a Teledyne Combiflash ISCO system eluting with MeOH/DCM (v/v = 0:100 to 15:85) to yield the desired title product (yield: 62 %).LC-MS (ES^+): *m/z* 352.21 [MH^+]

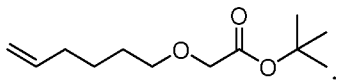
[0771] Step 2: Synthesis of tert-butyl 2-[(5-oxopentyl)oxy]acetate:



[0772] To a solution of tert-butyl 2-(hex-5-en-1-yloxy)acetate (300.0 mg, 1.40 mmol) in acetone (15.00 ml) were added potassium osmate(VI) dihydrate (15.5 mg, 0.042 mmol), follow by NMO (491.9 mg, 4.20 mmol) in water (4.5 ml) at rt. The resulting reaction mixture was stirred for 18h at rt. The reaction was monitored by TLC (EtOAc/Heptane, v/v = 25/75). Sodium periodate (898.2 mg, 4.20 mmol) was then added to the reaction mixture, the reaction was stirred at rt for another 3h. The reaction mixture was diluted with water (10 mL) and DCM (100 mL). The organic layer was separated and the aqueous layer was extracted with DCM (100 mL x 3). The combined organic layers were washed with brine (10 mL x 2) and then passed through a Universal Biotage Phase Separator and concentrated under reduced pressure to give a crude residue, which was purified by silica gel chromatography on a Teledyne Combiflash ISCO system eluting with EtOAc/Heptane (v/v = 0:100 to 50:50) to yield the titled product (yield 90%). ^1H

NMR (400 MHz, $CDCl_3$) δ 9.75 (t, J = 1.8 Hz, 1H), 3.89-3.93 (m, 2H), 3.51 (t, J = 6.1 Hz, 2H), 2.47 (dt, J = 1.6, 7.2 Hz, 2H), 1.69-1.78 (m, 2H), 1.64 (d, J = 8.2 Hz, 2H), 1.46 (s, 9H).

[0773] Step 1: Synthesis of tert-butyl 2-(hex-5-en-1-yloxy)acetate:

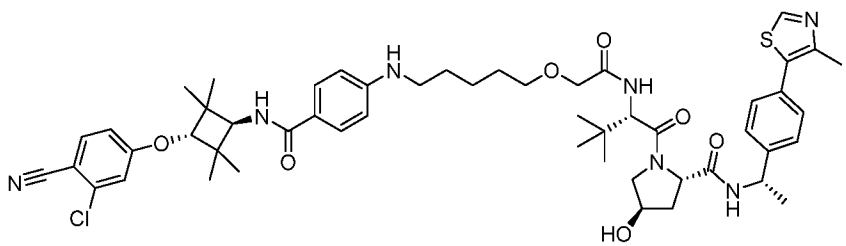


[0774] Tetrabutylammonium hydrogen sulfate (677.7 mg, 2.0 mmol) was added to a mixture of sodium hydroxide (23.9 g, 599 mmol) in water (20.0 mL) and toluene (20.00 ml) at 20 °C. To this mixture was added hex-5-en-1-ol (2.00 g, 20.0 mmol), the resulting mixture was stirred at 20 °C for 1h. The reaction was then cooled to 5 °C and *tert*-butyl 2-bromoacetate (20.0 mmol, 3.89 g) was added slowly while maintaining the internal temperature below 15 °C. The reaction mixture was then stirred at rt for additional 16h. The mixture was diluted with heptane (30 mL) and washed with water (20 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude residue, which was purified by silica gel chromatography on a Teledyne Combiflash ISCO system (gradient eluent: EtOAc/Heptane, v/v = 0/100 to 25/75) to afford the desired product (33%).^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75-5.87 (m, 1H), 4.82-5.10 (m, 2H), 3.95 (s, 2H), 3.52 (t, J = 6.7 Hz, 2H), 2.08 (d, J = 7.0 Hz, 2H), 1.57-1.69 (m, 2H), 1.45-1.53 (m, 11H). LC-MS (ES^+): *m/z* 237.14 [MNa^+]

[0775] Examples 173-178 were synthesized according to similar procedure described for synthesis of example 172, by using corresponding starting materials and intermediates.

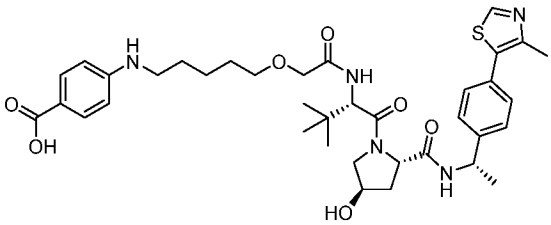
[0776] Alternatively, steps 5-7 of example 174 is synthesized as following:

[0777] Step 7: synthesis of (2S,4R)-1-((S)-2-(2-((5-((4-((trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)amino)pentyl)oxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide:



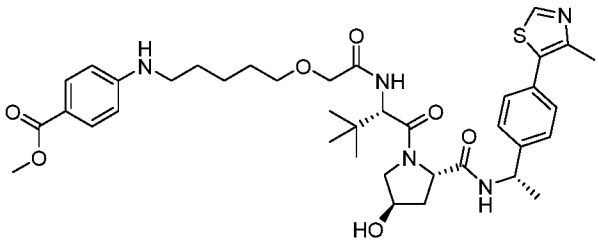
[0778] A solution of 4-((5-(2-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl) ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)pentyl) amino)benzoic acid (1.17 g, 1.65 mmol) in methylene chloride (10 mL) was charged with HATU (688 mg, 1.81 mmol) and diisopropylethylamine (859 µL, 4.94 mmol). The reaction mixture was allowed to stir at room temperature for 10 minutes, then 4-(trans-3-amino-2,2,4,4-tetramethylcyclobutoxy)-2-chlorobenzonitrile hydrochloride (545 mg, 1.73 mmol) was added. The reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with DCM (30 mL), then washed with water (10 mL), brine (10 mL), dried over Na2SO4, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography on a Teledyne Combiflash ISCO eluting with DCM/MeOH (100:0 to 90:10 to yield the desired product as a white solid (0.86 g, 54%). LC-MS (ES+): m/z 968.42 [MH+].

[0779] Step 6: synthesis of 4-((5-(2-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl) ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)pentyl) amino)benzoic acid



[0780] A solution of methyl 4-((5-(2-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)pentyl)amino)benzoate (1.2 g, 1.66 mmol) in methanol (5 mL) was charged with 3 M NaOH (2.0 mL, 50.0 mmol). The reaction mixture was allowed to stir at room temperature for 72 hours. The reaction mixture was quenched with 1.0 M HCl and then concentrated under reduced pressure to remove the methanol. The aqueous was extracted with EtOAc (25 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na2SO4, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography on a Teledyne Combiflash ISCO eluting with DCM/MeOH (100:0 to 90:10) to yield the desired product as a white solid (1.17 g, 100 %). LC-MS (ES+): m/z 708.32 [MH+].

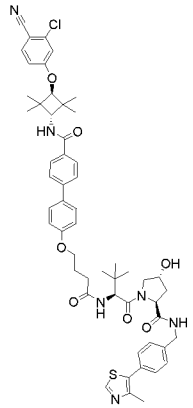
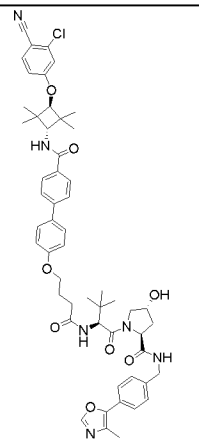
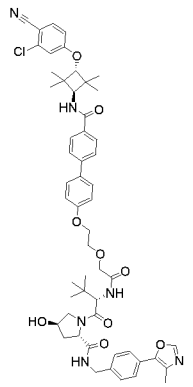
[0781] Step 5: Synthesis of methyl 4-((5-(2-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)pentyl)amino)benzoate.

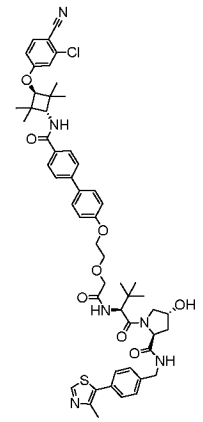


[0782] A solution of 2-((5-((4-(methoxycarbonyl)phenyl)amino)pentyl)oxy)acetic acid (1.68 g, 5.68 mmol) and (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide hydrochloride (2.73 g, 5.68 mmol) in methylene chloride (15 mL) was charged with O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate (1.82 g, 5.68 mmol) and diisopropylethylamine (2.95 mL, 17.0 mmol). The reaction mixture was allowed to stir at rt for 30 minutes. The reaction mixture was quenched with water (15 mL) and then extracted with DCM (15 mL). The organic layer was washed with brine (15 mL), dried over Na2SO4, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography on a Teledyne Combiflash ISCO eluting with DCM/MeOH (100:0 to 90:10) to yield the desired product as a white solid (1.2 g, 29%). LC-MS (ES+): m/z 722.34 [MH+].

[0783] Table 11. Exemplary Compounds.

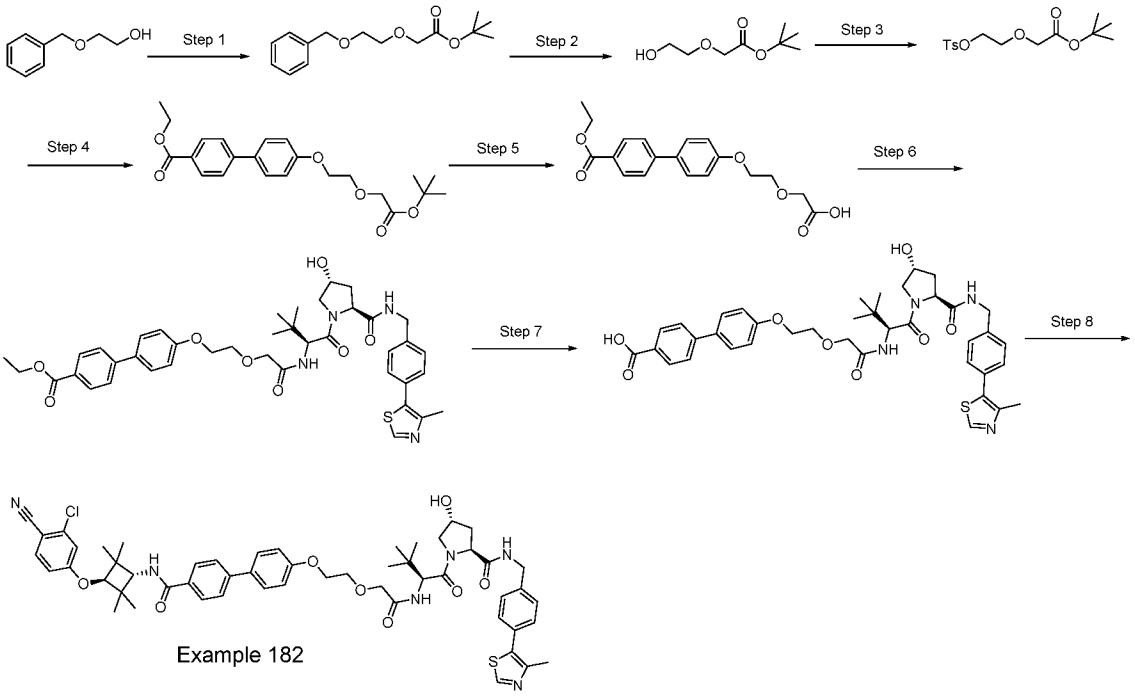
Ex#	Structure	Compound name and Analytical data

179		(2S,4R)-1-[(2S)-3,3-dimethyl-2-{4-[4-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenyl)phenoxy]butanamido}butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.87 (s, 1 H), 7.84 - 7.90 (m, 2 H), 7.73 (d, *J* = 8.61 Hz, 1 H), 7.66 - 7.71 (m, 2 H), 7.58 - 7.63 (m, 2 H), 7.45 - 7.49 (m, 2 H), 7.38 - 7.43 (m, 2 H), 7.14 (d, *J* = 2.35 Hz, 1 H), 7.01 - 7.06 (m, 2 H), 6.99 (dd, *J* = 8.80, 2.54 Hz, 1 H), 4.65 (s, 1 H), 4.56 - 4.60 (m, 1 H), 4.52 - 4.55 (m, 1 H), 4.51 (br. s., 1 H), 4.35 (d, *J* = 15.65 Hz, 1 H), 4.31 (s, 1 H), 4.18 (s, 1 H), 4.06 (ddt, *J* = 9.39, 6.36, 3.28, 3.28 Hz, 2 H), 3.93 (d, *J* = 10.96 Hz, 1 H), 3.81 (dd, *J* = 10.96, 3.91 Hz, 1 H), 2.48 - 2.57 (m, 2 H), 2.42 - 2.47 (m, 3 H), 2.22 (dd, *J* = 13.11, 7.63 Hz, 1 H), 2.06 - 2.15 (m, 3 H), 1.31 (s, 6 H), 1.25 (s, 6 H), 1.04 (s, 9 H); LC-MS (ES^+): *m/z* 973.41 [MH^+]
180		(2S,4R)-1-[(2S)-3,3-dimethyl-2-{4-[4-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenyl)phenoxy]butanamido}butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.14 (s, 1 H), 7.87 (d, *J* = 8.22 Hz, 2 H), 7.73 (d, *J* =8.61 Hz, 1 H), 7.67 - 7.71 (m, 2 H), 7.57 - 7.63 (m, 4 H), 7.45 - 7.51 (m, 2 H), 7.14 (d, *J* =2.74 Hz, 1 H), 7.03 (d, *J* =9.00 Hz, 2 H), 6.99 (dd, *J* =8.80, 2.54 Hz, 1 H), 4.65 (s, 1 H), 4.55 - 4.59 (m, 1 H), 4.47 - 4.55 (m, 2 H), 4.34 (d, *J* = 15.65 Hz, 1 H), 4.31 (s, 1 H), 4.19 (s, 1 H), 4.06 (tt, *J* = 6.16, 3.23 Hz, 2 H), 3.93 (d, *J* = 10.96 Hz, 1 H), 3.81 (dd, *J* = 10.96, 3.91 Hz, 1 H), 2.48 - 2.55 (m, 2 H), 2.39 (s, 3 H) 2.22 (dd, *J* = 13.30, 7.43 Hz, 1 H), 2.06 - 2.14 (m, 3 H), 1.31 (s, 6 H), 1.25 (s, 6 H), 1.04 (s, 9 H); LC-MS (ES^+): *m/z* 957.44 [MH^+]
181		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{2-[4-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenyl)phenoxy]ethoxy}acetamido)butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.05 (s, 1 H), 7.81 - 7.87 (m, 2 H), 7.73 (d, *J* = 9.00 Hz, 1 H), 7.58 - 7.64 (m, 2 H), 7.51 - 7.58 (m, 4 H), 7.43 - 7.51 (m, 2 H), 7.10 - 7.19 (m, 3 H), 6.99 (dd, *J* = 9.00, 2.35 Hz, 1 H), 4.76 (s, 1 H), 4.55 - 4.64 (m, 3 H), 4.51 (d, *J* = 1.96 Hz, 1 H), 4.31 (t, *J* = 7.83 Hz, 2 H), 4.25 (q, *J* = 4.17 Hz, 2 H), 4.19 (s, 1 H), 4.14 (s, 2 H), 3.96 (t, *J* = 4.30 Hz, 2 H), 3.86 - 3.91 (m, 1 H), 3.78 - 3.86 (m, 1 H), 2.26 - 2.32 (m, 3 H), 2.18 - 2.26 (m, 1 H), 2.05 - 2.13 (m, 1 H), 1.31 (s, 6 H), 1.25 (s, 6 H), 0.99 - 1.11 (m, 9 H); LC-MS (ES^+): *m/z* 973.43 [MH^+]

182		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{2-[4-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenyl)phenoxy]ethoxy}acetamido)butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.66 (s, 1 H), 7.82 (d, *J* = 8.22 Hz, 2 H), 7.60 (dd, *J* = 11.54, 8.41 Hz, 3 H), 7.53 (d, *J* = 8.61 Hz, 2 H), 7.27 - 7.41 (m, 6 H), 7.04 (d, *J* = 8.61 Hz, 2 H), 6.99 (d, *J* = 2.35 Hz, 1 H), 6.83 (dd, *J* = 8.80, 2.15 Hz, 1 H), 6.31 (d, *J* = 8.22 Hz, 1 H), 4.75 (t, *J* = 7.83 Hz, 1 H), 4.52 - 4.64 (m, 2 H), 4.50 (d, *J* = 8.61 Hz, 1 H), 4.34 (dd, *J* = 14.87, 5.48 Hz, 1 H), 4.17 - 4.24 (m, 3 H), 4.04 - 4.17 (m, 4 H), 3.88 - 3.97 (m, 2 H), 3.63 (dd, *J* = 11.35, 3.52 Hz, 1 H), 2.61 (ddd, *J* = 13.30, 7.83, 4.70 Hz, 1 H), 2.49 (s, 3 H), 2.12 (dd, *J* = 13.69, 8.22 Hz, 1 H), 1.31 (s, 6 H), 1.26 (s, 6 H), 0.96 (s, 9 H); LC-MS (ES$^+$): *m/z* 989.27 [MH$^+$]

[0784] Examples 179-181 were synthesized according to similar procedure described for synthesis of example 182, by using corresponding starting materials and intermediates.

[0785] Synthesis of example 182:

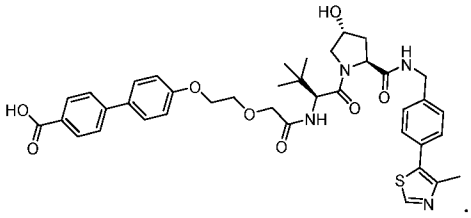


[0786] Step 8: Synthesis of example 182

[0787] To a stirred solution of 4-{4-[2-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)ethoxy]phenyl}benzoic acid (89.0 mg, 122 μmol) in methylene chloride (2.0 mL) was added HATU (55.5 mg, 146 μmol) and diisopropylethylamine (63.7 μL, 366 μmol). The reaction

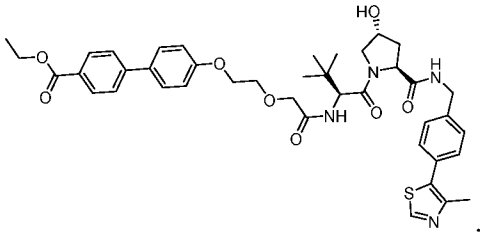
mixture was stirred at rt for 10 minutes. The reaction mixture was then charged with 2-chloro-4-[trans-3-amino-2,2,4,4-tetramethylcyclobutoxy]benzonitrile (34.0 mg, 122 μmol). The reaction was stirred at rt for 30 minutes. The reaction was monitored by LC-MS, which indicated completion of reaction. The reaction mixture was quenched with water (5 mL) and then extracted with DCM (25 mL). The organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude material, which was purified by flash silica gel chromatography on a Teledyne Combiflash ISCO (eluent: DCM/MeOH (v:v = 90:10)) to give titled product (yield: 37%) as a white solid.

[0788] Step 7: Synthesis of 4-{4-[2-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)ethoxy]phenyl}benzoic acid:



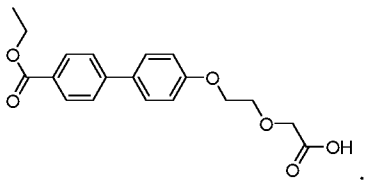
[0789] To a stirred solution of ethyl 4-{4-[2-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)ethoxy]phenyl}benzoate (188.4 mg, 248 μmol) in methanol (2.0 mL) was added 1 M NaOH in water (0.5 mL, 12.5 mmol). The reaction mixture was stirred at rt for 16 h. The reaction was monitored by LC-MS, which indicated completion of reaction. The reaction mixture was quenched with 1.0 M HCl in water and then concentrated under reduced pressure to remove the methanol. The aqueous was extracted with EtOAc (25 mL). The organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude material, which was purified by flash silica gel chromatography on a Teledyne Combiflash ISCO (eluent: DCM/MeOH (v:v = 90:10)) to give titled product (yield: 50%) as a white solid. LC-MS (ES^+): *m/z* 729.18 [MH^+]

[0790] Step 6: Synthesis of ethyl 4-{4-[2-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)ethoxy]phenyl}benzoate:



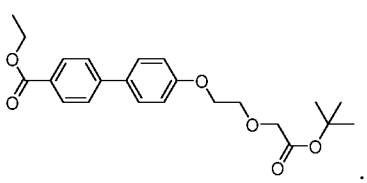
[0791] To a stirred solution of 2-(2-{4-[4-(ethoxycarbonyl)phenyl]phenoxy}ethoxy)acetic acid (100 mg, 290.3 µmol) and (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide hydrochloride (135.5 mg, 290.3 µmol) in Dichloromethane (2.0 mL) was added O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (93.20 mg, 290.3 µmol) and diisopropylethylamine (151.6 µL,870.9 µmol). The reaction mixture was stirred at rt for 30 minutes. The reaction was monitored by LC-MS, which indicated completion of reaction. The reaction mixture was concentrated under reduced pressure to give a crude material, which was purified by flash silica gel chromatography on a Teledyne Combiflash ISCO (gradient eluent: Heptane/Acetone (v:v = 100:0 to 0:100)) to give titled product (yield: 86%) as a white solid. LC-MS (ES^+): *m/z* 757.3283 [MH^+].

[0792] Step 5: Synthesis of 2-(2-{4-[4-(ethoxycarbonyl)phenyl]phenoxy}ethoxy)acetic acid:



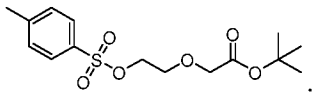
[0793] To a stirred solution of ethyl 4-(4-{2-[2-(tert-butoxy)-2-oxoethoxy]ethoxy}phenyl)benzoate (245 mg, 611 µmol) in methylene chloride (1.0 mL) was added trifluoroacetic acid (1.0 mL, 12.9 mmol). The reaction mixture was stirred at rt for 30 minutes. The reaction was monitored by LC-MS, which indicated completion of reaction. The reaction mixture was concentrated under reduced pressure to give titled product (yield: 100% based on crude) as an off white solid. The material was used in next step without any further purification. LC-MS (ES^+): *m/z* 345.1330 [MH^+].

[0794] Step 4: Synthesis of ethyl 4-(4-{2-[2-(tert-butoxy)-2-oxoethoxy]ethoxy}phenyl)benzoate:



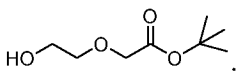
[0795] To a stirred mixture of ethyl 4'-hydroxy-[1,1'-biphenyl]-4-carboxylate (146.6 mg, 605.3 µmol) and tert-butyl 2-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}acetate (200.0 mg, 605.3 µmol) in acetonitrile (2.0 mL) was added potassium carbonate (125.4 mg, 907.9 µmol) at rt. The reaction mixture was then stirred at 80 °C for 16 h. The reaction was monitored by LC-MS, which indicated completion of reaction. The reaction mixture was concentrated under reduced pressure to give a crude material, which was purified by flash silica gel chromatography on a Teledyne Combiflash ISCO (gradient eluent: Heptane/EtOAc (v:v = 100:0 to 50:50)) to give titled product (yield: 99%) as a clear oil. LC-MS (ES^+): *m/z* 423.18 [MNa^+].

[0796] Step 3: synthesis of tert-butyl 2-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}acetate:



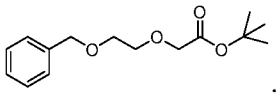
[0797] To a stirred solution of tert-butyl 2-(2-hydroxyethoxy)acetate (1.44 g, 0.19 mmol) in methylene chloride (10.0 mL) was added 4-methylbenzene-1-sulfonyl chloride (1.713 g, 0.21 mmol) and triethylamine (1.707 mL, 12.25 mmol) at rt. The reaction mixture was stirred at rt for 16 h. The reaction was monitored by LC-MS, which indicated completion of reaction. The reaction mixture was concentrated under reduced pressure give a crude material, which was purified by flash silica gel chromatography on a Teledyne Combiflash ISCO (gradient eluent: Heptane/Acetone (v:v = 100:0 to 0:100)) to give titled product (yield: 69%) as a clear oil. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.77 - 7.83 (m, 2 H), 7.44 (d, *J* = 7.83 Hz, 2 H), 4.14 - 4.19 (m, 2 H), 3.93 (s, 2 H), 3.68 - 3.74 (m, 2 H), 2.46 (s, 3 H), 1.46 (s, 9 H); LC-MS (ES^+): *m/z* 353.1053 [MNa^+], t_R = 2.56 min.

[0798] Step 2: Synthesis of tert-butyl 2-(2-hydroxyethoxy)acetate:



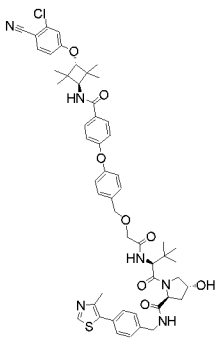
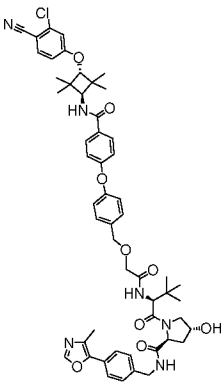
[0799] To a stirred solution of tert-butyl 2-[2-(benzyloxy)ethoxy]acetate in Ethanol (10.0 mL) was added palladium on carbon (10% wt.) (1.99 g, 1.87 mmol). The reaction mixture was evacuated and purged with H_2 gas (3 x). The reaction mixture was stirred at rt under an atmosphere of H_2 for 16 h. The reaction was monitored by TLC analysis, which indicated completion of reaction. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to give titled product (yield: 87% based on crude) as a clear oil. The crude material was used in next step reaction without any further purification.

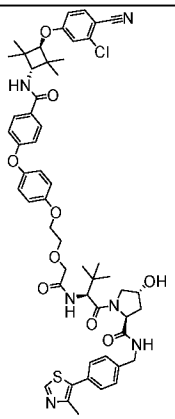
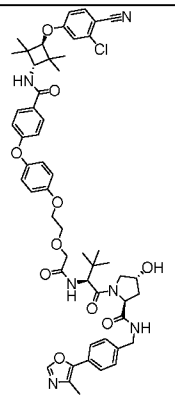
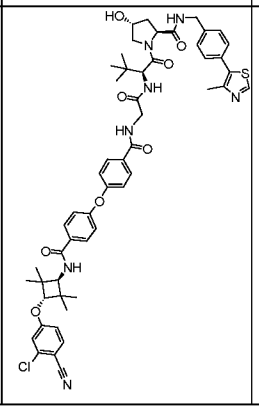
[0800] Step 1: Synthesis of tert-butyl 2-[2-(benzyloxy)ethoxy]acetate:



[0801] To a stirred solution of 2-(benzyloxy)ethanol (5.0 g, 32.8 mmol) and tert-butyl 2-bromoacetate (7.02 g, 36.0 mmol) in acetonitrile (10.0 mL) was added potassium carbonate (6.78 g, 49.1 mmol) at rt. The reaction mixture then stirred at 80 °C for 16 h. The reaction was monitored by TLC analysis, which indicated completion of reaction. The reaction mixture was diluted with water (10.0 mL) and extracted with EtOAc (20.0 mL). The organic layer was washed with water (5.0 mL), brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give titled product (yield: 100% based on crude) as a yellow oil. This crude material was used in next step reaction without any further purification.

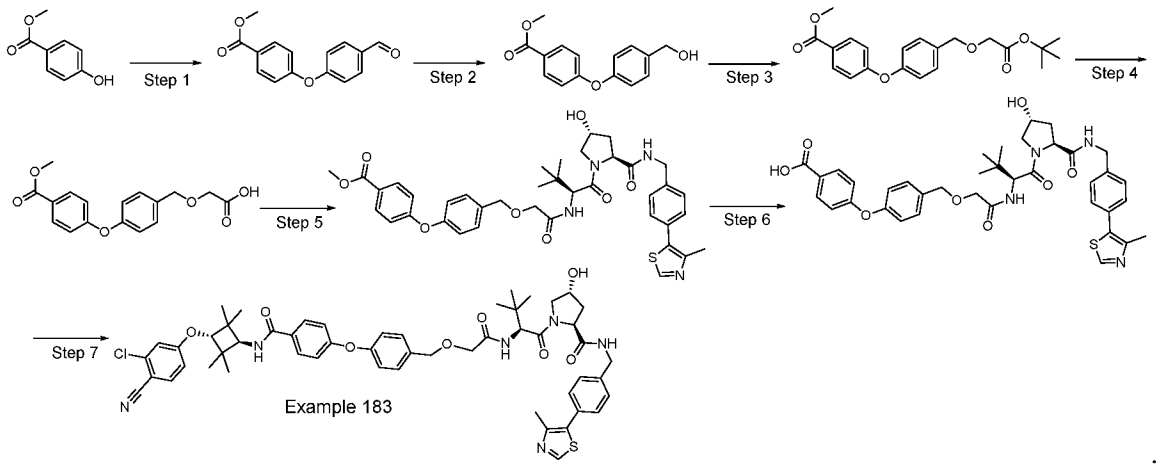
[0802] Table 12. Exemplary Compounds.

Ex#	Structure	Compound name and Analytical data
183		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{[4-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)phenyl]methoxy}acetamido)butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.83 - 8.90 (m, 1 H), 7.79 - 7.86 (m, 2 H), 7.72 (d, *J* = 8.61 Hz, 1 H), 7.43 - 7.50 (m, 4 H), 7.37 - 7.42 (m, 2 H), 7.13 (d, *J* = 2.35 Hz, 1 H), 7.00 - 7.09 (m, 4 H), 6.98 (dd, *J* = 9.00, 2.35 Hz, 1 H), 4.71 (s, 1 H), 4.63 (s, 2 H), 4.55 - 4.61 (m, 2 H), 4.47 - 4.54 (m, 2 H), 4.35 (d, *J* = 15.65 Hz, 1 H), 4.28 (s, 1 H), 4.15 (s, 1 H), 4.00 - 4.08 (m, 2 H), 3.86 - 3.92 (m, 1 H), 3.77 - 3.84 (m, 1 H), 2.44 - 2.48 (m, 3 H), 2.24 (dd, *J* = 13.30, 7.43 Hz, 1 H), 2.09 (ddd, *J* = 13.21, 9.10, 4.30 Hz, 1 H), 1.28 (s, 6 H), 1.22 (s, 6 H), 1.00 - 1.09 (m, 9 H); LC-MS (ES^+): *m/z* 975.39[MH^+]
184		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{[4-(4-{[(1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)phenyl]methoxy}acetamido)butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.10 - 8.15 (m, 1 H), 7.79 - 7.85 (m, 2 H), 7.72 (d, *J* = 9.00 Hz, 1 H), 7.55 - 7.61 (m, 2 H), 7.44 - 7.51 (m, 4 H), 7.12 (d, *J* = 2.35 Hz, 1 H), 7.00 - 7.09 (m, 4 H), 6.98 (dd, *J* = 9.00, 2.35 Hz, 1 H), 4.71 (s, 1 H), 4.63 (s, 2 H), 4.55 - 4.61 (m, 2 H), 4.46 - 4.54 (m, 2 H), 4.34 (d, *J* = 15.26 Hz, 1 H), 4.28 (s, 1 H), 4.15 (s, 1 H), 4.07 (s, 1 H), 4.02 - 4.06 (m, 1 H), 3.85 - 3.92 (m, 1 H), 3.77 - 3.84 (m, 1 H), 2.35 - 2.42 (m, 3 H), 2.23 (dd, *J* = 13.30, 7.43 Hz, 1 H), 2.04 - 2.12 (m, 1 H), 1.28 (s, 6 H), 1.22 (s, 6 H), 0.97 - 1.12 (m, 9 H); LC-MS (ES^+): *m/z* 959.41

185		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{2-[4-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)phenoxy]ethoxy}acetamido)butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.83 (s, 1 H), 7.74 - 7.82 (m, 2 H), 7.72 (d, *J* = 8.61 Hz, 1 H), 7.42 - 7.49 (m, 2 H), 7.33 - 7.40 (m, 2 H), 7.12 (d, *J* = 2.35 Hz, 1 H), 7.06 - 7.11 (m, 2 H), 6.87 - 7.01 (m, 5 H), 4.74 (s, 1 H), 4.55 - 4.61 (m, 2 H), 4.49 - 4.55 (m, 2 H), 4.32 (d, *J* = 15.26 Hz, 1 H), 4.28 (s, 1 H), 4.17 - 4.22 (m, 2 H), 4.14 (s, 1 H), 4.13 (s, 2 H), 3.91 - 3.96 (m, 2 H), 3.85 - 3.90 (m, 1 H), 3.79 - 3.85 (m, 1 H), 2.40 - 2.49 (m, 3 H), 2.23 (dd, *J* = 13.30, 7.83 Hz, 1 H), 2.05 - 2.14 (m, 1 H), 1.28 (d, *J* = 1.17 Hz, 6 H), 1.22 (s, 6 H), 1.01 - 1.09 (m, 9 H); LC-MS (ES^+): *m/z* 1005.40 [MH^+]
186		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{2-[4-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)phenoxy]ethoxy}acetamido)butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.10 (s, 1 H), 7.74 - 7.83 (m, 2 H), 7.72 (d, *J* = 8.61 Hz, 1 H), 7.52 - 7.59 (m, 2 H), 7.43 - 7.50 (m, 2 H), 7.07 - 7.15 (m, 3 H), 6.86 - 7.02 (m, 5 H), 4.75 (s, 1 H), 4.55 - 4.61 (m, 2 H), 4.52 (d, *J* = 8.61 Hz, 2 H), 4.33 (s, 1 H), 4.26 - 4.31 (m, 1 H), 4.21 (q, *J* = 3.78 Hz, 2 H), 4.10 - 4.17 (m, 3 H), 3.94 (dd, *J* = 4.70, 3.91 Hz, 2 H), 3.85 - 3.91 (m, 1 H), 3.78 - 3.85 (m, 1 H), 2.33 (s, 3 H), 2.23 (dd, *J* = 13.11, 7.63 Hz, 1 H), 2.09 (ddd, *J* = 13.30, 9.19, 4.50 Hz, 1 H), 1.28 (s, 6 H), 1.22 (s, 6 H), 1.00 - 1.10 (m, 9 H); LC-MS (ES^+): *m/z* 989.44 [MH^+]
187		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{[4-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)phenyl]formamido}acetamido)butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide Mass (ES^+): *m/z* 988.10 [MH^+]

[0803] Examples 184-187 were synthesized according to similar procedure described for synthesis of example 183, by using corresponding starting materials and intermediates.

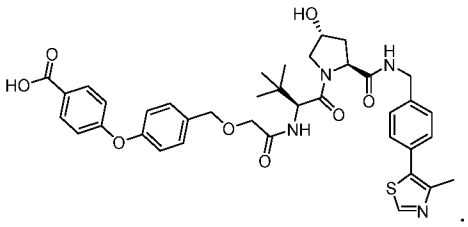
[0804] Synthesis of Example 183:



[0805] Step 7: Synthesis of Example 183

[0806] To a stirred solution of 2-chloro-4-[trans-3-amino-2,2,4,4-tetramethylcyclobutoxy]benzonitrile (25.3 mg, 90.9 µmol) and 4-{4-[({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)methyl]phenoxy}benzoic acid (65 mg, 90.9 µmol) in methylene chloride (2.0 mL) was added O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (29.1 mg, 90.9 µmol) and diisopropylethylamine (47.3 µL, 272 µmol) at rt. The reaction mixture was stirred at rt for 30 minutes. The reaction was monitored by LC-MS, which indicated completion of reaction. The reaction mixture was diluted with water (5 mL) and extracted with DCM (25 mL). The organic layer was separated and washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude material, which was purified by flash silica gel chromatography on a Teledyne Combiflash ISCO (eluent: DCM/MeOH (v:v = 90:10)) to give titled product (yield: 22%) as a white solid.

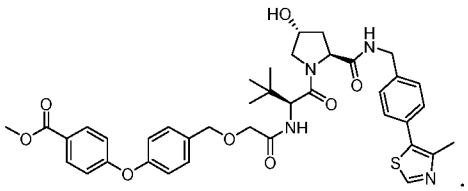
[0807] Step 6: Synthesis of 4-{4-[({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)methyl]phenoxy}benzoic acid:



[0808] To a stirred solution of methyl 4-{4-[({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)methyl]phenoxy}benzoate (68 mg, 93.2 µmol) in methanol (2.0 mL) was added 1

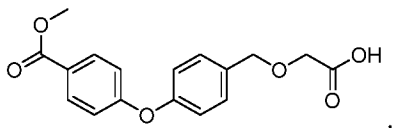
M NaOH solution in water (0.5 mL, 12.5 mmol) at rt. The reaction mixture was allowed to stir at rt for 16 hours. The reaction was monitored by LC-MS, which indicated completion of reaction. The reaction mixture was quenched with 1.0 M HCl solution in water (0.5 mL) and then concentrated under reduced pressure to remove the methanol. The aqueous was extracted with EtOAc (25 mL). The organic layer was separated, washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give titled product (yield: 98% based on crude) as a white solid. This material was used in next step reaction without any further purification. LC-MS (ES^+): *m/z* 715.28[MH^+].

[0809] Step 5: Synthesis of methyl 4-{4-[({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)methyl]phenoxy}benzoate:



[0810] To a stirred solution of 2-({4-[4-(methoxycarbonyl)phenoxy]phenyl}methoxy)acetic acid (30.0 mg, 94.8 µmol) and (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide hydrochloride (44.2 mg, 94.8 µmol) in methylene chloride (2.0 mL) was added O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate (30.4 mg, 94.8 µmol) and diisopropylethylamine (49.4 µL, 284 µmol) at rt. The reaction mixture was allowed to stir at rt for 30 minutes. The reaction was monitored by LC-MS, which indicated completion of reaction. The reaction mixture was concentrated under reduced pressure to give a crude material, which was purified by flash silica gel chromatography on a Teledyne Combiflash ISCO (gradient eluent: Heptane/Acetone (v:v = 100:0 to 0:100)) to give titled product (yield: 99%) as a white solid. LC-MS (ES^+): *m/z* 729.30 [MH^+].

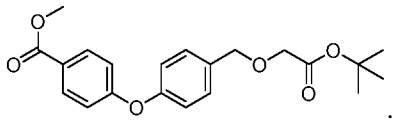
[0811] Step 4: 2-({4-[4-(methoxycarbonyl)phenoxy]phenyl}methoxy)acetic acid:



[0812] A solution of methyl 4-(4-{[2-(tert-butoxy)-2-oxoethoxy]methyl}phenoxy)benzoate (200.0 mg, 537 µmol) in hydrogen chloride solution (4 M in dioxane, 2.0 mL) was stirred at room temperature for 2 h. The reaction was monitored by LC-MS, which indicated completion of reaction. The reaction mixture was concentrated under reduced pressure to give titled product (yield: 95% based on crude) as an off white

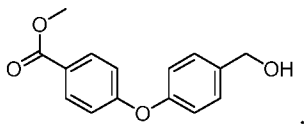
solid. This material used in next step reaction without any further purification. LC-MS (ES^+): *m/z* 339.0858 [MNa^+].

[0813] Step 3: Synthesis of methyl 4-(4-{[2-(tert-butoxy)-2-oxoethoxy]methyl}phenoxy)benzoate:



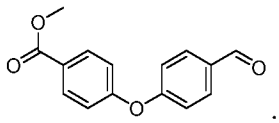
[0814] To a stirred mixture of sodium hydroxide (1.16 g, 29 mmol) in water (2.0 mL) and toluene (2.0 mL) at 20 °C was charged with tetrabutylammonium hydrogen sulfate (32.86 mg, 96.79 µmol), followed by methyl 4-[4-(hydroxymethyl)phenoxy]benzoate (250.0 mg, 967.9 µmol), the resulting mixture was stirred at 20 °C for 1h. The mixture was then cooled to 5 °C, tert-butyl 2-bromoacetate (207.5 mg, 1.064 mmol) was added slowly and the internal temperature was maintained below 15 °C. Upon the completion of this addition, the reaction mixture was allowed to warm up to rt and stirred for 16h at rt. The reaction was monitored by LC-MS, which indicated completion of reaction. The mixture was diluted with water (5 mL) and extracted with EtOAc (30 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to a give a crude material, which was purified by flash silica gel chromatography on a Teledyne Combiflash ISCO (eluent (gradient): Heptane/EtOAc (v:v = 100:0 to 70:30)) to give titled product (yield: 56%) as a white solid. LC-MS (ES^+): *m/z* 395.15 [MNa^+].

[0815] Step 2: Synthesis of methyl 4-[4-(hydroxymethyl)phenoxy]benzoate:



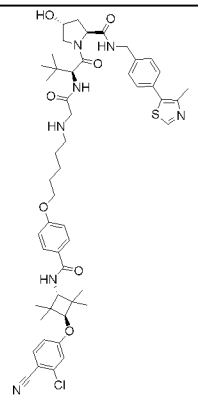
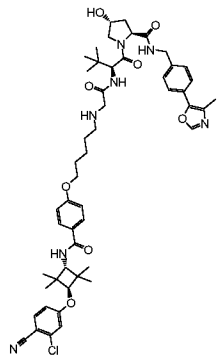
[0816] To a stirred solution of methyl 4-(4-formylphenoxy)benzoate (750.0 mg, 2.92 mmol) in methanol (2.0 mL) was added sodium borohydride (121 mg, 3.21 mmol) at rt. The reaction mixture was allowed to stir at rt for 30 min. The reaction was monitored by LC-MS, which indicated completion of reaction. The reaction mixture was slowly quenched with 1N HCl (solution in water), concentrated under reduced pressure to remove the bulk of methanol, and then extracted with DCM (30 mL). The organic layer was separated, washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude material, which was purified by flash silica gel chromatography on a Teledyne Combiflash ISCO (eluent (gradient): Heptane/EtOAc (v:v = 100:0 to 50:50)) to give titled product (yield: 94%) as a white solid. LC-MS (ES^+): *m/z* 259.10 [MH^+].

[0817] Step 1: Synthesis of methyl 4-(4-formylphenoxy)benzoate:



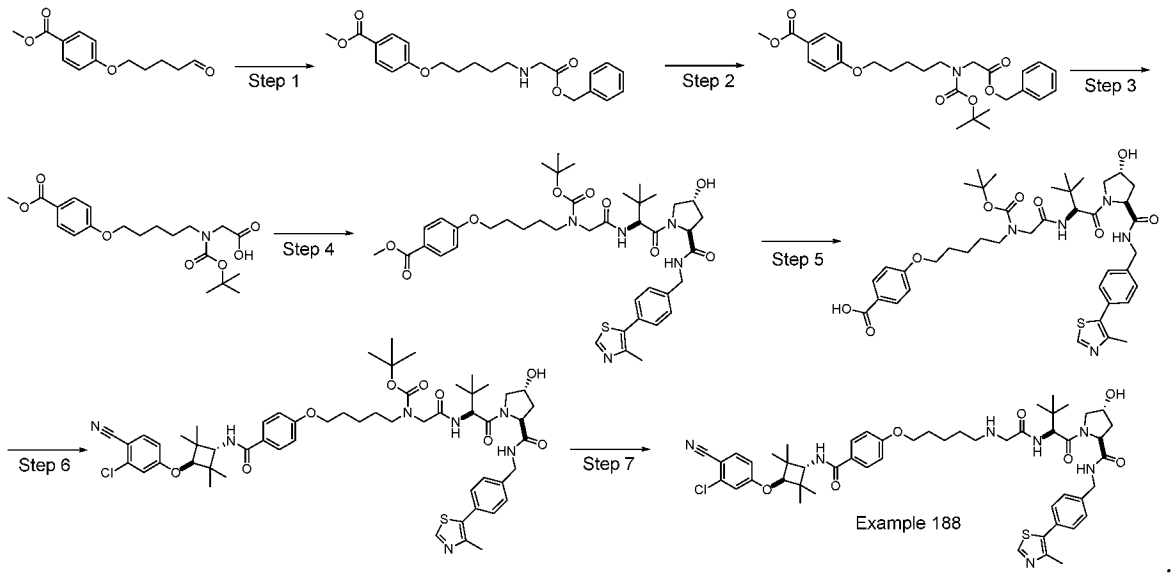
[0818] To a stirred mixture of methyl 4-hydroxybenzoate (1.0 g, 6.57 mmol) and potassium carbonate (1.36 g, 9.85 mmol) in dimethylformamide (2.0 mL) was added 4-fluorobenzaldehyde (815 mg, 6.57 mmol) at rt. The reaction mixture was then stirred at 80 ℃ for 16h. The reaction was monitored by LC-MS, which indicated completion of reaction. The reaction mixture was cooled to rt, diluted with water (10 mL) and extracted with EtOAc (50 mL x 2). The organic layer was separated, washed with brine (10 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude material, which was purified by flash silica gel chromatography on a Teledyne Combiflash ISCO (eluent (gradient): Heptane/EtOAc (v:v = 100:0 to 50:50)) to give titled product (yield: 90%) as a white solid. LC-MS (ES^+): *m/z* 257.08 [MH^+].

