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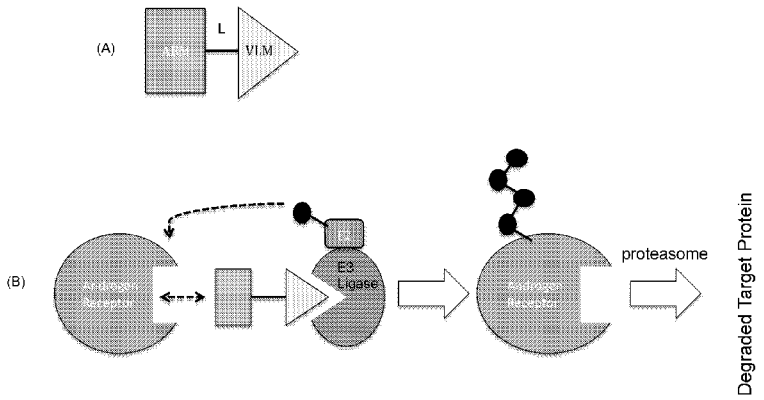
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(54) Title: COMPOUNDS AND METHODS FOR THE TARGETED DEGRADATION OF THE ANDROGEN RECEPTOR

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:

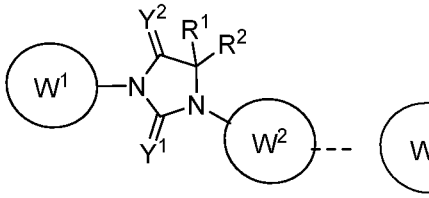
[010] **ABM – L-VLM (II),**

[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.

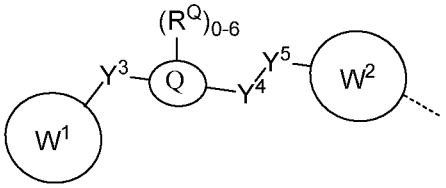
[012] In certain embodiments, the ULM is a moiety specific for an E3 ubiquitin ligase such as, e.g., cereblon, mouse double minute 2 homolog (Mdm2), or inhibitor of apoptosis (IAP), wherein the ULM moiety is coupled to an ABM as described herein.

[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.

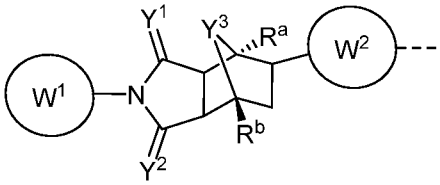
[014] In another aspect, the description provides AR binding moieties (ABM). In an additional embodiment, the description provides compounds having the following general structure: ABM-L, wherein ABM is an AR binding moiety as described herein, and L is a chemical linker moiety, or optionally a bond.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



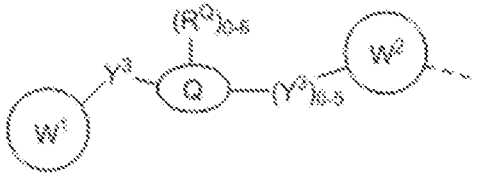
ABM-a ,



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);

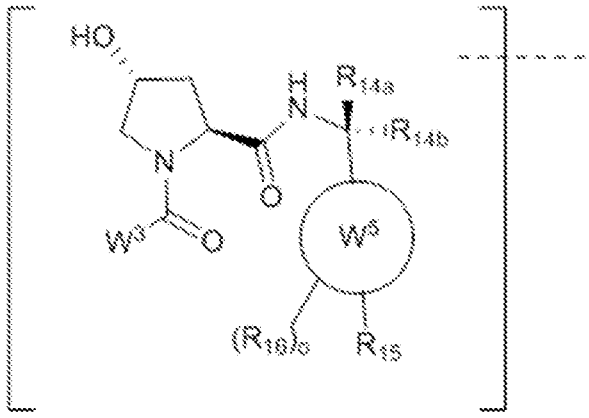
R^1, R^2, R^a, R^b, R^{Y1}, R^{Y2} are each independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or R^1, R^2 together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

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

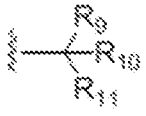
each R^{W2} is independently H, halo, C_{1-6} alkyl (optionally substituted by 1 or more F), OC_{1-3}alkyl (optionally substituted by 1 or more –F), OH, NH_2, $NR^{Y1}R^{Y2}$, CN.

[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,



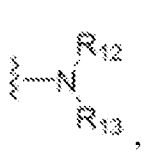
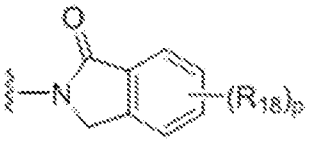
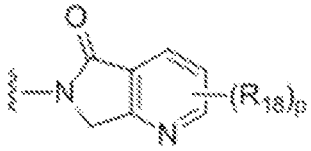
wherein, W^3 is optionally substituted aryl, optionally substituted heteroaryl, or



;

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;

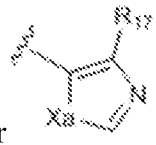
R_{11} is optionally substituted heterocyclic, optionally substituted alkoxy, optionally substituted heteroaryl, optionally substituted aryl,  ,  or  ;

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,

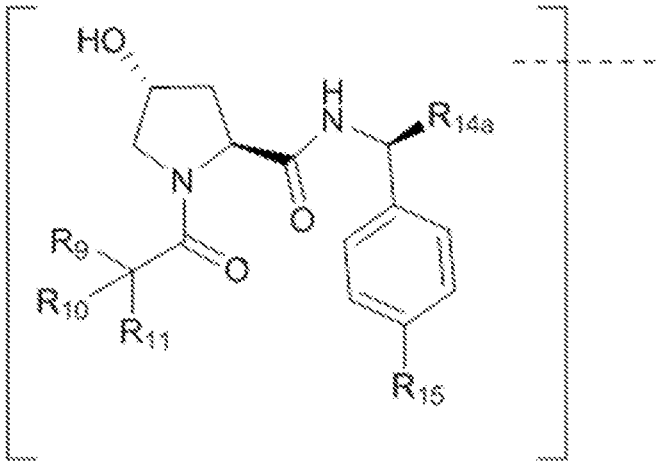
R_{15} is H, halogen, CN, OH, NO_2, N $R_{14a}R_{14b}$, OR_{14a}, $CONR_{14a}R_{14b}$, $NR_{14a}COR_{14b}$, $SO_2NR_{14a}R_{14b}$, NR_{14a} SO_2R_{14b}, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted haloalkoxy; aryl, heteroaryl, cycloalkyl, cycloheteroalkyl each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

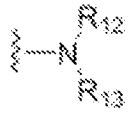


,

wherein

R_9 is H;

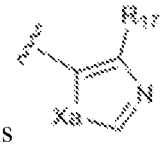
R_{10} is isopropyl, tert-butyl, sec-butyl, cyclopentyl, or cyclohexyl;

R_{11} is  ;

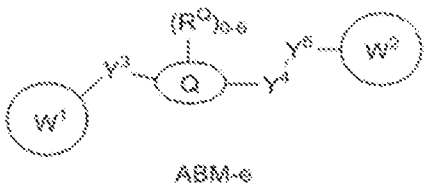
R_{12} is H;

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



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.

[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.

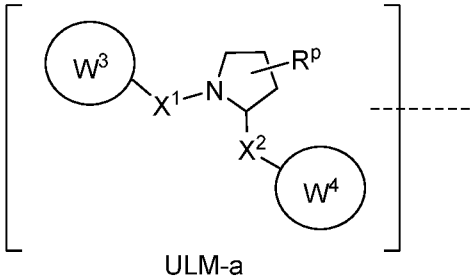
[075] It will be understood that the general structures are exemplary and the respective moieties can be arranged in any desired order or configuration, e.g., ULM-L-ABM, and VLM-L-ABM respectively. In certain additional embodiments, the compounds comprise a plurality of E3 ligase binding moieties and/or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

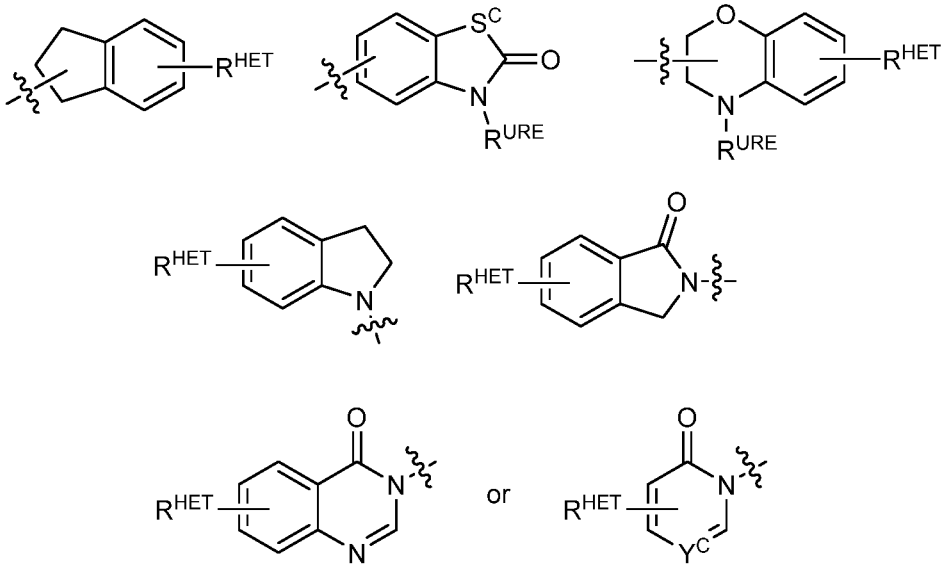
[089] Alternatively, T may also be a $-(CH_2O)_n-$ group, a $-(OCH_2)_n-$ group, a $-(CH_2CH_2O)_n-$ group, a $-(OCH_2CH_2)_n-$ group, all of which groups are optionally substituted.

[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;

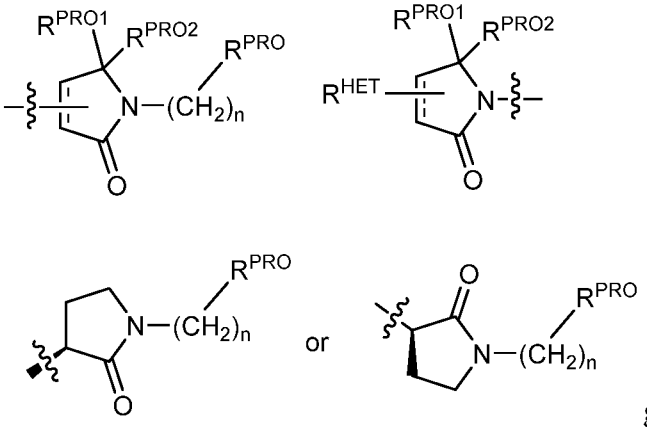
[095] R^{HET} is H, CN, NO_2, halo (preferably Cl or F), optionally substituted C_1-C_6 alkyl (preferably substituted with one or two hydroxyl groups or up to three halo groups (e.g. CF_3), optionally substituted O(C_1-C_6 alkyl) (preferably substituted with one or two hydroxyl groups or up to three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

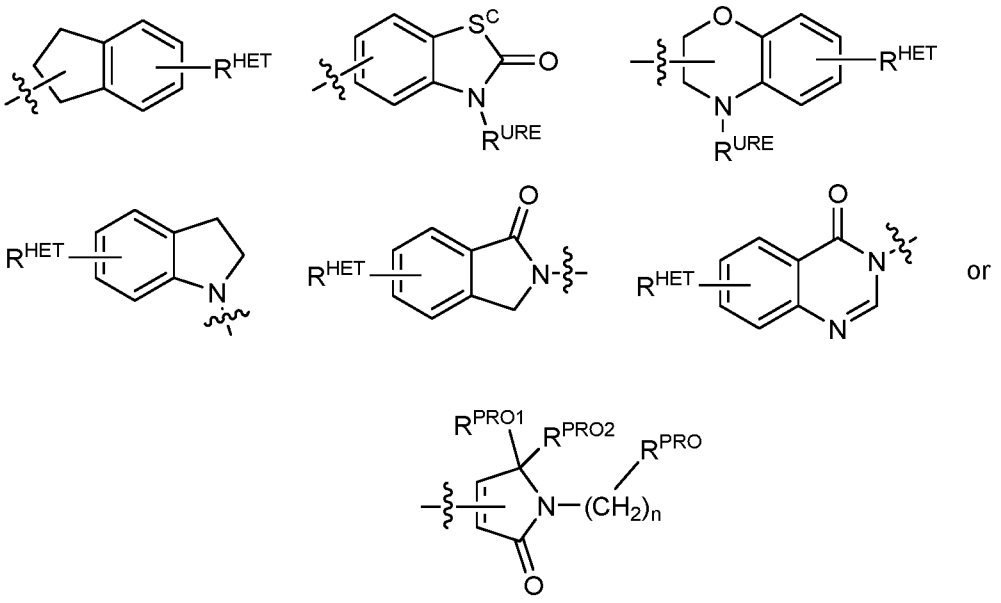
[0101] R^{PRO1} and R^{PRO2} are each independently H, an optionally subsituted C_1-C_3 alkyl group or together form a keto group, and

[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);

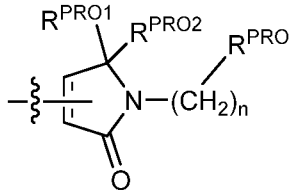
[0108] R^{URE} is H, a C_1-C_6 alkyl (preferably H or C_1-C_3 alkyl) or a –C(O)(C_1-C_6 alkyl) each of which groups is optionally substituted with one or two hydroxyl groups or up to three halogen, preferably fluorine groups, or an optionally substituted phenyl group, an optionally substituted heteroaryl,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

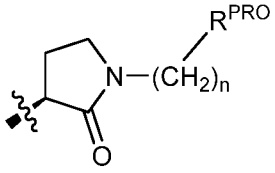
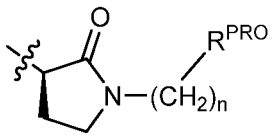
[0109] R^{PRO} is H, optionally substituted C_1-C_6 alkyl or an optionally substituted aryl (phenyl or napthyl), heteroaryl or heterocyclic group selected from the group consisting of oxazole, isoxazole, thiazole, isothiazole, imidazole, diazole, oximidazole, pyrrole, pyrollidine, furan, dihydrofuran,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

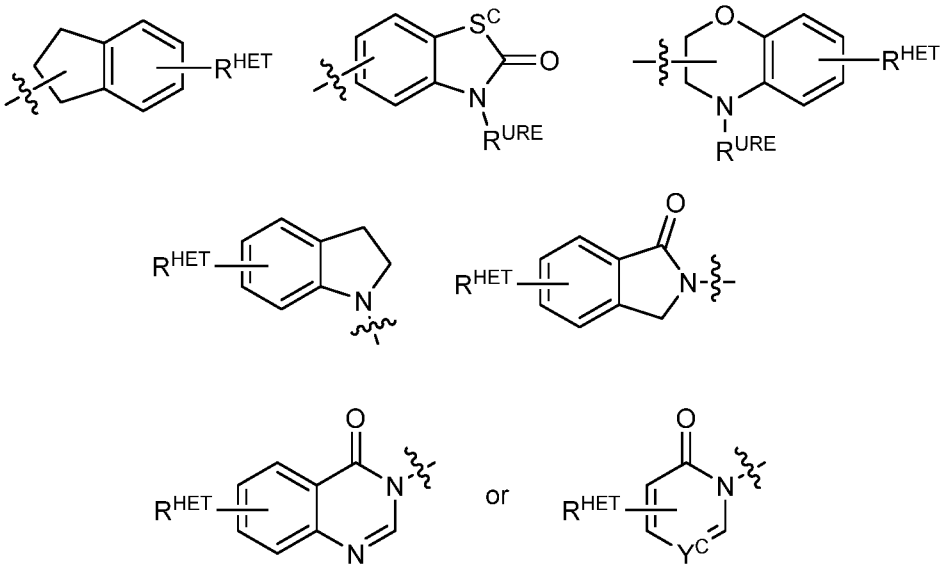
[0111] each n is independently 0, 1, 2, 3, 4, 5, or 6 (preferably 0 or 1), or an optionally substituted heterocycle, preferably tetrahydrofuran, tetrahydrothiene, piperidine, piperazine or morpholine (each of which groups when substituted, are preferably substituted with a methyl or halo (F, Br, Cl), 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);

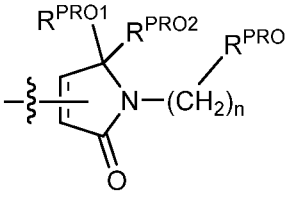
[0118] R^{SS} is H, CN, NO_2, halo (preferably F or Cl), optionally substituted C_1-C_6 alkyl (preferably substituted with one or two hydroxyl groups or up to three halo groups), optionally substituted O-(C_1-C_6 alkyl) (preferably substituted with one or two hydroxyl groups or up to three halo groups)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

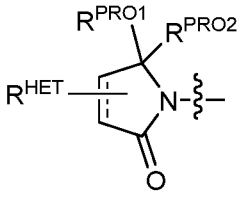
[0120] Y^C is N or C-R^{YC}, where R^{YC} is H, OH, CN, NO_2, halo (preferably Cl or F), optionally substituted C_1-C_6 alkyl (preferably substituted with one or two hydroxyl groups or up to three halo groups (e.g. CF_3), optionally substituted O(C_1-C_6 alkyl) (preferably substituted with one or two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

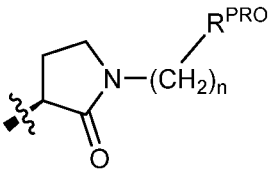
[0121] In certain embodiments, heterocycle groups for W^4 include tetrahydrofuran, tetrahydrothiene, tetrahydroquinoline, piperidine, piperazine, pyrrollidine, morpholine, oxane or thiane, each of which groups may be optionally substituted, or a group according to the chemical structure:



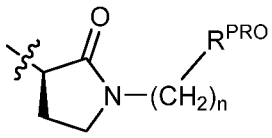
or



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;

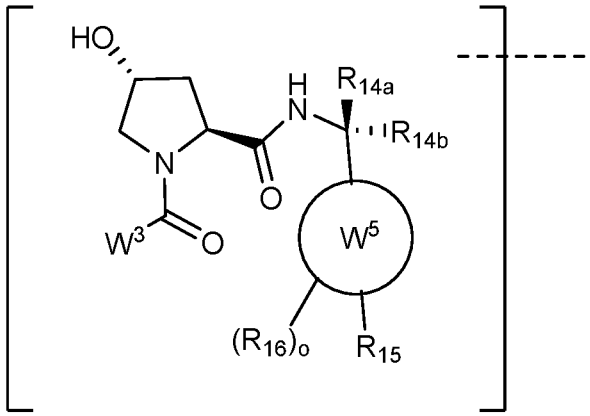
[0123] R^{PRO1} and R^{PRO2} are each independently H, an optionally subsituted C_1-C_3 alkyl group or together form a keto group and

[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.

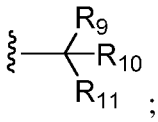
[0125] In certain additional embodiments, ULM-a, is optionally substituted by 1-3 R^P groups in the pyrrolidine moiety. Each R^P is independently H, halo, -OH, C_{1-3}alkyl.

[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:

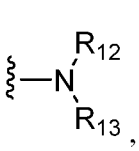


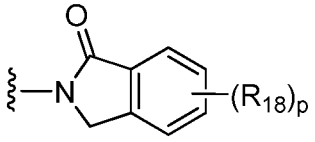
[0128] wherein, W^3 is optionally substituted aryl, optionally substituted heteroaryl, or



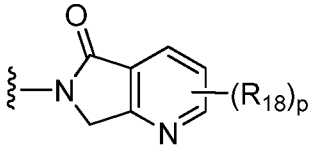
;

[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;

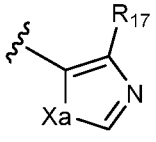
[0134] W^5 is a phenyl or a 5-10 membered heteroaryl,

[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.

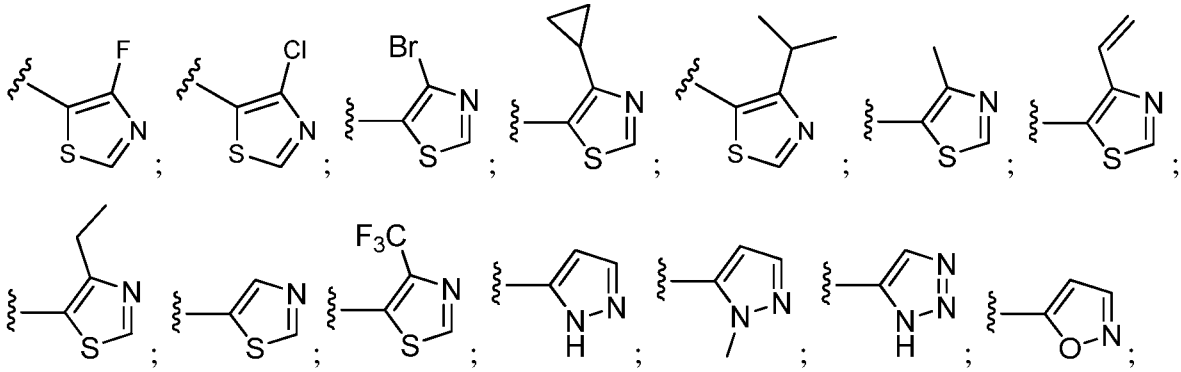
[0139] In certain embodiments, R_{15} is 

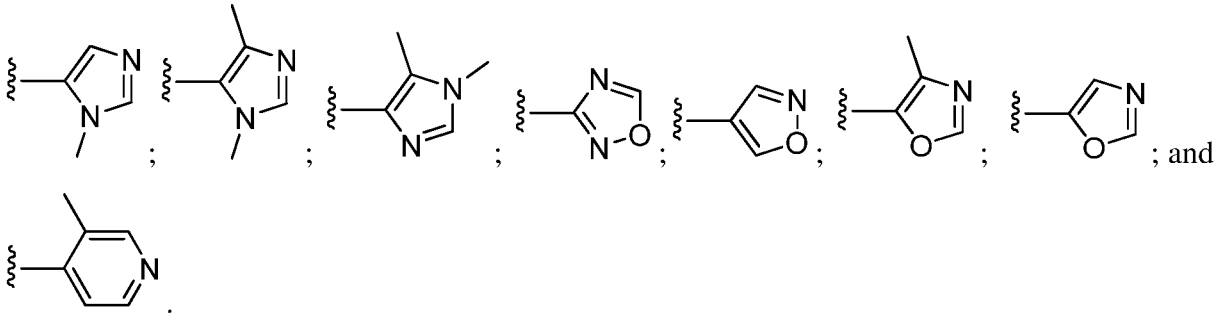
wherein R_{17} is H, halo, optionally substituted C_{3-6}cycloalkyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}alkenyl, and C_{1-6}haloalkyl; and

[0140] Xa is S or O.

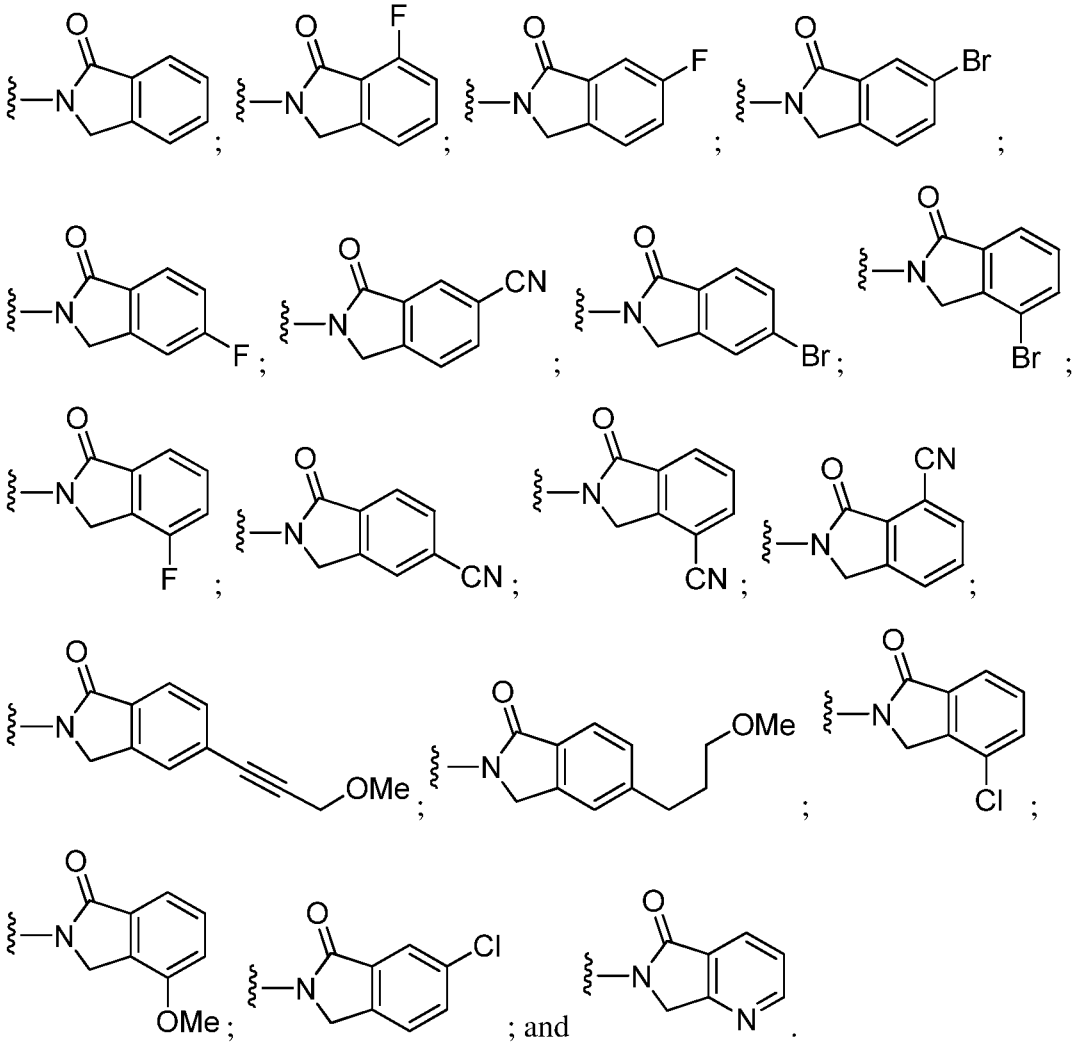
[0141] In certain embodiments, R_{17} is selected from the group methyl, ethyl, isopropyl, and cyclopropyl.

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

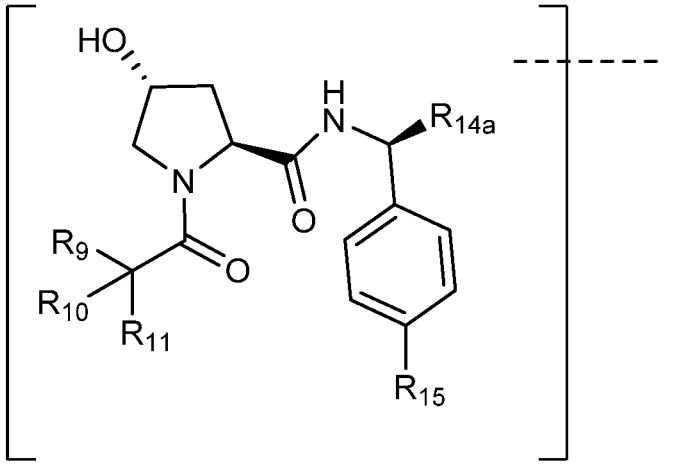




[0143] In certain embodiments, R_{11} is selected from the group consisting of:



[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:

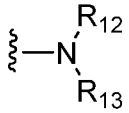


,

[0145] wherein

[0146] R_9 is H;

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

[0148] R_{11} is 

;

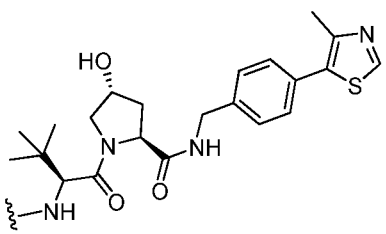
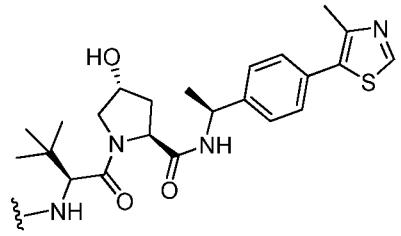
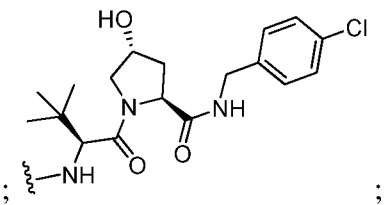
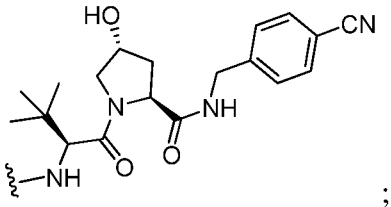
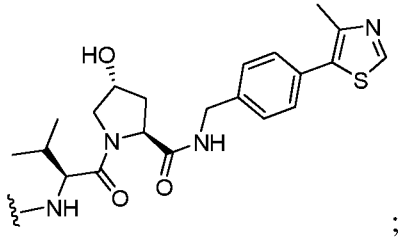
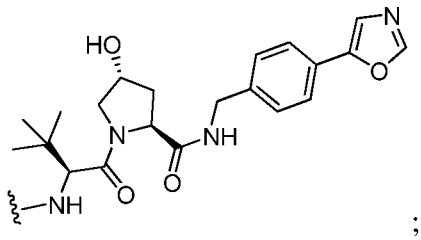
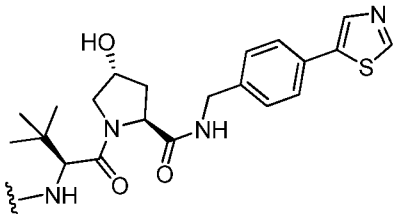
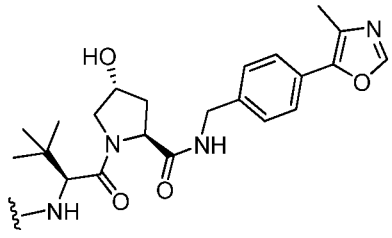
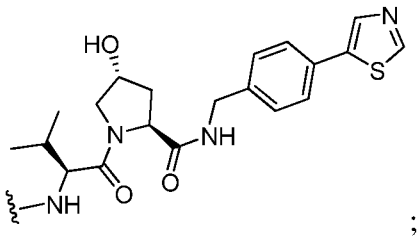
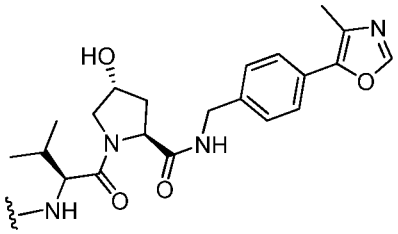
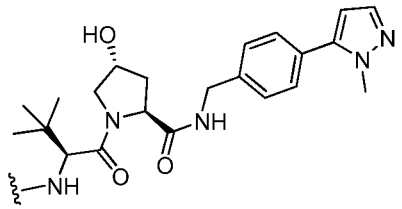
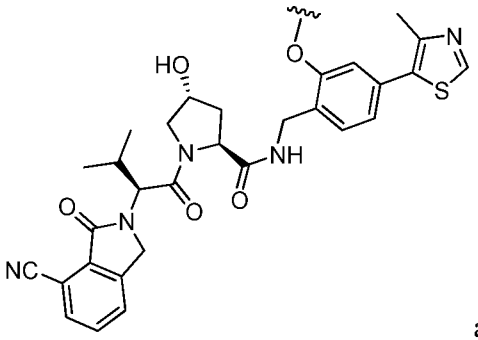
[0149] R_{12} is H;

[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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; and

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.

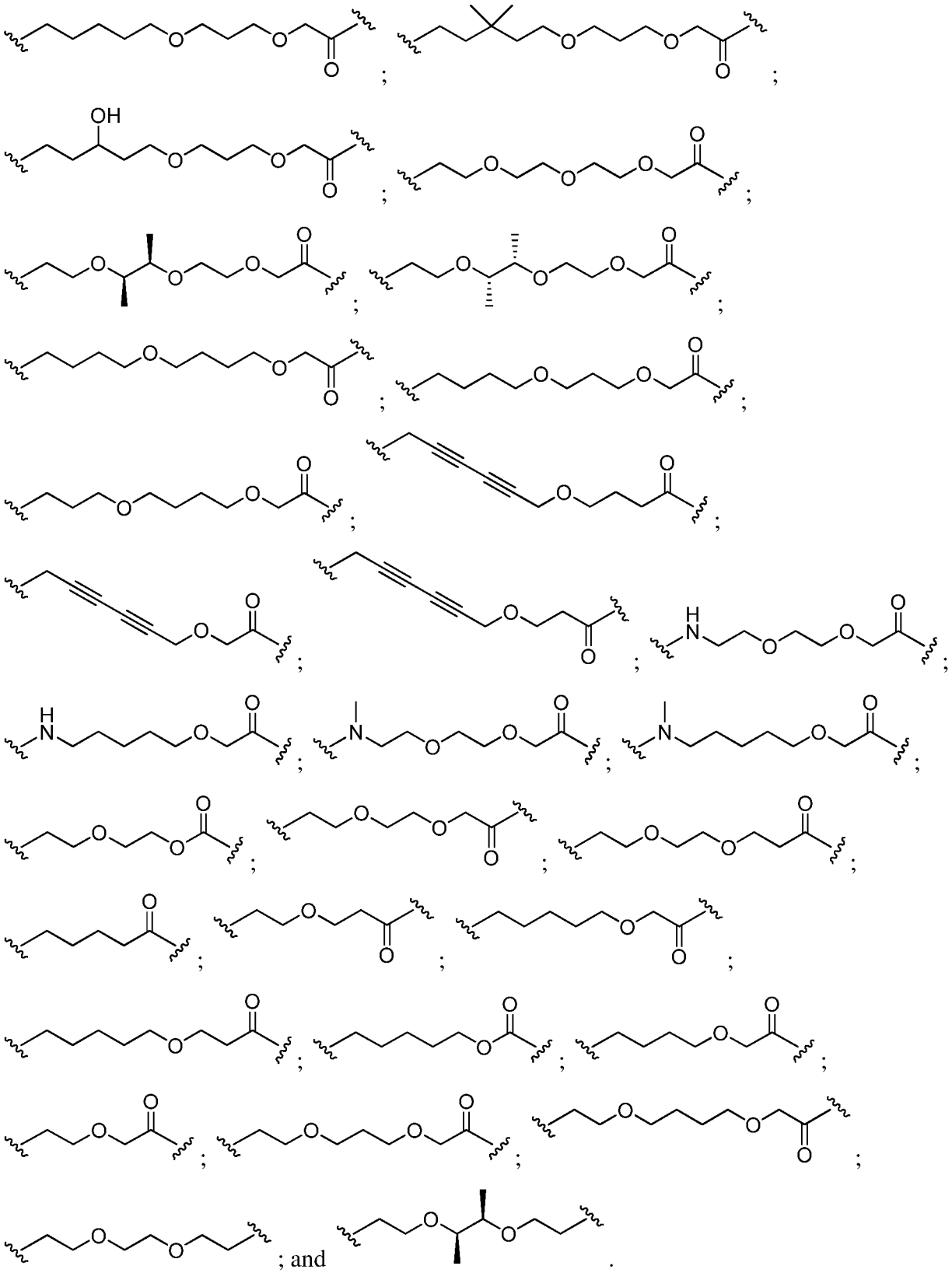
[0158] In certain embodiments, e. g., where q is 1, the structure of the linker group L is –A_1–, and A_1 is a group which is connected to a ULM or VLM moiety and an ABM moiety.

[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_{3-11}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} 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_{1-8}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 $SO_2N(C_{1-8}alkyl)_2$, 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.

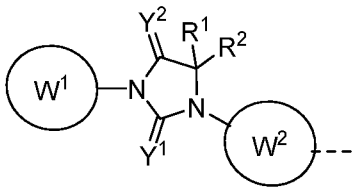
[0165] Exemplary Androgen Binding Moieties (ABMs)

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

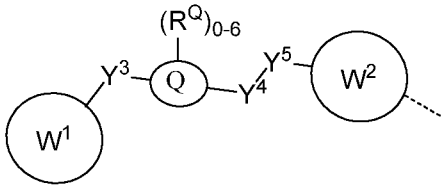
[0167] In any of the compounds described herein, the ABM comprises a chemical moiety that binds to the androgen receptor (AR). Various androgen receptor binding compounds have been described in literature, including various androgen derivatives such as testosterone, dihydrotestosterone, and metribolone (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.

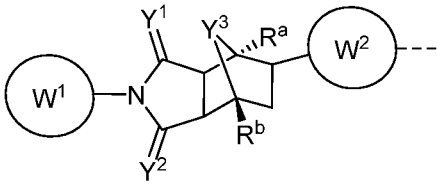
[0168] In certain embodiments, the ABM comprises a structure selected from, but not limited to the structures shown below, where a dashed line indicates the attachment point of linker moiety:



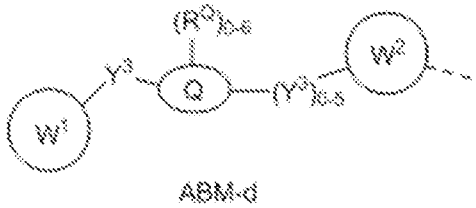
ABM-a ;



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;

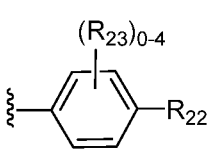
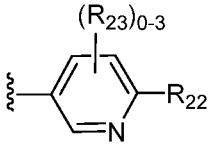
[0172] Q is a 3-6 membered ring with 0-4 heteroatoms, optionally substituted with 0-6 R^Q, each R^Q,is independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or 2 R^Q groups taken together with the atom they are attached to, form a 3-8 membered ring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

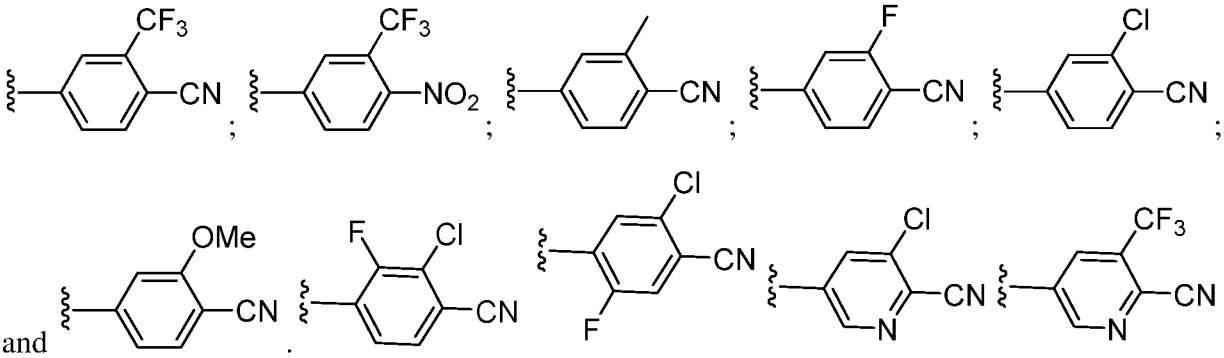
[0176] In any of the embodiments described herein, the W^2 is covalently coupled to one or more ULM or VLM groups, or a linker to which is attached one or more ULM or VLM groups as described herein.

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

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

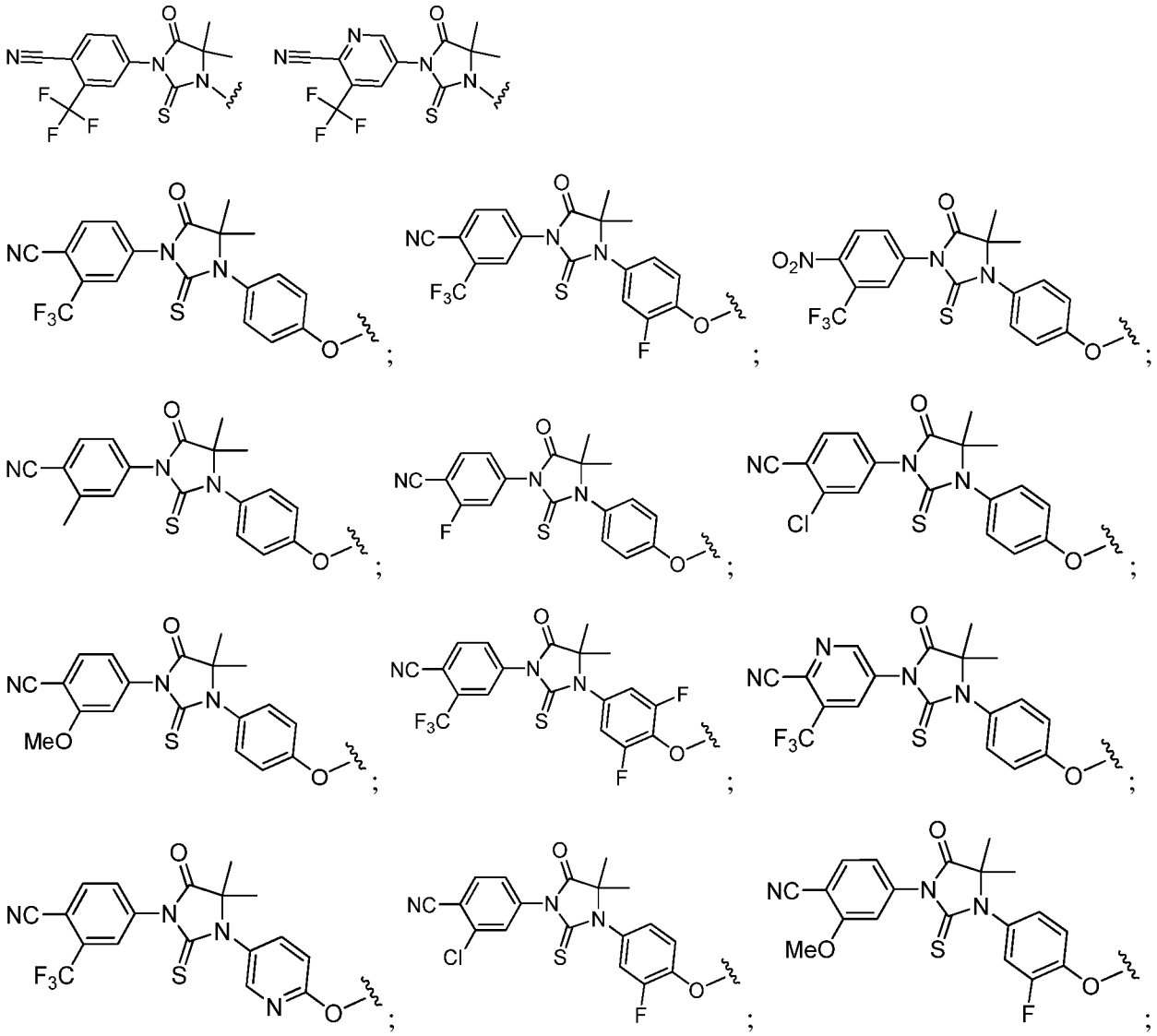
[0179] each R_{23} is independently H, halo, optionally substituted alkyl, haloalkyl, cyano, or nitro.

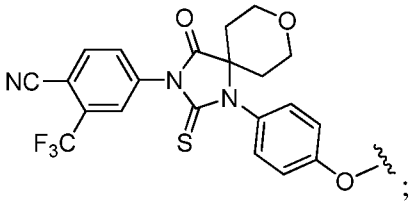
[0180] In certain additional embodiments, W^1 is selected from the group consisting of:

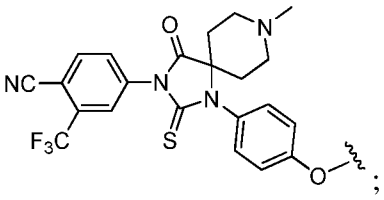


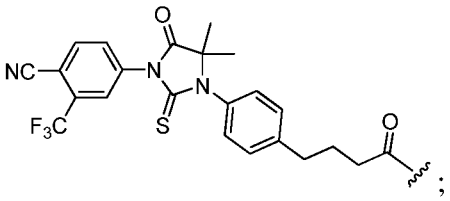
and .

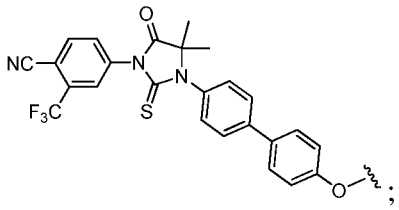
[0181] In certain embodiments, ABM is selected from the group consisting of:

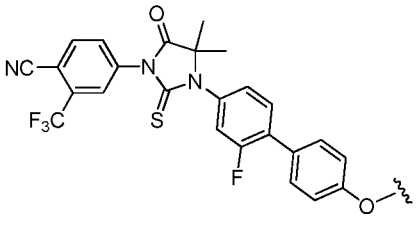


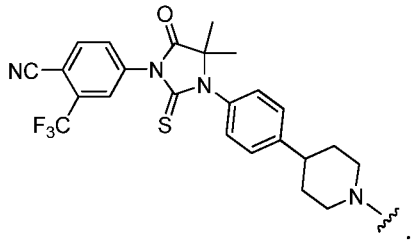

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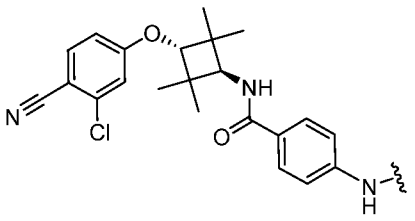

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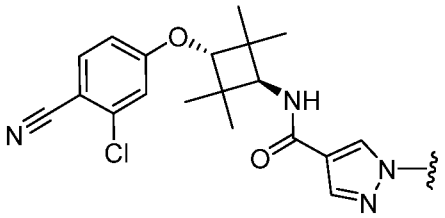

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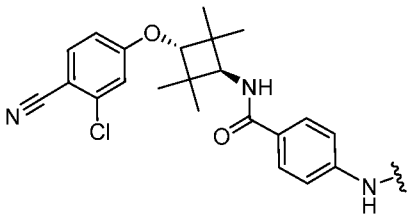

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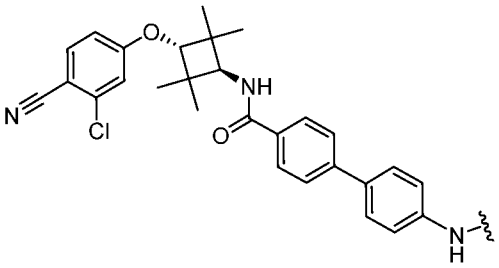

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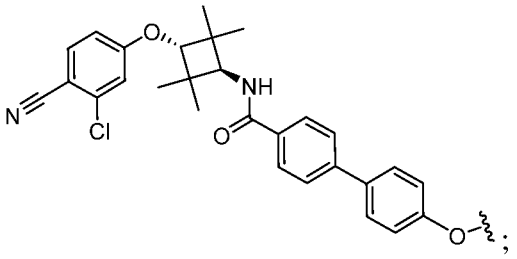

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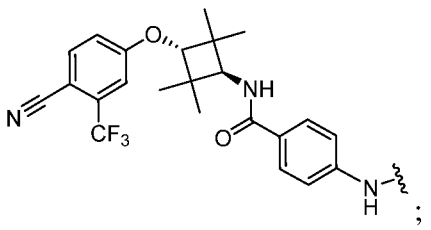


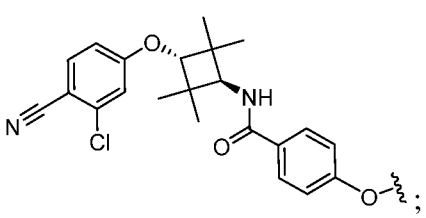


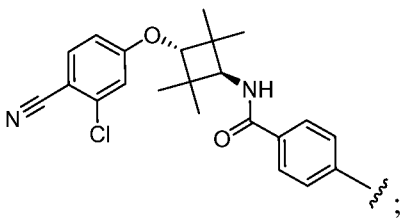


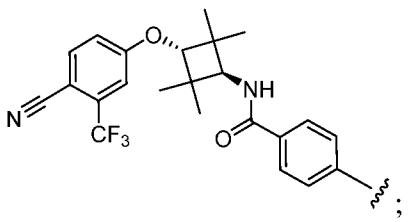


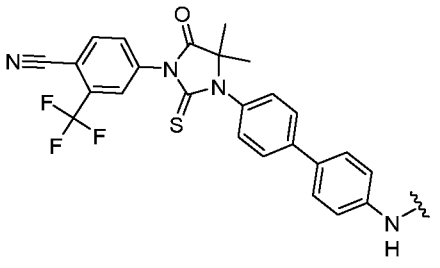
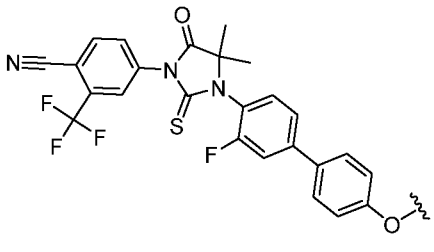
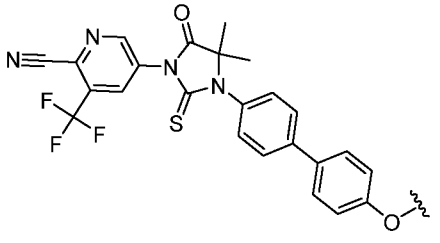

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; and

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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

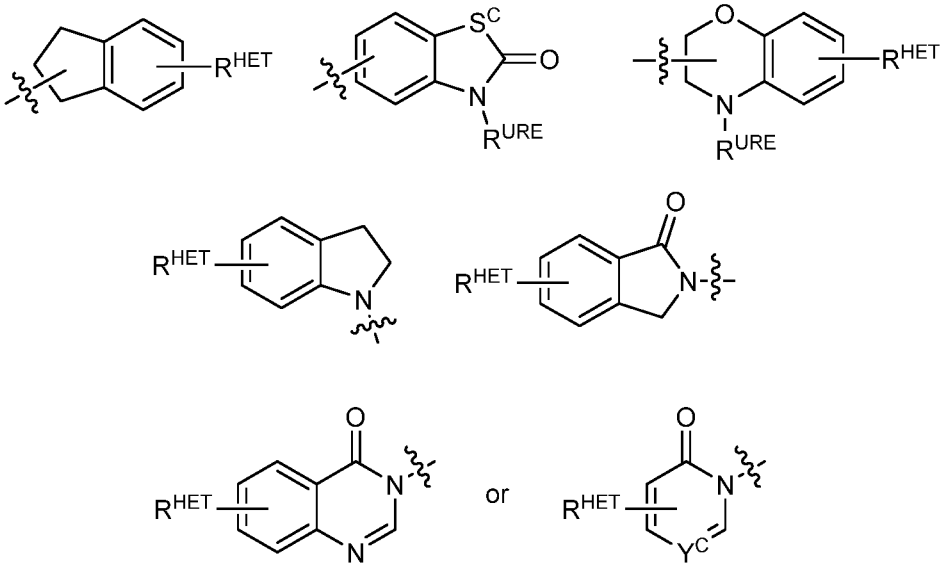
more substituents, preferably no more than 3 substituents and preferably with 1 or 2 substituents. It is noted that in instances where, in a compound at a particular position of the molecule substitution is required (principally, because of valency), but no substitution is indicated, then that substituent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

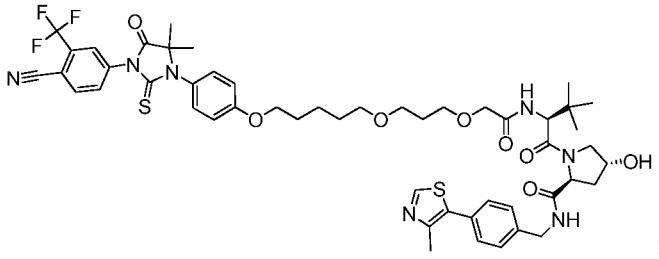
[0213] "Heterocycloalkyl" refers to a monocyclic or polycyclic alkyl group in which at least one ring carbon atom of its cyclic structure being replaced with a heteroatom selected from the group consisting of N, O, S or P. "Substituted heterocycloalkyl" refers to a monocyclic or polycyclic alkyl group 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.

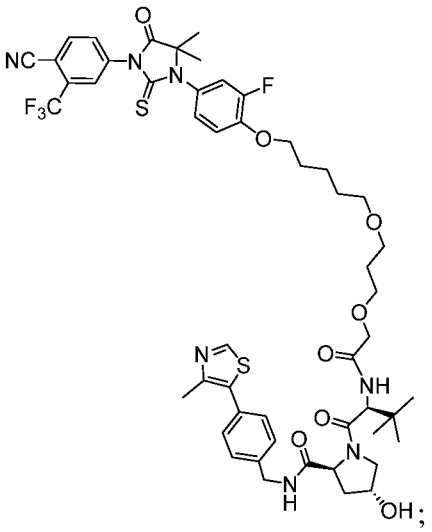
[0214] Exemplary AR-PROTAC Compounds

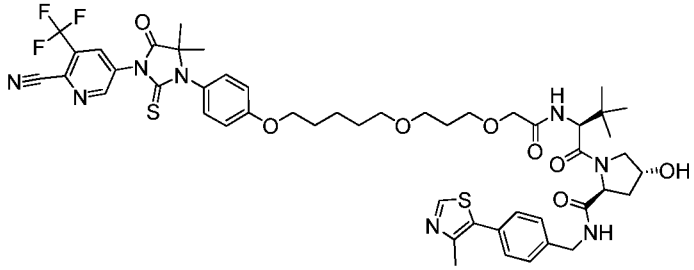
[0215] As described above, in certain aspects, the description provides bifuctional PROTAC compounds comprising at least one ABM group, a linker, and at least one ULM (or VLM) group as described herein.

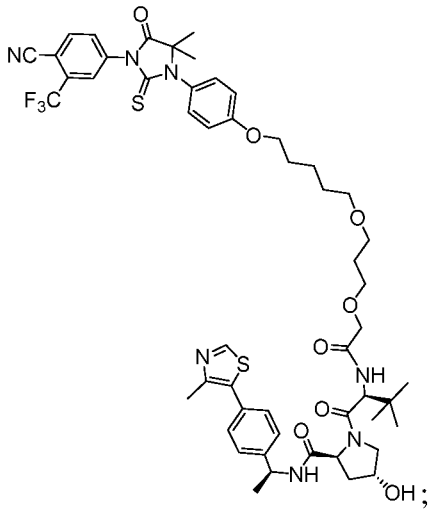
[0216] In certain embodiments, the compound is selected from the group consisting of compounds 1-593 (as described in Tables 2-17), and salts and polymorphs thereof.

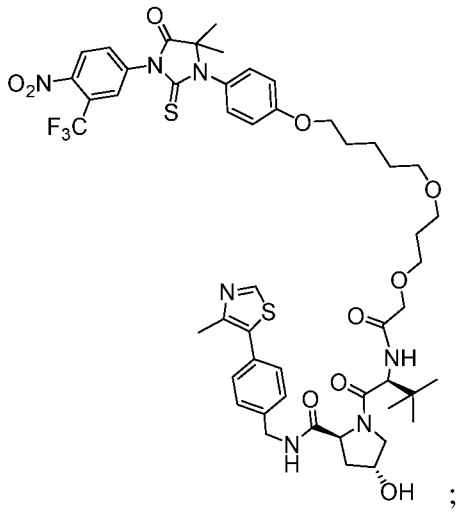
[0217] In certain embodiments, the compound is selected from the group consisting of:

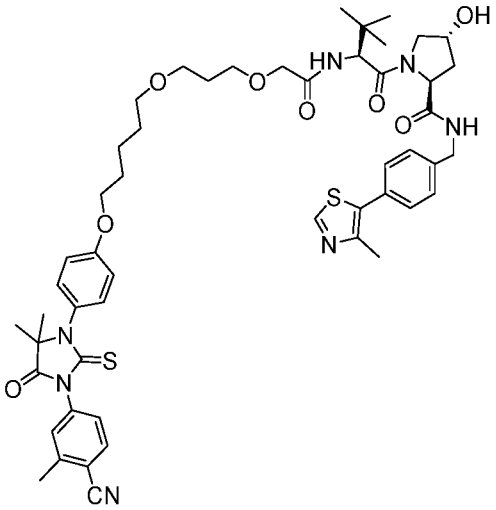
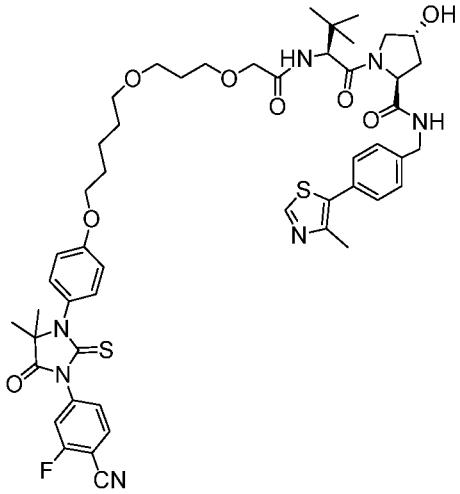
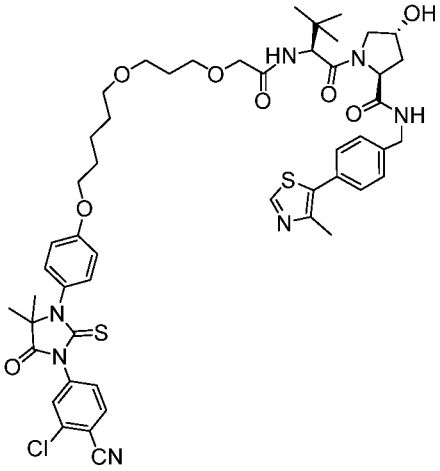
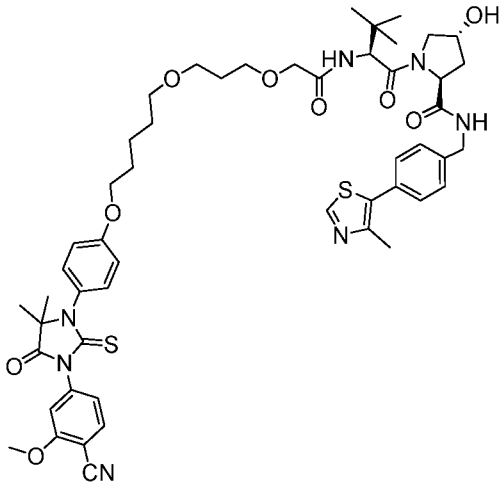
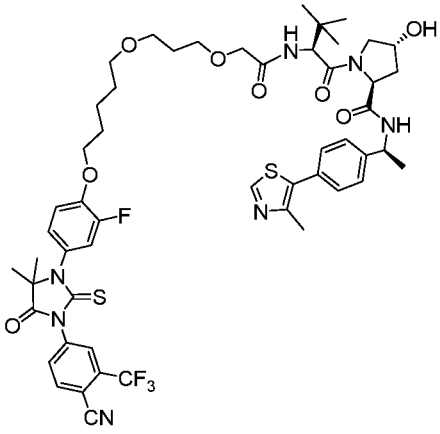
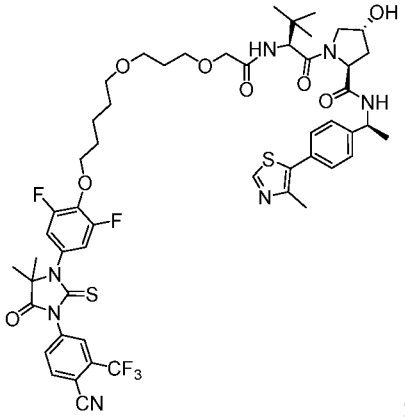

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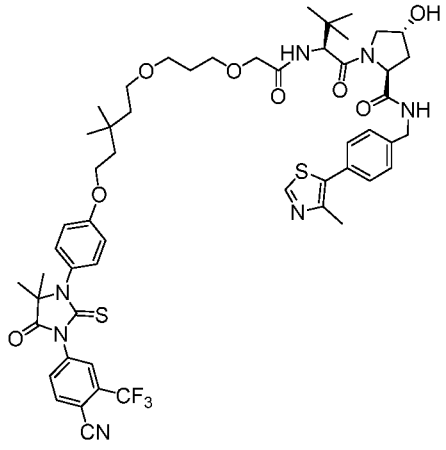
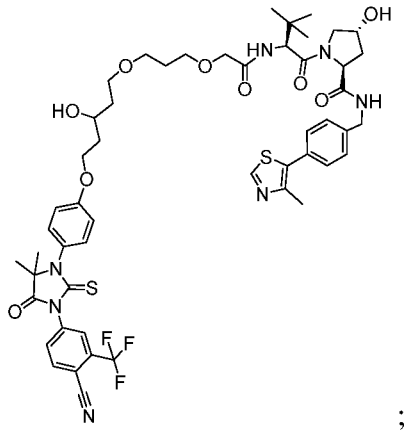
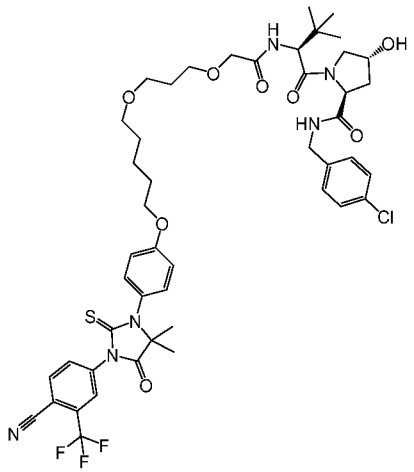
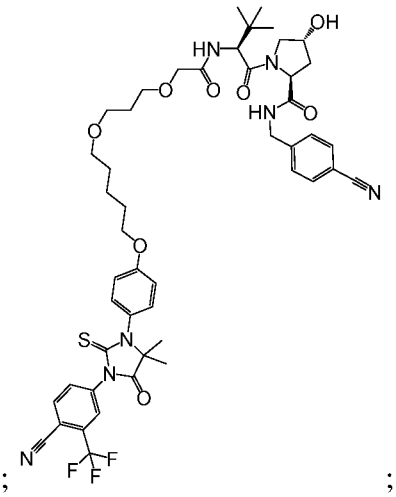
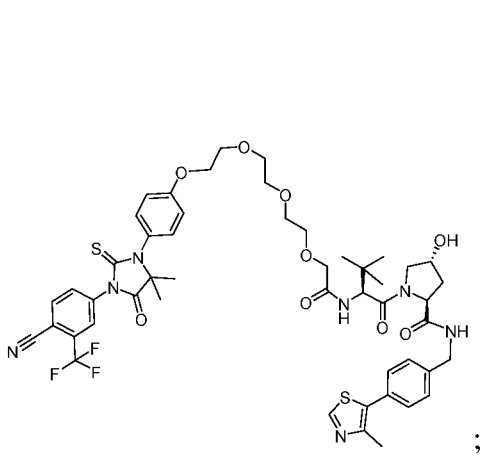
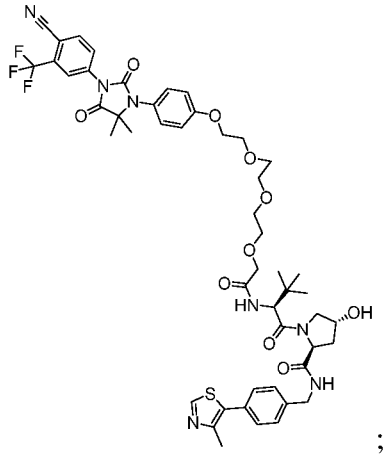

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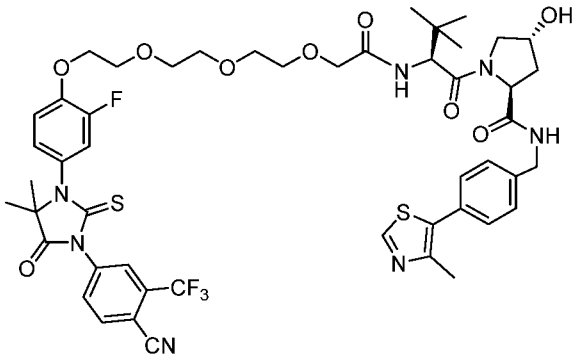
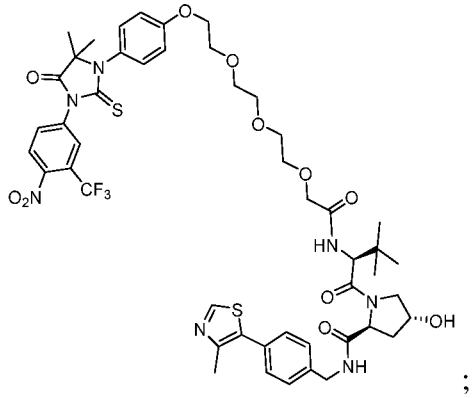
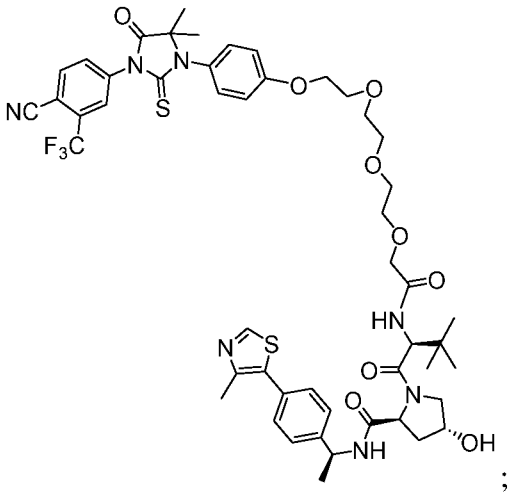
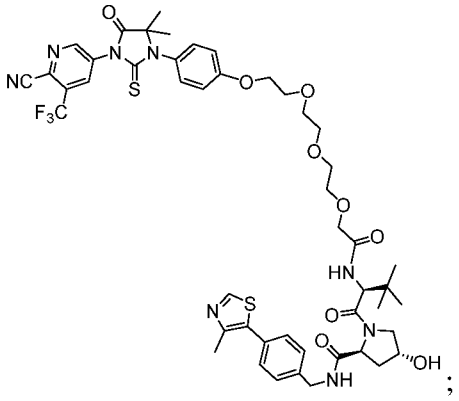
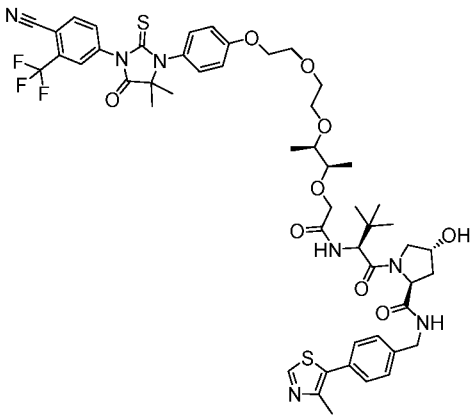
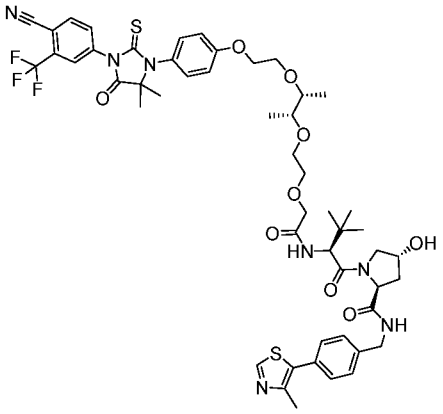

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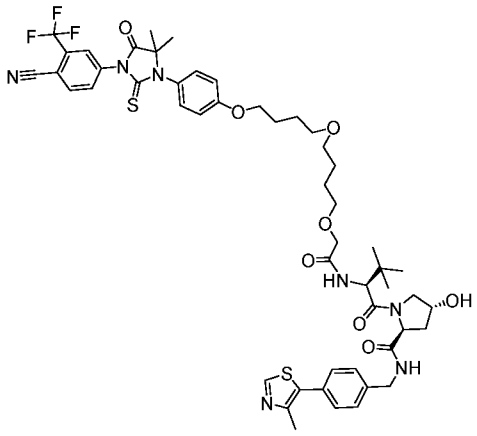

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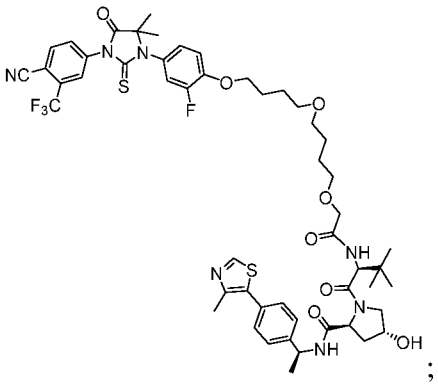

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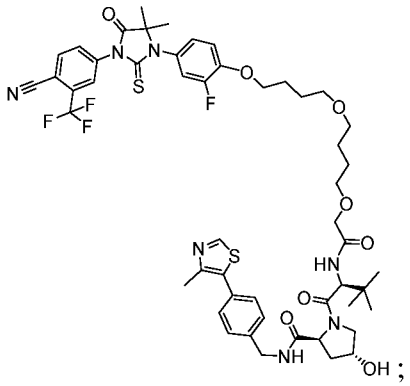

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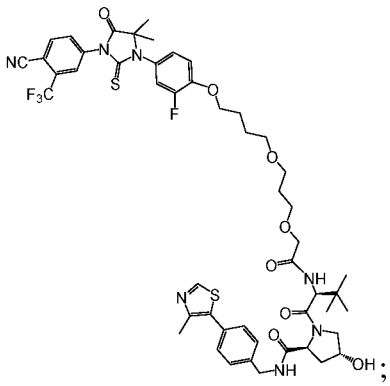

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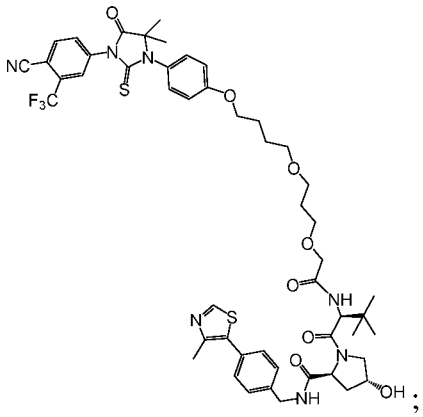

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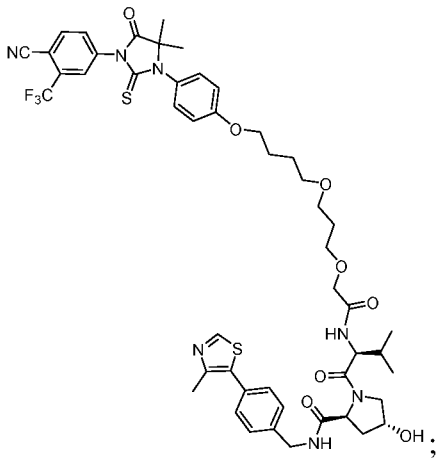

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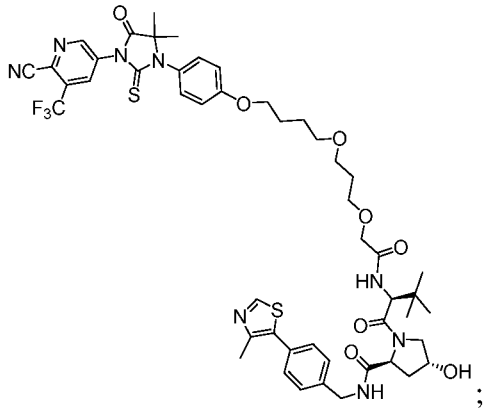

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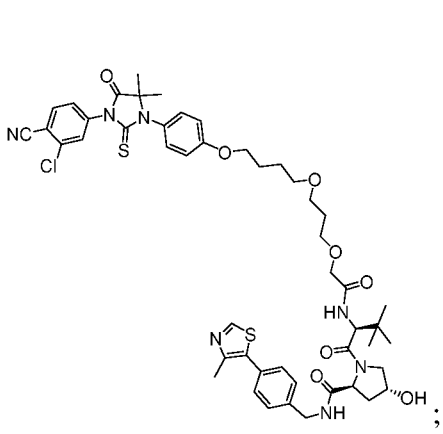

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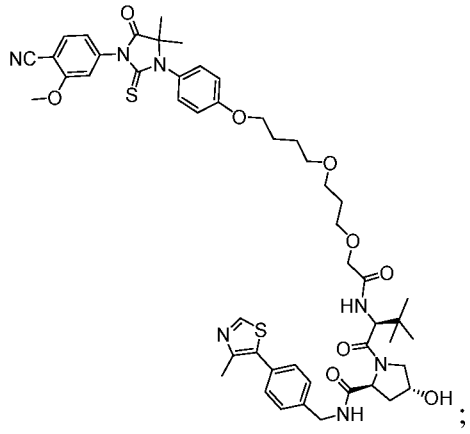

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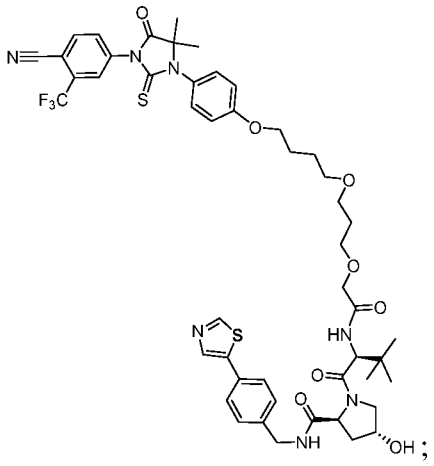

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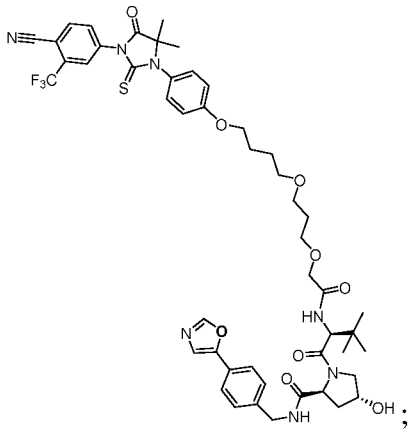

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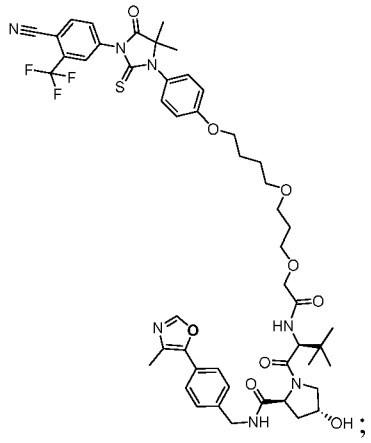

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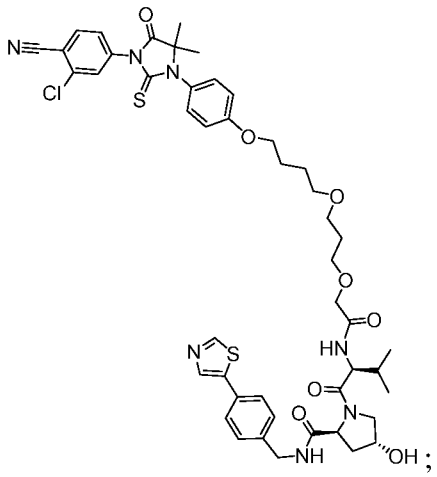


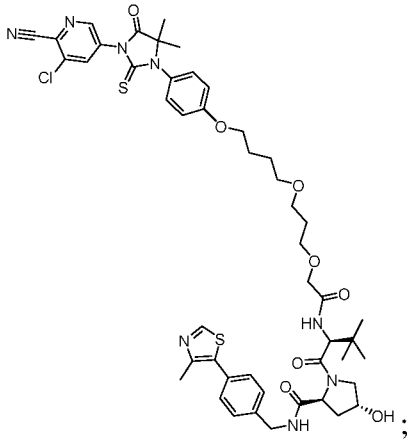


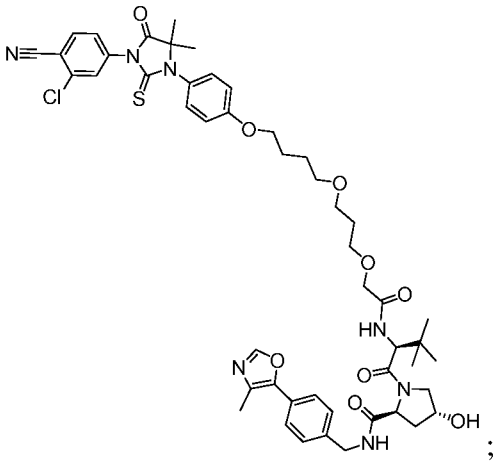




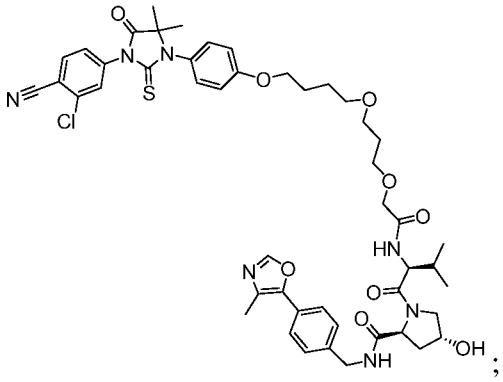




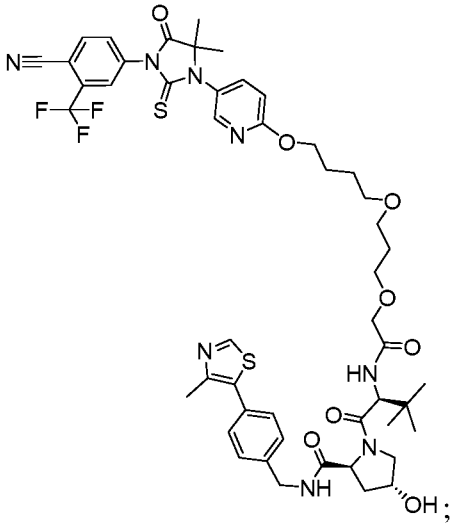




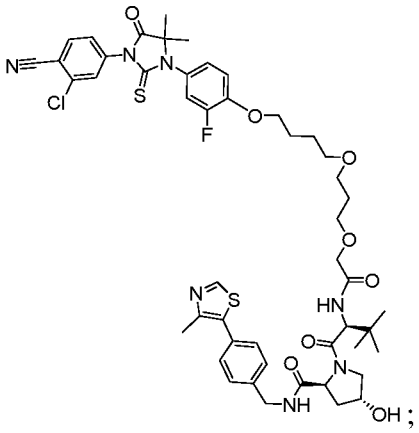
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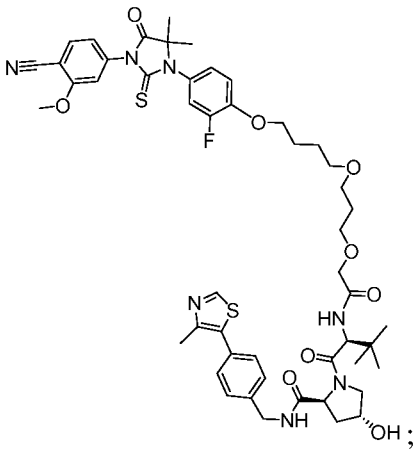
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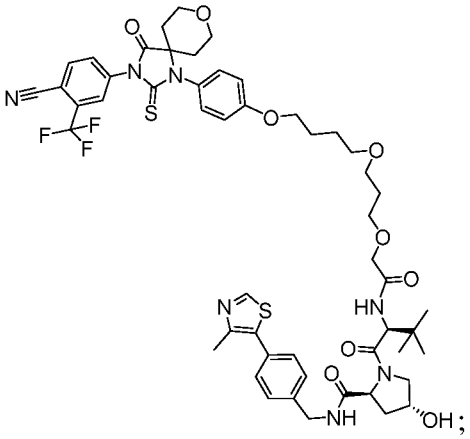
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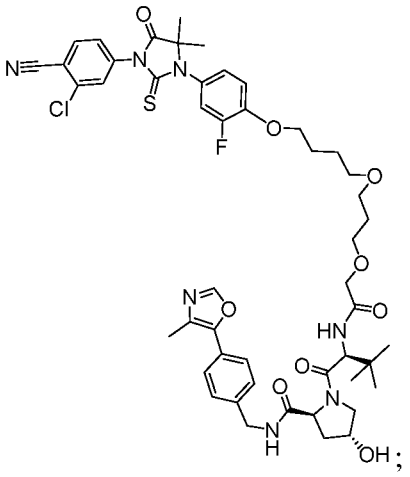
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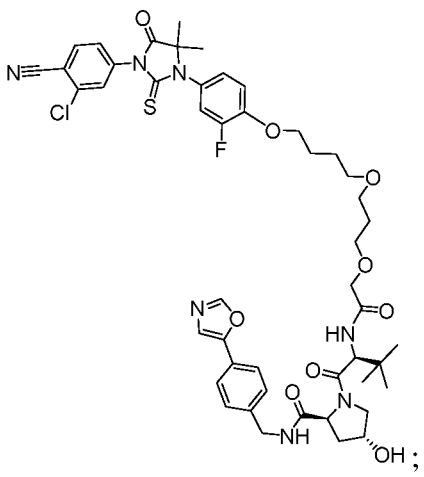


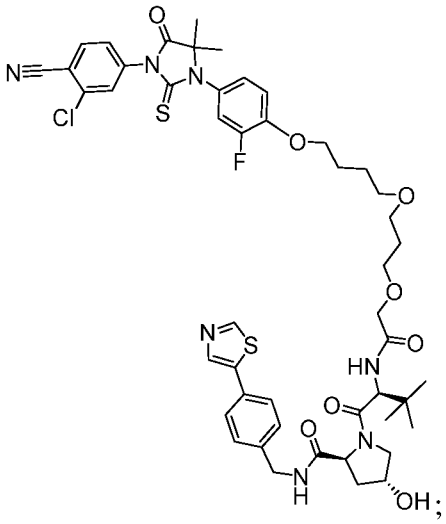
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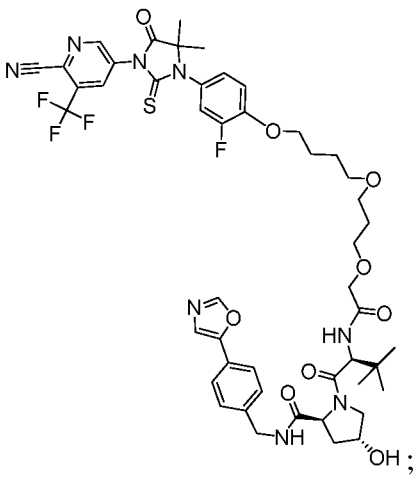


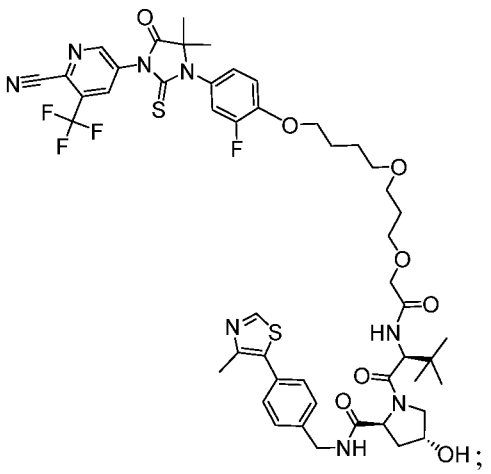
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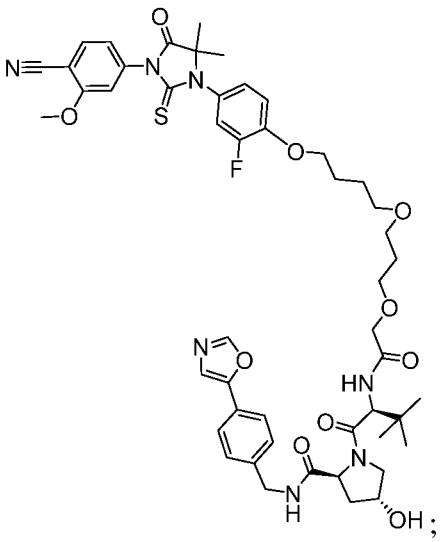


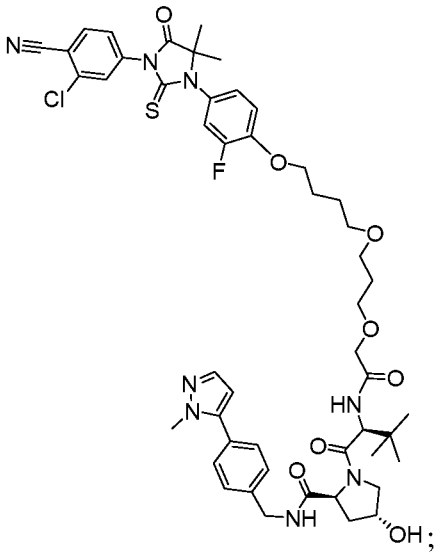


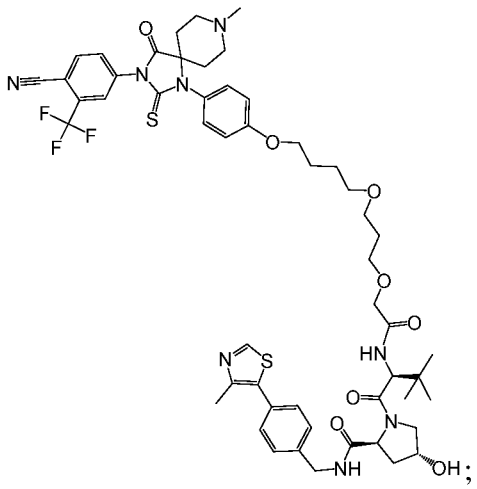


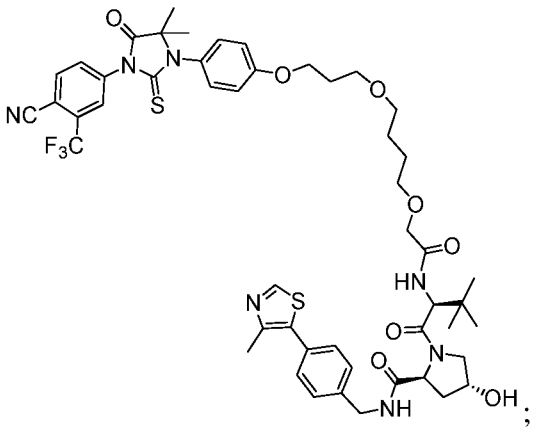


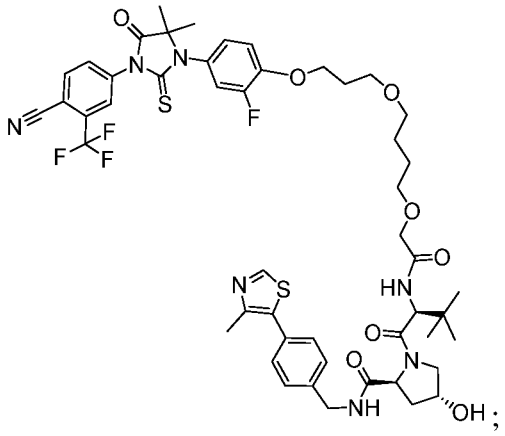


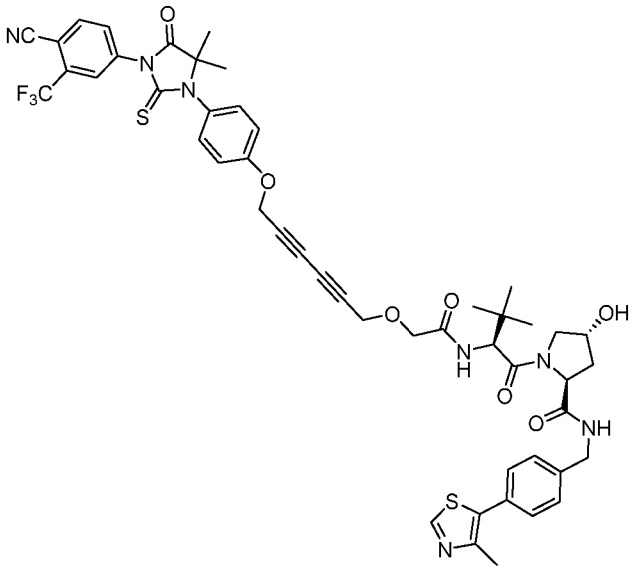


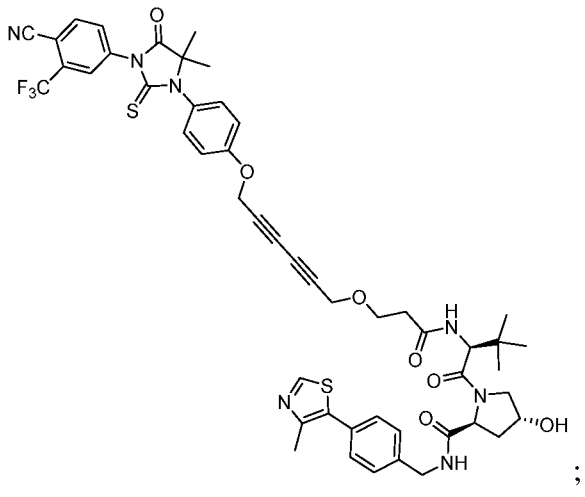


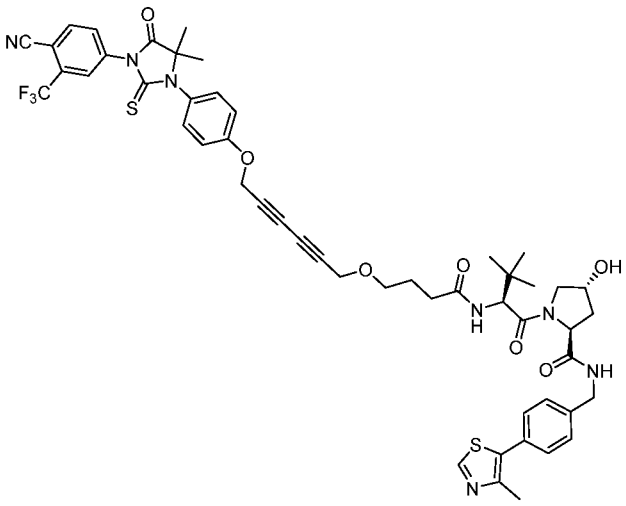


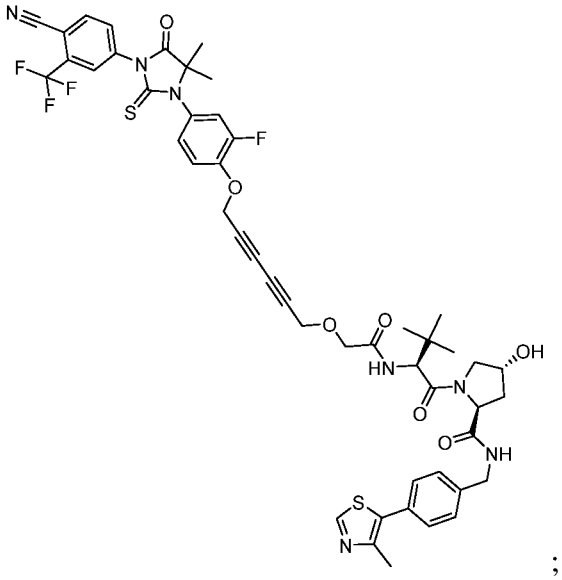


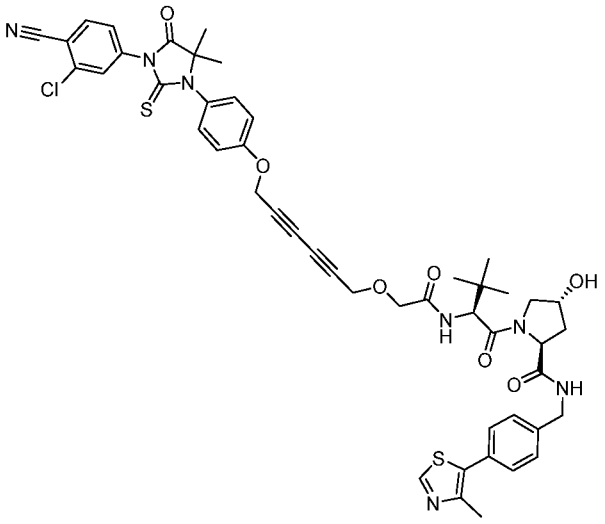


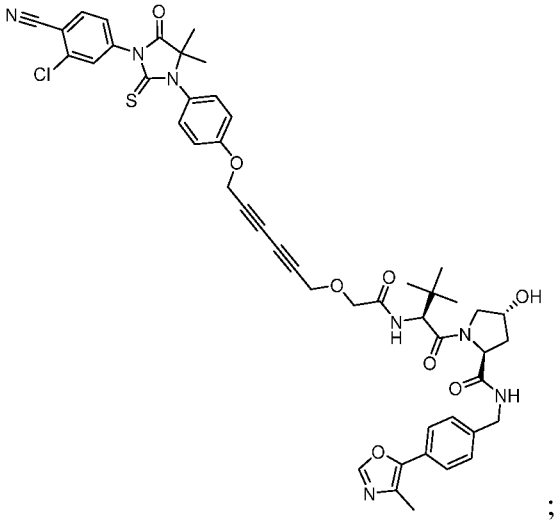


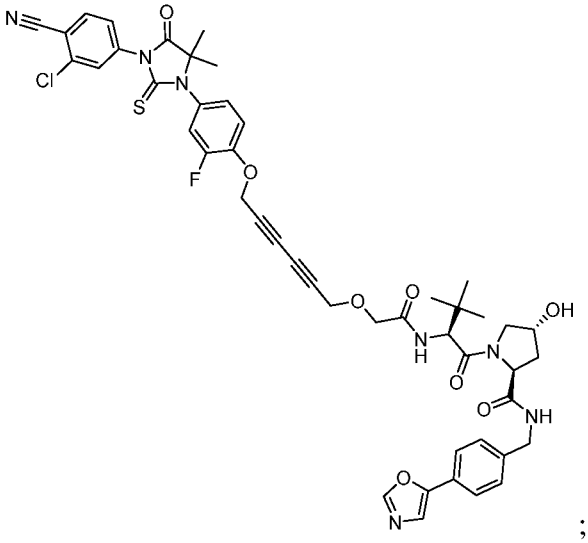


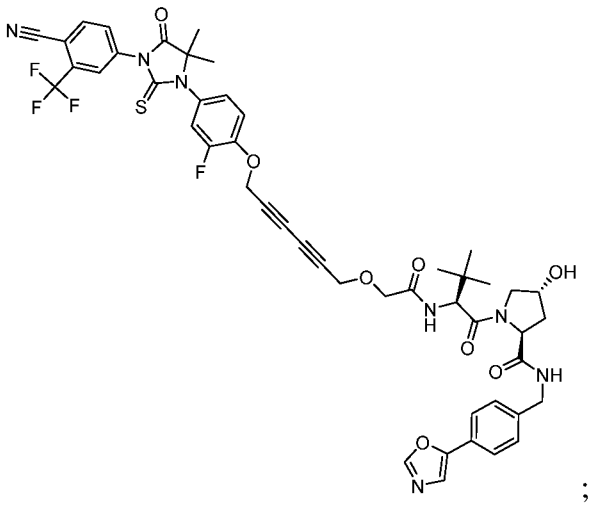

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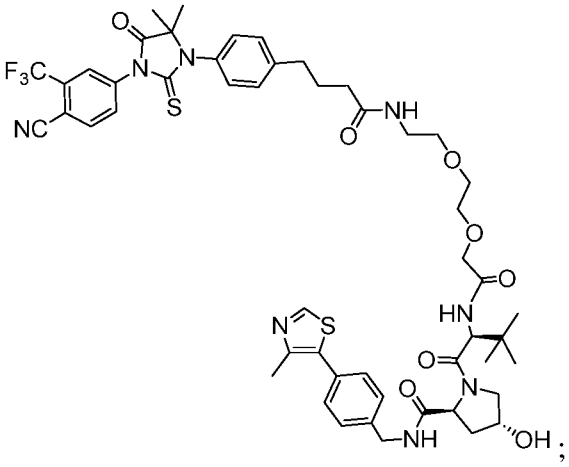

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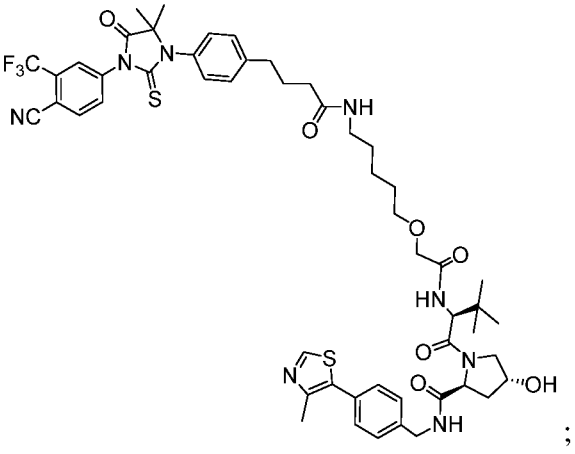

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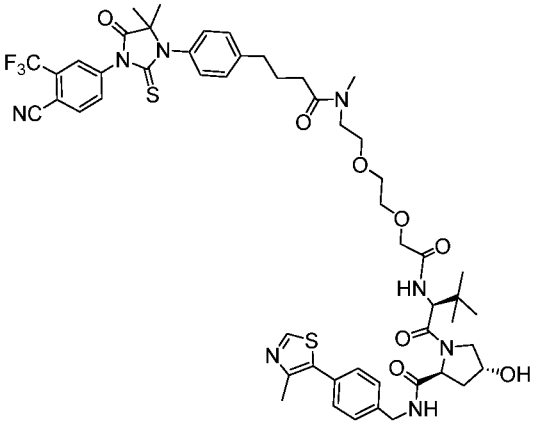

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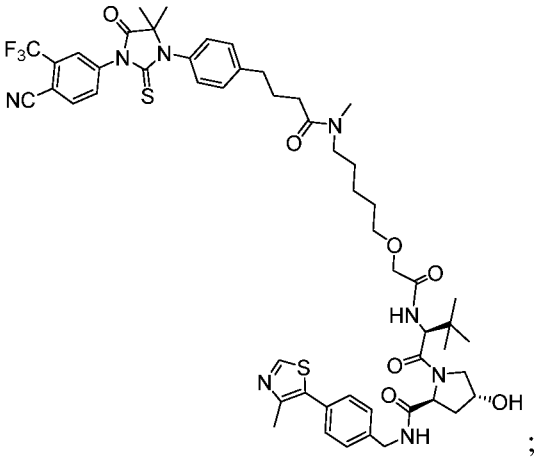

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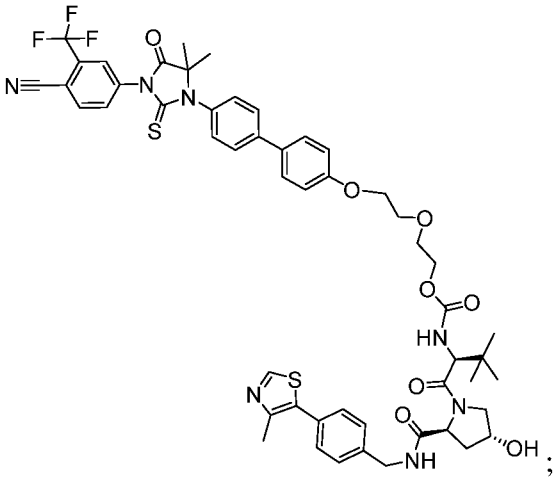

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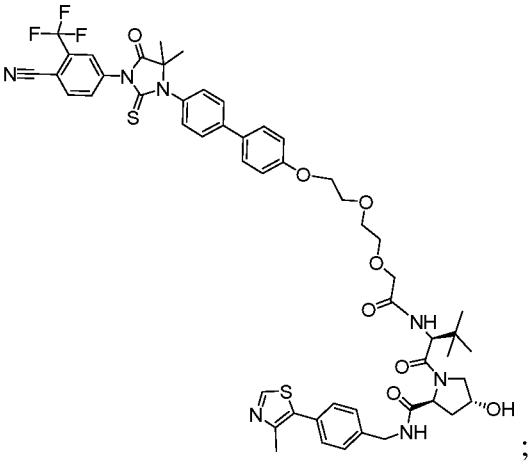

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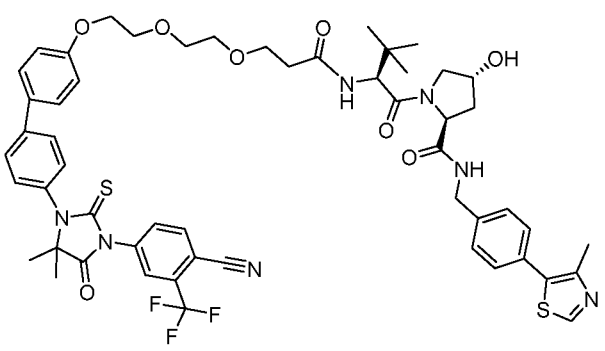
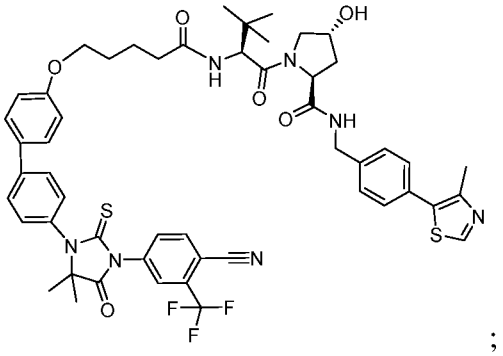
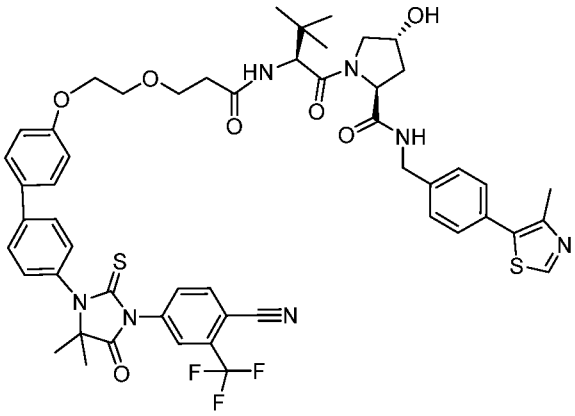
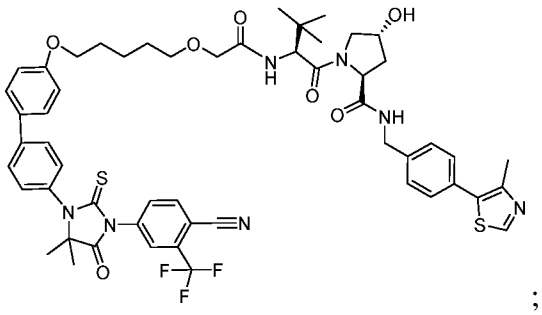
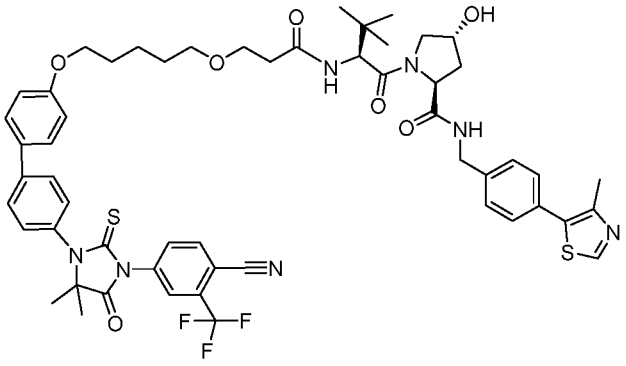
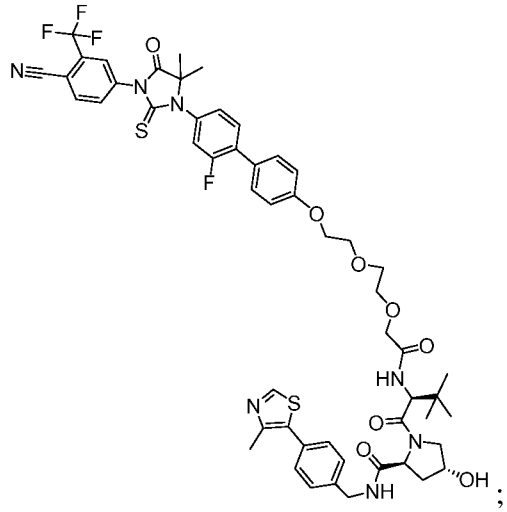

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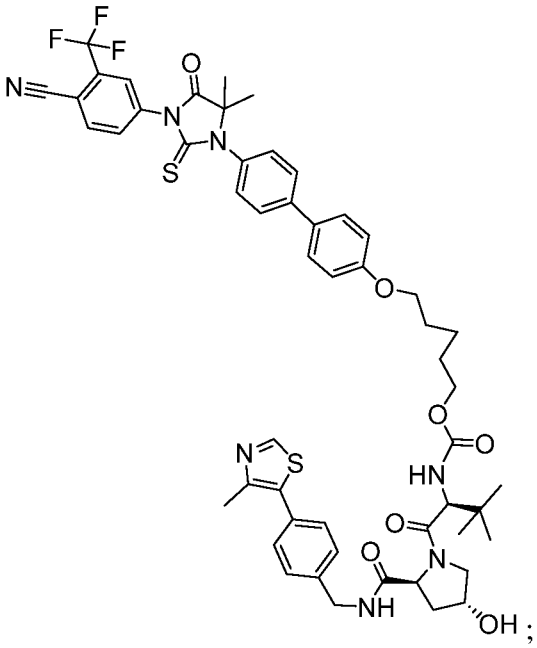

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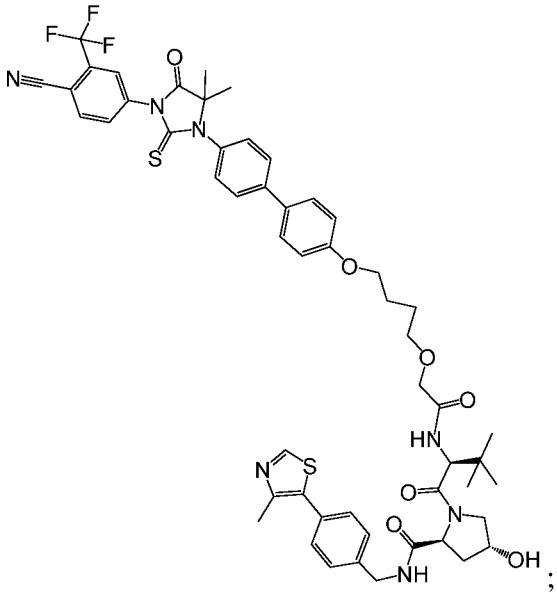

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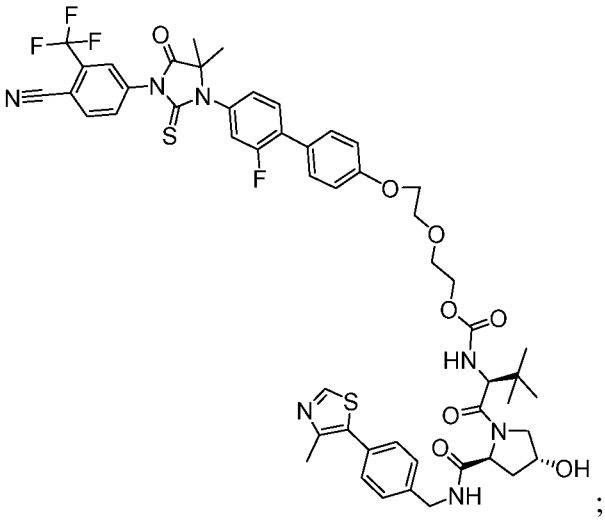

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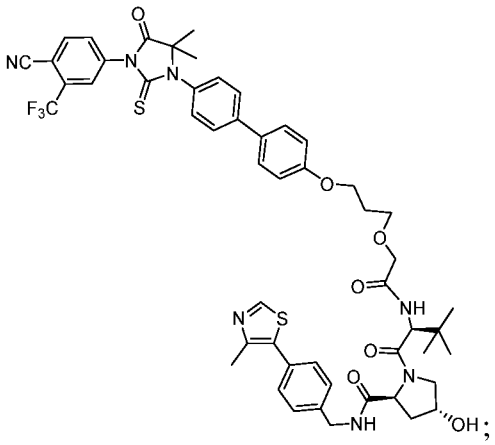

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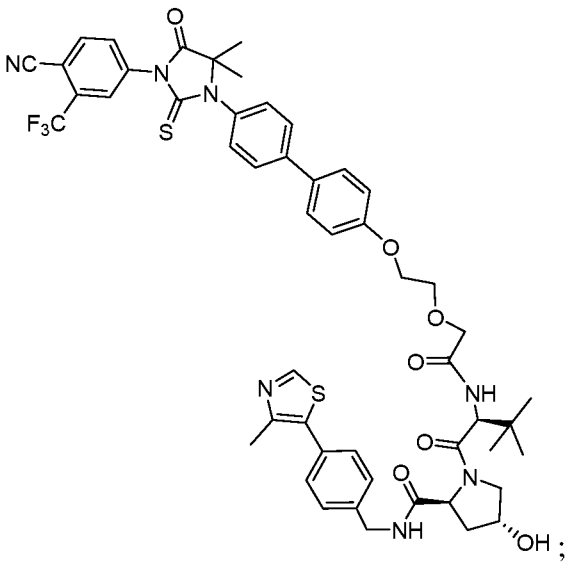

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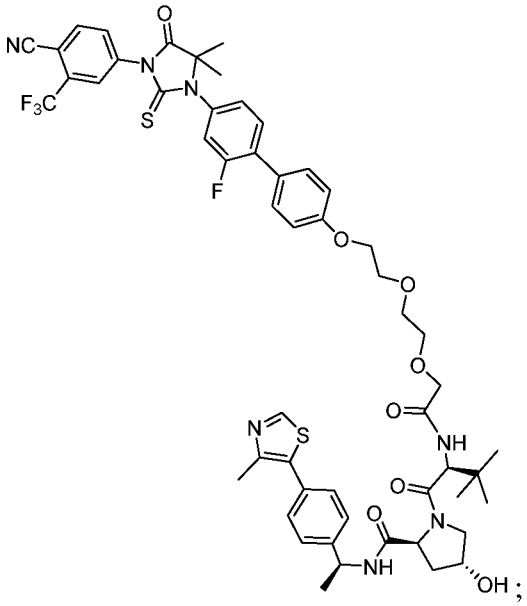


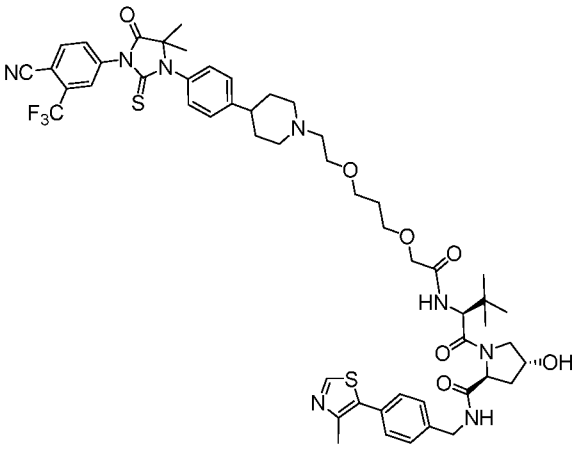


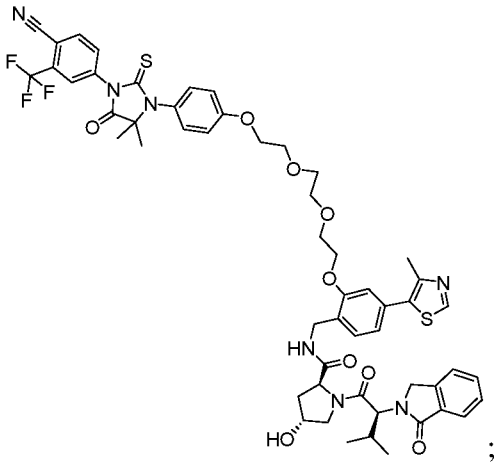


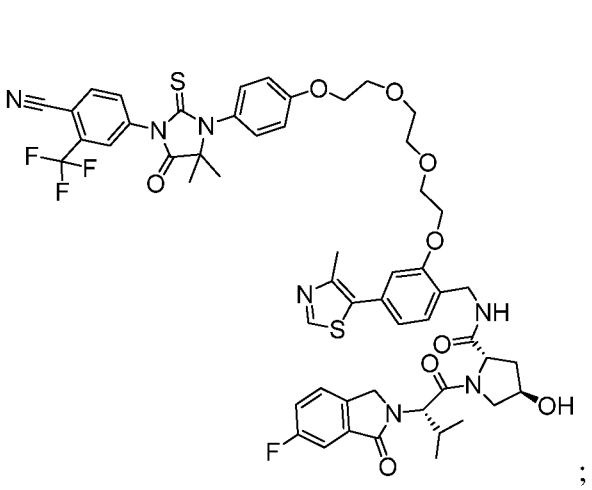


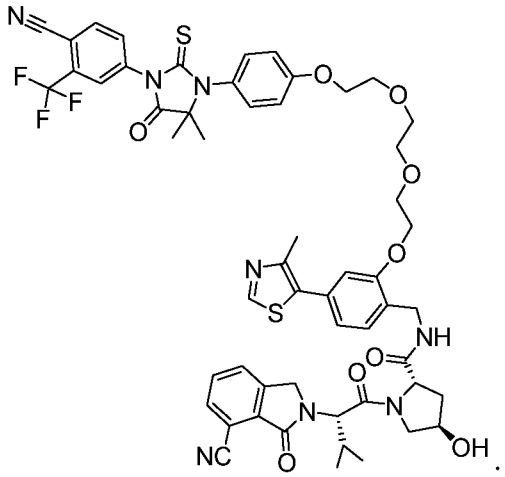


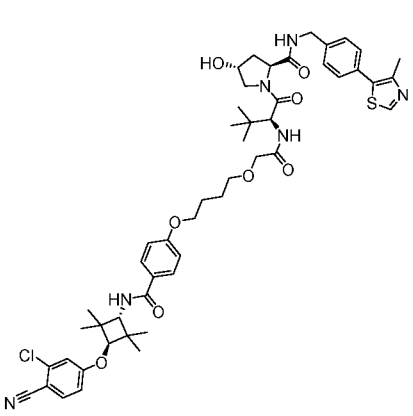


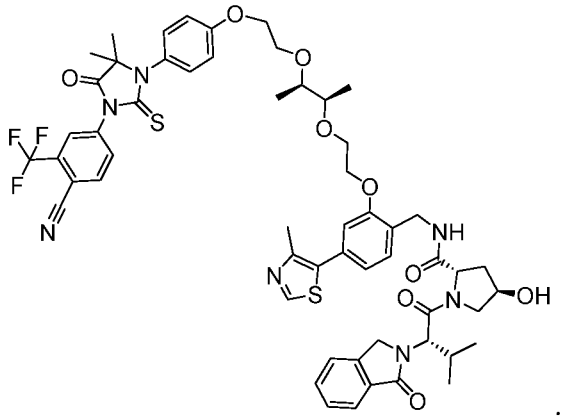





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; and .

[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]

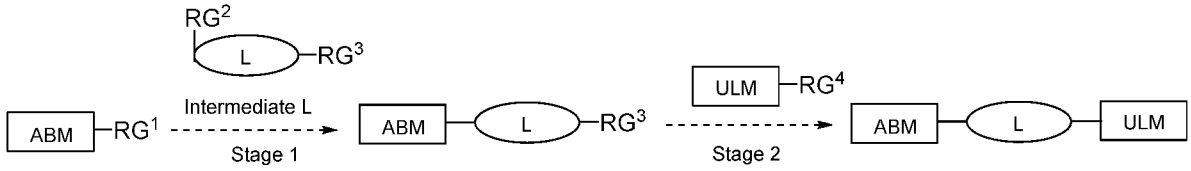
[0293] The UV detection is an averaged signal from wavelength of 210nm to 350nm and mass spectra are recorded on a mass spectrometer using positive mode electrospray ionization.

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

[0295] **Chemical Synthesis**

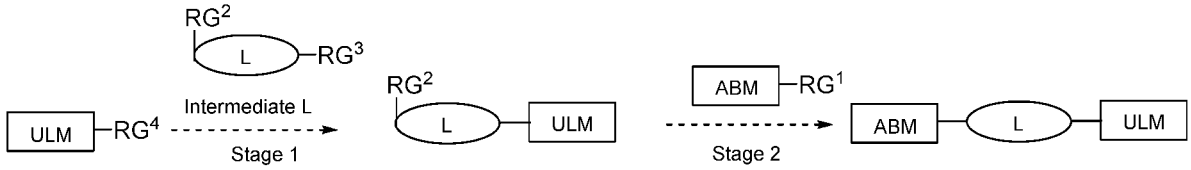
[0296] A PROTAC of ABM-L-ULM, or their pharmaceutically acceptable salts, polymorphic forms, prodrugs, solvate forms and isotope containing derivatives thereof, may be prepared by the general approaches described below (scheme 3-4), together with synthetic methods known in the art of organic chemistry,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

[0297] Scheme 3:



Scheme 3

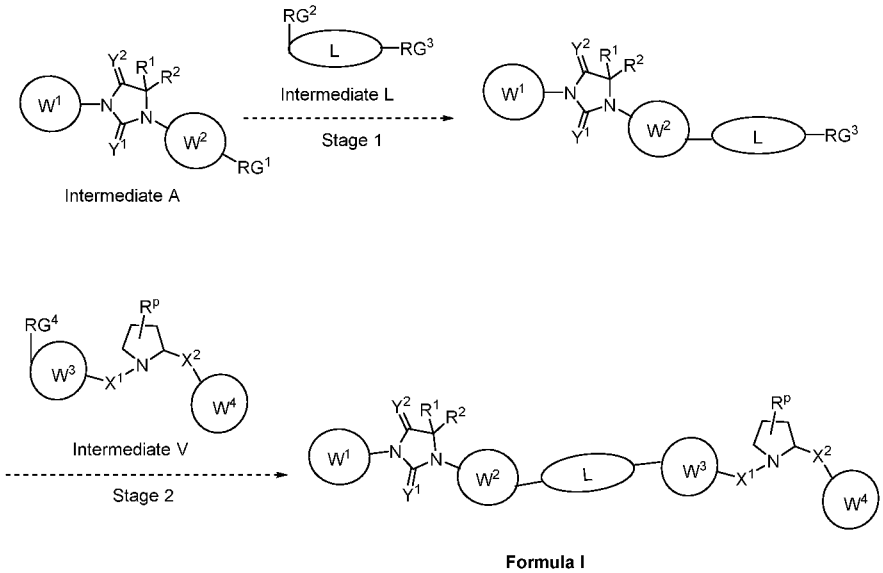
[0298] Scheme 4:



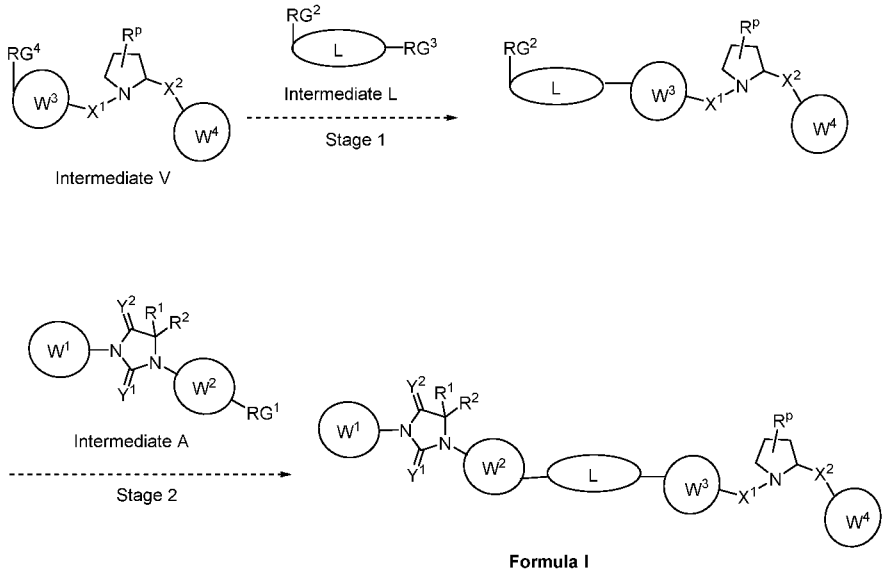
Scheme 4

[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



[0301] Scheme 6: **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.

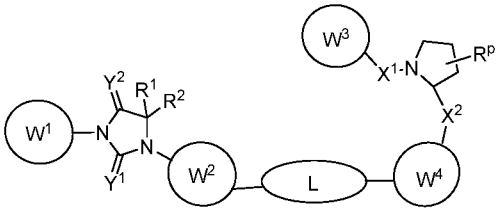
[0305] Although not explicitly shown in schemes 3-6, a chemist of ordinary skill would realize that during any of the synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This can be achieved by means of conventional protecting 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

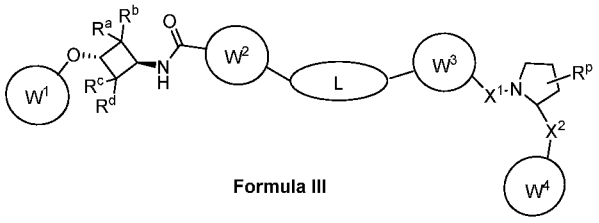
referred to in the general procedures is for convenience and does not preclude substitution as described elsewhere herein. For specific groups that can be present, either as R groups in the general procedures or as optional substituents not shown, refer to the descriptions in the remainder of this document,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

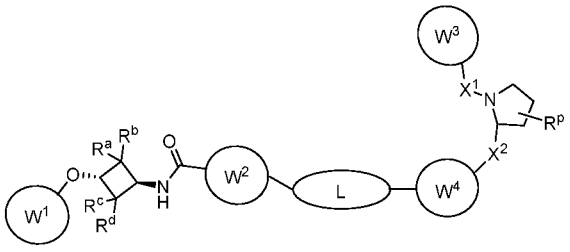
[0308] The compounds of Formulae II-IV (below), or their pharmaceutically acceptable salts, may be prepared by the methods similar to chemistry illustrated above for synthesis of compounds of Formula I (scheme 3-6), together with synthetic methods known in the art of organic chemistry, or modifications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



Formula II ;



Formula III ; and



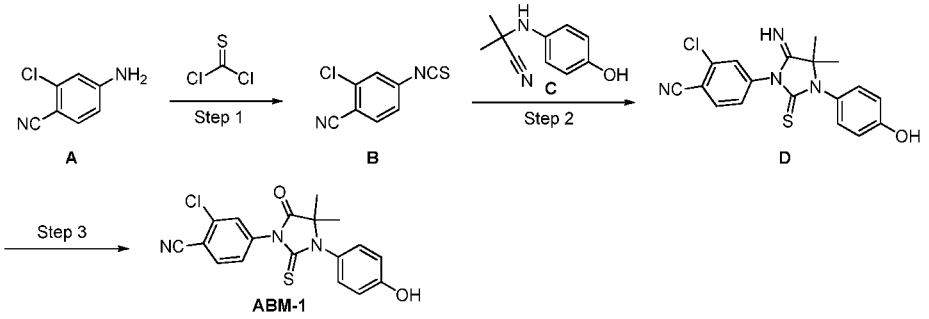
Formula IV .

[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);

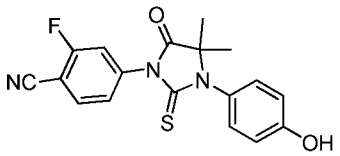
[0318] Step 3: Synthesis of 2-chloro-4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo- 2-sulfanylideneimidazolidin-1-yl]benzonitrile (**ABM-1**).

[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).

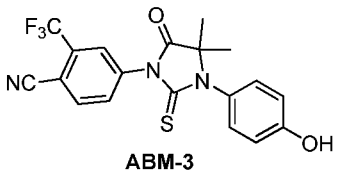
[0320] Unless otherwise noted, the following intermediates and their analogs (for examples, but not limited to, analogs with substitutions such as halogens) were synthesized according to similar procedures described above for the synthesis of **ABM-1**, by utilizing corresponding starting materials and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

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



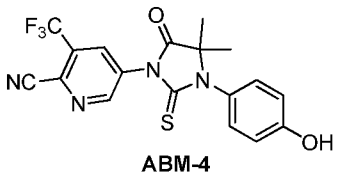
[0322] **ABM-2** .

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



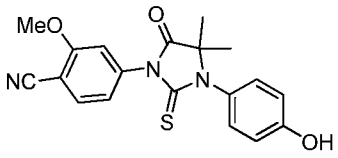
[0324] **ABM-3** .

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



[0326] **ABM-4** .

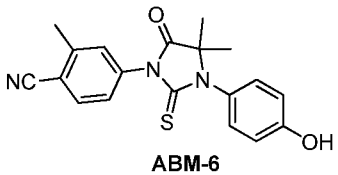
[0327] **ABM-5: 4-(3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-methoxybenzonitrile:**



ABM-5

[0328] .

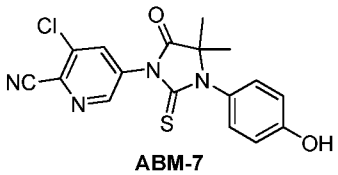
[0329] **ABM-6: 4-(3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-methylbenzonitrile:**



ABM-6

[0330] .

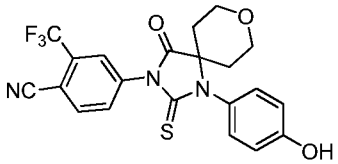
[0331] **ABM-7: 3-chloro-5-(3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)picolinonitrile:**



ABM-7

[0332] .

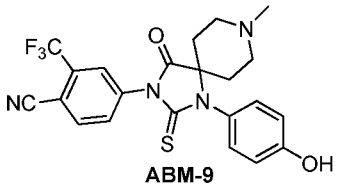
[0333] **ABM-8: 4-(1-(4-hydroxyphenyl)-4-oxo-2-thioxo-8-oxa-1,3-diazaspiro[4.5]decan-3-yl)-2-(trifluoromethyl)benzonitrile:**



ABM-8

[0334] .

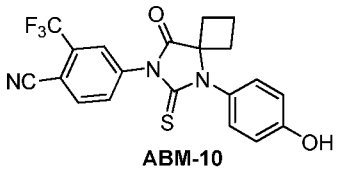
[0335] **ABM-9: 4-(1-(4-hydroxyphenyl)-8-methyl-4-oxo-2-thioxo-1,3,8-triazaspiro[4.5]decan-3-yl)-2-(trifluoromethyl)benzonitrile:**



ABM-9

[0336] .

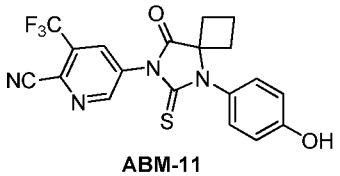
[0337] **ABM-10: 4-(5-(4-hydroxyphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-7-yl)-2-(trifluoromethyl)benzonitrile**



ABM-10

[0338]

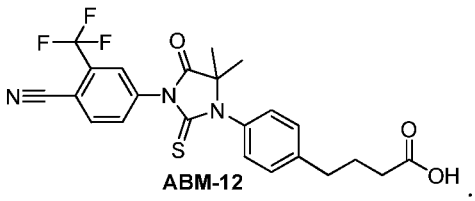
[0339] **ABM-11: 5-(5-(4-hydroxyphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-7-yl)-3-(trifluoromethyl)picolinonitrile:**



ABM-11

[0340]

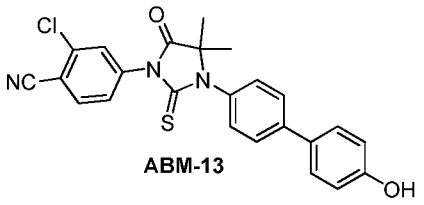
[0341] **ABM-12: 4-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenyl)butanoic acid:**



ABM-12

[0342]

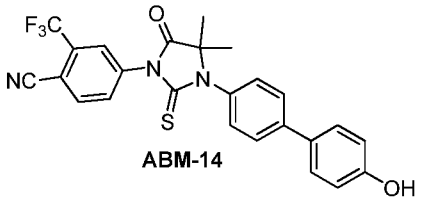
[0343] **ABM-13: 2-chloro-4-(3-(4'-hydroxybiphenyl-4-yl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)benzonitrile:**



ABM-13

[0344]

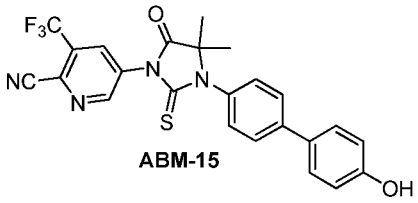
[0345] **ABM-14: 4-(3-(4'-hydroxybiphenyl-4-yl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile:**



ABM-14

[0346]

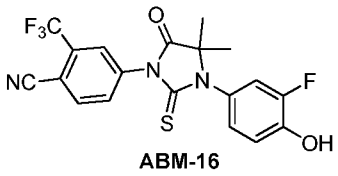
[0347] **ABM-15: 5-(3-(4'-hydroxybiphenyl-4-yl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-3-(trifluoromethyl)picolinonitrile:**



ABM-15

[0348]

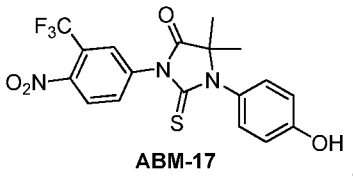
[0349] **ABM-16: 4-(3-(3-fluoro-4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile:**



ABM-16

[0350]

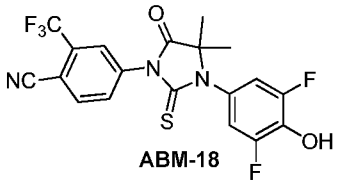
[0351] **ABM-17: 1-(4-hydroxyphenyl)-5,5-dimethyl-3-(4-nitro-3-(trifluoromethyl)phenyl)-2-thioxoimidazolidin-4-one:**



ABM-17

[0352]

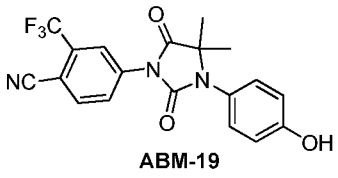
[0353] **ABM-18: 4-(3-(3,5-difluoro-4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile:**



ABM-18

[0354]

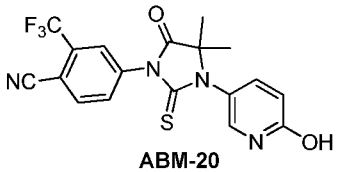
[0355] **ABM-19: 4-(3-(4-hydroxyphenyl)-4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile:**



ABM-19

[0356]

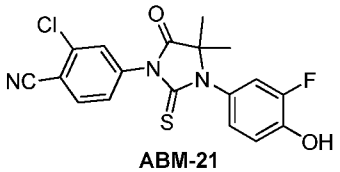
[0357] **ABM-20: 4-(3-(6-hydroxypyridin-3-yl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile:**



ABM-20

[0358]

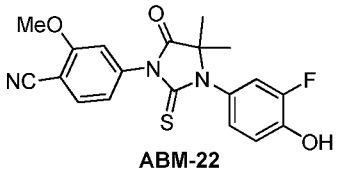
[0359] **ABM-21: 2-chloro-4-(3-(3-fluoro-4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)benzonitrile:**



ABM-21

[0360]

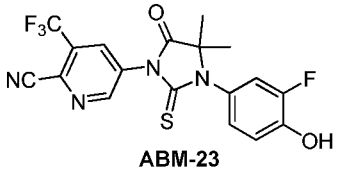
[0361] **ABM-22: 4-(3-(3-fluoro-4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-methoxybenzonitrile:**



ABM-22

[0362]

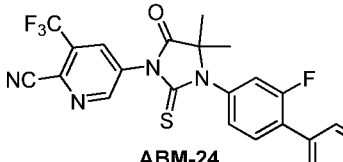
[0363] **ABM-23: 5-(3-(3-fluoro-4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-3-(trifluoromethyl)picolinonitrile:**



ABM-23

[0364]

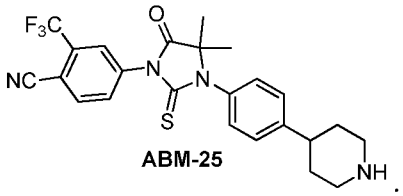
[0365] **ABM-24: 5-(3-(2-fluoro-4'-hydroxybiphenyl-4-yl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-3-(trifluoromethyl)picolinonitrile:**



ABM-24

[0366]

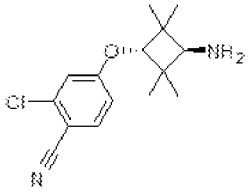
[0367] **ABM-25: 4-(4,4-dimethyl-5-oxo-3-(4-(piperidin-4-yl)phenyl)-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile:**



ABM-25

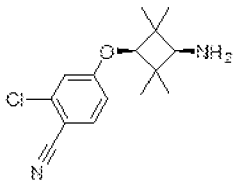
[0368]

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



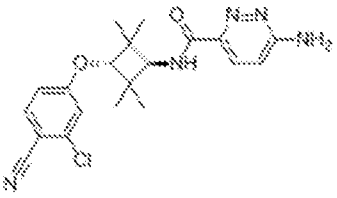
[0370]

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



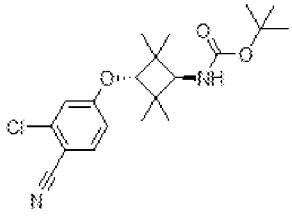
[0372]

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



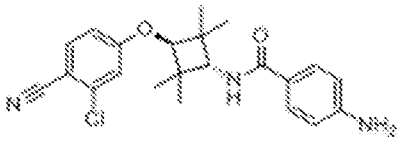
[0374]

[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] 

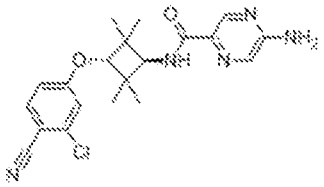
[0379] Step 1: Synthesis of *tert*-butyl (4-((*trans*-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)carbamate.

[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;

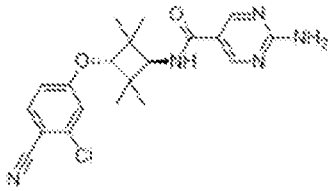
[0381] Step 2: synthesis of trans 4-Amino-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide.

[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^+].

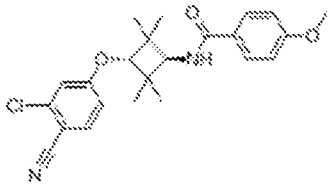
[0383] **ABM-31: trans 5-Amino-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]pyrazine-2-carboxamide**

[0384] 

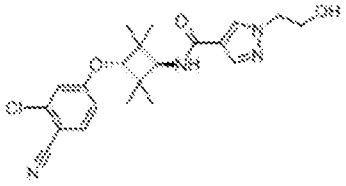
[0385] **ABM-32: trans 2-Amino-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]pyrimidine-5-carboxamid**

[0386] 

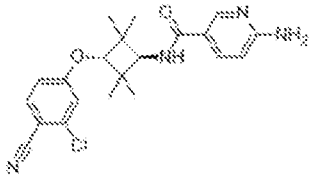
[0387] **ABM-33: 4-Methoxy-N-[(1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide**

[0388] 

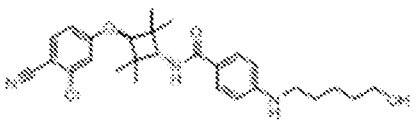
[0389] **ABM-34: trans 1-(2-Hydroxyethyl)-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]-1H-pyrazole-4-carboxamide**

[0390] 

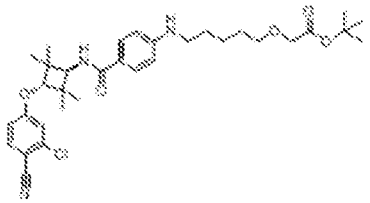
[0391] **ABM-35: trans 6-Amino-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]pyridine-3-carboxamide**.

[0392] 

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

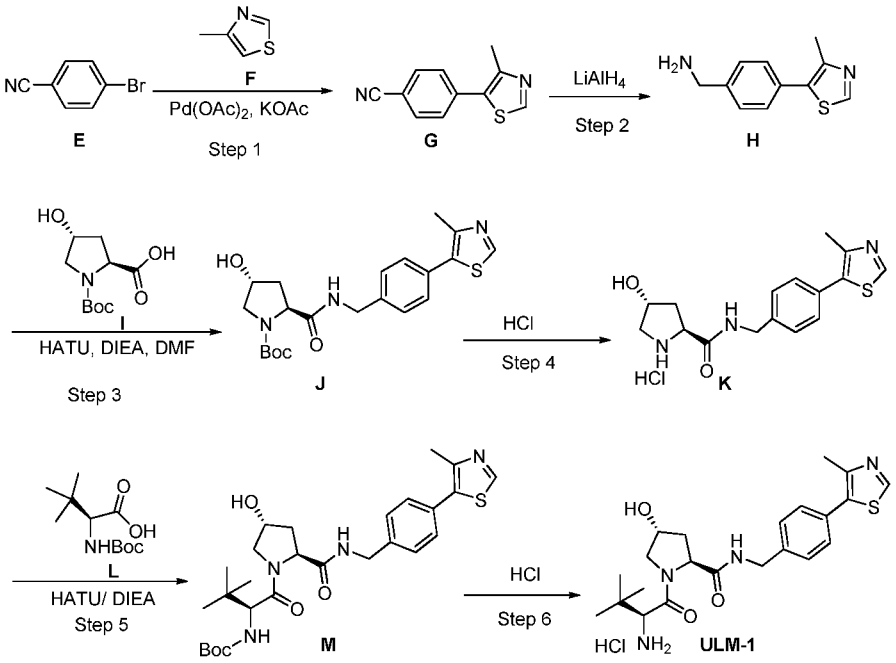
[0394] 

[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 °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**)

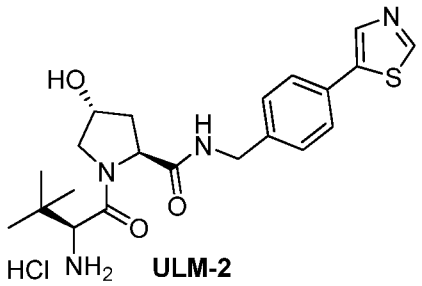
[0409] To a stirred solution of (2S)-2-{[(tert-butoxy)carbonyl]amino}-3,3-dimethylbutanoic acid (**L**, 15.7 g, 68.0 mmol) in N,N-dimethylformamide (500 mL) was added DIEA (29.2 g, 225.9 mmol), HATU (25.9 g, 68.1 mmol) and (2S,4R)-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl} pyrrolidine-2-carboxamide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

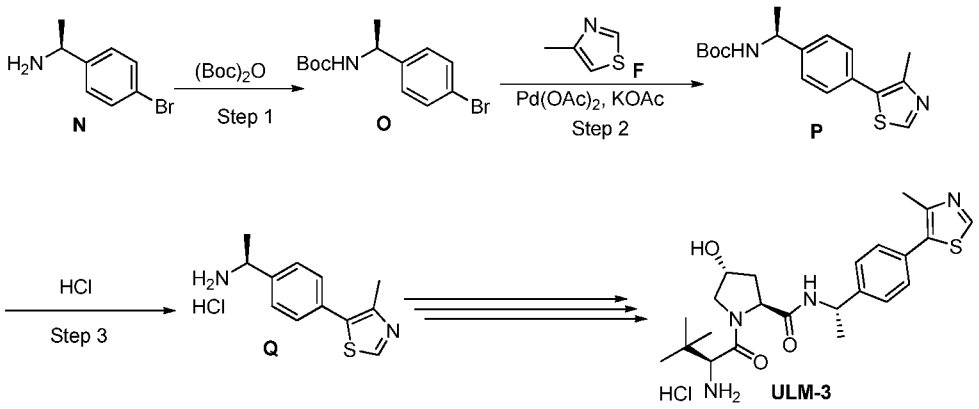


ULM-2

[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

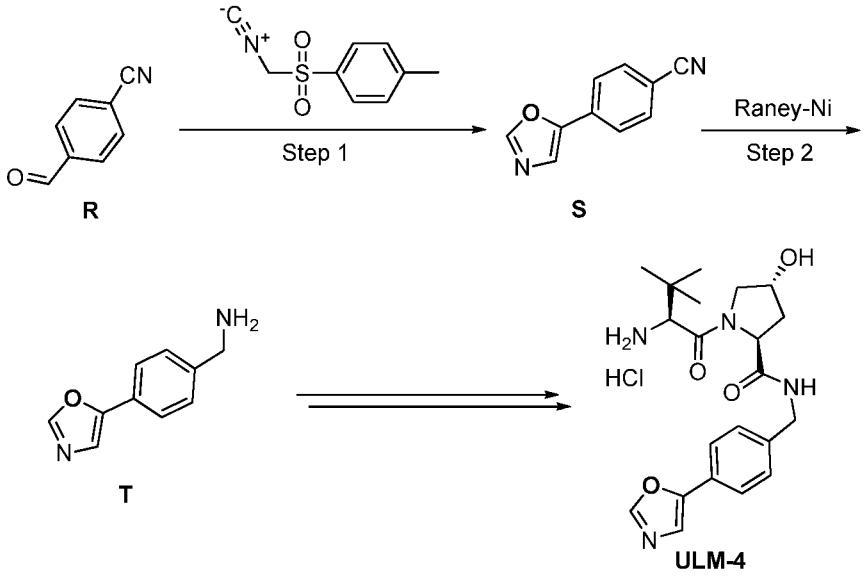
mixture was then cooled to rt, diluted by water (120mL), and extracted with ethyl acetate (200 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel chromatography (eluent: 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**)

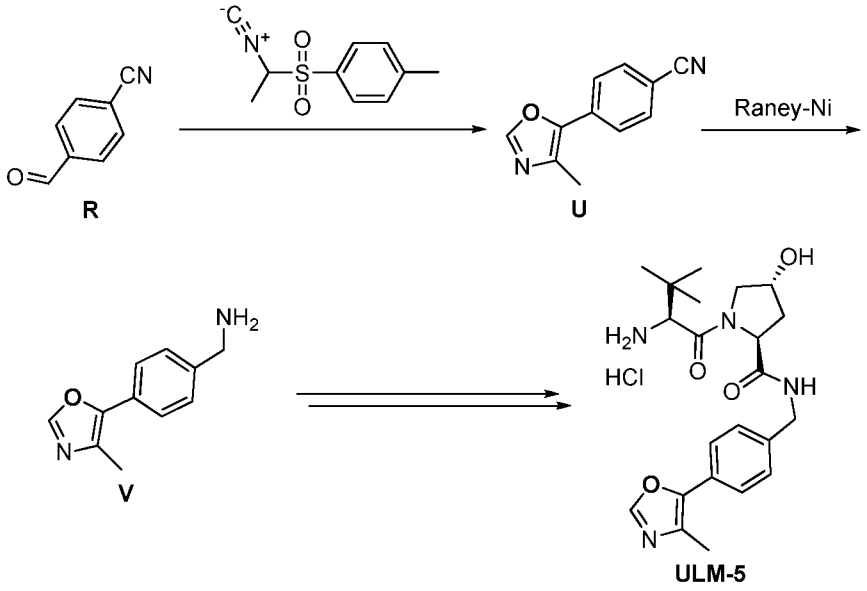
[0428] To a stirred solution of 4-formylbenzonitrile (**R**, 1.0 g, 7.63 mmol) in methanol (40 mL) was added [[(4-methylbenzene)sulfonyl]methyl](methyliumylidyne)azanuide (1.6 g, 8.40 mmol) and potassium carbonate (1.4 g, 9.91 mmol), the resulting mixture was stirred at rt for 1.5 h. The bulk of solvent 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:**

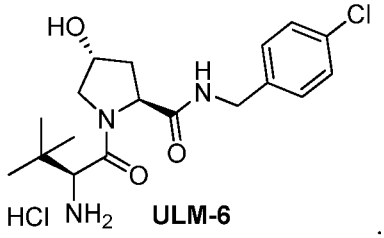


[0433]

[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).

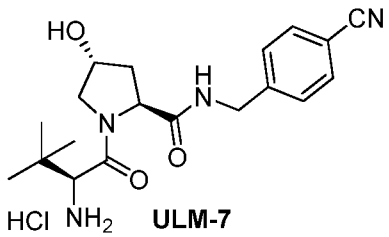
[0436] **ULM-6: (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-N-(4-chlorobenzyl)-4-hydroxypyrrolidine-2-carboxamide hydrochloride:**



[0437]

[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:**

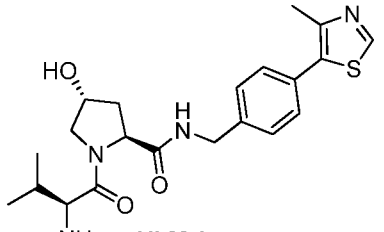


[0440]

[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]

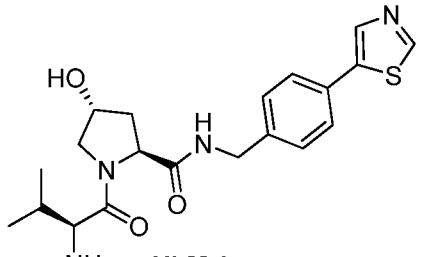


ULM-8

[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]

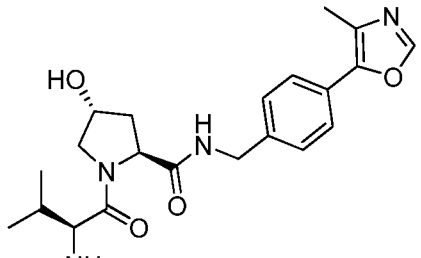


ULM-9

[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:**

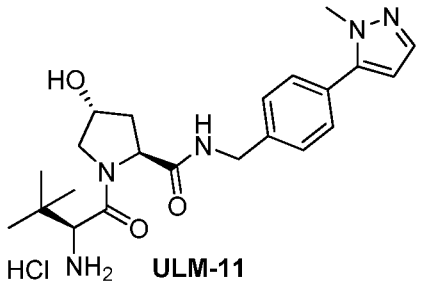
[0449]



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.

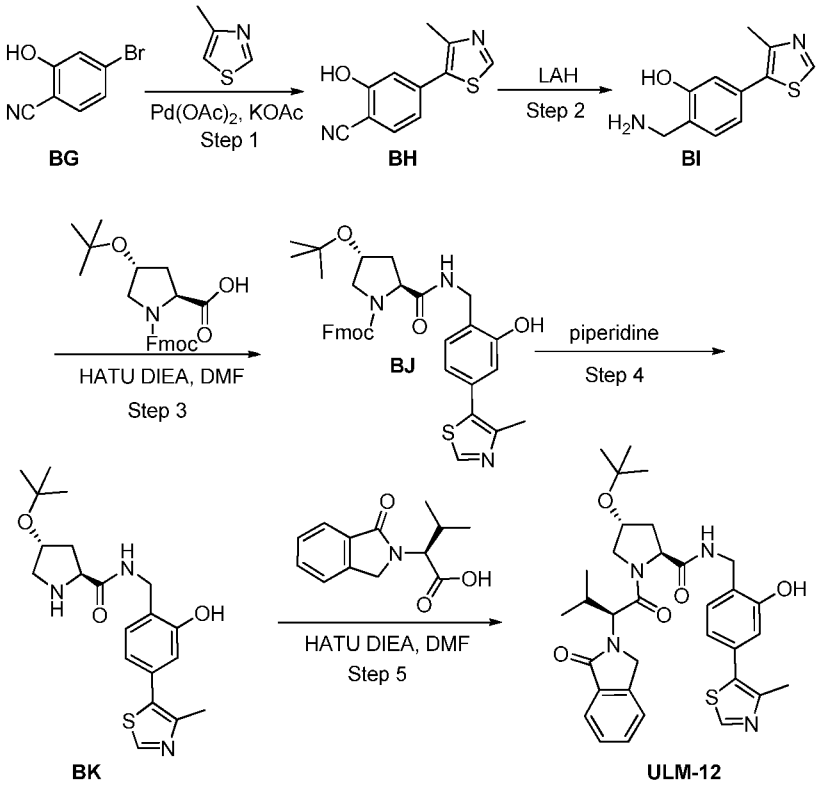
[0451] **ULM-11: (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(1-methyl-1H-pyrazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride:**

[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] 

[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).

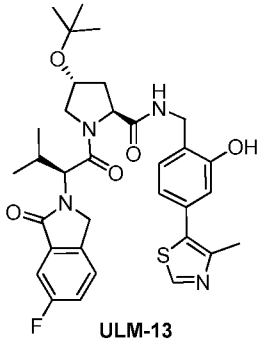
[0464] Step 5: Synthesis of (2S,4R)-4-(tert-butoxy)-N-{[2-hydroxy-4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}-1-[(2S)-3-methyl-2-(1-oxo-2,3-dihydro-1H-isoindol-2-yl)butanoyl]pyrrolidine-2-carboxamide **ULM-12**)

[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).

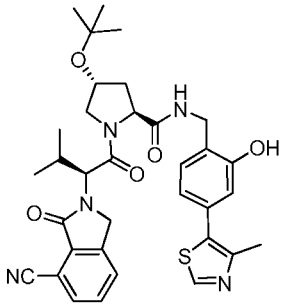
[0466] Unless otherwise noted, the following intermediates and their analogs (for examples, but not limited to, analogs with substitutions such as halogens) were synthesized

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:**

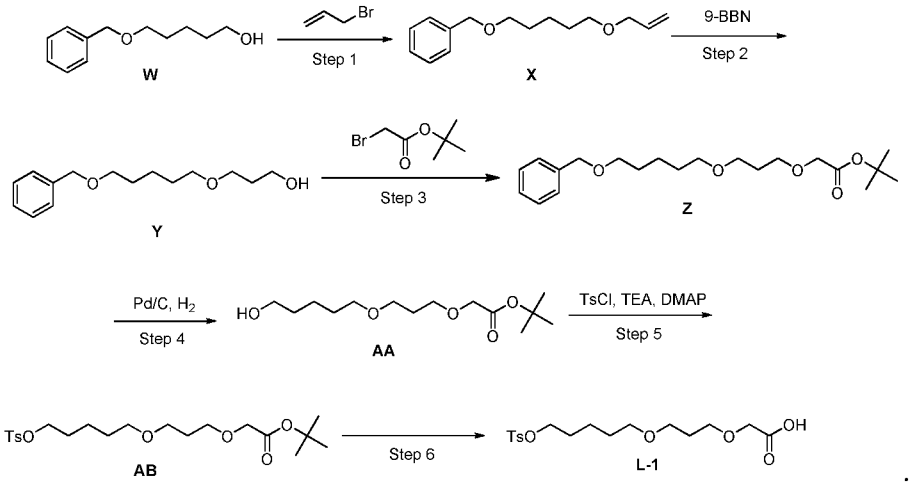
[0468] 
ULM-13 .

[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] 

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[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**)

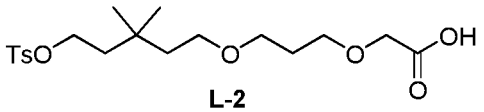
[0485] To a stirred solution of tert-butyl 2-[3-({5-[(4-methylbenzenesulfonyl)oxy]pentyl}oxy)propoxy]acetate (**AB**, 1.3 g, 3.02 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (10 mL) at rt. The resulting solution was stirred at rt for 3 h. The reaction mixture was then concentrated 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]

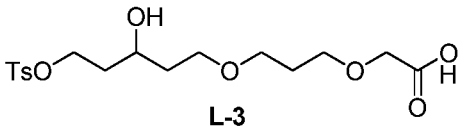
[0489] L-2: 2-(3-(3,3-dimethyl-5-(tosyloxy)pentyloxy)propoxy)acetic acid

[0490] 

L-2

[0491]

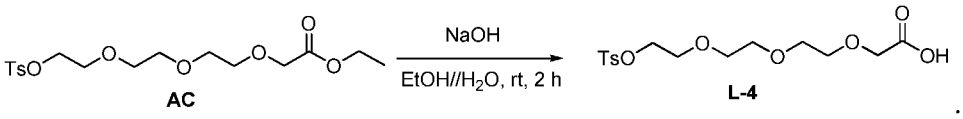
[0492] L-3: 2-(3-(3-hydroxy-5-(tosyloxy)pentyloxy)propoxy)acetic acid

[0493] 

L-3

[0494]

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

[0496] 

AC **L-4**

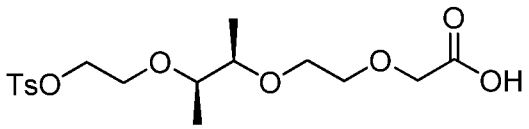
[0497] To a stirred solution of ethyl 2-[2-(2-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}ethoxy)ethoxy]acetate (**AC**, 2 g, 5.12 mmol, 1.00 equiv) in methanol (20 mL) was added a solution of NaOH (500 mg, 12.50 mmol) in water (4 mL), and the resulting mixture was stirred at rt for 2 h. Aqueous hydrogen 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]

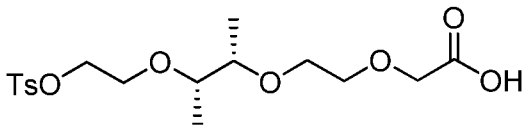
[0501] L-5: 2-(2-((2R,3R)-3-(2-(tosyloxy)ethoxy)butan-2-yloxy)ethoxy)acetic acid

[0502] 

L-5

[0503]

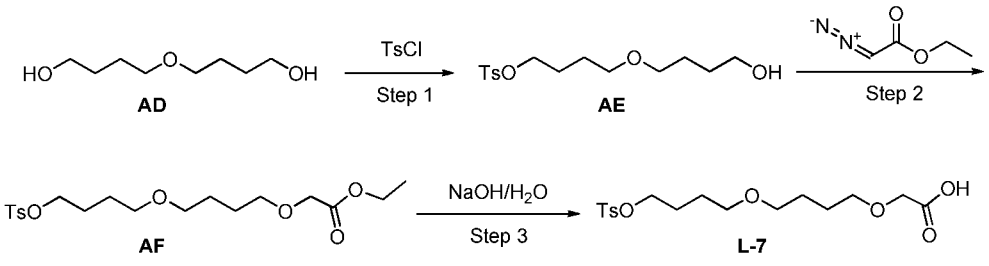
[0504] L-6: 2-(2-((2S,3S)-3-(2-(tosyloxy)ethoxy)butan-2-yloxy)ethoxy)acetic acid

[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)

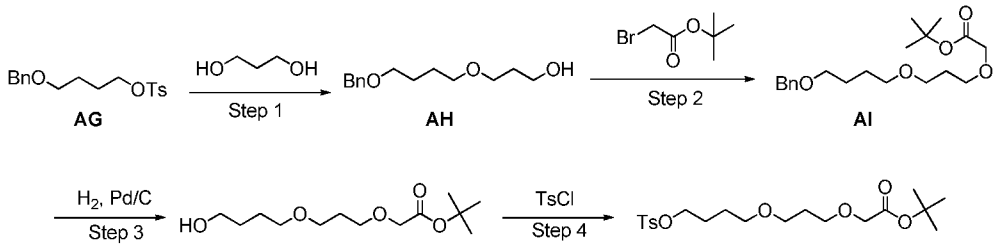
followed by ethyl 2-diazoacetate (794 mg, 6.96 mmol) at 0 °C. The resulting mixture was stirred overnight at rt. The reaction was then quenched by water (2.0 mL). The resulting mixture was extracted with dichloromethane (50mL x 3), the organic layers were combined, dried over anhydrous sodium sulfate 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^+].

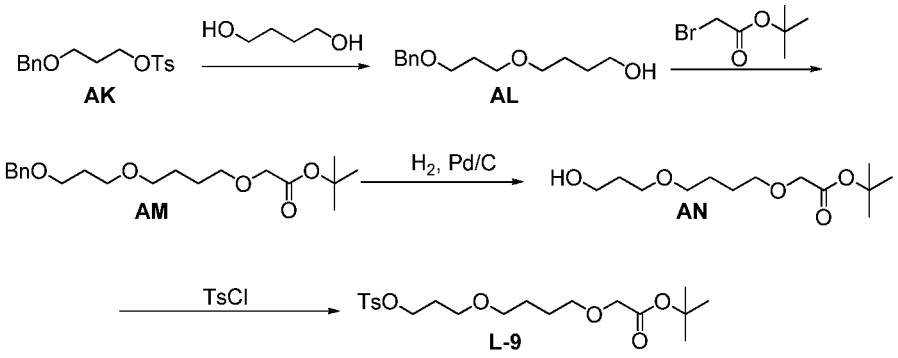
[0524] Step 4. Synthesis of tert-butyl 2-(3-{4-[(4-methylbenzenesulfonyl)oxy]butoxy}propoxy)acetate (**L-8**)

[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

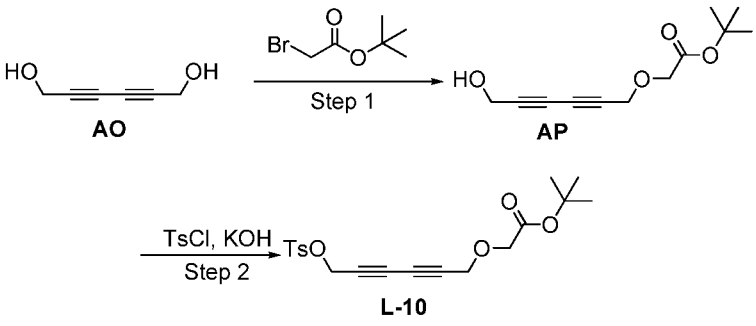


[0528]

[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**)

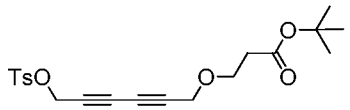
[0536] To a stirred solution of tert-butyl 2-[(6-hydroxyhexa-2, 4-diyn-1-yl) oxy] acetate (**AP**, 50 mg, 0.22 mmol) in ether (2 mL) was added 4-toluenesulfonyl chloride (51 mg, 0.27 mmol) at 0 ^{o}C, followed by potassium hydroxide (125 mg, 2.23 mmol) in several batches at 0 ^{o}C. The resulting mixture 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]

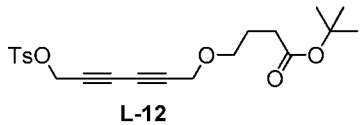
[0540] L-11: tert-butyl 3-(6-(tosyloxy)hexa-2,4-diynyloxy)propanoate



[0541] **L-11** .

[0542]

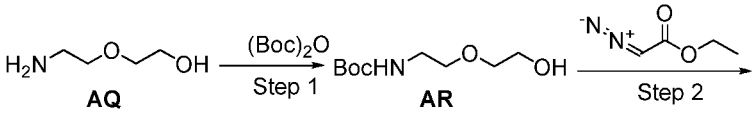
[0543] L-12: tert-butyl 4-(6-(tosyloxy)hexa-2,4-diynyloxy)butanoate



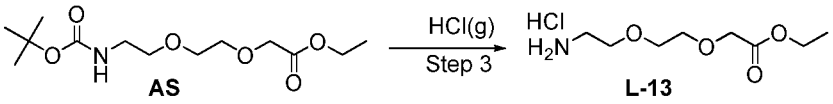
[0544] **L-12** .

[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. ^{1}H 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).

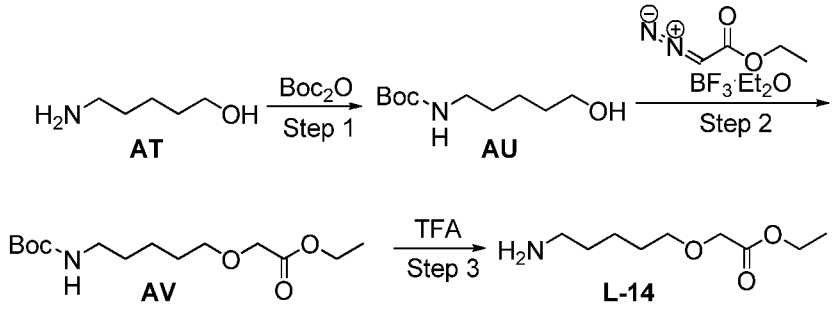
[0552] Step 3: Synthesis of ethyl 2-[2-(2-aminoethoxy)ethoxy]acetate hydrochloride (**L-13**)

[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]

[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).

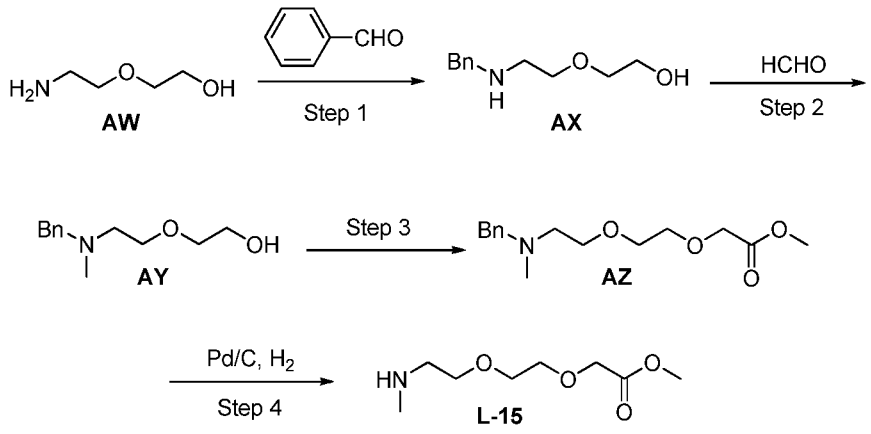
[0561] Step 3: Synthesis of ethyl 2-(5-aminopentyloxy)acetate (**L-14**)

[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).

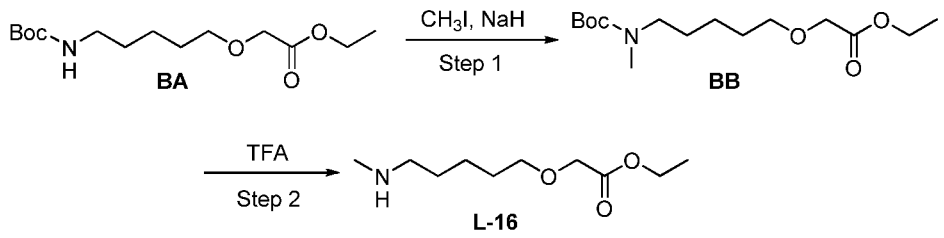
[0570] Step 3: Synthesis of methyl 2-(2-{2-[benzyl(methyl)amino]ethoxy}ethoxy)acetate (**AZ**)

[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]

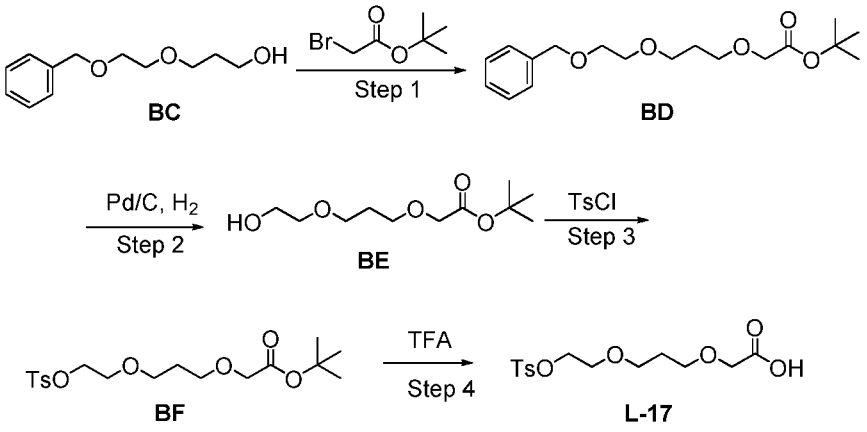
[0576] Step 1: Synthesis of ethyl 2-[(5-{[(tert-butoxy)carbonyl](methyl)amino}pentyl)oxy]acetate (**BB**)

[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).

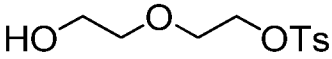
The resulting mixture was stirred overnight at rt. LC-MS indicated formation of the desired product. The reaction mixture was concentrated under reduced pressure to give a crude residue, which was purified by a flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v : v = 1 : 2) to 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**)

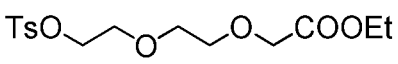
[0589] To a stirred solution of tert-butyl 2-(3-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}propoxy)acetate (**BF**, 400 mg, 1.03 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL) at rt. The resulting solution was stirred at rt for 1 h. LC-MS indicated completion of the reaction. The 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.

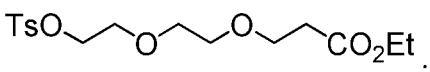
[0591] L-18: 2-(2-hydroxyethoxy)ethyl 4-methylbenzenesulfonate

[0592] 

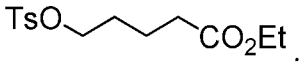
[0593] L-19: ethyl 2-(2-(2-(tosyloxy)ethoxy)ethoxy)acetate

[0594] 

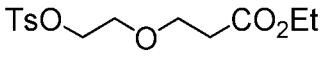
[0595] L-20: ethyl 3-(2-(2-(tosyloxy)ethoxy)ethoxy)propanoate

[0596] 

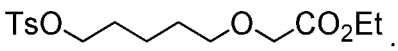
[0597] L-21: ethyl 5-(tosyloxy)pentanoate

[0598] 

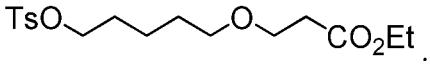
[0599] **L-22: ethyl 3-(2-(tosyloxy)ethoxy)propanoate**

[0600] 

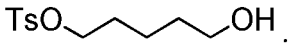
[0601] **L-23: ethyl 2-(5-(tosyloxy)pentyloxy)acetate**

[0602] 

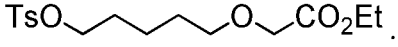
[0603] **L-24: ethyl 3-(5-(tosyloxy)pentyloxy)propanoate**

[0604] 

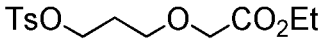
[0605] **L-25: 5-hydroxypentyl 4-methylbenzenesulfonate**

[0606] 

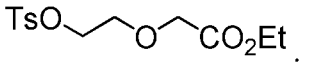
[0607] **L-26: ethyl 2-(5-(tosyloxy)pentyloxy)acetate**

[0608] 

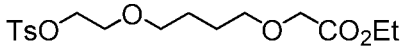
[0609] **L-27: ethyl 2-(3-(tosyloxy)propoxy)acetate**

[0610] 

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

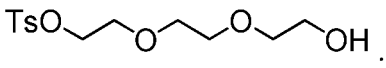
[0612] 

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

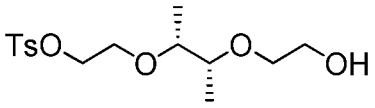


[0614] **L-29**

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

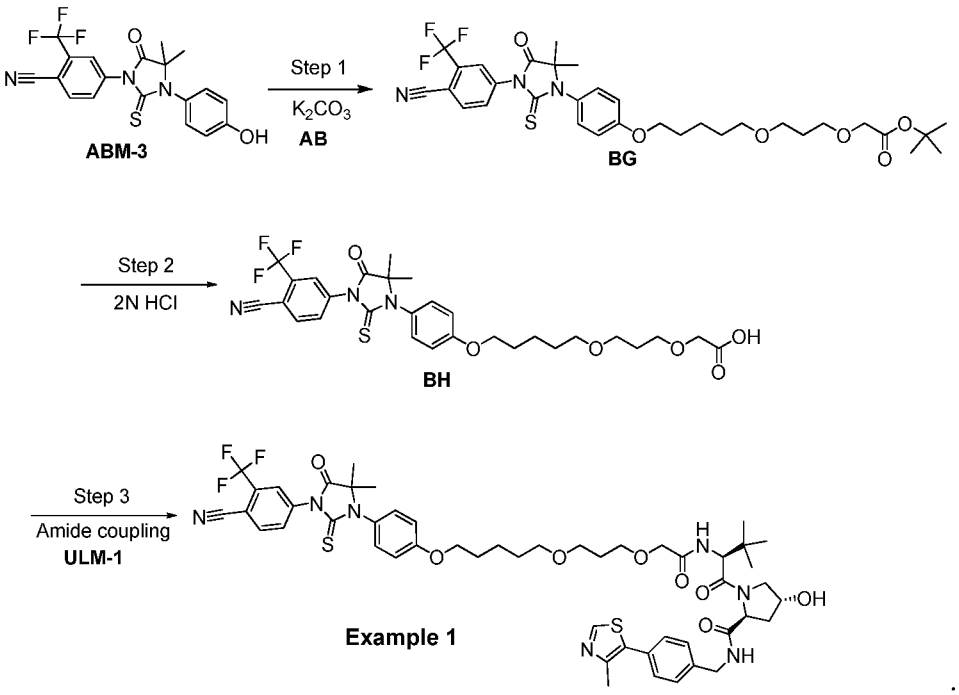
[0616] 

[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**)

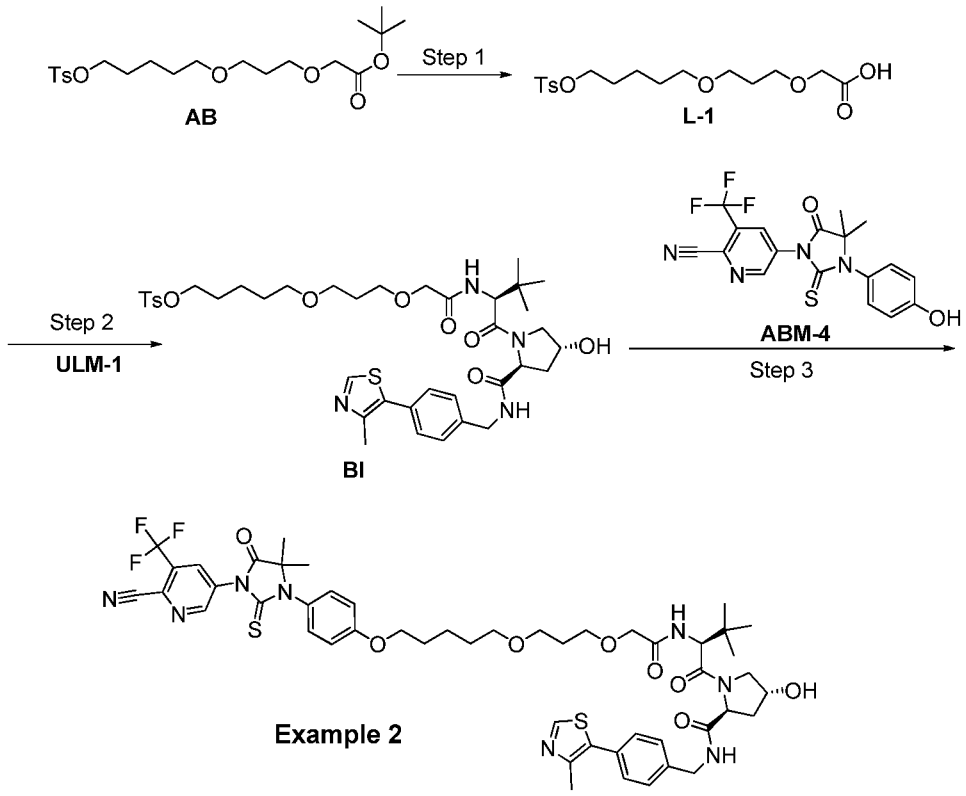
[0625] To a stirred solution of tert-butyl 2-(3-{[5-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)pentyl]oxy}propoxy)acetate (**BG**, 220 mg, 0.33 mmol) in dioxane (4.0 mL) was added hydrogen chloride (2N in water, 1.0 mL). The resulting mixture 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**)

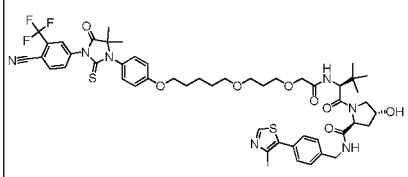
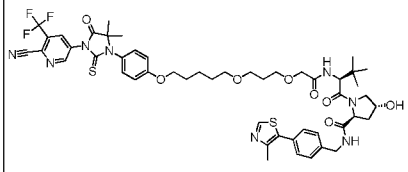
[0634] To a stirred solution of 5-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-sulfanylideneimidazolidin-1-yl]-3-(trifluoromethyl)pyridine-2-carbonitrile (**ABM-4**, 52 mg, 0.13 mmol), (2S,4R)-1-[(2S)-3,3-dimethyl-2-{2-[3-({5-[(4-methylbenzenesulfonyl)oxy]pentyl}oxy)propoxy]acetamido}butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**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-

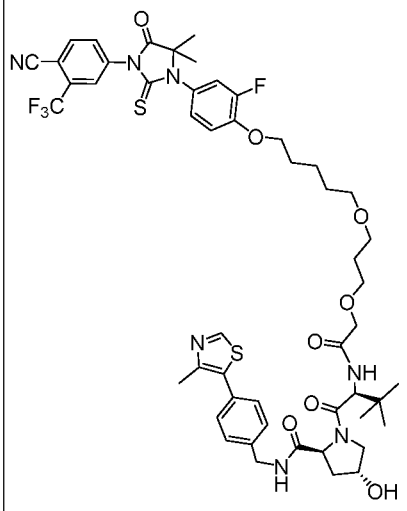
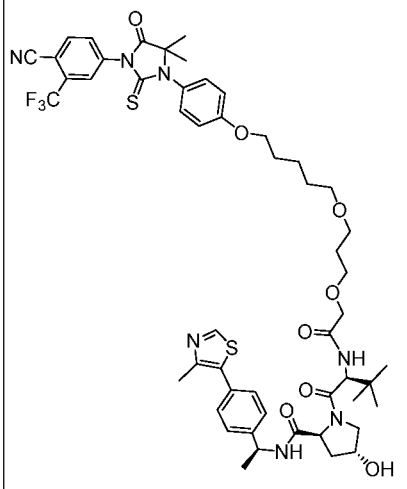
1.65 (m, 4H), 1.60-1.42 (m, 10H), 1.00 (s, 9H): LC-MS (ES^+): *m/z* 1021.12 [MH^+], t_R = 2.36 min (3.6 minute run).

