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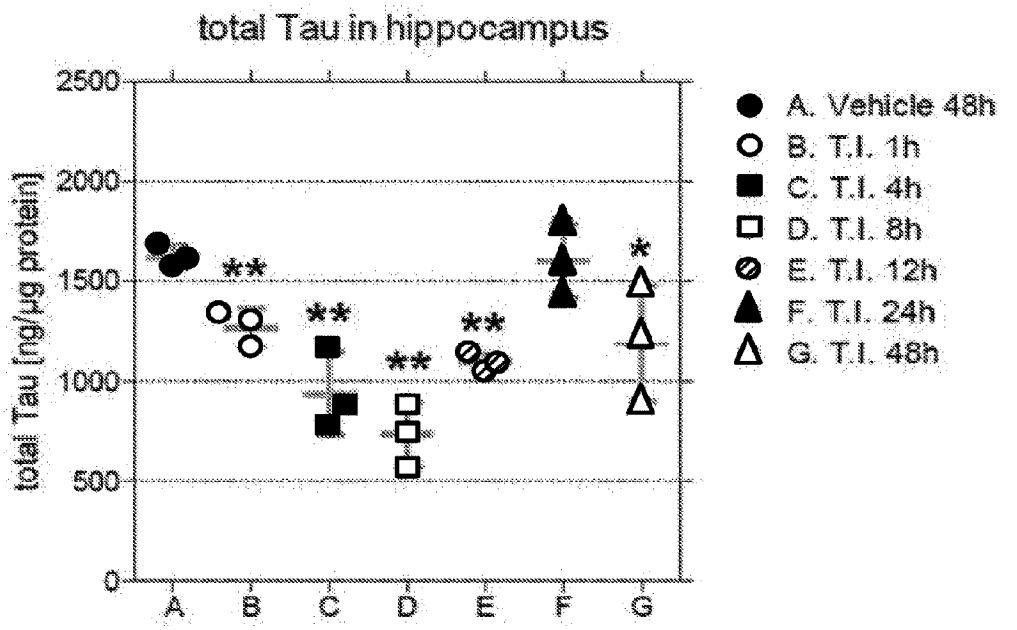
(54) **Titre : PROTACS CIBLANT LA PROTEINE TAU ET METHODES D'UTILISATION ASSOCIEES**
(54) **Title: TAU-PROTEIN TARGETING PROTACS AND ASSOCIATED METHODS OF USE**



(57) **Abrégé/Abstract:**
The present disclosure relates to bifunctional compounds, which find utility as modulators of tau protein. In particular, the present disclosure is directed to bifunctional compounds, which contain on one end a VHL or cereblon ligand which binds to the E3 ubiquitin ligase and on the other end a moiety which binds tau protein, such that tau protein is placed in proximity to the ubiquitin ligase to effect degradation (and inhibition) of tau. The present disclosure exhibits a broad range of pharmacological activities associated with degradation/inhibition of tau protein. Diseases or disorders that result from aggregation or accumulation of tau protein are treated or prevented with compounds and compositions of the present disclosure.

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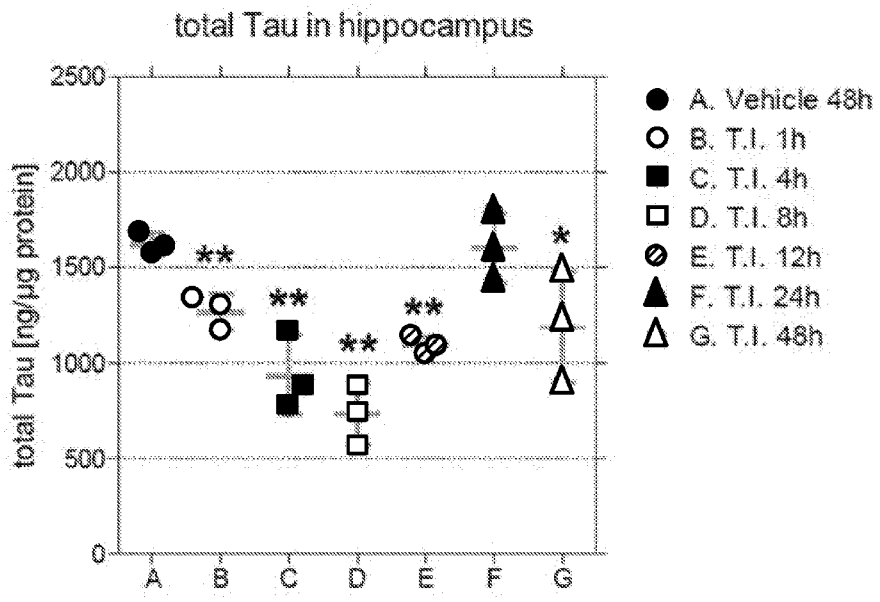
(54) Title: TAU-PROTEIN TARGETING PROTACS AND ASSOCIATED METHODS OF USE

FIG. 1



(57) Abstract: The present disclosure relates to bifunctional compounds, which find utility as modulators of tau protein. In particular, the present disclosure is directed to bifunctional compounds, which contain on one end a VHL or cereblon ligand which binds to the E3 ubiquitin ligase and on the other end a moiety which binds tau protein, such that tau protein is placed in proximity to the ubiquitin ligase to effect degradation (and inhibition) of tau. The present disclosure exhibits a broad range of pharmacological activities associated with degradation/inhibition of tau protein. Diseases or disorders that result from aggregation or accumulation of tau protein are treated or prevented with compounds and compositions of the present disclosure.

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JUMBO APPLICATIONS / PATENTS

THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1___ OF __2___

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TAU-PROTEIN TARGETING PROTACS AND ASSOCIATED METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] Paragraph intentionally left blank.

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BACKGROUND

1. Field of the discovery

[0003] The present description relates to bifunctional compounds, which are useful for modifying intracellular ubiquitination and subsequent degradation of target polypeptides and proteins, in particular, Tau protein. Compounds of the present disclosure place target protein/polypeptide in proximity to a ubiquitin ligase to effect the ubiquitination and degradation (and inhibition) of Tau protein.

2. Background information

[0004] Most small molecule drugs bind enzymes or receptors in tight and well-defined pockets. On the other hand, protein-protein interactions are notoriously difficult to target using small molecules due to their large contact surfaces and the shallow grooves or flat interfaces involved. E3 ubiquitin ligases (of which hundreds are known in humans) confer substrate specificity for

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ubiquitination, and therefore, are more attractive therapeutic targets than general proteasome inhibitors due to their specificity for certain protein substrates. The development of ligands of E3 ligases has proven challenging, in part due to the fact that they must disrupt protein-protein interactions. However, recent developments have provided specific ligands which bind to these ligases. For example, since the discovery of nutlins, the first small molecule E3 ligase inhibitors, additional compounds have been reported that target E3 ligases, but the field remains underdeveloped.

[0005] One E3 ligase with exciting therapeutic potential is the von Hippel-Lindau (VHL) tumor suppressor, the substrate recognition subunit of the E3 ligase complex VCB, which also consists of elongins B and C, Cul2 and Rbx1. The primary substrate of VHL is Hypoxia Inducible Factor 1α (HIF-1α), a transcription factor that upregulates genes such as the pro-angiogenic growth factor VEGF and the red blood cell inducing cytokine erythropoietin in response to low oxygen levels. The first small molecule ligands of Von Hippel Lindau (VHL) to the substrate recognition subunit of the E3 ligase were generated, and crystal structures were obtained confirming that the compound mimics the binding mode of the transcription factor HIF-1α, the major substrate of VHL.