[0819] Table 13. Exemplary Compounds.

Ex#	Structure	Compound name and Analytical data
188		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{[5-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)pentyl]amino}acetamido)butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.63 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.6 Hz, 1H), 7.35 (q, J = 8.5 Hz, 4H), 6.97 (d, J = 2.3 Hz, 1H), 6.81 (dd, J = 2.5, 8.8 Hz, 1H), 6.60 (d, J = 9.0 Hz, 2H), 6.07-6.12 (m, 1H), 4.74 (s, 1H), 4.50-4.59 (m, 3H), 4.37 (d, J = 5.1 Hz, 1H), 4.11-4.17 (m, 2H), 3.64 (dd, J = 3.5, 11.3 Hz, 1H), 3.53 (d, J = 7.0 Hz, 2H), 3.19 (t, J = 7.0 Hz, 2H), 2.55-2.61 (m, 1H), 2.52 (s, 3H), 2.10-2.19 (m, 2H), 1.65-1.71 (m, 4H), 1.50-1.53 (m, 2H), 1.24-1.33 (m, 9H), 1.22 (s, 6H), 0.96 (s, 9H), 0.86-0.91 (m, 3H). LC-MS (ES^+): *m/z* 954.43 [MH^+]
189		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{[5-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)pentyl]amino}acetamido)butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.72 (d, J = 8.6 Hz, 2H), 7.54-7.60 (m, 1H), 7.51 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 6.96 (d, J = 2.3 Hz, 1H), 6.88 (d, J = 9.0 Hz, 2H), 6.81 (dd, J = 2.3, 9.0 Hz, 1H), 4.53-4.67 (m, 2H), 4.40 (br. s., 1H), 4.14 (d, J = 8.2 Hz, 1H), 4.05 (s, 1H), 3.92 (br. s., 2H), 3.74 (br. s., 1H), 3.60 (d, J = 8.6 Hz, 1H), 2.39 (s, 3H), 2.23 (br. s., 2H), 1.71 (br. s., 4H), 1.43 (br. s., 2H), 1.27 (s, 12H), 1.22 (s, 6H), 0.99 (br. s., 8H), 0.86-0.93 (m, 6H). LC-MS (ES^+): *m/z* 938.45 [MH^+]

[0820] Example 189 was synthesized according to similar procedure described for synthesis of example 188, by using corresponding starting materials and intermediates.

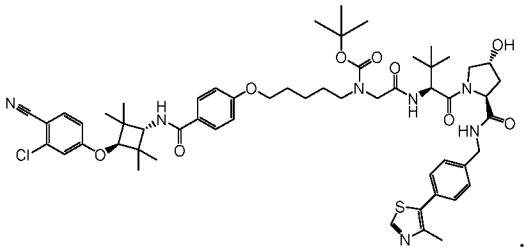
[0821] Synthesis of example 188:



[0822] Step 7: Synthesis of example 188

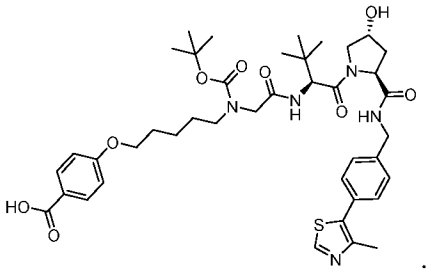
[0823] Trifluoroacetic acid (1.12 mL, 14.7 mmol) was added to a stirred solution of tert-butyl N-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl)-N-[5-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)pentyl]carbamate (34 mg, 0.0327 mmol) in DCM (3.00 ml) at rt. The resulting mixture was stirred at 45 °C for 48h. The reaction mixture was then concentrated under reduced pressure to give a crude material, which was purified by flash silica gel chromatography on a Teledyne Combiflash ISCO system, eluting with MeOH/DCM (gradient: v:v = 0:100 to 10:90) to yield the desired title product (yield: 62 %).

[0824] Step 6: Synthesis of tert-butyl N-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl)-N-[5-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)pentyl]carbamate:



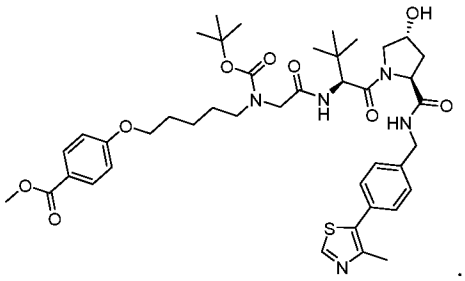
[0825] TBTU (23.0 mg, 0.072 mmol) was added to a stirred solution of 4-[(5-{[(tert-butoxy)carbonyl]({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl)amino}pentyl)oxy]benzoic acid (38 mg, 0.04786 mmol) and 2-chloro-4-[trans-3-amino-2,2,4,4-tetramethylcyclobutoxy]benzonitrile (13.3 mg, 0.04786 mmol) in DMF (3.0 mL) and DIPEA (16.5 µL, 0.095 mmol) at rt. The resulting mixture was stirred at rt for 1h. The reaction was then diluted with EtOAc (30 mL), washed with brine (5 mL x 2), filtered through a Biotage Universal Phase Separator and then concentrated under reduced pressure to give a crude material, which was purified by flash silica gel chromatography on a Teledyne Combiflash ISCO system, eluting with MeOH/DCM (gradient: v:v = 0:100 to 10:90) to yield the desired title product (yield: 60 %).

[0826] Step 5: Synthesis of 4-[(5-{[(tert-butoxy)carbonyl]({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl)amino}pentyl)oxy]benzoic acid:



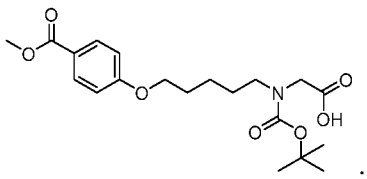
[0827] Lithium hydroxide (3.0 mg, 0.128 mmol) was added to a stirred solution of methyl 4-[(5-{[(tert-butoxy)carbonyl]({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl)amino}pentyl)oxy]benzoate (37 mg, 0.046 mmol) in a mixed solvent of THF/water (v:v = 1:1, 2.00 mL) at rt. The resulting reaction mixture was stirred at rt overnight. To the reaction mixture was added 1N HCl (aqueous solution) to adjust pH = ~3. The resulting mixture was extracted with EtOAc (20 mL x 2), washed with brine (5 mL x 2), filtered through a Biotage Universal Phase Separator and then concentrated under reduced pressure to give a crude material (yield: 100 % based on crude). This crude product was used for the next step reaction without any further purification.

[0828] Step 4: Synthesis of methyl 4-[(5-{[(tert-butoxy)carbonyl]({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl)amino}pentyl)oxy]benzoate:



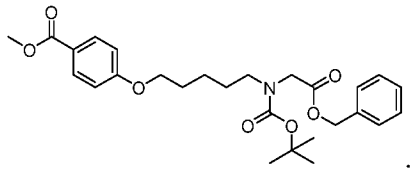
[0829] TBTU (36.6 mg, 0.1142 mmol) was added to a stirred solution of 2-{[(tert-butoxy)carbonyl]({5-[4-(methoxycarbonyl)phenoxy]pentyl})amino}acetic acid (37 mg, 0.076 mmol) and (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (32.8 mg, 0.076 mmol) in DMF (3.0 mL) and DIPEA (26.4 µL, 0.15 mmol) at rt. The resulting reaction mixture was stirred at rt for 1hr. The reaction was then diluted with EtOAc (30 mL), washed with brine (10 mL), filtered through a Biotage Universal Phase Separator and then concentrated under reduced pressure to give a crude material, which was purified by flash silica gel chromatography on a Teledyne Combiflash ISCO system, eluting with MeOH/DCM (gradient: v/v = 0/100 to 10/90) to yield the desired title product (yield: 64%).

[0830] Step 3: Synthesis of 2-{[(tert-butoxy)carbonyl]({5-[4-(methoxycarbonyl)phenoxy]pentyl})amino}acetic acid:



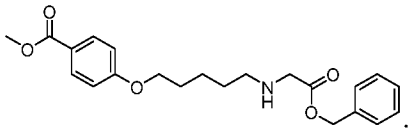
[0831] Palladium on carbon (96.8 mg, 0.91 mmol) was added to a stirred solution of methyl 4-[(5-{[2-(benzyloxy)-2-oxoethyl][(tert-butoxy)carbonyl]amino}pentyl)oxy]benzoate (83.0 mg, 0.171 mmol) in ethanol (20 ml) at rt. The reaction mixture was degassed and charged with $H_{(g)}$ and then stirred at rt for 16h under a hydrogen atmosphere. Solids were then removed by filtration and the solvent was concentrated under reduced pressure to give a crude material (yield: 98% based on crude). This crude product was used for the next step reaction without any further purification.

[0832] Step 2: Synthesis of methyl 4-[(5-{[2-(benzyloxy)-2-oxoethyl][(tert-butoxy)carbonyl]amino}pentyl)oxy]benzoate:

[0833]  .

[0834] Di-tert-butyl dicarbonate (47.7 µL, 0.21 mmol) was added to a stirred solution of methyl 4-[(5-{[2-(benzyloxy)-2-oxoethyl]amino}pentyl)oxy]benzoate (73.0 mg, 0.19 mmol) in THF (5.0 ml) at rt. The reaction mixture was heated to reflux at 80 °C and stirred at 80 °C for 14 h. The reaction was then cooled to rt, diluted with ethyl acetate (20 mL), washed with saturated aq. $NaHCO_3$ (10 mL). The organic layer was separated and filtered using a Biotage Universal Phase Separator and then concentrated under reduced pressure to give a crude material, which was purified by flash silica gel chromatography on a Teledyne Combiflash ISCO system, eluting with EtOAc/Heptane (gradient v:v = 0:100 to 40:60) to yield the desired title product (yield: 95%).

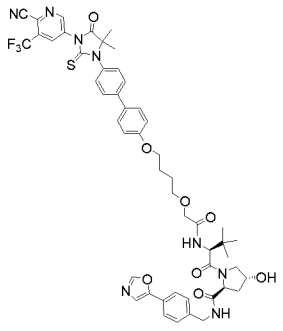
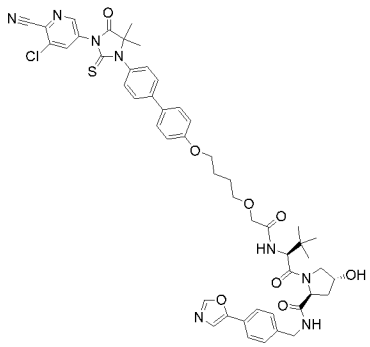
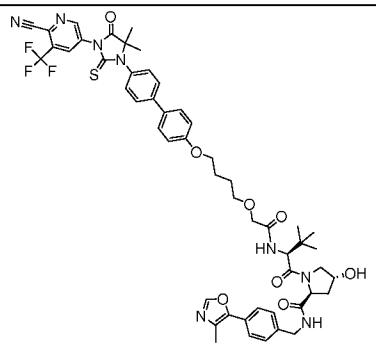
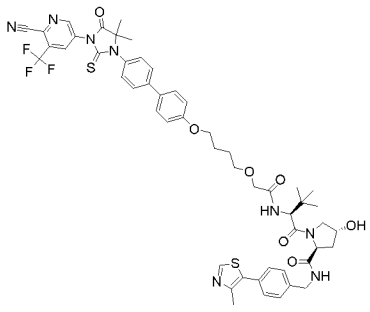
[0835] Step 1: Synthesis of methyl 4-[(5-{[2-(benzyloxy)-2-oxoethyl]amino}pentyl)oxy]benzoate:

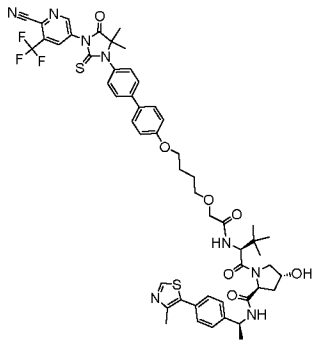
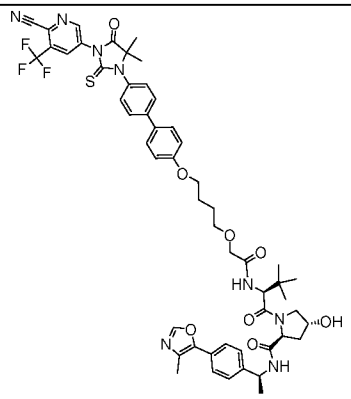
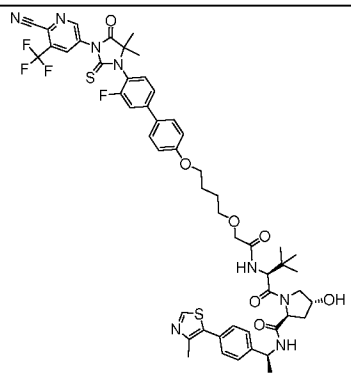
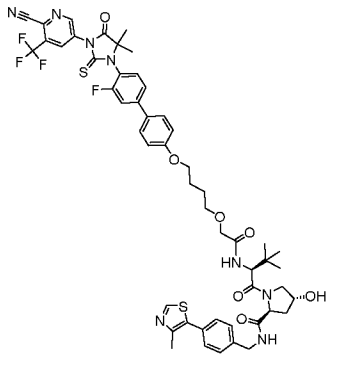
 .

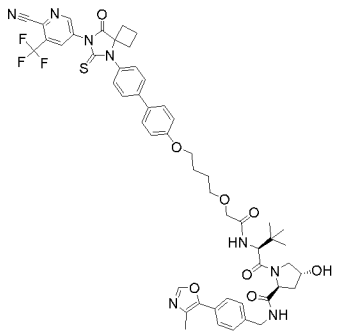
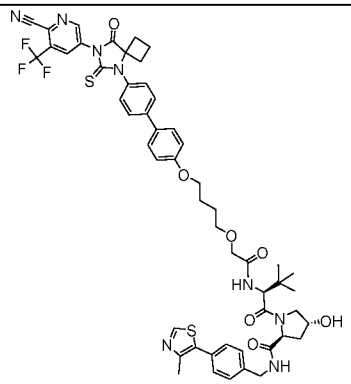
[0836] To a stirred mixture of methyl 4-[(5-oxopentyl)oxy]benzoate (269 mg, 1.13 mmol) and benzyl 2-aminoacetate hydrochloride (186 mg, 1.13 mmol) in DCE (5.00 mL) was added acetic acid (181 µL, 2.26 mmol) and sodium triacetoxyborohydride (358 mg, 1.69 mmol) at rt. The reaction mixture was stirred at rt for 18h. To the reaction mixture was added 1N NaOH aqueous solution to adjust pH = ~10, the resulting mixture was then extracted with DCM (30 mL x 3). The organic layer was separated, washed with brine (10 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude material, which was purified by flash silica gel chromatography on a Teledyne Combiflash ISCO, eluting with MeOH/DCM (gradient v:v = 0:100 to 15:85) to yield the titled product (17 %).

[0837] **Table 14. Exemplary Compounds.**

Ex#	Structure	Compound name and Analytical data

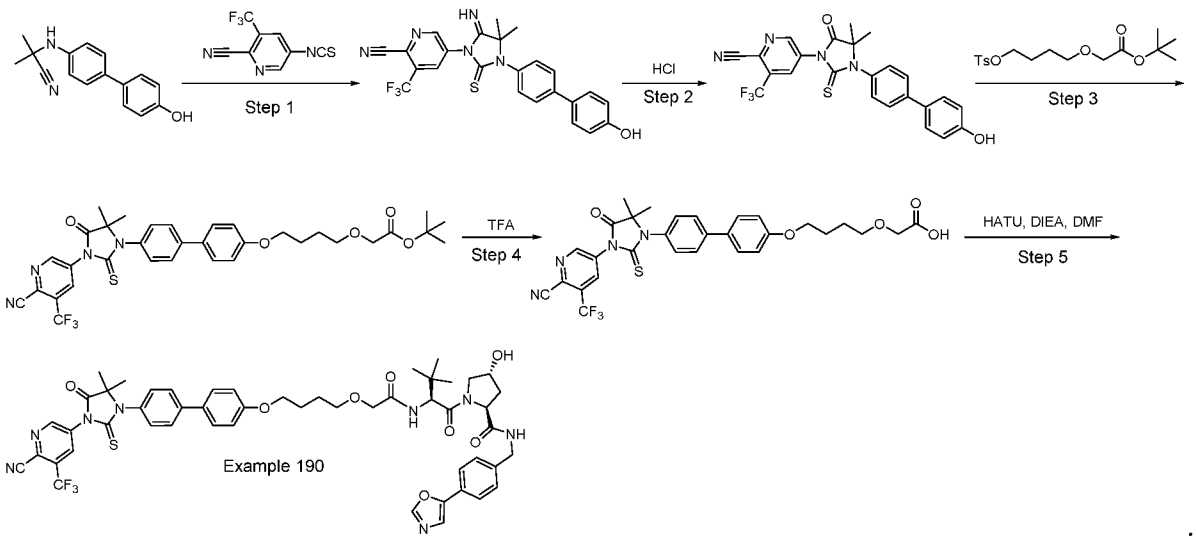
190		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD):δ9.14 (s, 1 H), 8.65 (d, *J* = 2.1 Hz, 1 H), 8.21-8.10 (m, 1 H), 7.74-7.50 (m, 6 H), 7.47-7.29 (m, 5 H), 7.10-6.97 (m, 2 H), 4.70-4.22 (m, 5 H), 4.15-3.96 (m, 4 H), 3.95-3.70 (m, 2 H), 3.70-3.50 (m, 2 H), 2.24-2.00 (m, 2 H), 2.00-1.80 (m, 4 H), 1.57 (s, 6 H), 1.00 (s, 9 H); LC-MS (ES^+): *m/z*, 995.20 [MH^+]
191		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(5-chloro-6-cyanopyridin-3-yl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide Mass (ES^+): *m/z* 961.20 [MH^+]
192		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide Mass (ES^+): *m/z* 1009.20 [MH^+]
193		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide Mass (ES^+): *m/z* 1025.45 [MH^+]

194		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 9.19 (s, 1H), 8.86 (s, 1H), 8.70 (s, 1H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.40 (m, 6H), 7.05 (d, *J* = 8.8 Hz, 2H), 5.00 (d, *J* = 7.2 Hz, 1H), 4.56 (s, 1H), 4.64 (m, 1H), 4.44 (m, 1H), 4.10 (m, 2H), 4.06 (m, 2H), 3.86 (m, 1H), 3.76 (m, 1H), 3.66 (m, 2H), 2.47 (s, 3H), 2.22 (m, 1H), 1.92 (m, 5H), 1.62 (s, 6H), 1.49 (d, *J* = 6.8 Hz, 3H), 1.02 (s, 9H); LC-MS (ES+): *m/z* 1039.50 [MH^+]
195		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-oxazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 9.19 (s, 1H), 8.70 (s, 1H), 8.12 (s, 1H), 7.75-7.71 (d, *J* = 8.4 Hz, 2H), 7.61-7.55 (m, 4H), 7.42-7.38 (m, 4H), 7.05-7.01 (d, *J* = 8.8 Hz, 2H), 5.00-4.96 (d, *J* = 7.2 Hz, 1H), 4.56 (s, 1H), 4.64-4.62 (m, 1H), 4.44-4.41 (m, 1H), 4.12-4.01 (m, 2H), 4.00-3.98 (m, 2H), 3.86-3.81 (m, 1H), 3.74-3.71 (m, 1H), 3.67-3.65 (m, 2H), 2.38 (s, 3H), 2.22-2.18 (m, 1H), 1.98-1.88(m, 3H), 1.88-1.82(m, 2H),1.62 (s, 6H), 1.48-1.46 (d, *J* = 6.8 Hz, 3H), 1.03 (s, 9H); LC-MS (ES+): *m/z* 1023.50 [MH^+]
196		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-3-fluorophenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide Mass (ES^+): *m/z* 1057.15 [MH^+]
197		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-3-fluorophenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide Mass (ES^+): *m/z* 1043.20 [MH^+]

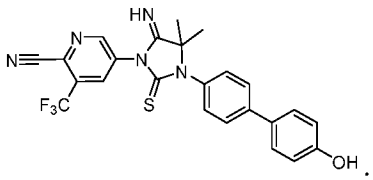
198		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 9.20 (s, 1H), 8.68 (s, 1H), 8.10 (s, 1H), 7.78-7.75 (d, *J* = 8.4 Hz, 2H), 7.69-7.60 (m, 4H), 7.48-7.45 (m, 4H), 7.08-7.01 (d, *J* = 8.8 Hz, 2H), 4.73 (s, 1H), 4.56-4.51 (m, 3H), 4.33-4.30 (m, 1H), 4.17-4.09 (m, 2H), 4.06-4.01 (m, 2H), 3.92-3.85 (m, 2H), 3.83-3.78 (m, 2H), 2.80-2.61 (m, 4H), 2.38 (s, 3H), 2.3-2.02 (m, 3H), 1.99-1.85 (m, 4H), 1.72-1.61 (m, 1H), 1.48-1.39 (m, 2H), 1.05 (s, 9H); LC-MS (ES^+): *m/z* 1021.40 [MH^+]
199		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 9.20 (s, 1H), 8.90 (s, 1H), 8.68 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.52-7.41 (m, 6H), 7.04 (d, *J* = 8.4 Hz, 2H), 4.73 (s, 1H), 4.60-4.51 (m, 3H), 4.37-4.35 (m, 1H), 4.17-4.11 (m, 2H), 4.05-4.01 (m, 2H), 3.90-3.88 (m, 1H), 3.84-3.78 (m, 1H), 3.68-3.65 (m, 2H), 2.76-2.60 (m, 4H), 2.42 (s, 3H), 2.30-2.05(m, 3H), 2.01-1.85 (m, 4H), 1.68-1.64 (m, 1H), 1.41-1.29 (m, 3H),1.05 (s, 9H); LC-MS (ES+): *m/z* 1037.10 [MH^+]

[0838] Examples 191-199 was synthesized according to similar procedure described for synthesis of example 190, by using corresponding starting materials and intermediates.

[0839] Synthesis of example 190:

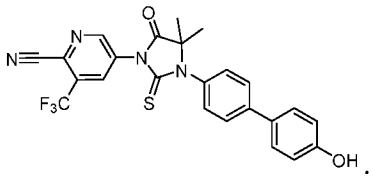


[0840] Step 1: Synthesis of 5-{3-[4-(4-hydroxyphenyl)phenyl]-5-imino-4,4-dimethyl-2-sulfanylideneimidazolidin-1-yl}-3-(trifluoromethyl)pyridine-2-carbonitrile:



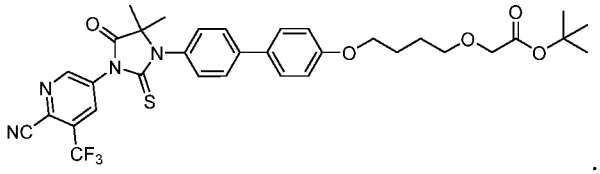
[0841] To a stirred solution of 5-isothiocyanato-3-(trifluoromethyl)pyridine-2-carbonitrile (440.0 mg, 1.92 mmol) in N,N-dimethylpyridin-4-amine (322.0 mg, 2.64 mmol) and toluene (10.0 mL) was added 2-[[4-(4-hydroxyphenyl)phenyl]amino]-2-methylpropanenitrile (400.0 mg, 1.59 mmol) under a nitrogen atmosphere at rt. The resulting solution was stirred at 100 °C for 12h. The reaction mixture was then concentrated under reduced pressure to give a crude material, which was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether, v/v = 1/1) to give the titiled product (yield: 17%). Mass (ES^+): *m/z* 482.20[MH^+] .

[0842] Step 2: Synthesis of 5-{3-[4-(4-hydroxyphenyl)phenyl]-4,4-dimethyl-5-oxo-2-sulfanylideneimidazolidin-1-yl}-3-(trifluoromethyl)pyridine-2-carbonitrile:



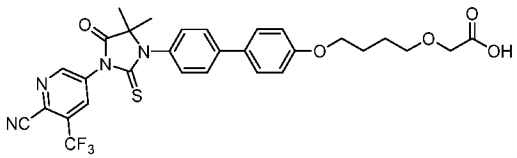
[0843] To a stirred solution of 5-{3-[4-(4-hydroxyphenyl)phenyl]-5-imino-4,4-dimethyl-2-sulfanylideneimidazolidin-1-yl}-3-(trifluoromethyl)pyridine-2-carbonitrile (160.0 mg, 0.33 mmol) in methanol (5.0 mL) was added hydrogen chloride aqueous solution (2N, 2.0 mL) at rt. The resulting solution was then refluxed for 2 h. The reaction was cooled to rt, concentrated under reduced pressure to give a crude material, which was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether, v/v = 1/1) to give the titled product (yield: 69%) as a yellow solid. LC-MS (ES^+): *m/z* 481.15[MH^+].

[0844] Step 3. Synthesis of tert-butyl 2-{4-[4-(4-{3-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetate:



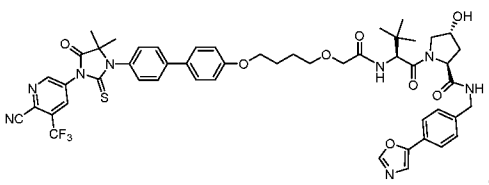
[0845] To a stirred solution of 5-{3-[4-(4-hydroxyphenyl)phenyl]-4,4-dimethyl-5-oxo-2-sulfanylideneimidazolidin-1-yl}-3-(trifluoromethyl)pyridine-2-carbonitrile (110.0 mg, 0.23 mmol) and tert-butyl 2-{4-[(4-methylbenzenesulfonyl)oxy]butoxy}acetate (163.0 mg, 0.45 mmol) in N,N-dimethylformamide (3.0 mL) was added potassium carbonate (62.9 mg, 0.46 mmol) at rt. The resulting mixture was stirred at 60°C for 3 h. The reaction was then cooled to rt, diluted with water (10 mL) and extracted with ethyl acetate (30 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate, concentrated under reduced pressure to give a crude material, which was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether, v/v =1/1) to give the titled product (yield: 98%) as a yellow solid.

[0846] Step 4. Synthesis of 2-{4-[4-(4-{3-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetic acid:



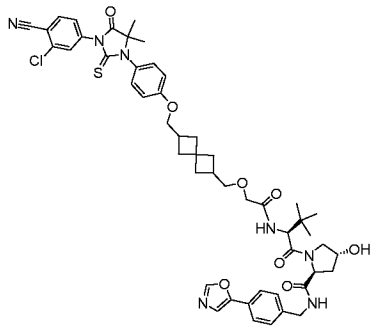
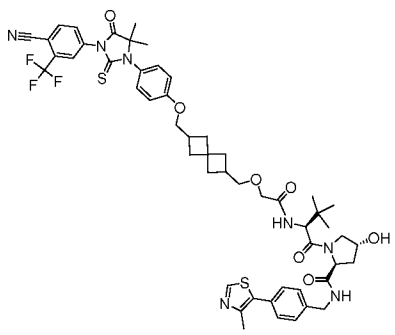
[0847] To a stirred solution of tert-butyl 2-{4-[4-(4-{3-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetate (150.0 mg, 0.22 mmol) in dichloromethane (2.0 mL) was added trifluoroacetic acid (2.0 mL) at rt. The resulting solution was stirred for 2h at rt. The resulting mixture was concentrated under reduced pressure to give a crude material, which was used for next step reaction without any further purifications. Mass (ES^+): *m/z* 613.00 [MH^+].

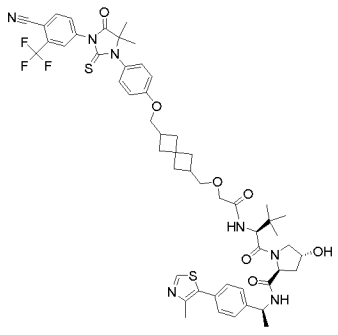
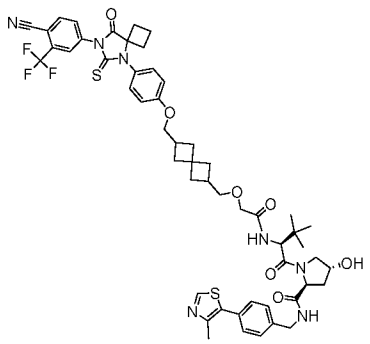
[0848] Step 5. Synthesis of example 190:



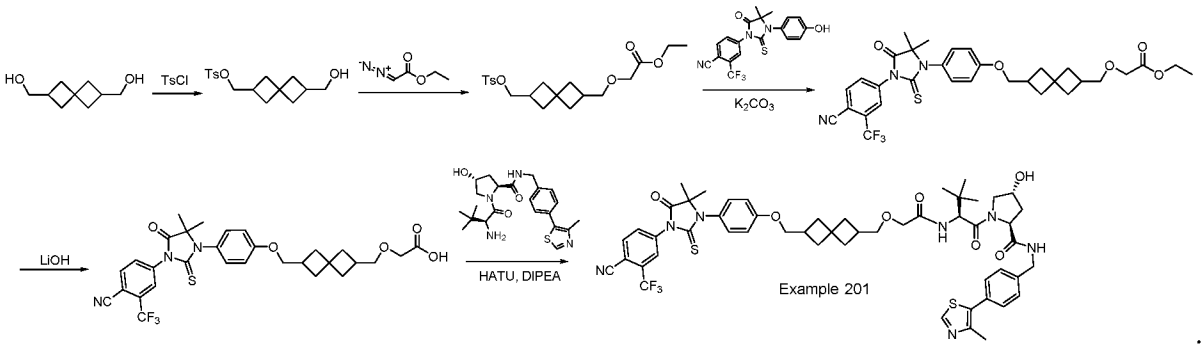
[0849] To a stirred solution of 2-{4-[4-(4-{3-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetic acid (80.0 mg, 0.13 mmol) and (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (53.8 mg, 0.13 mmol) in N,N-dimethylformamide (2.0 mL) was added O-(7-azabenzotriazol-1-yl)-N,N,N,N-tetramethyluronium hexafluorophosphate (51.0 mg, 0.13 mmol) and N-ethyl-N-isopropylpropan-2-amine (43.0 mg, 0.33 mmol) at rt. The resulting solution was stirred for 2h at rt. LC-MS indicated formation of the desired product. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (50 mL x 3). The organic layers were combined, washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude material, which was purified by a silica gel flash chromatography (eluent: ethyl acetate/petroleum ether, v/v = 1/1) to give the titled product as a white solid (yield: 45%).

[0850] Table 15. Exemplary Compounds.

Ex#	Structure	Compound name and Analytical data
200		(2S,4R)-1-[(2S)-2-(2-{[6-({4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenoxy}methyl)spiro[3.3]heptan-2-yl]methoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide Mass (ES^+): *m/z* 950.50 [MH^+]
201		(2S,4R)-1-[(2S)-2-[2-({6-[(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)methyl]spiro[3.3]heptan-2-yl}methoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^1H NMR (400 MHz, CD_3OD) δ 8.86 (s, 1H), 8.16 (d, *J* = 8 Hz, 2H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.51-7.42 (m, 4H), 7.27 (d, *J* = 8.8 Hz, 2H), 7.07-7.00 (m, 2H), 4.71 (s, 1H), 4.63-4.53 (m, 3H), 4.38-4.33 (m, 1H), 4.04-3.95 (m, 2H), 3.93-3.85 (m, 3H), 3.84-3.80 (m, 1H), 3.53 (s, 2H), 2.63-2.59 (m, 1H), 2.57-2.49 (m, 4H), 2.29-2.19 (m, 3H), 2.18-2.06 (m, 3H), 2.01-1.87 (m, 4H), 1.55 (s, 6H), 1.05 (s, 9H); LC-MS (ES^+): *m/z* 1014.20 [MH^+]

202		(2S,4R)-1-[(2S)-2-[2-({6-[(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)methyl]spiro[3.3]heptan-2-yl}methoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO) δ 8.99 (s, 1H), 8.45 (d, *J* = 7.6 Hz, 1H), 8.39 (d, *J* = 8.0 Hz, 1H), 8.29 (s, 1H), 8.08 (d, *J* = 9.6 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.38-7.25 (m, 5H), 7.07 (d, *J* = 8.8 Hz, 2H), 5.17 (s, 1H), 4.91 (s, 1H),4.54 (d, *J* = 9.6 Hz, 1H), 4.45-4.38 (m, 1H), 4.29 (s, 1H), 3.96-3.94 (m, 2H), 3.93-3.90 (m, 2H), 3.60-3.57 (m, 2H), 3.43 (s, 2H), 2.59-2.41 (m, 5H), 2.23-2.04 (m, 5H), 1.93-1.77 (m, 5H), 1.49 (s, 6H), 1.37 (d, *J* = 7.2 Hz, 3H), 0.95 (s, 9H); LC-MS (ES$^+$): *m/z* 1028.20 [MH$^+$]
203		(2S,4R)-1-[(2S)-2-[2-({6-[(4-{7-[4-cyano-3-(trifluoromethyl)phenyl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl}phenoxy)methyl]spiro[3.3]heptan-2-yl}methoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide Mass (ES$^+$): *m/z* 1026.25 [MH$^+$]

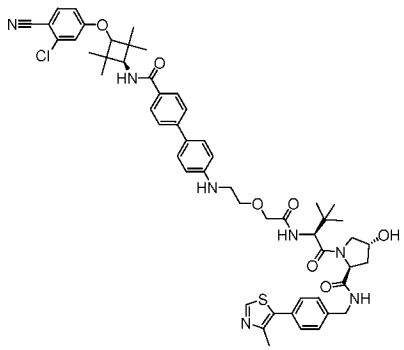
[0851] Example 201was synthesized according chemistry shown below, utilizing similar procedures used for the synthesis of example 75.



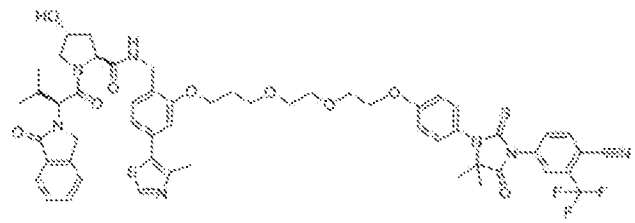
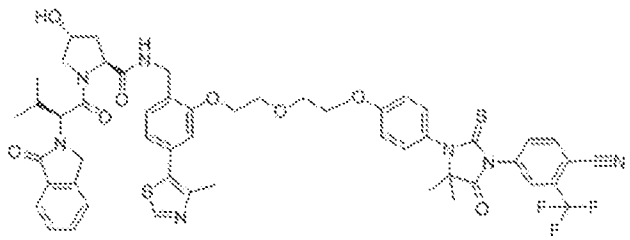
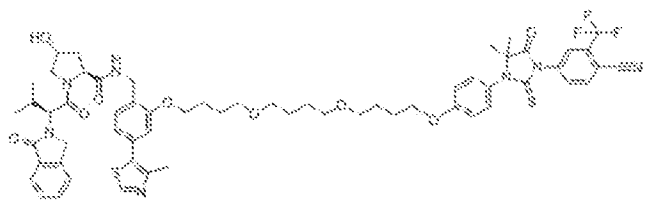
[0852] Examples 200, 202-203 was synthesized according to similar procedure described for synthesis of example 201, by using corresponding starting materials and intermediates.

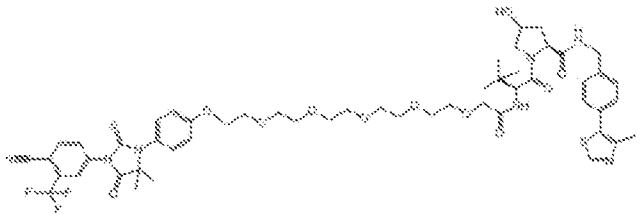
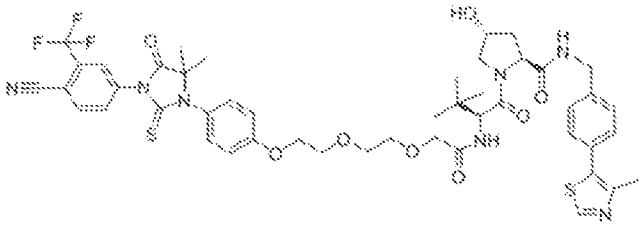
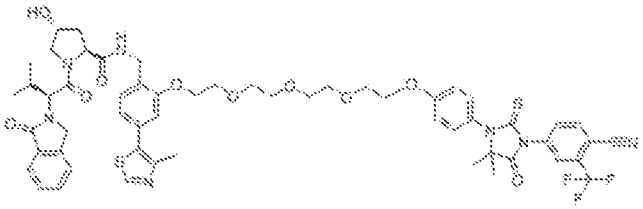
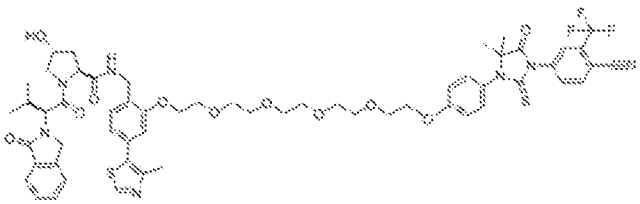
[0853] Table 16. Exemplary Compounds.

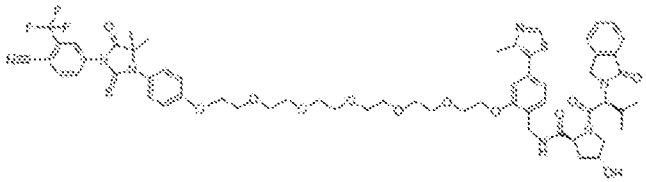
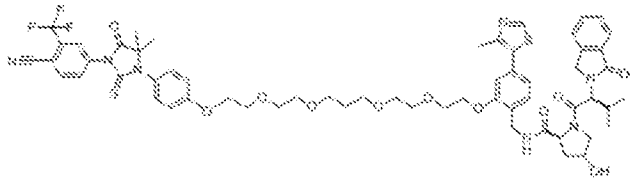
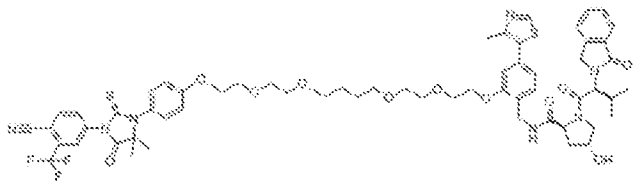
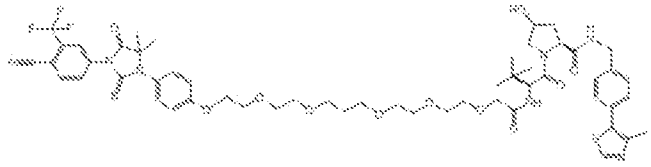
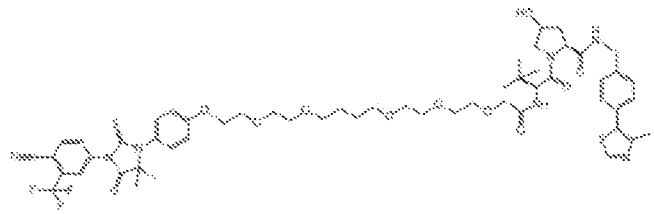
Ex#	Structure	Compound name and Analytical data

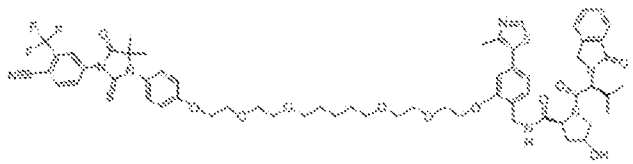
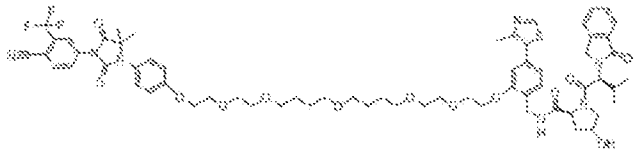
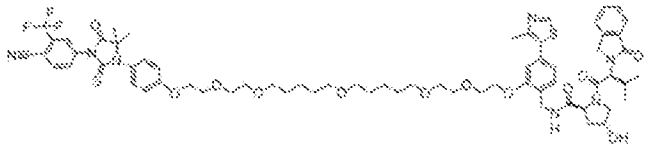
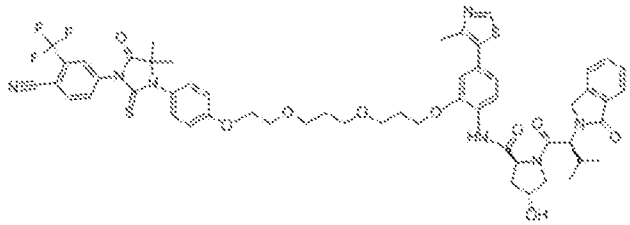
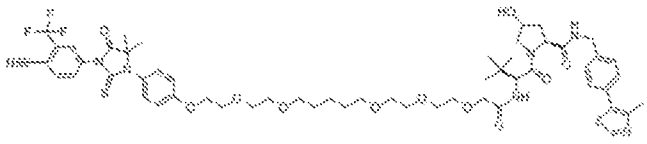
204		(2S,4R)-1-[(2S)-2-[2-(2-{[4-(4-{[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenyl)phenyl]amino}ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide Mass (ES^+): *m/z* 988.20 [MH^+]

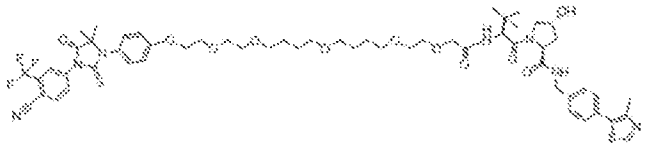
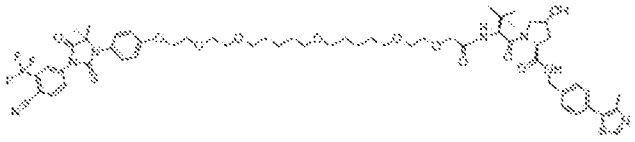
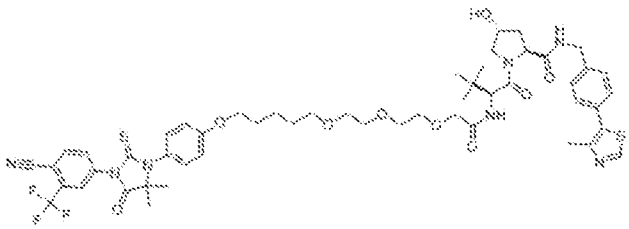
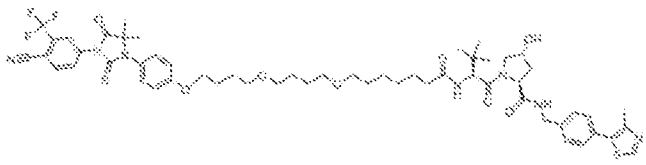
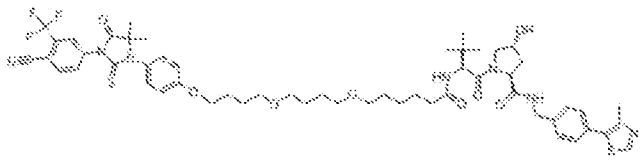
[0854] Table 17. Additional Exemplary Compounds.