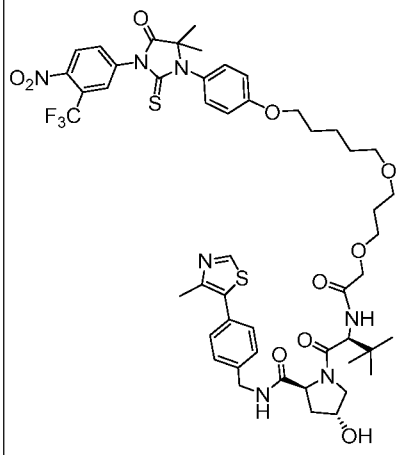
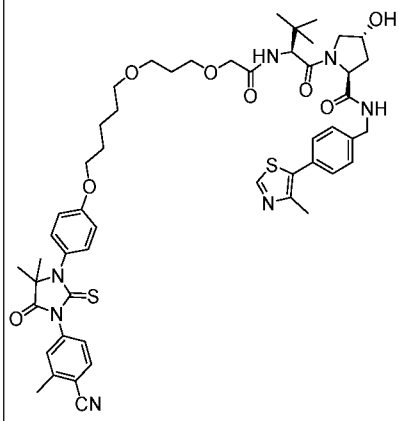
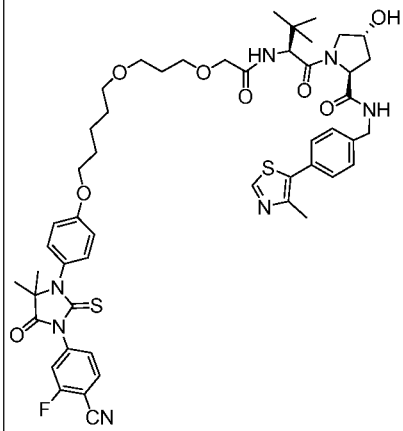
[0635] Unless otherwise noted, the following examples were synthesized according to analogous procedures described above for synthesis of examples 1 and 2, utilizing corresponding reagents, intermediates, and starting materials.

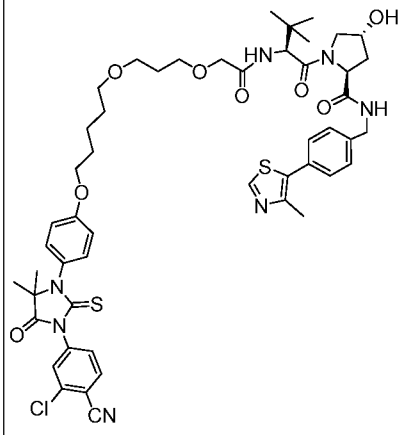
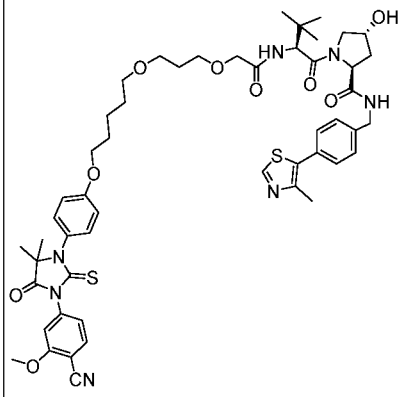
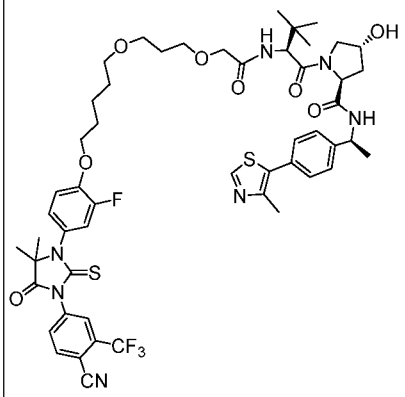
[0636] When referring to the specific exemplary compounds presented herein, the specification uses the terms "example #." For example, compound 1 (Table 2) is also referred to as Example 1.

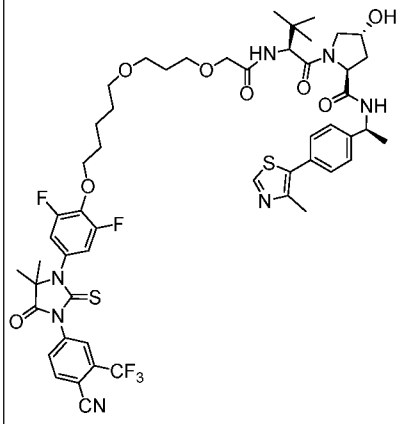
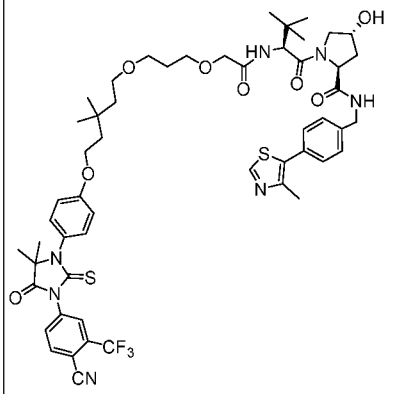
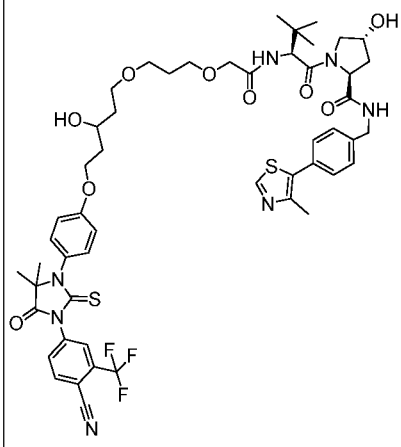
[0637] Table 2. Exemplary Compounds.

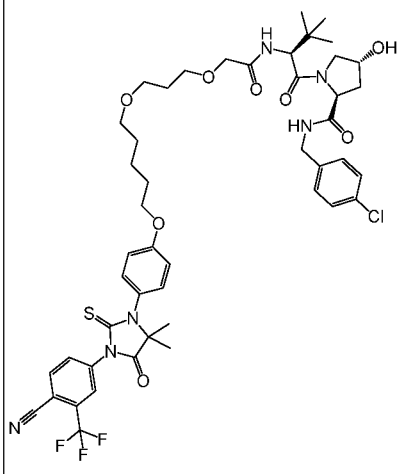
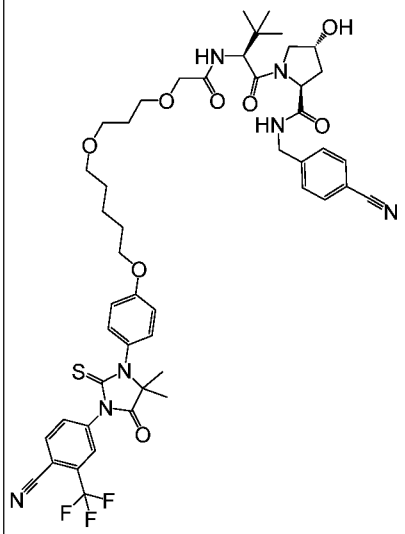
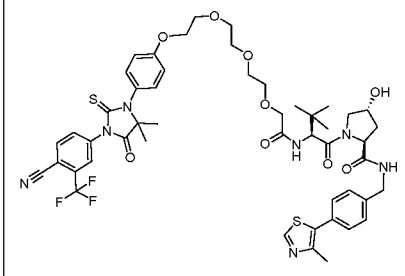
Ex #	Structure	Compound name and Analytical data
1		(2S,4R)-1-((S)-2-(2-(3-(5-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)pentyloxy)propoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide 1H NMR (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).

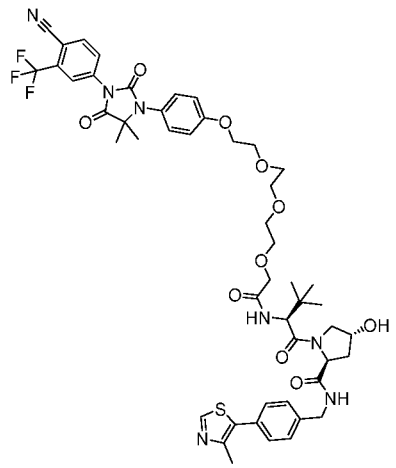
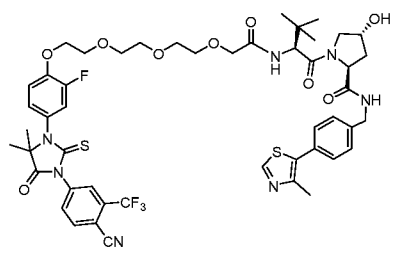
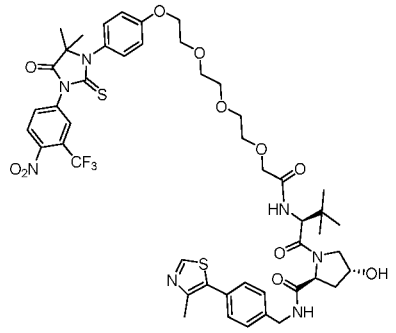
Ex #	Structure	Compound name and Analytical data
3		Prepared from **ABM-16**, **L-1**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluorophenoxy)pentyl]oxy}propoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{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)

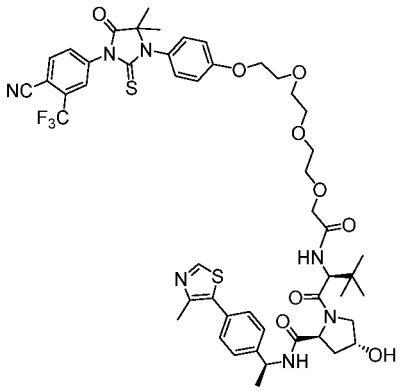
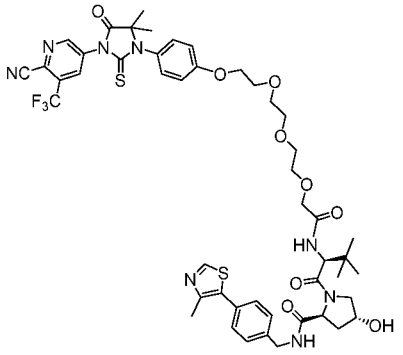
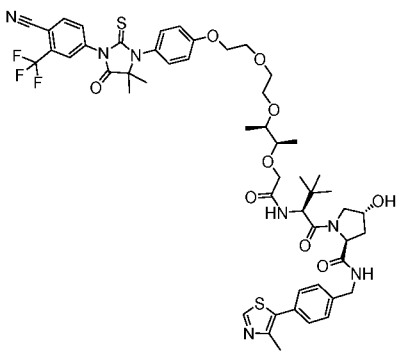
Ex #	Structure	Compound name and Analytical data
5		Prepared from **ABM-17**, **L-1**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{5,5-dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl]-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)pentyl]oxy}propoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{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)

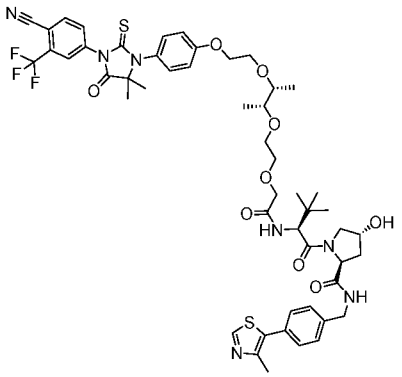
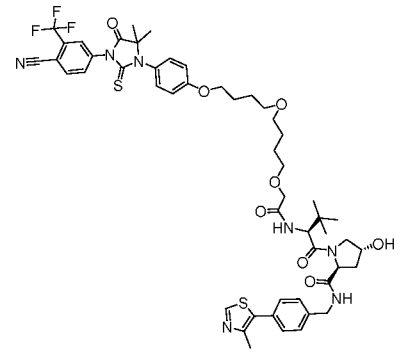
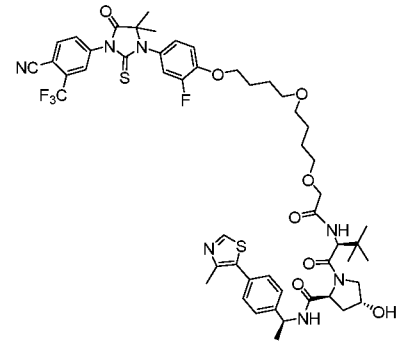
Ex #	Structure	Compound name and Analytical data
8		Prepared from **ABM-1**, **L-1**, and **ULM-1** 2S,4R)-1-[(2S)-2-(2-{3-[(5-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenoxy}pentyl)oxy]propoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{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

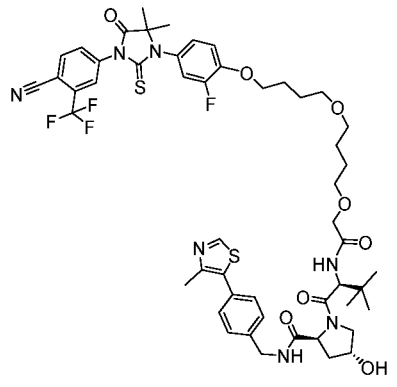
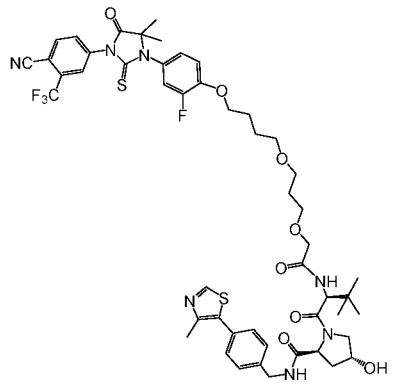
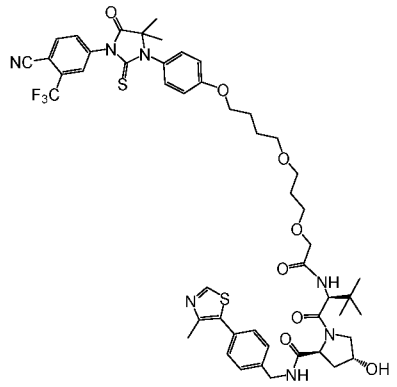
Ex #	Structure	Compound name and Analytical data
11		Prepared from **ABM-18**, **L-1**, and **ULM-3** (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2,6-difluorophenoxy)pentyl]oxy}propoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-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).

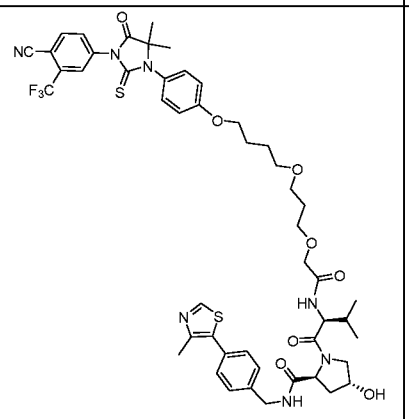
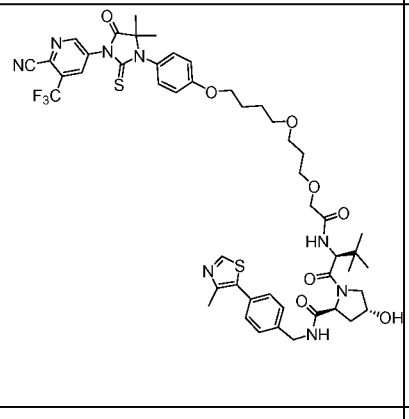
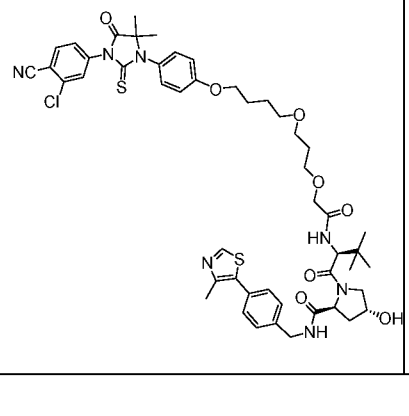
Ex #	Structure	Compound name and Analytical data
14		Prepared from **ABM-3**, **L-1**, and **ULM-6** (2S,4R)-N-[(4-chlorophenyl)methyl]-1-[(2S)-2-[2-(3-{[5-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)pentyl]oxy}propoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxypyrrolidine-2-carboxamide 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 ^1H 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 ^1H 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).

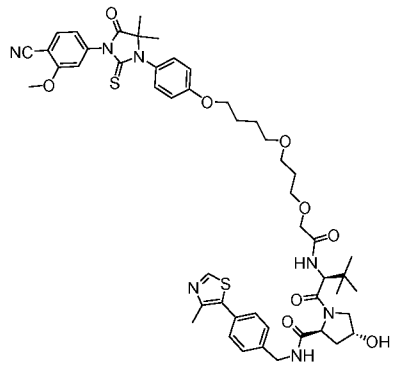
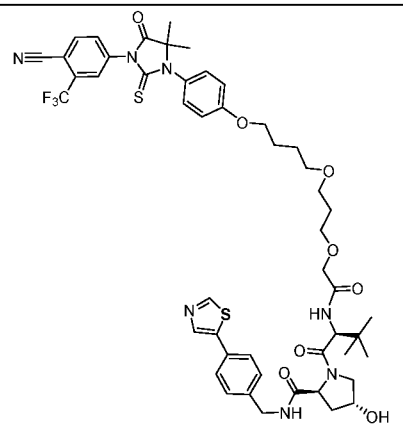
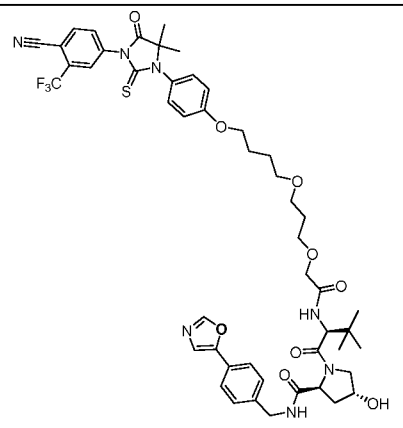
Ex #	Structure	Compound name and Analytical data
17		Prepared from **ABM-19**, **L-4**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-(2-{2-[2-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl}phenoxy)ethoxy]ethoxy}ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{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).

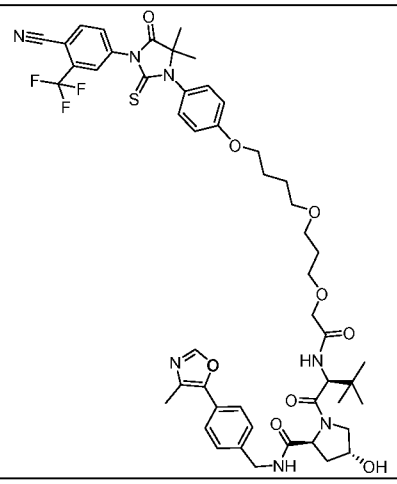
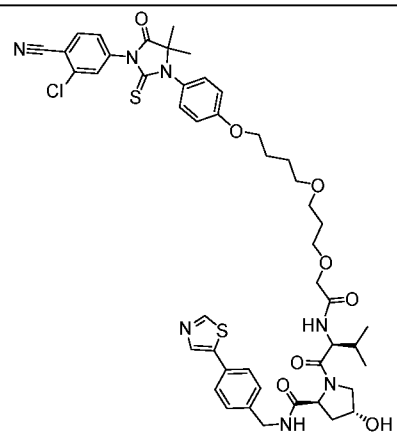
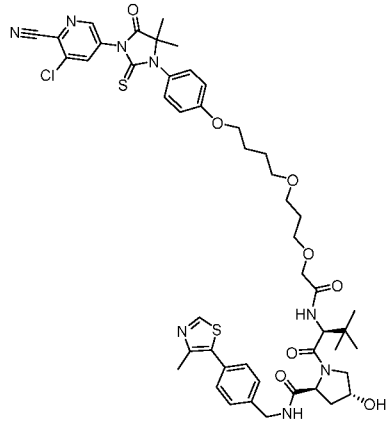
Ex #	Structure	Compound name and Analytical data
20		Prepared from **ABM-3**, **L-4**, and **ULM-3** (2S,4R)-1-[(2S)-2-[2-(2-{2-[2-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)ethoxy]ethoxy}ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-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^+]

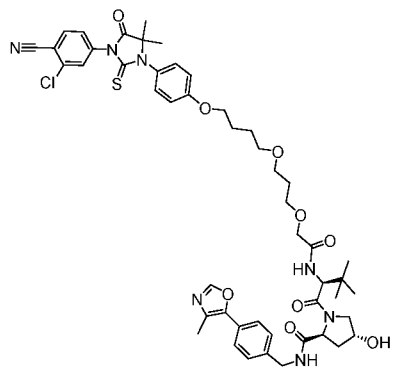
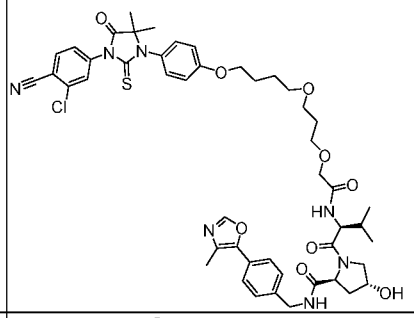
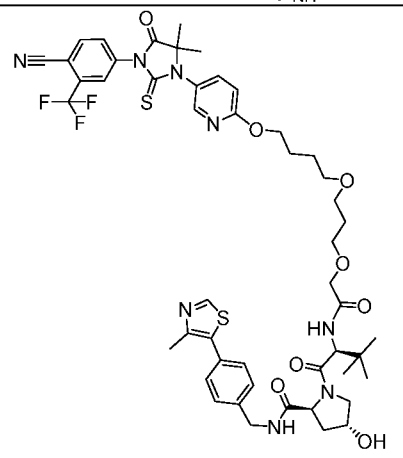
Ex #	Structure	Compound name and Analytical data
23		Prepared from **ABM-3**, **L-6**, and **ULM-1** (2S,4R)-1-[(2S)-2-[2-(2-{[(2R,3R)-3-[2-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)ethoxy]butan-2-yl]oxy}ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-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^+]

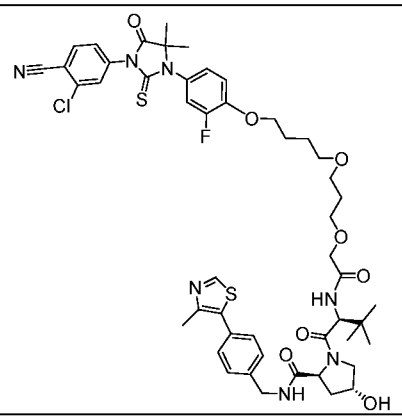
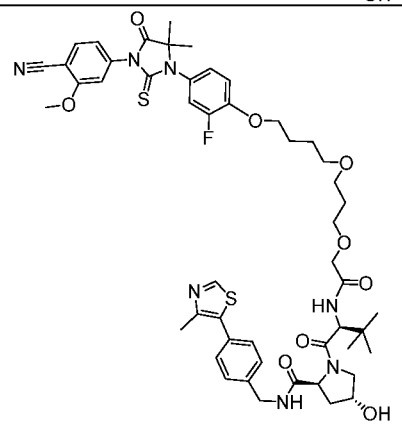
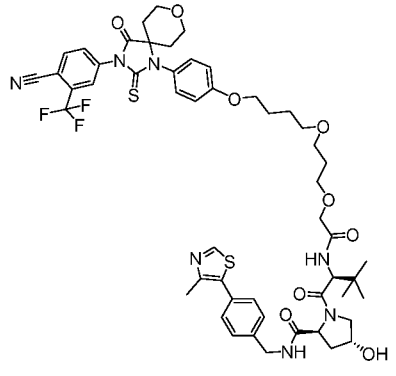
Ex #	Structure	Compound name and Analytical data
26		Prepared from **ABM-16**, **L-7**, and **ULM-3** (2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluorophenoxy)butoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{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).

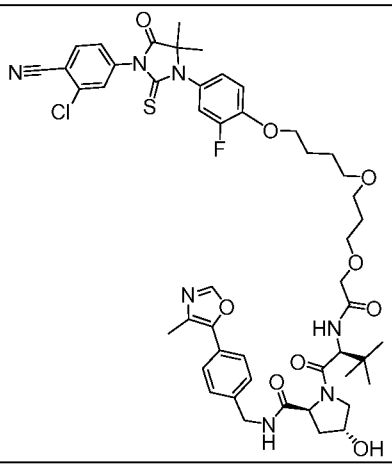
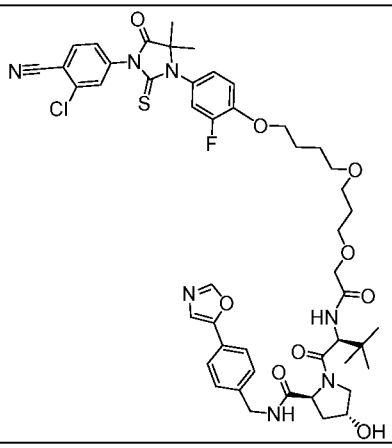
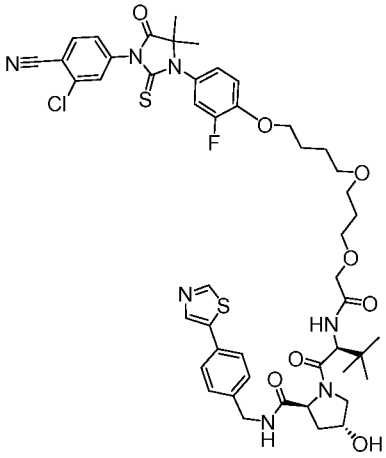
Ex #	Structure	Compound name and Analytical data
29		Prepared from **ABM-3**, **L-8**, and **ULM-8** (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)butoxy]propoxy}acetamido)-3-methylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{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).

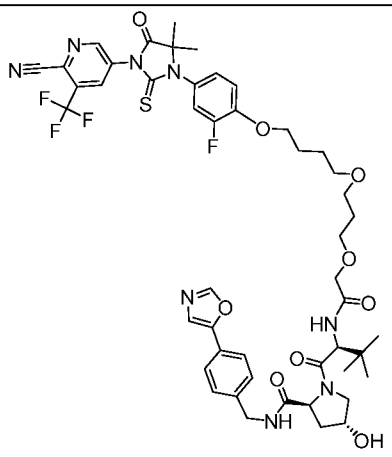
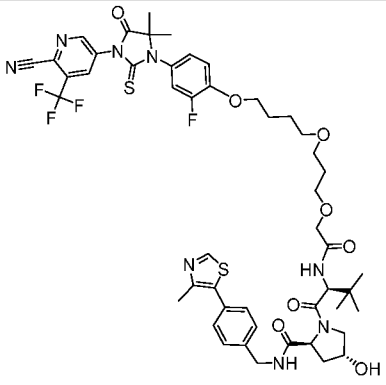
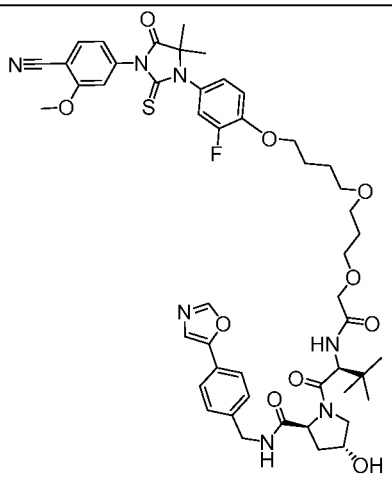
Ex #	Structure	Compound name and Analytical data
32		Prepared from **ABM-5**, **L-8**, and **ULM-1** (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(4-cyano-3-methoxyphenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenoxy}butoxy)propoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{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).

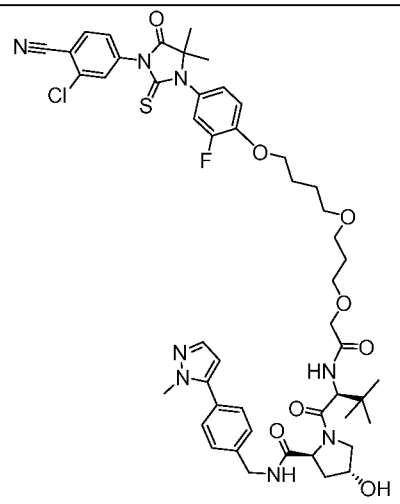
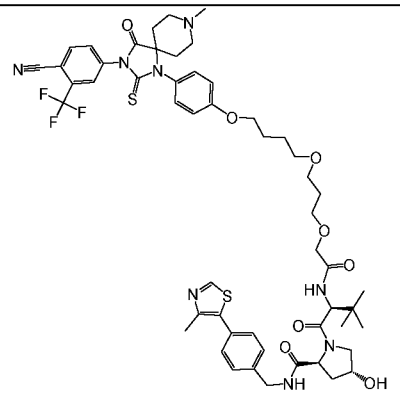
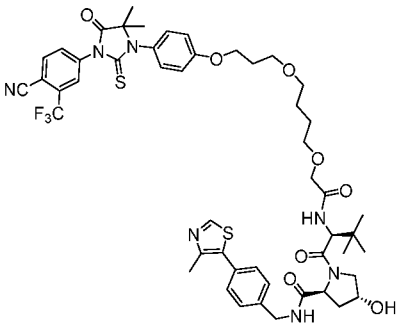
Ex #	Structure	Compound name and Analytical data
35		Prepared from **ABM-3**, **L-8**, and **ULM-5** (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)butoxy]propoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{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).

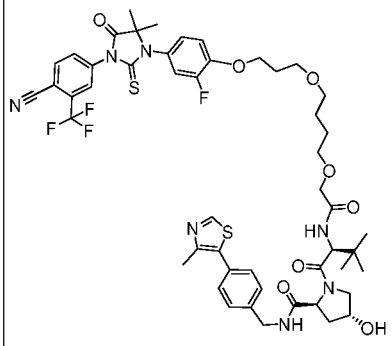
Ex #	Structure	Compound name and Analytical data
38		Prepared from **ABM-1**, **L-8**, and **ULM-5** (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenoxy}butoxy)propoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{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).

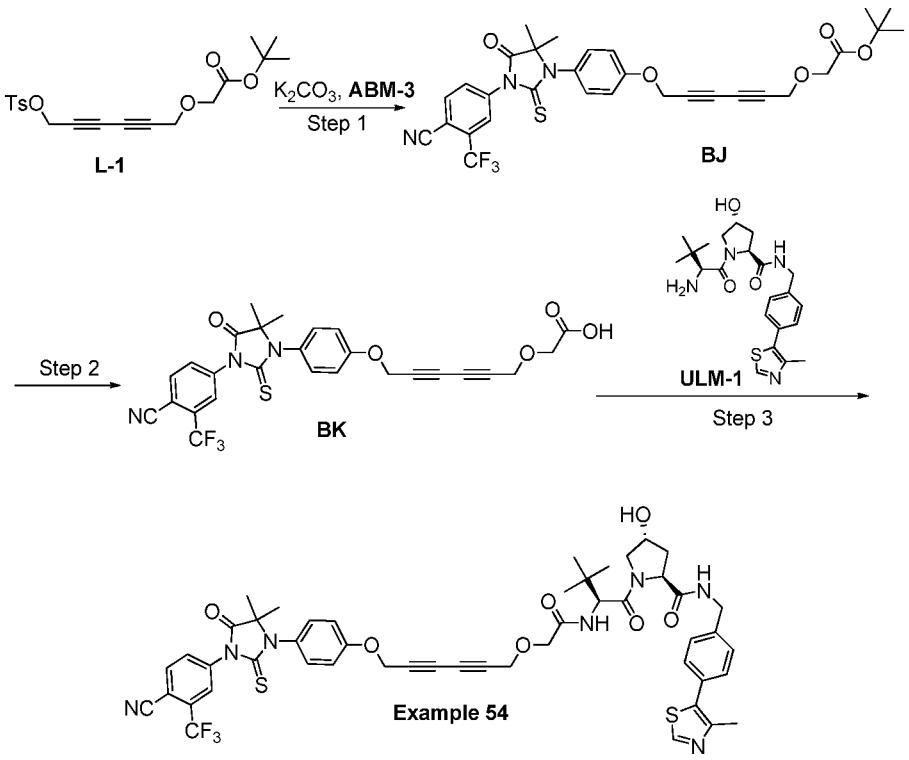
Ex #	Structure	Compound name and Analytical data
44		Prepared from **ABM-21**, **L-8**, and **ULM-5** (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]-2-fluorophenoxy}butoxy)propoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{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**)

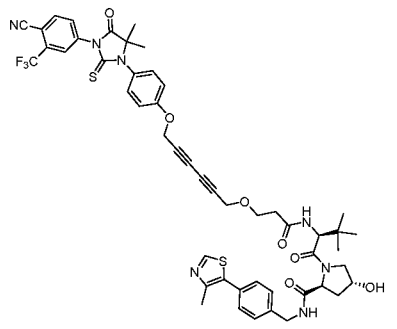
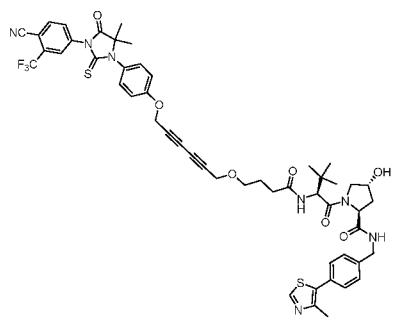
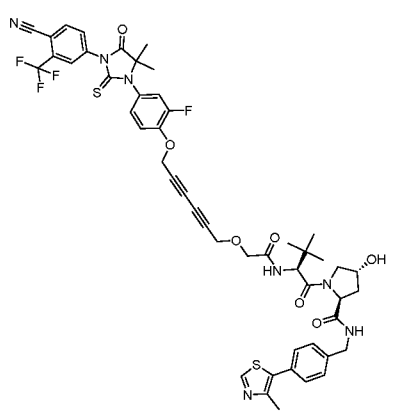
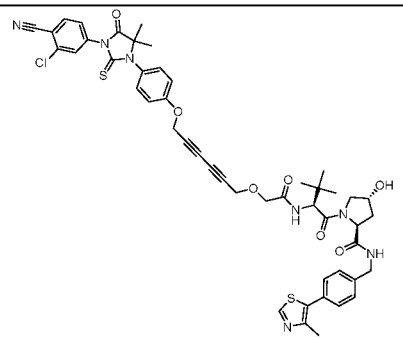
[0642] This material was synthesized according to a similar procedure described in reaction step 2 for the synthesis of example 1. LC-MS (ES^+): *m/z* 556.10 [MH^+], t_R = 1.54 min (2.6 minute run).

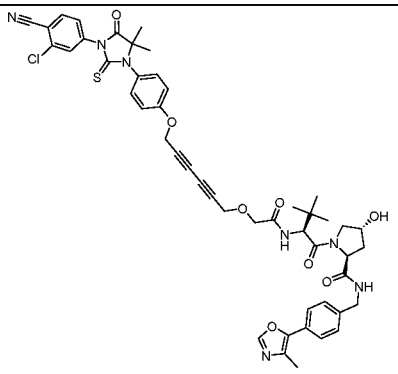
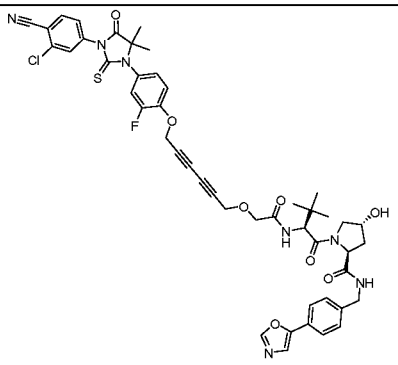
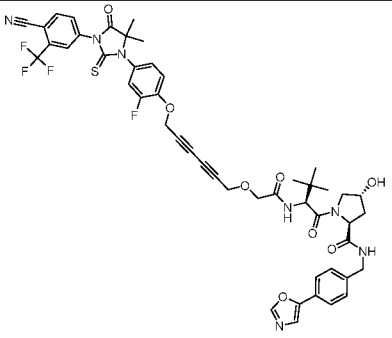
[0643] Step 3: Synthesis of (2S,4R)-1-[(2S)-2-(2-{[6-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)hexa-2,4-diyn-1-yl]oxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Example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

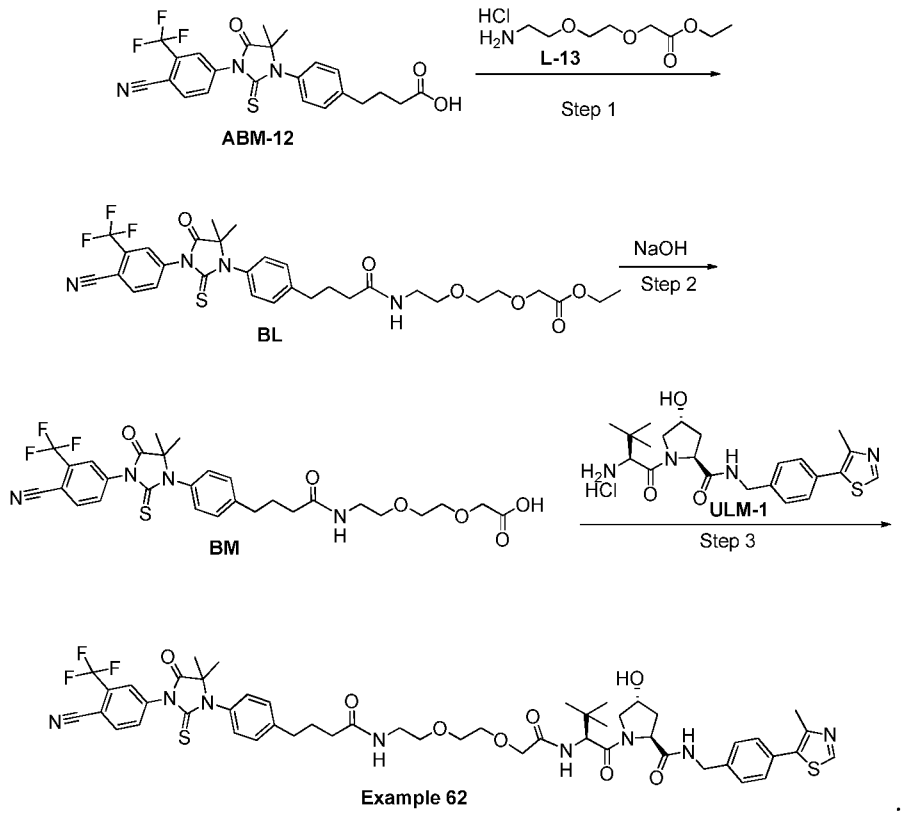
Ex #	Structure	Compound name and Analytical data

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).

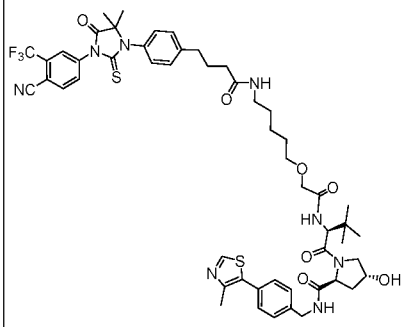
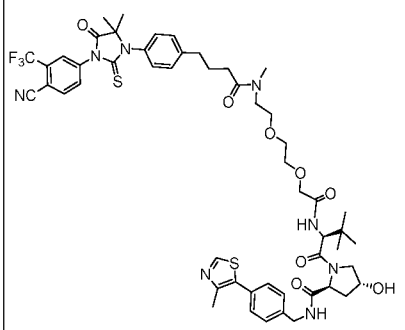
[0652] Step 3: Synthesis of (2S,4R)-1-[(2S)-2-[2-(2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)butanamido]ethoxy}ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Example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

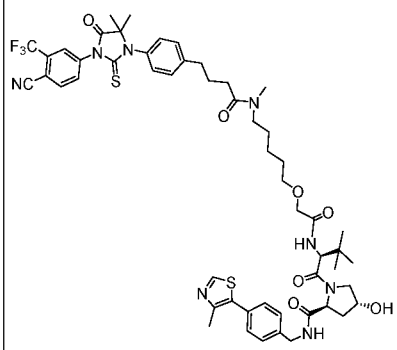
[0653] To a stirred solution of 2-(2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)butanamido]ethoxy}ethoxy)acetic acid (**BM**, 200 mg, 0.32 mmol) in N,N-dimethylformamide (20 mL) was added HATU (245 mg, 0.64 mmol), DIEA (166 mg, 1.28 mmol) 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).

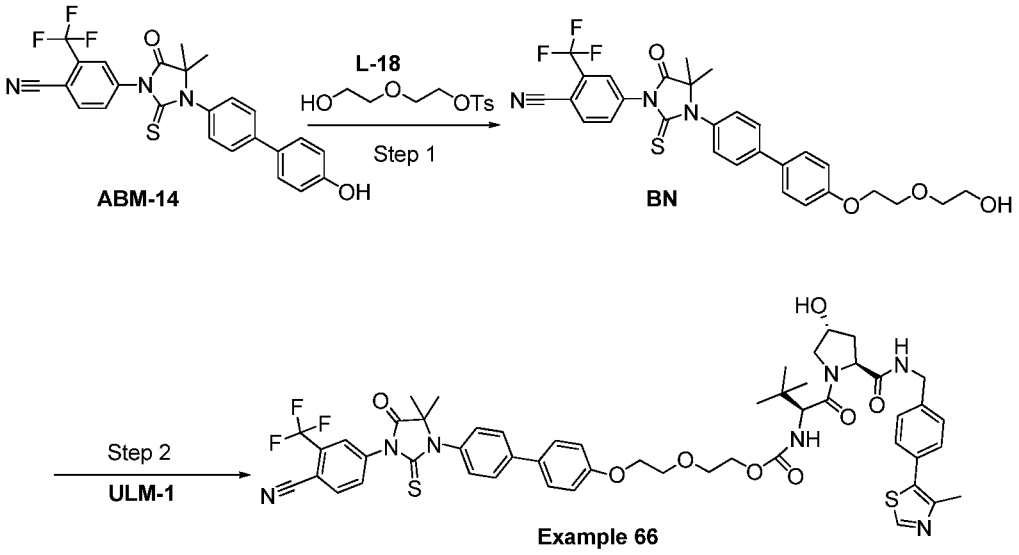
[0654] Examples 63-65 were synthesized according to similar procedure described for synthesis of example 62, by using corresponding starting materials and intermediates.

[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**)

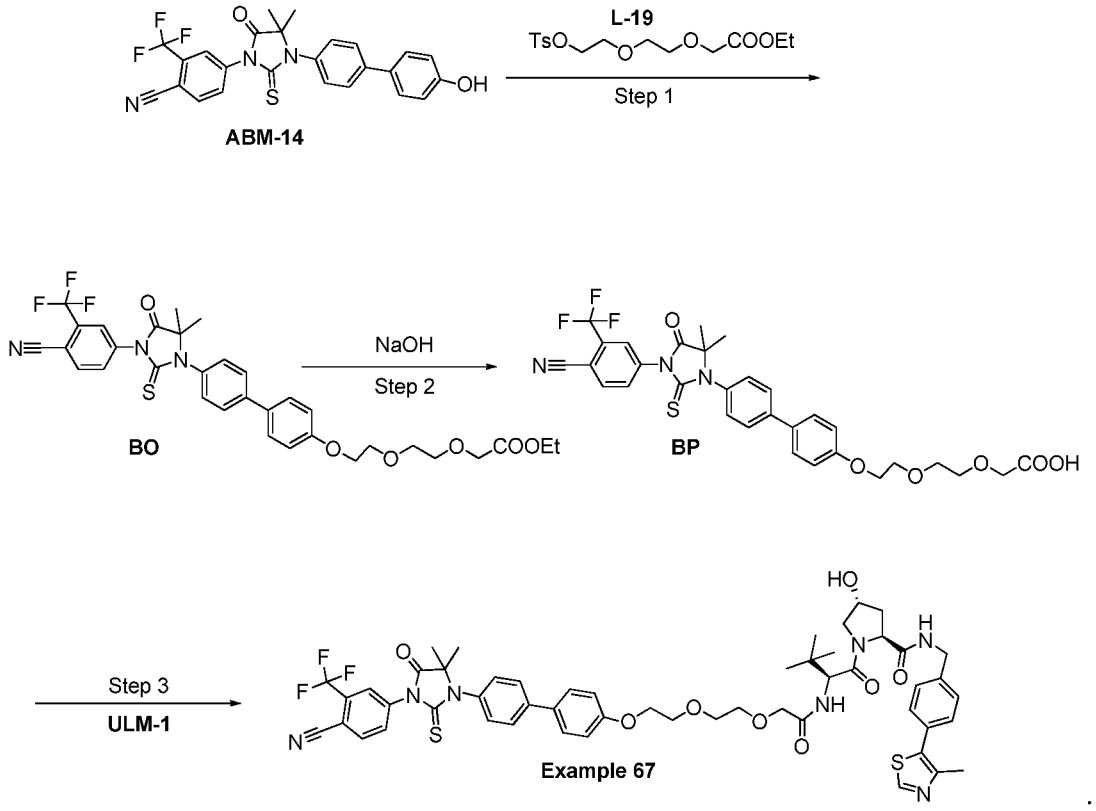
[0658] To a stirred solution of 4-{3-[4-(4-hydroxyphenyl)phenyl]-4,4-dimethyl-5-oxo-2-sulfanylideneimidazolidin-1-yl}-2-(trifluoromethyl)benzonitrile (**ABM-14**, 610.5 mg, 1.27 mmol) in N,N-dimethylformamide (10 mL) was added K_2CO_3 (318.46 mg, 2.29 mmol) and 2-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}ethan-1-ol (**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).

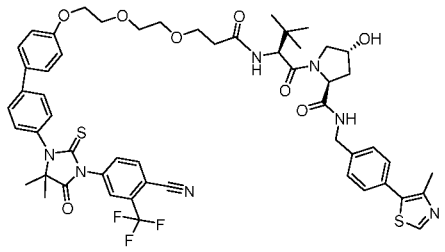
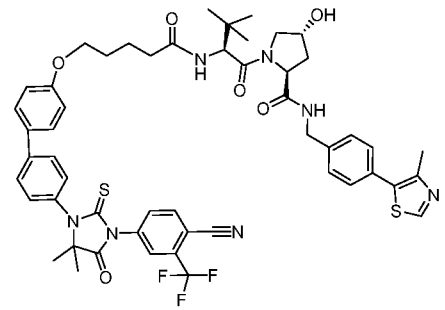
[0666] Step 3: Synthesis of (2S,4R)-1-[(2S)-2-[2-(2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]ethoxy}ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (**Example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

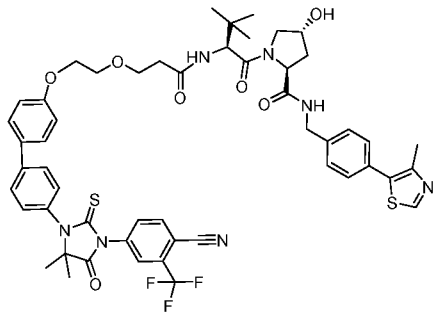
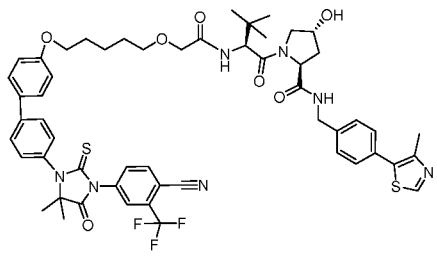
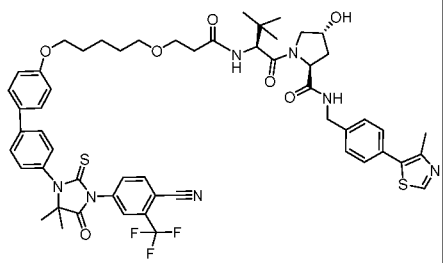
[0667] To a stirred solution of 2-(2-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]ethoxy}ethoxy)acetic acid (**BP**, 190 mg, 0.30 mmol) in N,N-dimethylformamide (10 mL) was added HATU (149.7 mg, 0.39 mmol), DIEA (156.4 mg, 1.21 mmol) 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

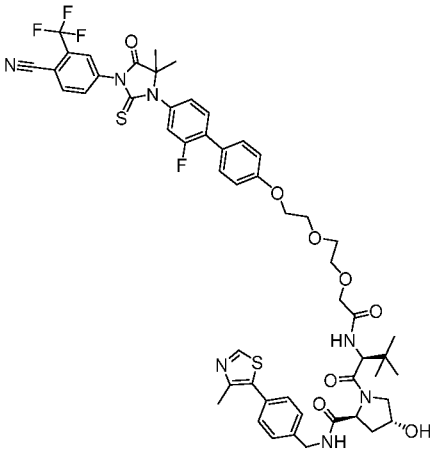
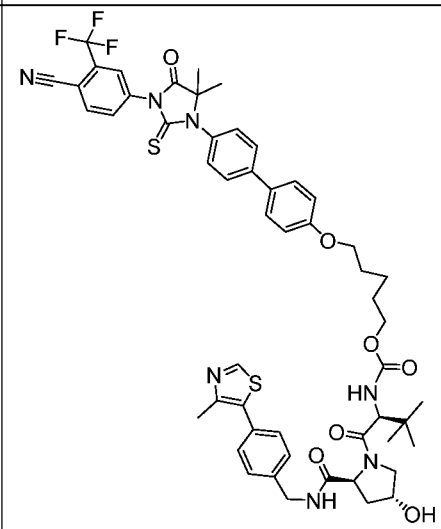
chloride (25 mL x 3), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified Prep-HPLC to give **Example 67** (yield: 17%) as a white solid. ^{1}H-NMR (400MHz, CD_3OD): δ 8.82 (s, 1 H), 8.19-8.16 (d, J = 9.0 Hz, 2 H), 8.02-8.00 (d, 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).

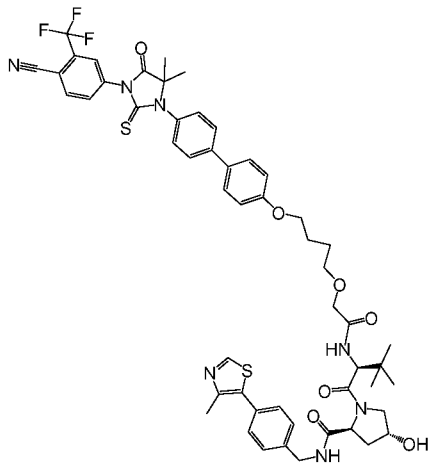
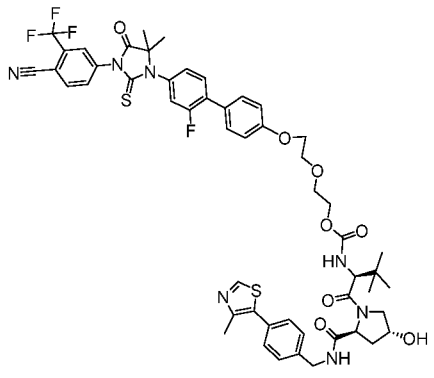
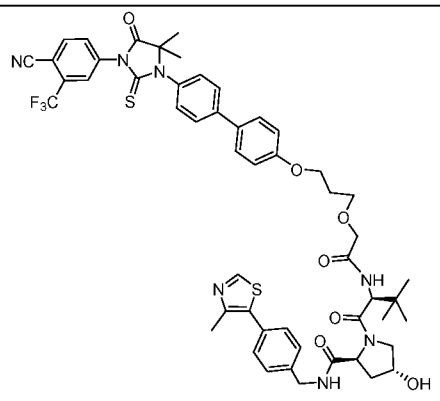
[0668] Examples 74 and 76 were synthesized according to similar procedure described for synthesis of Example 66, by using corresponding starting materials and intermediates. Examples 68-73, 75, 77-79 were synthesized according to similar procedure described for synthesis of Example 67, by using corresponding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

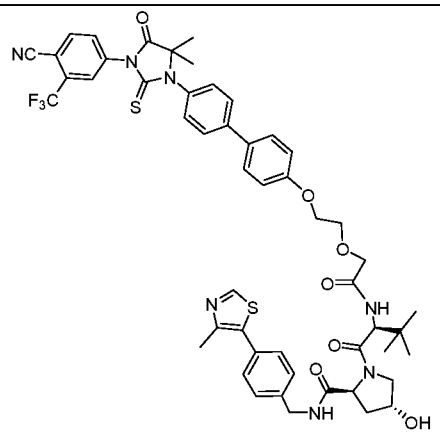
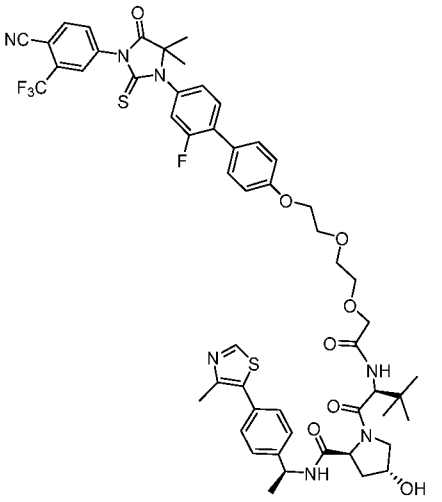
[0669] Table 5. Exemplary Compounds.

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$^+$):

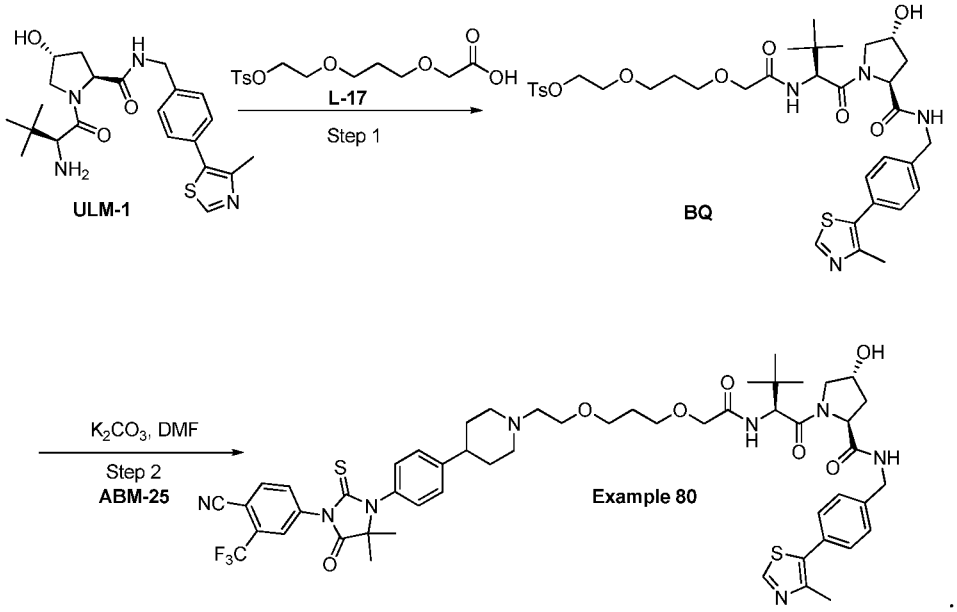
Ex #	Structure	Compound name and Analytical data
		m/z 994.40 [MH$^+$], t_R = 1.71 min (3.0 minute run).
70		Prepared from **ABM-14**, **L-22**, and **ULM-1** (2S,4R)-1-[(2S)-2-(3-{2-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]ethoxy}propanamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-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**)

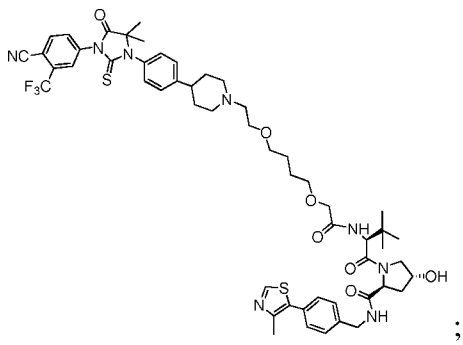
[0672] To a stirred solution of 2-(3-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}propoxy)acetic acid (**L-17**, 300 mg, 0.90 mmol) in N,N-dimethylformamide (5 mL) was added EDCI (350 mg, 1.83 mmol), HOBt (240 mg, 1.78 mmol) and DIEA (350 mg, 2.71 mmol) at rt. The resulting solution was stirred at rt for 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**

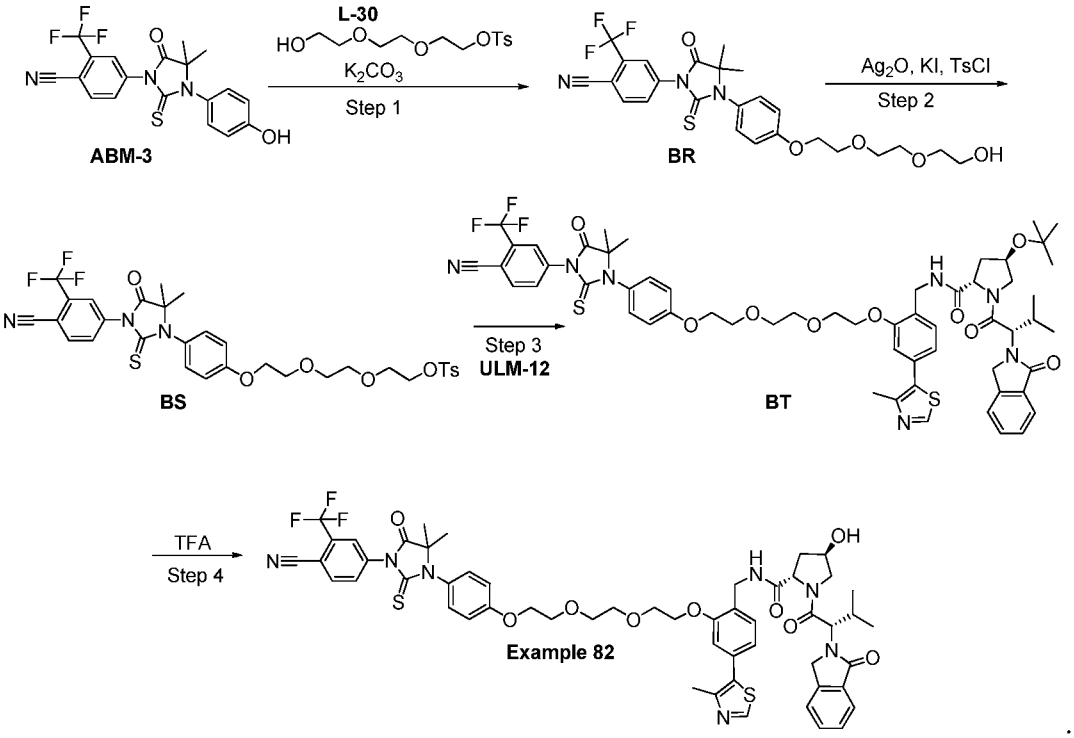
[0677] 

;

[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.

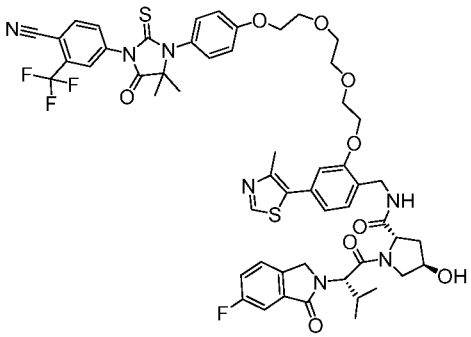
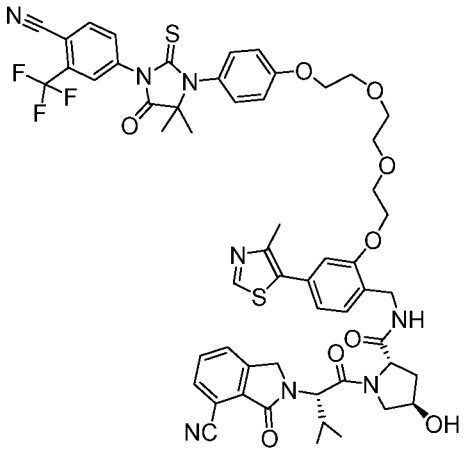
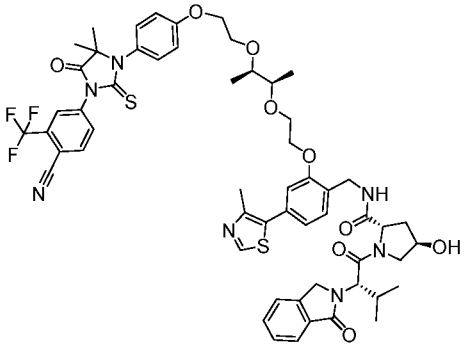
[0686] Step 4: Synthesis of (2S,4R)-N-{[2-(2-{2-[2-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenoxy)ethoxy]ethoxy}ethoxy)-4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}-4-hydroxy-1-[(2S)-3-methyl-2-(1-oxo-2,3-dihydro-1H-isoindol-2-yl)butanoyl]pyrrolidine-2-carboxamide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

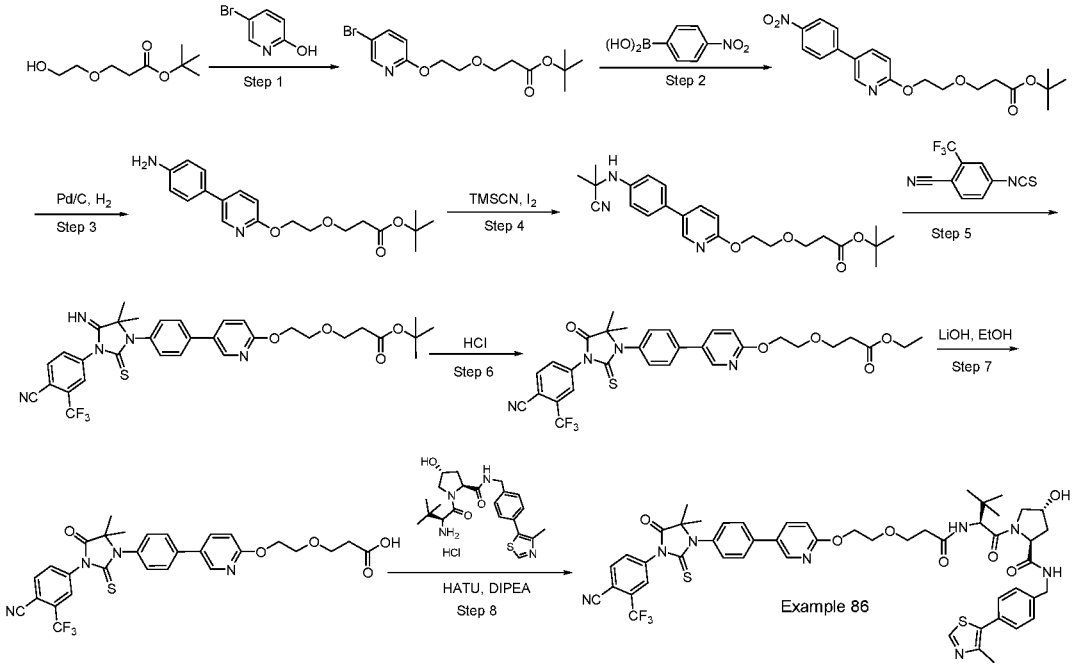
[0688] Examples 83-85 were synthesized according to similar procedure described for synthesis of Example 82, by using corresponding starting materials and intermediates.

[0689] Table 6. Exemplary Compounds.

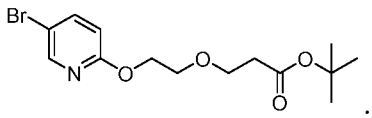
Ex #	Structure	Compound name and Analytical data

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.

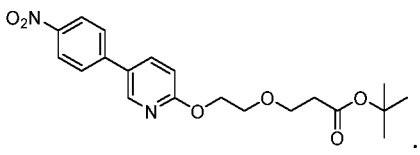


[0691] Step 1: Synthesis of tert-butyl 3-{2-[(5-bromopyridin-2-yl)oxy]ethoxy}propanoate:



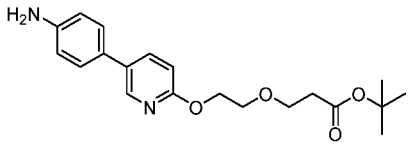
[0692] To a stirred solution of 5-bromopyridin-2-ol (3.0 g, 17.24 mmol), tert-butyl 3-(2-hydroxyethoxy)propanoate (3.3 g, 17.19 mmol) and triphenylphosphine (6.8 g, 25.81 mmol) in tetrahydrofuran (120.0 mL) was added diethyl diazene-1,2-dicarboxylate (4.49 g, 25.78 mmol) dropwise at 0 °C under an atmosphere 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^+].

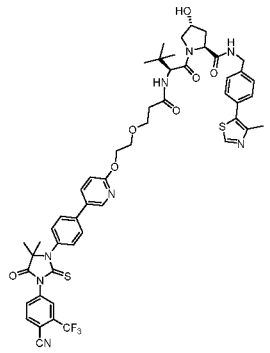
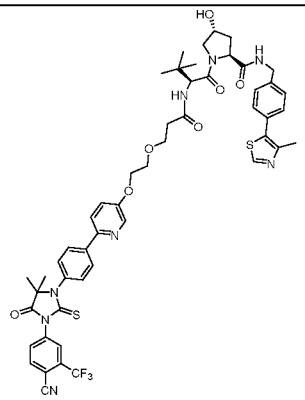
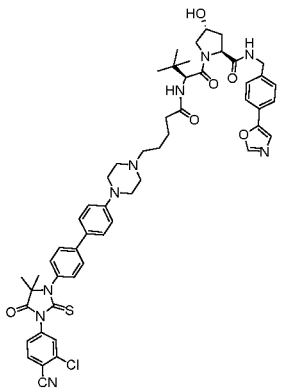
[0697] Example 86 was synthesized from tert-butyl 3-(2-{[5-(4-aminophenyl)pyridin-2-yl]oxy}ethoxy)propanoate, according to chemistry highlighted above (steps 4-8), utilizing similar procedures described for the similar chemistry carried out for the synthesis of examples 67, 75, 103, by using corresponding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

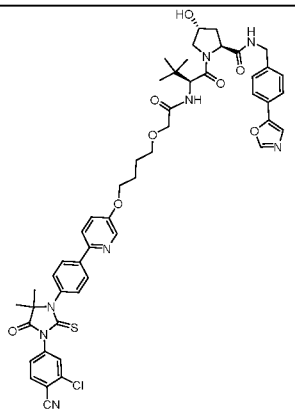
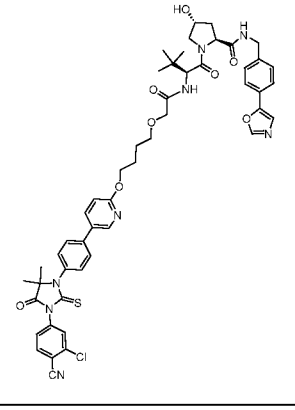
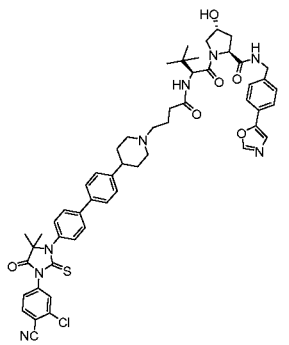
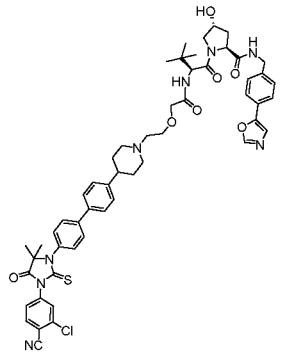
[0698] Example 90 was synthesized according to similar procedures described for the synthesis of examples 86, by using corresponding starting materials and intermediates.

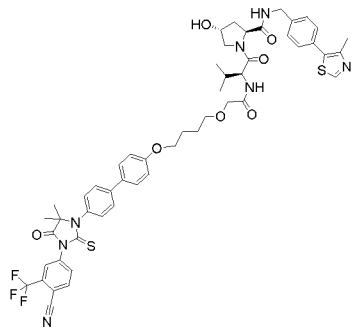
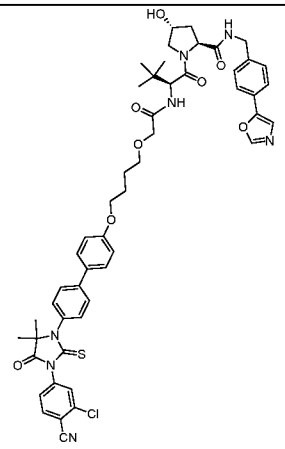
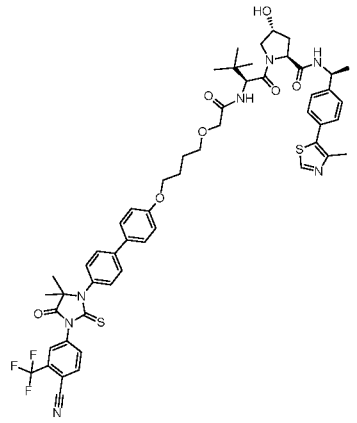
[0699] Examples 88, 91-92 were synthesized according to similar procedures described for the synthesis of examples 80, 75, 103, by using corresponding starting materials and intermediates.

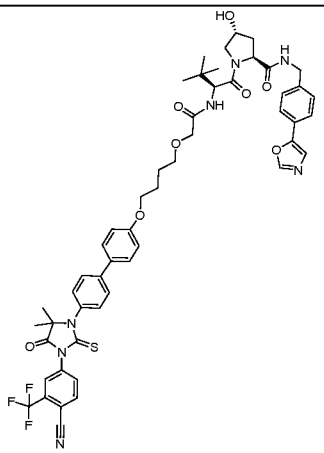
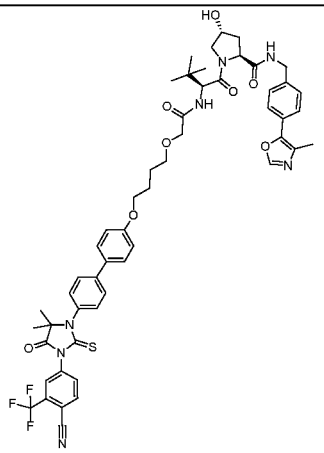
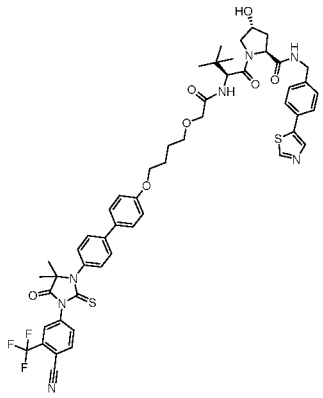
[0700] Examples 87, 89, 93-102, 104-134, 136-142, 146-149 were synthesized according to similar procedures described for the synthesis of examples 75, by using corresponding starting materials and intermediates.

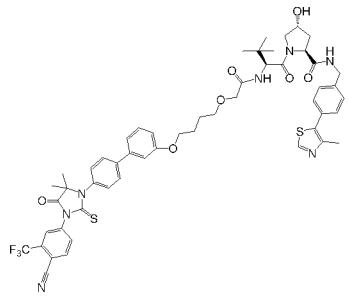
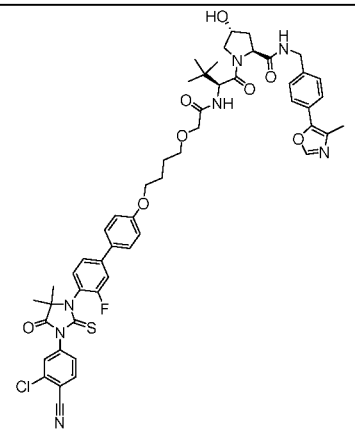
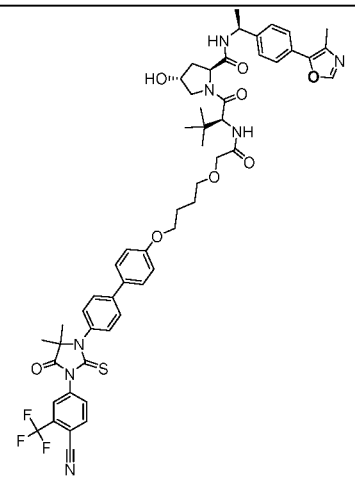
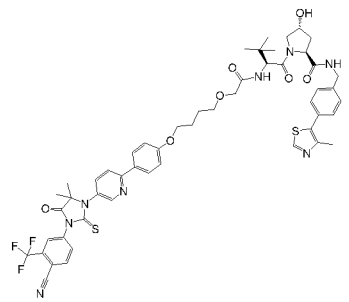
[0701] Table 7. Exemplary Compounds.

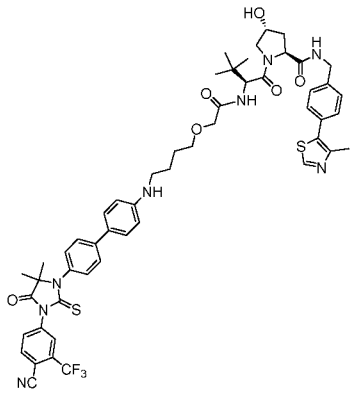
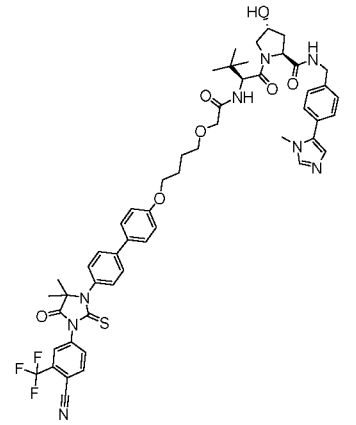
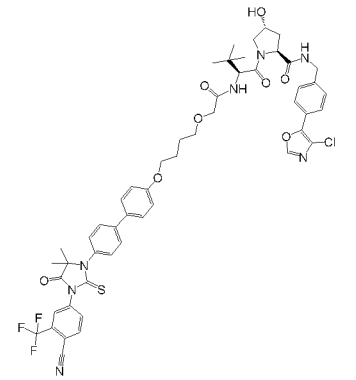
Ex #	Structure	Compound name and Analytical data
86		(2S,4R)-1-[(2S)-2-[3-(2-{[5-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)pyridin-2-yl]oxy}ethoxy)propanamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{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^+]

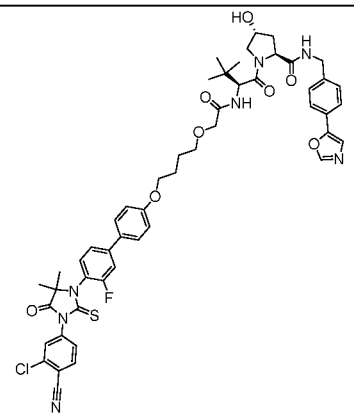
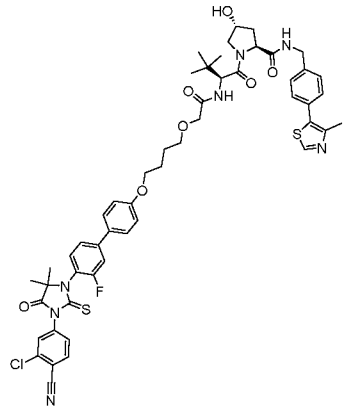
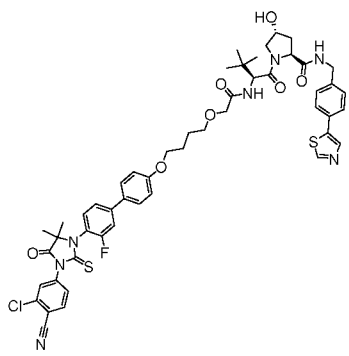
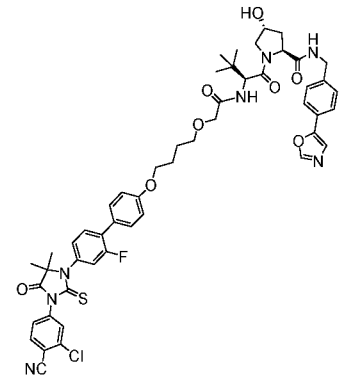
89		(2S,4R)-1-[(2S)-2-(2-{4-[(6-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}pyridin-3-yl)oxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD):δ8.38 (s, 1 H), 8.21 (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^+]

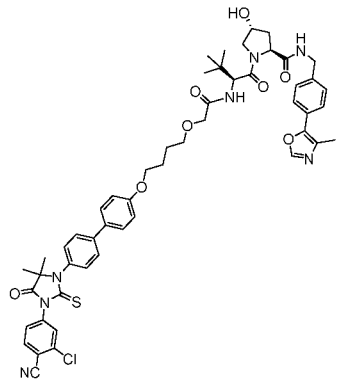
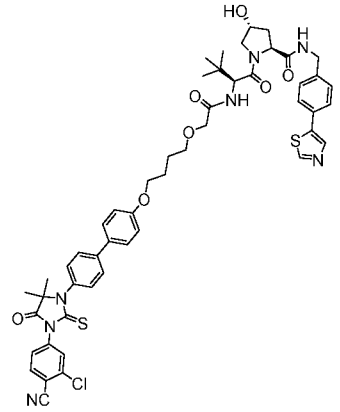
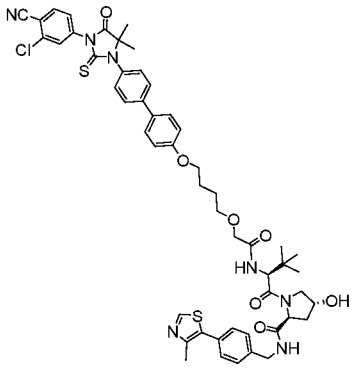
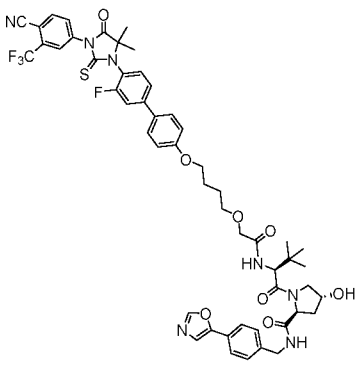
93		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3-methylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.83 (s, 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^+]

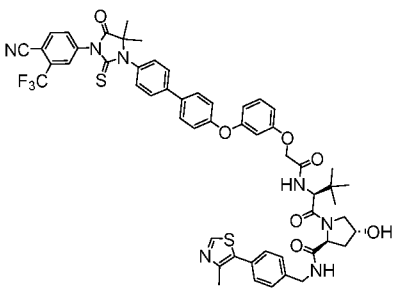
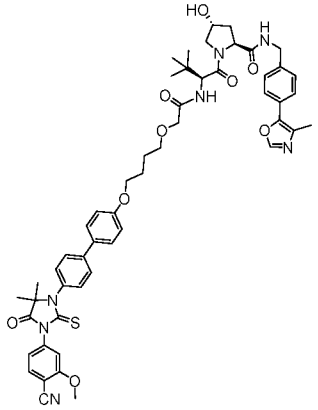
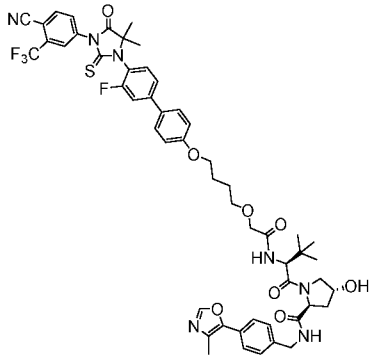
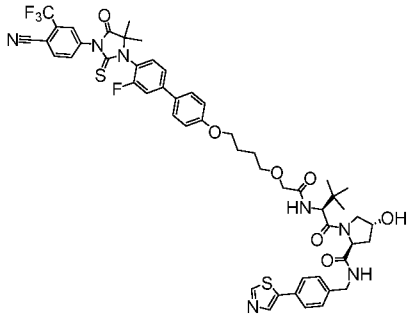
96		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.23-8.15 (m, 3H) , 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^+]

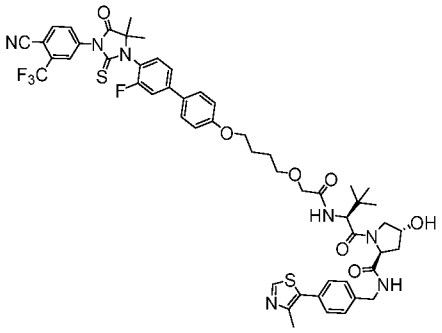
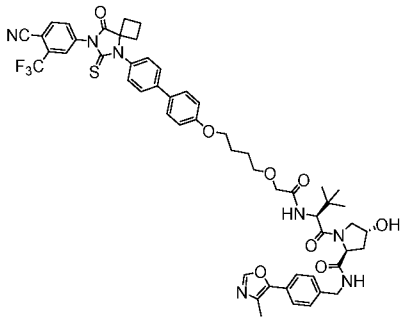
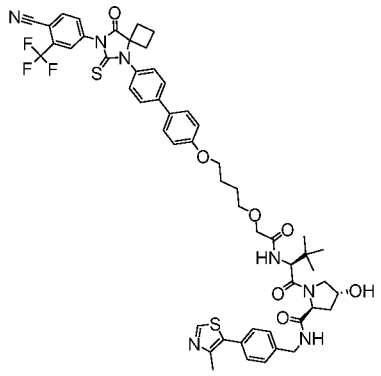
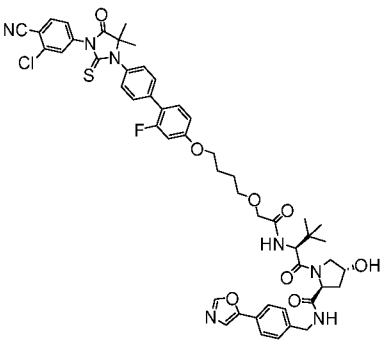
99		(2S,4R)-1-[(2S)-2-(2-{4-[3-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.82 (s, 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

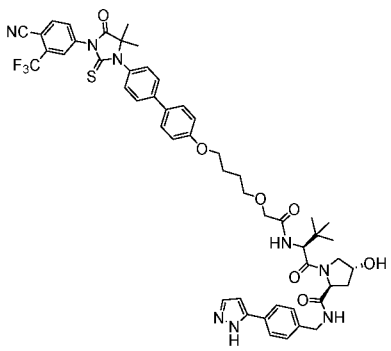
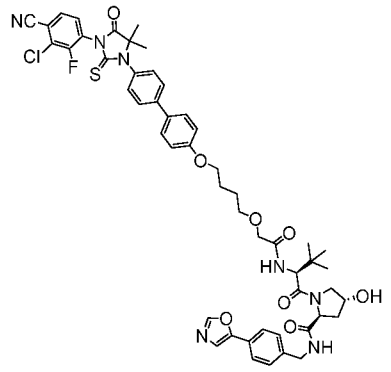
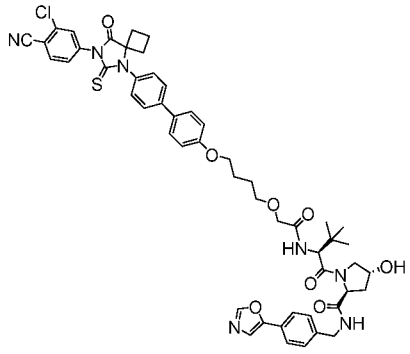
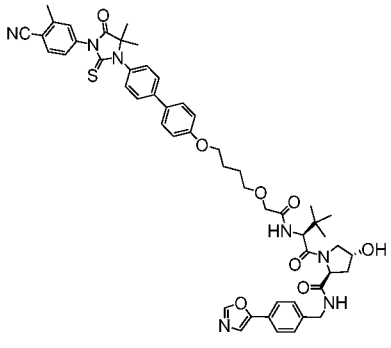
		(s, 9H); LC-MS (ES$^+$): *m/z* 1025.55 [MH$^+$]
103		(2S,4R)-1-[(2S)-2-[2-(4-{[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenyl]amino}butoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H 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 ^{1}H 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 ^{1}H 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$^+$]

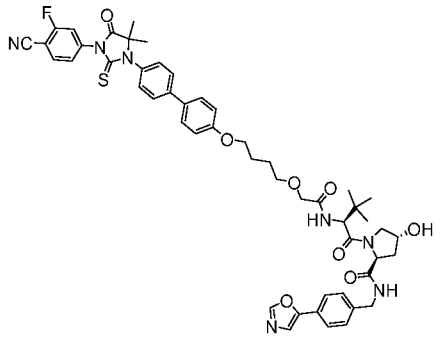
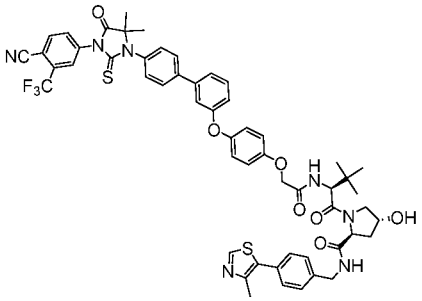
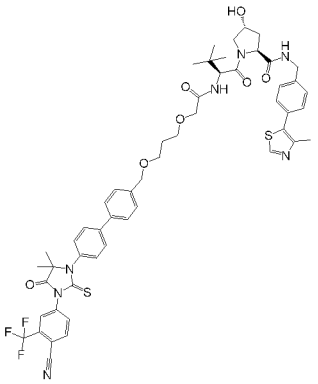
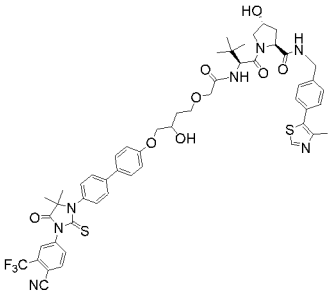
106		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]-3-fluorophenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (s, 1H), 8.00 (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^+]

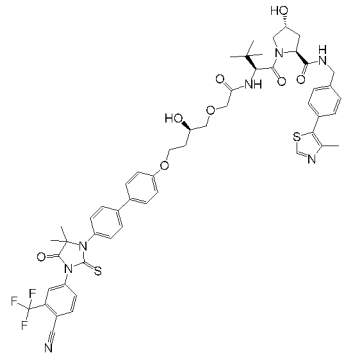
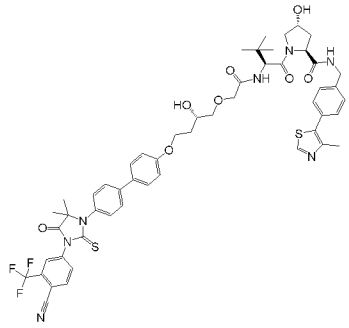
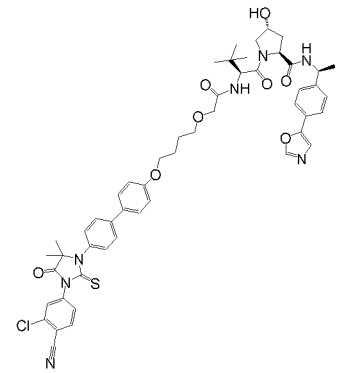
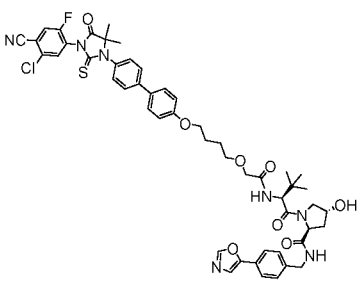
110		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD): δ 8.08 (s, 1H), 7.77-7.72 (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^+]

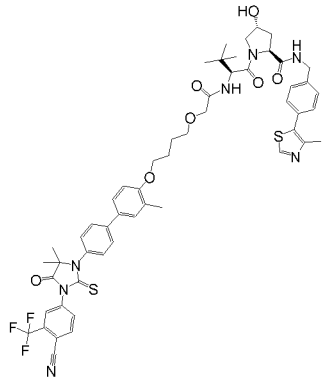
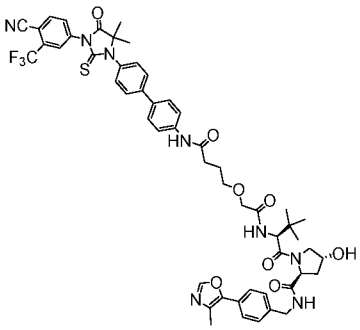
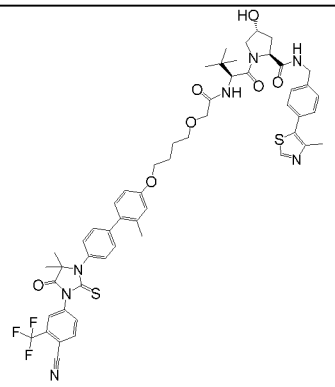
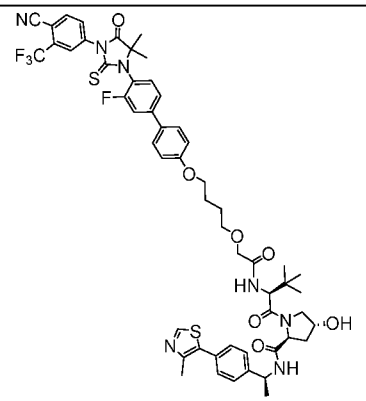
114		(2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]phenoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD):δ8.81 (s, 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^+],

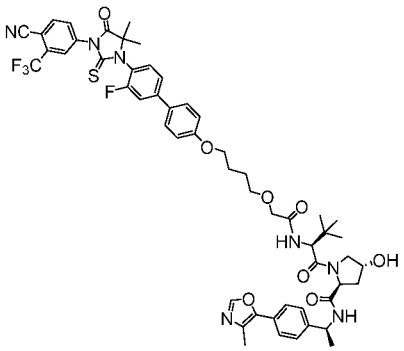
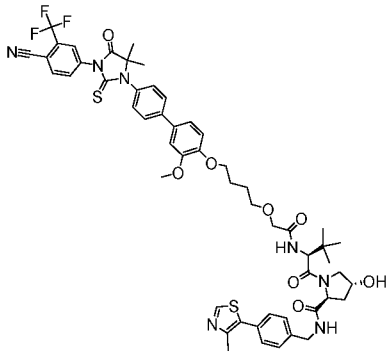
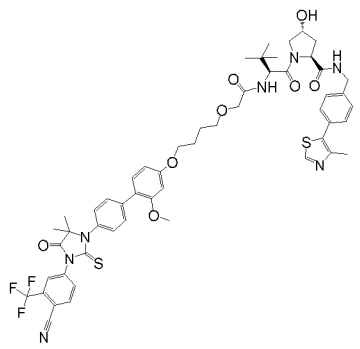
118		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-3-fluorophenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO) δ 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$^+$]

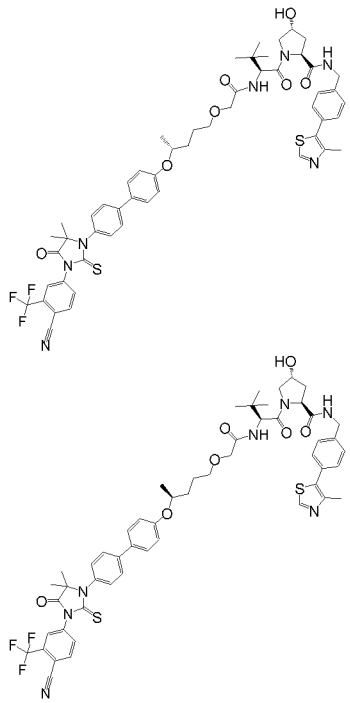
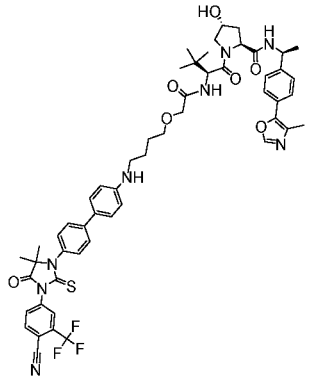
122		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1H-pyrazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): 8.25-8.15 (m, 2H), 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^+]

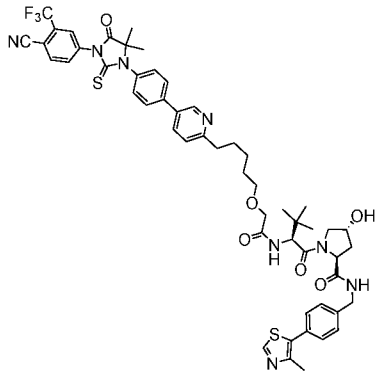
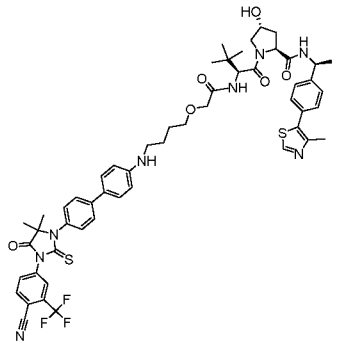
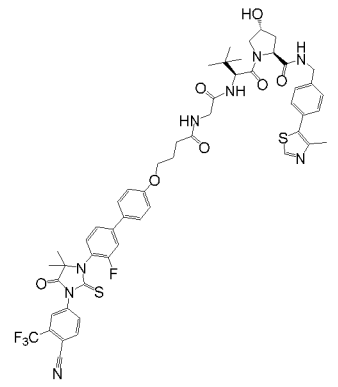
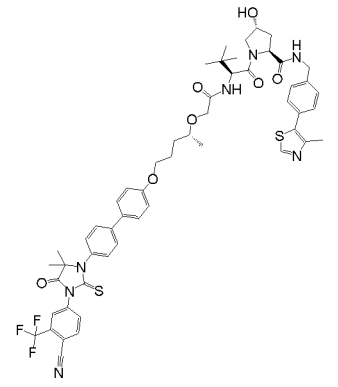
126		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(4-cyano-3-fluorophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]phenyl}phenoxy)butoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, DMSO) δ 8.60 (t, *J* = 6.0 Hz, 1H), 8.40 (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$^+$]

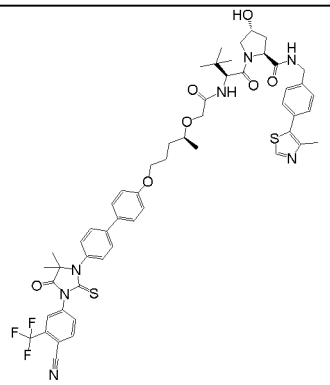
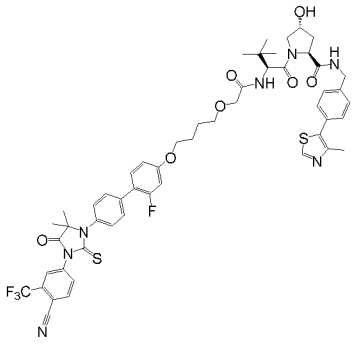
130		(2S,4R)-1-[(2S)-2-{2-[(2R)-4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]-2-hydroxybutoxy]acetamido}-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): 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^+]

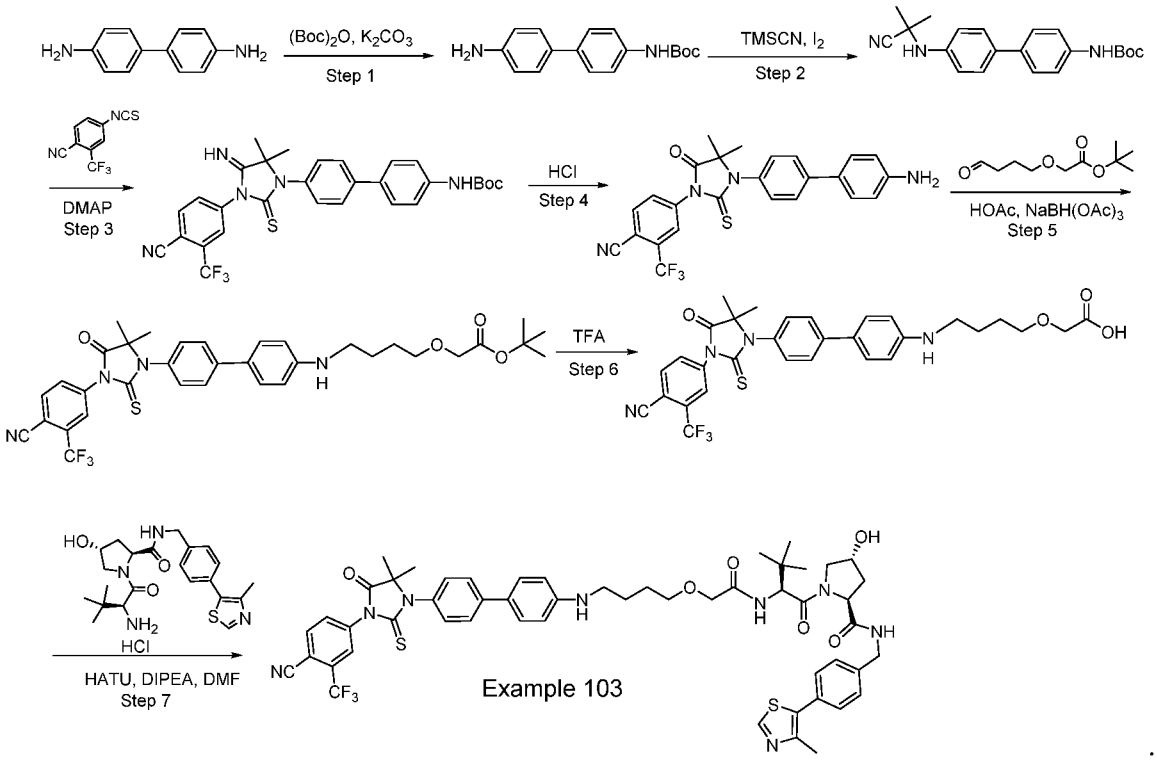
141, 142		(2S,4R)-1-[(2S)-2-(2-{[(4S)-4-[4-(4-{3-[4-cyano-3-trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]pentyl]oxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (2S,4R)-1-[(2S)-2-(2-{[(4R)-4-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-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,

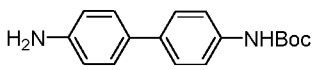
		*J* = 8.4 Hz, 1H), 7.72-7.70 (d, *J* = 8.8 Hz, 2H), 7.58-7.55 (d, *J* = 8.8 Hz, 2H), 7.47-7.38 (m , 6H), 7.01-6.99 (d, *J* = 4.8 Hz, 2H), 4.86 (s, 1H), 4.58-4.50 (m, 3H), 4.35-4.31 (m, 1H), 4.09-4.05 (m, 3H), 3.86-3.81 (m, 3H), 3.71-3.61 (m, 1H), 2.47 (s, 3H), 2.37-2.23 (m, 1H), 2.11-2.09 (m, 1H), 2.02-1.87 (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:

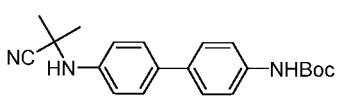


[0704] Step 1: Synthesis of tert-butyl N-[4-(4-aminophenyl)phenyl]carbamate:



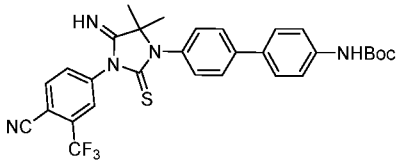
[0705] To a stirred solution of 4-(4-aminophenyl)aniline (15.0 g, 81.42 mmol) in a mixed solvent of N,N-dimethylformamide / tetrahydrofuran /water (v/v/v = 100/300/50 mL) was added potassium carbonate (9.5 g, 68.74 mmol) and di-tert-butyl dicarbonate (13.67 g, 62.63 mmol) at rt. The resulting mixtire 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^+].

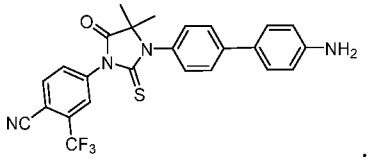
[0708] Step 3: Synthesis of tert-butyl N-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-4-imino-5,5-dimethyl-2-sulfanylideneimidazolidin-1-yl}phenyl)phenyl]carbamate:



.

[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^+].

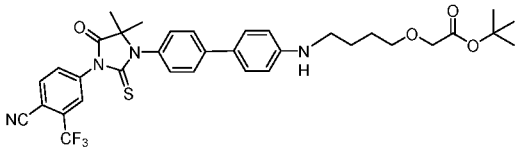
[0710] Step 4: Synthesis of 4-{3-[4-(4-aminophenyl)phenyl]-4,4-dimethyl-5-oxo-2-sulfanylideneimidazolidin-1-yl}-2-(trifluoromethyl)benzonitrile:



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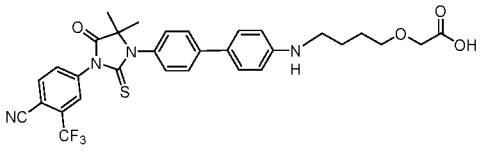
[0711] To a stirred solution of tert-butyl N-[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-4-imino-5,5-dimethyl-2-sulfanylideneimidazolidin-1-yl}phenyl)phenyl]carbamate (2.0 g) in methanol (20 mL) was added hydrogen chloride (3 N solution in water, 5 mL) at rt. The resulting solution was stirred for 2 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:



[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.

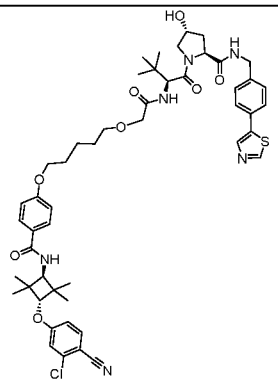
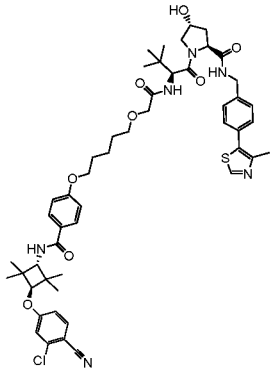
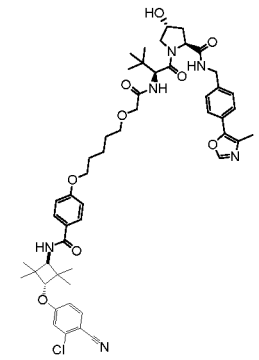
[0717] This compound was synthesized from 2-(4-{[4-(4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenyl]amino}butoxy)acetic acid and (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide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

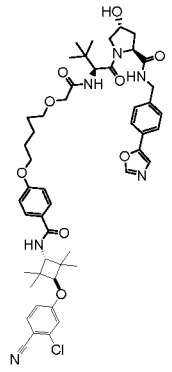
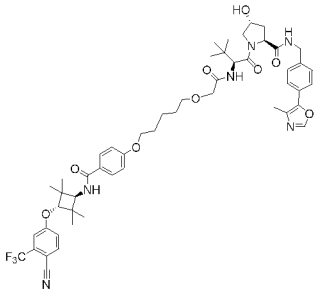
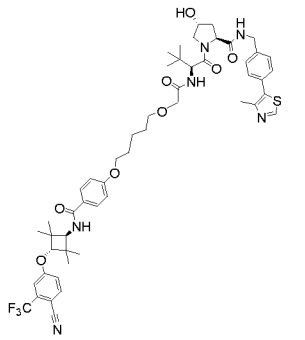
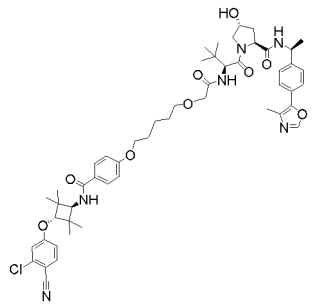
[0718] Synthesis of tert-butyl 2-(4-oxobutoxy) acetate:

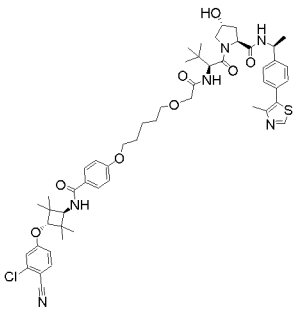
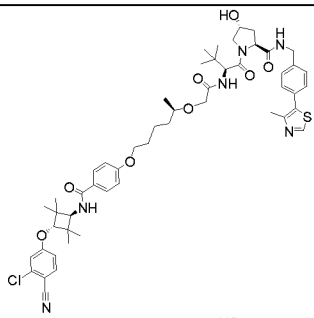
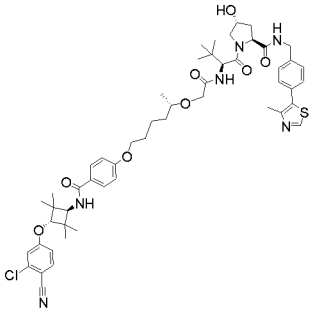
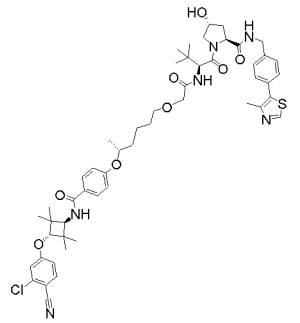
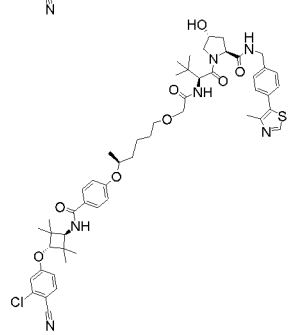


[0719] To a stirred solution of tert-butyl 2-(4-hydroxybutoxy)acetate (1.0 g, 4.90 mmol) in dichloromethane (10 mL) was added (1,1,1-triacetoxy)-1,1-dihydro-1,2-benziodoxol-3(1H)-one (2.7 g, 6.37 mmol) at rt. The resulting mixture was stirred for 12h at rt. The reaction mixture was then diluted with 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.

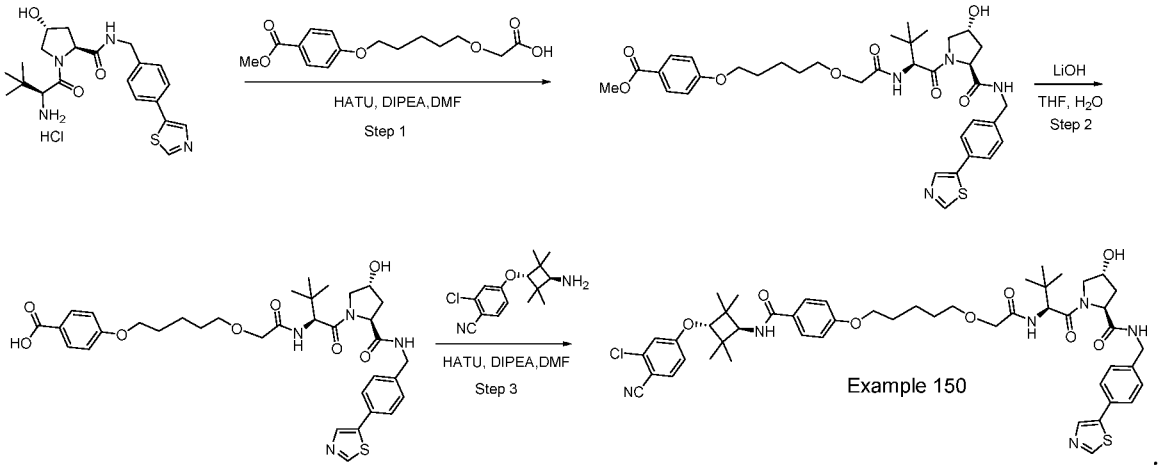
Ex #	Structure	Compound name and Analytical data
150		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{[5-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)pentyl]oxy}acetamido)butanoyl]-4-hydroxy-N-{[4-(1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, $CDCl_3$): 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^+]

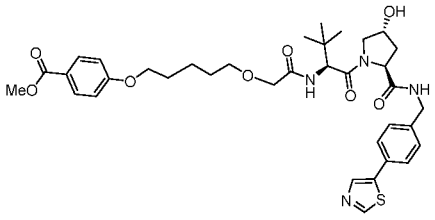
157		(2S,4R)-1-[(2S)-3,3-dimethyl-2-(2-{[5-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)pentyl]oxy}acetamido)butanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 8.90 (s, 1 H), 7.85-7.00 (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:



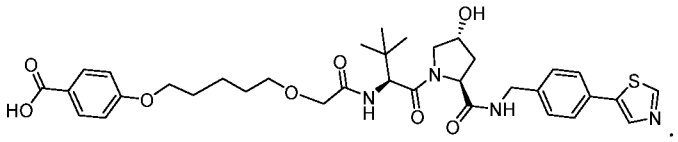
[0722] Step 1: Synthesis of methyl 4-{[5-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)pentyl]oxy}benzoate:



[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

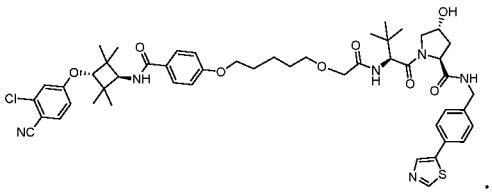
mL) was added HATU (2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (203 mg, 0.54 mmol) at 0 °C. The resulting mixture was allowed to warm up to rt and stirred at rt for 20 min. TLC and LC-MS showed formation of the desired product. The mixture was partitioned between 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:



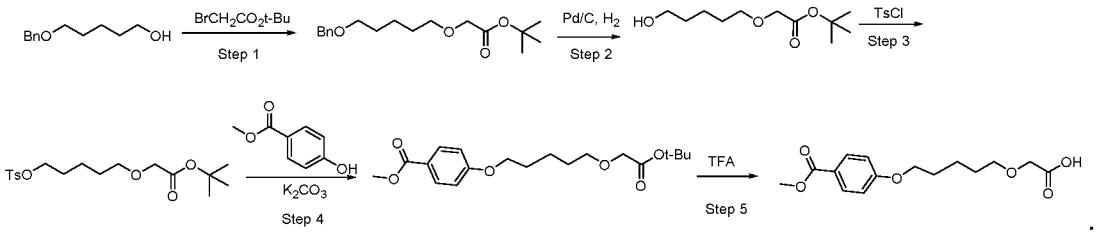
[0725] To a stirred solution of methyl 4-{[5-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)pentyl]oxy}benzoate (150 mg, 0.22 mmol) in a mixed solvents of tetrahydrofuran (4 mL)-water (2 mL)-methanol (1 ml) 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:

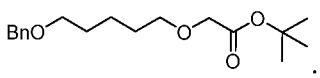


[0727] To a stirred mixture of 4-{[5-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)pentyl]oxy}benzoic acid (110 mg, 0.16 mmol), 2-chloro-4-[trans-3-amino-2,2,4,4-tetramethylcyclobutoxy]benzonitrile hydrogen 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



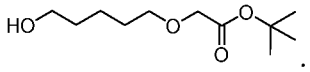
[0729] Step 1: Synthesis of tert-butyl 2-{[5-(benzyloxy)pentyl]oxy}acetate:



[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

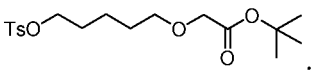
31.6%) as light yellow oil. LC-MS: (ES^+): m/z 331.10 [$M+Na^+$], ^1H NMR (400 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.63-1.67 (m, 6H), 3.46-3.53 (m, 4H), 4.10 (s, 2H), 4.50 (s, 2H), 7.28-7.34 (m, 5H).

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



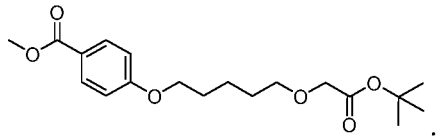
[0732] To a stirred solution of tert-butyl 2-{[5-(benzyloxy)pentyl]oxy}acetate (5 g, 16.2 mmol) in ethanol (100 ml) under a nitrogen atmosphere was added palladium on carbon (10%, 600 mg) at rt. The resulting mixture was stirred at 50°C overnight under hydrogen atmosphere (hydrogen balloon). TLC showed 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] 

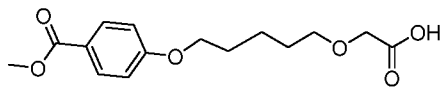
[0735] To a stirred solution of tert-butyl 2-[(5-hydroxypentyl)oxy]acetate (2.5 g, crude) and triethylamine (3.5 g, 34.5 mmol) in anhydrous methylene dichloride (50 mL) was added a solution of 4-toluenesulfonyl chloride (2.7 g, 13.8 mmol) in anhydrous methylene dichloride (8 mL) drop wise at 0 °C. The 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:

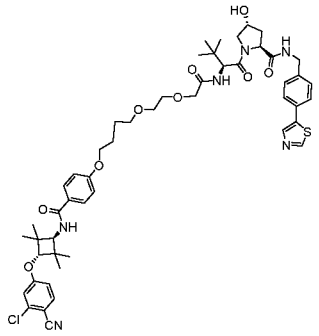
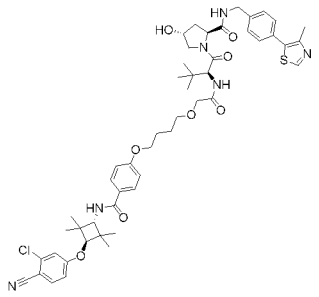
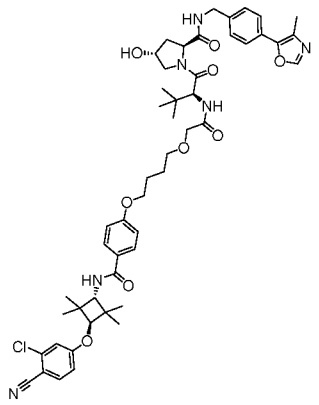
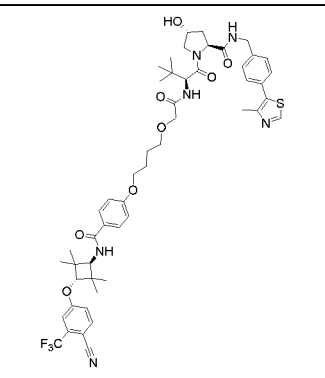
[0740]  .

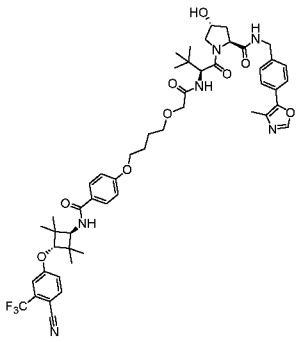
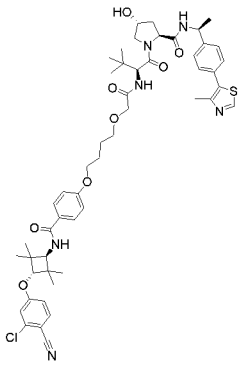
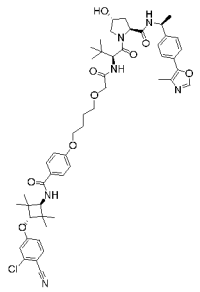
[0741] To a stirred solution of methyl 4-({5-[2-(tert-butoxy)-2-oxoethoxy]pentyl}oxy)benzoate (300 mg, 0.85 mmol) in DCM (4 mL) was added and TFA (2 ml) at rt, the resulting solution was stirred at room temperature for 1 h. TLC showed formation of the desired product. The solvent was evaporated to afford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

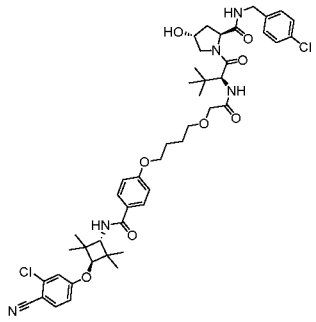
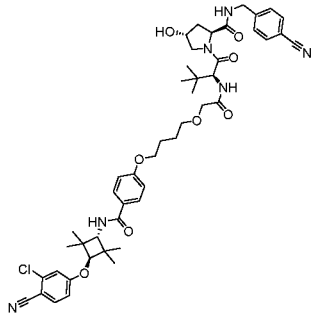
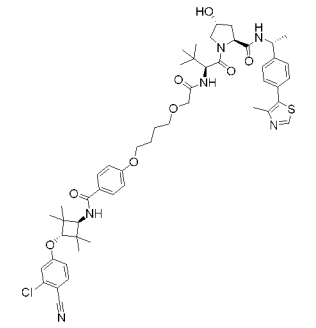
[0742] Examples 151-157 were synthesized according to similar procedure described for synthesis of example 150, by using corresponding starting materials and intermediates.

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

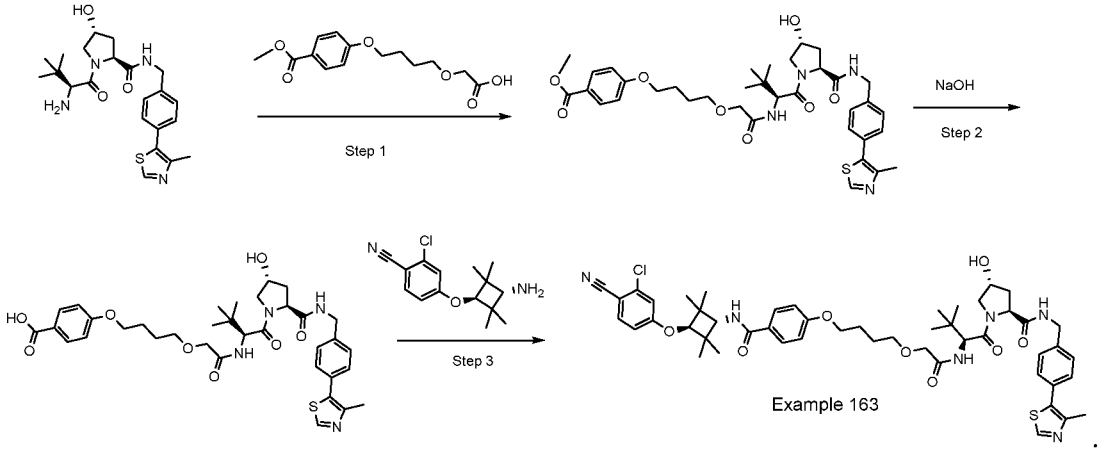
Ex #	Structure	Compound name and Analytical data

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

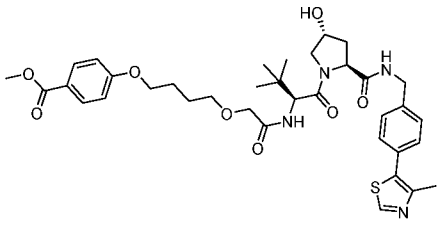
		[MH$^+$]
166		(2S,4R)-1-[(2S)-3,3-dimethyl-2-{2-[4-(4-{[trans-3-[4-cyano-3-(trifluoromethyl)phenoxy]-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)butoxy]acetamido}butanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD):8.09 (s, 1H),7.89 (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:

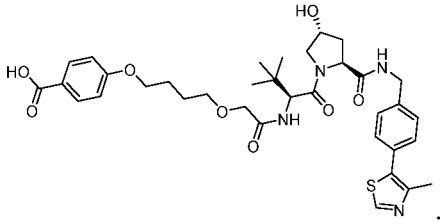


[0745] Step 1: synthesis of methyl 4-[4-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)butoxy]benzoate



[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:

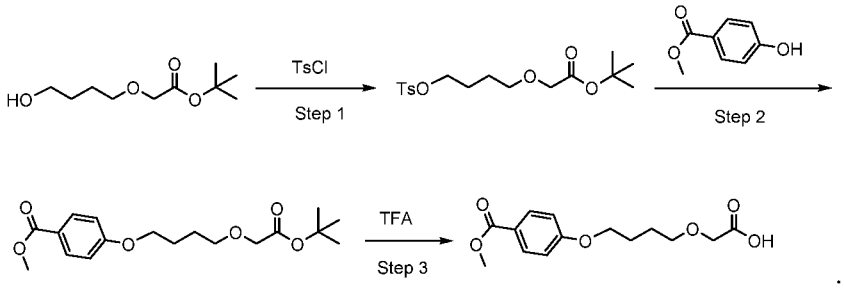


[0748] To a stirred solution of methyl 4-[4-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)butoxy]benzoate (42.4 mg, 61.0 µmol) in methanol (2.0 mL) was added 1 M NaOH in water (0.5 mL, 12.5 mmol) 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^+].

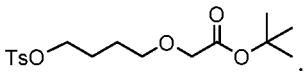
[0749] Step 3: Synthesis of example 163:

[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.

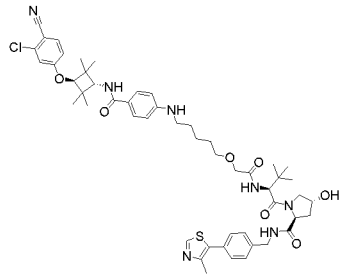
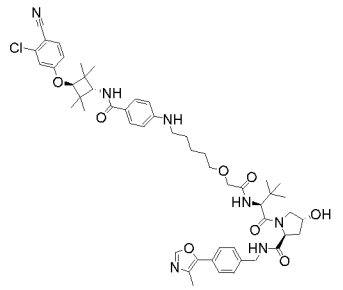
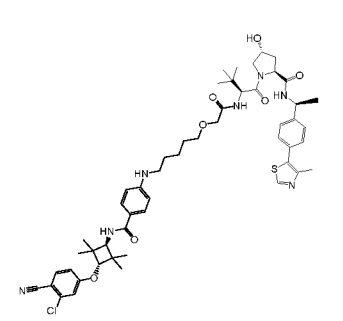
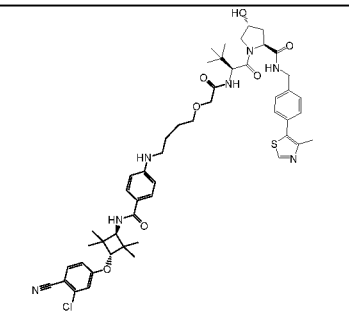
[0755] To a stirred mixture of methyl 4-hydroxybenzoate (27.99 mg, 184.0 µmol) and tert-butyl 2-{4-[(4-methylbenzenesulfonyl)oxy]butoxy}acetate in acetonitrile (2.0 mL) was added potassium carbonate (34.67 mg, 250.9 µmol) at rt. The reaction mixture was then stirred at 80 °C for 16 hours. LC-MS indicated 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].

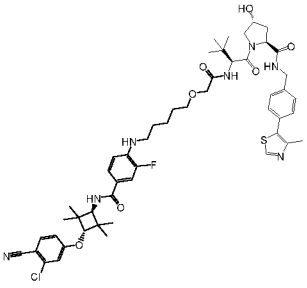
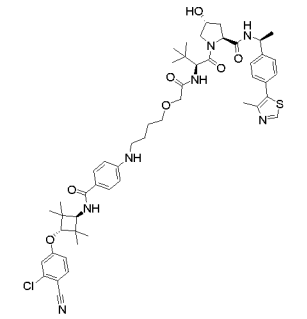
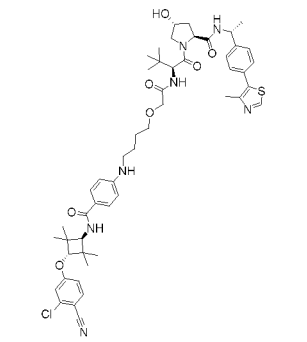
[0756] Step 3: Synthesis of Synthesis of 2-{4-[4-(methoxycarbonyl)phenoxy]butoxy}acetic acid:

[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.

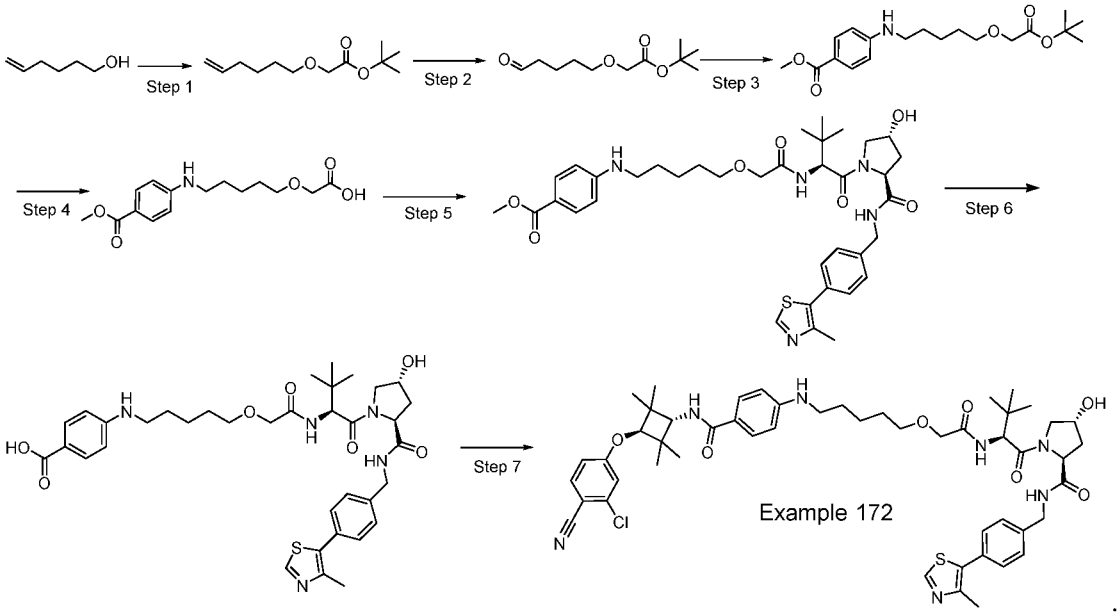
[0758] Examples 162, 164-171 were synthesized according to similar procedure described for synthesis of example 163, by using corresponding starting materials and intermediates.

[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+].

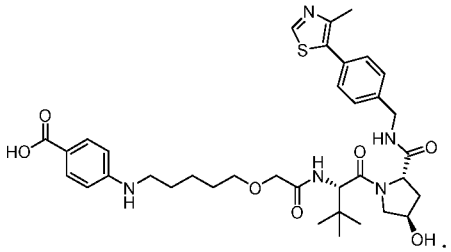
[0760] Synthesis of example 172:



[0761] Step 7: Synthesis of example 172:

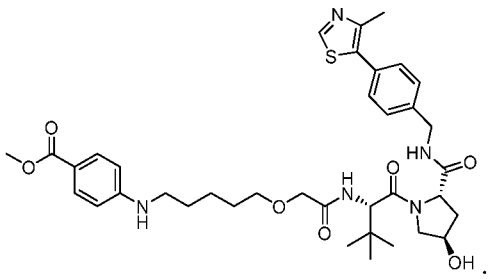
[0762] TBTU (21.5 mg, 0.067 mmol) was added to a solution of 4-{[5-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)pentyl]amino}benzoic acid (31 mg, 0.044 mmol), 2-chloro-4-[trans-3-amino-2,2,4,4-tetramethylcyclobutoxy]benzonitrile (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:



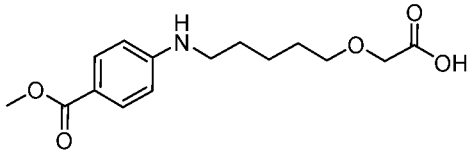
[0764] Lithium hydroxide (9.0 mg, 0.38 mmol) was added to a solution of methyl 4-{[5-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)pentyl]amino}benzoate (96 mg, 0.14 mmol) in a mixed solvent of THF/water/methanol (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.



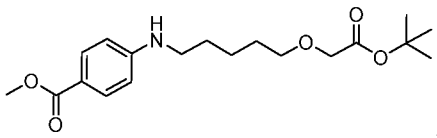
[0766] TBTU (81.5 mg, 0.25 mmol) was added to a solution of 2-[(5-{[4-(methoxycarbonyl)phenyl]amino}pentyl)oxy]acetic acid (50.0 mg, 0.17 mmol), (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (72.8 mg, 0.17 mmol) in DMF (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:



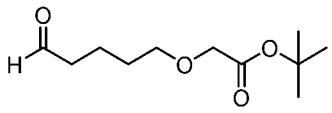
[0768] Trifluoroacetic acid (2.63 mL, 34.5 mmol) was added to a solution of methyl 4-{[5-(2-methoxy-2-oxoethoxy)pentyl]amino}benzoate (270 mg, 0.7682 mmol) in DCM (3.00 ml) at rt. The resulting mixture was stirred at 45 °C for 2h. The reaction mixture was then concentrated under reduced pressure to give 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^+]

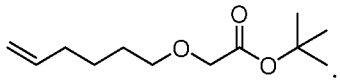
[0771] Step 2: Synthesis of tert-butyl 2-[(5-oxopentyl)oxy]acetate:



[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:

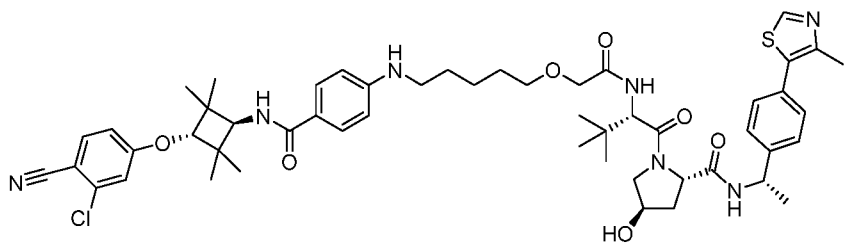


[0774] Tetrabutylammonium hydrogen sulfate (677.7 mg, 2.0 mmol) was added to a mixture of sodium hydroxide (23.9 g, 599 mmol) in water (20.0 mL) and toluene (20.00 ml) at 20 °C. To this mixture was added hex-5-en-1-ol (2.00 g, 20.0 mmol), the resulting mixture was stirred at 20 °C for 1h. The reaction 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.

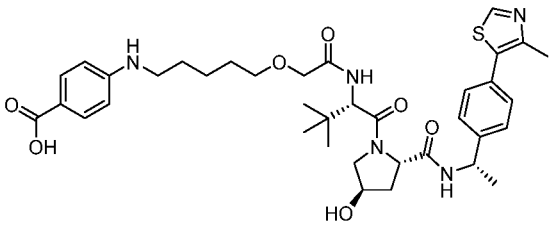
[0776] Alternatively, steps 5-7 of example 174 is synthesized as following:

[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:



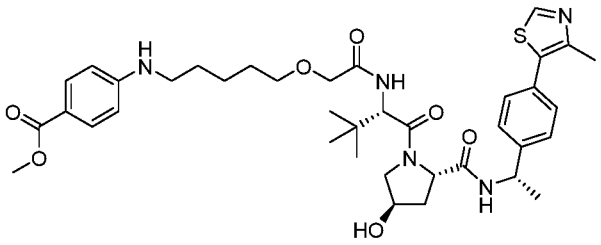
[0778] A solution of 4-((5-(2-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl) ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)pentyl) amino)benzoic acid (1.17 g, 1.65 mmol) in methylene chloride (10 mL) was charged with HATU (688 mg, 1.81 mmol) and 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+].

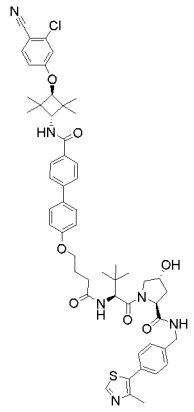
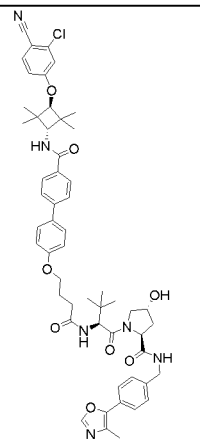
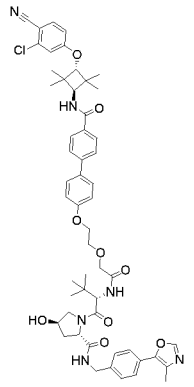
[0781] Step 5: Synthesis of methyl 4-((5-(2-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)pentyl)amino)benzoate.

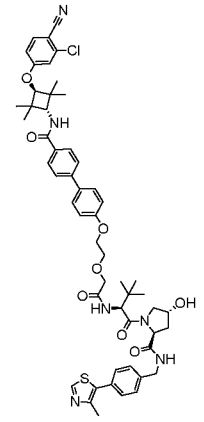


[0782] A solution of 2-((5-((4-(methoxycarbonyl)phenyl)amino)pentyl)oxy)acetic acid (1.68 g, 5.68 mmol) and (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide hydrochloride (2.73 g, 5.68 mmol) in methylene chloride (15 mL) was 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.

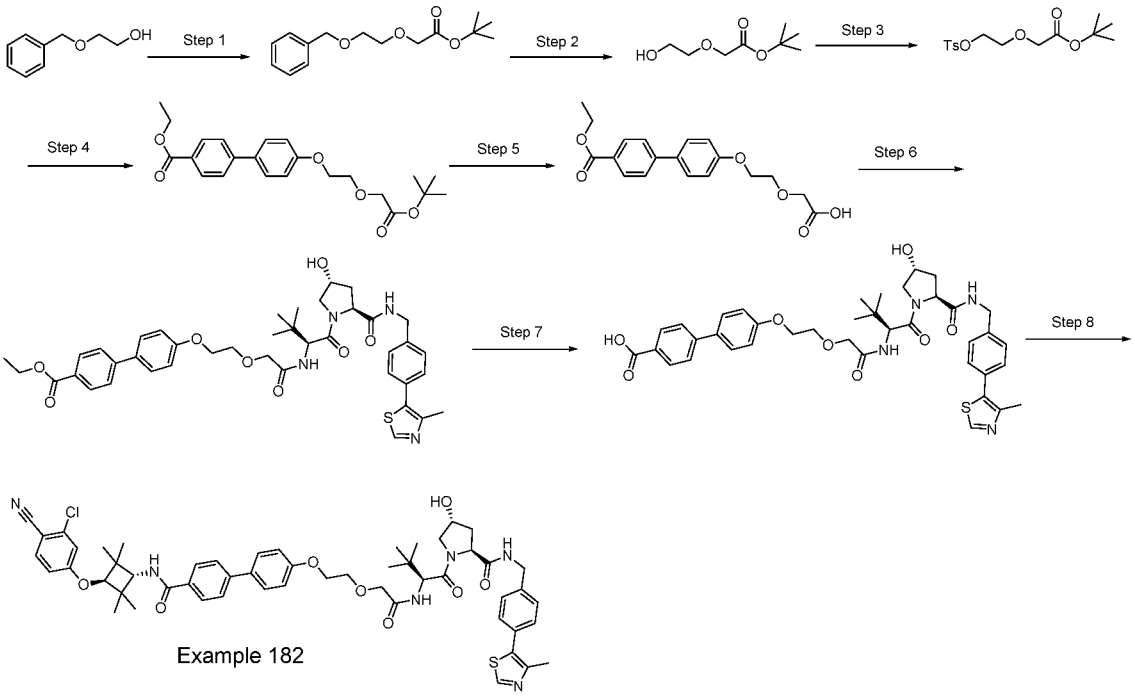
Ex#	Structure	Compound name and Analytical data

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:

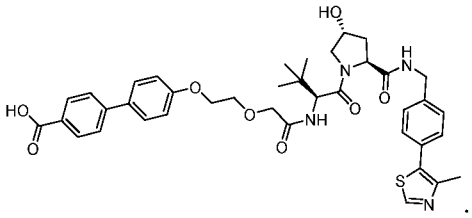


[0786] Step 8: Synthesis of example 182

[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

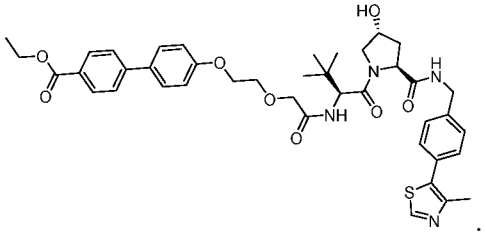
mixture was stirred at rt for 10 minutes. The reaction mixture was then charged with 2-chloro-4-[trans-3-amino-2,2,4,4-tetramethylcyclobutoxy]benzonitrile (34.0 mg, 122 μmol). The reaction was stirred at rt for 30 minutes. The reaction was monitored by LC-MS, which indicated completion of reaction. The 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:



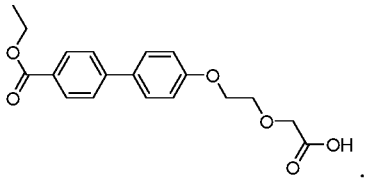
[0789] To a stirred solution of ethyl 4-{4-[2-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)ethoxy]phenyl}benzoate (188.4 mg, 248 μmol) in methanol (2.0 mL) was added 1 M NaOH in water (0.5 mL, 12.5 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:



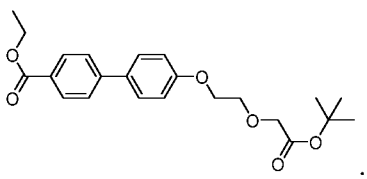
[0791] To a stirred solution of 2-(2-{4-[4-(ethoxycarbonyl)phenyl]phenoxy}ethoxy)acetic acid (100 mg, 290.3 µmol) and (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-[(1S)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide hydrochloride (135.5 mg, 290.3 µmol) in Dichloromethane (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:



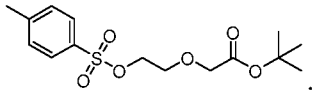
[0793] To a stirred solution of ethyl 4-(4-{2-[2-(tert-butoxy)-2-oxoethoxy]ethoxy}phenyl)benzoate (245 mg, 611 µmol) in methylene chloride (1.0 mL) was added trifluoroacetic acid (1.0 mL, 12.9 mmol). The reaction mixture was stirred at rt for 30 minutes. The reaction was monitored by LC-MS, which indicated 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:



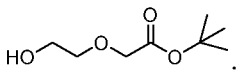
[0795] To a stirred mixture of ethyl 4'-hydroxy-[1,1'-biphenyl]-4-carboxylate (146.6 mg, 605.3 µmol) and tert-butyl 2-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}acetate (200.0 mg, 605.3 µmol) in acetonitrile (2.0 mL) was added potassium carbonate (125.4 mg, 907.9 µmol) at rt. The reaction mixture was then 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:



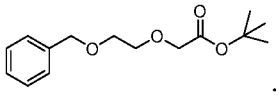
[0797] To a stirred solution of tert-butyl 2-(2-hydroxyethoxy)acetate (1.44 g, 0.19 mmol) in methylene chloride (10.0 mL) was added 4-methylbenzene-1-sulfonyl chloride (1.713 g, 0.21 mmol) and triethylamine (1.707 mL, 12.25 mmol) at rt. The reaction mixture was stirred at rt for 16 h. The reaction was 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:



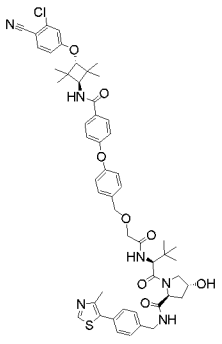
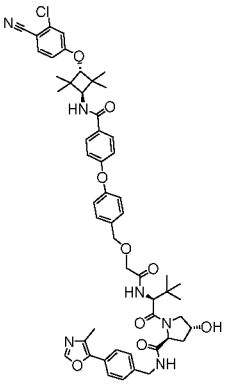
[0799] To a stirred solution of tert-butyl 2-[2-(benzyloxy)ethoxy]acetate in Ethanol (10.0 mL) was added palladium on carbon (10% wt.) (1.99 g, 1.87 mmol). The reaction mixture was evacuated and purged with H_2 gas (3 x). The reaction mixture was stirred at rt under an atmosphere of H_2 for 16 h. The 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.

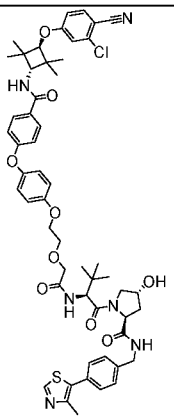
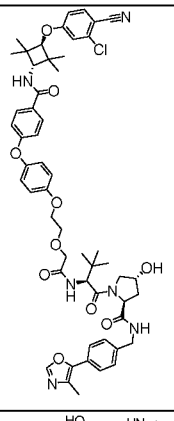
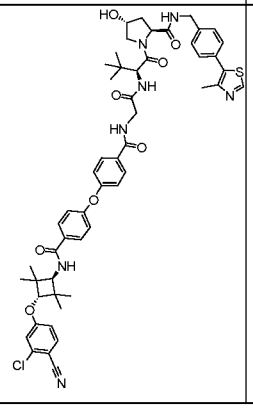
[0800] Step 1: Synthesis of tert-butyl 2-[2-(benzyloxy)ethoxy]acetate:



[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.

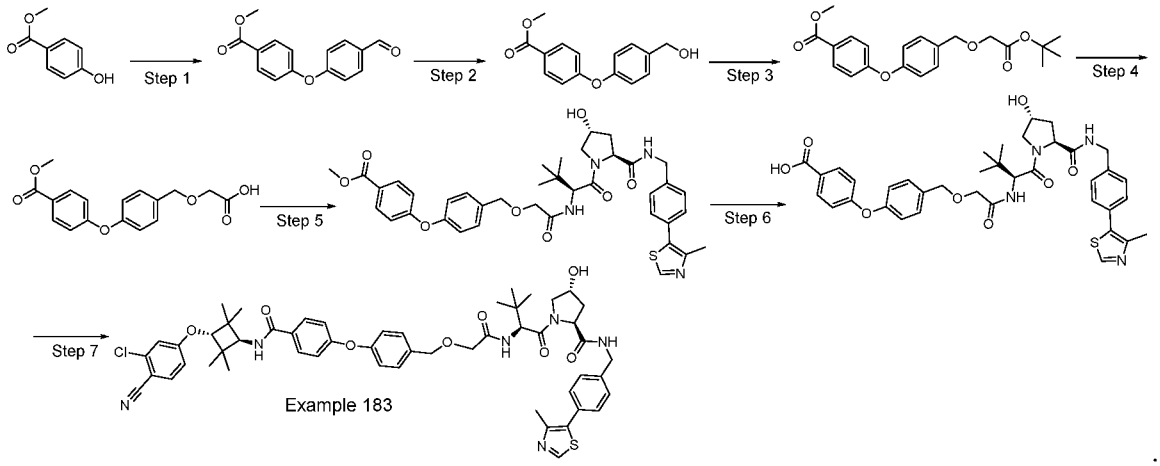
[0802] Table 12. Exemplary Compounds.

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.

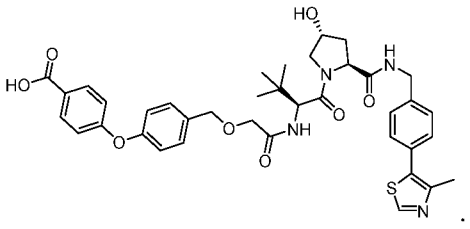
[0804] Synthesis of Example 183:



[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.

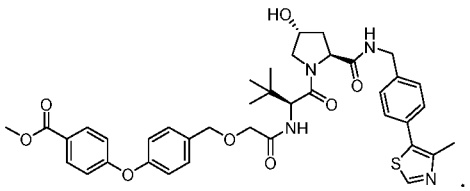
[0807] Step 6: Synthesis of 4-{4-[({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methoxy)methyl]phenoxy}benzoic acid:



[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

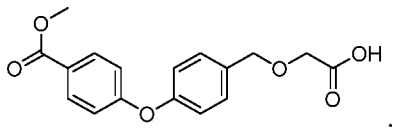
M NaOH solution in water (0.5 mL, 12.5 mmol) at rt. The reaction mixture was allowed to stir at rt for 16 hours. The reaction was monitored by LC-MS, which indicated completion of reaction. The reaction mixture was quenched with 1.0 M HCl solution in water (0.5 mL) and then concentrated under reduced 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^+].

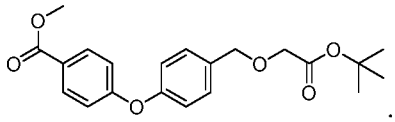
[0811] Step 4: 2-({4-[4-(methoxycarbonyl)phenoxy]phenyl}methoxy)acetic acid:



[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

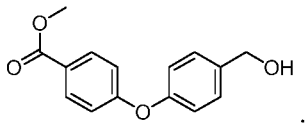
solid. This material used in next step reaction without any further purification. LC-MS (ES^+): *m/z* 339.0858 [MNa^+].

[0813] Step 3: Synthesis of methyl 4-(4-{[2-(tert-butoxy)-2-oxoethoxy]methyl}phenoxy)benzoate:



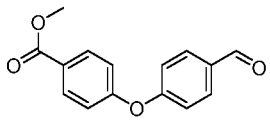
[0814] To a stirred mixture of sodium hydroxide (1.16 g, 29 mmol) in water (2.0 mL) and toluene (2.0 mL) at 20 °C was charged with tetrabutylammonium hydrogen sulfate (32.86 mg, 96.79 µmol), followed by methyl 4-[4-(hydroxymethyl)phenoxy]benzoate (250.0 mg, 967.9 µmol), the resulting mixture was stirred 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:



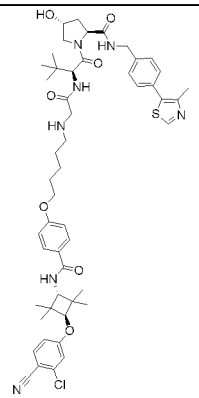
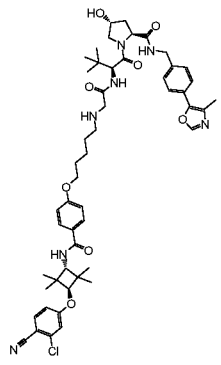
[0816] To a stirred solution of methyl 4-(4-formylphenoxy)benzoate (750.0 mg, 2.92 mmol) in methanol (2.0 mL) was added sodium borohydride (121 mg, 3.21 mmol) at rt. The reaction mixture was allowed to stir at rt for 30 min. The reaction was monitored by LC-MS, which indicated completion of reaction. 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:



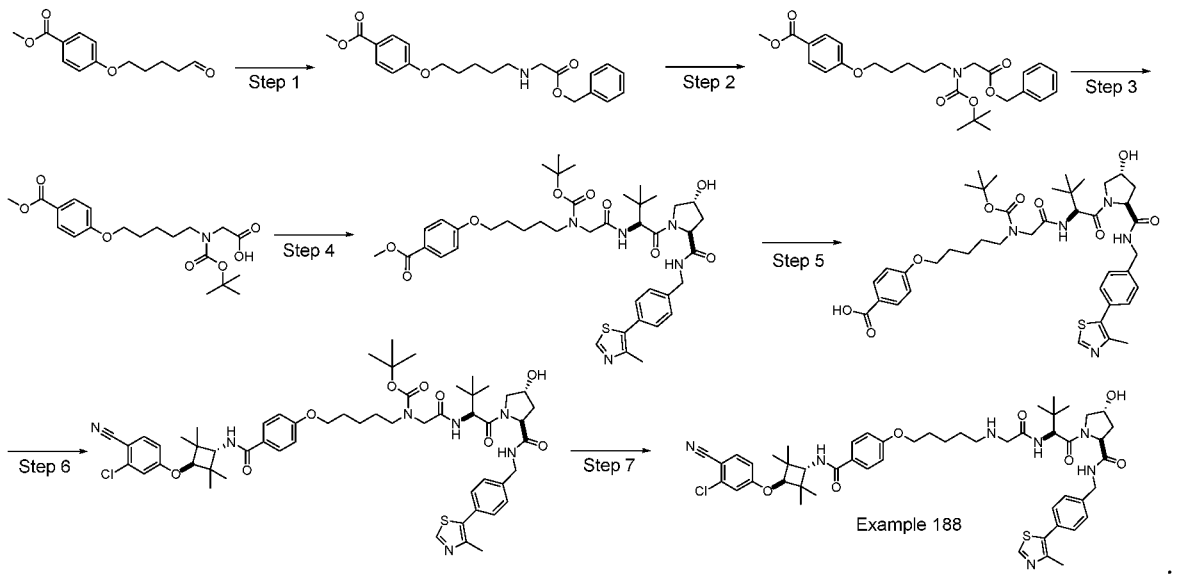
[0818] To a stirred mixture of methyl 4-hydroxybenzoate (1.0 g, 6.57 mmol) and potassium carbonate (1.36 g, 9.85 mmol) in dimethylformamide (2.0 mL) was added 4-fluorobenzaldehyde (815 mg, 6.57 mmol) at rt. The reaction mixture was then stirred at 80 °C for 16h. The reaction was monitored by LC-MS, which 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.

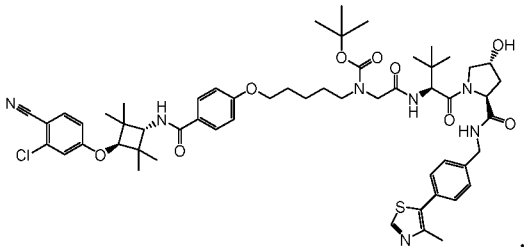
[0821] Synthesis of example 188:



[0822] Step 7: Synthesis of example 188

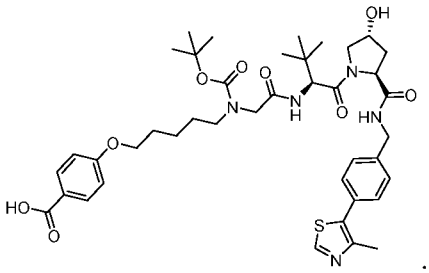
[0823] Trifluoroacetic acid (1.12 mL, 14.7 mmol) was added to a stirred solution of tert-butyl N-({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl)-N-[5-(4-{[trans-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenoxy)pentyl]carbamate (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:



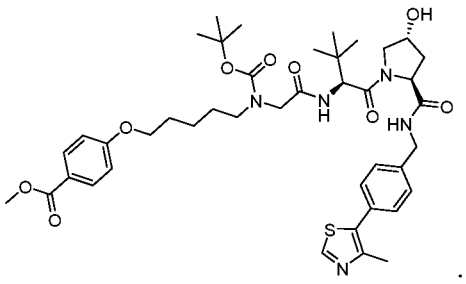
[0825] TBTU (23.0 mg, 0.072 mmol) was added to a stirred solution of 4-[(5-{[(tert-butoxy)carbonyl]({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl)amino}pentyl)oxy]benzoic acid (38 mg, 0.04786 mmol) 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:



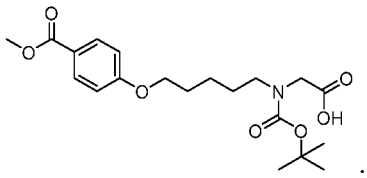
[0827] Lithium hydroxide (3.0 mg, 0.128 mmol) was added to a stirred solution of methyl 4-[(5-{[(tert-butoxy)carbonyl]({[(2S)-1-[(2S,4R)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamoyl}methyl)amino}pentyl)oxy]benzoate (37 mg, 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:



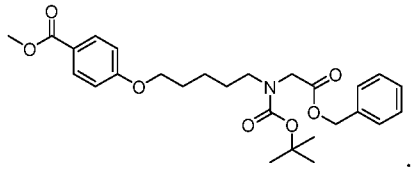
[0829] TBTU (36.6 mg, 0.1142 mmol) was added to a stirred solution of 2-{[(tert-butoxy)carbonyl]({5-[4-(methoxycarbonyl)phenoxy]pentyl})amino}acetic acid (37 mg, 0.076 mmol) and (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (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:



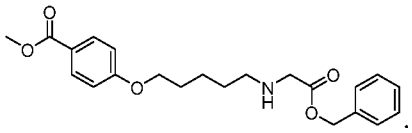
[0831] Palladium on carbon (96.8 mg, 0.91 mmol) was added to a stirred solution of methyl 4-[(5-{[2-(benzyloxy)-2-oxoethyl][(tert-butoxy)carbonyl]amino}pentyl)oxy]benzoate (83.0 mg, 0.171 mmol) in ethanol (20 ml) at rt. The reaction mixture was degassed and charged with $H_{(g)}$ and then stirred at 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%).

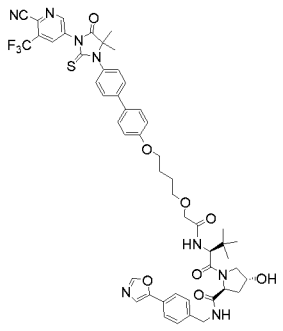
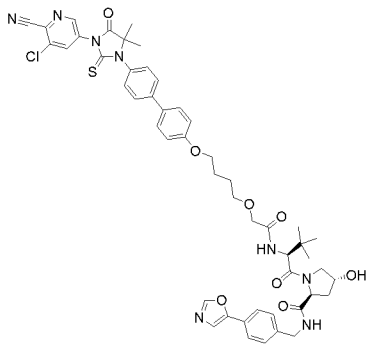
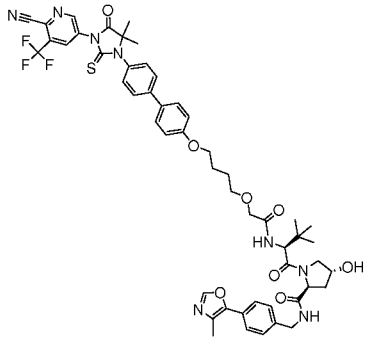
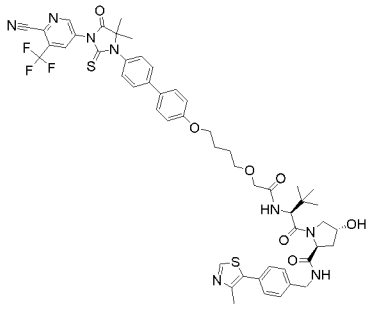
[0835] Step 1: Synthesis of methyl 4-[(5-{[2-(benzyloxy)-2-oxoethyl]amino}pentyl)oxy]benzoate:

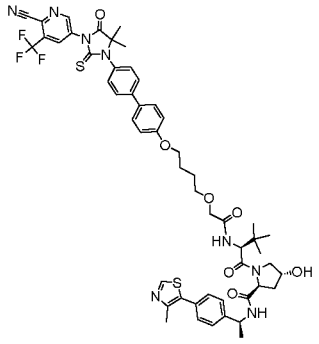
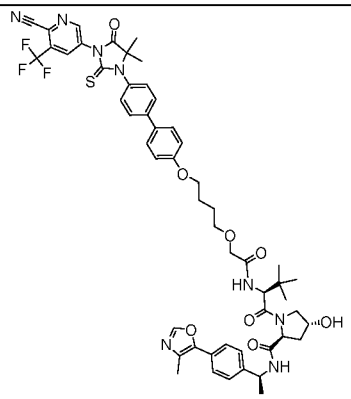
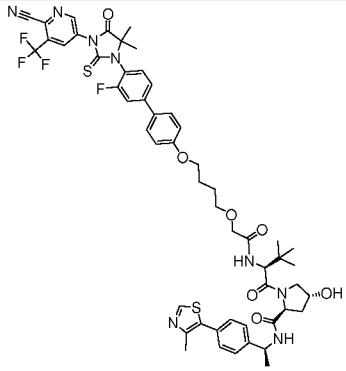
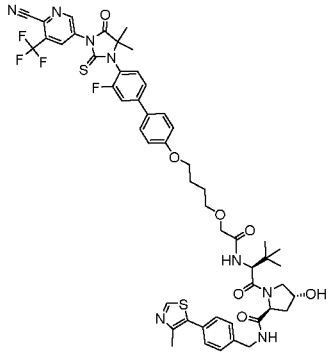
 .

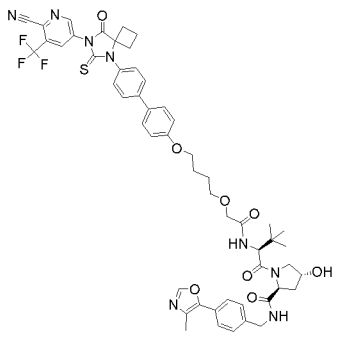
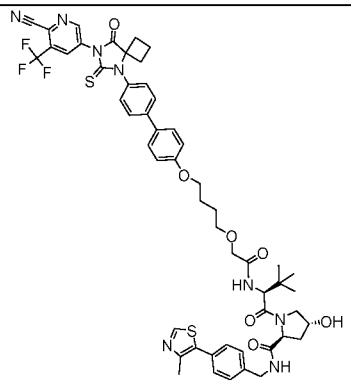
[0836] To a stirred mixture of methyl 4-[(5-oxopentyl)oxy]benzoate (269 mg, 1.13 mmol) and benzyl 2-aminoacetate hydrochloride (186 mg, 1.13 mmol) in DCE (5.00 mL) was added acetic acid (181 µL, 2.26 mmol) and sodium triacetoxyborohydride (358 mg, 1.69 mmol) at rt. The reaction mixture was stirred at 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

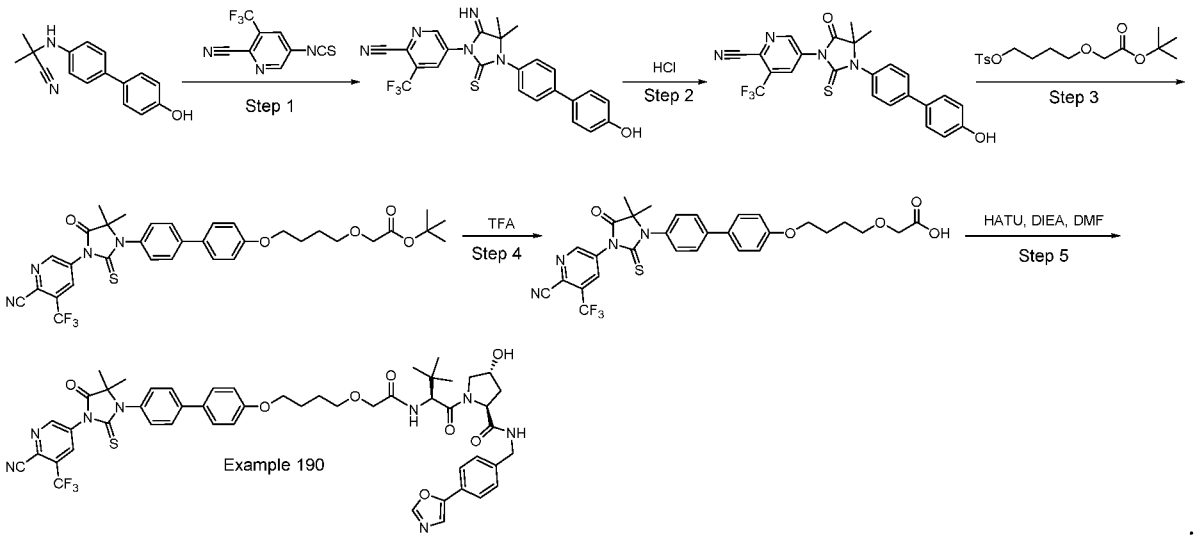
190		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (300 MHz, CD_3OD):δ9.14 (s, 1 H), 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^+]

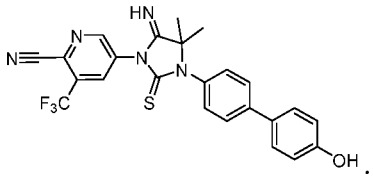
198		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl}phenyl)phenoxy]butoxy}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide ^{1}H NMR (400 MHz, CD_3OD): δ 9.20 (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:

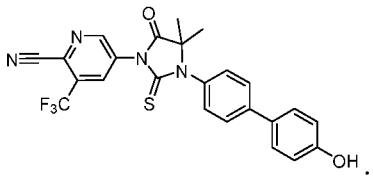


[0840] Step 1: Synthesis of 5-{3-[4-(4-hydroxyphenyl)phenyl]-5-imino-4,4-dimethyl-2-sulfanylideneimidazolidin-1-yl}-3-(trifluoromethyl)pyridine-2-carbonitrile:



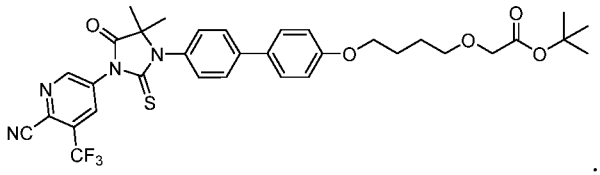
[0841] To a stirred solution of 5-isothiocyanato-3-(trifluoromethyl)pyridine-2-carbonitrile (440.0 mg, 1.92 mmol) in N,N-dimethylpyridin-4-amine (322.0 mg, 2.64 mmol) and toluene (10.0 mL) was added 2-[[4-(4-hydroxyphenyl)phenyl]amino]-2-methylpropanenitrile (400.0 mg, 1.59 mmol) under a nitrogen atmosphere 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:



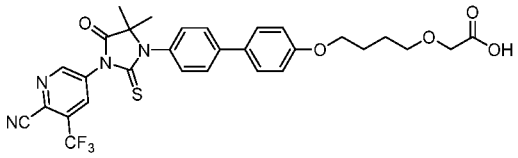
[0843] To a stirred solution of 5-{3-[4-(4-hydroxyphenyl)phenyl]-5-imino-4,4-dimethyl-2-sulfanylideneimidazolidin-1-yl}-3-(trifluoromethyl)pyridine-2-carbonitrile (160.0 mg, 0.33 mmol) in methanol (5.0 mL) was added hydrogen chloride aqueous solution (2N, 2.0 mL) at rt. The resulting solution was then 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:



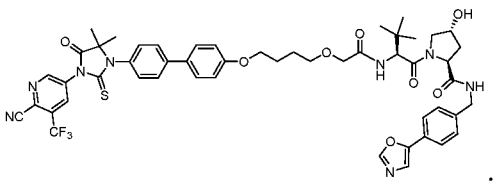
[0845] To a stirred solution of 5-{3-[4-(4-hydroxyphenyl)phenyl]-4,4-dimethyl-5-oxo-2-sulfanylideneimidazolidin-1-yl}-3-(trifluoromethyl)pyridine-2-carbonitrile (110.0 mg, 0.23 mmol) and tert-butyl 2-{4-[(4-methylbenzenesulfonyl)oxy]butoxy}acetate (163.0 mg, 0.45 mmol) in N,N-dimethylformamide (3.0 mL) 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:



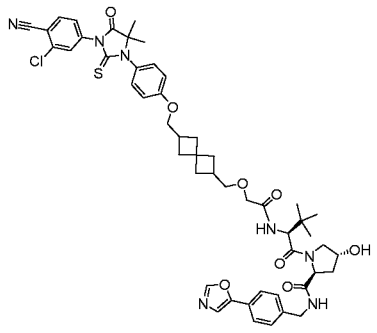
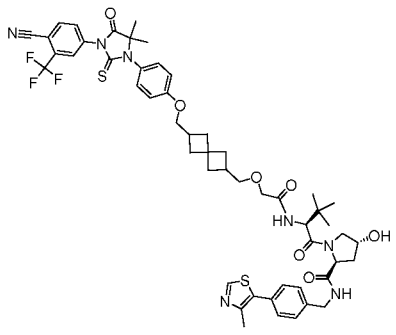
[0847] To a stirred solution of tert-butyl 2-{4-[4-(4-{3-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetate (150.0 mg, 0.22 mmol) in dichloromethane (2.0 mL) was added trifluoroacetic acid (2.0 mL) at rt. The resulting solution 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^+].

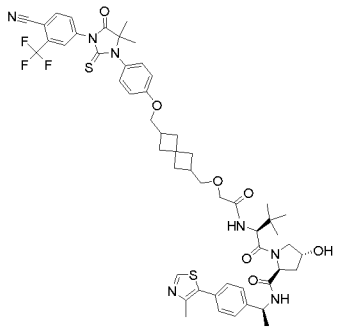
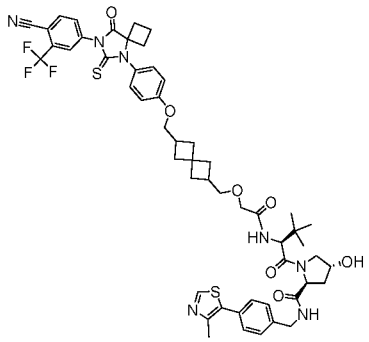
[0848] Step 5. Synthesis of example 190:



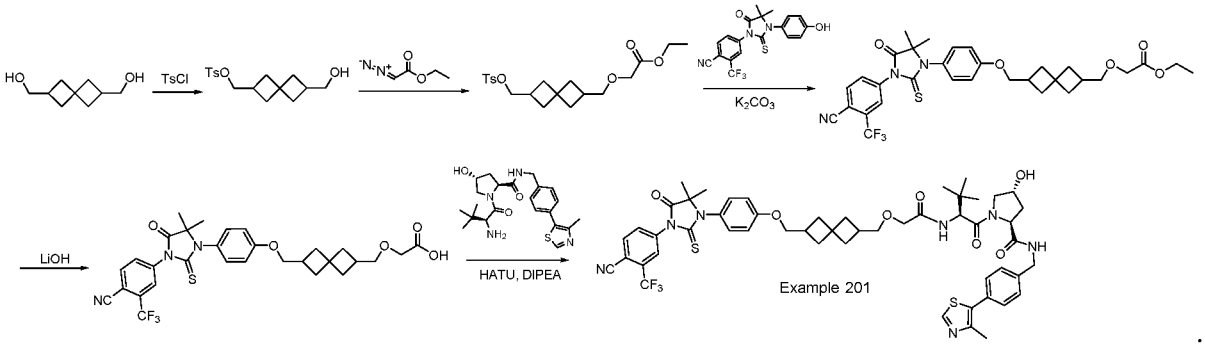
[0849] To a stirred solution of 2-{4-[4-(4-{3-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}phenyl)phenoxy]butoxy}acetic acid (80.0 mg, 0.13 mmol) and (2S,4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(1,3-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide (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$^+$]

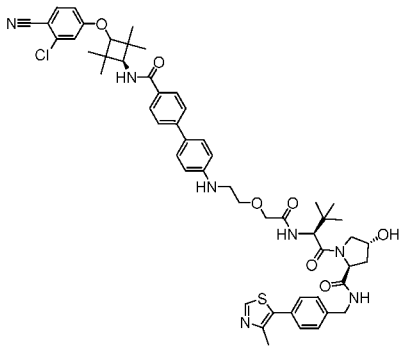
[0851] Example 201was synthesized according chemistry shown below, utilizing similar procedures used for the synthesis of example 75.



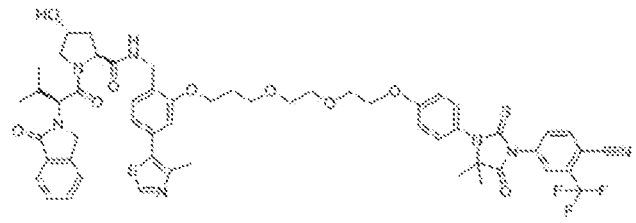
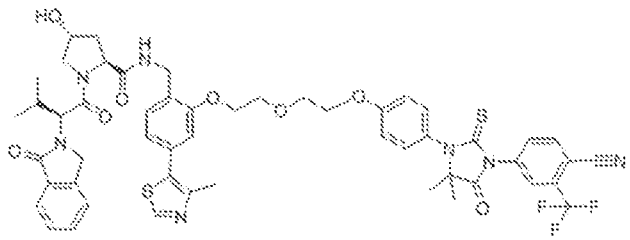
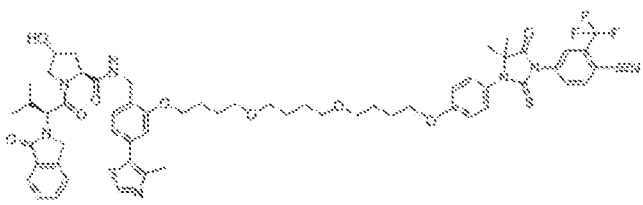
[0852] Examples 200, 202-203 was synthesized according to similar procedure described for synthesis of example 201, by using corresponding starting materials and intermediates.

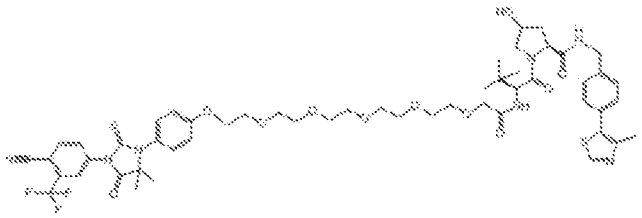
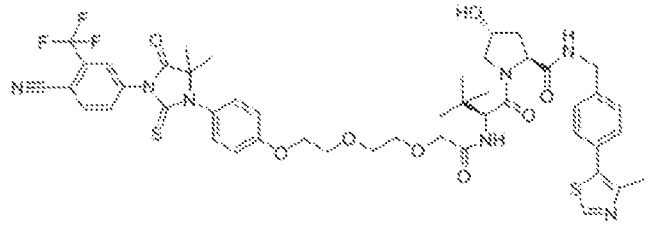
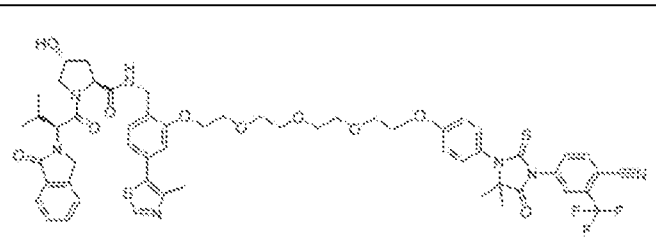
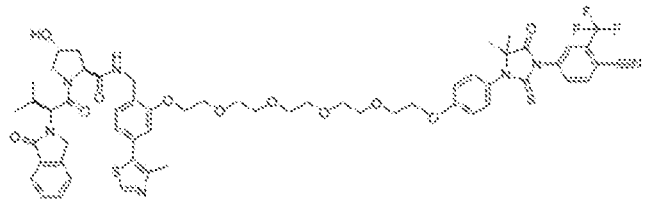
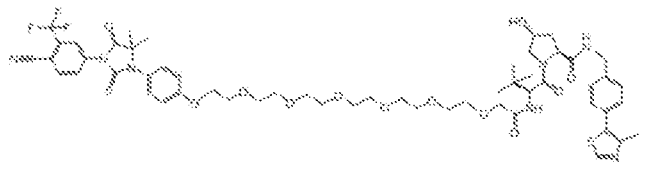
[0853] Table 16. Exemplary Compounds.