[0006] Cereblon is a protein that in humans is encoded by the CRBN gene. CRBN orthologs are highly conserved from plants to humans, which underscores its physiological importance. Cereblon forms an E3 ubiquitin ligase complex with damaged DNA binding protein 1 (DDB1), Cullin-4A (CUL4A), and regulator of cullins 1 (ROC1). This complex ubiquitinates a number of other proteins. Through a mechanism which has not been completely elucidated, cereblon ubquitination of target proteins results in increased levels of fibroblast growth factor 8 (FGF8) and fibroblast growth factor 10 (FGF10). FGF8 in turn regulates a number of developmental processes, such as limb and auditory vesicle formation. The net result is that this ubiquitin ligase complex is important for limb outgrowth in embryos. In the absence of cereblon, DDB1 forms a complex with DDB2 that functions as a DNA damage-binding protein.

[0007] The Tau protein is an abundant protein in the central nervous system primarily found in neuronal cells, although Tau is expressed at lower levels in other cells of the central nervous system. In a healthy neuron, Tau binds to microtubules and regulates microtubule stability, which is critical for axonal outgrowth and neuronal plasticity. When pathologically altered, Tau molecules are not able to stabilize microtubules and are prone to form insoluble aggregates. Once

the Tau protein forms insoluble aggregates in cells, cellular dysfunction occurs, axonal transport is compromised, and neuronal loss ensues. Accumulation of abnormal Tau aggregates in neurons is an important pathological signature in multiple neurodegenerative disorders including Alzheimer's disease. In certain pathological conditions, Tau aggregation results in paired-helical filaments (PHFs), straight filaments (SFs) and/or neurofibrillary tangles (NFTs). The accumulation of PHFs and NFTs in neurons directly correlates with microtubule dysfunction and neuronal degeneration. Neurons containing tau PHFs, SFs, and or NFTs activate diverse cellular mechanisms to try and rid the cell of the abnormal protein aggregates.

[0008] More recent studies suggest that, instead of the large insoluble filaments, soluble Tau oligomers might play a more critical role in the onset and progression of disease prior to the development of PHF- or NFT-induced neurotoxicity. Oligomeric species of Tau may act as seeds for the aggregation of native Tau, thereby promoting neurotoxic Tau aggregation. Accumulating evidence has suggested that Tau aggregates can be transmitted from one cell to another by propagating in a prion-like manner.

[0009] Tau alteration and dysfunction and extensive neuron loss has long been associated with several neurodegenerative diseases now collectively called tauopathies.

[0010] The term "tauopathy" or “tauopathies” refers herein to a class of neurodegenerative diseases associated with the pathological aggregation of Tau protein in neurofibrillary or gliofibrillary tangles in the human brain. Examples of tauopathies include but are not limited to AD, Down's syndrome, frontotemporal lobular dementia (FTLD), cotricobasal degeneration (CBD) and progressive supranuclear palsy (PSP)

[0011] Due to its pathological significance in multiple neurodegenerative diseases, Tau is an important therapeutic target. Preventing Tau aggregation becomes a potential strategy to treat neurodegenerative disorders associated with Tau. So far, great effort has been made to identify molecular mechanisms of Tau aggregation and find therapeutics to halt the progression of neurodegeneration.

[0012] Tau aggregation inhibitors which demonstrated promising pre-clinical data have proven ineffective in recent clinical trials for the treatment of various tauopathies. Therfore, a need exists in the art for effective treatments of diseases and conditions that are related to the aggregation of Tau in neurodegenerative disorders such as tauopathies.

SUMMARY

[0013] The present disclosure describes bifunctional compounds, including compositions comprising the same, which function to recruit endogenous proteins to an 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 Tau protein aggregates. In addition, the description provides methods of using an effective amount of the compounds as described herein for the treatment or amelioration of disease conditions due to accumulation or aggregation of Tau proteins such as tauopathies. These diseases or disorders include but are not limited to neurological or neurodegenerative disorders.

[0014] Thus, in one aspect, the disclosure provides compounds which function to recruit endogenous proteins, e.g., Tau, to E3 Ubiquitin Ligase for ubiquintination and degradation.

[0015] In any of the embodiments, the compounds have the following general structures

PTM-L-ULM

[0016] In certain embodiments, the compounds have the following general structures (A)

PTM-L-VLM (A)

[0017] In certain embodiments, the compounds have the following general structures (B)

PTM-L-CLM (B)

wherein, PTM represents protein targeting moiety, ULM represents E3 ubiquitin ligase targeting moiety including but not limited to VLM (VHL ligase-binding moiety) and CLM (cereblon ligase-binding moiety) and L represents a linker, e.g., a bond or a chemical linker moiety. As would be understood by the skilled artisan, the bifunctional compounds as described herein can be synthesized such that the number and position of the respective functional moieties can be varied as desired.

[0018] In certain embodiments, the PTMs in structure (A) are the ligands that bind to Tau as well as VHL E3 ubiquitin ligase.

[0019] In certain embodiments, the PTMs in structure (B) are the ligands that bind to Tau as well as CLM E3 ubiquitin ligase.

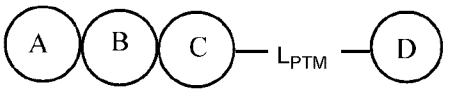
[0020] In certain embodiments, the compounds as described herein comprise multiple ULMs, multiple PTMs, multiple chemical linkers or a combination thereof. In an additional aspect, the description provides therapeutic compositions comprising an effective amount of a compound as described herein or salt form thereof, and a pharmaceutically acceptable carrier. The therapeutic compositions modulate protein degradation in a patient or subject, for example, an animal such as

a human, and can be used for treating or ameliorating disease states or conditions which are modulated through the degraded protein. In certain embodiments, the therapeutic compositions as described herein may be used to effectuate the degradation of proteins of interest for the treatment or amelioration of a disease, e.g., neuronal disease. In yet another aspect, the present disclosure provides a method of ubiquitinating/degrading a target protein in a cell. In certain embodiments, the method comprises administering a bifunctional compound as described herein comprising an ULM and a PTM, which may be linked through a linker moiety, as otherwise described herein, wherein the ULM is coupled to the PTM and wherein the ULM recognizes a ubiquitin pathway protein e.g., an ubiquitin ligase, such as an E3 ubiquitin ligase more preferably VLM and CLM and the PTM recognizes the target protein (TBM) such that degradation of the target protein will occur when the target protein (e.g., Tau) is placed in proximity to the ubiquitin ligase, thus resulting in degradation of the target protein, inhibition of its effects and the control of protein levels. In another aspect, the target protein is Tau. The present disclosure provides treatment of a disease state or condition through control of protein levels, i.e. by lowering the level of that protein (e.g., Tau protein) in the cells of a patient via degradation.