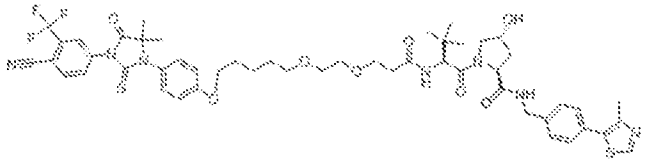
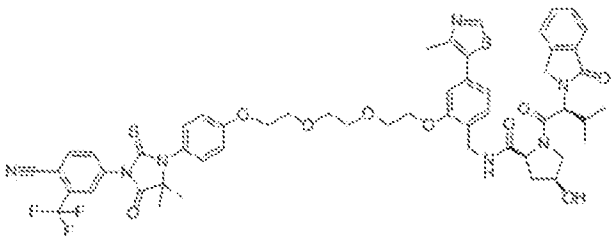
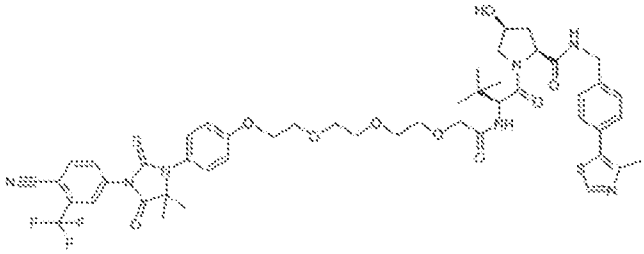
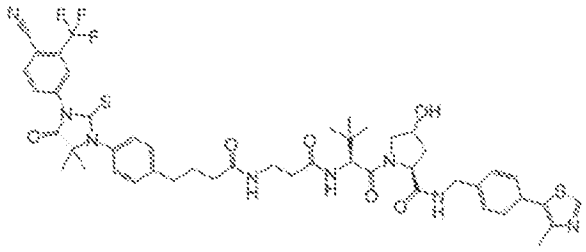
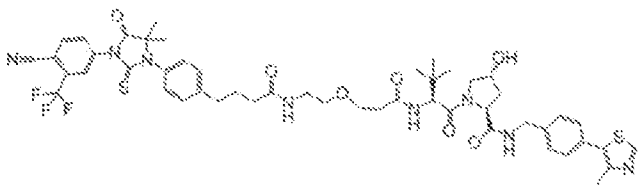
	Structure	Measured Mass Ion Data	
		MH^+ 1	MH^+ 2
205		1082.37	
206		1024.33	
207		1152.45	

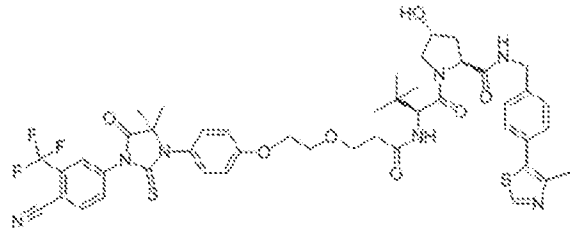
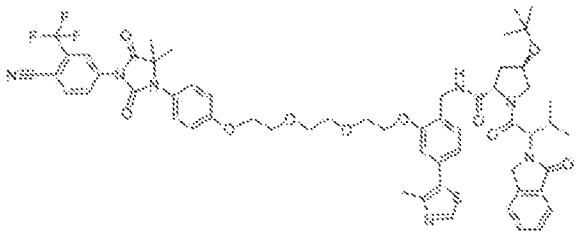
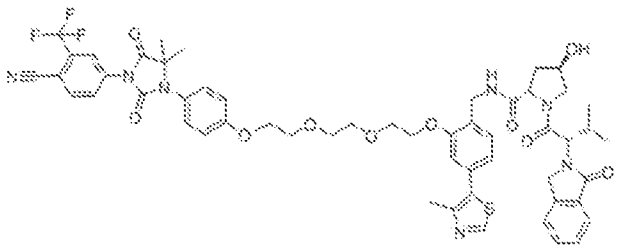
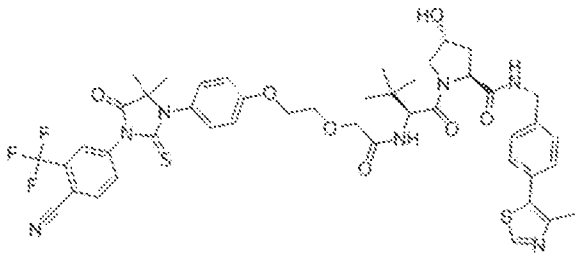
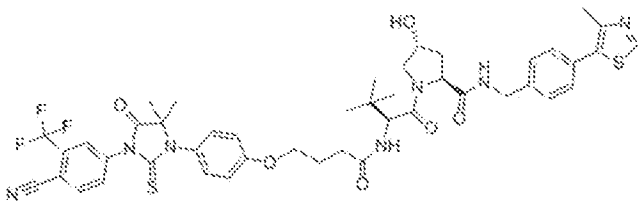
208		1096.41	
209		964.33	
210		1112.38	
211		1156.41	
212		1140.44	

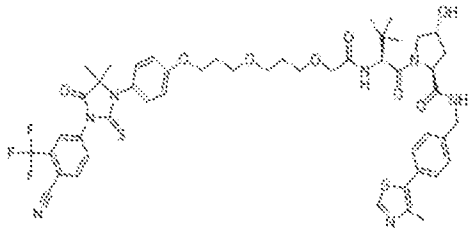
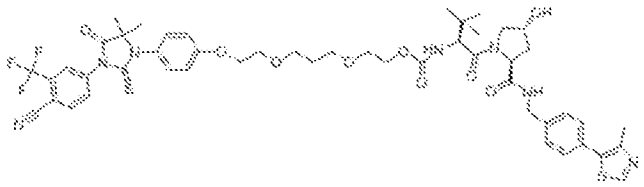
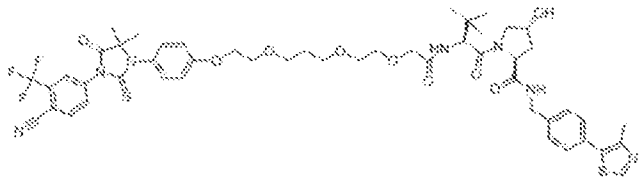
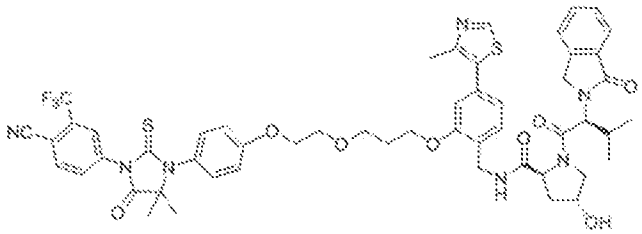
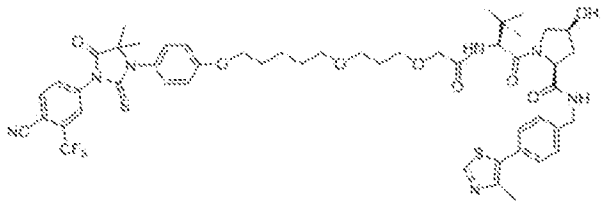
213		1200.44	
214		1170.42	
215		1184.44	
216		1110.43	
217		1124.44	

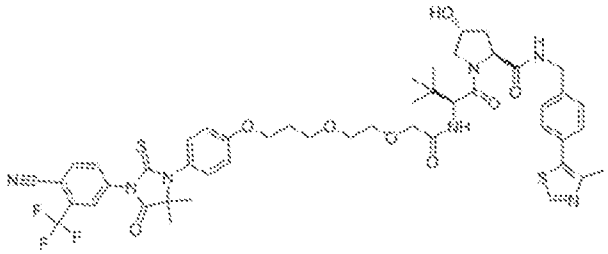
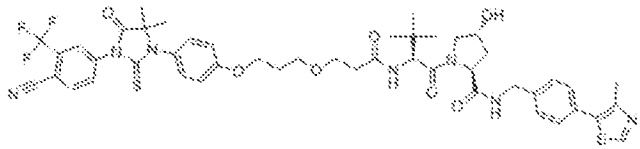
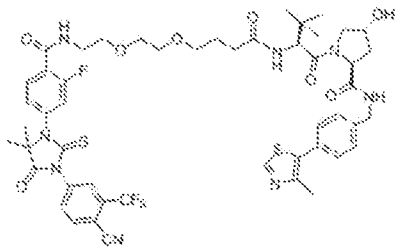
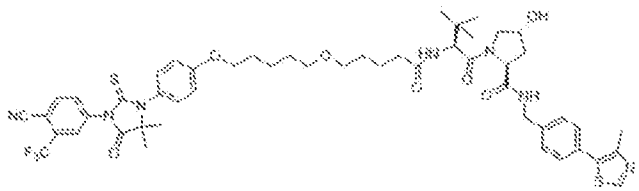
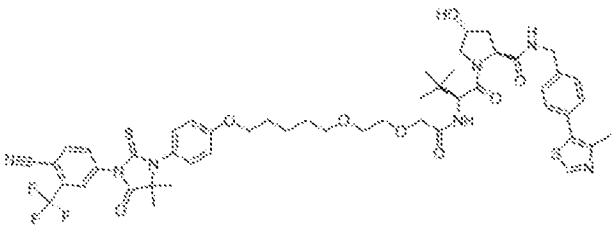
218		1198.46	
219		1256.50	
220		1284.53	
221		1096.39	
222		1138.46	

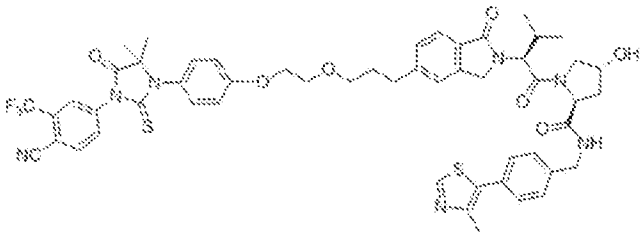
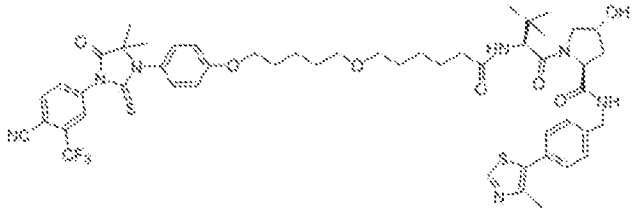
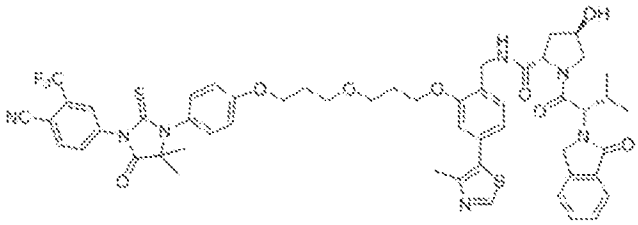
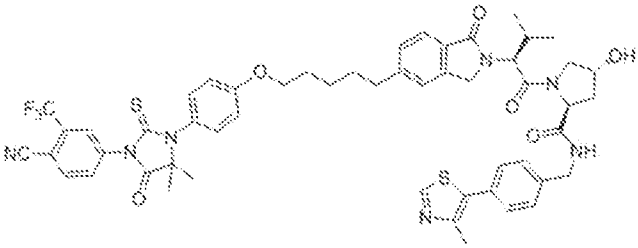
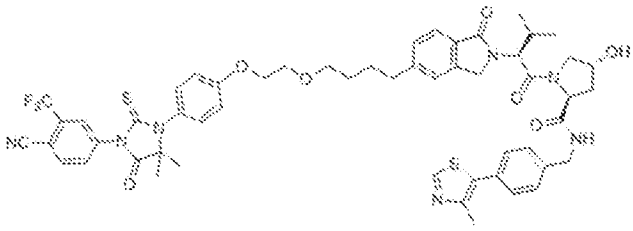
223		1152.47	
224		1180.50	
225		1050.40	
226		1090.47	
227		1076.46	

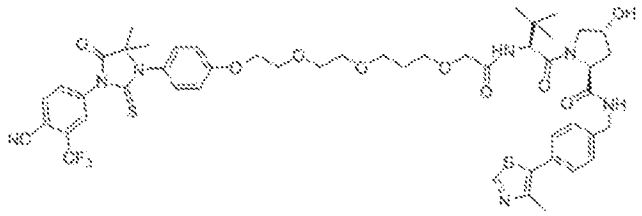
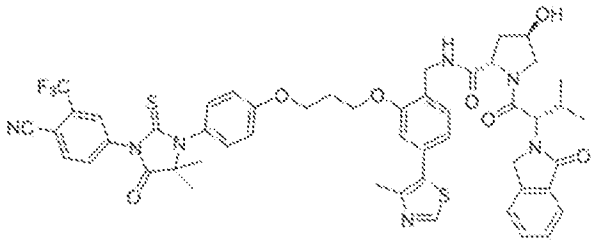
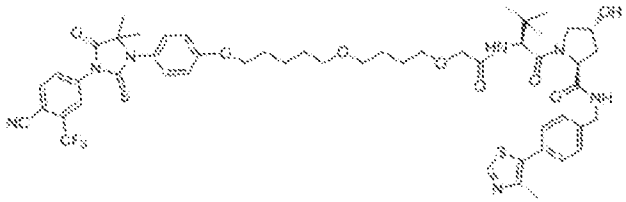
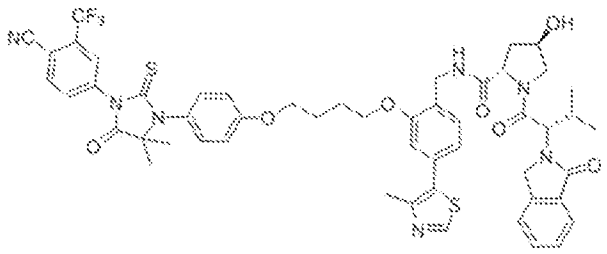
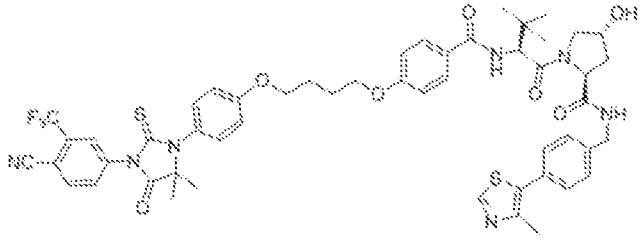
228		1020.40	
229		1068.36	
230		1008.36	
231		959.36	
232		1003.38	

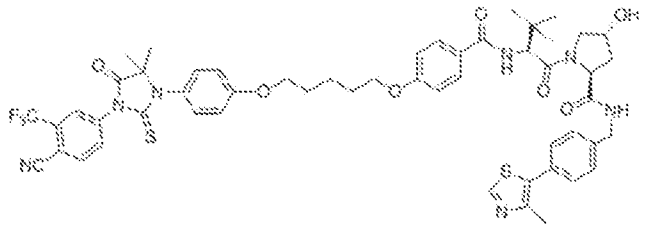
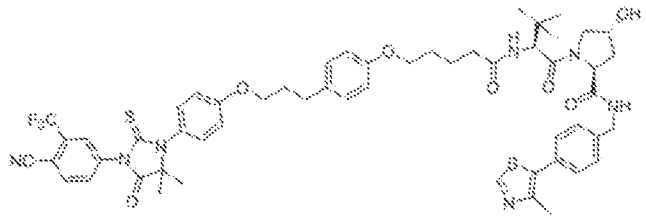
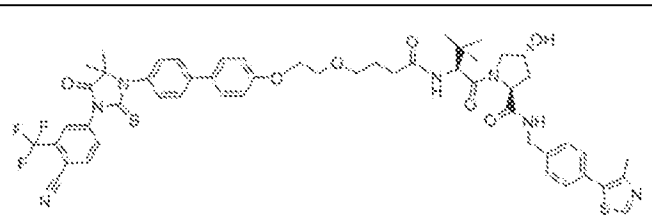
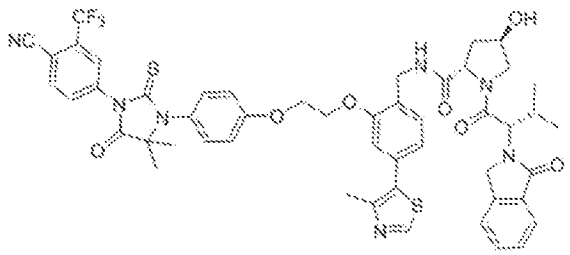
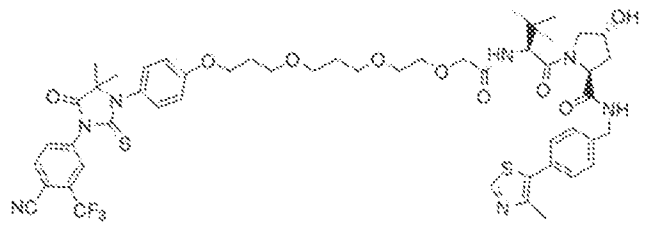
233		934.32	
234		1108.44	
235		1052.37	
236		920.29	
237		904.30	

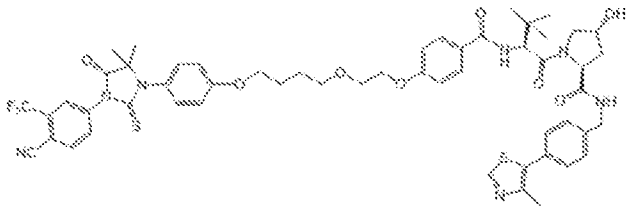
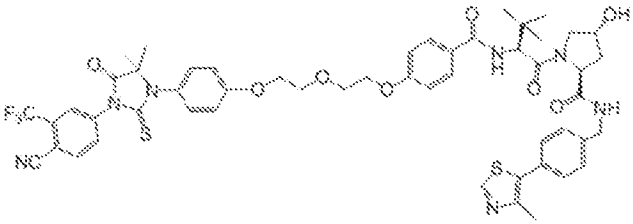
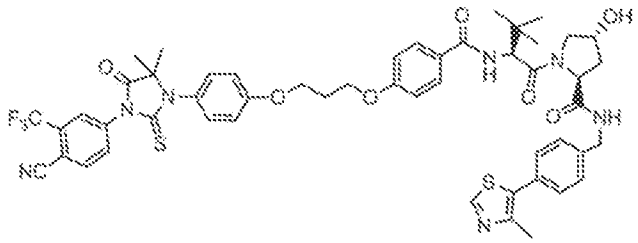
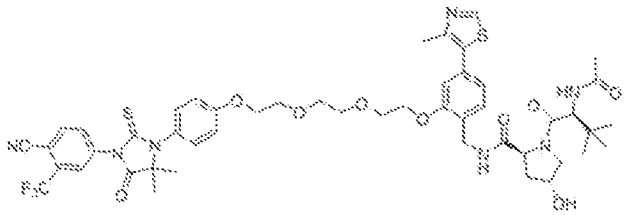
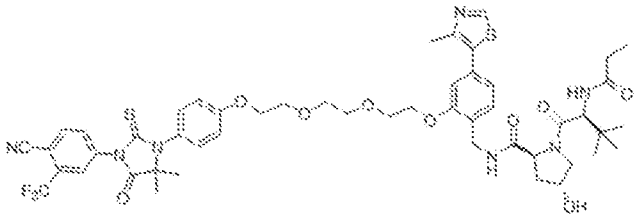
238		992.35	
239		1008.34	
240		1022.36	
241		1038.33	
242		1020.38	

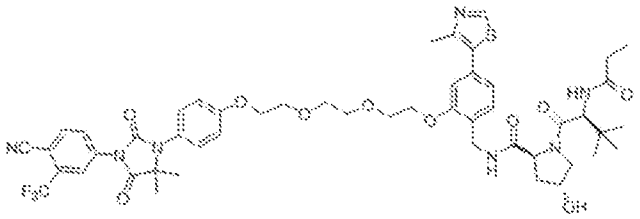
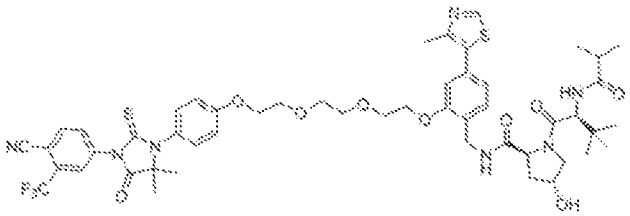
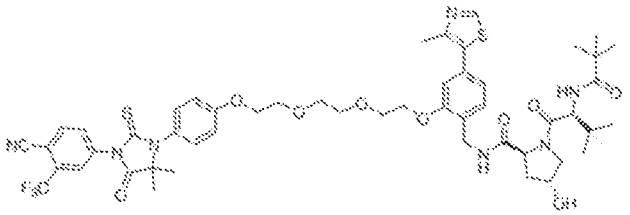
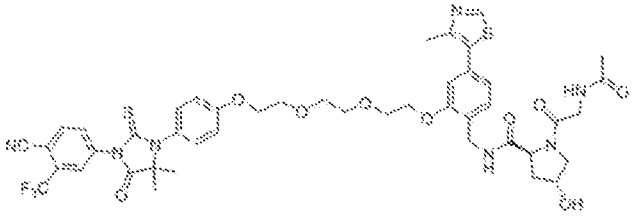
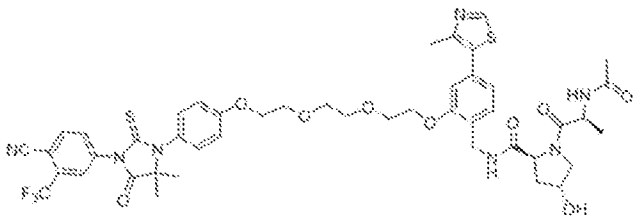
243		978.35	
244		948.34	
245		1037.37	
246		1004.40	
247		1006.38	

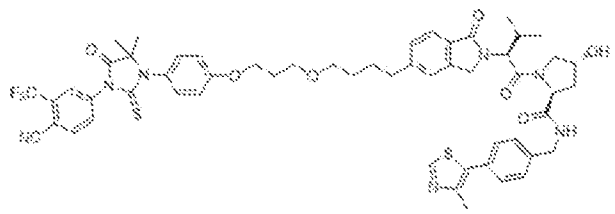
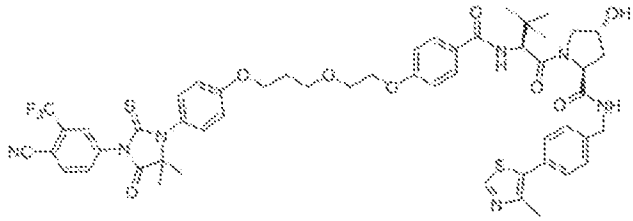
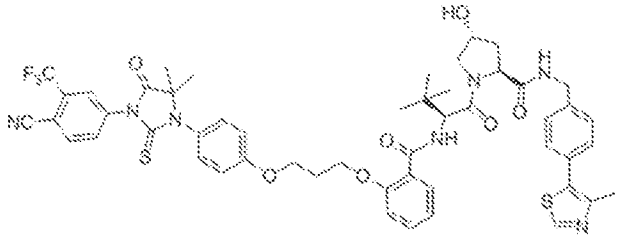
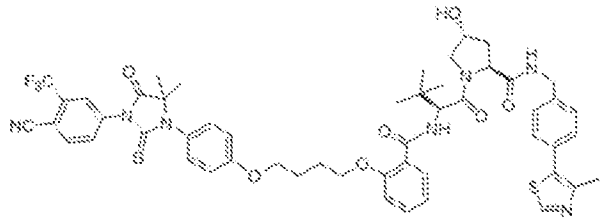
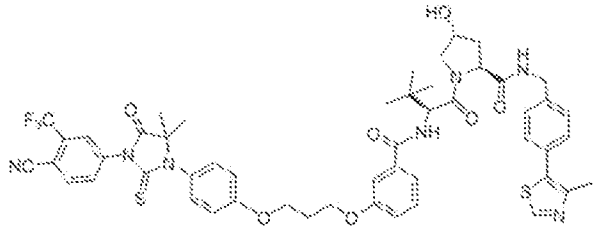
248		1022.35	
249		1040.40	
250		1052.35	
251		1006.35	
252		1036.36	

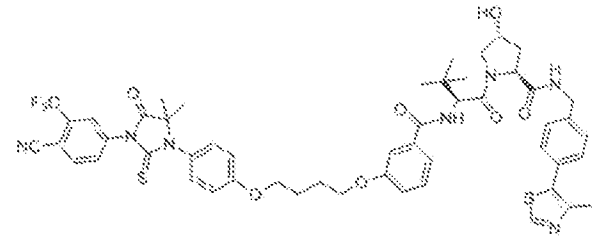
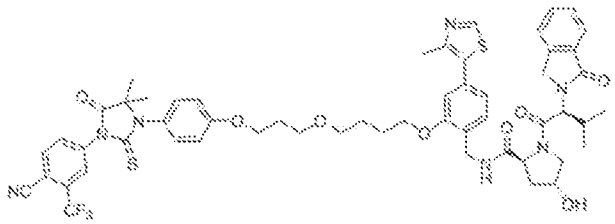
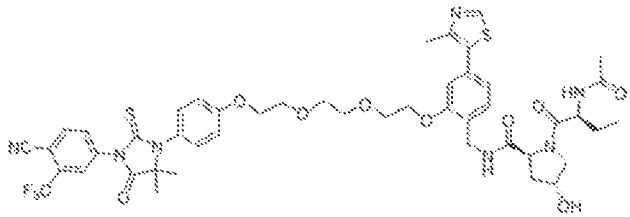
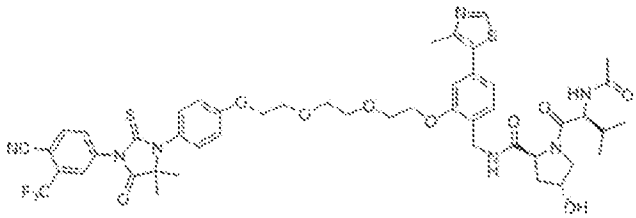
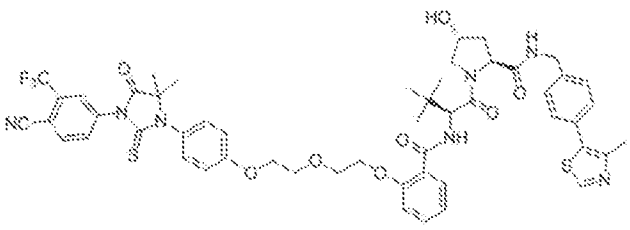
253		1022.36	
254		994.31	
255		1034.40	
256		1008.32	
257		1010.34	

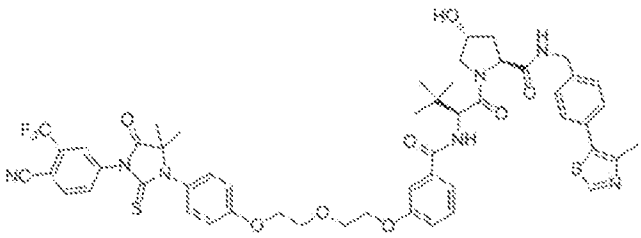
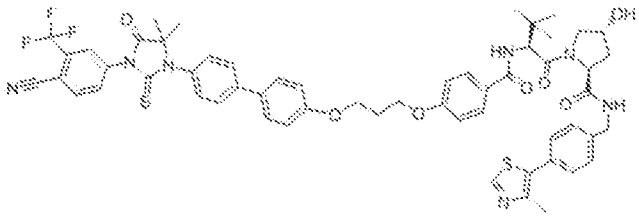
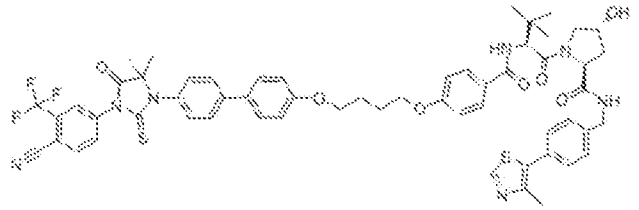
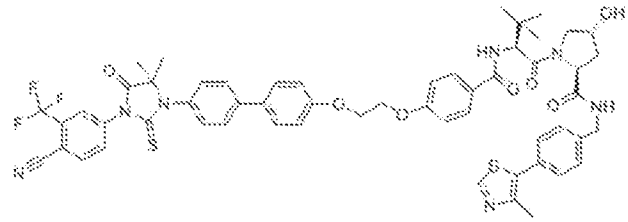
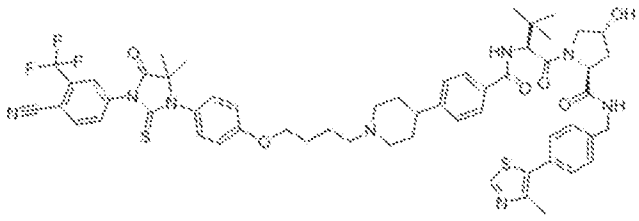
258		1024.35	
259		1052.38	
260		1024.34	
261		980.28	
262		1036.37	

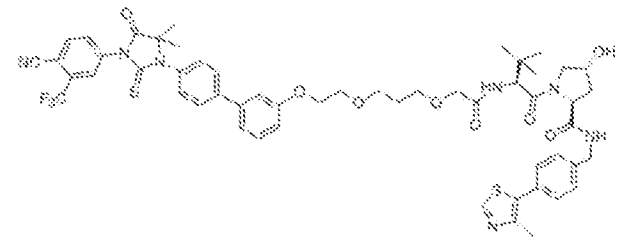
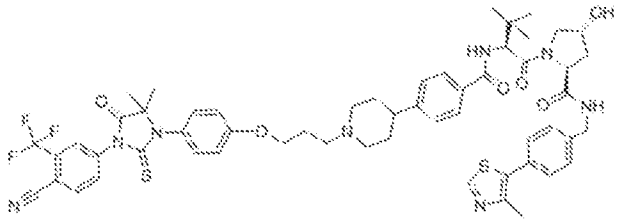
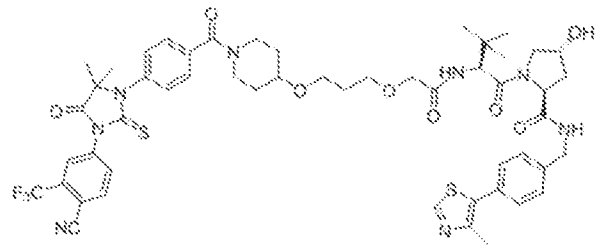
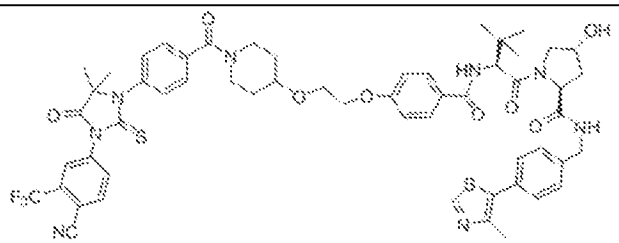
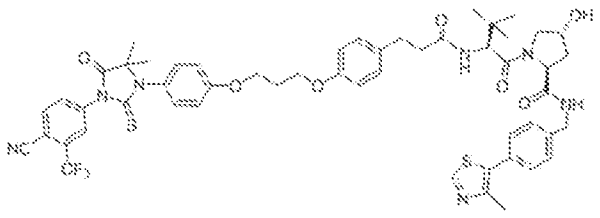
263		1054.35	
264		1026.32	
265			
266		1008.33	
267		1022.35	

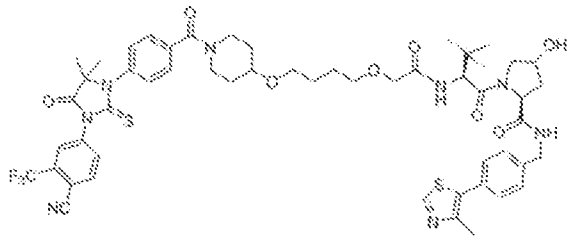
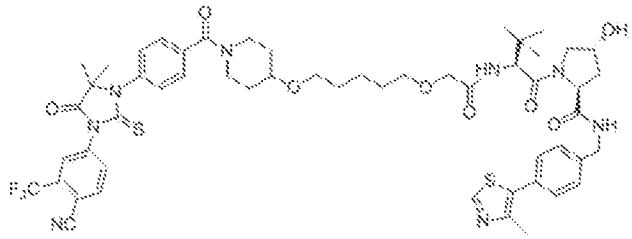
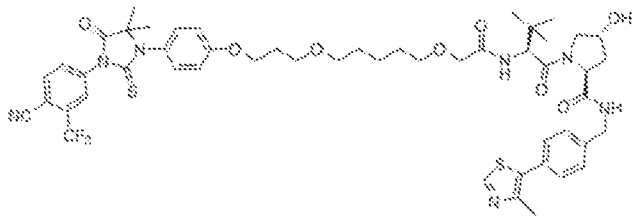
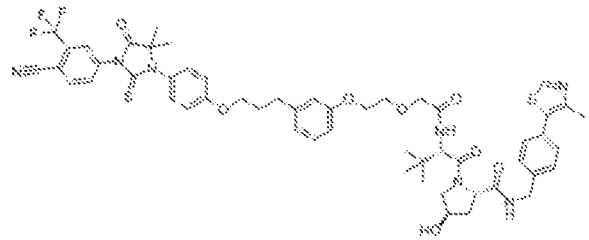
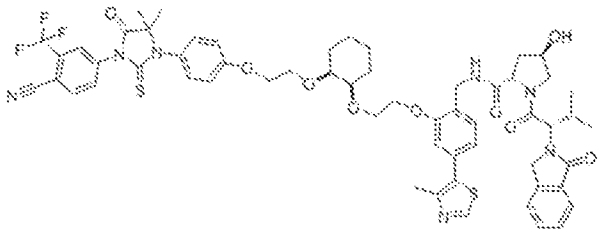
268		1006.37	
269		1036.36	
270		1050.38	
271		952.27	
272		966.29	

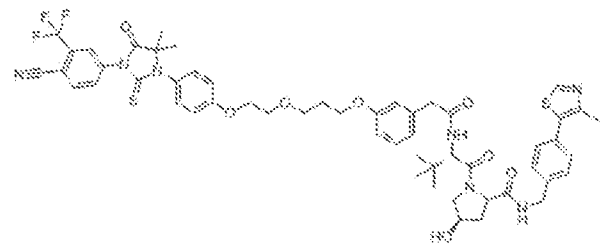
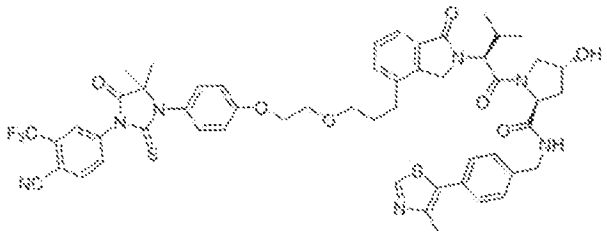
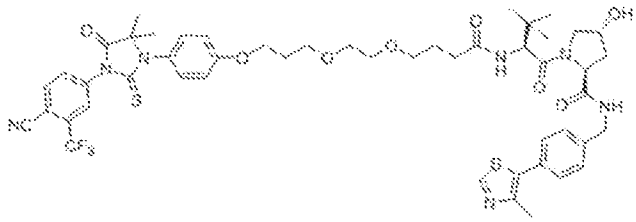
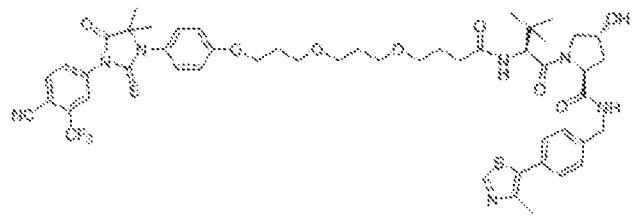
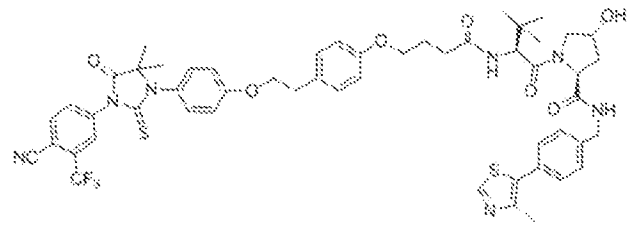
273		1050.36	
274		1040.34	
275		996.31	
276		1010.33	
277		996.32	

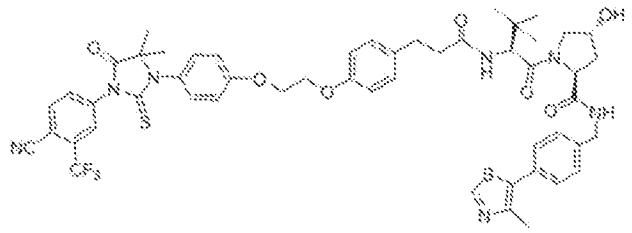
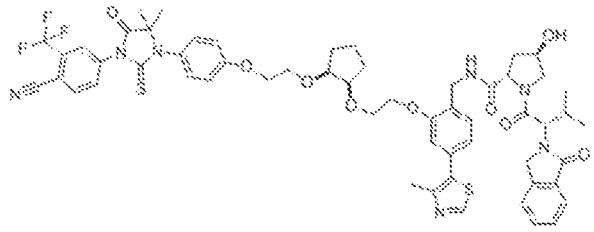
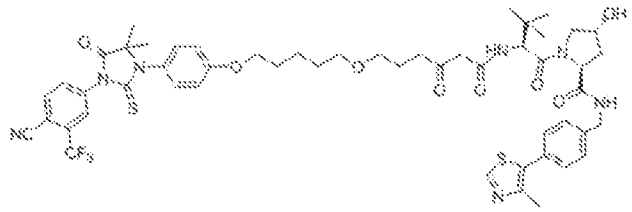
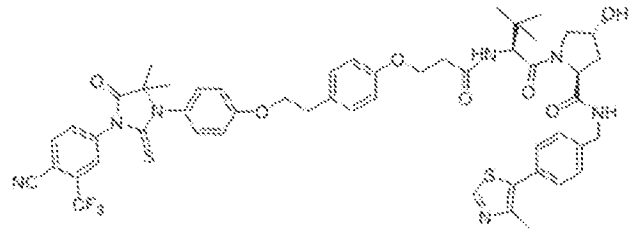
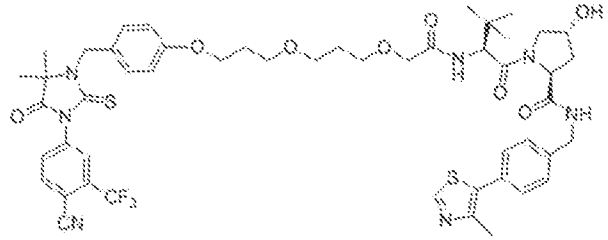
278		1010.33	
279		1066.36	
280		980.30	
281		994.32	
282		1048.30	

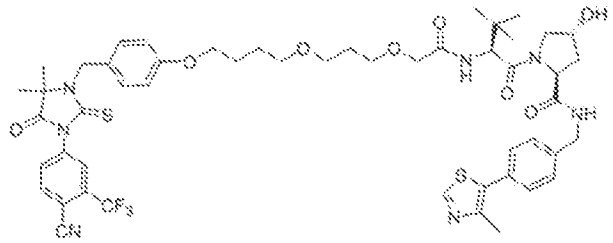
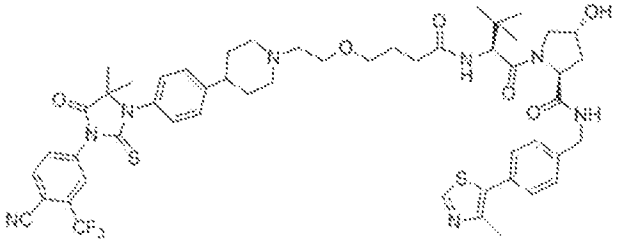
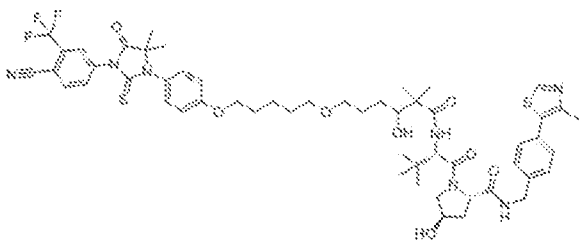
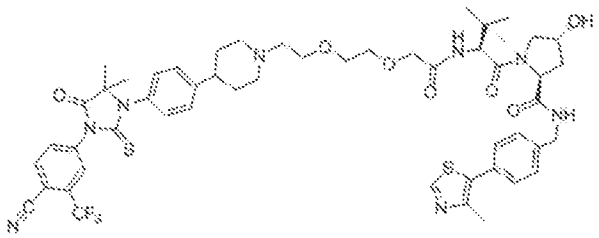
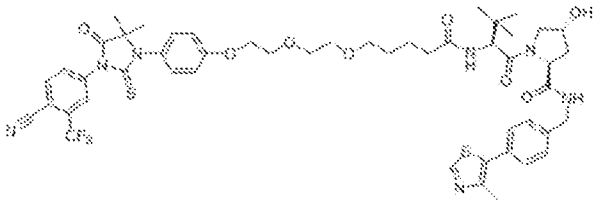
283		1026.32	
284		1072.34	
285		1086.36	
286		1058.33	
287		1077.41	

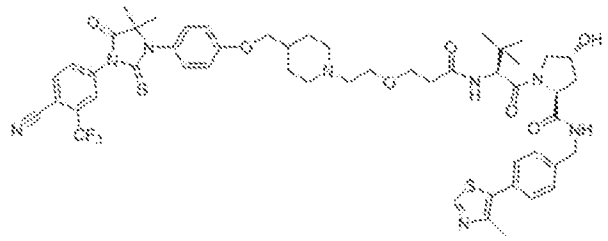
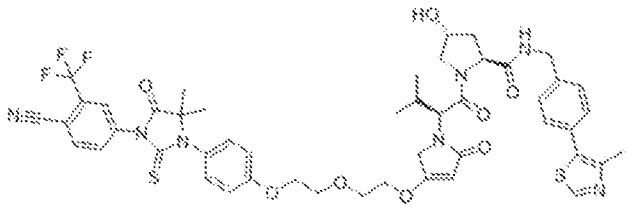
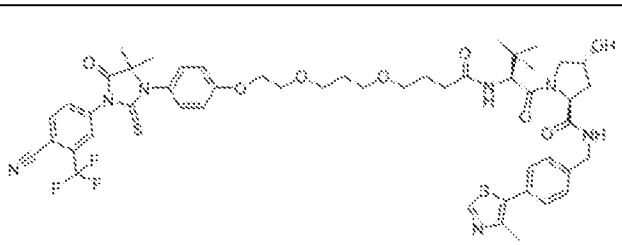
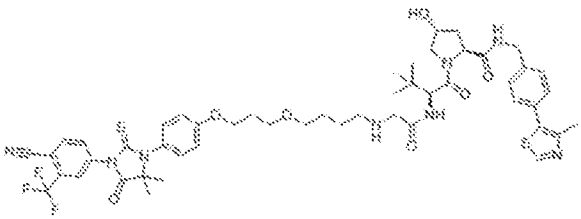
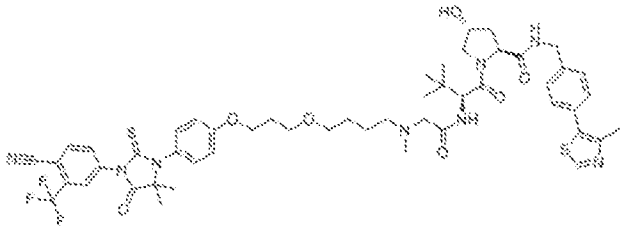
288		1054.37	
289		1063.41	
290		1045.38	
291		1093.38	
292		1024.44	