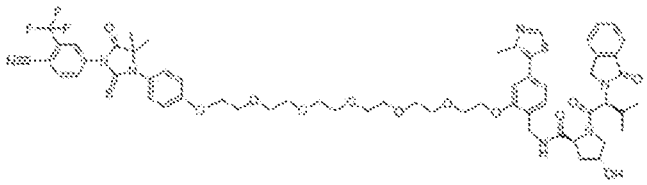
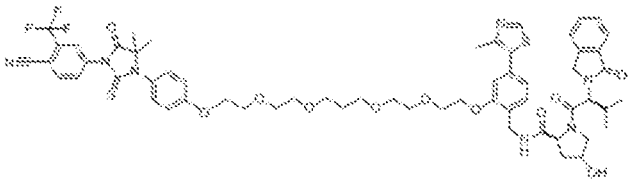
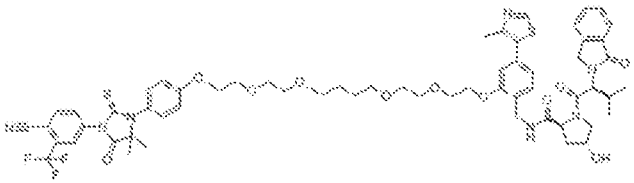
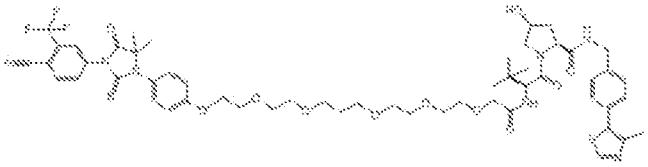
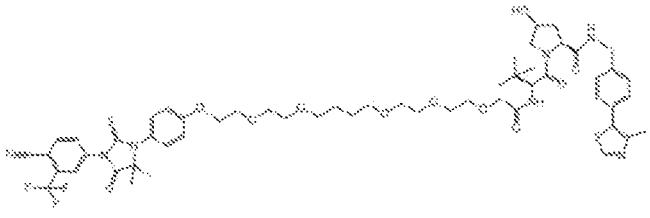
Ex#	Structure	Compound name and Analytical data

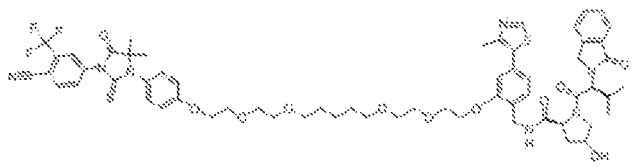
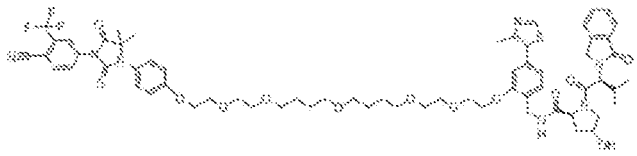
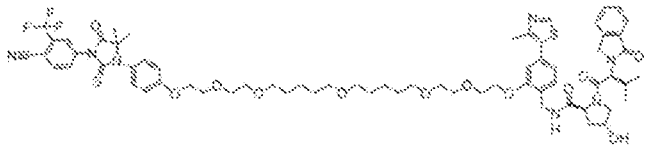
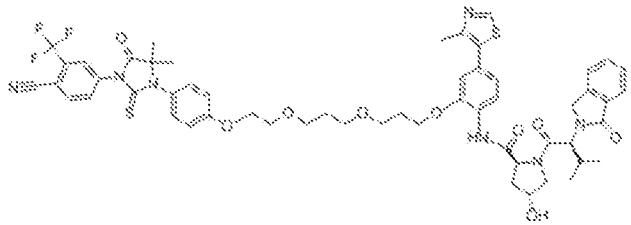
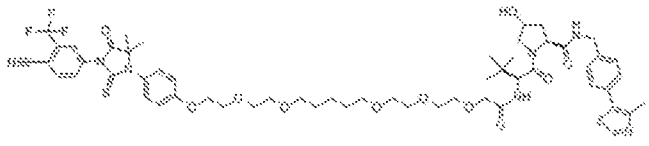
204		(2S,4R)-1-[(2S)-2-[2-(2-{[4-(4-{[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]carbamoyl}phenyl)phenyl]amino}ethoxy)acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide Mass (ES$^+$): *m/z* 988.20 [MH$^+$]

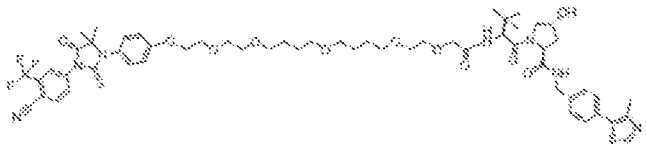
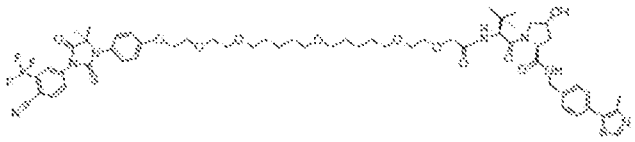
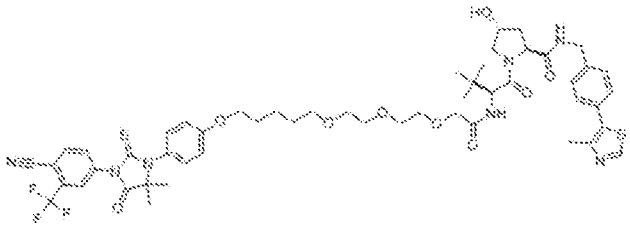
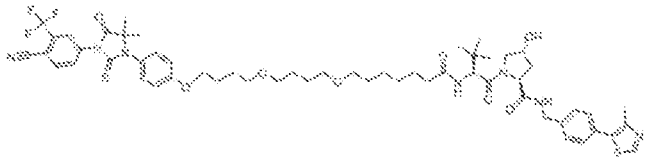
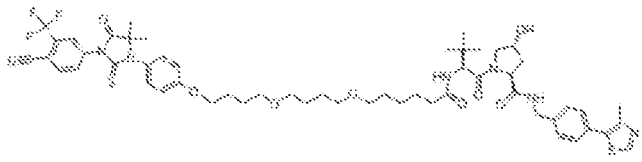
[0854] Table 17. Additional Exemplary Compounds.

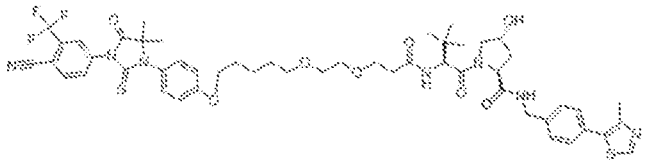
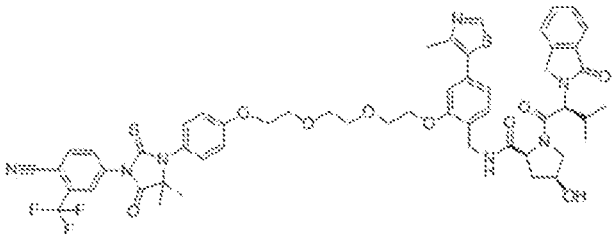
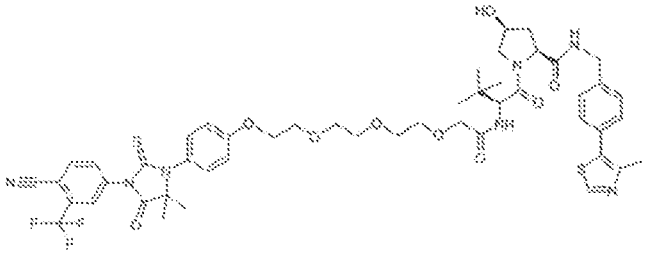
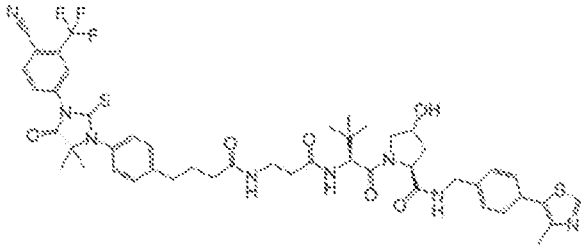
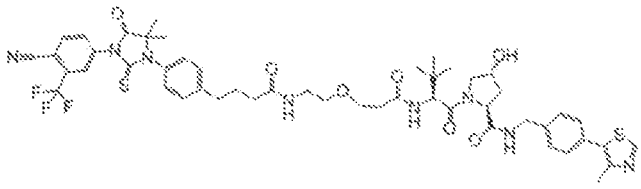
	Structure	Measured Mass Ion Data	
		MH$^+$ 1	MH$^+$ 2
205		1082.37	
206		1024.33	
207		1152.45	

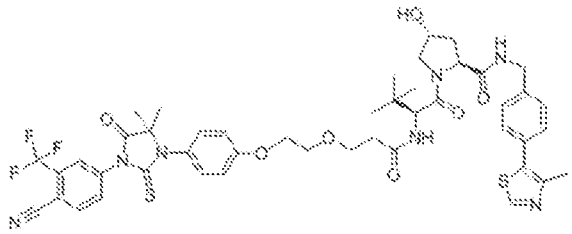
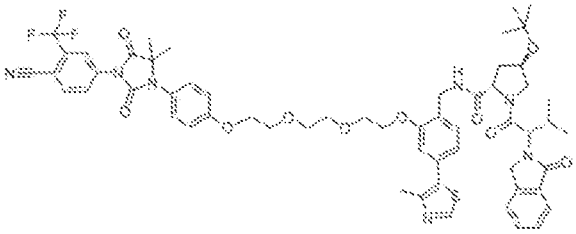
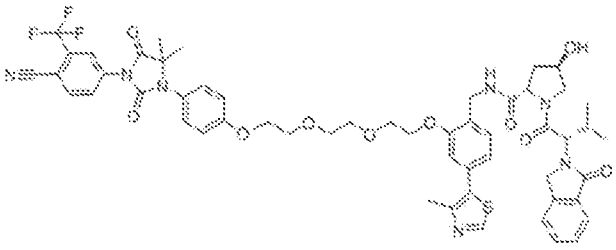
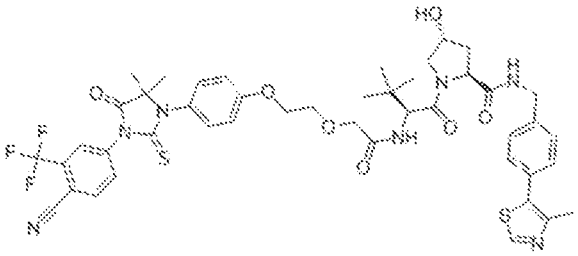
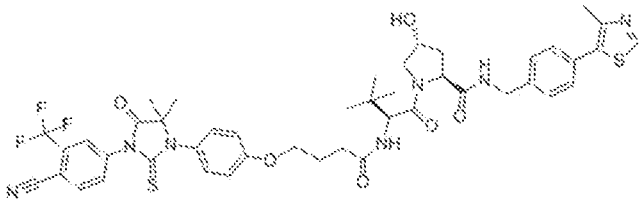
208		1096.41	
209		964.33	
210		1112.38	
211		1156.41	
212		1140.44	

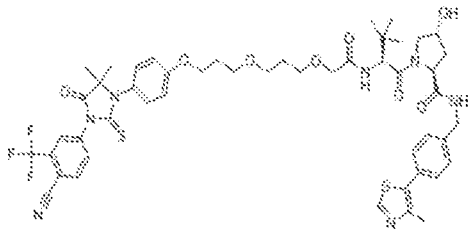
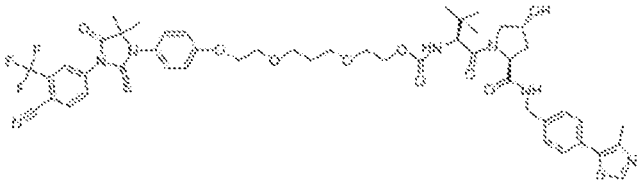
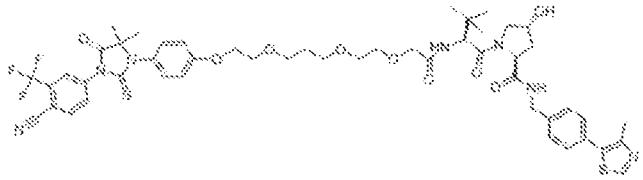
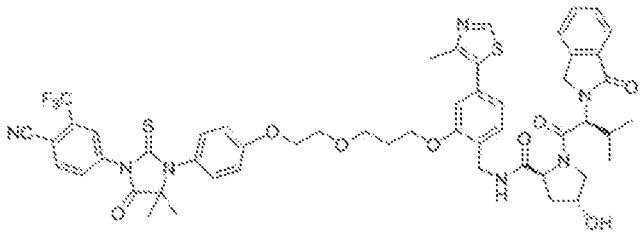
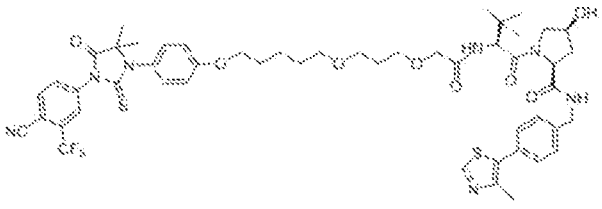
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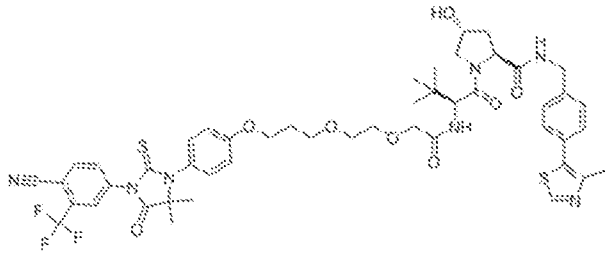
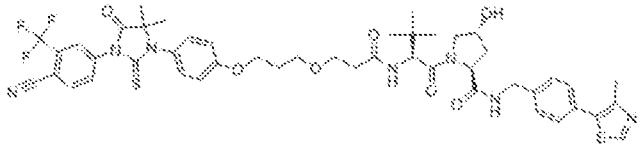
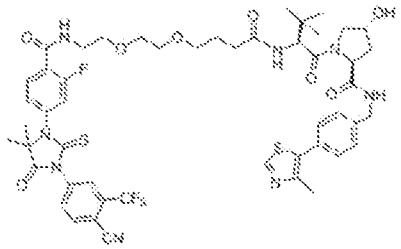
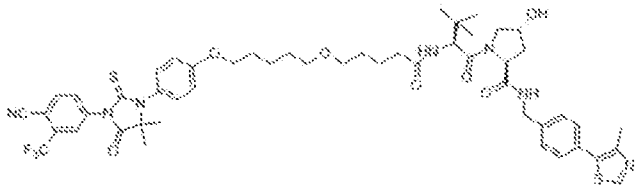
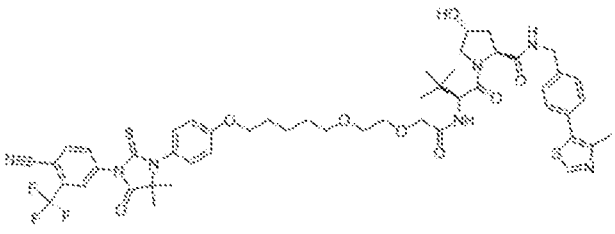
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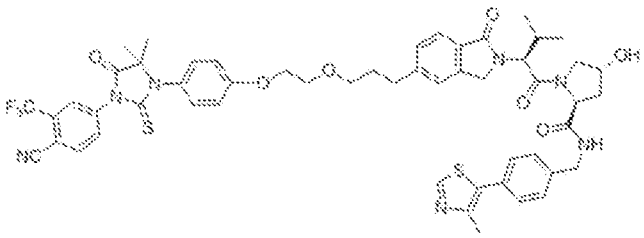
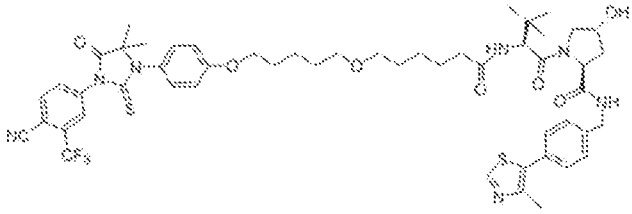
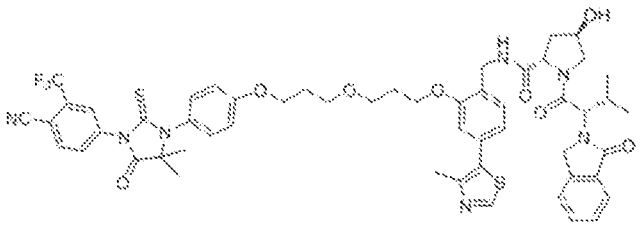
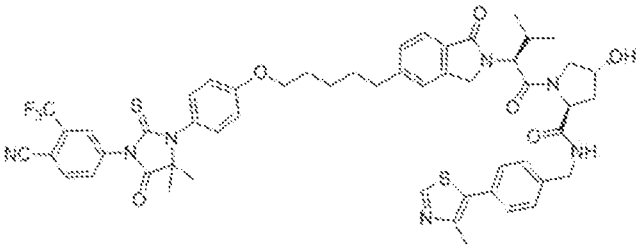
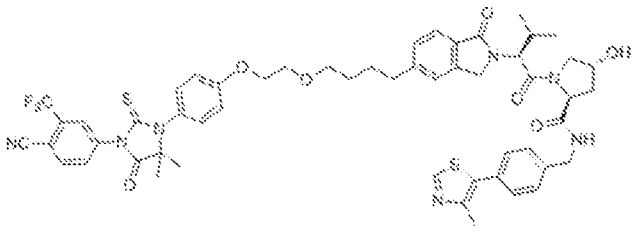
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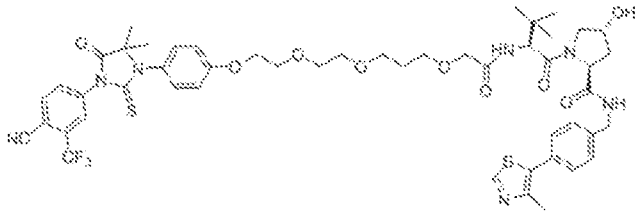
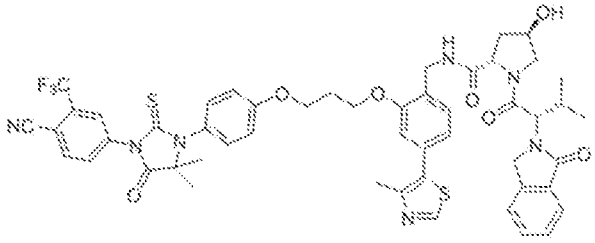
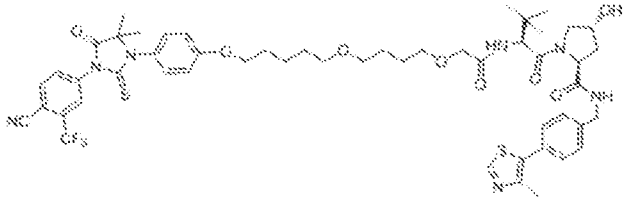
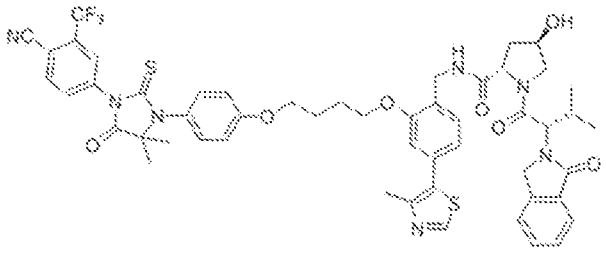
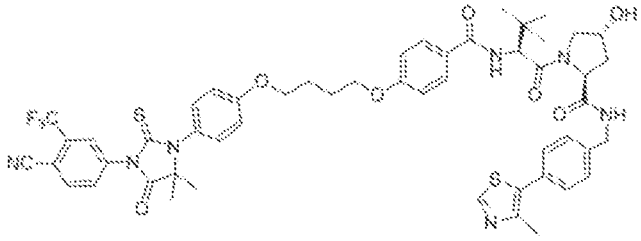
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232		1003.38	

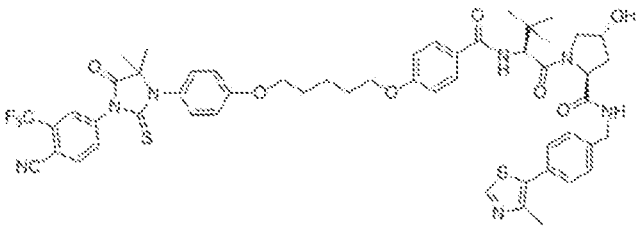
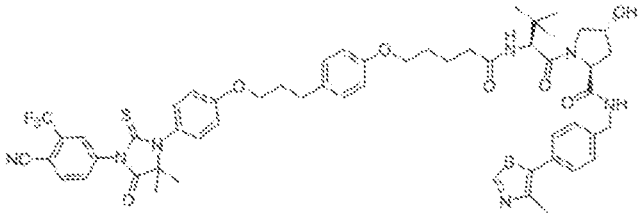
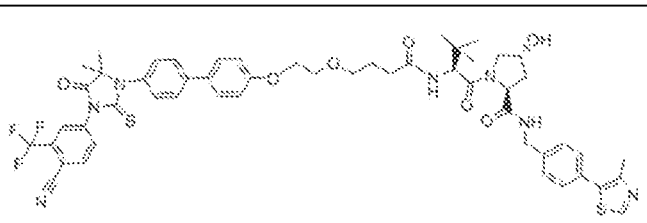
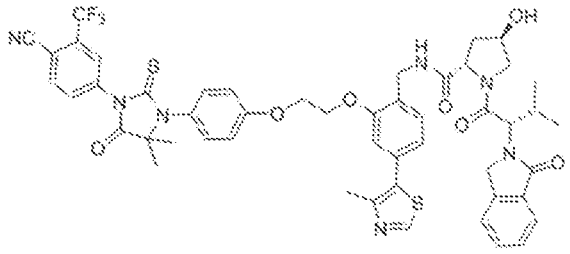
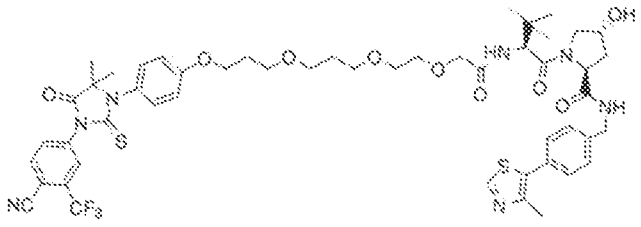
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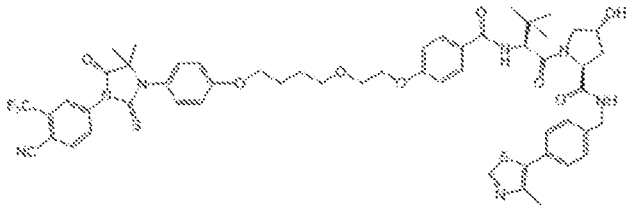
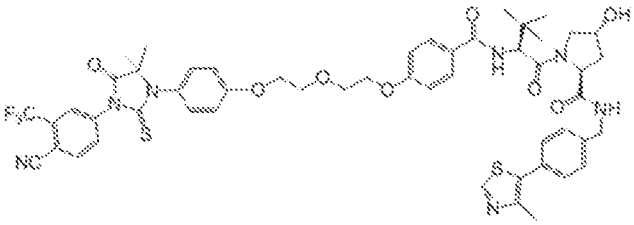
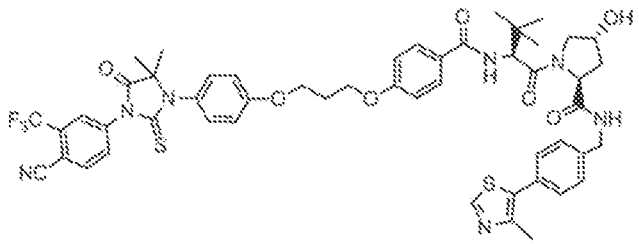
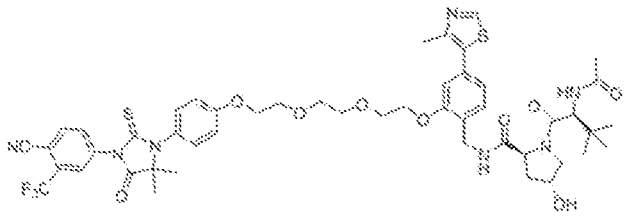
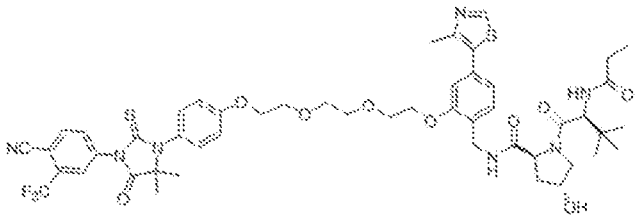
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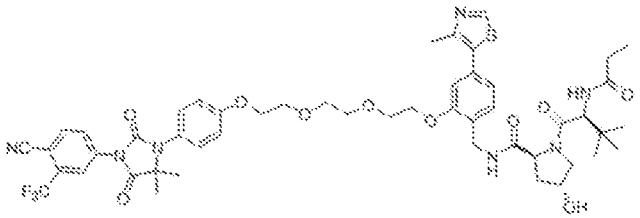
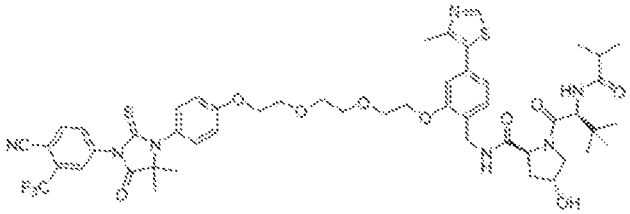
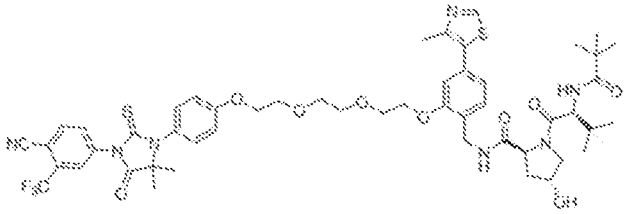
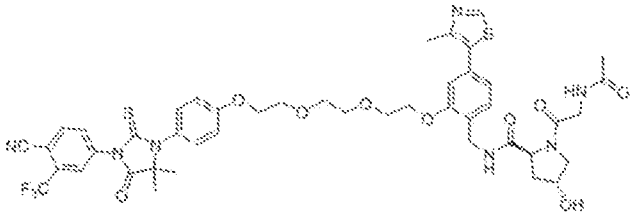
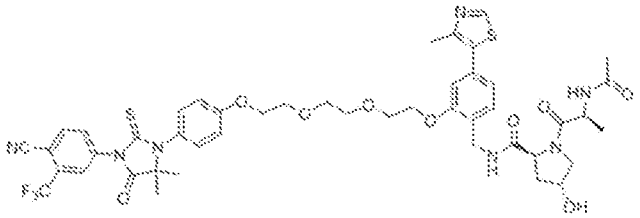
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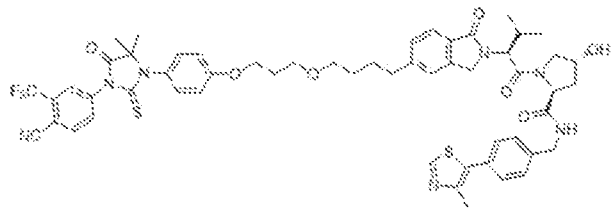
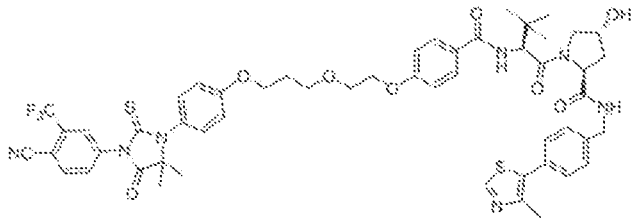
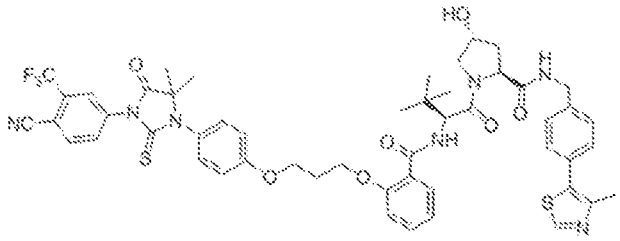
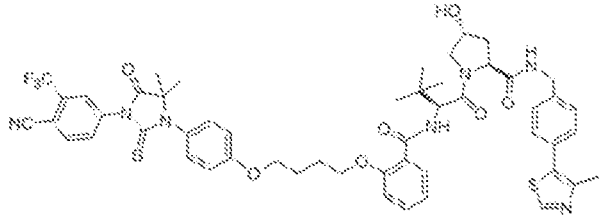
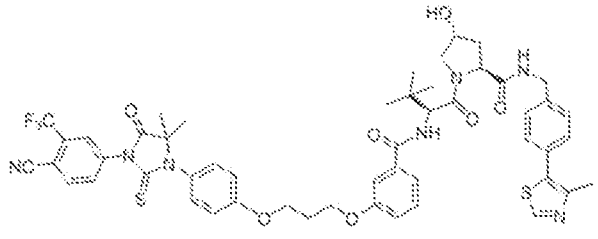
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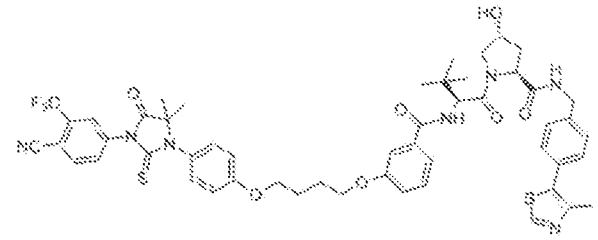
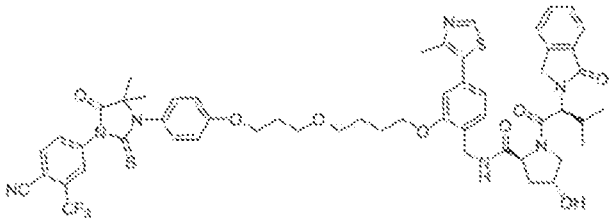
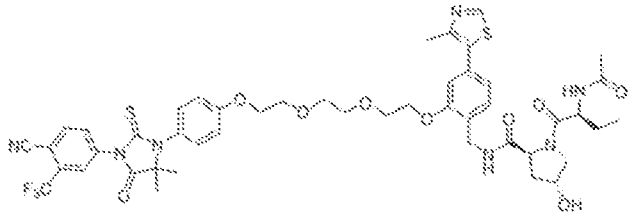
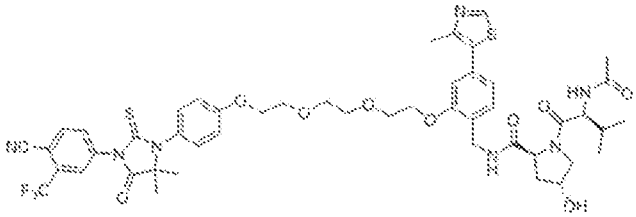
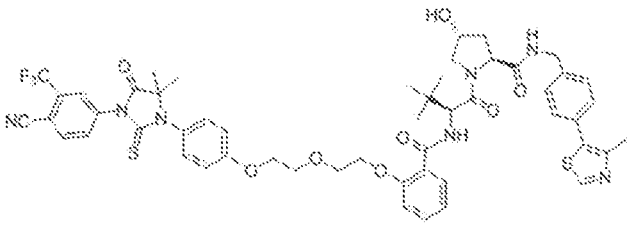
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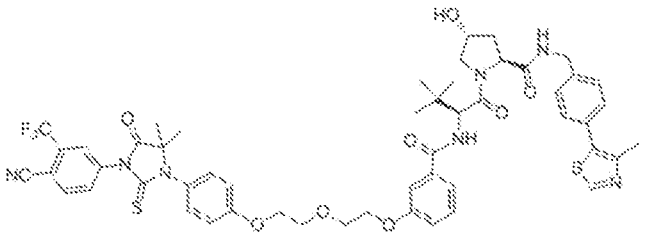
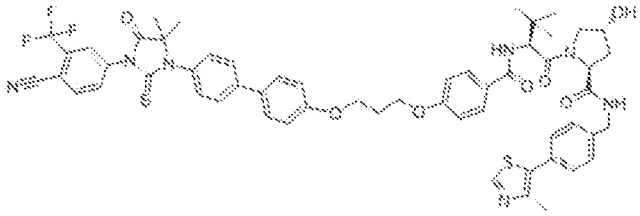
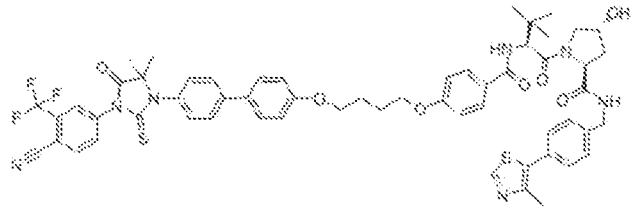
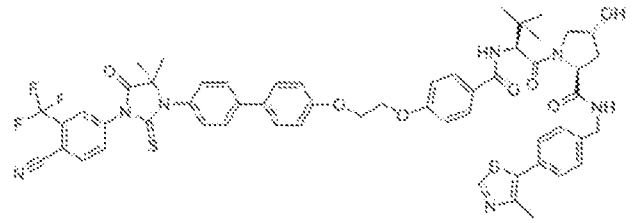
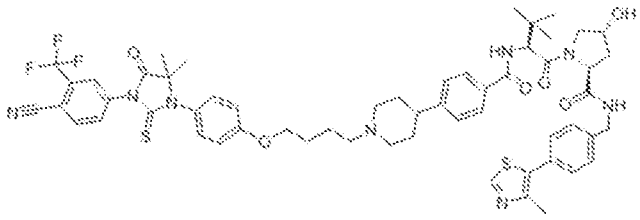
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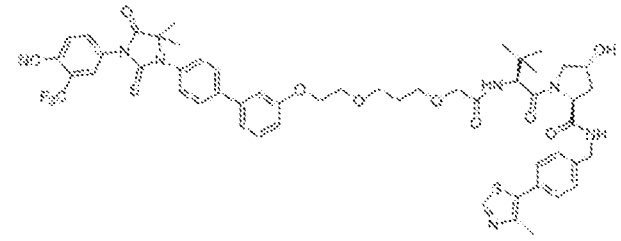
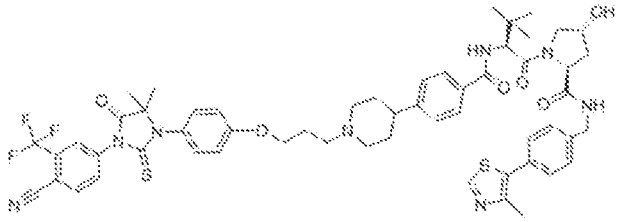
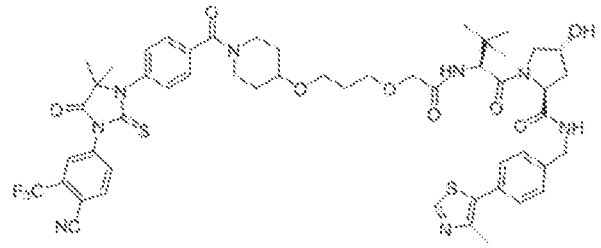
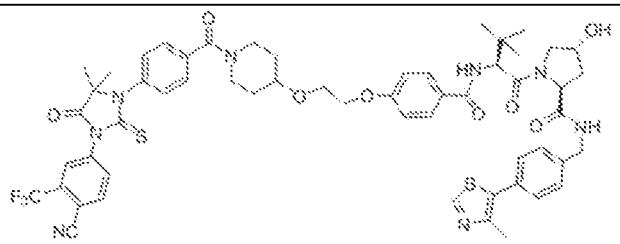
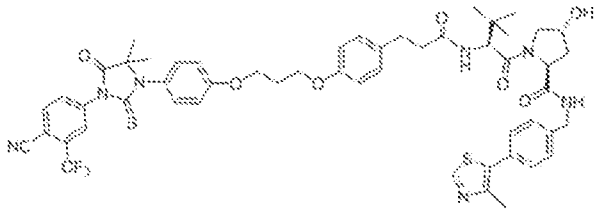
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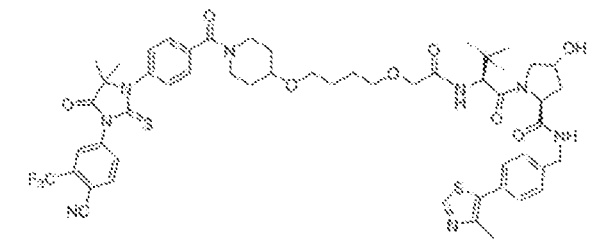
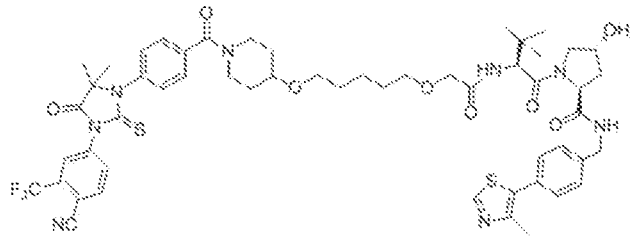
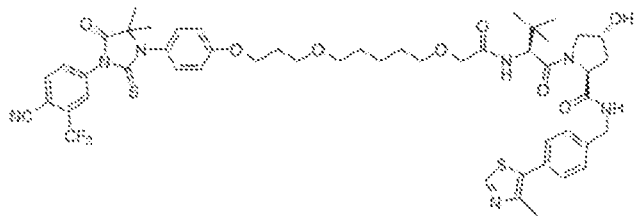
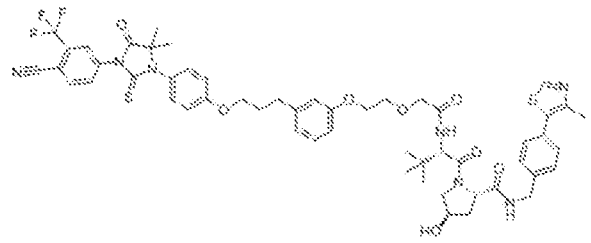
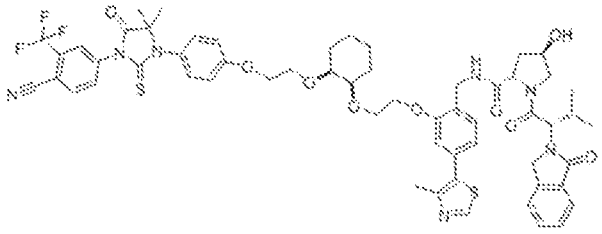
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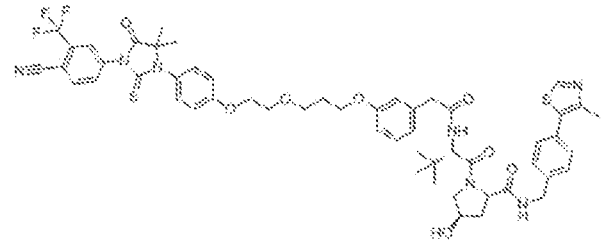
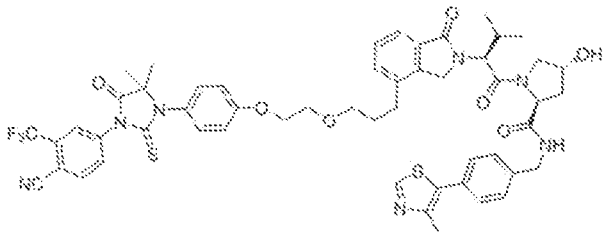
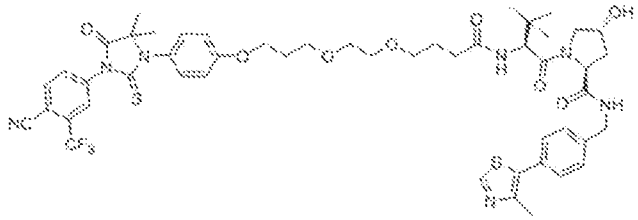
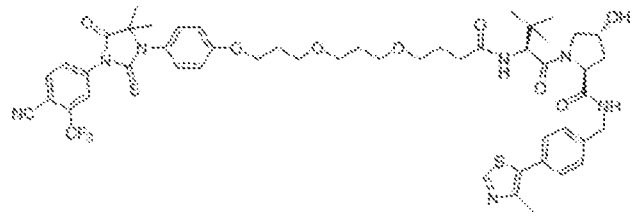
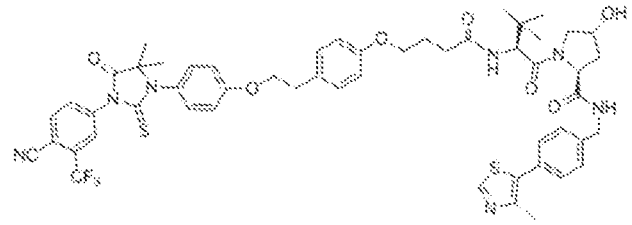
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277		996.32	

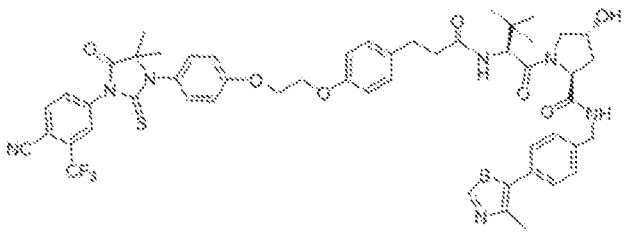
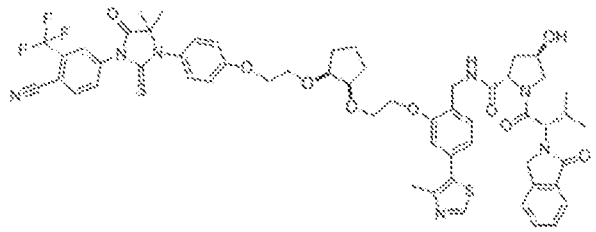
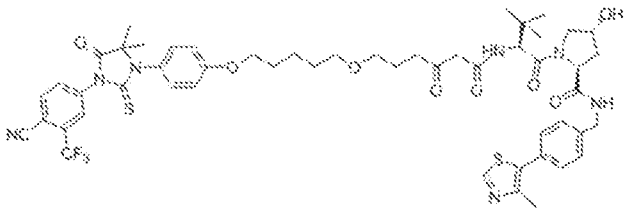
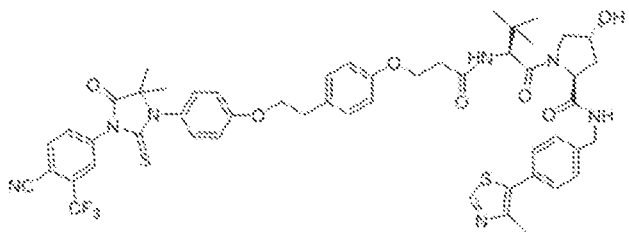
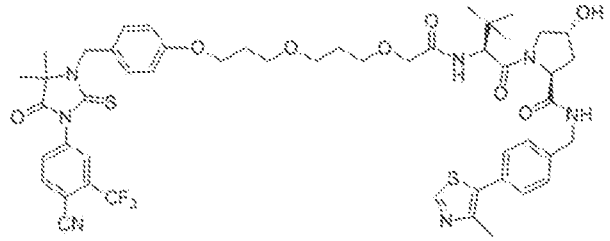
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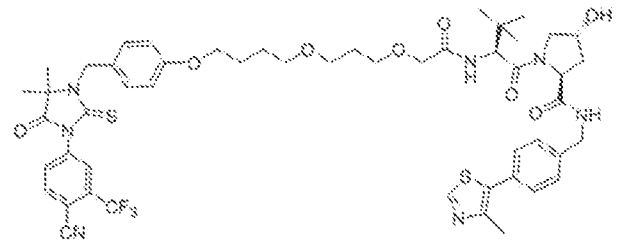
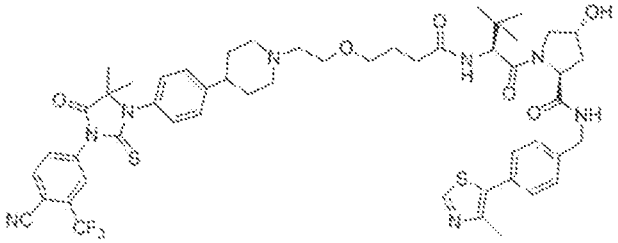
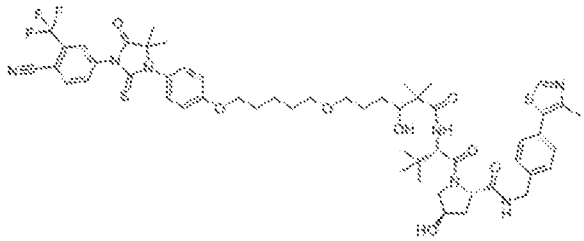
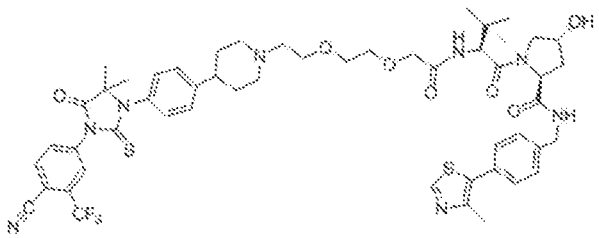
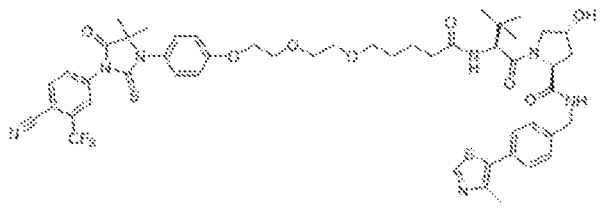
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287		1077.41	

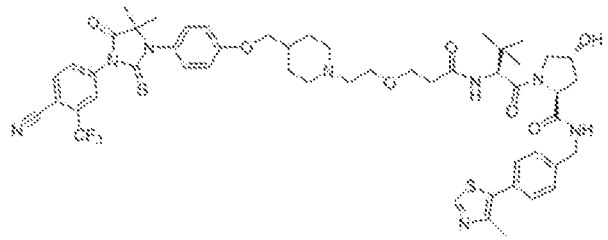
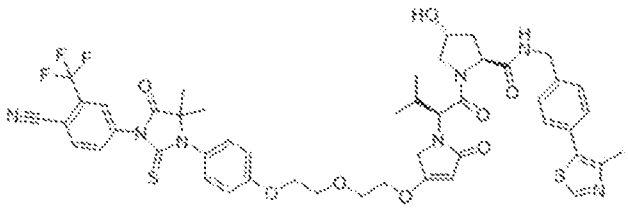
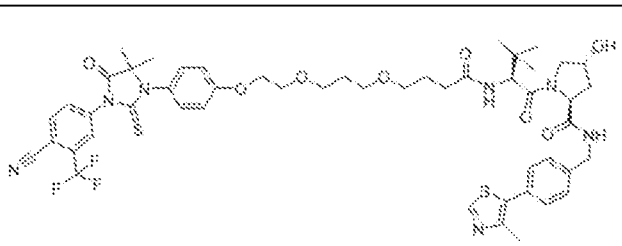
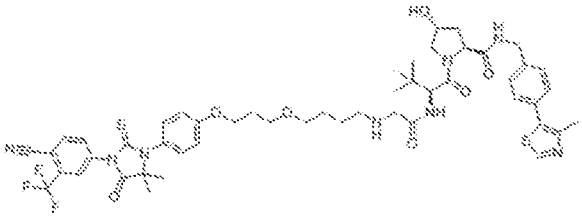
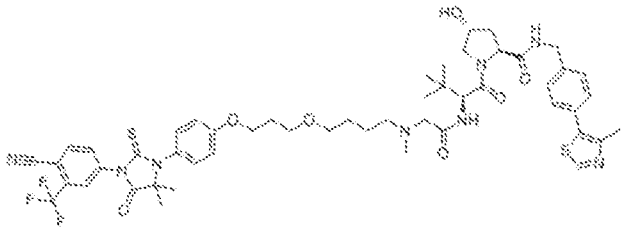
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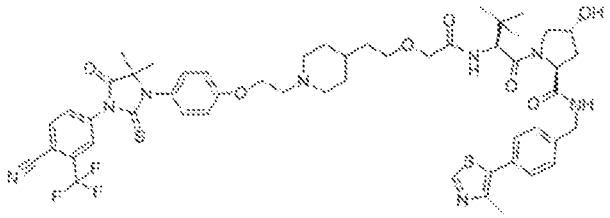
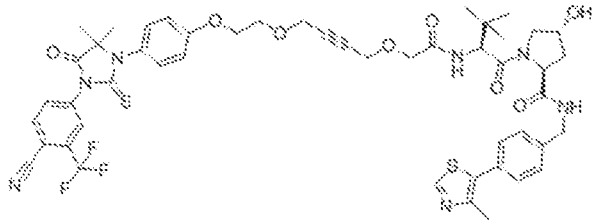
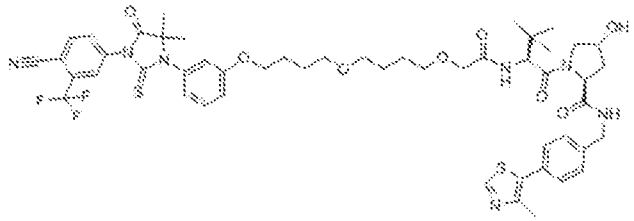
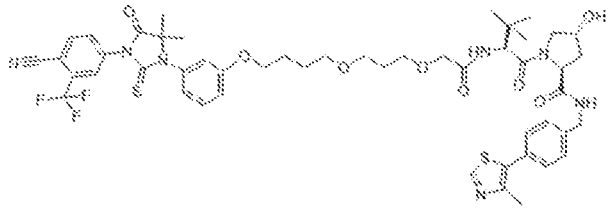
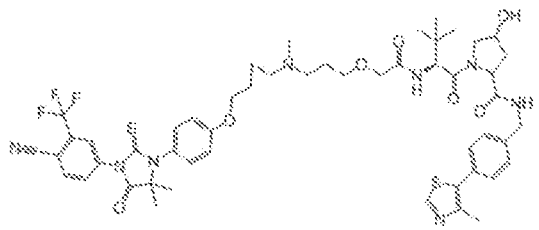
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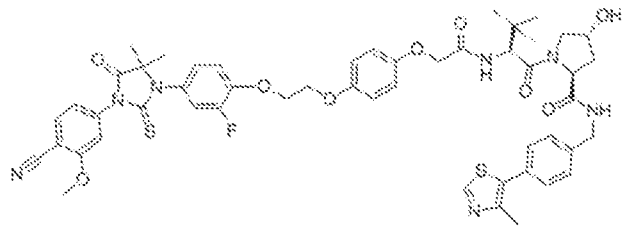
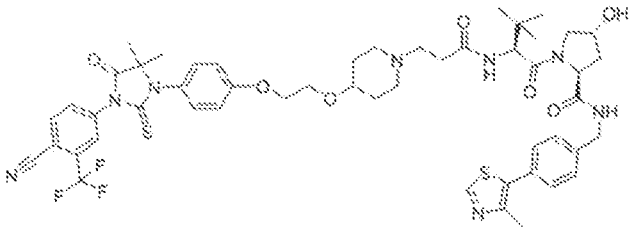
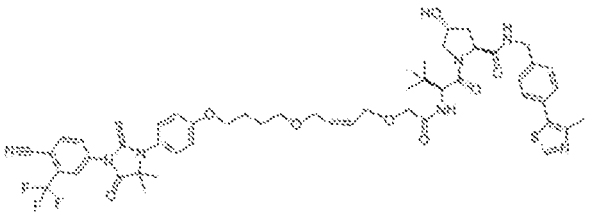
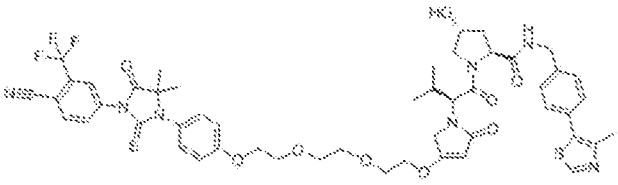
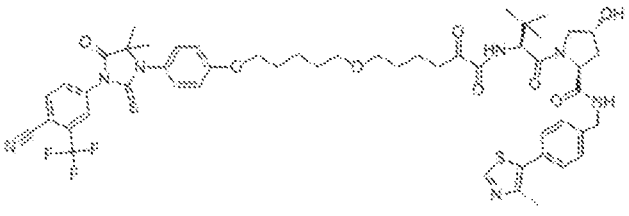
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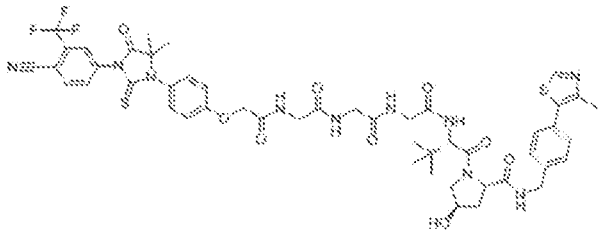
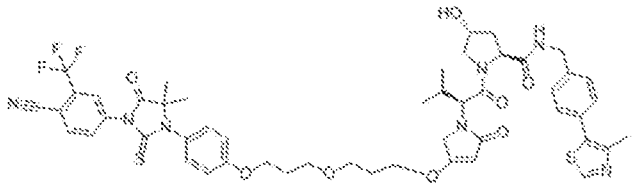
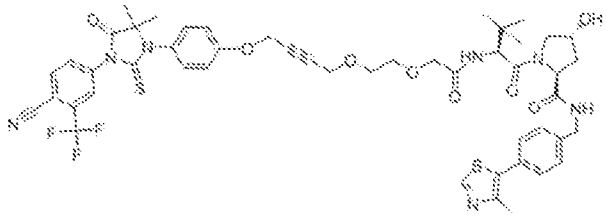
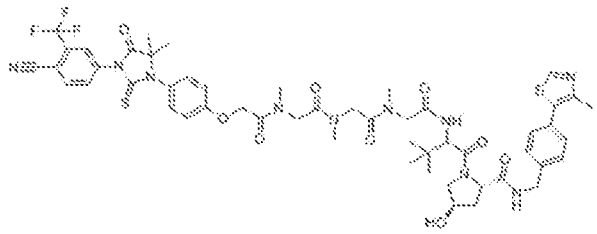
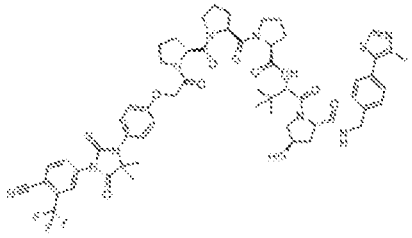
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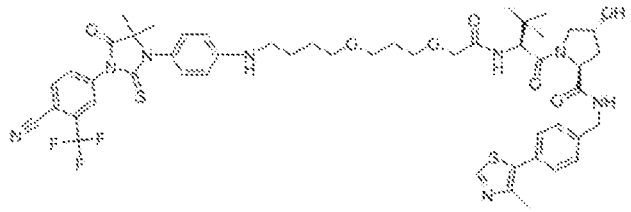
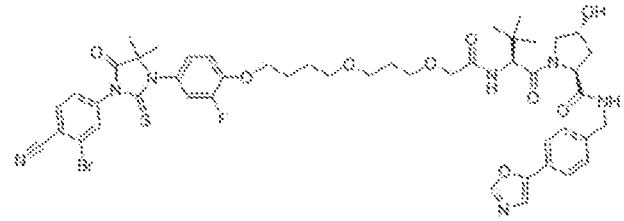
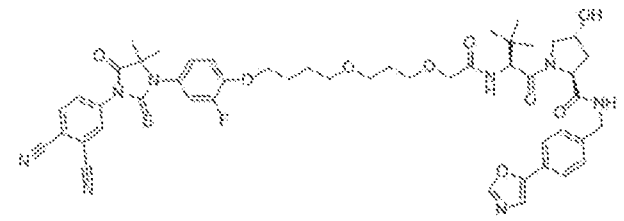
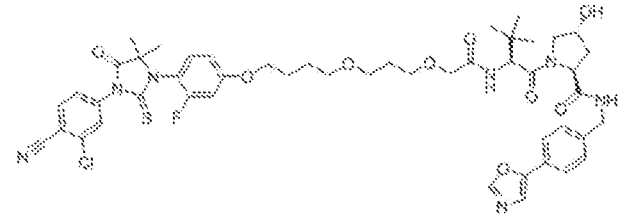
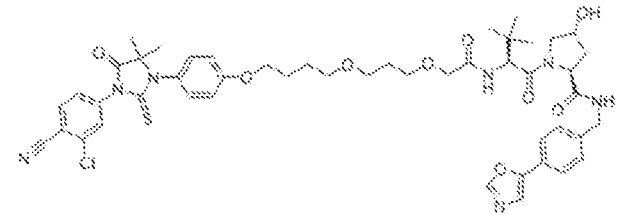
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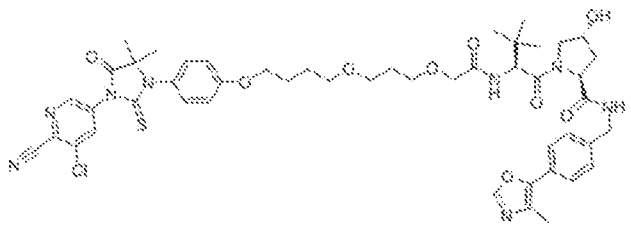
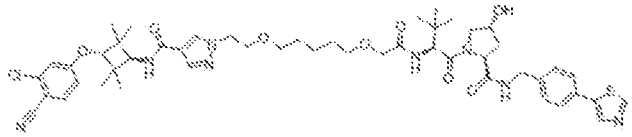
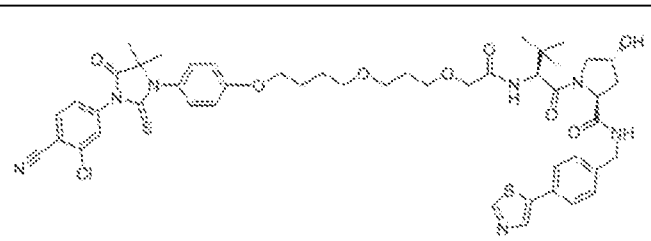
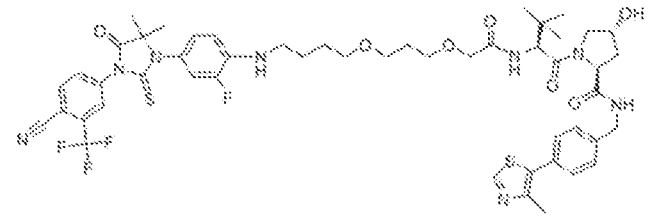
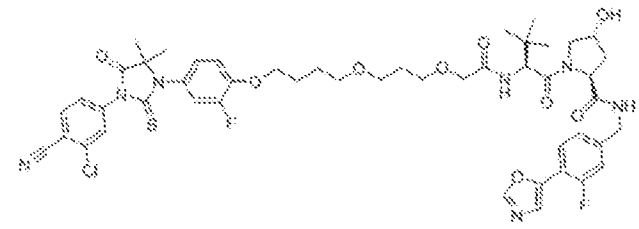
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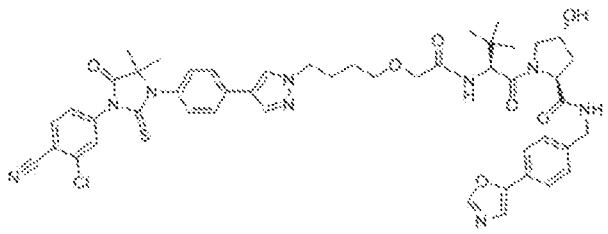
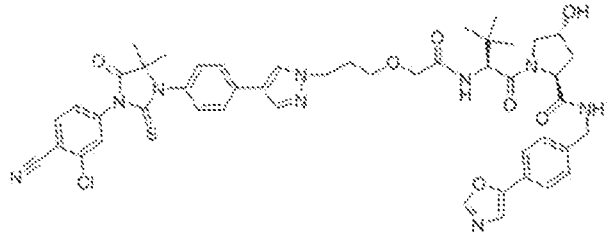
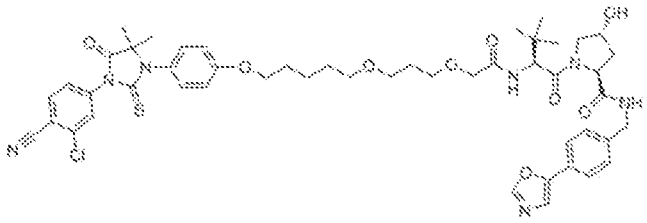
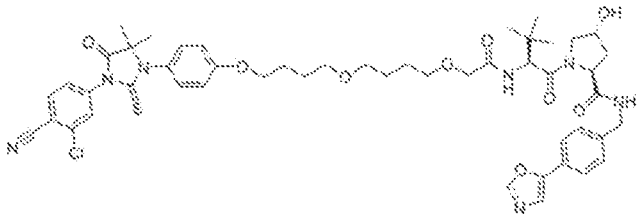
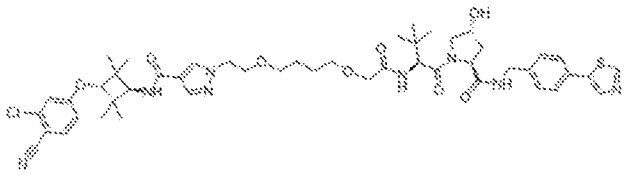
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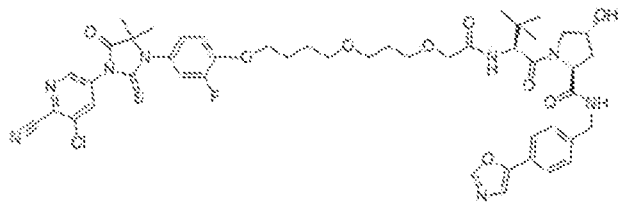
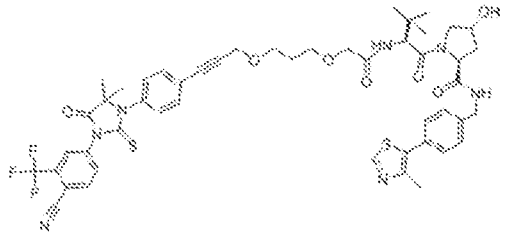
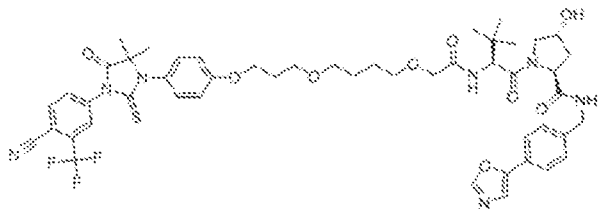
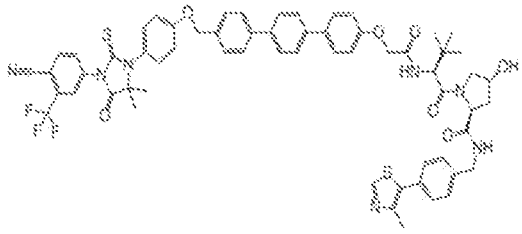
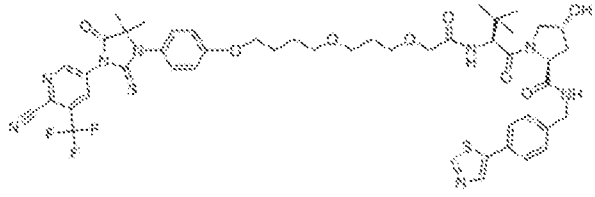
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326		1018.20	
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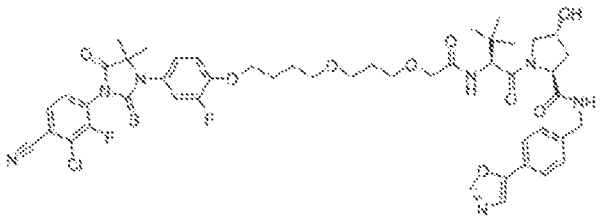
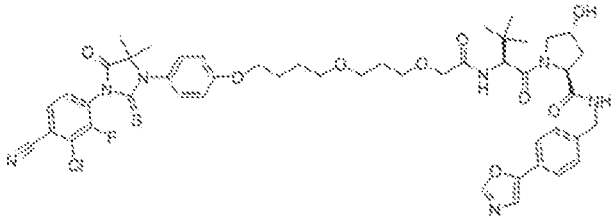
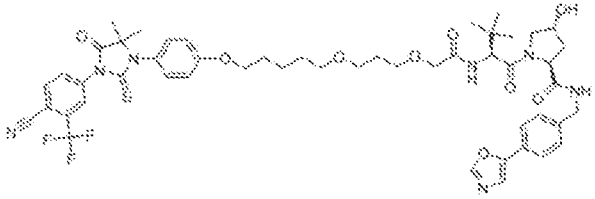
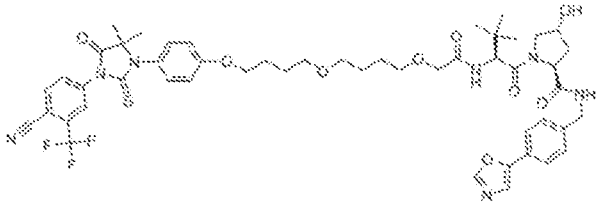
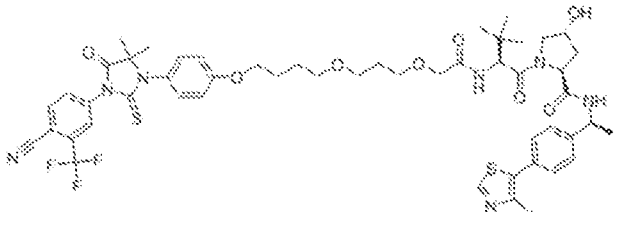
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332		1167.43	

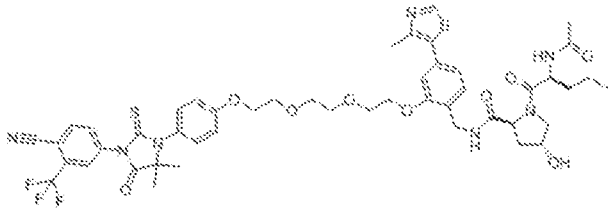
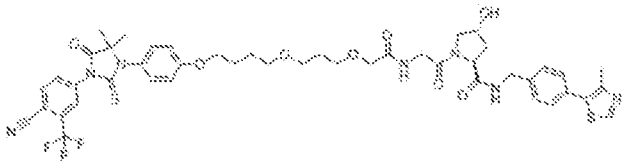
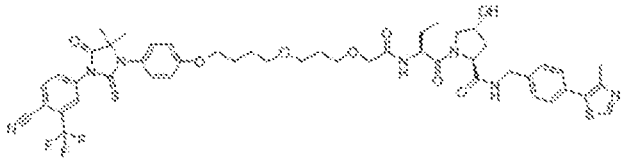
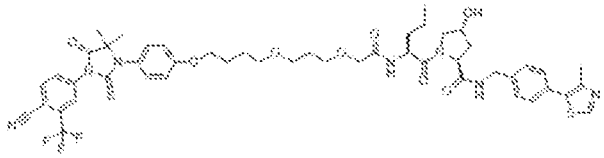
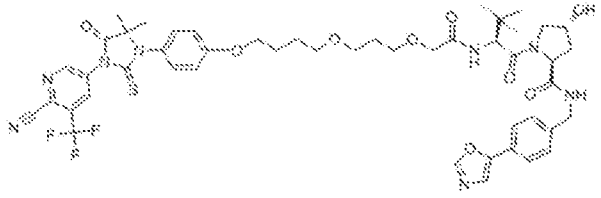
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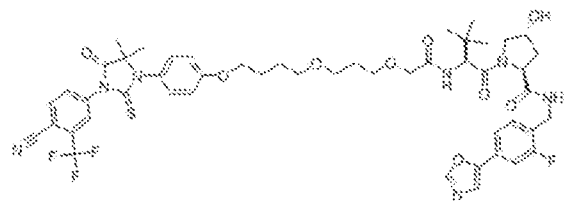
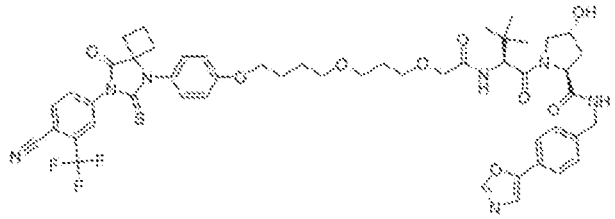
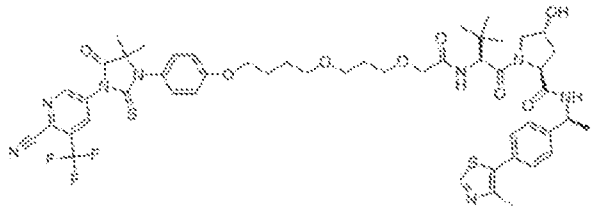
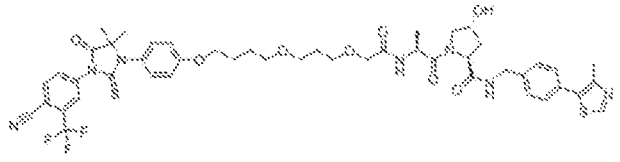
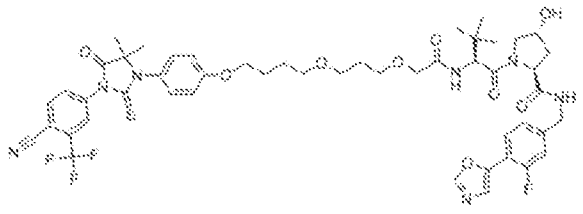
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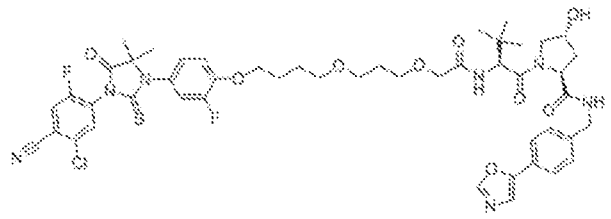
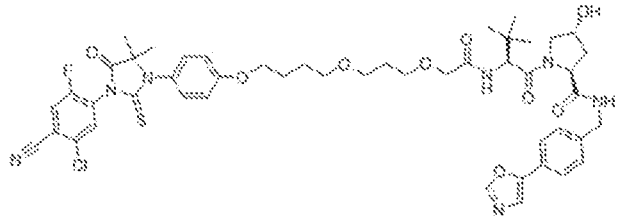
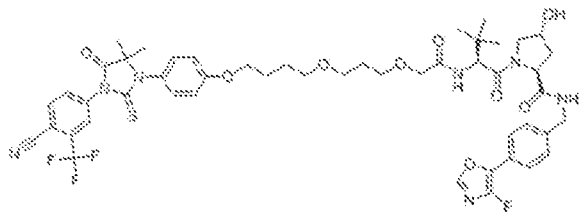
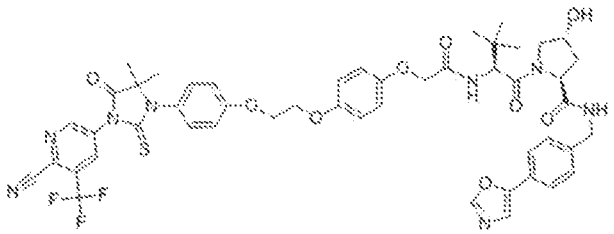
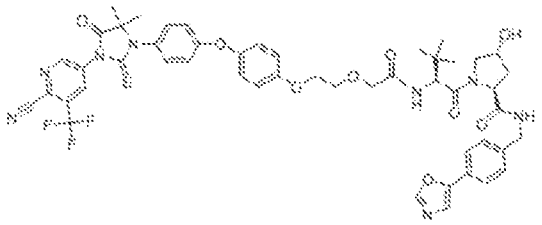
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346			
347		945.40	

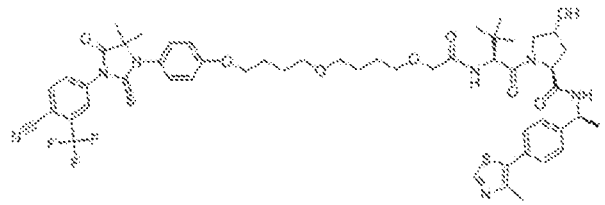
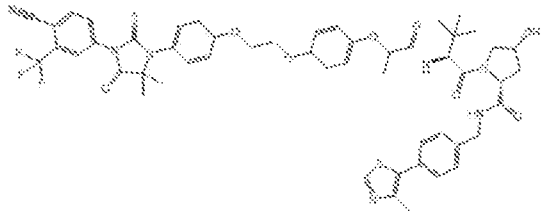
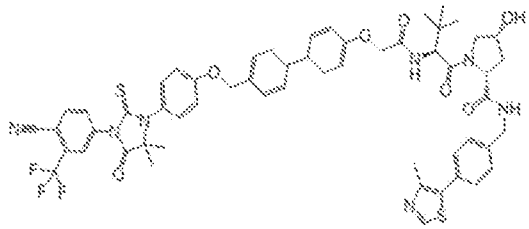
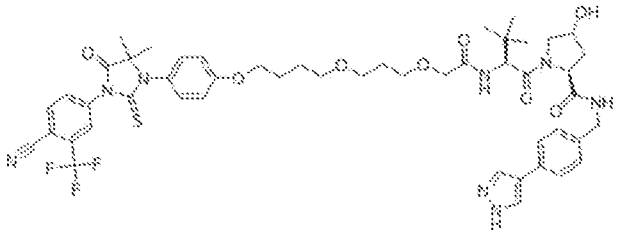
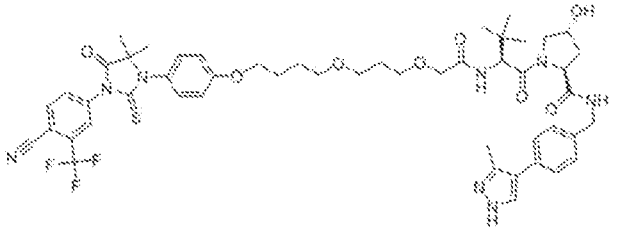
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351		-	
352		993.25	

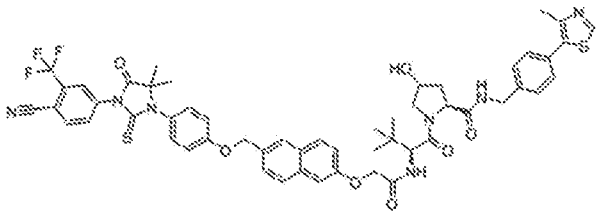
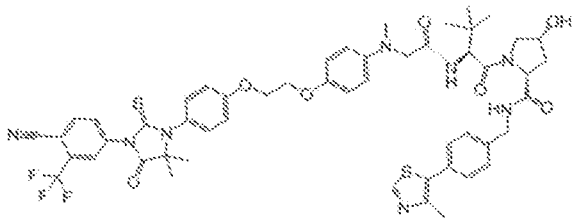
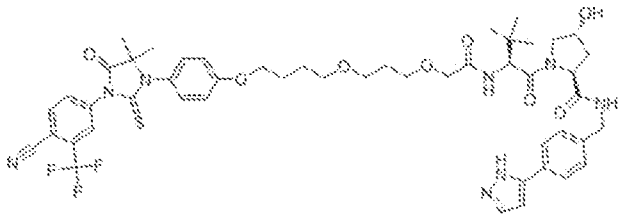
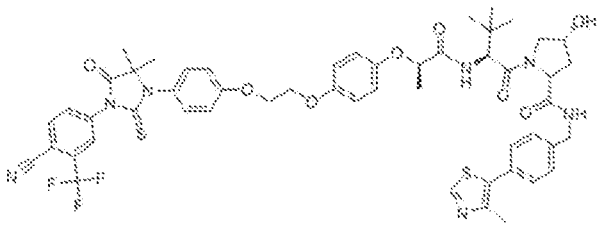
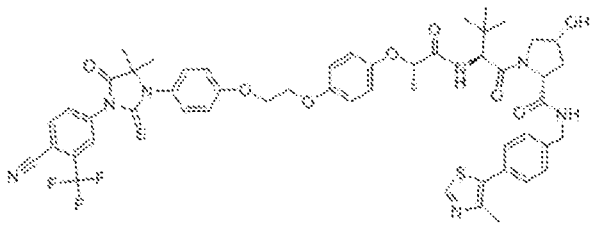
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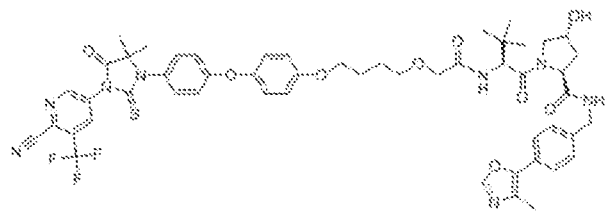
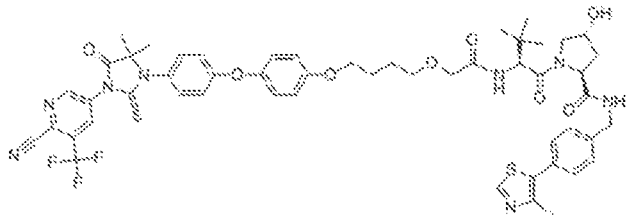
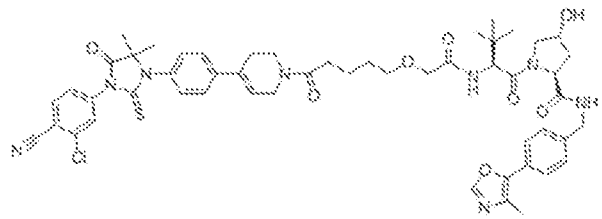
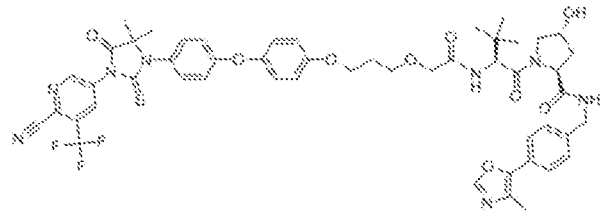
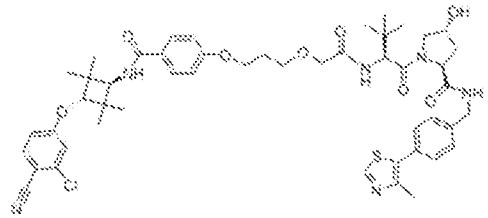
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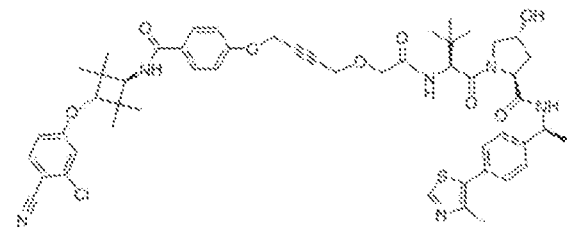
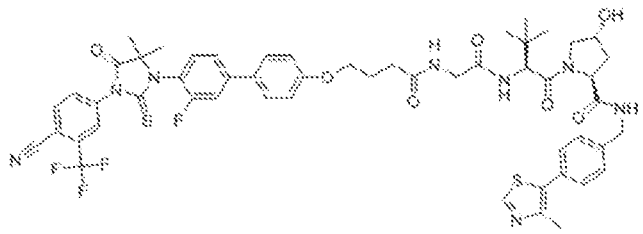
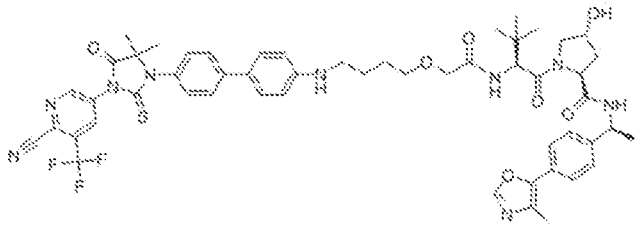
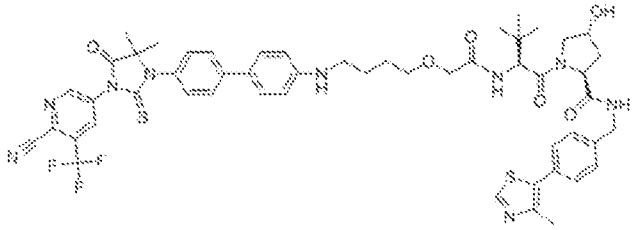
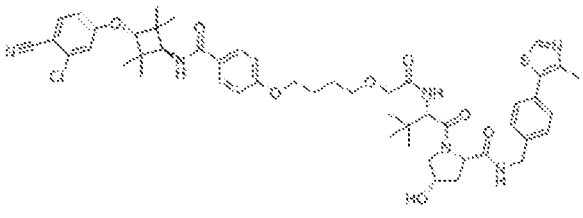
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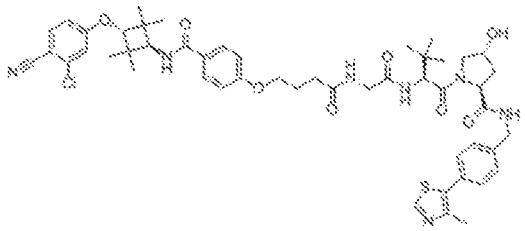
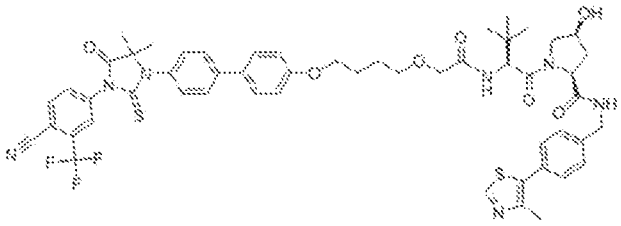
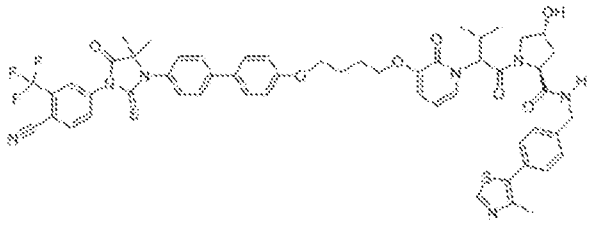
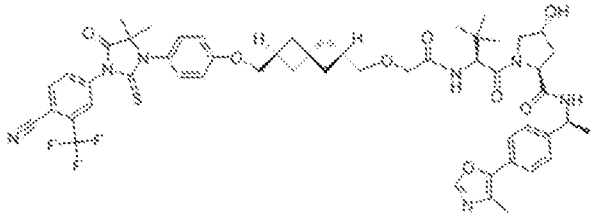
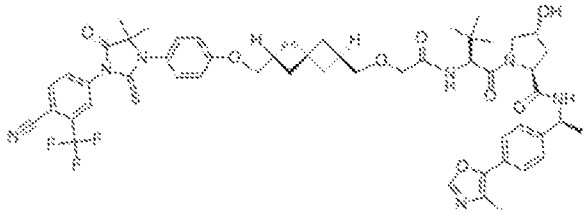
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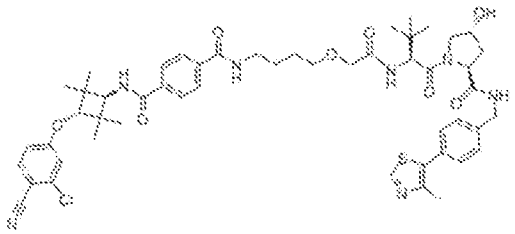
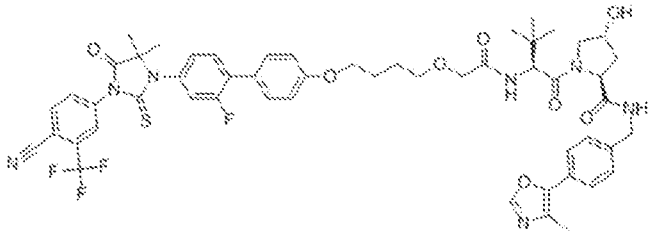
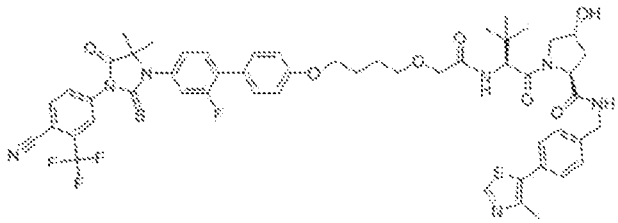
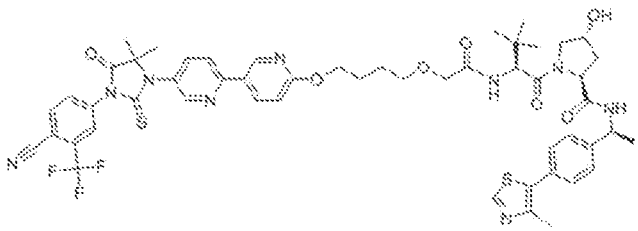
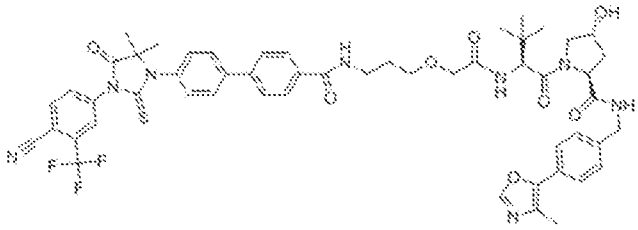
373		1034.40	
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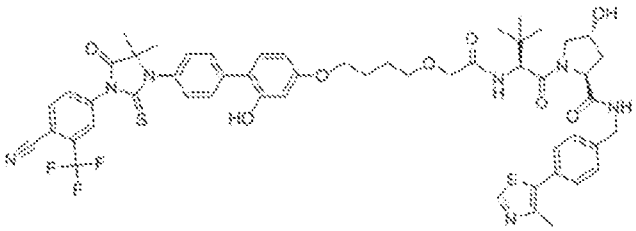
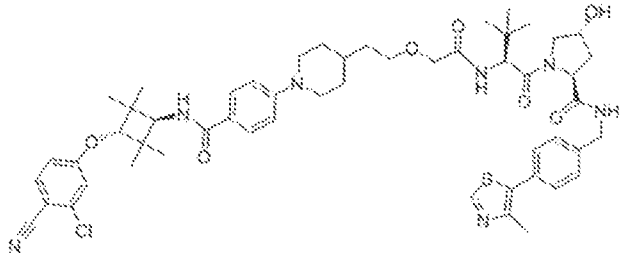
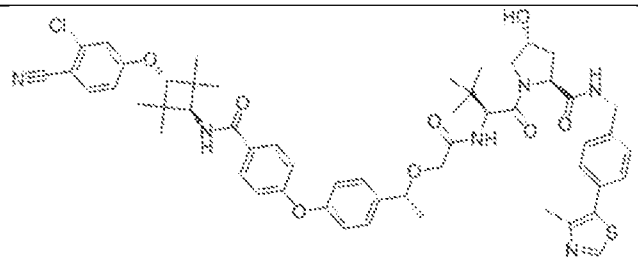
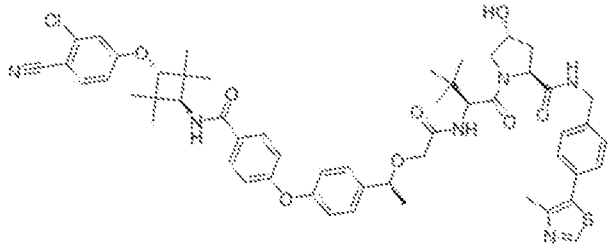
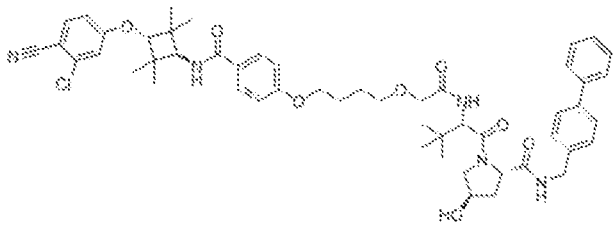
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379		1025.37	
380		975.30	
381		1026.16	
382		1026.16	

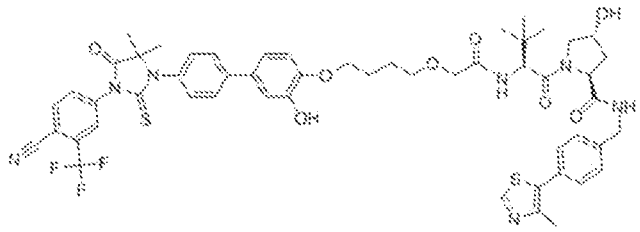
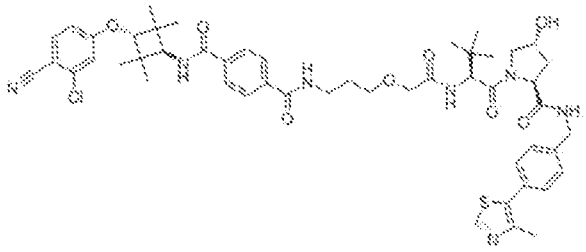
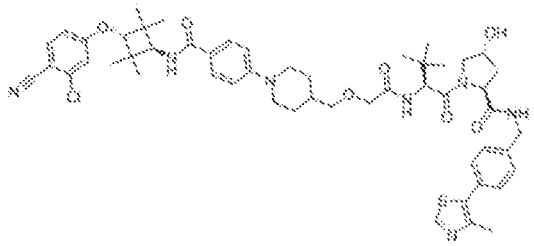
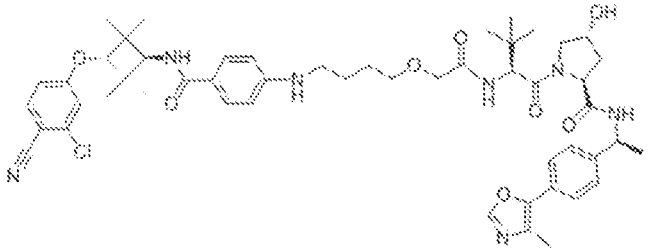
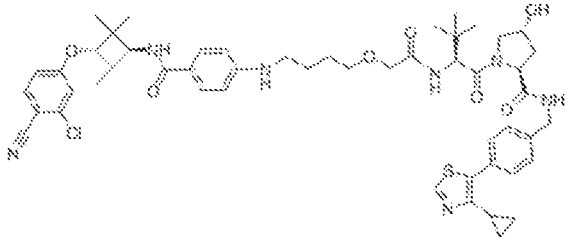
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384		1041.30	
385		991.26	993.26
386		1011.30	
387		927.37	929.37

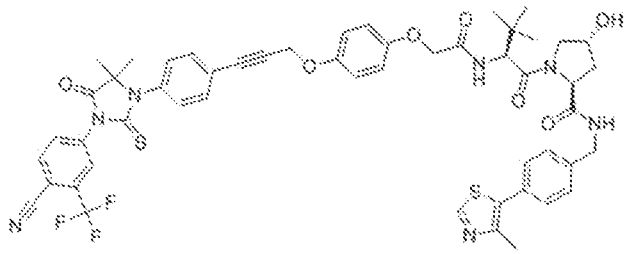
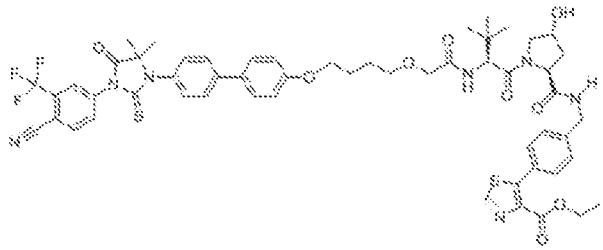
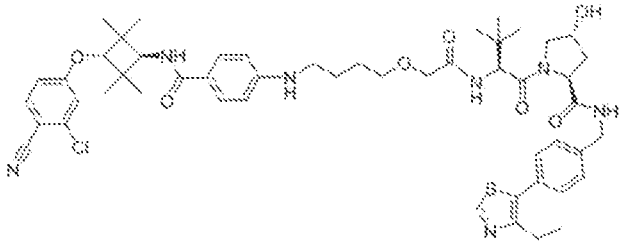
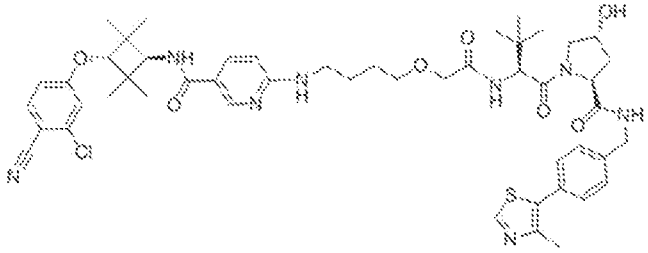
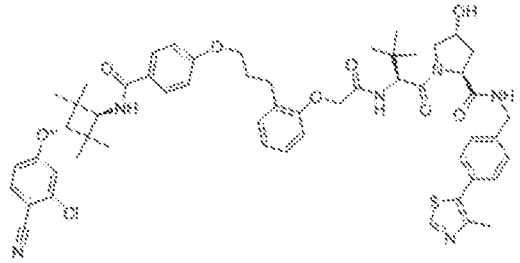
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389		1055.10	
390		1022.25	
391		1024.15	
392		941.39	943.39

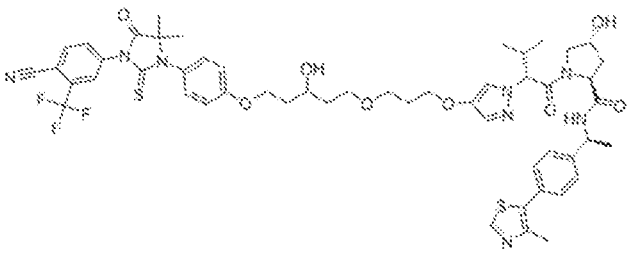
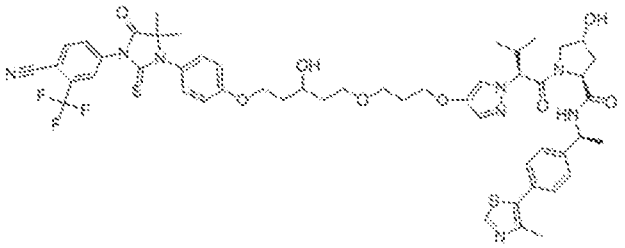
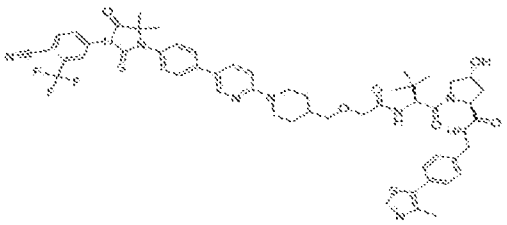
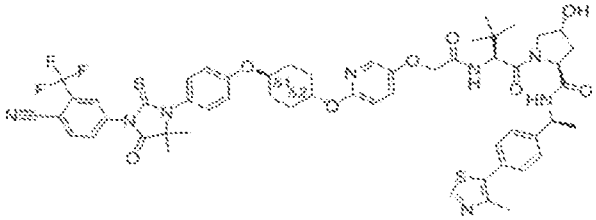
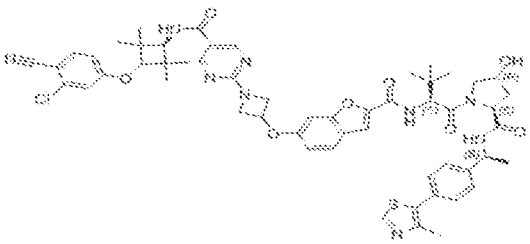
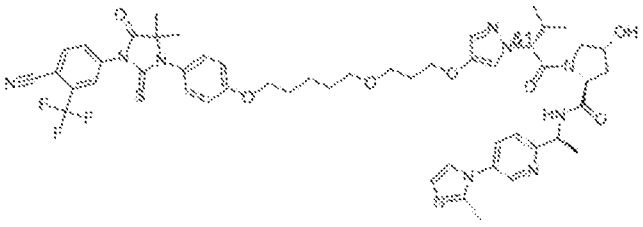
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394		988.37	990.37
395		1045.35	
396		1012.15	
397		1012.15	

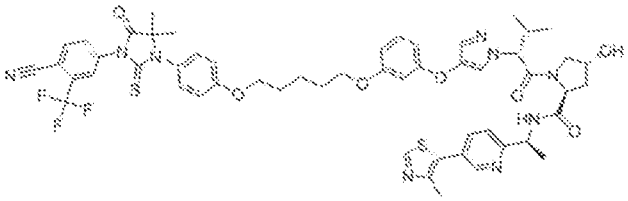
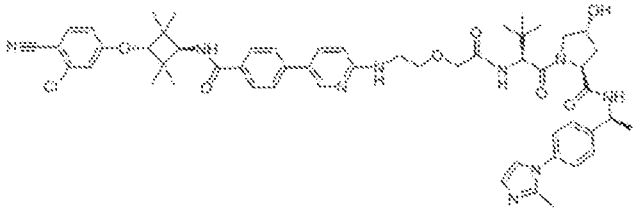
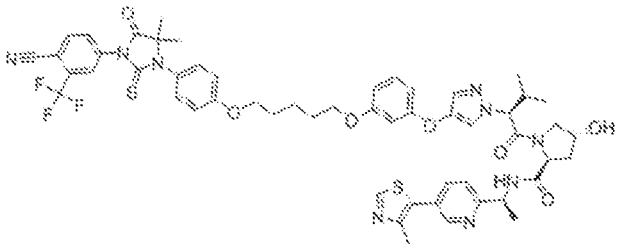
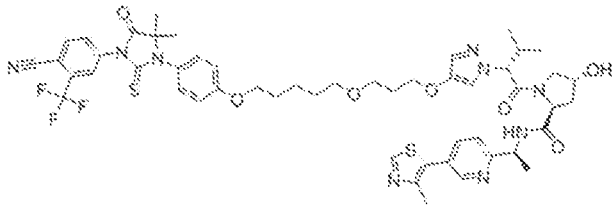
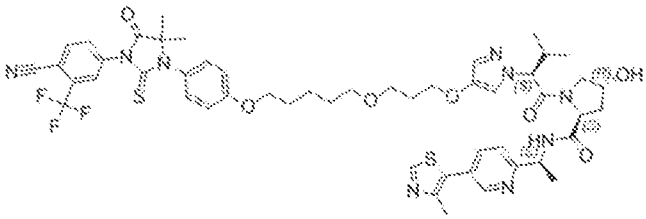
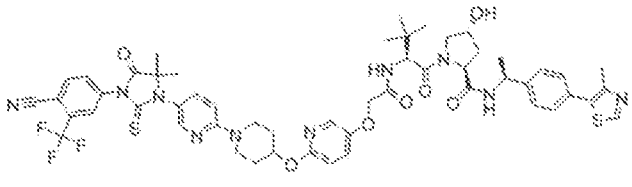
398		968.32	970.32
399		1026.15	
400		1042.20	
401		1040.35	
402		1021.20	

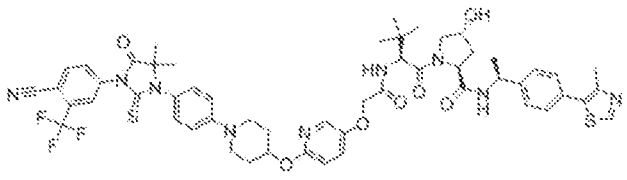
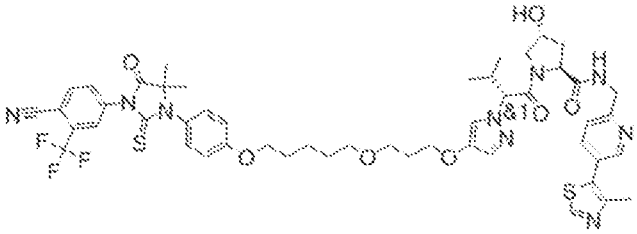
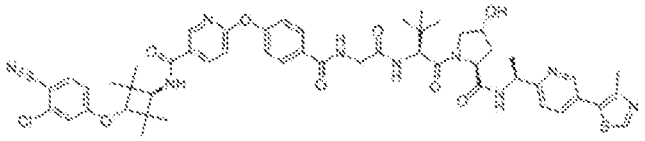
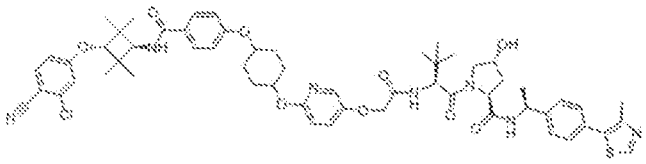
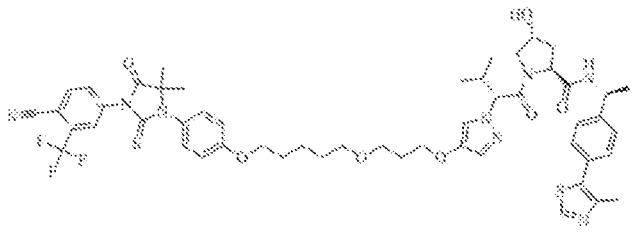
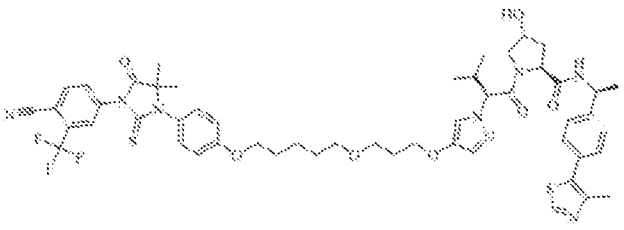
403		1040.15	
404		980.52	982.52
405		989.40	991.40
406		989.40	991.40
407		920.58	922.58

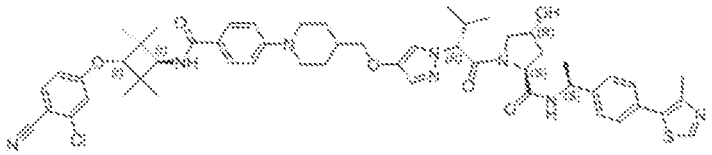
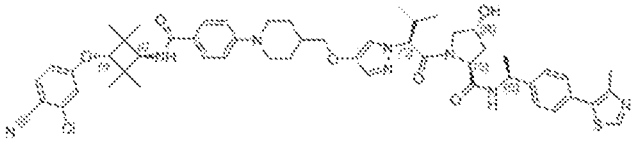
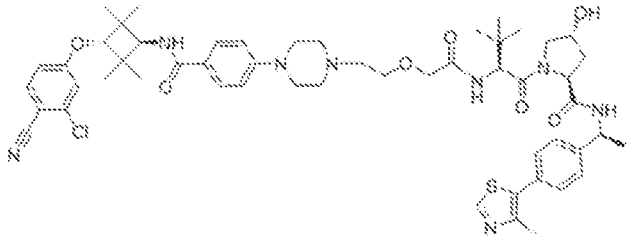
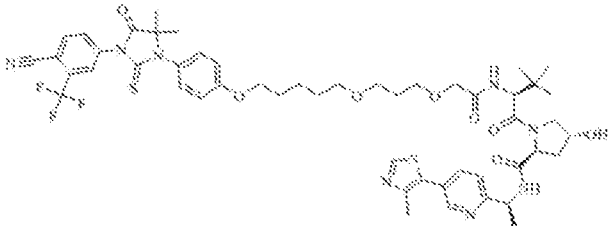
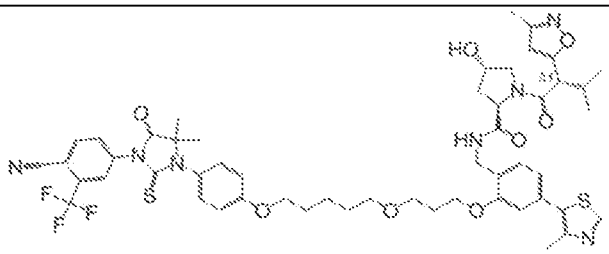
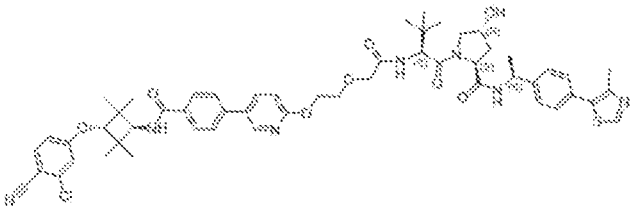
408		1040.10	
409		954.38	956.38
410		966.37	968.41
411		938.44	940.44
412		966.42	968.42

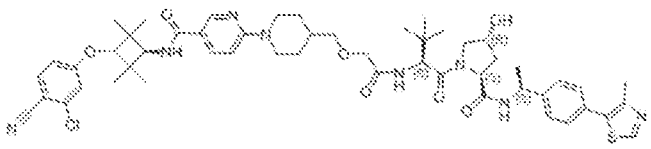
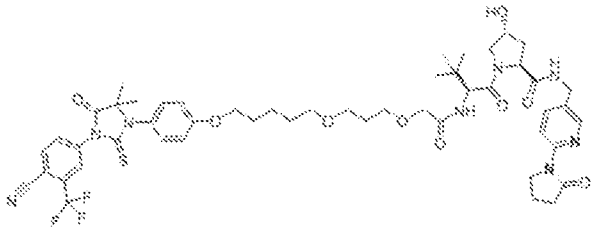
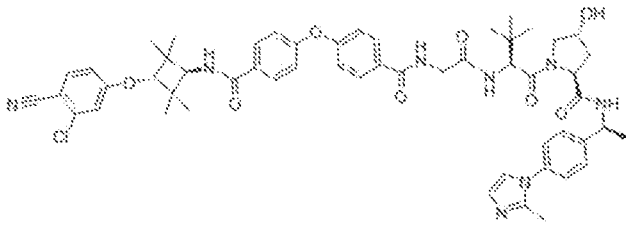
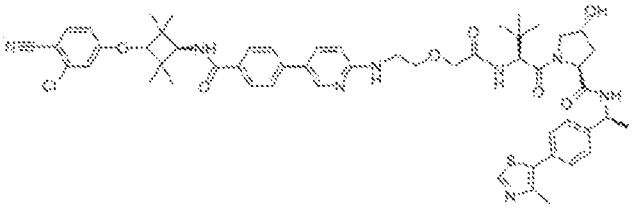
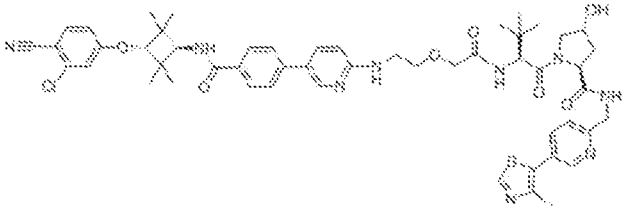
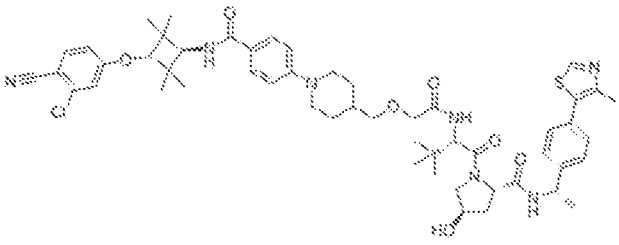
413		1006.30	
414		1083.34	
415		954.40	956.40
416		941.38	943.38
417		1003.39	1005.39

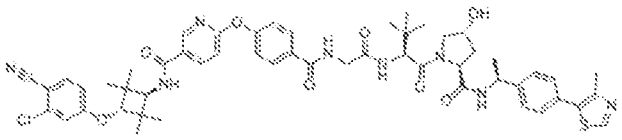
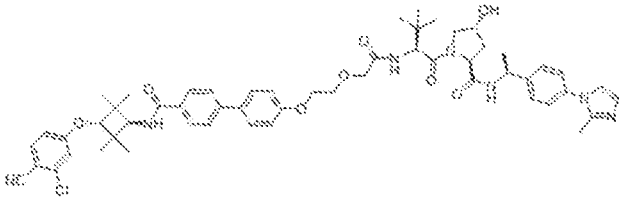
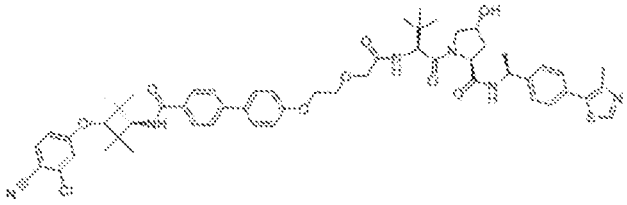
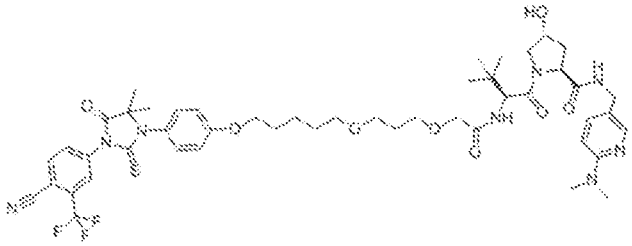
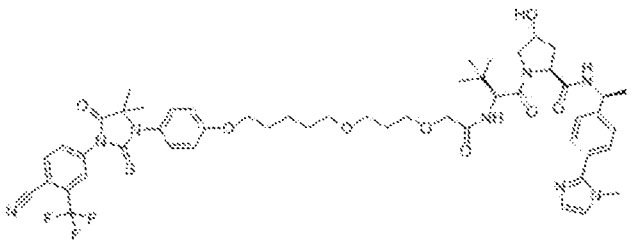
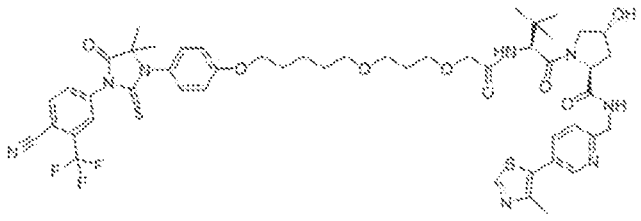
418		1045.38	
419		1045.38	
420		1050.39	
421		1081.38	
422		1042.39	1044.39
423		1013.42	

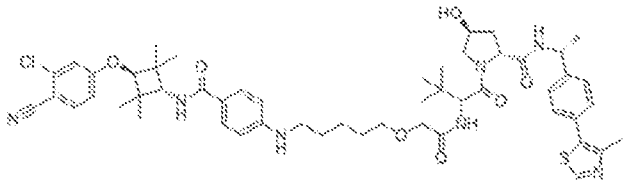
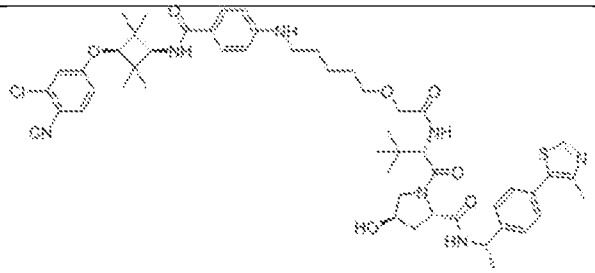
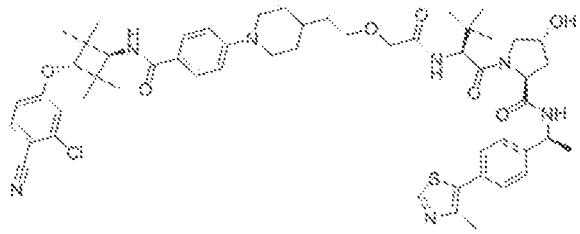
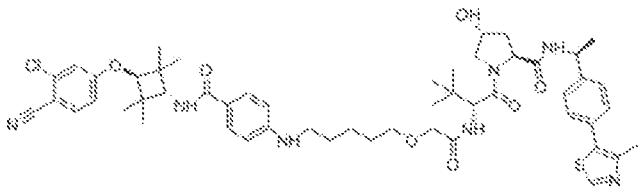
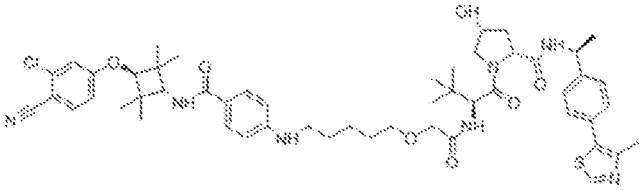
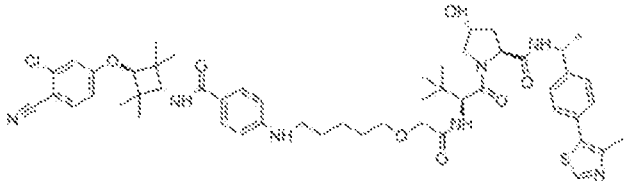
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426		1064.37	
427		1030.38	
428		1030.38	
429		1067.38	

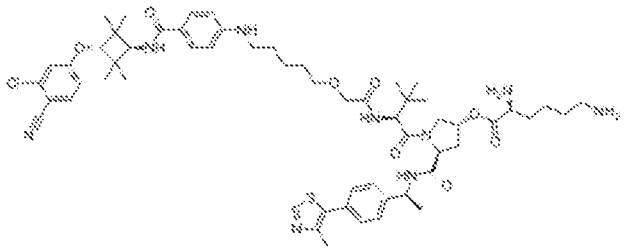
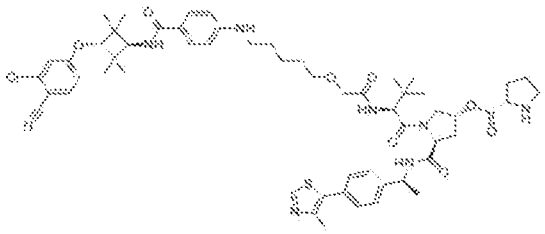
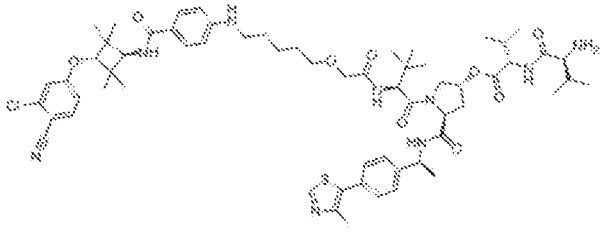
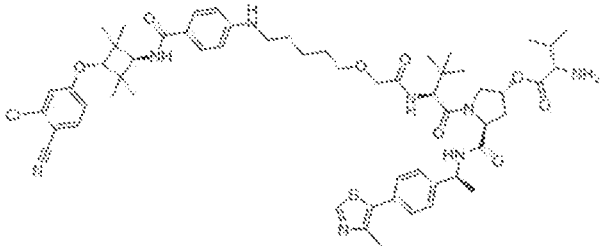
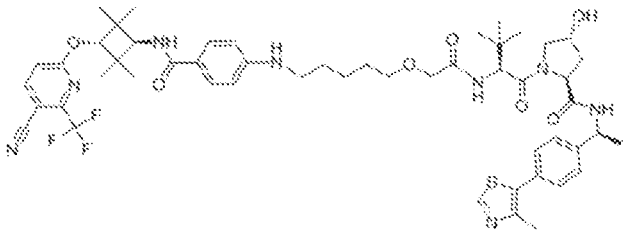
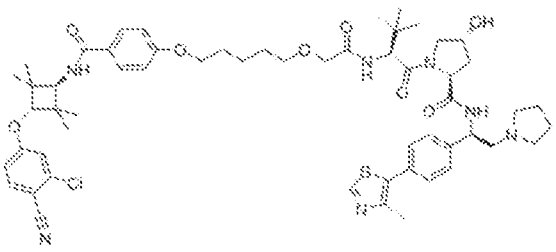
430		1066.38	
431		1016.37	
432		1004.38	1006.38
433		1074.45	1076.45
434		1029.39	
435		1029.39	

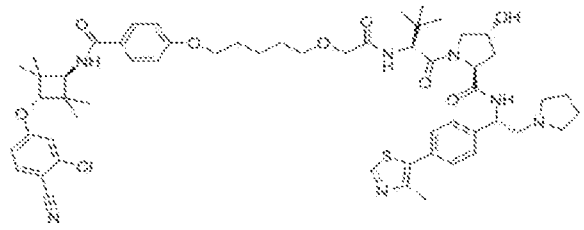
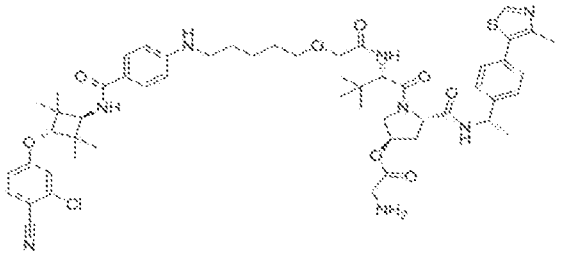
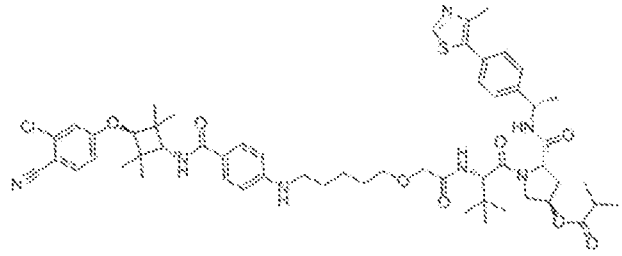
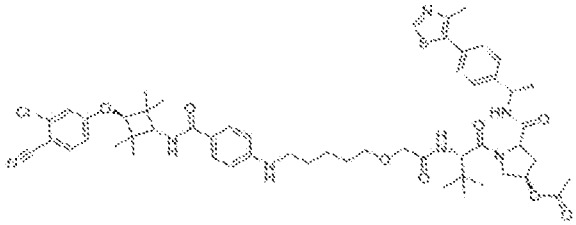
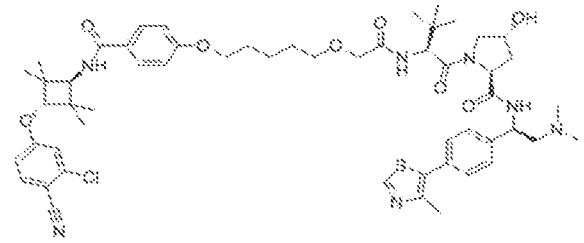
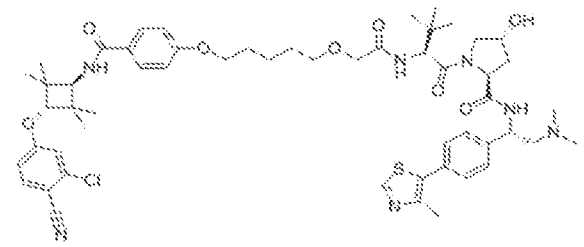
436		975.40	977.40
437		975.40	977.40
438		995.46	997.46
439		1036.40	
440		1030.38	
441		1004.30	1006.40

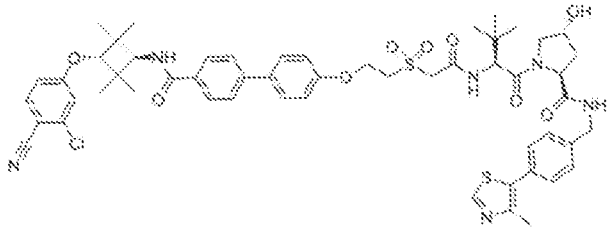
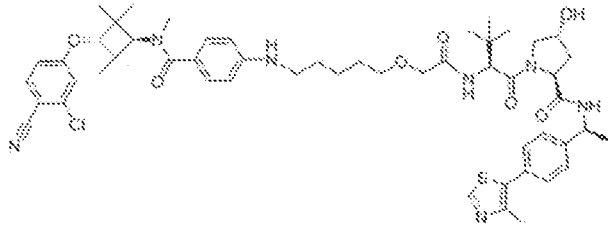
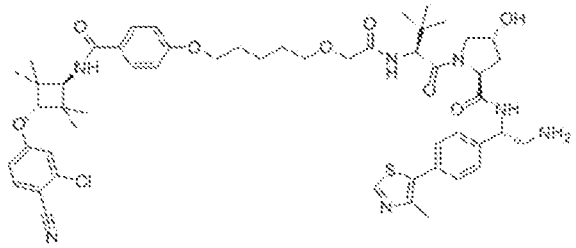
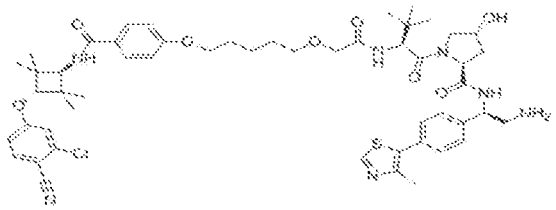
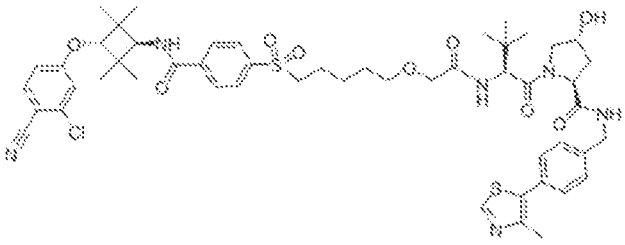
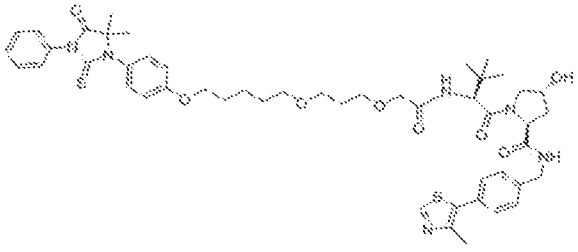
442		981.40	983.40
443		1007.42	
444		985.43	987.43
445		1003.42	1005.43
446		990.41	992.41
447		980.45	982.45

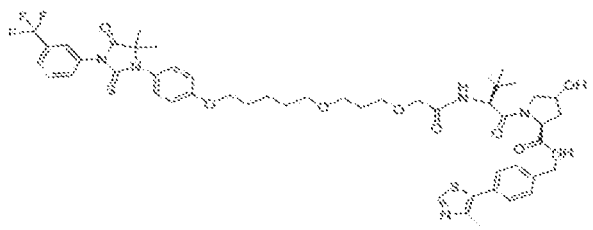
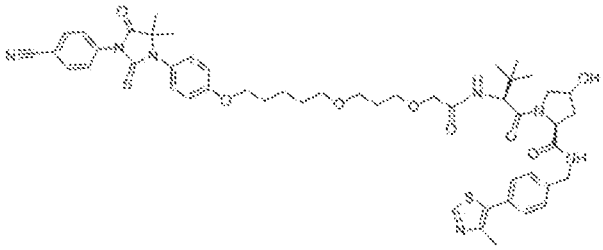
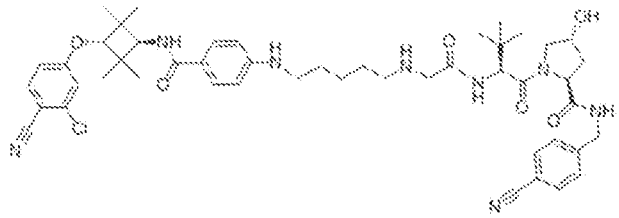
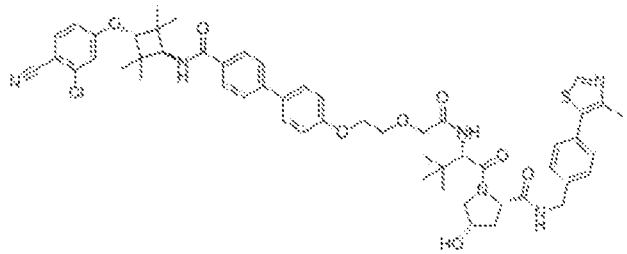
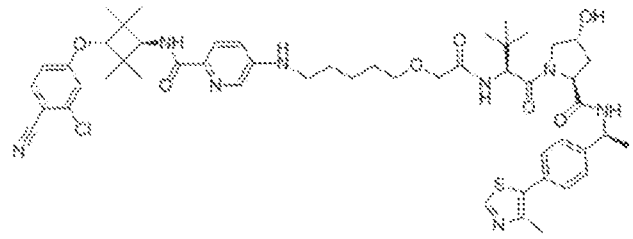
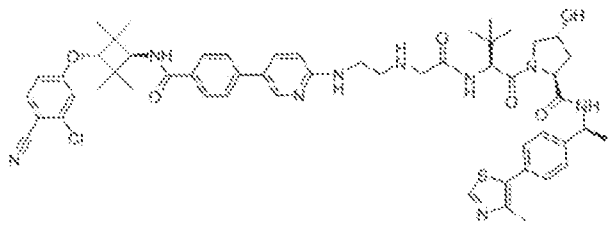
448		1003.30	1005.40
449		986.40	988.40
450		1003.40	1005.40
451		967.43	
452		1017.45	
453		1021.39	

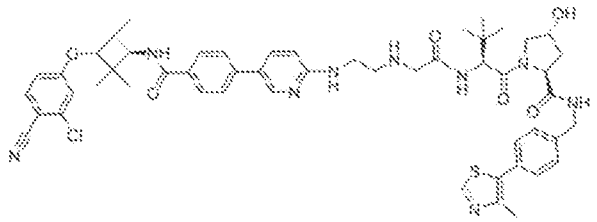
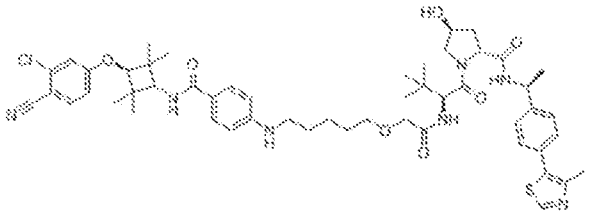
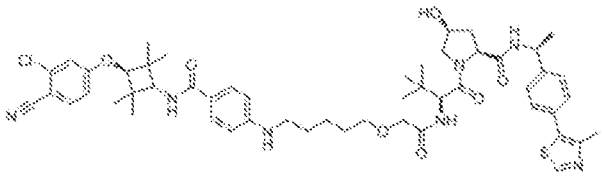
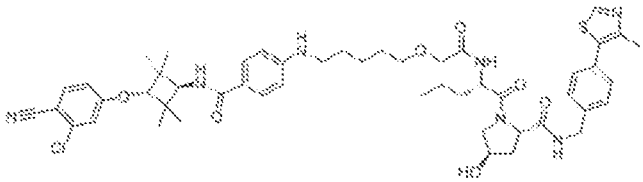
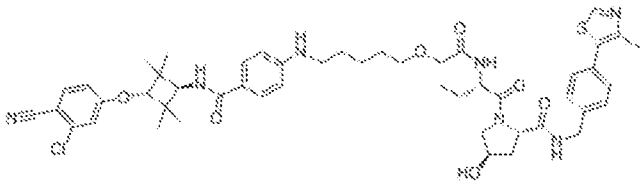
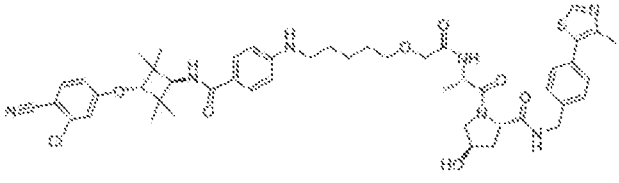
454		968.45	970.45
455		968.45	970.45
456		994.55	996.45
457		968.35	970.35
458		968.35	970.35
459		968.35	970.35

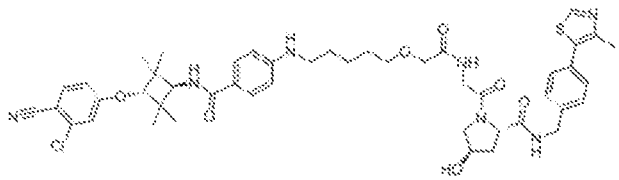
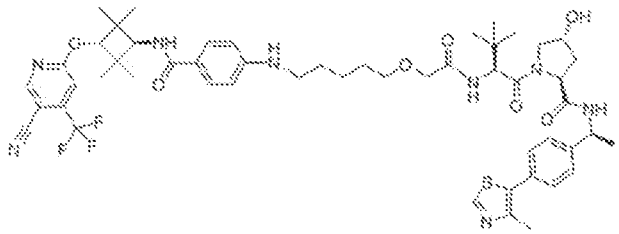
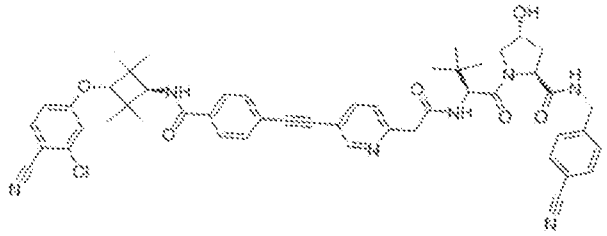
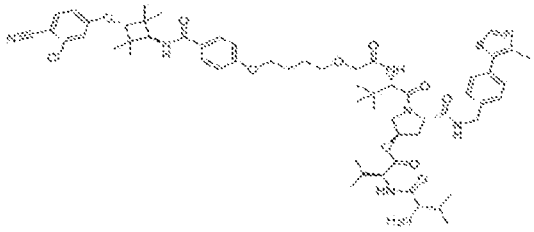
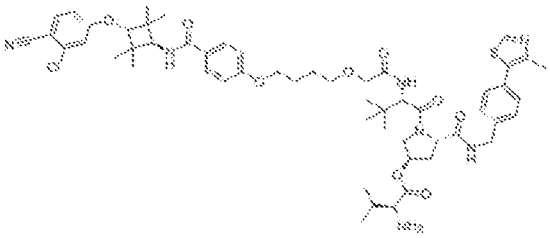
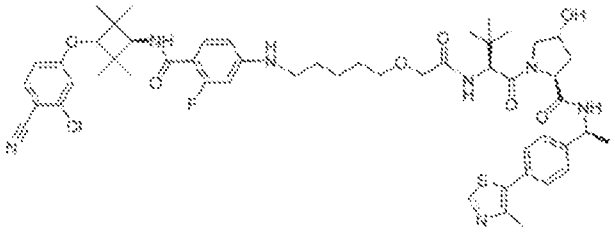
460		1096.43	1098.43
461		1065.38	1067.38
462		1166.46	1168.46
463		1067.40	1069.40
464		1003.50	
465		1038.50	1040.50

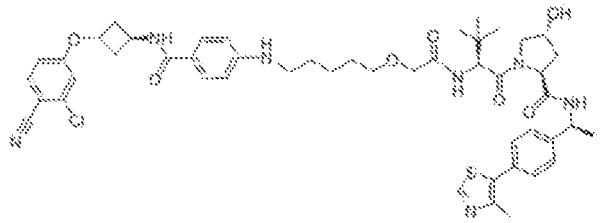
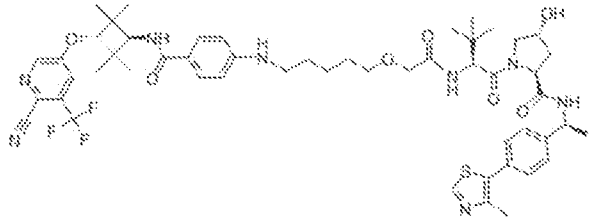
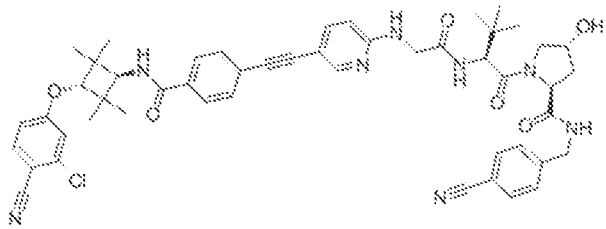
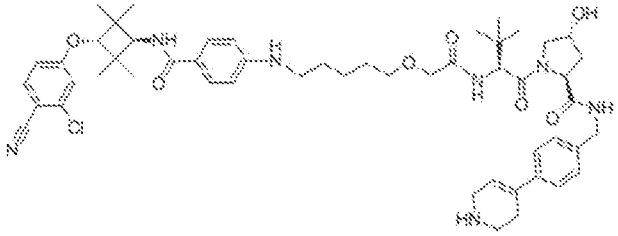
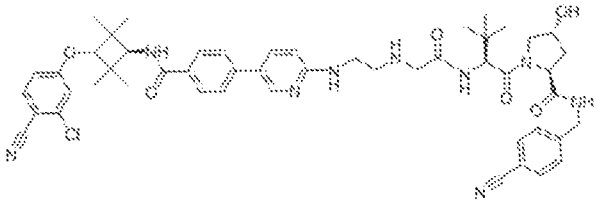
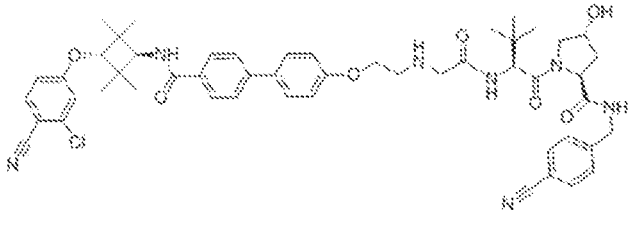
466		1038.55	1040.55
467		1025.36	1027.36
468		1038.37	1040.37
469		1010.34	1012.35
470		1012.35	1014.35
471		1012.35	1014.36

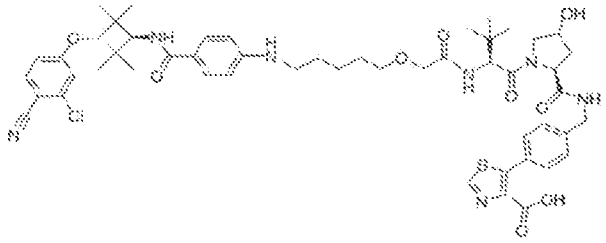
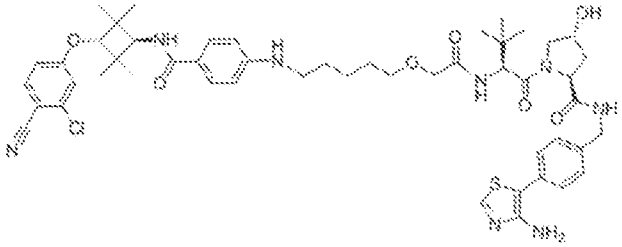
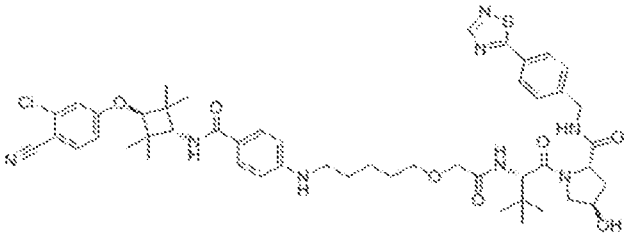
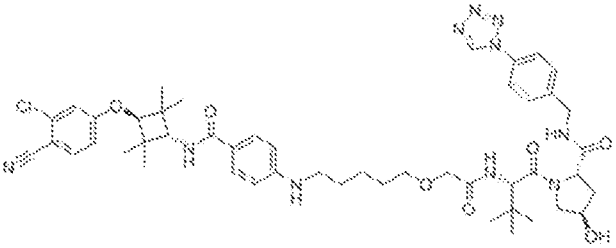
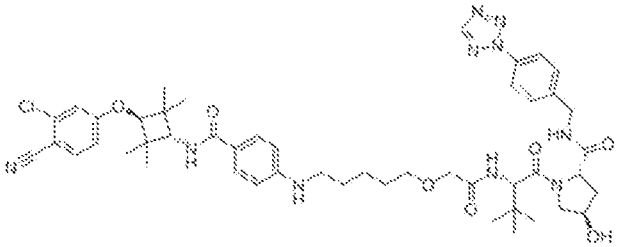
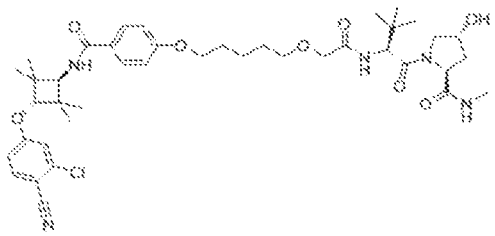
472		1037.25	1039.24
473		982.35	984.35
474		984.33	986.33
475		984.33	986.33
476		1003.26	1005.26
477		927.30	

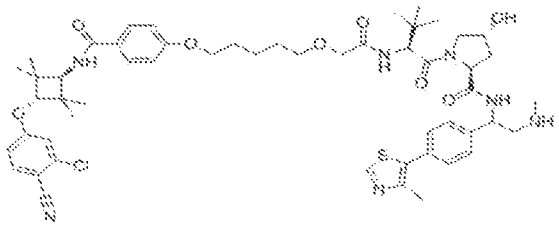
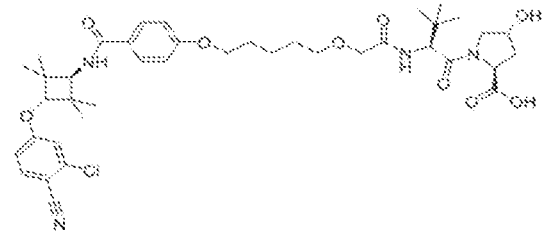
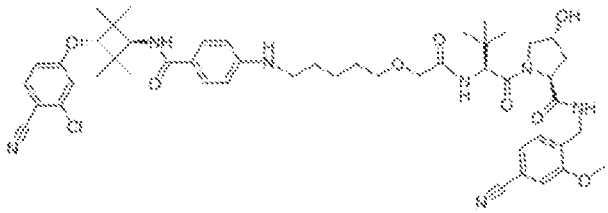
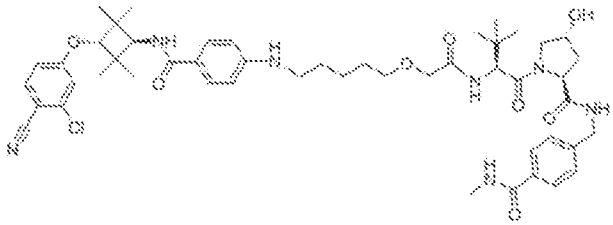
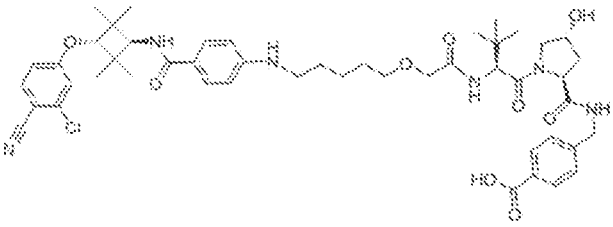
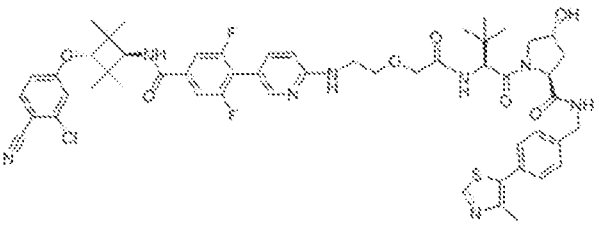
478		995.30	997.30
479		952.30	
480		881.34	883.34
481		989.28	991.28
482		969.33	971.33
483		1002.33	1004.33

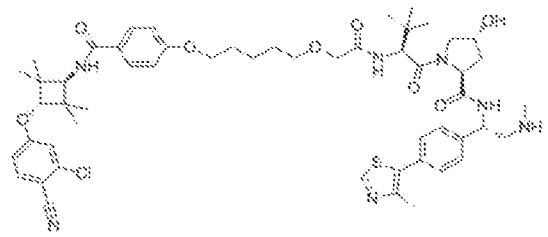
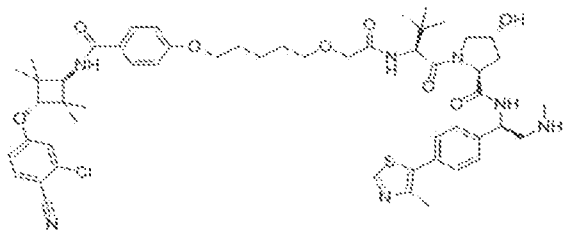
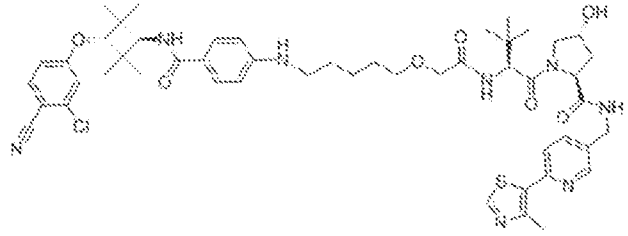
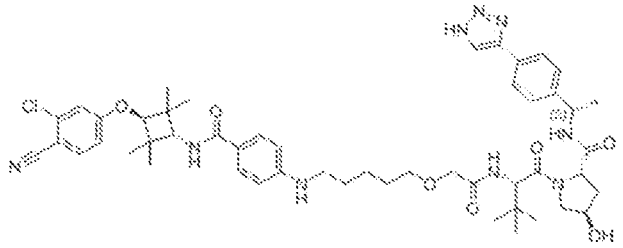
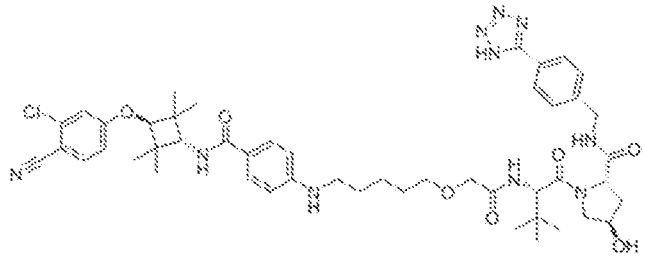
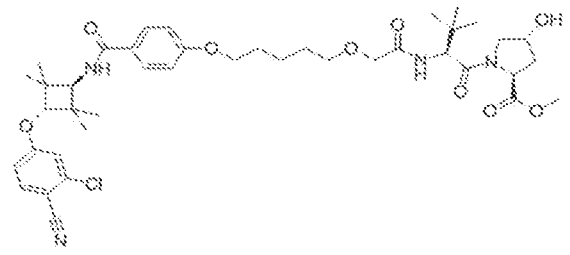
484		988.31	990.31
485		968.83	970.83
486		969.33	971.33
487		940.30	
488		926.29	928.29
489		912.23	914.23

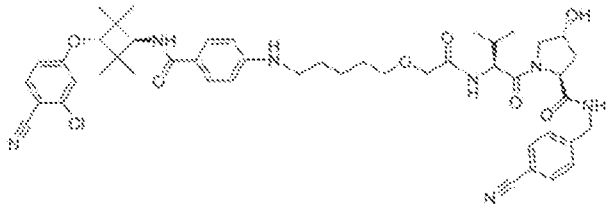
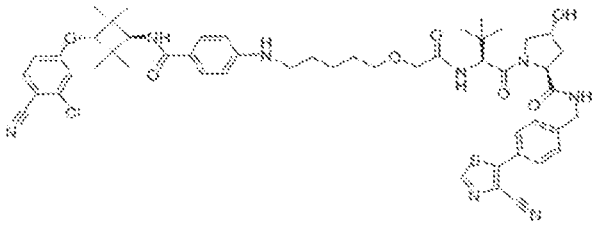
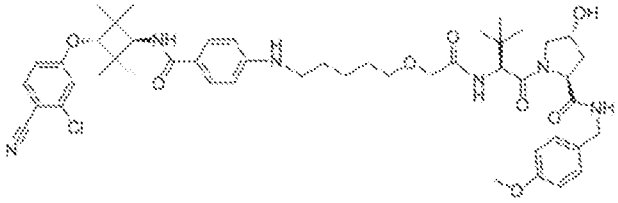
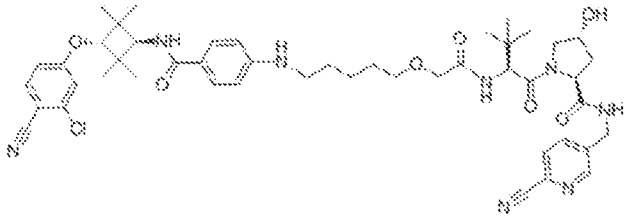
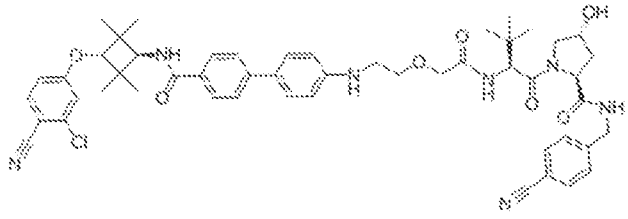
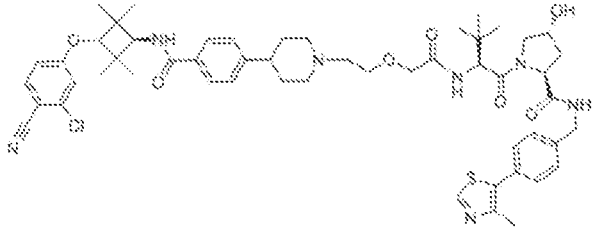
490		898.26	900.26
491		1003.60	
492		882.26	884.26
493		1139.41	1141.41
494		1040.35	1042.35
495		986.32	988.32

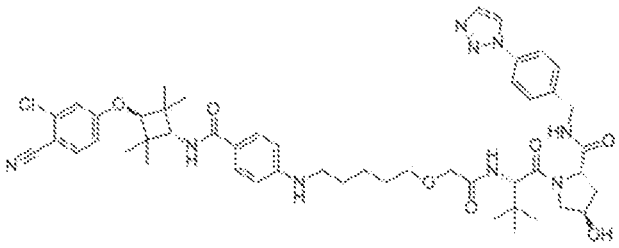
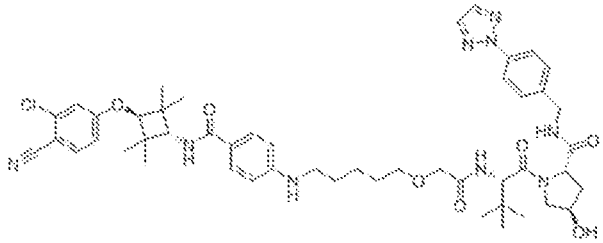
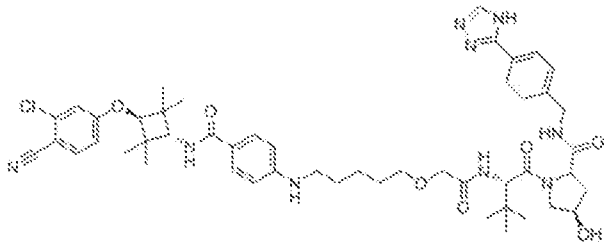
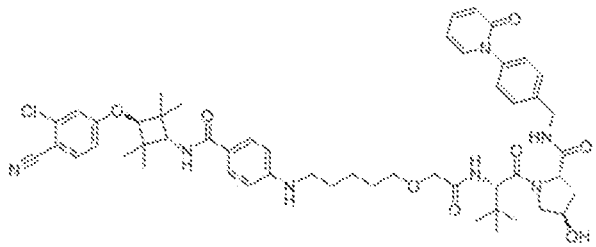
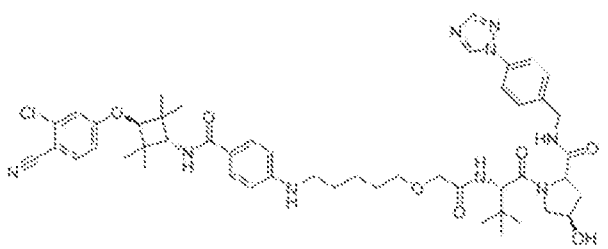
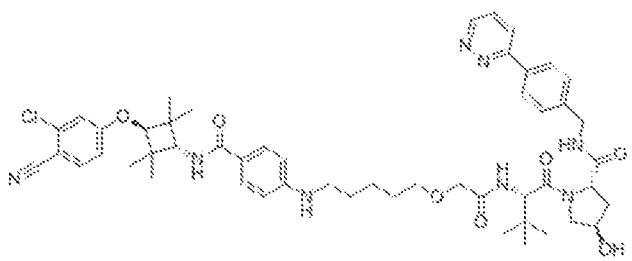
496		912.28	914.28
497		1003.45	
498		897.27	899.27
499		938.27	940.37
500		916.31	918.31
501		916.31	918.31

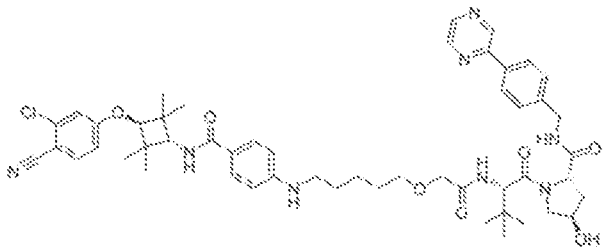
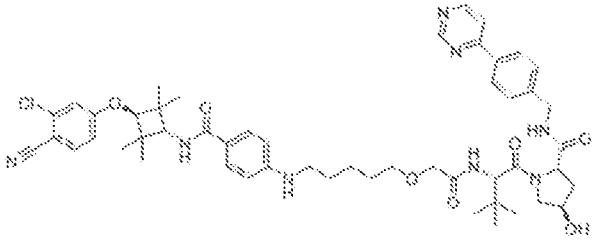
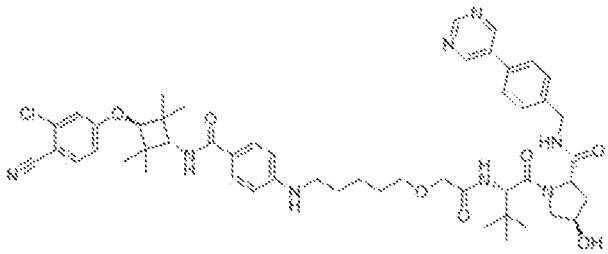
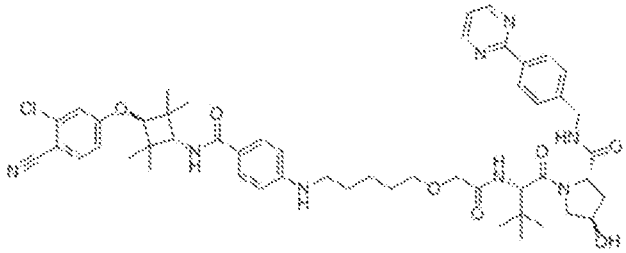
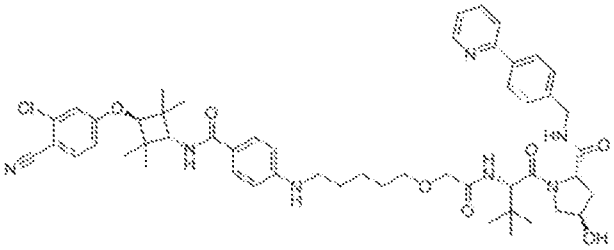
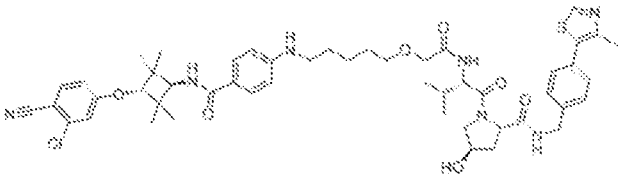
502		984.30	986.30
503		955.32	957.32
504		942.33	944.33
505		926.37	927.36
506		926.37	927.40
507		782.30	784.30

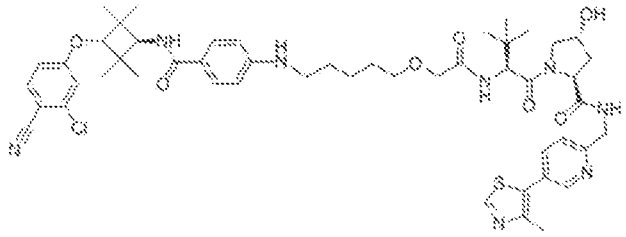
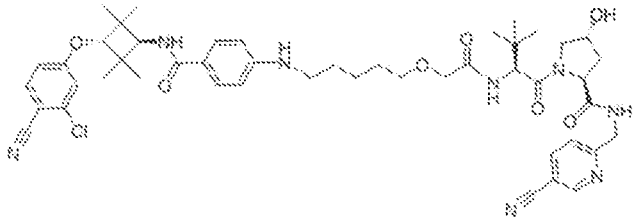
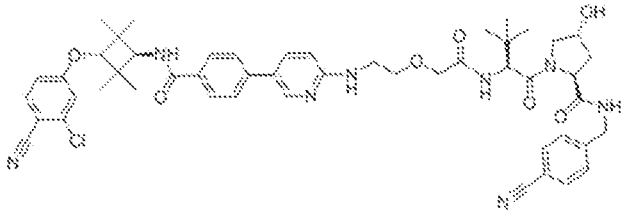
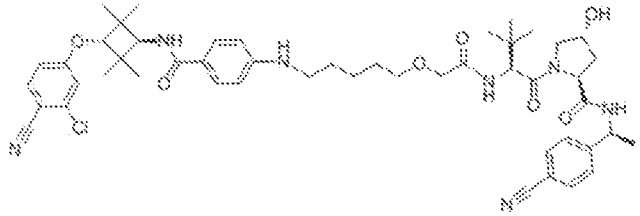
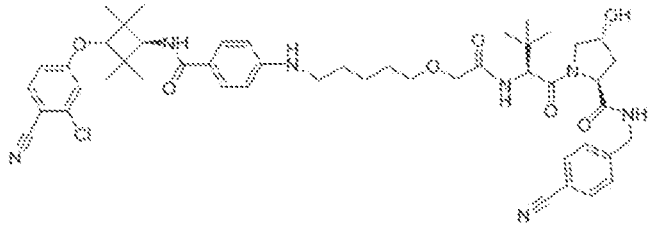
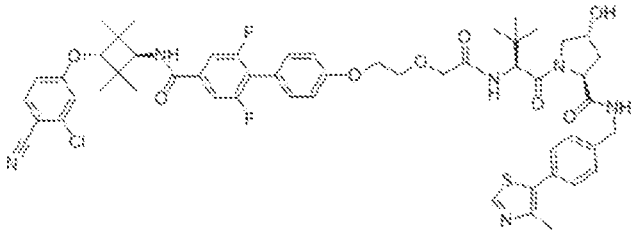
508		998.36	1000.36
509		769.27	771.27
510		912.35	914.35
511		914.36	916.36
512		901.33	903.33
513		1025.29	1027.29

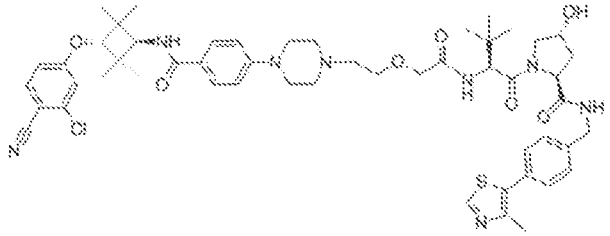
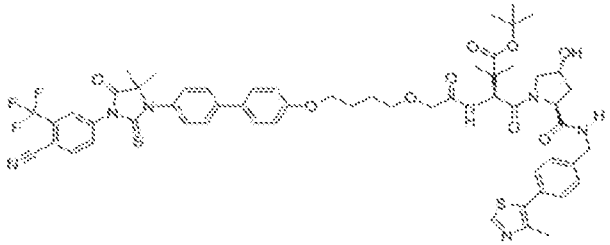
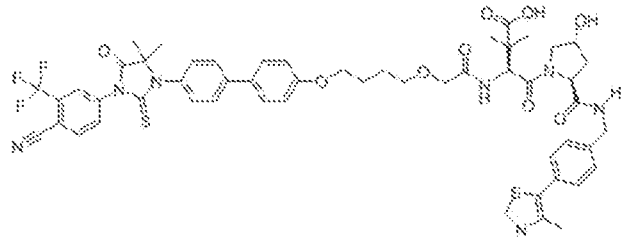
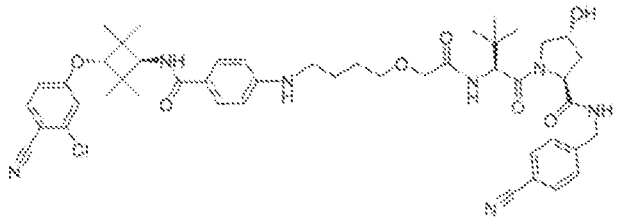
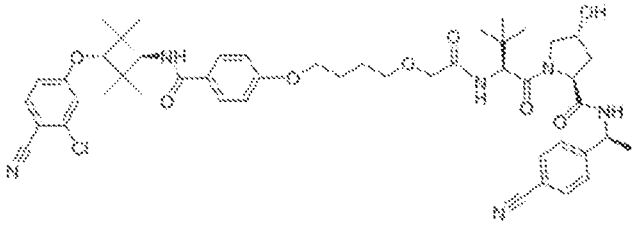
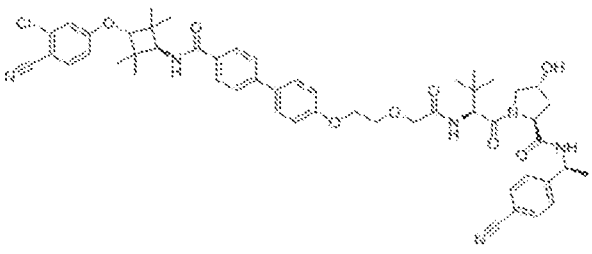
514		998.34	1000.34
515		998.34	1000.34
516		955.33	957.33
517		939.45	941.45
518		926.43	928.43
519		783.30	785.30

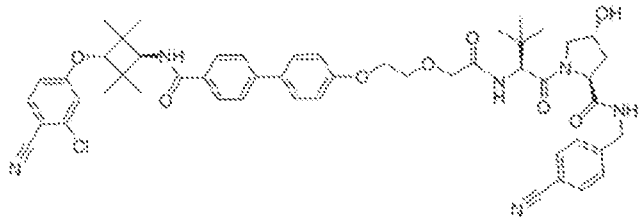
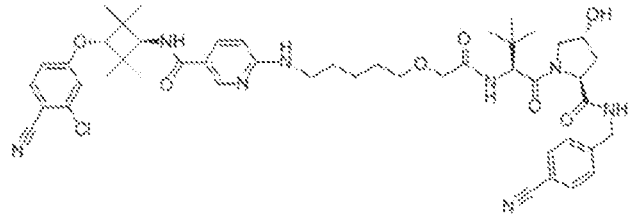
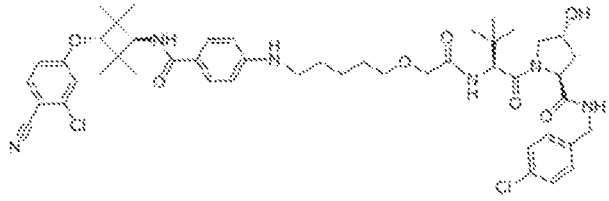
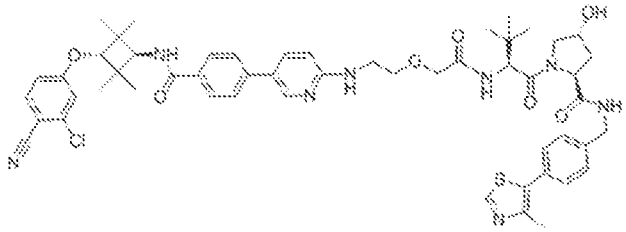
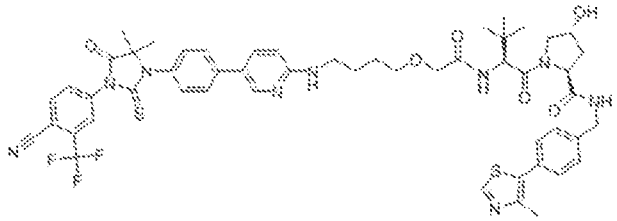
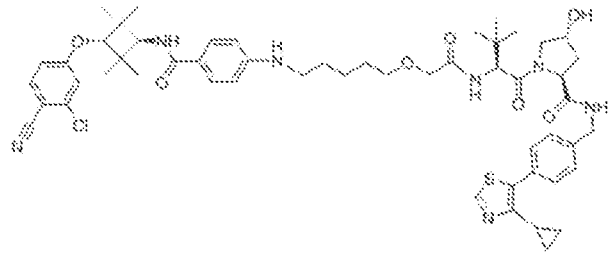
520		868.34	870.34
521		965.34	967.34
522		887.37	889.37
523		883.35	885.35
524		916.34	918.34
525		980.37	982.37

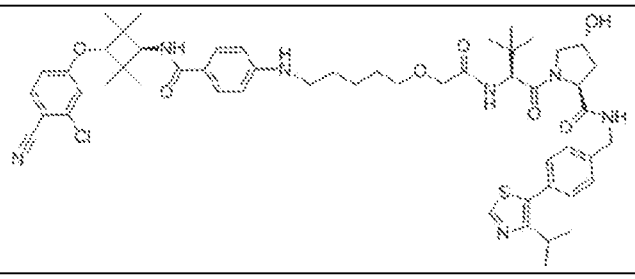
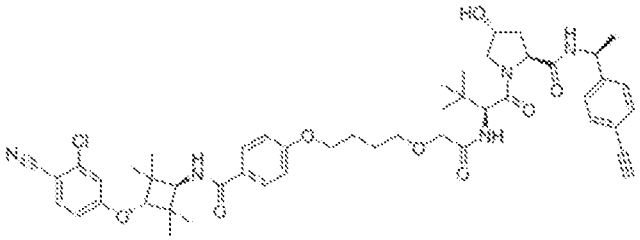
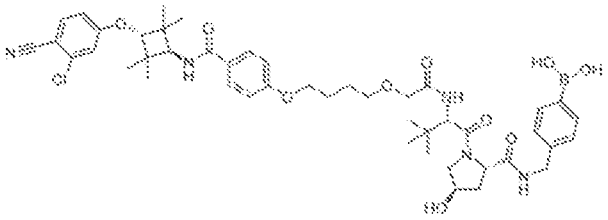
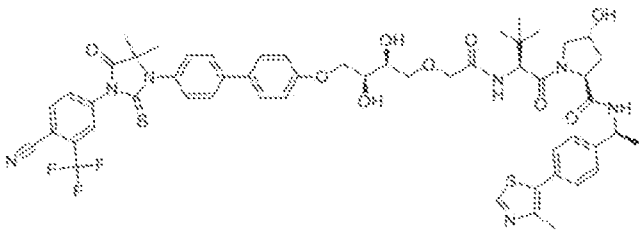
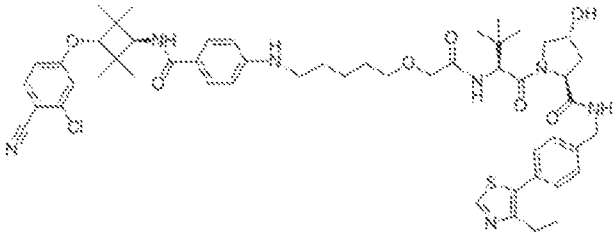
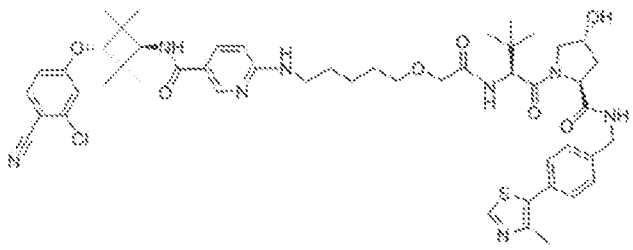
526		925.43	927.43
527		925.44	927.43
528		925.43	927.43
529		951.44	953.44
530		925.44	927.43
531		936.44	938.44

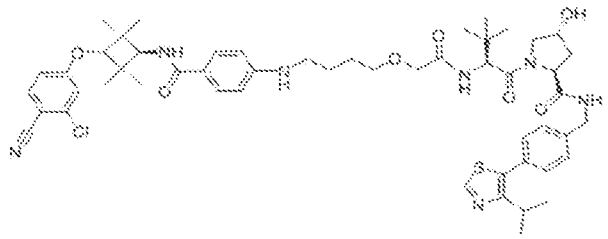
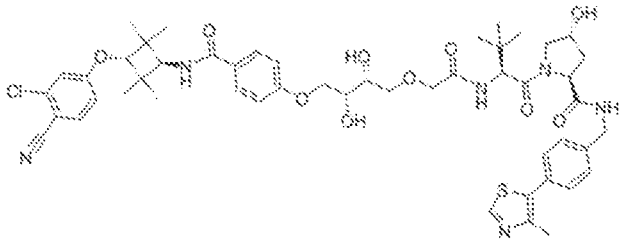
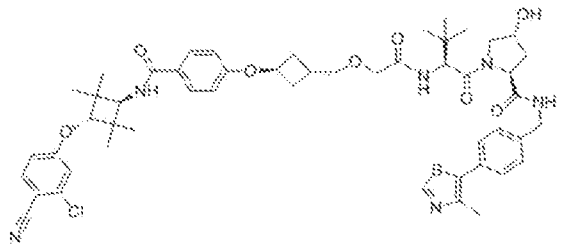
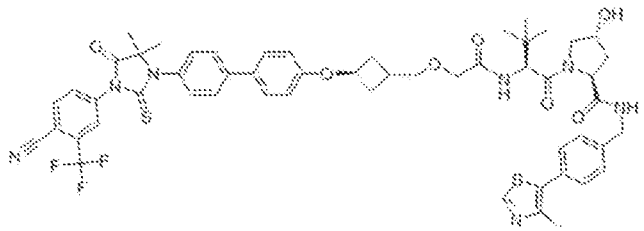
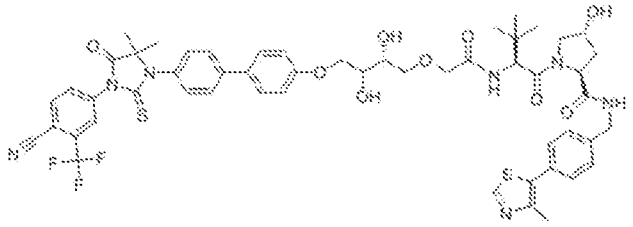
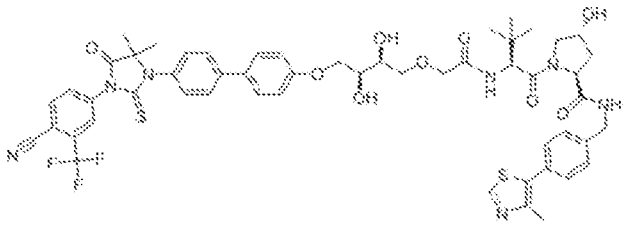
532		936.44	938.44
533		936.44	938.44
534		936.44	938.44
535		936.44	938.44
536		935.45	937.45
537		940.35	942.35

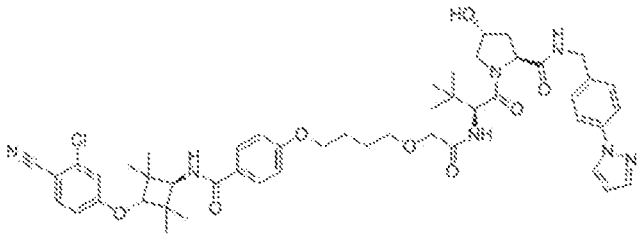
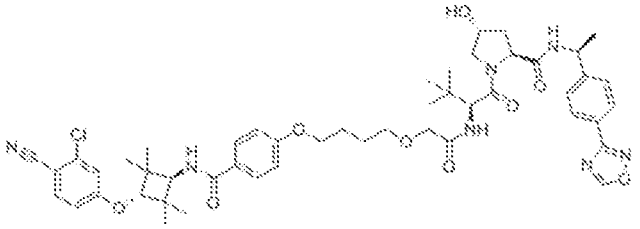
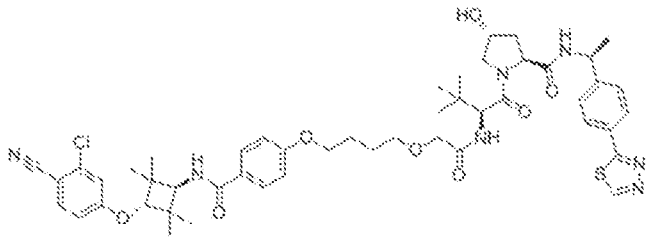
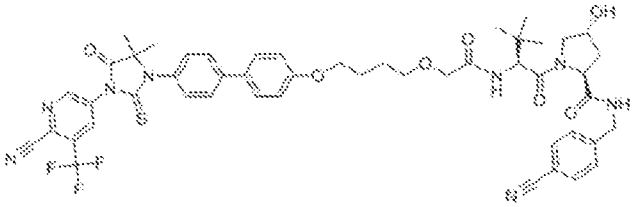
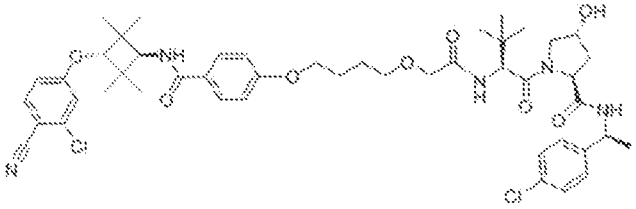
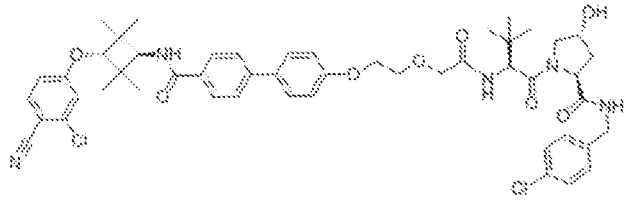
538		955.41	957.41
539		883.41	885.41
540		917.39	919.39
541		896.43	898.43
542		882.41	884.41
543		1025.38	1027.38

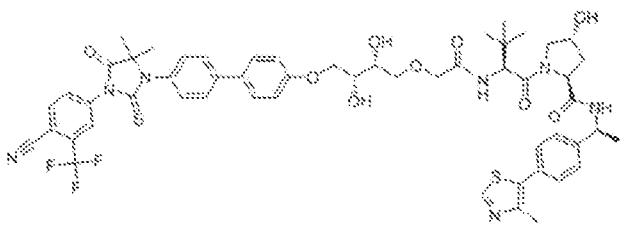
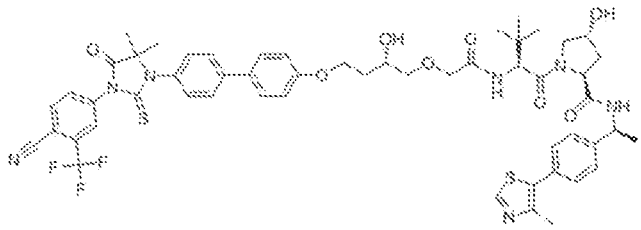
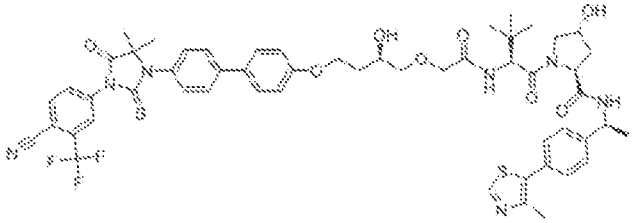
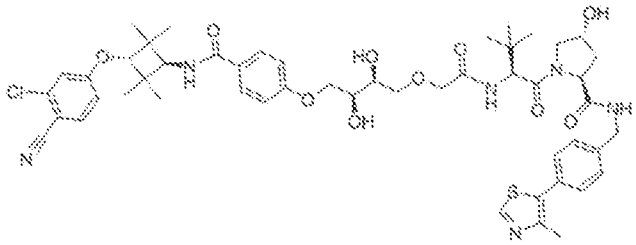
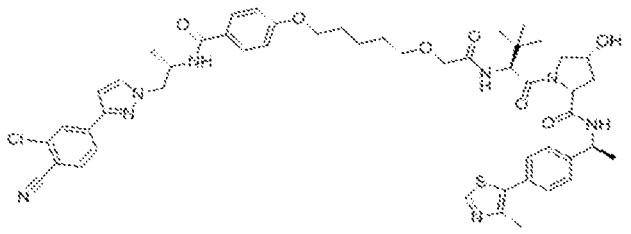
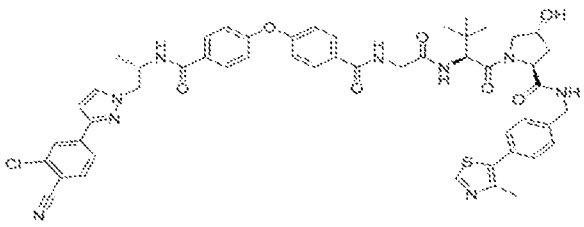
544		981.43	983.43
545		1110.30	
546		1055.30	
547		868.40	870.40
548		883.40	885.40
549		931.86	933.86

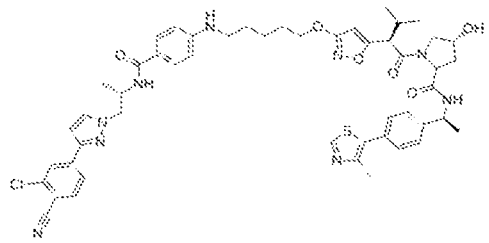
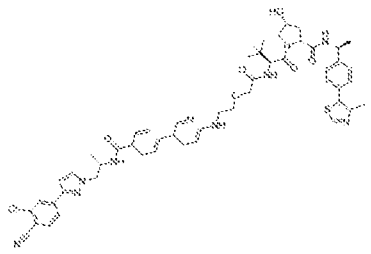
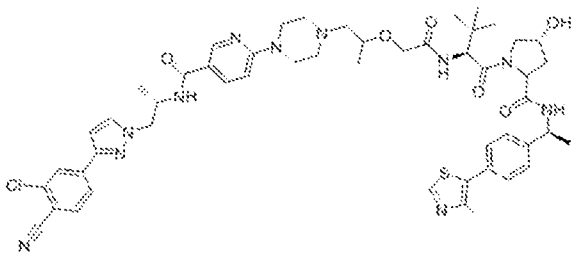
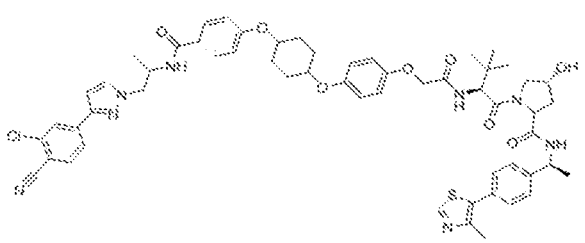
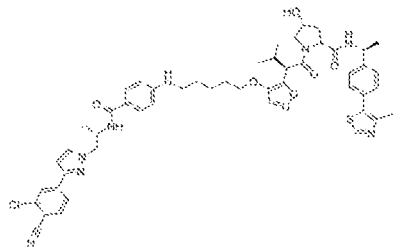
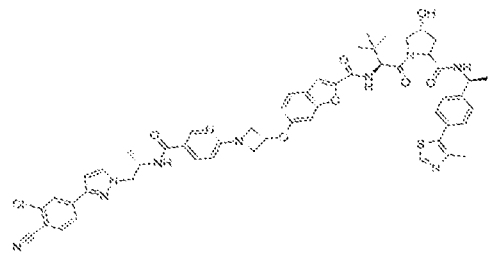
550		917.38	919.38
551		883.41	885.41
552		891.38	893.38
553		989.40	991.40
554		1024.15	
555		980.43	982.43

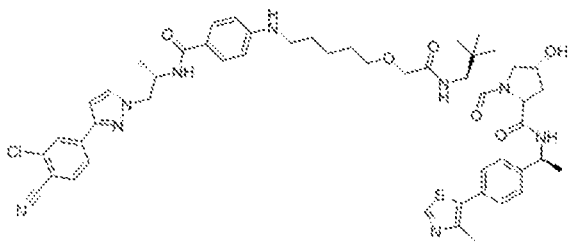
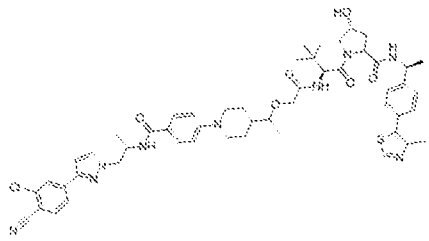
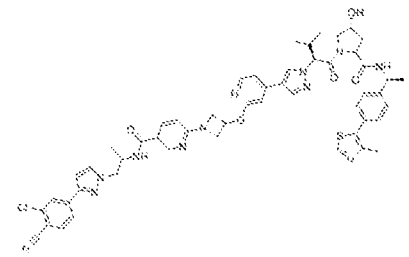
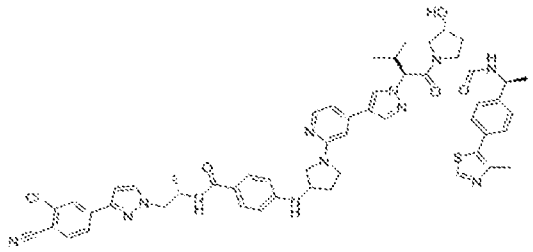
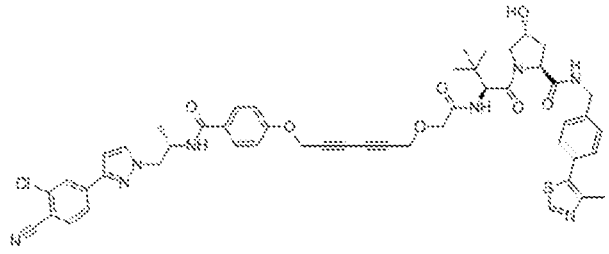
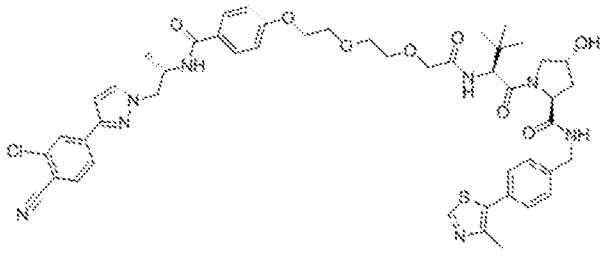
556		982.45	984.45
557		883.39	885.39
558		888.38	890.38
559		1070.15	
560		968.41	970.41
561		955.40	957.40

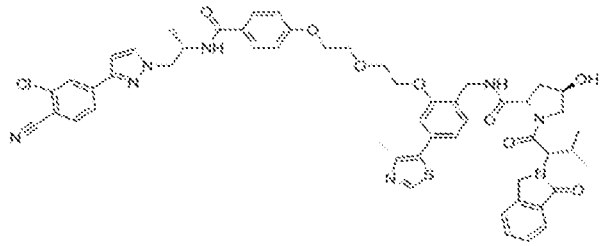
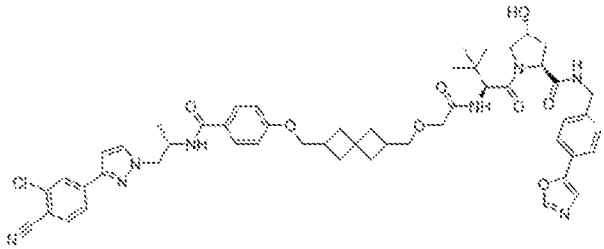
562		968.41	970.41
563		973.36	975.36
564		953.37	955.37
565		1036.20	
566		1056.15	
567		1056.15	

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			
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[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^{TM}) 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

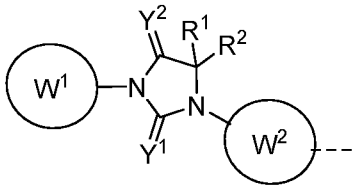
[0896] In summary, PROTACs designed to degrade AR are potent (low nM to pM), specific, rapid (within 2-4 hrs); long-lasting (days); active *in vitro* and *in vivo*, and have cellular efficacy superior to enzalutamide. AR PROTACs have efficacy in cell systems and work in vivo (AR degradation in prostate; 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:

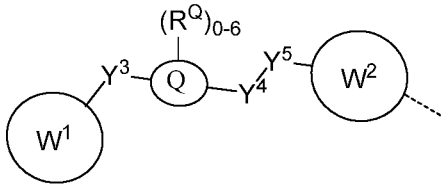
1. A compound having the structure:

[ABM]-[L],

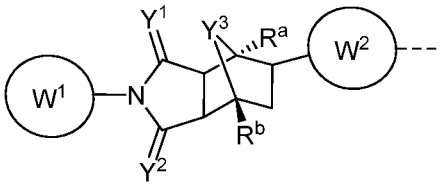
wherein ABM is an androgen receptor (AR) binding moiety, L is a chemical linker moiety, wherein the ABM comprises a structure selected from the group consisting of:



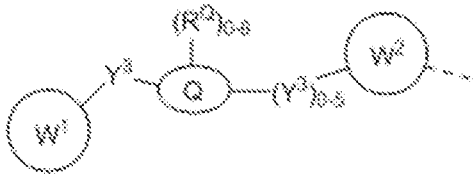
ABM-a ,



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;

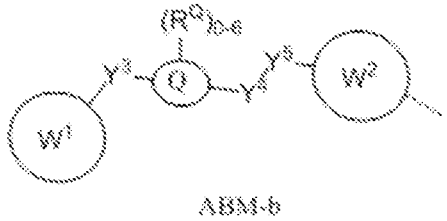
Q is a 3-6 membered alicyclic or aromatic ring with 0-4 heteroatoms, optionally substituted with 0-6 R^Q, each R^Q,is independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or 2 R^Q groups taken together with the atom they are attached to, form a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

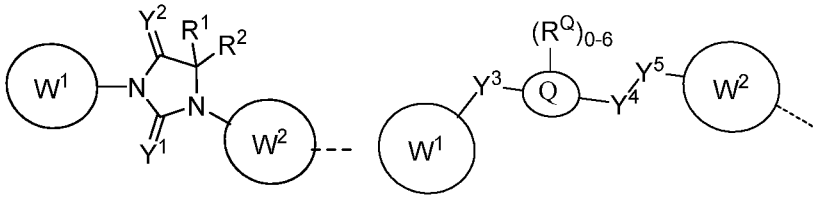
W^2 is a bond, C_{1-6} alkyl, C_{1-6} alicyclic, heterocyclic, aryl, or heteroaryl, each optionally substituted by 1, 2 or 3 R^{W2}; and

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.