[0021] In particular, PTM are molecules that bind to Tau protein (TBM), and ULM are molecules that bind to VHL E3 ubiquitin ligase and/or to CLM E3 ubiquitin ligase with the following general structures:

TBM-L-VLM/CLM

[0022] The PTM (protein-targeting moiety) of the PROTACs of current disclosure is represented by the general formulas I, II, III, IV, V, VI, VII, VIII, XI, X, and XI:



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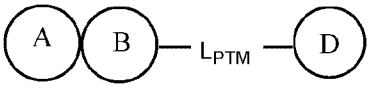

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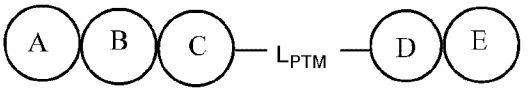

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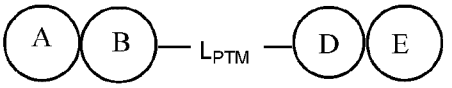

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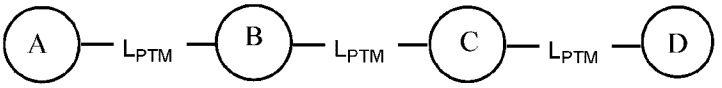

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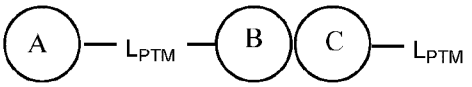

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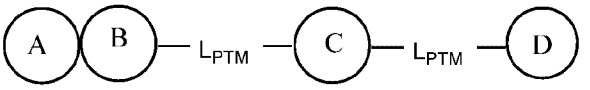

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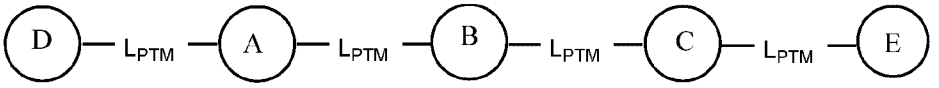

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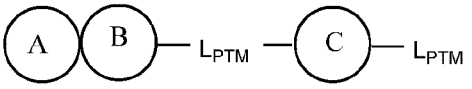

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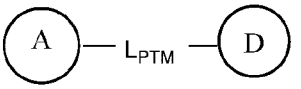

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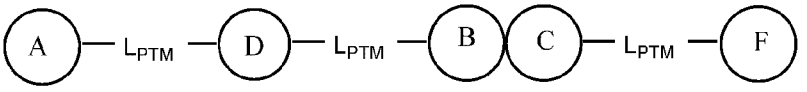

XI

,

wherein:

A, B, C, D, E, and F are each independently selected from an optionally substituted 5- or 6-membered aryl or heteroaryl ring, an optionally substituted 4- to 7-membered cycloalkyl or a heterocycloalkyl, where contact between circles indicates ring fusion; and

L_{PTM} is selected from a bond, an alkyl, an alkenyl or an alkynyl, optionally interrupted by one or more rings (i.e., cycloalkyl, heterocycloalkyl, aryl or heteroaryl), or one or more functional groups which could include -O-, -S-, -NR^1_{PTM}- (where R^1_{PTM} is selected from H or alkyl), -N=N-, -S(O)-, -SO_2-, -C(O)-, -NHC(O)-, -C(O)NH-, -$NHSO_2$-, -NHC(O)NH-, -NHC(O)O-, -OC(O)NH-, wherein the said functional group can be optionally located at either end of the linker (i.e., directly adjacent to the A, B, C, D, E, or F rings).

[0023] The above mentioned aryl and heteroaryl rings can be optionally substituted with 1–3 substituents each independently selected from alkyl, alkenyl, haloalkyl, halogen, hydroxyl, alkoxy, fluoroalkoxy, amino, alkylamino, dialkylamino, acylamino, trifluomethyl, and cyano, wherein the said alkyl and alkenyl groups can be further substituted.

[0024] In any aspect or embodiment described herein, at least one of A, B, C, F, or a combination thereof is selected from optionally substituted 5- or 6-membered aryl or heteroaryl rings.

[0025] In certain embodiments of the current disclosure, the PTM is represented by Formula I and/or II, where A, B and C are 5- or 6- membered fused aryl or heteroaryl rings, L_{PTM} is selected from a bond or an alkyl, and D is selected from a 6-membered aryl, heteroaryl or heterocycloalkyl, wherein A, B, C and D are optionally substituted with alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, trifluoromethyl, or cyano.

[0026] In other embodiments, the PTM is represented by Formula III and/or IV, wherein A, B and C are 5- or 6- membered fused aryl or heteroaryl rings, L_{PTM} is selected from a bond or an alkyl, and D and E are 5- or 6-membered fused aryl or heteroaryl rings, and wherein A, B, C, D and E are optionally substituted with alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, trifluoromethyl, or cyano.

[0027] In certain other embodiments of the current disclosure, the PTM isrepresented by Formula I, wherein A is a phenyl or a 6-membered heteroaryl ring, B is a 5-membered heteroaryl ring, C is a phenyl or a 6-membered heteroaryl ring, L_{PTM} is a bond, and D is a 6-membered heteroaryl or a 6-membered heterocycloalkyl ring, wherein each A, B, C and D is optionally independently substituted with alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, dialkylamino, trifluoromethyl, or cyano, with the proviso that a nitrogen atom of any of the A, B, C and D rings is not directly connected to a heteroatom or to a carbon atom of the L_{PTM}, to which another heteroatom is directly attached.

[0028] It will be understood that the general structures are exemplary and the respective moieties can be arranged spatially in any desired order, number or configuration.

[0029] In further embodiments, the description provides a bifunctional compound having a structure selected from the group consisting of Compounds 1-330 (e.g.., a compound selected from Tables 1 and 2), a salt, a polymorph, and a prodrug thereof.

[0030] In further embodiments, the description provides a bifunctional compound having a structure selected from the Table 1 or Table 2 (e.g., a chemical structure selected from Compounds 1-330), a salt, a polymorph, and a prodrug thereof.

[0031] 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 neuronal disease.

[0032] 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.

[0033] In another aspect, the description provides methods of modulating Tau protein, their ubiquitination and the subsequent 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 Tau ubquitination and degradation in the subject.

[0034] In yet another aspect, the description provides methods of treating or ameliorating a symptom of a disease related to TAU 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 TAU activity in the subject. In certain embodiments, the disease to be treated is neurological or neurodegenerative disease, e.g. Alzeimer, Parkinson, Dementia etc.

[0035] In a preferred embodiment, the subject is a human.

[0036] In an additional aspect, the description provides methods for identifying the effects of the degradation of proteins of interest in a biological system using compounds according to the present disclosure.

[0037] 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 disclosure. 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. Additional objects and advantages associated with the compositions, methods, and processes of the present disclosure 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 disclosure 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 disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] The accompanying drawings, which are incorporated into and form a part of the specification, illustrate several embodiments of the present disclosure and, together with the description, serve to explain the principles of the disclosure. The drawings are only for the purpose of illustrating an embodiment of the disclosure and are not to be construed as limiting the disclosure. Further objects, features and advantages of the disclosure will become apparent from the following detailed description taken in conjunction with the accompanying figures showing illustrative embodiments of the disclosure, in which:

[0039] **Figure 1** shows total tau levels in hippocampal homogenates. Data are displayed as scattered dot blot. Statistically significant differences between the test item (TI) treated groups versus the vehicle control group according to One-way ANOVA followed by Dunneett's Multiple Comparison Test are indicated by asterisk ** $p<0.01$, * $p<0.05$.

DETAILED DESCRIPTION

Date Reçue/Date Received 2021-01-27

[0040] The following is a detailed description provided to aid those skilled in the art in practicing the present disclosure. 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.