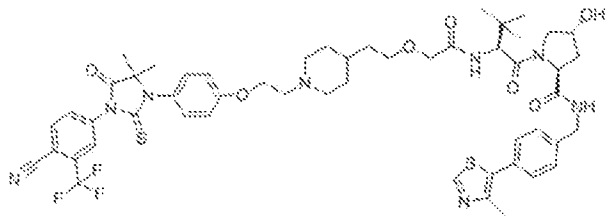
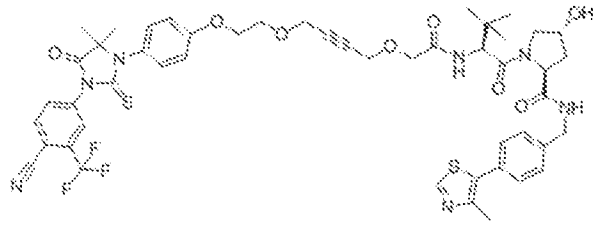
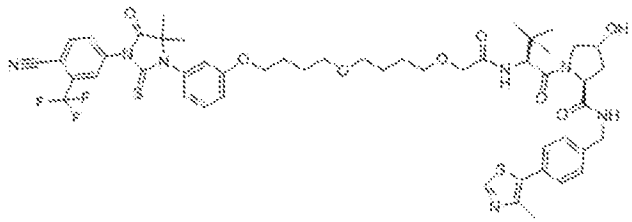
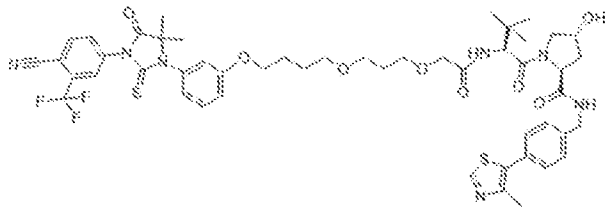
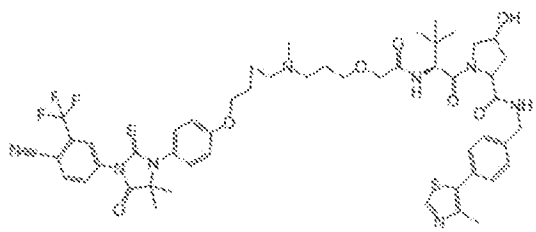
293		1059.48	
294		1073.49	
295		1020.46	
296		1054.46	
297		1122.49	

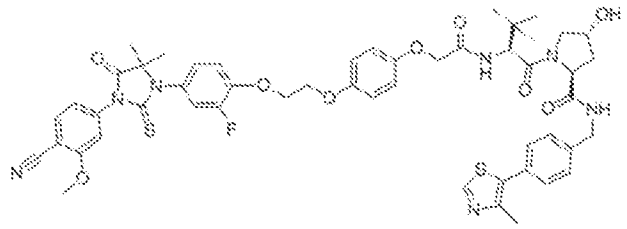
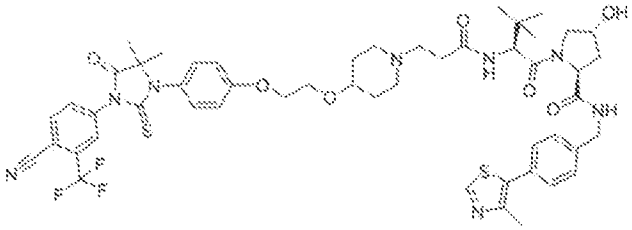
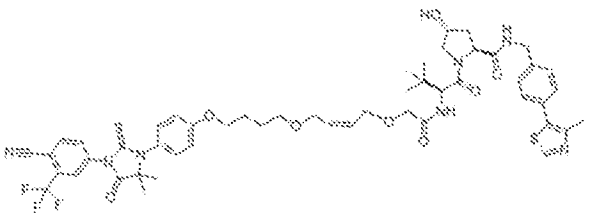
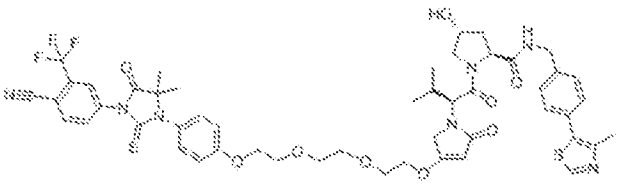
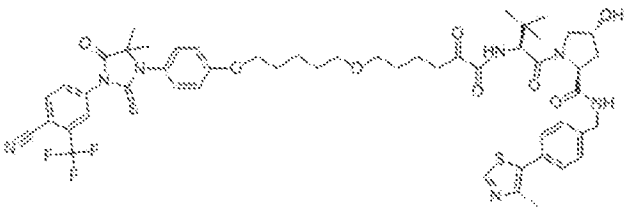
298		1054.46	
299		1022.41	
300		1006.44	
301		1020.45	
302		1024.42	

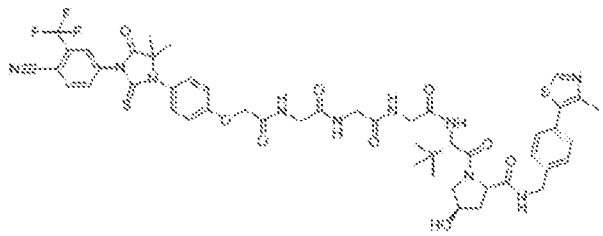
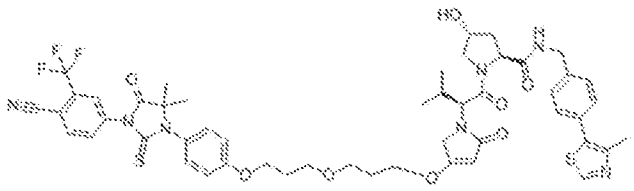
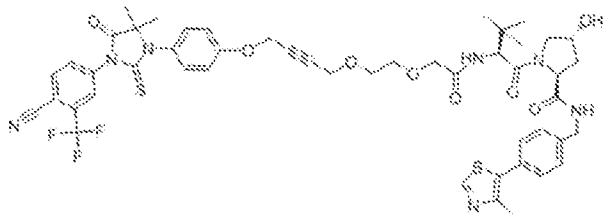
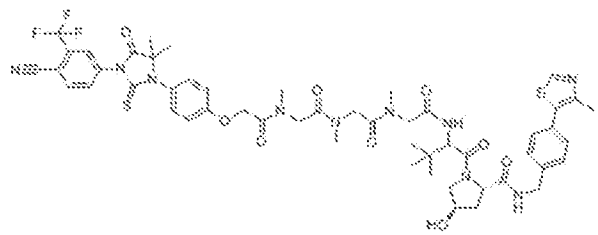
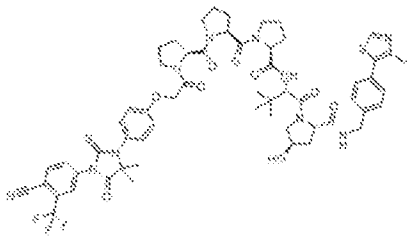
303		1010.41	
304		1108.44	
305		1032.46	
306		1010.41	
307		1006.44	

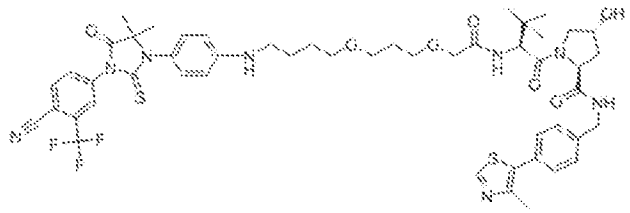
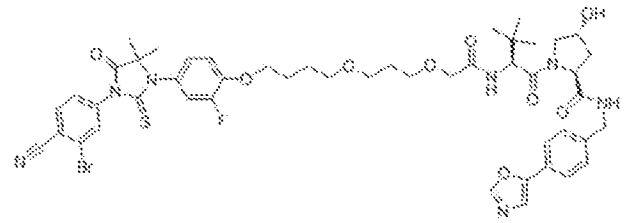
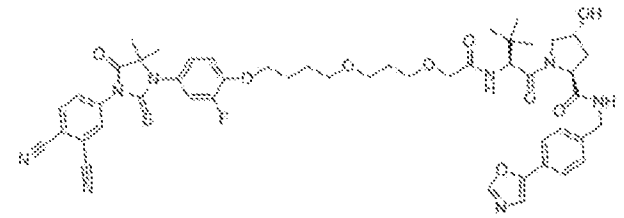
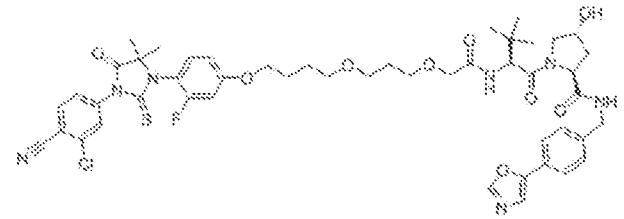
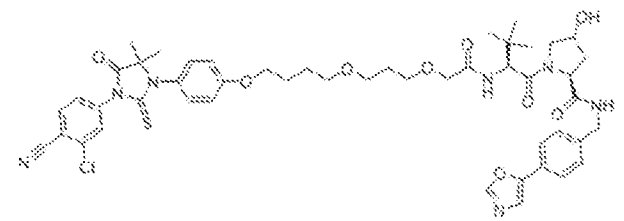
308		1020.47	
309		1015.49	
310		1062.51	
311		1031.48	
312		1006.45	

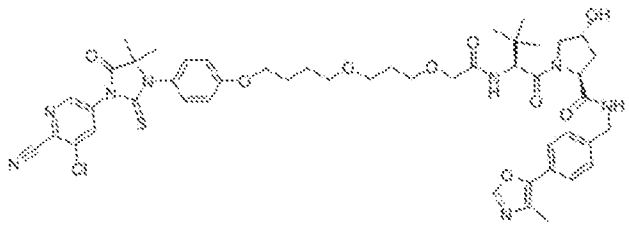
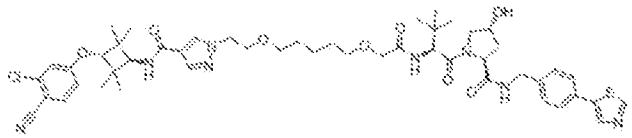
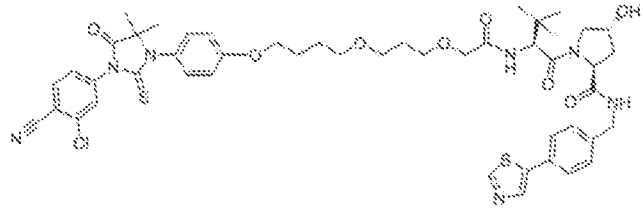
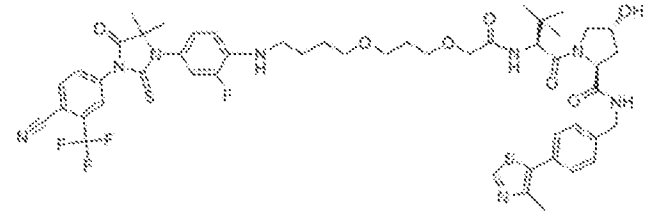
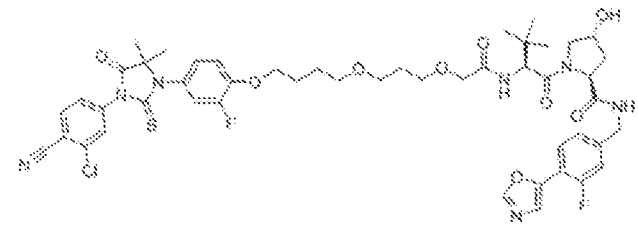
313		1031.48	
314		974.40	
315		1006.46	
316		1005.48	
317		1019.50	

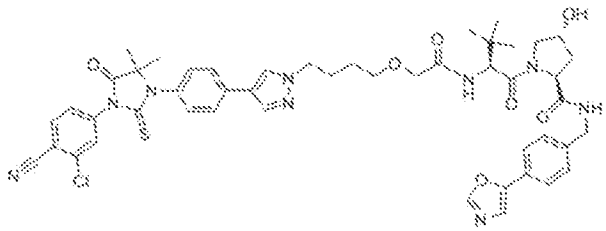
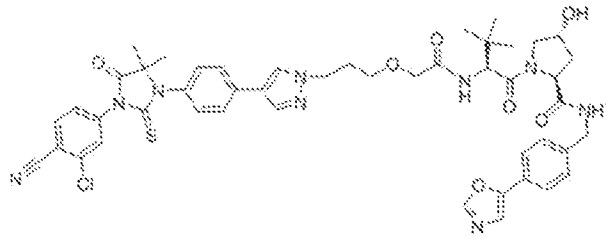
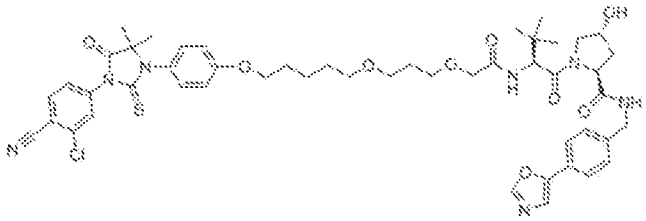
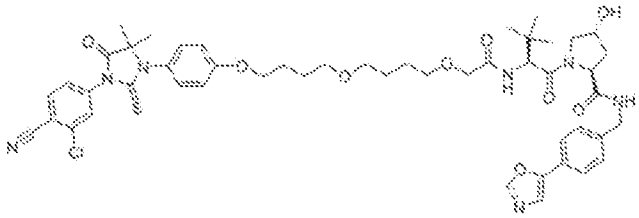
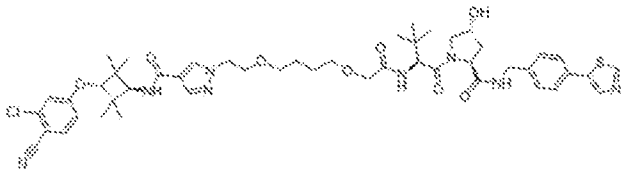
318		1031.40	
319		988.32	
320		1020.38	
321		1006.37	
322		1019.40	

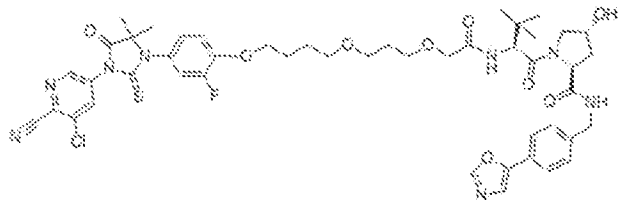
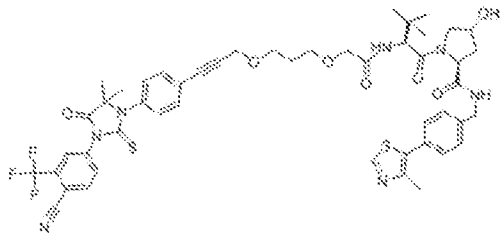
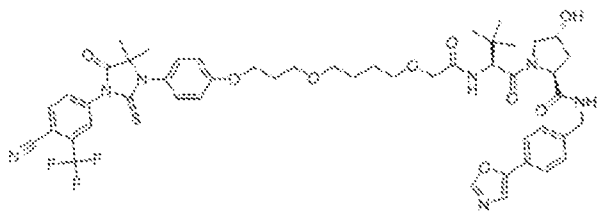
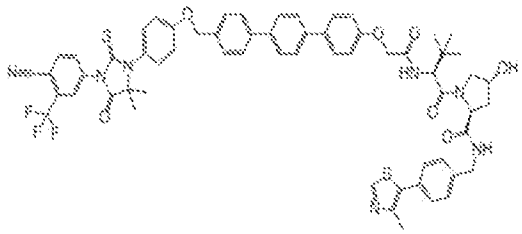
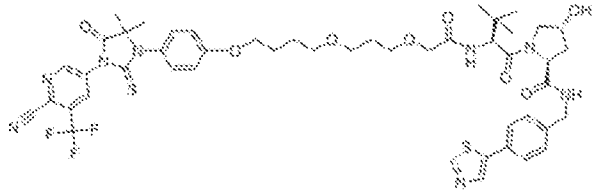
323		992.34	
324		1017.39	
325		1017.40	
326		1018.20	
327		1032.55	

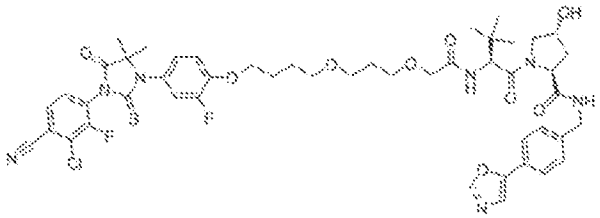
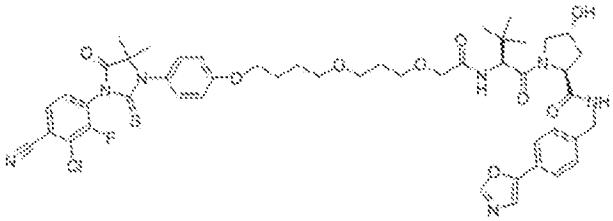
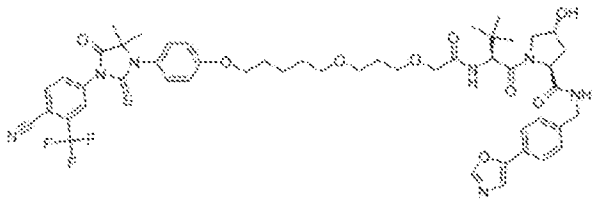
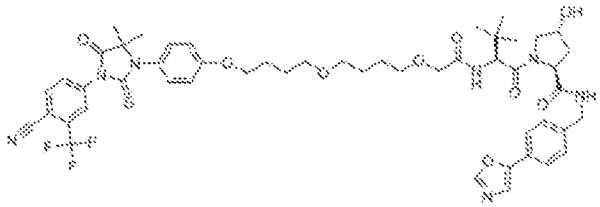
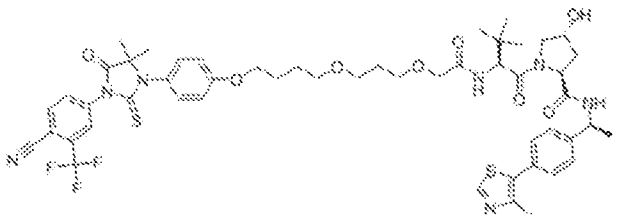
328		1047.34	
329		1002.10	
330		331.05	
331		1089.39	
332		1167.43	

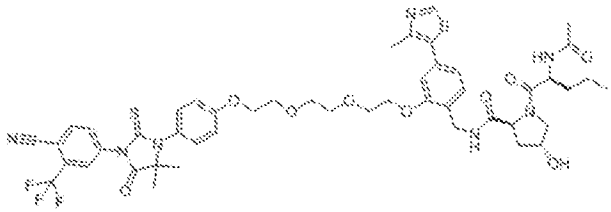
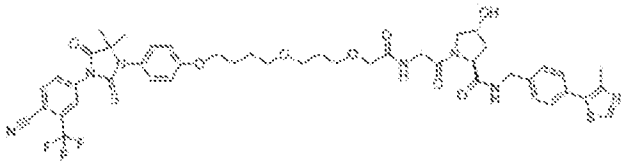
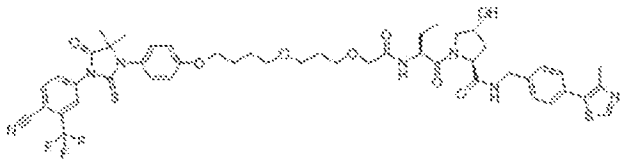
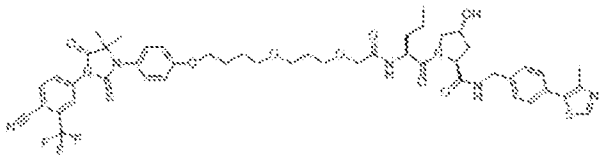
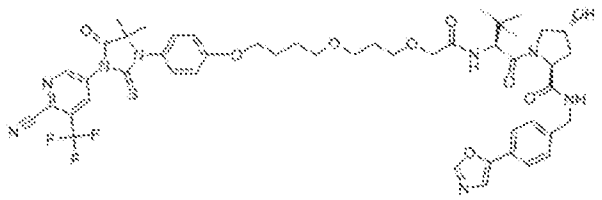
333		1005.40	
334		1004.40	
335		942.40	
336		960.50	
337		942.40	

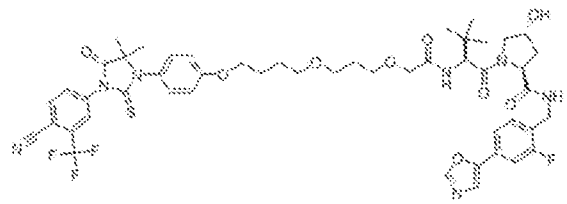
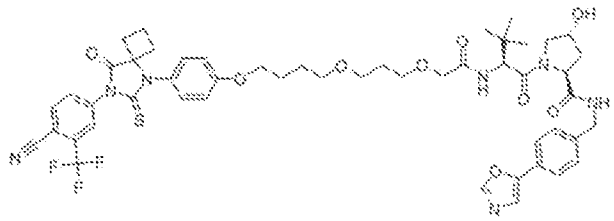
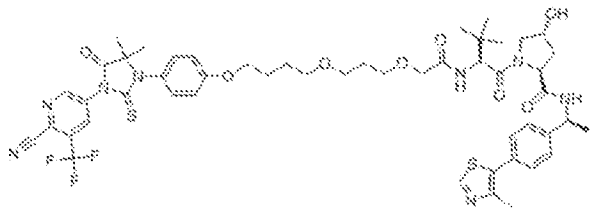
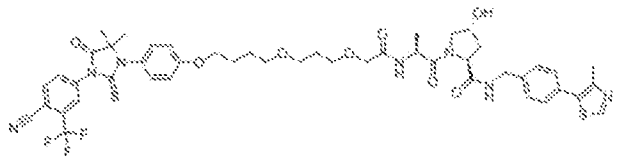
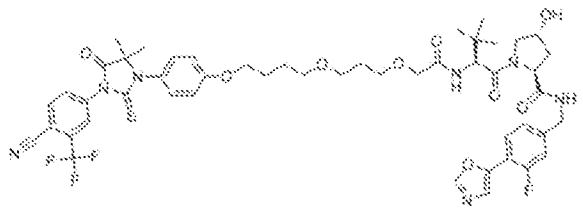
338		957.40	
339		959.20	
340		1023.40	
341		978.55	
342		934.30	

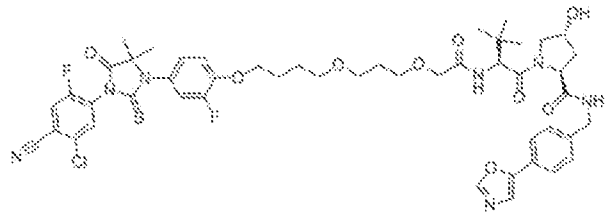
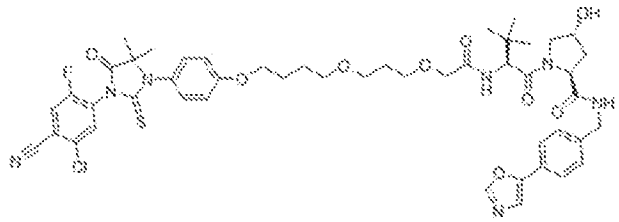
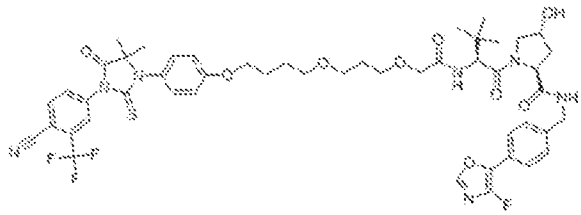
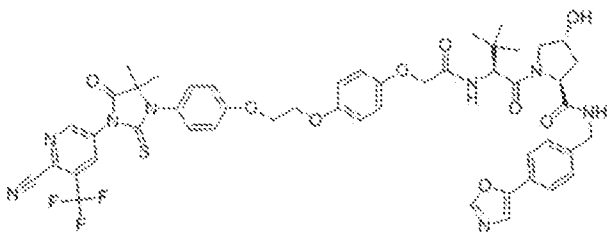
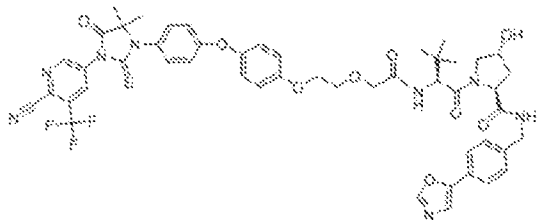
343		920.30	
344		956.30	
345		956.35	
346			
347		945.40	

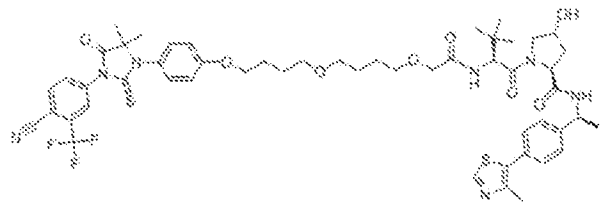
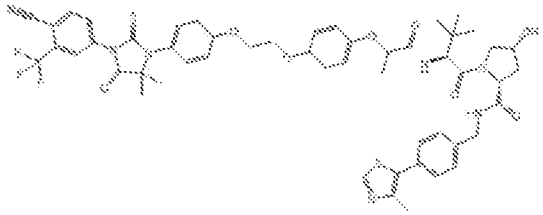
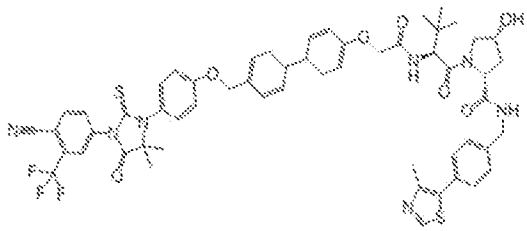
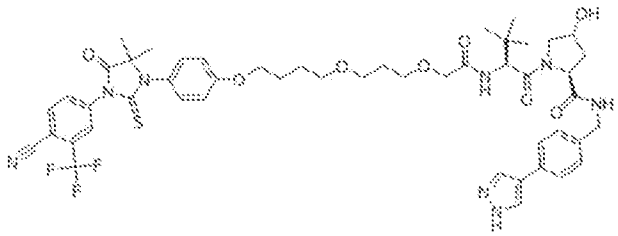
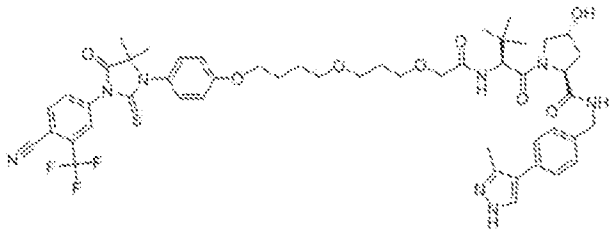
348		961.35	
349		972.40	
350		976.35	
351		-	
352		993.25	

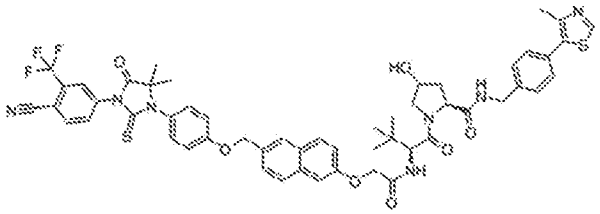
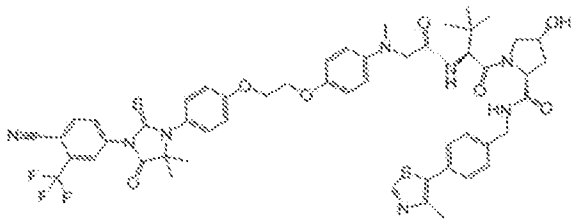
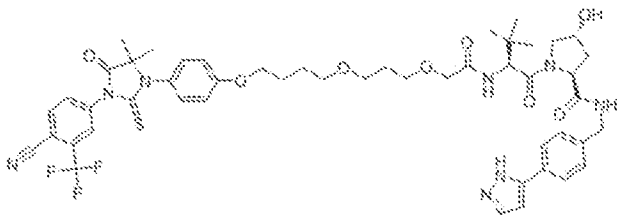
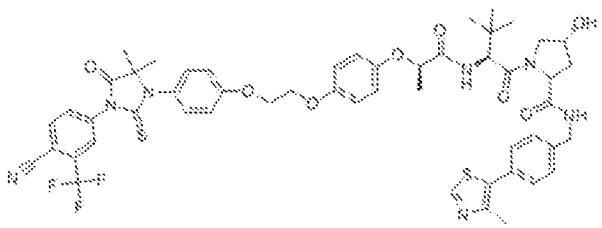
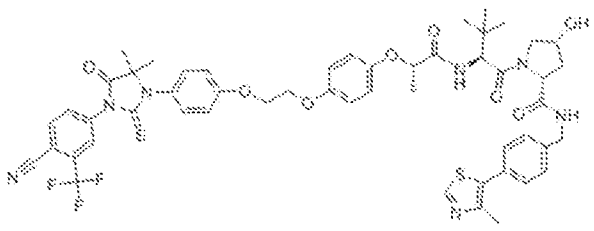
353		978.35	
354		960.35	
355		990.45	
356		990.45	
357		1020.40	

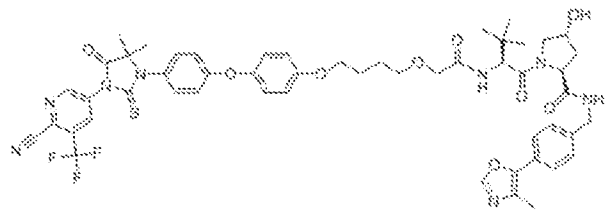
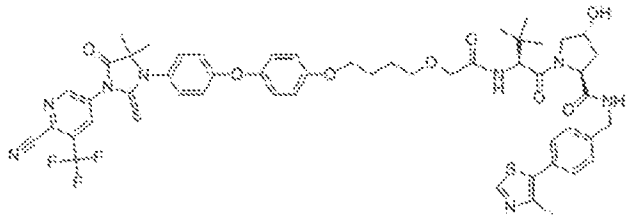
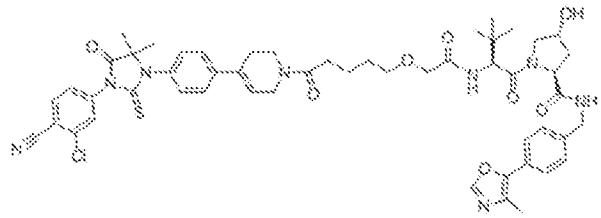
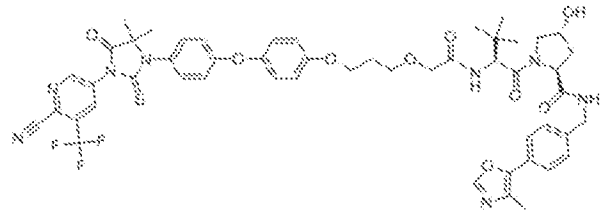
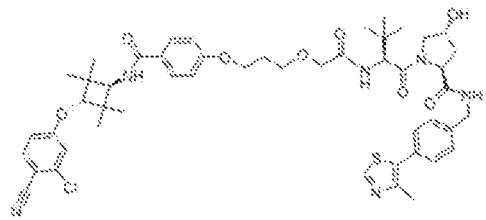
358		994.10	
359		950.20	
360		978.20	
361		992.20	
362		977.25	

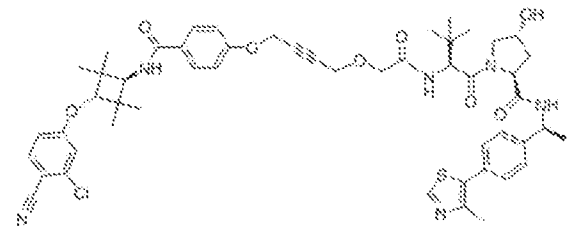
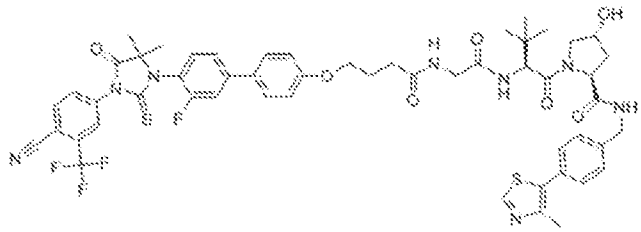
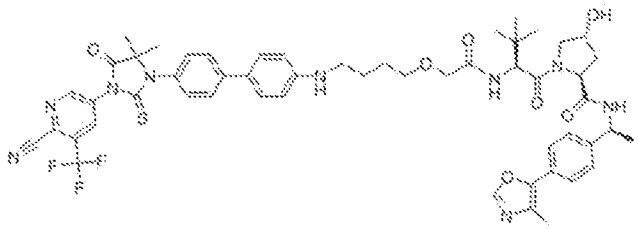
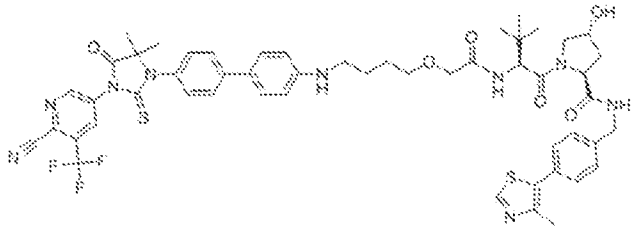
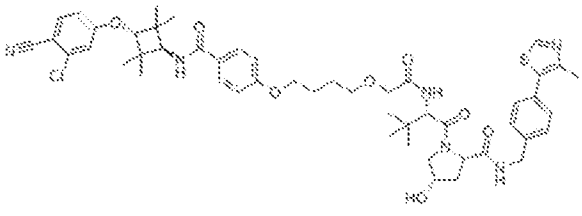
363		994.40	
364		988.40	
365		1021.20	
366		964.20	
367		994.40	

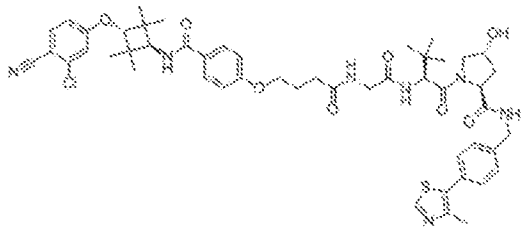
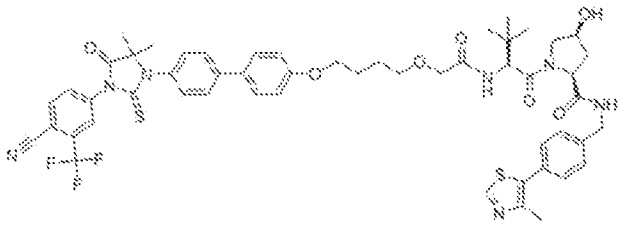
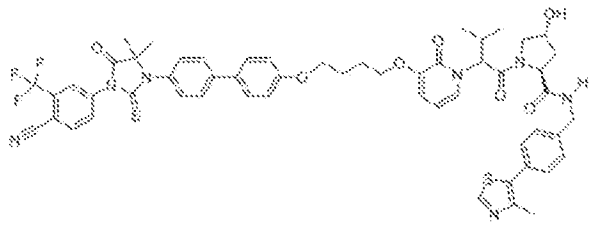
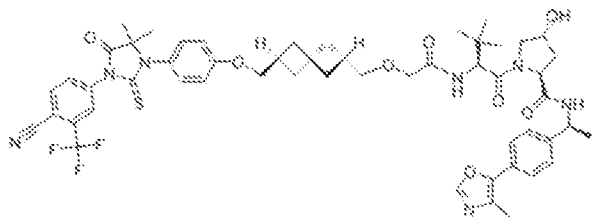
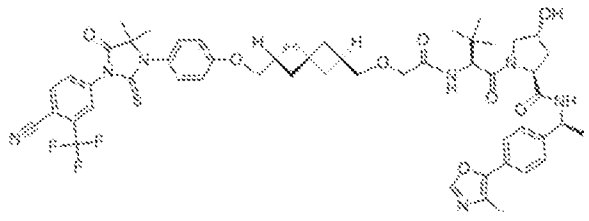
368		978.30	
369		960.30	
370		994.40	
371		983.30	
372		983.50	

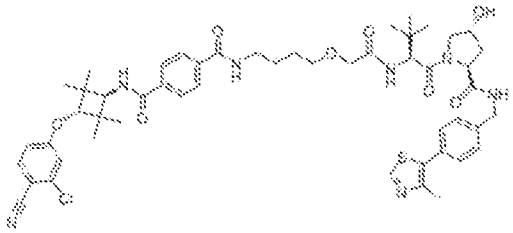
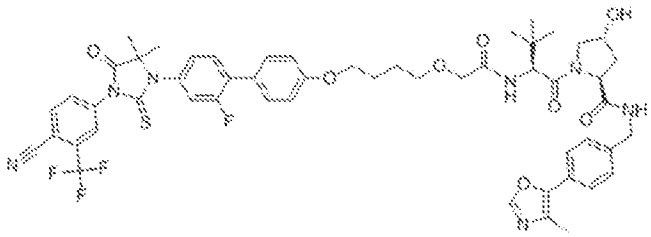
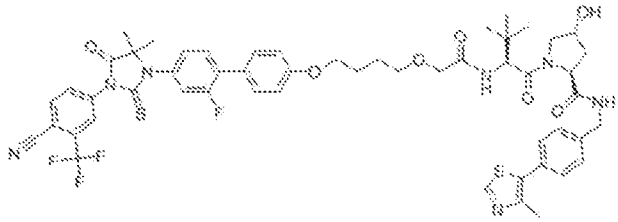
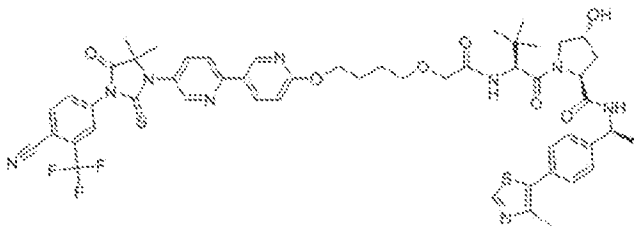
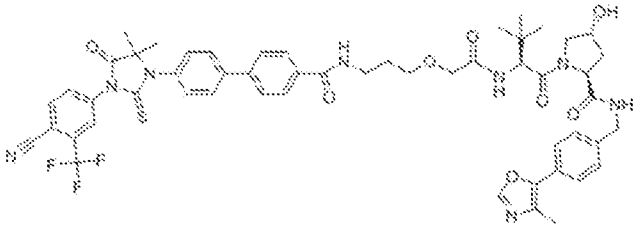
373		1034.40	
374		1026.35	
375		1059.36	
376		975.30	
377		989.30	

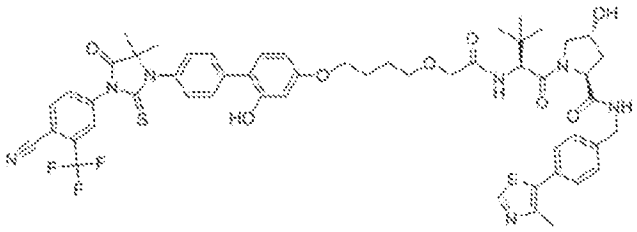
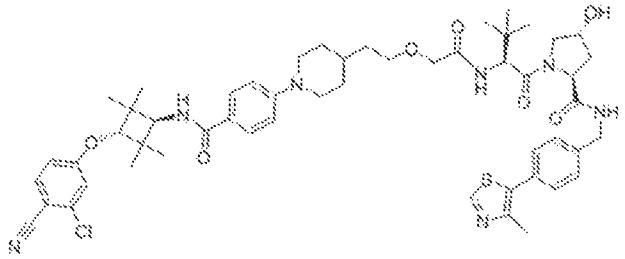
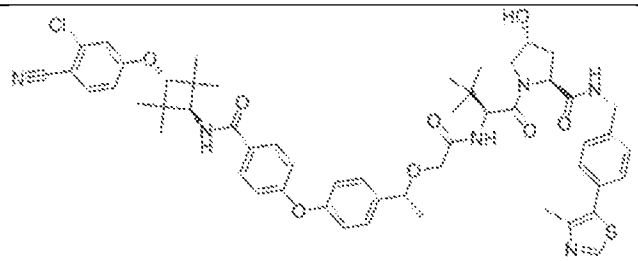
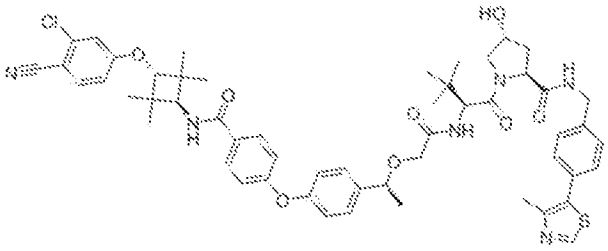
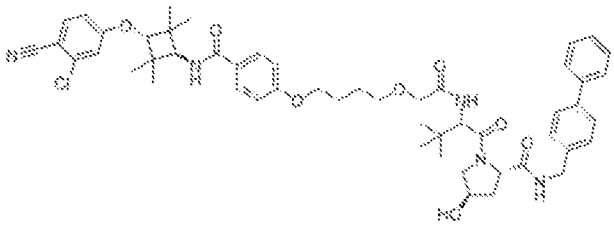
378		1032.34	
379		1025.37	
380		975.30	
381		1026.16	
382		1026.16	

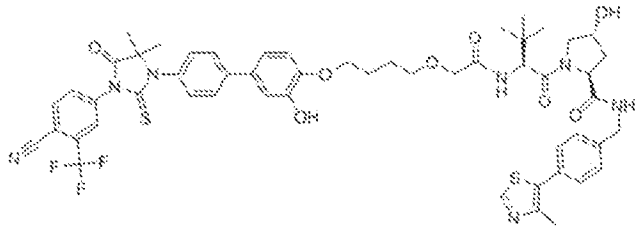
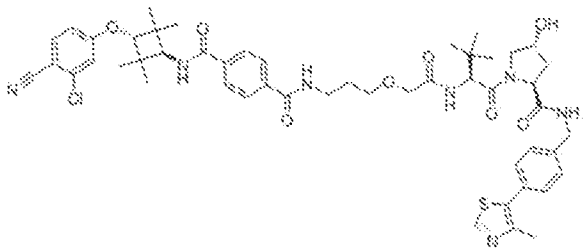
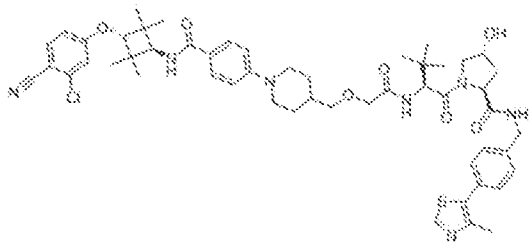
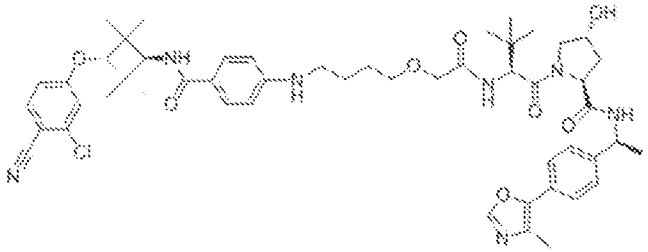
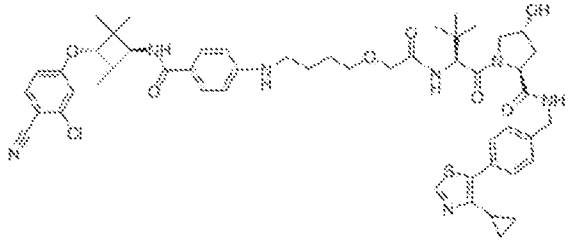
383		1025.30	
384		1041.30	
385		991.26	993.26
386		1011.30	
387		927.37	929.37