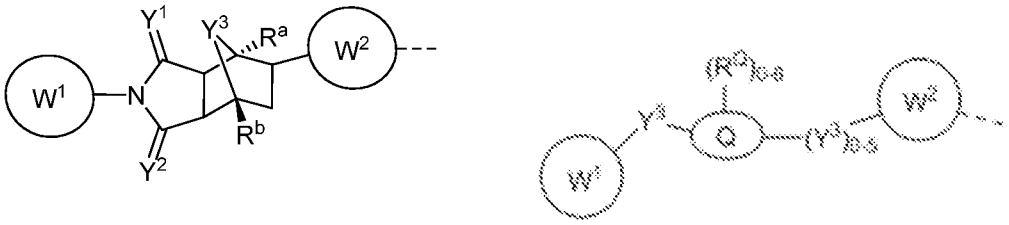
3. The compound of claim 1 or 2, further comprising an E3 ubiquintin ligase binding moiety (ULM) coupled to the ABM or L or both.

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;

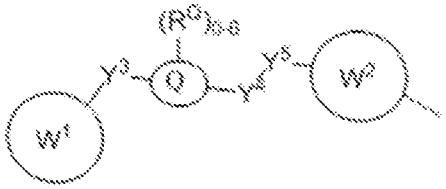
Q is a 3-6 membered alicyclic or aromatic ring with 0-4 heteroatoms, optionally substituted with 0-6 R^Q, each R^Q,is independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or 2 R^Q groups taken together with the atom they are attached to, form a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

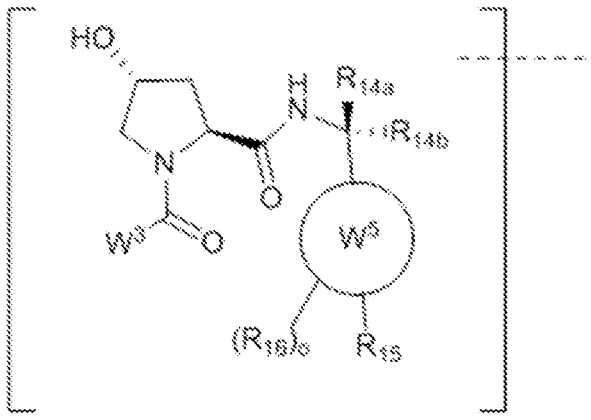
R^{Y1}, R^{Y2} are each independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl);

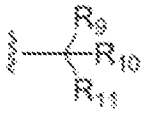
W^2 is a bond, C_{1-6} alkyl, C_{1-6} alicyclic, heterocyclic, aryl, or heteroaryl, each optionally substituted by 1, 2 or 3 R^{W2}; and

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.

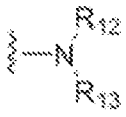
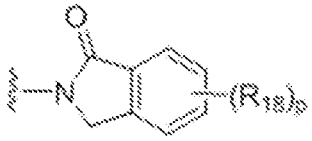
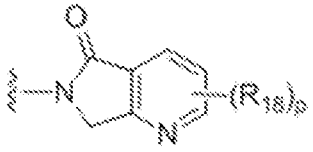
7. The bifunctional compound of claim 5 or 6, wherein ULM comprises a hydroxyl prolyl moiety that binds Von Hippel-Lindau (VHL) E3 ubiquitin ligase (VLM).

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;

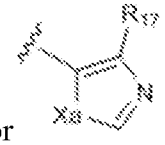
R_{11} is optionally substituted heterocyclic, optionally substituted alkoxy, optionally substituted heteroaryl, optionally substituted aryl,  ,  or  ;

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,

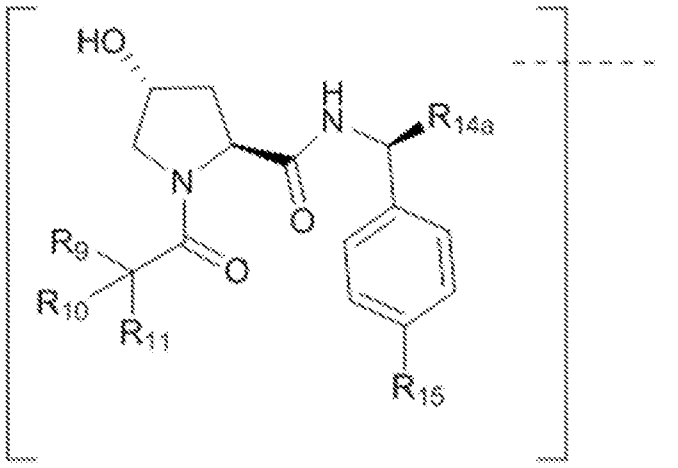
R_{15} is H, halogen, CN, OH, NO_2, N $R_{14a}R_{14b}$, OR_{14a}, $CONR_{14a}R_{14b}$, $NR_{14a}COR_{14b}$, $SO_2NR_{14a}R_{14b}$, NR_{14a} SO_2R_{14b}, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted haloalkoxy; aryl, heteroaryl, cycloalkyl, cycloheteroalkyl each 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:

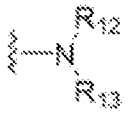


,

wherein

R_9 is H;

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

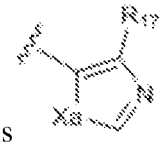
R_{11} is 

;

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

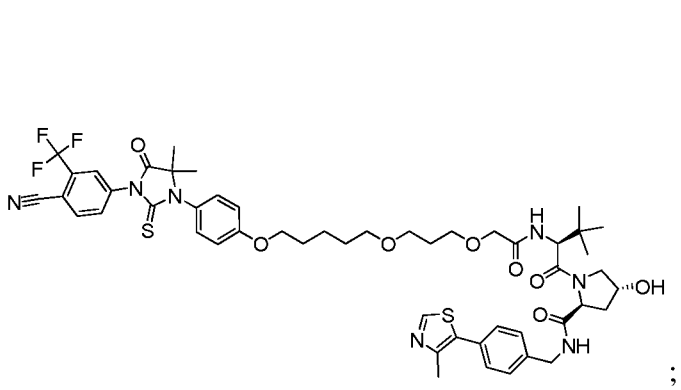
A is independently selected from the group consisting of a bond, $CR^{L1}R^{L2}$, O, S, SO, SO_2, NR^{L3}, SO_2NR^{L3}, $SONR^{L3}$, $CONR^{L3}$, $NR^{L3}CONR^{L4}$, $NR^{L3}SO_2NR^{L4}$, CO, $CR^{L1}=CR^{L2}$, C≡C, $SiR^{L1}R^{L2}$, $P(O)R^{L1}$, $P(O)OR^{L1}$, $NR^{L3}C(=NCN)NR^{L4}$, $NR^{L3}C(=NCN)$, $NR^{L3}C(=CNO_2)NR^{L4}$, 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

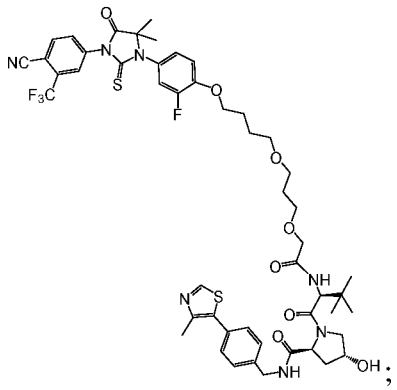
R^{L1}, R^{L2}, R^{L3}, R^{L4} and R^{L5} are each, independently, selected from the group consisting of H, halo, C_{1-8}alkyl, OC_{1-8}alkyl, SC_{1-8}alkyl, NHC_{1-8}alkyl, $N(C_{1-8}alkyl)_2$, C_{3-11}cycloalkyl, aryl, heteroaryl, C_{3-11}heterocyclyl, OC_{1-8}cycloalkyl, SC_{1-8}cycloalkyl, NHC_{1-8}cycloalkyl, $N(C_{1-8}cycloalkyl)_2$, $N(C_{1-8}cycloalkyl)(C_{1-8}alkyl)$, 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

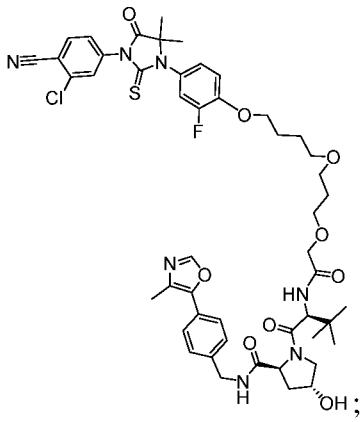
wherein when q is greater than 1, R^{L1} or R^{L2} each, independently, can be linked to another A group to form cycloalkyl and/or heterocyclyl moeity that can be further substituted with 0-4 R^{L5} groups.

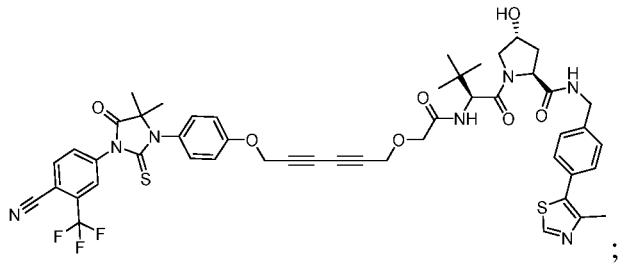
12. The bifunctional compound of claim 5, wherein the compound is a member selected from the group consisting of Examples 1-593 (Tables 2-17), a salt, a polymorph, isotopic derivative, and a prodrug thereof.

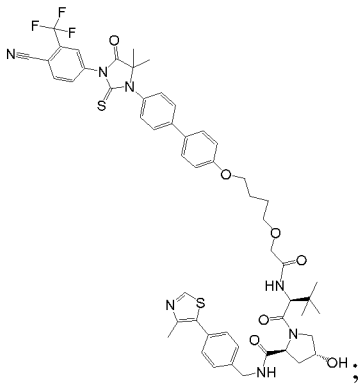
13. The bifunctional compound of claim 5, wherein the compound is selected from the group consisting of:

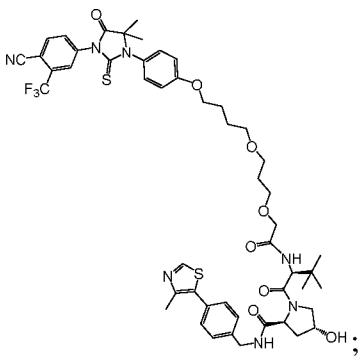

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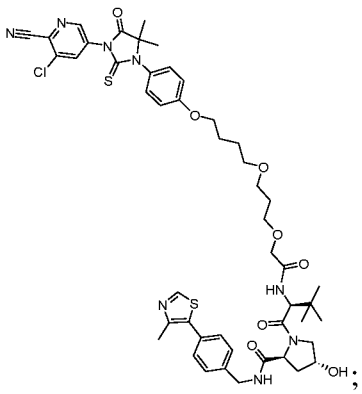

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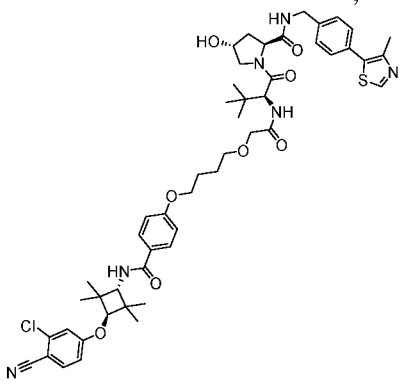

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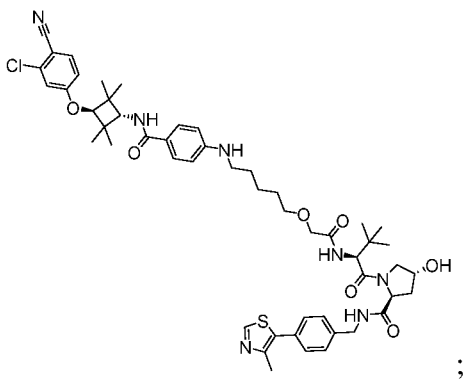

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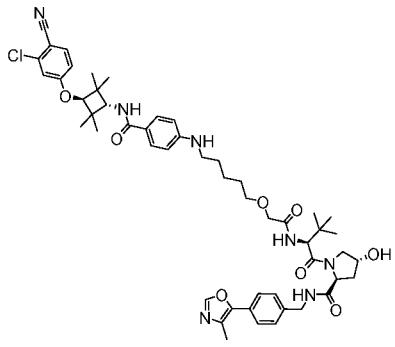
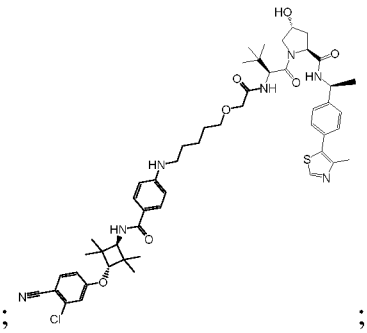
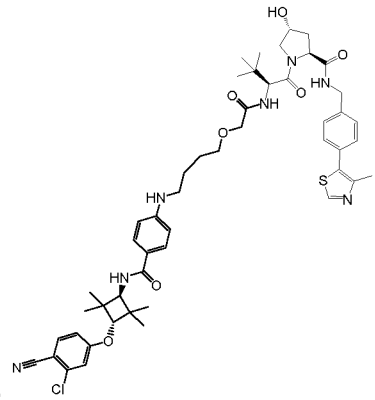
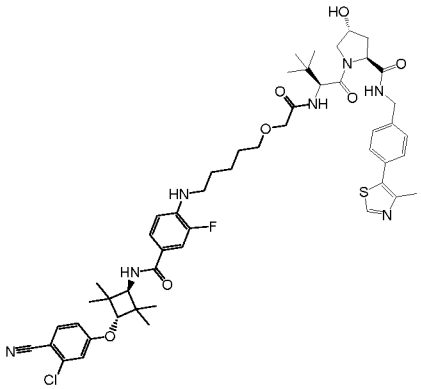
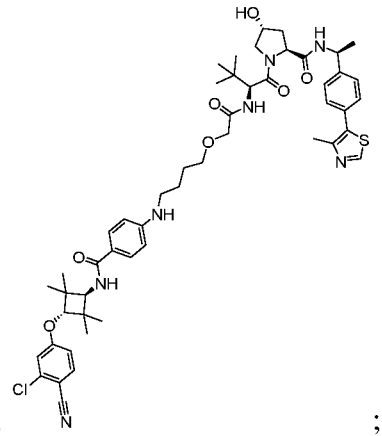
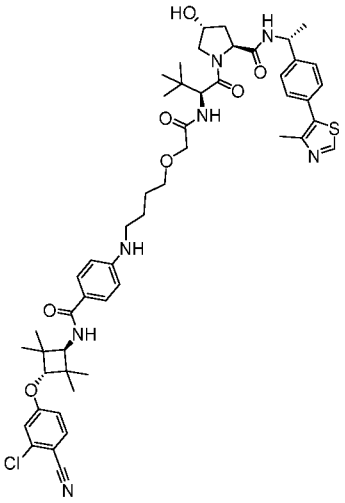
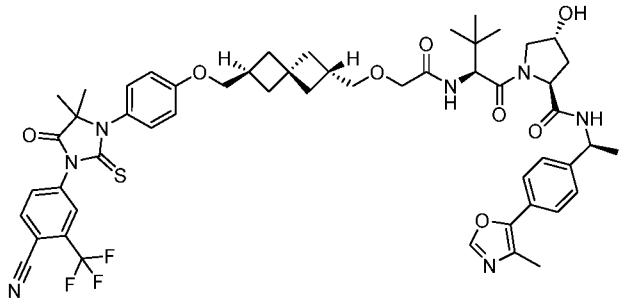
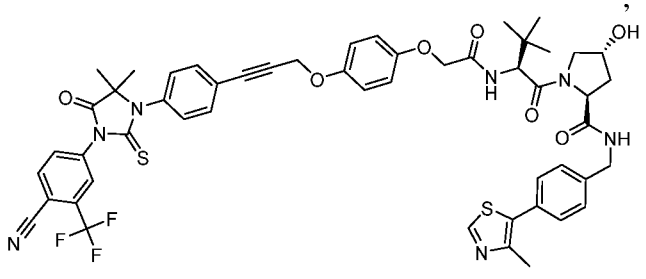

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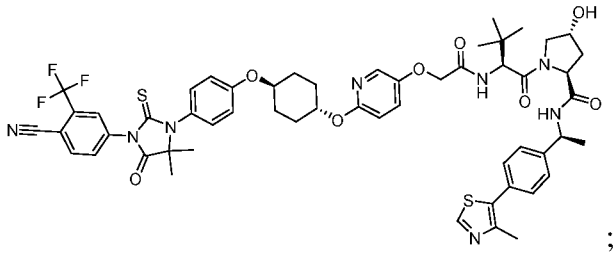

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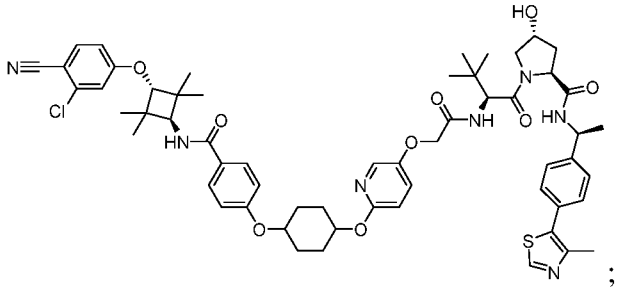

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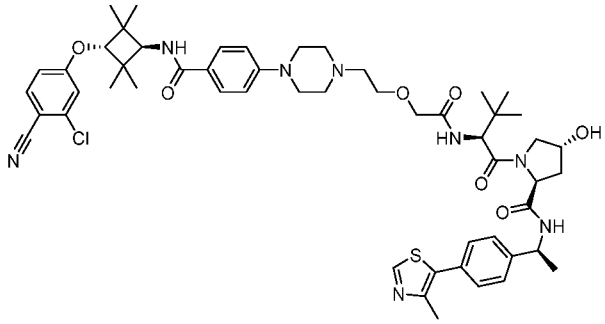

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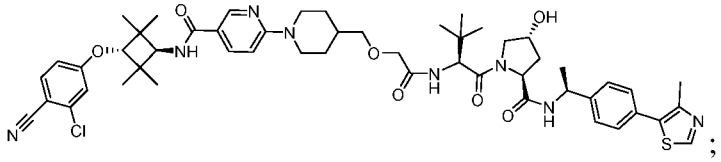

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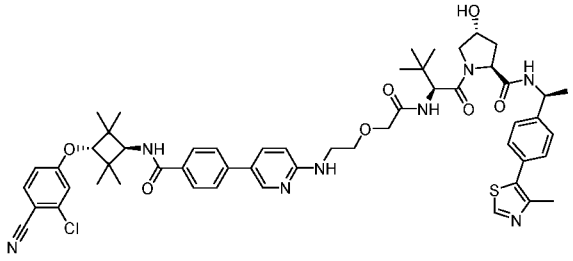

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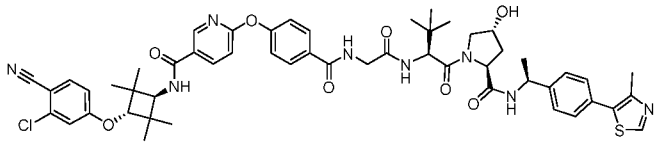

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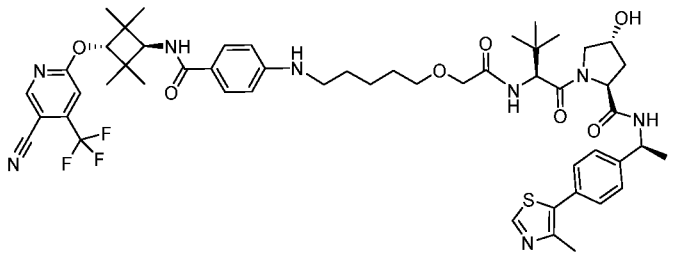

;


;


;


;


; 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.

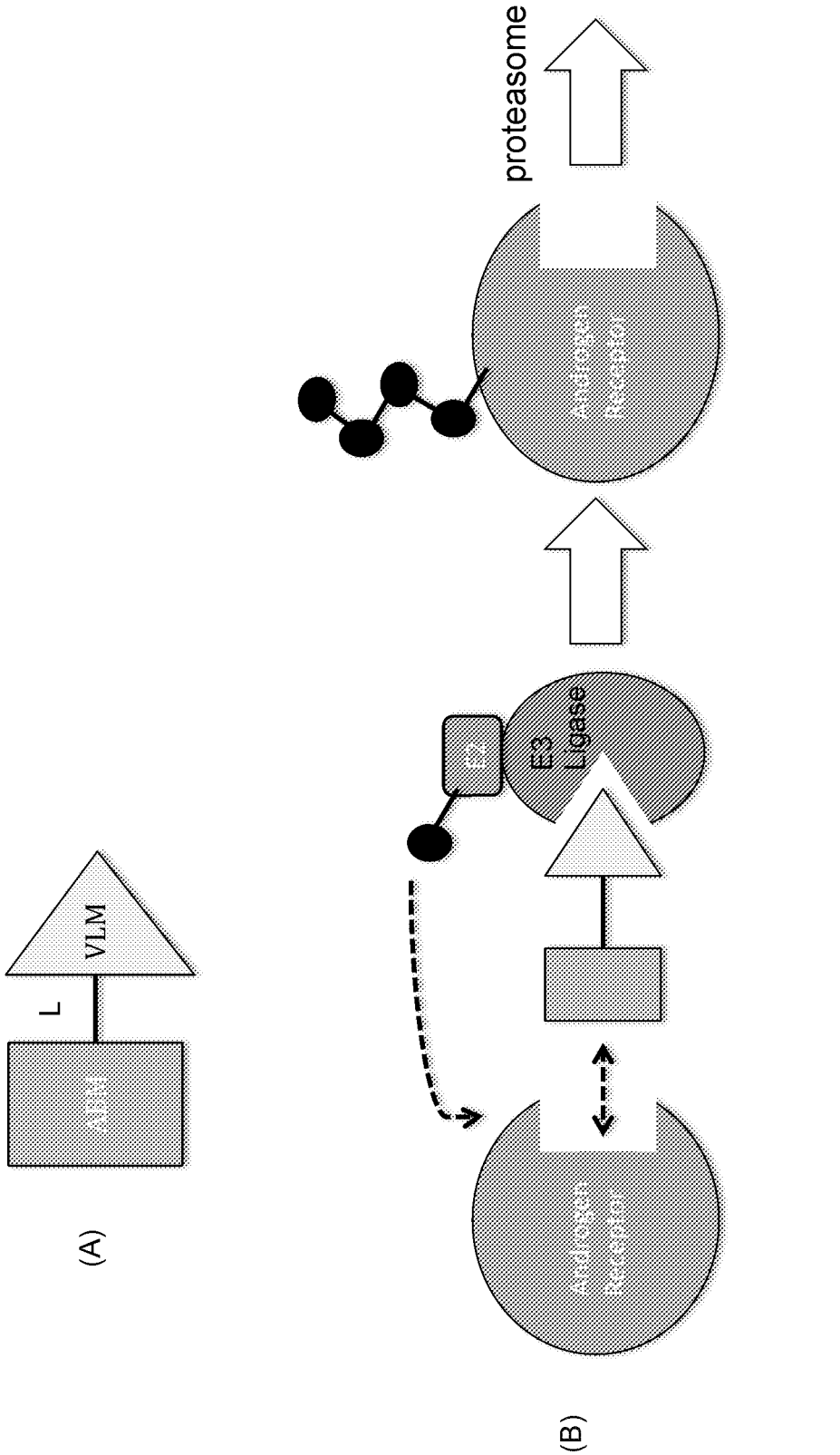
16. The composition of claim 15, wherein the composition further comprises at least one of another bioactive agent, an anti-cancer agent, another biofunctional compound of claim 5.

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
(B)
AHM
L
VLM
(A)

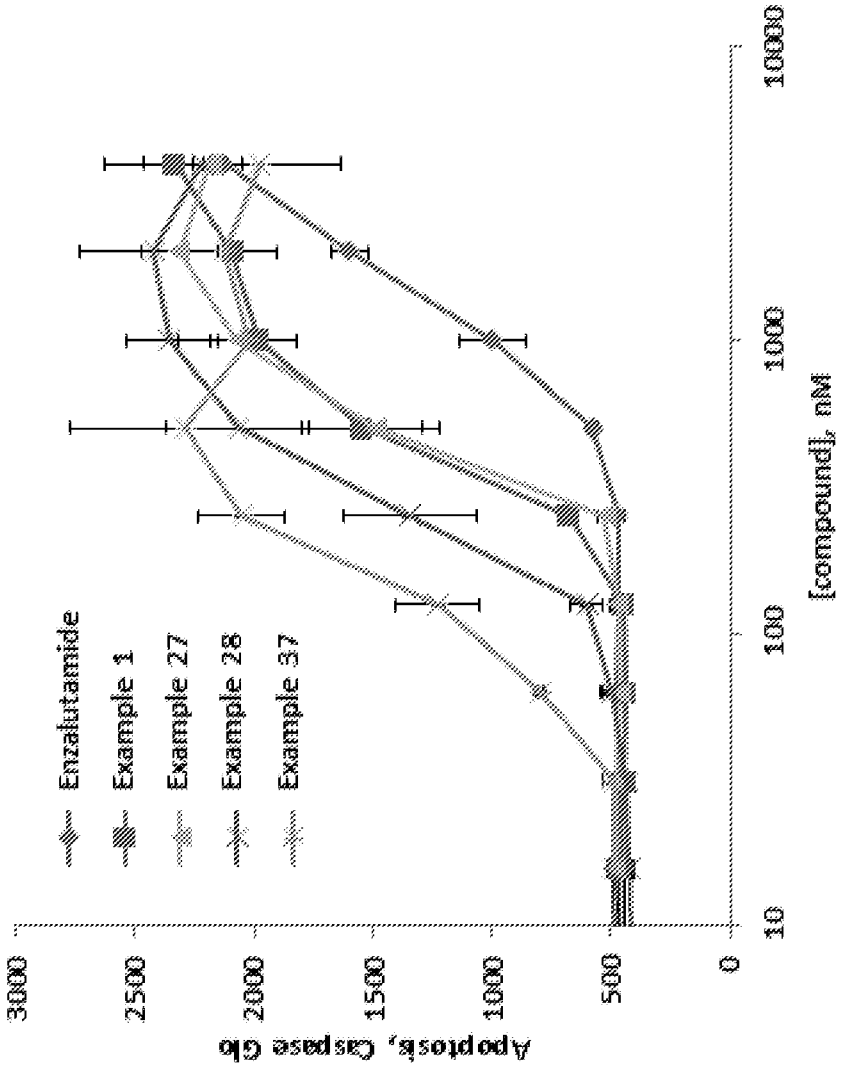

Apoptosis, Caspase Glo
3000
2500
2000
1500
1000
500
0
10
100
1000
10000
[compound], nM
Enzalutamide
Example 1
Example 27
Example 28
Example 37

Figure 2

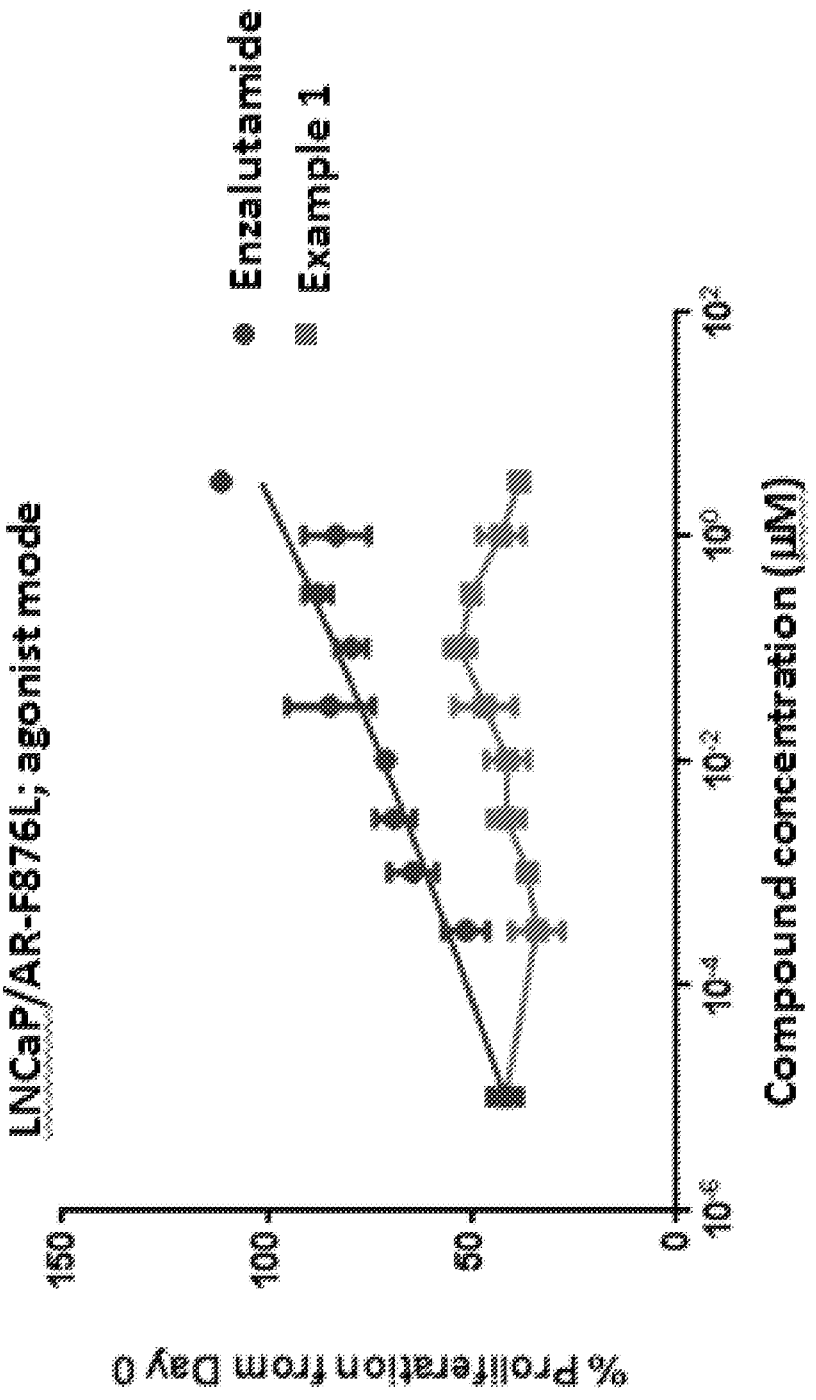

LNCaP/AR-F876L; agonist mode
Enzalutamide
Example 1
% Proliferation from Day 0
150
100
50
0
10^{-6}
10^{-4}
10^{-2}
10^{0}
10^{2}
Compound concentration (μM)

Figure 3

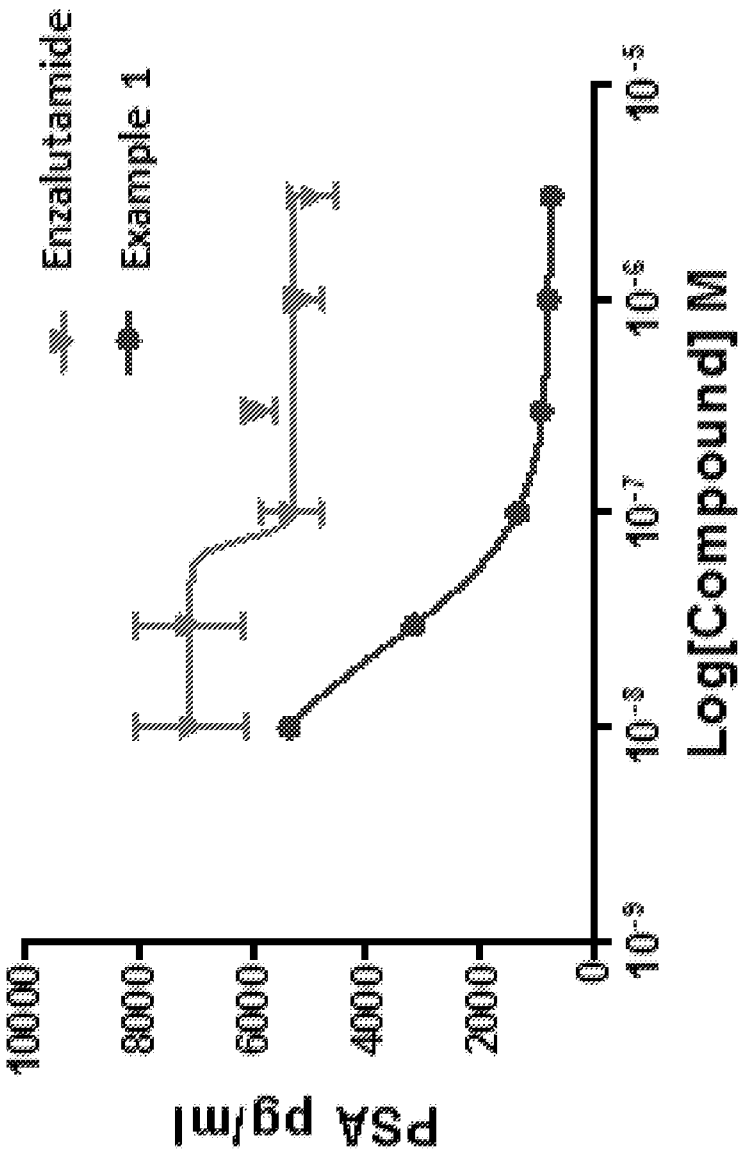
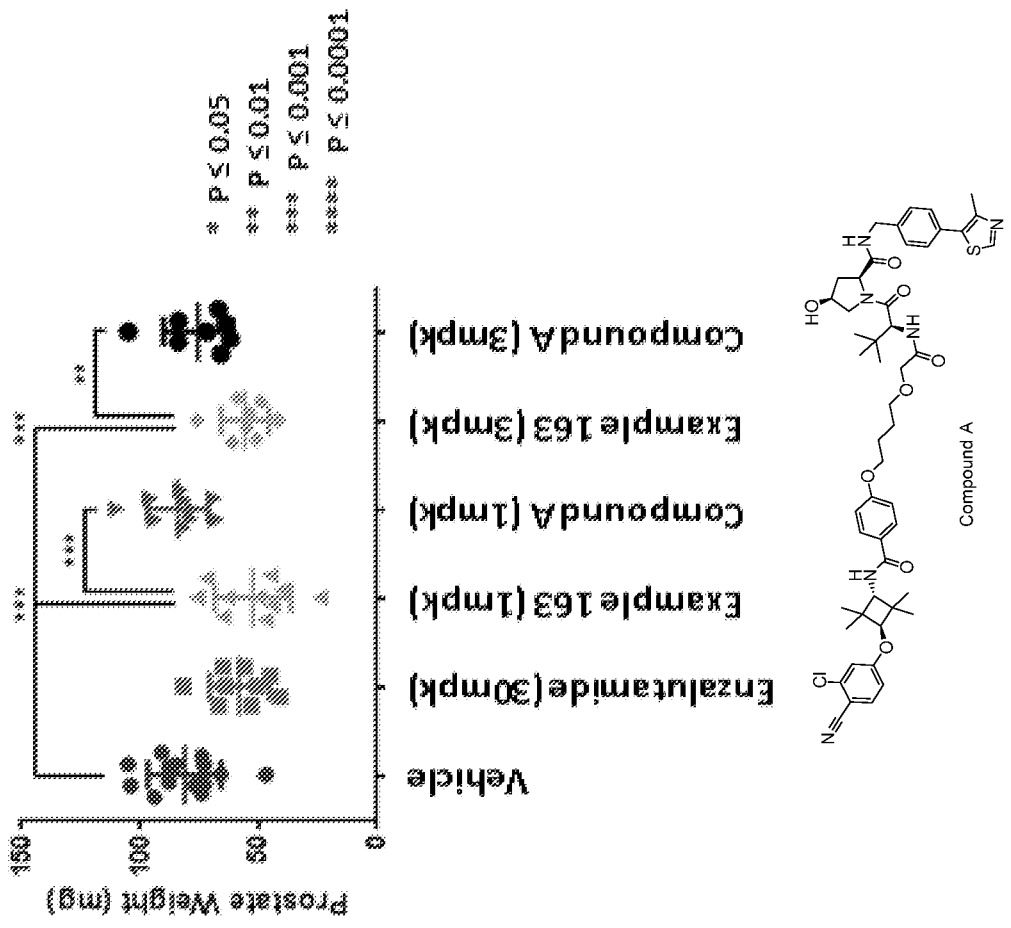

Enzalutamide
Example 1
PSA pg/ml
10000
8000
6000
4000
2000
0
10-9
10-8
10-7
10-6
10-5
Log[Compound] M

Figure 4

Figure 5


* P ≤ 0.05
** P ≤ 0.01
*** P ≤ 0.001
**** P ≤ 0.0001
Prostate Weight (mg)
150
100
50
0
Vehicle
Enzalutamide (30mpk)
Example 163 (1mpk)
Compound A (1mpk)
Example 163 (3mpk)
Compound A (3mpk)
Compound A

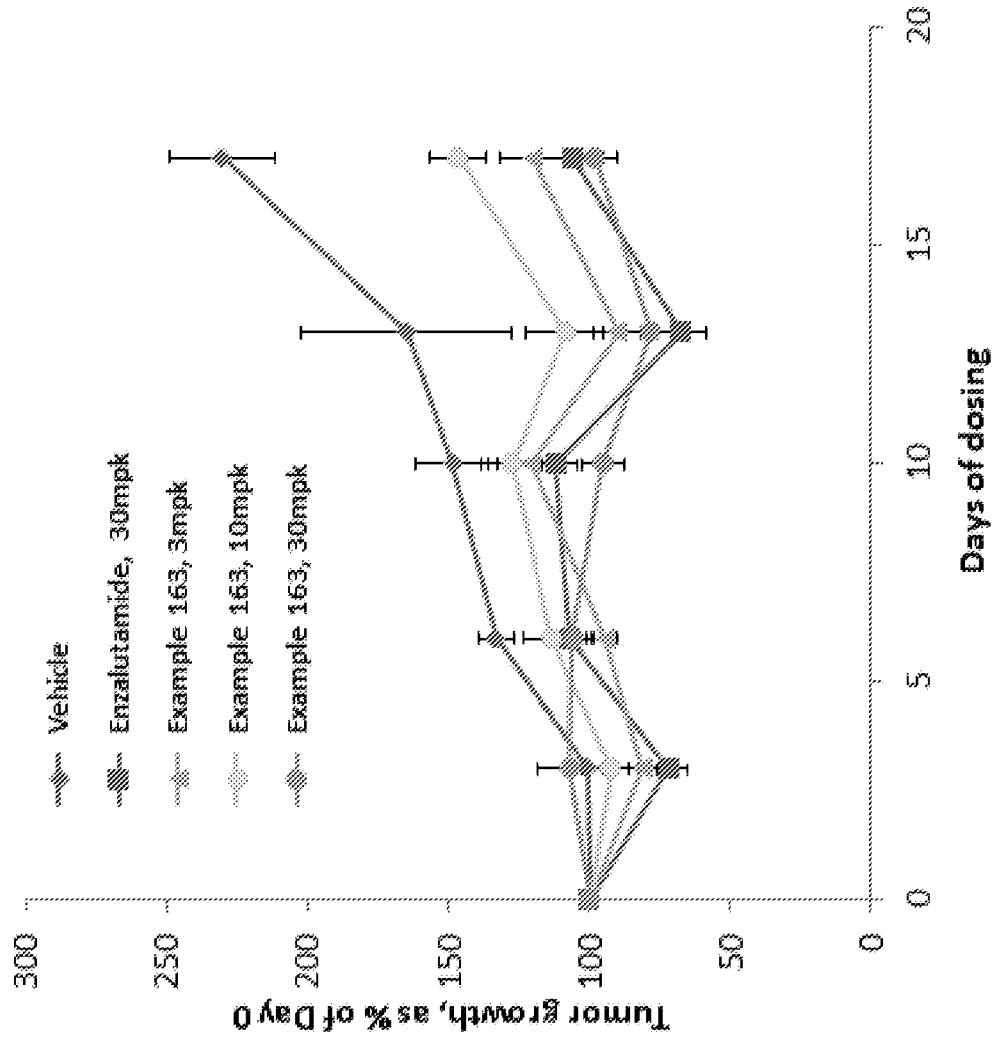
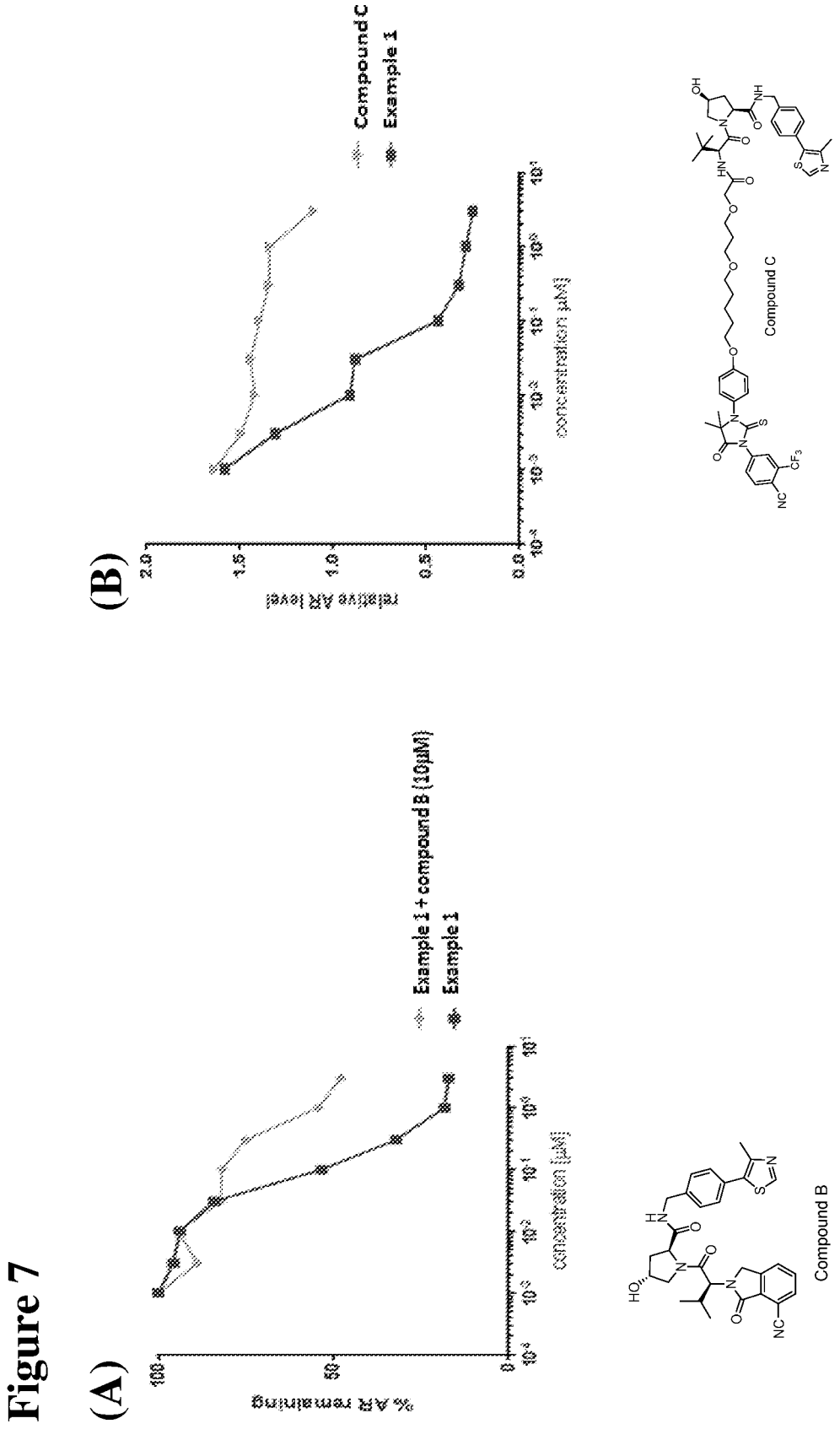

Tumor growth, as % of Day 0
300
250
200
150
100
50
0
0
5
10
15
20
Days of dosing
Vehicle
Enzalutamide, 30mpk
Example 163, 3mpk
Example 163, 10mpk
Example 163, 30mpk

Figure 6

Figure 7


(A)
% AR remaining
concentration [μM]
Example 1 + compound B (10μM)
Example 1
Compound B
(B)
relative AR level
concentration [μM]
Compound C
Example 1
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

Form PCT/ISA/210 (second sheet) (January 2015)

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.

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(12)发明专利申请

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代理人 谭玮

(51)Int.Cl.
C07D 403/06(2006.01)

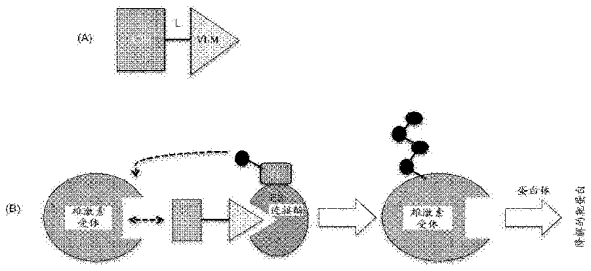
权利要求书10页 说明书255页 附图7页

(54)发明名称

用于雄激素受体的靶向降解的化合物和方法

(57)摘要

本发明涉及用于降解和(抑制)雄激素受体的双功能化合物。具体地,本发明涉及化合物,其在一端含有结合泛素连接酶的VHL配体,且在另一端含有结合雄激素受体的部分,从而将雄激素受体置于泛素连接酶附近以实现雄激素受体的降解(和抑制)。本发明表现出宽范围的与根据本发明的化合物有关的药理学活性,这与雄激素受体的降解/抑制一致。

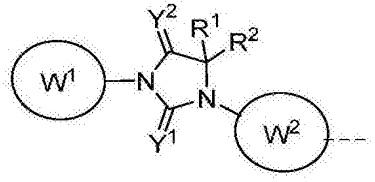


CN 107428734 A

1.具有以下结构的化合物：

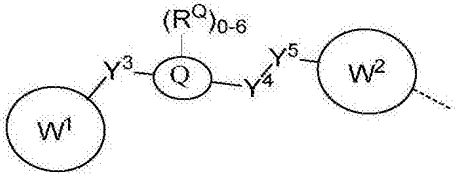
[ABM]-[L]，

其中ABM是雄激素受体(AR)结合部分，L是化学接头部分，其中所述ABM包含选自以下的结构：



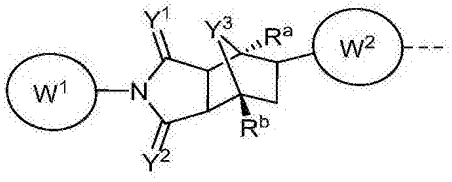
ABM-a

、



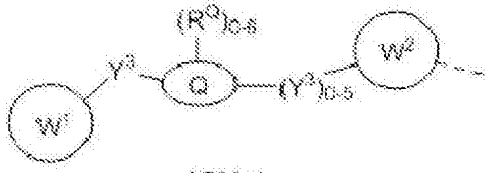
ABM-b

、



ABM-c

和



ABM-d

其中W^1是芳基或杂芳基，其独立地被1个或多个卤代、羟基、硝基、CN、C≡CH、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)、C_{1-6}烷氧基(直链的，支链的，任选地被1个或多个卤代取代)、C_{2-6}烯基、C_{2-6}炔基取代；

Y^1、Y^2各自独立地是NR^{Y1}、O、S；

Y^3、Y^4、Y^5各自独立地是键、O、NR^{Y2}、$CR^{Y1}R^{Y2}$、C=O、C=S、SO、SO_2；

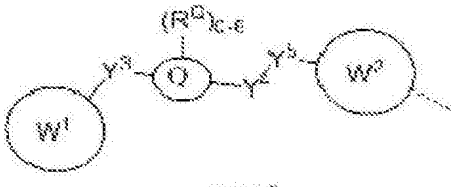
Q是具有0-4个杂原子的3-6元脂环族环或芳族环，其任选地被0-6个R^Q取代，每个R^Q独立地是H、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)，或者2个R^Q基团与它们所连接的原子一起形成含有0-2个杂原子的3-8元环系)；

R^1、R^2、R^a、R^b、R^{Y1}、R^{Y2}各自独立地是H、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)，或者R^1、R^2与它们所连接的原子一起形成含有0-2个杂原子的3-8元环系)；

W^2是键、C_{1-6}烷基、C_{1-6}脂环族基、杂环基、芳基或杂芳基，每个任选地被1、2或3个R^{W2}取代；且

每个R^{W2}独立地是H、卤代、C_{1-6}烷基(任选地被1个或多个F取代)、OC_{1-3}烷基(任选地被1个或多个-F取代)、OH、NH_2、$NR^{Y1}R^{Y2}$、CN。

2.根据权利要求1所述的化合物，其中所述ABM包含结构：



ABM-b

其中W^1是芳基或杂芳基，其独立地被1个或多个卤代、羟基、硝基、CN、C≡CH、C_{1-6}烷基(直

链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代）、C_{1-6}烷氧基（直链的，支链的，任选地被1个或多个卤代取代）、C_{2-6}烯基、C_{2-6}炔基取代；

Y^3、Y^4、Y^5各自独立地是键、O、NR^{Y2}、$CR^{Y1}R^{Y2}$、C＝O、C＝S、SO、SO_2；

Q是具有0-2个杂原子的4元脂环族环，其任选地被0-6个R^Q取代，每个R^Q独立地是H、C_{1-6}烷基（直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代），或者2个R^Q基团与它们所连接的原子一起形成含有0-2个杂原子的3-8元环系）；

R^{Y1}、R^{Y2}各自独立地是H、C_{1-6}烷基（直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代）；

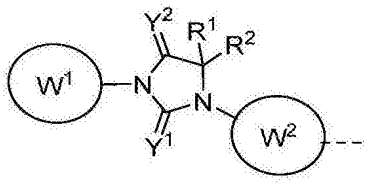
W^2是键、C_{1-6}烷基、C_{1-6}脂环族基、杂环基、芳基或杂芳基，每个任选地被1、2或3个R^{W2}取代；且

每个R^{W2}独立地是H、卤代、C_{1-6}烷基（任选地被1个或多个F取代）、OC_{1-3}烷基（任选地被1个或多个-F取代）、OH、NH_2、$NR^{Y1}R^{Y2}$、CN。

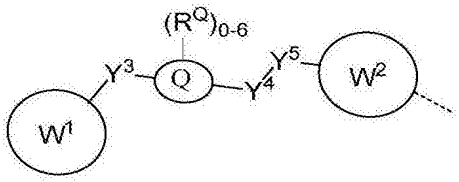
3.根据权利要求1或2所述的化合物，所述化合物还包含与ABM或L或二者偶联的E3泛素连接酶结合部分（ULM）。

4.根据权利要求1-3中的任一项所述的化合物，其中ULM包含结合Von Hippel-Lindau（VHL）E3泛素连接酶的羟基脯氨酰基部分。

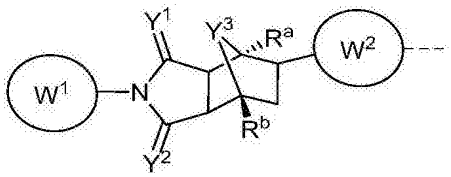
5.包含化学结构ABM-L-ULM的双功能化合物，其中ABM是雄激素受体（AR）结合部分，L不存在（键）或是化学接头，且ULM是E3泛素连接酶结合部分，其中所述ABM包含选自以下的结构：



ABM-a、

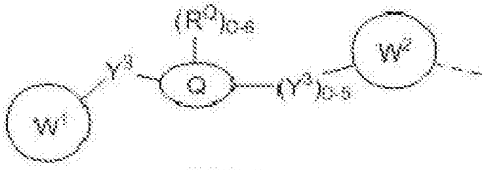


ABM-b、



ABM-c

和



ABM-d

其中W^1是芳基或杂芳基，其独立地被1个或多个卤代、羟基、硝基、CN、C≡CH、C_{1-6}烷基（直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代）、C_{1-6}烷氧基（直链的，支链的，任选地被1个或多个卤代取代）、C_{2-6}烯基、C_{2-6}炔基取代；

Y^1、Y^2各自独立地是NR^{Y1}、O、S；

Y^3、Y^4、Y^5各自独立地是键、O、NR^{Y2}、$CR^{Y1}R^{Y2}$、C＝O、C＝S、SO、SO_2；

Q是具有0-4个杂原子的3-6元脂环族环或芳族环，其任选地被0-6个R^Q取代，每个R^Q独立地是H、C_{1-6}烷基（直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代），或者2个R^Q基

团与它们所连接的原子一起形成含有0-2个杂原子的3-8元环系)；

R^1、R^2、R^a、R^b、R^{Y1}、R^{Y2}各自独立地是H、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)，或者R^1、R^2与它们所连接的原子一起形成含有0-2个杂原子的3-8元环系)；

W^2是键、C_{1-6}烷基、C_{1-6}脂环族基、杂环基、芳基或杂芳基，每个任选地被1、2或3个R^{W2}取代；且

每个R^{W2}独立地是H、卤代、C_{1-6}烷基(任选地被1个或多个F取代)、OC_{1-3}烷基(任选地被1个或多个-F取代)、OH、NH_2、$NR^{Y1}R^{Y2}$、CN。

6.根据权利要求5所述的化合物，其中所述ABM包含结构：



ABM-b

其中W^1是芳基或杂芳基，其独立地被1个或多个卤代、羟基、硝基、CN、C≡CH、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)、C_{1-6}烷氧基(直链的，支链的，任选地被1个或多个卤代取代)、C_{2-6}烯基、C_{2-6}炔基取代；

Y^3、Y^4、Y^5各自独立地是键、O、NR^{Y2}、$CR^{Y1}R^{Y2}$、C=O、C=S、SO、SO_2；

Q是具有0-2个杂原子的4元脂环族环，其任选地被0-6个R^Q取代，每个R^Q独立地是H、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)，或者2个R^Q基团与它们所连接的原子一起形成含有0-2个杂原子的3-8元环系)；

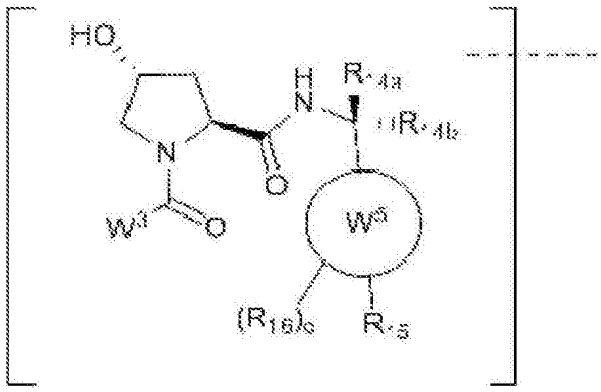
R^{Y1}、R^{Y2}各自独立地是H、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)；

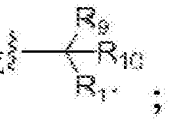
W^2是键、C_{1-6}烷基、C_{1-6}脂环族基、杂环基、芳基或杂芳基，每个任选地被1、2或3个R^{W2}取代；且

每个R^{W2}独立地是H、卤代、C_{1-6}烷基(任选地被1个或多个F取代)、OC_{1-3}烷基(任选地被1个或多个-F取代)、OH、NH_2、$NR^{Y1}R^{Y2}$、CN。

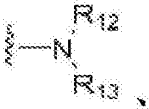
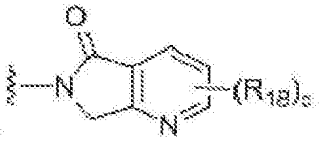
7.根据权利要求5或6所述的双功能化合物，其中ULM包含结合Von Hippel-Lindau (VHL)E3泛素连接酶的羟基脯氨酰基部分(VLM)。

8.根据权利要求5-7中的任一项所述的双功能化合物，其中所述ULM包含结构：



其中，W^3是任选地被取代的芳基、任选地被取代的杂芳基或  ；

每个R_9和R_{10}独立地是氢、任选地被取代的烷基、任选地被取代的环烷基、任选地被取代的羟基烷基、任选地被取代的杂芳基或卤代烷基；或R_9、R_{10}和它们所连接的碳原子形成任选地被取代的环烷基；

R_{11}是任选地被取代的杂环基、任选地被取代的烷氧基、任选地被取代的杂芳基、任选地被取代的芳基、  、  或  ；

R_{12}是H或任选地被取代的烷基；

R_{13}是H、任选地被取代的烷基、任选地被取代的烷基羰基、任选地被取代的(环烷基)烷基羰基、任选地被取代的芳烷基羰基、任选地被取代的芳基羰基、任选地被取代的(杂环基)羰基或任选地被取代的芳烷基；

R_{14a}、R_{14b}各自独立地是H、卤代烷基或任选地被取代的烷基；

W^5是苯基或5-10元杂芳基，

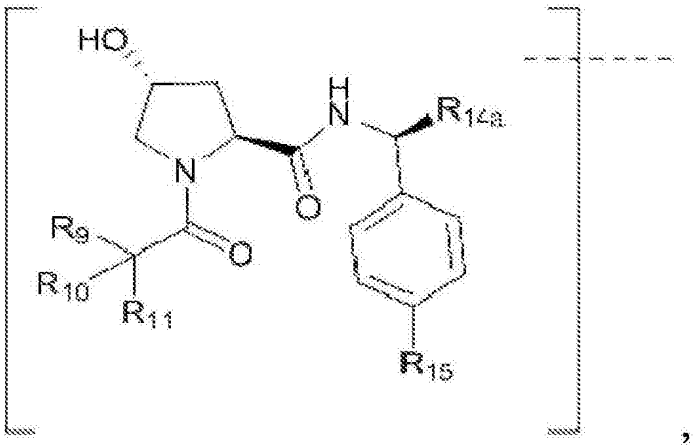
R_{15}是H、卤素、CN、OH、NO_2、N $R_{14a}R_{14b}$、OR_{14a}、$CONR_{14a}R_{14b}$、$NR_{14a}COR_{14b}$、$SO_2NR_{14a}R_{14b}$、$NR_{14a}SO_2R_{14b}$、任选地被取代的烷基、任选地被取代的卤代烷基、任选地被取代的卤代烷氧基；芳基、杂芳基、环烷基、环杂烷基，每个R_{16}独立地是卤代、任选地被取代的烷基、任选地被取代的卤代烷基、羟基或任选地被取代的卤代烷氧基；或  其中R_{17}是H、卤代、任选地被取代的C_{3-6}环烷基、任选地被取代的C_{1-6}烷基、任选地被取代的C_{1-6}烯基和C_{1-6}卤代烷基，且Xa是S或O；

o是0、1、2、3或4；

每个R_{18}独立地是卤代、任选地被取代的烷氧基、氰基、任选地被取代的烷基、卤代烷基、卤代烷氧基或接头；且

p是0、1、2、3或4。

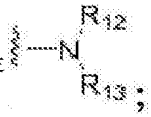
9.根据权利要求5-8中的任一项所述的双功能化合物，其中所述ULM包含结构：



其中

R_9是H；

R_{10}是异丙基、叔丁基、仲丁基、环戊基或环己基；

R_{11}是  ；

R_{12}是H；

R_{13}是H、任选地被取代的烷基、任选地被取代的烷基羰基、任选地被取代的(环烷基)烷基羰基、任选地被取代的芳烷基羰基、任选地被取代的芳基羰基、任选地被取代的(杂环基)羰基或任选地被取代的芳烷基；

R_{14a}是H、卤代烷基或任选地被取代的甲基、乙基、异丙基、环丙基或其它烷基；且

R_{15}是  其中R_{17}是H、卤代、任选地被取代的C_{3-6}环烷基、任选地被取代的C_{1-6}烷基、任选地被取代的C_{1-6}烯基和C_{1-6}卤代烷基；且Xa是S或O。

10.根据权利要求5-9中的任一项所述的双功能化合物，其中ULM选自：

(2S,4R)-1-((S)-2-氨基-3,3-二甲基丁酰基)-4-羟基-N-(4-(4-甲基噻唑-5-基)苄基)吡咯烷-2-甲酰胺；

(2S,4R)-1-((S)-2-氨基-3,3-二甲基丁酰基)-4-羟基-N-(4-(噻唑-5-基)苄基)吡咯烷-2-甲酰胺；

(2S,4R)-1-((S)-2-氨基-3,3-二甲基丁酰基)-4-羟基-N-((S)-1-(4-(4-甲基噻唑-5-基)苯基)乙基)吡咯烷-2-甲酰胺；

(2S,4R)-1-((S)-2-氨基-3,3-二甲基丁酰基)-4-羟基-N-(4-(噁唑-5-基)苄基)吡咯烷-2-甲酰胺盐酸盐；

(2S,4R)-1-((S)-2-氨基-3,3-二甲基丁酰基)-4-羟基-N-(4-(4-甲基噁唑-5-基)苄基)吡咯烷-2-甲酰胺；

(2S,4R)-1-((S)-2-氨基-3,3-二甲基丁酰基)-N-(4-氯苄基)-4-羟基吡咯烷-2-甲酰胺盐酸盐；

(2S,4R)-1-((S)-2-氨基-3,3-二甲基丁酰基)-N-(4-氰基苄基)-4-羟基吡咯烷-2-甲酰胺盐酸盐;

(2S,4R)-1-((S)-2-氨基-3-甲基丁酰基)-4-羟基-N-(4-(4-甲基噻唑-5-基)苄基)吡咯烷-2-甲酰胺盐酸盐;

(2S,4R)-1-((S)-2-氨基-3-甲基丁酰基)-4-羟基-N-(4-(噻唑-5-基)苄基)吡咯烷-2-甲酰胺盐酸盐;

(2S,4R)-1-((S)-2-氨基-3-甲基丁酰基)-4-羟基-N-(4-(4-甲基[illegible]唑-5-基)苄基)吡咯烷-2-甲酰胺盐酸盐;

(2S,4R)-1-((S)-2-氨基-3,3-二甲基丁酰基)-4-羟基-N-(4-(1-甲基-1H-吡唑-5-基)苄基)吡咯烷-2-甲酰胺盐酸盐;

(2S,4R)-4-叔丁氧基-N-(2-羟基-4-(4-甲基噻唑-5-基)苄基)-1-((S)-3-甲基-2-(1-氧代异吲哚啉-2-基)丁酰基)吡咯烷-2-甲酰胺;

(2S,4R)-4-叔丁氧基-1-((S)-2-(6-氟-1-氧代异吲哚啉-2-基)-3-甲基丁酰基)-N-(2-羟基-4-(4-甲基噻唑-5-基)苄基)吡咯烷-2-甲酰胺;和

(2S,4R)-4-叔丁氧基-1-((S)-2-(7-氰基-1-氧代异吲哚啉-2-基)-3-甲基丁酰基)-N-(2-羟基-4-(4-甲基噻唑-5-基)苄基)吡咯烷-2-甲酰胺。

11.根据权利要求1-10中的任一项所述的双功能化合物,其中所述接头基团(L)包含由下式表示的化学结构单元:

$-A_q-$

其中

q是大于1的整数;且

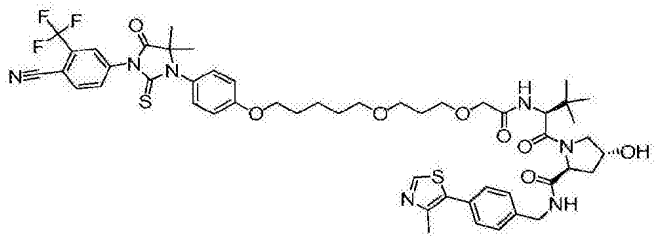
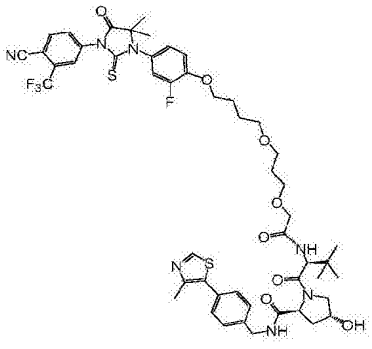
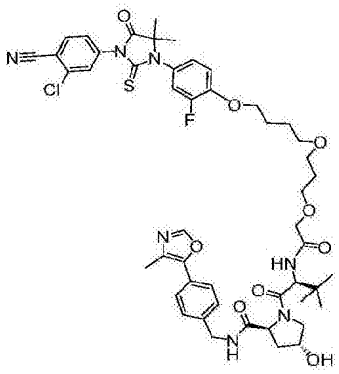
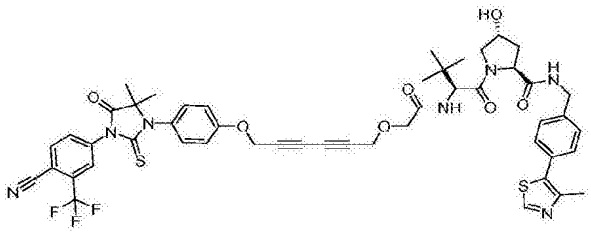
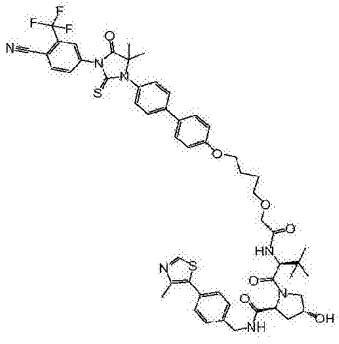
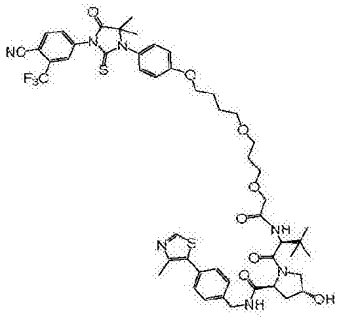
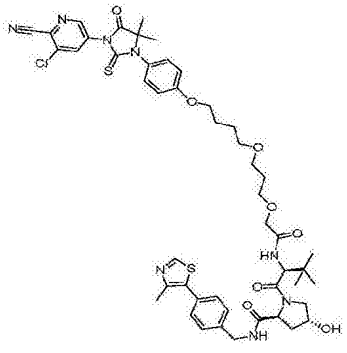
A独立地选自键、$CR^{L1}R^{L2}$、O、S、SO、SO_2、NR^{L3}、SO_2NR^{L3}、$SONR^{L3}$、$CONR^{L3}$、$NR^{L3}CONR^{L4}$、$NR^{L3}SO_2NR^{L4}$、CO、$CR^{L1}=CR^{L2}$、C≡C、$SiR^{L1}R^{L2}$、P(O)R^{L1}、P(O)OR^{L1}、$NR^{L3}C(=NCN)NR^{L4}$、$NR^{L3}C(=NCN)$、$NR^{L3}C(=CNO_2)NR^{L4}$、任选地被0-6个R^{L1}和/或R^{L2}基团取代的C_{3-11}环烷基、任选地被0-6个R^{L1}和/或R^{L2}基团取代的C_{3-11}杂环基、任选地被0-6个R^{L1}和/或R^{L2}基团取代的芳基、任选地被0-6个R^{L1}和/或R^{L2}基团取代的杂芳基;其中

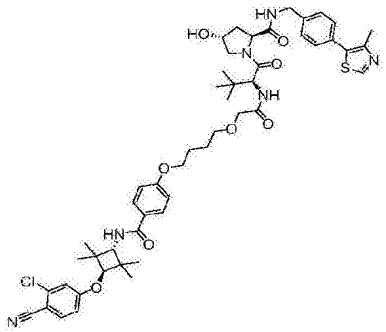
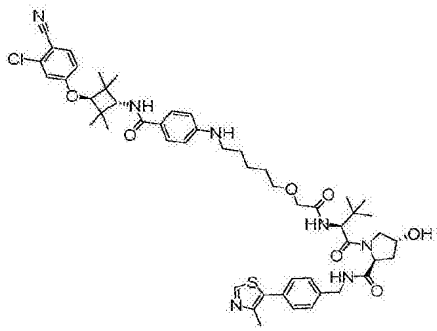
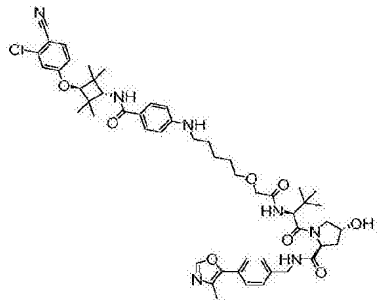
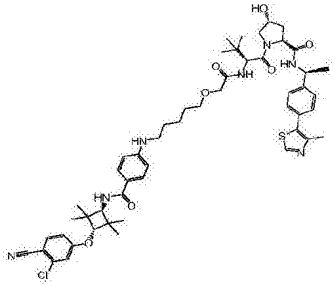
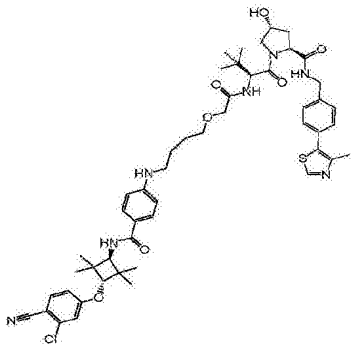
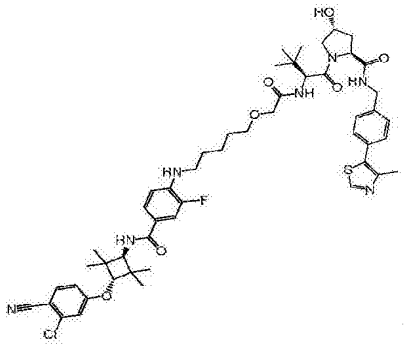
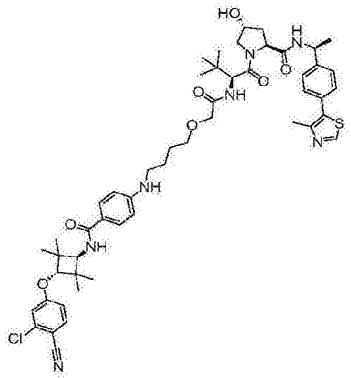
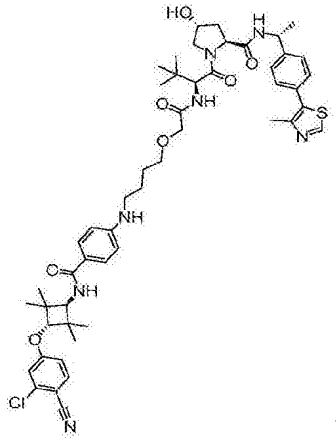
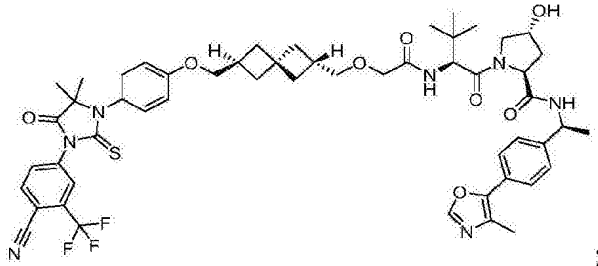
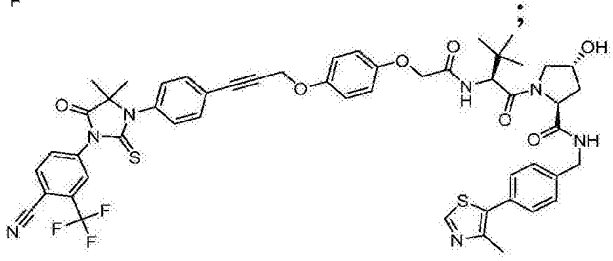
R^{L1}、R^{L2}、R^{L3}、R^{L4}和R^{L5}每个独立地选自H、卤代、C_{1-8}烷基、OC_{1-8}烷基、SC_{1-8}烷基、NHC_{1-8}烷基、$N(C_{1-8}烷基)_2$、C_{3-11}环烷基、芳基、杂芳基、C_{3-11}杂环基、OC_{1-8}环烷基、SC_{1-8}环烷基、NHC_{1-8}环烷基、$N(C_{1-8}环烷基)_2$、$N(C_{1-8}环烷基)(C_{1-8}烷基)$、OH、NH_2、SH、SO_2C_{1-8}烷基、P(O)$(OC_{1-8}烷基)(C_{1-8}烷基)$、$P(O)(OC_{1-8}烷基)_2$、CC-C_{1-8}烷基、CCH、CH=CH$(C_{1-8}烷基)$、C$(C_{1-8}烷基)$=CH$(C_{1-8}烷基)$、C$(C_{1-8}烷基)$=C$(C_{1-8}烷基)_2$、Si(OH)$_3$、Si$(C_{1-8}烷基)_3$、Si(OH)$_2(C_{1-8}烷基)_2$、COC_{1-8}烷基、CO_2H、卤素、CN、CF_3、CHF_2、CH_2F、NO_2、SF_5、SO_2NHC_{1-8}烷基、$SO_2N(C_{1-8}烷基)_2$、$SONHC_{1-8}$烷基、$SON(C_{1-8}烷基)_2$、$CONHC_{1-8}$烷基、$CON(C_{1-8}烷基)_2$、$N(C_{1-8}烷基)CONH(C_{1-8}烷基)$、$N(C_{1-8}烷基)CON(C_{1-8}烷基)_2$、$NHCONH(C_{1-8}烷基)$、$NHCON(C_{1-8}烷基)_2$、$NHCONH_2$、$N(C_{1-8}烷基)SO_2NH(C_{1-8}烷基)$、$N(C_{1-8}烷基)SO_2N(C_{1-8}烷基)_2$、NH $SO_2NH(C_{1-8}烷基)$、NH $SO_2N(C_{1-8}烷基)_2$和NH SO_2NH_2;且

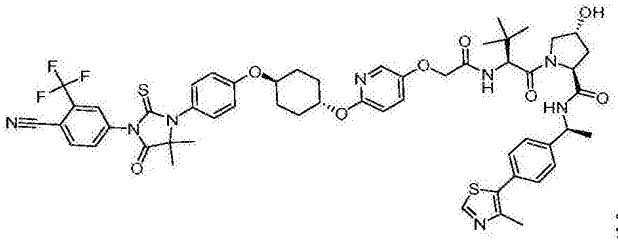
其中当q大于1时,R^{L1}或R^{L2}每个独立地可以连接至另一个A基团以形成环烷基和/或杂环基部分,所述部分可以进一步被0-4个R^{L5}基团取代。

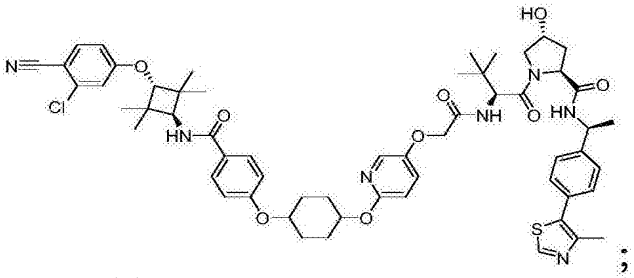
12.根据权利要求5所述的双功能化合物,其中所述化合物是选自实施例1-593(表2-17)的成员、其盐、多晶型物、同位素衍生物和前药。

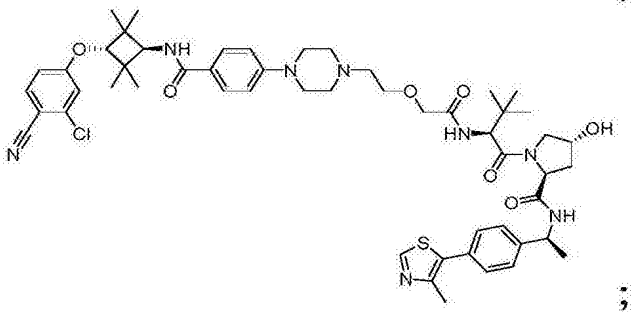
13.根据权利要求5所述的双功能化合物，其中所述化合物选自：

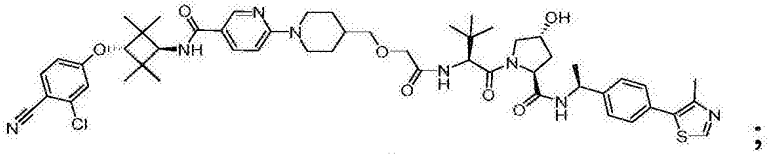

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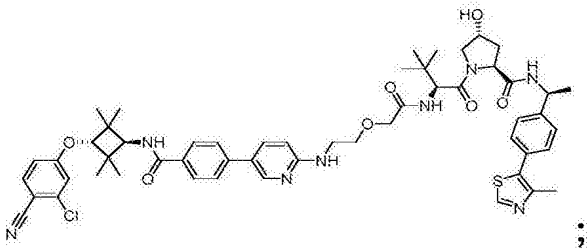

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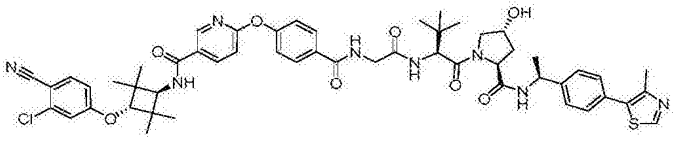

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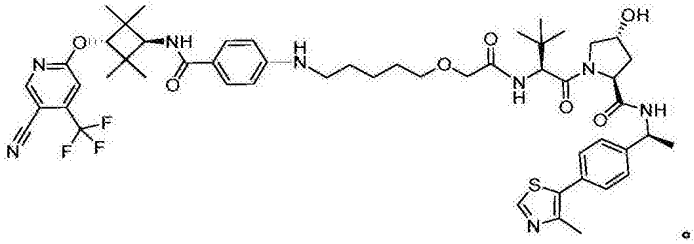

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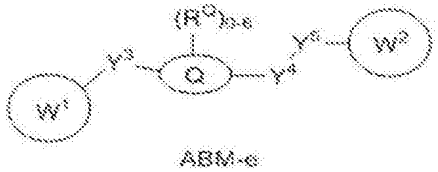

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14.包含以下结构的雄激素受体结合化合物：



ABM-c

其中W^1是芳基或杂芳基，其独立地被1个或多个卤代、羟基、硝基、CN、C≡CH、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)、C_{1-6}烷氧基(直链的，支链的，任选地被1个或多个卤代取代)、C_{2-6}烯基、C_{2-6}炔基取代；

Y^1、Y^2各自独立地是NR^{Y1}、O、S；

Y^3、Y^4、Y^5各自独立地是键、O、NR^{Y2}、$CR^{Y1}R^{Y2}$、C＝O、C＝S、SO、SO_2；

Q是具有0-4个杂原子的3-6元脂环族环或芳族环，其任选地被0-6个R^Q取代，每个R^Q独立地是H、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)，或者2个R^Q基团与它们所连接的原子一起形成含有0-2个杂原子的3-8元环系)；

R^1、R^2、R^a、R^b、R^{Y1}、R^{Y2}各自独立地是H、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)，或者R^1、R^2与它们所连接的原子一起形成含有0-2个杂原子的3-8元环系)；

W^2是键、C_{1-6}烷基、C_{1-6}脂环族基、杂环基、芳基或杂芳基，每个任选地被1、2或3个R^{W2}取代；且

每个R^{W2}独立地是H、卤代、C_{1-6}烷基(任选地被1个或多个F取代)、OC_{1-3}烷基(任选地被1个或多个-F取代)、OH、NH_2、$NR^{Y1}R^{Y2}$、CN。

15.组合物，其包含有效量的根据权利要求5-13中的任一项所述的双功能化合物和药学上可接受的载体。

16.根据权利要求15所述的组合物，其中所述组合物还包含至少一种另外的生物活性剂、抗癌剂、根据权利要求5所述的另一种双功能化合物。

17.用于治疗受试者中的疾病或障碍的组合物，其包含药学上可接受的载体和有效量的至少一种根据权利要求5所述的化合物，所述方法包括给有此需要的受试者施用所述组合物，其中所述化合物有效地治疗或改善所述疾病或障碍的至少一种症状。

18.根据权利要求19所述的组合物，其中所述疾病或障碍是癌症、前列腺癌、肯尼迪氏病或它们的组合中的至少一种。

用于雄激素受体的靶向降解的化合物和方法

[0001] 相关申请的交叉引用

[0002] 本申请要求2015年1月20日提交且标题为“Compounds and Methods for the Targeted Degradation of the Androgen Receptor”的美国临时专利申请系列号62/105,210的权益,其通过引用整体并入本文。

背景技术

[0003] 1.发现的领域.本说明书涉及双功能的化合物,其可用于修饰靶多肽和蛋白(具体地,雄激素受体)的泛素化和随后降解。在某些方面,所述化合物包含:Von Hippel-Lindau(VHL)结合部分,其结合VHL E3泛素连接酶;靶蛋白结合部分,其结合靶蛋白(例如,雄激素受体);和任选的接头部分(linker moiety),其连接所述VHL结合部分和靶蛋白结合部分。这些化合物以这样的方式起作用:将靶蛋白/多肽放在泛素连接酶附近以实现该蛋白(例如,雄激素受体)的降解(和抑制)。

[0004] 2.背景信息.雄激素受体(AR)属于被雄激素(诸如睾酮和二氢睾酮)活化的细胞核激素受体家族(Pharmacol.Rev.2006,58(4),782-97;Vitam.Horm.1999,55:309-52.)。在没有雄激素存在下,AR被胞质溶胶中的热休克蛋白90(Hsp90)结合。当雄激素结合AR时,它的构象变成从Hsp90释放AR并暴露核定位信号(NLS)。后者能使AR转移进细胞核中,在此处AR作为转录因子起作用以促进负责雄性性别特征的基因表达(Endocr.Rev.1987,8(1):1-28;Mol.Endocrinol.2002,16(10),2181-7)。AR缺乏会导致雄激素不敏感综合征,其以前被称作睾丸女性化。

[0005] 尽管AR负责雄性性别特征的发育,它也是某些形式的癌症中充分记载的癌基因,所述癌症包括前列腺癌(Endocr.Rev.2004,25(2),276-308)。AR活性的一种通常测量的靶基因是分泌的前列腺特异性抗原(PSA)蛋白。前列腺癌的当前治疗方案包括通过两种方法抑制雄激素-AR轴。第一个方案依赖于雄激素的减少,而第二个策略目标在于抑制AR功能(Nat.Rev.Drug Discovery,2013,12,823-824)。尽管开发了有效的靶向疗法,大多数患者发生抗性,且疾病进展。用于治疗前列腺癌的一个替代方案包括消除AR蛋白。因为AR是许多形式的前列腺癌中的肿瘤发生的关键驱动器,它的消除将会导致治疗上有益的应答。

[0006] 本领域中继续需要与异常AR调节或活性有关的疾病和病症(例如,癌症、前列腺癌和肯尼迪氏病(Kennedy's Disease))的有效治疗。

发明内容

[0007] 本公开内容描述了化合物,包括含有所述化合物的组合物,和使用它们的方法,所述化合物的作用是将内源性蛋白募集至E3泛素连接酶(例如,Von Hippel-Lindau(VHL)E3泛素连接酶)用于泛素化和随后降解。具体地,本公开内容提供了双功能化合物或蛋白酶解靶向嵌合(PROTAC)化合物,其用作雄激素受体(AR)的靶向泛素化和降解的调节剂。另外,本说明书提供了使用有效量的如本文中所述的化合物用于治疗或改善疾病状况(包括癌症,例如,前列腺癌和肯尼迪氏病)的方法。

[0008] 因而，在一个方面，本公开内容提供了起将内源性蛋白(例如，AR蛋白)募集至E3泛素连接酶用于泛素化和降解的作用的化合物。在某些实施方案中，所述化合物具有下述一般结构：

[0009] ABM-L-ULM (I)，

[0010] 其中ABM是AR结合部分，ULM是E3连接酶结合部分，例如，VHL E3连接酶结合部分(VLM)，且L是连接所述ABM和ULM的键或接头部分。这样，在某些实施方案中，本说明书提供了具有下述一般结构的化合物：

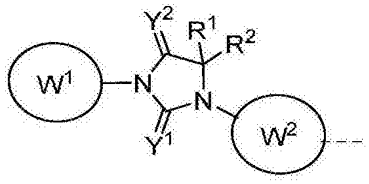
[0011] ABM-L-VLM (II)，

[0012] 其中ABM是AR结合部分，VLM是VHL E3连接酶结合部分，且L是连接所述ABM和VLM的键或接头部分。在某些实施方案中，所述VLM包含羟基脯氨酰基部分。

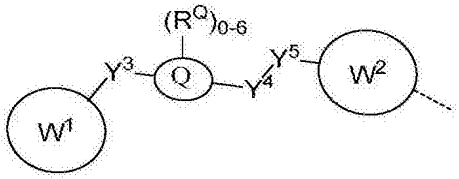
[0013] 在某些实施方案中，所述ULM是对E3泛素连接酶特异性的部分，例如，cereblon、小鼠双微体2同系物(Mdm2)或细胞凋亡抑制剂(IAP)，其中所述ULM部分与如本文中所述的ABM偶联。

[0014] 应该理解，所述一般结构是示例性的，且所述各个部分可以以任意期望的次序或构型在空间上排列，例如，分别ULM-L-ABM和VLM-L-ABM。

[0015] 在另一个方面，本说明书提供了AR结合部分(ABM)。在另一个实施方案中，本说明书提供了具有下述一般结构的化合物：ABM-L，其中ABM是如本文中所述的AR结合部分，且L是化学接头部分，或任选的键。在某些实施方案中，所述ABM和/或L与如本文中所述的ULM偶联。在某些实施方案中，所述ABM选自以下结构：

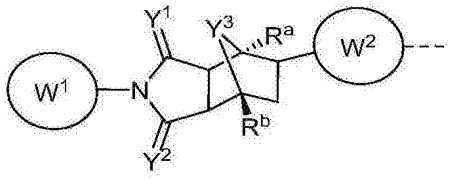


ABM-a、



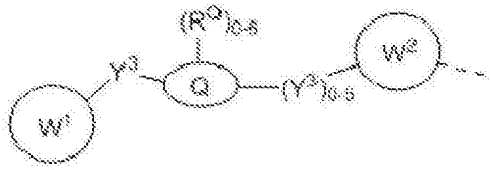
ABM-b、

[0016]



ABM-c

和



ABM-d。

[0017] 其中W^1是芳基或杂芳基，其独立地被1个或多个卤代(halo)、羟基、硝基、CN、C≡CH、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)、C_{1-6}烷氧基(直链的，支链的，任选地被1个或多个卤代取代)、C_{2-6}烯基、C_{2-6}炔基取代；

[0018] Y^1、Y^2各自独立地是NR^{Y1}、O、S；

[0019] Y^3、Y^4、Y^5各自独立地是键、O、NR^{Y2}、$CR^{Y1}R^{Y2}$、C=O、C=S、SO、SO_2；

[0020] Q是具有0-4个杂原子的3-6元脂环族环(alicyclic ring)或芳族环，其任选地被0-6个R^Q取代，每个R^Q独立地是H、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷

氧基取代)，或者2个R^Q基团与它们所连接的原子一起形成含有0-2个杂原子的3-8元环系)；

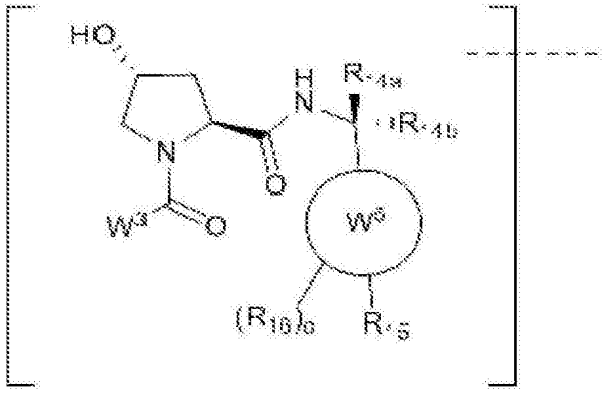
[0021] R^1、R^2、R^a、R^b、R^{Y1}、R^{Y2}各自独立地是H、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)，或者R^1、R^2与它们所连接的原子一起形成含有0-2个杂原子的3-8元环系)；

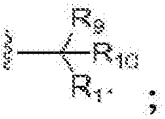
[0022] W^2是键、C_{1-6}烷基、C_{1-6}脂环族基(heterocyclic)、杂环基、芳基或杂芳基，每个任选地被1、2或3个R^{W2}取代；且

[0023] 每个R^{W2}独立地是H、卤代、C_{1-6}烷基(任选地被1个或多个F取代)、OC_{1-3}烷基(任选地被1个或多个-F取代)、OH、NH_2、$NR^{Y1}R^{Y2}$、CN。

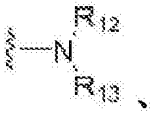
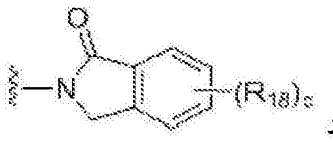
[0024] 在本文描述的方面或实施方案中的任一个中，所述ABM可以包含如本文中(特别是在实施例1-593所提供的ABM中的任一个中)所述的结构或由其组成。

[0025] 在某些实施方案中，所述ULM(被衍生化或构造成经由接头(如短划线所指示)与ABM连接或偶联)具有结构，

[0026] 

[0027] 其中，W^3是任选地被取代的芳基、任选地被取代的杂芳基或  ；

[0028] 每个R_9和R_{10}独立地是氢、任选地被取代的烷基、任选地被取代的环烷基、任选地被取代的羟基烷基、任选地被取代的杂芳基或卤代烷基；或R_9、R_{10}和它们所连接的碳原子形成任选地被取代的环烷基；

[0029] R_{11}是任选地被取代的杂环基、任选地被取代的烷氧基、任选地被取代的杂芳基、任选地被取代的芳基、  、  或  ；

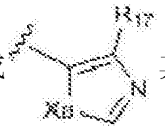
[0030] R_{12}是H或任选地被取代的烷基；

[0031] R_{13}是H、任选地被取代的烷基、任选地被取代的烷基羰基、任选地被取代的(环烷基)烷基羰基、任选地被取代的芳烷基羰基、任选地被取代的芳基羰基、任选地被取代的(杂环基)羰基或任选地被取代的芳烷基；

[0032] R_{14a}、R_{14b}各自独立地是H、卤代烷基或任选地被取代的烷基；

[0033] W^5是苯基或5-10元杂芳基，

[0034] R_{15}是H、卤素(halogen)、CN、OH、NO_2、N $R_{14a}R_{14b}$、OR_{14a}、$CONR_{14a}R_{14b}$、$NR_{14a}COR_{14b}$、

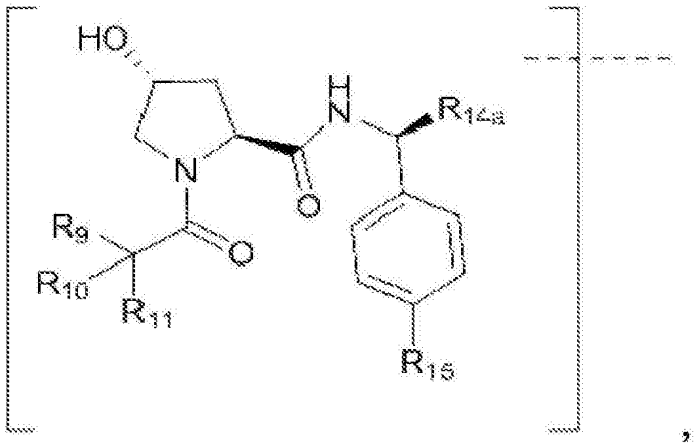
$SO_2NR_{14a}R_{14b}$、NR_{14a} SO_2R_{14b}、任选地被取代的烷基、任选地被取代的卤代烷基、任选地被取代的卤代烷氧基；芳基、杂芳基、环烷基、环杂烷基，每个R_{16}独立地是卤代、任选地被取代的烷基、任选地被取代的卤代烷基、羟基或任选地被取代的卤代烷氧基；或  其中R_{17}是H、卤代、任选地被取代的C_{3-6}环烷基、任选地被取代的C_{1-6}烷基、任选地被取代的C_{1-6}烯基和C_{1-6}卤代烷基，且Xa是S或O；

[0035] o是0、1、2、3或4；

[0036] 每个R_{18}独立地是卤代、任选地被取代的烷氧基、氰基、任选地被取代的烷基、卤代烷基、卤代烷氧基或接头；且

[0037] p是0、1、2、3或4。

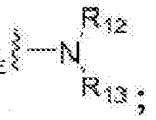
[0038] 在另一个实施方案中，所述ULM具有结构

[0039]  ，

[0040] 其中

[0041] R_9是H；

[0042] R_{10}是异丙基、叔丁基、仲丁基、环戊基或环己基；

[0043] R_{11}是  ；

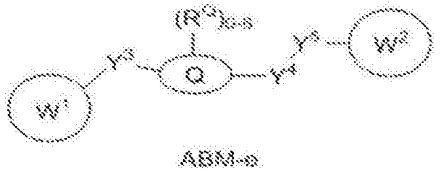
[0044] R_{12}是H；

[0045] R_{13}是H、任选地被取代的烷基、任选地被取代的烷基羰基、任选地被取代的(环烷基)烷基羰基、任选地被取代的芳烷基羰基、任选地被取代的芳基羰基、任选地被取代的(杂环基)羰基或任选地被取代的芳烷基；

[0046] R_{14a}是H、卤代烷基或任选地被取代的甲基、乙基、异丙基、环丙基或其它烷基；且

[0047] R_{15}是  其中R_{17}是H、卤代、任选地被取代的C_{3-6}环烷基、任选地被取代的C_{1-6}烷基、任选地被取代的C_{1-6}烯基和C_{1-6}卤代烷基；且Xa是S或O。

[0048] 在某些实施方案中，雄激素受体结合部分具有以下结构

[0049] 

[0050] 其中W^1是芳基或杂芳基，其独立地被1个或多个卤代、羟基、硝基、CN、C≡CH、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)、C_{1-6}烷氧基(直链的，支链的，任选地被1个或多个卤代取代)、C_{2-6}烯基、C_{2-6}炔基取代；

[0051] Y^1、Y^2各自独立地是NR^{Y1}、O、S；

[0052] Y^3、Y^4、Y^5各自独立地是键、O、NR^{Y2}、$CR^{Y1}R^{Y2}$、C=O、C=S、SO、SO_2；

[0053] Q是具有0-4个杂原子的3-6元脂环族环或芳族环，其任选地被0-6个R^Q取代，每个R^Q独立地是H、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)，或者2个R^Q基团与它们所连接的原子一起形成含有0-2个杂原子的3-8元环系)；

[0054] R^1、R^2、R^a、R^b、R^{Y1}、R^{Y2}各自独立地是H、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)，或者R^1、R^2与它们所连接的原子一起形成含有0-2个杂原子的3-8元环系)；

[0055] W^2是键、C_{1-6}烷基、C_{1-6}脂环族基、杂环基、芳基或杂芳基，每个任选地被1、2或3个R^{W2}取代；且

[0056] 每个R^{W2}独立地是H、卤代、C_{1-6}烷基(任选地被1个或多个F取代)、OC_{1-3}烷基(任选地被1个或多个-F取代)、OH、NH_2、$NR^{Y1}R^{Y2}$、CN。

[0057] 在某些另外的实施方案中，所述化合物包含多个E3连接酶结合部分和/或多个ABM。

[0058] 在某些实施方案中，所述接头基团(L)包含由下式表示的化学结构单元：

[0059] $-A_q-$

[0060] 其中

[0061] q是大于1的整数；且

[0062] A独立地选自键、$CR^{L1}R^{L2}$、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}、$NR^{L3}C(=NCN)NR^{L4}$、$NR^{L3}C(=NCN)$、$NR^{L3}C(=CNO_2)NR^{L4}$、任选地被0-6个R^{L1}和/或R^{L2}基团取代的C_{3-11}环烷基、任选地被0-6个R^{L1}和/或R^{L2}基团取代的C_{3-11}杂环基、任选地被0-6个R^{L1}和/或R^{L2}基团取代的芳基、任选地被0-6个R^{L1}和/或R^{L2}基团取代的杂芳基；

[0063] 其中R^{L1}、R^{L2}、R^{L3}、R^{L4}和R^{L5}每个独立地选自H、卤代、C_{1-8}烷基、OC_{1-8}烷基、SC_{1-8}烷基、NHC_{1-8}烷基、$N(C_{1-8}烷基)_2$、C_{3-11}环烷基、芳基、杂芳基、C_{3-11}杂环基、OC_{1-8}环烷基、SC_{1-8}环烷基、NHC_{1-8}环烷基、$N(C_{1-8}环烷基)_2$、$N(C_{1-8}环烷基)(C_{1-8}烷基)$、OH、NH_2、SH、SO_2C_{1-8}烷基、P(O)$(OC_{1-8}烷基)(C_{1-8}烷基)$、P(O)$(OC_{1-8}烷基)_2$、CC-C_{1-8}烷基、CCH、CH=CH(C_{1-8}烷基)、C(C_{1-8}烷基)=CH(C_{1-8}烷基)、C(C_{1-8}烷基)=C($C_{1-8}烷基)_2$、Si(OH)$_3$、Si($C_{1-8}烷基)_3$、Si(OH)$(C_{1-8}烷基)_2$、COC_{1-8}烷基、CO_2H、卤素、CN、CF_3、CHF_2、CH_2F、NO_2、SF_5、SO_2NHC_{1-8}烷基、$SO_2N(C_{1-8}烷基)_2$、$SONHC_{1-8}$烷基、$SON(C_{1-8}烷基)_2$、$CONHC_{1-8}$烷基、$CON(C_{1-8}烷基)_2$、$N(C_{1-8}烷基)CONH(C_{1-8}烷基)$、$N(C_{1-8}烷基)CON(C_{1-8}烷基)_2$、$NHCONH(C_{1-8}烷基)$、$NHCON(C_{1-8}烷基)_2$、$NHCONH_2$、$N(C_{1-8}烷基)SO_2NH(C_{1-8}烷基)$、$N(C_{1-8}烷基)SO_2N(C_{1-8}烷基)_2$、NH $SO_2NH(C_{1-8}烷基)$、NH $SO_2N(C_{1-8}烷基)_2$和NH SO_2NH_2；且

[0064] 其中当q大于1时，R^{L1}或R^{L2}每个独立地可以连接至另一个A基团以形成环烷基和/或杂环基部分，所述部分可以进一步被0-4个R^{L5}基团取代。

[0065] 在某些实施方案中，本说明书提供了具有选自实施例1-593的结构的双功能化合物、其盐、多晶型物和前药。

[0066] 在另一个方面，本说明书提供了组合物，其包含如本文中所述的化合物和药学上可接受的载体。在某些实施方案中，所述组合物是包含有效量的如本文中所述的化合物和药学上可接受的载体的治疗或药物组合物。在某些实施方案中，所述治疗或药物组合物包含另外的生物活性剂，例如，对于癌症的治疗有效的药剂。

[0067] 在本文描述的方面或实施方案中的任一个中，包含本文描述的化合物的治疗组合物可以呈任意合适的剂型，例如，固体或液体，且被构造成通过任意合适途径(例如，口服、胃肠外、静脉内、腹膜内、皮下、肌肉内等)和在任意期望的单元剂型(unit dosage)中递送。例如，在某些实施方案中，如本文中所述的治疗组合物被构造成由受试者在期望的时间段(例如，数天、数周、数月等)内施用或消费一次或多次。

[0068] 在另一个方面，本公开内容提供了调节受试者(例如，细胞、组织、哺乳动物或人患者)中的蛋白泛素化和降解的方法，所述方法包括给受试者施用有效量的如本文中所述的化合物或包含有效量的所述化合物的组合物，其中所述化合物或包含它们的组合物可有效地调节所述受试者中的蛋白的蛋白泛素化和降解。在某些实施方案中，所述蛋白是雄激素受体(AR)。

[0069] 在另一个方面，本公开内容提供了调节受试者(例如，细胞、组织、哺乳动物或人患者)中的AR蛋白泛素化和降解的方法，所述方法包括给受试者施用有效量的如本文中所述的化合物或包含有效量的所述化合物的组合物，其中所述化合物或包含它们的组合物可有效地调节所述受试者中的蛋白的AR蛋白泛素化和降解。

[0070] 在另一个方面，本公开内容提供了治疗或改善受试者(例如，细胞、组织、哺乳动物或人患者)中与AR活性有关的疾病的症状的方法，所述方法包括给有此需要的受试者施用有效量的如本文中所述的化合物或包含有效量的所述化合物的组合物，其中所述化合物或包含它们的组合物可有效地治疗或改善所述受试者中与AR活性有关的疾病的症状。在某些实施方案中，要治疗的疾病是癌症，例如，前列腺癌或肯尼迪氏病。在一个优选的实施方案中，所述受试者是人。

[0071] 在另一个方面，本公开内容提供了使用根据本发明的化合物鉴别生物系统中目标蛋白的降解的影响的方法。

[0072] 在另一个方面，本说明书提供了试剂盒，其包含如本文中所述的化合物或组合物。所述试剂盒可以作为用于执行本发明的方法的单元来宣传、分配或销售。另外，本发明的试剂盒可以优选地含有描述合适使用的说明书。这样的试剂盒可以方便地用在例如临床场合中，以治疗表现出例如癌症或肯尼迪氏病的症状的患者。

[0073] 在适用或没有特别放弃的情况下，预见到本文描述的任一个实施方案能够与任意其它一个或多个实施方案组合，尽管在本发明的不同方面下描述所述实施方案。这样，上述实用性的一般领域仅仅作为示例给出，且无意限制本公开内容和所附权利要求的范围。本领域普通技术人员考虑到本发明的权利要求、说明书和实施例会明白与本发明的组合物、方法和工艺有关的另外的目的和优点。例如，本发明的各个方面和实施方案可以以众多组

合使用，它们都被本说明书明确地预见到。在本发明范围内明确地包括这些另外的优点、目的和实施方案。在本文中用于阐明背景技术和在特定情况下用于提供关于实践的额外细节的出版物和其它材料通过引用并入。

附图说明

[0074] 并入说明书中并形成说明书的一部分的附图解释了本发明的若干实施方案，且与本说明书一起用于解释本发明的原理。附图仅仅用于解释本发明的实施方案的目的，不应解释为限制本发明。从下述详细描述，结合显示本发明的示例性实施方案的附图，会明白本发明的其它目的、特征和优点，在附图中：

[0075] 图1.PROTAC功能的一般原理的解释。(A)示例性的PROTAC包含雄激素受体靶向部分(ABM;深色阴影矩形)、Von Hippel-Lindau(VHL)E3泛素连接酶结合部分(VLM;浅色阴影三角形)和将所述ABM与所述VLM偶联或连接的接头部分(L;黑色线)(如本文中所述，L可以不存在或者是键或化学接头部分)。(B)解释了如本文中所述的PROTAC的功能应用。简而言之，所述VLM识别并结合Von Hippel-Lindau(VHL)E3泛素连接酶，且所述ABM结合并募集雄激素受体和将它带至Von Hippel-Lindau(VHL)E3泛素连接酶紧密附近。通常，所述E3泛素连接酶与E2泛素缀合蛋白形成复合物，且单独地或经由E2蛋白催化泛素(黑色圆圈)经由异肽键向靶蛋白上的赖氨酸的连接。然后多泛素化的蛋白(最右侧)被靶向以通过细胞的蛋白体机制进行降解。

[0076] 图2.VCaP细胞中的细胞凋亡。将VCaP细胞在补充了0.1nM R1881的、含木炭净化的血清的培养基(Charcoal Stripped Serum containing media)中培养48小时。

[0077] 图3.LNCaP F876L中的抗增殖。在含木炭净化的血清的培养基中培养用AR F876L构建体转导的LNCaP细胞。

[0078] 图4.LNCaP F876L中的PSA抑制。将用AR F876L构建体转导的LNCaP细胞在补充了0.1nM R1881的、含木炭净化的血清的培养基中培养7天。

[0079] 图5.C57B6小鼠模型中的前列腺退化(involution)。将12-周龄雄性C57BL/6小鼠用AR PROTAC实施例163和它的无活性的差向异构体类似物化合物A(其不能结合VHL E3连接酶)处理。将恩杂鲁胺(enzalutamide)(PO,QD,30mpk)、实施例163(IP,QD,1和3mpk)和化合物A(IP,QD,1和3mpk)施用10天，此后将前列腺分离并称重。

[0080] 图6.VCaP异种移植物模型中的肿瘤生长抑制。将VCaP细胞皮下地植入CB17scid小鼠中。一旦肿瘤是可触知的，将小鼠阉割，从而导致暂时的肿瘤停滞。在肿瘤的再生长后，按照指示给小鼠施用恩杂鲁胺(PO,QD,30mpk)或AR PROTAC实施例163(IP,QD,在30,10和3mpk)。

[0081] 图7.PROTAC的AR降解是E3连接酶依赖性的。(A)：在有或没有10μM VHL E3连接酶配体化合物B存在下将AR PROTAC实施例1在指示的浓度加给LNCaP细胞24小时。(B)：用AR PROTAC实施例1和它的无活性的差向异构体类似物化合物C(其不能结合VHL E3连接酶)处理LNCaP细胞。

[0082] 详细描述

[0083] 下述是为了辅助本领域技术人员实践本发明而提供的详细描述。本领域普通技术人员可以在本文描述的实施方案中做出修饰和变化，而不背离本公开内容的精神或范围。

本文中提及的所有出版物、专利申请、专利、附图和其它参考文献明确地通过引用整体并入。

[0084] 本说明书涉及以下惊人的和意外的发现：一旦如本文中所述的嵌合构建体(例如，PROTAC)使E3泛素连接酶蛋白和靶蛋白靠近，E3泛素连接酶蛋白就可以将靶蛋白(特别是雄激素受体)泛素化，在所述嵌合构建体中结合E3泛素连接酶蛋白的部分与结合雄激素受体靶蛋白的部分偶联(例如，共价地)。因此，本说明书提供了用于选择的靶蛋白(例如，雄激素受体)的泛素化和降解的化合物、包含它们的组合物和有关的使用方法(参见图1)。

[0085] 本说明书在某些方面涉及美国专利公开文本2014/0356322A1，其通过引用整体并入本文用于所有目的。

[0086] 除非另有定义，否则本文使用的所有技术和科学术语具有本发明所属领域的普通技术人员所通常理解的相同含义。在本说明书中使用的术语仅用于描述特定实施方案，且无意成为本发明的限制。

[0087] 在提供了值的范围的情况下，应当理解，介于该范围的上限与下限之间的每个居间值(intervening value)(直至下限单位的十分之一，除非上下文另外清楚地指明)(诸如在含有许多个碳原子的基团的情况下，在该情况下，提供落入所述范围内的每个碳原子数目)，并且在该所述范围中的任意其它所述值或居间值被包括在本发明内。这些较小范围的上限和下限(其可以独立地包括在较小范围内)也被包括在本发明内，具有在所述范围中的任何具体地排除的限制。在所述范围包括一个或两个端值的情况下，排除那些被包括的端值中的任一个或两个端值的范围也被包括在本发明中。

[0088] 下述术语用于描述本发明。在本文没有明确定义术语的情况下，普通技术人员在使用它描述本发明的背景下应用该术语时为该术语给出本领域公知的含义。

[0089] 在本文中和在所附权利要求中使用的冠词“一个”和“一种”在本文中用于表示一个/种或超过一个/种(即，至少一个/种)该冠词的语法对象，除非上下文另外清楚地指出。作为例子，“一个要素”是指一个要素或超过一个要素。

[0090] 本文在说明书中和在权利要求中使用的短语“和/或”应当被理解为是指如此结合的要素(即，在某些情况下结合地存在和在其它情况下分离地存在的要素)中的“任一个或二者”。用“和/或”列出的多个要素应当以相同的方式解释，即，如此结合的要素中的“一个或多个”。除了用“和/或”条款明确地指出的要素以外的其它要素可以任选地存在，无论与明确地指出的那些要素有关还是无关。因而，作为一个非限制性例子，当与开放式语言(诸如“包含”)结合使用时对“A和/或B”的提及在一个实施方案中可以表示仅A(任选地包括除了B以外的要素)；在另一个实施方案中，表示仅B(任选地包括除了A以外的要素)；在另一个实施方案中，表示A和B(任选地包括其它要素)；等等。

[0091] 本文在说明书中和在权利要求中使用的“或”应当理解为具有与上面定义的“和/或”相同的含义。例如，当在列表中分隔项目时，“或”或“和/或”应当解释为包含性的，即，包括数字或要素列表中的至少一个，但是也包括超过一个，且任选地包括另外的未列出的项目。清楚地指出相反含义的仅有性术语(诸如“……中仅一个”或“……中刚好一个”，或者，当在权利要求中使用时，“由……组成”)将表示包括数字或要素列表中的刚好一个要素。一般而言，当前面存在排它性术语(诸如“任一个”、“……中的一个”、“……中的仅一个”或“……中的刚好一个”)时，本文中使用的术语“或”应当仅解释为指示排它性替代物(即，“一

个或另一个，但不是二者”）。

[0092] 本文中与数字值或范围结合使用的术语“约”等反映了以下事实：由于实践和/或理论限制，存在本领域中公认的且允许的某种水平的变动。例如，由于某些装置运行的方式和/或进行测量的方式的固有差异，微小变动是允许的。根据上述，短语“约”通常用于包括在标准差或标准误差内的值。

[0093] 在权利要求中以及在上述说明书中，所有过渡短语(transitional phase)诸如“包含”、“包括”、“携带”、“具有”、“含有”、“包括”、“容纳”、“由……构成”等应当理解为开放式的，即，意在包括、但不限于。仅过渡短语“由……组成”和“基本上由……组成”应当分别是封闭式的或半封闭的过渡短语，如在美国专利局专利审查程序手册(United States Patent Office Manual of Patent Examining Procedures)第2111.03部分中所述。

[0094] 如本文在说明书中和在权利要求中使用的，提到一个或多个要素的列表的短语“至少一个”应当被理解为是指选自所述要素列表中的任一个或多个要素的至少一个要素，但不一定包括在所述要素列表内明确地列出的每个和每一个要素中的至少一个，且不排除所述要素列表中的要素的任意组合。该定义也允许可以任选地存在除了在短语“至少一个”所提及的要素列表内明确地指出的要素以外的要素，无论与明确地指出的那些要素有关还是无关。因而，作为一个非限制性例子，“A和B中的至少一个”(或，等同地，“A或B中的至少一个”，或，等同地“A和/或B中的至少一个”)在一个实施方案中可以表示至少一个(任选地包括超过一个)A，且不存在B(且任选地包括除了B以外的要素)；在另一个实施方案中，表示至少一个(任选地包括超过一个)B，且不存在A(且任选地包括除了A以外的要素)；在另一个实施方案中，表示至少一个(任选地包括超过一个)A和至少一个(任选地包括超过一个)B(且任选地包括其它要素)；等等。

[0095] 还应当理解，在本文描述的某些包括超过一个步骤或动作的方法中，所述步骤的次序或所述方法的动作不一定限于列举所述方法的步骤或动作的次序，除非上下文另外指出。

[0096] 术语“共同施用”和“共同给药”或“联合治疗”可以表示同时施用(两种或更多种治疗剂的同时施用)和不同时施用(与一种或多种治疗剂的施用不同时间地施用一种或多种其它治疗剂)，只要所述治疗剂在某种程度上存在于患者中，优选地在有效量、在相同时间。在某些优选的方面，将本文描述的本发明化合物中的一种或多种与至少一种另外的生物活性剂(特别包括抗癌剂)联合地共同施用。在特别优选的方面，化合物的共同施用产生协同的活性和/或疗法，包括抗癌活性。

[0097] 术语“有效的”可以是指，但决不限于，这样的活性药物成分的量/剂：当在它的预期用途的背景下使用时，其在需要这种治疗或接受这种治疗的受试者中实现或足以阻止、抑制病症、障碍或疾病状态的症状的发生，改善、延迟或治疗(减轻症状达到某种程度，优选地全部)病症、障碍或疾病状态的症状。术语“有效的”包含在本申请中另外描述或使用的所有其它有效量或有效浓度术语，例如，“有效量/剂”、“药学有效量/剂”或“治疗有效量/剂”。

[0098] 有效量取决于疾病的类型和严重程度、使用的组合物、施用途径、正在治疗的哺乳动物的类型、在考虑中的具体哺乳动物的体格特征、并行的药物治疗和医学领域的技术人员会认识到的其它因素。确切量可以由本领域技术人员使用已知技术确定(参见，例如，Lieberman,Pharmaceutical Dosage Forms(1992年第1-3卷)；Lloyd,The Art,Science

and Technology of Pharmaceutical Compounding(1999);Pickar,Dosage Calculations(1999);和Remington:The Science and Practice of Pharmacy,第20版,2003,Gennaro,编,Lippincott,Williams&Wilkins)。

[0099] 术语“药理学组合物”、“治疗组合物”、“治疗制剂”或“药学上可接受的制剂”可以是指,但决不限于,允许本发明提供的药剂的有效分布的组合物或制剂,其呈适合用于施用至最适合于它们的期望活性的身体位置的形式,例如,全身施用。

[0100] 术语“药学上可接受的”或“药理学上可接受的”可以是指,但决不限于,当施用给适当的动物或人时,不会产生不利的、变应性的或其它不良的反应的实体和组合物。

[0101] 术语“药学上可接受的载体”或“药理学上可接受的载体”可以是指,但决不限于,与药物施用相容的任意的和所有的溶剂、分散介质、包衣剂、抗细菌剂和抗真菌剂、等渗剂和吸收延迟剂等。在Remington's Pharmaceutical Sciences(本领域中的标准参考教科书,其通过引用并入本文)的最新版中描述了合适的载体。这样的载体或稀释剂的优选例子包括、但不限于水、盐水、林格氏(finger's)溶液、右旋糖溶液和5%人血清白蛋白。也可以使用脂质体和非水性媒介物诸如不挥发性油。这样的介质和药剂用于药学活性物质的用途是本领域众所周知的。除了任何常规介质或试剂与活性化合物不相容以外,预见到其在所述组合物中的应用。还可将补充性活性化合物掺入所述组合物中。

[0102] 术语“全身施用”表示这样的施用途径:其是例如肠内或胃肠外途径,并导致药剂的全身分布,从而导致血流中的药物的全身吸收或积累,然后分布遍及整个身体。适合形式部分地取决于用途或进入途径,例如口服、透皮或通过注射。这样的形式不应当阻止所述组合物或制剂到达靶细胞(即,期望向其递送带负电荷的聚合物的细胞)。例如,注射进血流中的药理学组合物应当是可溶性的。其它因素是本领域已知的,且包括考虑因素诸如毒性和阻止所述组合物或制剂发挥它的作用的形式。导致全身吸收的施用途径包括、但不限于静脉内、皮下、腹膜内、吸入、口服、肺内和肌肉内。已经证实药物向循环中的进入速率是分子量或大小的函数。包含本发明的化合物的脂质体或其它药物载体的应用可以潜在地将药物定位在例如某些组织类型中,诸如网状内皮系统(RES)的组织。可以促进药物与细胞(例如,淋巴细胞和巨噬细胞)的表面的结合的脂质体制剂也是有用的。

[0103] 术语“局部施用”表示这样的施用途径:其中将药剂递送至病变或疾病部位的适合(apposite)或近侧部位,例如,在约10cm内。

[0104] 除非另有说明,否则本文中使用的术语“化合物”表示本文中公开的任何具体化学化合物,且包括互变异构体、位置异构体、几何异构体和适用时的立体异构体,包括其光学异构体(对映异构体)和其它立体异构体(非对映异构体),以及当在上下文中适用时其药学上可接受的盐和衍生物(包括前药形式)。在它在上下文中的应用中,术语化合物通常表示单一化合物,但是也可以包括其它化合物诸如立体异构体、位置异构体和/或光学异构体(包括外消旋混合物)以及公开的化合物的具体对映异构体或对映异构地富集的混合物。该术语在上下文中也表示化合物的前药形式,其已经被修饰以促进化合物向活性部位的施用和递送。应当指出,在描述本发明化合物时,描述了众多取代基和与其有关的变量,以及其它。

[0105] 普通技术人员会理解,本文描述的分子是在下文中一般地描述的稳定化合物。当

显示键  时，在所示化合物的上下文中代表双键和单键。

[0106] 本文中使用的“衍生物”可以是指直接地、通过修饰或通过部分取代从天然化合物形成的组成。本文中使用的“类似物”可以是指具有与天然化合物类似、但是不同的结构的组成。

[0107] 术语“泛素连接酶”表示促进泛素向特定底物蛋白的转移、从而靶向所述底物蛋白用于降解的蛋白家族。作为例子，Von Hippel-Lindau E3泛素连接酶或VCB E3泛素连接酶是这样的蛋白：其单独地或与E2泛素缀合酶联合地造成泛素向靶蛋白上的赖氨酸的连接，并随后靶向特定蛋白底物用于被蛋白酶体降解。因而，单独的或与E2泛素缀合酶形成复合物的E3泛素连接酶负责泛素向靶蛋白的转移。一般而言，所述泛素连接酶参与多泛素化，使得第二个泛素连接至第一个；第三个连接至第二个，以此类推。多泛素化会标记蛋白用于被蛋白酶体降解。但是，存在一些限于单泛素化的泛素化事件，其中仅单个泛素被泛素连接酶添加至底物分子。单泛素化的蛋白没有被靶向蛋白酶体进行降解，但是相反可以在它们的细胞位置或功能方面被改变，例如，经由结合其它蛋白（其具有能够结合泛素的结构域）。使情况进一步复杂化的是，泛素上的不同赖氨酸可以被E3靶向以形成链。最常见的赖氨酸是泛素链上的Lys48。这是用于制备被蛋白酶体识别的多泛素的赖氨酸。

[0108] 术语“受试者”在本说明书中用于描述给其提供使用根据本发明的组合物的治疗（包括预防性处理）的细胞、组织或动物，优选哺乳动物，例如，人或驯化的动物。对于特定动物（诸如人患者）特有的那些感染、病症或疾病状态的治疗而言，术语患者表示该特定动物，包括驯化的动物诸如狗或猫或耕作动物诸如马、牛、绵羊等。一般而言，在本发明中，术语患者表示人患者，除非另有说明或从该术语的应用的上下文中暗示。

[0109] 化合物

[0110] 在一个方面，本发明提供了可用于调节蛋白活性的化合物。其组成（composition）包含连接或偶联在一起（优选地通过接头）的根据确定的化学结构的泛素途径蛋白结合部分（优选地针对E3泛素连接酶，其单独地或与E2泛素缀合酶形成复合物，其负责泛素向靶蛋白的转移）和蛋白靶向部分，其中所述泛素途径蛋白结合部分识别泛素途径蛋白，且所述靶向部分识别靶蛋白（例如，雄激素受体）。这样的化合物在本文中可以被称作PROTAC化合物或PROTAC。

[0111] 在一个方面，本说明书提供了AR结合部分（ABM）。在某些实施方案中，所述化合物具有下述一般结构：ABM-L，其中ABM是如本文中所述的AR结合部分，且L是化学接头部分，例如，如本文中所述的接头，或任选的键。在某些实施方案中，所述ABM和/或L与下文中所述的ULM偶联。

[0112] 在另一个方面，本公开内容提供了起将雄激素受体（AR）蛋白募集至E3泛素连接酶用于泛素化和降解的作用的化合物。在某些实施方案中，所述化合物具有下述一般结构：

[0113] ABM-L-ULM (I)，

[0114] 其中ULM是E3连接酶结合部分，ABM是结合AR蛋白的AR结合部分，且L是连接所述ABM和ULM的键或化学接头部分。

[0115] 在某些实施方案中，所述ULM是对E3泛素连接酶特异性的部分例如，Von Hippel-Lindau E3泛素连接酶（VHL）、cereblon、小鼠双微体2同系物（Mdm2）或细胞凋亡抑制剂

(IAP)，其中所述ULM部分与如本文中所述的ABM偶联。

[0116] 不受任何特定理论约束，假定至少部分地由于AR和E3泛素连接酶的靠近，所述AR被泛素连接酶泛素化和降解。在某些实施方案中，所述ABM直接与ULM基团化学连接或偶联。在某些另外的实施方案中，所述ABM经由化学接头部分与ULM化学连接或偶联。在另外的实施方案中，本说明书提供了具有下述一般结构的化合物：

[0117] ABM-L-VLM (II)，

[0118] 其中ABM是AR结合部分，且VLM是Von Hippel-Lindau E3泛素连接酶(VHL)结合部分，且L是连接所述ABM和VLM的键或化学接头部分。所述ULM或VLM基团和ABM基团可以通过适当的且对所述接头的化学性质稳定的任何共价键共价地连接至所述接头基团。

[0119] 在某些实施方案中，所述ULM或VLM包含羟基脯氨酰基部分。已经证实所述羟基脯氨酰基部分对于VHL蛋白的结合和募集而言是重要的。

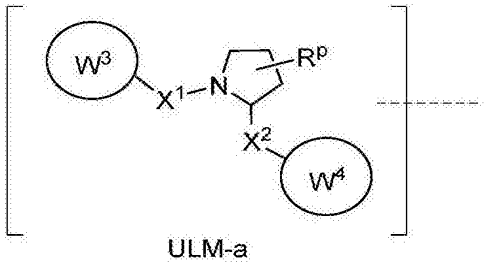
[0120] 应该理解，所述一般结构是示例性的，且所述各个部分可以以任意期望的次序或构型排列，例如，分别ULM-L-ABM和VLM-L-ABM。在某些另外的实施方案中，所述化合物包含多个E3连接酶结合部分和/或多个ABM。

[0121] 在某些实施方案中，单独的ABM(没有形成ABM-L-ULM)在调节蛋白活性中提供期望的性能。

[0122] 在本文描述的化合物的任何方面或实施方案中，除非另外指出，否则所述化合物意图包括其药学上可接受的盐、对映异构体、立体异构体、溶剂化物或多晶型物。

[0123] 示例性的ULM

[0124] 在如本文中所述的化合物的某些实施方案中，所述ULM包含选自集合ULM-a的化学结构：

[0125] 

ULM-a ，

[0126] 其中短划线指示至少一个ABM、另一个ULM或VLM(即，ULM'或VLM')或将至少一个ABM、ULM'或VLM'与所述接头的另一个末端偶联的化学接头部分的连接；

[0127] X^1、X^2各自独立地是键、O、NR^{Y3}、$CR^{Y3}R^{Y4}$、C=O、C=S、SO、SO_2；

[0128] R^{Y3}、R^{Y4}各自独立地是H、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)；

[0129] 在吡咯烷部分中任选地被1-3个R^P基团取代，其中每个R^P独立地是H、卤代、-OH、C_{1-3}烷基；

[0130] W^3是任选地被取代的-T-N($R^{1a}R^{1b}$)、-T-芳基、任选地被取代的-T-杂芳基、任选地被取代的-T-杂环、任选地被取代的-NR^1-T-芳基、任选地被取代的-NR^1-T-杂芳基或任选地被取代的-NR^1-T-杂环，其中T共价地键合至X^1；

[0131] 每个R^1、R^{1a}、R^{1b}独立地是H、C_1-C_6烷基(直链的，支链的，任选地被1个或多个卤代、-OH取代)、$R^{Y3}C$=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

$(R^{Y3}R^{Y4})SO_2$；

[0132] T是任选地被取代的-$(CH_2)_n$-基团，其中每个亚甲基可以任选地被一个或两个取代基取代，所述取代基优选地选自卤素、C_1-C_6烷基(直链的，支链的，任选地被1个或多个卤代、-OH取代)或如本文另外描述的氨基酸的侧链，优选甲基，其可以被任选地取代；且n是0-6，经常0、1、2或3，优选0。

[0133] 可替换地，T也可以是-$(CH_2O)_n$-基团、-$(OCH_2)_n$-基团、-$(CH_2CH_2O)_n$-基团、-$(OCH_2CH_2)_n$-基团，所述基团中的每个任选地被取代；且

[0134] W^4是任选地被取代的-NR^1-T-芳基、任选地被取代的-NR^1-T-杂芳基或任选地被取代的-NR^1-T-杂环，其中-NR^1共价地键合至X^2；R^1是H或CH_3，优选H，且T是任选地被取代的-$(CH_2)_n$-基团，其中每个亚甲基可以任选地被一个或两个取代基取代，所述取代基优选地选自卤素、如本文另外描述的氨基酸侧链或C_1-C_6烷基(直链的，支链的，任选地被1个或多个卤代、-OH取代)，优选一个或两个甲基，其可以任选地被取代；且n是0-6，经常0、1、2或3，优选0或1。

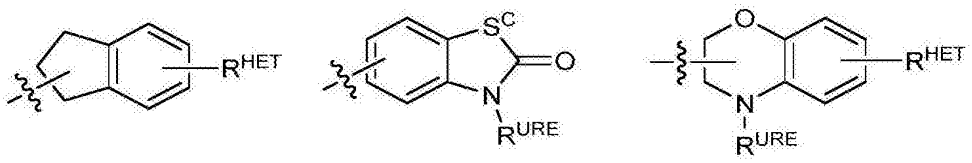
[0135] 可替换地，T也可以是-$(CH_2O)_n$-基团、-$(OCH_2)_n$-基团、-$(CH_2CH_2O)_n$-基团、-$(OCH_2CH_2)_n$-基团，所述基团都任选地被取代。

[0136] 在本文描述的任一个实施方案中，W^3和/或W^4可以连接至如本文中所述的接头部分。

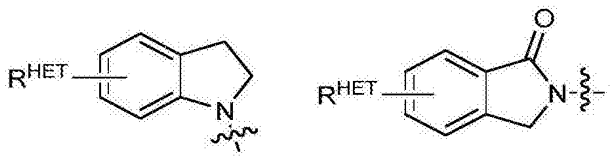
[0137] 在某些实施方案中，W^3的芳基包括任选地被取代的苯基或萘基，优选苯基，其中所述苯基或萘基任选地被以下基团取代：ABM基团(包括ULM'基团)和/或卤素(优选F或Cl)所连接的接头基团，胺，单烷基胺或二烷基胺(优选地，二甲基胺)，酰氨基(优选地-$(CH_2)_m$-$NR_1C(O)R_2$基团，其中m、R_1和R_2与关于R^1所述相同)，卤素(经常F或Cl)，OH，CH_3，CF_3，OMe，OCF_3，NO_2，CN或$S(O)_2R_S$基团(R_S是C_1-C_6烷基、任选地被取代的芳基、杂芳基或杂环基或-$(CH_2)_mNR_1R_2$基团)，它们中的每个可以在苯环的邻-、间-和/或对-位(优选地对-位)被取代，或芳基(优选地苯基)，杂芳基或杂环。优选地所述取代基苯基是任选地被取代的苯基(即，所述取代基苯基本身优选地被F、Cl、OH、SH、COOH、CH_3、CF_3、OMe、OCF_3、NO_2、CN或ABM基团(包括ULM'基团)所连接的接头基团中的至少一个取代，其中所述取代发生在苯环的邻-、间-和/或对-位，优选地对-位)，萘基，其可以任选地被取代，包括如上所述，任选地被取代的杂芳基(优选地任选地被取代的异噁唑，包括甲基取代的异噁唑，任选地被取代的噁唑，包括甲基取代的噁唑，任选地被取代的噻唑，包括甲基取代的噻唑，任选地被取代的吡咯，包括甲基取代的吡咯，任选地被取代的咪唑，包括甲基咪唑、苄基咪唑或甲氧基苄基咪唑、oximidazole或methyloximidazole，任选地被取代的二唑基团，包括甲基二唑基团，任选地被取代的三唑基团，包括甲基取代的三唑基团，吡啶基团，包括卤代-(优选地，F)或甲基取代的吡啶基团或氧杂吡啶基团(其中吡啶基团通过氧连接至苯基)或任选地被取代的杂环(四氢呋喃、四氢噻吩、吡咯烷、哌啶、吗啉、哌嗪、四氢喹啉、噁烷或硫杂环己烷(thiane))。所述芳基、杂芳基或杂环基中的每一个可以任选地被ABM基团(包括ULM'基团)所连接的接头基团取代。

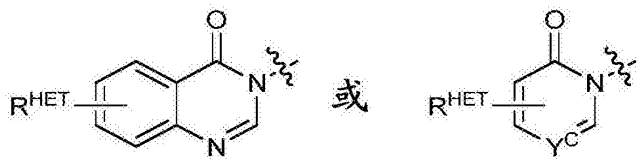
[0138] 在某些实施方案中，W^3的杂芳基包括任选地被取代的喹啉(其可以连接至药效团或在喹啉环内的任意碳原子上被取代)、任选地被取代的吲哚(包括二氢吲哚)、任选地被取

代的吲嗪、任选地被取代的氮杂吲嗪(2,3或4-氮杂吲嗪)、任选地被取代的苯并咪唑、苯并二唑、benzoxofuran、任选地被取代的咪唑、任选地被取代的异噁唑、任选地被取代的噁唑(优选地甲基取代)、任选地被取代的二唑、任选地被取代的三唑、四唑、任选地被取代的苯并呋喃、任选地被取代的噻吩、任选地被取代的噻唑(优选地甲基和/或巯基取代)、任选地被取代的异噻唑、任选地被取代的三唑(优选地被以下基团取代的1,2,3-三唑:甲基、三异丙基甲硅烷基、任选地被取代的-$(CH_2)_m$-O-C_1-C_6烷基或任选地被取代的-$(CH_2)_m$-C(O)-O-C_1-C_6烷基)、任选地被取代的吡啶(2-、3或4-吡啶)或根据以下化学结构的基团:



[0139]





[0140] 其中S^C是CHR^{SS}、NR^{URE}或O;

[0141] R^{HET}是H、CN、NO_2、卤代(优选地Cl或F)、任选地被取代的C_1-C_6烷基(优选地被一个或两个羟基或至多三个卤代基团(例如CF_3)取代)、任选地被取代的O(C_1-C_6烷基)(优选地被一个或两个羟基或至多三个卤代基团取代)或任选地被取代的炔属基团-C≡C-R_a,其中R_a是H或C_1-C_6烷基(优选地C_1-C_3烷基);

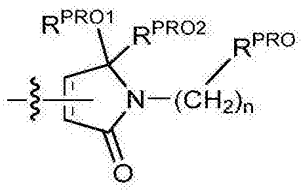
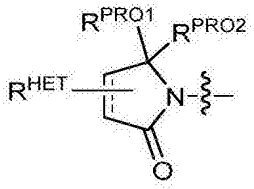
[0142] R^{SS}是H、CN、NO_2、卤代(优选F或Cl)、任选地被取代的C_1-C_6烷基(优选地被一个或两个羟基或至多三个卤代基团取代)、任选地被取代的O-(C_1-C_6烷基)(优选地被一个或两个羟基或至多三个卤代基团取代)或任选地被取代的-C(O)(C_1-C_6烷基)(优选地被一个或两个羟基或至多三个卤代基团取代);

[0143] R^{URE}是H、C_1-C_6烷基(优选地H或C_1-C_3烷基)或-C(O)(C_1-C_6烷基),所述基团中的每个任选地被一个或两个羟基或至多三个卤素(优选氟基团)取代,或任选地被取代的杂环,例如哌啶、吗啉、吡咯烷、四氢呋喃、四氢噻吩、哌啶、哌嗪,其中每个任选地被取代;且

[0144] Y^C是N或C-R^{YC},其中R^{YC}是H、OH、CN、NO_2、卤代(优选地Cl或F)、任选地被取代的C_1-C_6烷基(优选地被一个或两个羟基或至多三个卤代基团(例如CF_3)取代)、任选地被取代的O(C_1-C_6烷基)(优选地被一个或两个羟基或至多三个卤代基团取代)或任选地被取代的炔属基团-C≡C-R_a,其中R_a是H或C_1-C_6烷基(优选地C_1-C_3烷基)。所述杂芳基中的每个可以任选地被ABM基团(包括ULM'基团)所连接的接头基团取代。

[0145] 在另外的实施方案中,W^3的杂环基团包括四氢喹啉、哌啶、哌嗪、吡咯烷、吗啉、四氢呋喃、四氢噻吩、噁烷和硫杂环己烷,所述基团中的每个可以任选地被取代或是根据以

下化学结构的基团：

[0146]   基团；



[0147] 其中R^{PRO}是H、任选地被取代的C_1-C_6烷基或任选地被取代的芳基(苯基或萘基)、选自以下的杂芳基或杂环基团：噁唑、异噁唑、噻唑、异噻唑、咪唑、二唑、oximidazole、吡咯、吡咯烷、呋喃、二氢呋喃、四氢呋喃、噻吩、二氢噻吩、四氢噻吩、吡啶、哌啶、哌嗪、吗啉、喹啉(每个优选地被C_1-C_3烷基、优选甲基或卤代基团、优选F或Cl取代)、苯并呋喃、吲哚、吲嗪、氮杂吲嗪；

[0148] R^{PRO1}和R^{PRO2}各自独立地是H、任选地被取代的C_1-C_3烷基或一起形成酮基，且

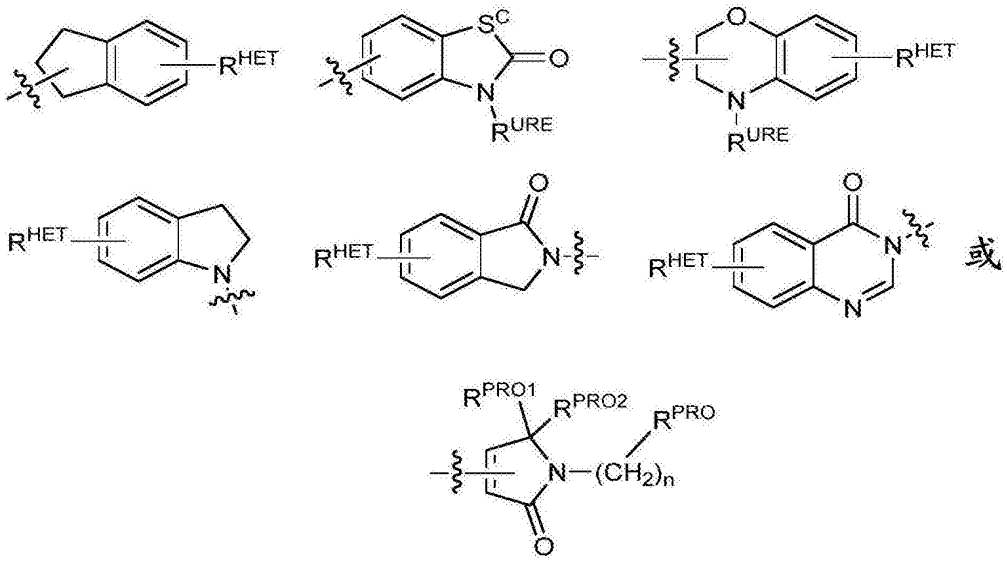
[0149] 每个n是0、1、2、3、4、5或6(优选地0或1)，其中所述杂环基团中的每个可以任选地被ABM基团(包括ULM'基团)所连接的接头基团取代，

[0150] 或其药学上可接受的盐、立体异构体、溶剂化物或多晶型物。

[0151] 在某些实施方案中，用于用在本发明中的W^3取代基也具体地包括(且不限于公开的具体化合物)在本文中公开的经鉴定的化合物(其包括在本说明书和随其附带的图中公开的具体化合物)中发现的W^3取代基。这些W^3取代基中的每个可以与任意数目的也在本文中公开的W^4取代基结合使用。

[0152] 在某些实施方案中，W^4的芳基包括任选地被取代的苯基或萘基，优选苯基，其中所述苯基任选地被以下基团取代：ABMABM基团(包括ULM'基团)所连接的接头基团，卤素(优选F或Cl)，胺，单烷基胺或二烷基胺(优选地，二甲基胺)，F，Cl，OH，COOH，C_1-C_6烷基(优选地CH_3)，CF_3，OMe，OCF_3，NO_2或CN基团(它们中的每个可以在苯环的邻-、间-和/或对-位(优选地对-位)被取代)，任选地被取代的苯基(所述苯基本身优选地被ABM基团(包括ULM'基团)所连接的接头基团取代)，和/或F、Cl、OH、COOH、CH_3、CF_3、OMe、OCF_3、NO_2或CN基团中的至少一个(在苯环的邻-、间-和/或对-位，优选地对-位)，萘基(其可以任选地被取代)，任选地被取代的杂芳基，优选地任选地被取代的异噁唑，包括甲基取代的异噁唑，任选地被取代的噁唑，包括甲基取代的噁唑，任选地被取代的噻唑，包括甲基取代的噻唑，任选地被取代的异噻唑，包括甲基取代的异噻唑，任选地被取代的吡咯，包括甲基取代的吡咯，任选地被取代的咪唑，包括甲基咪唑，任选地被取代的苯并咪唑或甲氧基苄基咪唑，任选地被取代的oximidazole或methyloximidazole，任选地被取代的二唑基团，包括甲基二唑基团，任选地被取代的三唑基团，包括甲基取代的三唑基团，任选地被取代的吡啶基团，包括卤代-(优选地，F)或甲基取代的吡啶基团或氧杂吡啶基团(其中所述吡啶基团通过氧连接至苯基)，任选地被取代的呋喃，任选地被取代的苯并呋喃，任选地被取代的二氢苯并呋喃，任选地被取

代的吲哚、吲嗪或氮杂吲嗪(2、3或4-氮杂吲嗪)，任选地被取代的喹啉，任选地被取代的根据以下化学结构的基团：

[0153] 

[0154] 其中S^c是CHR^{SS}、NR^{URE}或O；

[0155] R^{HET}是H、CN、NO_2、卤代(优选地Cl或F)、任选地被取代的C_1-C_6烷基(优选地被一个或两个羟基或至多三个卤代基团(例如CF_3)取代)、任选地被取代的O(C_1-C_6烷基)(优选地被一个或两个羟基或至多三个卤代基团取代)或任选地被取代的炔属基团-C≡C-R_a，其中R_a是H或C_1-C_6烷基(优选地C_1-C_3烷基)；

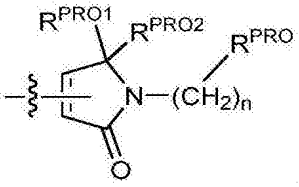
[0156] R^{SS}是H、CN、NO_2、卤代(优选F或Cl)、任选地被取代的C_1-C_6烷基(优选地被一个或两个羟基或至多三个卤代基团取代)、任选地被取代的O-(C_1-C_6烷基)(优选地被一个或两个羟基或至多三个卤代基团取代)或任选地被取代的-C(O)(C_1-C_6烷基)(优选地被一个或两个羟基或至多三个卤代基团取代)；

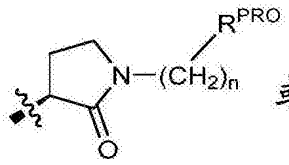
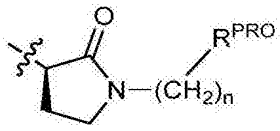
[0157] R^{URE}是H、C_1-C_6烷基(优选地H或C_1-C_3烷基)或-C(O)(C_1-C_6烷基)，所述基团中的每个任选地被一个或两个羟基或至多三个卤素(优选氟基团)取代，或任选地被取代的苯基、任选地被取代的杂芳基或任选地被取代的杂环、优选地例如哌啶、吗啉、吡咯烷、四氢呋喃)；

[0158] R^{PRO}是H、任选地被取代的C_1-C_6烷基或任选地被取代的芳基(苯基或萘基)、选自以下的杂芳基或杂环基团：噁唑、异噁唑、噻唑、异噻唑、咪唑、二唑、oximidazole、吡咯、吡咯烷、呋喃、二氢呋喃、四氢呋喃、噻吩、二氢噻吩、四氢噻吩、吡啶、哌啶、哌嗪、吗啉、喹啉(每个优选地被C_1-C_3烷基、优选甲基或卤代基团、优选F或Cl取代)、苯并呋喃、吲哚、吲嗪、氮杂吲嗪；

[0159] R^{PRO1}和R^{PRO2}各自独立地是H、任选地被取代的C_1-C_3烷基或一起形成酮基；且

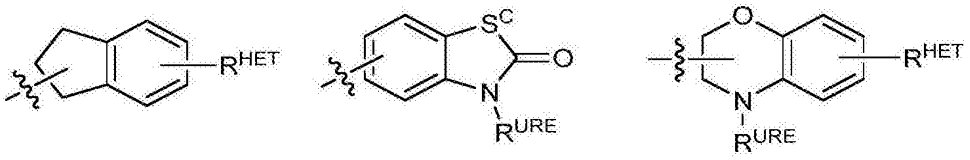
[0160] 每个n独立地是0、1、2、3、4、5或6(优选地0或1)，或任选地被取代的杂环，优选四氢呋喃、四氢噻吩、哌啶、哌嗪或吗啉(所述基团中的每个当被取代时，优选地被甲基或卤代(F、Br、Cl)取代)，所述基团中的每个可以任选地被ABM基团(包括ULM'基团)所连接的接头基团取代。

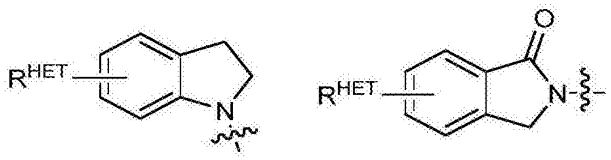
[0161] 在某些优选的方面，  是

[0162]  或  基团，

[0163] 其中R^{PRO}和n与上面相同。

[0164] 在某些实施方案中，W^4的杂芳基包括任选地被取代的喹啉(其可以连接至药效团或在喹啉环内的任意碳原子上被取代)、任选地被取代的吲哚、任选地被取代的吲嗪、任选地被取代的氮杂吲嗪、任选地被取代的苯并呋喃(包括任选地被取代的苯并呋喃)、任选地被取代的异噁唑、任选地被取代的噻唑、任选地被取代的异噻唑、任选地被取代的噻吩、任选地被取代的吡啶(2-、3或4-吡啶)、任选地被取代的咪唑、任选地被取代的吡咯、任选地被取代的二唑、任选地被取代的三唑、四唑、任选地被取代的oximidazole或根据以下化学结构的基团：



[0165] 



[0166] 其中S^c是CHR^{SS}、NR^{URE}或O；

[0167] R^{HET}是H、CN、NO_2、卤代(优选地Cl或F)、任选地被取代的C_1-C_6烷基(优选地被一个或两个羟基或至多三个卤代基团(例如CF_3)取代)、任选地被取代的O(C_1-C_6烷基)(优选地被一个或两个羟基或至多三个卤代基团取代)或任选地被取代的炔属基团-C≡C-R_a，其中R_a是H或C_1-C_6烷基(优选地C_1-C_3烷基)；

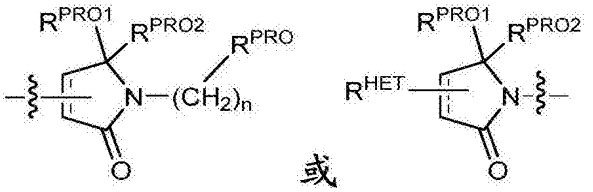
[0168] R^{SS}是H、CN、NO_2、卤代(优选F或Cl)、任选地被取代的C_1-C_6烷基(优选地被一个或两个羟基或至多三个卤代基团取代)、任选地被取代的O-(C_1-C_6烷基)(优选地被一个或两个羟基或至多三个卤代基团取代)或任选地被取代的-C(O)(C_1-C_6烷基)(优选地被一个或两个羟基或至多三个卤代基团取代)；

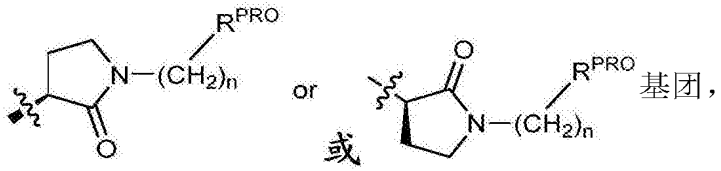
[0169] R^{URE}是H、C_1-C_6烷基(优选地H或C_1-C_3烷基)或-C(O)(C_1-C_6烷基)，所述基团中的每个

任选地被一个或两个羟基或至多三个卤素(优选氟基团)取代,或任选地被取代的杂环,例如哌啶、吗啉、吡咯烷、四氢呋喃、四氢噻吩、哌啶、哌嗪,它们中的每个任选地被取代,且

[0170] Y^C是N或C-R^{YC},其中R^{YC}是H、OH、CN、NO_2、卤代(优选地Cl或F)、任选地被取代的C_1-C_6烷基(优选地被一个或两个羟基或至多三个卤代基团(例如CF_3)取代)、任选地被取代的O(C_1-C_6烷基)(优选地被一个或两个羟基或至多三个卤代基团取代)或任选地被取代的炔属基团-C≡C-R_a,其中R_a是H或C_1-C_6烷基(优选地C_1-C_3烷基),所述基团中的每个可以任选地被ABM基团(包括ULM'基团)所连接的接头基团取代。

[0171] 在某些实施方案中,W^4的杂环基团包括四氢呋喃、四氢噻吩、四氢喹啉、哌啶、哌嗪、吡咯烷、吗啉、噁烷或硫杂环己烷,所述基团中的每个可以任选地被取代或是根据以下化学结构的基团:

[0172] 

[0173] 优选地, 

基团,

[0174] 其中R^{PRO}是H、任选地被取代的C_1-C_6烷基或任选地被取代的芳基、杂芳基或杂环基团;

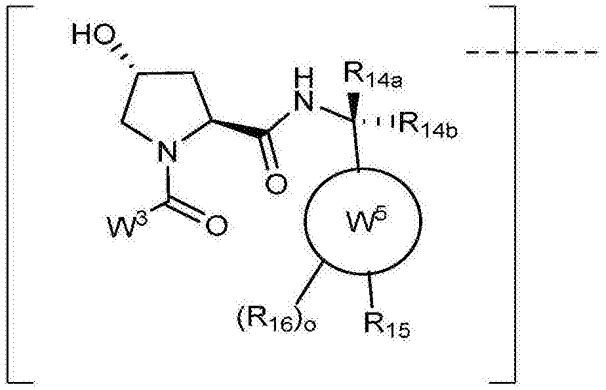
[0175] R^{PRO1}和R^{PRO2}各自独立地是H、任选地被取代的C_1-C_3烷基或一起形成酮基,且

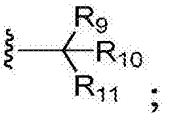
[0176] 每个n独立地是0、1、2、3、4、5或6(经常0或1),所述基团中的每个可以任选地被ABM基团(包括ULM'基团)所连接的接头基团取代。在另外的实施方案中,用于用在本发明中的W^4取代基也具体地包括(且不限于公开的具体化合物)在本文中公开的经鉴定的化合物(其包括在本说明书和随其附带的图中公开的具体化合物)中发现的W^4取代基。这些W^4取代基中的每个可以与任意数目的也在本文中公开的W^3取代基结合使用。

[0177] 在某些另外的实施方案中,ULM-a在吡咯烷部分中任选地被1-3个R^P基团取代。每个R^P独立地是H、卤代、-OH、C_{1-3}烷基。

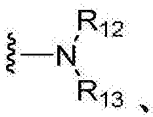
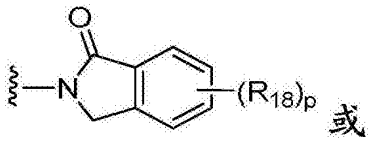
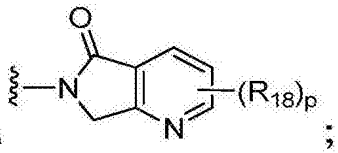
[0178] 在本文描述的任一个实施方案中,所述W^3、W^4可以独立地与一个或多个ABM基团所连接的接头共价地偶联。

[0179] 在某些实施方案中,ULM是根据以下化学结构的基团(被衍生化或构造成经由接头(如短划线所指示)与ABM连接或偶联):

[0180] 

[0181] 其中，W^3是任选地被取代的芳基、任选地被取代的杂芳基或  ；

[0182] 每个R_9和R_{10}独立地是氢、任选地被取代的烷基、任选地被取代的环烷基、任选地被取代的羟基烷基、任选地被取代的杂芳基或卤代烷基；或R_9、R_{10}和它们所连接的碳原子形成任选地被取代的环烷基；

[0183] R_{11}是任选地被取代的杂环基、任选地被取代的烷氧基、任选地被取代的杂芳基、任选地被取代的芳基、  、  或  ；

[0184] R_{12}是H或任选地被取代的烷基；

[0185] R_{13}是H、任选地被取代的烷基、任选地被取代的烷基羰基、任选地被取代的(环烷基)烷基羰基、任选地被取代的芳烷基羰基、任选地被取代的芳基羰基、任选地被取代的(杂环基)羰基或任选地被取代的芳烷基；

[0186] R_{14a}、R_{14b}各自独立地是H、卤代烷基或任选地被取代的烷基；

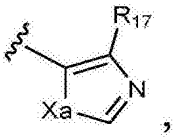
[0187] W^5是苯基或5-10元杂芳基，

[0188] R_{15}是H、卤素、CN、OH、NO_2、N $R_{14a}R_{14b}$、OR_{14a}、$CONR_{14a}R_{14b}$、$NR_{14a}COR_{14b}$、$SO_2NR_{14a}R_{14b}$、$NR_{14a}SO_2R_{14b}$、任选地被取代的烷基、任选地被取代的卤代烷基、任选地被取代的卤代烷氧基；芳基、杂芳基、环烷基、环杂烷基，每个R_{16}独立地是卤代、任选地被取代的烷基、任选地被取代的卤代烷基、羟基或任选地被取代的卤代烷氧基；

[0189] o是0、1、2、3或4；

[0190] 每个R_{18}独立地是卤代、任选地被取代的烷氧基、氰基、任选地被取代的烷基、卤代烷基、卤代烷氧基或接头；且

[0191] p是0、1、2、3或4。

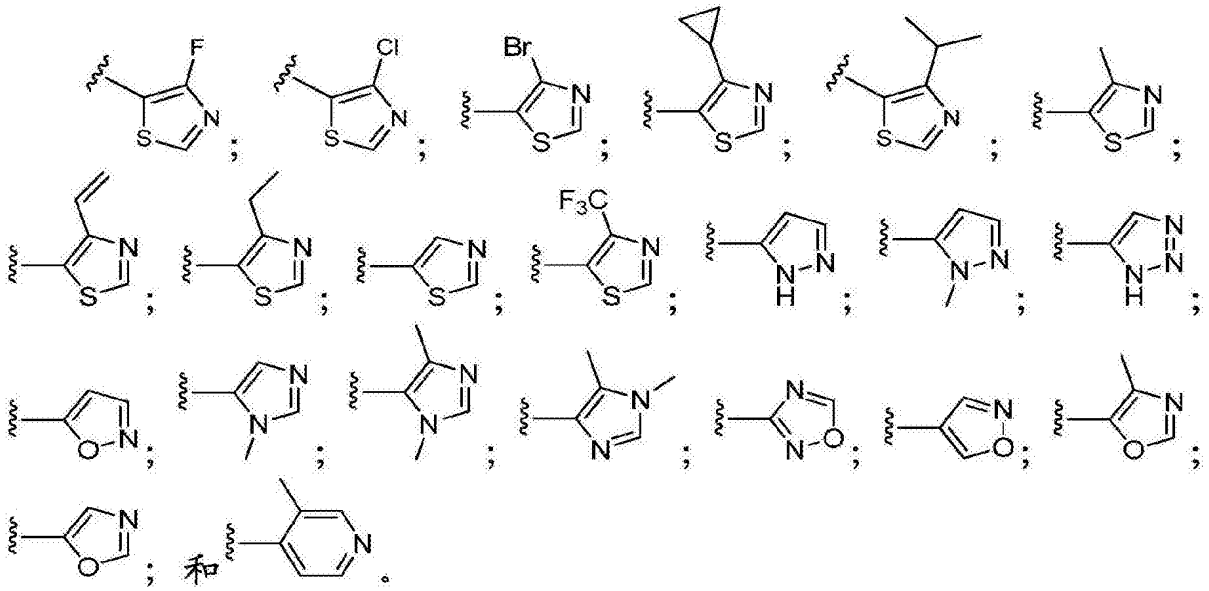
[0192] 在某些实施方案中，R_{15}是  ，其中R_{17}是H、卤代、任选地被取代的C_{3-6}环烷基、任选地被取代的C_{1-6}烷基、任选地被取代的C_{1-6}烯基和C_{1-6}卤代烷基；且

[0193] Xa是S或O。

[0194] 在某些实施方案中，R_{17}选自甲基、乙基、异丙基和环丙基。

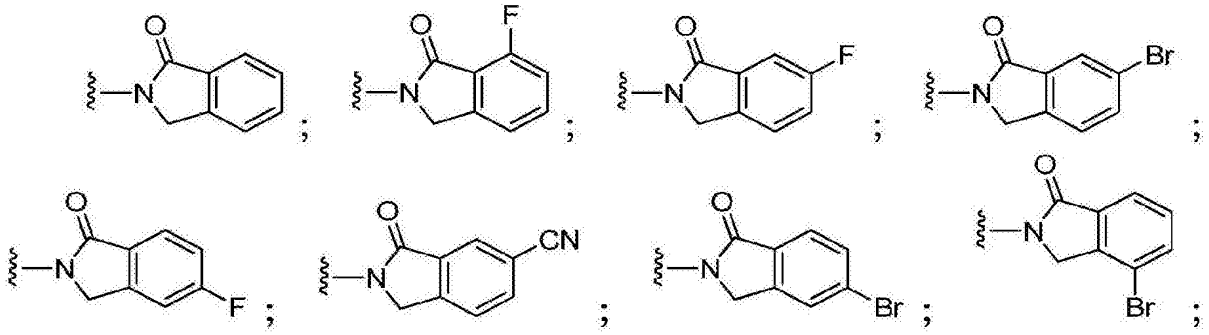
[0195] 在某些另外的实施方案中，R_{15}选自：

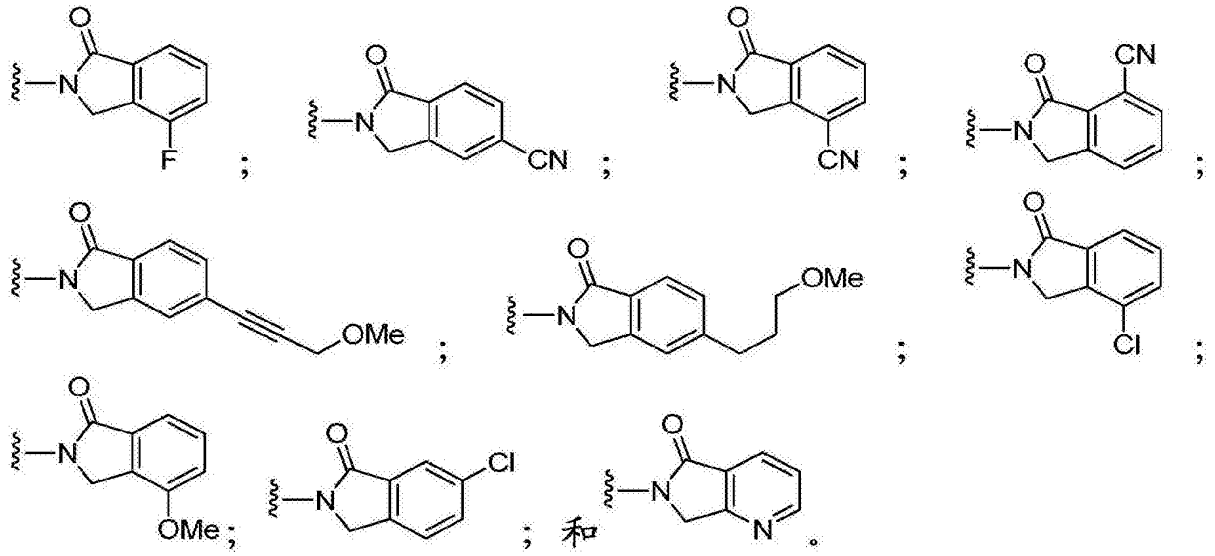
[0196]



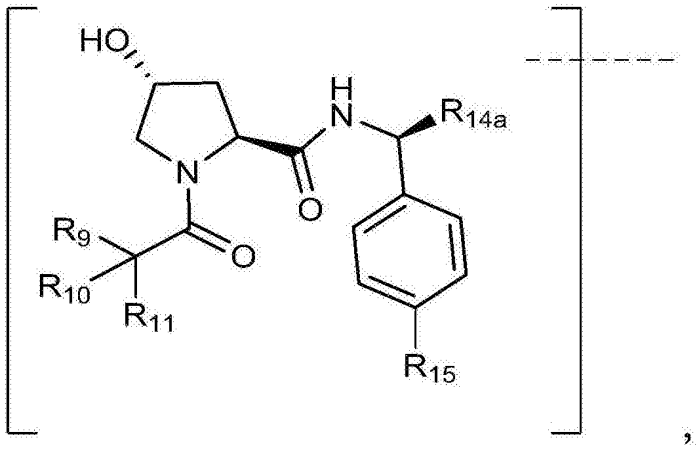
[0197] 在某些实施方案中，R_{11}选自：

[0198]



[0199] 

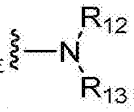
[0200] 在某些实施方案中，所述ULM(被衍生化或构造成经由接头(如短划线所指示)与ABM连接或偶联)具有以下结构：

[0201] 

[0202] 其中

[0203] R_9是H；

[0204] R_{10}是异丙基、叔丁基、仲丁基、环戊基或环己基；

[0205] R_{11}是  ；

[0206] R_{12}是H；

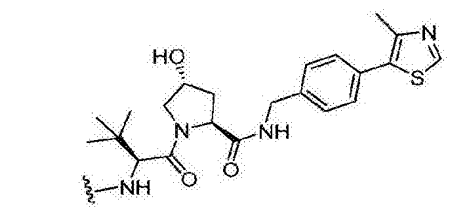
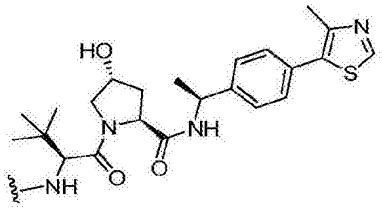
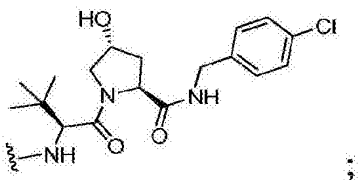
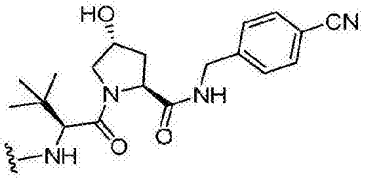
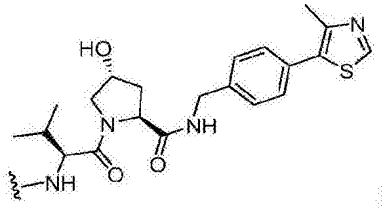
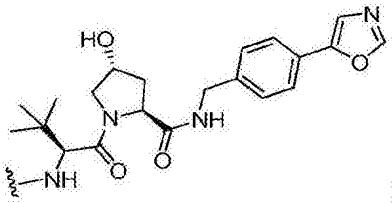
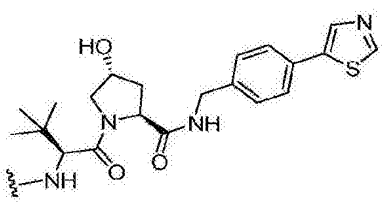
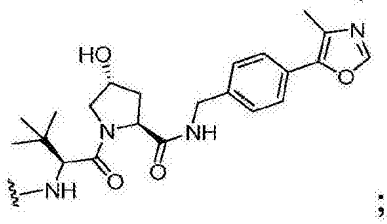
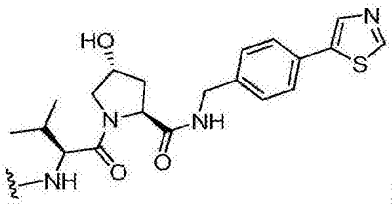
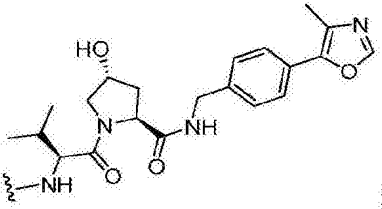
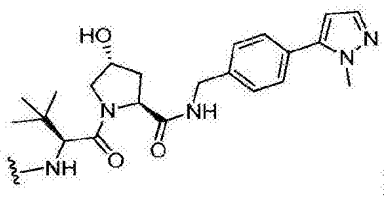
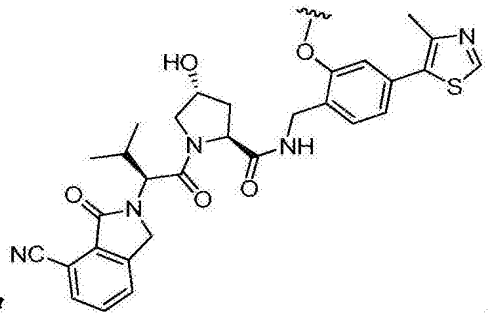
[0207] R_{13}是H、任选地被取代的烷基、任选地被取代的烷基羰基、任选地被取代的(环烷基)烷基羰基、任选地被取代的芳烷基羰基、任选地被取代的芳基羰基、任选地被取代的(杂环基)羰基或任选地被取代的芳烷基；