[0041] The present description relates to the surprising and unexpected discovery that an E3 ubiquitin ligase protein can ubiquitinate a target protein once the E3 ubiquitin ligase protein and the target protein are brought into proximity by a chimeric construct (e.g., PROTAC) as described herein, which binds the E3 ubiquitin ligase protein (e.g., VHL and cereblon) and the target protein e.g., TAU. Accordingly, the present description provides compounds, compositions comprising the same and associated methods of use for ubiquitination and degradation of a chosen target protein.

[0042] The following terms are used to describe the present disclosure. 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 disclosure.

[0043] 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 disclosure. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges is also encompassed within the disclosure, 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 disclosure.

[0044] 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.

[0045] 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

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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.

[0046] 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."

[0047] 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.

[0048] 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.

[0049] 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.

[0050] 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 stereoisomers (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. It is understood by those of ordinary skill that molecules which are described herein are stable compounds as generally described hereunder.

[0051] When the bond is shown, both a double bond and single bond are represented within the context of the compound shown.

[0052] The term "patient" or "subject" is used throughout the specification to describe an animal, preferably a human or a domesticated animal, to whom treatment, including prophylactic treatment, with the compositions according to the present disclosure 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 disclosure, the term patient refers to a human patient unless otherwise stated or implied from the context of the use of the term.

[0053] The term "effective" is used to describe an amount of a compound, composition or component which, when used within the context of its intended use, effects an intended result. The

term effective subsumes all other effective amount or effective concentration terms, which are otherwise described or used in the present application.

[0054] 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. For example, cereblon is an E3 Ubiquitin Ligase 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.

[0055] The term "protein target moiety" or PTM is used to describe a small molecule which binds to a target protein or other protein or polypeptide of interest and places/presents that protein or polypeptide in proximity to an ubiquitin ligase such that degradation of the protein or polypeptide by ubiquitin ligase may occur. Non-limiting examples of small molecule target protein binding moieties include compounds targeting Tau protein.

[0056] The term "target protein" is used to describe a protein or polypeptide, which is a target for binding to a compound according to the present disclosure and degradation by ubiquitin ligase hereunder. Such small molecule target protein binding moieties also include pharmaceutically acceptable salts, enantiomers, solvates and polymorphs of these compositions, as well as other small molecules that may target a protein of interest. These binding moieties are linked to ULM groups through linker groups L.

[0057] Tau protein target may be used in screens that identify compound moieties which bind to the protein and by incorporation of the moiety into compounds according to the present disclosure, the level of activity of the protein may be altered for therapeutic end result.

[0058] The term "disease state or condition" is used to describe any disease state or condition wherein protein dysregulation (i.e., the amount of protein expressed in a patient is elevated) occurs and where degradation of Tau protein in a patient may provide beneficial therapy or relief of symptoms to a patient in need thereof. In certain instances, the disease state or condition may be cured.

[0059] Disease states or conditions which may be treated using compounds according to the present disclosure include neuronal disease, for example, neurodegeneration, Huntington's disease and muscular dystrophy, Parkinson's disease, Alzheimer's disease, Batten disease, Injuries to the spinal cord and brain, Seizure disorders, epilepsy, brain tumors, meningitis, autoimmune diseases such as multiple sclerosis, Neurofibromatosis, Depression, Amyotrophic Lateral Sclerosis, Arteriovenous Malformation, Brain Aneurysm, Dural Arteriovenous Fistulae, Headache, Memory Disorders, Peripheral Neuropathy, Post-Herpetic Neuralgia, Spinal Cord Tumor, Stroke.

[0060] The term "neurological disorder" or "neurological disorders", as used herein, refers to any disorder, disease, and/or syndrome due to or resulting from neurologic, psychiatric, psychological, and/or cerebrovascular symptomology or origin. The term "neurological disorder" or "neurological disorders", as used herein, also refers to diseases, disorder or condition of the brain and nervous system or psychiatric disorders or conditions. Neurological disorders include, but are not limited to Absence of the Septum Pellucidum, Acquired Epileptiform Aphasia, Acute Disseminated Encephalomyelitis, ADHD, Adie's Pupil, Adie's Syndrome, Adrenoleukodystrophy, Agenesis of the Corpus Callosum, Agnosia, Aicardi Syndrome, AIDS—Neurological Complications, Alexander Disease, Alpers' Disease, Alternating Hemiplegia, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Anencephaly, Aneurysm, Angelman Syndrome, Angiomatosis, Anoxia, Aphasia, Apraxia, Arachnoid Cysts, Arachnoiditis, Arnold-Chiari Malformation, Arteriovenous Malformation, Asperger Syndrome, Ataxia, Ataxia, Telangiectasia, Ataxias and Cerebellar/Spinocerebellar Degeneration, Attention Deficit-Hyperactivity Disorder, Autism, Autonomic Dysfunction, Back Pain, Barth Syndrome Batten Disease, Becker's Myotonia, Behcet's Disease, Bell's Palsy, Benign Essential Blepharospasm, Benign Focal Amyotrophy, Benign Intracranial Hypertension, Bernhardt-Roth Syndrome, Binswanger's Disease, Blepharospasm, Bloch-Sulzberger Syndrome, Brachial Plexus Birth Injuries, Brachial Plexus Injuries, Bradbury-Eggleston Syndrome, Brain and Spinal Tumors, Brain Aneurysm, Brain Injury, Brown-Sequard Syndrome, Bulbospinal Muscular Atrophy, Canavan Disease, Carpal Tunnel Syndrome Causalgia, Cavernomas, Cavernous Angioma, Cavernous Malformation, Central Cervical Cord Syndrome,

Central Cord Syndrome, Central Pain Syndrome, Cephalic Disorders, Cerebellar Degeneration, Cerebellar Hypoplasia, Cerebral Aneurysm, Cerebral Arteriosclerosis, Cerebral Atrophy, Cerebral Beriberi, Cerebral Gigantism, Cerebral Hypoxia, Cerebral Patsy, Cerebro-Oculo-Facio-Skeletal Syndrome, Charcot-Marie-Tooth Disease, Chiari Malformation, Chorea, Choreoacanthocytosis, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Chronic Orthostatic Intolerance, Chronic Pain Cockayne Syndrome Type II, Coffin Lowry Syndrome, COFS, Colpocephaly, Coma and Persistent Vegetative State, Complex Regional Pain Syndrome, Congenital Facial Diplegia, Congenital Myasthenia, Congenital Myopathy, Congenital Vascular Cavernous, Malformations, Corticobasal Degeneration, Cranial Arteritis, Craniosynostosis, Creutzfeldt-Jakob Disease, Cumulative Trauma Disorders, Cushing's Syndrome, Cytomegalic Inclusion Body Disease, Cytomegalovirus Infection, Dancing Eyes-Dancing Feet Syndrome, Dandy-Walker Syndrome, Dawson Disease, De Morsier's Syndrome, Deep Brain Stimulation for Parkinson's Disease, Dejerine-Klumpke Palsy, Dementia, Dementia—Multi-Infarct, Dementia—Semantic, Dementia—Subcortical, Dementia With Lewy Bodies, Dentate Cerebellar Ataxia, Dentatorubral Atrophy, Dermatomyositis, Developmental Dyspraxia, Devic's Syndrome, Diabetic Neuropathy, Diffuse Sclerosis, Dysautonomia, Dysgraphia, Dyslexia, Dysphagia, Dyspraxia, Dyssynergia Cerebellaris, Myoclonica, Dyssynergia Cerebellaris Progressiva, Dystonias, Early Infantile Epileptic, Encephalopathy, Empty Sella Syndrome, Encephalitis Lethargica, Encephaloceles, Encephalopathy, Encephalotrigeminal Angiomatosis, Epilepsy, Erb-Duchenne and Dejerine-Klumpke Palsies, Erb's Palsy, Fabry's Disease, Fahr's Syndrome, Fainting, Familial Dysautonomia, Familial Hemangioma, Familial Idiopathic Basal Ganglia, Calcification, Familial Periodic Paralyses, Familial Spastic Paralysis, Febrile Seizures, Fisher Syndrome, Floppy Infant Syndrome, Friedreich's Ataxia, Frontotemporal, Dementia, Gaucher's Disease, Gerstmann's Syndrome, Gerstmann-Straussler-Scheinker, Disease, Giant Cell Arteritis, Giant Cell Inclusion Disease, Globoid Cell Leukodystrophy, Glossopharyngeal Neuralgia, Guillain-Barre Syndrome, Hallervorden-Spatz Disease, Head Injury, Headache, Hemicrania Continua, Hemifacial Spasm, Hemiplegia Alterans, Hereditary Neuropathies, Hereditary Spastic Paraplegia, Heredopathia Atactica Polyneuritiformis, Herpes Zoster, Herpes Zoster Oticus, Hirayama Syndrome, Holmes-Adie syndrome, Holoprosencephaly, HTLV-1 Associated, Myelopathy, Huntington's Disease, Hydranencephaly, Hydrocephalus, Hydrocephalus—Normal Pressure, Hydromyelia, Hyperactivity, Hypercortisolism, Hypersomnia, Hypertonia, Hypotonia,—Infantile, Hypoxia, Immune-Mediated Encephalomyelitis, Inclusion Body Myositis, Incontinentia Pigmenti, Infantile Hypotonia, Infantile