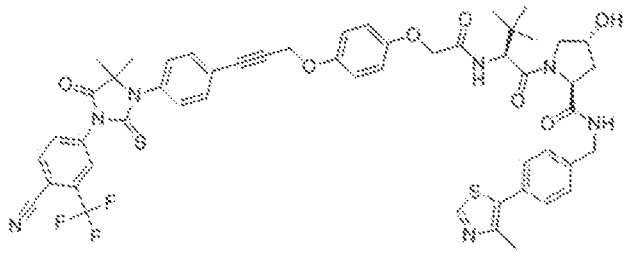
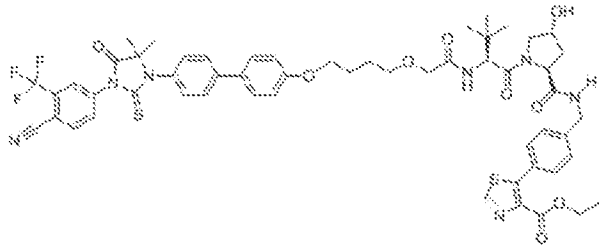
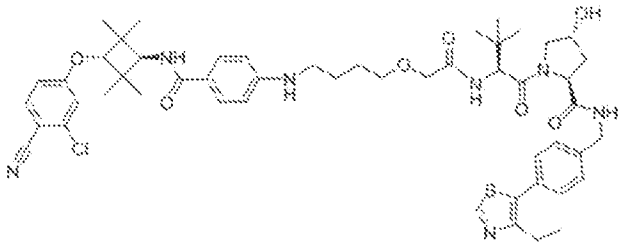
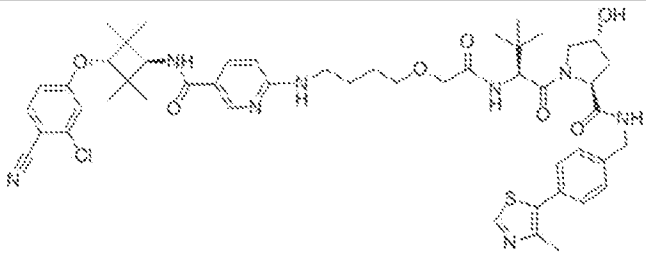
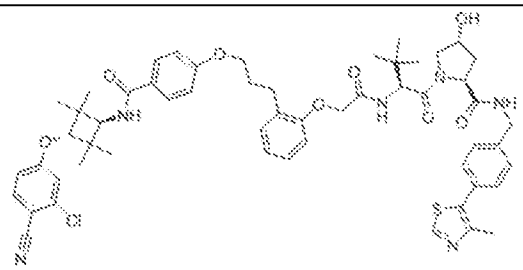
388		951.23	953.23
389		1055.10	
390		1022.25	
391		1024.15	
392		941.39	943.39

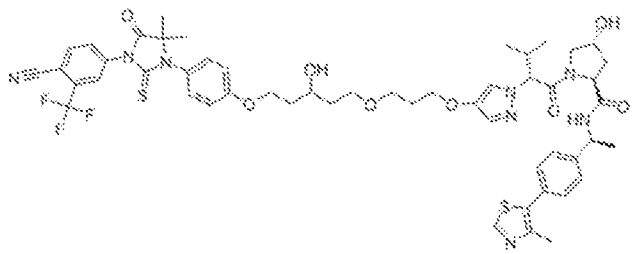
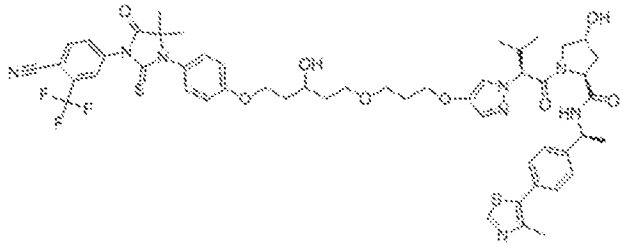
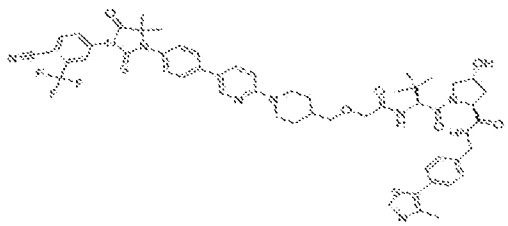
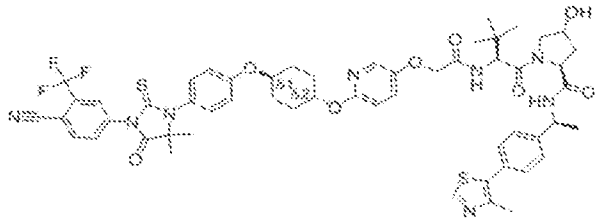
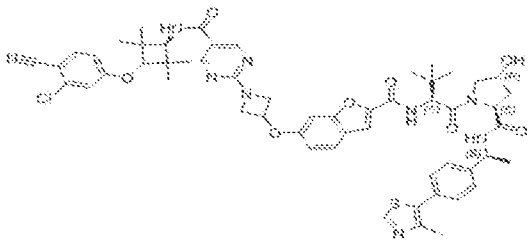
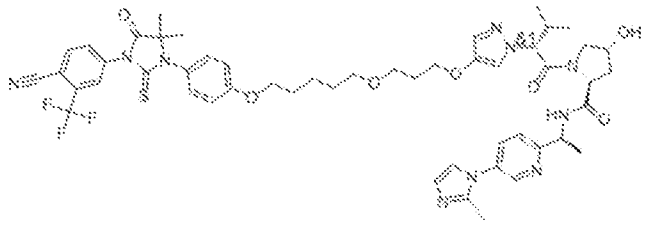
393		954.31	956.31
394		988.37	990.37
395		1045.35	
396		1012.15	
397		1012.15	

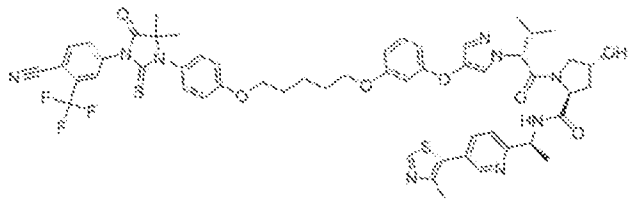
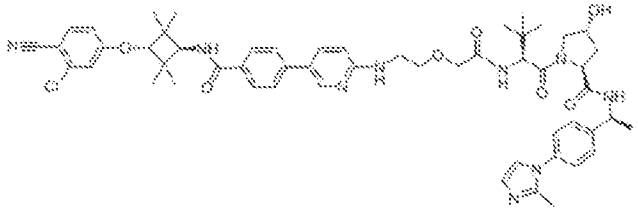
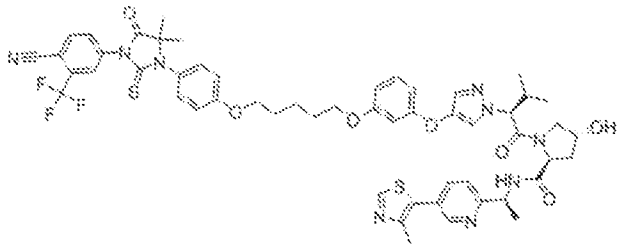
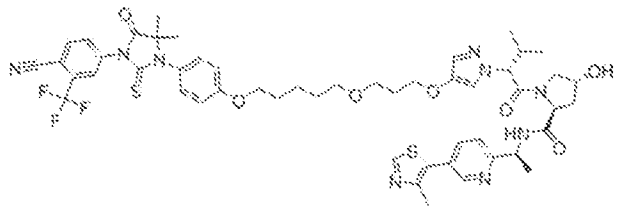
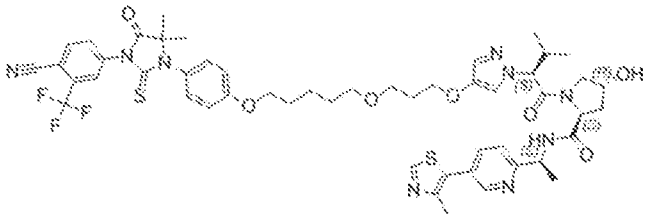
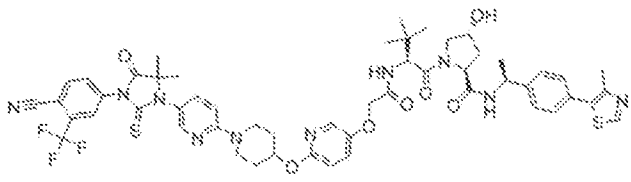
398		968.32	970.32
399		1026.15	
400		1042.20	
401		1040.35	
402		1021.20	

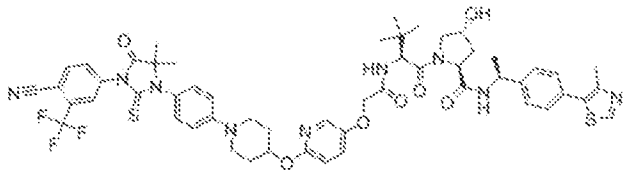
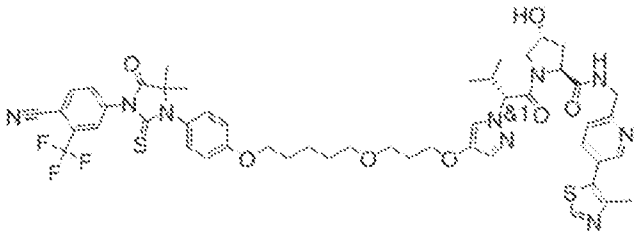
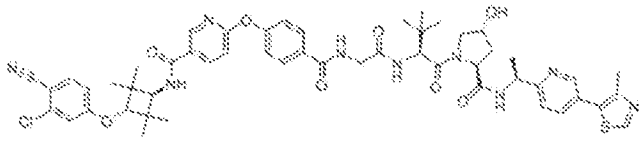
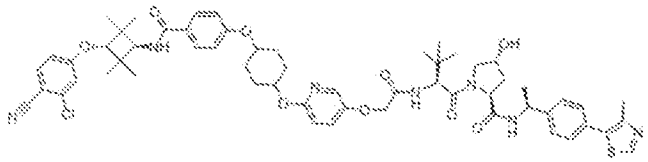
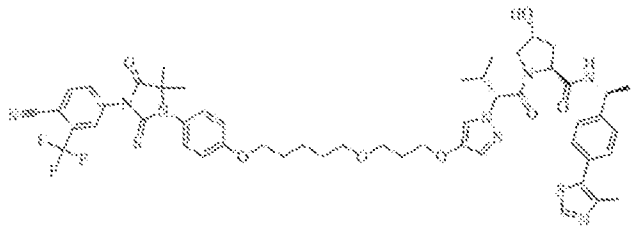
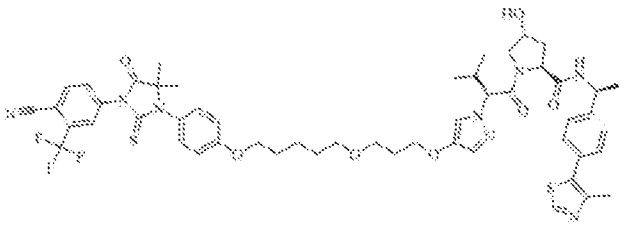
403		1040.15	
404		980.52	982.52
405		989.40	991.40
406		989.40	991.40
407		920.58	922.58

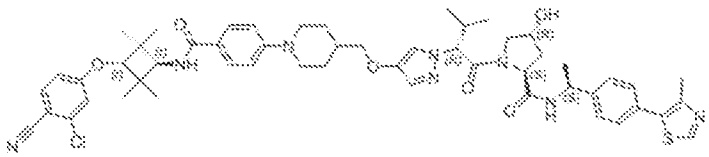
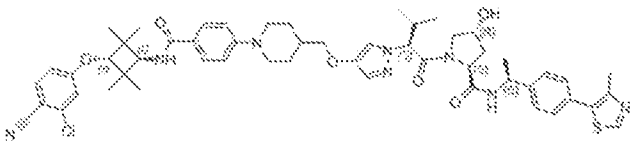
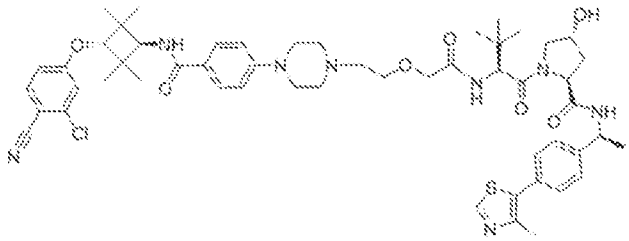
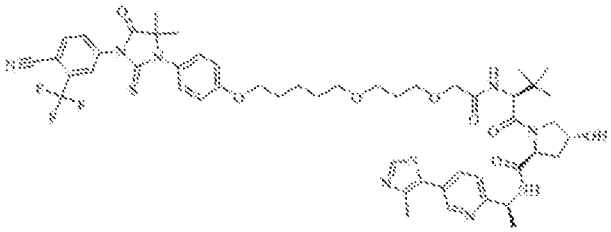
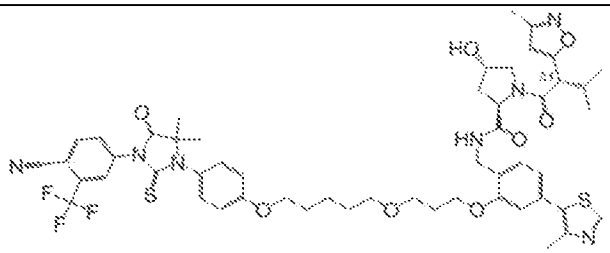
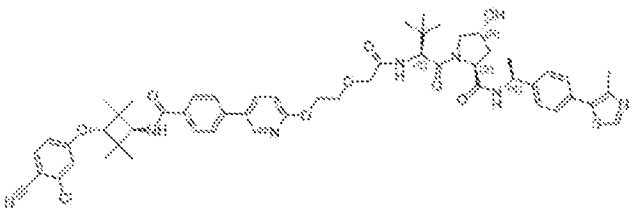
408		1040.10	
409		954.38	956.38
410		966.37	968.41
411		938.44	940.44
412		966.42	968.42

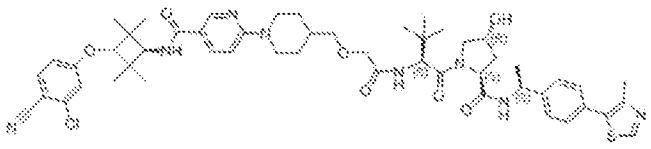
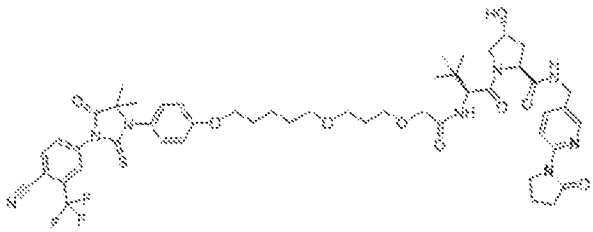
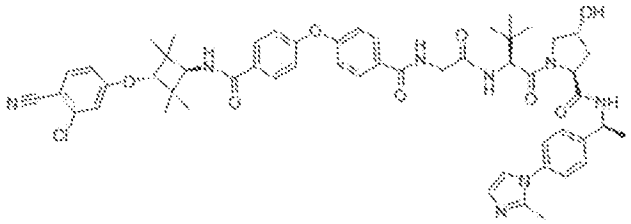
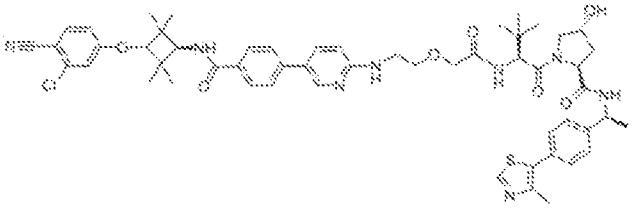
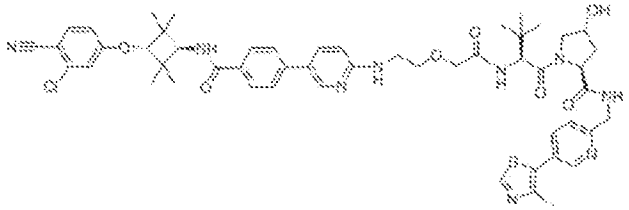
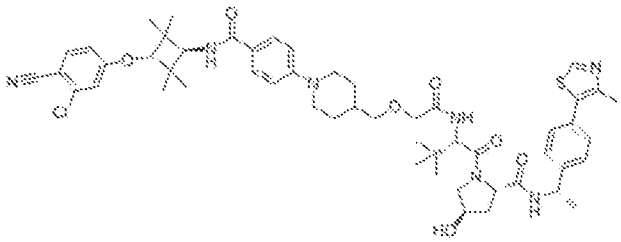
413		1006.30	
414		1083.34	
415		954.40	956.40
416		941.38	943.38
417		1003.39	1005.39

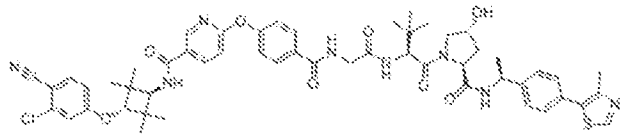
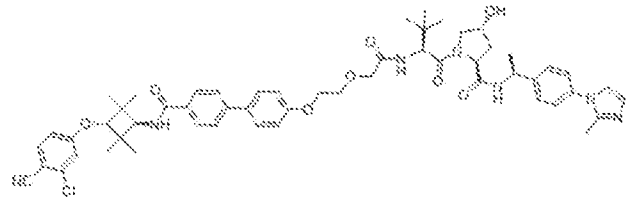
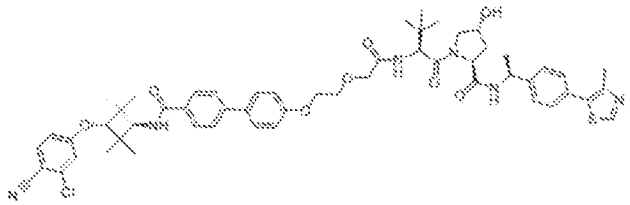
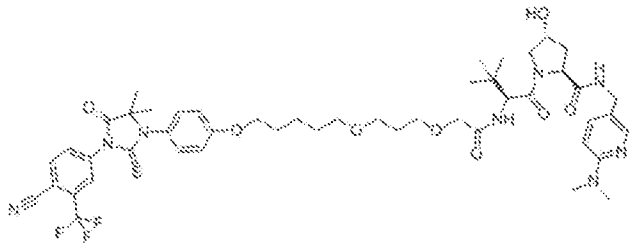
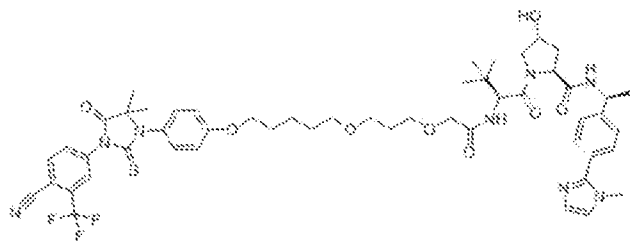
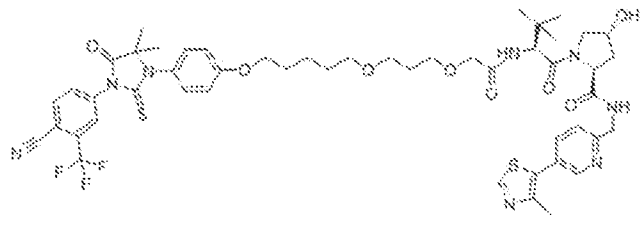
418		1045.38	
419		1045.38	
420		1050.39	
421		1081.38	
422		1042.39	1044.39
423		1013.42	

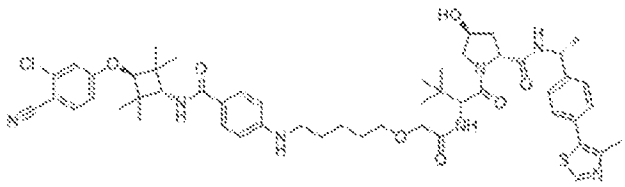
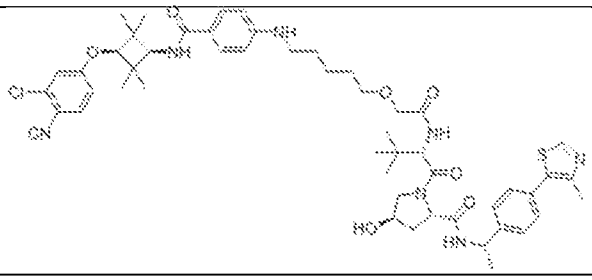
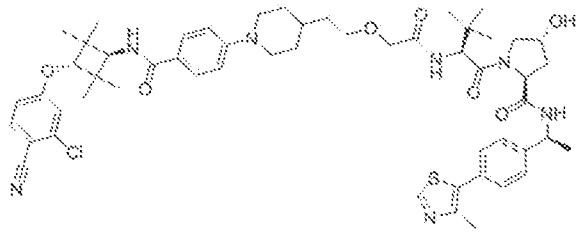
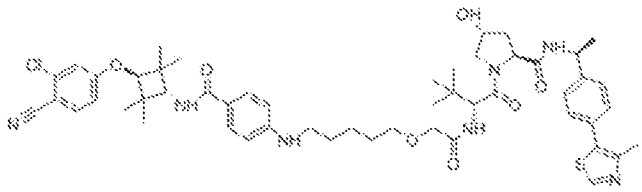
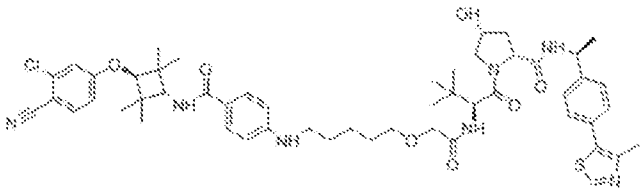
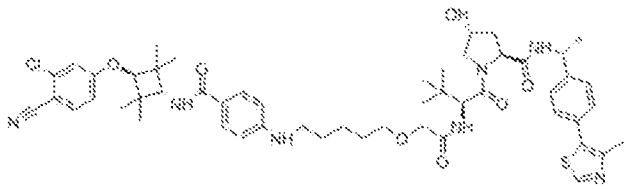
424		1064.36	
425		986.46	988.46
426		1064.37	
427		1030.38	
428		1030.38	
429		1067.38	

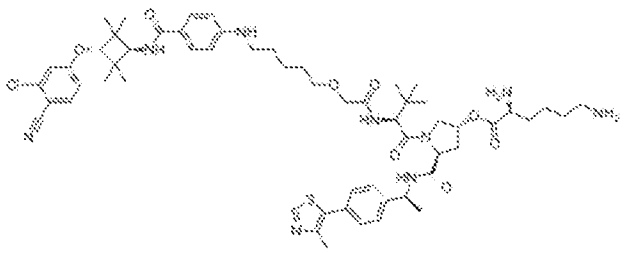
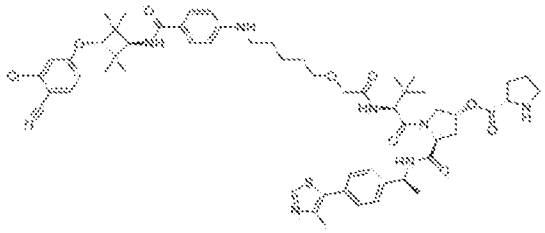
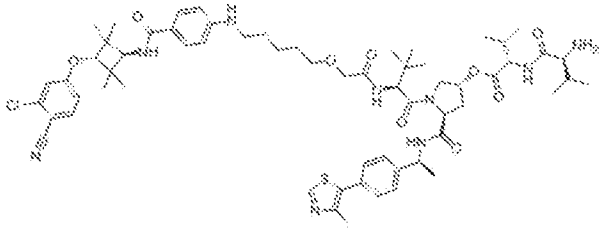
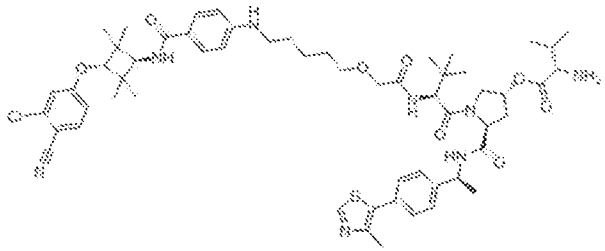
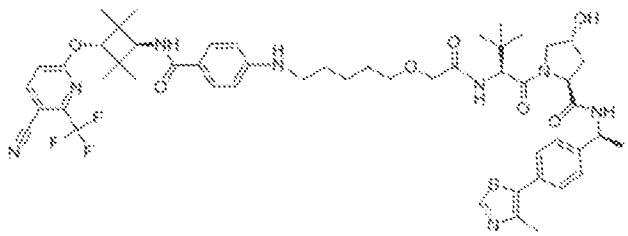
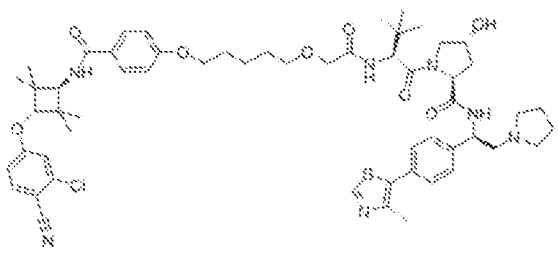
430		1066.38	
431		1016.37	
432		1004.38	1006.38
433		1074.45	1076.45
434		1029.39	
435		1029.39	

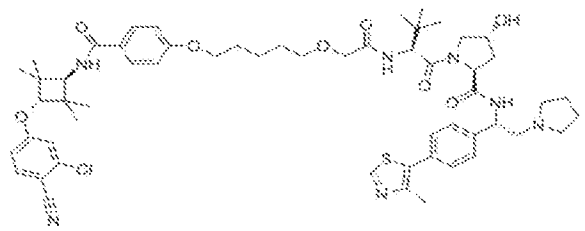
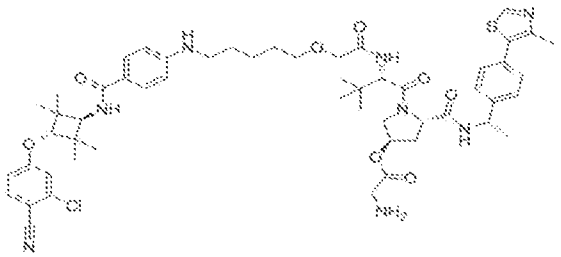
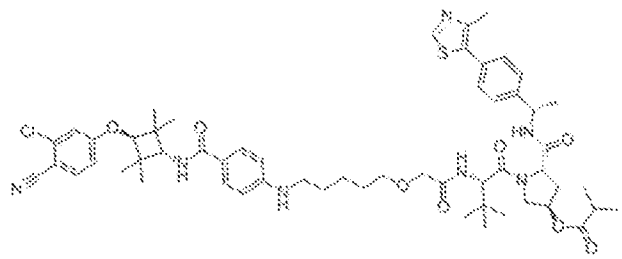
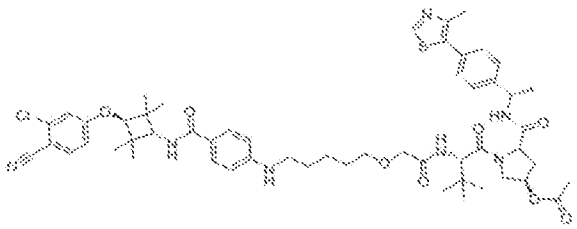
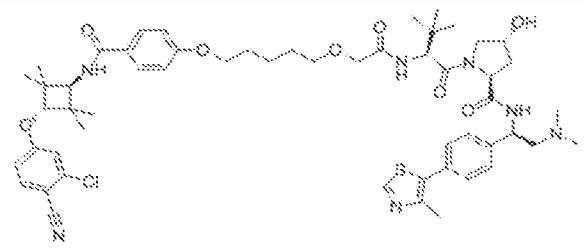
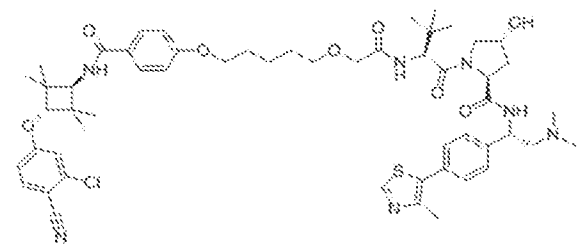
436		975.40	977.40
437		975.40	977.40
438		995.46	997.46
439		1036.40	
440		1030.38	
441		1004.30	1006.40

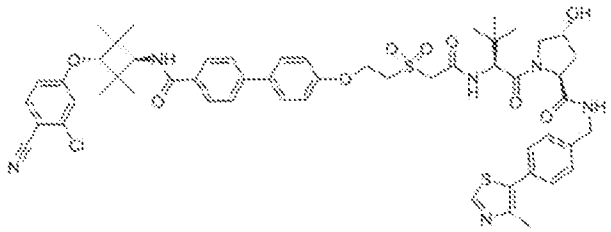
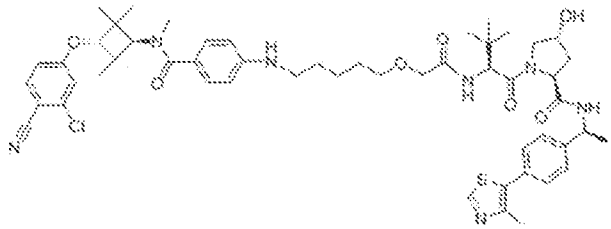
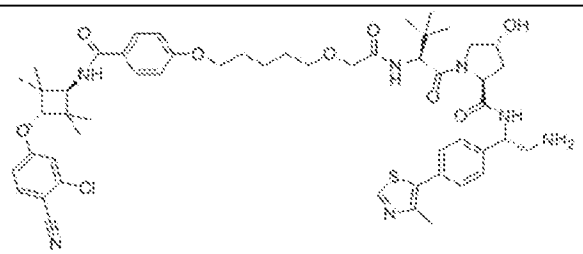
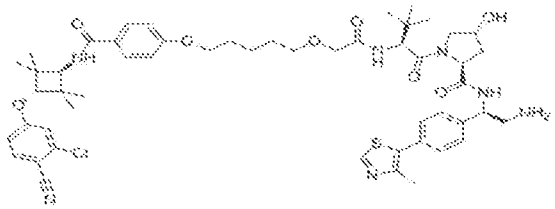
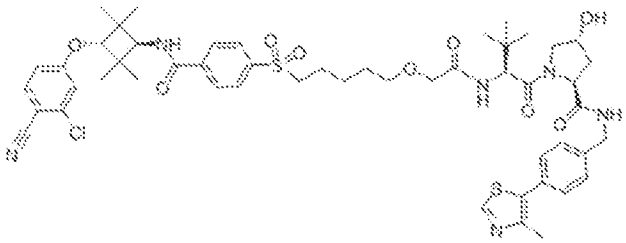
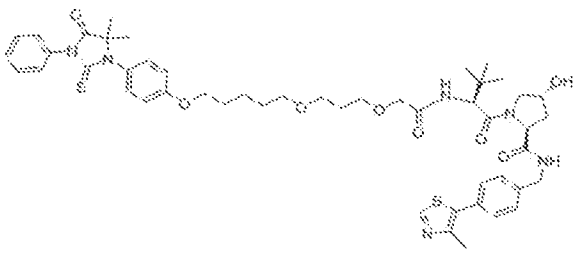
442		981.40	983.40
443		1007.42	
444		985.43	987.43
445		1003.42	1005.43
446		990.41	992.41
447		980.45	982.45

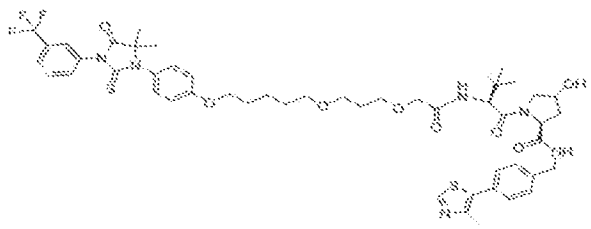
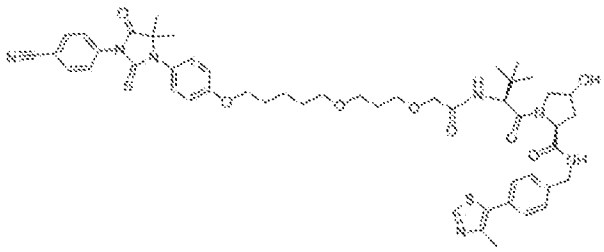
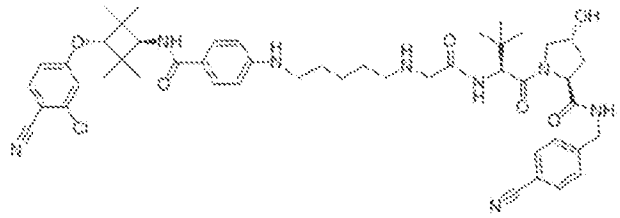
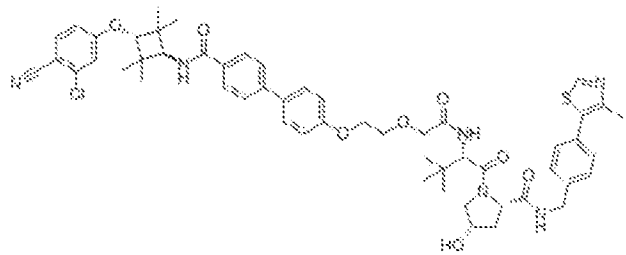
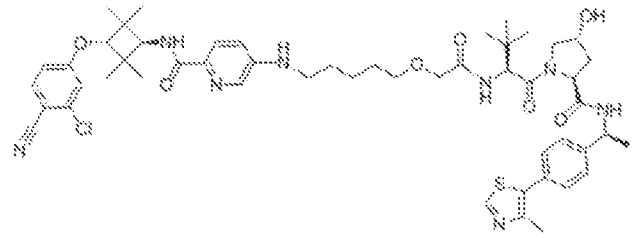
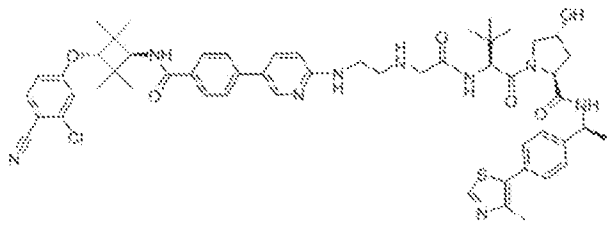
448		1003.30	1005.40
449		986.40	988.40
450		1003.40	1005.40
451		967.43	
452		1017.45	
453		1021.39	

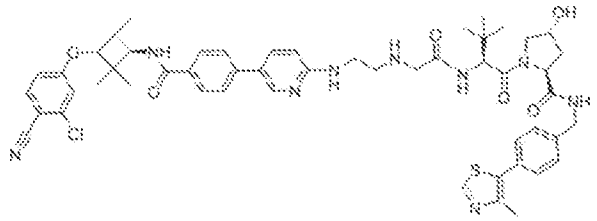
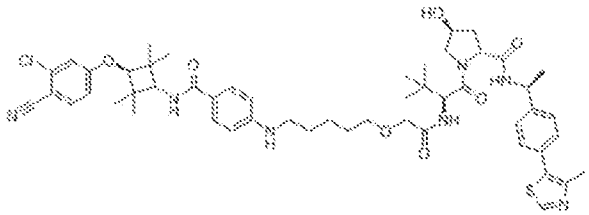
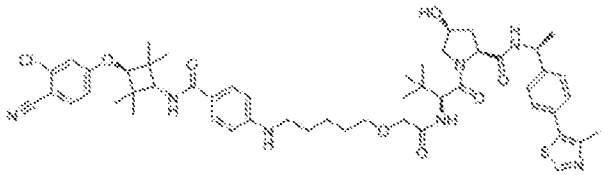
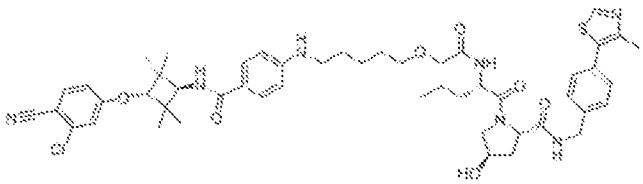
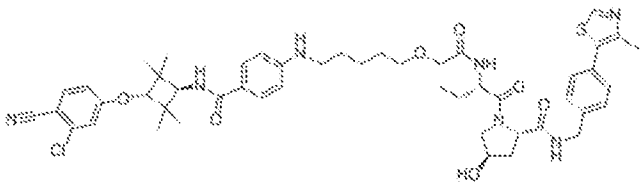
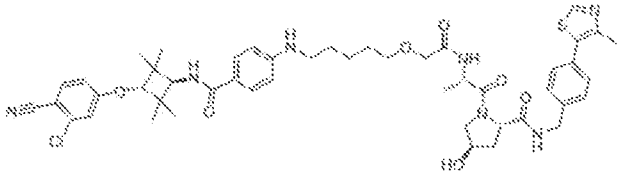
454		968.45	970.45
455		968.45	970.45
456		994.55	996.45
457		968.35	970.35
458		968.35	970.35
459		968.35	970.35

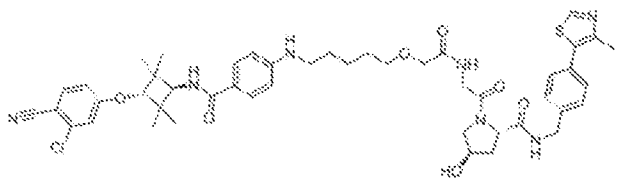
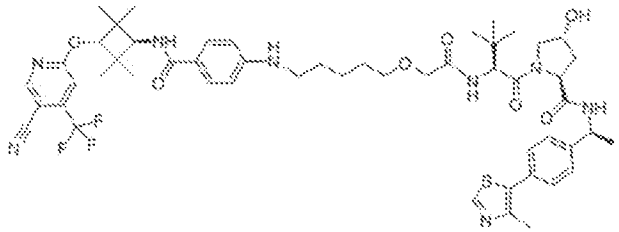
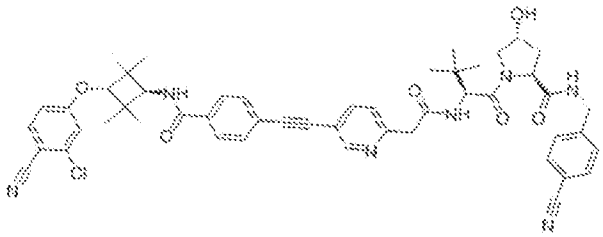
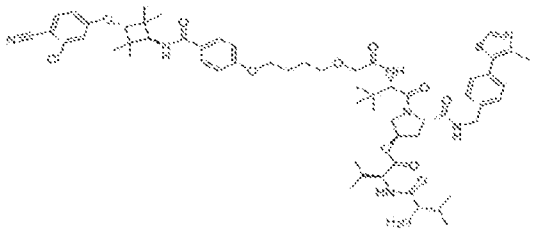
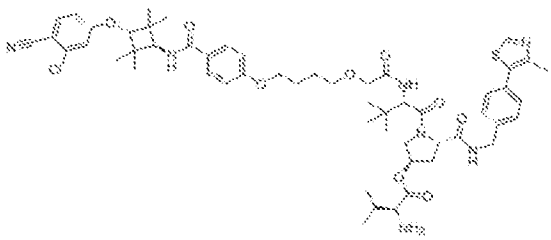
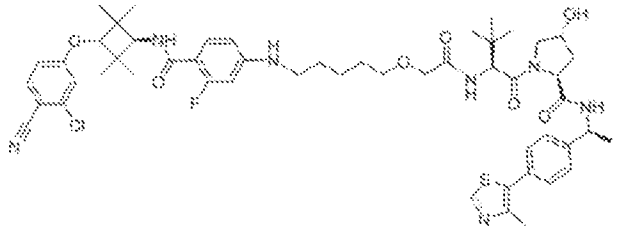
460		1096.43	1098.43
461		1065.38	1067.38
462		1166.46	1168.46
463		1067.40	1069.40
464		1003.50	
465		1038.50	1040.50

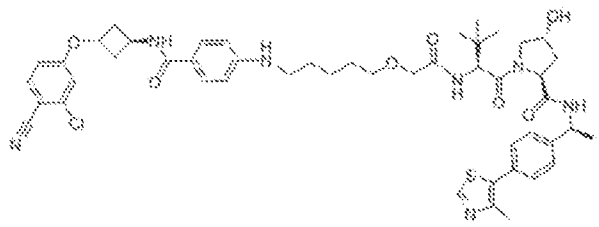
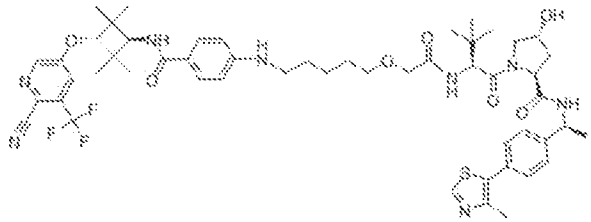
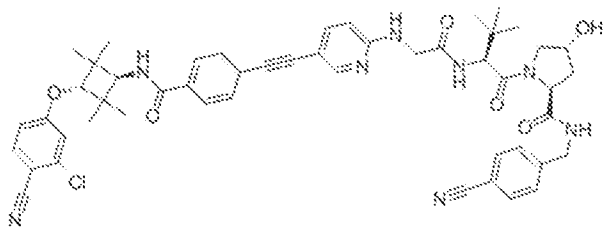
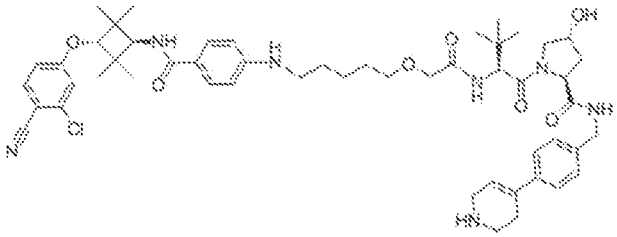
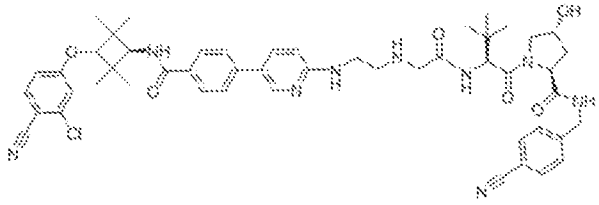
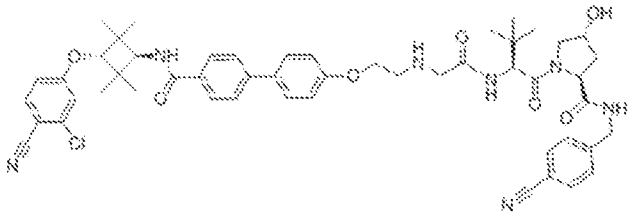
466		1038.55	1040.55
467		1025.36	1027.36
468		1038.37	1040.37
469		1010.34	1012.35
470		1012.35	1014.35
471		1012.35	1014.36

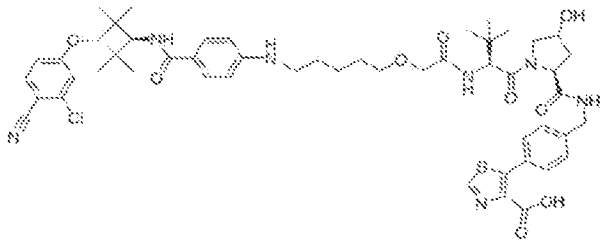
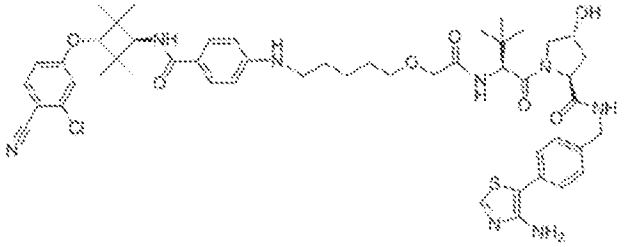
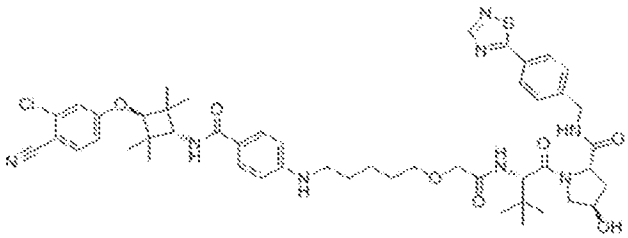
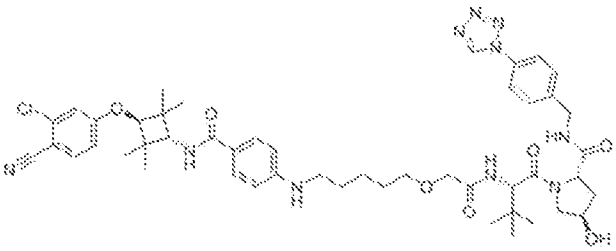
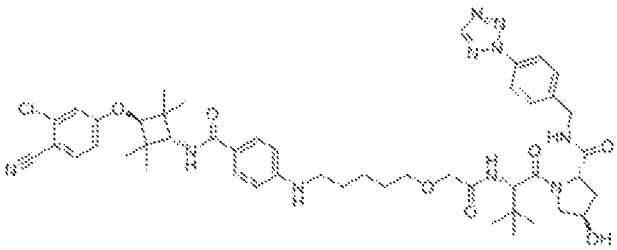
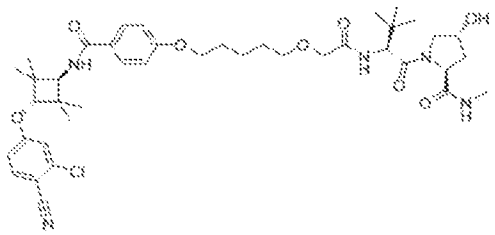
472		1037.25	1039.24
473		982.35	984.35
474		984.33	986.33
475		984.33	986.33
476		1003.26	1005.26
477		927.30	