[0208] R14a是H、卤代烷基或任选地被取代的甲基、乙基、异丙基、环丙基或其它烷基；且

[0209] R15是  ，其中R17是H、卤代、任选地被取代的C3-6环烷基、任选地被取代的C1-6烷基、任选地被取代的C1-6烯基和C1-6卤代烷基；且Xa是S或O。

[0210] 在某些实施方案中，所述ULM或VLM选自：

[0211]

 ；  ；  ；  ；  ；  ；  ；  ；  ；  ；  ；  和，其在指示的位置处连接至接头部分。

[0212] 示例性的接头

[0213] 在某些实施方案中，如本文中所述的化合物包括一个或多个ABM，所述ABM经由化学接头(L)化学连接或偶联至一个或多个ULM或VLM。在某些实施方案中，所述接头基团L是包含一个或多个共价地连接的A结构单元(例如-$A_1\cdots A_q$-)的基团，其中A_1偶联至ABM部分，且q是大于或等于0的整数。在某些实施方案中，q是大于或等于1的整数。

[0214] 在某些实施方案中，例如，在q大于2的情况下，A_q是与ULM或VLM部分连接的基团，

且A_1和A_q经由A结构单元(这样的A结构单元的数目:q-2)连接。

[0215] 在某些实施方案中,例如,在q是2的情况下,A_q是与A_1和与ULM或VLM部分连接的基团。

[0216] 在某些实施方案中,例如,在q是1的情况下,接头基团L的结构是-A_1-,且A_1是与ULM或VLM部分和ABM部分连接的基团。

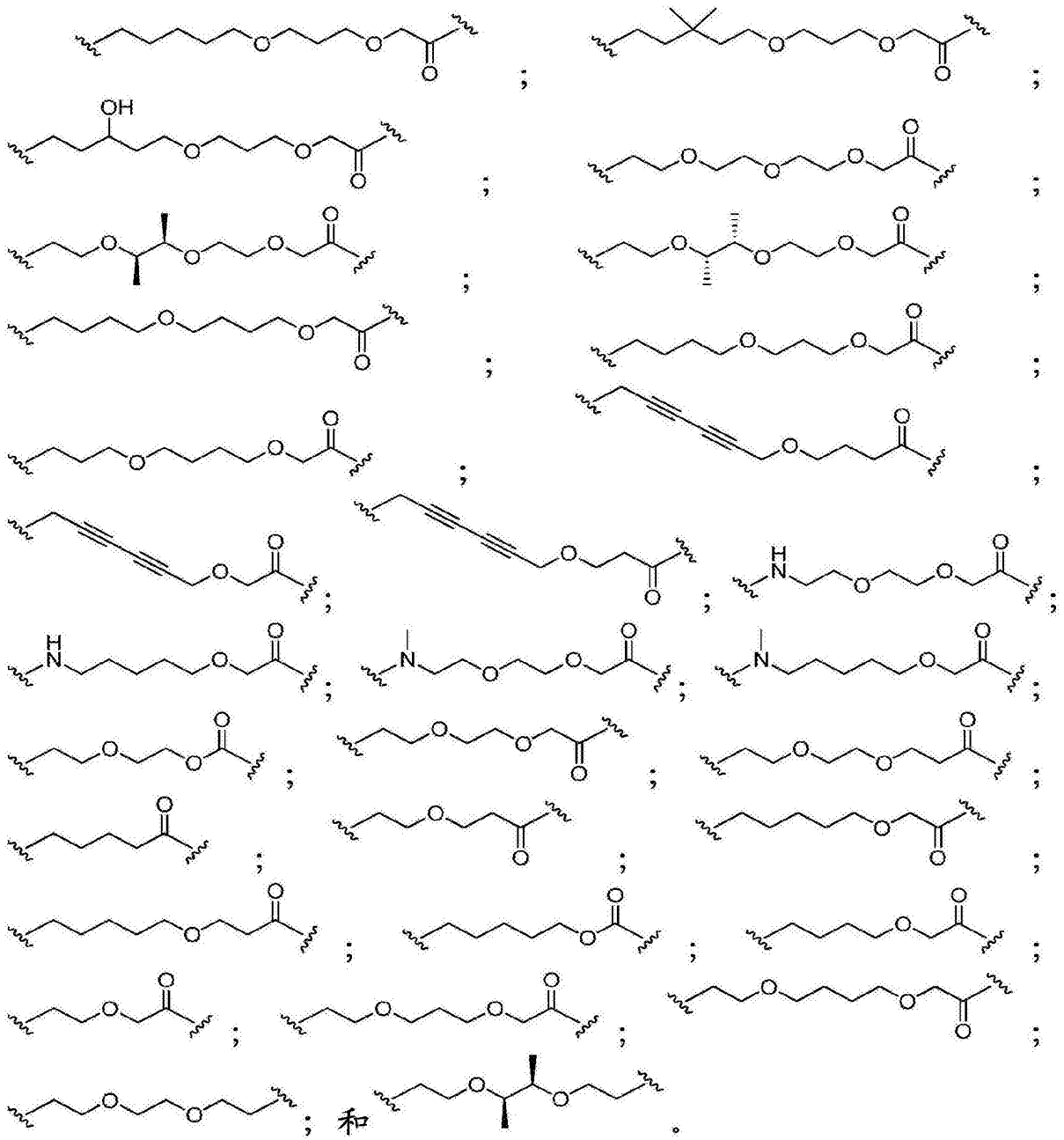
[0217] 在另外的实施方案中,q是1-100、1-90、1-80、1-70、1-60、1-50、1-40、1-30、1-20或1-10的整数。

[0218] 在某些实施方案中,A_1至A_q各自独立地是键、$CR^{L1}R^{L2}$、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}、$NR^{L3}C(=NCN)NR^{L4}$、$NR^{L3}C(=NCN)$、$NR^{L3}C(=CNO_2)NR^{L4}$、任选地被0-6个R^{L1}和/或R^{L2}基团取代的C_{3-11}环烷基、任选地被0-6个R^{L1}和/或R^{L2}基团取代的C_{3-11}杂环基、任选地被0-6个R^{L1}和/或R^{L2}基团取代的芳基、任选地被0-6个R^{L1}和/或R^{L2}基团取代的杂芳基,其中R^{L1}或R^{L2}各自独立地可以连接至其它A基团以形成环烷基和/或杂环基部分,所述部分可以进一步被0-4个R^{L5}基团取代;

[0219] 其中R^{L1}、R^{L2}、R^{L3}、R^{L4}和R^{L5}各自独立地是H、卤代、C_{1-8}烷基、OC_{1-8}烷基、SC_{1-8}烷基、NHC_{1-8}烷基、$N(C_{1-8}烷基)_2$、C_{3-11}环烷基、芳基、杂芳基、C_{3-11}杂环基、OC_{1-8}环烷基、SC_{1-8}环烷基、NHC_{1-8}环烷基、$N(C_{1-8}环烷基)_2$、$N(C_{1-8}环烷基)(C_{1-8}烷基)$、OH、NH_2、SH、SO_2C_{1-8}烷基、P(O)$(OC_{1-8}烷基)(C_{1-8}烷基)$、P(O)$(OC_{1-8}烷基)_2$、CC-C_{1-8}烷基、CCH、CH=CH$(C_{1-8}烷基)$、C$(C_{1-8}烷基)$=CH$(C_{1-8}烷基)$、C$(C_{1-8}烷基)$=C$(C_{1-8}烷基)_2$、Si(OH)$_3$、Si$(C_{1-8}烷基)_3$、Si(OH)$(C_{1-8}烷基)_2$、COC_{1-8}烷基、CO_2H、卤素、CN、CF_3、CHF_2、CH_2F、NO_2、SF_5、SO_2NHC_{1-8}烷基、$SO_2N(C_{1-8}烷基)_2$、$SONHC_{1-8}$烷基、$SON(C_{1-8}烷基)_2$、$CONHC_{1-8}$烷基、$CON(C_{1-8}烷基)_2$、$N(C_{1-8}烷基)CONH(C_{1-8}烷基)$、$N(C_{1-8}烷基)CON(C_{1-8}烷基)_2$、$NHCONH(C_{1-8}烷基)$、$NHCON(C_{1-8}烷基)_2$、$NHCONH_2$、$N(C_{1-8}烷基)SO_2NH(C_{1-8}烷基)$、$N(C_{1-8}烷基)SO_2N(C_{1-8}烷基)_2$、NH $SO_2NH(C_{1-8}烷基)$、NH $SO_2N(C_{1-8}烷基)_2$、NH SO_2NH_2。

[0220] 在某些实施方案中,所述接头(L)选自:

[0221]



[0222] 在另外的实施方案中，所述接头基团是具有1至约100个乙二醇单元、约1至约50个乙二醇单元、1至约25个乙二醇单元、约1至10个乙二醇单元、1至约8个乙二醇单元、和1至6个乙二醇单元、2-4个乙二醇单元的任选地被取代的聚乙二醇，或夹杂了(interdispersed)任选地取代的O、N、S、P或Si原子的任选地被取代的烷基。在某些实施方案中，所述接头被芳基、苯基、苄基、烷基、亚烷基或杂环基取代。在某些实施方案中，所述接头可以是不对称的或对称的。

[0223] 在某些方面，本说明书提供了一种PROTAC化合物，其中所述接头可在体内切割成功能性的E3连接酶结合部分和靶蛋白结合部分。在这点上，且不受任何特定理论约束，假定这样的构型可以增强完整的PROTAC分子的降解活性的有益效果。因而，在某些实施方案中，

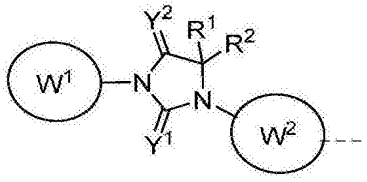
所述接头被构造或“调节”成具有切割成功能性组分分子或活性代谢物的期望动力学。在某些实施方案中，负责切割接头的酶是肝酶，例如，氧化酶、过氧化物酶、还原酶、转移酶、脱氢酶、过氧化物酶。在某些实施方案中，所述酶是细胞色素P450氧化酶中的至少一种，例如，CYP3A4、含黄素的单加氧酶、醇脱氢酶、醛脱氢酶、单胺氧化酶、过氧化物酶、谷胱甘肽S-转移酶、细胞色素P450还原酶、磺基转移酶、甲基转移酶、N-乙酰基转移酶、葡糖醛酸基转移酶、转肽酶或它们的组合。

[0224] 示例性的雄激素结合部分(ABM)

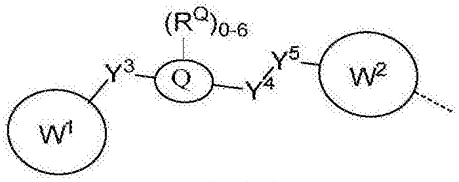
[0225] 在另一个方面，本说明书提供了AR结合部分(ABM)，其在某些方面和实施方案中偶联至ULM。

[0226] 在本文所述的任意化合物中，所述ABM包含结合雄激素受体(AR)的化学部分。已经在文献中描述了多种雄激素受体结合化合物，包括多种雄激素衍生物诸如睾酮、二氢睾酮和美曲勃龙(也被称作甲基三烯甘油酯酮或R1881)和非甾体类化合物诸如比卡鲁胺、恩杂鲁胺。本领域普通技术人员会理解，这些雄激素受体结合化合物可以潜在地用作PROTAC化合物中的ABM部分。这样的文献包括，但不限于，G.F.Allan等人，Nuclear Receptor Signaling，2003，1，e009；R.H。Bradbury等人，Bioorganic&Medicinal Chemistry Letters，2011 5442-5445；C.Guo等人，Bioorganic&Medicinal Chemistry Letters，2012 2572-2578；P.K.Poutiainen等人，J.Med.Chem.2012，55，6316-6327A.Pepe等人，J.Med.Chem.2013，56，8280-8297；M.E.Jung等人，J.Med.Chem.2010，53，2779-2796，它们通过引用并入本文。

[0227] 在某些实施方案中，所述ABM包含选自、但不限于下面所示结构的结构，其中短划线指示接头部分的连接点：

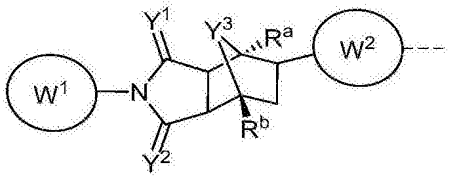


ABM-a ;

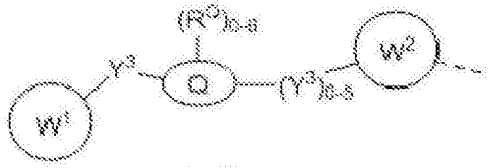


ABM-b ;

[0228]



ABM-c ; 和



ABM-d 。

[0229] 其中W^1是芳基或杂芳基，其独立地被1个或多个卤代、羟基、硝基、CN、C≡CH、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)、C_{1-6}烷氧基(直链的，支链的，任选地被1个或多个卤代取代)、C_{2-6}烯基、C_{2-6}炔基取代；

[0230] Y^1、Y^2各自独立地是NR^{Y1}、O、S；

[0231] Y^3、Y^4、Y^5各自独立地是键、O、NR^{Y2}、$CR^{Y1}R^{Y2}$、C=O、C=S、SO、SO_2；

[0232] Q是具有0-4个杂原子的3-6元环，其任选地被0-6个R^Q取代，每个R^Q独立地是H、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)，或者2个R^Q基团与它们所连接的原子一起形成含有0-2个杂原子的3-8元环系)；

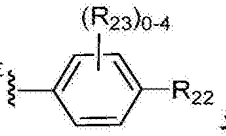
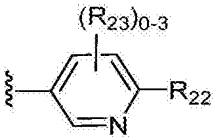
[0233] R^1、R^2、R^a、R^b、R^{Y1}、R^{Y2}各自独立地是H、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)，或者R^1、R^2与它们所连接的原子一起形成含有0-2个杂原子的3-8元环系)；

[0234] W^2是键、C_{1-6}烷基或芳基或杂芳基，每个任选地被1、2或3个R^{W2}取代；且

[0235] 每个R^{W2}独立地是H、卤代、C_{1-6}烷基(任选地被1个或多个F取代)、OC_{1-3}烷基(任选地被1个或多个-F取代)。

[0236] 在本文描述的任一个实施方案中，所述W^2共价地偶联至一个或多个ULM或VLM基团

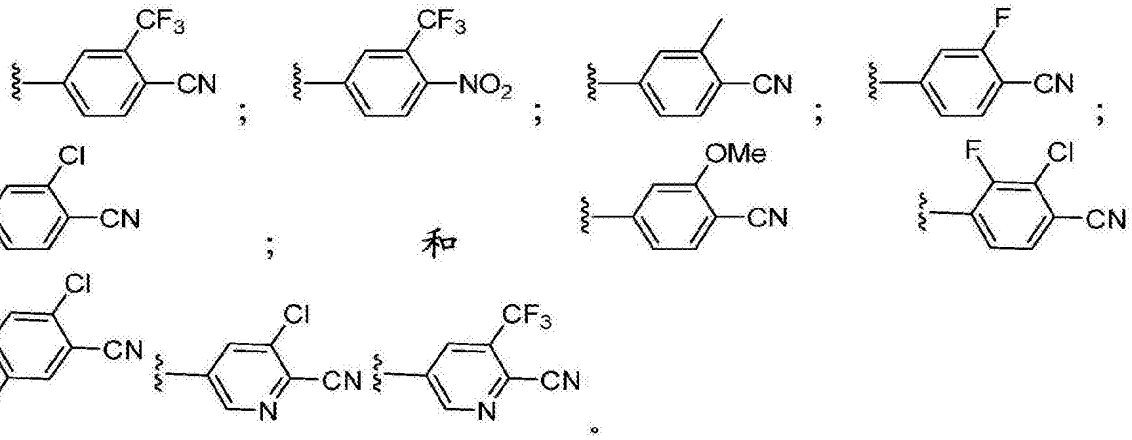
或如本文中所述的一个或多个ULM或VLM基团所连接的接头。

[0237] 在某些实施方案中，W^1是  或  ；

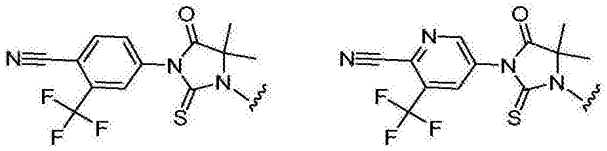
[0238] 其中每个R_{22}独立地是卤代、任选地被取代的烷基、卤代烷基、氰基或硝基；且

[0239] 每个R_{23}独立地是H、卤代、任选地被取代的烷基、卤代烷基、氰基或硝基。

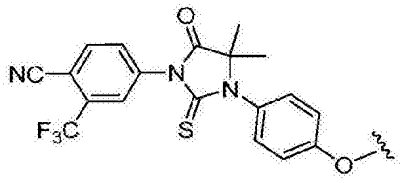
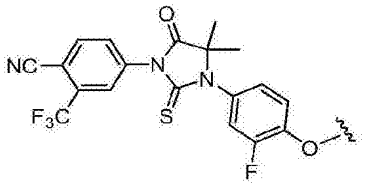
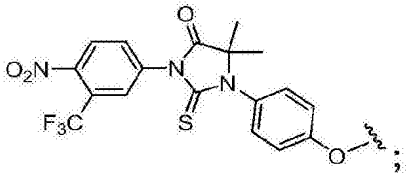
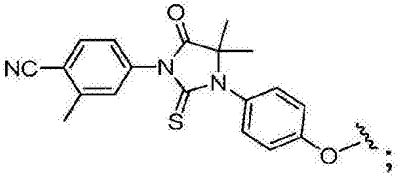
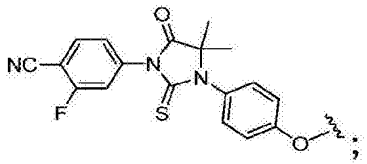
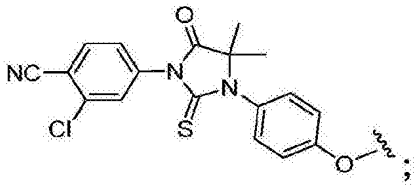
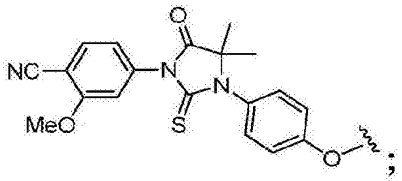
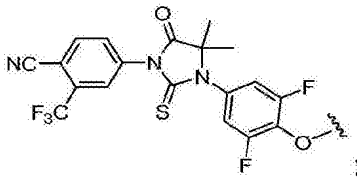
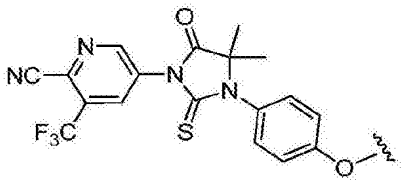
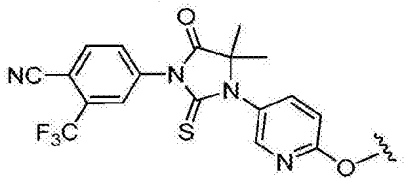
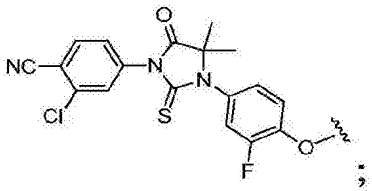
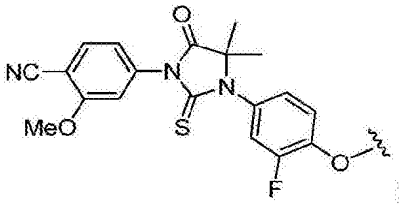
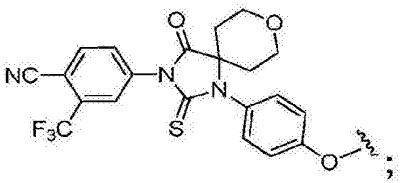
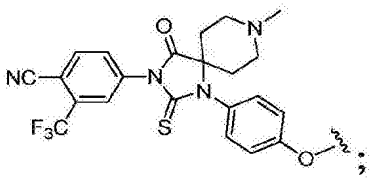
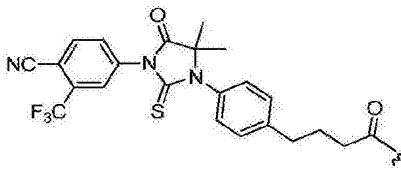
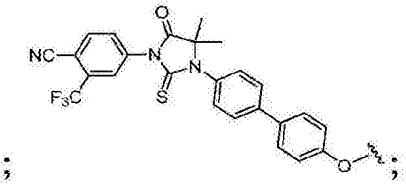
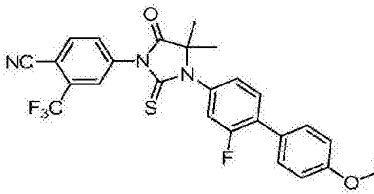
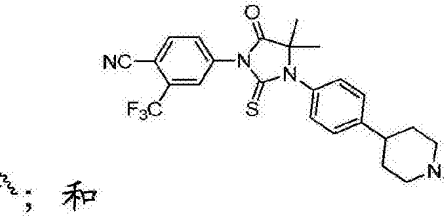
[0240] 在某些另外的实施方案中，W^1选自：

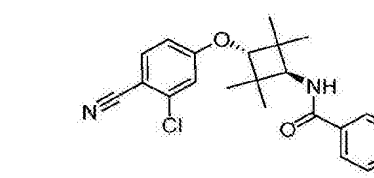
[0241]  。

[0242] 在某些实施方案中，ABM选自：

[0243] 

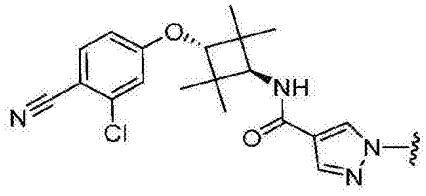
[0244]


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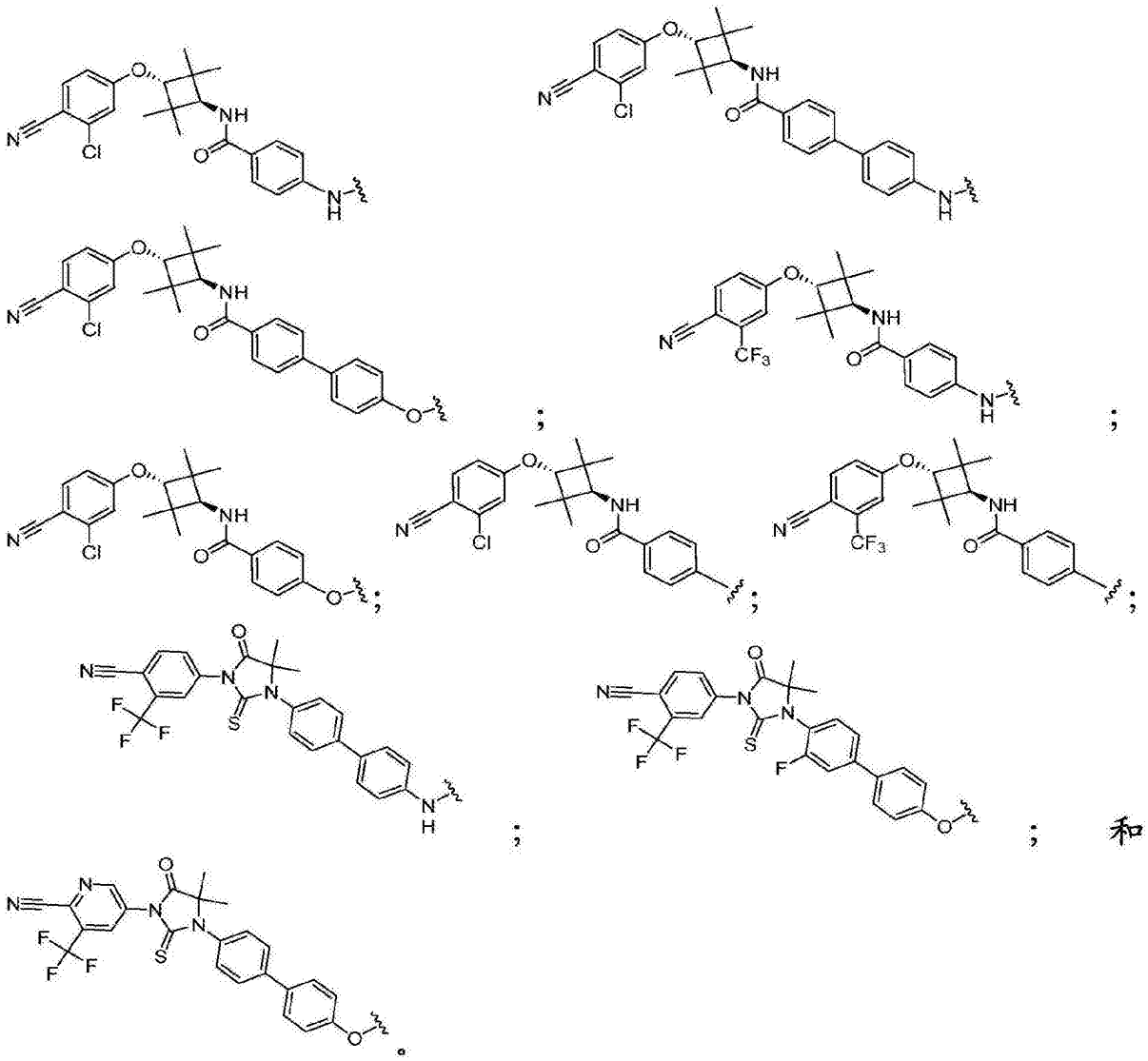
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和



[0245]



[0246] 在某些实施方案中，所述ABM包含结构：

[0247]



ABM b

[0248] 其中W^1是芳基或杂芳基，其独立地被1个或多个卤代、羟基、硝基、CN、C≡CH、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)、C_{1-6}烷氧基(直链的，支链的，任选地被1个或多个卤代取代)、C_{2-6}烯基、C_{2-6}炔基取代；

[0249] Y^3、Y^4、Y^5各自独立地是键、O、NR^{Y2}、$CR^{Y1}R^{Y2}$、C=O、C=S、SO、SO_2；

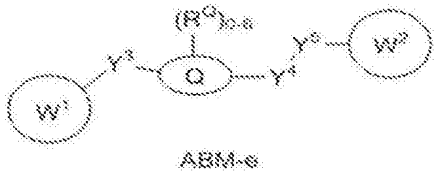
[0250] Q是具有0-2个杂原子的4元脂环族环，其任选地被0-6个R^Q取代，每个R^Q独立地是H、C_{1-6}烷基(直链的，支链的，任选地被1个或多个卤代、C_{1-6}烷氧基取代)，或者2个R^Q基团与它们所连接的原子一起形成含有0-2个杂原子的3-8元环系)；

[0251] R^{Y1}、R^{Y2}各自独立地是H、C_{1-6}烷基(直链的,支链的,任选地被1个或多个卤代、C_{1-6}烷氧基取代);

[0252] W^2是键、C_{1-6}烷基、C_{1-6}脂环族基、杂环基、芳基或杂芳基,每个任选地被1、2或3个R^{W2}取代;且

[0253] 每个R^{W2}独立地是H、卤代、C_{1-6}烷基(任选地被1个或多个F取代)、OC_{1-3}烷基(任选地被1个或多个-F取代)、OH、NH_2、$NR^{Y1}R^{Y2}$、CN。

[0254] 在另一个方面,本说明书提供了一种包含以下结构的雄激素受体结合化合物:

[0255] 

ABM-e

[0256] 其中W^1是芳基或杂芳基,其独立地被1个或多个卤代、羟基、硝基、CN、C≡CH、C_{1-6}烷基(直链的,支链的,任选地被1个或多个卤代、C_{1-6}烷氧基取代)、C_{1-6}烷氧基(直链的,支链的,任选地被1个或多个卤代取代)、C_{2-6}烯基、C_{2-6}炔基取代;

[0257] Y^1、Y^2各自独立地是NR^{Y1}、O、S;

[0258] Y^3、Y^4、Y^5各自独立地是键、O、NR^{Y2}、$CR^{Y1}R^{Y2}$、C=O、C=S、SO、SO_2;

[0259] Q是具有0-4个杂原子的3-6元脂环族环或芳族环,其任选地被0-6个R^Q取代,每个R^Q独立地是H、C_{1-6}烷基(直链的,支链的,任选地被1个或多个卤代、C_{1-6}烷氧基取代),或者2个R^Q基团与它们所连接的原子一起形成含有0-2个杂原子的3-8元环系);

[0260] R^1、R^2、R^a、R^b、R^{Y1}、R^{Y2}各自独立地是H、C_{1-6}烷基(直链的,支链的,任选地被1个或多个卤代、C_{1-6}烷氧基取代),或者R^1、R^2与它们所连接的原子一起形成含有0-2个杂原子的3-8元环系);

[0261] W^2是键、C_{1-6}烷基、C_{1-6}脂环族基、杂环基、芳基或杂芳基,每个任选地被1、2或3个R^{W2}取代;且

[0262] 每个R^{W2}独立地是H、卤代、C_{1-6}烷基(任选地被1个或多个F取代)、OC_{1-3}烷基(任选地被1个或多个-F取代)、OH、NH_2、$NR^{Y1}R^{Y2}$、CN。

[0263] 在某些实施方案中,ABM-e的雄激素受体结合化合物选自:

[0264] 反式-2-氯-4-[3-氨基-2,2,4,4-四甲基环丁氧基]苄腈;

[0265] 顺式-2-氯-4-[3-氨基-2,2,4,4-四甲基环丁氧基]苄腈;

[0266] 反式6-氨基-N-[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]哒嗪-3-甲酰胺;

[0267] 反式N-[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酸叔丁酯;

[0268] 反式4-氨基-N-[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]苯甲酰胺;

[0269] 反式5-氨基-N-[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]吡嗪-2-甲酰胺;

[0270] 反式2-氨基-N-[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]嘧啶-5-甲酰胺;

[0271] 4-甲氧基-N-[(1r,3r)-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]苯甲酰胺;

[0272] 反式1-(2-羟基乙基)-N-[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]-1H-吡唑-4-甲酰胺；

[0273] 反式6-氨基-N-[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]吡啶-3-甲酰胺；

[0274] 反式4-[(5-羟基戊基)氨基]-N-[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]苯甲酰胺；和

[0275] 反式2-({5-[(4-{[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯基)氨基戊基}氧基)乙酸叔丁酯。

[0276] 术语“烃基”应当是指这样的化合物：其含有碳和氢且其可以是完全饱和的、部分不饱和的或芳族的，且包括芳基、烷基、烯基和炔基。

[0277] 术语“烷基”在它的上下文中应当是指直链、支链或环状完全饱和的烃基或烷基，优选地C_1-C_{10}，更优选地C_1-C_6，可替换地C_1-C_3烷基，其可以任选地被取代。烷基的例子是甲基、乙基、正丁基、仲丁基、正己基、正庚基、正辛基、正壬基、正癸基、异丙基、2-甲基丙基、环丙基、环丙基甲基、环丁基、环戊基、环戊基乙基、环己基乙基和环己基，以及其它。在某些优选的实施方案中，根据本发明的化合物可以用于共价地结合脱卤素酶。这些化合物通常含有侧链(经常通过聚乙二醇基团连接)，所述侧链终止于在它的远端上具有卤素取代基(经常氯或溴)的烷基，这会导致含有这样的部分的化合物与所述蛋白的共价结合。

[0278] 术语“烯基”表示含有至少一个C=C键的直链、支链或环状C_2-C_{10}(优选地C_2-C_6)烃基。

[0279] 术语“炔基”表示含有至少一个C≡C键的直链、支链或环状C_2-C_{10}(优选地C_2-C_6)烃基。

[0280] 术语“亚烷基”在使用时表示-$(CH_2)_n$-基团(n是通常0-6的整数)，其可以任选地被取代。当被取代时，亚烷基优选地在一个或多个亚甲基上被C_1-C_6烷基(包括环丙基或叔丁基)、更优选地甲基取代，但是也可以被一个或多个卤代基团、优选地1-3个卤代基团或一个或两个羟基、O-(C_1-C_6烷基)基团或如本文中另外公开的氨基酸侧链取代。在某些实施方案中，亚烷基可以被氨基甲酸酯(urethane)或烷氧基(或其它基团)取代，所述氨基甲酸酯或烷氧基(或其它基团)进一步被聚乙二醇链(1-10个，优选地1-6个，经常1-4个乙二醇单元)取代，所述聚乙二醇链与取代的烷基链(优选地，但是非排它地在聚乙二醇链的远侧端部上)连接，所述烷基链被单个卤素基团、优选地氯基团取代。在其它实施方案中，所述亚烷基(经常，亚甲基)基团可以被氨基酸侧链基团诸如天然的或非天然的氨基酸(例如，丙氨酸、β-丙氨酸、精氨酸、天冬酰胺、天冬氨酸、半胱氨酸、胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、苯丙氨酸、组氨酸、异亮氨酸、赖氨酸、亮氨酸、甲硫氨酸、脯氨酸、丝氨酸、苏氨酸、缬氨酸、色氨酸或酪氨酸)的侧链基团取代。

[0281] 术语“未被取代”应当是指仅被氢原子取代。碳原子的范围包括C_0，这意味着碳不存在且被H替换。因而，C_0-C_6的碳原子范围包括1、2、3、4、5和6个碳原子，且对于C_0，H替代碳。术语“取代”或“任选地取代”应当是指独立地(即，在存在超过1个取代基的情况下，每个取代基独立于其它取代基)在上下文中在分子上的任何地方在碳(或氮)位置处的一个或多个取代基(在根据本发明的化合物中的部分上独立地多达5个取代基，优选地多达3个取代基，经常1或2个取代基，且可以包括其本身可以被进一步取代的取代基)，且包括以下基团作为

取代基：羟基、巯基、羧基、氰基(C≡N)、硝基(NO_2)、卤素(优选地，1、2或3个卤素，特别是在烷基、尤其是甲基上，诸如三氟甲基)、烷基(优选地，C_1-C_{10}，更优选地，C_1-C_6)、芳基(特别是苯基和被取代的苯基例如苄基或苯甲酰基)、烷氧基(优选地，C_1-C_6烷基或芳基，包括苯基和被取代的苯基)、硫醚(C_1-C_6烷基或芳基)、酰基(优选地，C_1-C_6酰基)、酯或硫代酸酯(优选地，C_1-C_6烷基或芳基)，包括亚烷基酯(使得连接是在亚烷基上，而不是在酯官能团处，所述酯官能团优选地被C_1-C_6烷基或芳基基团取代)，优选地，C_1-C_6烷基或芳基、卤素(优选地，F或Cl)、胺(包括5或6元环状亚烷基胺，进一步包括C_1-C_6烷基胺或C_1-C_6二烷基胺，所述烷基可以被一个或两个羟基取代)或任选地被取代的-N(C_0-C_6烷基)C(O)(O-C_1-C_6烷基)基团(其可以任选地被聚乙二醇链取代，所述聚乙二醇链进一步被含有单个卤素、优选氯取代基的烷基结合)、肼、酰氨基(其优选地被一个或两个C_1-C_6烷基取代)(包括羧酰胺，其任选地被一个或两个C_1-C_6烷基取代)、烷醇(优选地，C_1-C_6烷基或芳基)或链烷酸(优选地，C_1-C_6烷基或芳基)。根据本发明的取代基可以包括，例如-Si$R_1R_2R_3$基团，其中R_1和R_2中的每个如本文中另外所述，且R_3是H或C_1-C_6烷基，优选地R_1、R_2、R_3在该背景下是C_1-C_3烷基(包括异丙基或叔丁基)。上述基团中的每个可以直接连接至被取代的部分，或可替换地，所述取代基可以通过任选地被取代的-$(CH_2)_m$-或可替换地任选地被取代的-$(OCH_2)_m$-、-$(OCH_2CH_2)_m$-或-$(CH_2CH_2O)_m$-基团(其可以被上述取代基中的任意一种或多种取代)连接至被取代的部分(优选地在芳基或杂芳基部分的情况下)。如上指出的亚烷基-$(CH_2)_m$-或-$(CH_2)_n$-基团或其它链诸如乙二醇链可以在链上的任何地方被取代。在亚烷基上的优选取代基包括卤素或C_1-C_6(优选地C_1-C_3)烷基，其可以任选地被以下基团取代：一个或两个羟基、一个或两个醚基(O-C_1-C_6基团)、多达三个卤素基团(优选地F)、或如本文另外描述的氨基酸的侧链和任选地被取代的酰胺(优选地如上所述被取代的羧酰胺)或氨基甲酸酯基(经常具有一个或两个C_0-C_6烷基取代基，所述基团可以进一步被取代)。在某些实施方案中，所述亚烷基(经常单个亚甲基)被以下基团取代：一个或两个任选地被取代的C_1-C_6烷基，优选地C_1-C_4烷基，最经常甲基或O-甲基或如本文另外描述的氨基酸的侧链。在本发明中，分子中的部分可以任选地被多达5个取代基、优选地多达3个取代基取代。最经常地，在本发明中，被取代的部分是被一个或两个取代基取代。

[0282] 术语“取代”(每个取代基独立于任意其它取代基)在它的使用上下文中还应当是指C_1-C_6烷基、C_1-C_6烷氧基、卤素、酰氨基、羧酰氨基、砜(包括磺酰胺)、酮、羧基、C_1-C_6酯(氧基酯或羰基酯)、C_1-C_6酮、氨基甲酸酯-O-C(O)-NR_1R_2或-N(R_1)-C(O)-O-R_1、硝基、氰基和胺(特别包括C_1-C_6亚烷基-NR_1R_2、单-或二-C_1-C_6烷基取代的胺，其可以任选地被一个或两个羟基取代)。除非在上下文中另有说明，否则这些基团中的每个含有1-6个碳原子。在某些实施方案中，优选的取代基将包括例如，-NH-、-NHC(O)-、-O-、=O、-$(CH_2)_m$-(在这里，m和n在上下文中是1、2、3、4、5或6)、-S-、-S(O)-、SO_2-或-NH-C(O)-NH-、-$(CH_2)_n$OH、-$(CH_2)_n$SH、-$(CH_2)_n$COOH、C_1-C_6烷基、-$(CH_2)_n$O-(C_1-C_6烷基)、-$(CH_2)_n$C(O)-(C_1-C_6烷基)、-$(CH_2)_n$OC(O)-(C_1-C_6烷基)、-$(CH_2)_n$C(O)O-(C_1-C_6烷基)、-$(CH_2)_n$NHC(O)-R_1、-$(CH_2)_n$C(O)-NR_1R_2、-$(OCH_2)_n$OH、-$(CH_2O)_n$COOH、C_1-C_6烷基、-$(OCH_2)_n$O-(C_1-C_6烷基)、-$(CH_2O)_n$C(O)-(C_1-C_6烷基)、-$(OCH_2)_n$NHC(O)-R_1、-$(CH_2O)_n$C(O)-NR_1R_2、-S(O)$_2$-R_S、-S(O)-R_S(R_S是C_1-C_6烷基或-$(CH_2)_m$-NR_1R_2基团)、NO_2、CN或卤素(F、Cl、Br、I，优选F或Cl)，取决于所述取代基的使用上下文。R_1和R_2在上下文中各自是H或C_1-C_6烷基(其可以任选地被一个或两个羟基或至多三个卤素基团、优选地氟取

代)。术语“取代”还应当是指,在定义的化合物和使用的取代基的化学背景下,如本文另外描述的任选地被取代的芳基或杂芳基或任选地被取代的杂环基团。亚烷基也可以如本文中另外公开的被取代,优选地被以下基团取代:任选地被取代的C_1-C_6烷基(甲基、乙基或羟甲基或羟乙基是优选的,从而提供手性中心)、如本文另外描述的氨基酸基团的侧链、如上文中所述的酰氨基或氨基甲酸酯基O-C(O)-NR_1R_2基团,其中R_1和R_2如本文另外所述,尽管众多其它基团也可以用作取代基。多种任选地被取代的部分可以被3个或更多个取代基、优选地不超过3个取代基取代,且优选地被1或2个取代基取代。应当指出,在化合物中在分子的特定位置处需要取代(原则上,因为化合价)、但是没有指出取代的情况下,那么该取代基被解释或理解为H,除非取代的上下文另外提示。

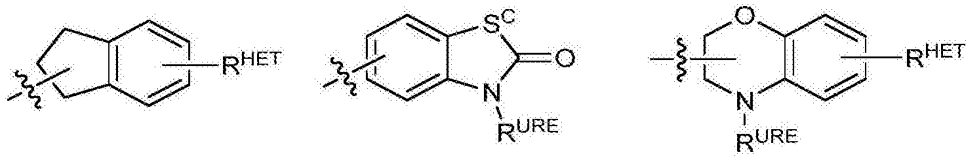
[0283] 术语“芳基”或“芳族”在上下文中表示被取代的(如本文另外描述)或未被取代的具有单环(例如,苯、苯基、苄基)或稠合环(例如,萘基、蒽基、菲基等)的单价芳族残基,且可以在所述环上的任何可利用的稳定位置处或如呈现的化学结构中另外指示地结合至根据本发明的化合物。芳基的其它例子在上下文中可以包括在环(单环)(诸如咪唑、呋喃基(furyl)、吡咯、呋喃基(furanyl)、噻吩、噻唑、吡啶、嘧啶、吡嗪、三唑、噁唑)或稠合环系(诸如吲哚、喹啉、吲嗪、氮杂吲嗪、苯并呋咱等,以及其它)中具有一个或多个氮、氧或硫原子的杂环芳族环系“杂芳基”基团,其可以如上所述任选地被取代。可以提及的杂芳基包括含氮的杂芳基诸如吡咯、吡啶、吡啶酮、哒嗪、嘧啶、吡嗪、吡唑、咪唑、三唑、三嗪、四唑、吲哚、异吲哚、吲嗪、氮杂吲嗪、嘌呤、吲唑、喹啉、二氢喹啉、四氢喹啉、异喹啉、二氢异喹啉、四氢异喹啉、喹嗪、酞嗪、萘啶、喹喔啉、喹唑啉、噌啉、喋啶、咪唑并吡啶、咪唑并三嗪、吡嗪并哒嗪、吖啶、菲啶、咔唑、咔唑啉、萘嵌间二氮杂苯、菲咯啉、phenacene、噁二唑、苯并咪唑、吡咯并吡啶、吡咯并嘧啶和吡啶并嘧啶;含硫的芳族杂环诸如噻吩和苯并噻吩;含氧的芳族杂环诸如呋喃、吡喃、环戊二烯并吡喃(cyclopentapyran)、苯并呋喃和异苯并呋喃;和包含2个或更多个选自氮、硫和氧的杂原子的芳族杂环,诸如噻唑、噻二唑、异噻唑、苯并噁唑、苯并噻唑、苯并噻二唑、吩噻嗪、异噁唑、呋咱、吩噁嗪、吡唑并噁唑、咪唑并噻唑、噻吩并呋喃、呋喃并吡咯、吡啶并噁嗪、呋喃并吡啶、呋喃并嘧啶、噻吩并嘧啶和噁唑,以及其它,它们都可以任选地被取代。

[0284] 术语“被取代的芳基”表示包含至少一个芳族环或多个稠合环(其中至少一个是芳族环)的芳族碳环基团,其中所述环被一个或多个取代基取代。例如,芳基可以包含选自以下的取代基:-$(CH_2)_n$OH,-$(CH_2)_n$-O-(C_1-C_6)烷基,-$(CH_2)_n$-O-$(CH_2)_n$-(C_1-C_6)烷基,-$(CH_2)_n$-C(O)(C_0-C_6)烷基,-$(CH_2)_n$-C(O)O(C_0-C_6)烷基,-$(CH_2)_n$-OC(O)(C_0-C_6)烷基,胺,单-或二-(C_1-C_6烷基)胺,其中所述胺上的烷基任选地被1或2个羟基或至多三个卤代(优选地F、Cl)基团取代,OH,COOH,C_1-C_6烷基(优选地CH_3),CF_3,OMe,OCF_3,NO_2或CN基团(它们中的每个可以在苯环的邻-、间-和/或对-位(优选地对-位)被取代),任选地被取代的苯基(所述苯基本身优选地被ABM基团(包括ULM基团)所连接的接头基团取代),和/或F、Cl、OH、COOH、CH_3、CF_3、OMe、OCF_3、NO_2或CN基团中的至少一个(在苯环的邻-、间-和/或对-位、优选地对-位),萘基(其可以任选地被取代),任选地被取代的杂芳基,优选地任选地被取代的异噁唑,包括甲基取代的异噁唑,任选地被取代的噁唑,包括甲基取代的噁唑,任选地被取代的噻唑,包括甲基取代的噻唑,任选地被取代的异噻唑,包括甲基取代的异噻唑,任选地被取代的吡咯,包括

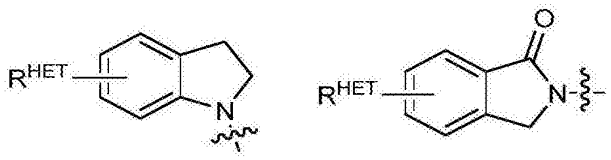
甲基取代的吡咯，任选地被取代的咪唑，包括甲基咪唑，任选地被取代的苯并咪唑或甲氧基苄基咪唑，任选地被取代的oximidazole或methyloximidazole，任选地被取代的二唑基团，包括甲基二唑基团，任选地被取代的三唑基团，包括甲基取代的三唑基团，任选地被取代的吡啶基团，包括卤代-(优选地，F)或甲基取代的吡啶基团或氧杂吡啶基团(其中所述吡啶基团通过氧连接至苯基)，任选地被取代的呋喃，任选地被取代的苯并呋喃，任选地被取代的二氢苯并呋喃，任选地被取代的吲哚，吲嗪或氮杂吲嗪(2、3或4-氮杂吲嗪)，任选地被取代的喹啉，和它们的组合。

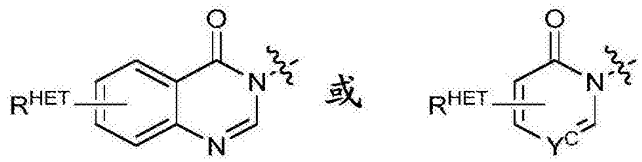
[0285] “羧基”表示基团--C(O)OR，其中R是氢、烷基、被取代的烷基、芳基、被取代的芳基、杂芳基或被取代的杂芳基，其中这些通用取代基具有与本文定义的对应基团的定义相同的含义。

[0286] 术语“杂芳基(heteroaryl或hetaryl)”可以是指但决不限于任选地被取代的喹啉(其可以连接至药效团或在喹啉环内的任意碳原子上被取代)、任选地被取代的吲哚(包括二氢吲哚)、任选地被取代的吲嗪、任选地被取代的氮杂吲嗪(2,3或4-氮杂吲嗪)、任选地被取代的苯并咪唑、苯并二唑、benzoxofuran、任选地被取代的咪唑、任选地被取代的异噁唑、任选地被取代的噁唑(优选地甲基取代)、任选地被取代的二唑、任选地被取代的三唑、四唑、任选地被取代的苯并呋喃、任选地被取代的噻吩、任选地被取代的噻唑(优选地甲基和/或巯基取代)、任选地被取代的异噻唑、任选地被取代的三唑(优选地被甲基取代的1,2,3-三唑)、三异丙基甲硅烷基、任选地被取代的$-(CH_2)_m-O-C_1-C_6$烷基或任选地被取代的$-(CH_2)_m-C(O)-O-C_1-C_6$烷基)、任选地被取代的吡啶(2-、3或4-吡啶)或根据以下化学结构的基团：



[0287]





[0288] 其中S^C是CHR^{SS}、NR^{URE}或O；

[0289] R^{HET}是H、CN、NO_2、卤代(优选地Cl或F)、任选地被取代的C_1-C_6烷基(优选地被一个或两个羟基或至多三个卤代基团(例如CF_3)取代)、任选地被取代的O(C_1-C_6烷基)(优选地被一个或两个羟基或至多三个卤代基团取代)或任选地被取代的炔属基团$-C\equiv C-R_a$，其中R_a是H或C_1-C_6烷基(优选地C_1-C_3烷基)；

[0290] R^{SS}是H、CN、NO_2、卤代(优选F或Cl)、任选地被取代的C_1-C_6烷基(优选地被一个或两

个羟基或至多三个卤代基团取代)、任选地被取代的O-(C1-C6烷基)(优选地被一个或两个羟基或至多三个卤代基团取代)或任选地被取代的-C(O)(C1-C6烷基)(优选地被一个或两个羟基或至多三个卤代基团取代);

[0291] R^{URE}是H、C1-C6烷基(优选地H或C1-C3烷基)或-C(O)(C1-C6烷基),所述基团中的每个任选地被一个或两个羟基或至多三个卤素(优选氟基团)取代,或任选地被取代的杂环,例如哌啶、吗啉、吡咯烷、四氢呋喃、四氢噻吩、哌啶、哌嗪,它们中的每个任选地被取代,且

[0292] Y^{C}是N或C-R^{YC},其中R^{YC}是H、OH、CN、NO_2、卤代(优选地Cl或F)、任选地被取代的C1-C6烷基(优选地被一个或两个羟基或至多三个卤代基团(例如CF_3)取代)、任选地被取代的O(C1-C6烷基)(优选地被一个或两个羟基或至多三个卤代基团取代)或任选地被取代的炔属基团-C≡C-Ra,其中Ra是H或C1-C6烷基(优选地C1-C3烷基)。

[0293] 术语"芳基烷基"和"杂芳基烷基"表示分别包含芳基或杂芳基以及根据以上定义的烷基和/或杂烷基和/或碳环和/或杂环烷基环系的基团。

[0294] 本文中使用的术语"芳基烷基"表示与上面定义的烷基连接的上面定义的芳基。所述芳基烷基通过烷基连接至母体部分,其中所述烷基是1-6个碳原子。所述芳基烷基中的芳基可以如上面所定义地被取代。

[0295] 术语"杂环"表示这样的环状基团:其含有至少一个杂原子(即,O、N或S),且可以是芳族的(杂芳基)或非芳族的。因而,杂芳基部分被包含在杂环的定义下,取决于它的应用上下文。示例性的杂环基包括:氮杂环丁基、苯并咪唑基、1,4-苯并二噁烷基、1,3-苯并间二氧杂环戊烯基、苯并噁唑基、苯并噻唑基、苯并噻吩基、二氢咪唑基、二氢吡喃基、二氢呋喃基、二噁烷基、二氧杂环戊烷基、亚乙基脲、1,3-二氧杂环戊烷、1,3-二噁烷、1,4-二噁烷、呋喃基、高哌啶基、咪唑基、咪唑啉基、咪唑烷基、吲哚啉基、吲哚基、异喹啉基、异噻唑烷基、异噻唑基、异噁唑烷基、异噁唑基、吗啉基、萘啶基、噁唑烷基、噁唑基、吡啶酮、2-吡咯烷酮、吡啶、哌嗪基,N-甲基哌嗪基、哌啶基、邻苯二甲酰亚胺、琥珀酰亚胺、吡嗪基、吡唑啉基、吡啶基、嘧啶基、吡咯烷基、吡咯啉基、吡咯基、喹啉基、四氢呋喃基、四氢吡喃基、四氢喹啉、噻唑烷基、噻唑基、噻吩基、四氢噻吩、噁烷、氧杂环丁基、氧杂硫杂环戊烷基、硫杂环己烷以及其它。

[0296] 杂环基团可以任选地被选自以下的成员取代:烷氧基、被取代的烷氧基、环烷基、被取代的环烷基、环烯基、被取代的环烯基、酰基、酰基氨基、酰氧基、氨基、被取代的氨基、氨基酰基、氨基酰氧基、氧基氨基酰基、叠氮基、氰基、卤素、羟基、酮、硫代酮、羧基、羧基烷基、硫代芳氧基、硫代杂芳氧基、硫代杂环氧基、巯基、硫代烷氧基、被取代的硫基烷氧基、芳基、芳氧基、杂芳基、杂芳氧基、杂环基、杂环氧基、羟氨基、烷氧氨基、硝基、—SO-烷基、—SO-取代的烷基、—SO芳基、—SO-杂芳基、—SO2-烷基、—SO2-取代的烷基、—SO2-芳基、氧代(=O)和-SO2-杂芳基。这样的杂环基团可以具有单环或多个稠合环。氮杂环和杂芳基的例子包括、但不限于吡咯、咪唑、吡唑、吡啶、吡嗪、嘧啶、哒嗪、吲嗪、异吲哚、吲哚、吲唑、嘌呤、喹嗪、异喹啉、喹啉、酞嗪、萘基吡啶、喹喔啉、喹唑啉、噌啉、喋啶、咔唑、咔啉、菲啶、吖啶、菲咯啉、异噻唑、吩嗪、异噁唑、吩噁嗪、吩噻嗪、咪唑烷、咪唑啉、哌啶、哌嗪、吲哚啉、吗啉代、哌啶基、四氢呋喃基等以及N-烷氧基-含氮杂环。术语"杂环"也包括二环基团,其中任意杂环与苯环或环己烷环或其它杂环(例如,吲哚基、喹啉基、异喹啉基、四氢喹啉基等)

稠合。

[0297] 术语“环烷基”可以是指但决不限于从本文定义的单环或多环烷基或环烷烃衍生出的单价基团，例如，在环中具有3-20个碳原子的饱和单环烃基，包括、但不限于，环丙基、环丁基、环戊基、环己基、环庚基等。术语“取代的环烷基”可以是指但决不限于单环或多环烷基且被一个或多个取代基(例如，氨基、卤素、烷基、被取代的烷基、二价碳基氧基(carbyloxy)、二价碳基巯基(carbylmercapto)、芳基、硝基、巯基或磺基)取代，其中这些通用取代基具有与在本说明书中定义的对应基团的定义相同的含义。

[0298] “杂环烷基”表示这样的单环或多环烷基：其中它的环结构的至少一个环碳原子被选自N、O、S或P的杂原子替代。“被取代的杂环烷基”表示这样的单环或多环烷基：其中它的环结构的至少一个环碳原子被选自N、O、S或P的杂原子替代，且所述基团含有一个或多个选自卤素、烷基、被取代的烷基、二价碳基氧基、二价碳基巯基、芳基、硝基、巯基或磺基的取代基，其中这些通用取代基具有与在本说明书中定义的对应基团的定义相同的含义。

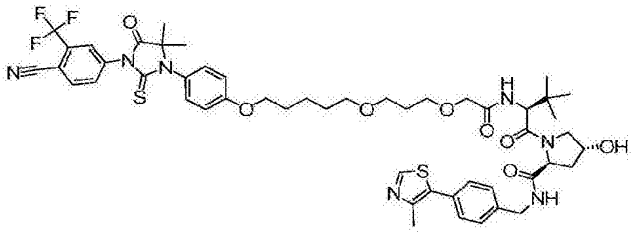
[0299] 示例性的AR-PROTAC化合物

[0300] 如上所述，在某些方面，本说明书提供了双功能的PROTAC化合物，其包含如本文中所述的至少一个ABM基团、接头和至少一个ULM(或VLM)基团。

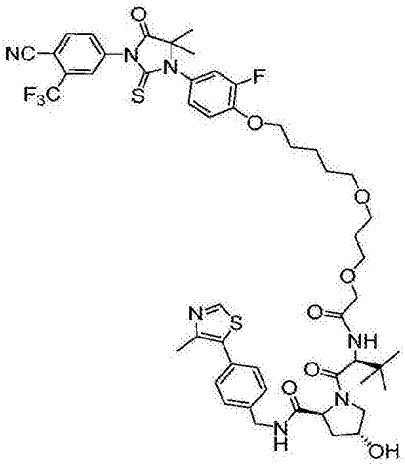
[0301] 在某些实施方案中，所述化合物选自化合物1-593(如在表2-17中所述)及其盐和多晶型物。

[0302] 在某些实施方案中，所述化合物选自：

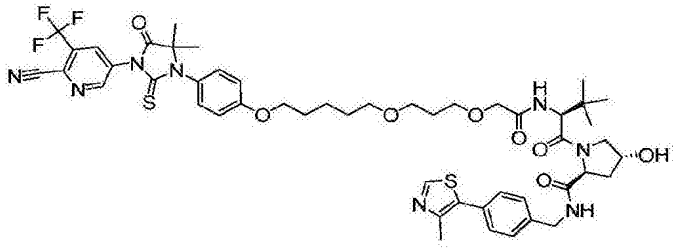
[0303]



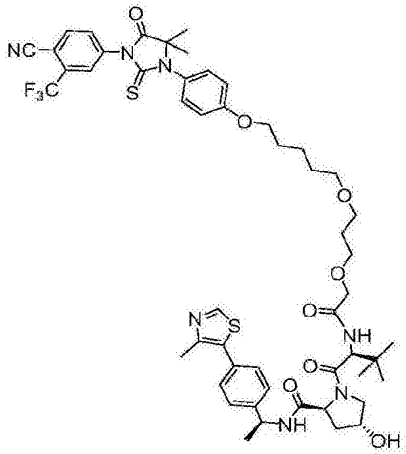
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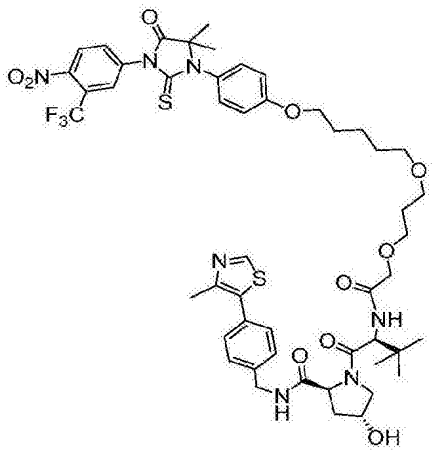
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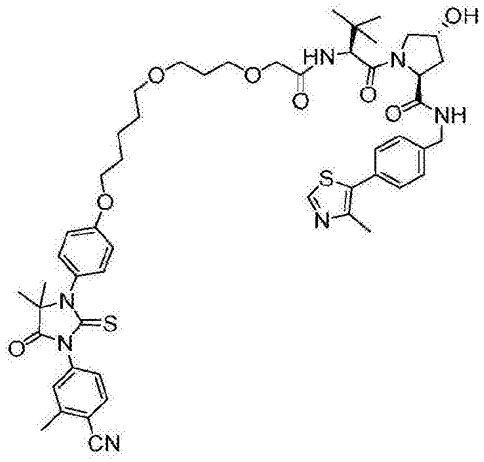
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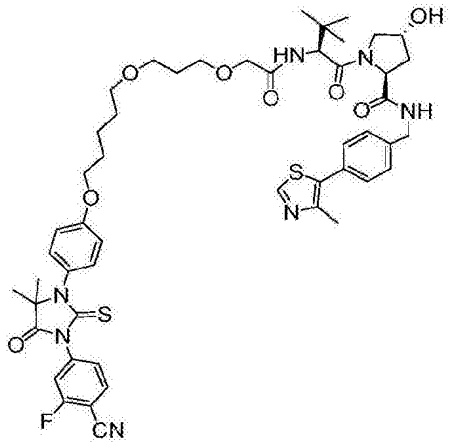
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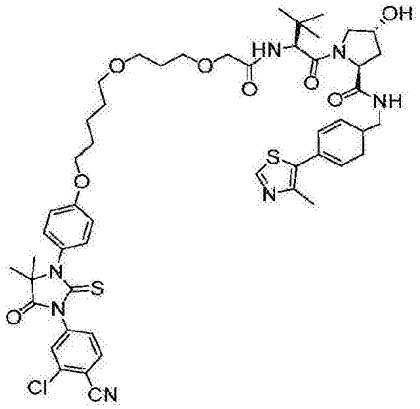


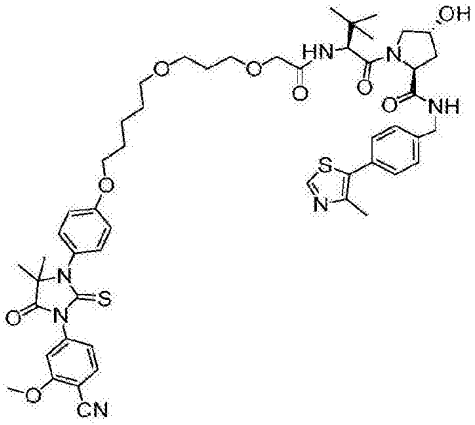
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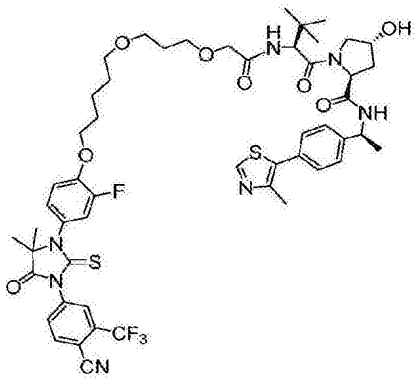


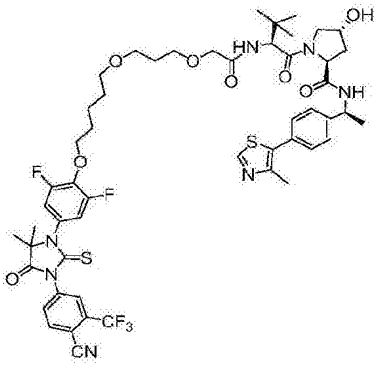
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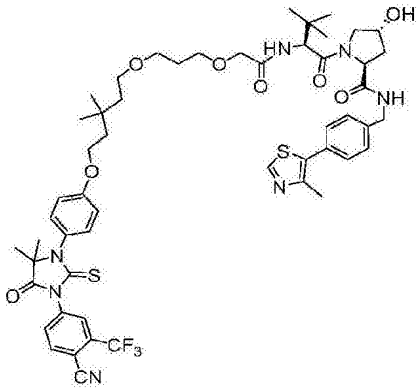
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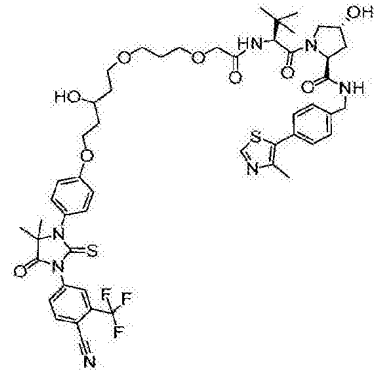

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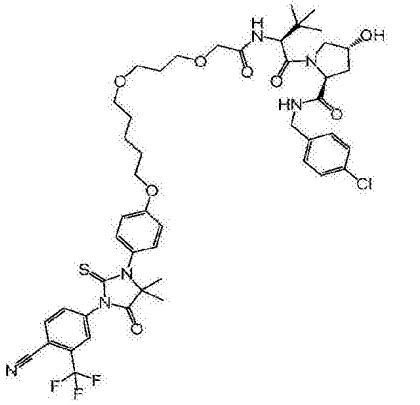

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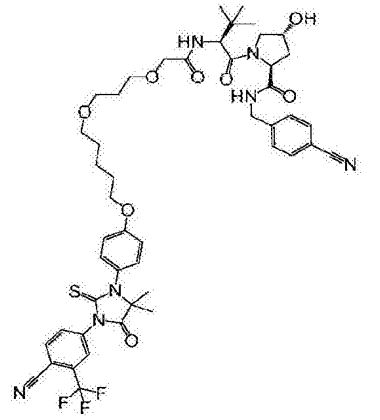

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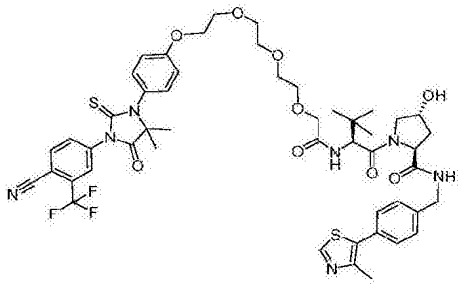
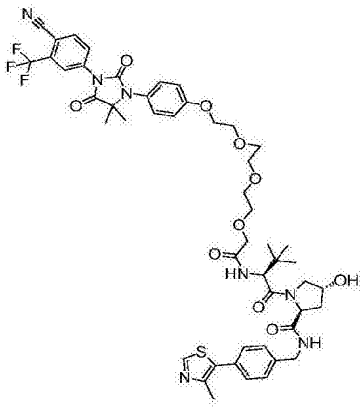
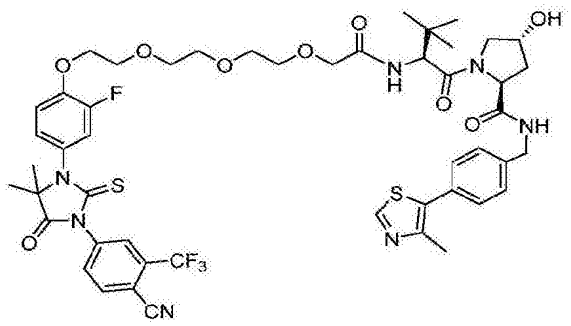
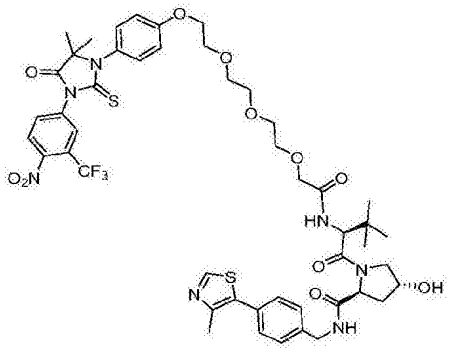
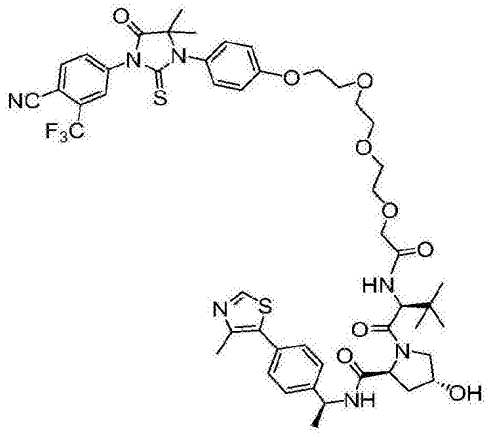
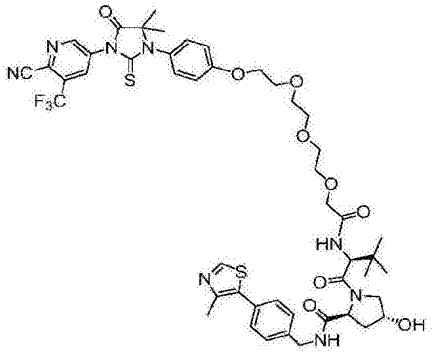
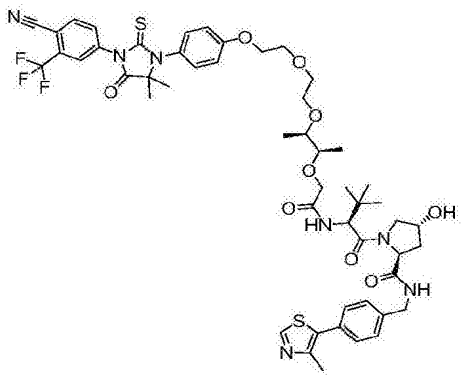
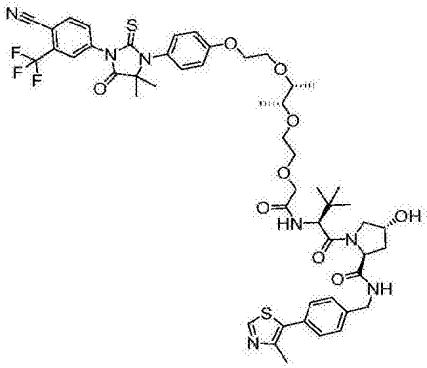

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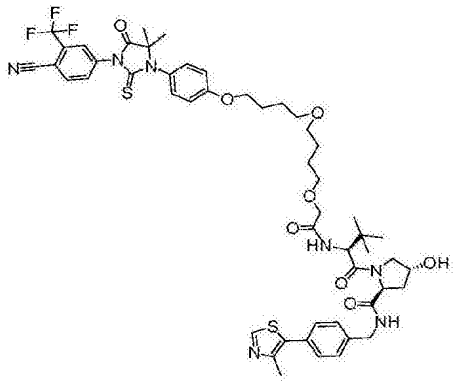
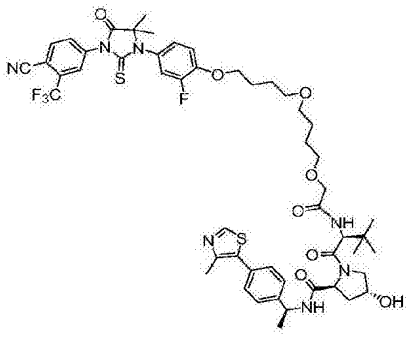
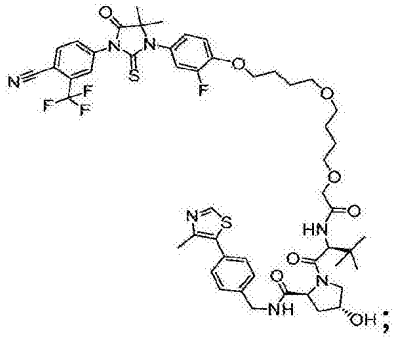
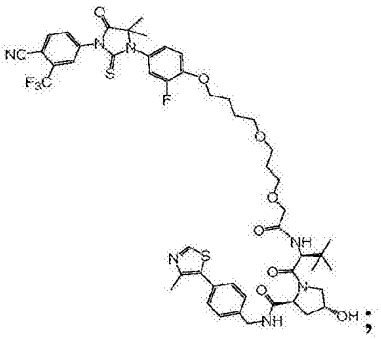
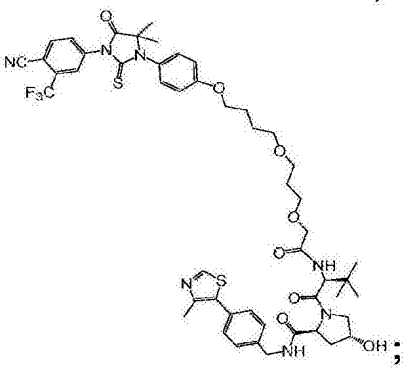
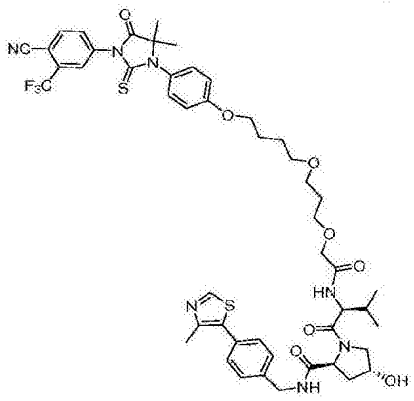
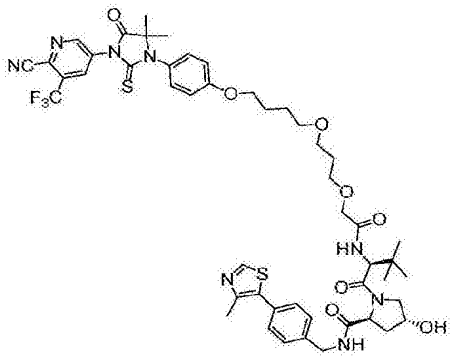
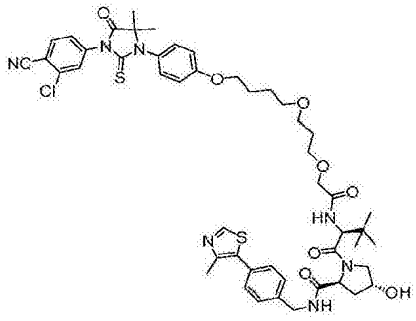
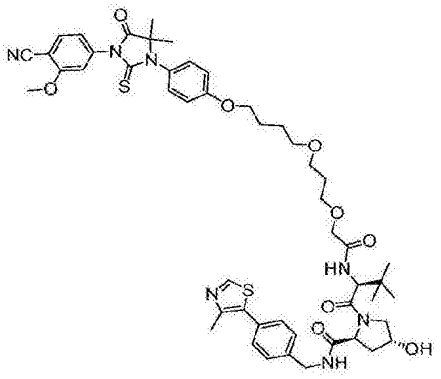

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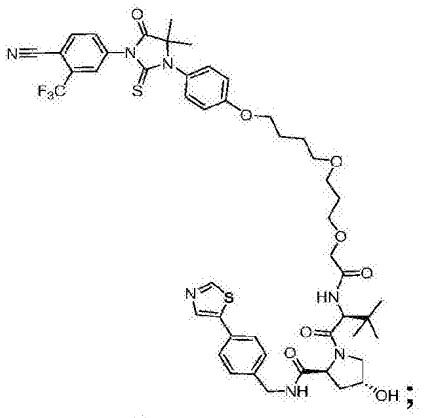
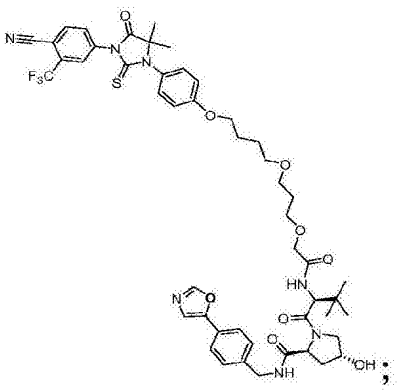
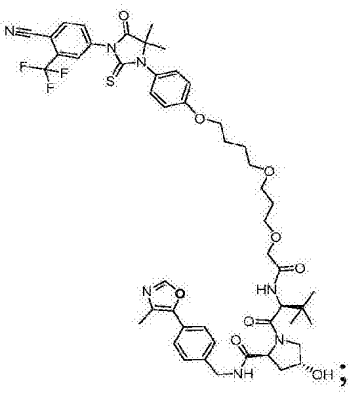
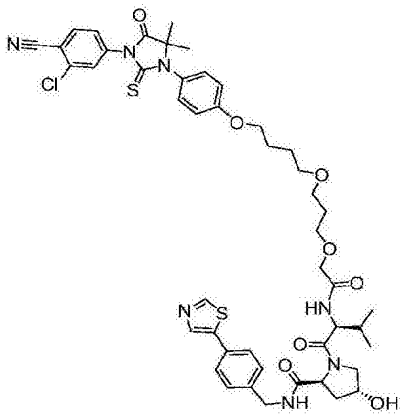
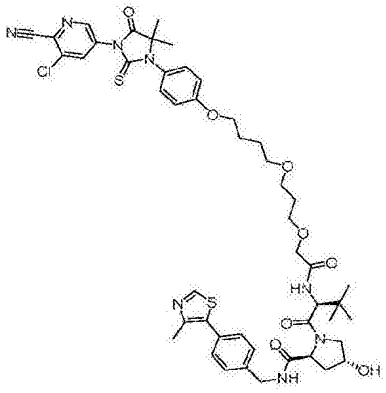
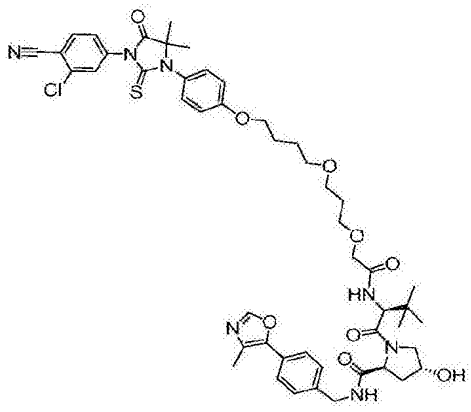
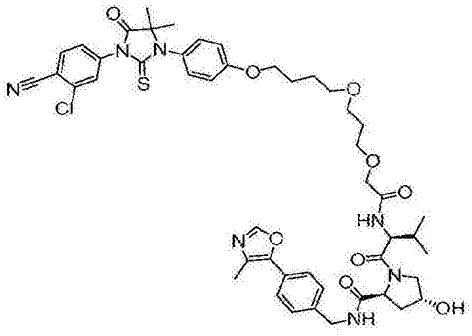
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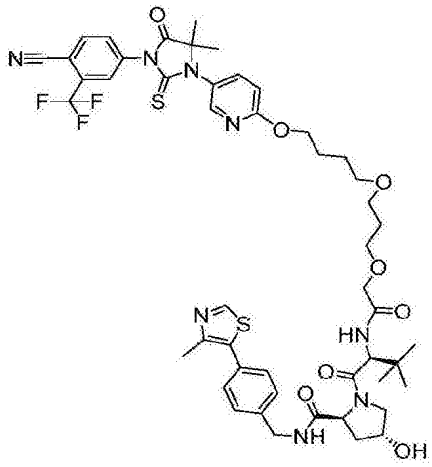
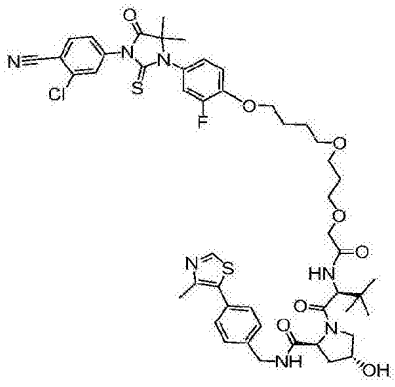
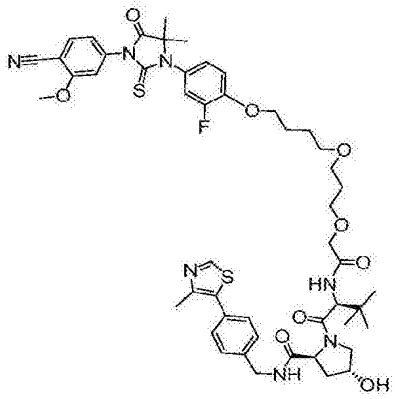
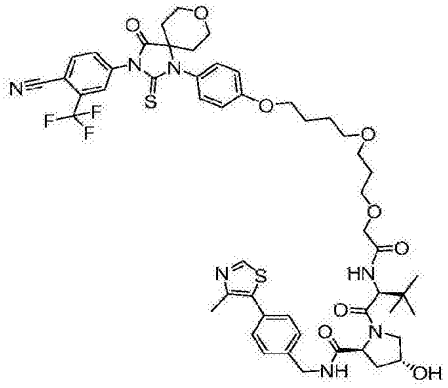
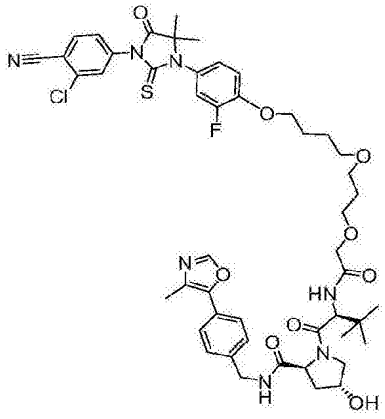
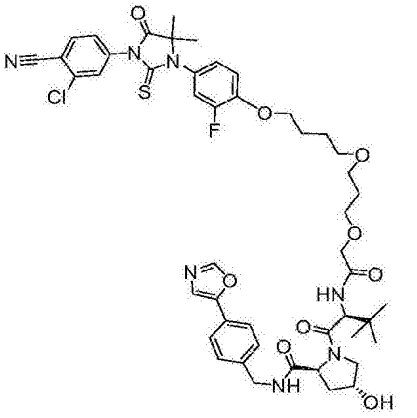
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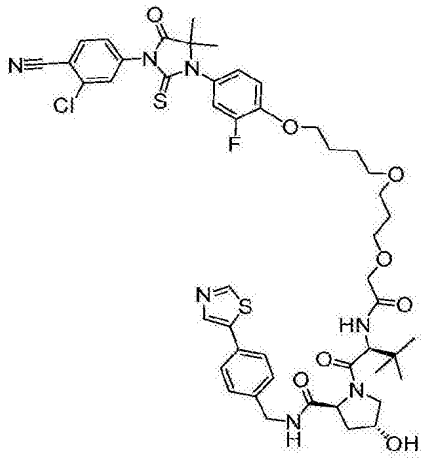
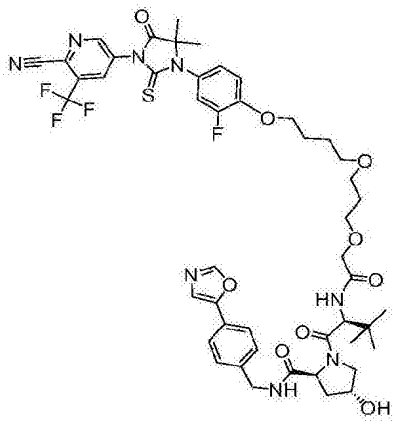
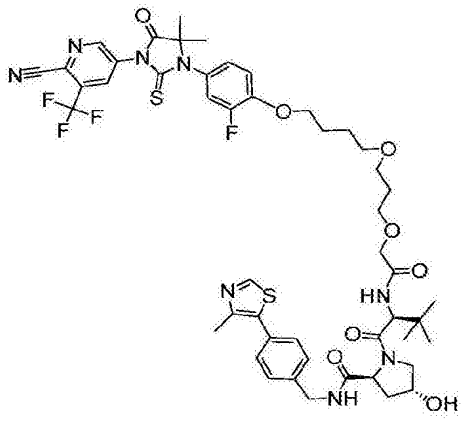
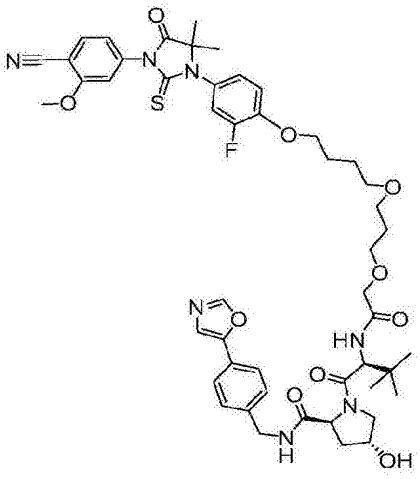
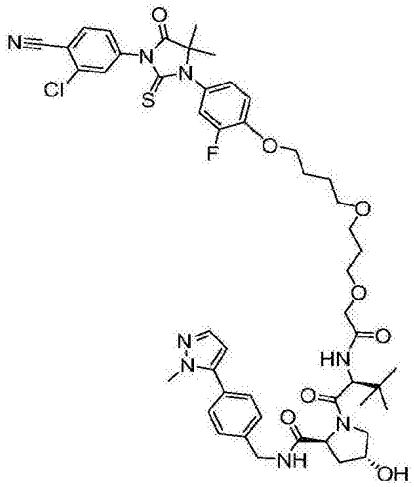
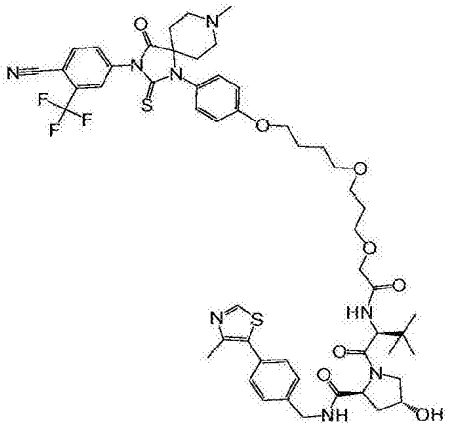
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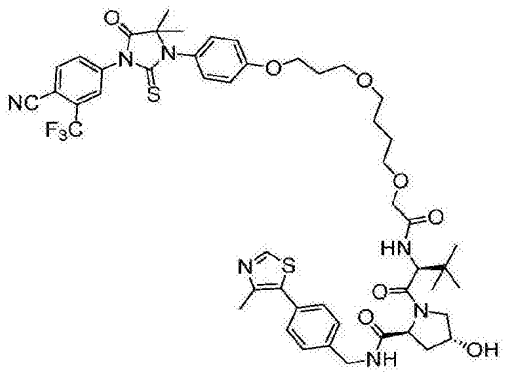
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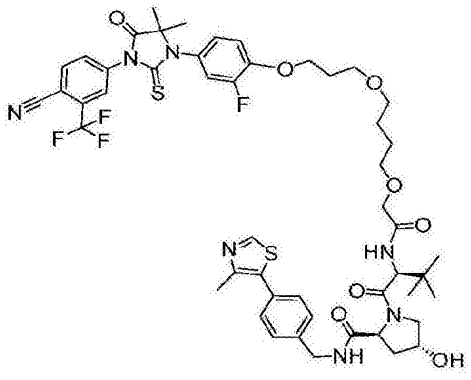

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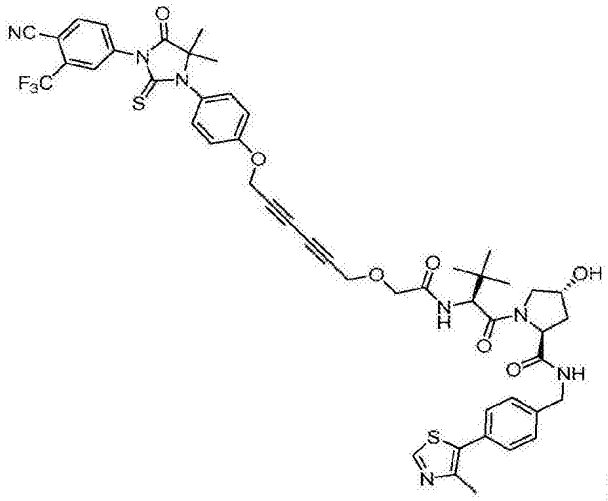
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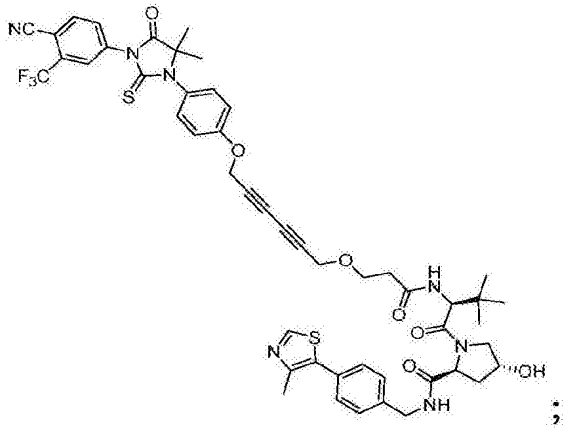

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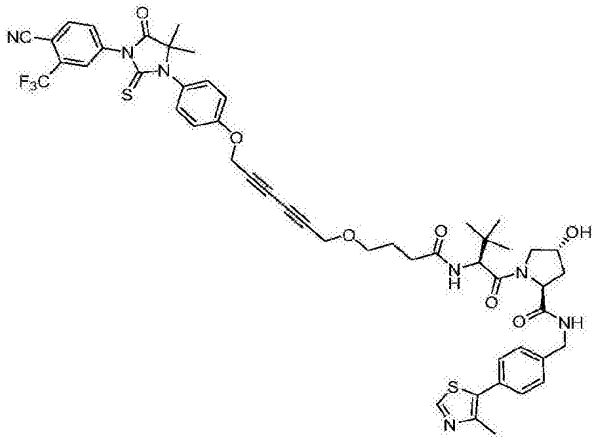
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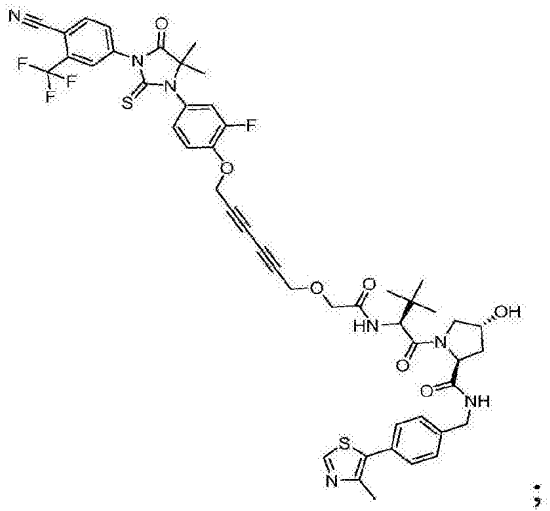

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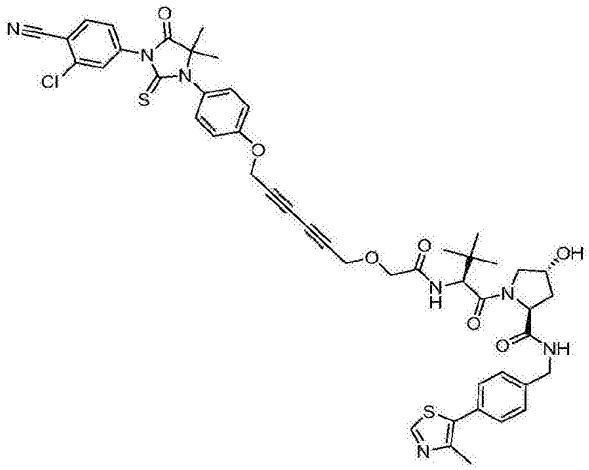

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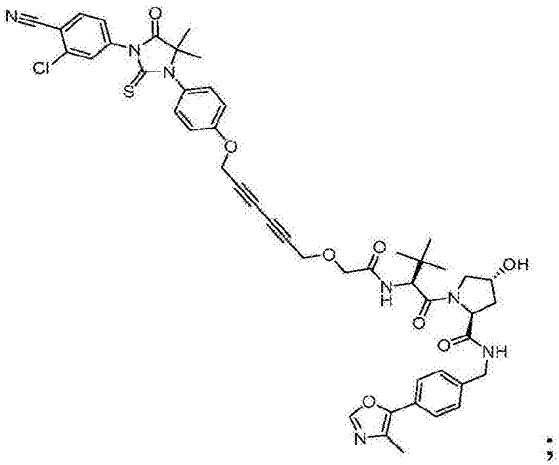

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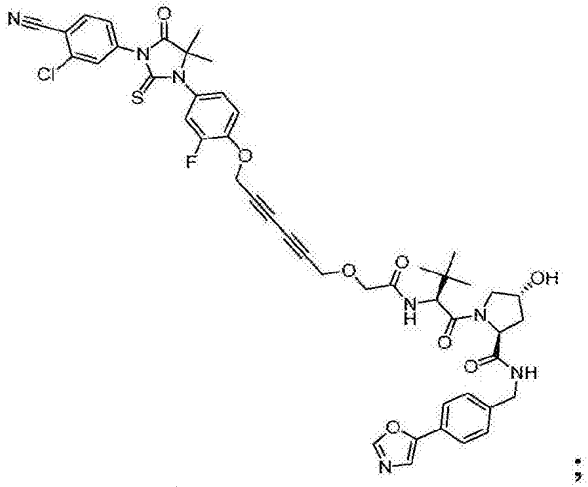

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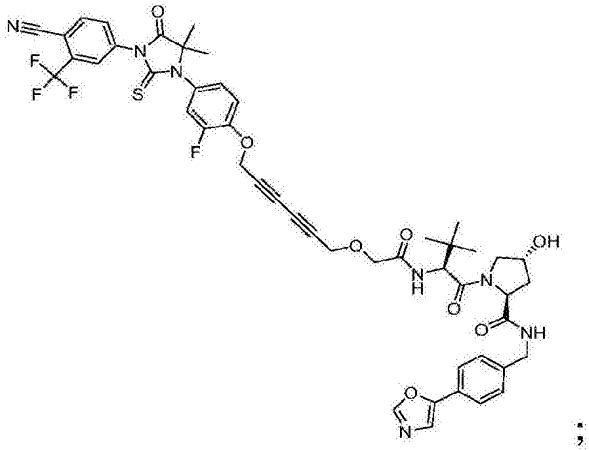

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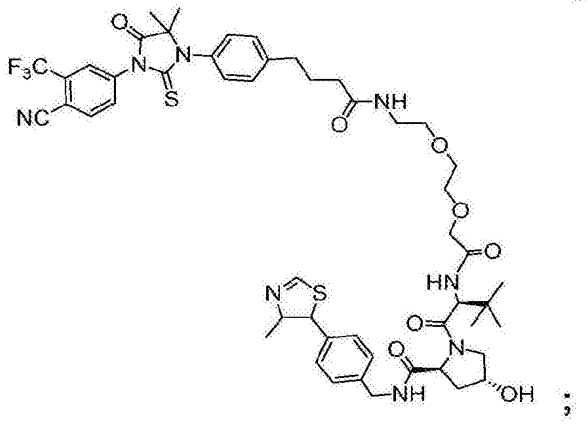
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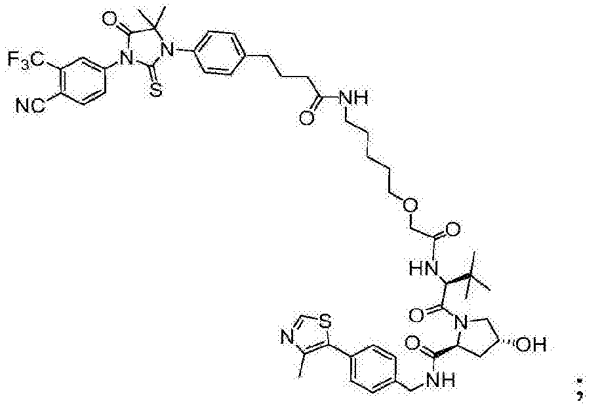

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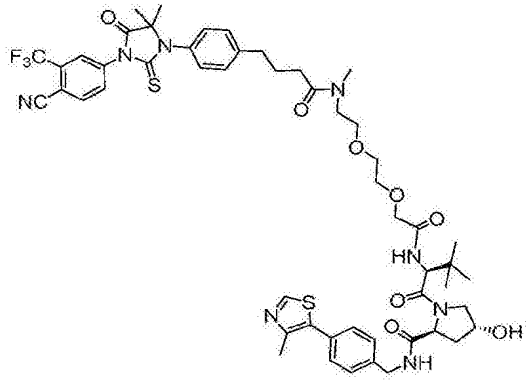
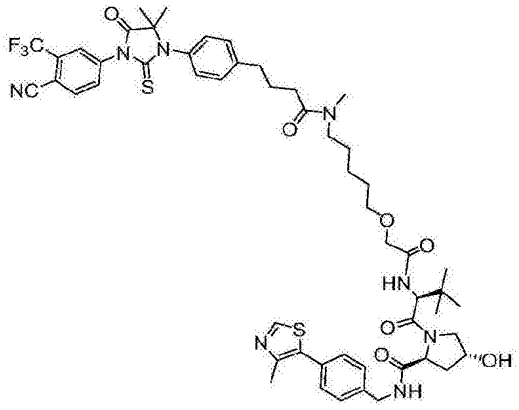
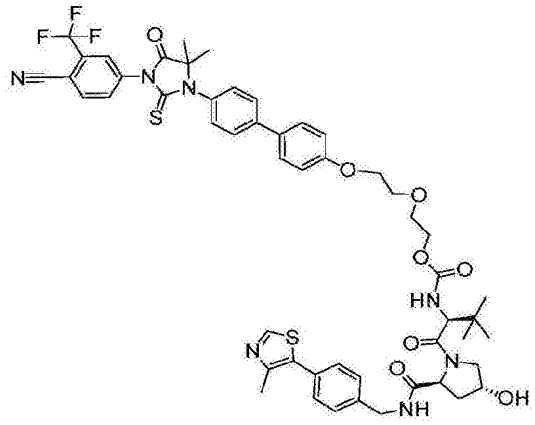
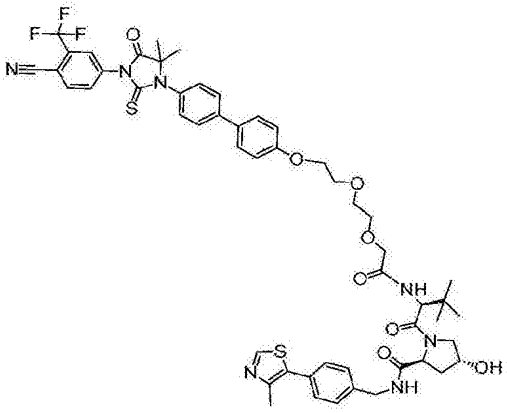
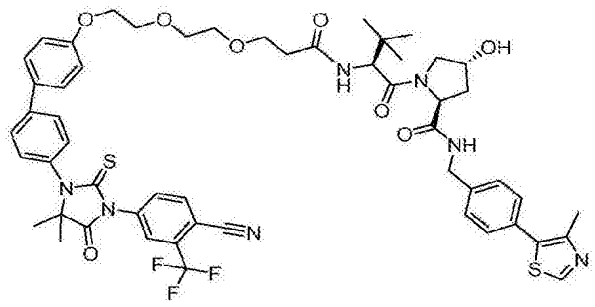
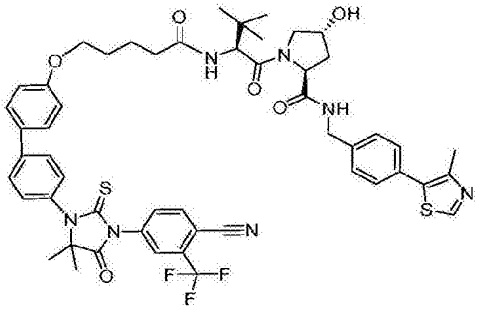
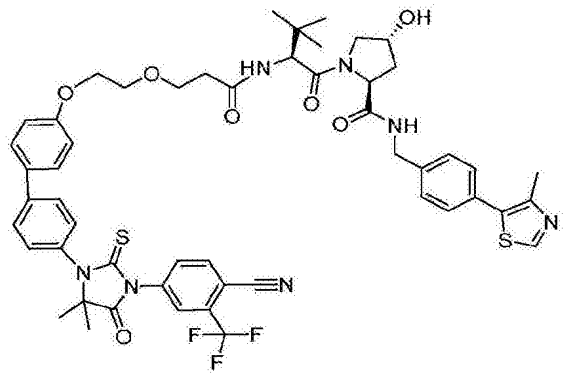
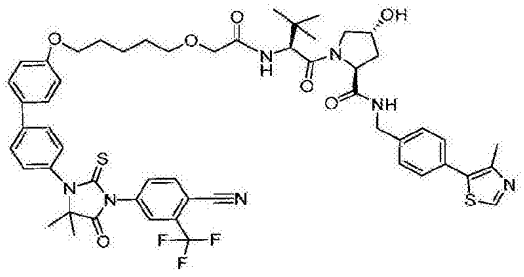

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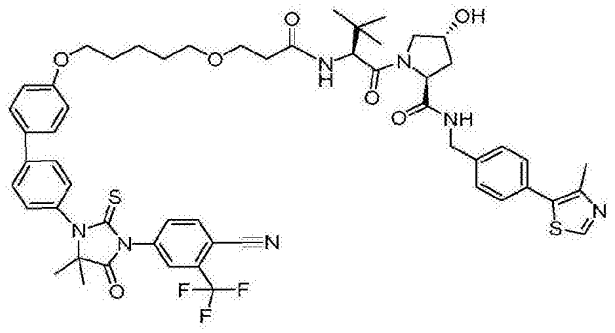
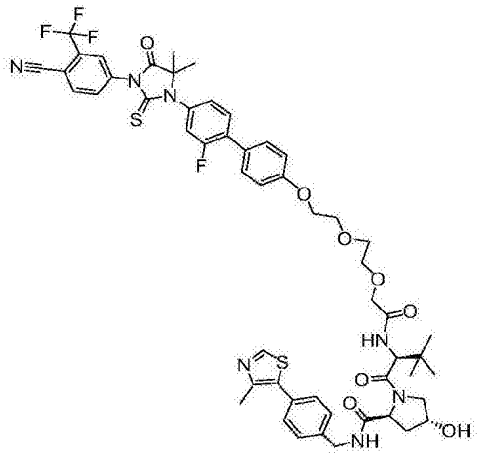
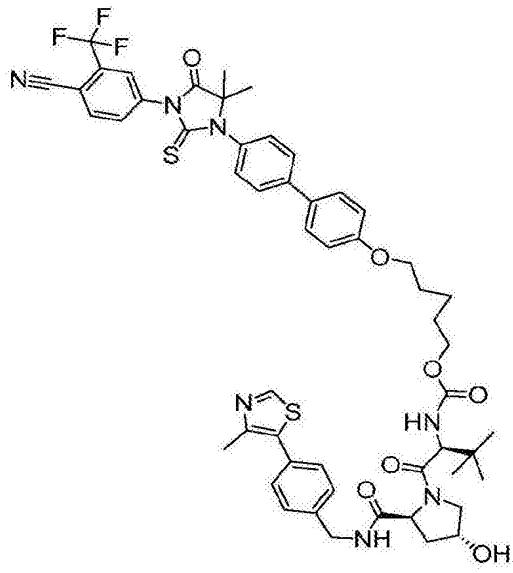
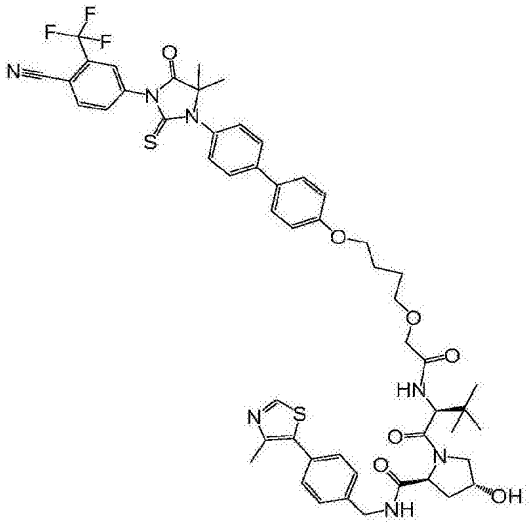
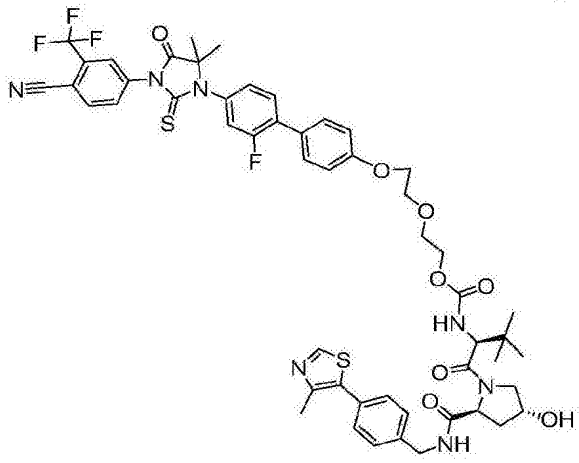
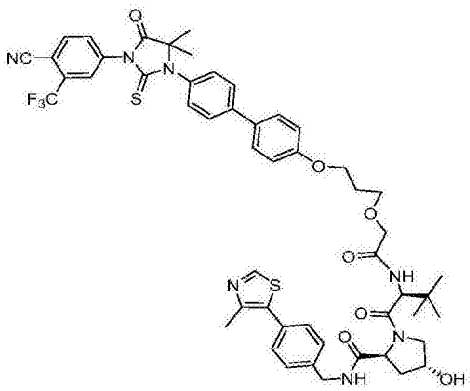

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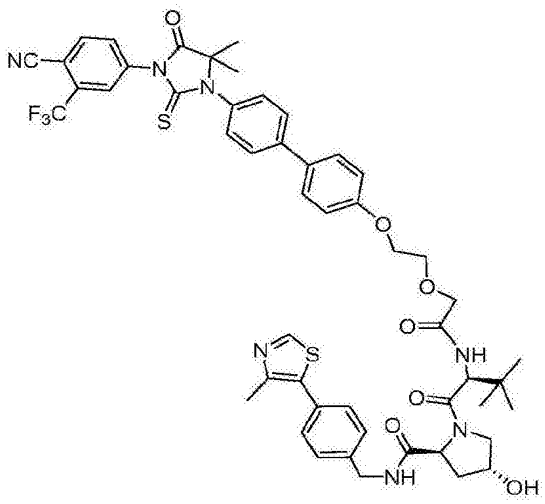
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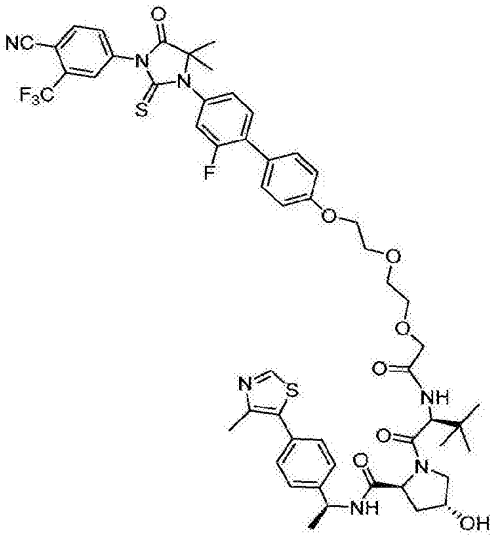

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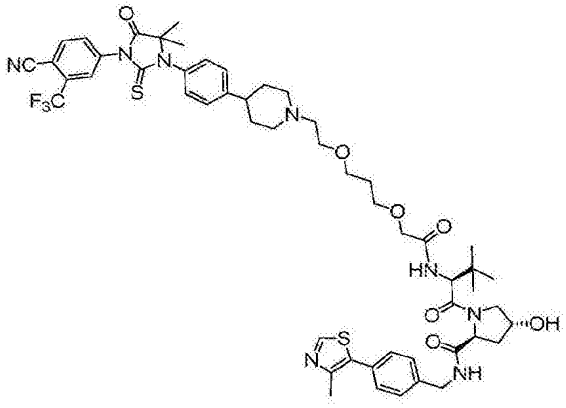
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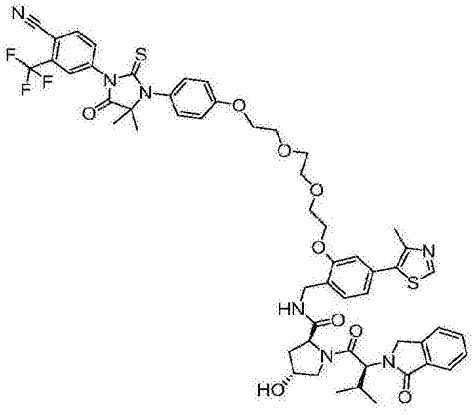

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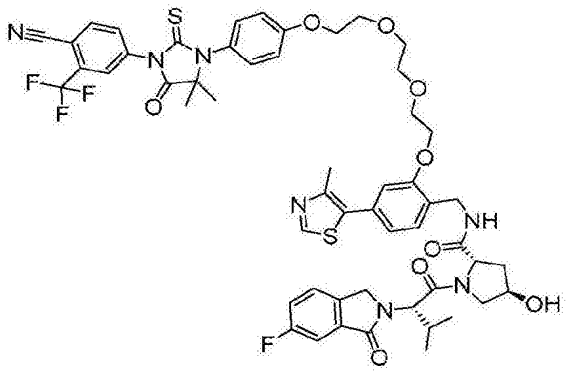
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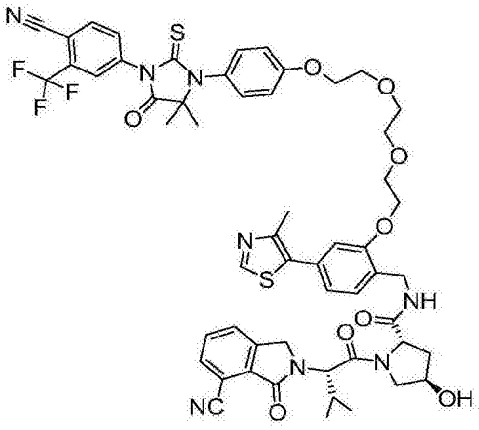

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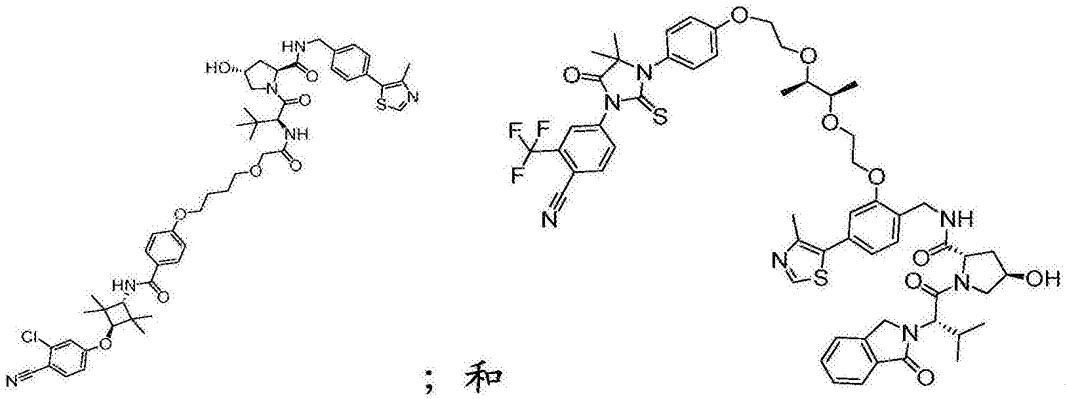

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[0316] 在另一个实施方案中，本发明提供了化合物的文库(library)。所述文库包含超过一种化合物，其中每种化合物具有式ABM-L-ULM，其中ULM是泛素途径蛋白结合部分(优选地，如本文中另外公开的E3泛素连接酶部分)，例如，VLM，且ABM是AR蛋白结合部分，其中ABM偶联(优选地，通过接头部分)至ULM，且其中所述泛素途径蛋白结合部分识别泛素途径蛋白，具体地，E3泛素连接酶。

[0317] 在适用时，本说明书包括组合物，其包含本发明的化合物的药学上可接受的盐，具体地，酸或碱加成盐。

[0318] 在适用时，术语“药学上可接受的盐”在本说明书中用于描述本文所述化合物中的一种或多种的盐形式，其呈现为增加所述化合物在患者的胃肠道的胃液中的溶解度，以便促进溶解和所述化合物的生物利用度。药学上可接受的盐包括从药学上可接受的无机或有机碱和酸(在适用时)衍生出的那些。合适的盐包括从碱金属(诸如钾和钠)、碱土金属(诸如钙、镁和铵盐)以及制药领域中众所周知的众多其它酸和碱衍生出的那些。作为根据本发明的磷酸盐的中和盐，钠和钾盐是特别优选的。

[0319] 用于制备在本发明中有用的前述碱化合物的药学上可接受的酸加成盐的酸是形成无毒的酸加成盐的那些，所述无毒的酸加成盐即含有药理学上可接受的阴离子的盐，诸如盐酸盐、氢溴酸盐、氢碘酸盐、硝酸盐、硫酸盐、硫酸氢盐、磷酸盐、酸式磷酸盐、乙酸盐、乳酸盐、柠檬酸盐、酸式柠檬酸盐、酒石酸盐、酒石酸氢盐、琥珀酸盐、马来酸盐、富马酸盐、葡萄糖酸盐、蔗糖酸盐、苯甲酸盐、甲磺酸盐、乙磺酸盐、苯磺酸盐、对甲苯磺酸盐和扑酸盐[即，1,1’-亚甲基-二-(2-羟基-3萘甲酸盐)]盐，以及众多其它盐。

[0320] 药学上可接受的碱加成盐也可以用于生产根据本发明的化合物或衍生物的药学上可接受的盐形式。可以用作试剂来制备在性质上是酸性的本发明化合物的药学上可接受的碱盐的化学碱是与这样的化合物形成无毒碱盐的那些。这样的无毒碱盐包括、但不限于从这样的药理学上可接受的阳离子诸如碱金属阳离子(例如，钾和钠)和碱土金属阳离子(例如，钙、锌和镁)、铵或水溶性胺加成盐诸如N-甲基还原葡糖胺-(葡甲胺)和低级烷醇铵和药学上可接受的有机胺的其它碱盐衍生出的那些，以及其它。

[0321] 组合物

[0322] 在另一个方面，本说明书提供了一种组合物，其包含如本文中所述的化合物(包括其盐(酸或碱)、多晶型物和前药)和药学上可接受的载体。在某些实施方案中，所述组合物是包含有效量的如本文中所述的化合物和药学上可接受的载体的治疗或药物组合物。在某些实施方案中，所述组合物还包含如本文中所述的另一种生物活性剂、抗癌剂、另一种双功

能化合物中的至少一种或它们的组合。

[0323] 在本发明的药物组合物中可以与载体材料组合以产生单一剂型的化合物的量将随治疗的宿主和疾病、特定施用模式而变化。通常，施用0.1mg/kg至1000mg/kg体重/天之间的量的活性成分，取决于药剂的效力。通过在细胞培养物或实验动物中的标准药物操作，可以测定这类化合物的毒性和治疗功效，例如测定LD50(对群体的50％致命的剂量)和ED50(对群体中的50％治疗上有效的剂量)。毒性和疗效之间的剂量比是治疗指数，且它可以表示为比率LD50/ED50。表现出大治疗指数的化合物是优选的。尽管可以使用具有毒性副作用的化合物，但应当小心地设计将这样的化合物靶向受影响的组织部位的递送系统，以便使对未受感染的细胞的潜在损伤最小化，且由此减少副作用。从细胞培养测定和动物研究获取的数据可以用在配制人类使用的剂量范围中。这样的化合物的剂量优选地在包括ED50又几乎没有或没有毒性的循环浓度范围内。根据所用剂型和所用给药途径，剂量可以在此范围内变化。对于在本发明的方法中使用的任何化合物，可以从细胞培养测定初步估计治疗有效剂量。可以在动物模型中配制剂量以达到包括在细胞培养物中确定的IC50(即，达到症状的半数最大抑制时的试验化合物浓度)的循环血浆浓度范围。这样的信息可以用来更准确地确定在人类中有用的剂量。可以例如通过高效液相色谱法来测量血浆的水平。

[0324] 本发明的组合物可以使用一种或多种药学上可接受的载体以常规方式配制，且还可以在控释制剂中施用。在这些药物组合物中可以使用的药学上可接受的载体包括、但不限于离子交换剂，氧化铝，硬脂酸铝，卵磷脂，血清蛋白，诸如人血清白蛋白，缓冲物质，诸如磷酸盐，甘氨酸，山梨酸，山梨酸钾，饱和植物脂肪酸的偏甘油酯混合物，水，盐或电解质，诸如谷醇溶蛋白硫酸盐，磷酸氢二钠，磷酸氢钾，氯化钠，锌盐，胶态二氧化硅(colloidal silica)，三硅酸镁，聚乙烯吡咯烷酮，基于纤维素的物质，聚乙二醇，羧甲纤维素钠，聚丙烯酸酯，蜡类，聚乙烯-聚氧丙烯-嵌段共聚物，聚乙二醇和羊毛脂。

[0325] 在药学上可接受的载体或稀释剂中包括足以给患者递送对于目标适应症而言治疗有效量的量的活性化合物，而不在治疗的患者中造成严重的毒性效应。用于本文提及的所有病症的活性化合物的优选剂量是在约10ng/kg至300mg/kg范围内，优选0.1-100mg/kg/天，更一般地0.5至约25mg/千克接受者/患者体重/天。一种典型局部剂量是在合适载体中的0.01-5％wt/wt范围内。

[0326] 所述化合物方便地在任意合适的单元剂型中施用，所述单元剂型包括、但不限于含有小于1mg、1mg至3000mg、优选5-500mg活性成分/单元剂型的剂型。约25-250mg的口服剂量经常是方便的。

[0327] 优选地施用活性成分以达到约0.00001-30mM、优选约0.1-30μM的活性化合物的峰血浆浓度。这可以如下实现：例如，通过静脉内注射活性成分任选地在盐水或水性介质中的溶液或制剂，或作为活性成分的推注剂(bolus)来施用。口服施用也是适当的以产生活性剂的有效血浆浓度。

[0328] 药物组合物中的活性化合物的浓度取决于药物的吸收、分布、灭活和排泄速率以及本领域技术人员已知的其它因素。应当指出，剂量值还将随要减轻的病症的严重程度而变化。进一步应当理解，对于任何特定受试者，应当根据个体需要以及管理或监督所述组合物的施用的人士的专业判断随时间调整具体剂量方案，并且本文中阐述的浓度范围仅仅是示例性的且无意限制要求保护的组合物的范围或实践。所述活性成分可以一次性地施用，

或可以分成许多较小剂量以在多个时间段施用。

[0329] 如果静脉内地施用，优选的载体是生理盐水或磷酸盐缓冲盐水(PBS)。

[0330] 在一个实施方案中，将活性化合物与载体一起制备，所述载体会保护化合物免于从身体中快速消除，诸如控释制剂，包括植入剂和微囊化的递送系统。可以使用可生物降解的、生物相容的聚合物，诸如乙烯醋酸乙烯酯、聚酸酐、聚乙醇酸、胶原、聚原酸酯和聚乳酸。本领域技术人员会明白用于制备这样的制剂的方法。

[0331] 脂质体悬浮液也可以是药学上可接受的载体。这些可以根据本领域技术人员已知的方法制备，例如，如在美国专利号4,522,811(其通过引用整体并入本文)中所述。例如，可以如下制备脂质体制剂：将适当的脂质(诸如硬脂酰基磷脂酰乙醇胺、硬脂酰基磷脂酰胆碱、花生酰基(arachadoyl)磷脂酰胆碱和胆固醇)溶解在无机溶剂中，然后蒸发所述溶剂，在容器的表面上剩下干燥的脂质的薄膜。然后将活性化合物的水溶液引入所述容器中。然后将所述容器用手涡旋以从所述容器的侧壁释放脂质物质和分散脂质聚集体，由此形成脂质体悬浮液。

[0332] 施用模式

[0333] 在本文描述的方面或实施方案中的任一个中，包含本文描述的化合物的治疗组合物可以是在被构造成通过任意合适途径递送的任意合适剂型中。例如，所述化合物可以通过任意适当途径施用，例如，口服地、胃肠外地、静脉内地、真皮内地、皮下地或局部地(topically)(包括透皮地)、以液体、乳膏剂、凝胶或固体形式、直肠地、鼻地、含服地、阴道地或经由植入的贮库或通过气雾剂形式。

[0334] 本文中使用的术语“胃肠外”包括皮下、静脉内、肌肉内、关节内、滑膜内、胸骨内、鞘内、肝内、病灶内和颅内注射或输注技术。优选地，口服地、腹膜内地或静脉内地施用所述组合物。

[0335] 可以通过口服、胃肠外或局部途径以单剂量或分份剂量施用如本文中所述的化合物。活性化合物的施用可以在从连续(静脉内滴注)至每天几次口服施用(例如，每天4次(Q.I.D.))的范围内，且可以包括口服、局部、胃肠外、肌肉内、静脉内、皮下、透皮(其可以包括穿透增强剂)、含服、舌下和栓剂施用，以及其它施用途径。包肠溶衣的口服片剂也可以用于增强来自口服施用途径的化合物的生物利用度。最有效的剂型将取决于选择的特定药剂的药代动力学以及患者中的疾病的严重程度。

[0336] 也可以使用化合物作为用于鼻内、气管内或肺施用的喷雾剂、薄雾或气雾剂的施用。可以以立即释放、中间释放或持续或受控释放形式施用如本文中所述的化合物。持续或受控释放形式优选地口服施用，但是也以栓剂和透皮或其它局部形式施用。脂质体形式的肌肉内注射剂也可以用于控制或支持化合物在注射部位处的释放。

[0337] 如本文中所述的组合物的无菌可注射形式可以是水性或油性悬浮液。这些悬浮液可以按照本领域已知的技术，使用合适的分散剂或润湿剂和助悬剂制备。所述无菌可注射制剂也可以是在无毒的胃肠外可接受的稀释剂或溶剂中的无菌可注射溶液或悬浮液，例如作为在1,3-丁二醇中的溶液。可用的可接受的载体和溶剂是水、林格氏液溶液和等渗氯化钠溶液。此外，无菌的不挥发性油通常被用作溶剂或悬浮介质。为此目的，可以采用任何温和的不挥发性油，包括合成的甘油单酯或甘油二酯。脂肪酸(诸如油酸和它的甘油酯衍生物)可用于制备注射剂，天然的药学上可接受的油(诸如橄榄油或蓖麻油)也是如此，特别是

其聚氧乙基化形式。这些油溶液或悬浮液还可以含有长链醇稀释剂或分散剂，诸如Ph.Helv或类似的醇。

[0338] 如本文中所述的药物组合物可以以任何口服可接受的剂型口服施用，所述剂型包括、但不限于，胶囊剂、片剂、水性悬浮液或溶液。在用于口服使用的片剂的情况下，常用的载体包括乳糖和玉米淀粉。通常也加入润滑剂，诸如硬脂酸镁。就胶囊形式的口服施用而言，有用的稀释剂包括乳糖和干燥的玉米淀粉。当口服使用需要水性悬浮液时，将活性成分与乳化剂和助悬剂组合。如果需要的话，还可以加入某些甜味剂、调味剂或着色剂。口服组合物通常包括惰性稀释剂或可食用的载体。它们可以包封在明胶胶囊中或压制成片剂。为了口服治疗施用的目的，可以给活性化合物或它的前药衍生物掺入赋形剂并以片剂、糖锭或胶囊剂的形式使用。包括药学上适合的粘合剂和/或辅料作为所述组合物的组成部分。

[0339] 片剂、丸剂、胶囊剂、锭剂等可含有任意下述成分或相似性质的化合物：粘合剂诸如微晶纤维素、黄蓍树胶或明胶；赋形剂诸如淀粉或乳糖，分散剂诸如海藻酸、Primogel或玉米淀粉；润滑剂诸如硬脂酸镁或Sterotes；助流剂诸如胶体二氧化硅(colloidal silicon dioxide)；甜味剂诸如蔗糖或糖精；或矫味剂诸如薄荷、水杨酸甲酯或橙味矫味剂。当剂量单元形式是胶囊时，除了上述类型的物质以外，它还可以含有液体载体诸如脂肪油。另外，剂量单元形式可以含有多种调节剂量单元的物理形式的其它物质，例如，糖、紫胶或肠溶药剂(enteric agent)的包衣。

[0340] 所述活性化合物或其药学上可接受的盐可以作为酏剂、悬浮液、糖浆剂、糯米纸囊剂、口香糖等的组分来施用。除了活性化合物以外，糖浆剂还可以含有作为甜味剂的蔗糖和某些防腐剂、染料和着色剂和矫味剂。

[0341] 可替换地，可以以用于直肠施用的栓剂的形式施用如本文中所述的药物组合物。这些可以如下制备：将所述药剂与合适的非刺激性的赋形剂混合，所述赋形剂在室温为固体，但是在直肠温度为液体且因此将在直肠中融化以释放药物。这样的材料包括可可脂、蜂蜡和聚乙二醇。

[0342] 也可以局部地施用本发明的药物组合物。针对这些区域或器官中的每一种，容易地制备合适的局部制剂。用于下肠道的局部应用可以在直肠栓剂制剂(参见上面)中或在合适的灌肠溶药剂制剂中实现。也可以使用局部地可接受的透皮贴剂。对于局部应用，可以在合适的软膏剂中配制药物组合物，所述软膏剂含有悬浮或溶解于一种或多种载体中的活性组分。用于本发明化合物的表面施用的载体包括、但不限于矿物油、液体矿脂、白矿脂、丙二醇、聚氧乙烯、聚氧丙烯化合物、乳化蜡和水。在本发明的某些优选方面，可以将化合物涂布在要通过外科手术植入患者中的支架上以便抑制或减小在患者的支架内发生阻塞的可能性。

[0343] 可替换地，可以在合适的洗剂或乳膏剂中配制药物组合物，所述洗剂或乳膏剂含有悬浮或溶解于一种或多种药学上可接受的载体中的活性组分。合适的载体包括、但不限于矿物油、脱水山梨糖醇单硬脂酸酯、聚山梨酯60、十六烷基酯蜡、鲸蜡硬脂醇、2-辛基十二醇、苯甲醇和水。

[0344] 对于眼科应用，可以将药物组合物配制为在等渗的、调过pH的无菌盐水中的微粉化的悬浮液，或，优选地，配制为在等渗的、调过pH的无菌盐水中的溶液，无论含有还是不含防腐剂诸如苯扎氯铵。可替换地，对于眼科应用，可以在软膏诸如矿脂中配制药物组合物。

[0345] 还可以通过鼻气雾剂或吸入来施用本发明的药物组合物。这样的组合物根据药物制剂领域众所周知的技术来制备，且可以采用苯甲醇或其它合适的防腐剂、吸收促进剂(以增强生物利用度)、碳氟化合物和/或其它常规增溶剂或分散剂制备为在盐水中的溶液。

[0346] 用于胃肠外、真皮内、皮下或局部应用的溶液或悬浮液可以包括下述组分：无菌稀释剂诸如注射用水、盐水溶液、不挥发性油、聚乙二醇、丙三醇、丙二醇或其它合成溶剂；抗细菌剂诸如苯甲醇或对羟基苯甲酸甲酯；抗氧化剂诸如抗坏血酸或亚硫酸氢钠；螯合剂诸如乙二胺四乙酸；缓冲剂诸如乙酸盐、柠檬酸盐或磷酸盐；以及用于调节张度的试剂，诸如氯化钠或葡萄糖。可以将胃肠外制品包封在玻璃或塑料制成的安瓿、一次性注射器或多次剂量小瓶中。

[0347] 还应当理解，针对任何特定患者的具体剂量和治疗方案将取决于多种因素，包括使用的具体化合物的活性、年龄、体重、一般健康、性别、饮食、施用时间、排泄速率、药物组合和治疗医师的判断以及正在治疗的特定疾病或病症的严重程度。

[0348] 可以如下治疗需要使用本文所述化合物的疗法的患者或受试者：给所述患者(受试者)施用有效量的化合物，包括其药学上可接受的盐、溶剂化物或多晶型物，其任选地在药学上可接受的载体或稀释剂中，无论是单独的，还是与其它已知的药剂组合。

[0349] 共同施用

[0350] 使用根据本说明书的化合物或组合物可以治疗的病症的疾病状态包括、但不限于，例如，癌症(例如，前列腺癌)和肯尼迪氏病。在某些实施方案中，所述治疗或药物组合物包含有效量的共同施用的另外的生物学上或生物活性的活性剂，例如，对于癌症的治疗有效的药剂。

[0351] 术语“共同施用”或“联合治疗”应当是指，将至少两种化合物或组合物同时施用给患者，使得有效量或浓度的所述两种或更多种化合物中的每一种可以在给定的时间点存在于患者中。尽管根据本发明的化合物可以同时共同施用给患者，该术语包括同时或在不同时间施用两种或更多种药剂，前提条件是，有效浓度的所有共同施用的化合物或组合物在给定的时间存在于受试者中。在本发明的某些优选方面，一种或多种上述的本发明化合物与至少一种另外的生物活性剂(具体地包括抗癌剂)联合地共同施用。在本发明的特别优选的方面，化合物的共同施用产生协同治疗，包括抗癌疗法。

[0352] 在另一个方面，本说明书提供了一种组合物，其包含有效量的两种或更多种如本文中所述的PROTAC化合物和药学上可接受的载体。在某些实施方案中，所述组合物还包含有效或协同量的另一种生物活性剂，其不是PROTAC化合物。

[0353] 包含有效量的至少一种根据本发明的双功能化合物与一种或多种本文另外描述的化合物(都在有效量)以及药学有效量的载体、添加剂或赋形剂的组合的药物组合物代表本发明的另一个方面。

[0354] 术语“生物活性剂”用于描述除了本文描述的PROTAC化合物以外的药剂，其与本发明化合物(作为具有生物活性的药剂)联合使用以辅助实现用于使用本发明化合物的预期治疗、抑制和/或阻止/预防。用于本文中的用途的优选生物活性剂包括其药理学活性与使用或施用的本发明化合物的活性类似的那些药剂，且包括例如抗癌剂。

[0355] 术语“另外的抗癌剂”用于描述可以与根据本说明书的PROTAC化合物组合以治疗癌症的抗癌剂。这些药剂包括，例如，依维莫司、曲贝替定、注射用紫杉醇(abraxane)、TLK

286、AV-299、DN-101、帕唑帕尼、GSK690693、RTA 744、ON 0910.Na、AZD 6244(ARRY-142886)、AMN-107、TKI-258、GSK461364、AZD 1152、恩扎妥林、凡他尼布、ARQ-197、MK-0457、MLN8054、PHA-739358、R-763、AT-9263、FLT-3抑制剂、雄激素受体抑制剂、VEGFR抑制剂、EGFR TK抑制剂、极光激酶抑制剂、PIK-1调节剂、Bcl-2抑制剂、HDAC抑制剂、c-MET抑制剂、PARP抑制剂、Cdk抑制剂、EGFR TK抑制剂、IGFR-TK抑制剂、抗-HGF抗体、PI3激酶抑制剂、AKT抑制剂、JAK/STAT抑制剂、检验点-1或2抑制剂、粘着斑激酶抑制剂、Map激酶激酶(mek)抑制剂、VEGF陷阱抗体、培美曲塞、厄洛替尼、达沙替尼、尼洛替尼、decatanib、帕木单抗、氨柔比星、奥戈伏单抗、Lep-etu、诺拉曲塞、azd2171、巴他布林、奥法木单抗、扎木单抗、艾特咔林、粉防己碱、卢比替康、替米利芬、奥利美生、替西木单抗、伊匹木单抗、棉酚、Bio 111、131-I-TM-601、ALT-110、BIO 140、CC 8490、西仑吉肽、吉马替康、IL13-PE38QQR、INO 1001、IPdR$_1$KRX-0402、硫蒽酮、LY317615、neuradiab、vitespan、Rta 744、Sdx 102、他仑帕奈、阿曲生坦、Xr 311、罗米地新、ADS-100380、舒尼替尼、5-氟尿嘧啶、伏林司他、依托泊苷、吉西他滨、多柔比星、脂质体多柔比星、5'-脱氧-5-氟尿苷、长春新碱、替莫唑胺、ZK-304709、塞利西利;PD0325901、AZD-6244、卡培他滨、L-谷氨酸、N-[4-[2-(2-氨基-4,7-二氢-4-氧代-1H-吡咯并[2,3-d]嘧啶-5-基)乙基]苯甲酰基]-,二钠盐,七水合物、喜树碱、PEG-标记的伊立替康、他莫昔芬、柠檬酸托瑞米芬、阿那曲唑、依西美坦、来曲唑、DES(己烯雌酚)、雌二醇、雌激素、缀合的雌激素、贝伐珠单抗、IMC-1C11、CHIR-258);3-[5-(甲基磺酰基哌啶甲基)-吲哚基]-喹诺酮、伐拉尼布、AG-013736、AVE-0005、[D-Ser(Bu t)6,Azgly 10]的乙酸盐(pyro-Glu-His-Trp-Ser-Tyr-D-Ser(But)-Leu-Arg-Pro-Azgly-NH_2乙酸盐[$C_{59}H_{84}N_{18}Oi_4$-($C_2H_4O_2$)$_x$,其中x=1-2.4]、乙酸戈舍瑞林、醋酸亮丙瑞林、双羟萘酸曲普瑞林、醋酸甲羟孕酮、己酸羟孕酮、乙酸甲地孕酮、雷洛昔芬、比卡鲁胺、氟他胺、尼鲁米特、乙酸甲地孕酮、CP-724714;TAK-165、HKI-272、厄洛替尼、拉帕替尼、卡纽替尼、ABX-EGF抗体、爱必妥、EKB-569、PKI-166、GW-572016、洛那法尼、BMS-214662、替匹法尼;氨磷汀、NVP-LAQ824、辛二酰苯胺异羟肟酸(suberoyl analide hydroxamic acid)、丙戊酸、曲古抑菌素A、FK-228、SU11248、索拉非尼、KRN951、氨鲁米特、arnsacrine、阿那格雷、L-天门冬酰胺酶、卡介苗(BCG)疫苗、阿霉素、博来霉素、布舍瑞林、白消安、卡铂、卡莫司汀、苯丁酸氮芥、顺铂、克拉屈滨、氯膦酸盐、环丙特龙、阿糖胞苷、达卡巴嗪、更生霉素、柔红霉素、己烯雌酚、表柔比星、氟达拉滨、氟氢可的松、氟甲睾酮、氟他胺、格列卫、吉西他滨、羟基脲、伊达比星、异环磷酰胺、伊马替尼、亮丙瑞林、左旋咪唑、洛莫司汀、氮芥、美法仑、6-巯基嘌呤、美司钠、甲氨蝶呤、丝裂霉素、米托坦、米托蒽醌、尼鲁米特、奥曲肽、奥沙利铂、帕米膦酸盐、喷司他丁、普卡霉素、卟菲尔钠、丙卡巴肼、雷替曲塞、利妥昔单抗、链佐星、替尼泊苷、睾酮、沙利度胺、硫鸟嘌呤、塞替派、维A酸、长春地辛、13-顺式-视黄酸、苯丙氨酸氮芥、尿嘧啶氮芥、雌莫司汀、六甲蜜胺、氟尿苷、5-脱氧尿苷、胞嘧啶阿糖胞苷、6-巯基嘌呤、脱氧考福霉素、骨化三醇、戊柔比星、普卡霉素、长春碱、长春瑞滨、托泊替康、雷佐生、马立马司他、COL-3、新伐司他、BMS-275291、角鲨胺、内皮他丁、SU5416、SU6668、EMD121974、白介素-12、IM862、血管生成抑制因子、vitaxin、屈洛昔芬、idoxyfene、螺内酯、非那雄胺、西咪替丁、曲妥珠单抗、地尼白介素2、吉非替尼、硼替佐米(bortezimib)、紫杉醇、无克列莫佛的紫杉醇、多西他赛、epithilone B、BMS-247550、BMS-310705、屈洛昔芬、4-羟基他莫昔芬、哌喷昔芬、ERA-923、阿佐昔芬、氟维司群、阿考比芬、拉索昔芬、艾多昔芬、TSE-424、HMR-3339、ZK186619、托泊替康、PTK787/ZK

222584、VX-745、PD 184352、雷帕霉素、40-O-(2-羟基乙基)-雷帕霉素、坦罗莫司、AP-23573、RAD001、ABT-578、BC-210、LY294002、LY292223、LY292696、LY293684、LY293646、渥曼青霉素、ZM336372、L-779,450、PEG-非格司亭、达依泊汀、促红细胞生成素、粒细胞集落刺激因子、唑来膦酸盐、泼尼松、西妥昔单抗、粒细胞巨噬细胞集落刺激因子、组氨瑞林、聚乙二醇化的干扰素α-2a、干扰素α-2a、聚乙二醇化的干扰素α-2b、干扰素α-2b、阿扎胞苷、PEG-L-天门冬酰胺酶、来那度胺、吉妥珠单抗、氢化可的松、白介素-11、右丙亚胺、阿仑珠单抗、全反式视黄酸、酮康唑、白介素-2、甲地孕酮、免疫球蛋白、氮芥、甲泼尼龙、替伊莫单抗、雄激素、地西他滨、六甲蜜胺、贝沙罗汀、托西莫单抗、三氧化二砷、可的松、editronate、米托坦、环孢菌素、脂质体柔红霉素、Edwina-天门冬酰胺酶、锶89、卡索匹坦、奈妥匹坦、NK-1受体拮抗剂、帕洛诺司琼、阿瑞匹坦、苯海拉明、羟嗪、甲氧氯普胺、劳拉西泮、阿普唑仑、氟哌啶醇、氟哌利多、屈大麻酚、地塞米松、甲泼尼龙、丙氯拉嗪、格拉司琼、昂丹司琼、多拉司琼、托烷司琼、培非司亭、促红细胞生成素、促红素α、达促红素α及其混合物。

[0356] 治疗方法

[0357] 在另一个方面,本公开内容提供了调节受试者(例如,细胞、组织、哺乳动物或人患者)中的蛋白泛素化和降解的方法,所述方法包括给受试者施用有效量的如本文中所述的PROTAC化合物或包含有效量的所述化合物的组合物,其中所述化合物或包含它们的组合物可有效地调节所述受试者中的蛋白的蛋白泛素化和降解。在某些实施方案中,所述蛋白是雄激素受体(AR)。

[0358] 在某些实施方案中,本说明书提供了一种用于调节有需要的患者中的雄激素受体的蛋白活性的方法,所述方法包括给所述患者施用一定量的如本文中所述的化合物。

[0359] 在另外的实施方案中,本说明书提供了一种治疗患者中的疾病状态或病症的方法,其中失调的蛋白活性引起所述疾病状态或病症,所述方法包括给所述患者施用有效量的如本文中所述的化合物以便调节所述患者中的所述蛋白活性。在某些实施方案中,所述蛋白是AR。

[0360] 本文中使用的术语“治疗”等表示给患者(可以给其施用本发明化合物)提供益处的任何动作,包括通过本发明化合物所结合的蛋白调节的任何疾病状态或病症的治疗。在上文中阐述了使用根据本发明的化合物可以治疗的疾病状态或病症,包括癌症。

[0361] 在另一个方面,本公开内容提供了调节受试者(例如,细胞、组织、哺乳动物或人患者)中的AR蛋白泛素化和降解的方法,所述方法包括给受试者施用有效量的如本文中所述的化合物或包含有效量的所述化合物的组合物,其中所述化合物或包含它们的组合物可有效地调节所述受试者中的蛋白的AR蛋白泛素化和降解。

[0362] 在另一个方面,本公开内容提供了治疗或改善受试者(例如,细胞、组织、哺乳动物或人患者)中与AR活性有关的疾病的症状的方法,所述方法包括给有此需要的受试者施用有效量的如本文中所述的化合物或包含有效量的所述化合物的组合物,其中所述化合物或包含它们的组合物可有效地治疗或改善所述受试者中与AR活性有关的疾病的症状。

[0363] 在另一个方面,本说明书提供了用于治疗受试者中的疾病或障碍的组合物,例如,治疗组合物,其包含药学上可接受的载体和有效量的至少一种如本文中所述的化合物,所述方法包括给有此需要的受试者施用所述组合物,其中所述化合物可有效地治疗或改善所述疾病或障碍的至少一种症状。在某些实施方案中,所述组合物包含至少一种来自表2-17

中的实施例的化合物。

[0364] 在另一个方面，本说明书提供了如本文中所述的化合物在药物的制备或生产中的用途，所述药物用于治疗受试者中的疾病或障碍。在某些实施方案中，所述药物包含有效量的如本文中所述的化合物和药学上可接受的载体。在另外的实施方案中，所述药物包含有效量的至少一种来自表2-17中的实施例的化合物。

[0365] 在某些实施方案中，所述疾病或障碍是哮喘、多发性硬化、癌症、前列腺癌、肯尼迪氏病、纤毛疾病、腭裂、糖尿病、心脏病、高血压、炎性肠病、精神发育迟滞、心境障碍、肥胖、屈光误差、不育、Angelman综合征、卡纳万病、腹腔病、夏-马-图三氏病、囊性纤维化、杜兴肌营养不良、血色病、血友病、克兰费尔特综合征、神经纤维瘤病、苯丙酮尿症、多囊性肾病、(PKD1)或4(PKD2)帕-魏二氏综合征、镰状细胞病、泰-萨克斯病、特纳综合征。根据权利要求48所述的方法，其中所述癌症是鳞状细胞癌、基底细胞癌、腺癌、肝细胞癌和肾细胞癌、膀胱癌、肠癌、乳腺癌、子宫颈癌、结肠癌、食管癌、头癌、肾癌、肝癌、肺癌、颈癌、卵巢癌、胰腺癌、前列腺癌和胃癌；白血病；良性和恶性淋巴瘤，特别是伯基特氏淋巴瘤和非霍奇金淋巴瘤；良性和恶性黑素瘤；骨髓增生性疾病；肉瘤，包括尤因肉瘤、血管肉瘤、卡波西氏肉瘤、脂肪肉瘤、肌肉瘤、周围神经上皮瘤、滑膜肉瘤、神经胶质瘤、星形细胞瘤、少突神经胶质瘤、室管膜瘤、成胶质细胞瘤、神经母细胞瘤、神经节瘤、神经节神经胶质瘤、髓母细胞瘤、松果体细胞肿瘤、脑膜瘤、脑膜肉瘤、神经纤维瘤和许旺细胞瘤；肠癌、乳腺癌、前列腺癌、宫颈癌、子宫癌、肺癌、卵巢癌、睾丸癌、甲状腺癌、星形细胞瘤、食管癌、胰腺癌、胃癌、肝癌、结肠癌、黑素瘤；癌肉瘤、霍奇金病、威尔曼瘤或畸胎癌。在某些实施方案中，要治疗的疾病是癌症，例如，前列腺癌或肯尼迪氏病。在一个优选的实施方案中，所述受试者是人。

[0366] 在另一个方面，本公开内容提供了治疗或改善受试者(例如，细胞、组织、哺乳动物或人患者)中与AR活性有关的疾病的症状的方法，所述方法包括给有此需要的受试者施用有效量的如本文中所述的化合物或包含有效量的所述化合物的组合物和有效或协同量的另一种生物活性剂，其中所述包含所述化合物的组合物可有效地治疗或改善所述受试者中与AR活性有关的疾病的症状。在某些实施方案中，要治疗的疾病是癌症，例如，前列腺癌或肯尼迪氏病。在一个优选的实施方案中，所述受试者是人。在某些另外的实施方案中，所述另外的生物活性剂是抗癌剂。

[0367] 在替代方面，本发明涉及通过降解蛋白或多肽(通过它来调节疾病状态或病症)来治疗疾病状态的方法，所述方法包括给所述患者或受试者施用有效量的至少一种如上所述的化合物，其任选地与另外的生物活性剂组合。通过施用有效量的至少一种本文描述的化合物，根据本发明的方法可以用于治疗大量疾病状态或病症，包括癌症。

[0368] 在另一个方面，本公开内容提供了使用根据本发明的化合物鉴别生物系统中的目标蛋白的降解的影响的方法。

[0369] 试剂盒

[0370] 在另一个方面，本说明书提供了试剂盒，其包含如本文中所述的化合物或组合物。所述试剂盒可以作为用于执行本发明的方法的单元来宣传、分配或销售。另外，本发明的试剂盒可以优选地含有描述合适使用的说明书。这样的试剂盒可以方便地用在例如临床场合中，以治疗表现出例如癌症或肯尼迪氏病的症状的患者。

实施例

[0371] 一般化学-分析和合成

[0372] 除非另外指出，否则所有材料/试剂都得自商业供应商且不经进一步纯化地使用。通过通过LC-MS和/或预包被了铝箔或用玻璃背衬的硅胶60F254(0.2mm)上的薄层色谱法(TLC)监测反应，并使用紫外线显影。使用ISCO CombiFiash RF 75PSI或具有RediSep正相硅胶柱的等同物进行快速色谱法(可替换地称作“ISCO色谱法”)。在具有1000μm或相当的厚度的Whatman LK6F Silica Gel 60A大小20×20cm平板上进行制备型TLC。

[0373] 用TMS或残余溶剂峰作为内部标准品，在室温在Bruker波谱仪上记录^{1}HNMR(300或400MHz)和^{13}CNMR(100.6MHz)波谱。以(δ)给出线位置或多重峰，以赫兹(Hz)为单位给出偶合常数(J)作为绝对值。在^{1}HNMR谱中的多重峰如下缩写：s(单峰)、d(双峰)、t(三重峰)、q(四重峰)、m(多重峰)、br或宽峰(宽峰)。

[0374] 在由MassLynx V4.1软件控制的、配备2545二元梯度模块(Binary Gradient Module)、2767样品管理器(Sample Manager)和2489UV/可见光检测器(UV/Visible Detector)的**Waters®** UV-指导的纯化系统(**Waters®** UV-Directed Purification System)上进行制备型HPLC纯化。使用下述柱完成所有纯化工作：Atlantis Prep T3 OBD柱、SunFire Prep C18 OBD柱和XBridge Prep Phenyl OBD柱。流动相是水(含有0.1％TFA或0.01％NH_4HCO_3)和乙腈；使用的所有试剂都是HPLC级。流速为30ml/min。柱以后，1:1000LC填料分流器允许将洗脱液的小部分转移进紫外检测器中。将电喷射源设定在3.0kV毛细管电压、30V锥电压、110℃源温度、350℃去溶剂化温度、600L/h去溶剂化气流和60L/h锥气流。对于分析仪，关于制备型调节方法，将倍增器设定在550。

[0375] 用以下流动相在Shimadzu LCMS-2020上收集分析型LC-MS数据：0.05％的TFA在乙腈中的溶液(A)和0.05％的TFA在HPLC级水中的溶液(B)；0.1％的FA在乙腈中的溶液(A)和0.1％的FA在HPLC级水中的溶液(B)；乙腈(A)和5mM碳酸氢铵在HPLC级水中的溶液(B)。

[0376] 配备LC-20AD或30AD泵、SPD-M20A PDA和Alltech 3300ELSD的Shimadzu LCMS-2020。对于2.0min、2.6min、3min、3.6min、5min或5.6min运行时间，所述系统使用下述条件。

[0377] 2.0分钟运行：Kinetex XB-C 18 100A柱，2.6μm，3.0×50mm。流速是1.5mL/min，运行时间是2.0min，且梯度特性是0.01min 10％A，1.10min 100％A，1.60min 100％A，1.70min 10％A，2.00min 10％A。

[0378] 2.6分钟运行：Shim-pack VP-ODS柱，2.2μm，3.0×50mm。流速是1.5mL/min，运行时间是2.6min，且梯度特性是0.01min 5％A，1.20min100％A，2.20min 100％A，2.30min 5％A，2.60min 5％A。

[0379] 3.0分钟运行：ACE UltraCore Super C18柱，2.5μm，3.0×50mm。流速是1.5mL/min，运行时间是3.0min，且梯度特性是0.01min 10％A，2.00min 95％A，2.60min 95％A，2.70min 10％A，3.00min 10％A。

[0380] 3.6分钟运行：Shim-pack VP-ODS柱，2.2μm，3.0×50mm。流速是1.5mL/min，运行时间是3.6min，且梯度特性是0.01min 5％A，2.20min100％A，3.20min 100％A，3.30min 5％A，3.60min 5％A。

[0381] 5.0分钟运行：ACE UltraCore Super C18柱，2.5μm，3.0×50mm。流速是1.5mL/

min,运行时间是5.0min,且梯度特性是0.01min 10%A,4.00min 60%A,4.70min 60%A,4.80min 10%A,5.00min 10%A。

[0382] 5.6分钟运行:Shim-pack VP-ODS柱,2.2μm,3.0×50mm。流速是1.5mL/min,运行时间是5.6min,且梯度特性是0.01min 5%A,3.00min50%A,5.00min 50%A,5.20min 5%A,5.60min 5%A

[0383] 可替换地,在Agilent infinity 1260 LC,Agilent 6230TOF质谱仪上收集分析型LC-MS数据。在45℃在Poroshell 120EC C18柱(50mm×3.0mm内径2.7μm填料直径)上进行分析。

[0384] 采用的溶剂是:

[0385] A=0.1%v/v的甲酸在水中的溶液。

[0386] B=0.1%v/v的甲酸在乙腈中的溶液。

[0387] 采用的梯度如下:

[0388] 表1.示例性的柱梯度.

[0389]

时间(分钟)	流速(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

[0390] 紫外检测是来自210nm至350nm的波长的平均信号,并使用正模式电喷射电离在质谱仪上记录质谱图。

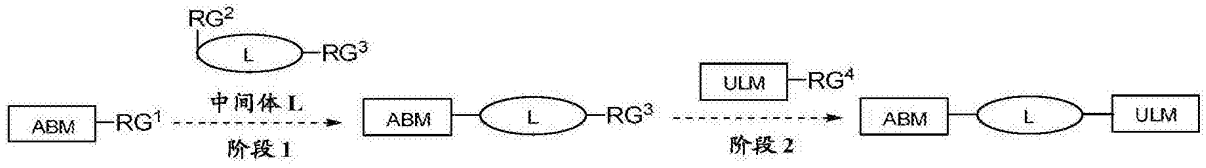
[0391] 除非另外指出,否则以>95%的LC-MS纯度制备所有化合物。

[0392] 化学合成

[0393] 通过下述的一般方案(方案3-4),以及有机化学领域已知的合成方法,或本领域普通技术人员熟悉的修饰和衍生化,可以制备ABM-L-ULM的PROTAC、或它们的药学上可接受的盐、多晶型形式、前药、溶剂化物形式及其含有同位素的衍生物。

[0394] 方案3:

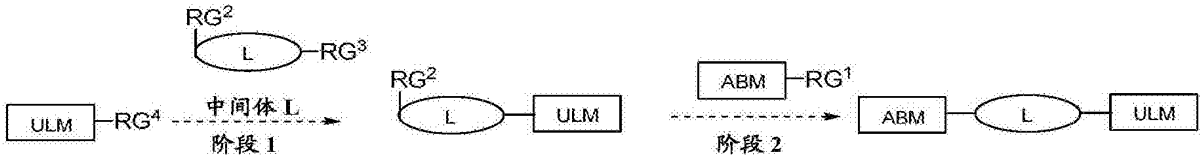
[0395]



方案 3

[0396] 方案4：

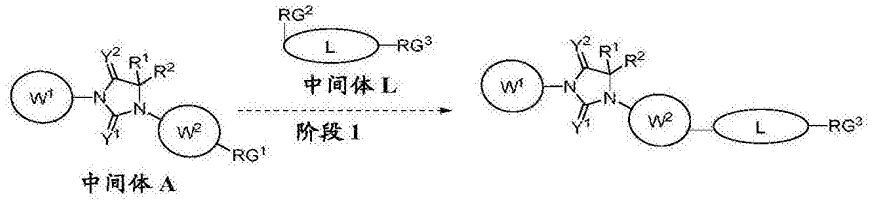
[0397]



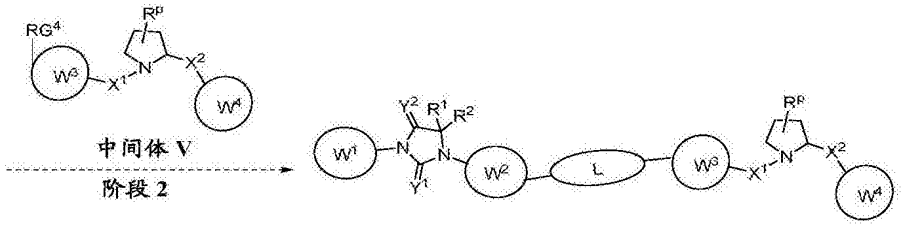
方案 4

[0398] 更具体地，通过下述的一般方案(方案5-6)，以及有机化学领域已知的合成方法，或本领域普通技术人员熟悉的修饰和衍生化，可以制备式I的化合物或它们的药学上可接受的盐。

[0399] 方案5：

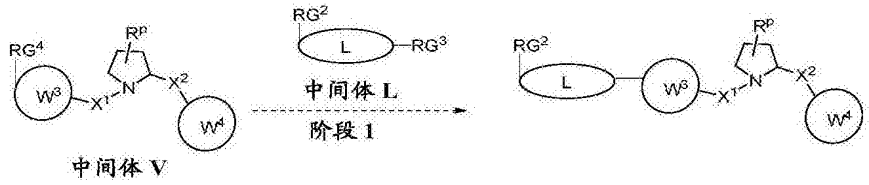


[0400]

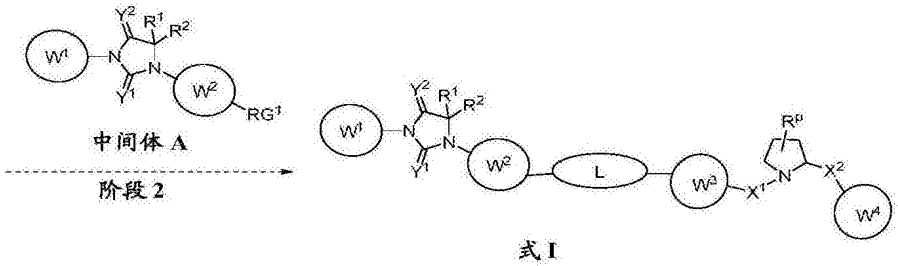


式 I

方案 5



[0401] 方案6：



式 I

方案 6

[0402] 在方案3-6中，L、ABM、ULM基团、W^1、W^2、W^3、W^4、X^1、X^2、Y^1、Y^2、R^1、R^2和R^P如上面所定义。RG^1、RG^2、RG^3和RG^4是具有合适的反应基团的部分，所述反应基团是实现合成化学以经由共价键形成化学将中间体A、中间体L和中间体V连接在一起成为式I的PROTAC化合物所必需的。这些化学取决于具体的反应基团，包括、但不限于，酰胺形成、酯形成、氨基甲酸酯形成、脲形成、醚形成、胺形成和各种C-C、C＝C键形成。方案5和方案6中的阶段1和阶段2转化可能涉及1个或多个合成步骤。这些是本领域已知的常规方法，诸如在标准参考书籍诸如Compendium of Organic Synthetic Methods，第I-VI卷(Wiley-lnterscience)；或Comprehensive Organic Transformations，R.C.Larock(Wiley-lnterscience)中公开的那些方法。除非另有说明，否则所述方案中的取代基如上面所定义。通过普通技术人员已知的标准程序完成产物的分离和纯化。

[0403] 在某些实施例中，对于在方案3-6中描述的化学，RG^1是具有合适亲核体诸如-OH的部分，且RG^2是具有合适离去基团诸如卤素、-OMs或-OTs的部分。在一个典型程序中，在合适的溶剂中使含有RG^1的中间体与含有RG^2的中间体反应。合适的溶剂包括、但不限于水、醚诸如THF、甘醇二甲醚(glyme)等；氯化的溶剂诸如DCM、1，2-二氯乙烷(DCE)或CHCI3等、甲苯、苯等、DMF、DMSO、MeCN。如果需要的话，使用这些溶剂的混合物。可以将碱加入反应物中以促进反应。合适的碱包括、但不限于Cs_2CO_3、K_2CO_3等。以上过程可以在约-78℃至约150℃之间的温度进行。优选地，所述反应在约20℃至约120℃之间进行。

[0404] 在另一个实施例中，对于在方案3-6中描述的化学，RG^3是含有-COOH基团的部分，且RG^4是含有合适胺基的部分。在一个典型的程序中，在有合适的酰胺偶联剂存在下在合适的溶剂中使含有RG^3的中间体与含有RG^4的中间体反应。合适的溶剂包括、但不限于水、醚诸如THF、甘醇二甲醚等；氯化的溶剂诸如DCM、1，2-二氯乙烷(DCE)或$CHCl_3$等、甲苯、苯等、DMF、DMSO、MeCN。如果需要的话，使用这些溶剂的混合物。在该情况下，优选的溶剂是DMF或DCM。合适的酰胺偶联剂包括、但不限于DCC、EDC、HATU、HBTU、PyBOP等。经常将碱加入反应物中。合适的碱包括、但不限于TEA、DIPEA等。以上过程可以在约-78℃至约150℃之间的温度进行。优选地，所述反应在约0℃至约100℃之间进行。

[0405] 尽管在方案3-6中没有明确地显示，普通技术人员会认识到，在任何合成顺序中，可能必须和/或需要保护涉及的任何分子上的敏感或反应基团。这可以借助于常规保护基实现，诸如在以下文献中描述的那些：T.W.Greene，Protective Groups in Organic Chemistry，John Wiley&Sons(1981)；T.W.Greene和P.G.M.Wuts，Protective Groups in Organic Chemistry，John Wiley&Sons(1991)，以及T.W.Greene和P.G.M.Wuts，Protective Groups in Organic Chemistry，John Wiley&Sons，1999，它们特此通过引用整体并入。

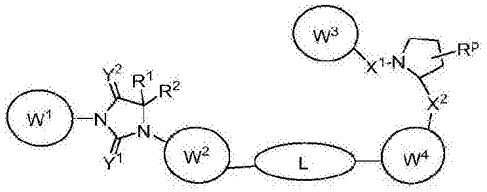
[0406] 当提及一般性的或示例性的合成程序时，本领域技术人员可以容易地确定适当的试剂，如果没有指出的话，从一般性的或示例性的程序推断。一些一般程序作为用于制备具体化合物的实施例给出。本领域技术人员可以容易地使这样的程序适应其它化合物的合成。在一般程序中显示或提及的结构中的未被取代的位置的表示是为了方便，且不排除如本文别处所述的取代。对于可以存在的具体基团，要么作为一般程序中的R基团，要么作为未显示的任选取代基，参考在本文件的其它部分(包括权利要求、发明内容和详细描述)中的描述。

[0407] 生产本发明的化合物的方法优选地在约大气压进行，尽管如果需要的话可以使用

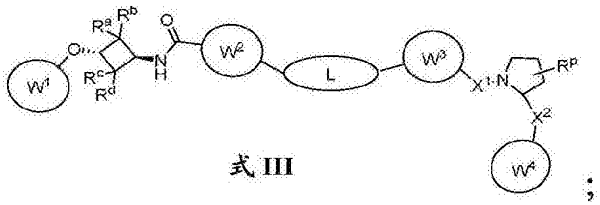
更高或更低的压力。优选地使用基本上等摩尔量的反应物，尽管还可以使用更高或更低的量。

[0408] 通过与上面关于式I的化合物的合成所示的化学法(方案3-6)类似的方法，以及有机化学领域已知的合成方法，或本领域普通技术人员熟悉的修饰和衍生化，可以制备式II-IV(下面)的化合物或它们的药学上可接受的盐：

[0409]

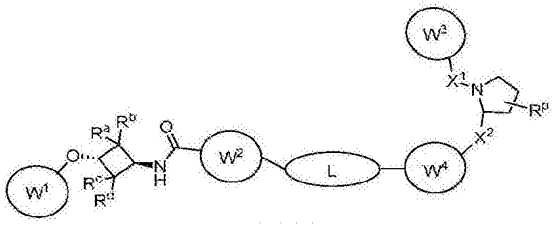


式II ；



式III ；

和



式IV 。

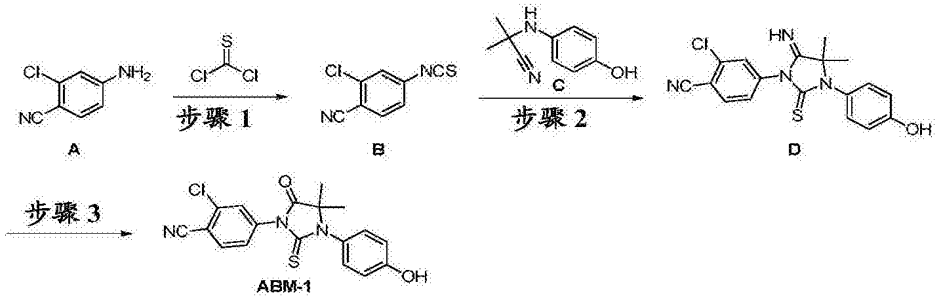
[0410] 对于式II-IV的化合物，L、ABM、ULM基团、W^1、W^2、W^3、W^4、X^1、X^2、Y^1、Y^2、R^1、R^2、R^P、R^a、R^b、R^c和R^d如上面所定义。

[0411] 在某些实施方案中，ABM化合物是有活性的，不形成式II-IV的双功能化合物。

[0412] ABM部分的合成

[0413] ABM-1：2-氯-4-(3-(4-羟基苯基)-4,4-二甲基-5-氧代-2-硫代(thioxo)咪唑烷-1-基)苄腈

[0414]



[0415] 步骤1：2-氯-4-异硫氰酰基苄腈(B)的合成.

[0416] 向4-氨基-2-氯苄腈(A,1g,6.55mmol)在二氯甲烷(9mL)中的搅拌溶液中加入碳酸氢钠(2.21g,26.31mmol)和水(9mL)。将得到的混合物冷却至0℃，在0℃在30min中向其中逐滴加入硫光气(817mg,7.11mmol)。然后将得到的混合物温热至室温并在室温搅拌1h。将反应混合物用二氯甲烷(200mL)稀释，用盐水(50mL×2)洗涤，经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物。将残余物通过快速硅胶色谱法(洗脱液：乙酸乙酯/石油醚(v:v=1:30))纯化以得到期望产物(收率：71%)^{1}HNMR(400MHz,$CDCl_3$)：δ7.69(d,J=8.0Hz,1H)，

7.38(s,1H),7.28(m,1H)；

[0417] 步骤2:2-氯-4-[3-(4-羟基苯基)-5-亚氨基-4,4-二甲基-2-亚硫烷基(sulfanylidene)咪唑烷-1-基]苄腈(D)的合成.

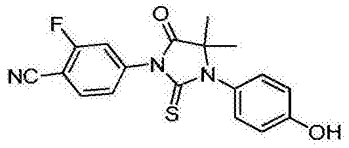
[0418] 向2-氯-4-异硫氰酰基苄腈(B,399mg,2.05mmol)在甲苯(5mL)中的搅拌溶液中加入2-[(4-羟基苯基)氨基]-2-甲基丙烷腈(C,300mg,1.70mmol)和4-二甲基氨基吡啶(312mg,2.55mmol)。然后将得到的溶液在油浴中加热至100℃并在相同温度搅拌16h。LC-MS指示期望产物的形成。将反应混合物在真空下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:1))纯化以得到作为棕色固体的期望产物(收率:48%)。LC-MS(ES^+):m/z 370.95[MH^+],t_R=0.74min(2.0分钟运行)；

[0419] 步骤3:2-氯-4-[3-(4-羟基苯基)-4,4-二甲基-5-氧代-2-亚硫烷基咪唑烷-1-基]苄腈(ABM-1)的合成.

[0420] 向2-氯-4-[3-(4-羟基苯基)-5-亚氨基-4,4-二甲基-2-亚硫烷基咪唑烷-1-基]苄腈(D,300mg,0.81mmol)在甲醇(6mL)中的搅拌溶液中加入氯化氢水溶液(2N,3.0mL)。然后将得到的溶液在油浴中加热至100℃并在相同温度搅拌2h。将反应混合物用水(30mL)稀释,用乙酸乙酯(60mL×3)萃取,用水(50mL)洗涤,经无水硫酸钠干燥并在真空下浓缩以得到作为黄色固体的标题产物(收率:93%),将其不经任何进一步纯化用于下一步。LC-MS(ES^+):m/z 372.00[MH^+],t_R=0.97min(2.0分钟运行)。

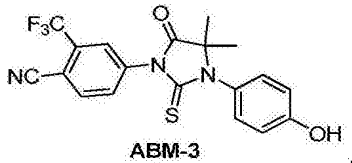
[0421] 除非另外指出,否则根据上面关于ABM-1的合成描述的类似程序利用对应的起始原料和试剂合成下述中间体和它们的类似物(例如、但不限于,具有取代诸如卤素的类似物)。

[0422] ABM-2:2-氟-4-(3-(4-羟基苯基)-4,4-二甲基-5-氧代-2-硫代咪唑烷-1-基)苄腈:

[0423] 

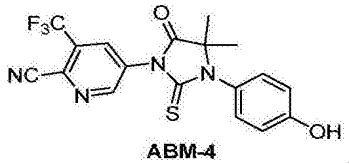
ABM-2。

[0424] ABM-3:4-(3-(4-羟基苯基)-4,4-二甲基-5-氧代-2-硫代咪唑烷-1-基)-2-(三氟甲基)苄腈:

[0425] 

ABM-3。

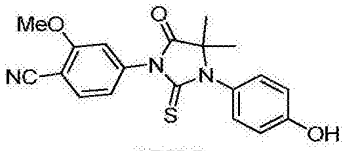
[0426] ABM-4:5-(3-(4-羟基苯基)-4,4-二甲基-5-氧代-2-硫代咪唑烷-1-基)-3-(三氟甲基)吡啶腈(picolinonitrile):

[0427] 

ABM-4。

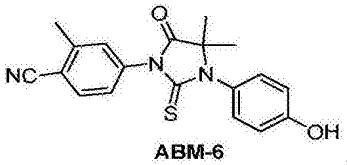
[0428] ABM-5:4-(3-(4-羟基苯基)-4,4-二甲基-5-氧代-2-硫代咪唑烷-1-基)-2-甲氧基

苄腈：

[0429] 

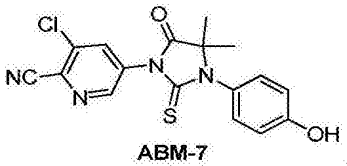
ABM-5。

[0430] ABM-6:4-(3-(4-羟基苯基)-4,4-二甲基-5-氧代-2-硫代咪唑烷-1-基)-2-甲基苄腈：

[0431] 

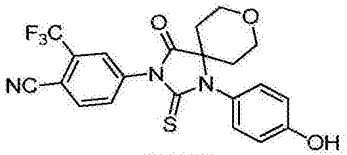
ABM-6。

[0432] ABM-7:3-氯-5-(3-(4-羟基苯基)-4,4-二甲基-5-氧代-2-硫代咪唑烷-1-基)吡啶腈：

[0433] 

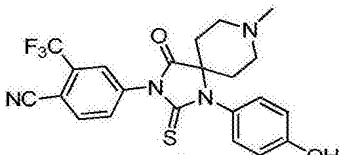
ABM-7。

[0434] ABM-8:4-(1-(4-羟基苯基)-4-氧代-2-硫代-8-氧杂-1,3-二氮杂螺[4.5]癸烷-3-基)-2-(三氟甲基)苄腈：

[0435] 

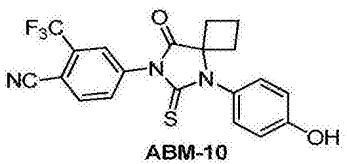
ABM-8。

[0436] ABM-9:4-(1-(4-羟基苯基)-8-甲基-4-氧代-2-硫代-1,3,8-三氮杂螺[4.5]癸烷-3-基)-2-(三氟甲基)苄腈：

[0437] 

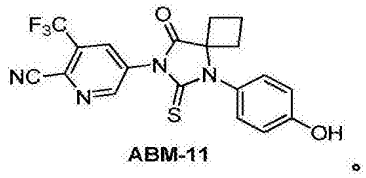
ABM-9。

[0438] ABM-10:4-(5-(4-羟基苯基)-8-氧代-6-硫代-5,7-二氮杂螺[3.4]辛烷-7-基)-2-(三氟甲基)苄腈

[0439] 

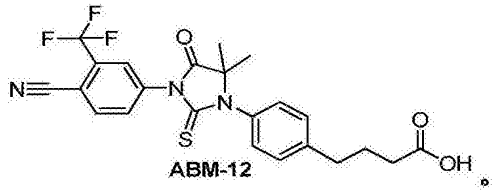
ABM-10。

[0440] ABM-11:5-(5-(4-羟基苯基)-8-氧代-6-硫代-5,7-二氮杂螺[3.4]辛烷-7-基)-3-(三氟甲基)吡啶腈：

[0441] 

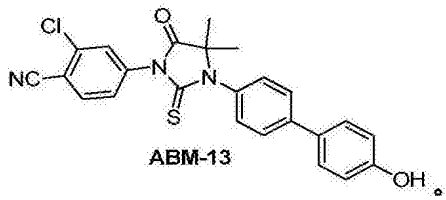
ABM-11。

[0442] ABM-12:4-(4-(3-(4-氰基-3-(三氟甲基)苯基)-5,5-二甲基-4-氧代-2-硫代咪唑烷-1-基)苯基)丁酸:

[0443] 

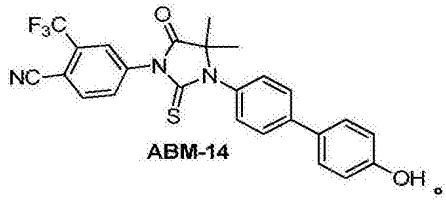
ABM-12。

[0444] ABM-13:2-氯-4-(3-(4'-羟基联苯-4-基)-4,4-二甲基-5-氧代-2-硫代咪唑烷-1-基)苄腈:

[0445] 

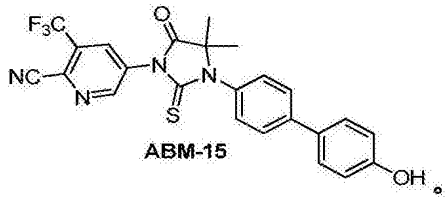
ABM-13。

[0446] ABM-14:4-(3-(4'-羟基联苯-4-基)-4,4-二甲基-5-氧代-2-硫代咪唑烷-1-基)-2-(三氟甲基)苄腈:

[0447] 

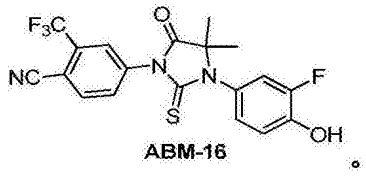
ABM-14。

[0448] ABM-15:5-(3-(4'-羟基联苯-4-基)-4,4-二甲基-5-氧代-2-硫代咪唑烷-1-基)-3-(三氟甲基)吡啶腈:

[0449] 

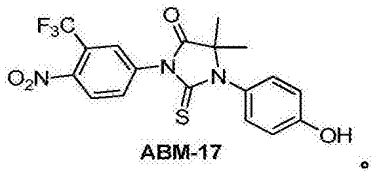
ABM-15。

[0450] ABM-16:4-(3-(3-氟-4-羟基苯基)-4,4-二甲基-5-氧代-2-硫代咪唑烷-1-基)-2-(三氟甲基)苄腈:

[0451] 

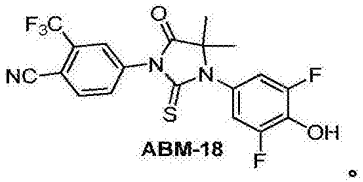
ABM-16。

[0452] ABM-17:1-(4-羟基苯基)-5,5-二甲基-3-(4-硝基-3-(三氟甲基)苯基)-2-硫代咪唑烷-4-酮:

[0453] 

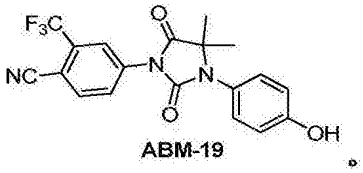
ABM-17。

[0454] ABM-18:4-(3-(3,5-二氟-4-羟基苯基)-4,4-二甲基-5-氧代-2-硫代咪唑烷-1-基)-2-(三氟甲基)苄腈:

[0455] 

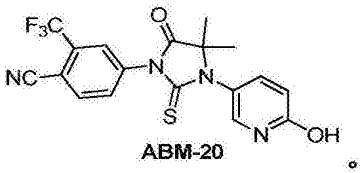
ABM-18。

[0456] ABM-19:4-(3-(4-羟基苯基)-4,4-二甲基-2,5-二氧代咪唑烷-1-基)-2-(三氟甲基)苄腈:

[0457] 

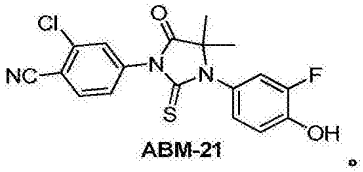
ABM-19。

[0458] ABM-20:4-(3-(6-羟基吡啶-3-基)-4,4-二甲基-5-氧代-2-硫代咪唑烷-1-基)-2-(三氟甲基)苄腈:

[0459] 

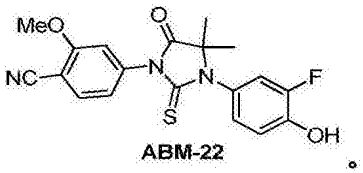
ABM-20。

[0460] ABM-21:2-氯-4-(3-(3-氟-4-羟基苯基)-4,4-二甲基-5-氧代-2-硫代咪唑烷-1-基)苄腈:

[0461] 

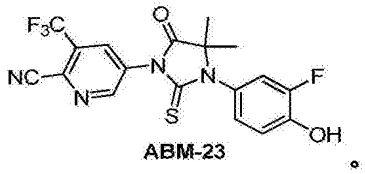
ABM-21。

[0462] ABM-22:4-(3-(3-氟-4-羟基苯基)-4,4-二甲基-5-氧代-2-硫代咪唑烷-1-基)-2-甲氧基苄腈:

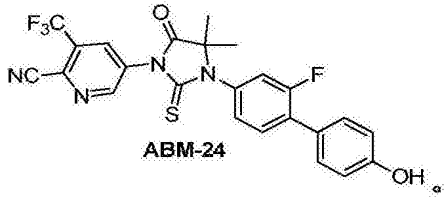
[0463] 

ABM-22。

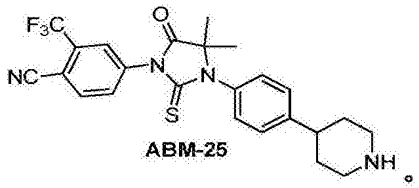
[0464] ABM-23:5-(3-(3-氟-4-羟基苯基)-4,4-二甲基-5-氧代-2-硫代咪唑烷-1-基)-3-(三氟甲基)吡啶腈:

[0465] 

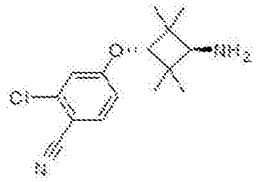
[0466] ABM-24:5-(3-(2-氟-4'-羟基联苯-4-基)-4,4-二甲基-5-氧代-2-硫代咪唑烷-1-基)-3-(三氟甲基)吡啶腈:

[0467] 

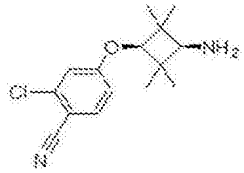
[0468] ABM-25:4-(4,4-二甲基-5-氧代-3-(4-(哌啶-4-基)苯基)-2-硫代咪唑烷-1-基)-2-(三氟甲基)苄腈:

[0469] 

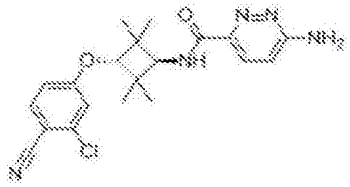
[0470] ABM-26:反式-2-氯-4-[3-氨基-2,2,4,4-四甲基环丁氧基]苄腈。

[0471] 

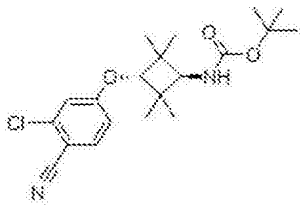
[0472] ABM-27:顺式-2-氯-4-[3-氨基-2,2,4,4-四甲基环丁氧基]苄腈

[0473] 

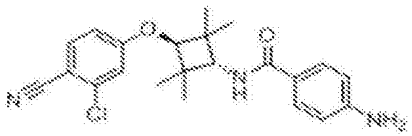
[0474] ABM-28:反式6-氨基-N-[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]哒嗪-3-甲酰胺

[0475] 

[0476] ABM-29:反式N-[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酸叔丁酯

[0477] 

[0478] ABM-30:反式4-氨基-N-[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]苯甲酰胺

[0479] 

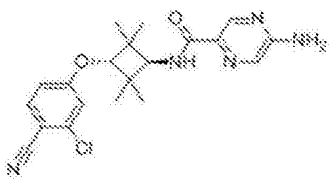
[0480] 步骤1:(4-((反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基)氨基甲酰基)苯基)氨基甲酸叔丁酯的合成.