Neuroaxonal Dystrophy, Infantile Phytanic Acid Storage Disease, Infantile Refsum Disease, Infantile Spasms, Inflammatory Myopathy, Iniencephaly, Intestinal Lipodystrophy, Intracranial Cysts, Intracranial Hypertension, Isaac's Syndrome, Joubert Syndrome, Kearns-Sayre Syndrome, Kennedy's Disease, Kinsbourne syndrome, Kleine-Levin Syndrome, Klippel-Feil Syndrome, Klippel-Trenaunay Syndrome (KTS), Klüver-Bucy Syndrome, Korsakoff's Amnesic Syndrome, Krabbe Disease, Kugelberg-Welander Disease, Kuru, Lambert-Eaton Myasthenic Syndrome, Landau-Kleffner Syndrome, Lateral Femoral, Cutaneous Nerve Entrapment, Lateral Medullary Syndrome, Learning Disabilities, Leigh's Disease, Lennox-Gastaut Syndrome, Lesch-Nyhan Syndrome, Leukodystrophy, Levine-Critchley Syndrome, Lewy Body Dementia, Lipid Storage Diseases, Lissencephaly, Locked-In Syndrome, Lou Gehrig's Disease, Lupus—Neurological, Sequelae, Lyme Disease—Neurological Complications, Machado-Joseph Disease, Macrencephaly, Mania, Megalencephaly, Melkersson-Rosenthal Syndrome, Meningitis, Meningitis and Encephalitis, Menkes Disease, Meralgia Paresthetica, Metachromatic, Leukodystrophy, Microcephaly, Migraine, Miller Fisher Syndrome, Mini-Strokes, Mitochondrial Myopathies, Mobius Syndrome, Monomelic Amyotrophy, Motor Neuron Diseases, Moyamoya Disease, Mucolipidoses, Mucopolysaccharidoses, Multifocal Motor Neuropathy, Multi-Infarct Dementia, Multiple Sclerosis, Multiple System Atrophy, Multiple System Atrophy with Orthostatic Hypotension, Muscular Dystrophy, Myasthenia—Congenital, Myasthenia Gravis, Myelinoclastic Diffuse Sclerosis, Myoclonic Encephalopathy of Infants, Myoclonus, Myopathy, Myopathy—Congenital, Myopathy-Thyrotoxic, Myotonia, Myotonia Congenita, Narcolepsy, Neuroacanthocytosis, Neurodegeneration with Brain Iron Accumulation, Neurofibromatosis, Neuroleptic Malignant Syndrome, Neurological Complications of AIDS, Neurological Complications Of Lyme Disease, Neurological Consequences of Cytomegalovirus Infection, Neurological Manifestations of Pompe Disease, Neurological Sequelae Of Lupus, Neuromyelitis Optica, Neuromyotonia, Neuronal Ceroid, Lipofuscinosis, Neuronal Migration Disorders, Neuropathy—Hereditary, Neurosarcoidosis, Neurotoxicity, Nevus Cavernosus, Niemann-Pick Disease, Normal Pressure Hydrocephalus, Occipital Neuralgia, Obesity, Occult Spinal Dysraphism Sequence, Ohtahara Syndrome, Olivopontocerebellar Atrophy, Opsoclonus Myoclonus, Orthostatic Hypotension, O'Sullivan-McLeod Syndrome, Overuse Syndrome, Pain—Chronic, Paine, Pantothenate Kinase-Associated Neurodegeneration, Paraneoplastic Syndromes, Paresthesia, Parkinson's Disease, Paroxysmal Choreoathetosis, Paroxysmal Hemicrania, Parry-Romberg, Pelizaeus-Merzbacher Disease, Pena Shokeir II Syndrome, Perineural Cysts, Periodic Paralyses,

Peripheral Neuropathy, Periventricular Leukomalacia, Persistent Vegetative State, Pervasive Developmental Disorders, Phytanic Acid Storage Disease, Pick's Disease, Pinched Nerve, Piriformis Syndrome, Pituitary Tumors, Polymyositis, Pompe Disease, Porencephaly, Postherpetic Neuralgia, Postinfectious Encephalomyelitis, Post-Polio Syndrome, Postural Hypotension, Postural Orthostatic, Tachycardia Syndrome, Postural Tachycardia Syndrome, Primary Dentatum Atrophy, Primary Lateral Sclerosis, Primary Progressive Aphasia, Prion Diseases, Progressive Hemifacial Atrophy, Progressive Locomotor Ataxia, Progressive Multifocal, Leukoencephalopathy, Progressive Sclerosing Poliodystrophy, Progressive Supranuclear, Palsy, Prosopagnosia, Pseudotumor Cerebri, Ramsay Hunt Syndrome I (formerly known as), Ramsay Hunt Syndrome II (formerly known as), Rasmussen's Encephalitis, Reflex Sympathetic Dystrophy Syndrome, Refsum Disease, Refsum Disease—Infantile, Repetitive Motion Disorders, Repetitive Stress Injuries, Restless Legs Syndrome, Retrovirus-Associated Myelopathy, Rett Syndrome, Reye's Syndrome, Riley-Day Syndrome, Sacral Nerve Root Cysts, Saint Vitus Dance, Salivary Gland Disease, Sandhoff Disease, Schilder's Disease, Schizencephaly, Seitelberger Disease, Seizure Disorder, Semantic Dementia, Septo-Optic Dysplasia, Shaken Baby Syndrome, Shingles Shy-Drager Syndrome, Sjogren's Syndrome, Sleep Apnea, Sleeping Sickness, Sotos Syndrome, Spasticity, Spina Bifida, Spinal Cord Infarction, Spinal Cord Injury, Spinal Cord Tumors, Spinal Muscular Atrophy, Spinocerebellar Atrophy, Spinocerebellar, Degeneration, Steele-Richardson-Olszewski Syndrome, Stiff-Person Syndrome, Striatonigral Degeneration, Stroke, Sturge-Weber Syndrome, Subacute Sclerosing Panencephalitis, Subcortical Arteriosclerotic Encephalopathy, SUNCT Headache Swallowing Disorders, Sydenham Chorea, Syncope, Syphilitic Spinal Sclerosis, Syringohydromyelia, Syringomyelia, Systemic Lupus Erythematosus, Tabes Dorsalis Tardive Dyskinesia, Tarlov Cysts, Tay-Sachs Disease, Temporal Arteritis, Tethered Spinal Cord Syndrome, Thomsen's Myotonia, Thoracic Outlet Syndrome, Thyrotoxic Myopathy, Tic Douloureux, Todd's Paralysis, Tourette Syndrome, Transient Ischemic Attack, Transmissible Spongiform Encephalopathies, Transverse Myelitis, Traumatic Brain Injury, Tremor, Trigeminal Neuralgia, Tropical Spastic Paraparesis, Tuberous Sclerosis, Vascular Erectile Tumor, Vasculitis including Temporal Arteritis, Von Economo's Disease, Von Hippel-Lindau Disease (VHL), Von Recklinghausen's Disease, Wallenberg's Syndrome, Werdnig-Hoffman Disease, Wernicke-Korsakoff Syndrome, West Syndrome, Whiplash, Whipple's Disease, Williams Syndrome, Wilson's Disease, X-Linked Spinal and Bulbar Muscular Atrophy, or Zellweger Syndrome.