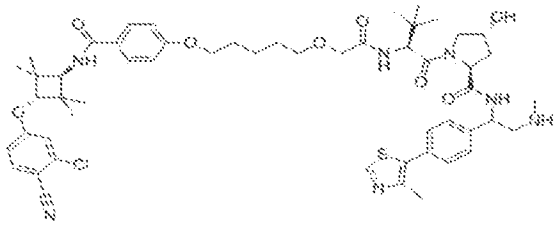
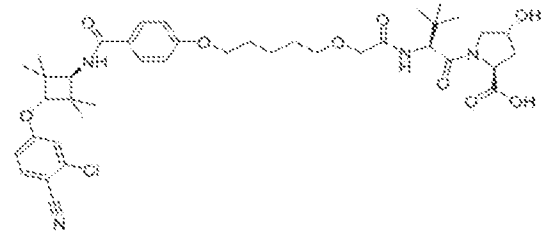
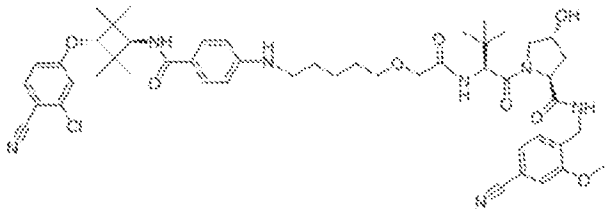
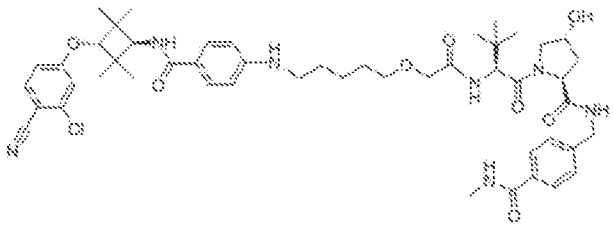
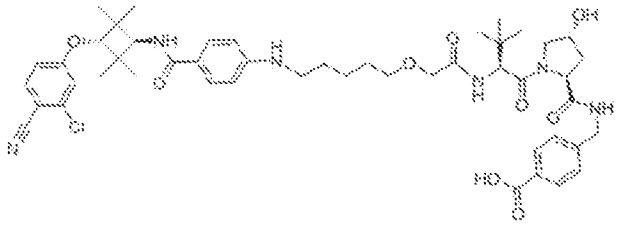
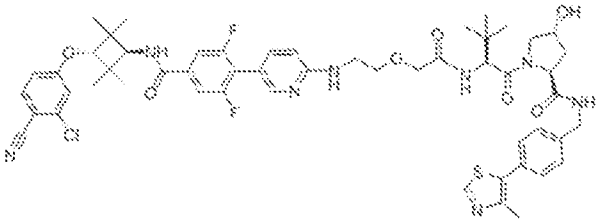
478		995.30	997.30
479		952.30	
480		881.34	883.34
481		989.28	991.28
482		969.33	971.33
483		1002.33	1004.33

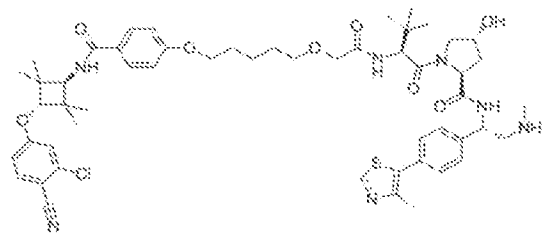
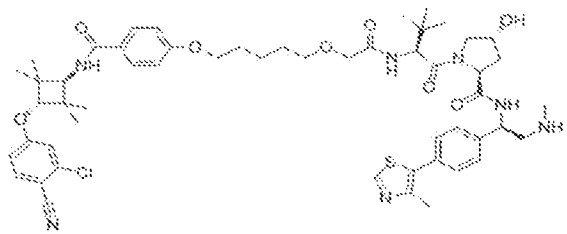
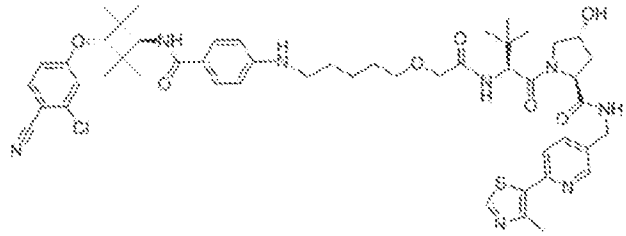
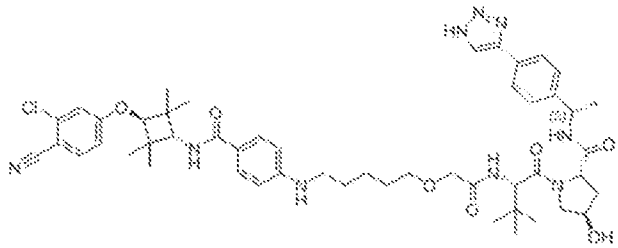
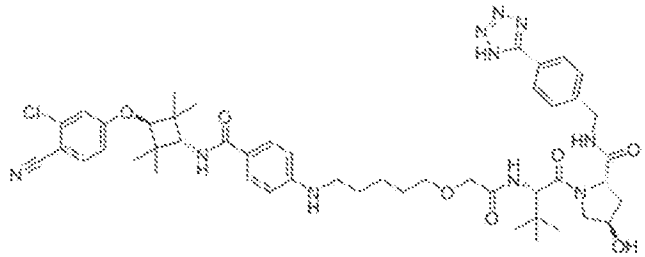
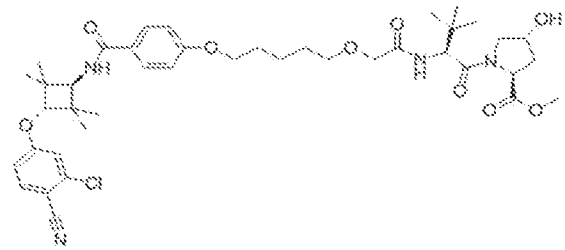
484		988.31	990.31
485		968.83	970.83
486		969.33	971.33
487		940.30	
488		926.29	928.29
489		912.23	914.23

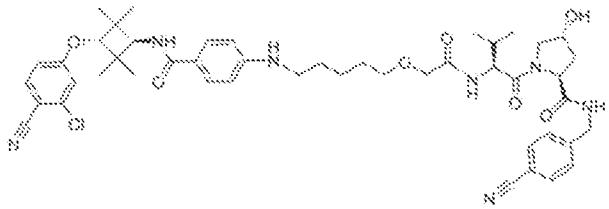
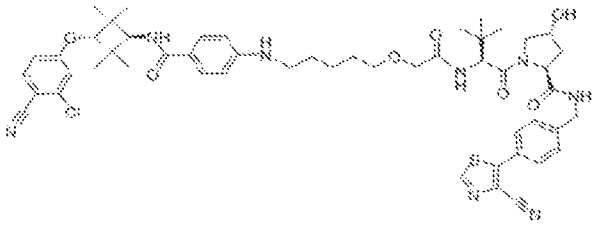
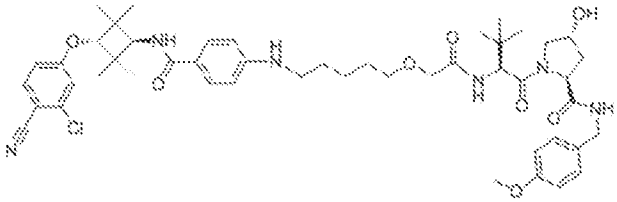
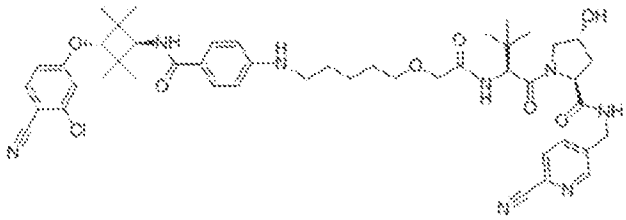
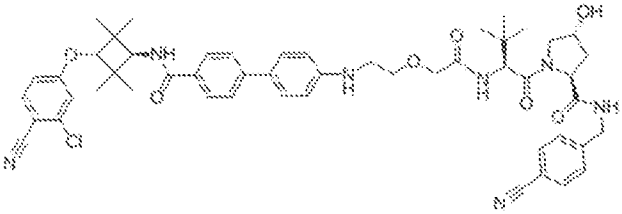
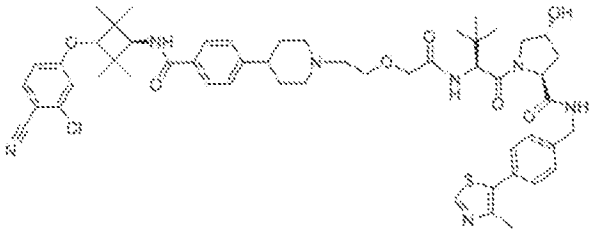
490		898.26	900.26
491		1003.60	
492		882.26	884.26
493		1139.41	1141.41
494		1040.35	1042.35
495		986.32	988.32

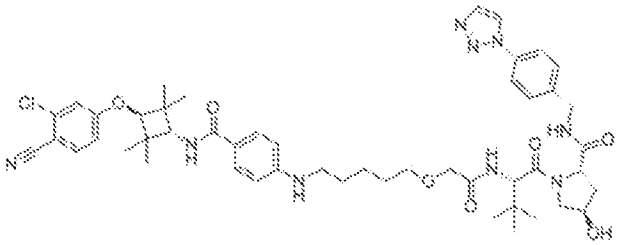
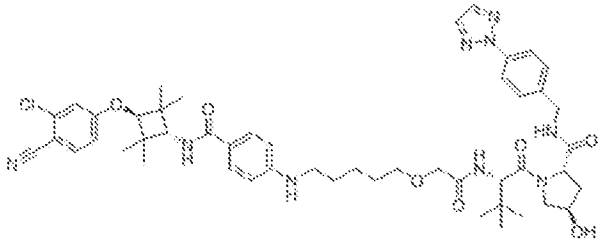
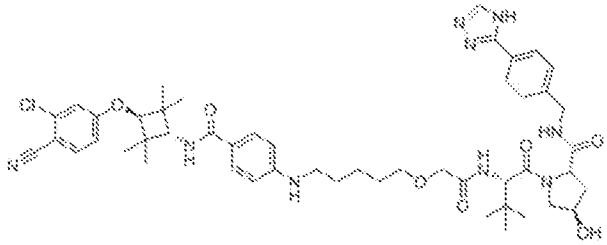
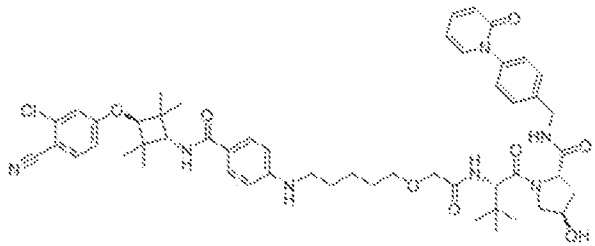
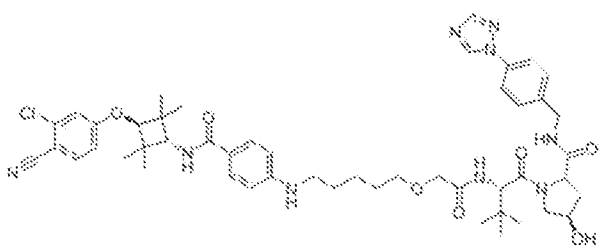
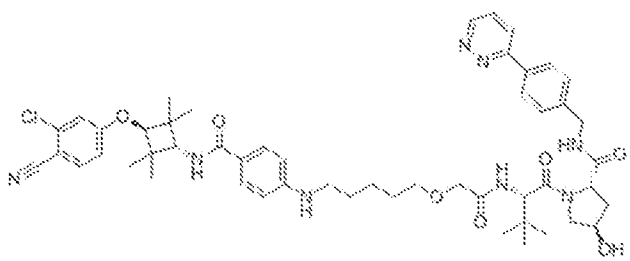
496		912.28	914.28
497		1003.45	
498		897.27	899.27
499		938.27	940.37
500		916.31	918.31
501		916.31	918.31

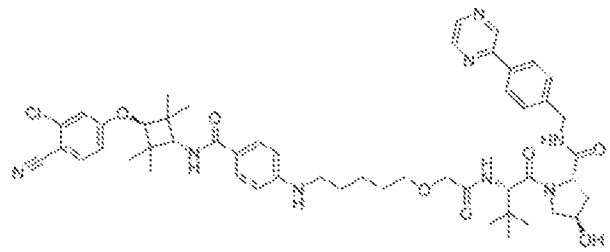
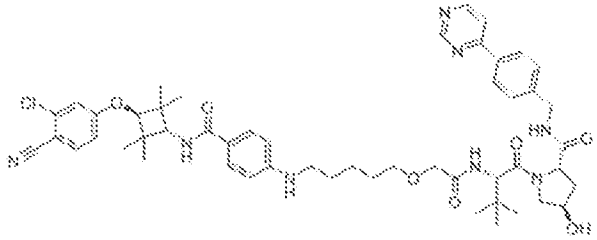
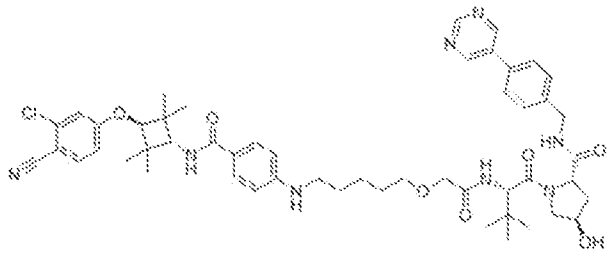
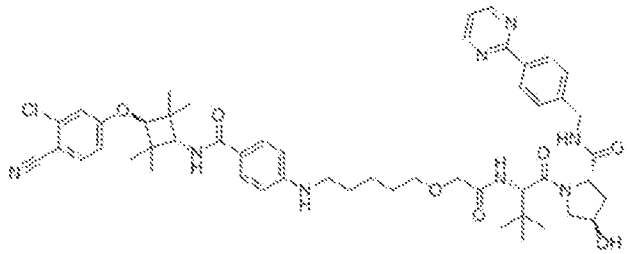
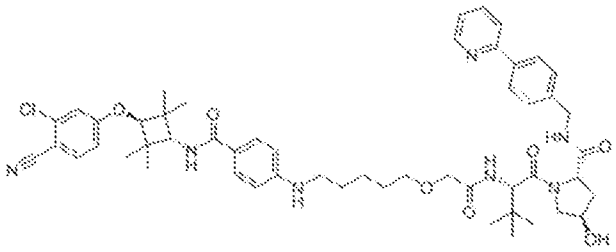
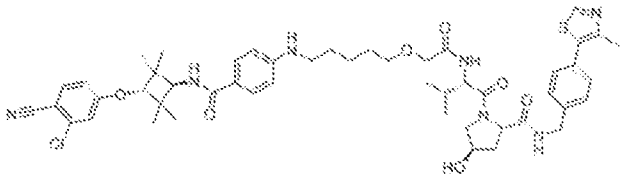
502		984.30	986.30
503		955.32	957.32
504		942.33	944.33
505		926.37	927.36
506		926.37	927.40
507		782.30	784.30

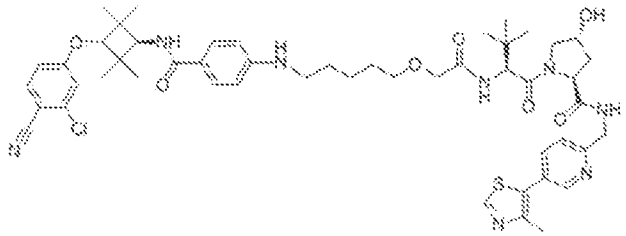
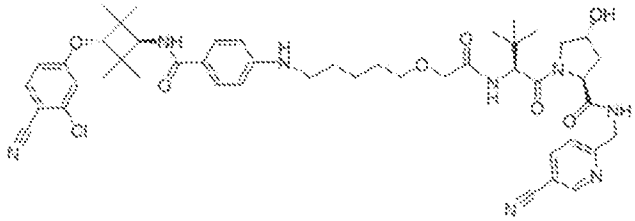
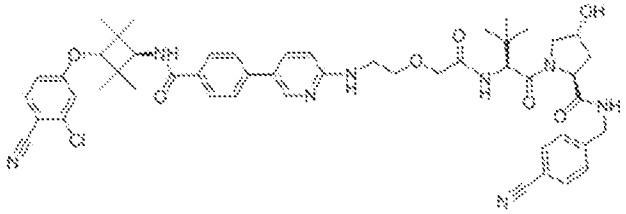
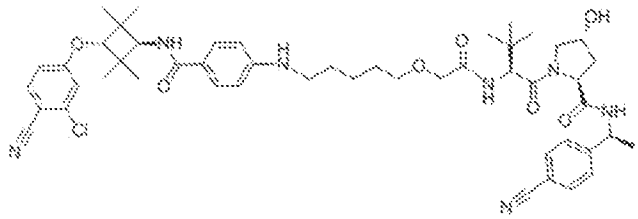
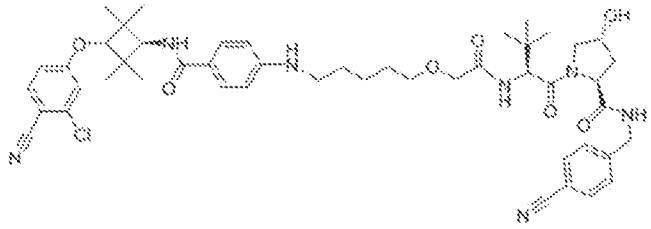
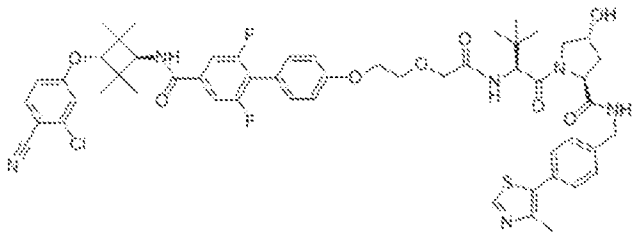
508		998.36	1000.36
509		769.27	771.27
510		912.35	914.35
511		914.36	916.36
512		901.33	903.33
513		1025.29	1027.29

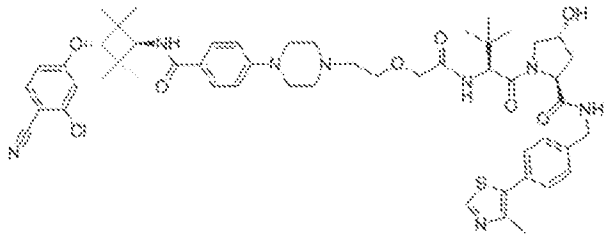
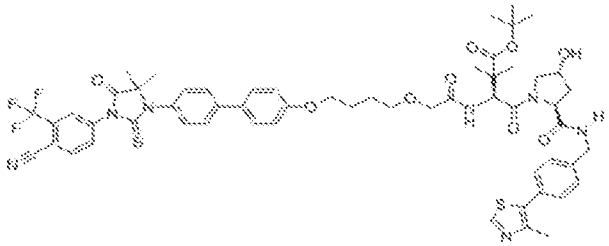
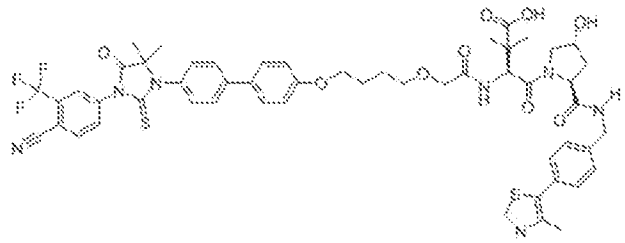
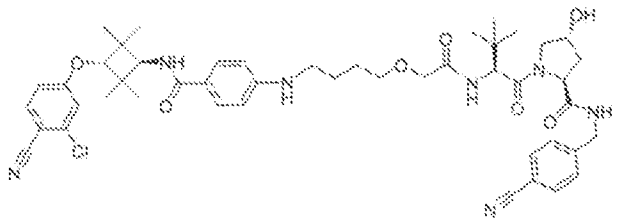
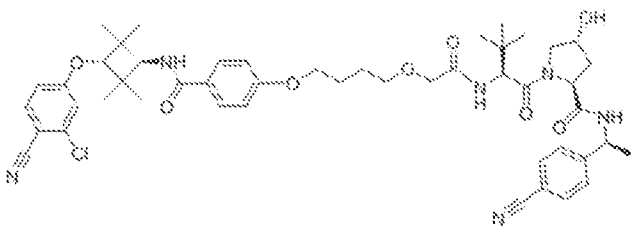
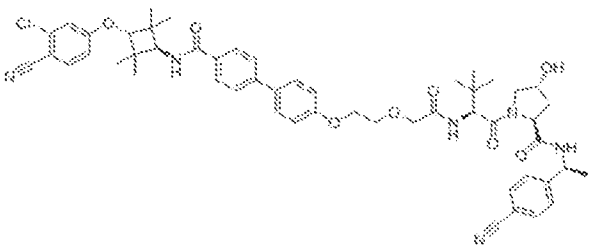
514		998.34	1000.34
515		998.34	1000.34
516		955.33	957.33
517		939.45	941.45
518		926.43	928.43
519		783.30	785.30

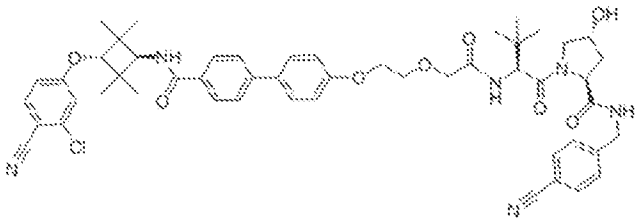
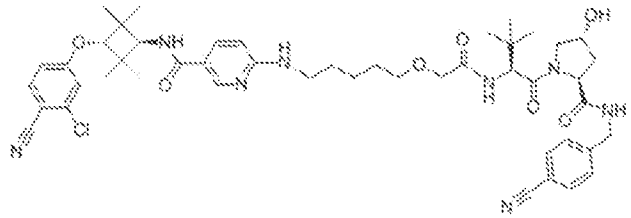
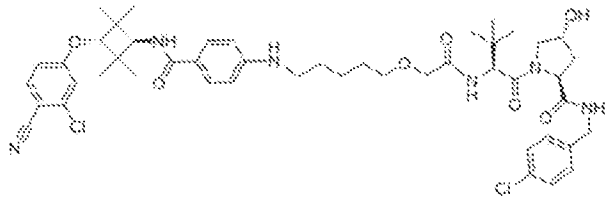
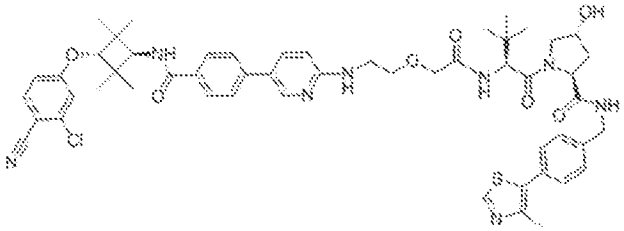
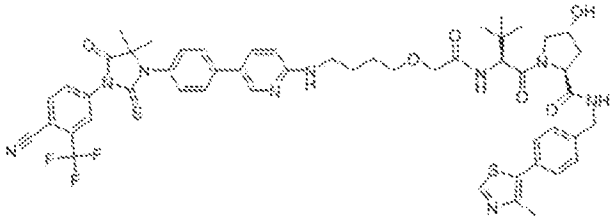
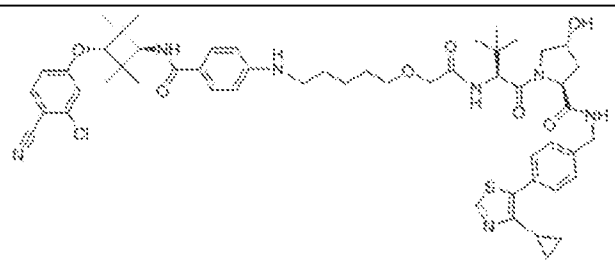
520		868.34	870.34
521		965.34	967.34
522		887.37	889.37
523		883.35	885.35
524		916.34	918.34
525		980.37	982.37

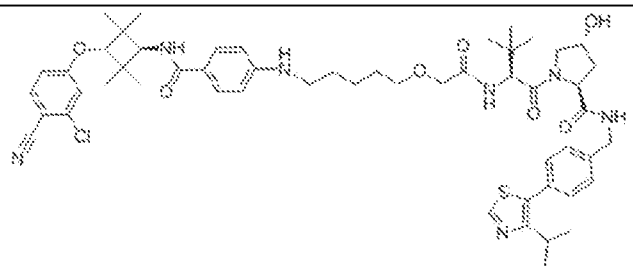
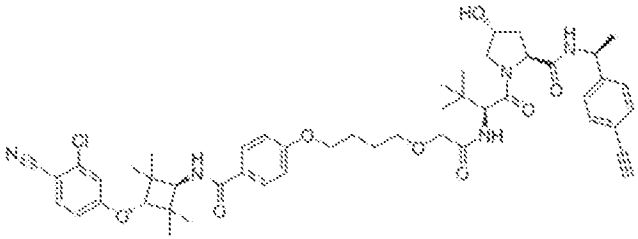
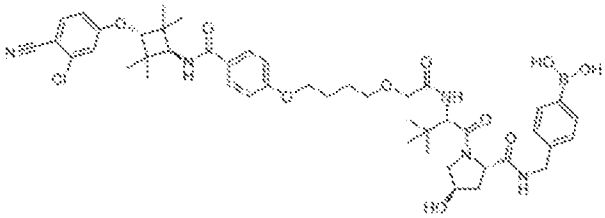
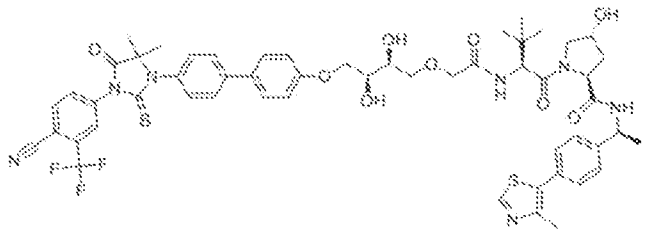
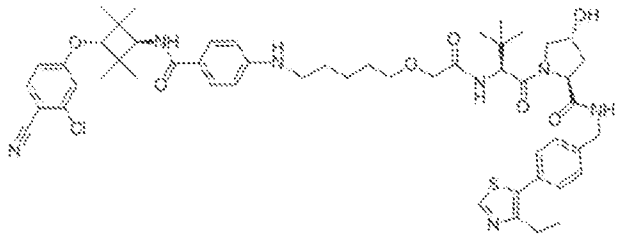
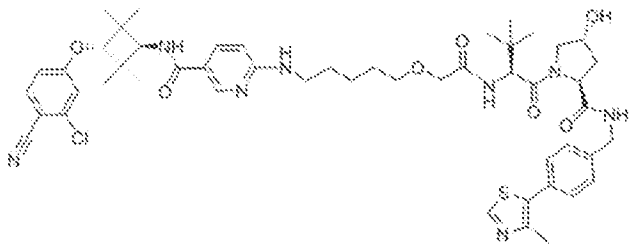
526		925.43	927.43
527		925.44	927.43
528		925.43	927.43
529		951.44	953.44
530		925.44	927.43
531		936.44	938.44

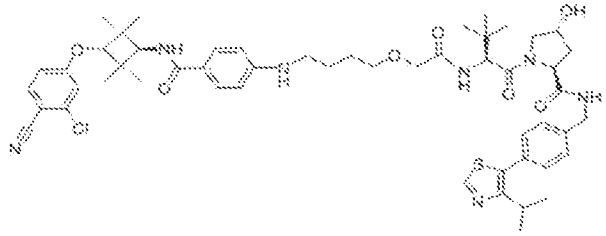
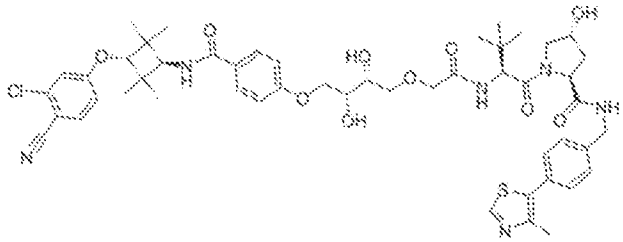
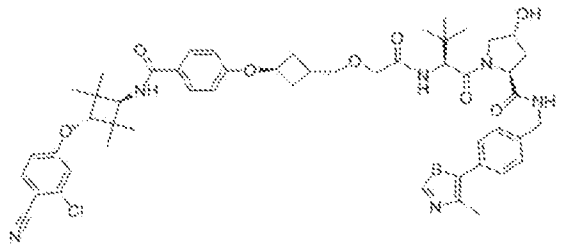
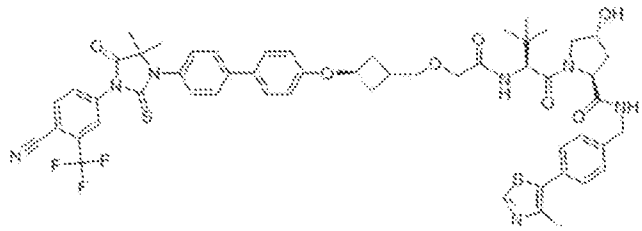
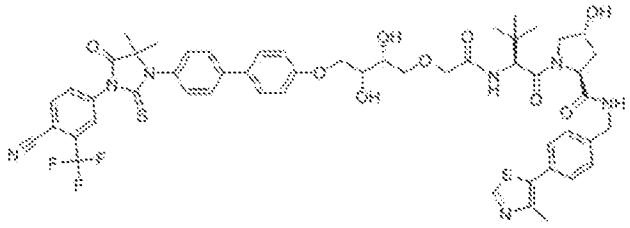
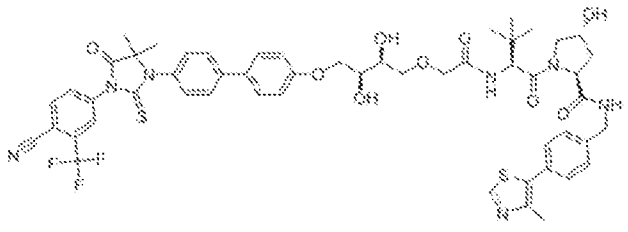
532		936.44	938.44
533		936.44	938.44
534		936.44	938.44
535		936.44	938.44
536		935.45	937.45
537		940.35	942.35

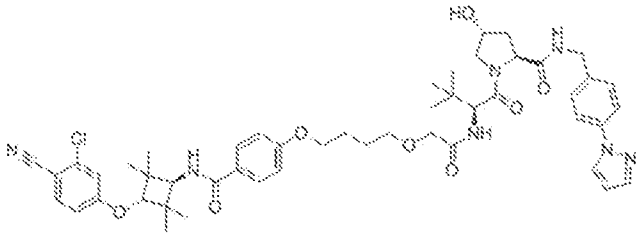
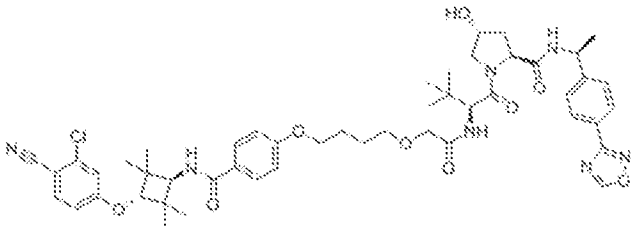
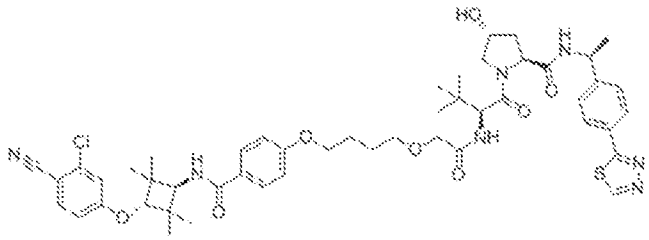
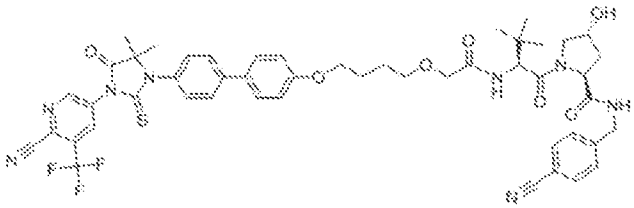
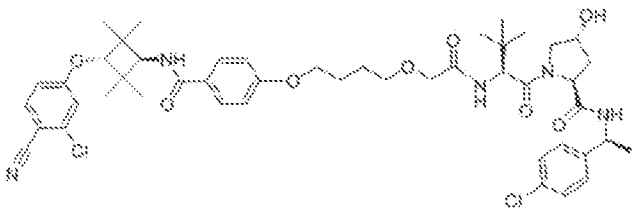
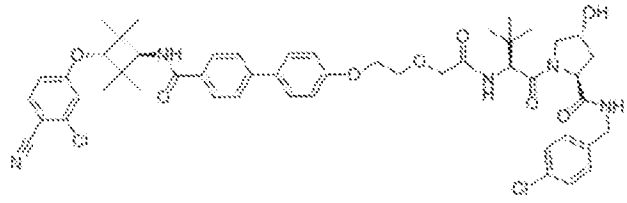
538		955.41	957.41
539		883.41	885.41
540		917.39	919.39
541		896.43	898.43
542		882.41	884.41
543		1025.38	1027.38

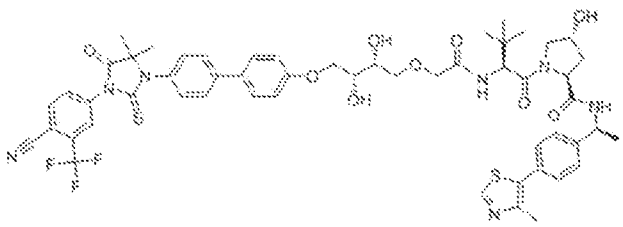
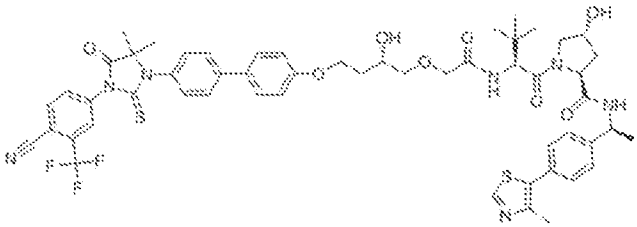
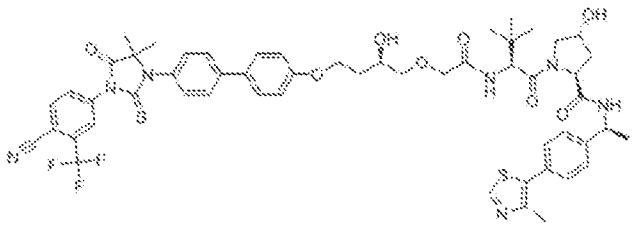
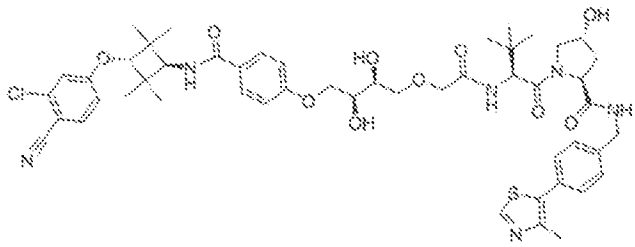
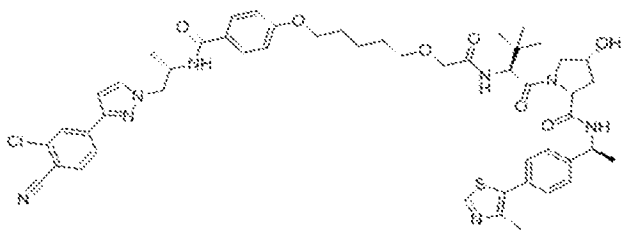
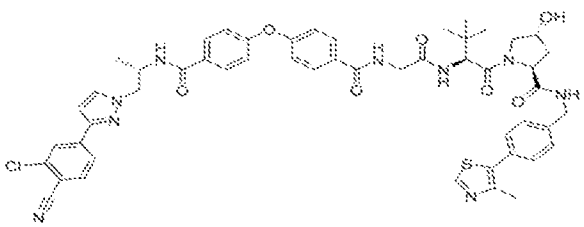
544		981.43	983.43
545		1110.30	
546		1055.30	
547		868.40	870.40
548		883.40	885.40
549		931.86	933.86

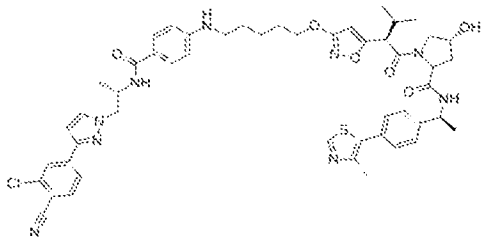
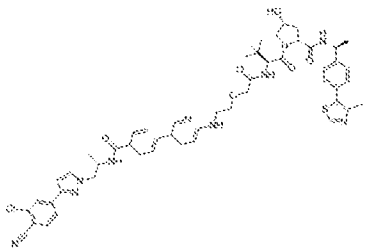
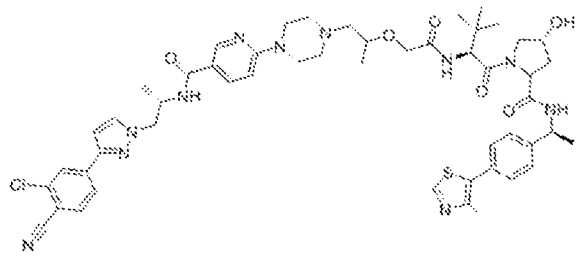
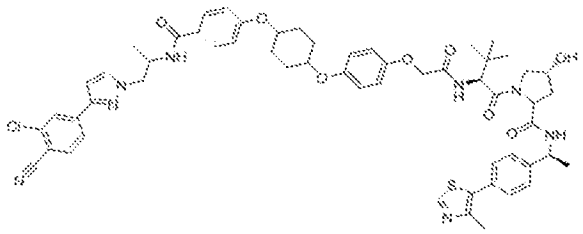
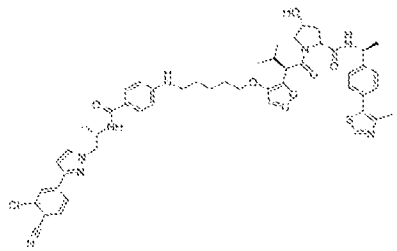
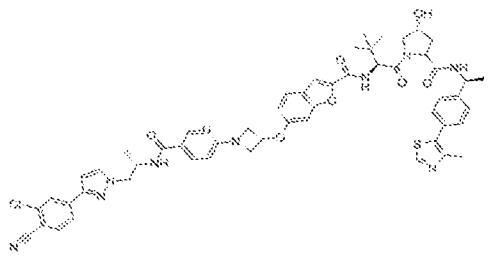
550		917.38	919.38
551		883.41	885.41
552		891.38	893.38
553		989.40	991.40
554		1024.15	
555		980.43	982.43

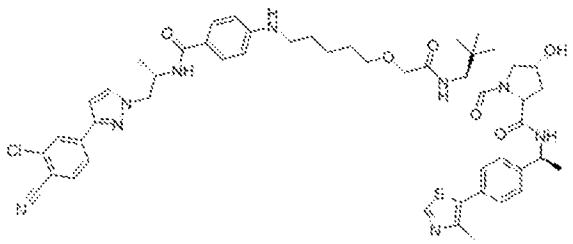
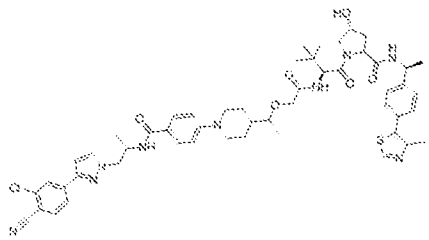
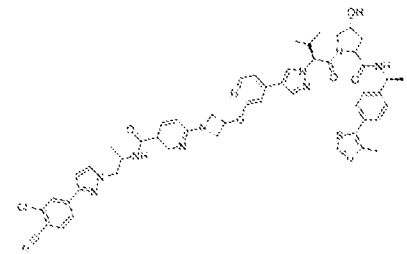
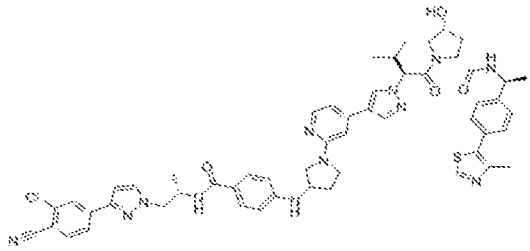
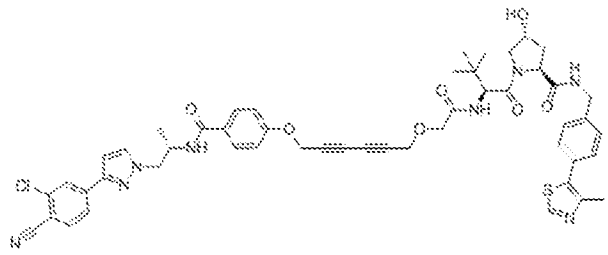
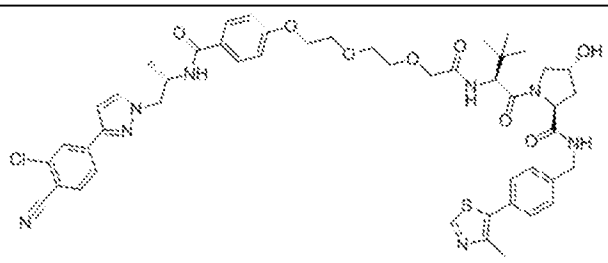
556		982.45	984.45
557		883.39	885.39
558		888.38	890.38
559		1070.15	
560		968.41	970.41
561		955.40	957.40

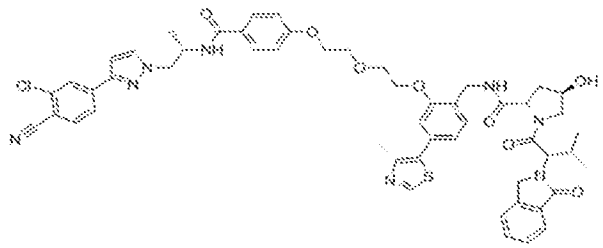
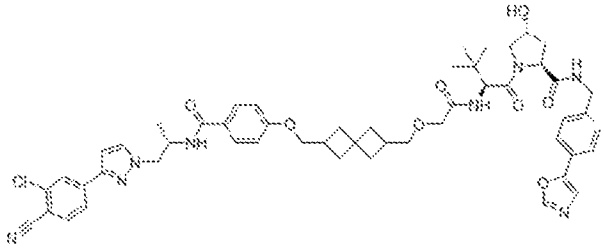
562		968.41	970.41
563		973.36	975.36
564		953.37	955.37
565		1036.20	
566		1056.15	
567		1056.15	

568		910.40	912.40
569		926.39	928.39
570		942.36	944.36
571		953.33	
572		892.35	894.35
573		926.34	928.34

574		1070.15	
575		1054.00	
576		1054.20	
577		973.63	975.36
578			
579			

580			
581			
582			
583			
584			
585			

586			
587			
588			
589			
590			
591			

592			
593			

[0855] In certain embodiments, the description provides a compound having a structure selected from the group consisting of Examples 1-593 (see Tables 2-17), a salt, a polymorph, and prodrug thereof. In certain additional embodiments, the description provides a composition comprising at least one of the compounds of Examples 1-593, including a salt, polymorph, and prodrug thereof. In still additional embodiments, the description provides a therapeutic composition comprising at least one of the compounds of Examples 1-593, including a salt, a polymorph, and a prodrug thereof, and a pharmaceutically acceptable carrier.