[0481] 给4-((叔丁氧基羰基)氨基)苯甲酸(1.50g,6.34mmol)在二氯甲烷(40mL)中的悬浮液加入N,N-二异丙基乙胺(3.30mL,19.0mmol),随后加入4-(反式-3-氨基-2,2,4,4-四甲基环丁氧基)-2-氯苄腈盐酸盐(2.0g,6.34mmol)。将混合物搅拌几分钟,并然后加入HATU(2.41g,6.34mmol)。将反应混合物在室温搅拌2h。将混合物用二氯甲烷(40mL)稀释,用1N HCl水溶液(2×)、饱和碳酸氢钠水溶液(2×)、盐水洗涤,并经无水Na_2SO_4干燥。将粗产物用在下一步中;

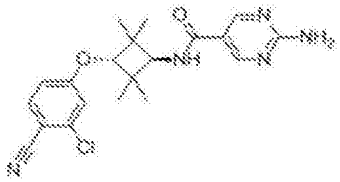
[0482] 步骤2:反式4-氨基-N-[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]苯甲酰胺的合成.

[0483] 将4M HCl在二噁烷中的溶液(1.38mL,40.0mmol)加入(4-((反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基)氨基甲酰基)苯基)氨基甲酸叔丁酯(2.00g,4.01mmol)在MeOH(2mL)中的预混合溶液中,并在室温搅拌1h直到结束。将反应混合物在真空中浓缩成固体,将其用5%的MeOH在DCM中的溶液溶解。将有机层用碳酸氢钠(2×)洗涤,穿过Biotage Universal分相器过滤,并然后在真空中浓缩成固体。将粗产物从EtOH/庚烷类重结晶以得到作为白色固体的期望产物,1.2g,75%收率。^{1}H NMR(400MHz,甲醇-d4)δ7.72(d,J=8.80Hz,1H),7.61(d,J=8.61Hz,2H),7.13(d,J=2.35Hz,1H),6.98(dd,J=2.45,8.71Hz,1H),6.69(d,J=8.61Hz,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^+]。

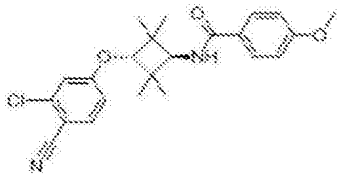
[0484] ABM-31:反式5-氨基-N-[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]吡嗪-2-甲酰胺

[0485] 

[0486] ABM-32:反式2-氨基-N-[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]嘧啶-5-甲酰胺

[0487] 

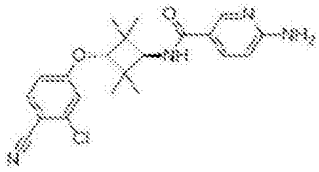
[0488] ABM-33:4-甲氧基-N-[(1r,3r)-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]苯甲酰胺

[0489] 

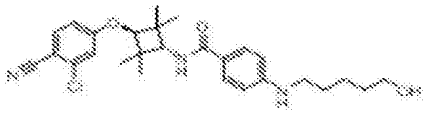
[0490] ABM-34:反式1-(2-羟基乙基)-N-[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]-1H-吡唑-4-甲酰胺

[0491] 

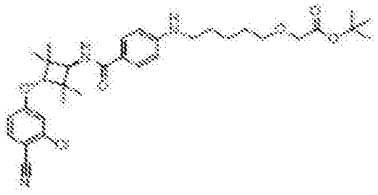
[0492] ABM-35:反式6-氨基-N-[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]吡啶-3-甲酰胺

[0493] 

[0494] ABM-36:反式4-[(5-羟基戊基)氨基]-N-[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]苯甲酰胺

[0495] 

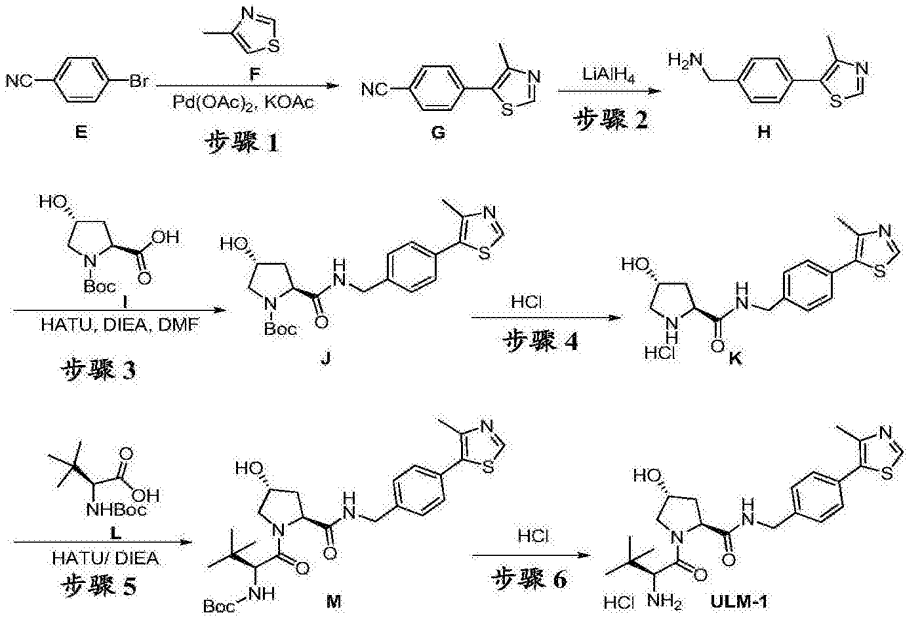
[0496] ABM-37:反式2-({5-[(4-{[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯基)氨基戊基}氧基)乙酸叔丁酯

[0497] 

[0498] ULM部分的合成

[0499] ULM-1:(2S,4R)-1-((S)-2-氨基-3,3-二甲基丁酰基)-4-羟基-N-(4-(4-甲基噻唑-5-基)苄基)吡咯烷-2-甲酰胺

[0500]



[0501] 步骤1:4-(4-甲基-1,3-噻唑-5-基)苄腈(G)的合成

[0502] 在室温在氮气氛下向4-溴苄腈(E,20g,109.88mmol)在DMA(250mL)中的搅拌溶液中加入4-甲基-1,3-噻唑(F,21.88g,220.67mmol)、乙酸钯(II)(743mg,3.31mmol)和乙酸钾(21.66g,220.71mmol)。将得到的溶液加热至150℃并在该温度搅拌5h,LC-MS指示期望产物的形成。将反应物冷却至室温,用1L水稀释,并用乙酸乙酯(300mL×3)萃取。将有机层合并,用饱和氯化钠水溶液(200mL)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚,v:v=1:5)纯化以得到作为白色固体的G(收率:91%)。

[0503] 步骤2:[4-(4-甲基-1,3-噻唑-5-基)苯基]甲胺(H)的合成

[0504] 在0℃在氮气氛下在10min中向4-(4-甲基-1,3-噻唑-5-基)苄腈(G,35.0g,174.8mmol)在四氢呋喃(1000mL)中的搅拌溶液中逐份加入$LiAlH_4$(20.0g,526.3mmol)。然后将得到的溶液在60℃搅拌3h。LC-MS指示期望产物的形成。然后将反应物冷却至0℃,通过加入水(20mL,缓慢地加入)、NaOH水溶液(15%,20mL)和水(60mL)进行猝灭。然后将得到的混合物用乙酸乙酯(300mL×2)萃取。将有机层合并,用饱和氯化钠水溶液(100mL)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:二氯甲烷/甲醇(v:v=10:1))纯化以得到作为黄色油的H(收率:56%)。

[0505] 步骤1:(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-甲酸叔丁酯(J)的合成

[0506] 在室温向(2S,4R)-1-[(叔丁氧基)羰基]-4-羟基吡咯烷-2-甲酸(I,2.7g,11.7mmol)在N,N-二甲基甲酰胺(20mL)中的搅拌溶液中加入DIEA(2.52g,19.50mmol)、HATU(4.47g,11.76mmol)和[4-(4-甲基-1,3-噻唑-5-基)苯基]甲胺(H,2.0g,9.79mmol)。将得到的混合物在室温搅拌过夜,LC-MS指示期望产物的形成。将反应混合物用水(20mL)稀释,并用乙酸乙酯(50mL×3)萃取。将有机层合并,用饱和氯化钠水溶液(50mL)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:二氯甲烷/甲醇(v:v=20:1))纯化以得到作为黄色固体的J(收率:56%)。

[0507] 步骤2：(2S,4R)-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺盐酸盐(K)的合成

[0508] 向(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-甲酸叔丁酯(J,45g,107.78mmol)的搅拌溶液中加入氯化氢在二噁烷中的溶液(4N,300mL)。将得到的溶液在20℃搅拌2h。将固体通过过滤进行收集以得到作为黄色固体的K(收率：98％)，将其不经任何进一步纯化用于下一步。

[0509] 步骤3：N-[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酸叔丁酯(M)的合成

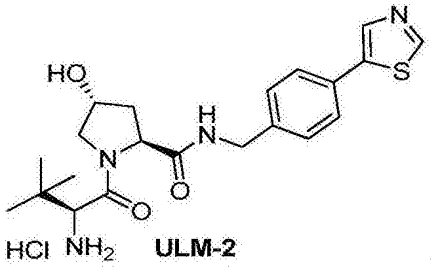
[0510] 在室温向(2S)-2-{[(叔丁氧基)羰基]氨基}-3,3-二甲基丁酸(L,15.7g,68.0mmol)在N,N-二甲基甲酰胺(500mL)中的搅拌溶液中加入DIEA(29.2g,225.9mmol)、HATU(25.9g,68.1mmol)和(2S,4R)-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺盐酸盐(K,20.0g,56.5mmol)。

[0511] 将得到的溶液在室温搅拌16h，LC-MS指示期望产物的形成。将反应混合物用水(200mL)稀释，并用乙酸乙酯(200mL×3)萃取。将有机层合并，用饱和氯化钠水溶液(50mL×2)洗涤，经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物，将其通过快速硅胶色谱法(洗脱液：乙酸乙酯/石油醚(v:v=2:1))纯化以得到作为黄色固体的M(收率：51％)。

[0512] 步骤4：(2S,4R)-1-[(2S)-2-氨基-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺盐酸盐(ULM-1)的合成

[0513] 在室温向N-[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酸叔丁酯(M,12g,22.61mmol)在二噁烷(20mL)中的搅拌溶液中加入氯化氢在二噁烷中的溶液(4N,80mL)。将得到的溶液在室温搅拌2h，LC-MS指示期望产物的形成。将沉淀的固体通过过滤进行收集以得到作为黄色固体的ULM-1(收率：48％)。^{1}HNMR(400MHz,CD_3OD)：δ9.84-9.82(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=0.73min(2.0分钟运行)。

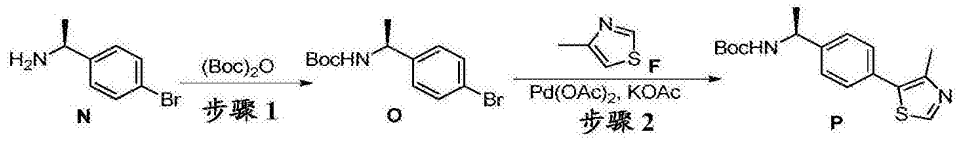
[0514] ULM-2：(2S,4R)-1-((S)-2-氨基-3,3-二甲基丁酰基)-4-羟基-N-(4-(噻唑-5-基)苄基)吡咯烷-2-甲酰胺：

[0515] 

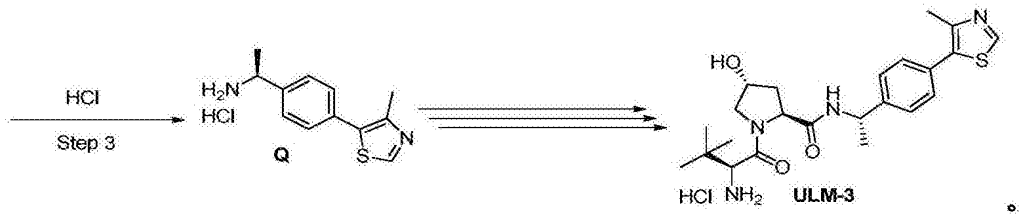
。

[0516] 根据上面关于ULM-1的合成描述的类似程序利用4-溴苄腈和1,3-噻唑作为起始原料合成ULM-2。LC-MS(ES^+)：m/z 417.10[MH^+]，t_R=0.51min(2.0分钟运行)。

[0517] ULM-3：(2S,4R)-1-((S)-2-氨基-3,3-二甲基丁酰基)-4-羟基-N-((S)-1-(4-(4-甲基噻唑-5-基)苯基)乙基)吡咯烷-2-甲酰胺：



[0518]



[0519] 步骤1:N-[(1S)-1-(4-溴苯基)乙基]氨基甲酸叔丁酯(O)的合成

[0520] 向(1S)-1-(4-溴苯基)乙烷-1-胺(N,10.0g,49.98mmol)在二氯甲烷(100mL)中的搅拌混合物中加入Et_3N(10.0g,99.01mmol)和$(Boc)_2O$(13.0g,59.63mmol)。将得到的混合物在室温搅拌2h。然后将大部分(bulk)溶剂在减压下除去以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚,v:v=1:10)纯化以得到作为白色固体的O(收率:99%)。

[0521] 步骤2:N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]氨基甲酸叔丁酯(P)的合成

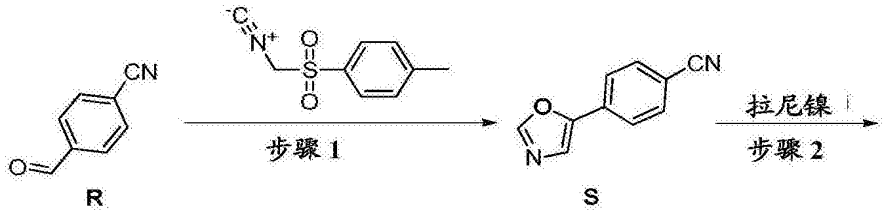
[0522] 在室温在氮气氛下向N-[(1S)-1-(4-溴苯基)乙基]氨基甲酸叔丁酯(O,15.0g,49.97mmol)在DMA(100mL)中的搅拌溶液中加入4-甲基-1,3-噻唑(9.9g,99.84mmol)、乙酸钾(9.8g,99.86mmol)和$Pd(OAc)_2$(112.5mg,0.50mmol)。然后将得到的混合物在120℃搅拌2h。然后将反应混合物冷却至室温,用水(120mL)稀释,并用乙酸乙酯(200mL×3)萃取。将有机层合并,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚,v:v=1:5)纯化以得到作为白色固体的P(收率:47%)。LC-MS(ES^+):m/z 319.13[MH^+],t_R=0.97min(2.0分钟运行)。

[0523] 步骤3.(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙烷-1-胺盐酸盐(Q)的合成

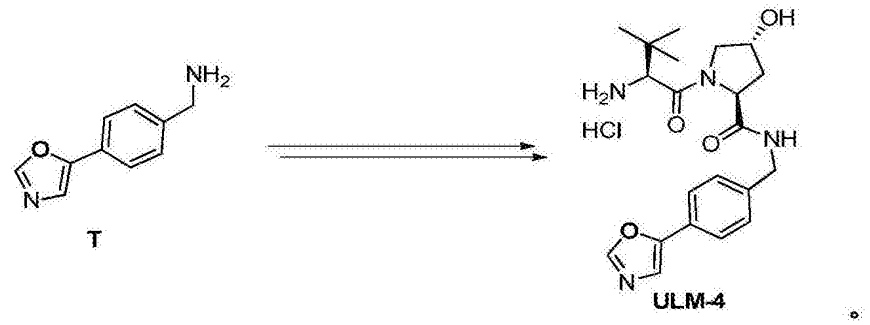
[0524] 在室温用氯化氢(气体)向N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]氨基甲酸叔丁酯(P,7.5g,23.55mmol)在甲醇(20mL)中的搅拌溶液中鼓泡2h。然后将得到的混合物在真空下浓缩以得到作为白色固体的Q(收率:86%),将其不经任何进一步纯化用于下一步。

[0525] 以关于H向ULM-1的转化所述类似的方式,将中间体Q转化成ULM-3。^1H NMR(300MHz,DMSO):δ8.99(s,1H),8.57-8.55(d,J=7.8Hz,1H),8.01(br.s,3H),7.46-7.43(d,J=8.4Hz,2H),7.39-7.37(d,J=8.4Hz,2H),4.98-4.90(m,1H),4.57-4.51(m,1H),4.34(br.s,1H),3.94-3.92(m,1H),3.69-3.66(m,1H),3.53-3.49(m,1H),2.52(s,3H),2.10-2.07(m,1H),1.83-1.81(m,1H),1.40-1.30(m,3H),1.03(s,9H)。LC-MS(ES^+):m/z 445.05[MH^+],t_R=0.53min(2.0分钟运行)。

[0526] ULM-4:(2S,4R)-1-((S)-2-氨基-3,3-二甲基丁酰基)-4-羟基-N-(4-(噁唑-5-基)苄基)吡咯烷-2-甲酰胺盐酸盐:



[0527]



[0528] 步骤1:1.4-(1,3-噁唑-5-基)苄腈(S)的合成

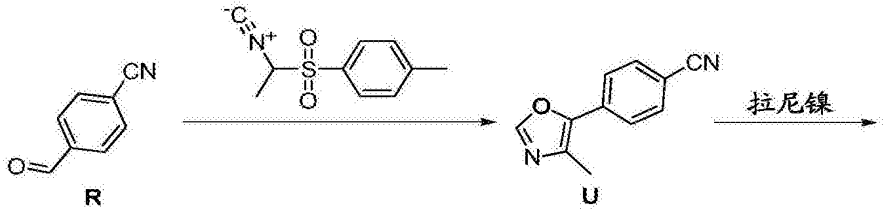
[0529] 向4-甲酰基苄腈(R,1.0g,7.63mmol)在甲醇(40mL)中的搅拌溶液中加入[[(4-甲基苯)磺酰基]甲基](亚甲基鎓(methyliumylidyne))azanuide(1.6g,8.40mmol)和碳酸钾(1.4g,9.91mmol),将得到的混合物在室温搅拌1.5h。然后将大部分溶剂在减压下除去。将残余物用饱和碳酸氢钠水溶液(20mL)稀释并用二氯甲烷(30mL×3)萃取。将有机层合并,用盐水(30mL)洗涤,经无水硫酸钠干燥并在真空下浓缩以得到粗产物,将其使用二氯甲烷和己烷通过重结晶纯化以得到作为白色固体的S(1.0g)。^{1}H NMR(400MHz,DMSO)δ8.56(s,1H),7.97-7.83(m,5H);LC-MS(ES^+):m/z 170.95[MH^+],t_R=0.79min(2.0分钟运行)。

[0530] 步骤2.[4-(1,3-噁唑-5-基)苯基]甲胺(T)的合成

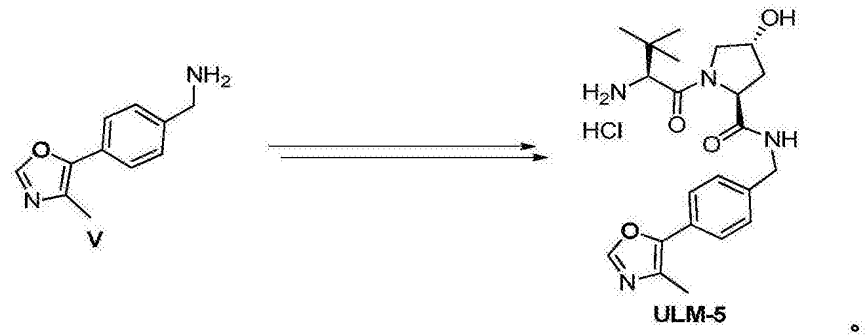
[0531] 向4-(1,3-噁唑-5-基)苄腈(S,900.0mg,5.29mmol)在甲醇(15mL)中的搅拌溶液中加入拉尼镍(900mg)和氢氧化铵水溶液(3.0mL)。然后经由气囊将氢气引入反应混合物中。将得到的混合物在室温搅拌16h。然后将固体通过过滤除去并将溶液在真空下浓缩以得到作为棕色油的T(收率:81%),将其不经任何进一步纯化用于下一步。LC-MS(ES^+):m/z175.90[MH^+],t_R=0.26min(2.0分钟运行)。

[0532] 以关于H向ULM-1的转化所述类似的方式将中间体T转化成ULM-4。LC-MS(ES^+):m/z 400.96[MH^+],t_R=0.66min(2.0分钟运行)。

[0533] ULM-5:(2S,4R)-1-((S)-2-氨基-3,3-二甲基丁酰基)-4-羟基-N-(4-(4-甲基噁唑-5-基)苄基)吡咯烷-2-甲酰胺:



[0534]

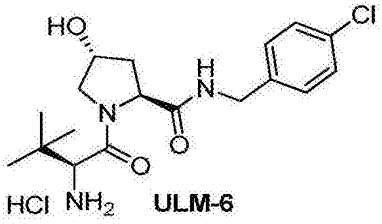


[0535] 根据上面关于[4-(1,3-噁唑-5-基)苯基]甲胺(T)的合成描述的类似程序,合成[4-(4-甲基-1,3-噁唑-5-基)苯基]甲胺(V)。

[0536] 以关于H向ULM-1的转化所述类似的方式将中间体V转化成ULM-5。LC-MS(ES^+):m/z 415.10[MH^+],t_R=1.17min(2.6分钟运行)。

[0537] ULM-6:(2S,4R)-1-((S)-2-氨基-3,3-二甲基丁酰基)-N-(4-氯苄基)-4-羟基吡咯烷-2-甲酰胺盐酸盐:

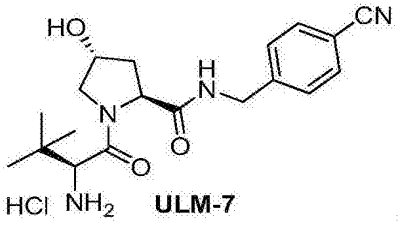
[0538]



[0539] 根据上面关于ULM-1的合成描述的类似程序,利用4-氯苄腈作为起始原料合成ULM-6。

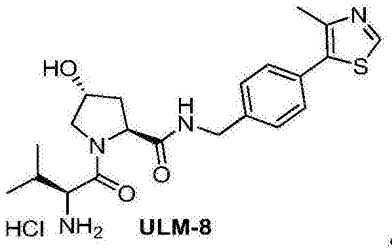
[0540] ULM-7:(2S,4R)-1-((S)-2-氨基-3,3-二甲基丁酰基)-N-(4-氰基苄基)-4-羟基吡咯烷-2-甲酰胺盐酸盐:

[0541]



[0542] 根据上面关于ULM-1的合成描述的类似程序,利用4-氰基苄腈作为起始原料合成ULM-7。

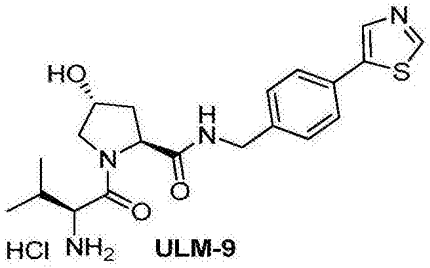
[0543] ULM-8:(2S,4R)-1-((S)-2-氨基-3-甲基丁酰基)-4-羟基-N-(4-(4-甲基噻唑-5-基)苄基)吡咯烷-2-甲酰胺盐酸盐:

[0544] 

ULM-8。

[0545] 根据上面关于ULM-1的合成描述的类似程序，利用(S)-2-(叔丁氧基羰基氨基)-3-甲基丁酸和4-甲基-1,3-噻唑(F)作为起始原料合成ULM-8。

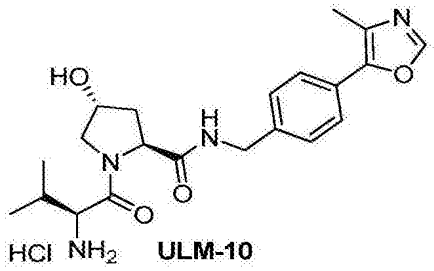
[0546] ULM-9：(2S,4R)-1-((S)-2-氨基-3-甲基丁酰基)-4-羟基-N-(4-(噻唑-5-基)苄基)吡咯烷-2-甲酰胺盐酸盐：

[0547] 

ULM-9。

[0548] 根据上面关于ULM-1的合成描述的类似程序，利用(S)-2-(叔丁氧基羰基氨基)-3-甲基丁酸和1,3-噻唑作为起始原料合成ULM-9。

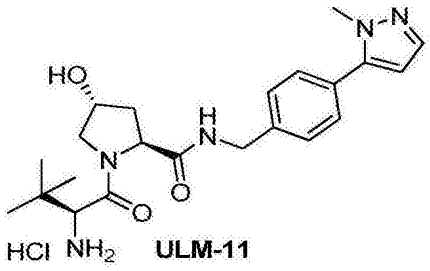
[0549] ULM-10：(2S,4R)-1-((S)-2-氨基-3-甲基丁酰基)-4-羟基-N-(4-(4-甲基噁唑-5-基)苄基)吡咯烷-2-甲酰胺盐酸盐：

[0550] 

ULM-10。

[0551] 根据上面关于ULM-5的合成描述的类似程序，利用(S)-2-(叔丁氧基羰基氨基)-3-甲基丁酸作为起始原料合成ULM-10。

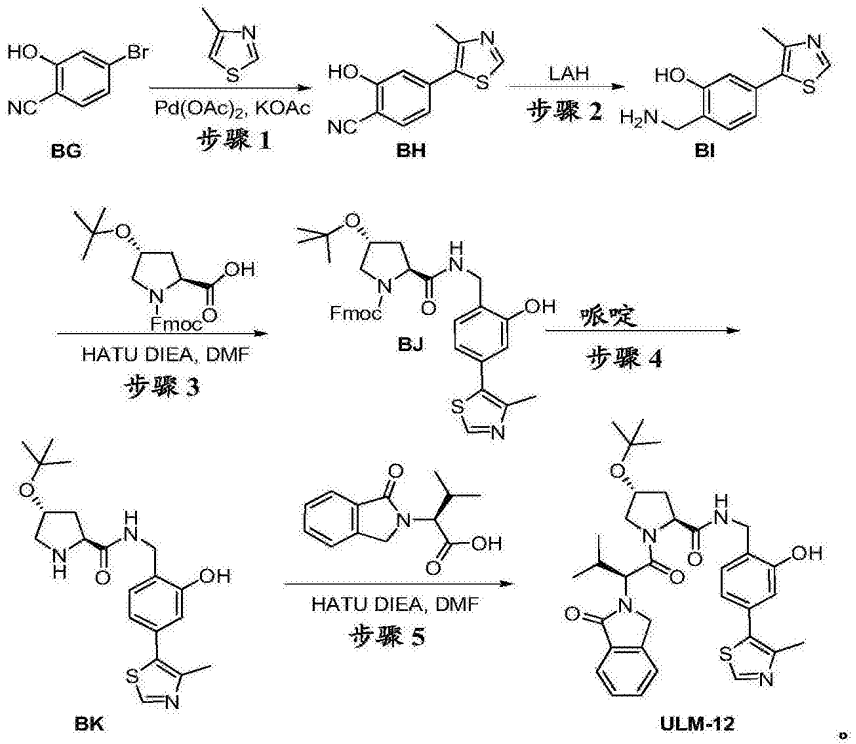
[0552] ULM-11：(2S,4R)-1-((S)-2-氨基-3,3-二甲基丁酰基)-4-羟基-N-(4-(1-甲基-1H-吡唑-5-基)苄基)吡咯烷-2-甲酰胺盐酸盐：

[0553] 

ULM-11。

[0554] 根据上面关于ULM-1的合成描述的类似程序，利用1-甲基吡唑作为起始原料合成ULM-11。

[0555] ULM-12:(2S,4R)-4-叔丁氧基-N-(2-羟基-4-(4-甲基噻唑-5-基)苄基)-1-((S)-3-甲基-2-(1-氧代异吲哚啉-2-基)丁酰基)吡咯烷-2-甲酰胺:

[0556] 

[0557] 步骤1:2-羟基-4-(4-甲基-1,3-噻唑-5-基)苄腈(BH)的合成

[0558] 在室温在氮气氛下向4-溴-2-羟基苄腈(BG,28g,141.40mmol)在DMA(300mL)中的搅拌溶液中加入4-甲基-1,3-噻唑(28.1g,283.40mmol)、乙酸钾(28g,285.31mmol)和乙酸钯(II)(940mg,4.19mol)。然后将得到的混合物加热至150℃并在该温度搅拌2.5h,LC-MS指示期望产物的形成。然后将反应物冷却至室温,用水(1000mL)稀释,并然后用乙酸乙酯(500mL×3)萃取。将有机层合并,经无水硫酸钠干燥并在减压下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:1)纯化以得到作为黄色固体的BH(收率:78%)。LC-MS(ES^+):m/z 216.95[MH^+],t_R=1.25min(2.6分钟运行)。

[0559] 步骤1:2-(氨基甲基)-5-(4-甲基-1,3-噻唑-5-基)苯酚(BI)

[0560] 在10℃在氮气氛下向2-羟基-4-(4-甲基-1,3-噻唑-5-基)苄腈(BH,15.6g,72.14mmol)在四氢呋喃(400mL)中的搅拌溶液中加入分成几个部分的$LiAlH_4$(11g,289.86mmol)。然后将得到的混合物加热至回流保持3h,LC-MS指示期望产物的形成。然后将反应物冷却至0℃,用水(10mL,缓慢地加入和逐滴)、15%NaOH(水溶液)(30mL)和水(10mL)猝灭。将沉淀的固体通过过滤除去,将溶液相在减压下继之以高真空泵浓缩以得到BI(收率:65%)。LC-MS(ES^+):m/z 220.85[MH^+],t_R=1.02min(2.6分钟运行)。

[0561] 步骤3.(2S,4R)-4-(叔丁氧基)-2-({[2-羟基-4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-甲酸-9H-芴-9-基甲酯(BJ)的合成

[0562] 在室温向(2S,4R)-4-(叔丁氧基)-1-[(9H-芴-9-基甲氧基)羰基]吡咯烷-2-甲酸(BI,18.6g)在N,N-二甲基甲酰胺(250mL)中的搅拌溶液中加入DIEA(7.9g,61.24mmol)、HATU(17.3g,45.53mmol)和2-(氨基甲基)-5-(4-甲基-1,3-噻唑-5-基)苯酚(20g,

90.79mmol)。将得到的混合物在室温搅拌过夜，且LC-MS指示期望产物的形成。将反应混合物用水(200mL)稀释，并然后用乙酸乙酯(300mL×3)萃取。将有机层合并，经无水硫酸钠干燥并在减压下浓缩以得到粗残余物，将其通过快速硅胶色谱法(洗脱液:二氯甲烷/甲醇(v:v=25:1))纯化以得到作为黄色油的BJ(收率:31%)。LC-MS(ES^+):m/z 611.20[MH^+]，t_R=1.12min(2.0分钟运行)。

[0563] 步骤4:(2S,4R)-4-(叔丁氧基)-N-{[2-羟基-4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺(BK)的合成

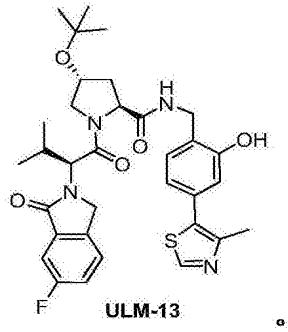
[0564] 在室温向(2S,4R)-4-(叔丁氧基)-2-({[2-羟基-4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-甲酸-9H-芴-9-基甲酯(BJ,17.2g,28.12mmol)在二氯甲烷(270mL)中的搅拌溶液中加入哌啶(30mL,280.00mmol)。将得到的溶液在室温搅拌3h，且LC-MS指示期望产物的形成。将反应混合物在真空下浓缩以得到粗残余物，然后将其用二氯甲烷(300mL)稀释，用水(300mL×2)洗涤，经无水硫酸钠干燥并在减压下浓缩以得到粗残余物，将其通过快速硅胶色谱法(洗脱液:二氯甲烷/甲醇(v:v=20:1))纯化以得到作为黄色油的BK(收率:71%)。LC-MS(ES^+):m/z389.95[MH^+]，t_R=0.88min(2.0分钟运行)。

[0565] 步骤5:(2S,4R)-4-(叔丁氧基)-N-{[2-羟基-4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}-1-[(2S)-3-甲基-2-(1-氧代-2,3-二氢-1H-异吲哚-2-基)丁酰基]吡咯烷-2-甲酰胺(ULM-12)的合成

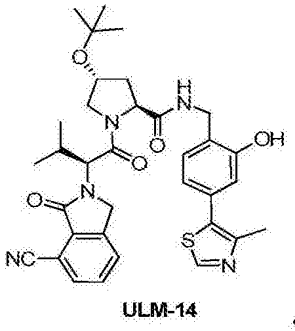
[0566] 在室温向(2S)-3-甲基-2-(1-氧代-2,3-二氢-1H-异吲哚-2-基)丁酸(3.6g,15.43mmol)在N,N-二甲基甲酰胺(50mL)中的搅拌溶液中加入DIEA(2.7g,20.93mmol)、HATU(5.89g,15.49mmol)和(2S,4R)-4-(叔丁氧基)-N-{[2-羟基-4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺(BK,4.0g,10.27mmol)。将得到的溶液在室温搅拌过夜，且LC-MS指示期望产物的形成。将反应物用水(100mL)稀释，并用二氯甲烷(100mL×3)萃取。将有机层合并，经无水硫酸钠干燥并在减压下浓缩以得到粗残余物，将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=2:1))纯化以得到作为黄色固体的ULM-12(收率:43%)。^1H NMR(400MHz,CD_3OD)δ8.88(s,1H),7.83-7.81(d,J=7.6Hz,1H),7.66-7.63(m,2H),7.61-7.59(m,1H),7.36-7.34(d,J=8.0Hz,1H),6.94-6.87(d,J=6.4Hz,1H),4.88(s,1H),4.56-4.39(m,6H),3.88-3.81(m,2H),2.51(s,3H),2.47-2.45(m,1H),2.15-2.13(m,2H),1.16-1.14(d,J=6.4Hz,3H)1.02(s,9H),0.89-0.86(d,J=6.4Hz,3H);LC-MS(ES^+):m/z 605.40[MH^+]，t_R=1.91min(3.6分钟运行)。

[0567] 除非另外指出，否则根据上面关于ULM-12的合成描述的类似程序利用对应的起始原料和试剂合成下述中间体和它们的类似物(例如、但不限于，具有取代诸如卤素的类似物)。

[0568] ULM-13:(2S,4R)-4-叔丁氧基-1-((S)-2-(6-氟-1-氧代异吲哚啉-2-基)-3-甲基丁酰基)-N-(2-羟基-4-(4-甲基噻唑-5-基)苄基)吡咯烷-2-甲酰胺:

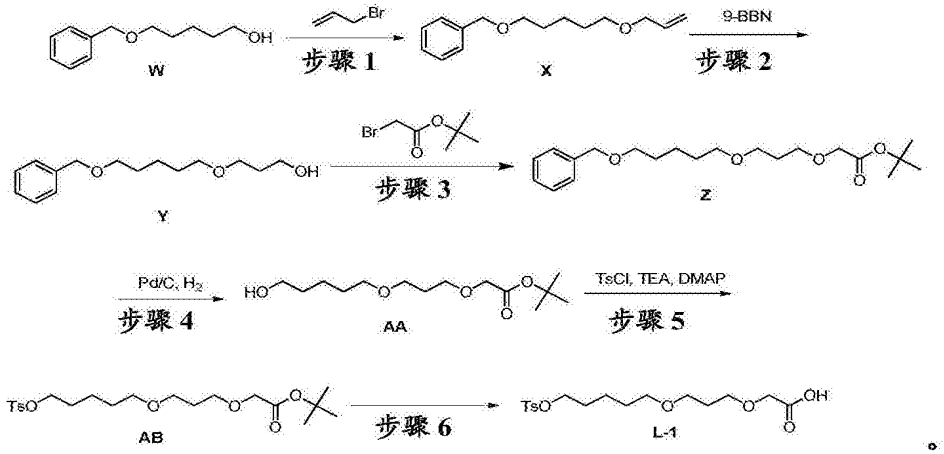
[0569] 

[0570] ULM-14:(2S,4R)-4-叔丁氧基-1-((S)-2-(7-氰基-1-氧代异吲哚啉-2-基)-3-甲基丁酰基)-N-(2-羟基-4-(4-甲基噻唑-5-基)苄基)吡咯烷-2-甲酰胺:

[0571] 

[0572] 接头化学L的合成

[0573] L-1:2-(3-(5-(甲苯磺酰氧基)戊氧基)丙氧基)乙酸

[0574] 

[0575] 步骤1:({[5-(丙-2-烯-1-基氧基)戊基]氧基}甲基)苯的合成

[0576] 在0℃在氮气氛下向5-(苄氧基)戊烷-1-醇(W,4.0g,20.59mmol)在N,N-二甲基甲酰胺(50mL)中的搅拌溶液中逐份加入氢化钠(1.24g,51.67mmol)。然后将得到的混合物在室温搅拌1h。向该混合物中加入3-溴丙-1-烯(3.71g,30.67mmol),将反应混合物在油浴中在60℃搅拌过夜。LC-MS指示期望产物的形成。将反应混合物冷却至0℃,并然后用水(100mL)猝灭,将得到的混合物用乙酸乙酯(200mL×2)萃取。将有机层合并,用饱和氯化钠水溶液(60mL)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物。将残余物通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:40))纯化以得到4.57g X。^{1}H NMR(300MHz,$CDCl_3$):δ7.36(s,4H),7.32(m,1H),5.98(m,1H),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=1.18min(2.0分钟运行)。

[0577] 步骤2:3-{[5-(苄氧基)戊基]氧基}丙烷-1-醇(Y)的合成

[0578] 在0℃在氮气氛下在搅拌下向装有9-BBN(0.5M的在THF中的溶液,77mL)的250-mL圆底烧瓶中加入({[5-(丙-2-烯-1-基氧基)戊基]氧基}甲基)苯(X,3.0g,12.80mmol)在无水四氢呋喃(20mL)中的溶液。将得到的溶液在室温搅拌过夜。LC-MS指示期望产物的形成。将甲醇(15mL,含有30%氢氧化钠和30%H_2O_2)加入反应物中并将得到的混合物在室温搅拌2h。然后将该混合物用乙酸乙酯(20mL×3)萃取。将有机层合并,用饱和氯化钠水溶液(100mL)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物。将残余物通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:1))纯化以得到1.96g作为浅黄色油的Y。^1H 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,1H),1.84(m,2H),1.68(m,4H),1.50(m,2H)。LC-MS(ES^+):m/z 253.17[MH^+],t_R=1.44min(2.6分钟运行)。

[0579] 步骤3:2-(3-{[5-(苄氧基)戊基]氧基}丙氧基)乙酸叔丁酯(Z)的合成

[0580] 向3-{[5-(苄氧基)戊基]氧基}丙烷-1-醇(Y,3.7g,14.66mmol)在二氯甲烷(30mL)中的搅拌溶液中加入NaOH在水中的溶液(37%,30mL),随后加入2-溴乙酸叔丁酯(11.39g,58.39mmol)和TBACl(4.17g)。将得到的混合物在室温搅拌过夜。LC-MS指示期望产物的形成。然后将反应混合物用乙酸乙酯(50mL×3)萃取。将有机层合并,用饱和氯化钠水溶液(60mL)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物。将残余物通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:2)纯化以得到3.2g作为黄色油的Z。^1H NMR(400MHz,$CDCl_3$):δ7.34(s,4H),7.29(m,1H),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=1.28min(2.0分钟运行)。

[0581] 步骤4:2-[3-[(5-羟基戊基)氧基]丙氧基]乙酸叔丁酯(AA)的合成

[0582] 在氮气氛下向2-(3-{[5-(苄氧基)戊基]氧基}丙氧基)乙酸叔丁酯(Z,3.2g,8.73mmol)在甲醇(30mL)中的搅拌溶液中加入AcOH(1.5mL)、炭载钯(1.5g)。然后经由氢气囊将氢气引入反应混合物中,并将反应物在室温搅拌3h。将固体物质通过过滤除去,将溶液在真空下浓缩以得到作为浅黄色油的2.3g AA,将其不经任何进一步纯化用于下一步。LC-MS(ES^+):m/z 277.10[MH^+],t_R=0.86min(2.0分钟运行)。

[0583] 步骤5:2-[3-({5-[(4-甲基苯磺酰基)氧基]戊基}氧基)丙氧基]乙酸叔丁酯(AB)的合成

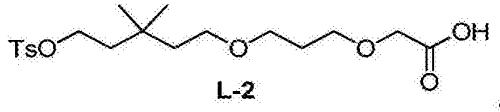
[0584] 在室温向2-[3-[(5-羟基戊基)氧基]丙氧基]乙酸叔丁酯(AA,2.3g,8.32mmol)在二氯甲烷(30mL)中的搅拌溶液中加入4-甲基苯-1-磺酰氯(3.17g,16.63mmol)、三乙胺(2.52g,24.90mmol)和4-二甲基氨基吡啶(203mg,1.66mmol)。将得到的混合物在室温搅拌过夜。将得到的混合物在减压下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:2)纯化以得到2.6g作为黄色油的AB。^1H NMR(300MHz,$CDCl_3$):δ7.77(d,J=8.1Hz,2H),7.36(d,J=8.1Hz,2H),4.51(s,2H),4.31(m,2H),4.13(m,2H),3.52(m,4H),2.05(s,3H),1.97(m,2H),1.69(m,4H),1.48(s,9H),1.46(m,2H)。LC-MS(ES^+):m/z 431.20[MH^+],t_R=1.21min(2.0分钟运行)。

[0585] 步骤1:2-[3-({5-[(4-甲基苯磺酰基)氧基]戊基}氧基)丙氧基]乙酸(L-1)的合成

[0586] 在室温向2-[3-({5-[(4-甲基苯磺酰基)氧基]戊基}氧基)丙氧基]乙酸叔丁酯(AB,1.3g,3.02mmol)在二氯甲烷(10mL)中的搅拌溶液中加入三氟乙酸(10mL)。将得到的溶液在室温搅拌3h。然后将反应混合物在真空下浓缩以得到1.5g(粗制物)L-1,将其不经任何进一步纯化用于下一步。LC-MS(ES^+):m/z 375.34[MH^+],t_R=1.39min(2.6分钟运行)。

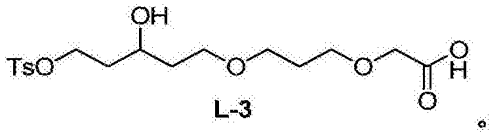
[0587] 以关于L-1的制备类似的方式制备下述接头(L)。

[0588] L-2:2-(3-(3,3-二甲基-5-(甲苯磺酰氧基)戊氧基)丙氧基)乙酸

[0589] 

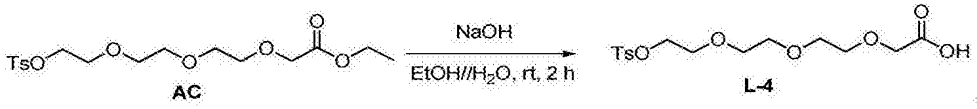
L-2。

[0590] L-3:2-(3-(3-羟基-5-(甲苯磺酰氧基)戊氧基)丙氧基)乙酸

[0591] 

L-3。

[0592] L-4:2-(2-(2-(2-(甲苯磺酰氧基)乙氧基)乙氧基)乙氧基)乙酸

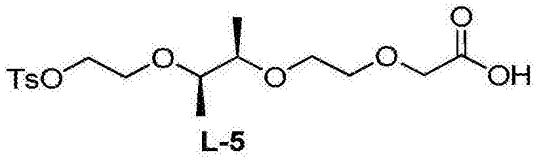
[0593] 

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[0594] 向2-[2-(2-{2-[(4-甲基苯磺酰基)氧基]乙氧基}乙氧基)乙氧基]乙酸乙酯(AC,2g,5.12mmol,1.00当量)在甲醇(20mL)中的搅拌溶液中加入NaOH(500mg,12.50mmol)在水(4mL)中的溶液,并将得到的混合物在室温搅拌2h。然后将氯化氢水溶液(1M)加入反应混合物中以将pH调至~5。将沉淀的固体通过过滤进行收集以得到L-4(收率:98%)。质量(ES+):m/z 363,[MH+]。

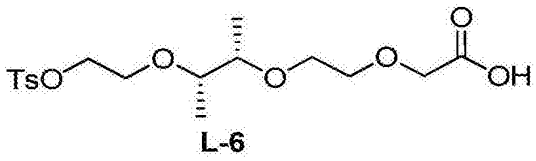
[0595] 以关于L-4的制备类似的方式制备下述接头(L)。

[0596] L-5:2-(2-((2R,3R)-3-(2-(甲苯磺酰氧基)乙氧基)丁-2-基氧基)乙氧基)乙酸

[0597] 

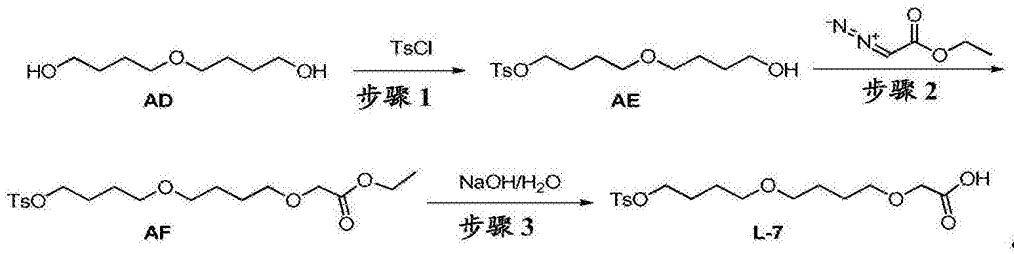
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[0598] L-6:2-(2-((2S,3S)-3-(2-(甲苯磺酰氧基)乙氧基)丁-2-基氧基)乙氧基)乙酸

[0599] 

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[0600] L-7:2-(4-(4-(甲苯磺酰氧基)丁氧基)丁氧基)乙酸

[0601] 

[0602] 步骤1:4-{4-[(4-甲基苯磺酰基)氧基]丁氧基}丁-1-醇(AE)的合成

[0603] 向4-(4-羟基丁氧基)丁-1-醇(AD,2g,12.33mmol)在二氯甲烷(20mL)中的搅拌溶液中加入Ag_2O(4.25g,18.49mmol)、KI(409mg,2.46mmol)和TsCl(2.345g,12.30mmol)。将得到的混合物在室温搅拌12h。将形成的无机盐通过过滤除去并将有机溶液在减压下浓缩以得到粗残余物。将残余物通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:1))纯化以得到作为无色油的AE(收率:28%)。

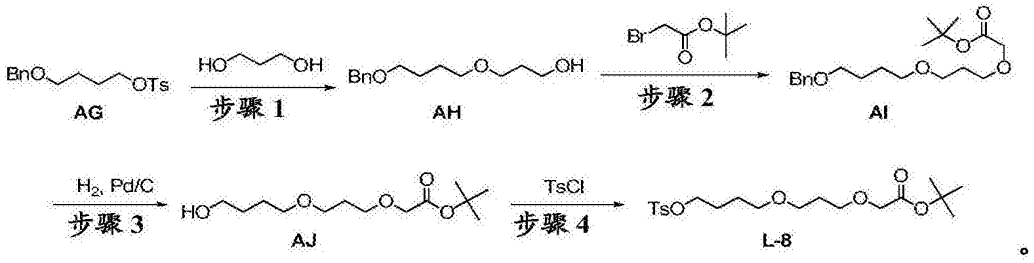
[0604] 步骤2:2-(4-{4-[(4-甲基苯磺酰基)氧基]丁氧基}丁氧基)乙酸乙酯(AF)的合成

[0605] 在0℃向4-{4-[(4-甲基苯磺酰基)氧基]丁氧基}丁-1-醇(AE,1.1g,3.48mmol)在二氯甲烷(10mL)中的搅拌溶液中缓慢地加入$BF_3.Et_2O$(49.4mg,0.35mmol),随后加入2-重氮基乙酸乙酯(794mg,6.96mmol)。将得到的混合物在室温搅拌过夜。然后将反应物用水(2.0mL)猝灭。将得到的混合物用二氯甲烷(50mL×3)萃取,将有机层合并,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物。将残余物通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:4)纯化以得到作为浅黄色油的AF(收率:93%)。质量(ES^+):m/z 403.10[MH^+]。

[0606] 步骤3:2-(4-{4-[(4-甲基苯磺酰基)氧基]丁氧基}丁氧基)乙酸(L-7)的合成

[0607] 在室温向2-(4-{4-[(4-甲基苯磺酰基)氧基]丁氧基}丁氧基)乙酸乙酯(AF,1.3g,3.23mmol)在甲醇(25mL)中的搅拌溶液中加入NaOH(388mg,9.70mmol)在水(6mL)中的溶液。将得到的溶液在室温搅拌4h。将大部分(bulk)有机溶剂在减压下除去,向得到的混合物中加入氯化氢水溶液(1.0M)以调节pH=~5。然后将溶液用乙酸乙酯(250mL×3)萃取,将有机层合并和经无水硫酸钠干燥,在减压下浓缩以得到作为浅黄色油的I-7(收率:93%)。质量(ES^+):m/z 375.05[MH^+]。

[0608] L-8:2-(3-(4-(甲苯磺酰氧基)丁氧基)丙氧基)乙酸叔丁酯

[0609] 

[0610] 步骤1.3-[4-(苄氧基)丁氧基]丙烷-1-醇(AH)的合成

[0611] 在室温向丙烷-1,3-二醇(1.52g,19.98mmol)在N,N-二甲基甲酰胺(20mL)中的搅拌溶液中加入氢化钠(840mg,35.00mmol),将得到的混合物在室温搅拌30min。然后向所述混合物中加入4-甲基苯-1-磺酸4-(苄氧基)丁酯(AG,6.68g,19.97mmol),并将反应物在50℃搅拌过夜。TLC指示期望产物的形成,此时使反应物冷却至室温。将水(10mL)缓慢地加入

以猝灭反应;然后将得到的混合物用乙酸乙酯(80mL×2)萃取。将有机层合并,用饱和氯化钠水溶液(20mL)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:2))纯化以得到作为浅黄色油的AH(收率:67%)。^{1}H NMR(300MHz,$CDCl_3$)δ7.38-7.29(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);质量(ES^+):m/z 239.05[MH^+]。

[0612] 步骤2.2-[3-[4-(苄氧基)丁氧基]丙氧基]乙酸叔丁酯(AI)的合成.

[0613] 向3-[4-(苄氧基)丁氧基]丙烷-1-醇(AH,2.38g,9.99mmol)在二氯甲烷(15mL)中的搅拌溶液中加入2-溴乙酸叔丁酯(7.76g,39.78mmol)、TBAC(2.78g,10.00mmol),随后加入氢氧化钠水溶液(37%,15mL)。将得到的混合物在室温搅拌过夜。然后将反应混合物用二氯甲烷(100mL×3)萃取,将有机层合并,用饱和氯化钠水溶液(20mL)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物。将残余物通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:5))纯化以得到作为黄色油的AI(收率57%)。质量(ES^+):m/z 353.10[MH^+]。

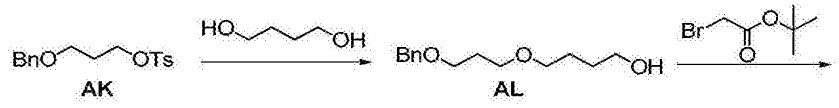
[0614] 步骤3.2-[3-(4-羟基丁氧基)丙氧基]乙酸叔丁酯(AJ)的合成

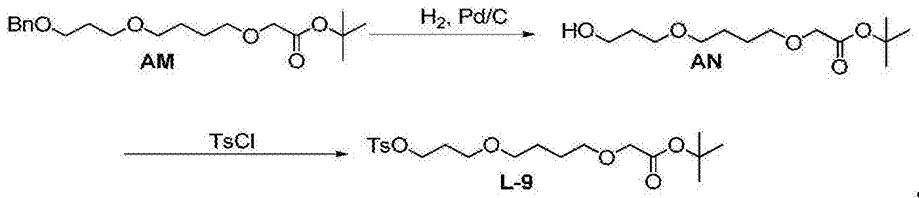
[0615] 在氮气氛下向2-[3-[4-(苄氧基)丁氧基]丙氧基]乙酸叔丁酯(AI,1g,2.84mmol)、炭载钯(10%,200mg)在甲醇(20mL)中的搅拌混合物中加入乙酸(0.05mL)。然后经由气囊将氢气引入反应混合物中,然后将反应物在室温搅拌过夜。将不溶性固体通过过滤除去并将溶液相在减压下浓缩以得到作为黄色油的期望产物(收率:94%)。质量(ES^+):m/z 263.05[MH^+]。

[0616] 步骤4.2-(3-{4-[(4-甲基苯磺酰基)氧基]丁氧基}丙氧基)乙酸叔丁酯(L-8)的合成

[0617] 向2-[3-(4-羟基丁氧基)丙氧基]乙酸叔丁酯(AJ,700mg,2.67mmol)在二氯甲烷(10mL)中的搅拌溶液中加入4-甲基苯-1-磺酰氯(558.4mg,2.93mmol)、TEA(539.5mg,5.33mmol)和4-二甲基氨基吡啶(32.6mg,0.27mmol)。将得到的混合物在室温搅拌过夜。将大部分溶剂在减压下除去以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:2))纯化以得到作为黄色油的标题产物(收率:52%)。^{1}H NMR(300MHz,$CDCl_3$)δ7.79(d,J=8.4Hz,2H),7.35(d,J=8.0Hz,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);质量(ES^+):m/z417.05[MH^+]。

[0618] L-9:2-(4-(3-(甲苯磺酰氧基)丙氧基)丁氧基)乙酸叔丁酯

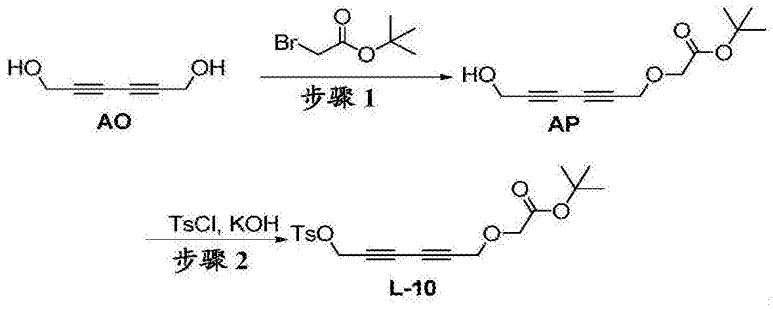


[0619] 

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[0620] 除了使用AK替代AG以外，以与用于制备L-8的方式类似的方式制备L-9。质量(ES$^+$):m/z 439.15[MNa$^+$]。

[0621] L-10:2-(6-(甲苯磺酰氧基)己-2,4-二炔基氧基)乙酸叔丁酯

[0622] 

[0623] 步骤1:2-[(6-羟基己-2,4-二炔-1-基)氧基]乙酸叔丁酯(AP)的合成

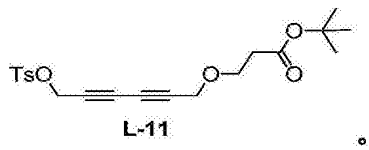
[0624] 在0℃向己-2,4-二炔-1,6-二醇(AO,100mg,0.91mmol)在N,N-二甲基甲酰胺(5mL)中的搅拌溶液中加入氢化钠(32mg,1.33mmol)。然后将得到的混合物温热至室温并在室温搅拌30min。将反应混合物冷却至0℃，随后加入2-溴乙酸叔丁酯(176mg,0.90mmol)，并将得到的混合物在0℃搅拌2h。LC-MS指示期望产物的形成。然后将反应物在0℃用水(10mL，缓慢地加入)猝灭，并用乙酸乙酯(20×2mL)萃取。将有机层合并，经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物，将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:2))纯化以得到作为黄色油的AP(收率:49%)。

[0625] 步骤2.2-({6-[(4-甲基苯磺酰基)氧基]己-2,4-二炔-1-基}氧基)乙酸叔丁酯(L-10)的合成

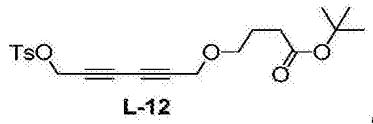
[0626] 在0℃向2-[(6-羟基己-2,4-二炔-1-基)氧基]乙酸叔丁酯(AP,50mg,0.22mmol)在乙醚(2mL)中的搅拌溶液中加入4-甲苯磺酰氯(51mg,0.27mmol)，随后在0℃加入分成几批的氢氧化钾(125mg,2.23mmol)。将得到的混合物在0℃搅拌4h。LC-MS指示期望产物的形成。将水(10mL)加入反应物中，并将得到的混合物用乙酸乙酯(20mL×2)萃取。将有机层合并，经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物，将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:2))纯化以得到作为黄色油的L-10(收率:71%)。^{1}H NMR(300MHz,$CDCl_3$):δ7.83(d,J=6.0Hz,2H),7.39(d,J=6.0Hz,2H),4.79(s,2H),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=1.71min(2.6分钟运行)。

[0627] 以关于L-10的制备类似的方式制备下述接头(L)。

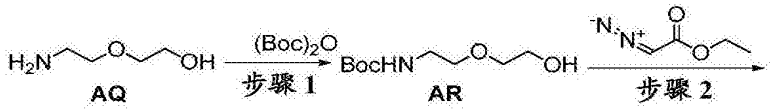
[0628] L-11:3-(6-(甲苯磺酰氧基)己-2,4-二炔基氧基)丙酸叔丁酯

[0629] 

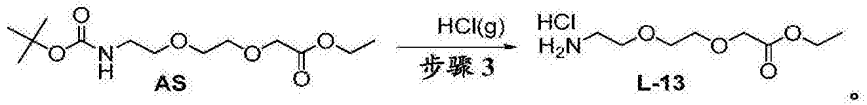
[0630] L-12:4-(6-(甲苯磺酰氧基)己-2,4-二炔基氧基)丁酸叔丁酯

[0631] 

[0632] L-13:2-(2-(2-氨基乙氧基)乙氧基)乙酸乙酯盐酸盐



[0633]



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[0634] 步骤1:N-[2-(2-羟基乙氧基)乙基]氨基甲酸叔丁酯(AR)的合成

[0635] 在0℃向2-(2-氨基乙氧基)乙烷-1-醇(AQ,5.25g,49.94mmol)在四氢呋喃(100mL)中的搅拌溶液中加入碳酸氢钠(20%(w/w),40ml)和(Boc)$_2$O(11.4g,52.23mmol,分几批加入)的水溶液。然后将得到的混合物缓慢地温热至室温并在室温搅拌5h。将大部分有机溶剂在减压下除去并将得到的残余物用水(300mL)稀释,用乙酸乙酯(100mL×3)萃取。将有机层合并,用饱和氯化钠水溶液(20mL×2)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到作为无色油的AR(收率:98%)。

[0636] 步骤2:2-[2-(2-{[(叔丁氧基)羰基]氨基}乙氧基)乙氧基]乙酸乙酯(AS)的合成

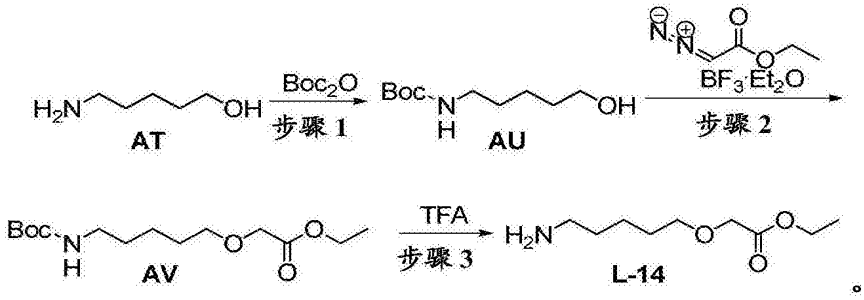
[0637] 在室温向N-[2-(2-羟基乙氧基)乙基]氨基甲酸叔丁酯(AR,4.0g,19.49mmol)在二氯甲烷(30mL)中的搅拌溶液中加入1-重氮基-3-甲氧基丙烷-2-酮(3.34g,29.27mmol)和BF_3-Et_2O(0.2mL)。将得到的溶液在室温搅拌2h。将水(20mL)加入反应混合物中,将有机层分离,并用盐水(20mL)洗涤,经无水硫酸钠干燥并在减压下浓缩以得到粗残余物。将残余物通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:2))纯化以得到作为黄色固体的AS(收率:18%)。^{1}H NMR(400MHz,$CDCl_3$):δ4.25-4.22(q,J=7.2Hz,2H),4.14(s,2H),3.74(b,2H),3.72(b,1H),3.67-3.32(m,4H),1.414(s,9H),1.31(t,J=7.2Hz,3H)。

[0638] 步骤3:2-[2-(2-氨基乙氧基)乙氧基]乙酸乙酯盐酸盐(L-13)的合成

[0639] 在室温通过鼓泡向2-[2-(2-{[(叔丁氧基)羰基]氨基}乙氧基)乙氧基]乙酸乙酯(AS,500mg,1.72mmol)在1,4-二噁烷(10mL)中的搅拌溶液中引入氯化氢(气体)2h。然后将溶剂在真空下除去以得到L-13(收率:99%)。LC-MS(ES^+):m/z 192.00[MH^+],t_R=0.41min(2.0分钟运行)。

[0640] L-14:2-(5-氨基戊氧基)乙酸乙酯

[0641]



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[0642] 步骤1:5-羟基戊基氨基甲酸叔丁酯(AU)的合成

[0643] 在0℃向5-氨基戊烷-1-醇(AT,3.1g,30.05mmol)在二氯甲烷(30mL)中的搅拌溶液中加入二碳酸二叔丁酯(6.56g,30.06mmol)。然后将得到的混合物在室温搅拌4h。将溶剂在减压下除去以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=

1:2))纯化以得到作为无色油的AU(收率:98%)。LC-MS(ES^+):m/z 204.00[MH^+],t_R=1.29min(2.6分钟运行)。

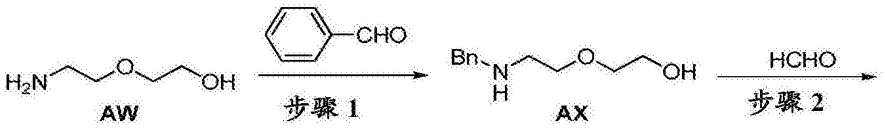
[0644] 步骤2:2-[(5-{[(叔丁氧基)羰基]氨基}戊基)氧基]乙酸乙酯(AV)的合成

[0645] 在0℃向N-(5-羟基戊基)氨基甲酸叔丁酯(AU,1.5g,7.38mmol)在二氯甲烷(10mL)中的搅拌溶液中加入$BF_3 \cdot Et_2O$(0.1mL)。然后在0℃向该混合物中加入2-重氮基乙酸乙酯(850mg,7.45mmol)在二氯甲烷(2mL)中的溶液。将得到的混合物温热至室温并在室温搅拌2h。将饱和碳酸氢钠水溶液(30mL)加入反应物中,将得到的混合物用乙酸乙酯(150mL×3)萃取。将有机层合并,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:7))纯化以得到作为无色油的AV(收率:15%)。LC-MS(ES^+):m/z 290.05[MH^+],t_R=1.55min(2.6分钟运行)。

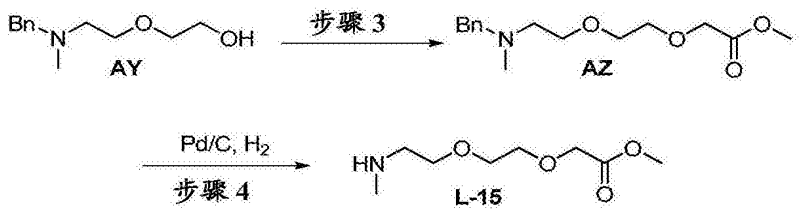
[0646] 步骤3:2-(5-氨基戊氧基)乙酸乙酯(L-14)的合成

[0647] 在室温向2-[(5-{[(叔丁氧基)羰基]氨基}戊基)氧基]乙酸乙酯(AV,400mg,1.38mmol)在二氯甲烷(5mL)中的搅拌溶液中加入三氟乙酸(5mL)。将得到的溶液在室温搅拌2h。然后将反应混合物在真空下浓缩以得到作为黄色油的L-14(收率:84%)。LC-MS(ES^+):m/z 190.00[MH^+],t_R=1.01min(2.6分钟运行)。

[0648] L-15:2-(2-(2-(甲基氨基)乙氧基)乙氧基)乙酸甲酯



[0649]



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[0650] 步骤1:2-[2-(苄基氨基)乙氧基]乙烷-1-醇(AX)的合成

[0651] 在0℃向2-(2-氨基乙氧基)乙烷-1-醇(AW,5.0g)和苯甲醛(5.0g)在THF(50mL)中的搅拌溶液中加入三乙酰氧基硼氢化钠(15.8g,74.5mmol)。然后将得到的溶液在室温搅拌4h。将水(50mL)加入反应物中并将得到的混合物用乙酸乙酯(50mL×2)萃取。将有机层合并,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:二氯甲烷/甲醇(v:v=3:1)纯化以得到作为白色固体的AX(收率:85%)。LC-MS(ES^+):m/z 195.95[MH^+],t_R=0.22min(2.0分钟运行)。

[0652] 步骤2:2-{2-[苄基(甲基)氨基]乙氧基}乙烷-1-醇(AY)的合成

[0653] 在室温向2-[2-(苄基氨基)乙氧基]乙烷-1-醇(AX,10.0g)在甲醇(200mL)中的搅拌溶液中加入甲醛(38%在水中)(4.9mL)和三乙酰氧基硼氢化物(17.0g)。将得到的溶液在室温搅拌2h。将饱和碳酸氢钠水溶液(100mL)加入反应物中,并然后将大部分有机溶剂在减压下除去。将得到的混合物用乙酸乙酯(200mL×3)萃取。将有机层合并,经无水硫酸钠干燥并然后在减压下继之以高真空泵浓缩以得到作为黄色油的AY(收率:33%)。LC-MS(ES^+):m/z 210.00[MH^+],t_R=0.43min(2.0分钟运行)。

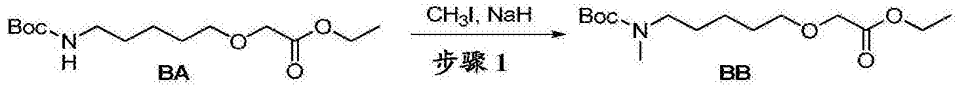
[0654] 步骤3:2-(2-{2-[苄基(甲基)氨基]乙氧基}乙氧基)乙酸甲酯(AZ)的合成

[0655] 在室温向2-{2-[苄基(甲基)氨基]乙氧基}乙烷-1-醇(AY,2g)在二氯甲烷(20mL)中的搅拌溶液中加入氢氧化钠(37%)在水(20mL)中的溶液,随后加入2-溴乙酸叔丁酯(7.76g)和TBAC(2.78g)。将得到的混合物在室温搅拌15h。将水层分离,并向其中加入氯化氢水溶液(4N)以调节pH至~3,然后将其在减压下浓缩以得到粗残余物。然后将甲醇(20mL)加入该残余物中,并将不溶性的盐滤出。将溶液在真空下浓缩以得到作为黄色油的2-(2-[2-[苄基(甲基)氨基]乙氧基]乙氧基)乙酸(收率:78%)。在室温向上面制备的2-(2-{2-[苄基(甲基)氨基]乙氧基}乙氧基)乙酸(2g,7.48mmol,1.00当量)在甲醇(50mL)中的搅拌溶液中缓慢地加入硫酸(2mL)。将得到的溶液在油浴中在70℃搅拌3h。将大部分溶剂在减压下除去以得到残余物,将其用H_2O(30mL)稀释。然后将碳酸钠加入混合物中以调节pH至~8。然后将混合物用乙酸乙酯(50mL×2)萃取,将有机层合并,经无水硫酸钠干燥并然后在减压下继之以高真空泵浓缩以得到作为黄色油的AZ(收率:29%)。LC-MS(ES^+):m/z 281.95[MH^+],t_R=0.30min(2.0分钟运行)。

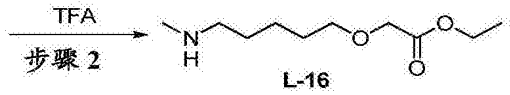
[0656] 步骤4:2-{2-[2-(甲基氨基)乙氧基]乙氧基}乙酸甲酯(L-15)的合成

[0657] 经由气囊在氮气氛下向2-(2-{2-[苄基(甲基)氨基]乙氧基}乙氧基)乙酸甲酯(AZ,600mg,2.13mmol)和炭载钯(300mg)在甲醇(30mL)中的搅拌混合物中充入氢气。将得到的混合物在室温搅拌15h。将固体物质通过过滤除去并将溶液在真空下浓缩以得到作为黄色油的L-15(400mg),将其不经任何进一步纯化用于下一步。LC-MS(ES^+):m/z 191.95[MH^+],t_R=0.31min(2.0分钟运行)。

[0658] L-16:2-(5-(甲基氨基)戊氧基)乙酸乙酯



[0659]



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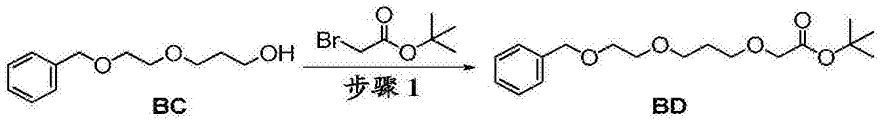
[0660] 步骤1:2-[(5-{[(叔丁氧基)羰基](甲基)氨基}戊基)氧基]乙酸乙酯(BB)的合成

[0661] 在0℃向2-[(5-{[(叔丁氧基)羰基]氨基}戊基)氧基]乙酸乙酯(BA,1.1g,3.8mmol)在N,N-二甲基甲酰胺(10mL)中的搅拌溶液中加入CH_3I(0.71mL,11.4mmol),随后在0℃加入分成几个部分的氢化钠(304mg,7.60mmol,60%在矿物油中)。将得到的混合物在室温搅拌16h。加入水(1.0mL)并将得到的混合物用乙酸乙酯(50mL×2)萃取。将有机层合并,用饱和氯化钠水溶液(100mL)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:10))纯化以得到作为黄色油的BB(收率:21%)。LC-MS(ES^+):m/z 326.20[MNa^+],t_R=1.55min(2.6分钟运行)。

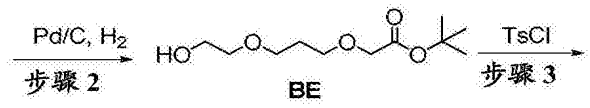
[0662] 步骤2:2-{[5-(甲基氨基)戊基]氧基}乙酸乙酯(L-16)的合成

[0663] 向2-[(5-{[(叔丁氧基)羰基](甲基)氨基}戊基)氧基]乙酸乙酯(BB,240mg,0.79mmol)在二氯甲烷(5mL)中的搅拌溶液中加入三氟乙酸(0.5mL)。将得到的溶液在室温搅拌16h。将溶剂在减压下继之以高真空泵除去以得到作为黄色油的L-16(收率:99%)。LC-MS(ES^+):m/z 204.20[MH^+],t_R=0.56min(2.0分钟运行)。

[0664] L-17:2-(3-(2-(甲苯磺酰氧基)乙氧基)丙氧基)乙酸



[0665]





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[0666] 步骤1:2-{3-[2-(苄氧基)乙氧基]丙氧基}乙酸叔丁酯(BD)的合成

[0667] 向3-[2-(苄氧基)乙氧基]丙烷-1-醇(BC,1.8g,8.56mmol)和2-溴乙酸叔丁酯(6.6g,33.84mmol,4.00当量)在二氯甲烷(40mL)中的搅拌溶液中加入TBAC(2.4g)和氢氧化钠水溶液(37%,40mL)。将得到的混合物在室温搅拌过夜。LC-MS指示期望产物的形成。然后将反应混合物用乙酸乙酯(150×3mL)萃取,将有机层合并,经无水硫酸钠干燥并在减压下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:2)纯化以得到作为无色油的BD(收率:90%)。^{1}H NMR(300MHz,$CDCl_3$):δ7.35-7.27(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=1.72min(2.6分钟运行)。

[0668] 步骤2:2-[3-(2-羟基乙氧基)丙氧基]乙酸叔丁酯(BE)的合成

[0669] 在氮气氛下经由气囊向2-{3-[2-(苄氧基)乙氧基]丙氧基}乙酸叔丁酯(BD,2.5g,7.71mmol)和炭载钯(2.0g)在甲醇(20mL)中的搅拌混合物中引入氢气。将得到的混合物在氢气气氛下在室温搅拌过夜。LC-MS指示反应结束。将固体通过过滤除去,将溶液在真空下浓缩以得到作为无色油的BE(收率:99%)。LC-MS(ES^+):m/z 257.10[MNa^+],t_R=1.21min(2.6分钟运行)。

[0670] 步骤3:2-(3-{2-[(4-甲基苯磺酰基)氧基]乙氧基}丙氧基)乙酸叔丁酯(BF)的合成

[0671] 向2-[3-(2-羟基乙氧基)丙氧基]乙酸叔丁酯(BE,1.8g,7.68mmol)在二氯甲烷(50mL)中的搅拌溶液中加入4-甲苯磺酰氯(2.2g,11.54mmol)、三乙胺(2.33g,23.03mmol)和4-二甲基氨基吡啶(95mg,0.78mmol)。将得到的混合物在室温搅拌过夜。LC-MS指示期望产物的形成。将反应混合物在减压下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:2)纯化以得到作为黄色油的BF(收率:80%)。^{1}H NMR(400MHz,$CDCl_3$):δ7.80(d,J=8.0Hz,2H),7.34(d,J=8.4Hz,2H),4.15(t,J=3.6Hz,2H),3.93(s,2H),3.61(t,J=3.6Hz,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=1.12min(2.0分钟运行)。

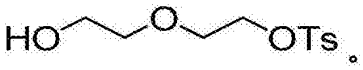
[0672] 步骤4:2-(3-{2-[(4-甲基苯磺酰基)氧基]乙氧基}丙氧基)乙酸(L-17)的合成

[0673] 在室温向2-(3-{2-[(4-甲基苯磺酰基)氧基]乙氧基}丙氧基)乙酸叔丁酯(BF,400mg,1.03mmol)在二氯甲烷(3mL)中的搅拌溶液中加入三氟乙酸(1mL)。将得到的溶液在室温搅拌1h。LC-MS指示反应结束。将反应混合物在减压下浓缩以得到作为黄色油的L-17(350mg),将其不经进一步纯化用于下一步。LC-MS(ES^+):m/z 332.90[MH^+],t_R=0.81min

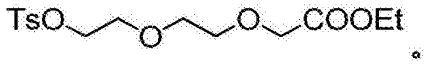
(2.0分钟运行)。

[0674] 除非另外指出,否则根据上面关于L-17的合成描述的类似程序利用对应的起始原料和试剂合成下述中间体和它们的类似物(例如、但不限于,具有取代诸如卤素的类似物)。

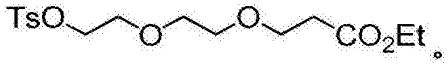
[0675] L-18:4-甲基苯磺酸-2-(2-羟基乙氧基)乙酯

[0676]  。

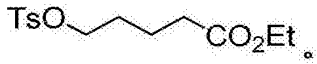
[0677] L-19:2-(2-(2-(甲苯磺酰氧基)乙氧基)乙氧基)乙酸乙酯

[0678]  。

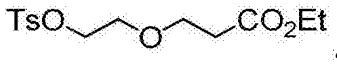
[0679] L-20:3-(2-(2-(甲苯磺酰氧基)乙氧基)乙氧基)丙酸乙酯

[0680]  。

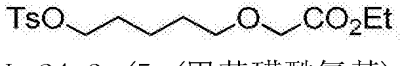
[0681] L-21:5-(甲苯磺酰氧基)戊酸乙酯

[0682]  。

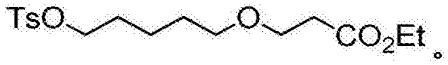
[0683] L-22:3-(2-(甲苯磺酰氧基)乙氧基)丙酸乙酯

[0684]  。

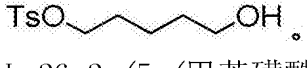
[0685] L-23:2-(5-(甲苯磺酰氧基)戊氧基)乙酸乙酯

[0686]  。

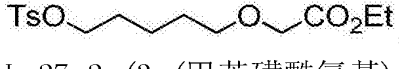
[0687] L-24:3-(5-(甲苯磺酰氧基)戊氧基)丙酸乙酯

[0688]  。

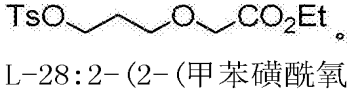
[0689] L-25:4-甲基苯磺酸-5-羟基戊酯

[0690]  。

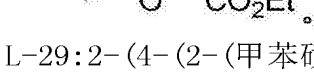
[0691] L-26:2-(5-(甲苯磺酰氧基)戊氧基)乙酸乙酯

[0692]  。

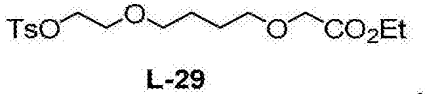
[0693] L-27:2-(3-(甲苯磺酰氧基)丙氧基)乙酸乙酯

[0694]  。

[0695] L-28:2-(2-(甲苯磺酰氧基)乙氧基)乙酸乙酯

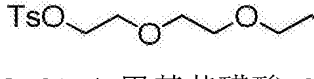
[0696]  。

[0697] L-29:2-(4-(2-(甲苯磺酰氧基)乙氧基)丁氧基)乙酸乙酯

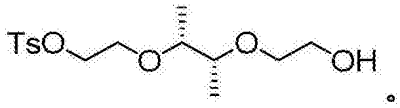
[0698] 

L-29。

[0699] L-30:4-甲基苯磺酸-2-(2-(2-羟基乙氧基)乙氧基)乙酯

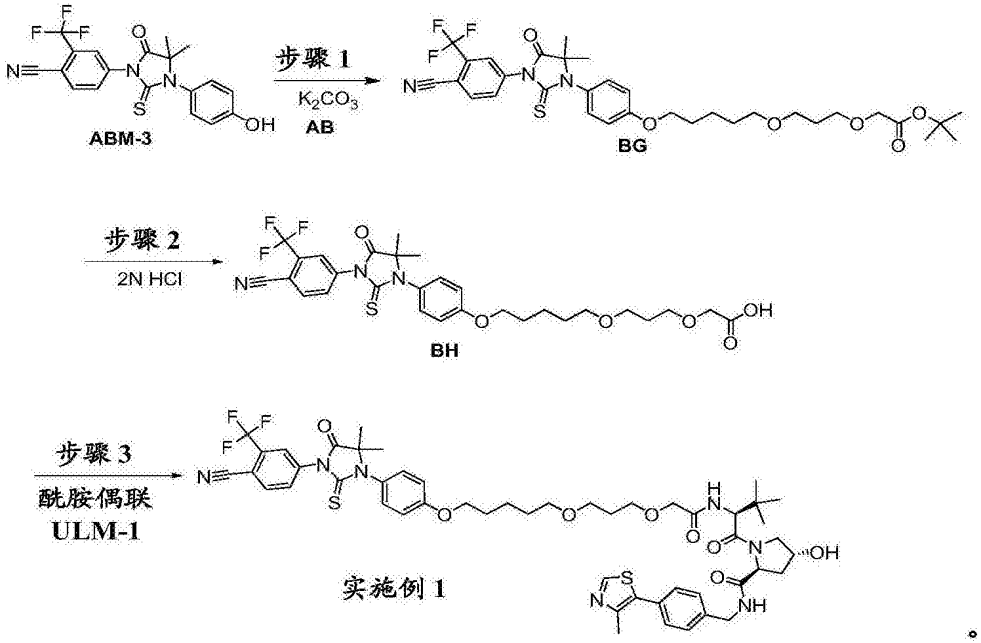
[0700]  。

[0701] L-31:4-甲基苯磺酸-2-((2R,3R)-3-(2-羟基乙氧基)丁-2-基氧基)乙酯

[0702] 

[0703] 实施例的合成

[0704] 实施例1:(2S,4R)-1-((S)-2-(2-(3-(5-(4-(3-(4-氰基-3-(三氟甲基)苯基)-5,5-二甲基-4-氧代-2-硫代咪唑烷-1-基)苯氧基)戊氧基)丙氧基)乙酰氨基)-3,3-二甲基丁酰基)-4-羟基-N-(4-(4-甲基噻唑-5-基)苄基)吡咯烷-2-甲酰胺

[0705] 

[0706] 步骤1:2-(3-{[5-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)戊基]氧基}丙氧基)乙酸叔丁酯(BG)的合成

[0707] 向2-[3-[(5-[[(4-甲基苯)磺酰基]氧基]戊基)氧基]丙氧基]乙酸叔丁酯(AB,150mg,0.35mmol)在乙腈(10mL)中的搅拌溶液中加入4-[3-(4-羟基苯基)-4,4-二甲基-5-氧代-2-亚硫烷基咪唑烷-1-基]-2-(三氟甲基)苄腈(ABM-3,141mg,0.35mmol)和碳酸钾(144mg,1.04mmol)。将得到的混合物在油浴中在80℃搅拌过夜。LC-MS指示期望产物的形成。然后将反应混合物用乙酸乙酯(20mL×2)萃取。将有机层合并,用饱和氯化钠水溶液(20mL)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚,v:v=1:1)纯化以得到0.22g作为黄色油的BG。^{1}H NMR(400MHz,$CDCl_3$):δ7.96(s,2H),7.86(d,J=8.6Hz,1H),7.19(d,J=8.8Hz,2H),7.02(d,J=8.6Hz,2H),4.50(s,2H),4.30(t,J=6.4Hz,2H),4.02(t,J=6.4Hz,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);质量(ES^+):m/z 686.35[MNa^+]。

[0708] 步骤2:2-(3-[[5-(4-[3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯氧基)戊基]氧基]丙氧基)乙酸(BH)的合成

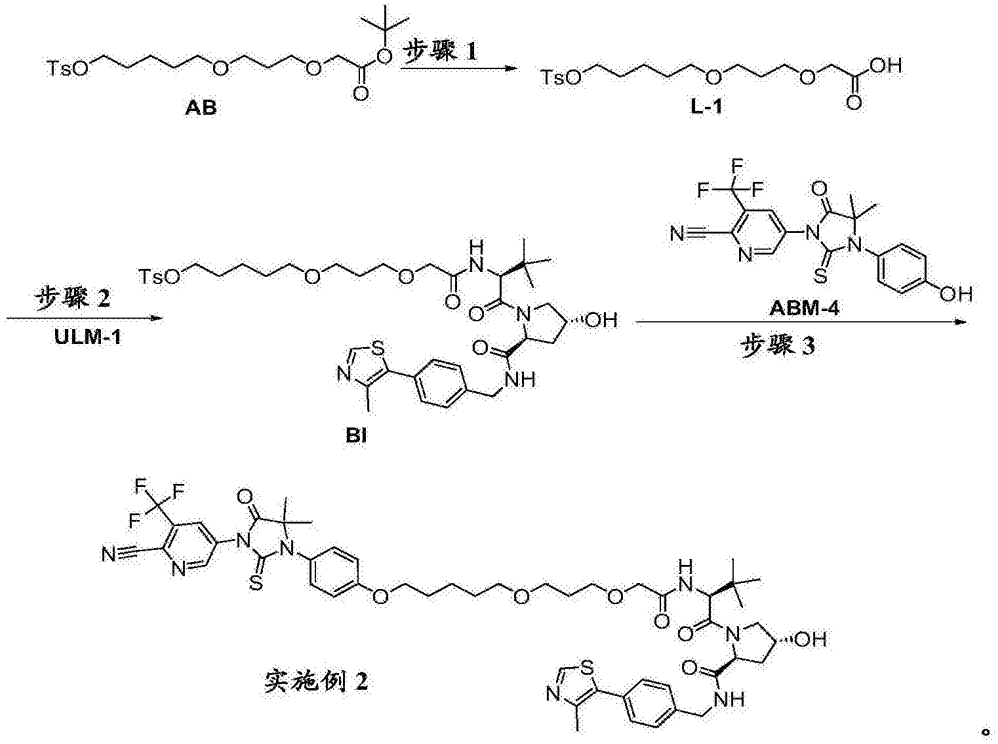
[0709] 向2-(3-{[5-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)戊基]氧基}丙氧基)乙酸叔丁酯(BG,220mg,0.33mmol)在二噁烷(4.0mL)中的搅拌溶液中加入氯化氢(2N在水中,1.0mL)。将得到的混合物在80℃搅拌2h。

LC-MS指示期望产物的形成。将得到的混合物在减压下浓缩以得到200mg作为浅黄色油的BH。质量(ES+):m/z 608.25[MH+]。

[0710] 步骤3:实施例1的合成:

[0711] 向2-(3-[[5-(4-[3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯氧基)戊基]氧基]丙氧基)乙酸(BH,160mg,0.26mmol)在N,N-二甲基甲酰胺(5mL)中的搅拌溶液中加入(2S,4R)-1-[(2S)-2-氨基-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺盐酸盐(ULM-1,182mg,0.39mmol)、DIPEA(151mg,1.17mmol)、EDCI(101mg,0.53mmol)和HOBt(70mg,0.52mmol)。将得到的混合物在室温搅拌5h且LC-MS指示期望产物的形成。将水(20mL)加入反应物,将得到的混合物用乙酸乙酯(20mL×2)萃取。将有机层合并,用饱和氯化钠水溶液(20mL)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物。将残余物通过制备型HPLC纯化以得到60mg作为白色固体的实施例1。^{1}H NMR(400MHz,CD_3OD):δ8.88(s,1H),8.16(d,J=8.0Hz,2H),8.00(s,1H),7.49-7.42(m,4H),7.28(d,J=8.8Hz,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=2.28min(3.6分钟运行)。

[0712] 实施例2:(2S,4R)-1-((S)-2-(2-(3-(5-(4-(3-(6-氰基-5-(三氟甲基)吡啶-3-基)-5,5-二甲基-4-氧代-2-硫代咪唑烷-1-基)苯氧基)戊氧基)丙氧基)乙酰氨基)-3,3-二甲基丁酰基)-4-羟基-N-(4-(4-甲基噻唑-5-基)苄基)吡咯烷-2-甲酰胺:

[0713] 

[0714] 步骤1:2-[3-({5-[(4-甲基苯磺酰基)氧基]戊基}氧基)丙氧基]乙酸(L-1)的合成

[0715] 在室温向2-[3-({5-[(4-甲基苯磺酰基)氧基]戊基}氧基)丙氧基]乙酸叔丁酯(AB,1.3g,3.02mmol)在二氯甲烷(10mL)中的搅拌溶液中加入三氟乙酸(10mL)。将得到的溶

液在室温搅拌3h。然后将反应混合物在真空下浓缩以得到1.5g(粗制物)L-1,将其不经任何进一步纯化用于下一步。LC-MS(ES+):m/z 375.34[MH+],tR=1.39min(2.6分钟运行)。

[0716] 步骤2:(2S,4R)-1-[(2S)-3,3-二甲基-2-{2-[3-({5-[(4-甲基苯磺酰基)氧基]戊基}氧基)丙氧基]乙酰氨基}丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺(BI)的合成

[0717] 在室温向2-[3-({5-[(4-甲基苯磺酰基)氧基]戊基}氧基)丙氧基]乙酸(L-1,1.5g,4.01mmol)在N,N-二甲基甲酰胺(20mL)中的搅拌溶液中加入HATU(1.36g,3.58mmol)、DIEA(0.7mL)和(2S,4R)-1-[(2S)-2-氨基-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺(ULM-1,1.3g,3.02mmol)。将得到的混合物在室温搅拌2h。然后将它用水(100mL)稀释,并用乙酸乙酯(100mL×3)萃取。将有机层合并,用饱和氯化钠水溶液(60mL)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:二氯甲烷/甲醇(v:v=10:1))纯化以得到0.5g BI。LC-MS(ES+):m/z 787.34[MH+],tR=1.87min(3.0分钟运行)。

[0718] 步骤3:(2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{3-[6-氰基-5-(三氟甲基)吡啶-3-基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)戊基]氧基}丙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺(实施例2)的合成

[0719] 在氮气氛下向5-[3-(4-羟基苯基)-4,4-二甲基-5-氧代-2-亚硫烷基咪唑烷-1-基]-3-(三氟甲基)吡啶-2-甲腈(ABM-4,52mg,0.13mmol)、(2S,4R)-1-[(2S)-3,3-二甲基-2-{2-[3-({5-[(4-甲基苯磺酰基)氧基]戊基}氧基)丙氧基]乙酰氨基}丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺(BI,100mg,0.13mmol)在N,N-二甲基甲酰胺(10mL)中的搅拌溶液中加入碳酸钾(34mg,0.25mmol)。将得到的溶液在80℃搅拌2h。将得到的混合物在真空下浓缩以得到粗残余物,将其通过制备型HPLC纯化以得到38.1mg作为白色固体的实施例2。^{1}H NMR(300MHz,CD_3OD):δ9.12(s,1H),8.83(s,1H),8.63(s,1H),7.44-7.39(m,4H),7.00(d,J=9.0Hz,2H),7.20(d,J=9.0Hz,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/z1021.12[MH+],tR=2.36min(3.6分钟运行)。

[0720] 除非另外指出,否则根据上面关于实施例1和2的合成描述的类似程序,利用对应的试剂、中间体和起始原料合成下述实施例。

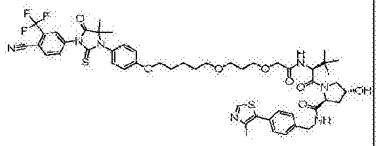
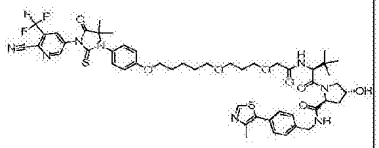
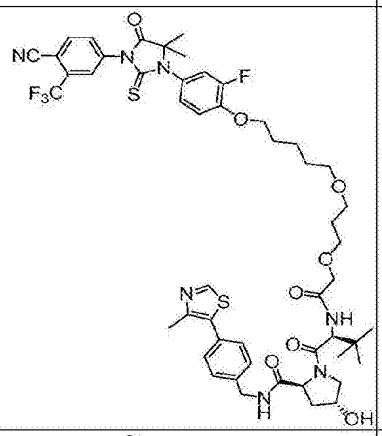
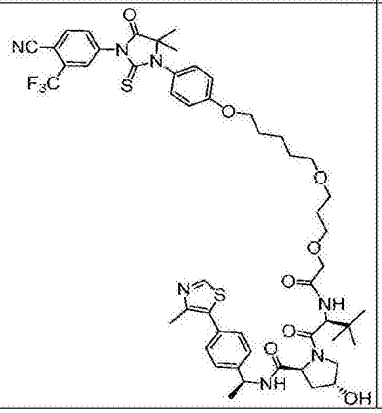
[0721] 当提及本文中呈现的具体示例性化合物时,本说明书使用术语“实施例#”。例如,化合物1(表2)也被称作实施例1。

[0722] 表2.示例性的化合物.

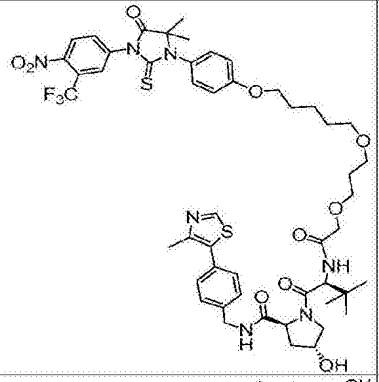
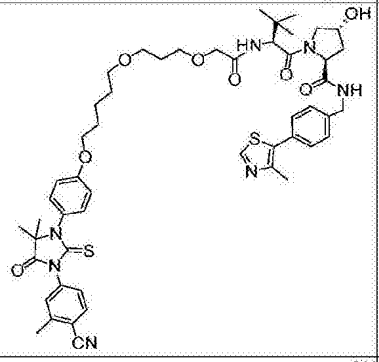
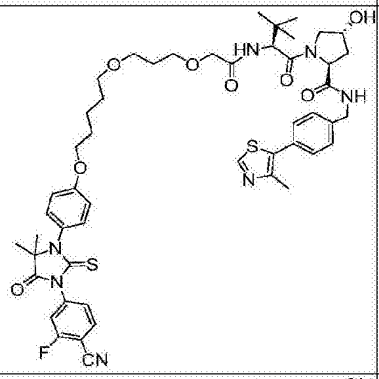
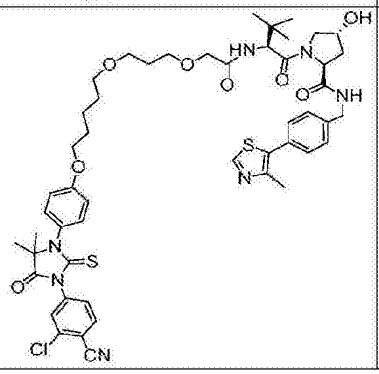
[0723]

实施例#	结构	化合物名称和分析数据

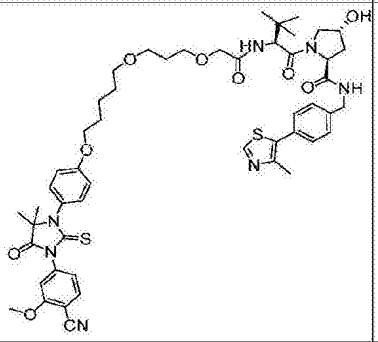
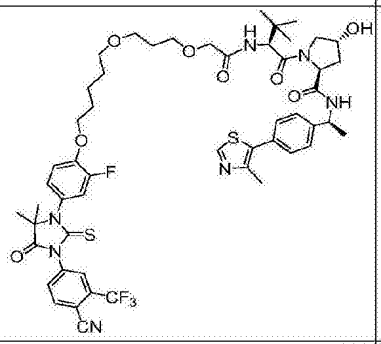
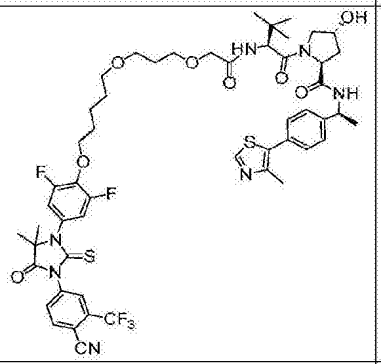
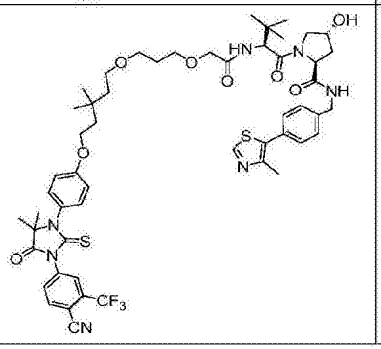
[0724]

实施例#	结构	化合物名称和分析数据
1		(2S,4R)-1-((S)-2-(2-(3-(5-(4-(3-(4-氰基-3-(三氟甲基)苯基)-5,5-二甲基-4-氧代-2-硫代咪唑烷-1-基)苯氧基)戊氧基)丙氧基)乙酰氨基)-3,3-二甲基丁酰基)-4-羟基-N-(4-(4-甲基噻唑-5-基)苄基)吡咯烷-2-甲酰胺 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); 质量(ES+): m/z 686.35 [MNa+]
2		(2S,4R)-1-((S)-2-(2-(3-(5-(4-(3-(6-氰基-5-(三氟甲基)吡啶-3-基)-5,5-二甲基-4-氧代-2-硫代咪唑烷-1-基)苯氧基)戊氧基)丙氧基)乙酰氨基)-3,3-二甲基丁酰基)-4-羟基-N-(4-(4-甲基噻唑-5-基)苄基)吡咯烷-2-甲酰胺 1H NMR (300 MHz, CD3OD): δ9.12 (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 分钟运行).
3		从 ABM-16、L-1 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-2-氟苯氧基)戊基]氧基}丙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{1}H NMR (300 MHz, CD_3OD): δ8.84 (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 分钟运行)
4		从 ABM-3、L-1 和 ULM-3 制备 (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)戊基]氧基}丙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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 分钟运行)

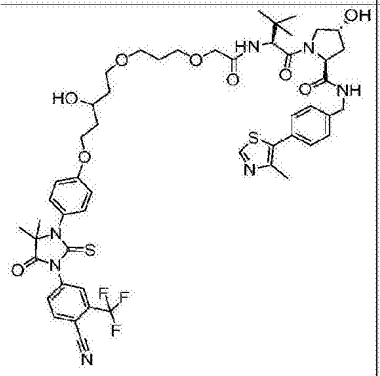
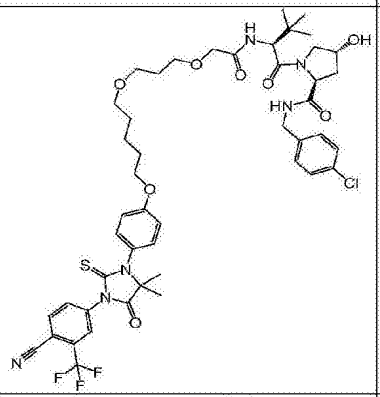
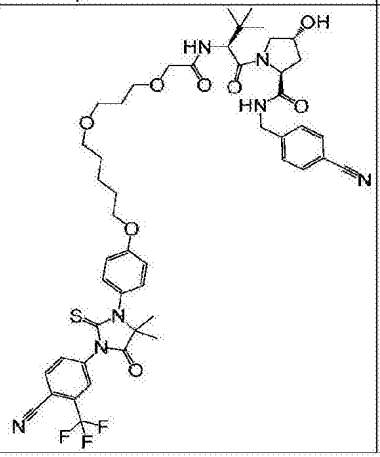
[0725]

实施例#	结构	化合物名称和分析数据
5		从 ABM-17、L-1 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{5,5-二甲基-3-[4-硝基-3-(三氟甲基)苯基]-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)戊基]氧基}丙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{1}H NMR (300 MHz, CD_3OD): δ8.82 (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 分钟运行)
6		从 ABM-6、L-1 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(2-{3-[(5-{4-[3-(4-氰基-3-甲基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯氧基}戊基)氧基]丙氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
7		从 ABM-2、L-1 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(2-{3-[(5-{4-[3-(4-氰基-3-氟苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯氧基}戊基)氧基]丙氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行)
8		从 ABM-1、L-1 和 ULM-1 制备 2S,4R)-1-[(2S)-2-(2-{3-[(5-{4-[3-(3-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯氧基}戊基)氧基]丙氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行)

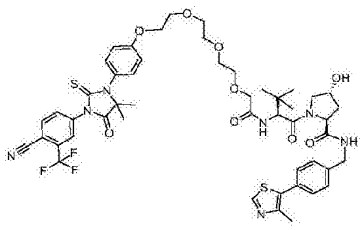
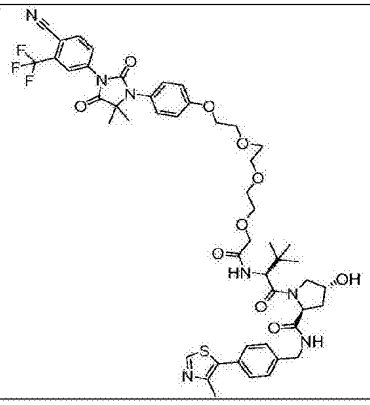
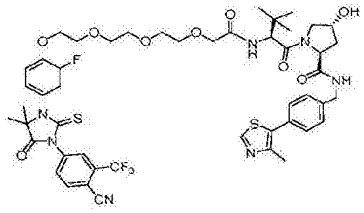
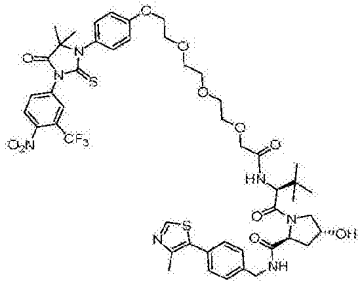
[0726]

实施例#	结构	化合物名称和分析数据
9		从 ABM-5、L-1 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(2-{3-[(5-{4-[3-(4-氰基-3-甲氧基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯氧基}戊基)氧基]丙氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行)
10		从 ABM-16、L-1 和 ULM-3 制备 (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-2-氟苯氧基)戊基]氧基}丙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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
11		从 ABM-18、L-1 和 ULM-3 制备 (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-2,6-二氟苯氧基)戊基]氧基}丙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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); 质量(ES^+): *m/z* 1070.50 [MH^+]
12		从 ABM-3、L-2 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)-3,3-二甲基戊基]氧基}丙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).

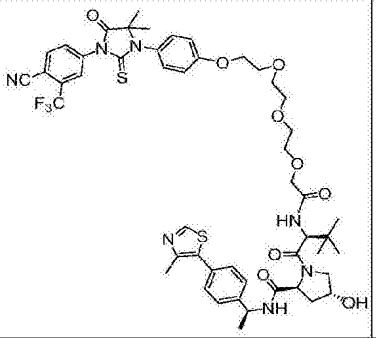
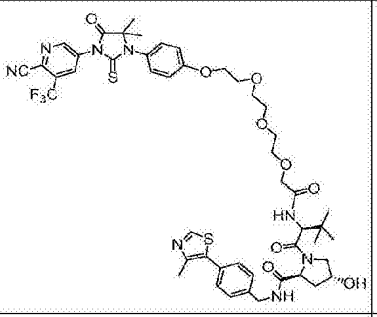
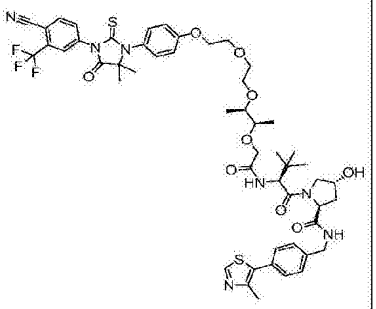
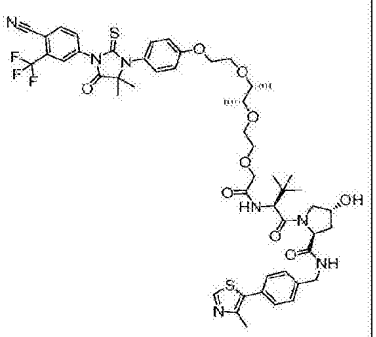
[0727]

实施例#	结构	化合物名称和分析数据
13		从 ABM-3、L-3 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)-3-羟基戊基]氧基}丙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
14		从 ABM-3、L-1 和 ULM-6 制备 (2S,4R)-N-[(4-氯苯基)甲基]-1-[(2S)-2-[2-(3-{[5-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)戊基]氧基}丙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基吡咯烷-2-甲酰胺 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		从 ABM-3、L-1 和 ULM-7 制备 (2S,4R)-1-[(2S)-2-[2-(3-{[5-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)戊基]氧基}丙氧基)乙酰氨基]-3,3-二甲基丁酰基]-N-[(4-氰基苯基)甲基]-4-羟基吡咯烷-2-甲酰胺 ^{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^+].

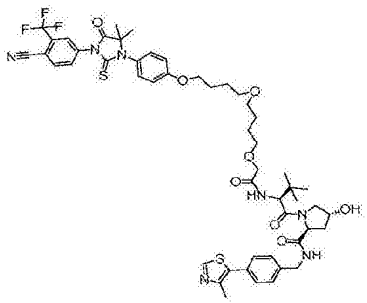
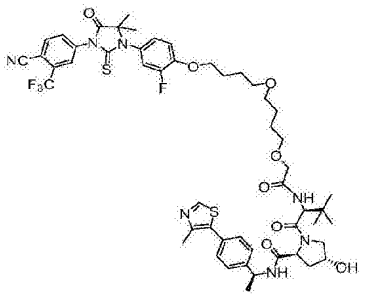
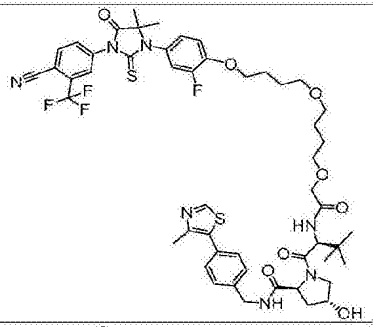
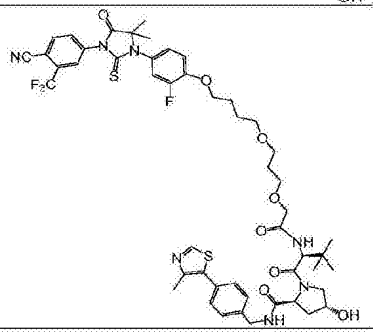
[0728]

实施例#	结构	化合物名称和分析数据
16		从 ABM-3、L-4 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-[2-(2-{2-[2-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)乙氧基]乙氧基}乙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
17		从 ABM-19、L-4 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-[2-(2-{2-[2-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-2,4-二氧代咪唑烷-1-基}苯氧基)乙氧基]乙氧基}乙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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); 质量(ES^+): m/z 992.38 [MH^+]
18		从 ABM-16、L-4 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-[2-(2-{2-[2-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-2-氟苯氧基)乙氧基]乙氧基}乙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
19		从 ABM-17、L-4 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-[2-(2-{2-[2-(4-{5,5-二甲基-3-[4-硝基-3-(三氟甲基)苯基]-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)乙氧基]乙氧基}乙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 (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 分钟运行).

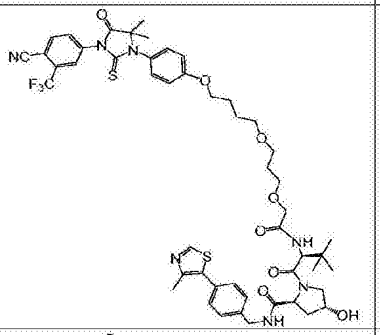
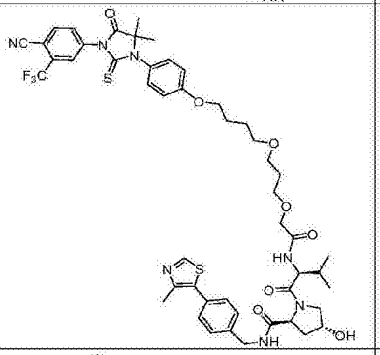
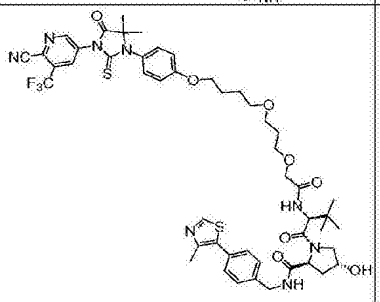
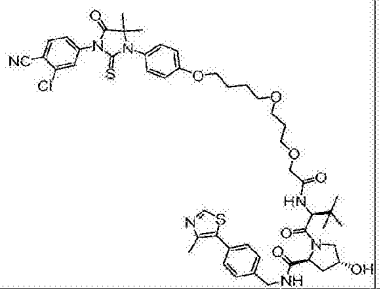
[0729]

实施例#	结构	化合物名称和分析数据
20		从 ABM-3、L-4 和 ULM-3 制备 (2S,4R)-1-[(2S)-2-[2-(2-{2-[2-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)乙氧基]乙氧基}乙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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 分钟运行).
21		从 ABM-4、L-4 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-[2-(2-{2-[2-(4-{3-[6-氰基-5-(三氟甲基)吡啶-3-基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)乙氧基]乙氧基}乙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
22		从 ABM-3、L-5 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(2-{[(2R,3R)-3-{2-[2-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)乙氧基]乙氧基}丁-2-基]氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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); 质量(ES^+): *m/z* 1036.47 [MH^+]
23		从 ABM-3、L-6 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-[2-(2-{[(2R,3R)-3-[2-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)乙氧基]丁-2-基]氧基}乙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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); 质量(ES^+): *m/z* 1036.47

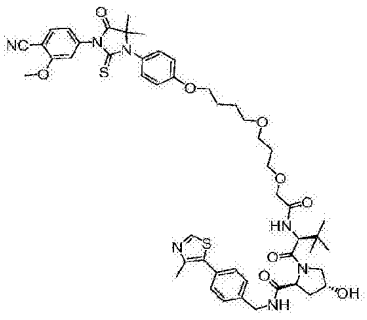
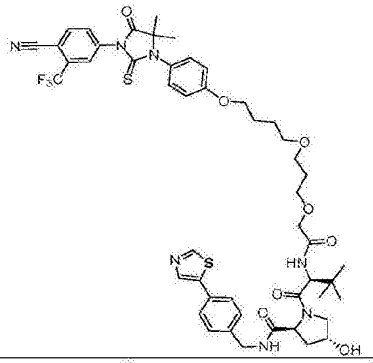
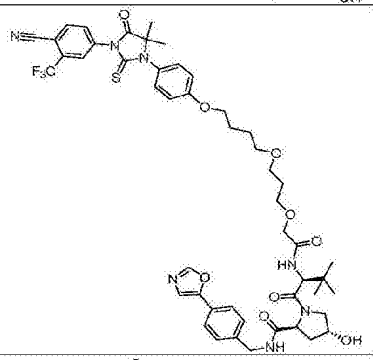
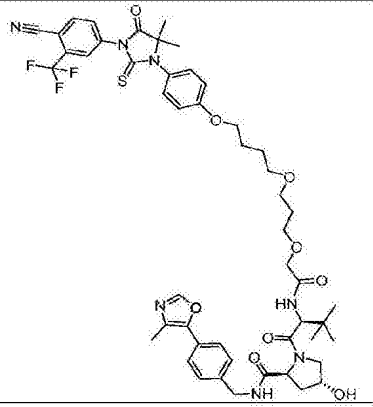
[0730]

实施例#	结构	化合物名称和分析数据
24		从 ABM-3、L-7 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)丁氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
25		从 ABM-16、L-7 和 ULM-3 制备 (2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-2-氟苯氧基)丁氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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); 质量(ES^+): *m/z* 1052.20 [MH^+]
26		从 ABM-16、L-7 和 ULM-3 制备 (2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-2-氟苯氧基)丁氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
27		从 ABM-16、L-8 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-2-氟苯氧基)丁氧基]丙氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{1}H NMR (300 MHz, CD_3OD): δ 8.87 (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 分钟运行).

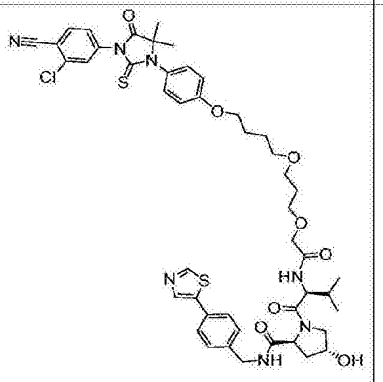
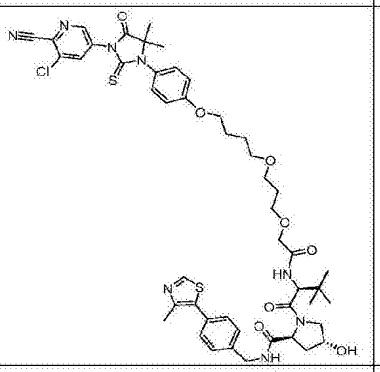
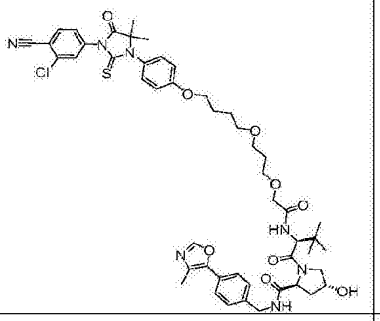
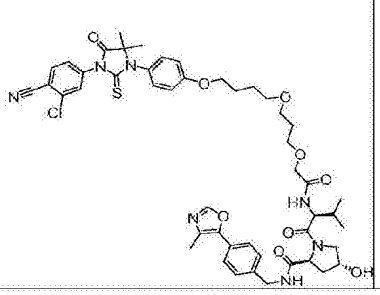
[0731]

实施例#	结构	化合物名称和分析数据
28		从 ABM-3、L-8 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)丁氧基]丙氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
29		从 ABM-3、L-8 和 ULM-8 制备 (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)丁氧基]丙氧基}乙酰氨基)-3-甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行)。
30		从 ABM-4、L-8 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[6-氰基-5-(三氟甲基)吡啶-3-基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)丁氧基]丙氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
31		从 ABM-1、L-8 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯氧基}丁氧基)丙氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).

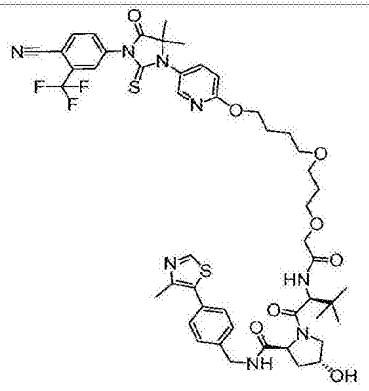
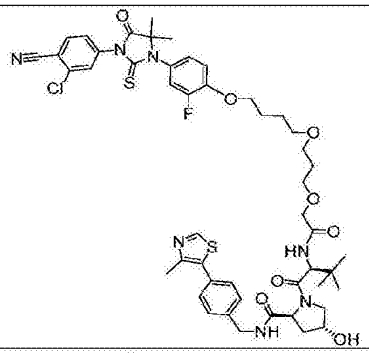
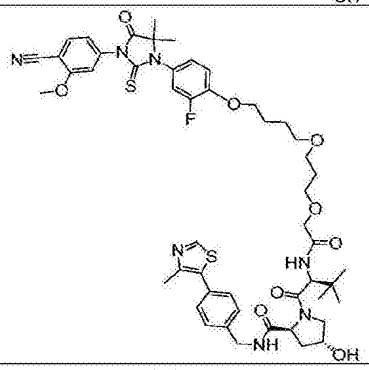
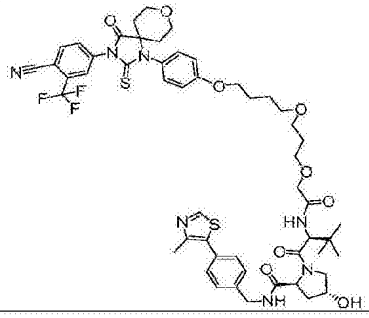
[0732]

实施例#	结构	化合物名称和分析数据
32		从 ABM-5、L-8 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(4-氰基-3-甲氧基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯氧基}丁氧基)丙氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
33		从 ABM-3、L-8 和 ULM-2 制备 (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)丁氧基]丙氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
34		从 ABM-3、L-8 和 ULM-4 制备 (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)丁氧基]丙氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
35		从 ABM-3、L-8 和 ULM-5 制备 (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)丁氧基]丙氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).

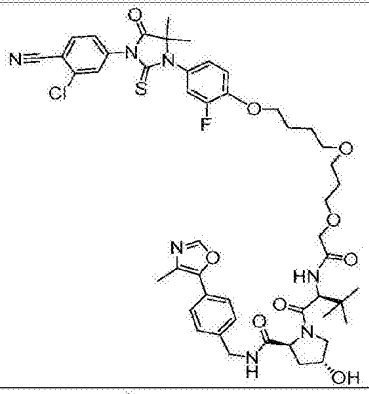
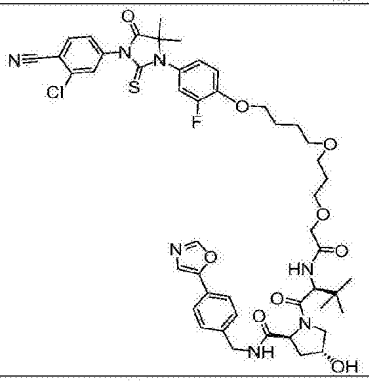
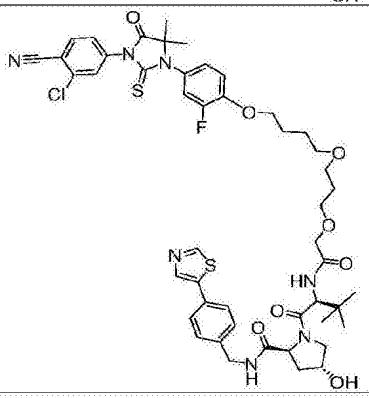
[0733]

实施例#	结构	化合物名称和分析数据
36		从 ABM-1、L-8 和 ULM-9 制备 (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯氧基}丁氧基)丙氧基]乙酰氨基}-3-甲基丁酰基]-4-羟基-N-{[4-(1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
37		从 ABM-1、L-8 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(5-氯-6-氰基吡啶-3-基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯氧基}丁氧基)丙氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
38		从 ABM-1、L-8 和 ULM-5 制备 (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯氧基}丁氧基)丙氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
39		从 ABM-1、L-8 和 ULM-10 制备 (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯氧基}丁氧基)丙氧基]乙酰氨基}-3-甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).

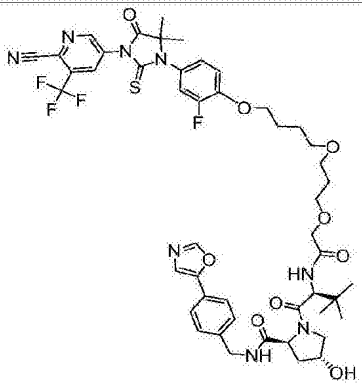
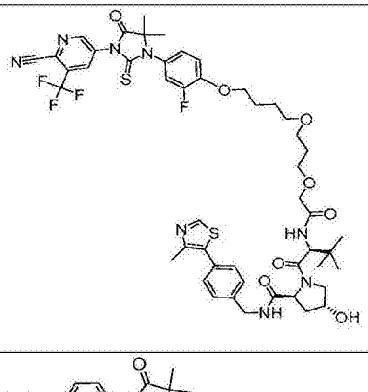
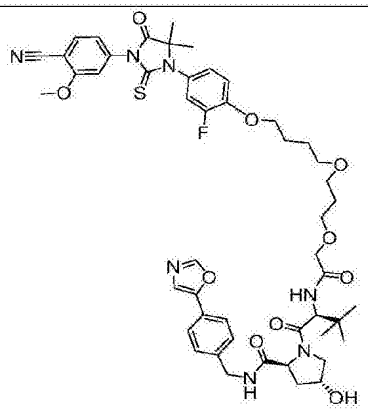
[0734]

实施例#	结构	化合物名称和分析数据
40		从 ABM-20、L-8 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-[2-(3-{4-[(5-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}吡啶-2-基)氧基]丁氧基}丙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
41		从 ABM-21、L-8 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]-2-氟苯氧基}丁氧基)丙氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
42		从 ABM-22、L-8 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(4-氰基-3-甲氧基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]-2-氟苯氧基}丁氧基)丙氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
43		从 ABM-8、L-8 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-4-氧代-2-亚硫烷基-8-氧杂-1,3-二氮杂螺[4.5]癸烷-1-基}苯氧基)丁氧基]丙氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).

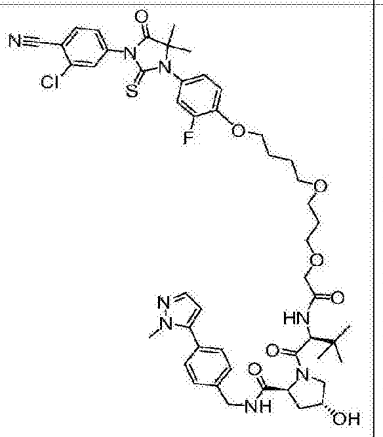
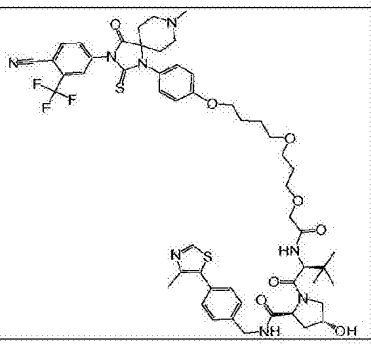
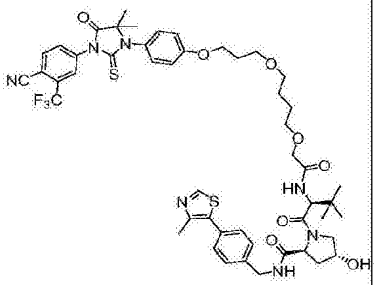
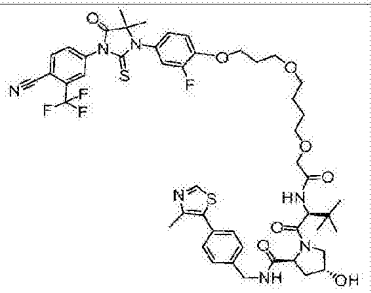
[0735]

实施例#	结构	化合物名称和分析数据
44		从 ABM-21、L-8 和 ULM-5 制备 (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]-2-氟苯氧基}丁氧基)丙氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
45		从 ABM-21、L-8 和 ULM-4 制备 (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]-2-氟苯氧基}丁氧基)丙氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
46		从 ABM-21、L-8 和 ULM-2 制备 (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]-2-氟苯氧基}丁氧基)丙氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).

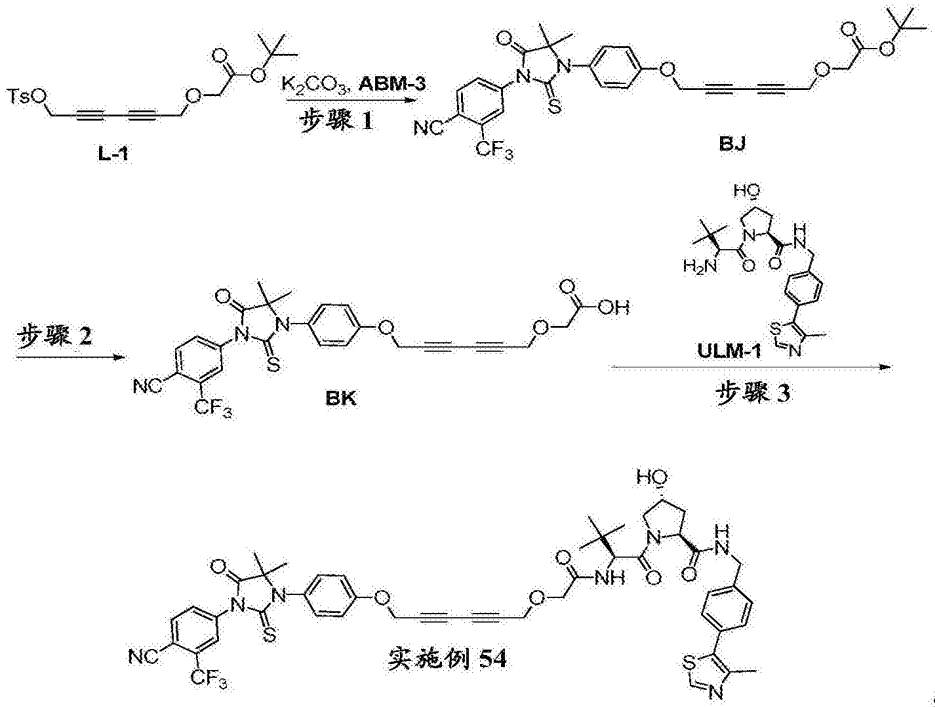
[0736]

实施例#	结构	化合物名称和分析数据
47		从 ABM-23、L-8 和 ULM-4 制备 (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[6-氰基-5-(三氟甲基)吡啶-3-基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-2-氟苯氧基)丁氧基]丙氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
48		从 ABM-23、L-8 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[6-氰基-5-(三氟甲基)吡啶-3-基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-2-氟苯氧基)丁氧基]丙氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行)
49		从 ABM-22、L-8 和 ULM-4 制备 (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(4-氰基-3-甲氧基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]-2-氟苯氧基}丁氧基)丙氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).

[0737]

实施例#	结构	化合物名称和分析数据
50		从 ABM-21、L-8 和 ULM-11 制备 (2S,4R)-1-[(2S)-2-{2-[3-(4-{4-[3-(3-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]-2-氟苯氧基}丁氧基)丙氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1-甲基-1H-吡唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行)
51		从 ABM-9、L-8 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-8-甲基-4-氧代-2-亚硫烷基-1,3,8-三氮杂螺[4.5]癸烷-1-基}苯氧基)丁氧基]丙氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
52		从 ABM-3、L-9 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(2-{4-[3-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)丙氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
53		从 ABM-16、L-9 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(2-{4-[3-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-2-氟苯氧基)丙氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).

[0738] 实施例54:(2S,4R)-1-((S)-2-(2-(6-(4-(3-(4-氰基-3-(三氟甲基)苯基)-5,5-二甲基-4-氧代-2-硫代咪唑烷-1-基)苯氧基)己-2,4-二炔基氧基)乙酰氨基)-3,3-二甲基丁酰基)-4-羟基-N-(4-(4-甲基噻唑-5-基)苄基)吡咯烷-2-甲酰胺:

[0739] 

[0740] 步骤1:2-{[6-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)己-2,4-二炔-1-基]氧基}乙酸叔丁酯(BJ)的合成

[0741] 根据关于实施例1的合成在反应步骤1中描述的类似程序合成该物质。LC-MS(ES+):m/z 634.05[MNa^+],t_R=1.26min(2.0分钟运行)。

[0742] 步骤2:2-{[6-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)己-2,4-二炔-1-基]氧基}乙酸(BK)的合成

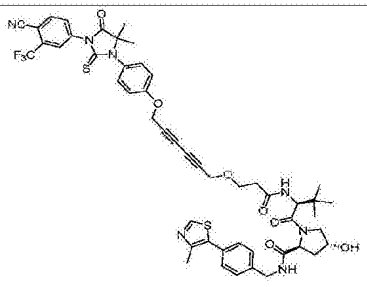
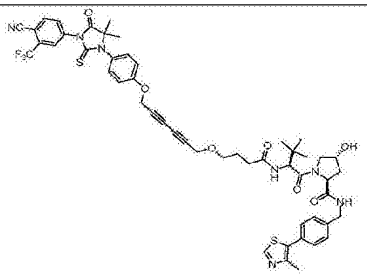
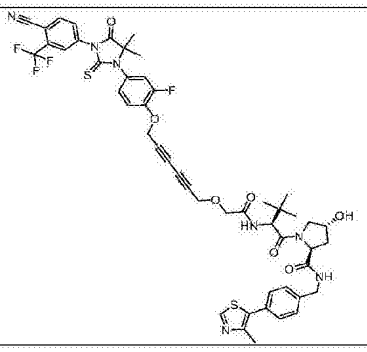
[0743] 根据关于实施例1的合成在反应步骤2中描述的类似程序合成该物质。LC-MS(ES+):m/z 556.10[MH^+],t_R=1.54min(2.6分钟运行)。

[0744] 步骤3:(2S,4R)-1-[(2S)-2-(2-{[6-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)己-2,4-二炔-1-基]氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺(实施例54)的合成

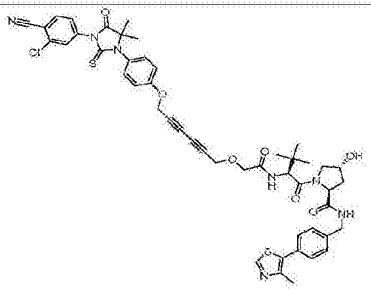
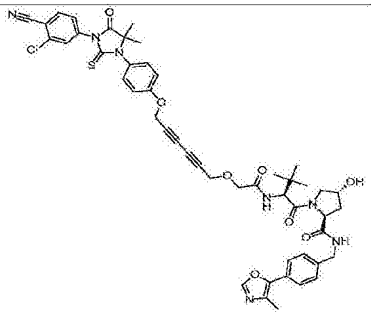
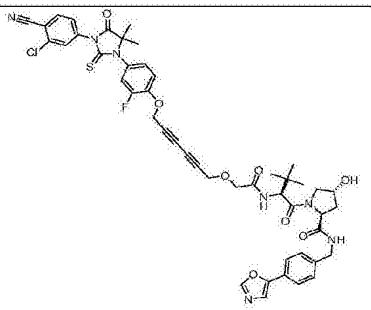
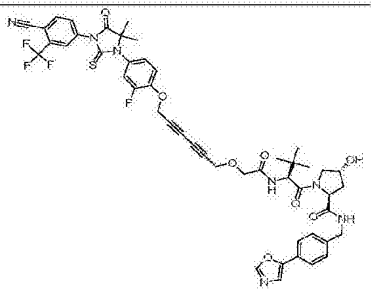
[0745] 根据关于实施例1的合成在反应步骤3中描述的类似程序合成该物质。^1H NMR(400MHz,CD_3OD):δ8.88(s,1H),8.15(d,J=8.4Hz,2H),8.00(d,J=1.6Hz,1H),7.49-7.43(m,4H),7.34(d,J=8.8Hz,2H),7.14(d,J=8.8Hz,2H),4.93(s,2H),4.71(s,1H),4.60-4.34(m,6H),4.08(s,2H),3.90-3.80(m,2H),2.49(s,3H),2.25-2.22(m,1H),2.13-2.05(m,1H),1.56(s,6H),1.03(s,9H);LC-MS(ES+):m/z 968.45[MH^+],t_R=1.67min(3.0分钟运行)。

[0746] 表3.示例性的化合物.

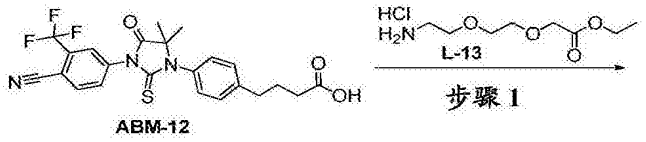
[0747]

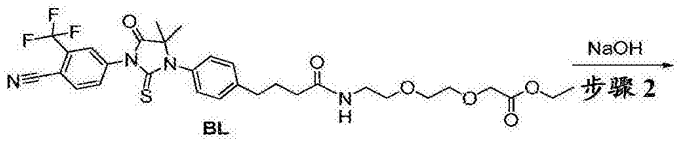
实施例#	结构	化合物名称和分析数据
55		从 ABM-3、L-11 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(3-{[6-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)己-2,4-二炔-1-基]氧基}丙酰氨基（propanamido）)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{1}H NMR (400 MHz, CD_3OD): δ 8.88 (s, 1H), 8.16 (d, *J* = 8.8 Hz, 2H), 7.99 (d, *J* = 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 分钟运行).
56		从 ABM-3、L-12 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(4-{[6-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)己-2,4-二炔-1-基]氧基}丁酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
57		从 ABM-16、L-10 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(2-{[6-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-2-氟苯氧基)己-2,4-二炔-1-基]氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).

[0748]

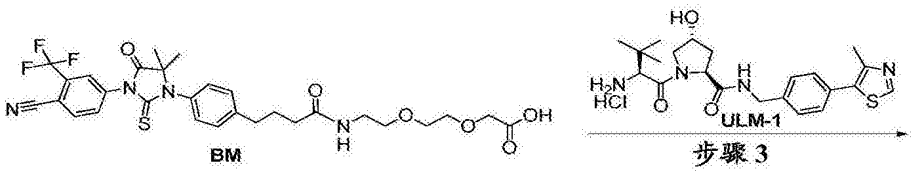
实施例#	结构	化合物名称和分析数据
58		从 ABM-1、L-10 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-{2-[(6-{4-[3-(3-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯氧基}己-2,4-二炔-1-基)氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{1}H NMR (400 MHz, CD_3OD): δ 8.88 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.87 (s, 1H), 7.66-7.64 (m, 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), 1.01 (s, 9H); LC-MS (ES$^+$): *m/z* 934.20 [MH$^+$], t_R = 1.54 min (3.0 分钟运行).
59		从 ABM-1、L-10 和 ULM-5 制备 (2S,4R)-1-[(2S)-2-{2-[(6-{4-[3-(3-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯氧基}己-2,4-二炔-1-基)氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
60		从 ABM-21、L-10 和 ULM-4 制备 (2S,4R)-1-[(2S)-2-{2-[(6-{4-[3-(3-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]-2-氟苯氧基}己-2,4-二炔-1-基)氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
61		从 ABM-16、L-10 和 ULM-4 制备 (2S,4R)-1-[(2S)-2-(2-{[6-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-2-氟苯氧基)己-2,4-二炔-1-基]氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).

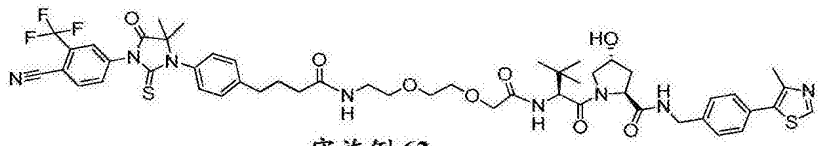
[0749] 实施例62:(2S,4R)-1-((S)-2-叔丁基-16-(4-(3-(4-氰基-3-(三氟甲基)苯基)-5,5-二甲基-4-氧代-2-硫代咪唑烷-1-基)苯基)-4,13-二氧代-6,9-二氧杂-3,12-二氮杂十六烷)-4-羟基-N-(4-(4-甲基噻唑-5-基)苄基)吡咯烷-2-甲酰胺:





[0750]





实施例 62

[0751] 步骤1:2-(2-{2-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)丁酰氨基]乙氧基}乙氧基)乙酸乙酯(BL)的合成

[0752] 在0℃向4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)丁酸(ABM-12,417mg,0.88mmol)在N,N-二甲基甲酰胺(10mL)中的搅拌溶液中加入HATU(669mg,1.76mmol)、DIEA(454mg,3.51mmol)和2-[2-(2-氨基乙氧基)乙氧基]乙酸乙酯盐酸盐(L-13,400mg,1.76mmol)。将得到的溶液在0℃搅拌30min,然后将它温热至室温并在室温搅拌15h。将水/冰的混合物(1:1,50mL)加入反应物中,将得到的混合物用乙酸乙酯(100mL×3)萃取。将有机层合并,用饱和氯化钠水溶液(20mL×2)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:1)纯化以得到作为黄色固体的BL(收率:35%)。LC-MS(ES^+):m/z 649.15[MH^+],t_R=1.05min(2.0分钟运行)。

[0753] 步骤2:2-(2-{2-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)丁酰氨基]乙氧基}乙氧基)乙酸(BM)的合成

[0754] 在室温向2-(2-{2-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)丁酰氨基]乙氧基}乙氧基)乙酸乙酯(BL,200mg,0.31mmol)在甲醇(10mL)中的搅拌溶液中加入NaOH(123mg,3.08mmol)在水(10mL)中的溶液。然后将得到的溶液加热至50℃并在该温度搅拌2h。将大部分有机溶剂在减压下除去。向剩余的残余物中加入氯化氢水溶液(1M)以调节pH至~3。将得到的混合物用乙酸乙酯(50mL×2)萃取,将有机层合并,用饱和氯化钠水溶液(20mL×2)洗涤,经无水硫酸钠干燥并然后在减压下继之以高真空泵浓缩以得到作为黄色固体的BM(收率:78%)。LC-MS(ES^+):m/z 621.20[MH^+],t_R=0.96min(2.0分钟运行)。

[0755] 步骤3:(2S,4R)-1-[(2S)-2-[2-(2-{2-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-

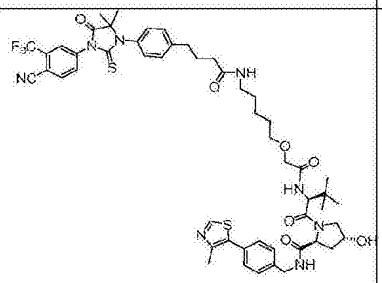
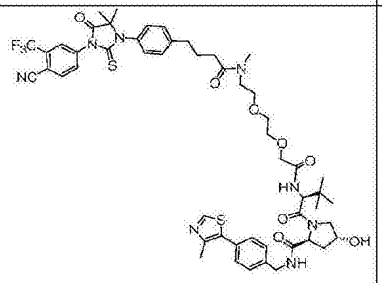
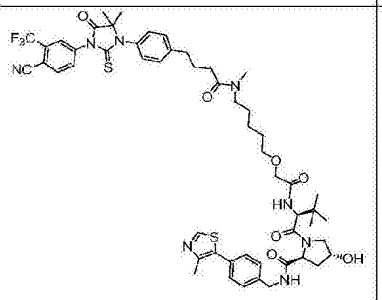
5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)丁酰氨基]乙氧基}乙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺(实施例62)的合成

[0756] 在0℃向2-(2-{2-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)丁酰氨基]乙氧基}乙氧基)乙酸(BM,200mg,0.32mmol)在N,N-二甲基甲酰胺(20mL)中的搅拌溶液中加入HATU(245mg,0.64mmol)、DIEA(166mg,1.28mmol)和(2S,4R)-1-[(2S)-2-氨基-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺盐酸盐(ULM-1,226mg,0.48mmol)。将得到的溶液在0℃搅拌30min,然后将它温热至室温并在室温搅拌15h。将水/冰的混合物(1:1,50mL)加入反应物中,将得到的混合物用乙酸乙酯(100mL×3)萃取。将有机层合并,用饱和氯化钠水溶液(50mL)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物,将其通过制备型HPLC纯化以得到作为黄色固体的实施例62(收率:6%)。^{1}H NMR(400MHz,CD_3OD):δ8.89(s,1H),8.18-8.16(d,J=8.4Hz,2H),8.01-7.99(d,J=8.0Hz,1H),7.47-7.41(m,4H),7.38-7.36(d,J=8.4Hz,2H),7.30-7.28(d,J=8.4Hz,2H),4.87(s,1H),4.78-4.60(m,3H),4.39-4.35(d,J=15.2Hz,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=3.06min(5.6分钟运行)。

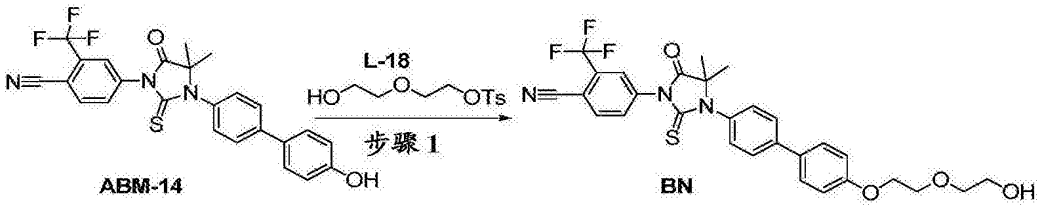
[0757] 根据关于实施例62的合成描述的类似程序,使用对应的起始原料和中间体合成实施例63-65。

[0758] 表4.示例性的化合物.

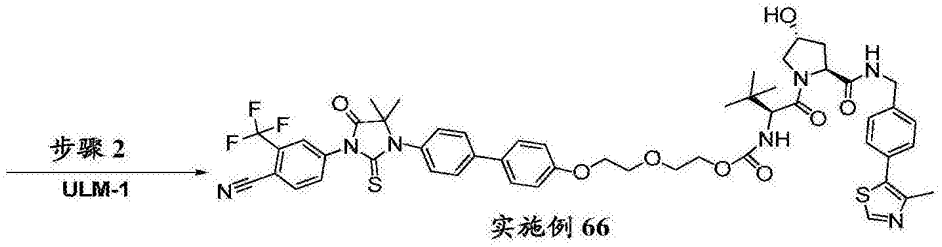
[0759]

实施例#	结构	化合物名称和分析数据
63		从 ABM-12、L-14 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-[2-({5-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)丁酰氨基]戊基}氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
64		从 ABM-12、L-15 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-[2-(2-{2-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)-N-甲基丁酰氨基]乙氧基}乙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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), 1.02 (s, 9H); LC-MS (ES$^+$): *m/z* 1047.80 [MH$^+$], t_R = 2.09 min (3.6 分钟运行)。
65		从 ABM-12、L-16 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-[2-({5-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)-N-甲基丁酰氨基]戊基}氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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); 质量(ES$^+$): *m/z* 1045.40 [MH$^+$]

[0760] 实施例66:(S)-1-((2S,4R)-4-羟基-2-(4-(4-甲基噻唑-5-基)苄基氨基甲酰基)吡咯烷-1-基)-3,3-二甲基-1-氧代丁-2-基氨基甲酸-2-(2-(4'-(3-(4-氰基-3-(三氟甲基)苯基)-5,5-二甲基-4-氧代-2-硫代咪唑烷-1-基)联苯-4-基氧基)乙氧基)乙酯:



[0761]



[0762] 步骤1:4-[3-(4-{4-[2-(2-羟基乙氧基)乙氧基]苯基}苯基)-4,4-二甲基-5-氧代-2-亚硫烷基咪唑烷-1-基]-2-(三氟甲基)苄腈(BN)的合成

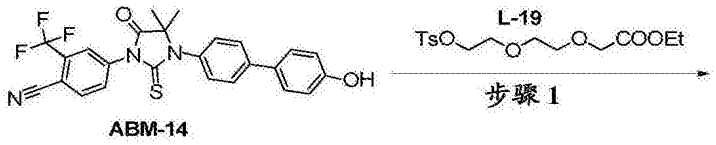
[0763] 在室温向4-{3-[4-(4-羟基苯基)苯基]-4,4-二甲基-5-氧代-2-亚硫烷基咪唑烷-1-基}-2-(三氟甲基)苄腈(ABM-14,610.5mg,1.27mmol)在N,N-二甲基甲酰胺(10mL)中的搅拌溶液中加入K_2CO_3(318.46mg,2.29mmol)和2-{2-[(4-甲基苯磺酰基)氧基]乙氧基}乙烷-1-醇(L-18,300mg,1.15mmol)。然后将得到的混合物在油浴中在80℃搅拌2小时,LC-MS指示期望产物的形成。将反应混合物冷却至室温,加入水(20mL)并将得到的混合物用乙酸乙酯(100mL×2)萃取。将有机层合并,用饱和氯化钠水溶液(20mL)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=7:3)纯化以得到作为浅黄色油的BN(收率:66%)。LC-MS(ES^+):m/z 570,[MH^+],t_R=1.60min(2.0分钟运行)。

[0764] 步骤2:N-[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酸-2-{2-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]乙氧基}乙酯(实施例66)的合成

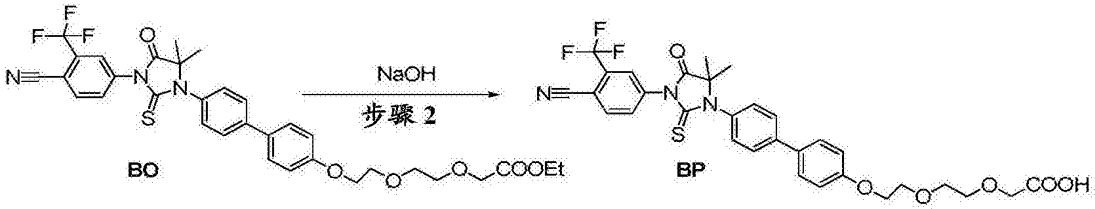
[0765] 向4-[3-(4-{4-[2-(2-羟基乙氧基)乙氧基]苯基}苯基)-4,4-二甲基-5-氧代-2-亚硫烷基咪唑烷-1-基]-2-(三氟甲基)苄腈(200mg,0.35mmol)在二氯甲烷(10mL)中的搅拌溶液中加入三乙胺(106.5mg,1.05mmol),随后在0℃在30min中缓慢地加入三光气(36.5mg,0.12mmol)。然后在0℃向该混合物中加入(2S,4R)-1-[(2S)-2-氨基-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺盐酸盐(ULM-1,196.9mg,0.42mmol)。然后将得到的混合物温热至室温并在室温搅拌2小时。将水(20mL)加入反应物中并将得到的混合物用二氯甲烷(50mL×3)萃取。将有机层合并,用饱和氯化钠水溶液(20mL)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物,将其通过制备型HPLC纯化以得到作为白色固体的实施例66(收率:6%)。^{1}H-NMR(400MHz,CD_3OD):δ8.88(s,1H),8.20-8.17(m,2H),8.04-8.02(d,J=8.0Hz,1H),7.77-7.72(m,2H),7.65-7.59(m,2H),7.48-7.42(m,6H),7.08-7.06(d,J=8.4Hz,2H),4.61-4.53(m,1H),4.47-4.44(s,1H),4.38-4.34(m,2H),4.25-4.20(m,4H),3.92-3.90(m,3H),3.82-3.79(m,3H),2.48(s,3H),

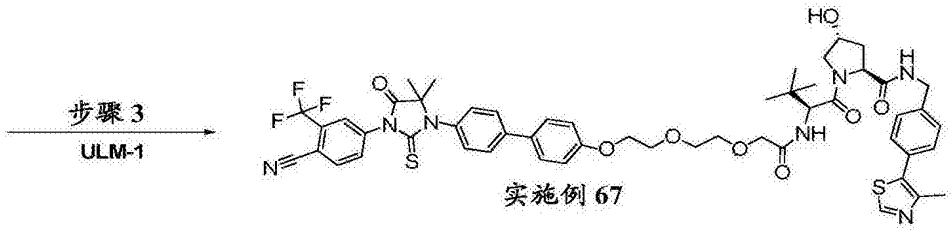
2.26-2.21(m,1H),2.13-1.09(m,1H),1.61(s,6H),1.30(s,1H),1.04(s,9H);LC-MS(ES+):m/z 1026.40[MH+],tR=2.23min(3.0分钟运行)。

[0766] 实施例67:(2S,4R)-1-((S)-2-(2-(2-(2-(4'-(3-(4-氰基-3-(三氟甲基)苯基)-5,5-二甲基-4-氧代-2-硫代咪唑烷-1-基)联苯-4-基氧基)乙氧基)乙氧基)乙酰氨基)-3,3-二甲基丁酰基)-4-羟基-N-(4-(4-甲基噻唑-5-基)苄基)吡咯烷-2-甲酰胺:



[0767]





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[0768] 步骤1:2-(2-{2-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]乙氧基}乙氧基)乙酸乙酯(BO)的合成

[0769] 向4-{3-[4-(4-羟基苯基)苯基]-4,4-二甲基-5-氧代-2-亚硫烷基咪唑烷-1-基}-2-(三氟甲基)苄腈(ABM-14,300mg,0.62mmol)在N,N-二甲基甲酰胺(10mL)中的搅拌溶液中加入K_2CO_3(172mg,1.24mmol)和2-(2-{2-[(4-甲基苯磺酰基)氧基]乙氧基}乙氧基)乙酸乙酯(L-19,237.4mg,0.69mmol)。将得到的混合物在油浴中在80℃搅拌2小时。将反应物冷却至室温,加入水(50mL)并将得到的混合物用乙酸乙酯(100mL×2)萃取。将有机层合并,用饱和氯化钠水溶液(30mL×3)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=3:7))纯化以得到作为浅黄色油的BO(收率:48%)。LC-MS(ES+):m/z 656,[MH+],tR=1.19min(2.0分钟运行)。

[0770] 步骤2:2-(2-{2-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]乙氧基}乙氧基)乙酸(BP)的合成

[0771] 在室温向2-(2-{2-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]乙氧基}乙氧基)乙酸乙酯(BO,198mg,0.30mmol)在乙醇(5mL)中的搅拌溶液中加入氢氧化钠(36.3mg,0.91mmol)在水(2mL)中的溶液。将得到的溶液在室温搅拌过夜,然后将大部分有机溶剂在减压下除去。向剩余的含水残余物中加入氯化氢水溶液(1N)以调节pH至~5.0,并将得到的混合物用乙酸乙酯(250mL×2)萃取。将

有机层合并，经无水硫酸钠干燥并在减压下继之以高真空泵浓缩以得到作为浅黄色油的BP(收率：99％)。LC-MS(ES+)：m/z 628，[MH+]，tR＝1.08min(2.0分钟运行)。

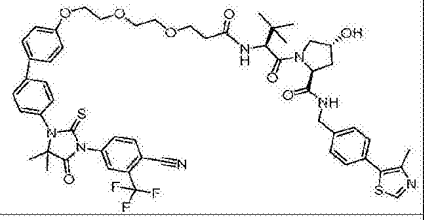
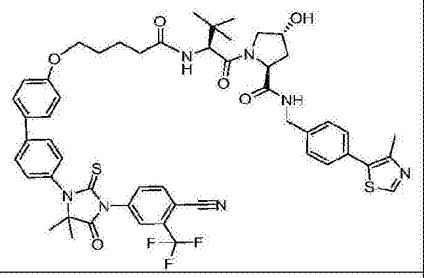
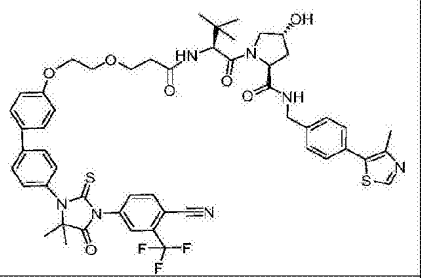
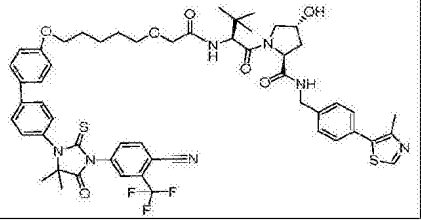
[0772] 步骤3：(2S,4R)-1-[(2S)-2-[2-(2-{2-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]乙氧基}乙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺(实施例67)的合成

[0773] 向2-(2-{2-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]乙氧基}乙氧基)乙酸(BP，190mg，0.30mmol)在N,N-二甲基甲酰胺(10mL)中的搅拌溶液中加入HATU(149.7mg，0.39mmol)、DIEA(156.4mg，1.21mmol)和(2S,4R)-1-[(2S)-2-氨基-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺盐酸盐(ULM-1，183.9mg，0.39mmol)。将得到的溶液在室温搅拌2小时。加入水(50mL)并将得到的混合物用乙酸乙酯(100mL×2)萃取。将有机层合并，用饱和氯化钠水溶液(25mL×3)洗涤，经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物，将其通过制备型HPLC纯化以得到作为白色固体的实施例67(收率：17％)。^{1}H-NMR(400MHz，CD_3OD)：δ8.82(s,1H)，8.19-8.16(d,J＝9.0Hz,2H)，8.02-8.00(d,J＝8.1Hz,1H)，7.72-7.69(d,J＝8.1Hz,2H)，7.61-7.55(m,2H)，7.46-7.37(m,6H)，7.08-7.01(m,2H)，4.71(s,1H)，4.61-4.51(m,1H)，4.47(s,2H)，4.38-4.31(m,1H)，4.23-4.20(m,2H)，4.01(s,2H)，3.96-3.78(m,4H)，3.63(s,4H)，2.43(s,3H)，2.27-2.20(m,1H)，2.13-2.04(m,1H)，1.61(s,6H)，1.04(s,9H)；LC-MS(ES+)：m/z 1040.10[MH+]，tR＝2.26min(3.0分钟运行)。

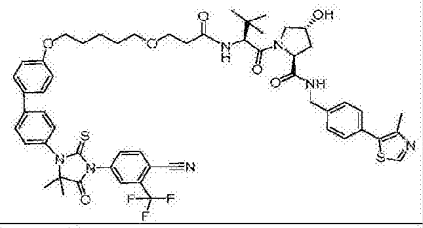
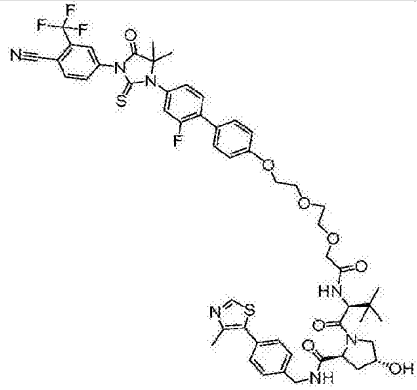
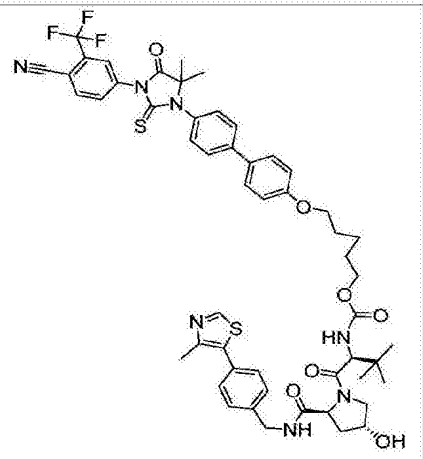
[0774] 根据关于实施例66的合成所述的类似程序，使用对应的起始原料和中间体合成实施例74和76。根据关于实施例67的合成所述的类似程序，使用对应的起始原料和中间体合成实施例68-73、75、77-79。

[0775] 表5.示例性的化合物.

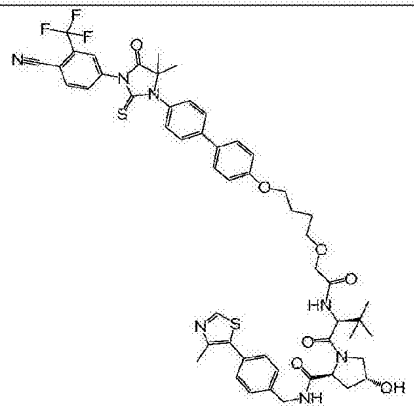
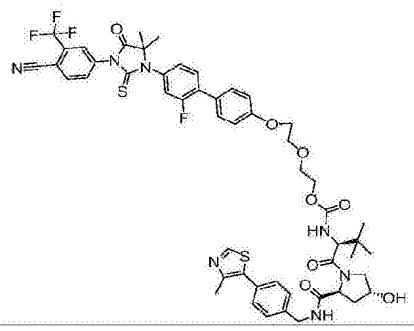
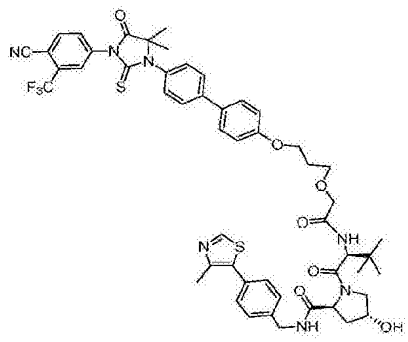
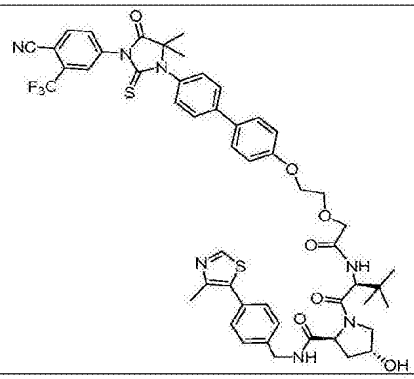
[0776]

实施例#	结构	化合物名称和分析数据
68		从 ABM-14、L-20 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-[3-(2-{2-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]乙氧基}乙氧基)丙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行).
69		从 ABM-14、L-21 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-{5-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]戊酰氨基（pentanamido）}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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^+): *m/z* 994.40 [MH^+], t_R = 1.71 min (3.0 分钟运行)。
70		从 ABM-14、L-22 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(3-{2-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]乙氧基}丙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行)。
71		从 ABM-14、L-23 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-[2-({5-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]戊基}氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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),

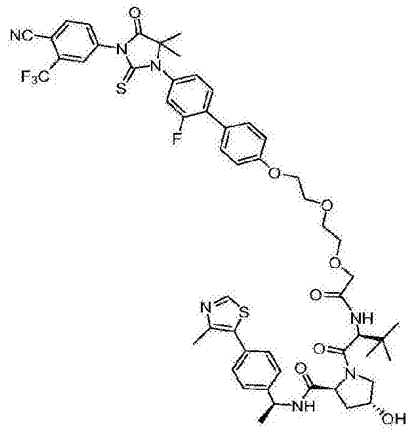
[0777]

实施例#	结构	化合物名称和分析数据
		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 分钟运行)。
72		从 ABM-14、L-24 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-[3-({5-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]戊基}氧基)丙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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* 1052.39 [MH^+], t_R = 1.81 min (3.0 分钟运行)。
73		从 ABM-24、L-29 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-[2-(2-{2-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-2-氟苯基)苯氧基]乙氧基}乙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行)。
74		从 ABM-14、L-25 和 ULM-1 制备 N-[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酸-5-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]戊酯 ^{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 分钟运行)

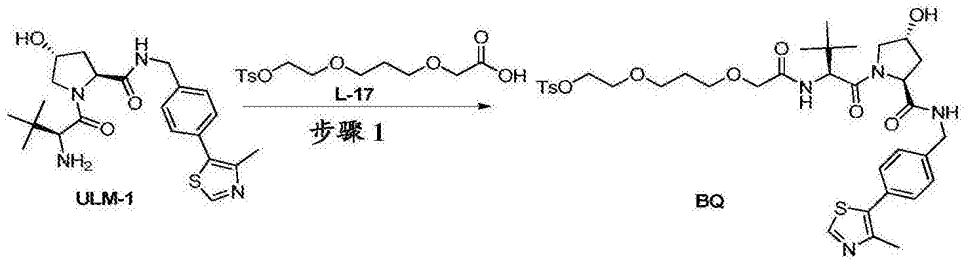
[0778]

实施例#	结构	化合物名称和分析数据
75		从 ABM-14、L-26 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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 分钟运行)
76		从 ABM-24、L-18 和 ULM-1 制备 N-[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酸-2-{2-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-2-氟苯基)苯氧基]乙氧基}乙酯 ^{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 分钟运行).
77		从 ABM-14、L-27 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丙氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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); 质量(ES$^+$): m/z 1010.30 [MH$^+$]
78		从 ABM-14、L-28 和 ULM-1 制备 (2S,4R)-1-[(2S)-2-(2-{2-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]乙氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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);

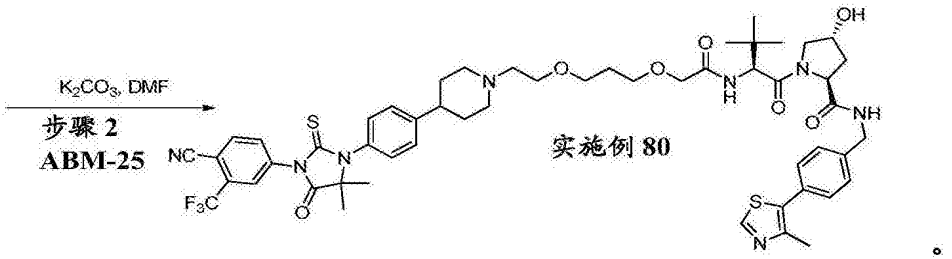
[0779]

实施例#	结构	化合物名称和分析数据
		LC-MS (ES^+): m/z 996.33 [MH^+], t_R = 2.92 min (5.0 分钟运行).
79		从 ABM-24、L-19 和 ULM-3 制备 (2S,4R)-1-[(2S)-2-[2-(2-{2-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-2-氟苯基)苯氧基]乙氧基}乙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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 分钟运行).

[0780] 实施例80：(2S,4R)-1-((S)-2-(2-(3-(2-(4-(4-(3-(4-氰基-3-(三氟甲基)苯基)-5,5-二甲基-4-氧代-2-硫代咪唑烷-1-基)苯基)哌啶-1-基)乙氧基)丙氧基)乙酰氨基)-3,3-二甲基丁酰基)-4-羟基-N-(4-(4-甲基噻唑-5-基)苄基)吡咯烷-2-甲酰胺：



[0781]



。

[0782] 步骤1：(2S,4R)-1-[(2S)-3,3-二甲基-2-[2-(3-{2-[(4-甲基苯磺酰基)氧基]乙氧基}丙氧基)乙酰氨基]丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺(BQ)的合成

[0783] 在室温向2-(3-{2-[(4-甲基苯磺酰基)氧基]乙氧基}丙氧基)乙酸(L-17,300mg,

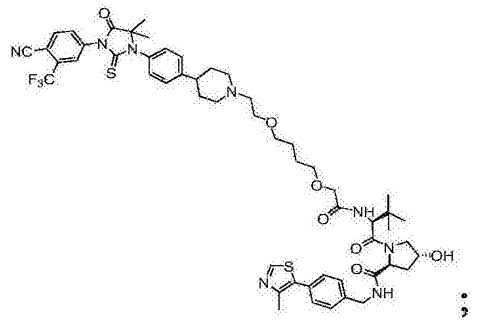
0.90mmol)在N,N-二甲基甲酰胺(5mL)中的搅拌溶液中加入EDCI(350mg,1.83mmol)、HOBt(240mg,1.78mmol)和DIEA(350mg,2.71mmol)。将得到的溶液在室温搅拌10min。然后向溶液中加入(2S,4R)-1-[(2S)-2-氨基-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺(ULM-1,390mg,0.91mmol),并将得到的溶液在室温搅拌1h。加入水(30mL),并将得到的混合物用乙酸乙酯(30mL×3)萃取。将有机层合并,用饱和氯化钠水溶液(30mL)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:二氯甲烷/甲醇(v:v=10:1)纯化以得到作为黄色固体的BQ(收率:64%)。LC-MS(ES^+):m/z 745.35[MH^+],t_R=0.96min(2.0分钟运行)。

[0784] 步骤2:(2S,4R)-1-[(2S)-2-[2-(3-{2-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)哌啶-1-基]乙氧基}丙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺(实施例80)的合成

[0785] 向4-{4,4-二甲基-5-氧代-3-[4-(哌啶-4-基)苯基]-2-亚硫烷基咪唑烷-1-基}-2-(三氟甲基)苄腈(ABM-25,150mg,0.32mmol)、(2S,4R)-1-[(2S)-3,3-二甲基-2-[2-(3-{2-[(4-甲基苯磺酰基)氧基]乙氧基}丙氧基)乙酰氨基]丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺(BQ,236mg,0.32mmol)在N,N-二甲基甲酰胺(5mL)中的搅拌溶液中加入碳酸钾(131mg,0.95mmol)。将得到的混合物在60℃搅拌过夜。将反应混合物冷却至室温,加入水(20mL)并将得到的混合物用乙酸乙酯(30mL×3)萃取。将有机层合并,用饱和氯化钠水溶液(20mL)洗涤,经无水硫酸钠干燥并然后在减压下浓缩以得到粗残余物,将其通过制备型HPLC纯化以得到作为白色固体的实施例80(收率:7%)。^1H NMR(300MHz,CD_3OD):δ8.91(s,1H),8.15(d,J=4.5Hz,2H),8.02(d,J=4.5Hz,1H),7.40(m,7H),4.45(d,J=12.0Hz,1H),4.45(m,4H),4.02(d,J=3.9Hz,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=2.74min(5.6分钟运行)。

[0786] 根据关于实施例80的合成所述的类似程序,使用对应的起始原料和中间体合成实施例81。

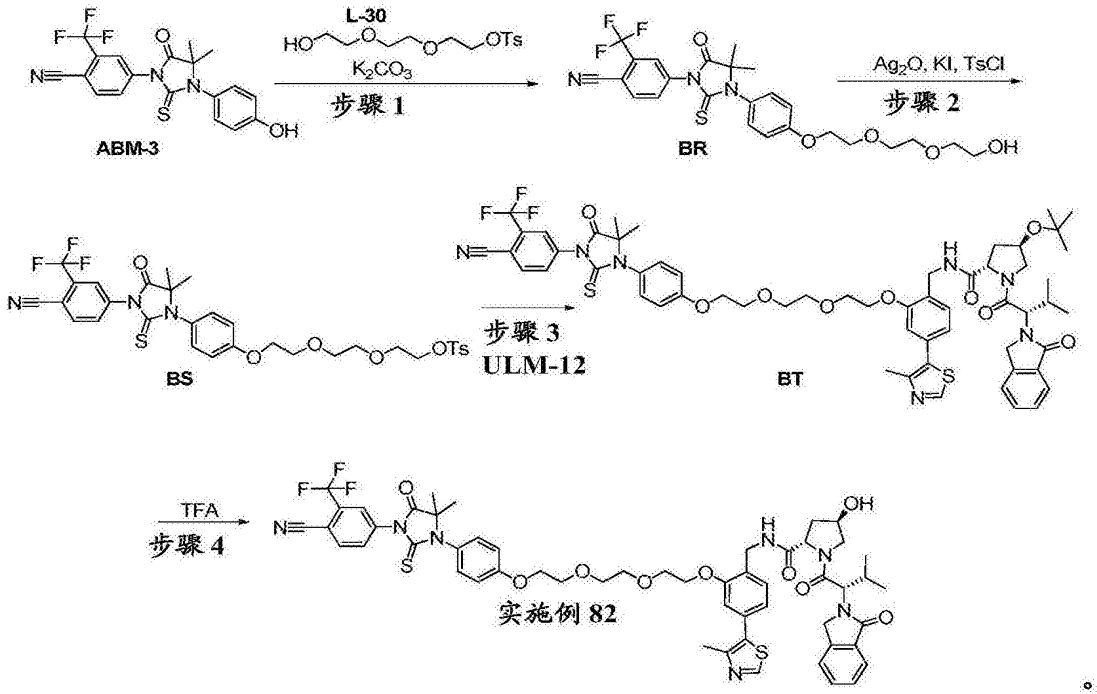
[0787] 实施例81:(2S,4R)-1-((S)-2-(2-(4-(2-(4-(4-(3-(4-氰基-3-(三氟甲基)苯基)-5,5-二甲基-4-氧代-2-硫代咪唑烷-1-基)苯基)哌啶-1-基)乙氧基)丁氧基)乙酰氨基)-3,3-二甲基丁酰基)-4-羟基-N-(4-(4-甲基噻唑-5-基)苄基)吡咯烷-2-甲酰胺

[0788]  ;

[0789] ^1H NMR(300MHz,DMSO):δ8.98(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=9.6Hz,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);质量(ES$^+$):m/z 1059.44[MH$^+$]。

[0790] 实施例82:(2S,4R)-N-(2-(2-(2-(2-(4-(3-(4-氰基-3-(三氟甲基)苯基)-5,5-二甲基-4-氧代-2-硫代咪唑烷-1-基)苯氧基)乙氧基)乙氧基)乙氧基)-4-(4-甲基噻唑-5-基)苄基)-4-羟基-1-((S)-3-甲基-2-(1-氧代异吲哚啉-2-基)丁酰基)吡咯烷-2-甲酰胺:

[0791] 

[0792] 步骤1:4-[3-(4-{2-[2-(2-羟基乙氧基)乙氧基]乙氧基}苯基)-4,4-二甲基-5-氧代-2-亚硫烷基咪唑烷-1-基]-2-(三氟甲基)苄腈(BR)的合成

[0793] 在室温向4-[3-(4-羟基苯基)-4,4-二甲基-5-氧代-2-亚硫烷基咪唑烷-1-基]-2-(三氟甲基)苄腈(ABM-3,405mg,1.00mmol)在CH_3CN(20mL)中的搅拌溶液中加入碳酸钾(276mg,1.98mmol)和2-(2-{2-[(4-甲基苯磺酰基)氧基]乙氧基}乙氧基)乙烷-1-醇(L-30,456mg,1.50mmol)。然后将得到的混合物加热至80℃并在该温度搅拌过夜。LC-MS指示期望产物的形成。将反应混合物冷却至室温,在真空下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:1))纯化以得到作为棕色油的BR(收率:91%)。

[0794] 步骤2:4-甲基苯-1-磺酸-2-{2-[2-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)乙氧基]乙氧基}乙酯(BS)的合成

[0795] 在室温向4-[3-(4-{2-[2-(2-羟基乙氧基)乙氧基]乙氧基}苯基)-4,4-二甲基-5-氧代-2-亚硫烷基咪唑烷-1-基]-2-(三氟甲基)苄腈(BR,490mg,0.91mmol)在二氯甲烷(10mL)中的搅拌溶液中加入甲苯磺酰氯(190mg,1.00mmol)、碘化钾(30.2mg)和氧化银(314mg)。然后将得到的混合物在30℃搅拌6h,LC-MS指示期望产物的形成。将无机盐通过过滤从反应物中除去,将溶液相在真空下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:3))纯化以得到作为浅黄色固体的BS(收率:60%)。

[0796] 步骤3:(2S,4R)-4-(叔丁氧基)-N-{[2-(2-{2-[2-(4-{3-[4-氰基-3-(三氟甲基)

苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)乙氧基]乙氧基}乙氧基)-4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}-1-[(2S)-3-甲基-2-(1-氧代-2,3-二氢-1H-异吲哚-2-基)丁酰基]吡咯烷-2-甲酰胺(BT)的合成

[0797] 在室温向4-甲基苯-1-磺酸-2-{2-[2-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)乙氧基]乙氧基}乙酯(BS,207mg,0.30mmol)和(2S,4R)-4-(叔丁氧基)-N-{[2-羟基-4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}-1-[(2S)-3-甲基-2-(1-氧代-2,3-二氢-1H-异吲哚-2-基)丁酰基]吡咯烷-2-甲酰胺(ULM-12,181mg,0.30mmol)在N,N-二甲基甲酰胺(2mL)中的搅拌溶液中加入碳酸钾(83mg,0.60mmol)。然后将得到的混合物加热至80℃并在相同温度搅拌过夜,且LC-MS指示期望产物的形成。然后将反应物冷却至室温,用水(10mL)稀释,并然后用乙酸乙酯(20mL×3)萃取。将有机层合并,经无水硫酸钠干燥并在减压下浓缩以得到粗残余物,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚(v:v=1:1)纯化以得到作为白色固体的BT(收率:54%)。

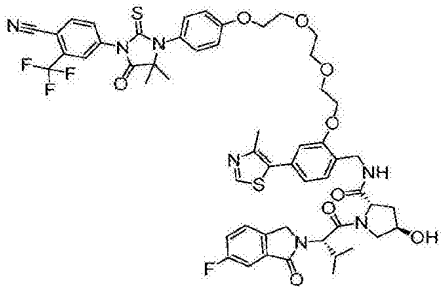
[0798] 步骤4:(2S,4R)-N-{[2-(2-{2-[2-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)乙氧基]乙氧基}乙氧基)-4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}-4-羟基-1-[(2S)-3-甲基-2-(1-氧代-2,3-二氢-1H-异吲哚-2-基)丁酰基]吡咯烷-2-甲酰胺(实施例82)的合成

[0799] 在室温向(2S,4R)-4-(叔丁氧基)-N-{[2-(2-{2-[2-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)乙氧基]乙氧基}乙氧基)-4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}-1-[(2S)-3-甲基-2-(1-氧代-2,3-二氢-1H-异吲哚-2-基)丁酰基]吡咯烷-2-甲酰胺(BT,180mg,0.16mmol)在二氯甲烷(5mL)中的搅拌溶液中加入三氟乙酸(0.5mL)。将得到的溶液在室温搅拌6h,LC-MS指示期望产物的形成。将饱和碳酸氢钠水溶液加入反应物中以中和三氟乙酸。将有机层分离,将水层用二氯甲烷(10mL×2)萃取。将有机层合并,经无水硫酸钠干燥并在减压下浓缩以得到粗残余物,将其通过制备型HPLC纯化以得到作为白色固体的实施例82(收率:31%)。^{1}H NMR(400MHz,CD_3OD):δ8.90(s,1H),8.40-8.38(d,J=8.0Hz,2H),8.29(s,1H),8.09-8.07(d,J=8.4Hz,1H),7.72-7.70(d,J=7.6Hz,1H),7.62-7.61(d,J=4.0Hz,2H),7.50-7.40(m,1H),7.35-7.33(d,J=7.6Hz,1H),7.27-7.25(d,J=8.8Hz,2H),7.10-7.06(m,3H),7.05-7.00(m,1H),5.09(s,1H),4.72-4.69(d,J=10.8Hz,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,1H),2.10-2.00(m,1H),2.00-1.95(m,1H),1.48(s,6H),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=1.59min(3.0分钟运行)。

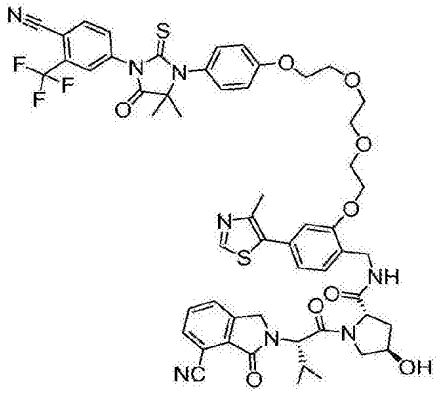
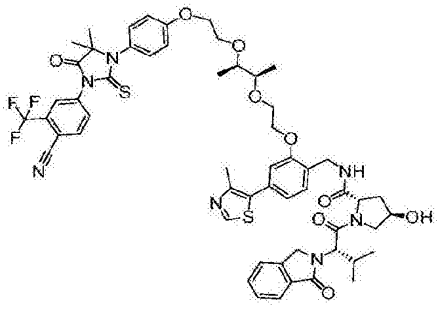
[0800] 根据关于实施例82的合成所述的类似程序,使用对应的起始原料和中间体合成实施例83-85。

[0801] 表6.示例性的化合物.