[0061] The term "bioactive agent" is used to describe an agent, other than a compound according to the present disclosure, which is used in combination with the compounds of the present disclosure 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.

[0062] 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 disclosure.

[0063] The term "pharmaceutically acceptable derivative" is used throughout the specification to describe any pharmaceutically acceptable prodrug form (such as an ester, amide other prodrug group), which, upon administration to a patient, provides directly or indirectly the present compound or an active metabolite of the present compound.

[0064] The term "independently" is used herein to indicate that the variable, which is independently applied, varies independently from application to application.

[0065] 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.

[0066] 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.

[0067] The term "lower alkyl" means the alkyl groups with no more than six carbon atoms.

[0068] 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 disclosure 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 disclosure 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 heteroaryl 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 disclosure, a moiety in a molecule may be optionally substituted with up to five substituents, preferably up to three substituents. Most often, in the present disclosure moieties which are substituted are substituted with one or two substituents.

[0069] 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.

[0070] 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 disclosure 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.

[0071] 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 heteroaryl groups are described hereinabove. Exemplary non-aromatic heterocyclic groups for use in the present disclosure include, for example, pyrrolidinyl, pyrrolinyl, piperidinyl, piperazinyl, N-methylpiperazinyl, pyrazolidinyl, imidazolidinyl, morpholinyl, tetrahydropyranyl, azetidinyl, oxetanyl, oxathiolanyl, pyridone, 2-pyrrolidone, ethyleneurea, 1,3-dioxolane, 1,3-dioxane, 1,4-dioxane, phthalimide and succinimide, among others, as described herein.

[0072] The term "co-administration" 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 disclosure 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 co-administered compounds or compositions are found in the subject at a given time. In certain preferred aspects of the present disclosure, 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 aspects of the disclosure, the co-administration of compounds results in synergistic therapeutic, including anticancer therapy

[0073] The present disclosure describes bifunctional compounds which function to recruit endogenous proteins to an E3 ubiquitin ligase for 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 of Tau proteins. An advantage of the compounds provided herein is that a broad range of pharmacological activities is possible, consistent with the degradation/inhibition of Tau protein.

[0074] As such, the present disclosure provides such compounds and compositions comprising an E3 ubiquitin ligase targeing moiety ("ULM") coupled to a Tau protein target binding moiety ("PTM"), which result in the ubiquitination of Tau protein, which leads to degradation (and/or inhibition) of the Tau protein. The present disclosure also provides a library of compositions and the use thereof.

[0075] The present description provides compounds which comprise a ligand, e.g., a small molecule ligand (i.e., having a molecular weight of below 2,000, 1,000, 500, or 200 Daltons),

which is capable of binding to a ubiquitin ligase, such as VHL or cereblon. The compounds also comprise a moiety that is capable of binding to target protein, in such a way that the target protein is placed in proximity to the ubiquitin ligase to effect degradation (and/or inhibition) of that protein. Small molecule can mean, in addition to the above, that the molecule is non-peptidyl, that is, it is not generally considered a peptide, e.g., comprises fewer than 4, 3, or 2 amino acids. In accordance with the present description, the PTM, ULM or PROTAC molecule can be a small molecule.

[0076] In one embodiment, the description provides a composition useful for regulating protein activity. The composition comprises a ubiquitin pathway protein binding moiety (preferably for VHL or cereblon) according to a defined chemical structure and a Tau protein targeting moiety which are linked together, preferably through a linker, wherein the ubiquitin pathway protein binding moiety recognizes a ubiquitin pathway protein and the targeting moiety recognizes Tau target protein and wherein the ubiquitin pathway protein binding moiety is coupled to the Tau targeting moiety.

[0077] In another embodiment, the present disclosure provides a library of compounds. The library comprises more than one compound wherein each composition has a ubiquitin pathway protein binding moiety (preferably, VHL or cereblon) and a Tau protein binding moiety, wherein ULM is coupled (preferably, through a linker moiety) to Tau, and wherein the ubiquitin pathway protein binding moiety recognizes an ubiquitin pathway protein, in particular, an E3 ubiquitin ligase.

[0078] In another embodiment, the present disclosure provides a method of ubiquitinating/degrading a target protein (e.g. Tau) in a cell. The method comprises administering a bifunctional composition comprising an ubiquitin pathway protein binding moiety and a targeting moiety, preferably linked through a linker moiety, as otherwise described herein, wherein the ubiquitin pathway protein binding moiety is coupled to the targeting moiety and wherein the ubiquitin pathway protein binding moiety recognizes a ubiquitin pathway protein (e.g., VHL, cereblon) and the targeting moiety recognizes the target protein (e.g., Tau) such that degradation of the target protein will occur when the target protein is placed in proximity to the ubiquitin ligase, thus resulting in degradation/inhibition of the effects of the target protein and the control of protein levels. The control of protein levels afforded by the present disclosure provides treatment of a disease state or condition, which is modulated through the target protein by lowering the level of that protein in the cells of a patient.

[0079] In yet another embodiment, the present disclosure is directed to a method of treating a patient in need for a disease state or condition modulated through a protein (e.g., Tau) where the degradation of that protein will produce a therapeutic effect in that patient, the method comprising administering to a patient in need an effective amount of a compound according to the present disclosure, optionally in combination with another bioactive agent. The disease state or condition may be a disease caused by a microbial agent or other exogenous agent such as a virus, bacteria, fungus, protozoa or other microbe or may be a disease state, which is caused by overexpression of a protein i.e. accumulation or aggregation of Tau protein, which leads to a disease state and/or condition.