[0856] Examples – In vitro and in vivo assays.

[0857] The experimental results presented below are made with reference to the Tables and Figures 1-7.

[0858] 1. Androgen Receptor ELISA Assay.

[0859] Compounds have been evaluated in this assay in LNCaP and/or VCaP cells utilizing similar protocols. The protocols used with VCaP cells are described below. The androgen receptor ELISA assay was performed using PathScan AR ELISA (Cell Signaling Catalog#12850) according to the following assay steps:

[0860] VCaP cells are seeded at 30,000 cells/well at a volume of 200 µL/well in VCaP assay medium [Phenol red free RPMI (Gibco Cat#11835-030); 5% Charcoal Stripped (Dextran treated) FBS (Omega Scientific, Cat#FB-04); Pen/Strep Life Technologies (Gibco Cat#: 10378-016); 0. 1nM R1881 (Sigma, Cat# R0908) is added upon the start of the assay, not during initial plating of the cells) in Corning 3904 plates. The cells are grown for a minimum of 3 days.

[0861] First, cells are dosed with compounds diluted in 0.1% DMSO – use a polypropylene plate according to the following protocol: (1)(i) make 1000x stock plate in DMSO; (ii) 20mM stock diluted 1/6.7 with DMSO (5 μL + 28.3 μL DMSO) =3mM into row H; (iii) perform serial dilutions in ½ log doses (10 μL of PROTAC + 20 μL DMSO) from row H towards row B. Reserve row A for DMSO; (iv) 7 doses total (final concentration in this 1000x plate will be 3 mM, 1 mM, 333 μM, 111 μM, etc). (2)(i) Make 10x stock plate in media; (ii) transfer 2.5 μL of the 1000x stock to a new 10x stock plate (use 12 channel pipet, start at A (DMSO control) work thru H. When 247.5 μL of media is added to this plate, it will serve as a 10x stock; (iii) make media + 1nM R1881 for making 10x stock plate; (iv) add 247.5 μL of media with 1 nM R1881 to each well of the 10x stock plate, mix.

[0862] Then 22 μL of 10x stock is added to cells and incubated for 24h. 1x Cell Signaling Cell lysis buffer is made (Catalogue #9803; comes with the kit) - prepare for 50 μL/well. Keep on ice. Media is aspirated, and 50 μL lx cell lysis buffer/well is added. The cells are placed on ice for 10 minues. The solution is mixed and transferred to PCR plate, and centrifuged at 4C for 10 minutes at 4000 rpm.

[0863] 5 μL is transferred to fresh plate (use immediately or freeze -80C); 115 μL ELISA Dilutant is added (0.15ug/ml – 0.075ug/ml; comes with the PathScan ELISA).

[0864] Add 100 μL/well AR Elisa; cover and shake, 37C for 2hrs; dump, tap, wash 4x 200 μL ELISA wash buffer; add 100 μL/well mouse AR detection Ab; cover and shake, 37C for 1hr; dump, tap, wash 4x 200 μL ELISA wash buffer; add 100 μL/well anti-mouse – HRP conjugated Ab (comes with the kit); cover and shake, 37C for 30 min; allow TMB reagent to come to RT; dump, tap, wash 4x 200 μL Elisa wash buffer; tap; add 100 μL TMB, shake 5min – while watching color. Add the stop reagent when light blue color develops. Add 100 μL Stop solution; shake and read at 450nM.

[0865] Progression of prostate cancer in patients treated with anti-androgen therapy usually involves one of several mechanisms of enhanced Androgen Receptor (AR) signaling, including increased intratumoral androgen synthesis, increased AR expression and AR mutations. PROTACs (PROteolysis TArgeting Chimera), which uses bi-functional molecules that simultaneously bind a target of choice and an E3 ligase, cause ubiquitination via induced proximity and degradation of the targeted, pathological protein. As opposed to traditional target

inhibition, which is a competitive process, degradation is a progressive process. As such, it is less susceptible to increases in endogenous ligand, target expression, or mutations in the target. Thus this technology seems ideal for addressing the mechanisms of AR resistance in patients with prostate cancer.

[0866] AR PROTACs degrade AR in LNCaP and VCaP cells, with nM to pM potency, and had a >85% reduction in AR concentration (D_{max}). Degradation was rapid, with 50% of AR lost within 15 minutes and maximal degradation observed by 4 hours. The duration of AR knockdown was long-lasting, with no recovery of AR observed over several days. The degradation process in cells was specific, as PROTACs with an inactive epimer for E3 ligase binding did not degrade AR. AR PROTACs induced rapid apoptosis and cell death in VCaP cells. In LNCap and VCaP cell systems, AR PROTACs were anti-proliferative under conditions in which enzalutamide was inactive, such as increasing concentrations of the AR agonist R1881 and cells containing the AR^{F876L} mutation. AR PROTACs typically had $t_{1/2}$ values of several hours and bioavailability of >50% after ip or sc injection. In mice, AR PROTACs have shown *in vivo* activity, including involution of seminal vesicles, reduction of AR protein levels in the prostate, and regression of VCaP tumors.

[0867] The following assay results were generated using the androgen receptor ELISA Assay described above, where compound potencies were charactrized in highest percentage of Androgen Receptor degradation (D_{max}) observed and compound concentration that caused 50% Androgen Receptor degradation (DC_{50}).

[0868] **Table 18. Androgen Receptor degradation (D_{max}) observed and compound concentration that caused 50% Androgen Receptor degradation (DC_{50}).** D_{max}: + ($D_{max} \leq 25\%$); ++ ($26\% \leq D_{max} \leq 50\%$); +++ ($51\% \leq D_{max} \leq 70\%$); ++++ ($71\% \leq D_{max}$); DC_{50}: A ($D_{max} \leq 50$nM); B (51nM $\leq DC_{50} \leq$ 500nM); C (501nM $\leq DC_{50}$).

Ex #	LNCaP Dmax (%)	LNCaP DC_{50} (μM)	VCaP Dmax (%)	VCaP DC_{50} (μM)
1	++++	A		
2	++++	A		
3	++++	A		

4	++++	A		
5	++++	B		
6	++++	A		
7	+++	A		
8	++++	A		
9	++++	A		
10	++++	A		
11	++++	A		
12	++++	B		
13			++	
14				C
15			++	
16	+++	A	++	
17	++			
18	+++	B		
19	+++	A		
20	++++	B		
21	++			
22	+++	A		
23	++++	B		
24	++++	A		
25	++++	A		
26			+++	A
27	++++	A		
28	++++	A		
29	+++	B		
30	++++	A		
31	++++	A		
32	++++	A		

33			+++	A
34			+++	A
35			+++	A
36			++	B
37			++++	A
38			+++	A
39			++	A
40			+++	A
41			++++	A
42			+++	A
43			+++	A
44			++++	A
45			++++	A
46			++++	A
47			+++	A
48			++++	A
49			+++	A
50			++++	A
51			++	A
52	++++	A		
53			++++	A
54			++++	A
55	++			
56	++			
57				
58				
59				
60			+++	B
61			+++	B

62	+++	C		
63	++++	B		
64	+++	B		
65	+++	B		
66	+++	B		
67	72.1	A		
68	++	B		
69	++++	B		
70	++++	A		
71	++++	A		
72	++++	B		
73	++++	A		
74	++++	A		
75	++++	A		
76	+++	A		
77	++++	A		
78	++++	A		
79	++++	A		
80	+++	C		
81	+++	C		
82	+++	B		
83	+++	B		
84	+++	B		
85	+++	C		

Ex#	VCaP Dmax (%)	VCaP DC_{50} (μM)
86	++	
87	++	
88		

89	++++	A
93		
94	++++	A
95	++++	A
96	+++	A
99	+++	A
100	++++	A
101	++++	A
102	++++	A
103	++++	A
104	++++	A
105	+++	B
106	++++	A
107	++++	A
108	++++	A
109	++++	A
110	++++	A
111	++++	A
112	++++	B
114	+++	A
115	++++	A
116	++++	A
117	++++	A
118	++++	A
119	+++	A
120	++++	A
121	++++	A
122	++++	A
123	++++	A
124	+++	A
125	++++	A
126	+++	A
127	++++	A
128	+++	A
129	+++	A
130	+++	A
131	+++	A
132	++++	A
133	+	
134	++++	A
135	+++	A
136	++++	A
137	++++	A

138	++++	A
139	++++	A
140	++++	A
141	++++	A
142	++++	A
145	++++	A
147	++++	A
148	++++	A

Ex#	VCaP Dmax (%)	VCaP DC_{50} (μM)
150	++++	A
151	++++	A
152	++++	A
153	++++	A
154	++++	A
155	++++	A
156	++++	A
157	++++	A
158	++++	A
159	++++	A

Ex#	VCaP Dmax (%)	VCaP DC_{50} (μM)
162	++++	A
163	++++	A
164	++++	A
165	++++	A
166	+++	A

Ex#	VCaP Dmax (%)	VCaP DC_{50} (μM)
172	++++	A
173	++++	A
174	+++	A
175	+++	A

Ex#	VCaP Dmax (%)	VCaP DC_{50} (μM)
180	++++	A
181	++++	A
182	++++	A

Ex#	VCaP Dmax (%)	VCaP DC_{50} (μM)
183	++++	A
184	++++	A
185	++++	A
186	++++	A

Ex#	VCaP Dmax (%)	VCaP DC_{50} (μM)
188	++++	A
189	+++	A

Ex#	VCaP Dmax (%)	VCaP DC_{50} (μM)
418	+++	C
419	++	C
420	++++	A
421	++++	A
422	++++	A
423	+	C
424	+	C
425	++++	A
426	+	C
427	+	C
428	+	C

429	++	C
430	+	C
431	+	C
432	+	C
433	+++	A
434	+	C
435	+	C
436	+++	
437	+	C
438	++++	A
439		
440		
441		
442	++++	A
443		
444	++++	A
445	++++	A
446	++	C
447	++++	A
448	++++	A
449	++++	A
450	++++	A
451	+	C
452	+	C
453	+	C
454	++++	A
455	++	C
456	+++	C
457	++++	A
458	+	C
459	+	C
460	++	C
461		
462	++++	A

463		
464		
465	++++	C
466	++++	A
467	++++	B
468		
469	++++	A
470	++++	A
471	++++	A
472	++	C
473	++++	A
474	++	A
475	++	B
476	++++	A
477	++++	A
478	+	C
479	++	C
480	++	C
481	++	C
482	+	C
483	++++	A
484	++++	A
485	+++	A
486		
487		
488		
489		
490		
491		
492		
493		
494		
495		
496	++++	A

497	+++	A
498	+++	A
499	++++	A
500	++	C
501	++	C
502	+++	A
503	++	B
504	++++	A
505	+++	A
506	++	C
507	+++	A
508	++	C
509	++++	A
510	++	C
511	+++	A
512	+++	A
513	+++	B
514	++++	A
515	++	C
516	++++	A
517	+++	A
518	++++	A
519	+	C
520	++	C
521	++	C
522	+++	A
523	+++	A
524	+++	A
525	+++	A
526	++++	A
527	+++	A
528	++	C
529	+++	A
530	+	C

531	++++	A
532	++	C
533	+++	A
534	++	C
535	+++	A
536	++	C
537	++	C
538	++	C
539	+++	A
540	++	C
541	++++	A
542	++++	A
543	++++	A
544	++++	A
545	++++	A
546	+++	A
547	+	C
548	+++	A
549	++++	A
550	++++	A
551	++++	A
552	+++	A
553	+++	A
554	++++	A
555	+++	A
556	++++	A
557	++++	A
558		
559		
560	++++	A
561		
562		
563		
564	+++	A

565	++++	A
566	++++	A
567	+++	A
568	++++	A
569	++++	A
570	++++	A
571	++++	A
572	++++	A
573	++++	A
574	++++	A
575	++++	A
576	++++	A
577	++++	A
578	++++	A

[0869] 2. VCaP Cell Proliferation Assay.

[0870] VCaP cells are plated 7,500/well 200 μL/well in **VCaP assay medium** [Phenol red free RPMI (Gibco Cat#11835-030); 5% Charcoal Stripped (Dextran treated) FBS (Omega Scientific, Cat#FB-04); Pen/Strep Life Technologies (Gibco Cat#: 10378-016); 0. 1nM R1881 (Sigma, Cat# R0908) is added upon the start of the assay, not during initial plating of the cells).

[0871] The assay was performed as follows: the cells are grown for a minimum of 3 days to deplete androgens; dosing of PROTACs and R1881 is performed as for AR ELISA; the baseline reading of Cell Titer Glo can be performed on day of dosing.

[0872] VCaP cells with 0.1 nM R1881 will double once in 4 days. Gently draw off 110 μL of media so as not to disturb the adherent cells; add 110 μL of CTG; incubate with slow shaking for 20 minutes; and read luminescence on a plate reader.

[0873] VCaP anti-proliferation data:

[0874] GI_{50} definition: A ($GI_{50} \leq$ 50nM); B (51nM $\leq$ $GI_{50} \leq$ 250nM); C (251nM $\leq$ GI_{50})

[0875] Table 19. Inhibition of VCaP Proliferation.

Ex #	GI_{50}
75	B
131	B
134	B
150	A

156	A
157	A
163	A
169	B
170	A
172	A
174	A
182	A
183	A
194	B
195	B
197	B
201	B
202	B
204	A

Ex #	Mass Data		GI_{50}
	Observed Mass 1: MH+	Observed Mass 2: MH+	
ABM-26	279.11	281.11	B
ABM-27	279.30	281.30	C
ABM-28	400.14	402.14	
ABM-29	379.17	381.16	B
ABM-30	398.13	400.12	A
ABM-31	400.14	402.14	B
ABM-32	400.14	402.14	
ABM-33	413.20	415.20	B
ABM-34	417.16	419.16	C
ABM-35	399.15	401.15	
ABM-36	484.16	486.16	A
ABM-37	598.29	600.29	A

[0876] These results support that both the difunctional compounds (ABM-L-ULM) and androgen receptor binding moieties (ABM-e) inhibit VCaP Proliferation.

[0877] 3. Apoptosis in VCaP cells.

[0878] Figure 2 illustrates that compounds as described herein induce apoptosis in VCaP cells. VCaP cells were cultured in Charcoal Stripped Serum containing media supplemented with 0.1 nM R1881 for 48 hrs. The degree of apoptosis was ascertained with CaspaseGlo assay (Promega).

These results demonstrated that PROTACs are much more potent in inducing apoptosis than an AR antagonist enzalutamide. Further, the degree of AR degradation correlates with their ability to induce apoptosis in VCaP cells.

[0879] 4. Anti-proliferation in LNCaP F876L.

[0880] Figure 3 demonstrates the anti-proliferation in LNCaP F876L cells observed with treatment with a compounds as described herein. LNCaP cells transduced with AR F876L construct were cultured in Charcoal Stripped Serum containing media. Indicated doses of enzalutamide or Example 1 were added for 7 days. CellTiterGlo reagent (Promega) was employed to assess proliferation. As shown, LNCaP cells expressing F876L construct proliferate in response to increasing doses of enzalutamide, whereas Example 1 did not exhibit agonist activity. These results demonstrated that AR PROTACs do not possess agonist activity.

[0881] 5. PSA suppression in LNCaP F876L

[0882] Compounds as described herein also suppress PSA in LNCaP F876L cells (See Figure 4). LNCaP cells transduced with AR F876L construct were cultured in Charcoal Stripped Serum containing media supplemented with 0.1 nM R1881 for 7 days. Secreted PSA in the media was detected by PSA ELISA (Sigma). These results demonstrated that AR PROTAC is able to suppress the transcriptional activity of AR in F876L containing cells.

[0883] 6. Prostate involution in C57B6 mouse model.

[0884] Figure 5 demonstrates that compounds as described herein induce prostate involution in C57B6 mouse model. 12-week old male C57BL/6 mice were treated with AR PROTAC Example 163 and its inactive epimer analog Compound A which is unable to bind to VHL E3 ligase. Enzalutamide (PO, QD, 30 mpk), Example 163 (IP, QD, 1 and 3 mpk) and Compound A (IP, QD, 1 and 3 mpk) were administered for 10 days, upon which the prostates were isolated and weighed. PROTAC Example 163 demonstrated a significant reduction in prostate weights, whereas Compound A showed no significant activity. These results demonstrated that the ability of PROTAC Example 163 to degrade AR leads to significant prostate involution in mice at very low doses.

[0885] 7. Tumor growth inhibition in VCaP xenograft model.

[0886] Figure 6 illustrates tumor growth inhibition in a VCaP xenograft model, which was achieved with compounds as described herein. VCaP cells were implanted into CB17 scid mice subcutaneously. Once the tumors were palpable, the mice were castrated, leading to temporary

tumor stasis. Upon regrowth of tumors, the mice were dosed with enzalutamide (PO, QD, 30 mpk) or AR PROTAC Example 163 (IP, QD, at 30, 10 and 3 mpk) as indicated. Tumor growth inhibition was observed in all treatment arms.

[0887] 8. AR degradation of PROTAC is E3 ligase dependent.

[0888] Figure 7 demonsrates that AR degration achieved with compounds as described herein is E3 ligase dependent. For example, in (A) AR PROTAC Example 1 was added to LNCaP cells at indicated concentrations for 24 hours in the presence or absence of 10 uM VHL E3 ligase ligand compound B. The presence of compound B competes with AR PROTAC Example 1 in VHL E3 ligase binding and greatly diminishes the AR degradation activity of AR PROTAC Example 1. In (B) LNCaP cells were treated with AR PROTAC Example 1 and its inactive epimer analog compound C which is unable to bind to VHL E3 ligase. While AR PROTAC Example 1 led to significant degradation of AR, compound C did not. These results demonstrated that AR PROTAC activity in AR degradation is VHL E3 ligase dependent.

[0889] 9. PROTAC prodrug oral pharmacokinetics and PROTAC Subcutaneous phamacokinetics.

[0890] Representative Pharmacokinetic Procedure

[0891] Male CD-1 mice (6-8 weeks old, weighing 20-30 g, 3 per study) with free access to food and water were administered with the test article at 10 mg/kg either by oral gavage or sub-cutaneous injection in the formulation specified in tables 20 and 21, at 10 mL/kg.

[0892] Approximately 0.04 mL blood samples were collected from the dorsal metatarsal vein serially at 0.25, 0.5, 1, 2, 4, 8 and 24 h timepoints; heparin was used as the anticoagulant. The samples were centrifuged at 4000 g for 5 min at 4 °C then stored at -75 °C prior to analysis.

[0893] The plasma samples were analysed via an LC/MS/MS method quantitating for unchanged, administered test article, and/or a derivative species as appropriate. WinNonlin (Phoenix™) was used for the pharmacokinetic calculations and modeling, to generate parameters such as C_{max} and AUC.

[0894] Table 20: Examples of PROTAC prodrug pharmacokinetics (ESP-4: 5% EtOH, 5% solutol HS15 in PBS; ESD-4 5% EtOH, 15% solutol in D5W).

Ex #	Dose/Route		Plasma Exposure	
		Vehicle	Prodrug	Derivative

			C_{max} (ng/mL)	AUC (ng.h/mL)	C_{max} (ng/mL)	AUC (ng.h/mL)
464	10mpk PO	ESP-4	48	118	157	571
463	10mpk PO	ESP-4	12	49	15	42
462	10mpk PO	ESP-4	0	0	178	1479
461	10mpk PO	ESP-4	0	0	524	2412
468	10mpk PO	ESP-4	0	0	209	616
470	10mpk PO	ESP-4	346	469	565	1600
469	10mpk PO	ESD-4	181	353	528	4279

[0895] Table 21: Examples of PROTAC Subcutaneous pharmacokinetics (ELP-1: 5% EtOH, 20% labrasol in PBS; ESD-2: 5% EtOH, 20% solutol in D5W).

Vehicle	Ex #	CD-1 Mouse Plasma Exposure following a 10 mg/kg SC dose	
		C_{max} (ug/mL)	AUC_{0-24} (ng.h/mL)
ESD-1	1	1.15	15600
ELP-1	80	0.18	2530
ESD-1	150	2.75	40200
ELP-1	182	1.53	29162
ESD-1	174	1.9	35065

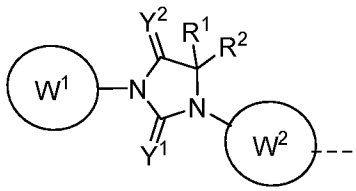
[0896] In summary, PROTACs designed to degrade AR are potent (low nM to pM), specific, rapid (within 2-4 hrs); long-lasting (days); active *in vitro* and *in vivo*, and have cellular efficacy superior to enzalutamide. AR PROTACs have efficacy in cell systems and work in vivo (AR degradation in prostate; prostate involution in prostate and seminal vesicle; tumor xenograft models). Thus, targeted degradation of AR may provide a novel mechanism for providing efficacious therapy for patients with prostate cancer for whom current therapies have failed.

In the claims:

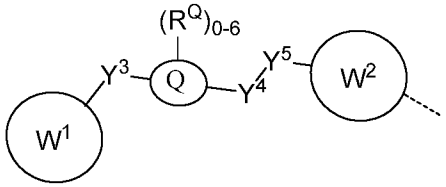
1. A compound having the structure:

[ABM]-[L],

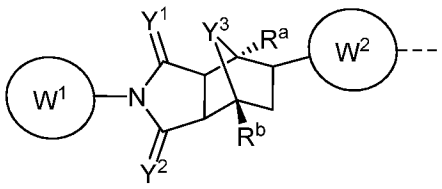
wherein ABM is an androgen receptor (AR) binding moiety, L is a chemical linker moiety, wherein the ABM comprises a structure selected from the group consisting of:



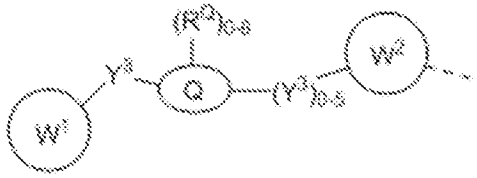
ABM-a ,



ABM-b ,



ABM-c , and



ABM-d

wherein W^1 is aryl or heteroaryl, independently substituted by 1 or more halo, hydroxyl, nitro, CN, C≡CH, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), C_{1-6} alkoxyl (linear, branched, optionally substituted by 1 or more halo), C_{2-6} alkenyl, C_{2-6} alkynyl;

Y^1, Y^2 are each independently NR^{Y1}, O, S;

Y^3, Y^4, Y^5 are each independently a bond, O, NR^{Y2}, $CR^{Y1}R^{Y2}$, C=O, C=S, SO, SO_2;

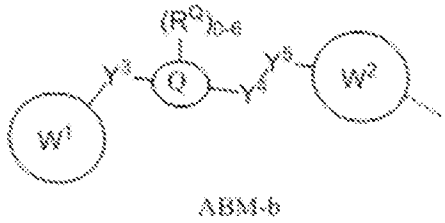
Q is a 3-6 membered alicyclic or aromatic ring with 0-4 heteroatoms, optionally substituted with 0-6 R^Q, each R^Q,is independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or 2 R^Q groups taken together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

R^1, R^2, R^a, R^b, R^{Y1}, R^{Y2} are each independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or R^1, R^2 together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

W^2 is a bond, C_{1-6} alkyl, C_{1-6} alicyclic, heterocyclic, aryl, or heteroaryl, each optionally substituted by 1, 2 or 3 R^{W2}; and

each R^{W2} is independently H, halo, C_{1-6} alkyl (optionally substituted by 1 or more F), OC_{1-3}alkyl (optionally substituted by 1 or more –F), OH, NH_2, $NR^{Y1}R^{Y2}$, CN.

2. The compound of claim 1, wherein the ABM comprises the structure:



ABM-b

wherein W^1 is aryl or heteroaryl, independently substituted by 1 or more halo, hydroxyl, nitro, CN, C≡CH, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), C_{1-6} alkoxyl (linear, branched, optionally substituted by 1 or more halo), C_{2-6} alkenyl, C_{2-6} alkynyl;

Y^3, Y^4, Y^5 are each independently a bond, O, NR^{Y2}, $CR^{Y1}R^{Y2}$, C=O, C=S, SO, SO_2;

Q is a 4 membered alicyclic ring with 0-2 heteroatoms, optionally substituted with 0-6 R^Q, each R^Q,is independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or 2 R^Q groups taken together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

R^{Y1}, R^{Y2} are each independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl);

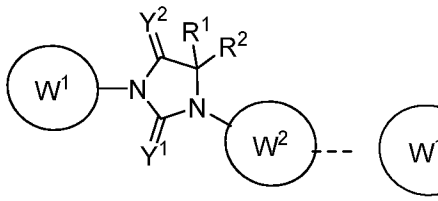
W^2 is a bond, C_{1-6} alkyl, C_{1-6} alicyclic, heterocyclic, aryl, or heteroaryl, each optionally substituted by 1, 2 or 3 R^{W2}; and

each R^{W2} is independently H, halo, C_{1-6} alkyl (optionally substituted by 1 or more F), OC_{1-3}alkyl (optionally substituted by 1 or more –F), OH, NH_2, $NR^{Y1}R^{Y2}$, CN.

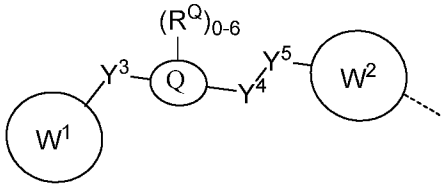
3. The compound of claim 1 or 2, further comprising an E3 ubiquintin ligase binding moiety (ULM) coupled to the ABM or L or both.

4. The compound of any of claims 1-3, wherein ULM comprises a hydroxyl prolyl moiety that binds Von Hippel-Lindau (VHL) E3 ubiquitin ligase.

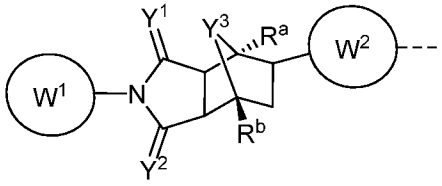
5. A bifunctional compound comprising the chemical structure: ABM-L-ULM, wherein ABM is an androgen receptor (AR) binding moiety, L is absent (a bond) or a chemical linker, and ULM is an E3 ubiquitin ligase binding moiety,wherein the ABM comprises a structure selected from the group consisting of:



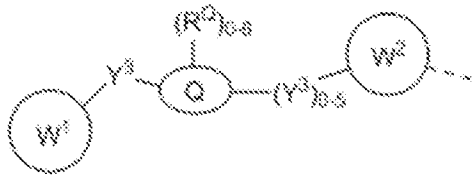
ABM-a ,



ABM-b ,



ABM-c , and



ABM-d

wherein W^1 is aryl or heteroaryl, independently substituted by 1 or more halo, hydroxyl, nitro, CN, C≡CH, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), C_{1-6} alkoxyl (linear, branched, optionally substituted by 1 or more halo), C_{2-6} alkenyl, C_{2-6} alkynyl;

Y^1, Y^2 are each independently NR^{Y1}, O, S;

Y^3, Y^4, Y^5 are each independently a bond, O, NR^{Y2}, $CR^{Y1}R^{Y2}$, C=O, C=S, SO, SO_2;

Q is a 3-6 membered alicyclic or aromatic ring with 0-4 heteroatoms, optionally substituted with 0-6 R^Q, each R^Q,is independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or 2 R^Q groups taken together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

R^1, R^2, R^a, R^b, R^{Y1}, R^{Y2} are each independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or R^1, R^2 together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

W^2 is a bond, C_{1-6} alkyl, C_{1-6} alicyclic, heterocyclic, aryl, or heteroaryl, each optionally substituted by 1, 2 or 3 R^{W2}; and

each R^{W2} is independently H, halo, C_{1-6} alkyl (optionally substituted by 1 or more F), OC_{1-3}alkyl (optionally substituted by 1 or more –F), OH, NH_2, $NR^{Y1}R^{Y2}$, CN.

6. The compound of claim 5, wherein the ABM comprises the structure:

ABM-b

wherein W^1 is aryl or heteroaryl, independently substituted by 1 or more halo, hydroxyl, nitro, CN, C≡CH, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), C_{1-6} alkoxyl (linear, branched, optionally substituted by 1 or more halo), C_{2-6} alkenyl, C_{2-6} alkynyl;

Y^3, Y^4, Y^5 are each independently a bond, O, NR^{Y2}, $CR^{Y1}R^{Y2}$, C=O, C=S, SO, SO_2;

Q is a 4 membered alicyclic ring with 0-2 heteroatoms, optionally substituted with 0-6 R^Q, each R^Q,is independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or 2 R^Q groups taken together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

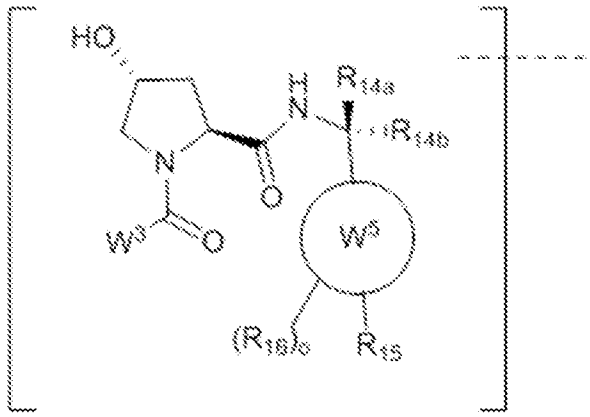
R^{Y1}, R^{Y2} are each independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl);

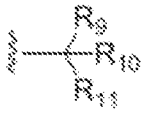
W^2 is a bond, C_{1-6} alkyl, C_{1-6} alicyclic, heterocyclic, aryl, or heteroaryl, each optionally substituted by 1, 2 or 3 R^{W2}; and

each R^{W2} is independently H, halo, C_{1-6} alkyl (optionally substituted by 1 or more F), OC_{1-3}alkyl (optionally substituted by 1 or more –F), OH, NH_2, $NR^{Y1}R^{Y2}$, CN.

7. The bifunctional compound of claim 5 or 6, wherein ULM comprises a hydroxyl prolyl moiety that binds Von Hippel-Lindau (VHL) E3 ubiquitin ligase (VLM).

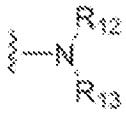
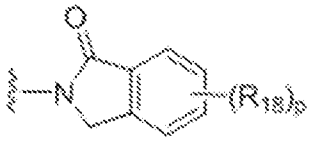
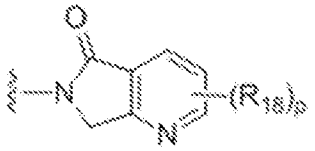
8. The bifunctional compound of any of claims 5-7, wherein the ULM comprises the structure:





wherein, W^3 is optionally substituted aryl, optionally substituted heteroaryl, or ;

each R_9 and R_{10} is independently hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted hydroxyalkyl, optionally substituted heteroaryl, or haloalkyl; or R_9, R_{10}, and the carbon atom to which they are attached form an optionally substituted cycloalkyl;

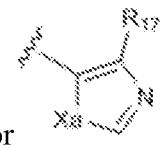
R_{11} is optionally substituted heterocyclic, optionally substituted alkoxy, optionally substituted heteroaryl, optionally substituted aryl,  ,  or  ;

R_{12} is H or optionally substituted alkyl;

R_{13} is H, optionally substituted alkyl, optionally substituted alkylcarbonyl, optionally substituted (cycloalkyl)alkylcarbonyl, optionally substituted aralkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted (heterocyclyl)carbonyl, or optionally substituted aralkyl;

R_{14a}, R_{14b}, is each independently H, haloalkyl, or optionally substituted alkyl;

W^5 is a phenyl or a 5-10 membered heteroaryl,

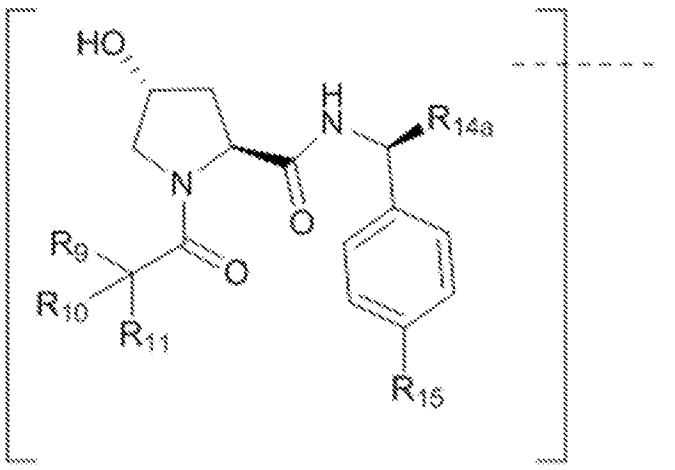
R_{15} is H, halogen, CN, OH, NO_2, N $R_{14a}R_{14b}$, OR_{14a}, $CONR_{14a}R_{14b}$, $NR_{14a}COR_{14b}$, $SO_2NR_{14a}R_{14b}$, NR_{14a} SO_2R_{14b}, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted haloalkoxy; aryl, heteroaryl, cycloalkyl, cycloheteroalkyl each R_{16} is independently halo, optionally substituted alkyl, optionally substituted haloalkyl, hydroxy, or optionally substituted haloalkoxy; or  wherein R_{17} is H, halo, optionally substituted $C_{3\text{-}6}$cycloalkyl, optionally substituted $C_{1\text{-}6}$alkyl, optionally substituted $C_{1\text{-}6}$alkenyl, and $C_{1\text{-}6}$haloalkyl, and Xa is S or O;

o is 0, 1, 2, 3, or 4;

each R_{18} is independently halo, optionally substituted alkoxy, cyano, optionally substituted alkyl, haloalkyl, haloalkoxy or a linker; and

p is 0, 1, 2, 3, or 4.

9. The bifunctional compound of any of claims 5-8, wherein the ULM comprises the structure:

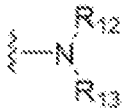


,

wherein

R_9 is H;

R_{10} is isopropyl, tert-butyl, sec-butyl, cyclopentyl, or cyclohexyl;

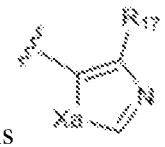
R_{11} is 

;

R_{12} is H;

R_{13} is H, optionally substituted alkyl, optionally substituted alkylcarbonyl, optionally substituted (cycloalkyl)alkylcarbonyl, optionally substituted aralkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted (heterocyclyl)carbonyl, or optionally substituted aralkyl;

R_{14a} is H, haloalkyl, or optionally substituted methyl, ethyl, isopropyl, cyclopropyl, or other alkyl; and

R_{15} is 

wherein R_{17} is H, halo, optionally substituted C_{3-6}cycloalkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}alkenyl, and C_{1-6}haloalkyl; and Xa is S or O.

10. The bifunctional compound of any of claims 5-9, wherein ULM is selected from the group consisting of:

(2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide;

(2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(thiazol-5-yl)benzyl)pyrrolidine-2-carboxamide;

(2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide;

(2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(oxazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride;

(2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methyloxazol-5-yl)benzyl)pyrrolidine-2-carboxamide;

(2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-N-(4-chlorobenzyl)-4-hydroxypyrrolidine-2-carboxamide hydrochloride;

(2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-N-(4-cyanobenzyl)-4-hydroxypyrrolidine-2-carboxamide hydrochloride;

(2S,4R)-1-((S)-2-amino-3-methylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride;

(2S,4R)-1-((S)-2-amino-3-methylbutanoyl)-4-hydroxy-N-(4-(thiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride;

(2S,4R)-1-((S)-2-amino-3-methylbutanoyl)-4-hydroxy-N-(4-(4-methyloxazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride;

(2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(1-methyl-1H-pyrazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride;

(2S,4R)-4-tert-butoxy-N-(2-hydroxy-4-(4-methylthiazol-5-yl)benzyl)-1-((S)-3-methyl-2-(1-oxoisoindolin-2-yl)butanoyl)pyrrolidine-2-carboxamide;

(2S,4R)-4-tert-butoxy-1-((S)-2-(6-fluoro-1-oxoisoindolin-2-yl)-3-methylbutanoyl)-N-(2-hydroxy-4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide; and

(2S,4R)-4-tert-butoxy-1-((S)-2-(7-cyano-1-oxoisoindolin-2-yl)-3-methylbutanoyl)-N-(2-hydroxy-4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide.

11. The bifunctional compound of any of claims 1-10, wherein the linker group (L) comprises a chemical structural unit represented by the formula:

$$-A_q-$$

wherein

q is an integer greater than 1; and

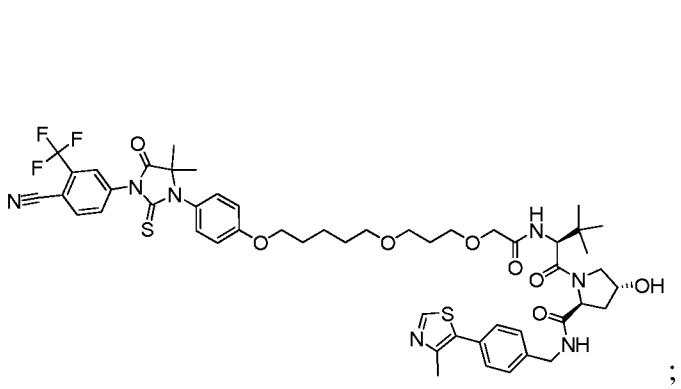
A is independently selected from the group consisting of a bond, $CR^{L1}R^{L2}$, O, S, SO, SO_2, NR^{L3}, SO_2NR^{L3}, $SONR^{L3}$, $CONR^{L3}$, $NR^{L3}CONR^{L4}$, $NR^{L3}SO_2NR^{L4}$, CO, $CR^{L1}=CR^{L2}$, C≡C, $SiR^{L1}R^{L2}$, $P(O)R^{L1}$, $P(O)OR^{L1}$, $NR^{L3}C(=NCN)NR^{L4}$, $NR^{L3}C(=NCN)$, $NR^{L3}C(=CNO_2)NR^{L4}$, C_{3-11}cycloalkyl optionally substituted with 0-6 R^{L1} and/or R^{L2} groups, C_{3-11}heteocyclyl optionally substituted with 0-6 R^{L1} and/or R^{L2} groups, aryl optionally substituted with 0-6 R^{L1} and/or R^{L2} groups, heteroaryl optionally substituted with 0-6 R^{L1} and/or R^{L2} groups; wherein

R^{L1}, R^{L2}, R^{L3}, R^{L4} and R^{L5} are each, independently, selected from the group consisting of H, halo, C_{1-8}alkyl, OC_{1-8}alkyl, SC_{1-8}alkyl, NHC_{1-8}alkyl, $N(C_{1-8}alkyl)_2$, C_{3-11}cycloalkyl, aryl, heteroaryl, C_{3-11}heterocyclyl, OC_{1-8}cycloalkyl, SC_{1-8}cycloalkyl, NHC_{1-8}cycloalkyl, $N(C_{1-8}cycloalkyl)_2$, $N(C_{1-8}cycloalkyl)(C_{1-8}alkyl)$, OH, NH_2, SH, SO_2C_{1-8}alkyl, $P(O)(OC_{1-8}alkyl)(C_{1-8}alkyl)$, $P(O)(OC_{1-8}alkyl)_2$, CC-C_{1-8}alkyl, CCH, $CH=CH(C_{1-8}alkyl)$, $C(C_{1-8}alkyl)=CH(C_{1-8}alkyl)$, $C(C_{1-8}alkyl)=C(C_{1-8}alkyl)_2$, $Si(OH)_3$, $Si(C_{1-8}alkyl)_3$, $Si(OH)(C_{1-8}alkyl)_2$, COC_{1-8}alkyl, CO_2H, halogen, CN, CF_3, CHF_2, CH_2F, NO_2, SF_5, SO_2NHC_{1-8}alkyl, $SO_2N(C_{1-8}alkyl)_2$, $SONHC_{1-8}$alkyl, $SON(C_{1-8}alkyl)_2$, $CONHC_{1-8}$alkyl, $CON(C_{1-8}alkyl)_2$, $N(C_{1-8}alkyl)CONH(C_{1-8}alkyl)$, $N(C_{1-8}alkyl)CON(C_{1-8}alkyl)_2$, $NHCONH(C_{1-8}alkyl)$, $NHCON(C_{1-8}alkyl)_2$, $NHCONH_2$, $N(C_{1-8}alkyl)SO_2NH(C_{1-8}alkyl)$, $N(C_{1-8}alkyl)$ $SO_2N(C_{1-8}alkyl)_2$, NH $SO_2NH(C_{1-8}alkyl)$, NH $SO_2N(C_{1-8}alkyl)_2$, and NH SO_2NH_2; and

wherein when q is greater than 1, R^{L1} or R^{L2} each, independently, can be linked to another A group to form cycloalkyl and/or heterocyclyl moeity that can be further substituted with 0-4 R^{L5} groups.

12. The bifunctional compound of claim 5, wherein the compound is a member selected from the group consisting of Examples 1-593 (Tables 2-17), a salt, a polymorph, isotopic derivative, and a prodrug thereof.