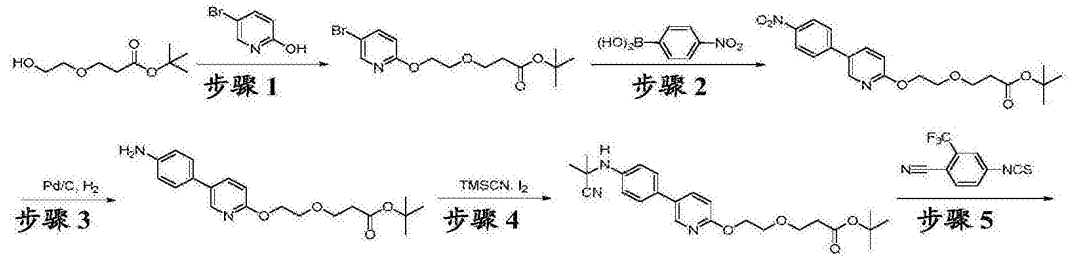
[0802]

实施例#	结构	化合物名称和分析数据
83		从ABM-3、L-30和ULM-13制备 (2S,4R)-N-{[2-(2-{2-[2-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)乙氧基]乙氧基}乙氧基)-4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}-1-[(2S)-2-(6-氟-1-氧代-2,3-二氢-1H-异吲哚-2-基)-3-甲基丁酰基]-4-羟基吡咯烷-2-甲酰胺 ^{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 分钟运行).

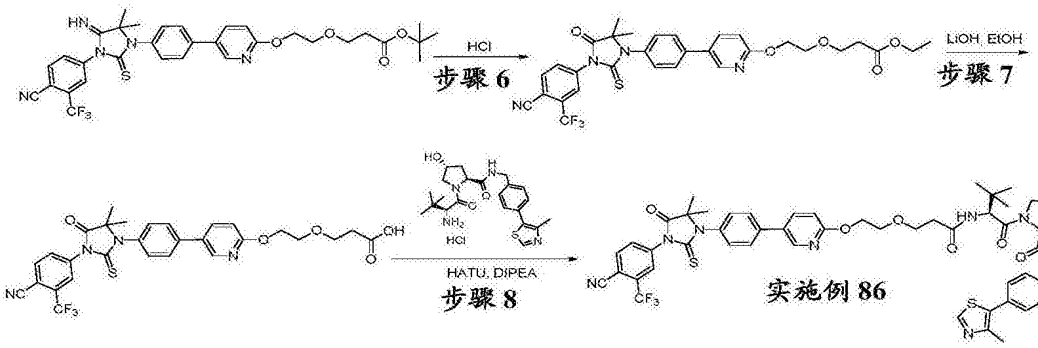
[0803]

实施例#	结构	化合物名称和分析数据
84		从ABM-3、L-30和ULM-14制备 (2S,4R)-1-[(2S)-2-(7-氰基-1-氧代-2,3-二氢-1H-异吲哚-2-基)-3-甲基丁酰基]-N-{[2-(2-{2-[2-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)乙氧基]乙氧基}乙氧基)-4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}-4-羟基吡咯烷-2-甲酰胺 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 分钟运行).
85		从ABM-3、L-31和ULM-12制备 (2S,4R)-N-{[2-(2-{[(2R,3R)-3-[2-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)乙氧基]丁-2-基]氧基}乙氧基)-4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}-4-羟基-1-[(2S)-3-甲基-2-(1-氧代-2,3-二氢-1H-异吲哚-2-基)丁酰基]吡咯烷-2-甲酰胺 ^{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); 质量(ES^+): m/z 1096.37 [MH^+]

[0804] 实施例86的合成.

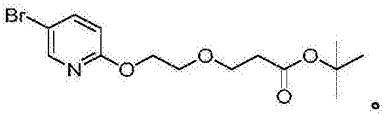


[0805]



[0806] 步骤1:3-{2-[(5-溴吡啶-2-基)氧基]乙氧基}丙酸叔丁酯的合成:

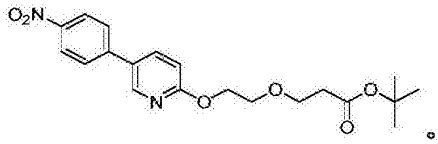
[0807]



[0808] 在0℃在氮气氛下向5-溴吡啶-2-醇(3.0g,17.24mmol)、3-(2-羟基乙氧基)丙酸叔丁酯(3.3g,17.19mmol)和三苯基膦(6.8g,25.81mmol)在四氢呋喃(120.0mL)中的搅拌溶液中逐滴加入二氮烯-1,2-二甲酸二乙酯(4.49g,25.78mmol)。将得到的溶液在室温搅拌过夜。将反应混合物在减压下浓缩以得到粗残余物,将其通过硅胶快速色谱法(洗脱液:乙酸乙酯/石油醚,v/v=1/3)纯化以得到作为无色油的标题产物(收率:50%)。

[0809] 步骤2:3-(2-{[5-(4-硝基苯基)吡啶-2-基]氧基}乙氧基)丙酸叔丁酯的合成:

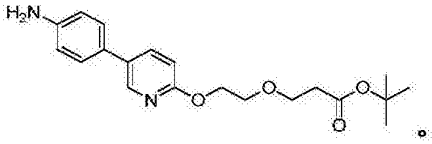
[0810]



[0811] 在氮气氛下向3-{2-[(5-溴吡啶-2-基)氧基]乙氧基}丙酸叔丁酯(3.0g,8.67mmol)和(4-硝基苯基)硼酸(1.5g,8.87mmol)在二噁烷(90.0mL)和水(9.0mL)的混合溶剂中的搅拌混合物中加入碳酸钾(2.4g,17.36mmol)和Pd(PPh3)4(450.0mg,0.39mmol)。将得到的混合物在100℃搅拌12h。将大部分溶剂在减压下除去,并将得到的含水残余物用乙酸乙酯(100mL×2)萃取。将有机层合并,用盐水(70mL×2)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗残余物,将其通过硅胶快速色谱法(洗脱液:乙酸乙酯/石油醚,v/v=1/5)纯化以得到作为黄色固体的标题产物(收率:83%)。质量(ES^+):m/z 389.00[MH^+]。

[0812] 步骤3:3-(2-{[5-(4-氨基苯基)吡啶-2-基]氧基}乙氧基)丙酸叔丁酯的合成:

[0813]



[0814] 在氮气氛下在室温向3-(2-{[5-(4-硝基苯基)吡啶-2-基]氧基}乙氧基)丙酸叔丁酯(2.8g,7.21mmol)在乙醇(200.0mL)中的搅拌溶液中加入炭载钯(1.5g)。然后给反应混合物充入氢气并在室温搅拌12h。将固体通过过滤除去并将溶液相在减压下浓缩以得到粗残余物,将其通过硅胶快速色谱法(洗脱液:乙酸乙酯/石油醚,v/v=1/3)纯化以得到作为黄色油的标题产物(收率:89%)。LC-MS(ES^+):m/z 358.97[MH^+]。

[0815] 根据在上面突出显示的化学(步骤4-8),利用关于实施例67、75、103的合成进行的类似化学描述的类似程序,使用对应的起始原料和中间体,从3-(2-{[5-(4-氨基苯基)吡啶-2-基]氧基}乙氧基)丙酸叔丁酯合成实施例86。

[0816] 根据关于实施例86的合成描述的类似程序,使用对应的起始原料和中间体合成实施例90。

[0817] 根据关于实施例80、75、103的合成描述的类似程序,使用对应的起始原料和中间体合成实施例88、91-92。

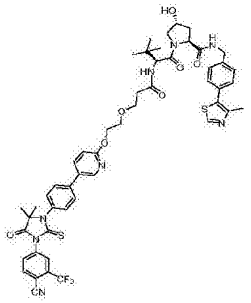
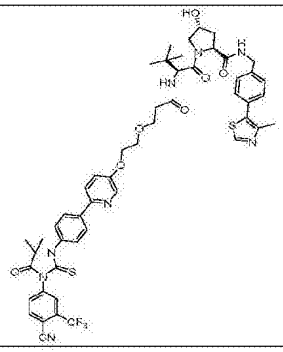
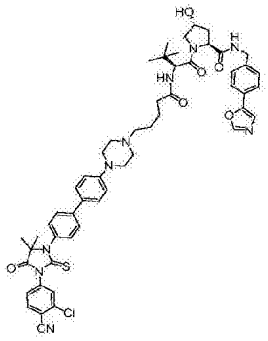
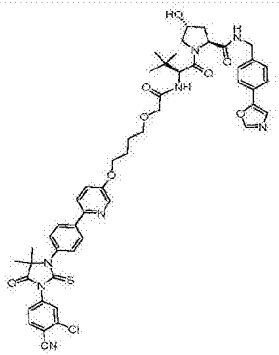
[0818] 根据关于实施例75的合成描述的类似程序,使用对应的起始原料和中间体合成实施例87、89、93-102、104-134、136-142、146-149。

[0819] 表7.示例性的化合物.

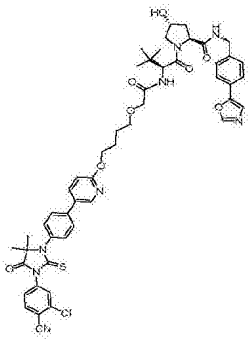
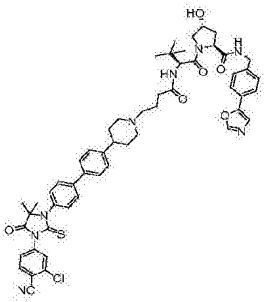
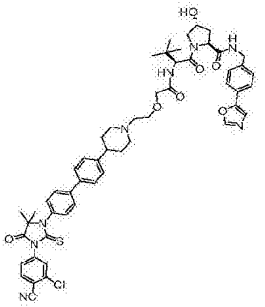
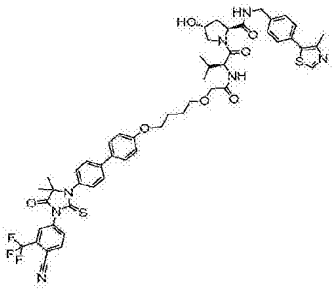
[0820]

实施例#	结构	化合物名称和分析数据

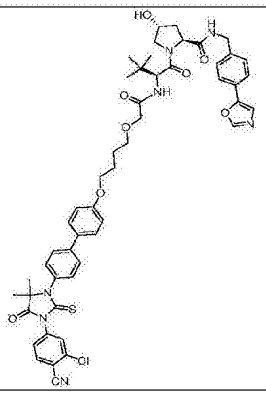
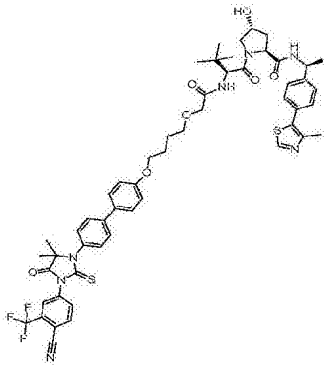
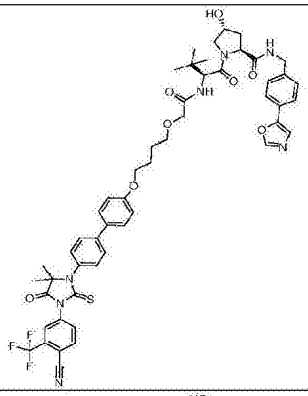
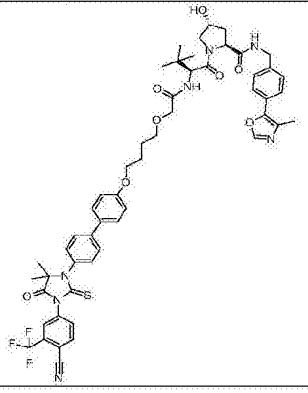
[0821]

86		(2S,4R)-1-[(2S)-2-[3-(2-{[5-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)吡啶-2-基]氧基}乙氧基)丙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)吡啶-3-基]氧基}乙氧基)丙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯基}苯基)哌嗪-1-基]戊酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯基}吡啶-3-基)氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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^+]

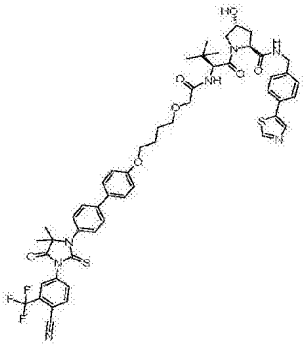
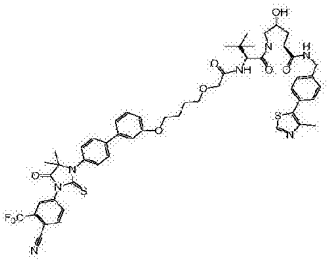
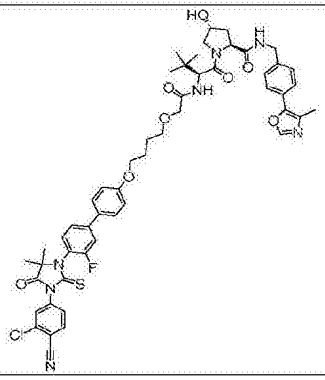
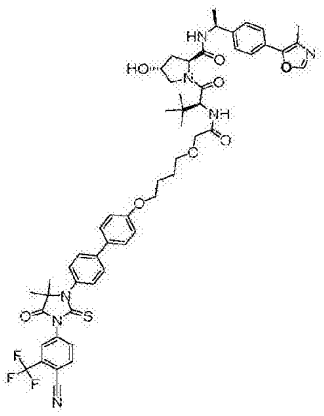
[0822]

90		(2S,4R)-1-[(2S)-2-(2-{4-[(5-{4-[3-(3-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯基}吡啶-2-基)氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯基}苯基)哌啶-1-基]丁酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯基}苯基)哌啶-1-基]乙氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酰氨基)-3-甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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$^+$]

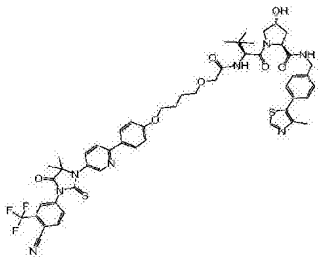
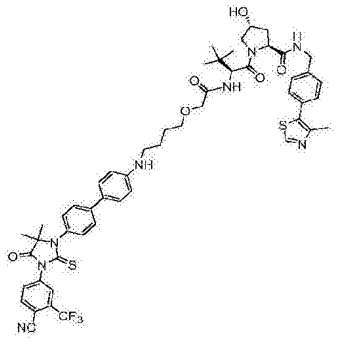
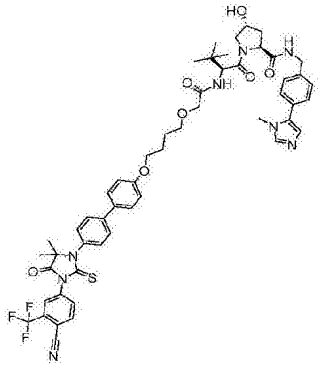
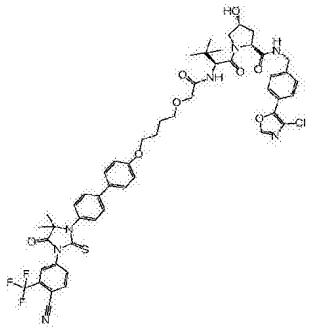
[0823]

94		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(3-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯基}苯氧基)丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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^+]

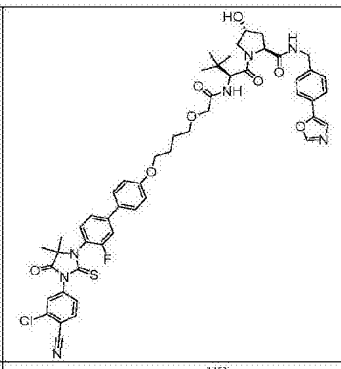
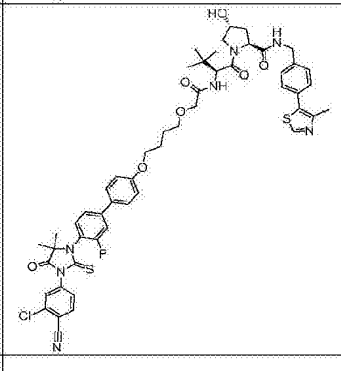
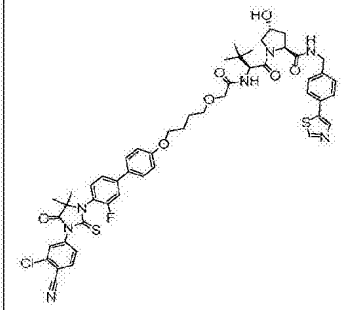
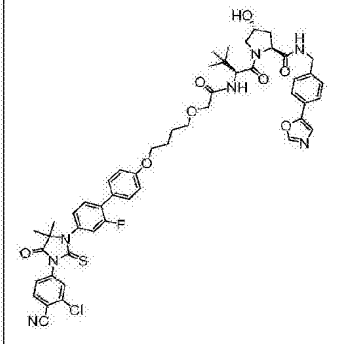
[0824]

98		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]-3-氟苯基}苯氧基)丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噁唑-5-基（1）)苯基]乙基]吡咯烷-2-甲酰胺 ^{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^+]

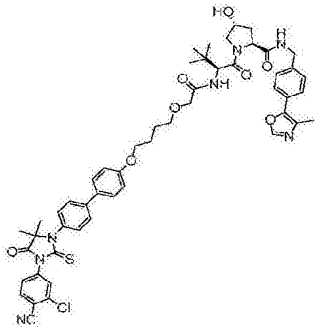
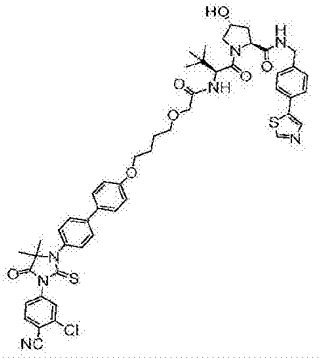
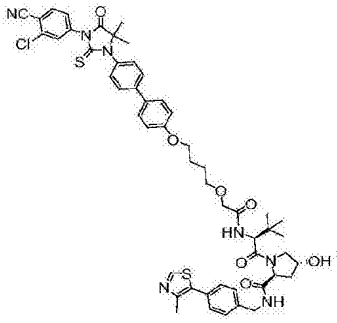
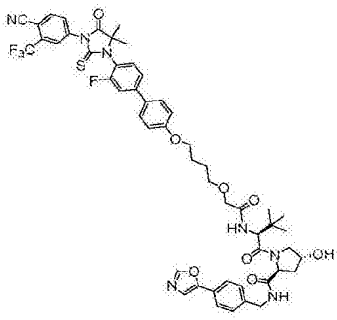
[0825]

102		(2S,4R)-1-[(2S)-2-(2-{4-[4-(5-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}吡啶-2-基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯基]氨基}丁氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{1}H 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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1-甲基-1H-咪唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{1}H 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-氯-1,3-噁唑-5-基)苯基]甲基}-1-[(2S)-2-(2-{4-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基吡咯烷-2-甲酰胺 ^{1}H 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^+]

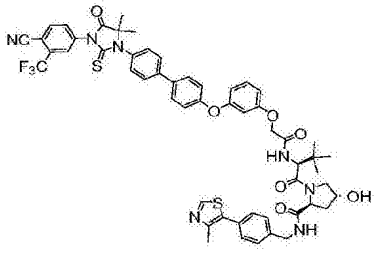
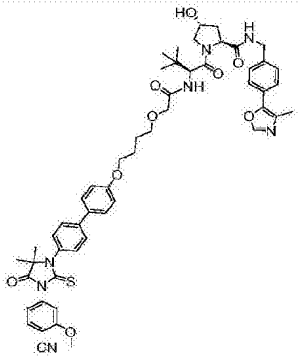
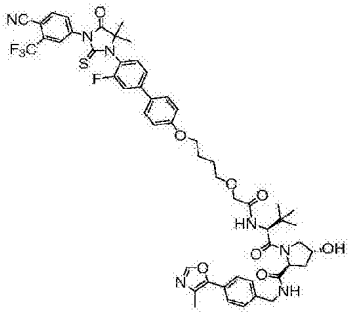
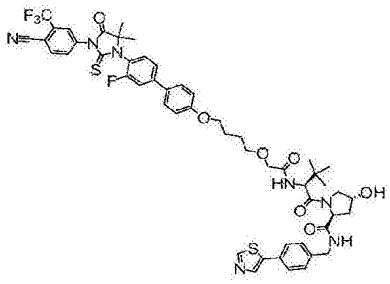
[0826]

106		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(3-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]-3-氟苯基}苯氧基)丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]-3-氟苯基}苯氧基)丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-羧酰胺 ^{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-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]-3-氟苯基}苯氧基)丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]-2-氟苯基}苯氧基)丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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^+]

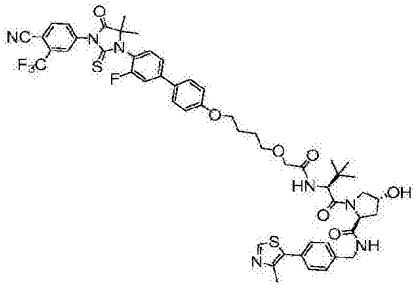
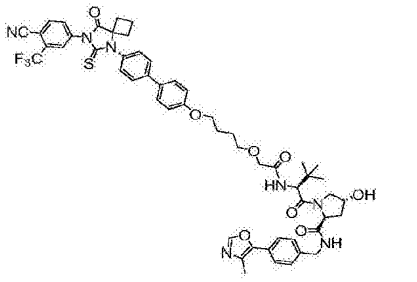
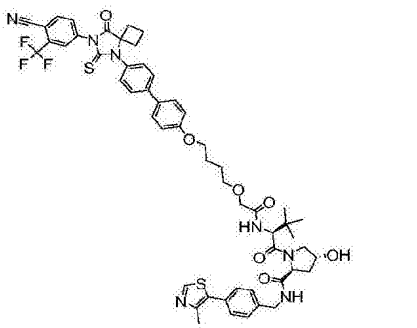
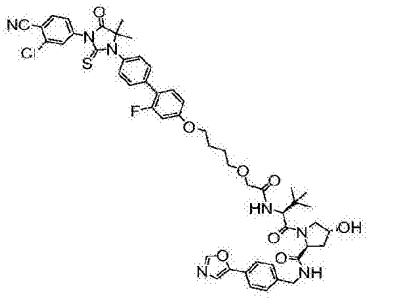
[0827]

110		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(3-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯基}苯氧基)丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯基}苯氧基)丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯基}苯氧基)丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-3-氟苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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$^+$]

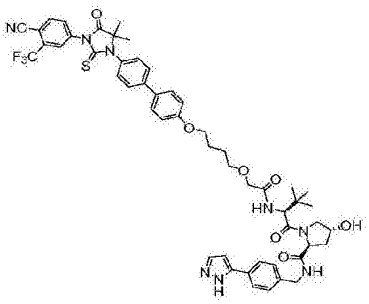
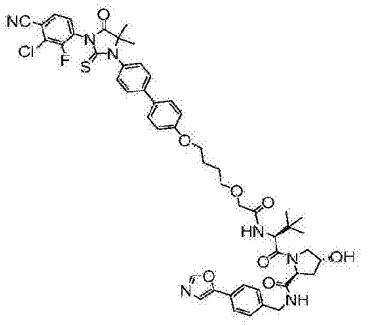
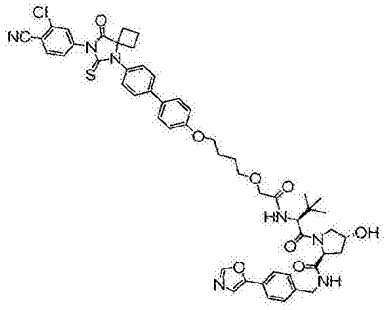
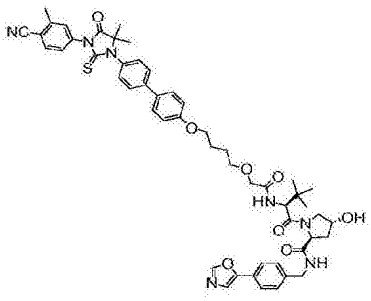
[0828]

114		(2S,4R)-1-[(2S)-2-(2-{3-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]苯氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-甲氧基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯基}苯氧基)丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-3-氟苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-3-氟苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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$^+$],

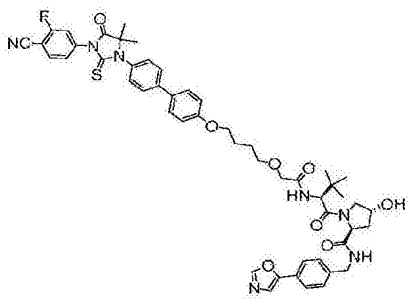
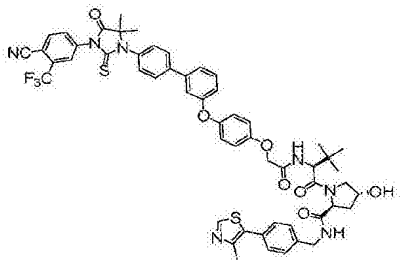
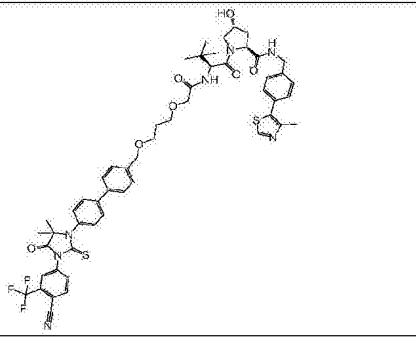
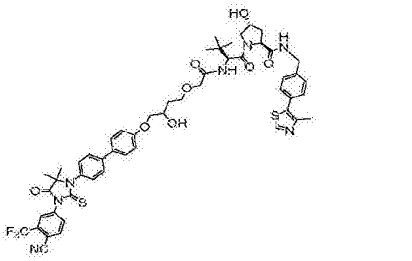
[0829]

118		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-3-氟苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-8-氧代-6-亚硫烷基-5,7-二氮杂螺[3.4]辛烷-5-基}苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{1}H NMR (300 MHz, CD_3OD): δ 8.17-8.15 (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-氰基-3-(三氟甲基)苯基]-8-氧代-6-亚硫烷基-5,7-二氮杂螺[3.4]辛烷-5-基}苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯基}-3-氟苯氧基)丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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$^+$]

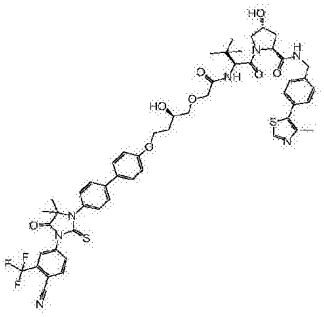
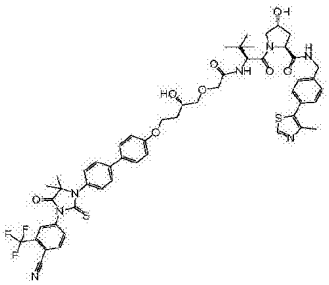
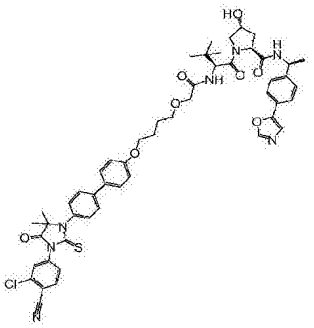
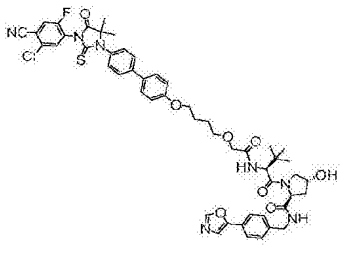
[0830]

122		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1H-吡唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氯-4-氰基-2-氟苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯基}苯氧基)丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氯-4-氰基苯基)-8-氧代-6-亚硫烷基-5,7-二氮杂螺[3.4]辛烷-5-基]苯基}苯氧基)丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-甲基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯基}苯氧基)丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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^+]

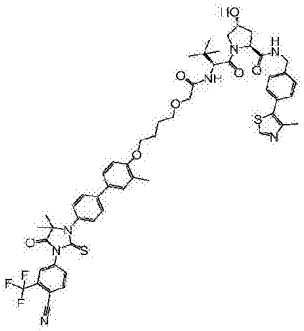
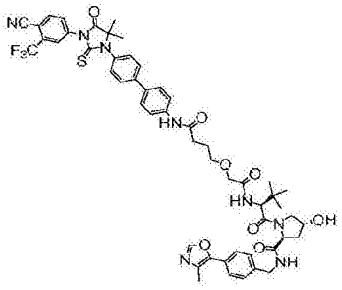
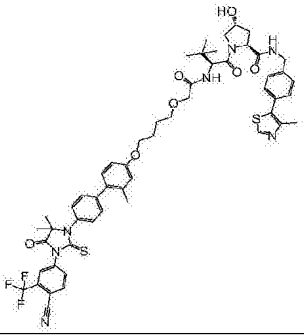
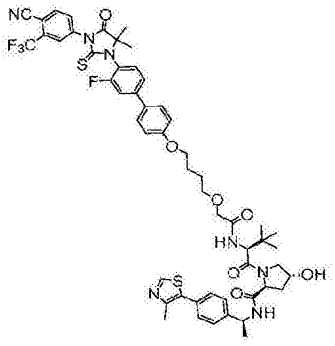
[0831]

126		(2S,4R)-1-[(2S)-2-{2-[4-(4-{4-[3-(4-氰基-3-氟苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯基}苯氧基)丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]苯氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯基]甲氧基}丙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]-3-羟基丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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$^+$]

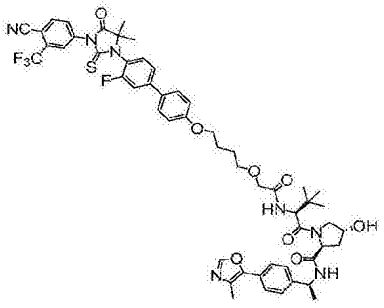
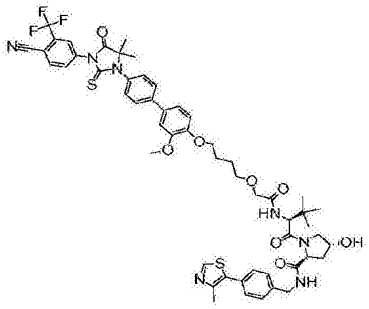
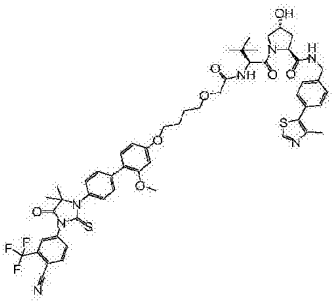
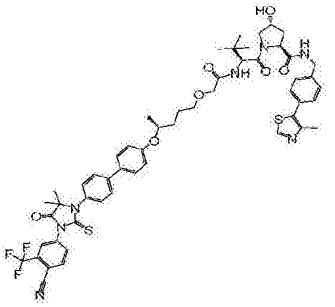
[0832]

130		(2S,4R)-1-[(2S)-2-{2-[(2R)-4-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]-2-羟基丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]-2-羟基丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯基}苯氧基)丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(1,3-噁唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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-氯-4-氰基-2-氟苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯基}苯氧基)丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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^+]

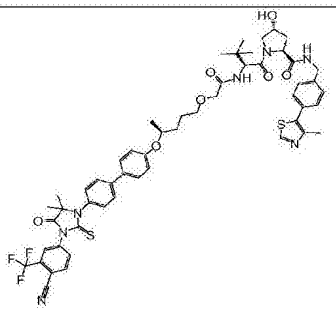
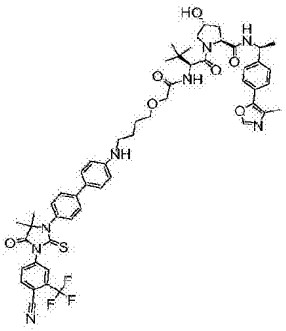
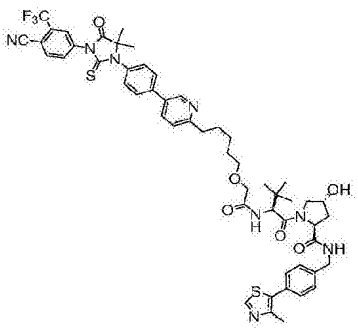
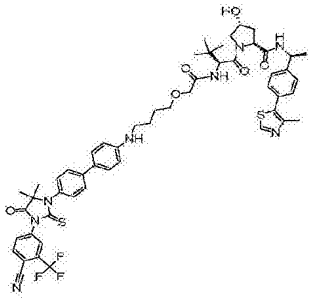
[0833]

134		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)-2-甲基苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯基]氨基甲酰基}丙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)-3-甲基苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-3-氟苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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$^+$]

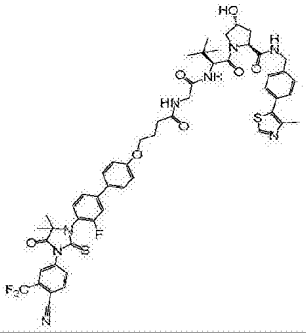
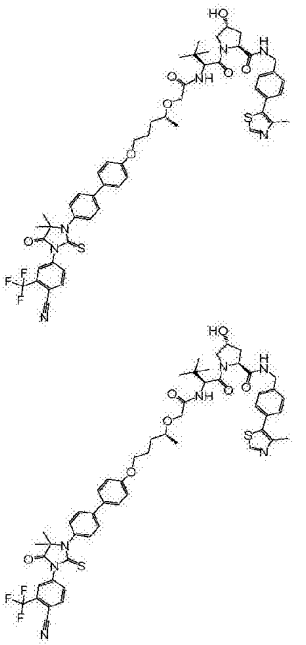
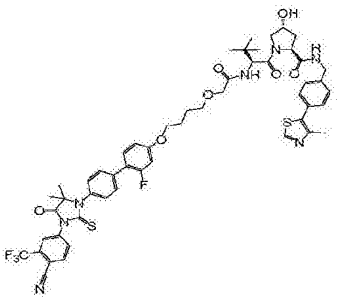
[0834]

138		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-3-氟苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噁唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)-2-甲氧基苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)-3-甲氧基苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]戊基]氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 (2S,4R)-1-[(2S)-2-(2-{[(4R)-4-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]戊基]氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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

[0835]

		(ES+): *m/z* 1038.15[MH+] 1H NMR (400 MHz, CD3OD) 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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯基]氨基}丁氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噁唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 1H NMR (400 MHz, CD3OD) 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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)吡啶-2-基]戊基}氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 1H NMR (400 MHz, CD3OD): 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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯基]氨基}丁氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 1H NMR (300 MHz, CD3OD) 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+]

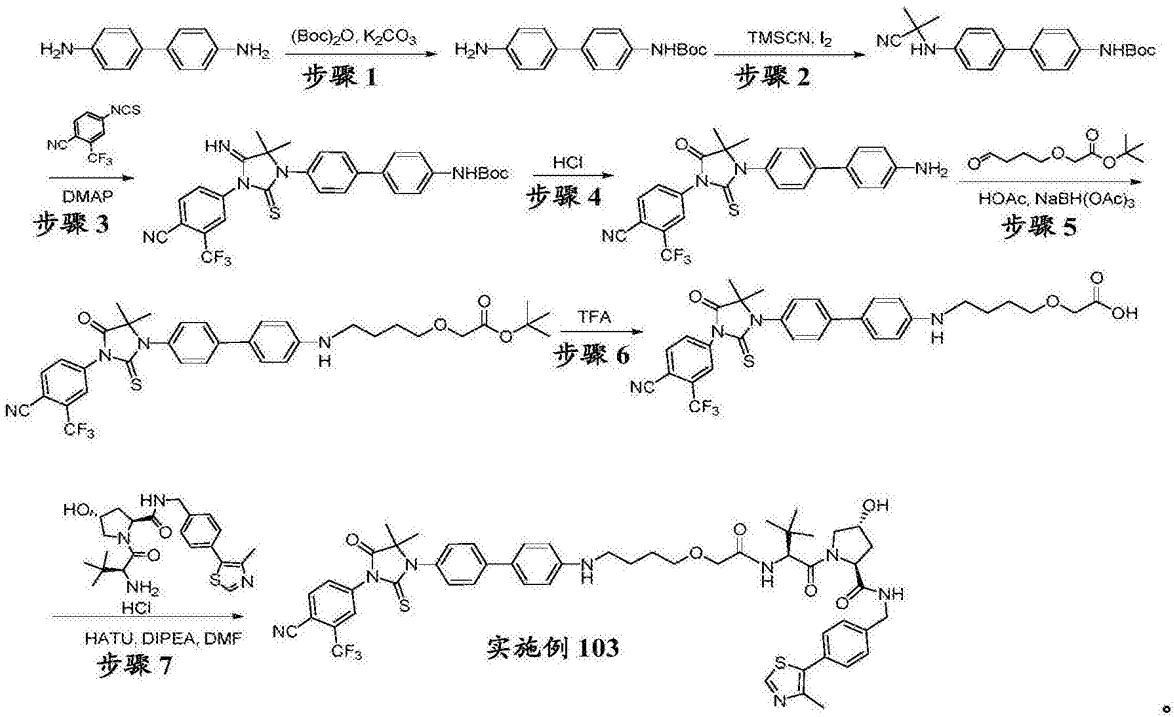
[0836]

146		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-3-氟苯基)苯氧基]丁酰氨基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]戊烷-2-基]氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 (2S,4R)-1-[(2S)-2-(2-{[(2R)-5-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]戊烷-2-基]氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)-3-氟苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{1}H NMR (400 MHz, CD_3OD): 8.80 (s, 1H),8.18-8.12 (m,2H), 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$^+$]

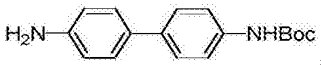
[0837] 根据关于实施例103的合成描述的类似程序，使用对应的起始原料和中间体合成实施例135、143-145。

[0838] 实施例103的合成：

[0839]

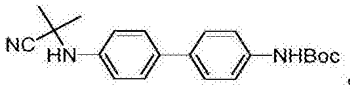


[0840] 步骤1:N-[4-(4-氨基苯基)苯基]氨基甲酸叔丁酯的合成:

[0841] 

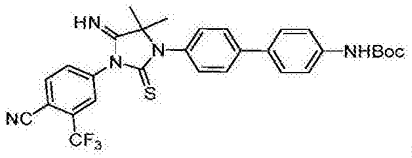
[0842] 在室温向4-(4-氨基苯基)苯胺(15.0g,81.42mmol)在N,N-二甲基甲酰胺/四氢呋喃/水(v/v/v=100/300/50mL)的混合溶剂中的搅拌溶液中加入碳酸钾(9.5g,68.74mmol)和二碳酸二叔丁酯(13.67g,62.63mmol)。将得到的混合物在室温搅拌5h。然后将反应物用水(500mL)稀释,并用乙酸乙酯(200mL×3)萃取。将有机层合并,用盐水(50mL×2)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗残余物,将其通过硅胶快速色谱法(洗脱液:乙酸乙酯/石油醚,v:v=1:2)纯化以得到作为黄色固体的标题产物(收率:97%)。

[0843] 步骤2:N-(4-{4-[(1-氰基-1-甲基乙基)氨基]苯基}苯基)氨基甲酸叔丁酯的合成:

[0844] 

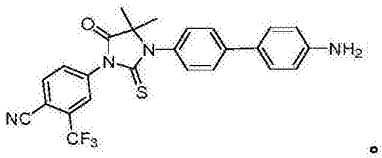
[0845] 在氮气气氛下在0℃向N-[4-(4-氨基苯基)苯基]氨基甲酸叔丁酯(7.0g,24.62mmol)在丙酮(100mL)中的搅拌溶液中逐滴加入三甲基硅烷甲腈(4.9g,49.49mmol),随后在0℃加入分成几批的碘(630.0mg,2.48mmol)。将得到的混合物在室温搅拌15h。然后将反应物通过加入水(100mL)进行猝灭,并将得到的溶液用乙酸乙酯(100mL×2)萃取。将有机层合并,用盐水(70mL×2)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗残余物,将其通过硅胶快速色谱法(洗脱液:乙酸乙酯/石油醚,v:v=1:3)纯化以得到作为黄色固体的标题产物(收率:87%)。质量(ES^+):m/z 352.20[MH^+]。

[0846] 步骤3:N-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-4-亚氨基-5,5-二甲基-2-亚硫烷基咪唑烷-1-基}苯基)苯基]氨基甲酸叔丁酯的合成:

[0847] 

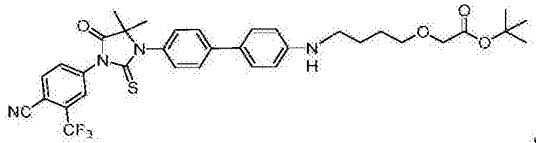
[0848] 在室温在氮气氛下向N-(4-{4-[(1-氰基-1-甲基乙基)氨基]苯基}苯基)氨基甲酸叔丁酯(3.1g,8.82mmol)在甲苯(40.0mL)中的搅拌溶液中加入4-二甲基氨基吡啶(1.6g,13.10mmol)和4-异硫氰酰基-2-(三氟甲基)苄腈(2.0g,8.76mmol)。将得到的溶液在油浴中在100℃搅拌12h。然后将反应混合物在减压下浓缩以得到粗残余物,将其通过硅胶快速色谱法(洗脱液:乙酸乙酯/石油醚,v:v=1:1)纯化以得到作为黄色固体的标题产物(收率:36%)。质量(ES^+):m/z 580.30[MH^+]。

[0849] 步骤4:4-{3-[4-(4-氨基苯基)苯基]-4,4-二甲基-5-氧代-2-亚硫烷基咪唑烷-1-基}-2-(三氟甲基)苄腈的合成:

[0850] 

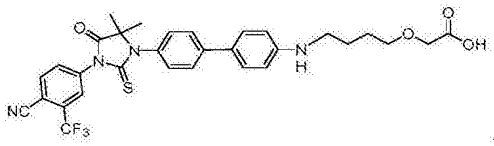
[0851] 在室温向N-[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-4-亚氨基-5,5-二甲基-2-亚硫烷基咪唑烷-1-基}苯基)苯基]氨基甲酸叔丁酯(2.0g)在甲醇(20mL)中的搅拌溶液中加入氯化氢(3N水溶液,5mL)。将得到的溶液在油浴中在70℃搅拌2h。然后将反应混合物在减压下浓缩以除去大部分甲醇。向得到的含水混合物中加入碳酸氢钠(饱和水溶液)以调节pH至~8,并将得到的混合物用乙酸乙酯(80mL×3)萃取。将有机层合并,用盐水(30mL×2)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗残余物,将其通过硅胶快速色谱法(洗脱液:乙酸乙酯/石油醚,v:v=1:2)纯化以得到作为黄色固体的标题产物(收率:45%)。质量(ES^+):m/z 481.15[MH^+]。

[0852] 步骤5:2-(4-{[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯基]氨基}丁氧基)乙酸叔丁酯的合成:

[0853] 

[0854] 在室温向4-{3-[4-(4-氨基苯基)苯基]-4,4-二甲基-5-氧代-2-亚硫烷基咪唑烷-1-基}-2-(三氟甲基)苄腈(200.0mg,0.42mmol)在二氯甲烷(10mL)中的搅拌溶液中加入乙酸(0.01mL)和2-(4-氧代丁氧基)乙酸叔丁酯(93.0mg,0.46mmol)。将得到的混合物在室温搅拌10min,然后向混合物中加入三乙酰氧基硼氢化钠(124.0mg,0.59mmol)。将得到的混合物在室温搅拌过夜。将反应混合物用水(30mL)稀释,用二氯甲烷(20mL×3)萃取。将有机层合并,用盐水(20mL×2)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗残余物,将其通过硅胶快速色谱法(洗脱液:乙酸乙酯/石油醚,v:v=1:2)纯化以得到标题产物(收率:36%)。质量(ES^+):m/z667.20[MH^+]。

[0855] 步骤6:2-(4-{[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯基]氨基}丁氧基)乙酸的合成:

[0856] 

[0857] 在室温向2-(4-{[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯基]氨基}丁氧基)乙酸叔丁酯(100.0mg,0.15mmol)在二氯甲烷(10mL)中的搅拌溶液中加入三氟乙酸(2.0mL)。将得到的溶液在室温搅拌2h。然后将反应混合物在减压下浓缩以得到粗制物质(收率:99%,基于粗制物),将其不经任何进一步纯化用于下一步反应。质量(ES^+):m/z 611.10[MH^+]

[0858] 步骤7:实施例103的合成.

[0859] 根据关于实施例75的合成描述的最后一步(酰胺偶联)中的类似程序,从2-(4-{[4-(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯基]氨基}丁氧基)乙酸和(2S,4R)-1-[(2S)-2-氨基-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺盐酸盐合成该化合物。

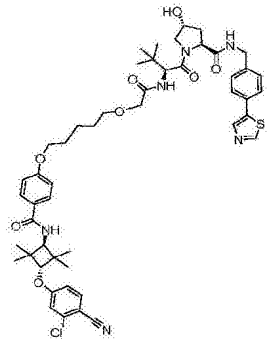
[0860] 2-(4-氧代丁氧基)乙酸叔丁酯的合成:

[0861] 

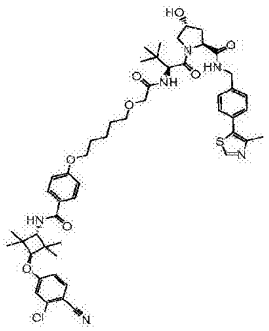
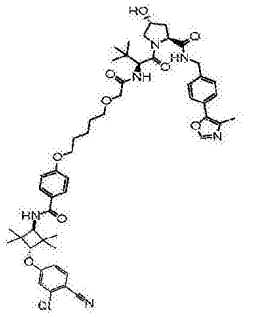
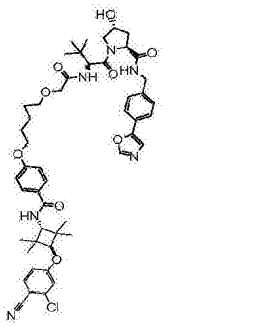
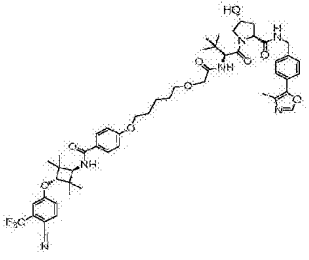
[0862] 在室温向2-(4-羟基丁氧基)乙酸叔丁酯(1.0g,4.90mmol)在二氯甲烷(10mL)中的搅拌溶液中加入(1,1,1-三乙酰氧基)-1,1-二氢-1,2-苯并碘杂氧杂环戊烷(benziodoxol)-3(1H)-酮(2.7g,6.37mmol)。将得到的混合物在室温搅拌12h。然后将反应混合物用水(20mL)稀释,用乙酸乙酯(20mL×3)萃取。将有机层合并,用盐水(20mL×2)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗残余物,将其通过硅胶快速色谱法(洗脱液:乙酸乙酯/石油醚,v/v=1:2)纯化以得到作为无色油的标题产物(收率:50%)。^1H NMR(300MHz,CD_3OD)δ9.68(s,1H),3.95(s,2H),3.48-3.45(m,2H),2.51-2.50(m,2H),1.81-1.63(m,2H),1.42(s,9H)。

[0863] 表8.示例性的化合物.

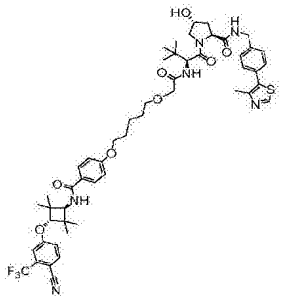
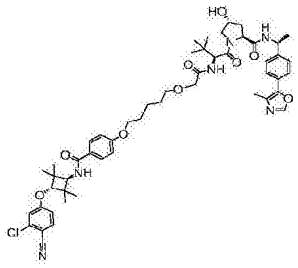
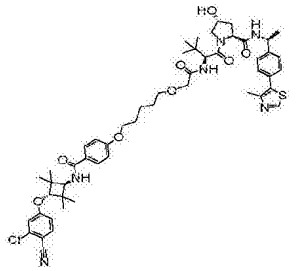
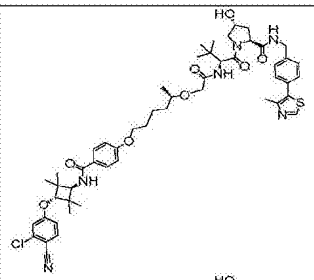
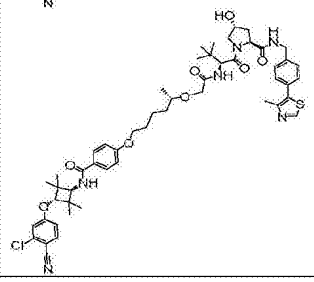
[0864]

实施例#	结构	化合物名称和分析数据
150		(2S,4R)-1-[(2S)-3,3-二甲基-2-(2-{[5-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)戊基]氧基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^1H 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 [$M+H^+$]

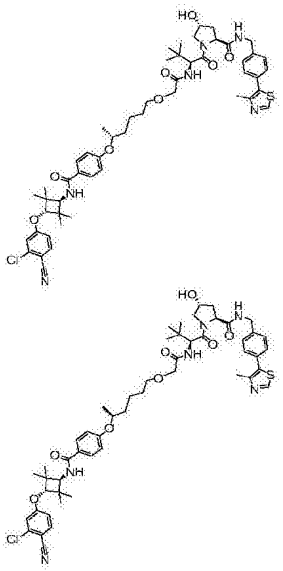
[0865]

151		(2S,4R)-1-[(2S)-3,3-二甲基-2-(2-{[5-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)戊基]氧基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-(2-{[5-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)戊基]氧基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-(2-{[5-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)戊基]氧基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-(2-{[5-(4-{[反式--3-[4-氰基-3-(三氟甲基)苯氧基]-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)戊基]氧基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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^+]

[0866]

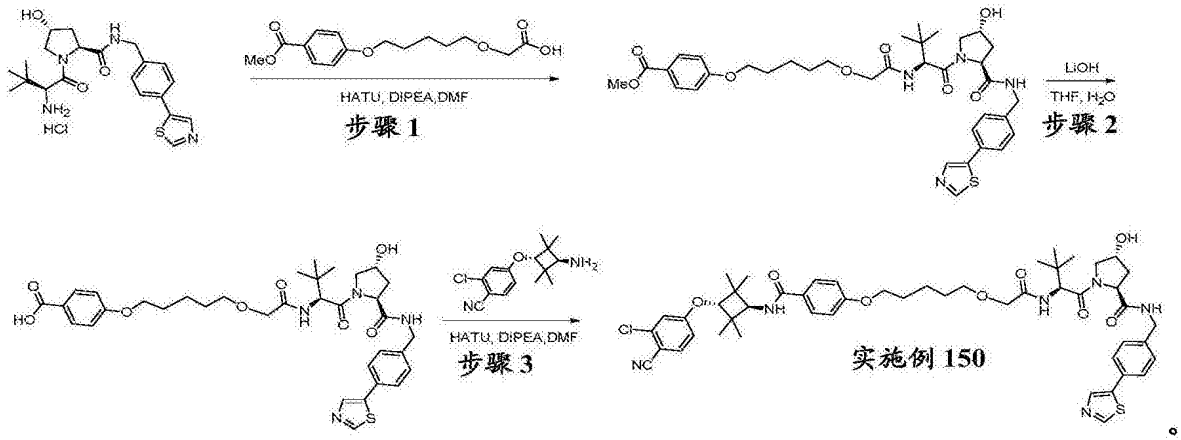
155		(2S,4R)-1-[(2S)-3,3-二甲基-2-(2-{[5-(4-{[反式-3-[4-氰基-3-(三氟甲基)苯氧基]-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)戊基]氧基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{1}H NMR (300 MHz, CD_3OD): δ 8.84 (s, 1 H), 7.90-7.84 (m, 1 H), 7.80-7.70 (m, 2 H), 7.45-7.32 (m, 4 H), 7.26-7.22 (m, 1 H), 7.28-7.20 (m, 1 H), 7.00-6.89 (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)-3,3-二甲基-2-(2-{[5-(4-{[反式--3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)戊基]氧基}乙酰氨基)丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噁唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-(2-{[5-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)戊基]氧基}乙酰氨基)丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-(2-{[(2R)-6-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)己烷-2-基]氧基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 (2S,4R)-1-[(2S)-3,3-二甲基-2-(2-{[(2S)-6-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)己烷-2-基]氧基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺

[0867]

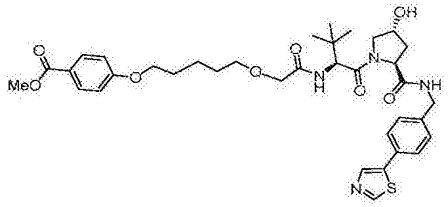
160, 161		(2S,4R)-1-[(2S)-3,3-二甲基-2-(2-{[(5S)-5-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)己基]氧基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 (2S,4R)-1-[(2S)-3,3-二甲基-2-(2-{[(5R)-5-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)己基]氧基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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^+]

[0868] 实施例150的合成：

[0869]



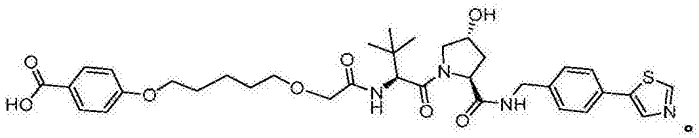
[0870] 步骤1:4-{[5-({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)戊基]氧基}苯甲酸甲酯的合成：

[0871] 

[0872] 在0℃向2-({5-[4-(甲氧基羰基)苯氧基]戊基}氧基)乙酸(200mg)、(2S,4R)-1-

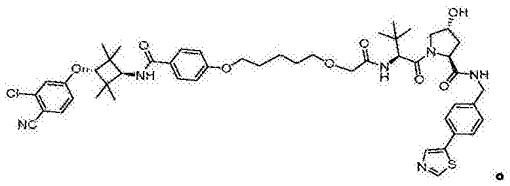
[(2S)-2-氨基-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺盐酸盐(149mg,0.32mmol)、N-乙基-N-异丙基丙烷-2-胺(185mg,1.44mmol)在无水N,N-二甲基甲酰胺(5mL)中的搅拌溶液中加入HATU(2-(7-氮杂-1H-苯并三唑-1-基)-1,1,3,3-四甲基脲鎓六氟磷酸盐)(203mg,0.54mmol)。将得到的混合物温热至室温并在室温搅拌20min。TLC和LC-MS表明期望产物的形成。将混合物在乙酸乙酯(100mL)和水(50mL)之间分配。将有机层收集,用盐水(50mL)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗残余物,将其通过硅胶快速色谱法(洗脱液2%的甲醇在二氯甲烷中的溶液)纯化以得到作为白色固体的标题产物(收率25%,2步骤)。质量:(ES^+):m/z 695.30$[M+H^+]$。

[0873] 步骤2:4-{[5-({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)戊基]氧基}苯甲酸的合成:

[0874] 

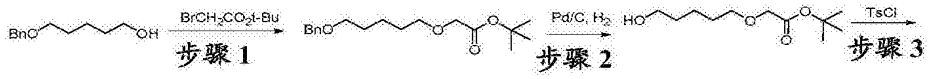
[0875] 在室温向4-{[5-({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)戊基]氧基}苯甲酸甲酯(150mg,0.22mmol)在四氢呋喃(4mL)-水(2mL)-甲醇(1ml)的混合溶剂中的搅拌溶液中加入氢氧化锂一水合物(36mg,0.86mmol)。将得到的混合物在35℃搅拌过夜。TLC和LC-MS表明期望产物的形成。将反应混合物用HCl水溶液(3N)酸化至pH=3-4,并用二氯甲烷(50mL×2)萃取。将有机层合并,用盐水洗涤,经Na_2SO_4干燥并浓缩以得到作为白色固体的标题产物(110mg,粗制物),将其不经进一步纯化用于下一步。质量:(ES^+):m/z 681.20$[M+H^+]$。

[0876] 步骤3:实施例150的合成:

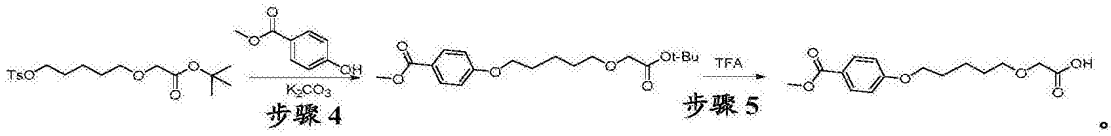
[0877] 

[0878] 在0℃向4-{[5-({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)戊基]氧基}苯甲酸(110mg,0.16mmol)、2-氯-4-[反式-3-氨基-2,2,4,4-四甲基环丁氧基]苄腈盐酸盐(50mg,0.16mmol)、N-乙基-N-异丙基丙烷-2-胺(77mg,0.64mmol)在无水N,N-二甲基甲酰胺(4mL)中的搅拌混合物中加入HATU((2-(7-氮杂-1H-苯并三唑-1-基)-1,1,3,3-四甲基脲鎓六氟磷酸盐))(68mg,0.18mmol)。将得到的混合物温热至室温并在室温搅拌20min。TLC和LC-MS表明期望产物的形成。将反应混合物在乙酸乙酯(100mL)和水(40mL)之间分配。将有机相分离,用盐水(50mL)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗残余物,将其通过制备型TLC(洗脱液:5%的甲醇在二氯甲烷中的溶液)纯化以得到作为白色固体的标题产物(收率25%,2步骤)。

[0879] 2-({5-[4-(甲氧基羰基)苯氧基]戊基}氧基)乙酸的合成

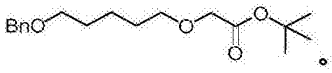


[0880]



[0881] 步骤1:2-{[5-(苄氧基)戊基]氧基}乙酸叔丁酯的合成:

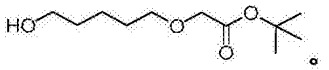
[0882]



[0883] 在室温向5-(苄氧基)戊烷-1-醇(10g,51.5mmol)、2-溴乙酸叔丁酯(40.2g,206mmol)和四丁基氯化铵(14.2g,51.5mmol)在二氯甲烷(60mL)中的搅拌混合物中加入氢氧化钠(40ml,35%在水中),并将得到的混合物在室温搅拌16h。然后将反应混合物在二氯甲烷(200mL)和水(100mL)之间分配。将有机层收集,并用盐水(50mL)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗残余物,将其通过硅胶快速色谱法(洗脱液:5%乙酸乙酯在己烷中的溶液)纯化以得到作为浅黄色油的2-{[5-(苄氧基)戊基]氧基}乙酸叔丁酯(收率31.6%)。LC-MS:(ES^+):m/z 331.10[$M+Na^+$],^1H NMR(400MHz,$CDCl_3$):δ1.48(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)。

[0884] 步骤2:2-[(5-羟基戊基)氧基]乙酸叔丁酯的合成:

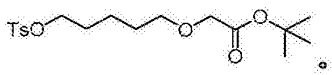
[0885]



[0886] 在氮气氛下在室温向2-{[5-(苄氧基)戊基]氧基}乙酸叔丁酯(5g,16.2mmol)在乙醇(100ml)中的搅拌溶液中加入炭载钯(10%,600mg)。将得到的混合物在氢气氛(氢气囊)下在50℃搅拌过夜。TLC表明期望产物的形成。将炭载钯通过过滤除去并用乙酸乙酯(50mL)洗涤。将滤液在减压下浓缩以得到作为无色油的2-[(5-羟基戊基)氧基]乙酸叔丁酯(2.5g,粗制物),将其不经进一步纯化用于下一步。

[0887] 步骤3:2-({5-[(4-甲基苯磺酰基)氧基]戊基}氧基)乙酸叔丁酯的合成:

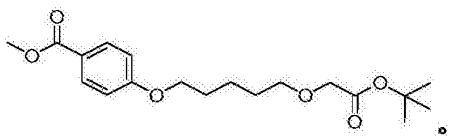
[0888]



[0889] 在0℃向2-[(5-羟基戊基)氧基]乙酸叔丁酯(2.5g,粗制物)和三乙胺(3.5g,34.5mmol)在无水二氯甲烷(50mL)中的搅拌溶液中逐滴加入4-甲苯磺酰氯(2.7g,13.8mmol)在无水二氯甲烷(8mL)中的溶液。将反应混合物温热至室温并在室温搅拌过夜。TLC表明期望产物的形成。将混合物在室温用碳酸钾水溶液(1N,50mL)猝灭,并用乙酸乙酯(50mL×3)萃取。将有机层合并,用盐水(50mL)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗残余物,将其通过硅胶快速色谱法(洗脱液:1%的甲醇在二氯甲烷中的溶液)纯化以得到作为无色油的2-({5-[(4-甲基苯磺酰基)氧基]戊基}氧基)乙酸叔丁酯(收率35.1%)。质量:(ES^+):m/z 395.10[MNa^+]。

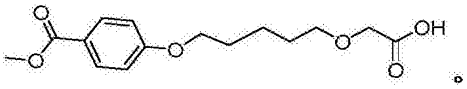
[0890] 步骤4:4-({5-[2-(叔丁氧基)-2-氧代乙氧基]戊基}氧基)苯甲酸甲酯的合成:

[0891]



[0892] 在室温向2-({5-[(4-甲基苯磺酰基)氧基]戊基}氧基)乙酸叔丁酯(1.0g,2.7mmol)和碳酸钾(266mg,1.6mmol)在乙腈(15mL)中的搅拌混合物中加入4-羟基苯甲酸甲酯(500mg,3.29mmol)。将得到的混合物回流过夜。TLC表明期望产物的形成。将反应混合物冷却至室温,并在乙酸乙酯(150mL)和水(50mL)之间分配。将有机层用盐水(50mL)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗残余物,将其通过硅胶快速色谱法(洗脱液10%乙酸乙酯在已烷中的溶液)纯化以得到作为无色油的4-({5-[2-(叔丁氧基)-2-氧代乙氧基]戊基}氧基)苯甲酸甲酯(收率33%)。质量(ES^+):m/z353.10[$M+Na^+$];^1H NMR(400MHz,$CDCl_3$):δ1.48(s,9H),1.55-1.61(m,2H),1.68-1.72(m,2H),1.80-1.87(m,2H),3.55(t,J=6.4Hz,2H),3.88(s,3H),3.96(s,2H),4.02(t,J=6.4Hz,2H),6.89(d,J=9.2Hz,2H),7.97(d,J=9.2Hz,2H)。

[0893] 步骤5:2-({5-[4-(甲氧基羰基)苯氧基]戊基}氧基)乙酸的合成:

[0894] 

[0895] 在室温向4-({5-[2-(叔丁氧基)-2-氧代乙氧基]戊基}氧基)苯甲酸甲酯(300mg,0.85mmol)在DCM(4mL)中的搅拌溶液中加入和TFA(2ml),将得到的溶液在室温搅拌1h。TLC表明期望产物的形成。将溶剂蒸发以得到作为黄色油的2-({5-[4-(甲氧基羰基)苯氧基]戊基}氧基)乙酸(200mg,粗制物),将其不经进一步纯化用在下一步中。

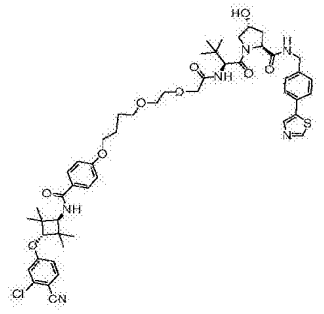
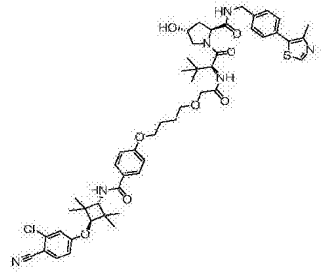
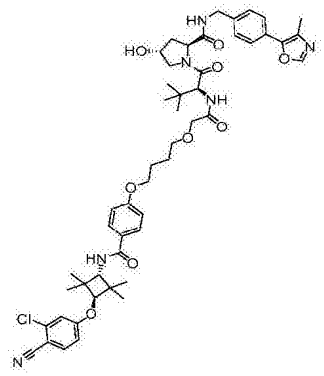
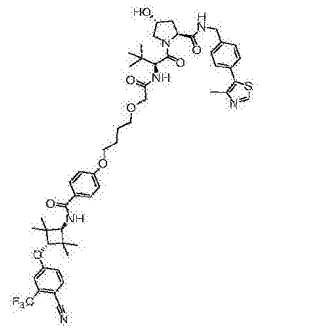
[0896] 根据关于实施例150的合成所述的类似程序,使用对应的起始原料和中间体合成实施例151-157。

[0897] 表9.示例性的化合物.

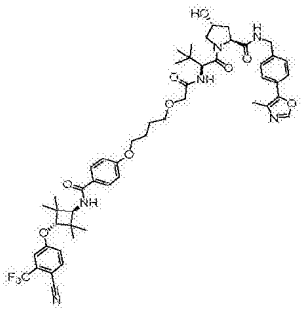
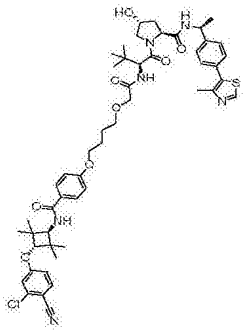
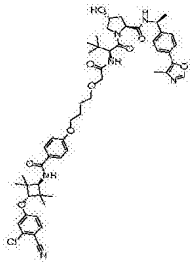
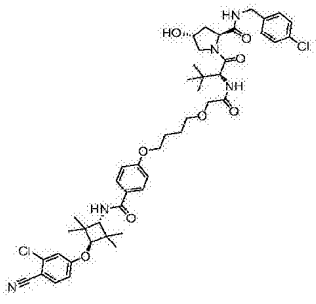
[0898]

实施例#	结构	化合物名称和分析数据

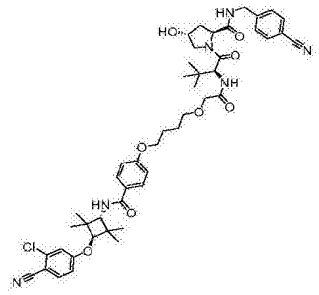
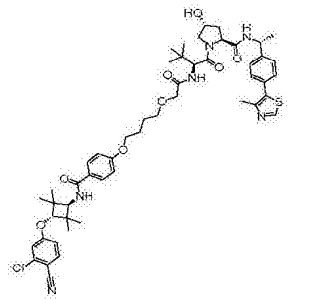
[0899]

162		(2S,4R)-1-[(2S)-3,3-二甲基-2-(2-{2-[4-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)丁氧基]乙氧基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-{2-[4-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)丁氧基]乙酰氨基}丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-{2-[4-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)丁氧基]乙酰氨基}丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-{2-[4-(4-{[反式-3-[4-氰基-3-(三氟甲基)苯氧基]-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)丁氧基]乙酰氨基}丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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$^+$]

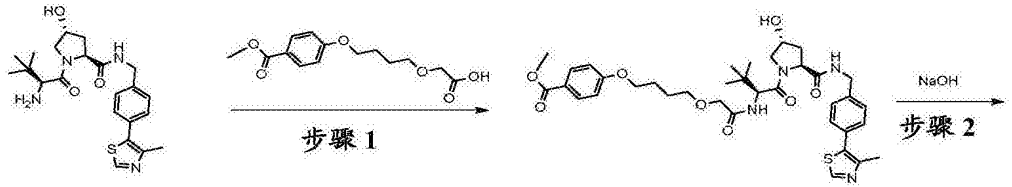
[0900]

166		(2S,4R)-1-[(2S)-3,3-二甲基-2-{2-[4-(4-{[反式-3-[4-氰基-3-(三氟甲基)苯氧基]-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)丁氧基]乙酰氨基}丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-{2-[4-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)丁氧基]乙酰氨基}丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-{2-[4-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)丁氧基]乙酰氨基}丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噁唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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-氯苯基)甲基]-1-[(2S)-3,3-二甲基-2-{2-[4-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)丁氧基]乙酰氨基}丁酰基]-4-羟基吡咯烷-2-甲酰胺 ^{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^+]

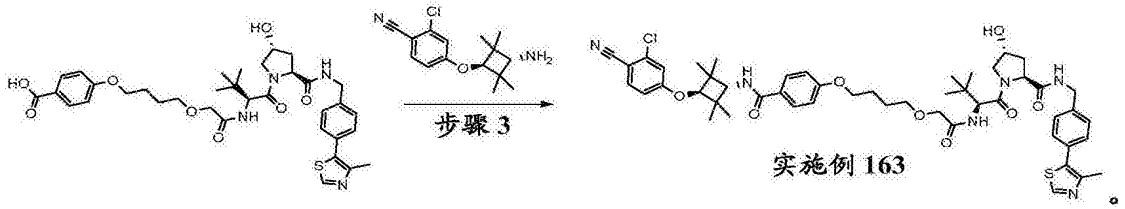
[0901]

170		(2S,4R)-N-[(4-氰基苯基)甲基]-1-[(2S)-3,3-二甲基-2-{2-[4-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)丁氧基]乙酰氨基}丁酰基]-4-羟基吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-{2-[4-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)丁氧基]乙酰氨基}丁酰基]-4-羟基-N-[(1R)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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); 质量(ES^+): *m/z* 955.45 [MH^+]

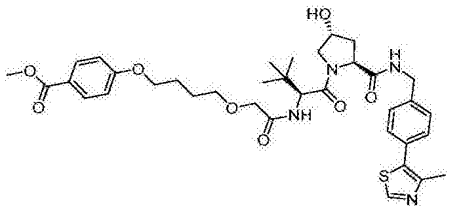
[0902] 实施例163的合成：



[0903]



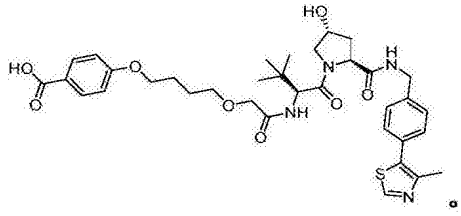
[0904] 步骤1:4-[4-({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)丁氧基]苯甲酸甲酯的合成

[0905] 

[0906] 在室温向2-{4-[4-(甲氧基羰基)苯氧基]丁氧基}乙酸(22.0mg,77.9μmol)和(2S,4R)-1-[(2S)-2-氨基-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺盐酸盐(36.3mg,77.9μmol)在二氯甲烷(2.0mL)中的搅拌

溶液中加入O-(苯并三唑-1-基)-N,N,N′,N′-四甲基脲鎓四氟硼酸盐(25.0mg,77.9μmol)和二异丙基乙胺(40.5μL,233μmol)。将反应混合物在室温搅拌30分钟,LC-MS指示期望产物的形成。将反应混合物在减压下浓缩。将粗制物质通过Teledyne Combiflash ISCO上的快速硅胶色谱法(梯度洗脱液:庚烷/丙酮(v:v=100:0至0:100))纯化以得到作为白色固体的标题产物(收率:78%)。LC-MS(ES+):m/z 695.3138[MH+]。

[0907] 步骤2:4-[4-({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)丁氧基]苯甲酸的合成:

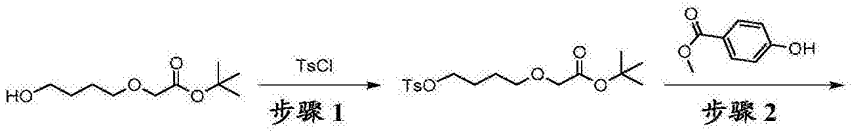
[0908] 

[0909] 在室温向4-[4-({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)丁氧基]苯甲酸甲酯(42.4mg,61.0μmol)在甲醇(2.0mL)中的搅拌溶液中加入1M的NaOH在水中的溶液(0.5mL,12.5mmol)。将反应混合物在室温搅拌16小时。LC-MS指示期望产物的形成。将反应混合物用1.0M的HCl水溶液猝灭并然后在减压下浓缩以除去甲醇。将含水残余物用EtOAc(15mL×2)萃取。将有机层用盐水(5mL)洗涤,经Na_2SO_4干燥,过滤并在减压下浓缩以得到作为白色固体的标题产物(收率:82%)。将该物质不经任何进一步纯化用于下一步。质量(ES+):m/z681.2986[MH+]。

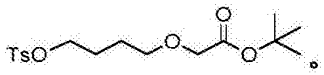
[0910] 步骤3:实施例163的合成:

[0911] 在室温向2-氯-4-[反式-3-氨基-2,2,4,4-四甲基环丁氧基]苄腈(13.9mg,50.2μmol)和4-[4-({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)丁氧基]苯甲酸(34.2mg,50.2μmol)在二氯甲烷(2.0mL)中的搅拌溶液中加入O-(苯并三唑-1-基)-N,N,N',N'-四甲基脲鎓四氟硼酸盐(16.1mg,50.2μmol)和二异丙基乙胺(26.0μL,150μmol)。将反应混合物在室温搅拌1.5小时。LC-MS指示期望产物的形成。将反应混合物用水(5mL)猝灭,并用DCM(15mL×3)萃取。将有机层合并,用$NaHCO_3$水溶液(5mL)、盐水(5mL)洗涤,经Na_2SO_4干燥、过滤并在减压下浓缩以得到粗制物质,将其通过Teledyne Combiflash ISCO上的快速硅胶色谱法(洗脱液:DCM/MeOH(v:v=90:10))纯化以得到作为灰白色固体的标题产物(收率:39%)。

[0912] 2-{4-[4-(甲氧基羰基)苯氧基]丁氧基}乙酸的合成:

[0913] 

[0914] 步骤1:2-{4-[(4-甲基苯磺酰基)氧基]丁氧基}乙酸叔丁酯的合成:

[0915] 

[0916] 根据上面关于2-({5-[(4-甲基苯磺酰基)氧基]戊基}氧基)乙酸叔丁酯的合成描述的类似程序,从2-(4-羟基丁氧基)乙酸叔丁酯和4-甲苯磺酰氯合成该物质。

[0917] 步骤2:4-{4-[2-(叔丁氧基)-2-氧代乙氧基]丁氧基}苯甲酸甲酯的合成.

[0918] 在室温向4-羟基苯甲酸甲酯(27.99mg,184.0μmol)和2-{4-[(4-甲基苯磺酰基)氧基]丁氧基}乙酸叔丁酯在乙腈(2.0mL)中的搅拌混合物中加入碳酸钾(34.67mg,250.9μmol)。然后将反应混合物在80℃搅拌16小时。LC-MS指示期望产物的形成。将反应混合物在减压下浓缩以得到粗残余物,将其通过Teledyne Combiflash ISCO上的快速硅胶色谱法(梯度洗脱液:庚烷/丙酮(v:v=100:0至50:50))纯化以得到作为澄清油的标题产物(收率:94%)。质量(ES^+):m/z 361.16[M+Na]。

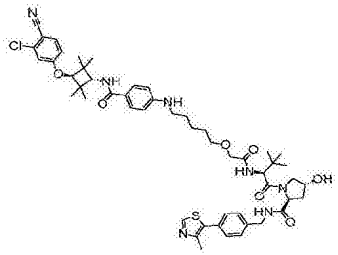
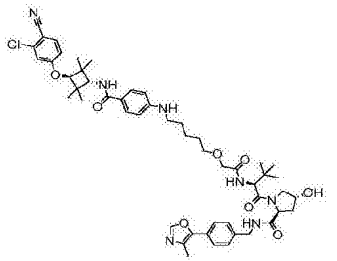
[0919] 步骤3:2-{4-[4-(甲氧基羰基)苯氧基]丁氧基}乙酸的合成:

[0920] 在室温向4-{4-[2-(叔丁氧基)-2-氧代乙氧基]丁氧基}苯甲酸甲酯(53.1mg,156μmol)在二氯甲烷(1.0mL)中的搅拌溶液中加入三氟乙酸(1.0mL,12.9mmol)。然后将反应混合物在室温搅拌30分钟。LC-MS指示期望产物的形成。将反应混合物在减压下浓缩以得到作为灰白色固体的标题产物(收率:99%,基于粗制物质)。然后将粗制物质不经任何进一步纯化用于下一步。质量(ES^+):m/z 305.10。

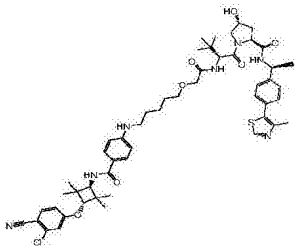
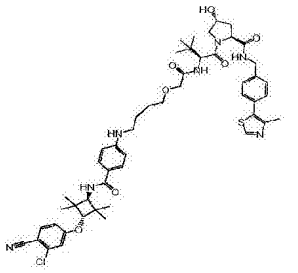
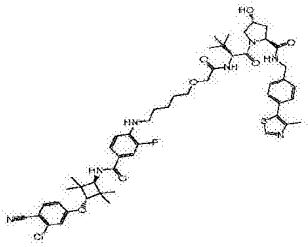
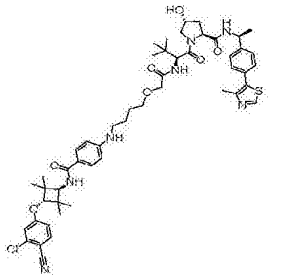
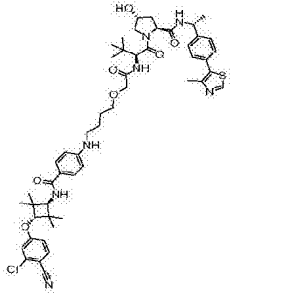
[0921] 根据关于实施例163的合成所述的类似程序,使用对应的起始原料和中间体合成实施例162、164-171。

[0922] 表10.示例性的化合物.

[0923]

实施例#	结构	化合物名称和分析数据
172		(2S,4R)-1-[(2S)-3,3-二甲基-2-[2-({5-[(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯基)氨基]戊基}氧基)乙酰氨基]丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-[2-({5-[(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯基)氨基]戊基}氧基)乙酰氨基]丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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^+]

[0924]

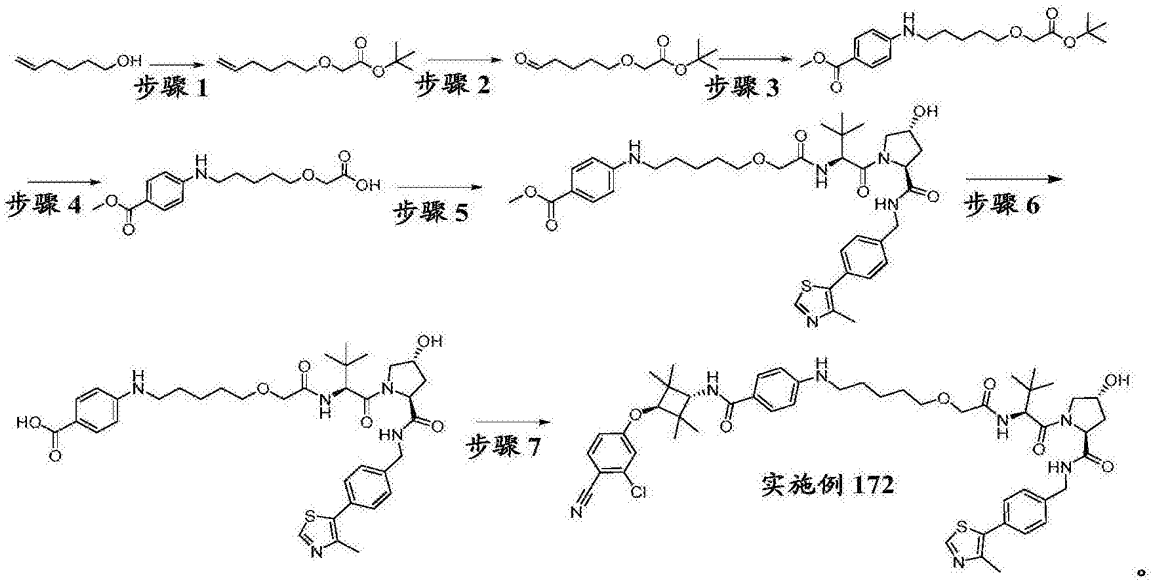
174		(2S,4R)-1-[(2S)-3,3-二甲基-2-[2-({5-[(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯基)氨基]戊基}氧基)乙酰氨基]丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{1}H NMR (300 MHz, CD_3OD):δ8.88 (s, 1 H), 7.80-7.65 (m, 3 H), 7.50-7.33 (m, 4 H), 7.16 (s, 1H), 7.03-6.93 (m, 1 H), 6.54-6.43 (m, 2 H), 5.02 -4.95 (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)-3,3-二甲基-2-(2-{4-[(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯基)氨基]丁氧基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氟-4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯基)氨基]戊基}氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-(2-{4-[(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯基)氨基]丁氧基}乙酰氨基)丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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); 质量(ES^+): *m/z* 955.20 [MH^+]
178		(2S,4R)-1-[(2S)-3,3-二甲基-2-(2-{4-[(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯基)氨基]丁氧基}乙酰氨基)丁酰基]-4-羟基-N-[(1R)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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* =

[0925]

		6.8 Hz, 3H), 1.20 (s, 6H), 1.11 (s, 6H), 0.91 (s, 9H); 质量(ES^+): *m/z* 954.15 [MH^+].

[0926] 实施例172的合成：

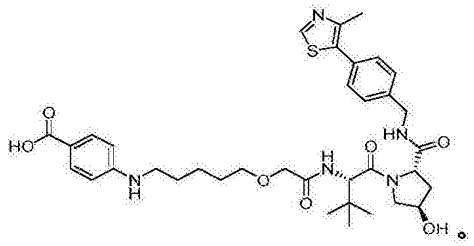
[0927]



[0928] 步骤7：实施例172的合成：

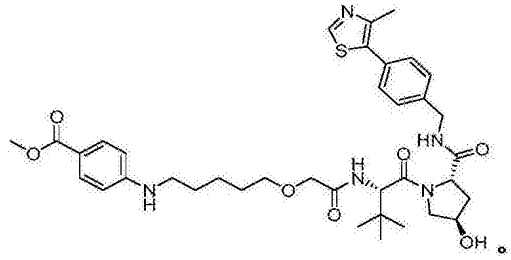
[0929] 在室温将TBTU(21.5mg,0.067mmol)加入4-{[5-({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)戊基]氨基}苯甲酸(31mg,0.044mmol)、2-氯-4-[反式-3-氨基-2,2,4,4-四甲基环丁氧基]苄腈(12.4mg,0.044mmol)在DMF(3.0mL)和DIPEA(15.4μL,0.089mmol)中的溶液中。将得到的反应混合物在室温搅拌1小时。LC-MS指示期望产物的形成。将反应混合物用EtOAc(30mL)稀释，用水(15mL×2)、盐水(15mL×1)洗涤，穿过Biotage Universal分相器过滤并然后在减压下浓缩以得到粗残余物，将其通过Teledyne Combiflash ISCO系统上的硅胶色谱法纯化，用MeOH/DCM(v/v=0:100至10:90)洗脱，以得到期望的标题产物(收率：41%)。

[0930] 步骤6：4-{[5-({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)戊基]氨基}苯甲酸的合成：

[0931] 

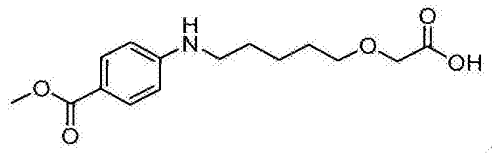
[0932] 在室温将氢氧化锂(9.0mg,0.38mmol)加入4-{[5-({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)戊基]氨基}苯甲酸甲酯(96mg,0.14mmol)在THF/水/甲醇(v/v/v=1/1/1,2.00mL)的混合溶剂中的溶液中。将得到的混合物在室温搅拌过夜。将HCl水溶液(1N)加入反应混合物中以将pH调至~3。将得到的混合物用EtOAc(30mL)稀释,用盐水(15mL×2)洗涤,经硫酸钠干燥,穿过Biotage Universal分相器过滤并然后在减压下浓缩以得到粗产物,将其不经任何进一步纯化用于下一步。LC-MS(ES+):m/z 694.33[MH+]。

[0933] 步骤5:4-{[5-({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)戊基]氨基}苯甲酸甲酯的合成。

[0934] 

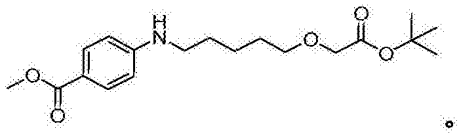
[0935] 在室温将TBTU(81.5mg,0.25mmol)加入2-[(5-{[4-(甲氧基羰基)苯基]氨基}戊基)氧基]乙酸(50.0mg,0.17mmol)、(2S,4R)-1-[(2S)-2-氨基-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺(72.8mg,0.17mmol)在DMF(3.0mL)和DIPEA(59μL,0.34mmol)中的溶液中。将得到的混合物在室温搅拌1h。将反应混合物用EtOAc(30mL)稀释,用水(15mL×2)、盐水(15mL×1)洗涤,经硫酸钠干燥,穿过Biotage Universal分相器过滤并然后在减压下浓缩以得到粗残余物,将其通过Teledyne Combiflash ISCO系统上的硅胶色谱法纯化,用MeOH/DCM(v/v=0:100至10:90)洗脱,以得到标题产物(收率:51%,2步骤)。LC-MS(ES+):m/z 708.35[MH+]。

[0936] 步骤4:2-[(5-{[4-(甲氧基羰基)苯基]氨基}戊基)氧基]乙酸的合成:

[0937] 

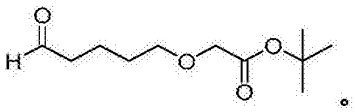
[0938] 在室温将三氟乙酸(2.63mL,34.5mmol)加入4-{[5-(2-甲氧基-2-氧代乙氧基)戊基]氨基}苯甲酸甲酯(270mg,0.7682mmol)在DCM(3.00ml)中的溶液中。将得到的混合物在45℃搅拌2h。然后将反应混合物在减压下浓缩以得到粗产物,将其不经任何进一步纯化用于下一步。LC-MS(ES+):m/z 296.15[MH+]。

[0939] 步骤3:4-({5-[2-(叔丁氧基)-2-氧代乙氧基]戊基}氨基)苯甲酸甲酯的合成:

[0940] 

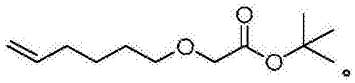
[0941] 在室温向2-[(5-氧代戊基)氧基]乙酸叔丁酯(269mg,1.24mmol)和4-氨基苯甲酸甲酯(187mg,1.24mmol)在二氯乙烷(5.00mL)中的溶液中加入乙酸(199μL,2.48mmol)和三乙酰氧基硼氢化钠(394mg,1.86mmol)。将反应混合物在室温搅拌18h。然后将NaOH(1N水溶液)加入以中和乙酸,将得到的反应混合物用DCM(100mL×3)萃取。将有机层合并,经无水硫酸钠干燥并在减压下浓缩以得到粗残余物,将其通过Teledyne Combiflash ISCO系统上的硅胶色谱法纯化,用MeOH/DCM(v/v=0:100至15:85)洗脱,以得到期望的标题产物(收率:62%)。LC-MS(ES^+):m/z352.21[MH^+]

[0942] 步骤2:2-[(5-氧代戊基)氧基]乙酸叔丁酯的合成:

[0943] 

[0944] 向2-(己-5-烯-1-基氧基)乙酸叔丁酯(300.0mg,1.40mmol)在丙酮(15.00ml)中的溶液中加入锇酸钾(VI)二水合物(15.5mg,0.042mmol),随后在室温加入NMO(491.9mg,4.20mmol)在水(4.5ml)中的溶液。将得到的反应混合物在室温搅拌18h。通过TLC(EtOAc/庚烷,v/v=25/75)监测反应。然后将高碘酸钠(898.2mg,4.20mmol)加入反应混合物中,将反应物在室温搅拌另外3h。将反应混合物用水(10mL)和DCM(100mL)稀释。将有机层分离并将水层用DCM(100mL×3)萃取。将合并的有机层用盐水(10mL×2)洗涤,并然后穿过Universal Biotage分相器并在减压下浓缩以得到粗残余物,将其通过Teledyne Combiflash ISCO系统上的硅胶色谱法纯化,用EtOAc/庚烷(v/v=0:100至50:50)洗脱,以得到标题产物(收率90%)。^1H NMR(400MHz,$CDCl_3$)δ9.75(t,J=1.8Hz,1H),3.89-3.93(m,2H),3.51(t,J=6.1Hz,2H),2.47(dt,J=1.6,7.2Hz,2H),1.69-1.78(m,2H),1.64(d,J=8.2Hz,2H),1.46(s,9H)。

[0945] 步骤1:2-(己-5-烯-1-基氧基)乙酸叔丁酯的合成:

[0946] 

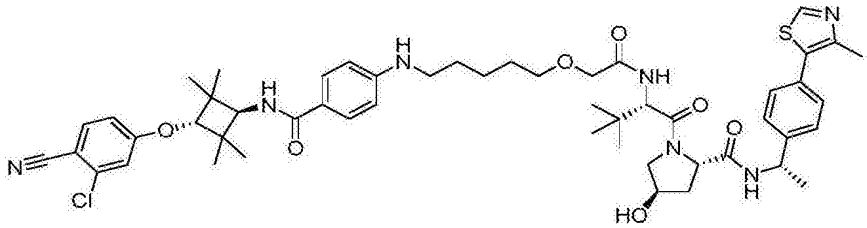
[0947] 在20℃将四丁基硫酸氢铵(677.7mg,2.0mmol)加入氢氧化钠(23.9g,599mmol)在水(20.0mL)和甲苯(20.00ml)中的混合物中。向该混合物中加入己-5-烯-1-醇(2.00g,20.0mmol),将得到的混合物在20℃搅拌1h。然后将反应物冷却至5℃,并缓慢地加入2-溴乙酸叔丁酯(20.0mmol,3.89g),同时维持内部温度低于15℃。然后将反应混合物在室温搅拌另外16h。将混合物用庚烷(30mL)稀释,并用水(20mL)洗涤。将有机相经无水硫酸钠干燥、过滤并在减压下浓缩以得到粗残余物,将其通过Teledyne Combiflash ISCO系统上的硅胶色谱法(梯度洗脱液:EtOAc/庚烷,v/v=0/100-25/75)纯化以得到期望产物(33%)。^1H NMR(400MHz,$CDCl_3$)δ5.75-5.87(m,1H),4.82-5.10(m,2H),3.95(s,2H),3.52(t,J=6.7Hz,2H),2.08(d,J=7.0Hz,2H),1.57-1.69(m,2H),1.45-1.53(m,11H)。LC-MS(ES^+):m/z237.14[MNa^+]

[0948] 根据关于实施例172的合成所述的类似程序,使用对应的起始原料和中间体合成

实施例173-178。

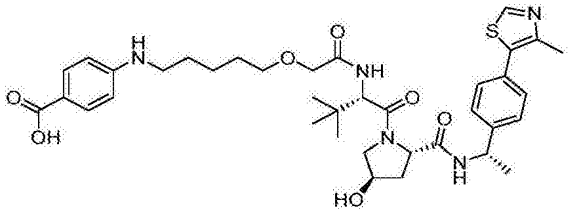
[0949] 可替换地，如下合成实施例174的步骤5-7：

[0950] 步骤7：(2S,4R)-1-((S)-2-(2-((5-((4-((反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基)氨基甲酰基)苯基)氨基)戊基)氧基)乙酰氨基)-3,3-二甲基丁酰基)-4-羟基-N-((S)-1-(4-(4-甲基噻唑-5-基)苯基)乙基)吡咯烷-2-甲酰胺的合成：

[0951] 

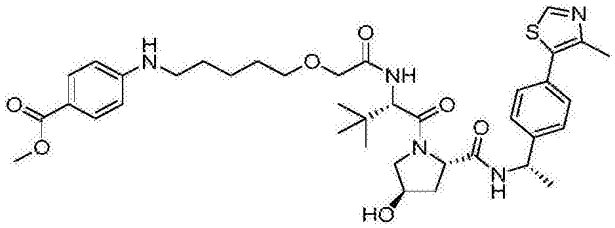
[0952] 给4-((5-(2-(((S)-1-((2S,4R)-4-羟基-2-(((S)-1-(4-(4-甲基噻唑-5-基)苯基)乙基)氨基甲酰基)吡咯烷-1-基)-3,3-二甲基-1-氧代丁-2-基)氨基)-2-氧代乙氧基)戊基)氨基)苯甲酸(1.17g,1.65mmol)在二氯甲烷(10mL)中的溶液加入HATU(688mg,1.81mmol)和二异丙基乙胺(859μL,4.94mmol)。将反应混合物在室温搅拌10分钟，然后加入4-(反式-3-氨基-2,2,4,4-四甲基环丁氧基)-2-氯苄腈盐酸盐(545mg,1.73mmol)。将反应混合物在室温搅拌30分钟。将反应混合物用DCM(30mL)稀释，然后用水(10mL)、盐水(10mL)洗涤，经Na_2SO_4干燥、过滤并在减压下浓缩。将粗制物质通过Teledyne Combiflash ISCO上的硅胶色谱法纯化，用DCM/MeOH(100:0至90:10)洗脱，以得到作为白色固体的期望产物(0.86g,54%)。LC-MS(ES+):m/z 968.42[MH+]。

[0953] 步骤6:4-((5-(2-(((S)-1-((2S,4R)-4-羟基-2-(((S)-1-(4-(4-甲基噻唑-5-基)苯基)乙基)氨基甲酰基)吡咯烷-1-基)-3,3-二甲基-1-氧代丁-2-基)氨基)-2-氧代乙氧基)戊基)氨基)苯甲酸的合成

[0954] 

[0955] 给4-((5-(2-(((S)-1-((2S,4R)-4-羟基-2-(((S)-1-(4-(4-甲基噻唑-5-基)苯基)乙基)氨基甲酰基)吡咯烷-1-基)-3,3-二甲基-1-氧代丁-2-基)氨基)-2-氧代乙氧基)戊基)氨基)苯甲酸甲酯(1.2g,1.66mmol)在甲醇(5mL)中的溶液加入3M NaOH(2.0mL,50.0mmol)。将反应混合物在室温搅拌72小时。将反应混合物用1.0M HCl猝灭并然后在减压下浓缩以除去甲醇。将水相用EtOAc(25mL×3)萃取。将合并的有机层用盐水(15mL)洗涤，经Na_2SO_4干燥、过滤并在减压下浓缩。将粗制物质通过Teledyne Combiflash ISCO上的硅胶色谱法纯化，用DCM/MeOH(100:0至90:10)洗脱，得到作为白色固体的期望产物(1.17g,100%)。LC-MS(ES+):m/z708.32[MH+]。

[0956] 步骤5:4-((5-(2-(((S)-1-((2S,4R)-4-羟基-2-(((S)-1-(4-(4-甲基噻唑-5-基)苯基)乙基)氨基甲酰基)吡咯烷-1-基)-3,3-二甲基-1-氧代丁-2-基)氨基)-2-氧代乙氧基)戊基)氨基)苯甲酸甲酯的合成

[0957] 

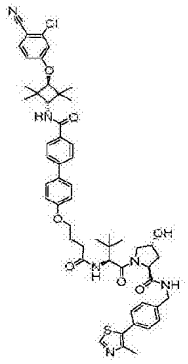
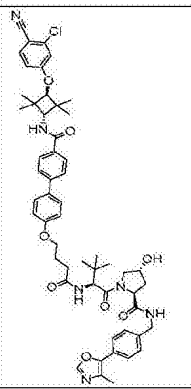
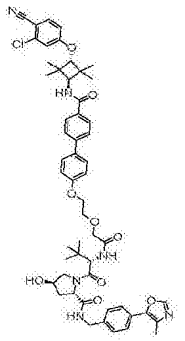
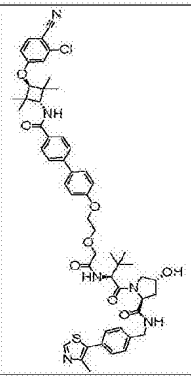
[0958] 给2-((5-((4-(甲氧基羰基)苯基)氨基)戊基)氧基)乙酸(1.68g,5.68mmol)和(2S,4R)-1-((S)-2-氨基-3,3-二甲基丁酰基)-4-羟基-N-((S)-1-(4-(4-甲基噻唑-5-基)苯基)乙基)吡咯烷-2-甲酰胺盐酸盐(2.73g,5.68mmol)在二氯甲烷(15mL)中的溶液加入O-(苯并三唑-1-基)-N,N,N′,N′-四甲基脲鎓四氟硼酸盐(1.82g,5.68mmol)和二异丙基乙胺(2.95mL,17.0mmol)。将反应混合物在室温搅拌30分钟。将反应混合物用水(15mL)猝灭,并然后用DCM(15mL)萃取。将有机层用盐水(15mL)洗涤,经Na_2SO_4干燥、过滤并在减压下浓缩。将粗制物质通过Teledyne Combiflash ISCO上的硅胶色谱法纯化,用DCM/MeOH(100:0至90:10)洗脱,得到作为白色固体的期望产物(1.2g,29%)。LC-MS(ES+):m/z722.34[MH+]。

[0959] 表11.示例性的化合物.

[0960]

实施例#	结构	化合物名称和分析数据

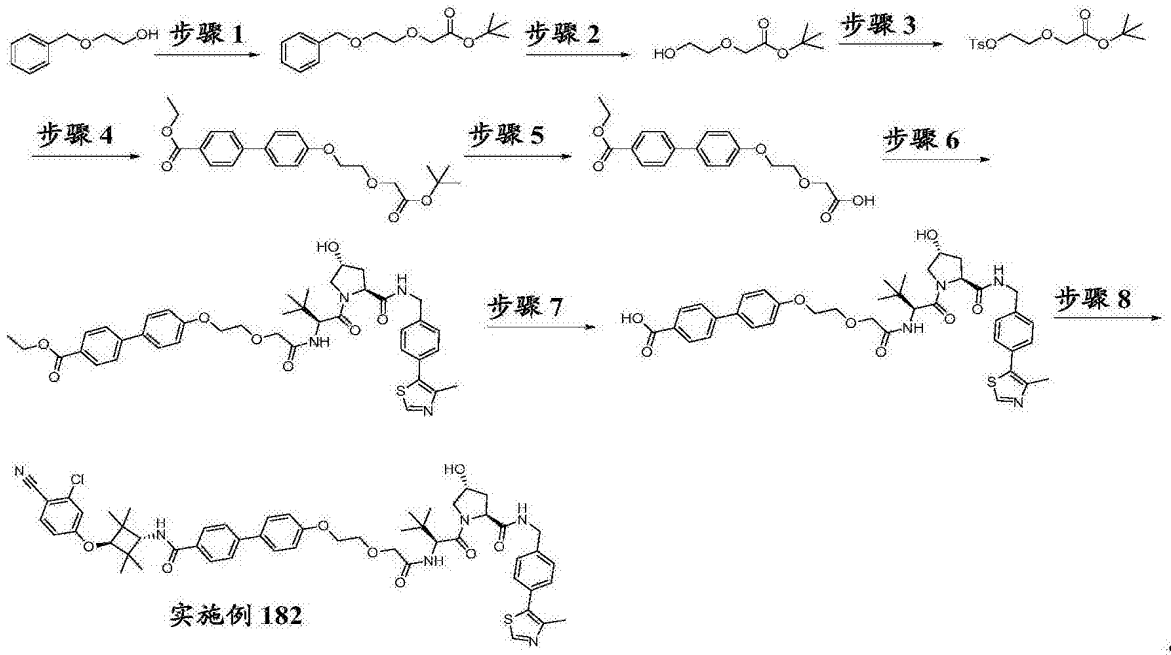
[0961]

179		(2S,4R)-1-[(2S)-3,3-二甲基-2-{4-[4-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯基)苯氧基]丁酰氨基}丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-{4-[4-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯基)苯氧基]丁酰氨基}丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-(2-{2-[4-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯基)苯氧基]乙氧基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-(2-{2-[4-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯基)苯氧基]乙氧基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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^+]

[0962] 根据关于实施例182的合成所述的类似程序，使用对应的起始原料和中间体合成实施例179-181。

[0963] 实施例182的合成：

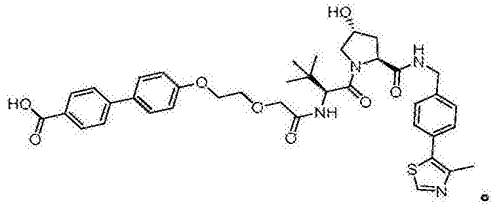
[0964]



[0965] 步骤8:实施例182的合成

[0966] 向4-{4-[2-({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)乙氧基]苯基}苯甲酸(89.0mg,122μmol)在二氯甲烷(2.0mL)中的搅拌溶液中加入HATU(55.5mg,146μmol)和二异丙基乙胺(63.7μL,366μmol)。将反应混合物在室温搅拌10分钟。然后给反应混合物加入2-氯-4-[反式-3-氨基-2,2,4,4-四甲基环丁氧基]苄腈(34.0mg,122μmol)。将反应物在室温搅拌30分钟。通过LC-MS监测反应,其指示反应结束。将反应混合物用水(5mL)猝灭,并然后用DCM(25mL)萃取。将有机层用盐水(5mL)洗涤,经Na_2SO_4干燥、过滤并在减压下浓缩以得到粗制物质,将其通过Teledyne Combiflash ISCO上的快速硅胶色谱法(洗脱液:DCM/MeOH(v:v=90:10))纯化以得到作为白色固体的标题产物(收率:37%)。

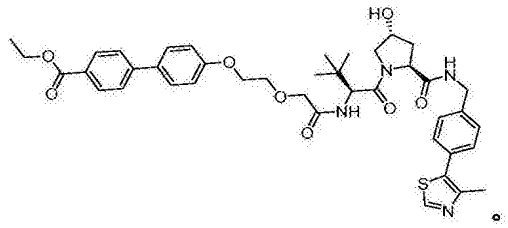
[0967] 步骤7:4-{4-[2-({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)乙氧基]苯基}苯甲酸的合成:

[0968] 

[0969] 向4-{4-[2-({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)乙氧基]苯基}苯甲酸乙酯(188.4mg,248μmol)在甲醇(2.0mL)中的搅拌溶液中加入1M的NaOH在水中的溶液(0.5mL,12.5mmol)。将反应混合物在室温搅拌16h。通过LC-MS监测反应,其指示反应结束。将反应混合物用1.0M的HCl在水中的溶液猝灭,并然后在减压下浓缩以除去甲

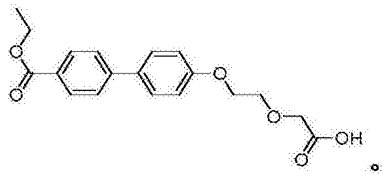
醇。将水相用EtOAc(25mL)萃取。将有机层用盐水(5mL)洗涤,经Na_2SO_4干燥、过滤并在减压下浓缩以得到粗制物质,将其通过Teledyne Combiflash ISCO上的快速硅胶色谱法(洗脱液:DCM/MeOH(v:v=90:10))纯化以得到作为白色固体的标题产物(收率:50%)。LC-MS(ES^+):m/z 729.18[MH^+]

[0970] 步骤6:4-{4-[2-({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)乙氧基]苯基}苯甲酸乙酯的合成:

[0971] 

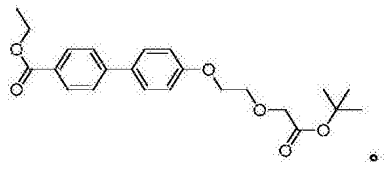
[0972] 向2-(2-{4-[4-(乙氧基羰基)苯基]苯氧基}乙氧基)乙酸(100mg,290.3μmol)和(2S,4R)-1-[(2S)-2-氨基-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺盐酸盐(135.5mg,290.3μmol)在二氯甲烷(2.0mL)中的搅拌溶液中加入O-(苯并三唑-1-基)-N,N,N',N'-四甲基脲鎓四氟硼酸盐(93.20mg,290.3μmol)和二异丙基乙胺(151.6μL,870.9μmol)。将反应混合物在室温搅拌30分钟。通过LC-MS监测反应,其指示反应结束。将反应混合物在减压下浓缩以得到粗制物质,将其通过Teledyne Combiflash ISCO上的快速硅胶色谱法(梯度洗脱液:庚烷/丙酮(v:v=100:0至0:100))纯化以得到作为白色固体的标题产物(收率:86%)。LC-MS(ES^+):m/z 757.3283[MH^+]。

[0973] 步骤5:2-(2-{4-[4-(乙氧基羰基)苯基]苯氧基}乙氧基)乙酸的合成:

[0974] 

[0975] 向4-(4-{2-[2-(叔丁氧基)-2-氧代乙氧基]乙氧基}苯基)苯甲酸乙酯(245mg,611μmol)在二氯甲烷(1.0mL)中的搅拌溶液中加入三氟乙酸(1.0mL,12.9mmol)。将反应混合物在室温搅拌30分钟。通过LC-MS监测反应,其指示反应结束。将反应混合物在减压下浓缩以得到作为灰白色固体的标题产物(收率:100%,基于粗制物)。将该物质不经任何进一步纯化用于下一步。LC-MS(ES^+):m/z 345.1330[MH^+]。

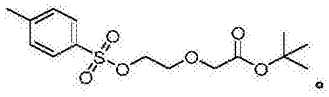
[0976] 步骤4:4-(4-{2-[2-(叔丁氧基)-2-氧代乙氧基]乙氧基}苯基)苯甲酸乙酯的合成:

[0977] 

[0978] 在室温向4'-羟基-[1,1'-联苯基]-4-甲酸乙酯(146.6mg,605.3μmol)和2-{2-[(4-甲基苯磺酰基)氧基]乙氧基}乙酸叔丁酯(200.0mg,605.3μmol)在乙腈(2.0mL)中的搅

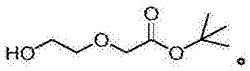
拌混合物中加入碳酸钾(125.4mg,907.9μmol)。然后将反应混合物在80℃搅拌16h。通过LC-MS监测反应,其指示反应结束。将反应混合物在减压下浓缩以得到粗制物质,将其通过Teledyne Combiflash ISCO上的快速硅胶色谱法(梯度洗脱液:庚烷/EtOAc(v:v=100:0至50:50))纯化以得到作为澄清油的标题产物(收率:99%)。LC-MS(ES^+):m/z 423.18[MNa^+]。

[0979] 步骤3:2-{2-[(4-甲基苯磺酰基)氧基]乙氧基}乙酸叔丁酯的合成:

[0980] 

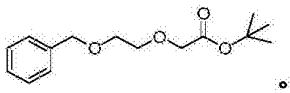
[0981] 在室温向2-(2-羟基乙氧基)乙酸叔丁酯(1.44g,0.19mmol)在二氯甲烷(10.0mL)中的搅拌溶液中加入4-甲基苯-1-磺酰氯(1.713g,0.21mmol)和三乙胺(1.707mL,12.25mmol)。将反应混合物在室温搅拌16h。通过LC-MS监测反应,其指示反应结束。将反应混合物在减压下浓缩以得到粗制物质,将其通过Teledyne Combiflash ISCO上的快速硅胶色谱法(梯度洗脱液:庚烷/丙酮(v:v=100:0至0:100))纯化以得到作为澄清油的标题产物(收率:69%)。^1H NMR(400MHz,CD_3OD)δppm 7.77-7.83(m,2H),7.44(d,J=7.83Hz,2H),4.14-4.19(m,2H),3.93(s,2H),3.68-3.74(m,2H),2.46(s,3H),1.46(s,9H);LC-MS(ES^+):m/z 353.1053[MNa^+],t_R=2.56min。

[0982] 步骤2:2-(2-羟基乙氧基)乙酸叔丁酯的合成:

[0983] 

[0984] 向2-[2-(苄氧基)乙氧基]乙酸叔丁酯在乙醇(10.0mL)中的搅拌溶液中加入炭载钯(10重量%)(1.99g,1.87mmol)。将反应混合物抽真空并用H_2气体(3×)净化。将反应混合物在H_2气氛下在室温搅拌16h。通过TLC分析监测反应,其指示反应结束。将反应混合物穿过硅藻土垫过滤并将滤液在减压下浓缩以得到作为澄清油的标题产物(收率:87%,基于粗制物)。将粗制物质不经任何进一步纯化用在下一步反应中。

[0985] 步骤1:2-[2-(苄氧基)乙氧基]乙酸叔丁酯的合成:

[0986] 

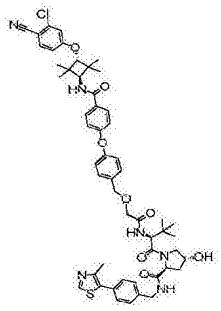
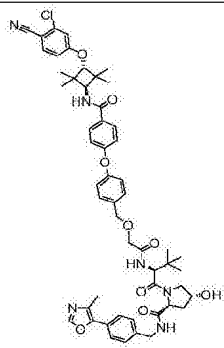
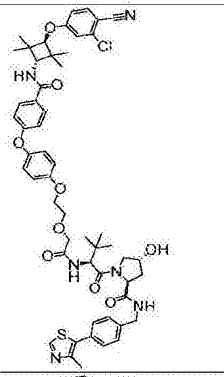
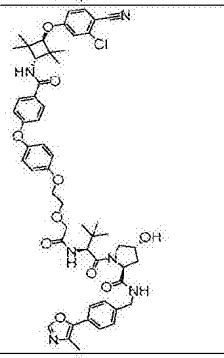
[0987] 在室温向2-(苄氧基)乙醇(5.0g,32.8mmol)和2-溴乙酸叔丁酯(7.02g,36.0mmol)在乙腈(10.0mL)中的搅拌溶液中加入碳酸钾(6.78g,49.1mmol)。然后将反应混合物在80℃搅拌16h。通过TLC分析监测反应,其指示反应结束。将反应混合物用水(10.0mL)稀释,并用EtOAc(20.0mL)萃取。将有机层用水(5.0mL)、盐水(5.0mL)洗涤,经Na_2SO_4干燥,过滤,并在减压下浓缩以得到作为黄色油的标题产物(收率:100%,基于粗制物)。将该粗制物质不经任何进一步纯化用在下一步反应中。

[0988] 表12.示例性的化合物.

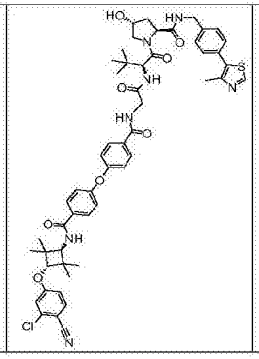
[0989]

实施例#	结构	化合物名称和分析数据

[0990]

183		(2S,4R)-1-[(2S)-3,3-二甲基-2-(2-{[4-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)苯基]甲氧基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-(2-{[4-(4-{[(1r,3r)-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)苯基]甲氧基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-(2-{2-[4-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)苯氧基]乙氧基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-(2-{2-[4-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)苯氧基]乙氧基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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^+]

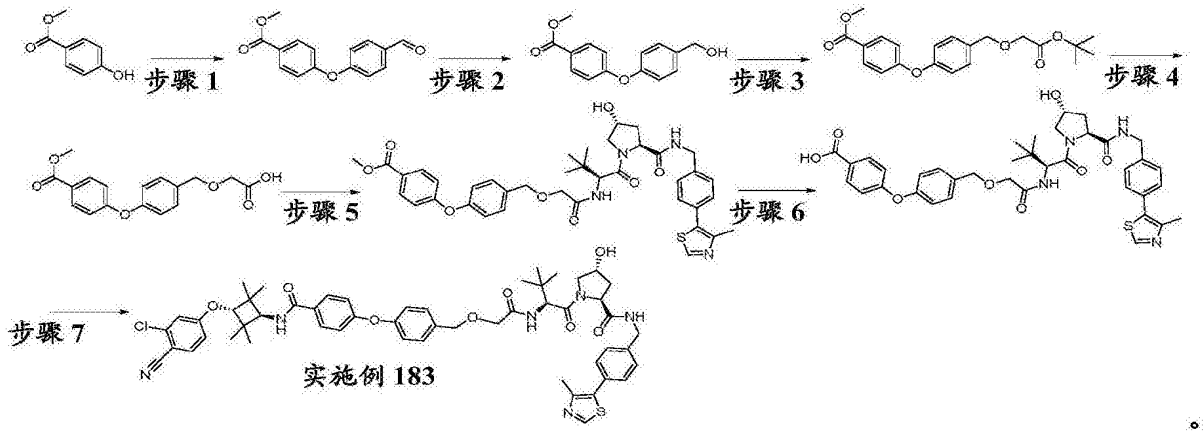
[0991]

187		(2S,4R)-1-[(2S)-3,3-二甲基-2-(2-{[4-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)苯基]甲酰氨基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 质量(ES$^+$): *m/z* 988.10 [MH$^+$]

[0992] 根据关于实施例183的合成所述的类似程序，使用对应的起始原料和中间体合成实施例184-187。

[0993] 实施例183的合成：

[0994]

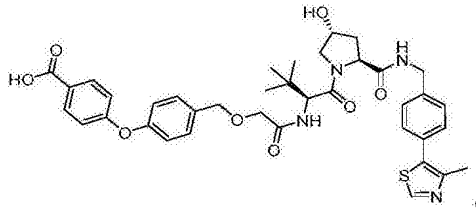


。

[0995] 步骤7：实施例183的合成

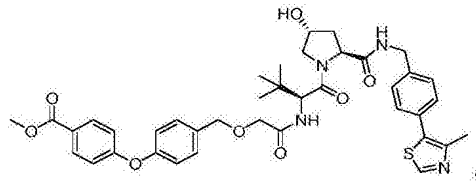
[0996] 在室温向2-氯-4-[反式-3-氨基-2,2,4,4-四甲基环丁氧基]苄腈(25.3mg,90.9μmol)和4-{4-[({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)甲基]苯氧基}苯甲酸(65mg,90.9μmol)在二氯甲烷(2.0mL)中的搅拌溶液中加入O-(苯并三唑-1-基)-N,N,N',N'-四甲基脲鎓四氟硼酸盐(29.1mg,90.9μmol)和二异丙基乙胺(47.3μL,272μmol)。将反应混合物在室温搅拌30分钟。通过LC-MS监测反应，其指示反应结束。将反应混合物用水(5mL)稀释，并用DCM(25mL)萃取。将有机层分离，并用盐水(5mL)洗涤，经Na_2SO_4干燥、过滤并在减压下浓缩以得到粗制物质，将其通过Teledyne Combiflash ISCO上的快速硅胶色谱法(洗脱液：DCM/MeOH(v:v=90:10))纯化以得到作为白色固体的标题产物(收率：22%)。

[0997] 步骤6：4-{4-[({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)甲基]苯氧基}苯甲酸的合成：

[0998] 

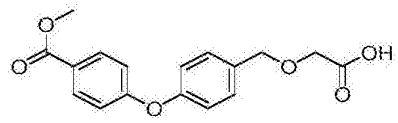
[0999] 在室温向4-{4-[({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)甲基]苯氧基}苯甲酸甲酯(68mg,93.2μmol)在甲醇(2.0mL)中的搅拌溶液中加入1M NaOH水溶液(0.5mL,12.5mmol)。将反应混合物在室温搅拌16小时。通过LC-MS监测反应,其指示反应结束。将反应混合物用1.0M HCl水溶液(0.5mL)猝灭,并然后在减压下浓缩以除去甲醇。将水相用EtOAc(25mL)萃取。将有机层分离,用盐水(5mL)洗涤,经Na_2SO_4干燥、过滤并在减压下浓缩以得到作为白色固体的标题产物(收率:98%,基于粗制物)。将该物质不经任何进一步纯化用于下一步反应。LC-MS(ES^+):m/z 715.28[MH^+]。

[1000] 步骤5:4-{4-[({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲氧基)甲基]苯氧基}苯甲酸甲酯的合成:

[1001] 

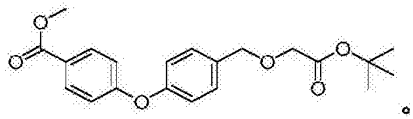
[1002] 在室温向2-({4-[4-(甲氧基羰基)苯氧基]苯基}甲氧基)乙酸(30.0mg,94.8μmol)和(2S,4R)-1-[(2S)-2-氨基-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺盐酸盐(44.2mg,94.8μmol)在二氯甲烷(2.0mL)中的搅拌溶液中加入O-(苯并三唑-1-基)-N,N,N′,N′-四甲基脲鎓四氟硼酸盐(30.4mg,94.8μmol)和二异丙基乙胺(49.4μL,284μmol)。将反应混合物在室温搅拌30分钟。通过LC-MS监测反应,其指示反应结束。将反应混合物在减压下浓缩以得到粗制物质,将其通过Teledyne Combiflash ISCO上的快速硅胶色谱法(梯度洗脱液:庚烷/丙酮(v:v=100:0至0:100))纯化以得到作为白色固体的标题产物(收率:99%)。LC-MS(ES^+):m/z 729.30[MH^+]。

[1003] 步骤4:2-({4-[4-(甲氧基羰基)苯氧基]苯基}甲氧基)乙酸:

[1004] 

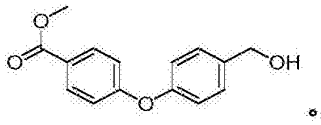
[1005] 将4-(4-{[2-(叔丁氧基)-2-氧代乙氧基]甲基}苯氧基)苯甲酸甲酯(200.0mg,537μmol)在氯化氢溶液(4M在二噁烷中,2.0mL)中的溶液在室温搅拌2h。通过LC-MS监测反应,其指示反应结束。将反应混合物在减压下浓缩以得到作为灰白色固体的标题产物(收率:95%,基于粗制物)。将该物质不经任何进一步纯化用于下一步反应。LC-MS(ES^+):m/z 339.0858[MNa^+]。

[1006] 步骤3:4-(4-{[2-(叔丁氧基)-2-氧代乙氧基]甲基}苯氧基)苯甲酸甲酯的合成:

[1007]  。

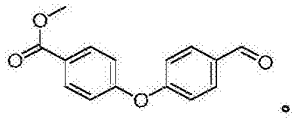
[1008] 在20℃向氢氧化钠(1.16g,29mmol)在水(2.0mL)和甲苯(2.0mL)中的搅拌混合物中加入四丁基硫酸氢铵(32.86mg,96.79μmol),随后加入4-[4-(羟基甲基)苯氧基]苯甲酸甲酯(250.0mg,967.9μmol),将得到的混合物在20℃搅拌1h。然后将混合物冷却至5℃,缓慢地加入2-溴乙酸叔丁酯(207.5mg,1.064mmol),并将内部温度维持在15℃以下。在该加入结束后,将反应混合物温热至室温并在室温搅拌16h。通过LC-MS监测反应,其指示反应结束。将混合物用水(5mL)稀释,并用EtOAc(30mL)萃取。将有机层分离,经无水硫酸钠干燥、过滤并在减压下浓缩以得到粗制物质,将其通过Teledyne Combiflash ISCO上的快速硅胶色谱法(洗脱液(梯度):庚烷/EtOAc(v:v=100:0至70:30))纯化以得到作为白色固体的标题产物(收率:56%)。LC-MS(ES^+):m/z 395.15[MNa^+]。

[1009] 步骤2:4-[4-(羟基甲基)苯氧基]苯甲酸甲酯的合成:

[1010]  。

[1011] 在室温向4-(4-甲酰基苯氧基)苯甲酸甲酯(750.0mg,2.92mmol)在甲醇(2.0mL)中的搅拌溶液中加入硼氢化钠(121mg,3.21mmol)。将反应混合物在室温搅拌30min。通过LC-MS监测反应,其指示反应结束。将反应混合物用1N HCl(在水中的溶液)缓慢地猝灭,在减压下浓缩以除去大部分甲醇,然后用DCM(30mL)萃取。将有机层分离,用盐水(5mL)洗涤,经Na_2SO_4干燥、过滤并在减压下浓缩以得到粗制物质,将其通过Teledyne Combiflash ISCO上的快速硅胶色谱法(洗脱液(梯度):庚烷/EtOAc(v:v=100:0至50:50))纯化以得到作为白色固体的标题产物(收率:94%)。LC-MS(ES^+):m/z 259.10[MH^+]。

[1012] 步骤1:4-(4-甲酰基苯氧基)苯甲酸甲酯的合成:

[1013]  。

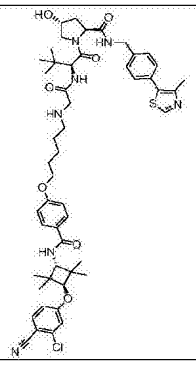
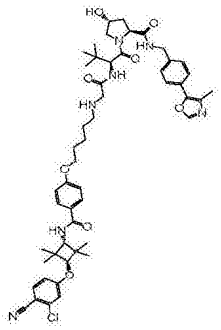
[1014] 在室温向4-羟基苯甲酸甲酯(1.0g,6.57mmol)和碳酸钾(1.36g,9.85mmol)在二甲基甲酰胺(2.0mL)中的搅拌混合物中加入4-氟苯甲醛(815mg,6.57mmol)。然后将反应混合物在80℃搅拌16h。通过LC-MS监测反应,其指示反应结束。将反应混合物冷却至室温,用水(10mL)稀释,并用EtOAc(50mL×2)萃取。将有机层分离,用盐水(10mL×2)洗涤,经Na_2SO_4干燥、过滤并在减压下浓缩以得到粗制物质,将其通过Teledyne Combiflash ISCO上的快速硅胶色谱法(洗脱液(梯度):庚烷/EtOAc(v:v=100:0至50:50))纯化以得到作为白色固体的标题产物(收率:90%)。LC-MS(ES^+):m/z 257.08[MH^+]。

[1015] 表13.示例性的化合物.

[1016]

实施例#	结构	化合物名称和分析数据

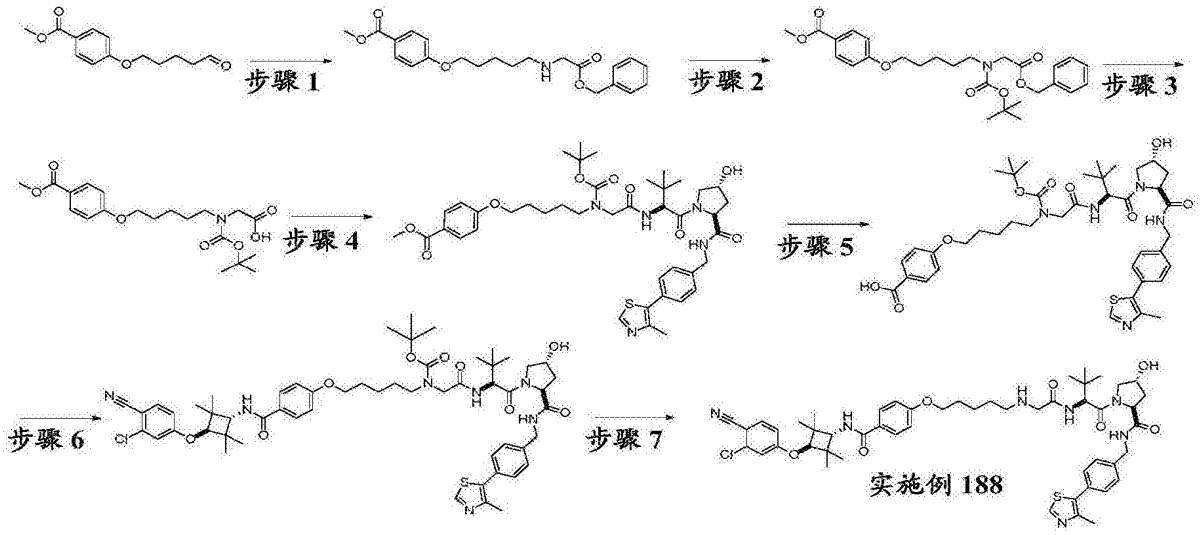
[1017]

188		(2S,4R)-1-[(2S)-3,3-二甲基-2-(2-{[5-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)戊基]氨基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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)-3,3-二甲基-2-(2-{[5-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)戊基]氨基}乙酰氨基)丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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$^+$]

[1018] 根据关于实施例188的合成所述的类似程序，使用对应的起始原料和中间体合成实施例189。

[1019] 实施例188的合成：

[1020]



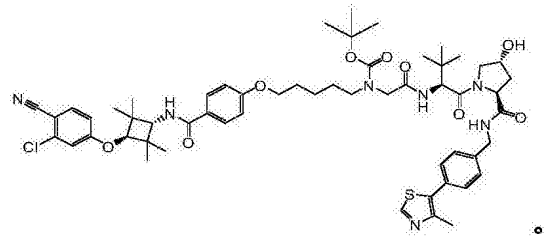
。

[1021] 步骤7：实施例188的合成

[1022] 在室温将三氟乙酸(1.12mL，14.7mmol)加入N-({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲基)-N-[5-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)戊基]氨基甲酸叔丁酯(34mg，0.0327mmol)在DCM(3.00ml)

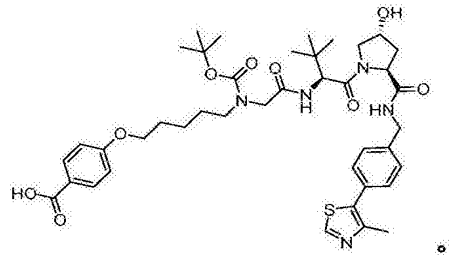
中的搅拌溶液中。将得到的混合物在45℃搅拌48h。然后将反应混合物在减压下浓缩以得到粗制物质，将其通过Teledyne Combiflash ISCO系统上的快速硅胶色谱法纯化，用MeOH/DCM(梯度:v:v＝0:100至10:90)洗脱，得到期望的标题产物(收率:62%)。

[1023] 步骤6:N-({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲基)-N-[5-(4-{[反式-3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯氧基)戊基]氨基甲酸叔丁酯的合成:

[1024] 

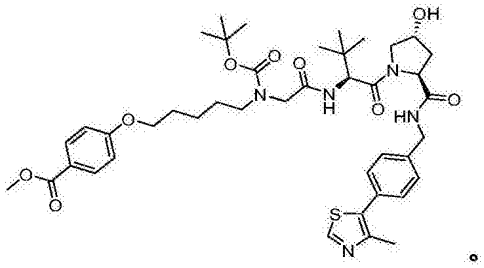
[1025] 在室温将TBTU(23.0mg,0.072mmol)加入4-[(5-{[(叔丁氧基)羰基]({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲基)氨基}戊基)氧基]苯甲酸(38mg,0.04786mmol)和2-氯-4-[反式-3-氨基-2,2,4,4-四甲基环丁氧基]苄腈(13.3mg,0.04786mmol)在DMF(3.0mL)和DIPEA(16.5μL,0.095mmol)中的搅拌溶液中。将得到的混合物在室温搅拌1h。然后将反应物用EtOAc(30mL)稀释，用盐水(5mL×2)洗涤，穿过Biotage Universal分相器过滤并然后在减压下浓缩以得到粗制物质，将其通过Teledyne Combiflash ISCO系统上的快速硅胶色谱法纯化，用MeOH/DCM(梯度:v:v＝0:100至10:90)洗脱，得到期望的标题产物(收率:60%)。

[1026] 步骤5:4-[(5-{[(叔丁氧基)羰基]({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲基)氨基}戊基)氧基]苯甲酸的合成:

[1027] 

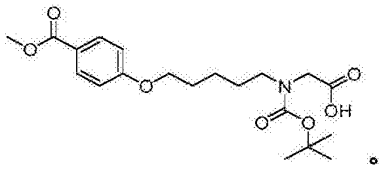
[1028] 在室温将氢氧化锂(3.0mg,0.128mmol)加入4-[(5-{[(叔丁氧基)羰基]({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲基)氨基}戊基)氧基]苯甲酸甲酯(37mg,0.046mmol)在THF/水(v:v＝1:1,2.00mL)的混合溶剂中的搅拌溶液中。将得到的反应混合物在室温搅拌过夜。向反应混合物中加入1N HCl(水溶液)以调节pH＝～3。将得到的混合物用EtOAc(20mL×2)萃取，用盐水(5mL×2)洗涤，穿过Biotage Universal分相器过滤并然后在减压下浓缩以得到粗制物质(收率:100%，基于粗制物)。将该粗产物不经任何进一步纯化用于下一步反应。

[1029] 步骤4:4-[(5-{[(叔丁氧基)羰基]({[(2S)-1-[(2S,4R)-4-羟基-2-({[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}氨基甲酰基)吡咯烷-1-基]-3,3-二甲基-1-氧代丁-2-基]氨基甲酰基}甲基)氨基}戊基)氧基]苯甲酸甲酯的合成:

[1030] 

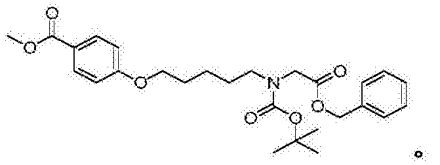
[1031] 在室温将TBTU(36.6mg,0.1142mmol)加入2-{[(叔丁氧基)羰基]({5-[4-(甲氧基羰基)苯氧基]戊基})氨基}乙酸(37mg,0.076mmol)和(2S,4R)-1-[(2S)-2-氨基-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺(32.8mg,0.076mmol)在DMF(3.0mL)和DIPEA(26.4μL,0.15mmol)中的搅拌溶液中。将得到的反应混合物在室温搅拌1小时。然后将反应物用EtOAc(30mL)稀释,用盐水(10mL)洗涤,穿过Biotage Universal分相器过滤并然后在减压下浓缩以得到粗制物质,将其通过Teledyne Combiflash ISCO系统上的快速硅胶色谱法纯化,用MeOH/DCM(梯度:(v/v)=0/100-10/90)洗脱,得到期望的标题产物(收率:64%)。

[1032] 步骤3:2-{[(叔丁氧基)羰基]({5-[4-(甲氧基羰基)苯氧基]戊基})氨基}乙酸的合成:

[1033] 

[1034] 在室温将炭载钯(96.8mg,0.91mmol)加入4-[(5-{[2-(苄氧基)-2-氧代乙基][(叔丁氧基)羰基]氨基}戊基)氧基]苯甲酸甲酯(83.0mg,0.171mmol)在乙醇(20ml)中的搅拌溶液中。将反应混合物脱气并充入$H_{(g)}$,并然后在氢气氛下在室温搅拌16h。然后将固体通过过滤除去并将溶剂在减压下浓缩以得到粗制物质(收率:98%,基于粗制物)。将该粗产物不经任何进一步纯化用于下一步反应。

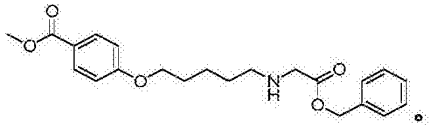
[1035] 步骤2:4-[(5-{[2-(苄氧基)-2-氧代乙基][(叔丁氧基)羰基]氨基}戊基)氧基]苯甲酸甲酯的合成:

[1036] 

[1037] 在室温将二碳酸二叔丁酯(47.7μL,0.21mmol)加入4-[(5-{[2-(苄氧基)-2-氧代乙基]氨基}戊基)氧基]苯甲酸甲酯(73.0mg,0.19mmol)在THF(5.0ml)中的搅拌溶液中。将反应混合物在80℃加热至回流并在80℃搅拌14h。然后将反应物冷却至室温,用乙酸乙酯(20mL)稀释,用饱和$NaHCO_3$水溶液(10mL)洗涤。将有机层分离并使用Biotage Universal分相器过滤,并然后在减压下浓缩以得到粗制物质,将其通过Teledyne Combiflash ISCO系

统上的快速硅胶色谱法纯化，用EtOAc/庚烷(梯度v:v＝0:100至40:60)洗脱，得到期望的标题产物(收率:95%)。

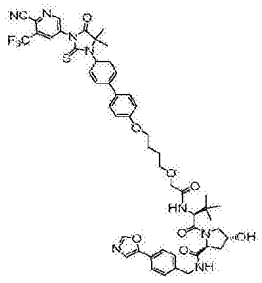
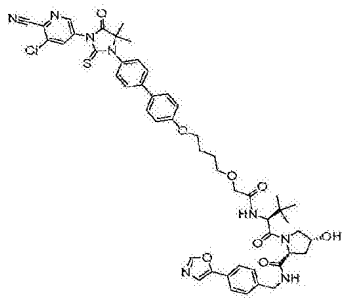
[1038] 步骤1:4-[(5-{[2-(苄氧基)-2-氧代乙基]氨基}戊基)氧基]苯甲酸甲酯的合成：

[1039]  。

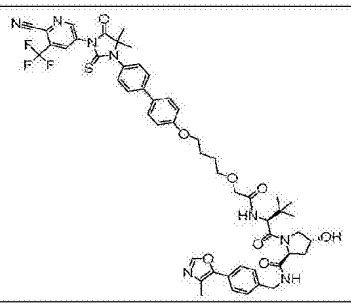
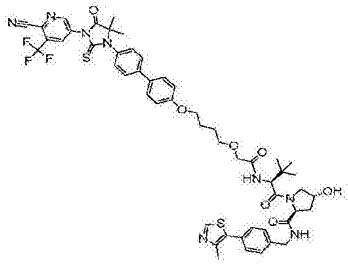
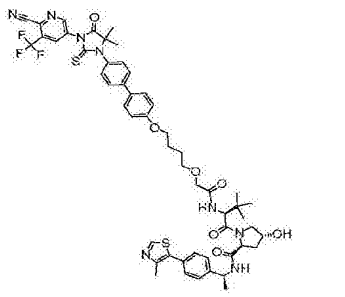
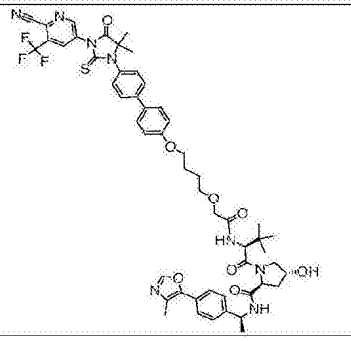
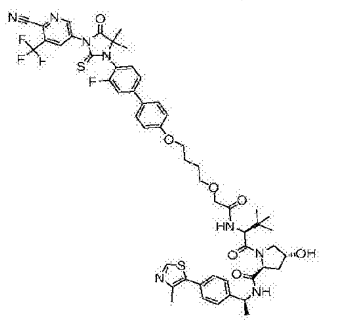
[1040] 在室温向4-[(5-氧代戊基)氧基]苯甲酸甲酯(269mg,1.13mmol)和2-氨基乙酸苄酯盐酸盐(186mg,1.13mmol)在DCE(5.00mL)中的搅拌混合物中加入乙酸(181μL,2.26mmol)和三乙酰氧基硼氢化钠(358mg,1.69mmol)。将反应混合物在室温搅拌18h。向反应混合物中加入1N NaOH水溶液以调节pH＝～10，然后将得到的混合物用DCM(30mL×3)萃取。将有机层分离，用盐水(10mL×2)洗涤，经Na_2SO_4干燥、过滤并在减压下浓缩以得到粗制物质，将其通过Teledyne Combiflash ISCO上的快速硅胶色谱法纯化，用MeOH/DCM(梯度v:v＝0:100至15:85)洗脱，得到标题产物(17%)。

[1041] 表14.示例性的化合物.

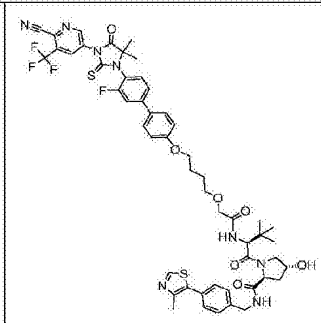
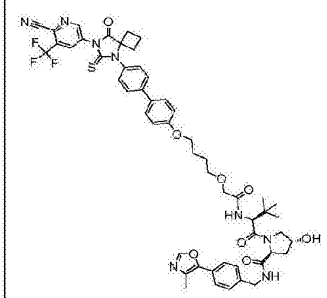
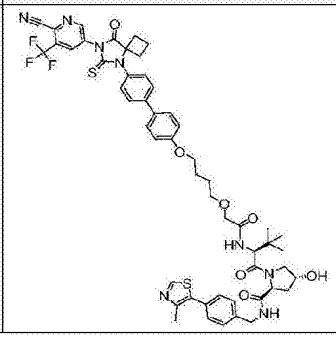
[1042]

实施例#	结构	化合物名称和分析数据
190		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[6-氰基-5-(三氟甲基)吡啶-3-基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氯-6-氰基吡啶-3-基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯基}苯氧基)丁氧基]乙酰氨基}-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 质量(ES^+): *m/z* 961.20 [MH^+]

[1043]

192		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[6-氰基-5-(三氟甲基)吡啶-3-基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 质量(ES$^+$): *m/z* 1009.20 [MH$^+$]
193		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[6-氰基-5-(三氟甲基)吡啶-3-基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 质量(ES$^+$): *m/z* 1025.45 [MH$^+$]
194		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[6-氰基-5-(三氟甲基)吡啶-3-基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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-氰基-5-(三氟甲基)吡啶-3-基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噁唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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-氰基-5-(三氟甲基)吡啶-3-基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-3-氟苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 质量(ES$^+$): *m/z* 1057.15 [MH$^+$]

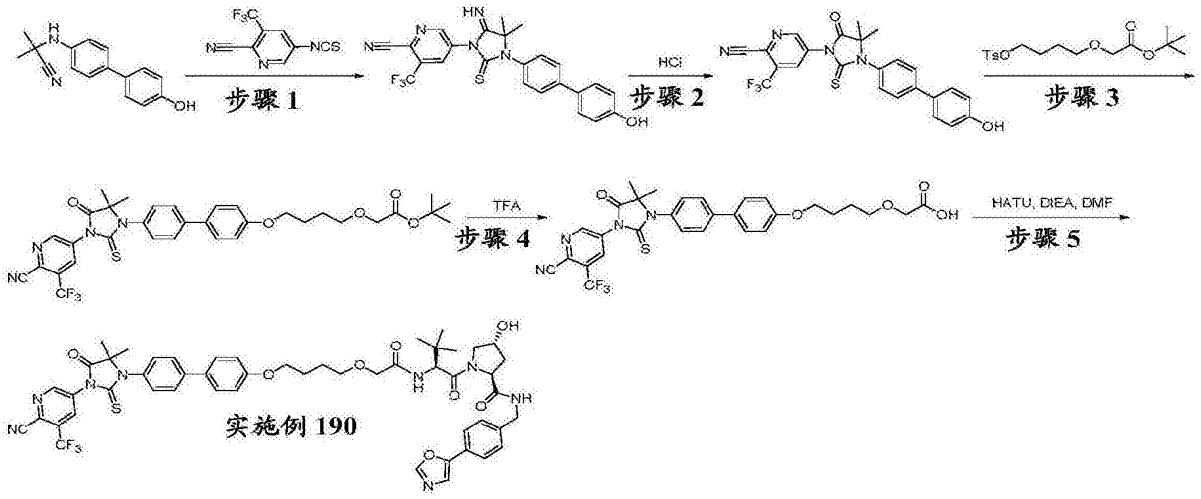
[1044]

197		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{3-[6-氰基-5-(三氟甲基)吡啶-3-基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}-3-氟苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 质量(ES$^+$): *m/z* 1043.20 [MH$^+$]
198		(2S,4R)-1-[(2S)-2-(2-{4-[4-(4-{7-[6-氰基-5-(三氟甲基)吡啶-3-基]-8-氧代-6-亚硫烷基-5,7-二氮杂螺[3.4]辛烷-5-基}苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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-氰基-5-(三氟甲基)吡啶-3-基]-8-氧代-6-亚硫烷基-5,7-二氮杂螺[3.4]辛烷-5-基}苯基)苯氧基]丁氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{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$^+$]

[1045] 根据关于实施例190的合成所述的类似程序，使用对应的起始原料和中间体合成实施例191-199。

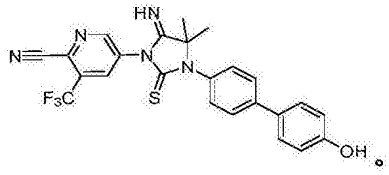
[1046] 实施例190的合成：

[1047]



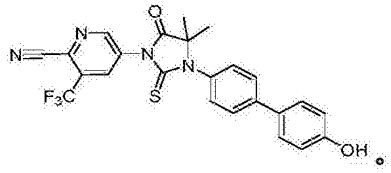
。

[1048] 步骤1:5-{3-[4-(4-羟基苯基)苯基]-5-亚氨基-4,4-二甲基-2-亚硫烷基咪唑烷-1-基}-3-(三氟甲基)吡啶-2-甲腈的合成:

[1049] 

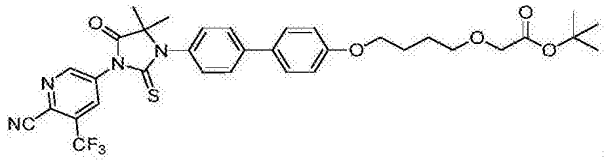
[1050] 在氮气氛下在室温向5-异硫氰酰基-3-(三氟甲基)吡啶-2-甲腈(440.0mg,1.92mmol)在N,N-二甲基吡啶-4-胺(322.0mg,2.64mmol)和甲苯(10.0mL)中的搅拌溶液中加入2-[[4-(4-羟基苯基)苯基]氨基]-2-甲基丙烷腈(400.0mg,1.59mmol)。将得到的溶液在100℃搅拌12h。然后将反应混合物在减压下浓缩以得到粗制物质,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚,v/v=1/1)纯化以得到标题产物(收率:17%)。质量(ES+):m/z 482.20[MH+]。

[1051] 步骤2:5-{3-[4-(4-羟基苯基)苯基]-4,4-二甲基-5-氧代-2-亚硫烷基咪唑烷-1-基}-3-(三氟甲基)吡啶-2-甲腈的合成:

[1052] 

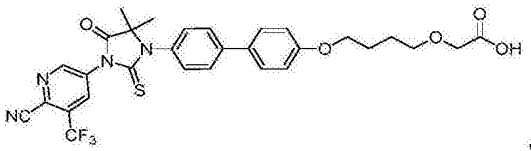
[1053] 在室温向5-{3-[4-(4-羟基苯基)苯基]-5-亚氨基-4,4-二甲基-2-亚硫烷基咪唑烷-1-基}-3-(三氟甲基)吡啶-2-甲腈(160.0mg,0.33mmol)在甲醇(5.0mL)中的搅拌溶液中加入盐酸水溶液(2N,2.0mL)。然后将得到的溶液回流2h。将反应物冷却至室温,在减压下浓缩以得到粗制物质,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚,v/v=1/1)纯化以得到作为黄色固体的标题产物(收率:69%)。LC-MS(ES+):m/z 481.15[MH+]。

[1054] 步骤3.2-{4-[4-(4-{3-[6-氰基-5-(三氟甲基)吡啶-3-基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酸叔丁酯的合成:

[1055] 

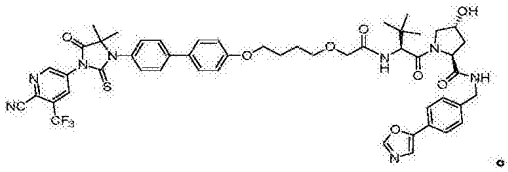
[1056] 在室温向5-{3-[4-(4-羟基苯基)苯基]-4,4-二甲基-5-氧代-2-亚硫烷基咪唑烷-1-基}-3-(三氟甲基)吡啶-2-甲腈(110.0mg,0.23mmol)和2-{4-[(4-甲基苯磺酰基)氧基]丁氧基}乙酸叔丁酯(163.0mg,0.45mmol)在N,N-二甲基甲酰胺(3.0mL)中的搅拌溶液中加入碳酸钾(62.9mg,0.46mmol)。将得到的混合物在60℃搅拌3h。然后将反应物冷却至室温,用水(10mL)稀释,并用乙酸乙酯(30mL×3)萃取。将有机层合并,经无水硫酸钠干燥,在减压下浓缩以得到粗制物质,将其通过快速硅胶色谱法(洗脱液:乙酸乙酯/石油醚,v/v=1/1)纯化以得到作为黄色固体的标题产物(收率:98%)。

[1057] 步骤4.2-{4-[4-(4-{3-[6-氰基-5-(三氟甲基)吡啶-3-基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酸的合成:

[1058] 

[1059] 在室温向2-{4-[4-(4-{3-[6-氰基-5-(三氟甲基)吡啶-3-基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酸叔丁酯(150.0mg,0.22mmol)在二氯甲烷(2.0mL)中的搅拌溶液中加入三氟乙酸(2.0mL)。将得到的溶液在室温搅拌2h。将得到的混合物在减压下浓缩以得到粗制物质,将其不经任何进一步纯化用于下一步反应。质量(ES^+):m/z613.00[MH^+]。

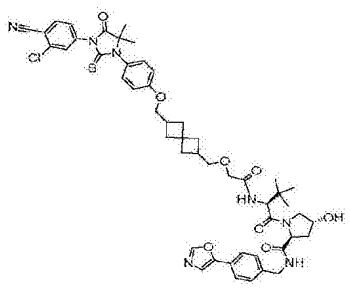
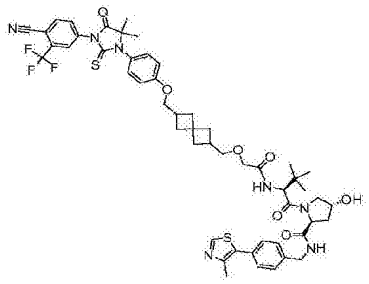
[1060] 步骤5.实施例190的合成:

[1061] 

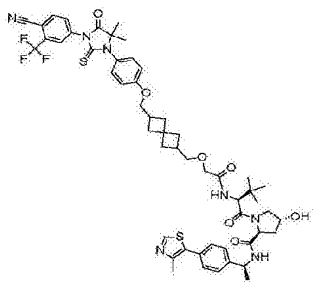
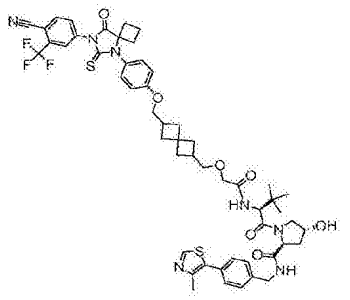
[1062] 在室温向2-{4-[4-(4-{3-[6-氰基-5-(三氟甲基)吡啶-3-基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯基)苯氧基]丁氧基}乙酸(80.0mg,0.13mmol)和(2S,4R)-1-[(2S)-2-氨基-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺(53.8mg,0.13mmol)在N,N-二甲基甲酰胺(2.0mL)中的搅拌溶液中加入O-(7-氮杂苯并三唑-1-基)-N,N,N,N-四甲基脲鎓六氟磷酸盐(51.0mg,0.13mmol)和N-乙基-N-异丙基丙烷-2-胺(43.0mg,0.33mmol)。将得到的溶液在室温搅拌2h。LC-MS指示期望产物的形成。将反应混合物用水(10mL)稀释,并用乙酸乙酯(50mL×3)萃取。将有机层合并,用盐水(10mL)洗涤,经无水硫酸钠干燥并在减压下浓缩以得到粗制物质,将其通过硅胶快速色谱法(洗脱液:乙酸乙酯/石油醚,v/v=1/1)纯化以得到作为白色固体的标题产物(收率:45%)。

[1063] 表15.示例性的化合物.

[1064]

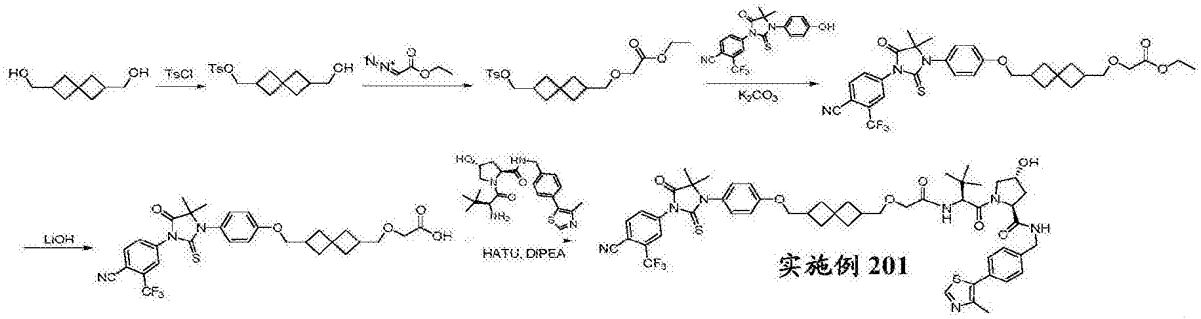
实施例#	结构	化合物名称和分析数据
200		(2S,4R)-1-[(2S)-2-(2-{[6-({4-[3-(3-氯-4-氰基苯基)-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基]苯氧基}甲基)螺[3.3]庚烷-2-基]甲氧基}乙酰氨基)-3,3-二甲基丁酰基]-4-羟基-N-{[4-(1,3-噁唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 质量(ES$^+$): *m/z* 950.50 [MH$^+$]
201		(2S,4R)-1-[(2S)-2-[2-({6-[(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)甲基]螺[3.3]庚烷-2-基}甲氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 ^{1}H NMR (400 MHz, CD$_3$OD) 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$^+$]

[1065]

202		(2S,4R)-1-[(2S)-2-[2-({6-[(4-{3-[4-氰基-3-(三氟甲基)苯基]-5,5-二甲基-4-氧代-2-亚硫烷基咪唑烷-1-基}苯氧基)甲基]螺[3.3]庚烷-2-基}甲氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-[(1S)-1-[4-(4-甲基-1,3-噻唑-5-基)苯基]乙基]吡咯烷-2-甲酰胺 ^{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-氰基-3-(三氟甲基)苯基]-8-氧代-6-亚硫烷基-5,7-二氮杂螺[3.4]辛烷-5-基}苯氧基)甲基]螺[3.3]庚烷-2-基}甲氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 质量(ES$^+$): *m/z* 1026.25 [MH$^+$]

[1066] 根据下面显示的化学，利用用于合成实施例75的类似程序合成实施例201。

[1067]



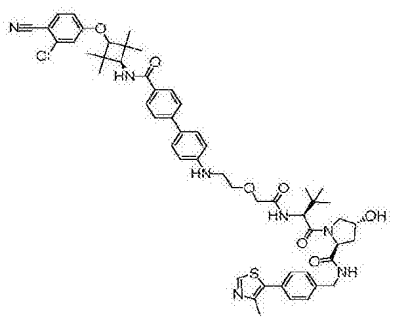
[1068] 根据关于实施例201的合成所述的类似程序，使用对应的起始原料和中间体合成实施例200、202-203。

[1069] 表16.示例性的化合物.

[1070]

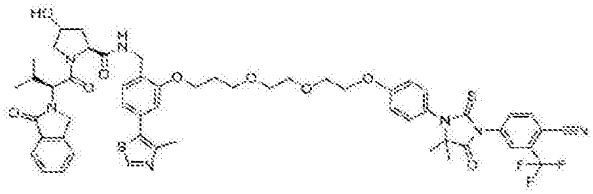
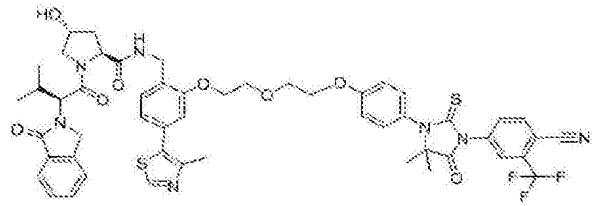
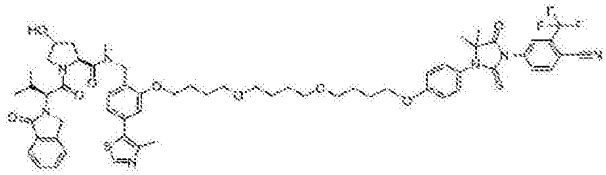
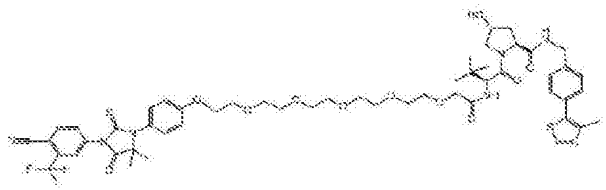
实施例#	结构	化合物名称和分析数据

[1071]

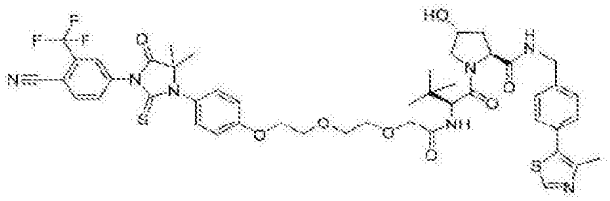
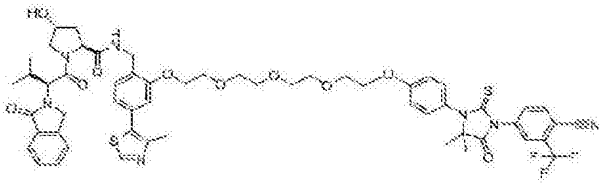
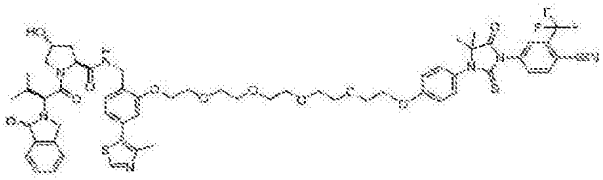
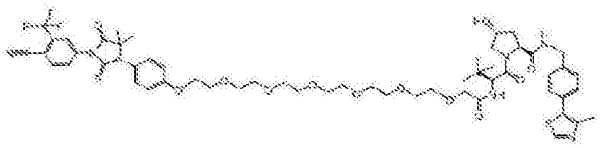
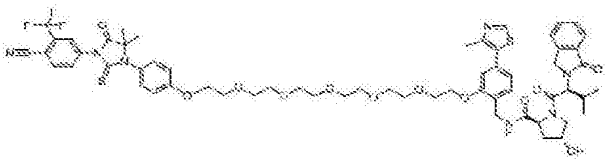
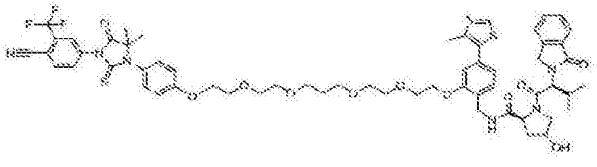
204		(2S,4R)-1-[(2S)-2-[2-(2-{[4-(4-{[3-(3-氯-4-氰基苯氧基)-2,2,4,4-四甲基环丁基]氨基甲酰基}苯基)苯基]氨基}乙氧基)乙酰氨基]-3,3-二甲基丁酰基]-4-羟基-N-{[4-(4-甲基-1,3-噻唑-5-基)苯基]甲基}吡咯烷-2-甲酰胺 质量(ES^+): *m/z* 988.20 [MH^+]

[1072] 表17.另外的示例性化合物.