[0080] In one aspect, the present disclosure provides compounds useful for regulating protein activity. The composition comprises an E3 ubiquitin ligase, a ubiquitin pathway protein binding moiety, and a protein targeting moiety which are linked or coupled together, preferably through a linker, wherein the ubiquitin pathway protein binding moiety recognizes a ubiquitin pathway protein and the targeting moiety recognizes a target protein (e.g., Tau). Such compounds may be referred to herein as PROTAC compounds or PROTACs with the following general chemical structure:

ULM—L—PTM,

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, solvate, polymorph or prodrug thereof,

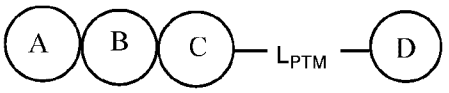
wherein ULM is a small molecule E3 ubiquitin ligase binding moiety that binds an E3 ubiquitin ligase;

PTM is a small molecule comprising a Tau protein targeting moiety that degrades the Tau protein; and

L is a bond or a chemical linking moiety connecting ULM and PTM.

[0081] In certain embodiments, the E3 ubiquitin ligase binding moiety targets a member of the group consisting of Von Hippel-Lindau (VLM), cereblon (CLM), mouse double-minute homolog2 (MLM), and IAP (ILM).

[0082] In one aspect, the description provides Tau protein binding moieties (PTM). In certain embodiments, PTM is represented by Formula I, Formula II, Formula III, Formula IV, Formula V, Formula VI, Formula, VII, Formula, VIII, Formula IX, Formula X, or Formula XI:



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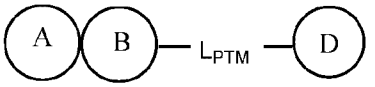

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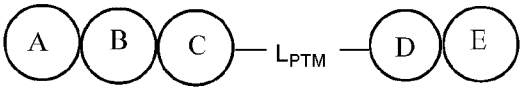

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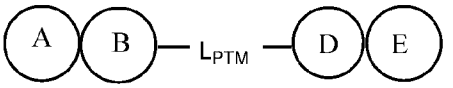

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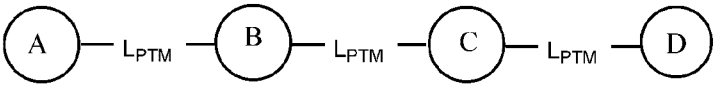

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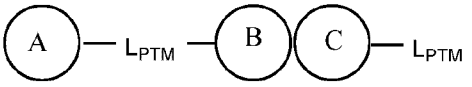

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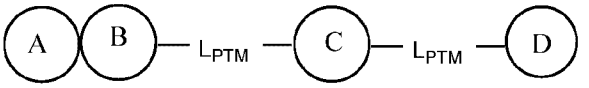

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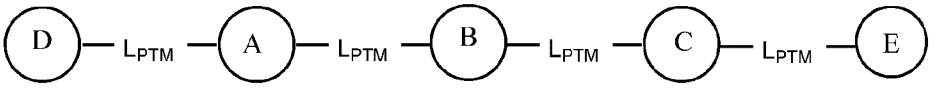

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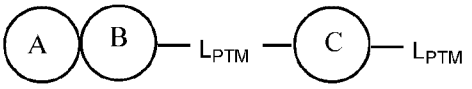

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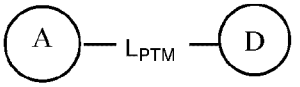

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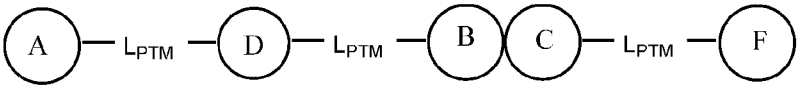

XI

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wherein:

A, B, C, D, E, and F are independently selected from an optionally substituted 5- or 6-membered aryl or heteroaryl ring, an optionally substituted 4- to 7-membered cycloalkyl or a heterocycloalkyl, where contact between circles indicates ring fusion; and

L_{PTM} is selected from a bond, an alkyl, an alkenyl or an alkynyl, optionally interrupted by one or more rings (i.e., cycloalkyl, heterocycloalkyl, aryl or heteroaryl), or one or more functional groups selected from the groups -O-, -S-, -NR^1_{PTM}- (where R^1_{PTM} is selected from H or alkyl), -N=N-, -S(O)-, -SO_2-, -C(O)-, -NHC(O)-, -C(O)NH-, -$NHSO_2$-, -NHC(O)NH-, -NHC(O)O-, or -OC(O)NH-, wherein the said functional group are optionally located at either end of the linker.

[0083] In certain embodiments, aryl and heteroaryl rings of A, B, C, D, E, and F of PTM are optionally substituted with 1–3 substituents each independently selected from alkyl, alkenyl, haloalkyl, halogen, hydroxyl, alkoxy, fluoroalkoxy, amino, alkylamino, dialkylamino, acylamino, trifluoromethyl, and cyano, wherein the said alkyl and alkenyl groups are further optionally substituted.

[0084] In certain embodiments, the rings of at least one of A, B, C, F, or a combination thereof is selected from optionally substituted 5- or 6-membered aryl or heteroaryl rings;

[0085] In certain embodiments, the PTM has the chemical structure of Formula I, wherein:

A, B and C rings are independently 5- or 6- membered fused aryl or heteroaryl rings;

L_{PTM} is selected from a bond or an alkyl, and

D is selected from a 6-membered aryl, heteroaryl or heterocycloalkyl,

wherein A, B, C and D are optionally substituted with alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, alkylamino, dialkylamino or cyano.

[0086] In certain additional embodiments, The PTM has the chemical structure of Formula I, wherein:

A and C are a phenyl or a 6-membered heteroaryl ring;

B is a 5-membered heteroaryl ring;

L_{PTM} is a bond; and

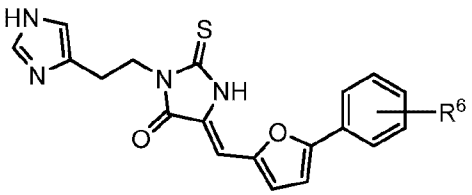
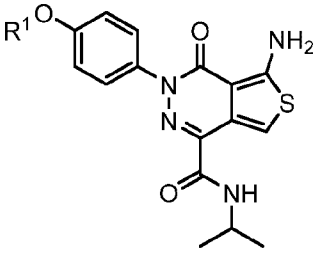
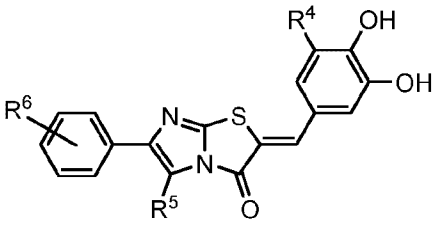
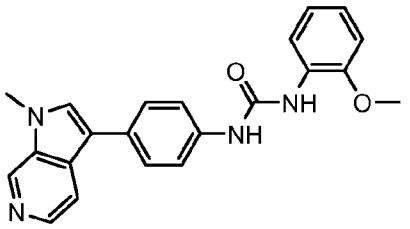
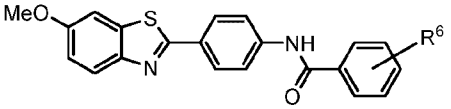
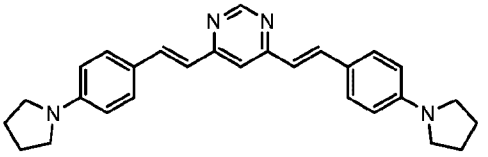
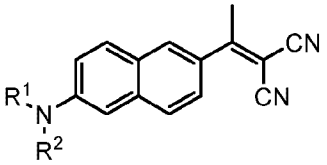
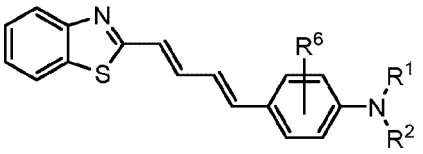
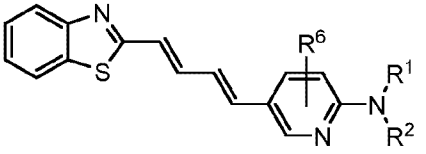
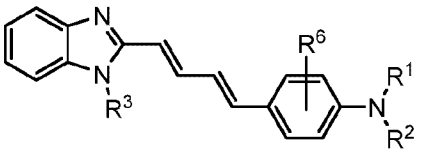
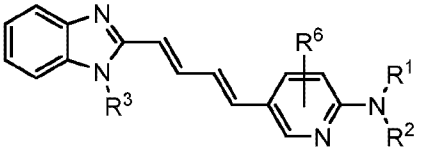
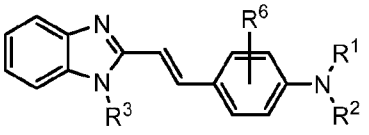
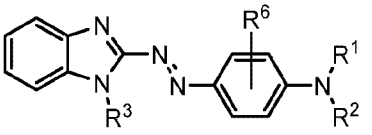
D is a 6-membered heteroaryl or a 6-membered heterocycloalkyl ring;