13. The bifunctional compound of claim 5, wherein the compound is selected from the group consisting of: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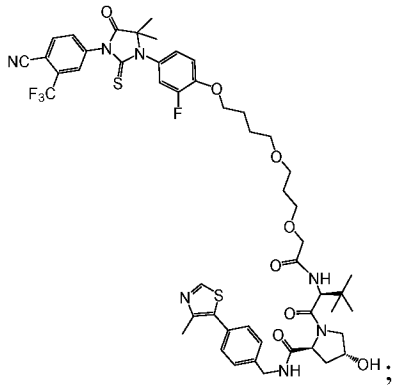
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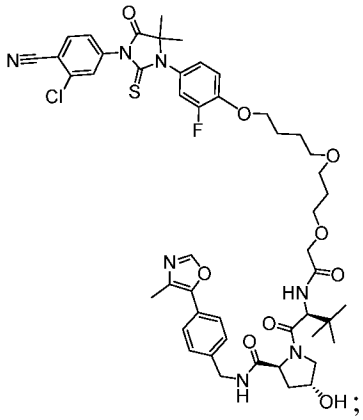
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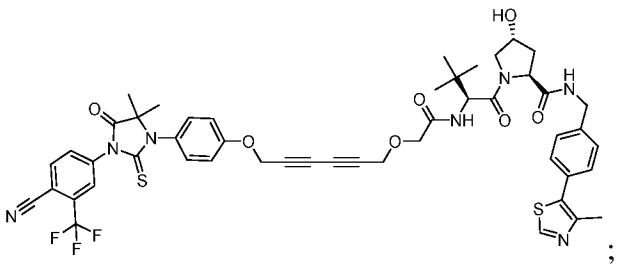
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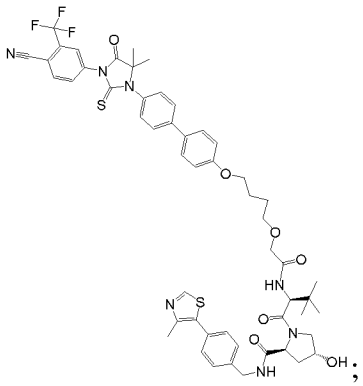
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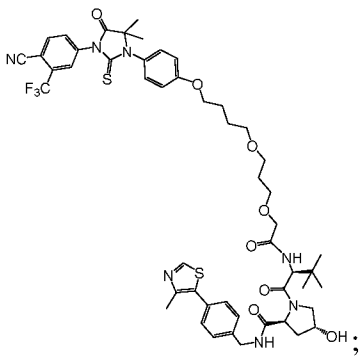
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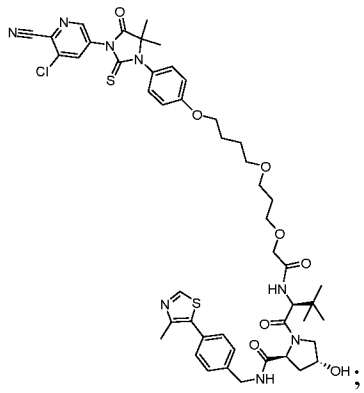
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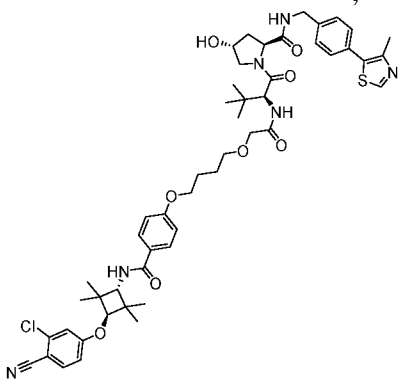
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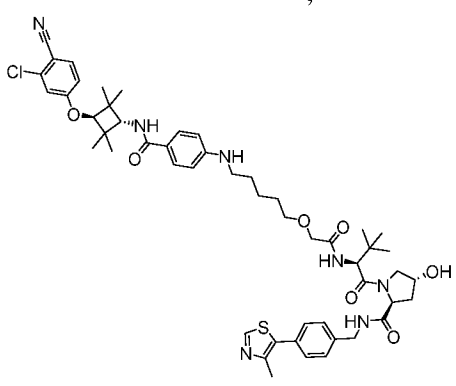
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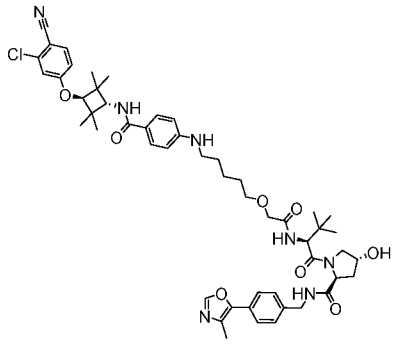
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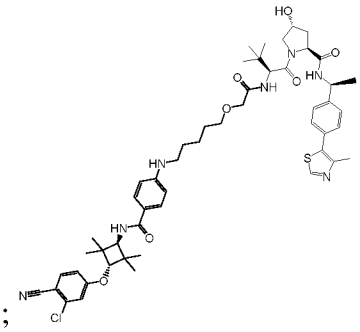
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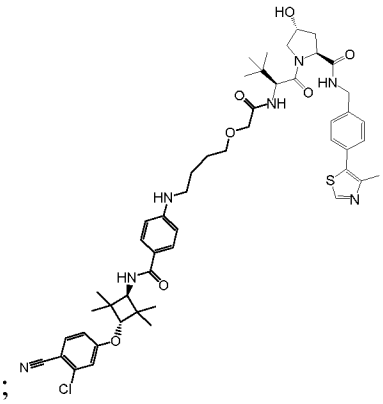
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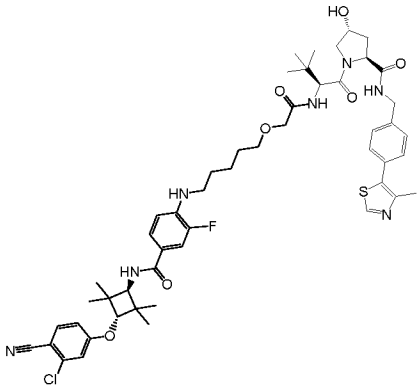
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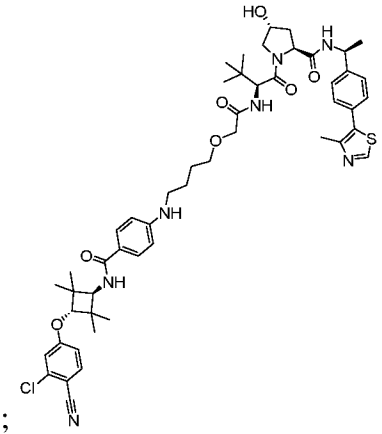
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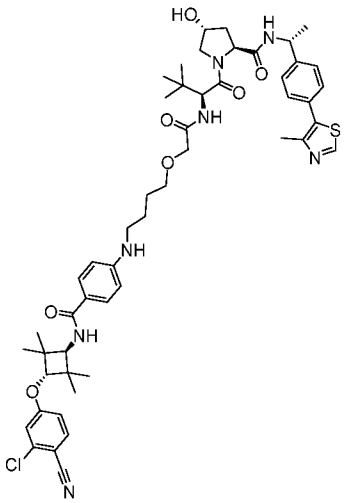
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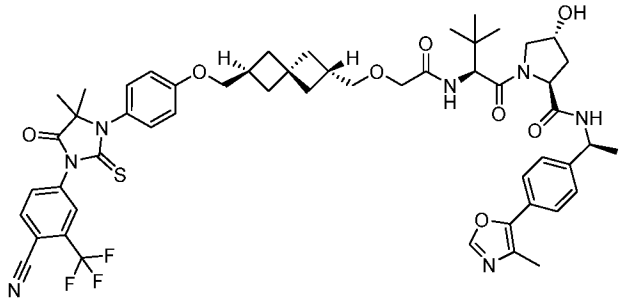
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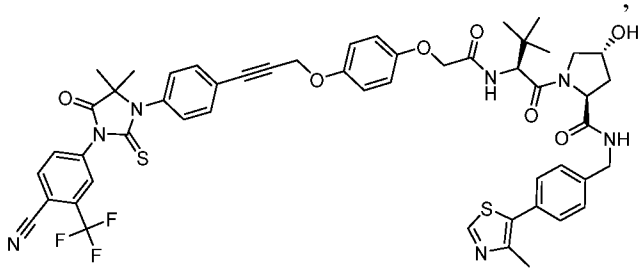
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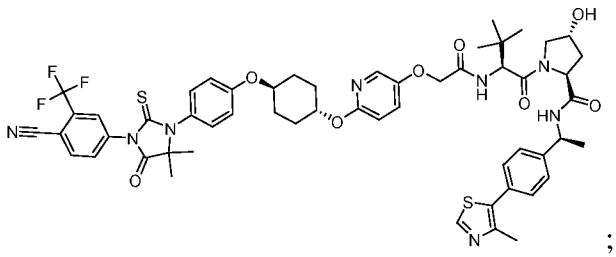
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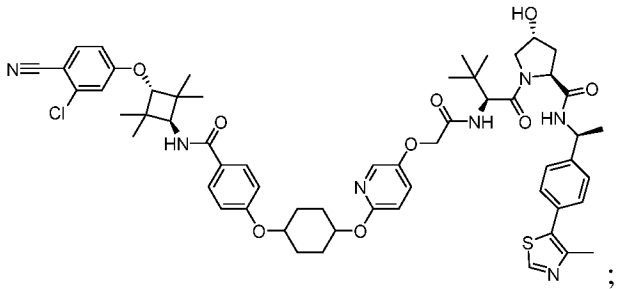
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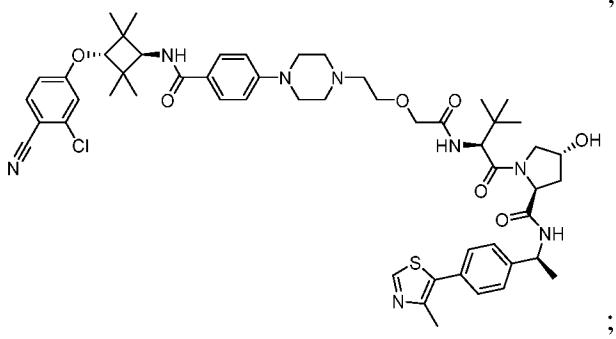
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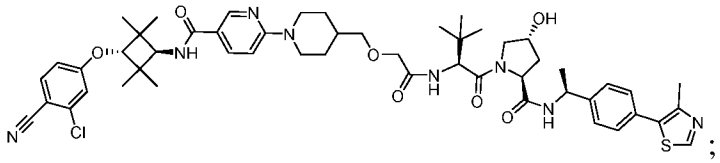
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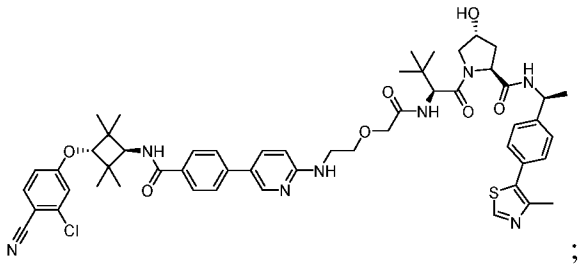
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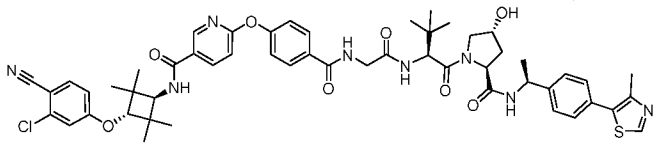
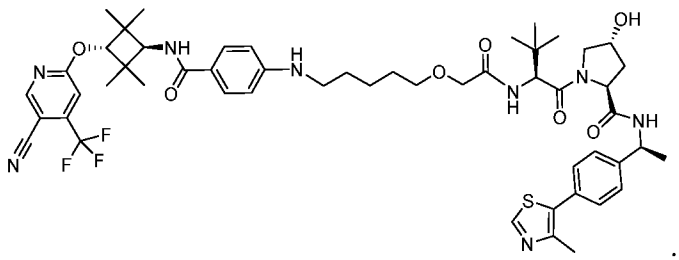

; and


.

14. An androgen receptor bindingcompound comprising a structure of:

ABM-e

wherein W^1 is aryl or heteroaryl, independently substituted by 1 or more halo, hydroxyl, nitro, CN, C≡CH, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), C_{1-6} alkoxyl (linear, branched, optionally substituted by 1 or more halo), C_{2-6} alkenyl, C_{2-6} alkynyl;

Y^1, Y^2 are each independently NR^{Y1}, O, S;

Y^3, Y^4, Y^5 are each independently a bond, O, NR^{Y2}, $CR^{Y1}R^{Y2}$, C=O, C=S, SO, SO_2;

Q is a 3-6 membered alicyclic or aromatic ring with 0-4 heteroatoms, optionally substituted with 0-6 R^Q, each R^Q,is independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or 2 R^Q groups taken together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

R^1, R^2, R^a, R^b, R^{Y1}, R^{Y2} are each independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or R^1, R^2 together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

W^2 is a bond, C_{1-6} alkyl, C_{1-6} alicyclic, heterocyclic, aryl, or heteroaryl, each optionally substituted by 1, 2 or 3 R^{W2}; and

each R^{W2} is independently H, halo, C_{1-6} alkyl (optionally substituted by 1 or more F), OC_{1-3}alkyl (optionally substituted by 1 or more –F), OH, NH_2, $NR^{Y1}R^{Y2}$, CN.

15. A composition comprising an effective amount of a bifunctional compound of any of claims 5-13, and a pharmaceutically acceptable carrier.

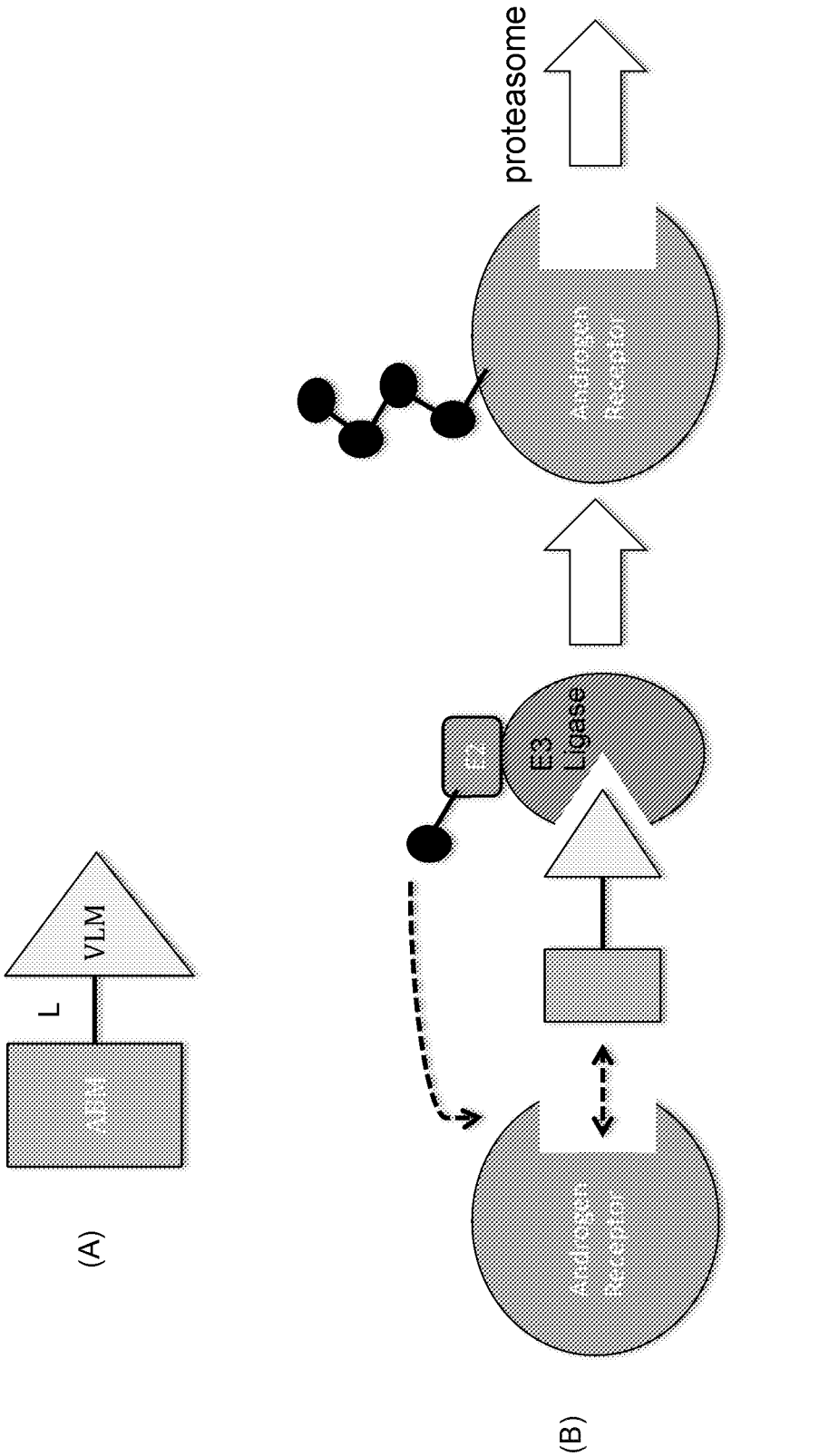
16. The composition of claim 15, wherein the composition further comprises at least one of another bioactive agent, an anti-cancer agent, another biofunctional compound of claim 5.

17. A composition comprising a pharmaceutically acceptable carrier and an effective amount of at least one compound of claim 5 for treating a disease or disorder in a subject, the method

comprising administering the composition to a subject in need thereof, wherein the compound is effective in treating or ameliorating at least one symptom of the disease or disorder.

18. The composition of claim 19, wherein the disease or disorder is at least one of cancer, prostate cancer, Kennedy's Disease or a combination thereof.

FIGURE 1


Degraded Target Protein
proteasome
Androgen Receptor
E3 Ligase
E2
Androgen Receptor
L
VLM
(A)
(B)

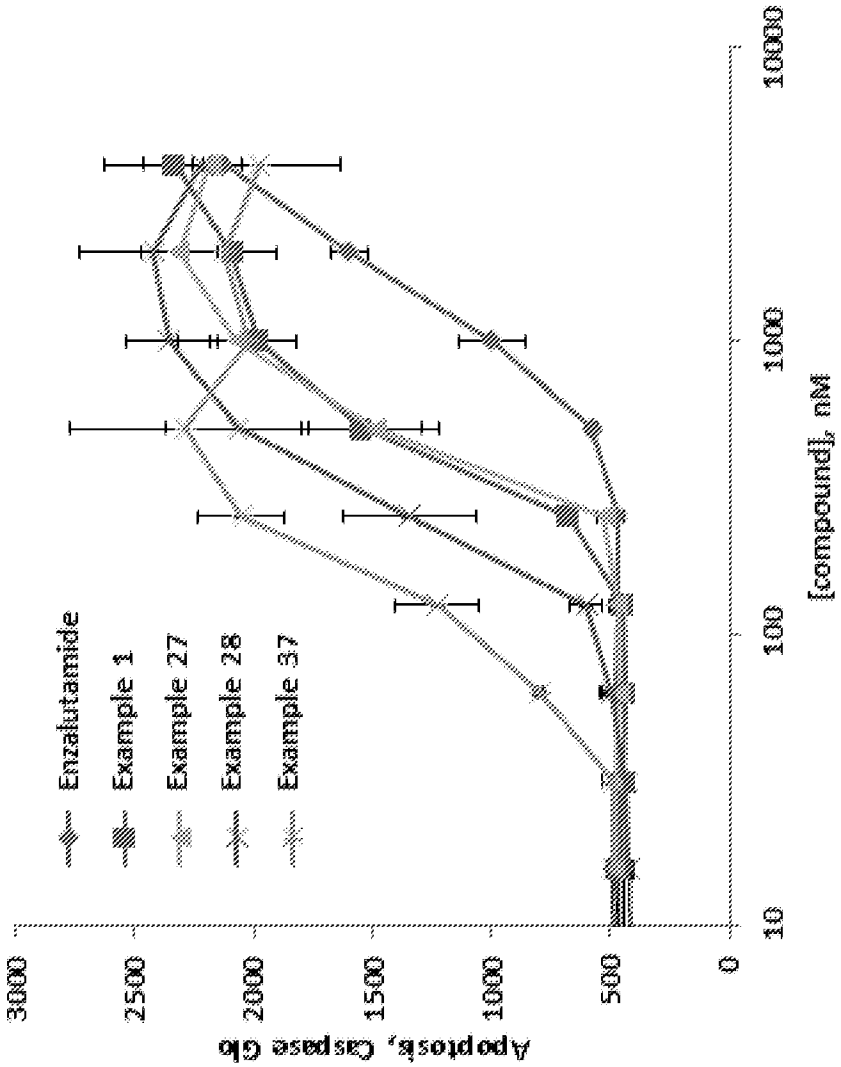
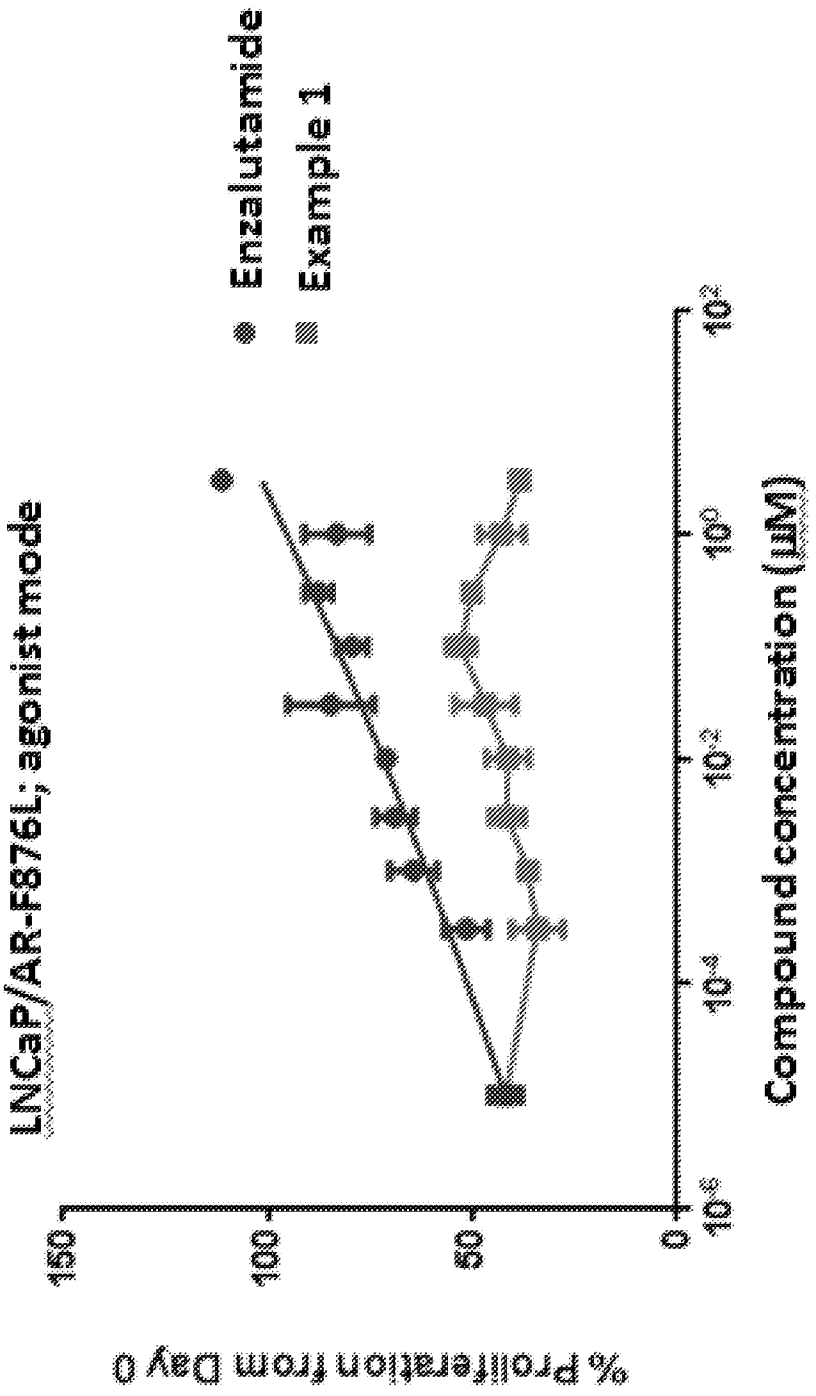

Apoptosis, Caspase Glo
3000
2500
2000
1500
1000
500
0
10
100
1000
10000
[compound], nM
Enzalutamide
Example 1
Example 27
Example 28
Example 37

Figure 2

Figure 3


LNCaP/AR-F876L; agonist mode
Enzalutamide
Example 1
% Proliferation from Day 0
150
100
50
0
10^{-6}
10^{-4}
10^{-2}
10^{0}
10^{2}
Compound concentration (μM)

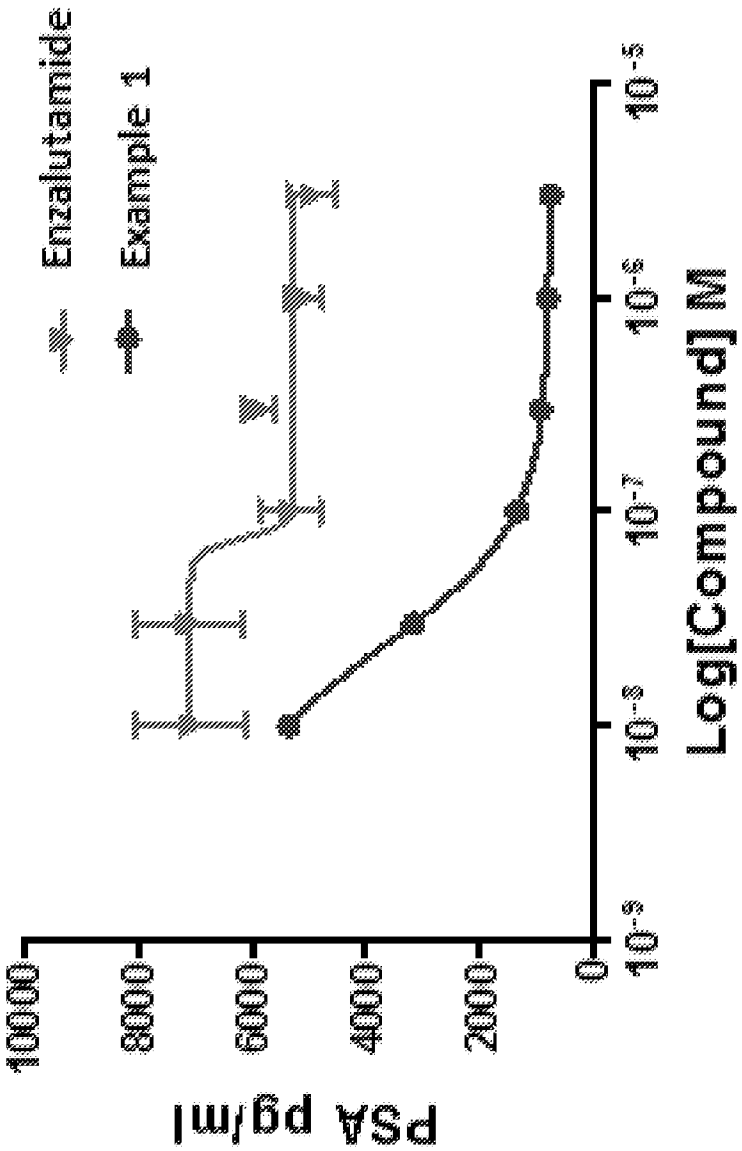
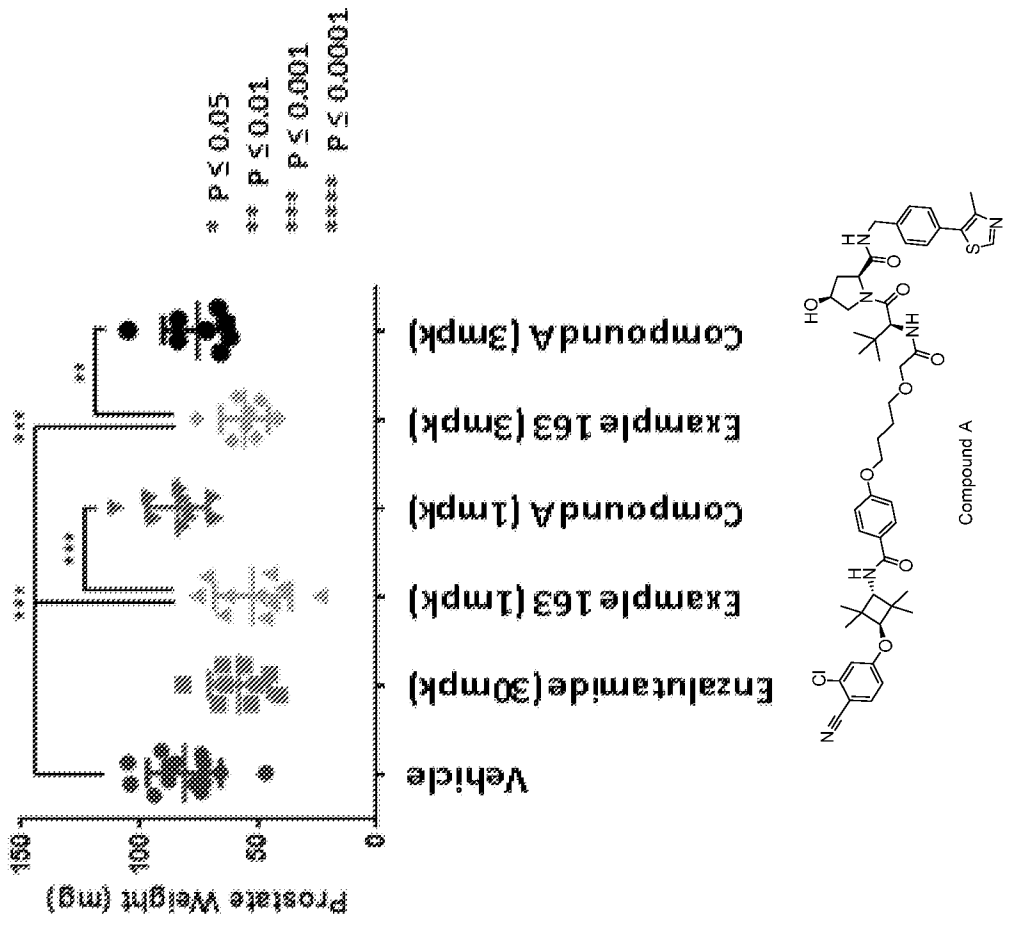

Enzalutamide
Example 1
PSA pg/ml
10000
8000
6000
4000
2000
0
10-9
10-8
10-7
10-6
10-5
Log[Compound] M

Figure 4

Figure 5


Prostate Weight (mg)
150
100
50
0
Vehicle
Enzalutamide (30mpk)
Example 163 (1mpk)
Compound A (1mpk)
Example 163 (3mpk)
Compound A (3mpk)
* P ≤ 0.05
** P ≤ 0.01
*** P ≤ 0.001
**** P ≤ 0.0001
Compound A

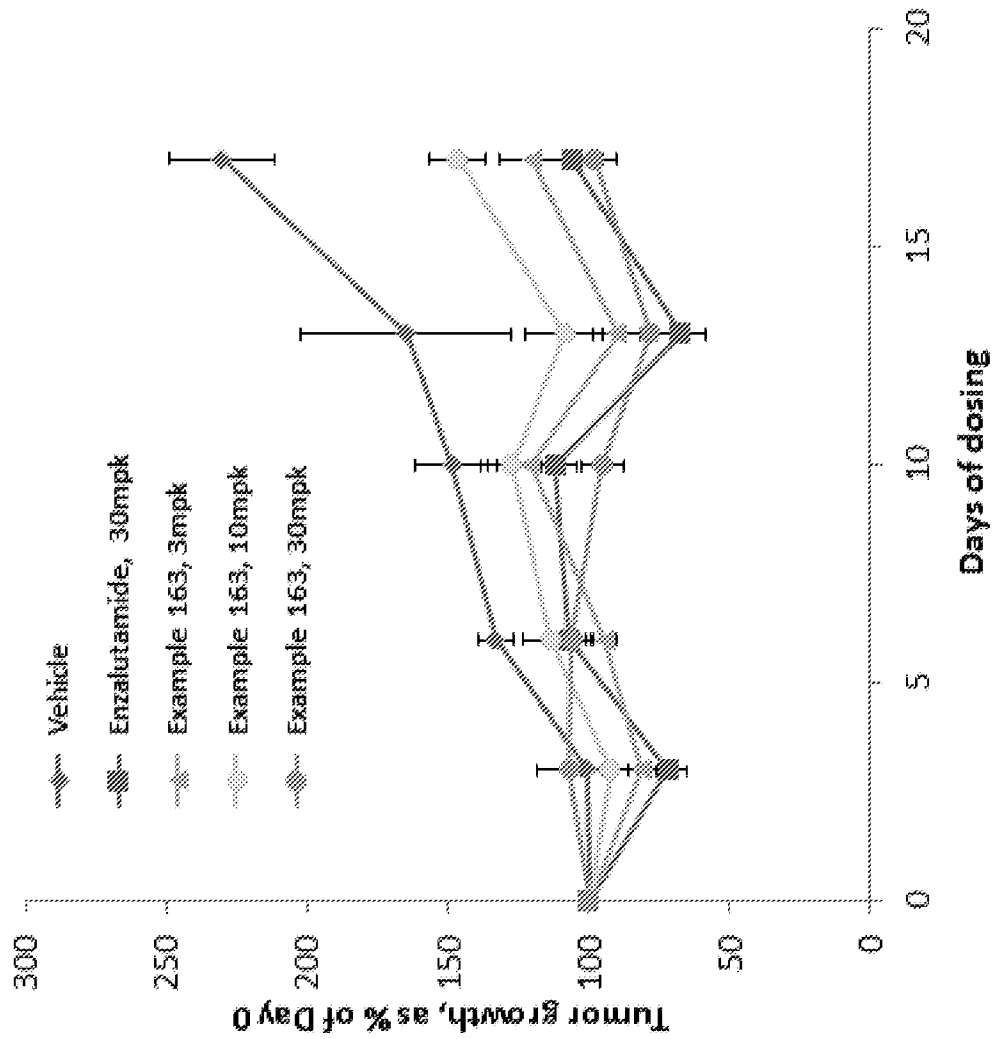
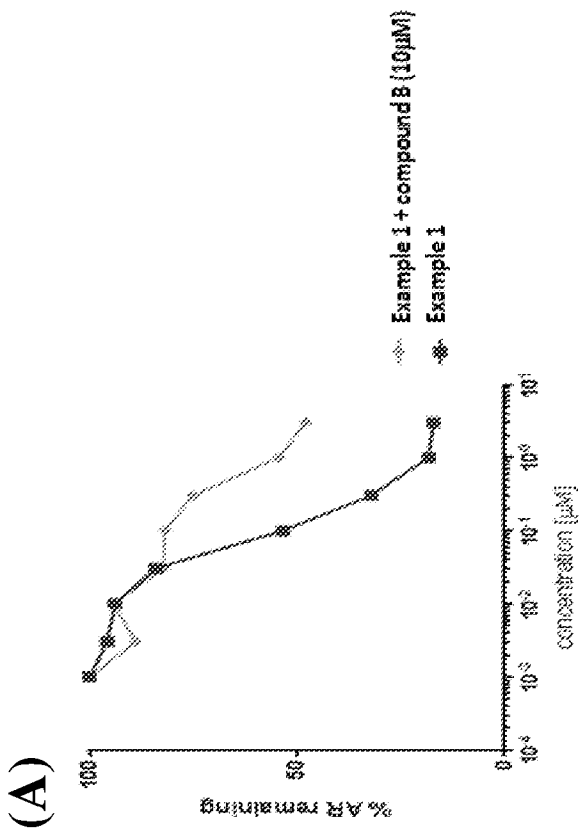
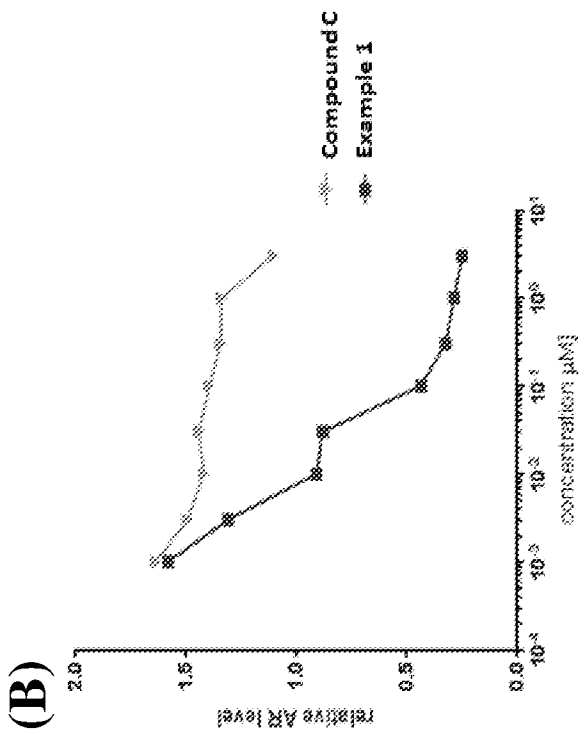

Tumor growth, as % of Day 0
300
250
200
150
100
50
0
0
5
10
15
20
Days of dosing
Vehicle
Enzalutamide, 30mpk
Example 163, 3mpk
Example 163, 10mpk
Example 163, 30mpk

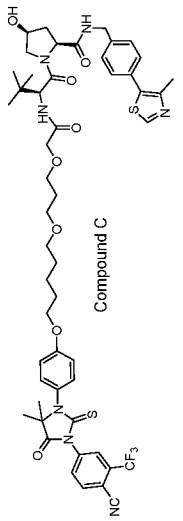
Figure 6

Figure 7


(A)
% AR remaining
concentration [μM]
Example 1 + compound B (10μM)
Example 1


(B)
relative AR level
concentration [μM]
Compound C
Example 1

Compound B


Compound C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/014187

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 403/06 (2016.01)
CPC - A61K 31/4439; C07D 207/26; C07D 207/46 (2016.02)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/4439; C07D 207/26, 207/46, 401/10, 403/06, 413/12; C12N 9/00 (2016.01)
CPC - A61K 31/4439; C07D 207/26, 207/46, 401/10, 403/06, 413/12; C12N 9/93 (2016.02)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/365, 378; 540/108; 546/113; IPC(8) - A61K 31/4439; C07D 207/26, 207/46, 401/10, 403/06, 413/12; C12N 9/00; CPC - A61K 31/4439; C07D 207/26, 207/46, 401/10, 403/06, 413/12; C12N 9/93 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Orbit, Google Patents, Google, STN, PubChem, SureChem
Search terms used: androgen receptor, e3 ubiquitin ligase, von hippel-lindau, imidazolidine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SCHNEEKLOTH et al.: Targeted intracellular protein degradation induced by a small molecule: En route to chemical proteomics. Bioorganic & Medicinal Chemistry Letters; 18; 5904–5908. 31 July 2008. [retrieved on 23.02.2016]. Retrieved from the Internet. <URL: https://www.researchgate.net/publication/23219558_Targeted_intracellular_protein_degradation_induced_by_a_small_molecule_En_route_to_chemical_proteomics>. entire document	1, 3, 5, 7, 17, 18
A	BUCKLEY et al.: Targeting the von Hippel–Lindau E3 Ubiquitin Ligase Using Small Molecules To Disrupt the VHL/HIF-1α Interaction. J. Am. Chem. Soc. 134, 4465–4468. 27 February 2012. [retrieved on 19.04.2016]. Retrieved from the Internet. <URL: http://pubs.acs.org/doi/pdf/10.1021/ja209924v>. entire document	1, 3, 5, 7, 17, 18
A	US 2014/0356322 A1 (YALE UNIVERSITY) 04 December 2014 (04.12.2014) entire document	1, 3, 5, 7, 17, 18
A	US 2009/0035362 A1 (SHIH et al) 05 February 2009 (05.02.2009) entire document	1, 3, 5, 7, 17, 18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2016	17 MAY 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/014187

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4, 8-11, 15, 16
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 3, 5, 7, 17, 18

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Continued from Box No. III Observations where unity of invention is lacking

Claims 1, 3, 5, 7, 17, and 18 have been analyzed subject to the restriction that the claims read on a compound having the structure: [ABM]-[L], wherein ABM is an androgen receptor (AR) binding moiety, L is a chemical linker moiety, wherein the chemical linker moiety is a bond, wherein the ABM comprises a structure ABM-a, wherein W1 is aryl substituted with 1 halo, wherein the halo is Cl, wherein the aryl is phenyl; Y1, Y2 are each NRY1; R1, R2, RY1 are each independently H; W2 is a bond; wherein the compound further comprising an E3 ubiquitin ligase binding moiety (ULM) coupled to the ABM; wherein the ULM comprising the chemical structure: ABM-L-ULM, wherein ULM comprises a hydroxyl prolyl moiety that binds Von Hippel-Lindau (VHL) E3 ubiquitin ligase (VLM) wherein the ULM comprises the structure as shown in claim 8 of the instant invention: wherein W3 is unsubstituted aryl; R14a, R14b is each independently H; W5 is phenyl; R15 is H; R16 is absent; and o is 0; and compositions thereof.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-3, 5-7, 12-14, 17, and 18 are drawn to compounds and compositions thereof.

The first invention of Group I+ is restricted to a compound having the structure: [ABM]-[L], wherein ABM is an androgen receptor (AR) binding moiety, L is a chemical linker moiety, wherein the chemical linker moiety is a bond, wherein the ABM comprises a structure ABM-a, wherein W1 is aryl substituted with 1 halo, wherein the halo is Cl, wherein the aryl is phenyl; Y1, Y2 are each NRY1; R1, R2, RY1 are each independently H; W2 is a bond; wherein the compound further comprising an E3 ubiquitin ligase binding moiety (ULM) coupled to the ABM; wherein the ULM comprising the chemical structure: ABM-L-ULM, wherein ULM comprises a hydroxyl prolyl moiety that binds Von Hippel-Lindau (VHL) E3 ubiquitin ligase (VLM) wherein the ULM comprises the structure as shown in claim 8 of the instant invention: wherein W3 is unsubstituted aryl; R14a, R14b is each independently H; W5 is phenyl; R15 is H; R16 is absent; and o is 0; and compositions thereof. It is believed that claims 1, 3, 5, 7, 17, and 18 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound having the structure: [ABM]-[L], wherein ABM is an androgen receptor (AR) binding moiety, L is a chemical linker moiety, wherein the chemical linker moiety is a bond, wherein the ABM comprises a structure ABM-b, wherein W1 is aryl substituted with 1 halo, wherein the halo is Cl, wherein the aryl is phenyl; Y3, Y4, and T5 are each independently a bond; Q is a 3-membered alicyclic ring with 0 heteroatoms which is unsubstituted comprising 2 RQ groups; RQ is H; W2 is a bond; wherein the compound further comprising an E3 ubiquitin ligase binding moiety (ULM) coupled to the ABM; wherein the ULM comprising the chemical structure: ABM-L-ULM, wherein ULM comprises a hydroxyl prolyl moiety that binds Von Hippel-Lindau (VHL) E3 ubiquitin ligase (VLM) wherein the ULM comprises the structure as shown in claim 8 of the instant invention: wherein W3 is unsubstituted aryl; R14a, R14b is each independently H; W5 is phenyl; R15 is H; R16 is absent; and o is 0; and compositions thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables ABM, L, ULM, W1, W2, Q, Y3, Y4, Y5, and RQ.

The Groups I+ share the technical features of a compound having the core structure of the structure: [ABM]-[L]; a bifunctional compound comprising the core structure of the chemical structure: ABM-L-ULM; a androgen receptor binding compound comprising the core structure of a structure of: ABM-e; and a composition comprising a pharmaceutically acceptable carrier and an effective amount of at least one compound for treating a disease or disorder in a subject, the method comprising administering the composition to a subject in need thereof, wherein the compound is effective in treating or ameliorating at least one symptom of the disease or disorder. However, these shared technical features do not represent a contribution over the prior art.

Specifically, "Targeted intracellular protein degradation induced by a small molecule: En route to chemical proteomics" to Schneekloth et al. teach a compound having the core structure of the structure: [ABM]-[L] (See Abstract, This cell permeable PROTAC consists of a non-steroidal androgen receptor ligand (SARM) and the MDM2 ligand known as nutlin, connected by a PEG-based linker. The SARM–nutlin PROTAC recruits the androgen receptor to MDM2, which functions as an E3 ubiquitin ligase.; Pg. 5905, For this PROTAC, we opted to use a selective androgen receptor modulator (SARM), whichbinds AR with a Ki of 4 nM. We chose to recruit the androgen receptor via this class of PROTACs to the E3 ligase MDM2, which is a 90 kDa protein whose natural substrate is p53.12 Recently a new class of imidazoline derivatives that bind MDM2 has been identified. These compounds, called nutlins...A short soluble PEG linker was chosen to bridge the two terminal protein ligands...Coupling of 13 to the acid 4 afforded a diastereomeric mixture of the SARM–nutlin PROTAC, 14.; Pg. 5905, Fig. 1; Pg. 5906, Scheme 3, Compound 14 SARM–nutlin PROTAC 14;...see shown structure...); a bifunctional compound comprising the core structure of the chemical structure: ABM-L-ULM (See Abstract; Pg. 5906, Scheme 3, Compound 14 SARM–nutlin PROTAC 14;...see shown structure...); a androgen receptor binding compound comprising the core structure of a structure of: ABM-e (See Abstact, a heterobifunctional all-small molecule PROTAC (PROteolysis TArgeting Chimera) capable of inducing proteasomal degradation of the androgen receptor...).

Additionally, US 2014/0356322 A1 to Yale University teaches a bifunctional compound comprising the core structure of the chemical structure: ABM-L-ULM (See Abstract, Para. [0003]; Para. [0148]); a composition comprising a pharmaceutically acceptable carrier and an effective amount of at least one compound for treating a disease or disorder in a subject, the method comprising administering the composition to a subject in need thereof, wherein the compound is effective in treating or ameliorating at least one symptom of the disease or disorder (See Paras. [0123] and [0124]).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.