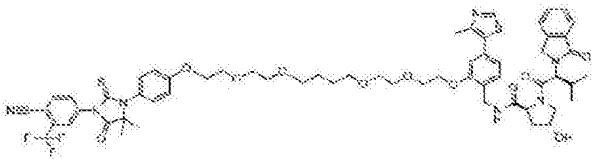
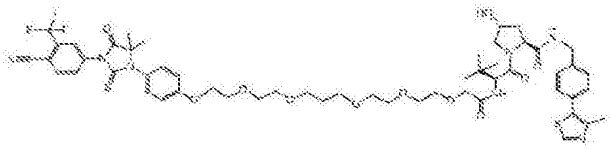
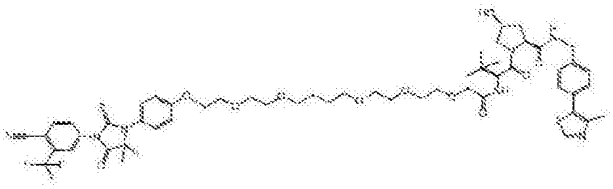
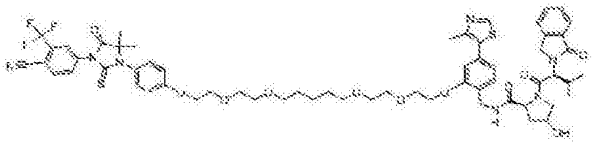
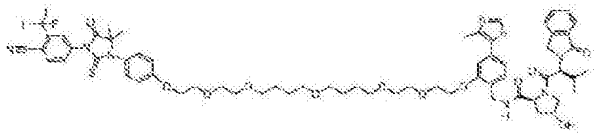
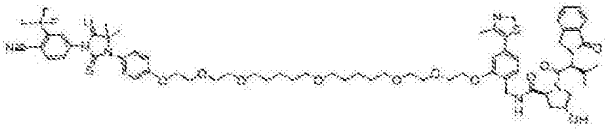
[1073]

	结构	测量的质量离子数据	
		MH^+ 1	MH^+ 2
205		1082.37	
206		1024.33	
207		1152.45	
208		1096.41	

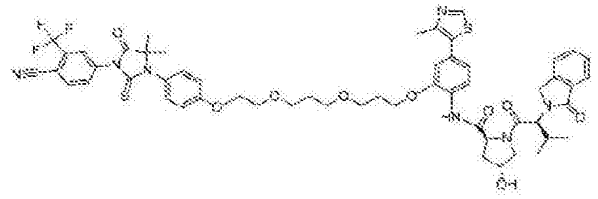
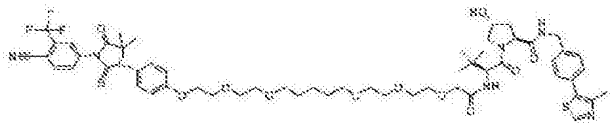
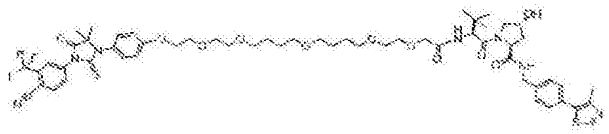
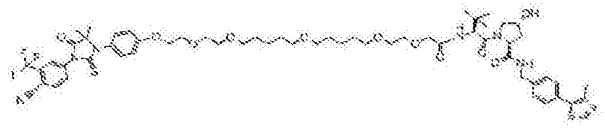
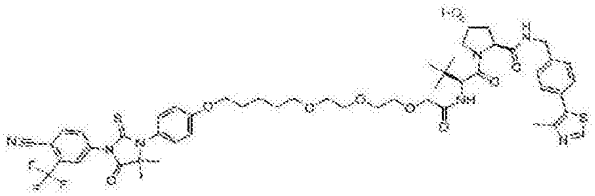
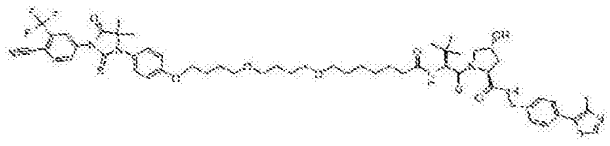
[1074]

209		964.33	
210		1112.38	
211		1156.41	
212		1140.44	
213		1200.44	
214		1170.42	

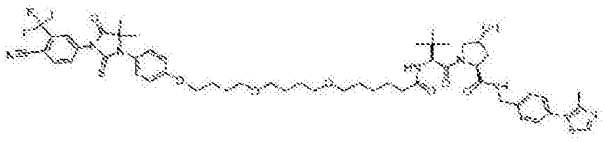
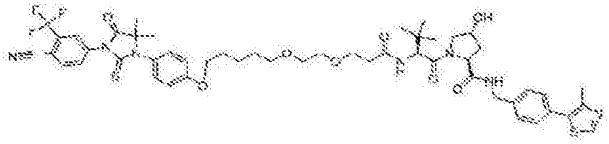
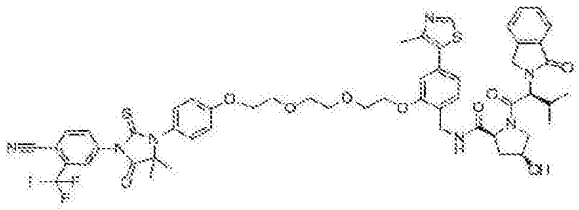
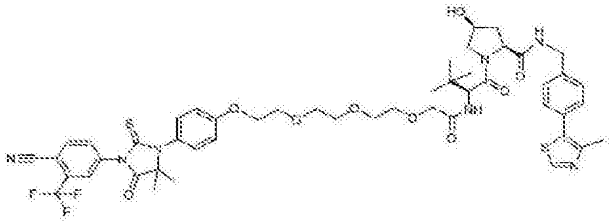
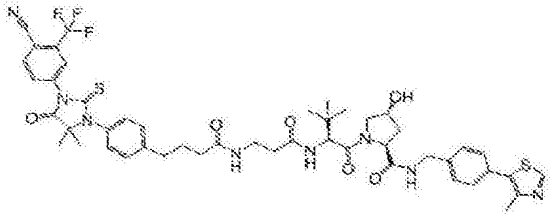
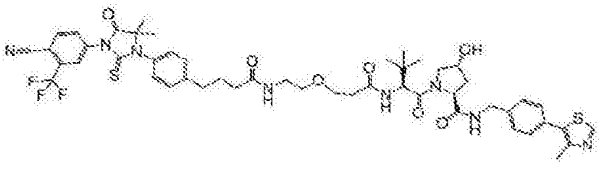
[1075]

215		1184.44	
216		1110.43	
217		1124.44	
218		1198.46	
219		1256.50	
220		1284.53	

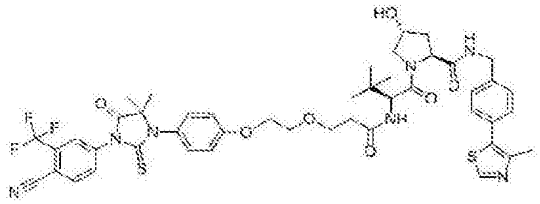
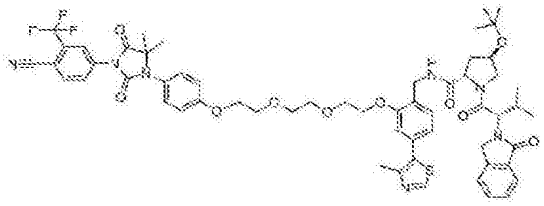
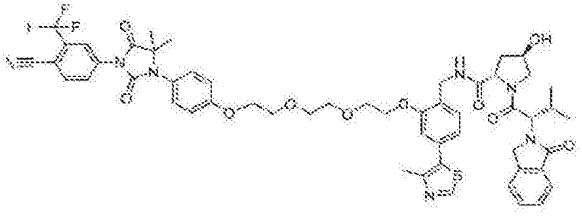
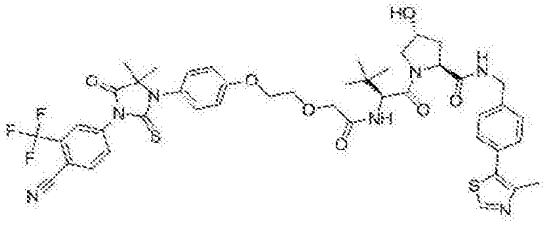
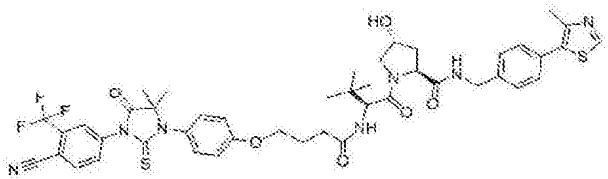
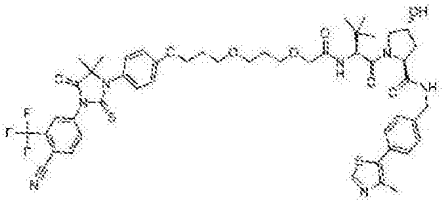
[1076]

221		1096.39	
222		1138.46	
223		1152.47	
224		1180.50	
225		1050.40	
226		1090.47	

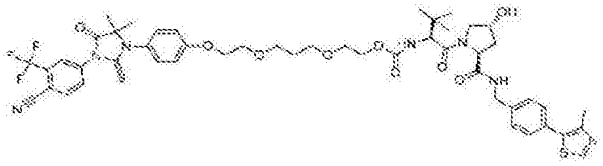
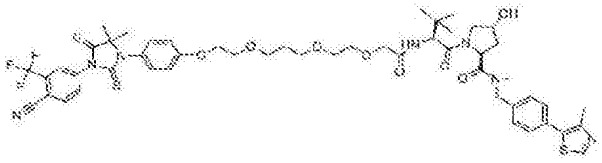
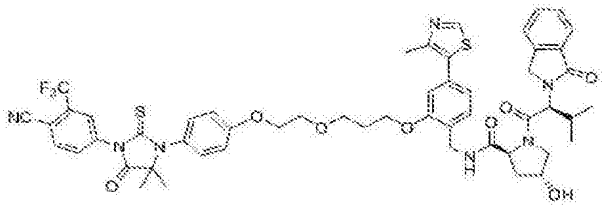
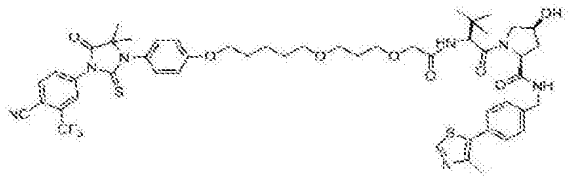
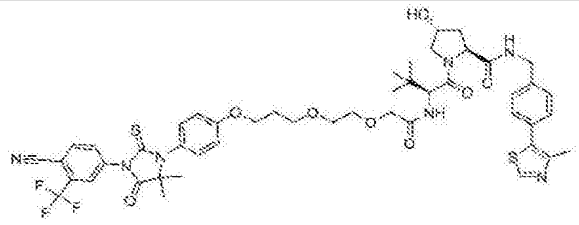
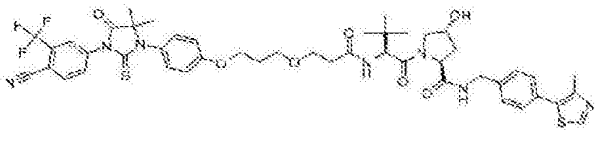
[1077]

227		1076.46	
228		1020.40	
229		1068.36	
230		1008.36	
231		959.36	
232		1003.38	

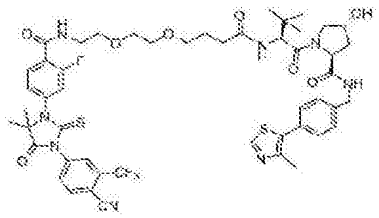
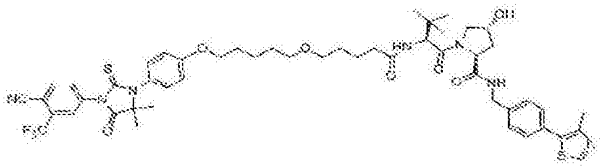
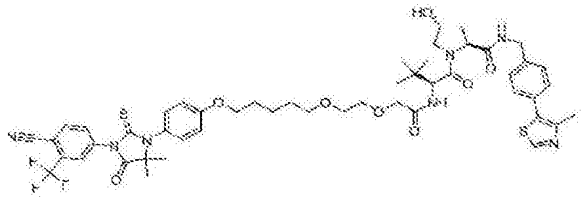
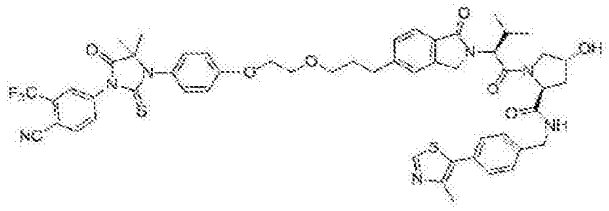
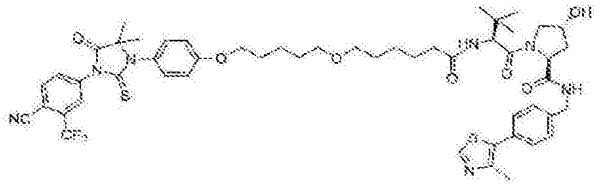
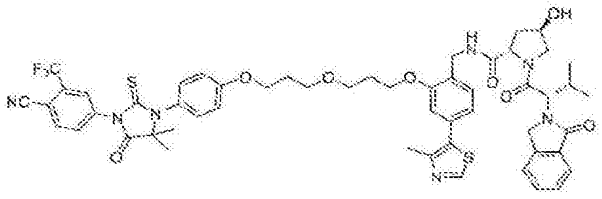
[1078]

233		934.32	
234		1108.44	
235		1052.37	
236		920.29	
237		904.30	
238		992.35	

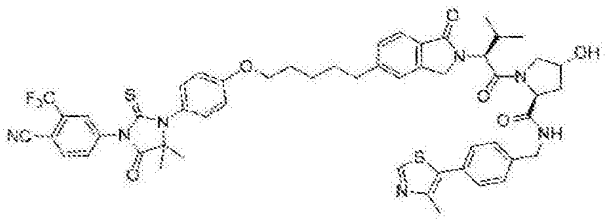
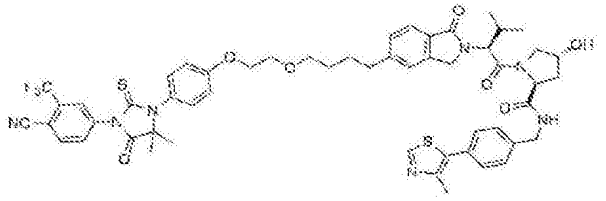
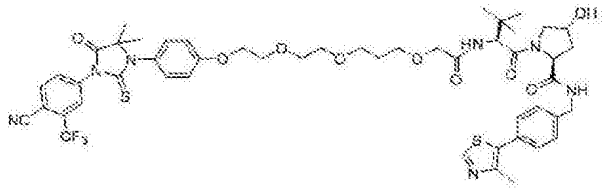
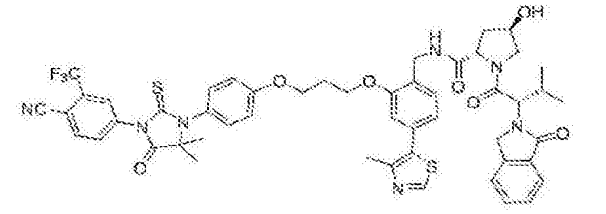
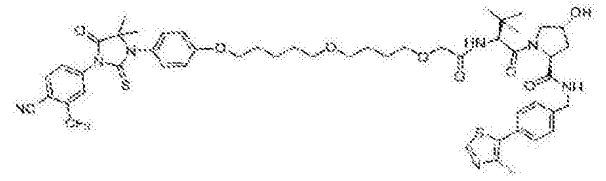
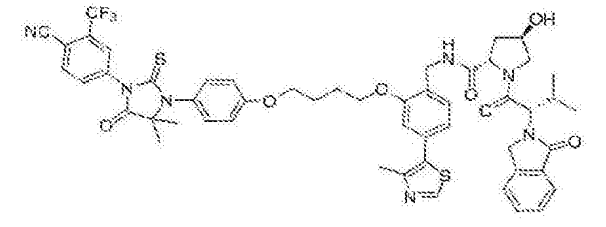
[1079]

239		1008.34	
240		1022.36	
241		1038.33	
242		1020.38	
243		978.35	
244		948.34	

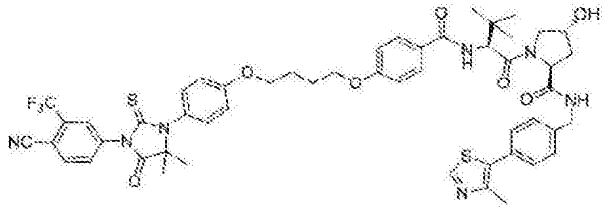
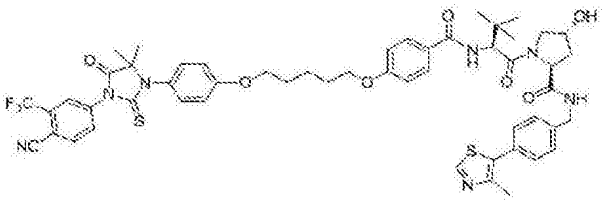
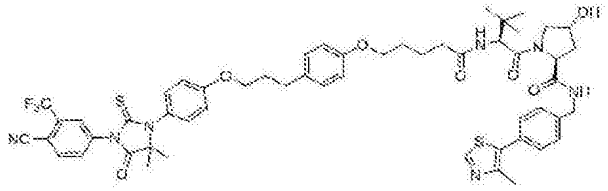
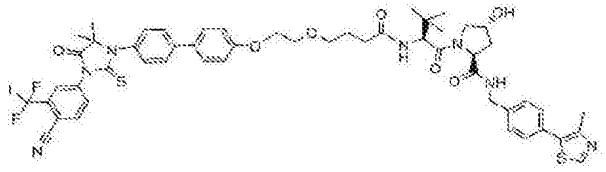
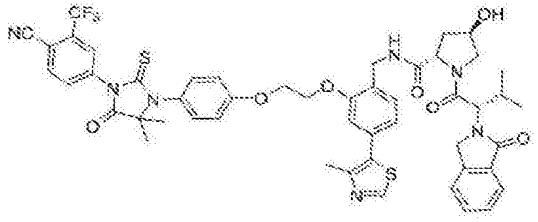
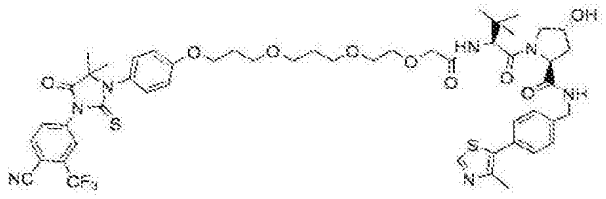
[1080]

245		1037.37	
246		1004.40	
247		1006.38	
248		1022.35	
249		1040.40	
250		1052.35	

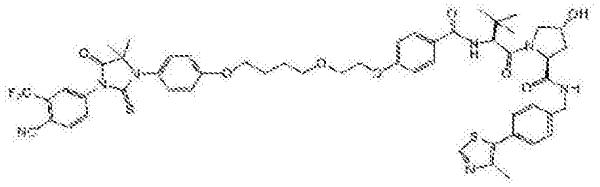
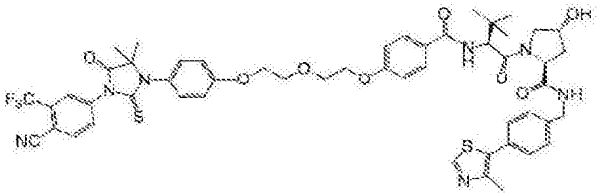
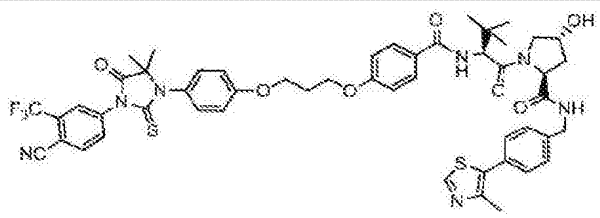
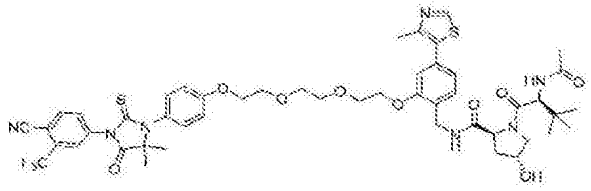
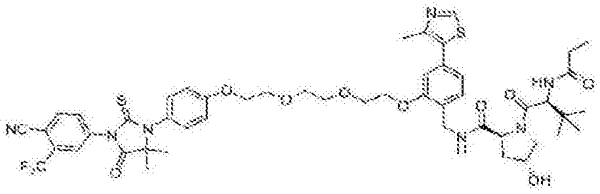
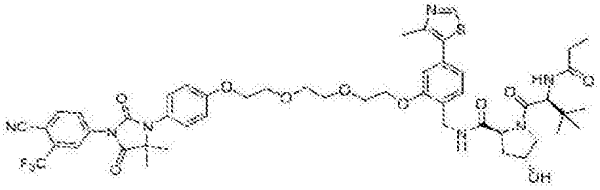
[1081]

251		1006.35	
252		1036.36	
253		1022.36	
254		994.31	
255		1034.40	
256		1008.32	

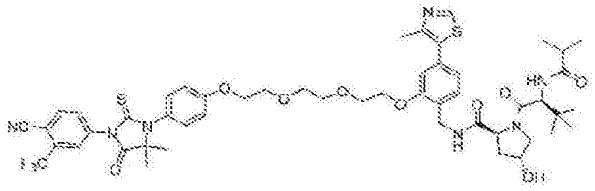
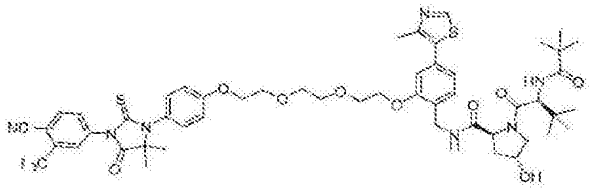
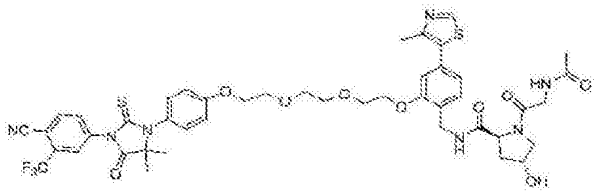
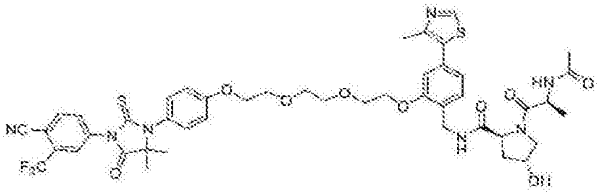
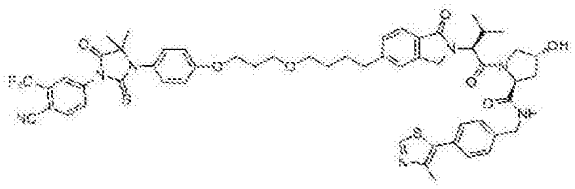
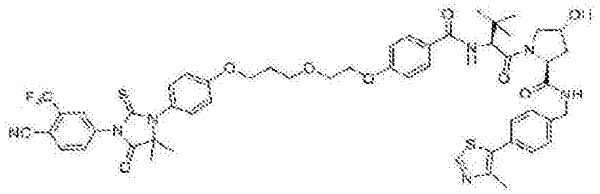
[1082]

257		1010.34	
258		1024.35	
259		1052.38	
260		1024.34	
261		980.28	
262		1036.37	

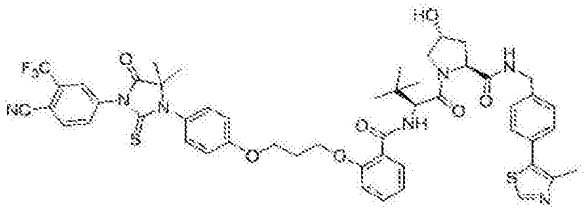
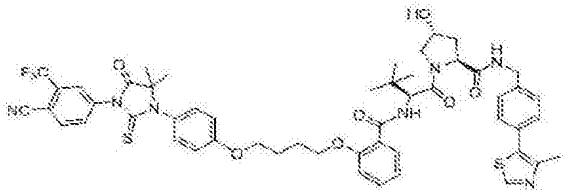
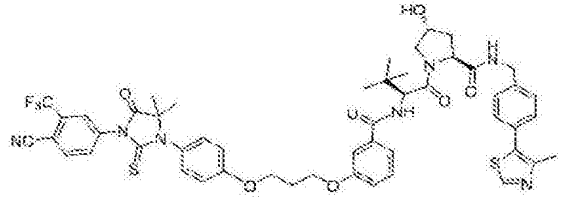
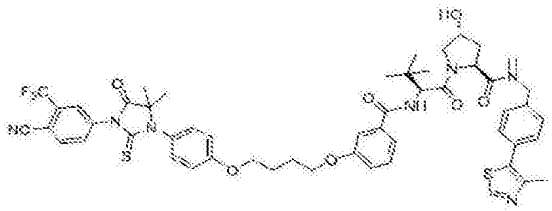
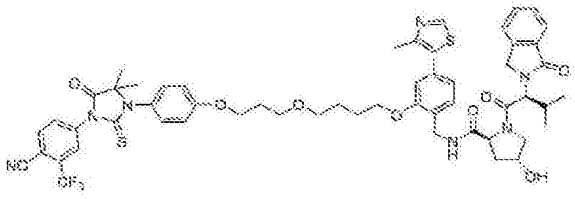
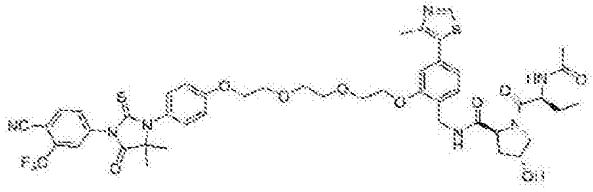
[1083]

263		1054.35	
264		1026.32	
265			
266		1008.33	
267		1022.35	
268		1006.37	

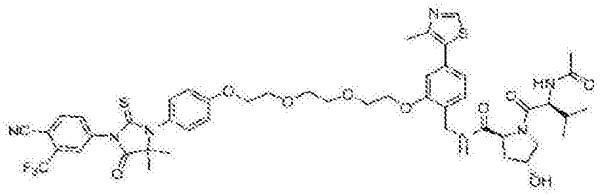
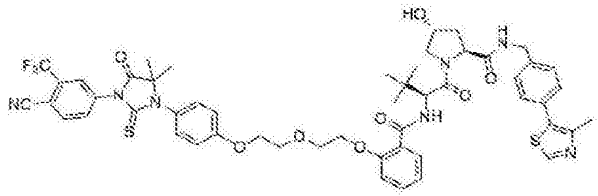
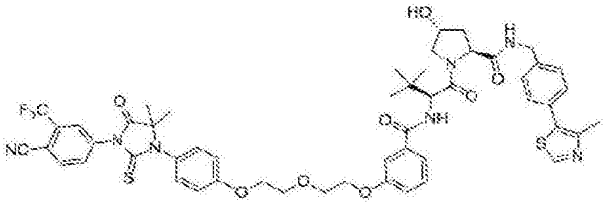
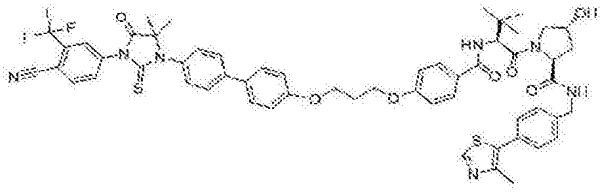
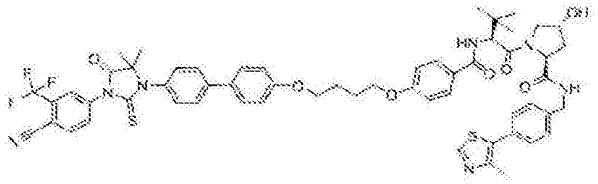
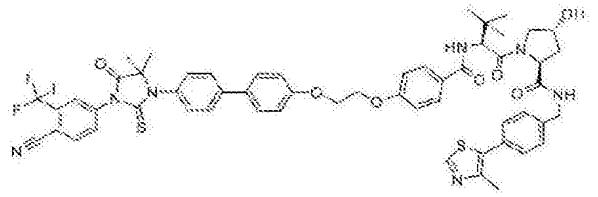
[1084]

269		1036.36	
270		1050.38	
271		952.27	
272		966.29	
273		1050.36	
274		1040.34	

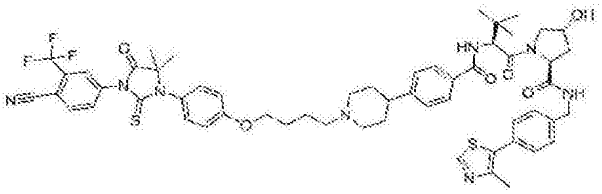
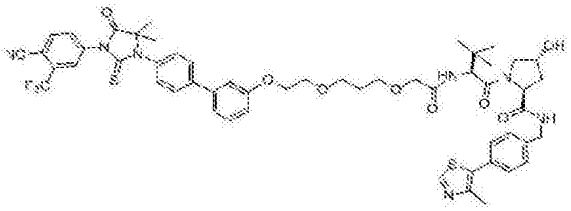
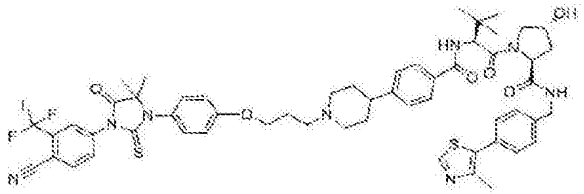
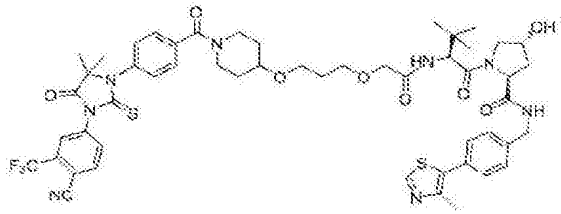
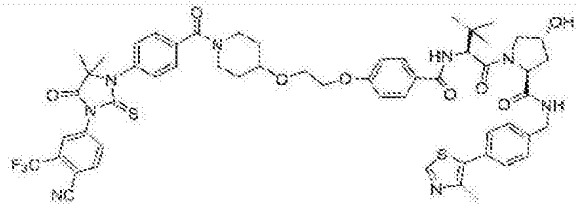
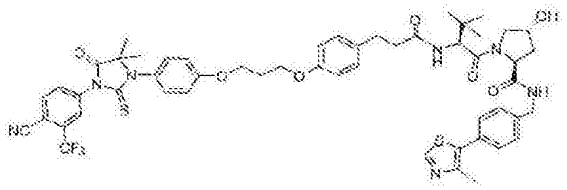
[1085]

275		996.31	
276		1010.33	
277		996.32	
278		1010.33	
279		1066.36	
280		980.30	

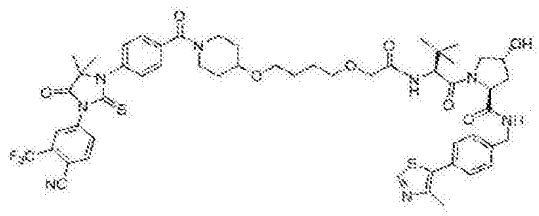
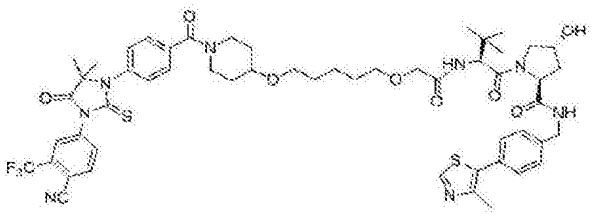
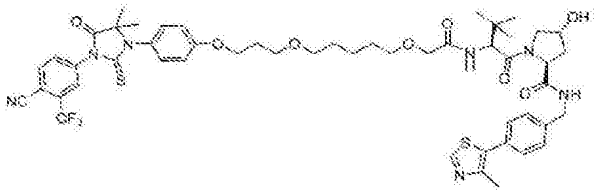
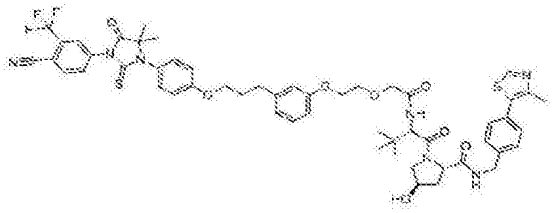
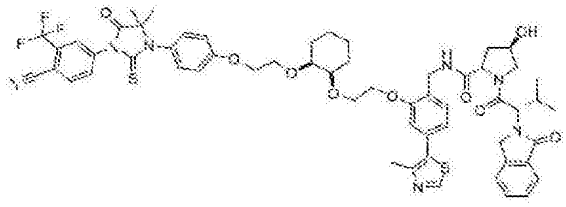
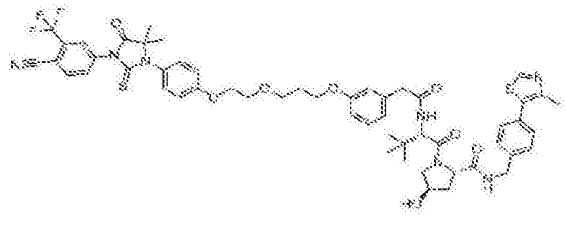
[1086]

281		994.32	
282		1048.30	
283		1026.32	
284		1072.34	
285		1086.36	
286		1058.33	

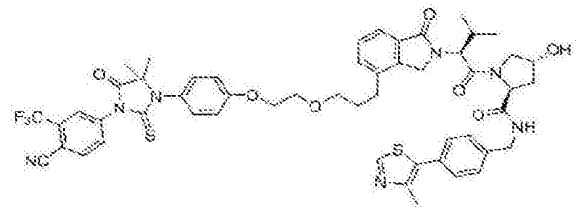
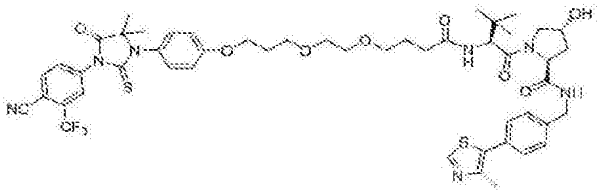
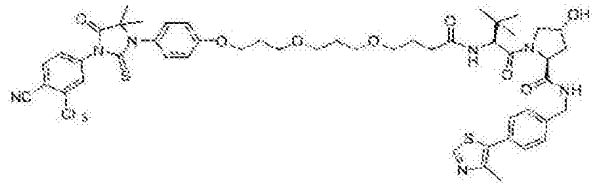
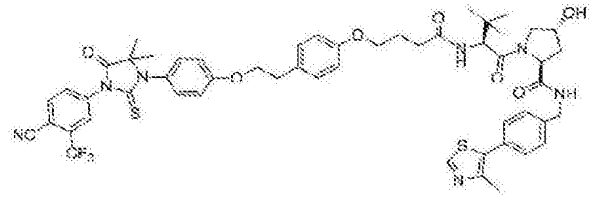
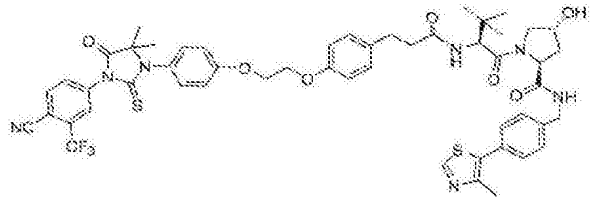
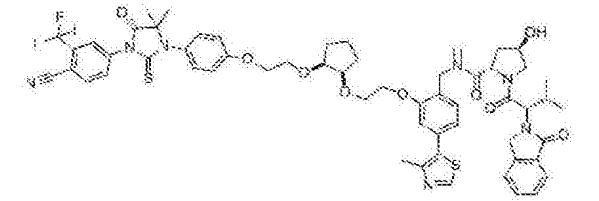
[1087]

287		1077.41	
288		1054.37	
289		1063.41	
290		1045.38	
291		1093.38	
292		1024.44	

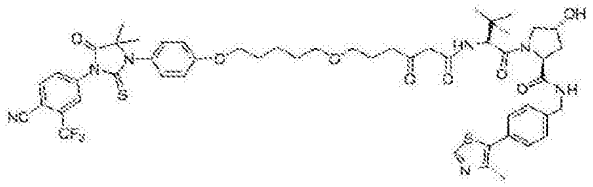
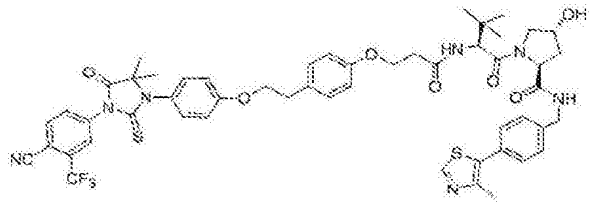
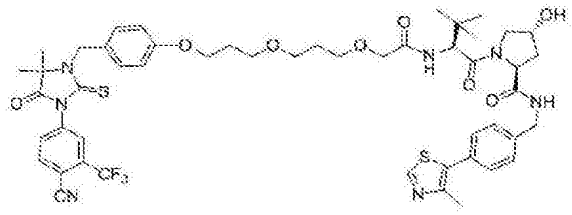
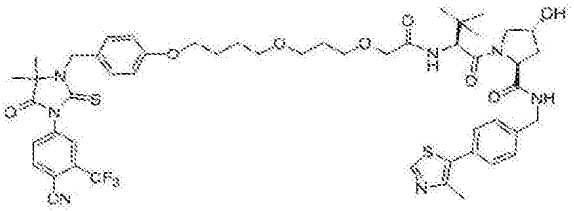
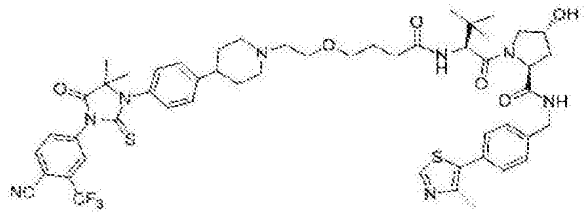
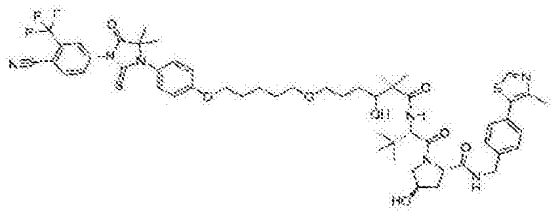
[1088]

293		1059.48	
294		1073.49	
295		1020.46	
296		1054.46	
297		1122.49	
298		1054.46	

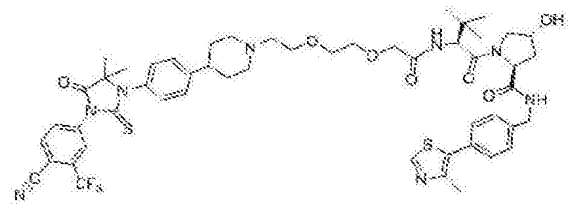
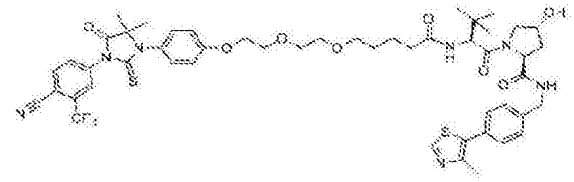
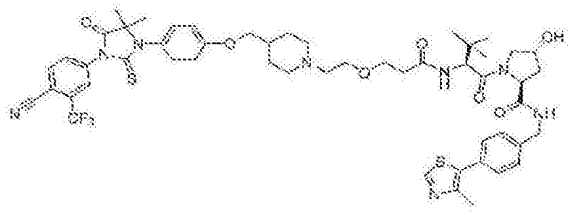
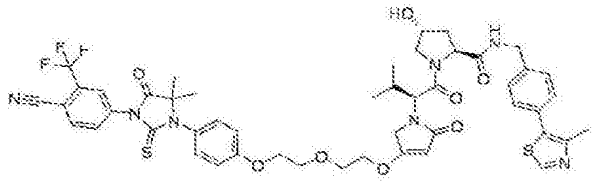
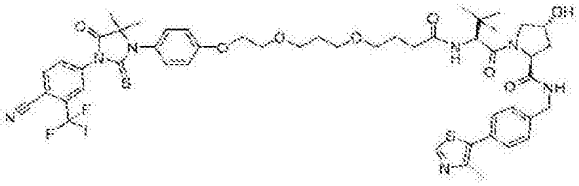
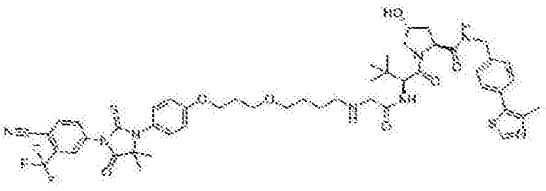
[1089]

299		1022.41	
300		1006.44	
301		1020.45	
302		1024.42	
303		1010.41	
304		1108.44	

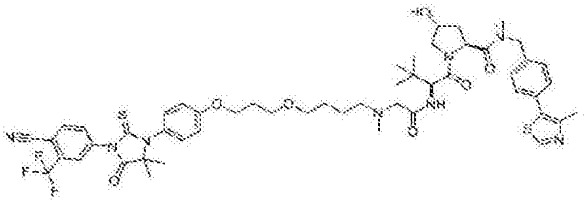
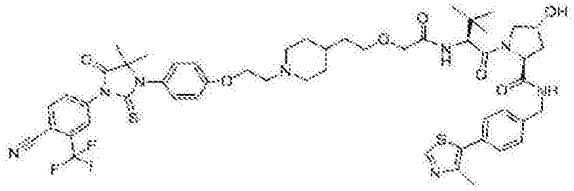
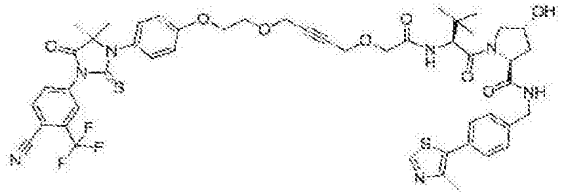
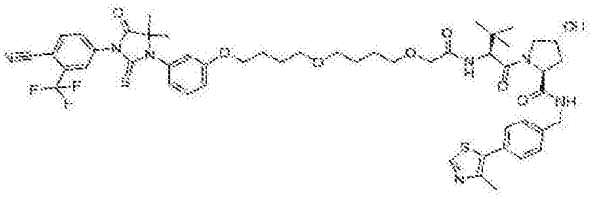
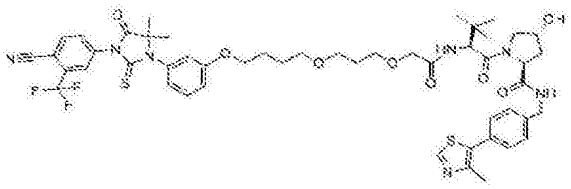
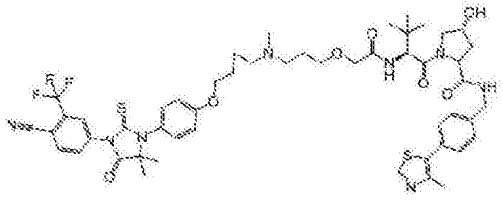
[1090]

305		1032.46	
306		1010.41	
307		1006.44	
308		1020.47	
309		1015.49	
310		1062.51	

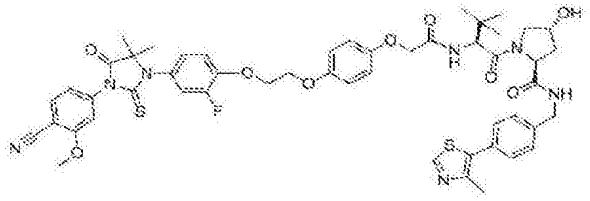
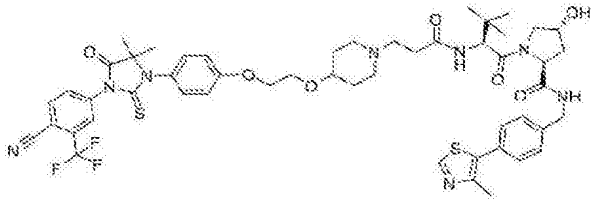
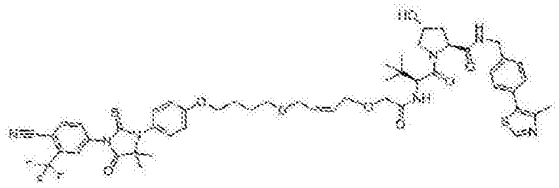
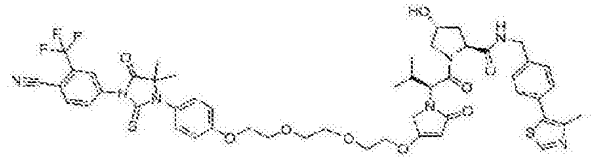
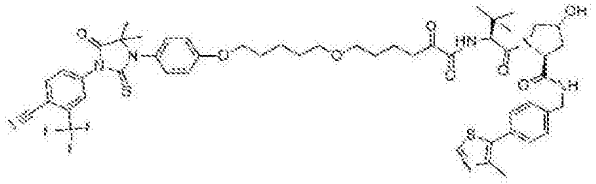
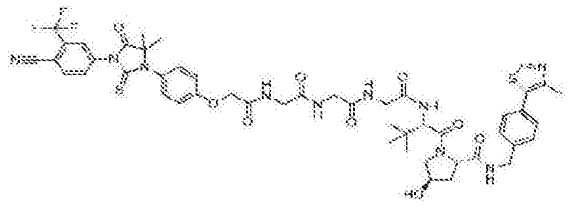
[1091]

311		1031.48	
312		1006.45	
313		1031.48	
314		974.40	
315		1006.46	
316		1005.48	

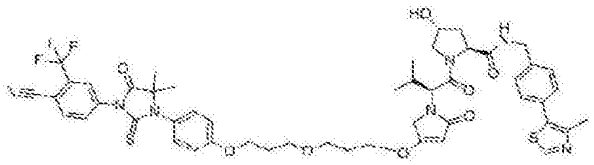
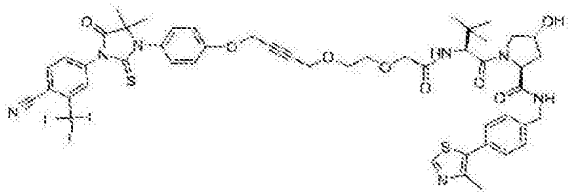
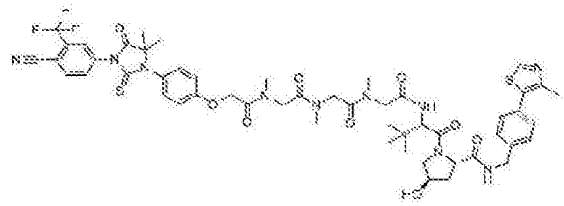
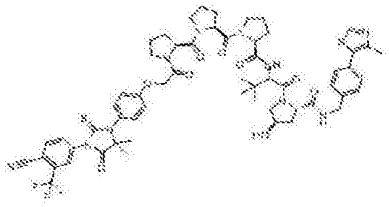
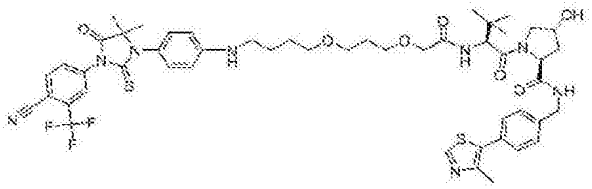
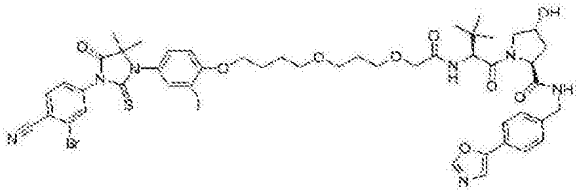
[1092]

317		1019.50	
318		1031.40	
319		988.32	
320		1020.38	
321		1006.37	
322		1019.40	

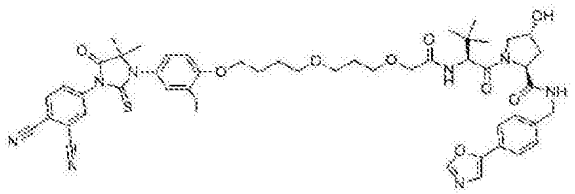
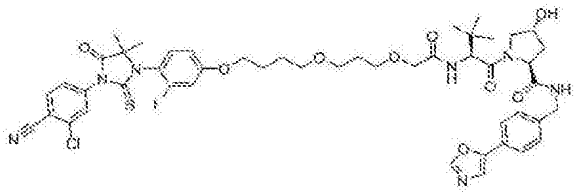
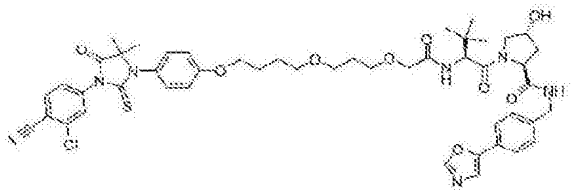
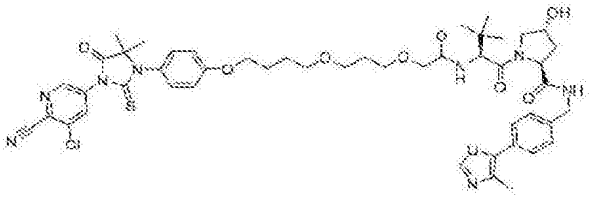
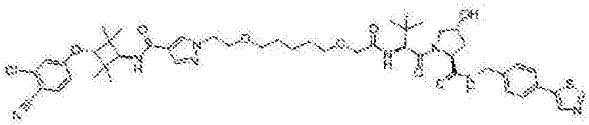
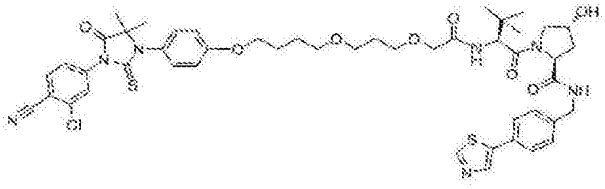
[1093]

323		992.34	
324		1017.39	
325		1017.40	
326		1018.20	
327		1032.55	
328		1047.34	

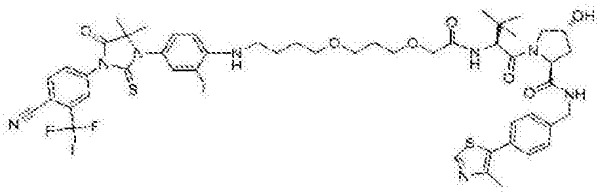
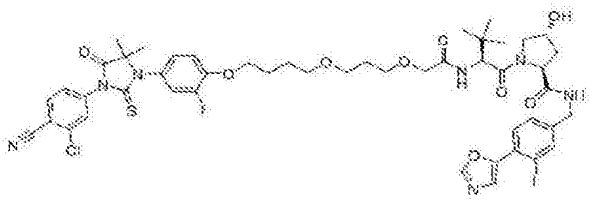
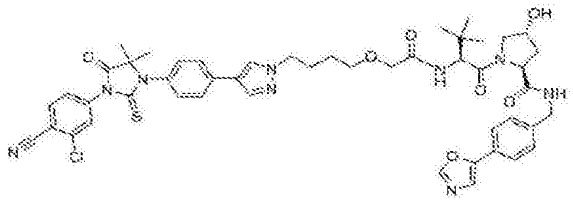
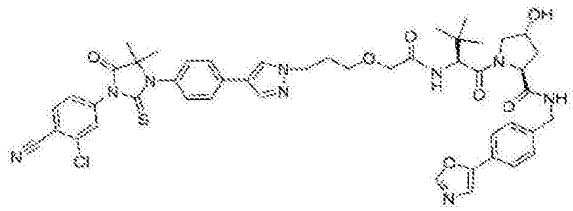
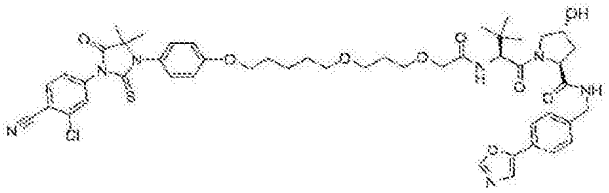
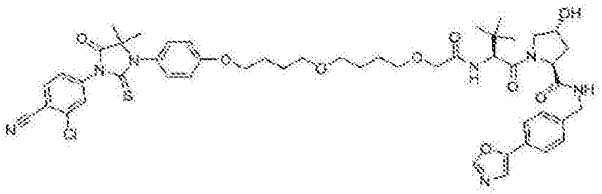
[1094]

329		1002.10	
330		331.05	
331		1089.39	
332		1167.43	
333		1005.40	
334		1004.40	

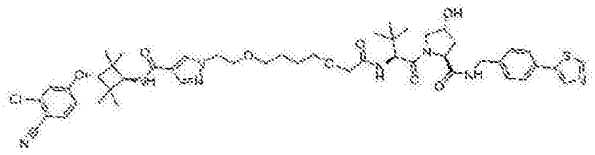
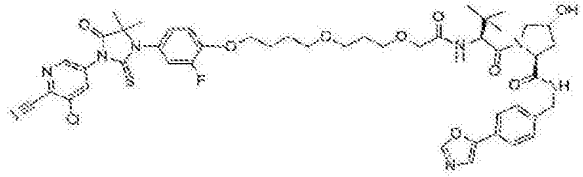
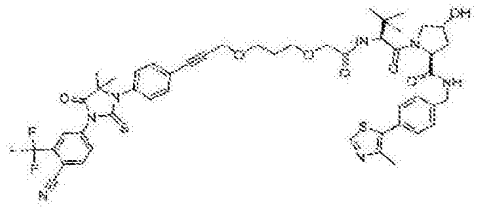
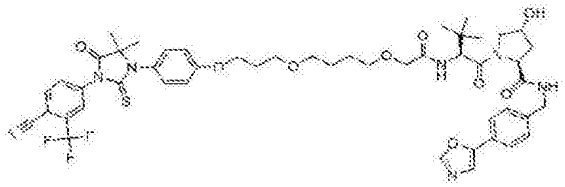
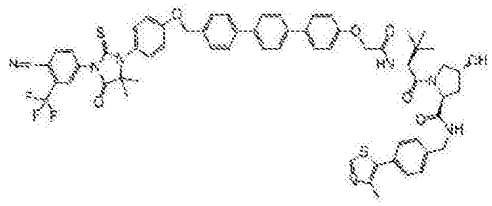
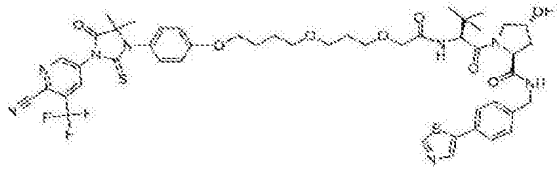
[1095]

335		942.40	
336		960.50	
337		942.40	
338		957.40	
339		959.20	
340		1023.40	

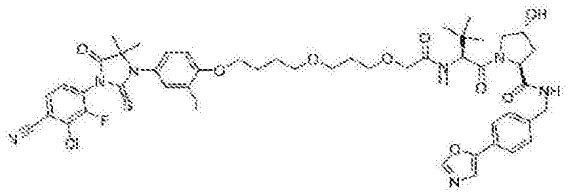
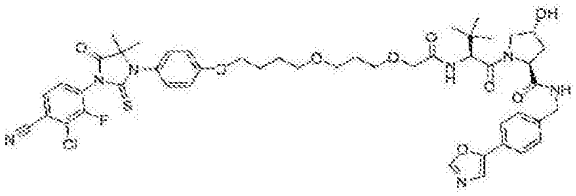
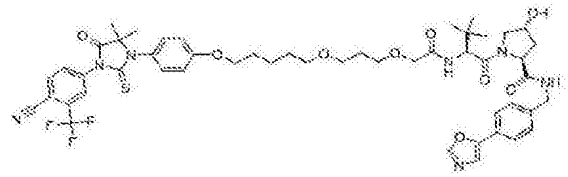
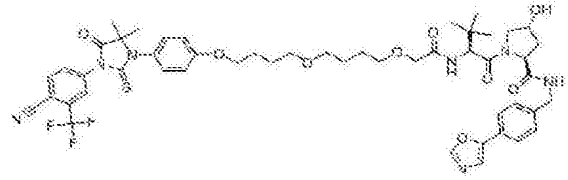
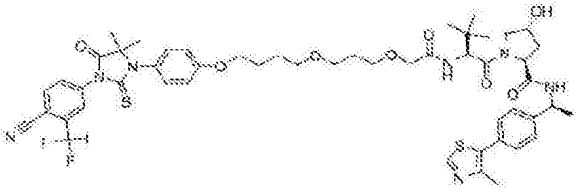
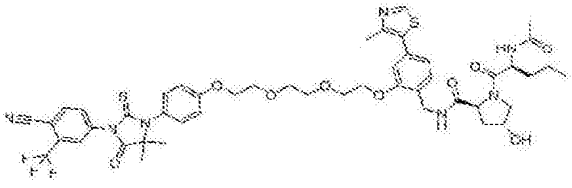
[1096]

341		978.55	
342		934.30	
343		920.30	
344		956.30	
345		956.35	
346			

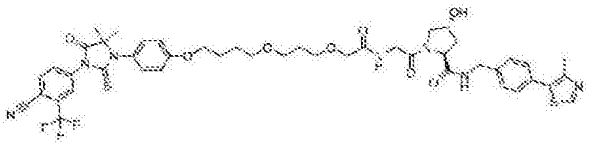
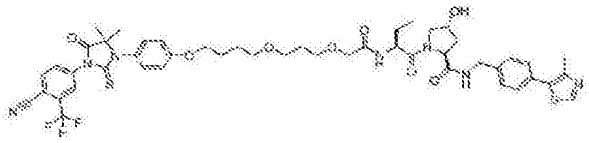
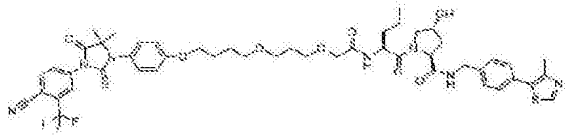
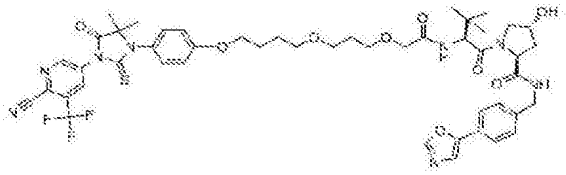
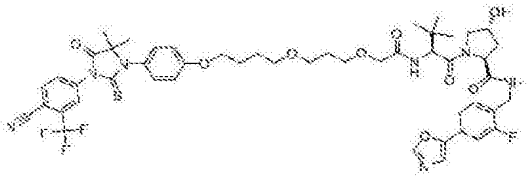
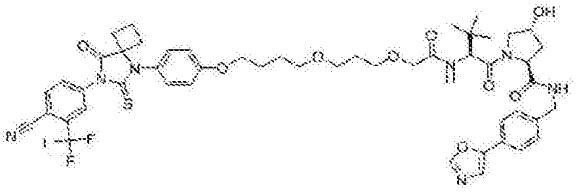
[1097]

347		945.40	
348		961.35	
349		972.40	
350		976.35	
351		-	
352		993.25	

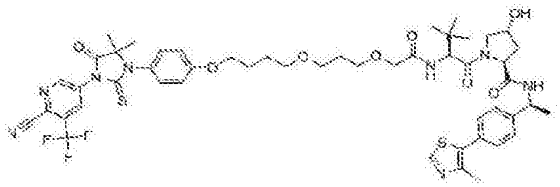
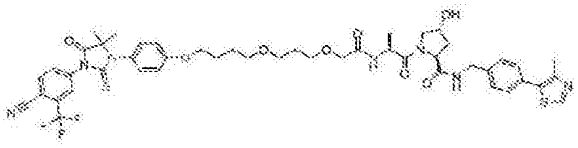
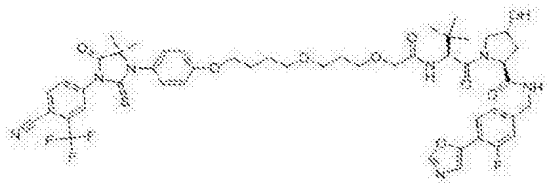
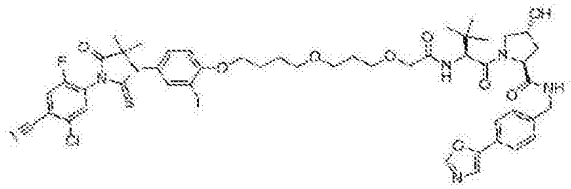
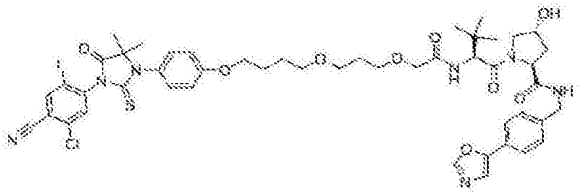
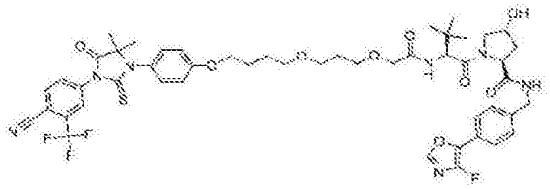
[1098]

353		978.35	
354		960.35	
355		990.45	
356		990.45	
357		1020.40	
358		994.10	

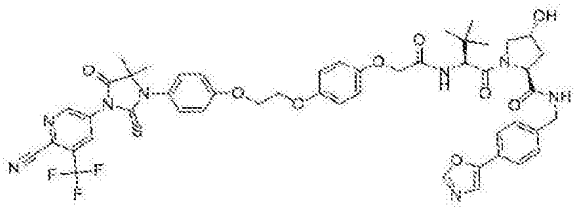
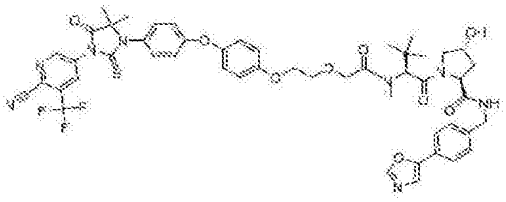
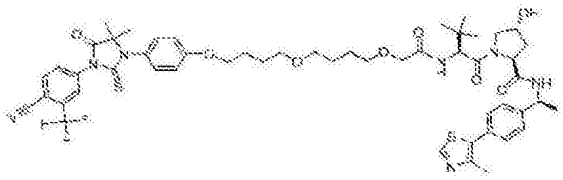
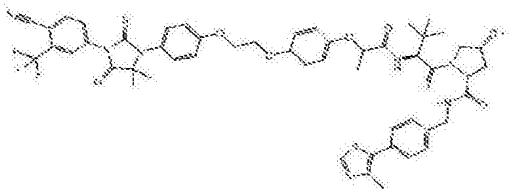
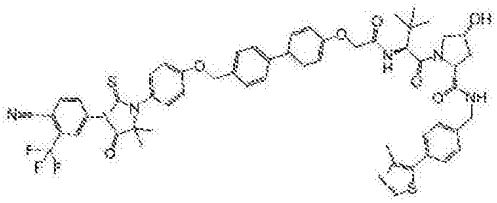
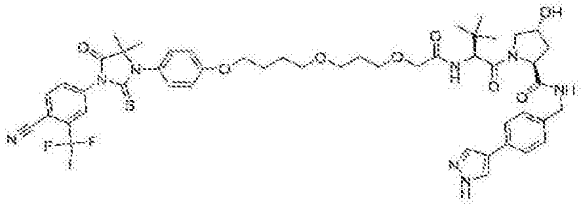
[1099]

359		950.20	
360		978.20	
361		992.20	
362		977.25	
363		994.40	
364		988.40	

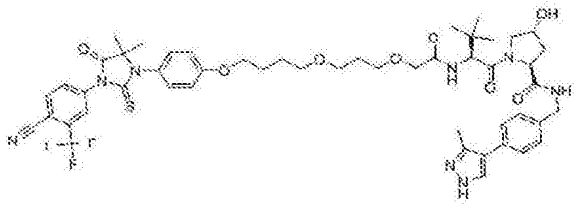
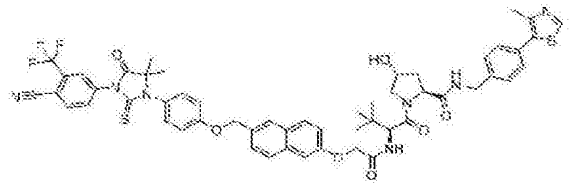
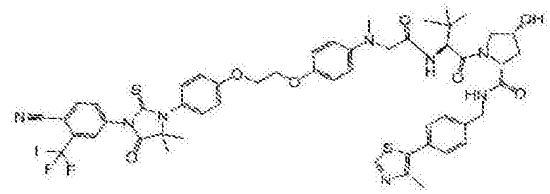
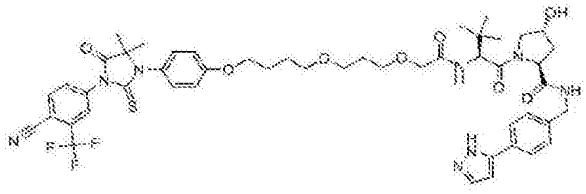
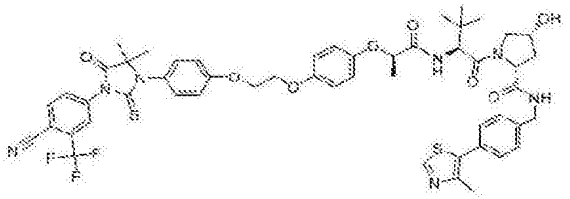
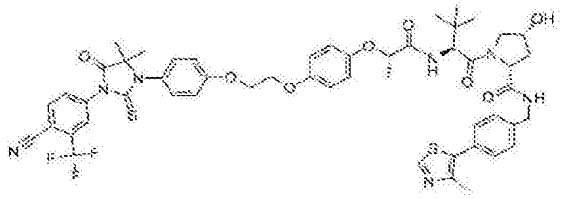
[1100]

365		1021.20	
366		964.20	
367		994.40	
368		978.30	
369		960.30	
370		994.40	

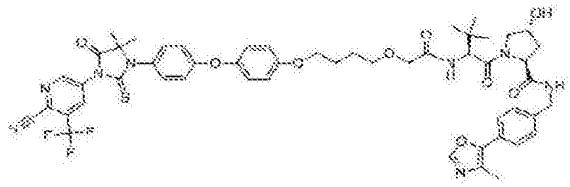
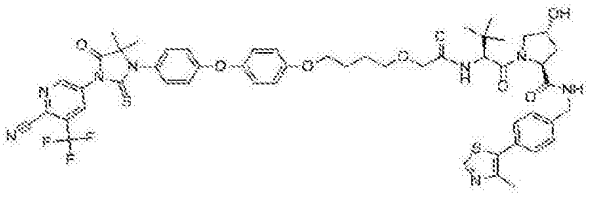
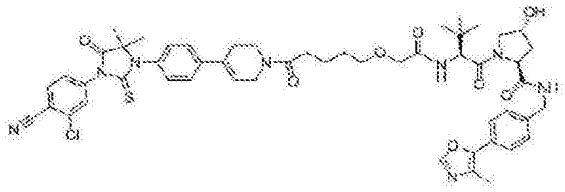
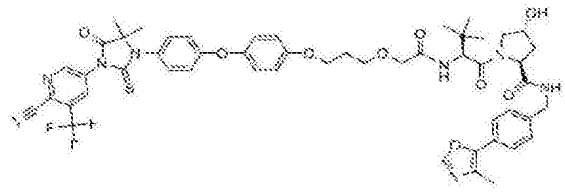
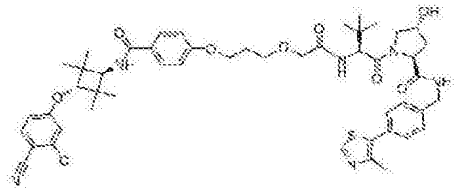
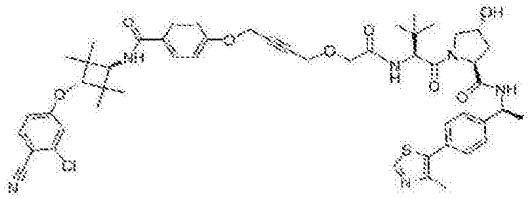
[1101]

371		983.30	
372		983.50	
373		1034.40	
374		1026.35	
375		1059.36	
376		975.30	

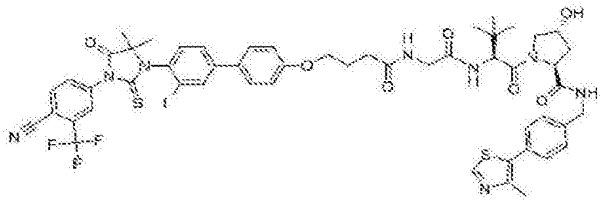
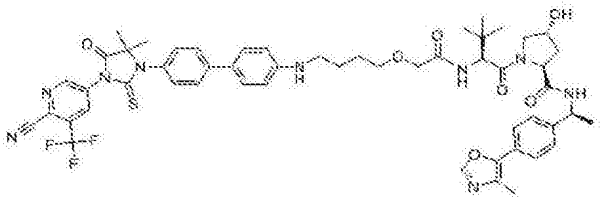
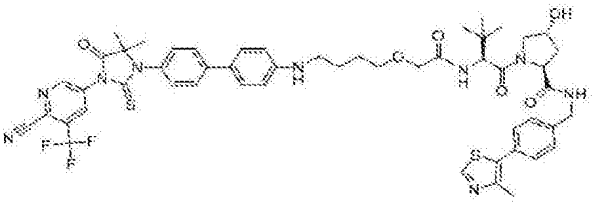
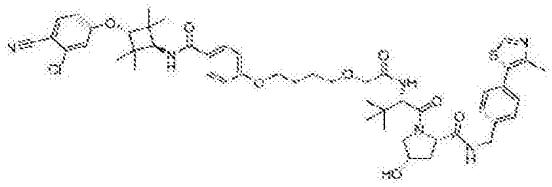
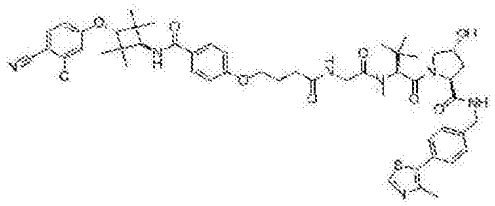
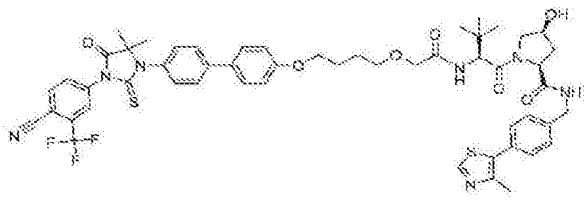
[1102]

377		989.30	
378		1032.34	
379		1025.37	
380		975.30	
381		1026.16	
382		1026.16	

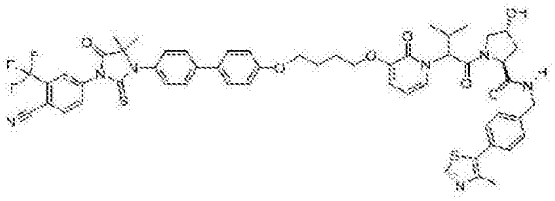
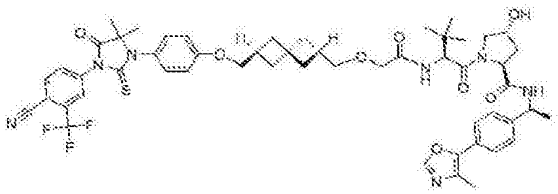
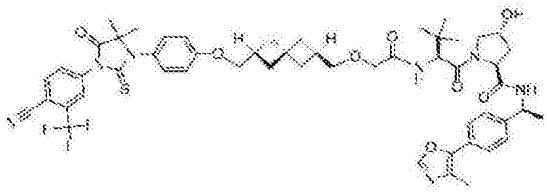
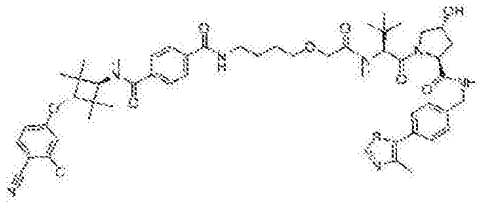
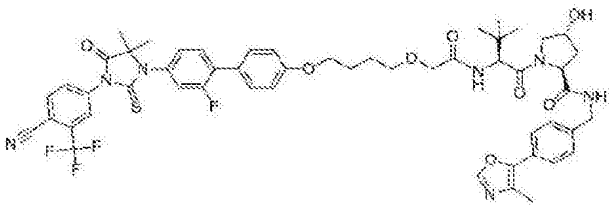
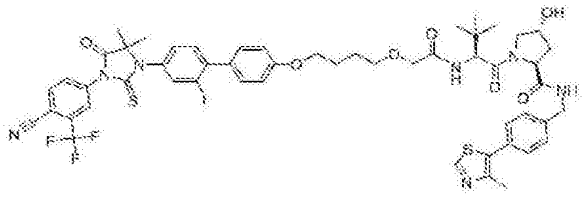
[1103]

383		1025.30	
384		1041.30	
385		991.26	993.26
386		1011.30	
387		927.37	929.37
388		951.23	953.23

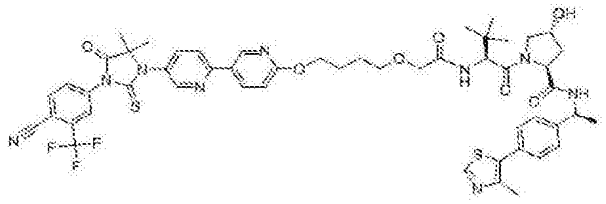
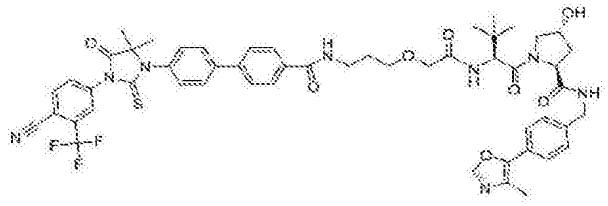
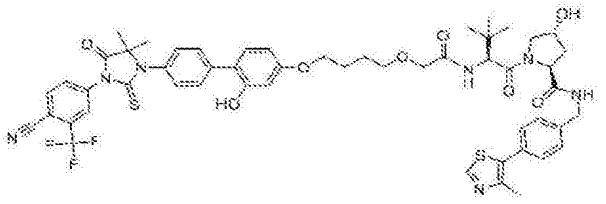
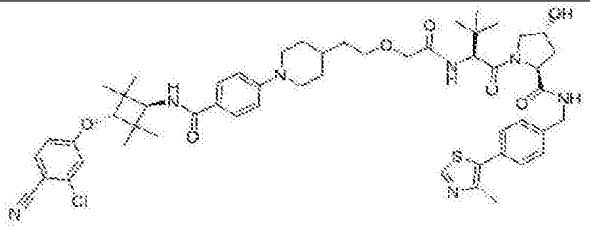
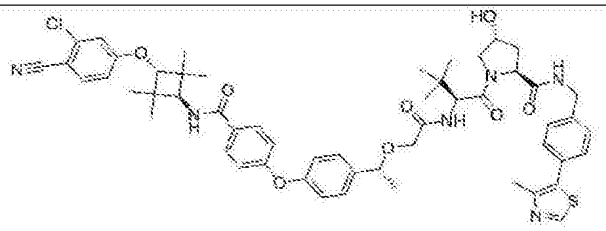
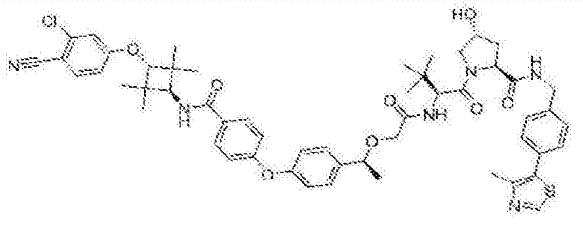
[1104]

389		1055.10	
390		1022.25	
391		1024.15	
392		941.39	943.39
393		954.31	956.31
394		988.37	990.37

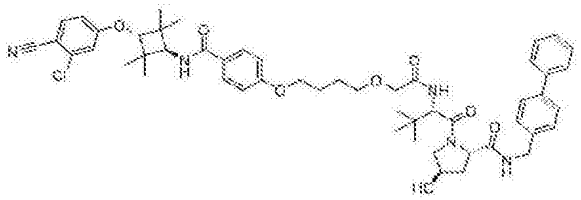
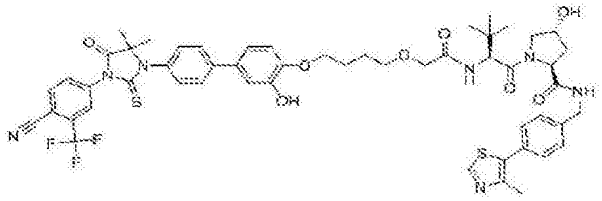
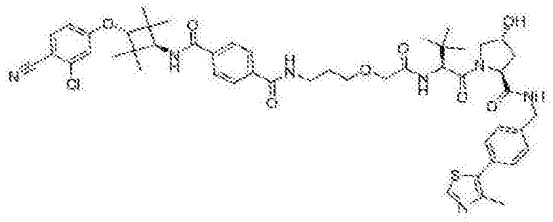
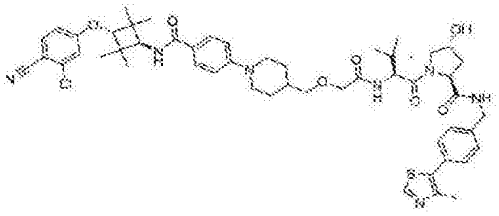
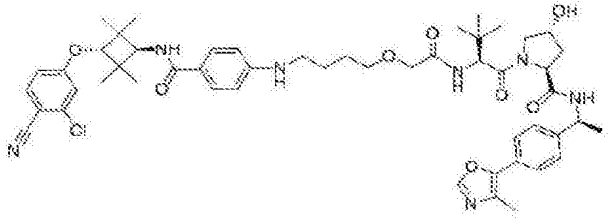
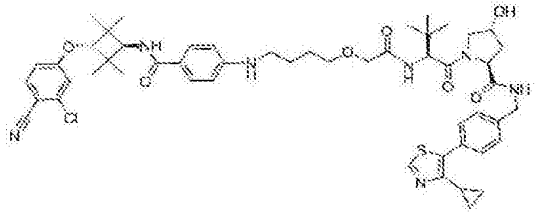
[1105]

395		1045.35	
396		1012.15	
397		1012.15	
398		968.32	970.32
399		1026.15	
400		1042.20	

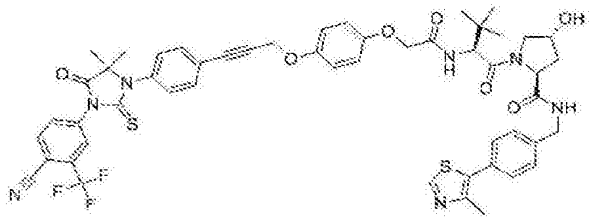
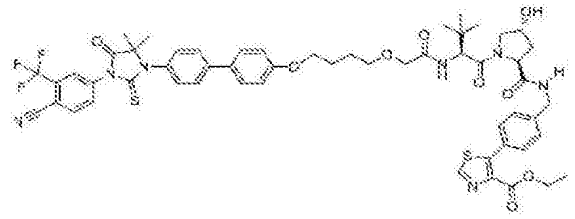
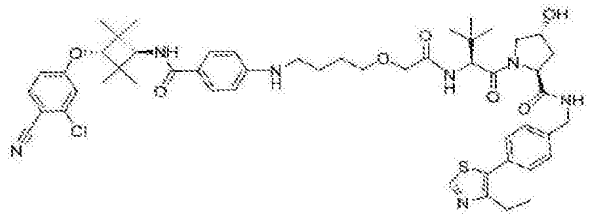
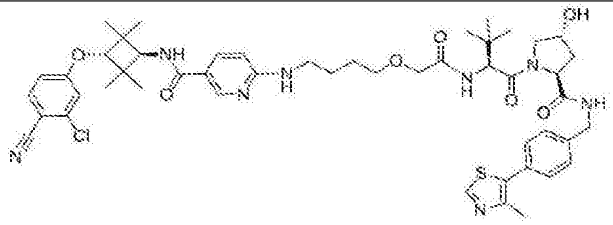
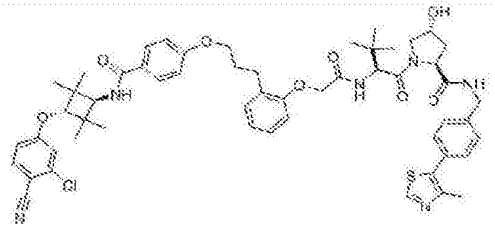
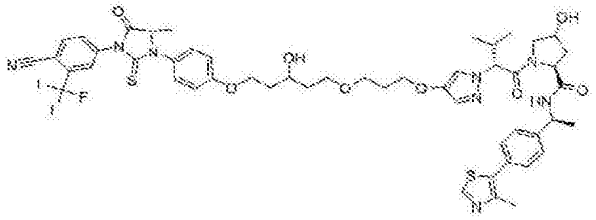
[1106]

401		1040.35	
402		1021.20	
403		1040.15	
404		980.52	982.52
405		989.40	991.40
406		989.40	991.40

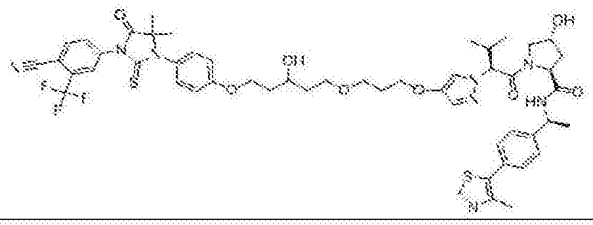
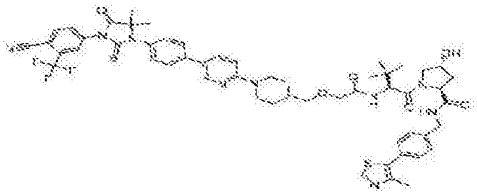
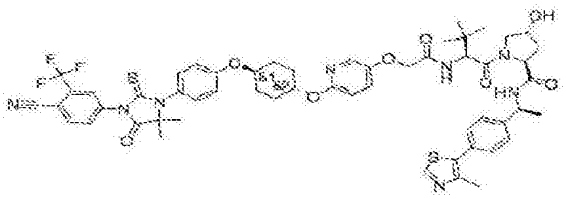
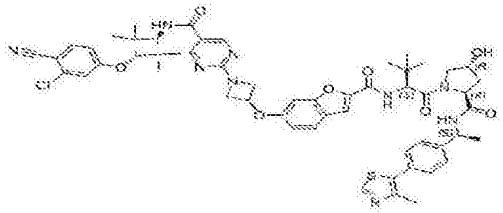
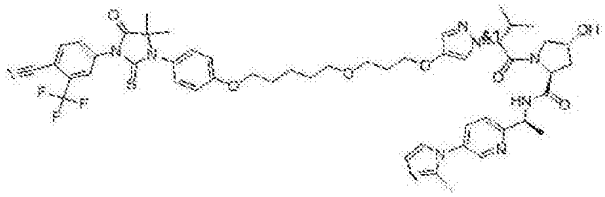
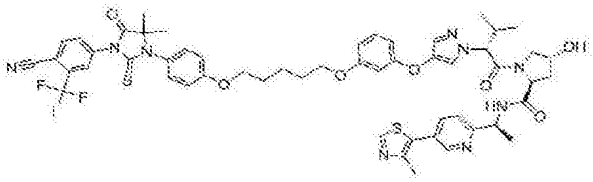
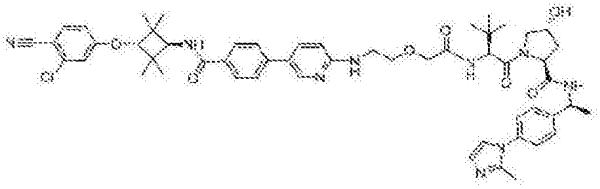
[1107]

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

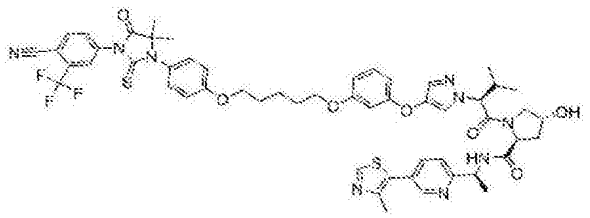
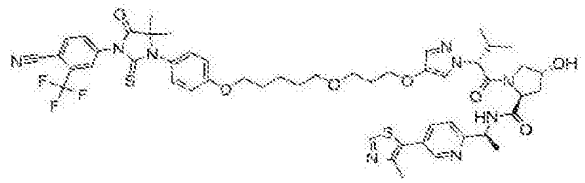
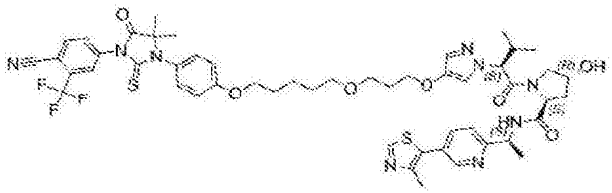
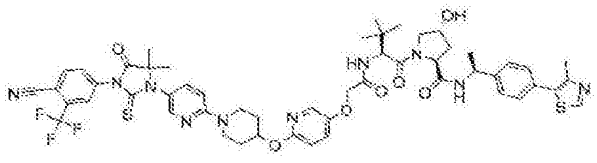
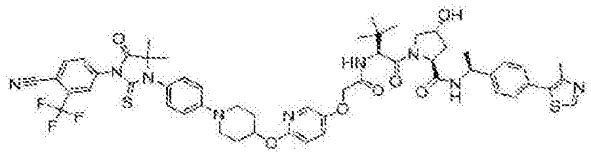
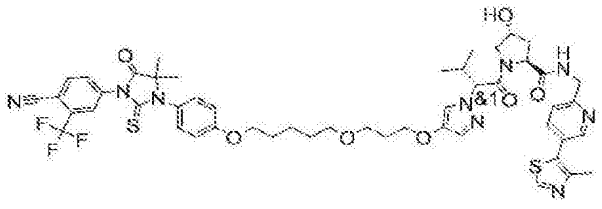
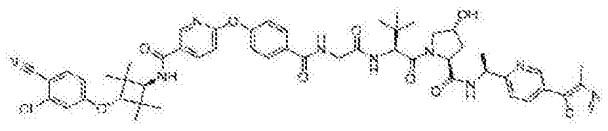
[1108]

413		1006.30	
414		1083.34	
415		954.40	956.40
416		941.38	943.38
417		1003.39	1005.39
418		1045.38	

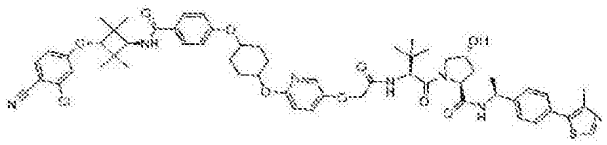
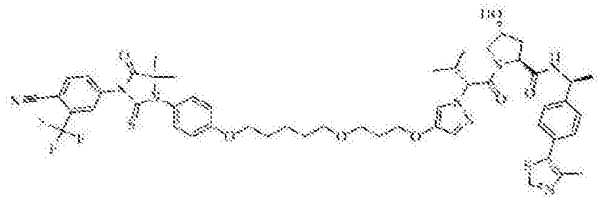
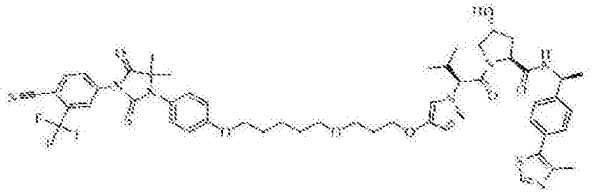
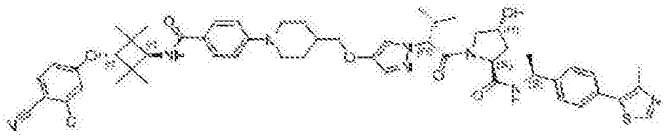
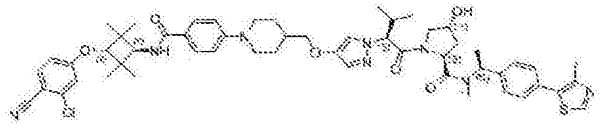
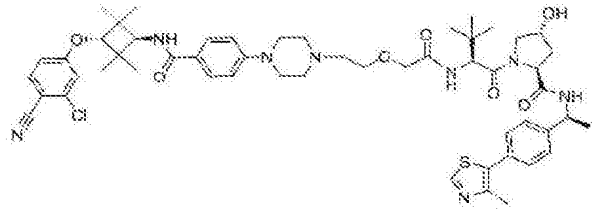
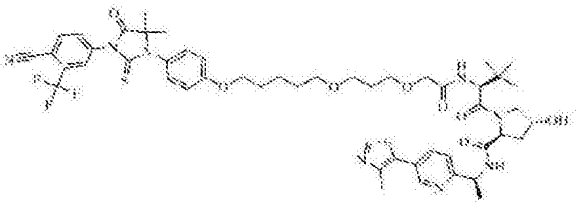
[1109]

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

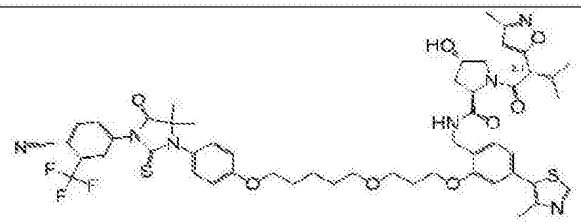
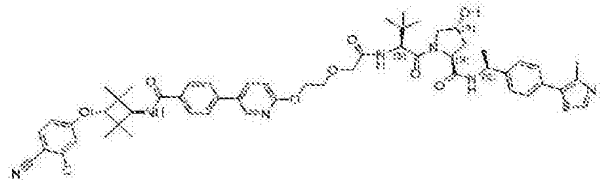
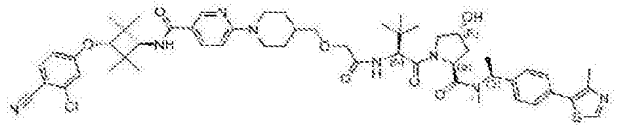
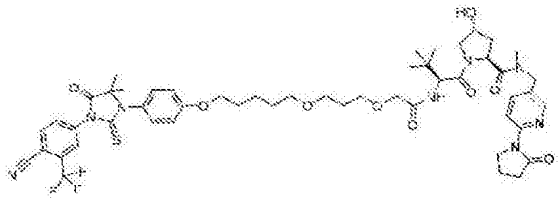
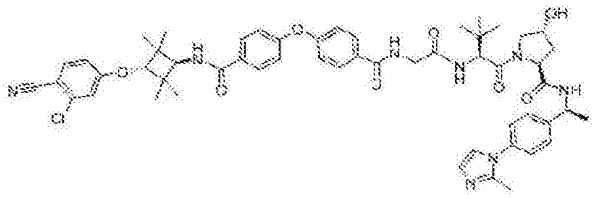
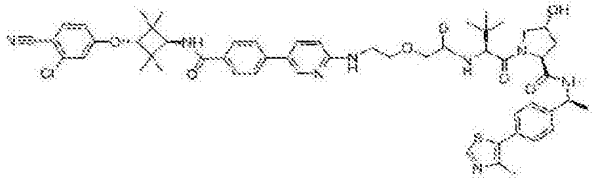
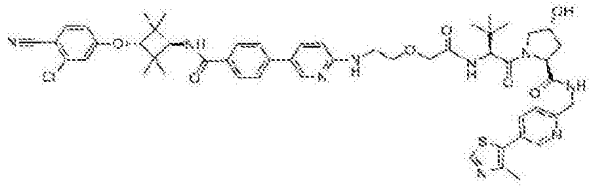
[1110]

426		1064.37	
427		1030.38	
428		1030.38	
429		1067.38	
430		1066.38	
431		1016.37	
432		1004.38	1006.38

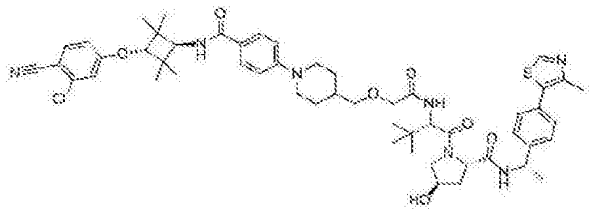
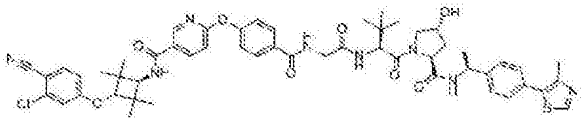
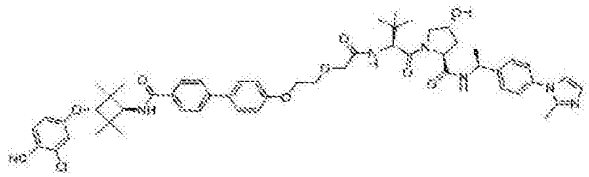
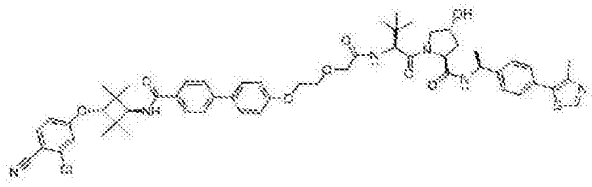
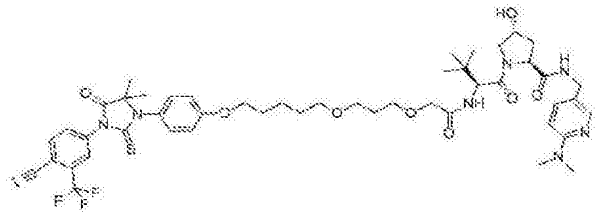
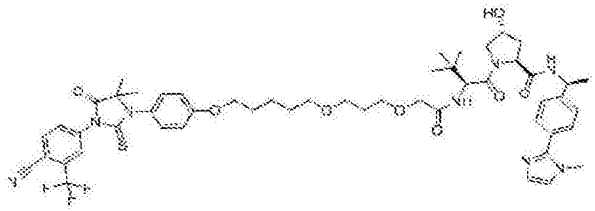
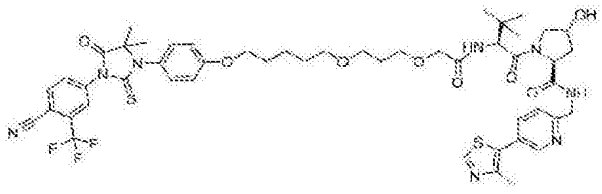
[1111]

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	

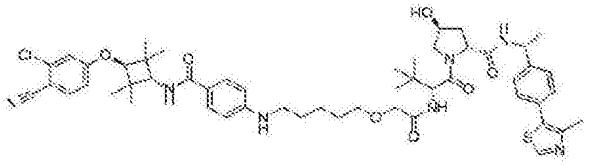
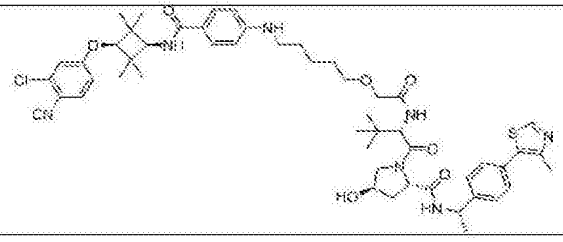
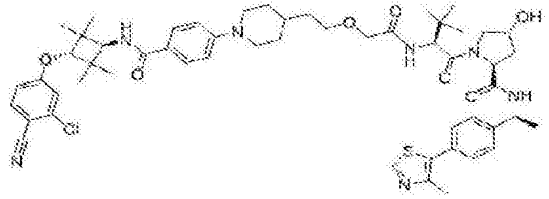
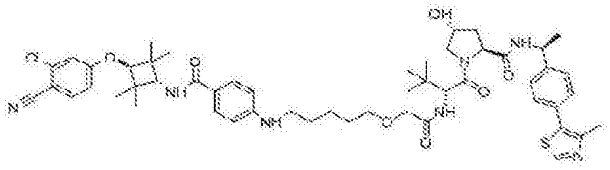
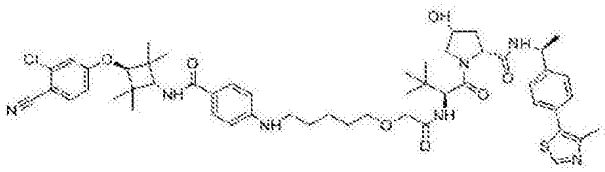
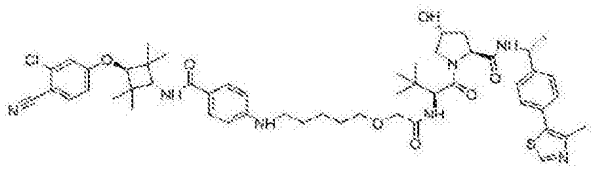
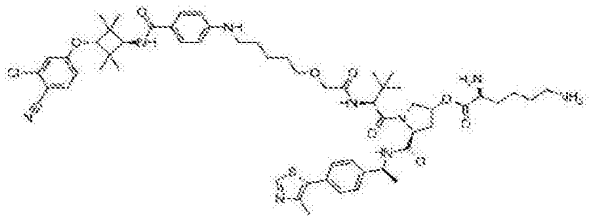
[1112]

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

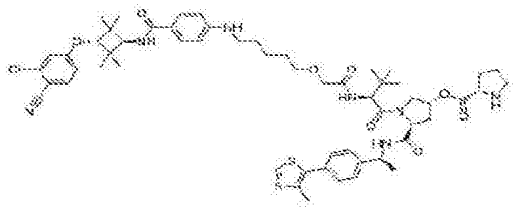
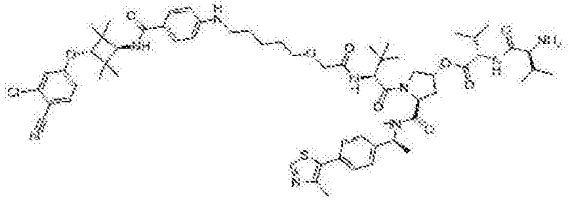
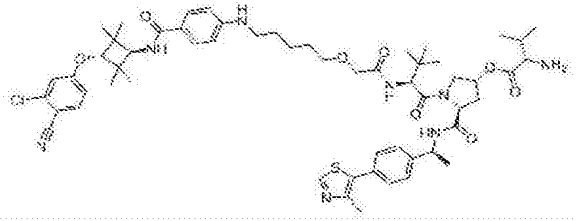
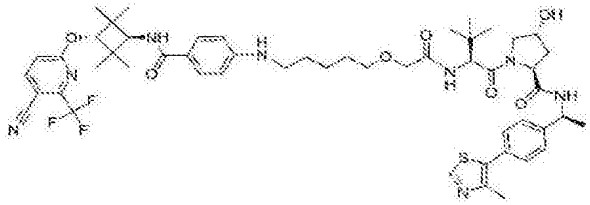
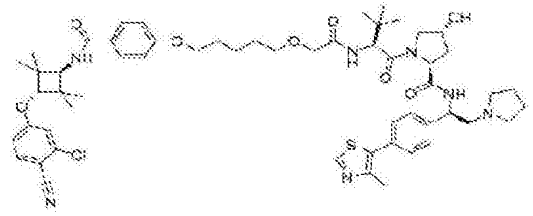
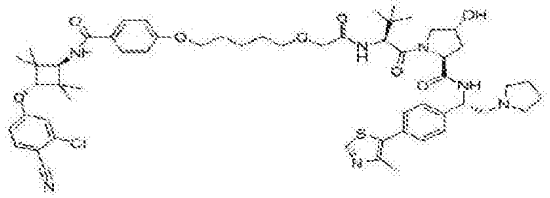
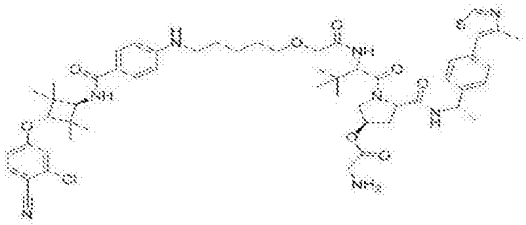
[1113]

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	

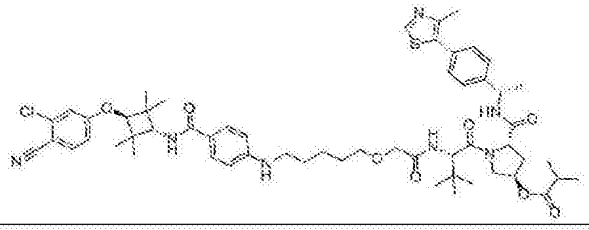
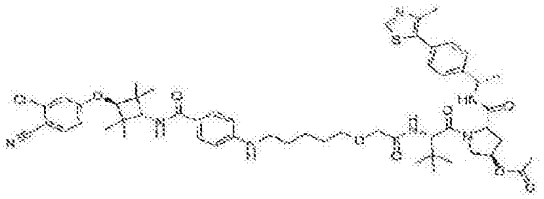
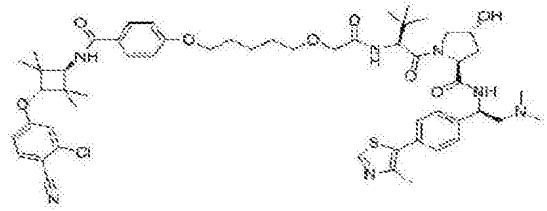
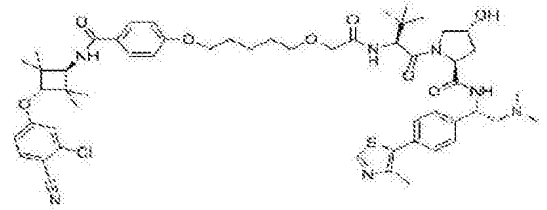
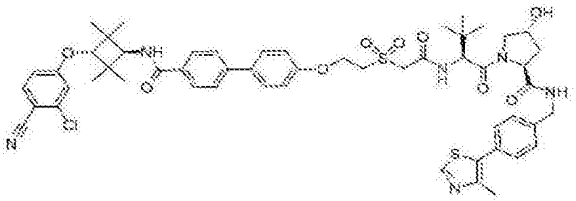
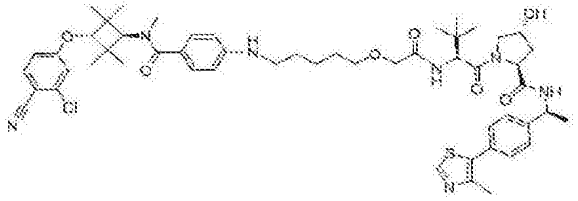
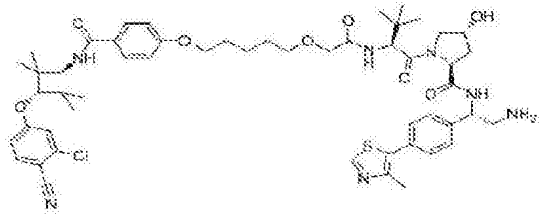
[1114]

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

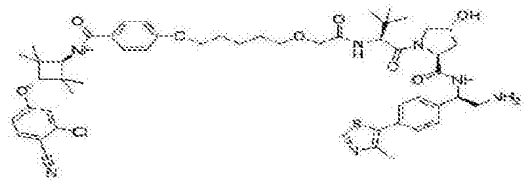
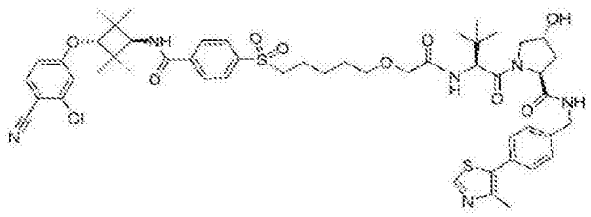
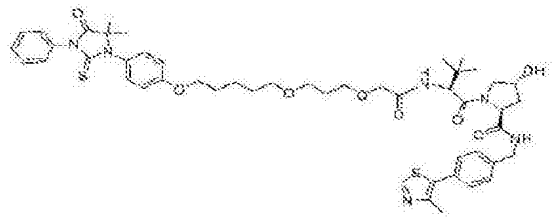
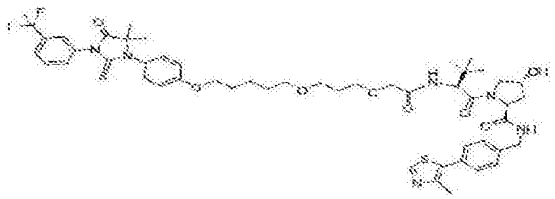
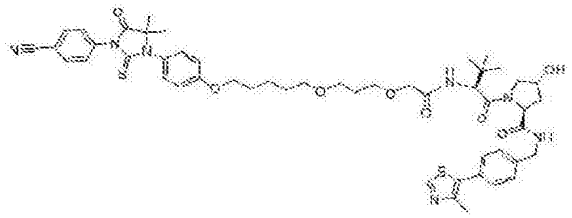
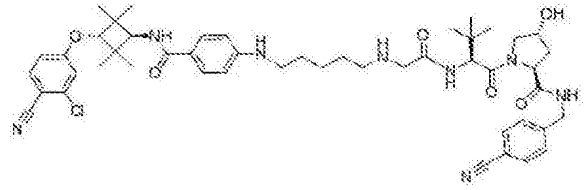
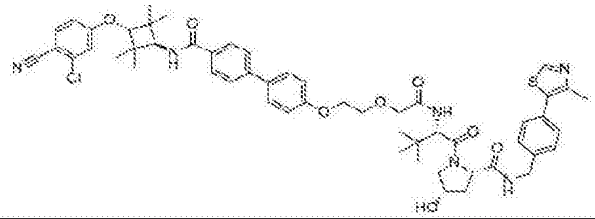
[1115]

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

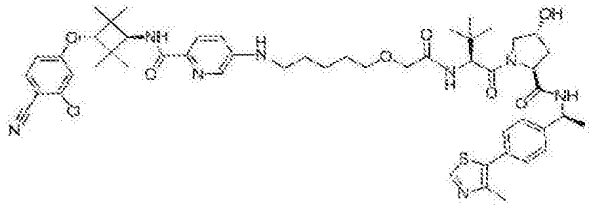
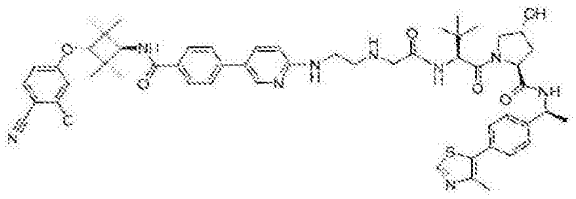
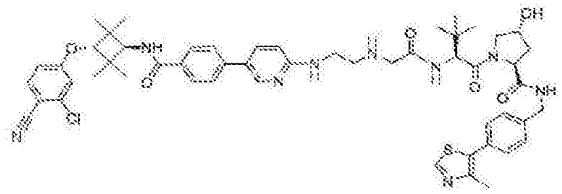
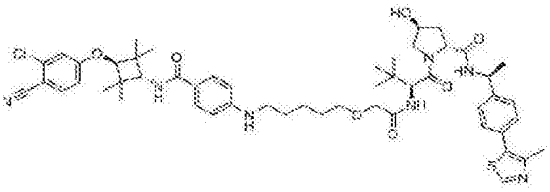
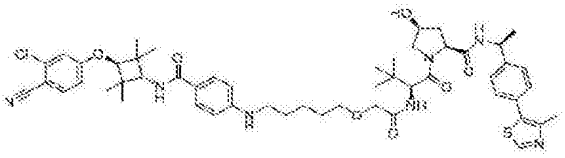
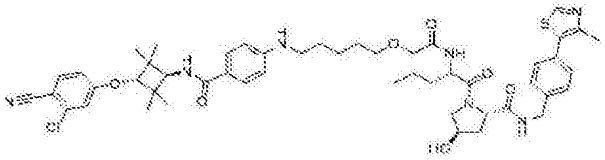
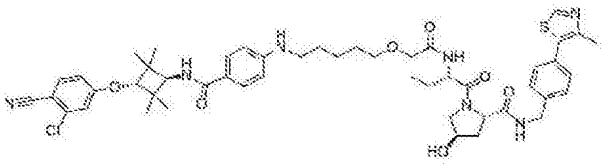
[1116]

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

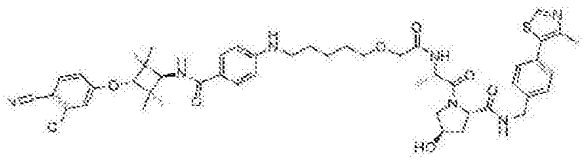
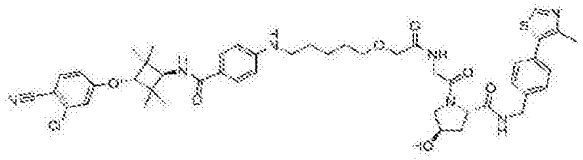
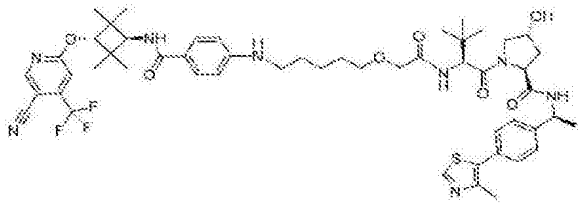
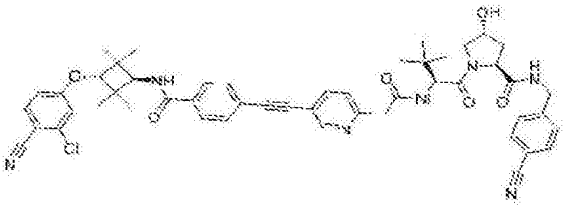
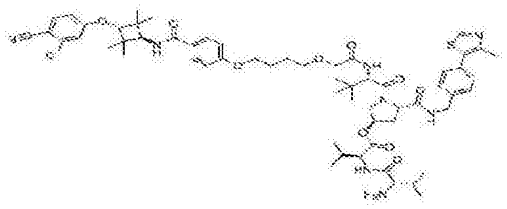
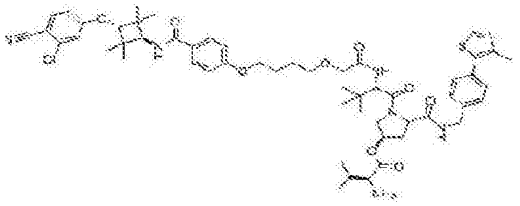
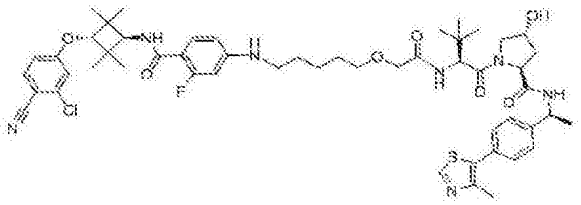
[1117]

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

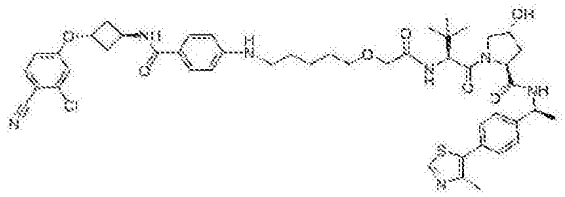
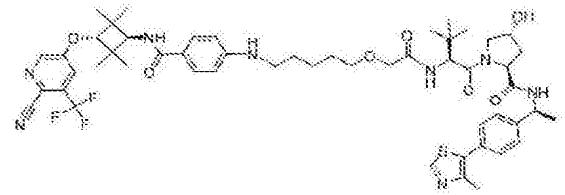
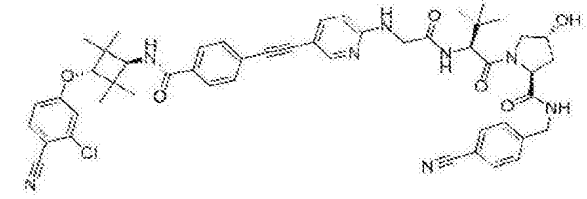
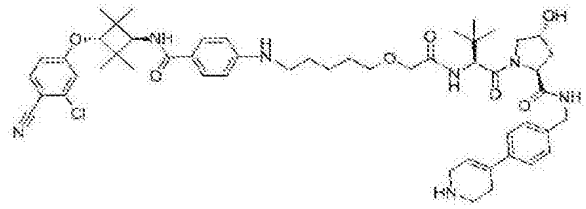
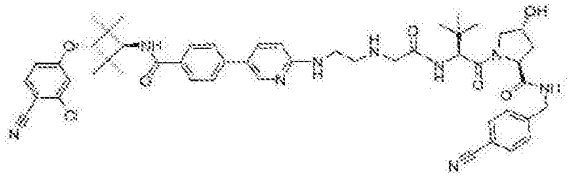
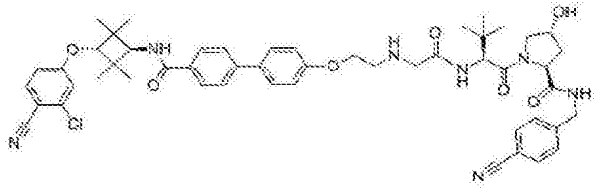
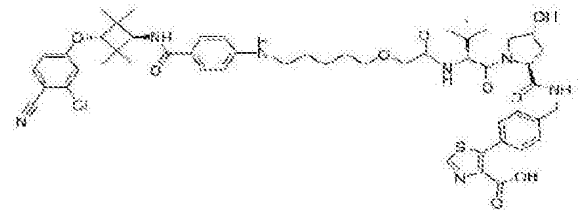
[1118]

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

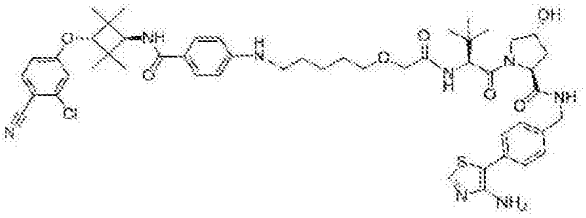
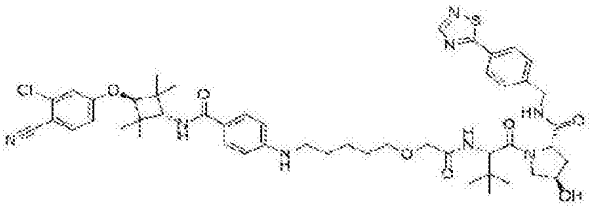
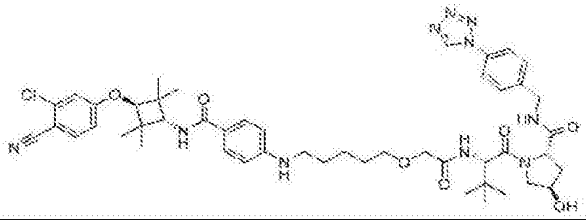
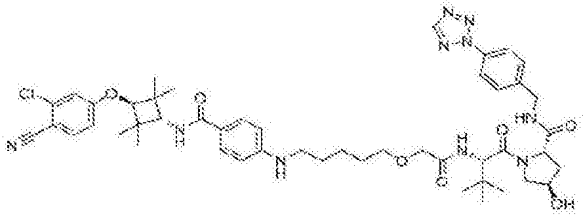
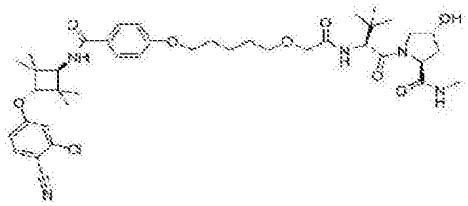
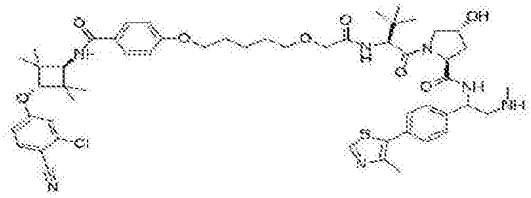
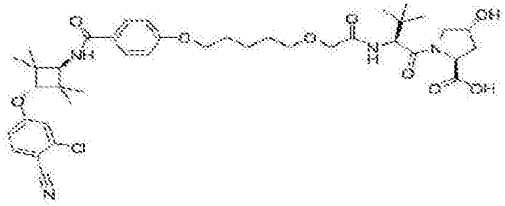
[1119]

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

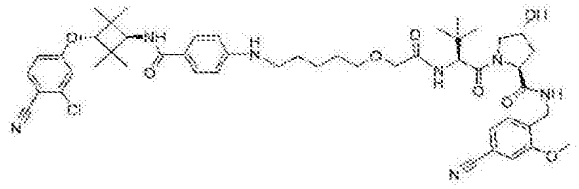
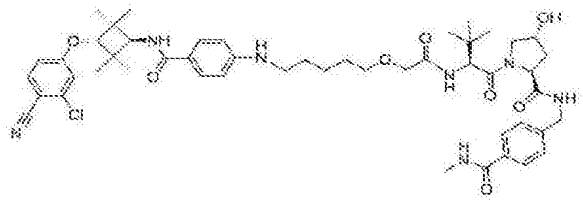
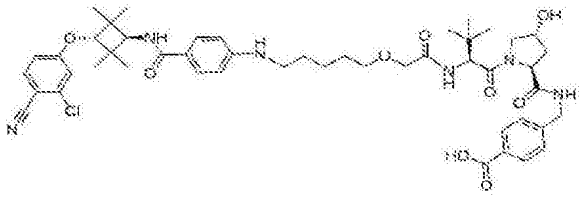
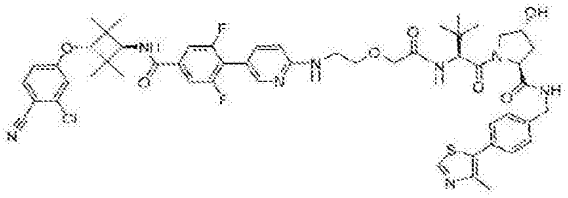
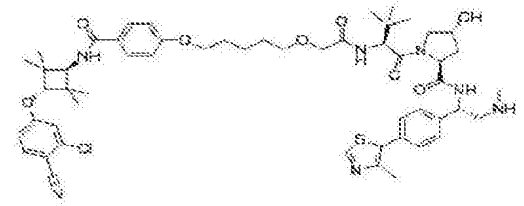
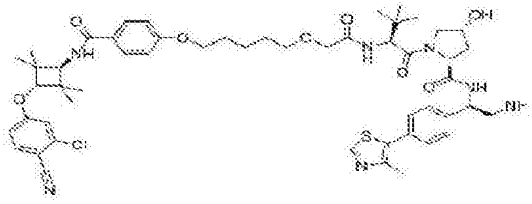
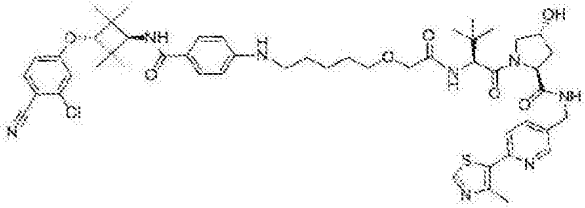
[1120]

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

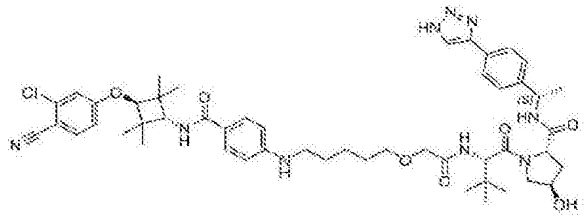
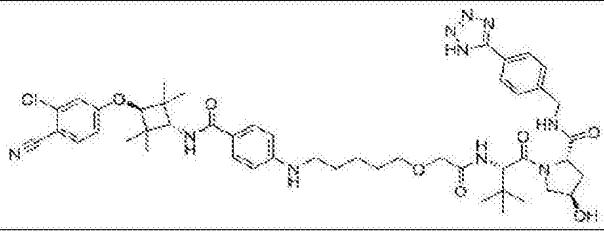
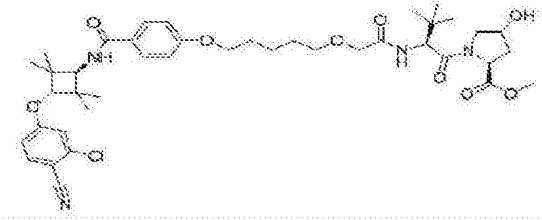
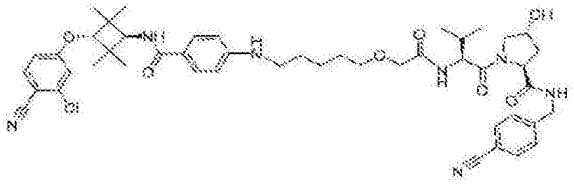
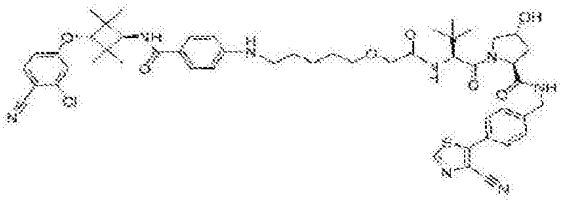
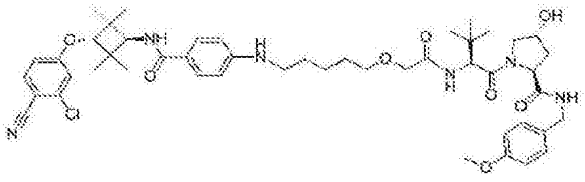
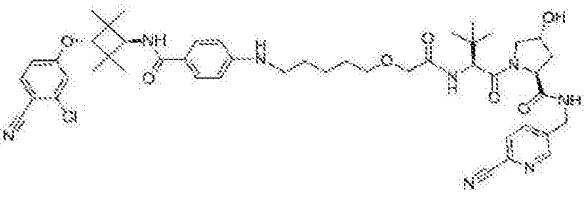
[1121]

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

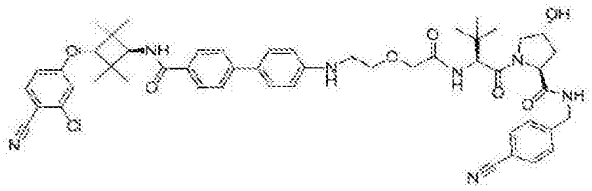
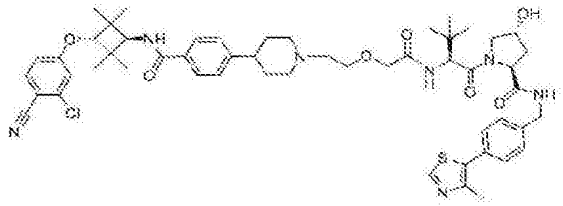
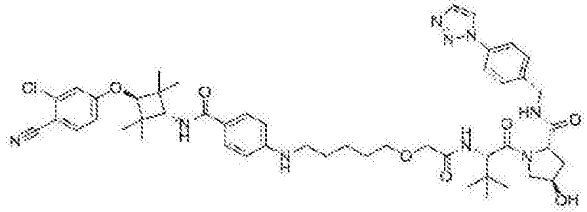
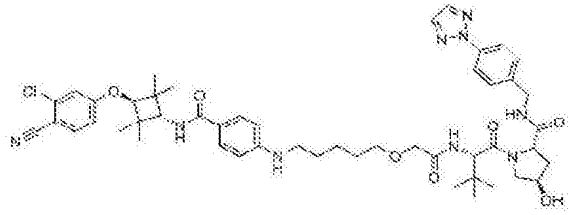
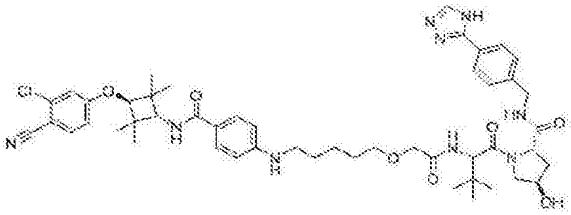
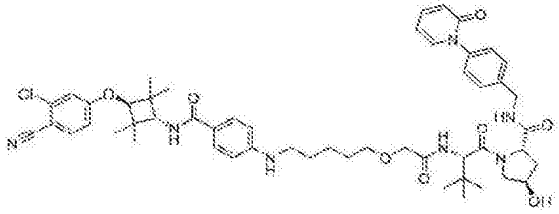
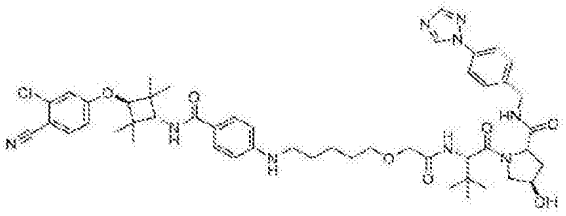
[1122]

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

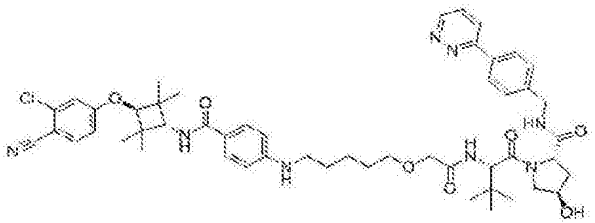
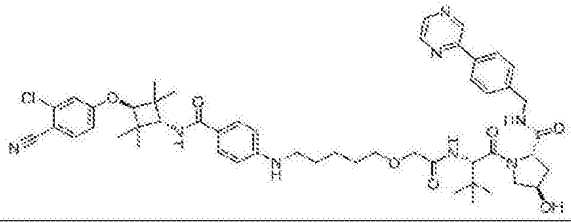
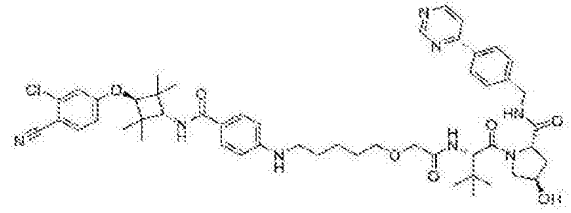
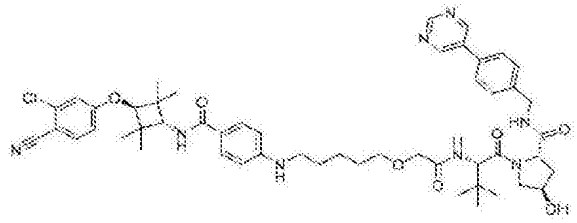
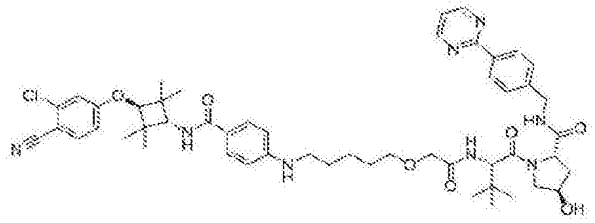
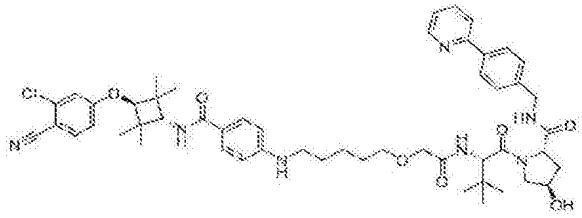
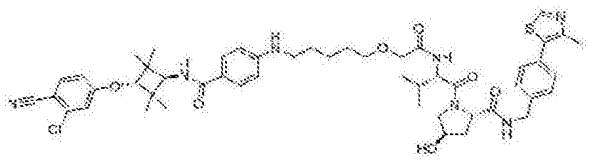
[1123]

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

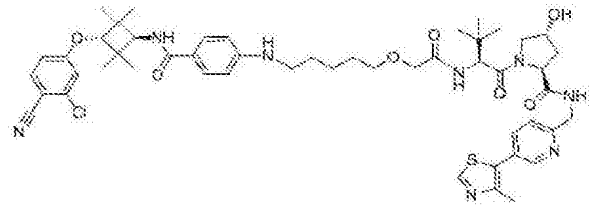
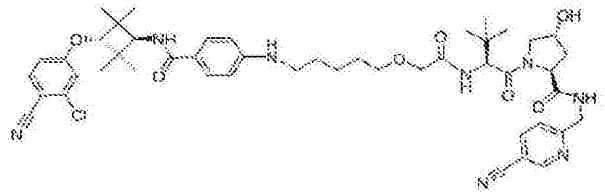
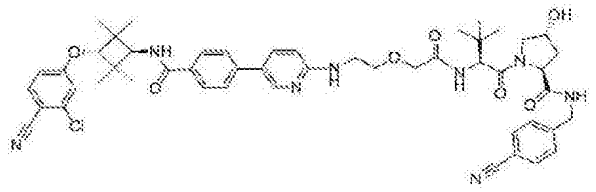
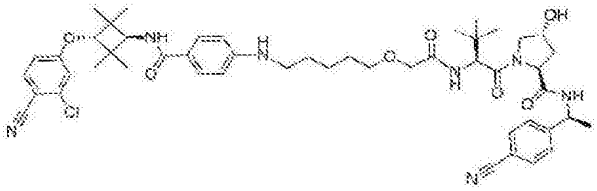
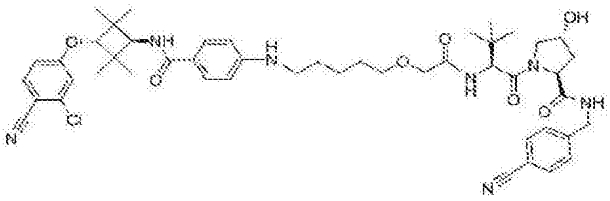
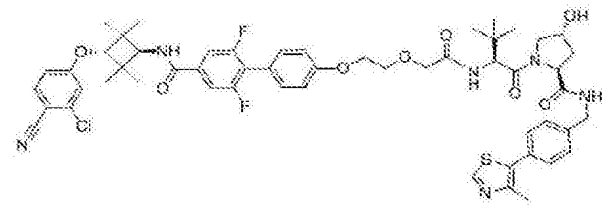
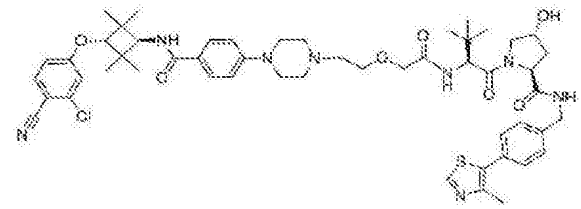
[1124]

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

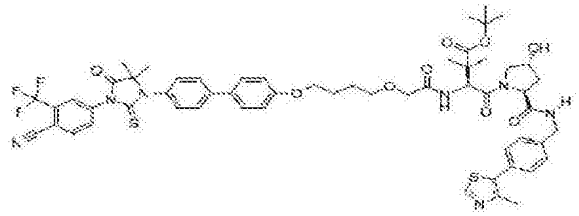
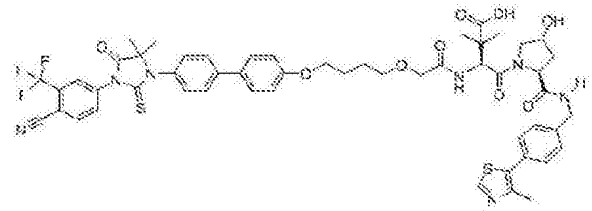
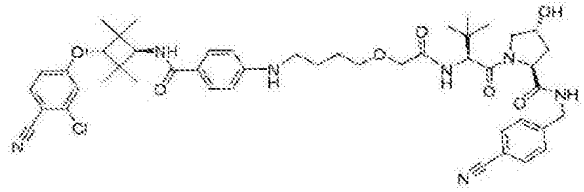
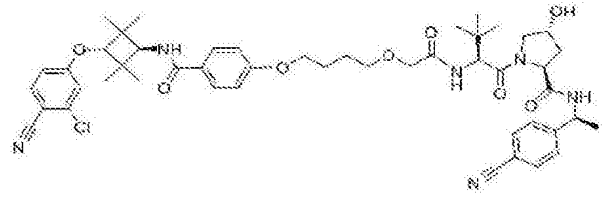
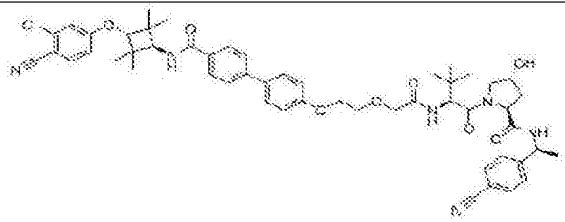
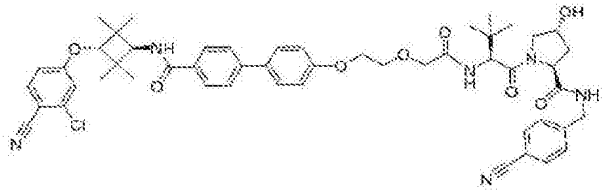
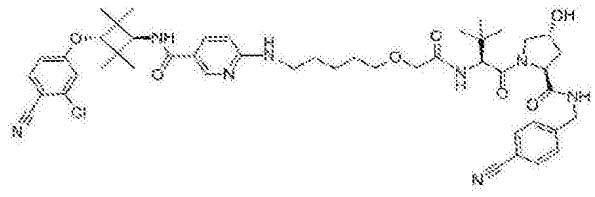
[1125]

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

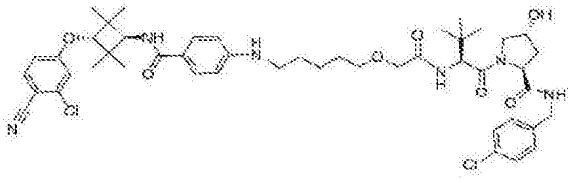
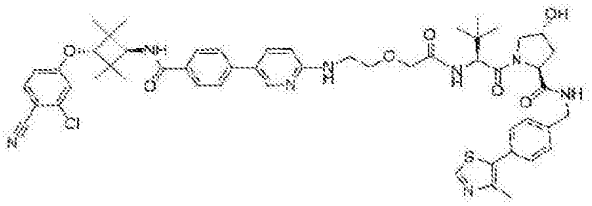
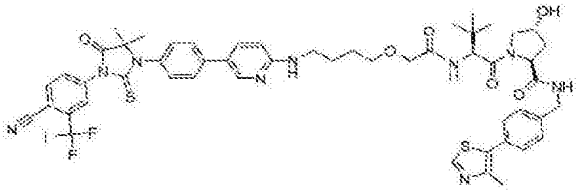
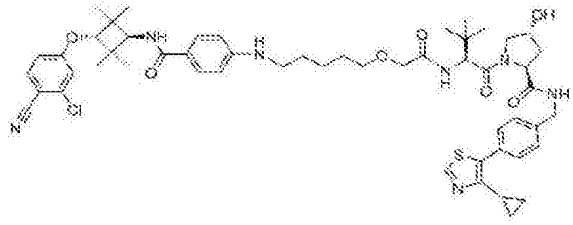
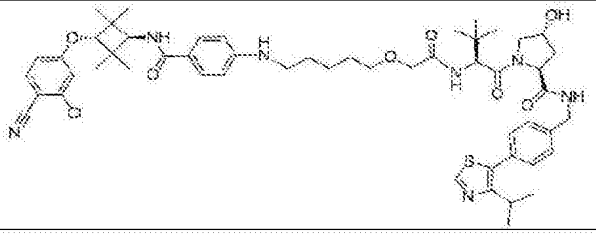
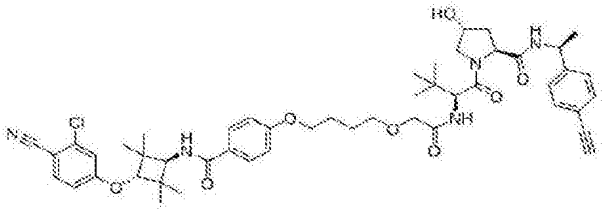
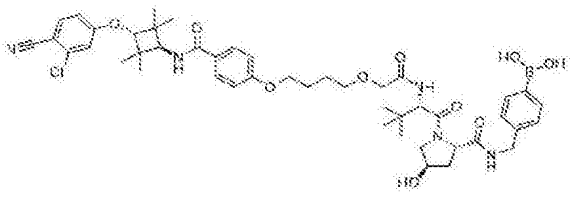
[1126]

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

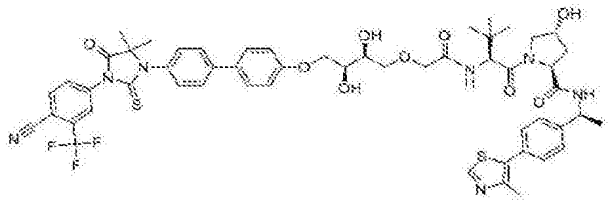
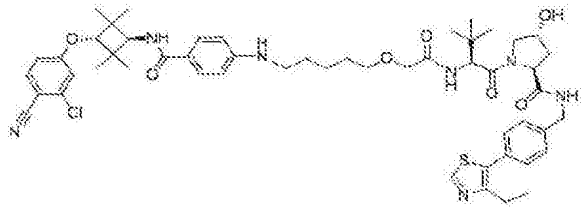
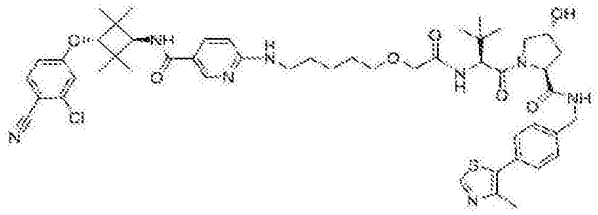
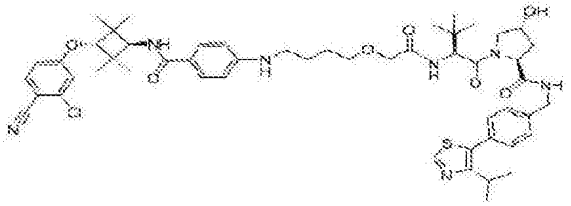
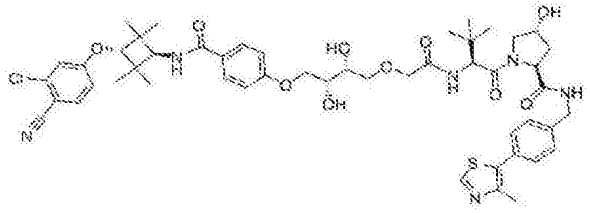
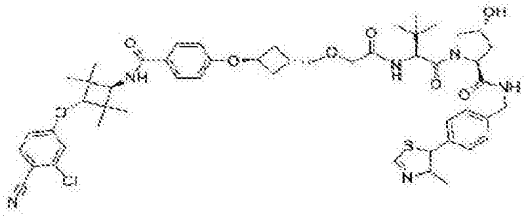
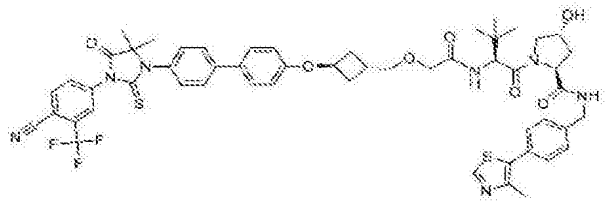
[1127]

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

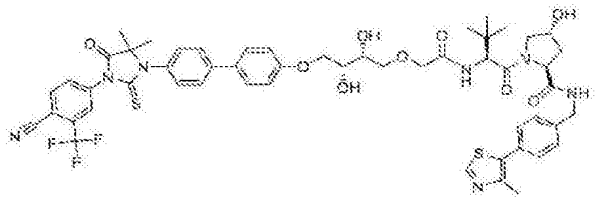
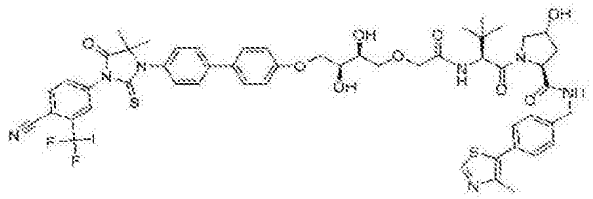
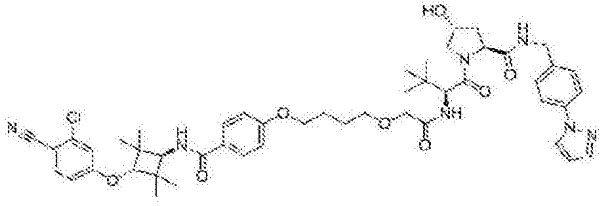
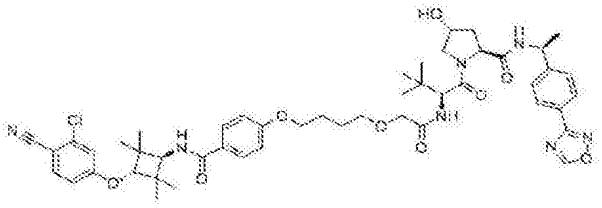
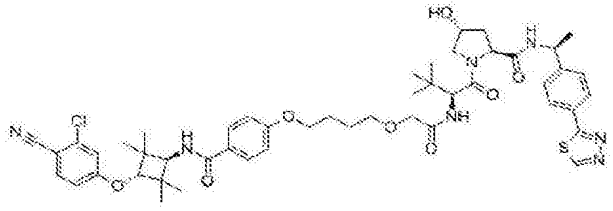
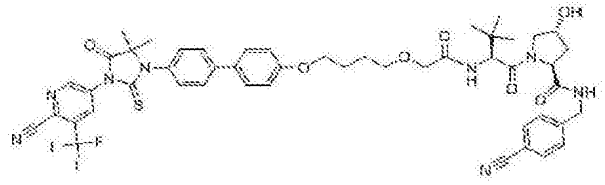
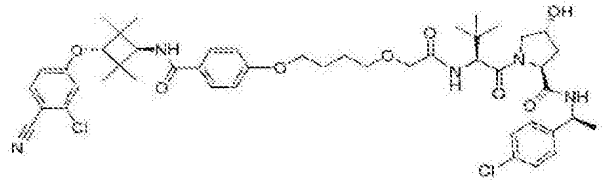
[1128]

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

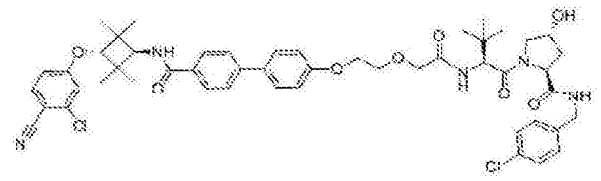
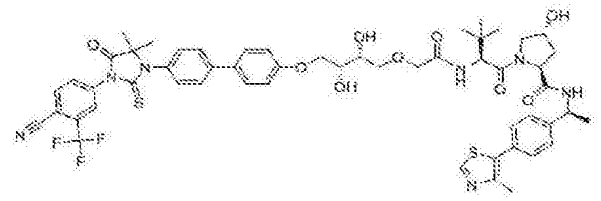
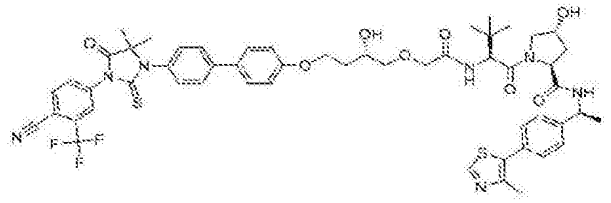
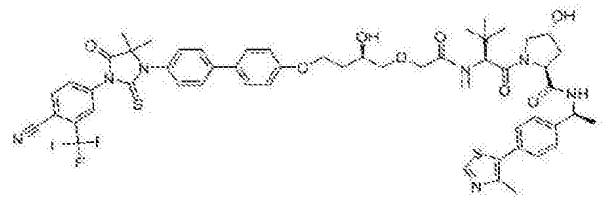
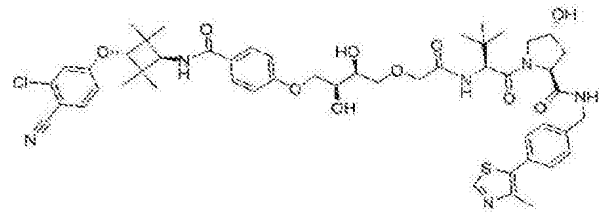
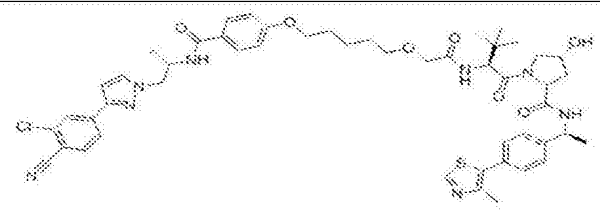
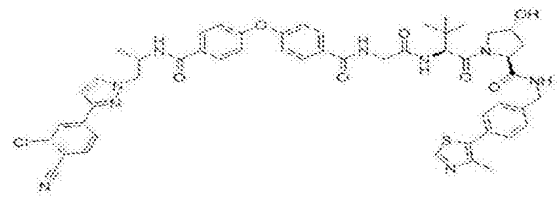
[1129]

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	

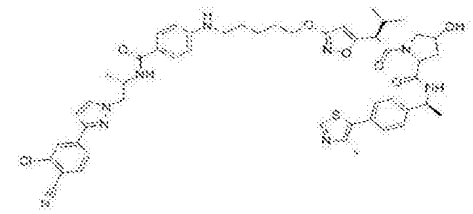
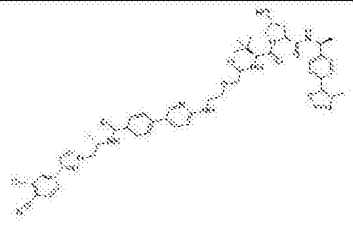
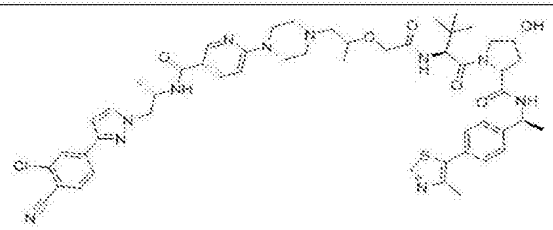
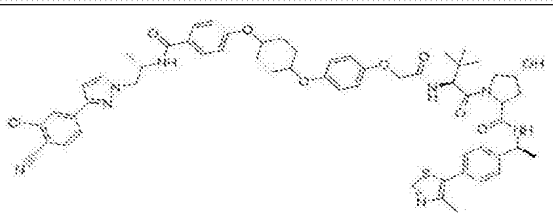
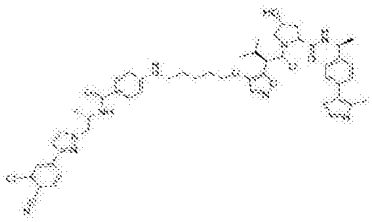
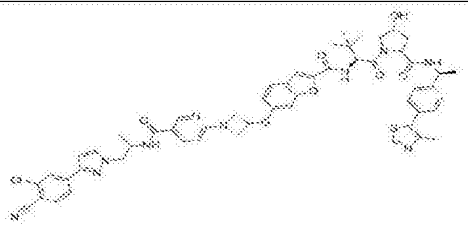
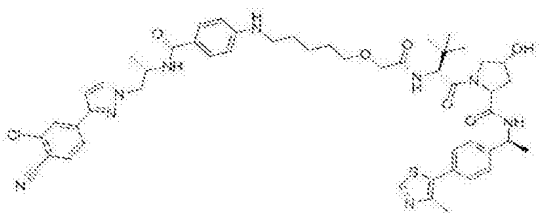
[1130]

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

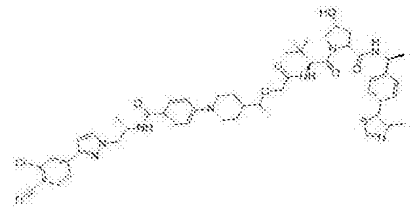
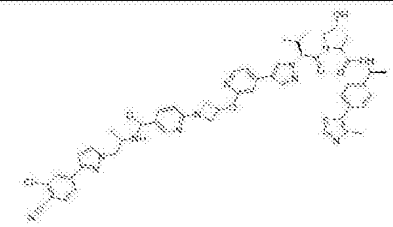
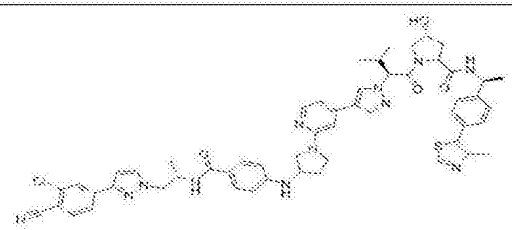
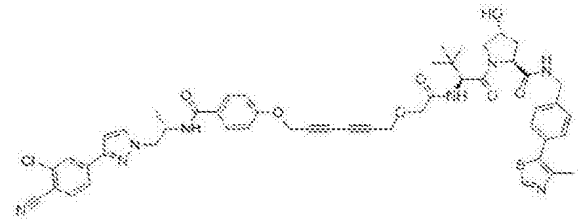
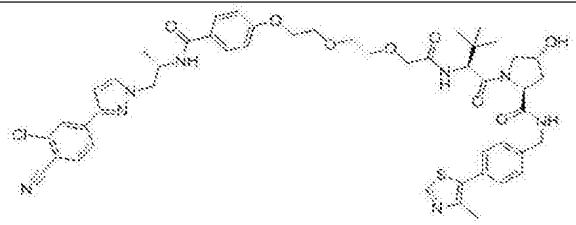
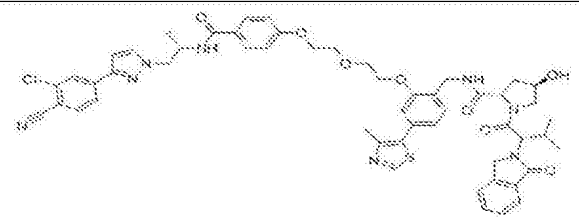
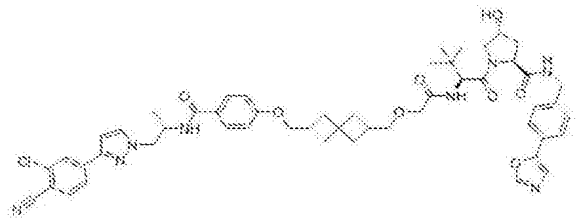
[1131]

573		926.34	928.34
574		1070.15	
575		1054.00	
576		1054.20	
577		973.63	975.36
578			
579			

[1132]

580			
581			
582			
583			
584			
585			
586			

[1133]

587			
588			
589			
590			
591			
592			
593			

[1134] 在某些实施方案中，本说明书提供了具有选自实施例1-593的结构(参见表2-17)

的化合物、其盐、多晶型物和前药。在某些另外的实施方案中，本说明书提供了一种组合物，其包含至少一种实施例1-593的化合物，包括其盐、多晶型物和前药。在另外的实施方案中，本说明书提供了一种治疗组合物，其包含至少一种实施例1-593的化合物(包括其盐、多晶型物和前药)和药学上可接受的载体。

[1135] 实施例-体外和体内测定.

[1136] 参考表和图1-7得出下面呈现的实验结果。

[1137] 1.雄激素受体ELISA测定.

[1138] 在该测定中已经利用类似的方案在LNCaP和/或VCaP细胞中评价了化合物。下面描述了与VCaP细胞一起使用的方案。根据下述测定步骤，使用PathScan AR ELISA(Cell Signaling Catalog#12850)进行雄激素受体ELISA测定：

[1139] 在Corning 3904平板中将VCaP细胞以200μL/孔的体积以30,000个细胞/孔接种在VCaP测定培养基[不含酚磺酞的RPMI(Gibco目录号11835-030)；5％木炭净化的(葡聚糖处理过的)FBS(Omega Scientific,目录号FB-04)；Pen/Strep Life Technologies(Gibco目录号:10378-016)；0.1nM R1881(Sigma,目录号R0908)在测定开始后加入，不是在细胞的最初涂平板过程中加入)中。将细胞培养最少3天。

[1140] 首先，给细胞施用在0.1％DMSO中稀释的化合物—根据下述方案使用聚丙烯平板：(1)(i)在DMSO中制备1000×储备液平板；(ii)将20mM储备液用DMSO进行1/6.7稀释(5μL+28.3μL DMSO)＝3mM进入H行中；(iii)从H行向B行在1/2log剂量(10μL PROTAC+20μL DMSO)进行系列稀释。保留A行用于DMSO；(iv)共7个剂量(在该1000×平板中的终浓度将是3mM、1mM、333μM、111μM等)。(2)(i)在培养基中制备10×储备液平板；(ii)将2.5μL 1000×储备液转移至新的10×储备液平板(使用12通道移液管，从A(DMSO对照)开始直到H。当将247.5μL培养基加入该平板时，它将充当10×储备液；(iii)制备培养基+1nM R1881用于制备10×储备液平板；(iv)将247.5μL含有1nM R1881的培养基加入10×储备液平板的每个孔中，混合。

[1141] 然后，将22μL 10×储备液加给细胞并温育24h。制备1×Cell Signaling细胞裂解缓冲液(目录#9803；与试剂盒一起得到)—为50μL/孔准备。保持在冰上。抽吸培养基，并加入50μL 1×细胞裂解缓冲液/孔。将细胞在冰上放置10分钟。将溶液混合并转移至PCR平板，并在4℃在4000rpm离心10分钟。

[1142] 将5μL转移至新鲜平板(立即使用或在-80℃冷冻)；加入115μL ELISA Dilutant(0.15ug/ml-0.075ug/ml；与PathScan ELISA一起得到)。

[1143] 加入100μL/孔AR Elisa；覆盖并在37℃摇动2小时；倾倒，轻敲，用4×200μL ELISA洗涤缓冲液洗涤；加入100μL/孔小鼠AR检测Ab；覆盖并在37℃摇动1小时；倾倒，轻敲，用4×200μL ELISA洗涤缓冲液洗涤；加入100μL/孔抗-小鼠-HRP缀合的Ab(与试剂盒一起得到)；覆盖并在37℃摇动30min；允许TMB试剂达到室温；倾倒，轻敲，用4×200μL Elisa洗涤缓冲液洗涤；轻敲；加入100μL TMB，摇动5min-同时观察颜色。当浅蓝色显影时，加入停止试剂。加入100μL停止溶液；摇动并在450nM读出。

[1144] 用抗-雄激素疗法治疗的患者中的前列腺癌的进展经常涉及增强的雄激素受体(AR)信号传递的几种机制之一，包括增加的肿瘤内雄激素合成、增加的AR表达和AR突变。使用同时结合选择的靶标和E3连接酶的双功能分子的PROTAC(蛋白酶解靶向嵌合体

(PROteolysis TArgeting Chimera))经由靶向的病理学蛋白的诱导靠近和降解而造成泛素化。与传统的靶标抑制(其是一个竞争性过程)相反,降解是一个进行性过程。因此,它对内源性配体的增加、靶标表达或靶标中的突变不太敏感。因而,该技术似乎对于解释前列腺癌患者中的AR抗性机制而言是理想的。

[1145] AR PROTAC会降解LNCaP和VCaP细胞中的AR,具有nM至pM效力,且具有AR浓度(D_{max})的>85%下降。降解是快速的,50%的AR在15分钟内消失,且在4小时之前观察到最大降解。AR敲低的持续时间是持久的,经过几天没有观察到AR的恢复。细胞中的降解过程是特异性的,因为使用无活性差向异构体(用于E3连接酶结合)的PROTAC没有降解AR。AR PROTAC在VCaP细胞中诱导快速的细胞凋亡和细胞死亡。在LNCap和VCaP细胞系统中,AR PROTAC在恩杂鲁胺无活性的条件下是抗增殖的,诸如增加AR激动剂R1881和含有AR^{F876L}突变的细胞的浓度。AR PROTAC在腹膜内或皮下注射以后通常具有几小时的$t_{1/2}$值和>50%的生物利用度。在小鼠中,AR PROTAC已经表现出体内活性,包括精囊的退化、前列腺中AR蛋白水平的下降和VCaP肿瘤的消退。

[1146] 使用上述的雄激素受体ELISA测定产生了下述测定结果,其中用观察到的雄激素受体降解的最高百分比(D_{max})和造成50%雄激素受体降解的化合物浓度(DC_{50})表征化合物效力。

[1147] 表18.观察到的雄激素受体降解(D_{max})和造成50%雄激素受体降解的化合物浓度(DC_{50})。

[1148] D_{max}:+($D_{max}\leq 25\%$);++(26%≤$D_{max}\leq 50\%$);+++(51%≤$D_{max}\leq 70\%$);++++(71%≤D_{max});DC_{50}:A($D_{max}\leq 50nM$);B(51nM≤$DC_{50}\leq 500nM$);C(501nM≤DC_{50}).

[1149]

实施例#	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	++	

[1150]

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

[1151]

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		

[1152]

83	+++	B		
84	+++	B		
85	+++	C		

[1153]

实施例#	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

[1154]

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

[1155]

实施例#	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

[1156]

实施例#	VCaP Dmax (%)	VCaP DC_{50} (μM)
162	++++	A
163	++++	A
164	++++	A
165	++++	A
166	+++	A

[1157]

实施例#	VCaP Dmax (%)	VCaP DC_{50} (μM)
172	++++	A
173	++++	A
174	+++	A
175	+++	A

[1158]

实施例#	VCaP Dmax (%)	VCaP DC_{50} (μM)
180	++++	A
181	++++	A

[1159]

182	++++	A

[1160]

实施例#	VCaP Dmax (%)	VCaP DC_{50} (μM)
183	++++	A
184	++++	A
185	++++	A
186	++++	A

[1161]

实施例#	VCaP Dmax (%)	VCaP DC_{50} (μM)
188	++++	A
189	+++	A

[1162]

实施例#	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

[1163]

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

[1164]

[1165]

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

[1166]

[1167] 2.VCaP细胞增殖测定

[1168] 将VCaP细胞以7,500个/孔、200μL/孔铺板在VCaP测定培养基[不含酚磺酞的RPMI(Gibco目录号11835-030);5%木炭净化的(葡聚糖处理过的)FBS(Omega Scientific,目录号FB-04);Pen/Strep Life Technologies(Gibco目录号:10378-016);0.1nM R1881(Sigma,目录号R0908)在测定开始后加入,不是在细胞的最初涂平板过程中加入)中。

[1169] 如下进行测定:将细胞培养最少3天以除去雄激素;如关于AR ELISA那样进行PROTAC和R1881的施用;可以在施用当天进行Cell Titer Glo的基线读出。

[1170] 使用0.1nM R1881的VCaP细胞将在4天中倍增一次。轻轻抽出110μL培养基从而不会扰乱粘附细胞;加入110μL CTG;在缓慢摇动下温育20分钟;并在平板读数器上读出发光。

[1171] VCaP抗增殖数据:

[1172] GI_{50}定义:A($GI_{50}\leqslant 50nM$);B($51nM\leqslant GI_{50}\leqslant 250nM$);C($251nM\leqslant GI_{50}$)

[1173] 表19.VCaP增殖的抑制.

[1174]

实施例#	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

[1175]

实施例#	质量数据		GI_{50}
	观察到的质量 1: MH+	观察到的质量 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

[1176] 这些结果支持所述双功能化合物(ABM-L-ULM)和雄激素受体结合部分(ABM-e)会抑制VCaP增殖。

[1177] 3.VCaP细胞中的细胞凋亡

[1178] 图2表明，如本文中所述的化合物在VCaP细胞中诱导细胞凋亡。在补充了0.1nM R1881的、含木炭净化的血清的培养基中培养VCaP细胞48小时。用CaspaseGlo测定物(Promega)确定细胞凋亡的程度。这些结果证实，PROTAC在诱导细胞凋亡方面比AR拮抗剂恩杂鲁胺更有效得多。此外，AR降解的程度与它们在VCaP细胞中诱导细胞凋亡的能力相关。

[1179] 4.LNCaP F876L中的抗增殖

[1180] 图3证实了用如本文中所述的化合物处理观察到的LNCaP F876L细胞中的抗增殖。在含木炭净化的血清的培养基中培养用AR F876L构建体转导的LNCaP细胞。加入指示剂量的恩杂鲁胺或实施例1保持7天。采用CellTiterGlo试剂(Promega)来评估增殖。如显示的，表达F876L构建体的LNCaP细胞响应于递增剂量的恩杂鲁胺而增殖，而实施例1没有表现出激动剂活性。这些结果证实，AR PROTAC不具有激动剂活性。

[1181] 5.LNCaP F876L中的PSA抑制

[1182] 如本文中所述的化合物也抑制LNCaP F876L细胞中的PSA(参见图4)。将用AR F876L构建体转导的LNCaP细胞在补充了0.1nM R1881的含木炭净化的血清的培养基中培养7天。通过PSA ELISA(Sigma)检测培养基中分泌的PSA。这些结果证实，AR PROTAC能够抑制含F876L的细胞中的AR的转录活性。

[1183] 6.C57B6小鼠模型中的前列腺退化

[1184] 图5证实，如本文中所述的化合物在C57B6小鼠模型中诱导前列腺退化。用AR PROTAC实施例163和它的无活性的差向异构体类似物化合物A(其不能结合VHL E3连接酶)处理12-周龄雄性C57BL/6小鼠。将恩杂鲁胺(PO,QD,30mpk)、实施例163(IP,QD,1和3mpk)和化合物A(IP,QD,1和3mpk)施用10天，此后将前列腺分离并称重。PROTAC实施例163表现出前列腺重量的显著减小，而化合物A没有表现出显著活性。这些结果证实，PROTAC实施例163的降解AR的能力在非常低的剂量导致小鼠中显著的前列腺退化。

[1185] 7.VCaP异种移植物模型中的肿瘤生长抑制

[1186] 图6解释了VCaP异种移植物模型中的肿瘤生长抑制，其用如本文中所述的化合物实现。将VCaP细胞皮下地植入CB17scid小鼠中。一旦所述肿瘤是可触知的，将小鼠阉割，从而导致暂时肿瘤停滞。在肿瘤的再生长后，给小鼠施用指示的恩杂鲁胺(PO,QD,30mpk)或AR PROTAC实施例163(IP,QD,在30,10和3mpk)。在所有治疗组中观察到肿瘤生长抑制。

[1187] 8.PROTAC的AR降解是E3连接酶依赖性的

[1188] 图7证实了用如本文中所述的化合物实现的AR降解是E3连接酶依赖性的。例如，在(A)中，在有或没有10μM VHL E3连接酶配体化合物B存在下将AR PROTAC实施例1在指示的浓度加给LNCaP细胞24小时。化合物B的存在与AR PROTAC实施例1在VHL E3连接酶结合中竞争，且极大地减少AR PROTAC实施例1的AR降解活性。在(B)中，用AR PROTAC实施例1和它的无活性的差向异构体类似物化合物C(其不能结合VHL E3连接酶)处理LNCaP细胞。尽管AR PROTAC实施例1导致AR的显著降解，但是化合物C不会。这些结果证实，AR降解中的AR PROTAC活性是VHL E3连接酶依赖性的。

[1189] 9.PROTAC前药口服药代动力学和PROTAC皮下药代动力学

[1190] 代表性的药代动力学程序

[1191] 通过经口腔管饲法或皮下注射在表20和21中详细说明的制剂中以10mL/kg给自由

获取食物和水的雄性CD-1小鼠(6-8周龄,体重20-30g,每个研究3只)施用10mg/kg的试验物。

[1192] 在0.25、0.5、1、2、4、8和24h时间点从背侧跖静脉连续地收集大约0.04mL血液样品;将肝素用作抗凝血剂。将样品在4℃在4000g离心5min,然后在分析之前在-75℃储存。

[1193] 通过LC/MS/MS方法分析血浆样品,在适当时定量未变化的、施用的试验物和/或衍生物种类。使用WinNonlin(Phoenix™)进行药代动力学计算和建模,以产生参数诸如C_{max}和AUC。

[1194] 表20:PROTAC前药药代动力学的例子(ESP-4:5%EtOH,5%solutol HS15在PBS中;ESD-4 5%EtOH,15%solutol在D5W中)。

[1195]

实施例#	剂量/途径		血浆暴露			
		媒介物	前药		衍生物	
			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

[1196] 表21:PROTAC皮下药代动力学的例子(ELP-1:5%EtOH,20%辛酸癸酸聚乙二醇甘油酯(labrasol)在PBS中;ESD-2:5%EtOH,20%solutol在D5W中).

[1197]

媒介物	实施例#	在10 mg/kg皮下剂量以后的CD-1小鼠血浆暴露	
		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

[1198] 总之,被设计成降解AR的PROTAC是有效的(低nM至pM),特异性的,快速的(在2-4小

时内)；持久的(数天)；在体外和在体内是有活性的，且具有比恩杂鲁胺优秀的细胞效力。AR PROTAC在细胞系统中具有效力且在体内工作(前列腺中的AR降解；前列腺和精囊中的前列腺退化；肿瘤异种移植物模型)。因而，AR的靶向降解可以提供新机制用于给当前的疗法对其已经失败的那些前列腺癌患者提供有效的疗法。

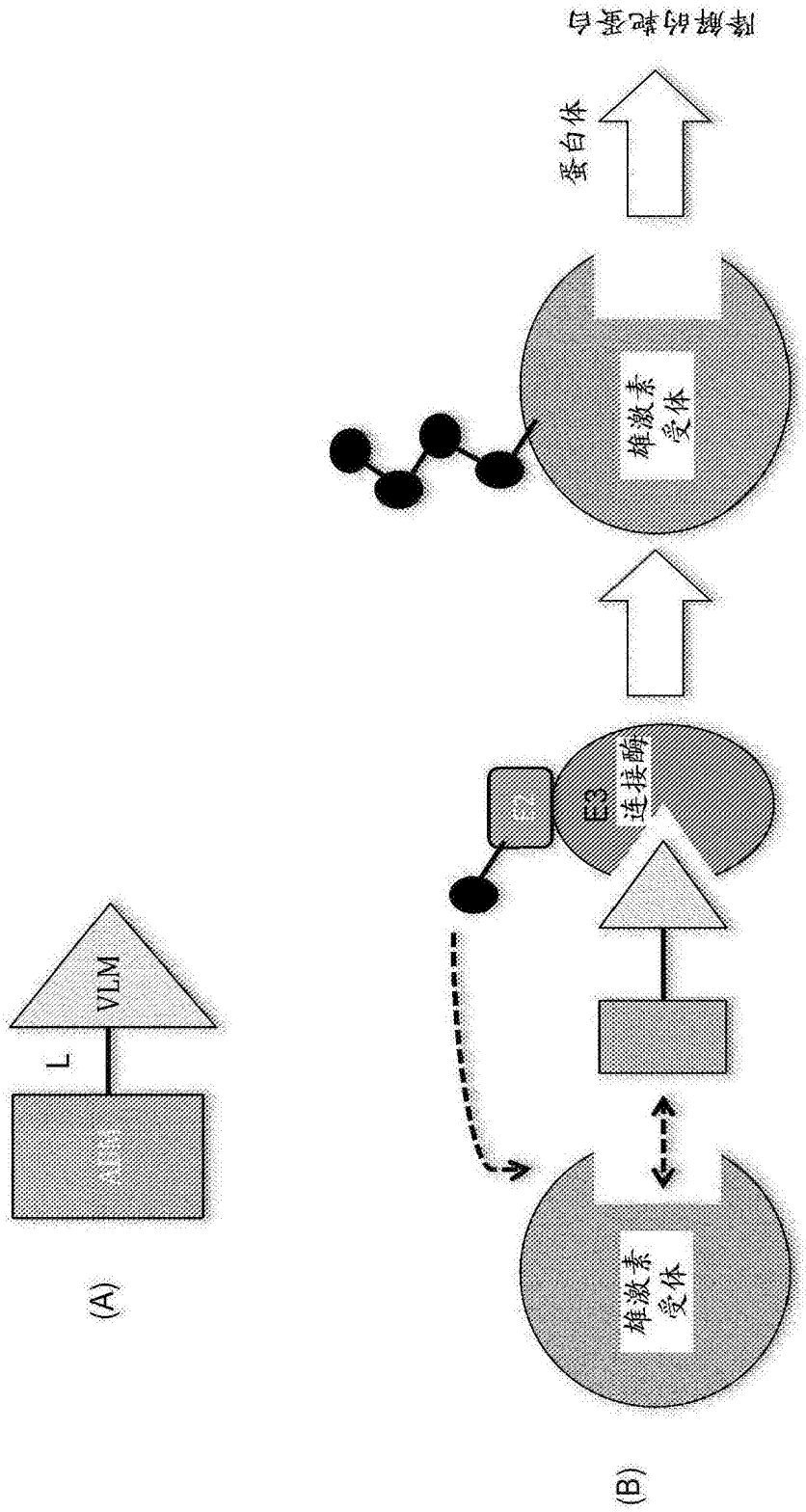


图1

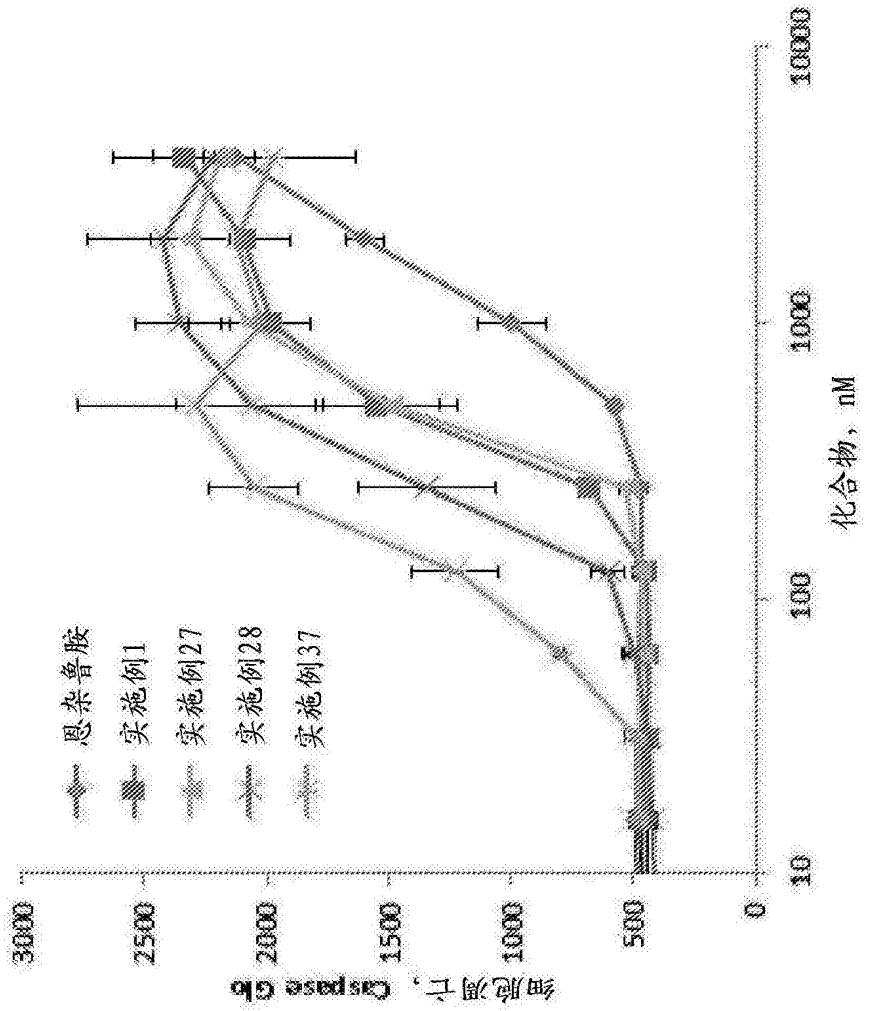

恩杂鲁胺
实施例1
实施例27
实施例28
实施例37
细胞凋亡，Caspase Glo
3000
2500
2000
1500
1000
500
0
10
100
1000
10000
化合物，nM

图2

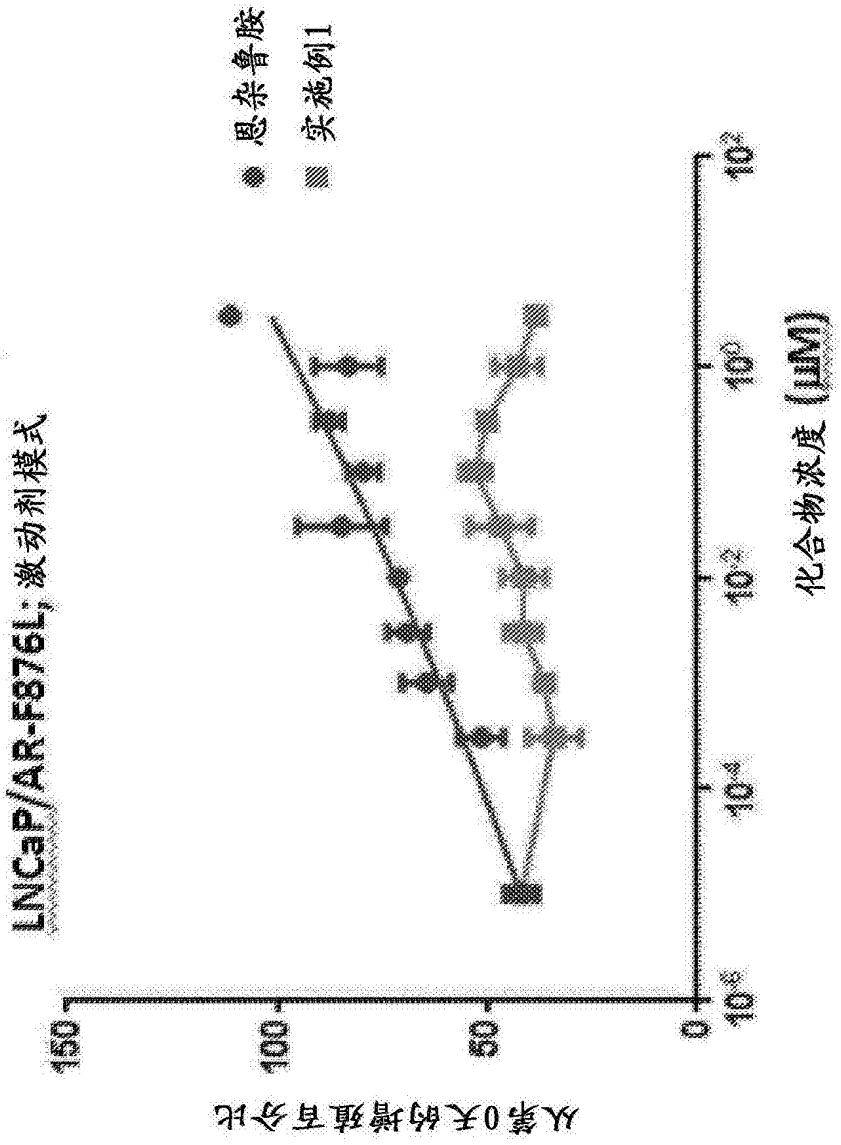

恩杂鲁胺
实施例1
LNCaP/AR-F876L; 激动剂模式
从第0天的增殖百分比
150
100
50
0
10^{-5}
10^{-4}
10^{-3}
10^{-2}
10^{-1}
10^{0}
化合物浓度 [uM]

图3

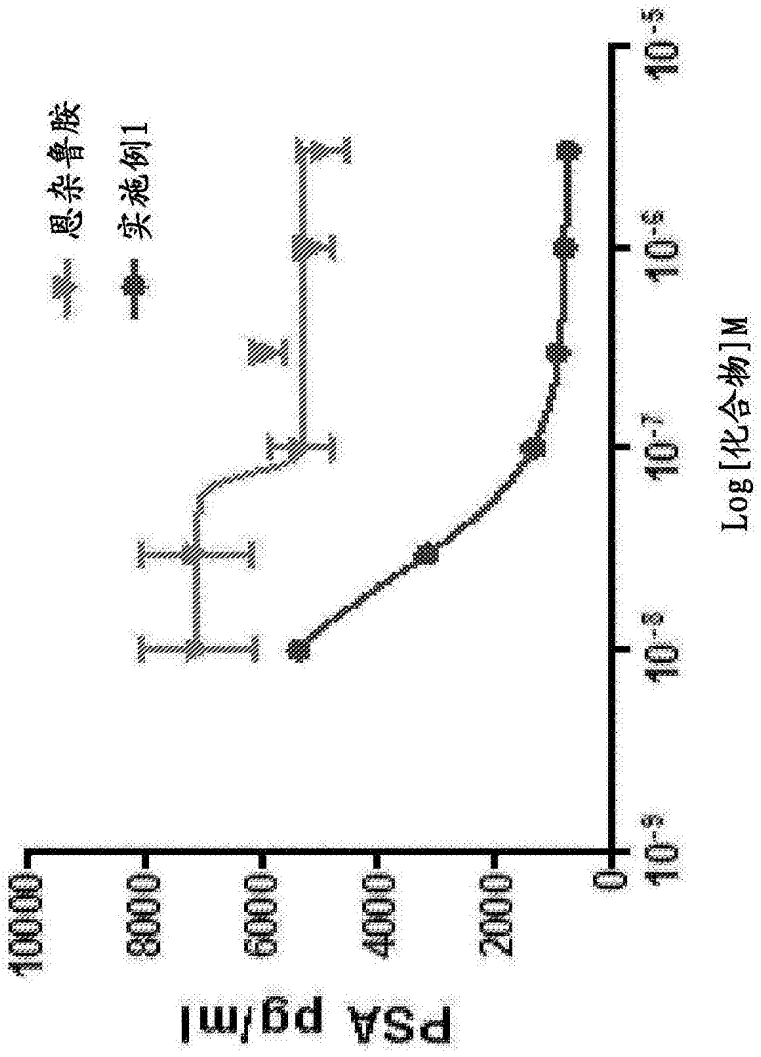

恩杂鲁胺
实施例1
PSA pg/ml
10000
8000
6000
4000
2000
0
10-5
10-3
10-7
10-6
10-5
Log [化合物] M

图4

* P ≤ 0.05
** P ≤ 0.01
*** P ≤ 0.001
**** P ≤ 0.0001
前列腺重量 (mg)
0
50
100
150
媒介物
恩杂鲁胺 (30mpk)
实施例 163 (1mpk)
化合物 A (1mpk)
实施例 163 (3mpk)
化合物 A (3mpk)
化合物 V

图5

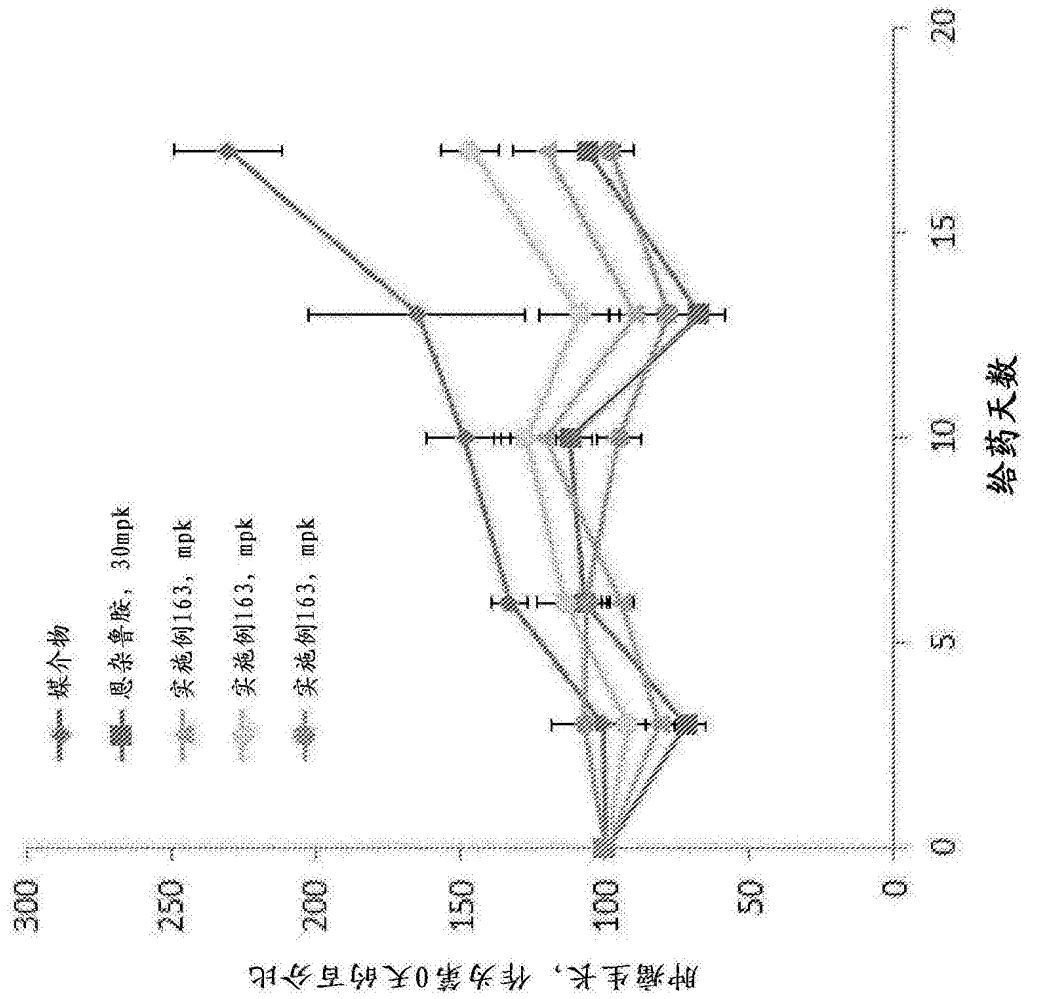

肿瘤生长，作为第0天的百分比
300
250
200
150
100
50
0
0
5
10
15
20
给药天数
媒介物
恩杂鲁胺，30mpk
实施例163，mpk
实施例163，mpk
实施例163，mpk

图6

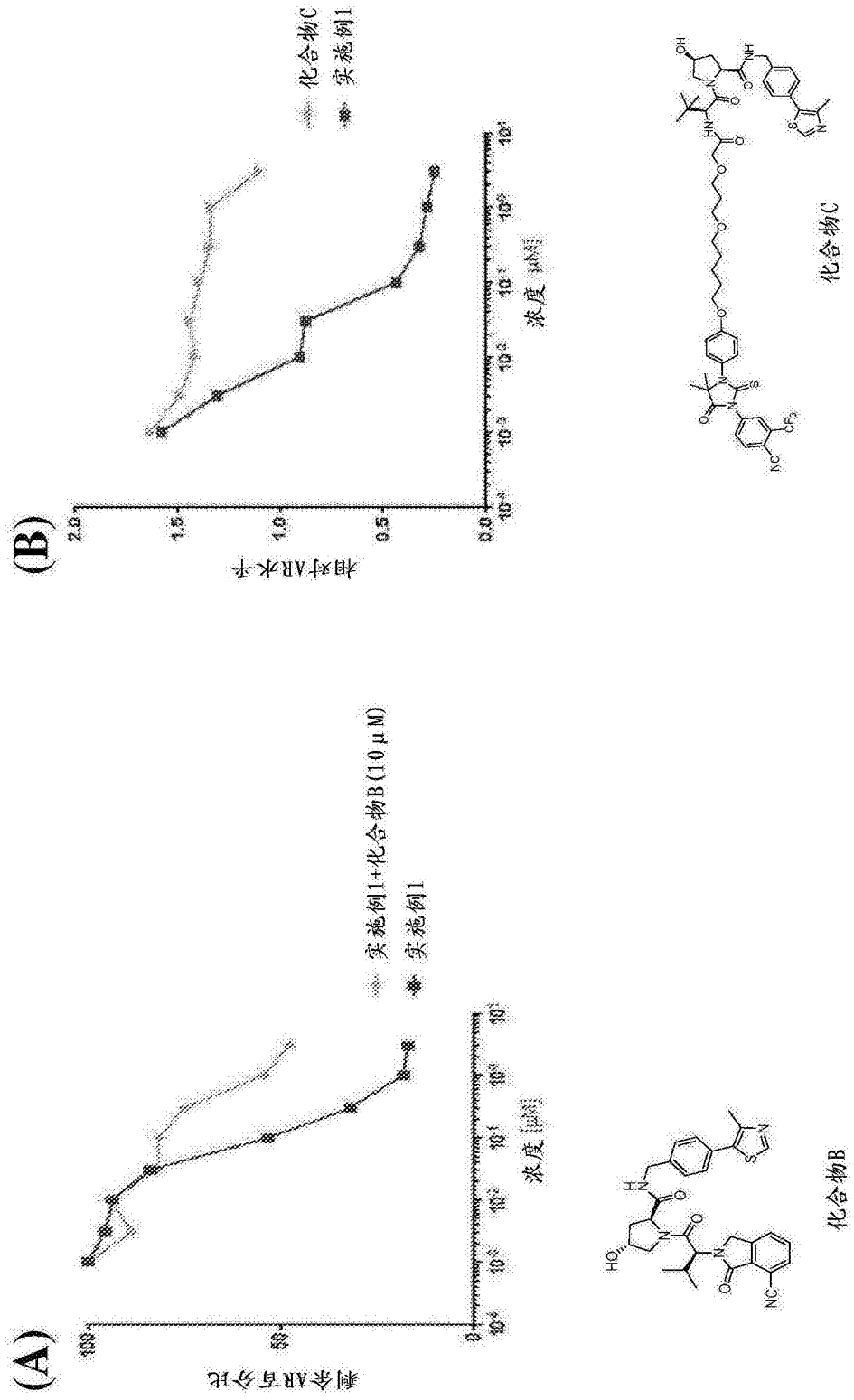

(A)
剩余AR百分比
浓度 [nM]
实施例1+化合物B(10μM)
实施例1
化合物B
(B)
相对AR水平
浓度 [μM]
化合物C
实施例1
化合物C

图7