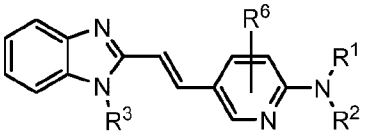
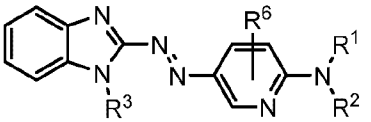
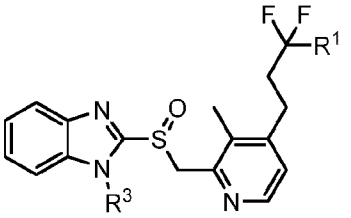
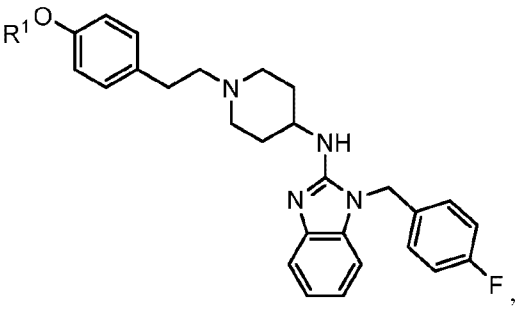
wherein each A, B, C and D is optionally independently substituted with alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, dialkylamino or cyano, and wherein a nitrogen atom of any of the A, B, C and D rings is not directly connected to a heteroatom or to a carbon atom, to which another heteroatom is directly attached.

[0087] In other embodiments, the PTM has the chemical structure of Formula III or IV, wherein A, B and C are 5- or 6- membered fused aryl or heteroaryl rings, L_{PTM} is selected from a bond or an alkyl, and D and E are 5- or 6-membered fused aryl or heteroaryl rings, wherein A, B, C, D and

E are optionally substituted with alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, alkylamino, dialkylamino or cyano.

[0088] In certain embodiments, the PTM is represented by following chemical structure:

wherein:

R^1, R^2 and R^3 are independently selected from H, methyl, ethyl, 2-fluoroethyl and 2,2,2-trifluoroethyl;

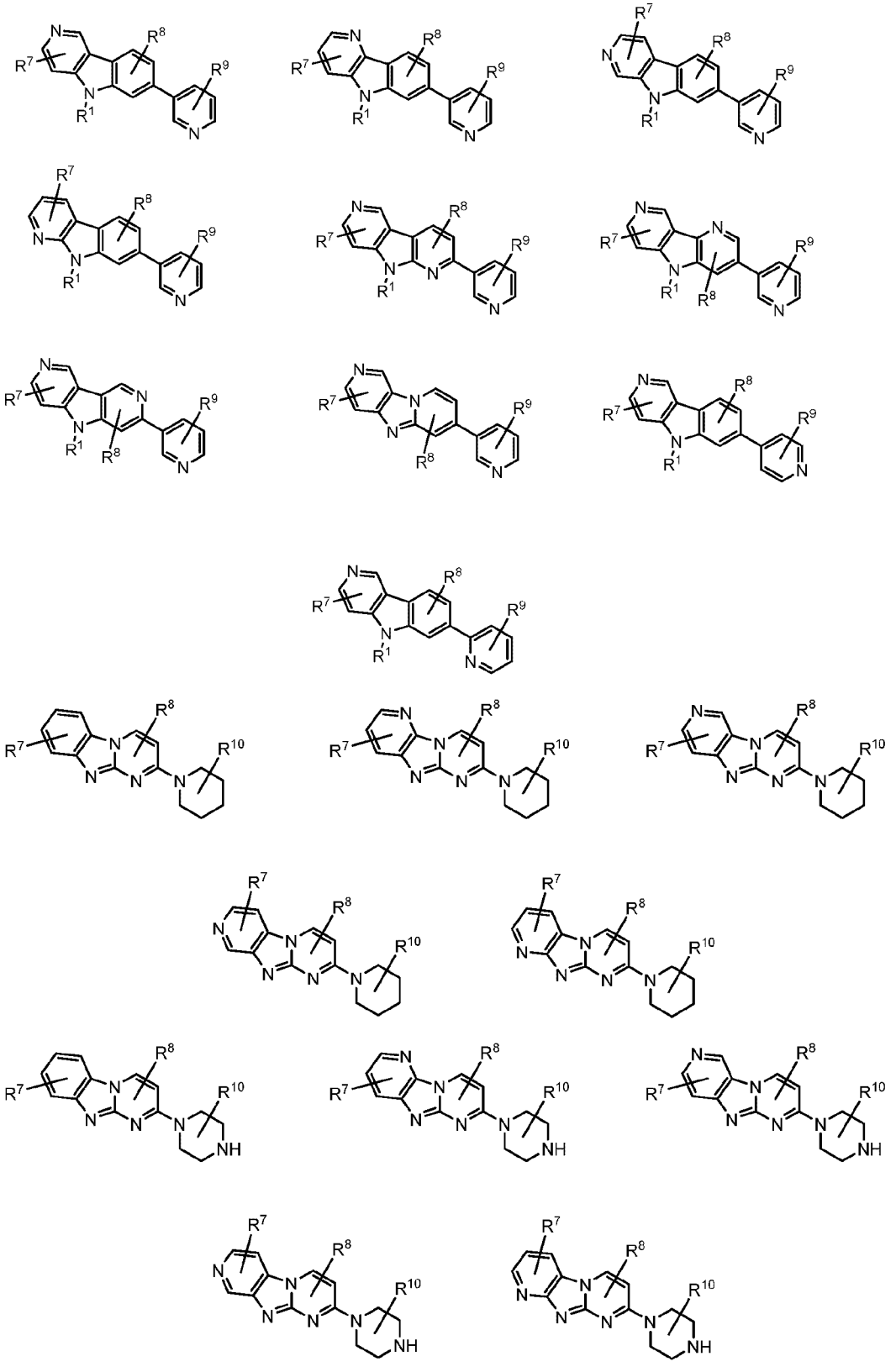
R^4 and R^5 are independently selected from H, methyl, ethyl and halogen; and

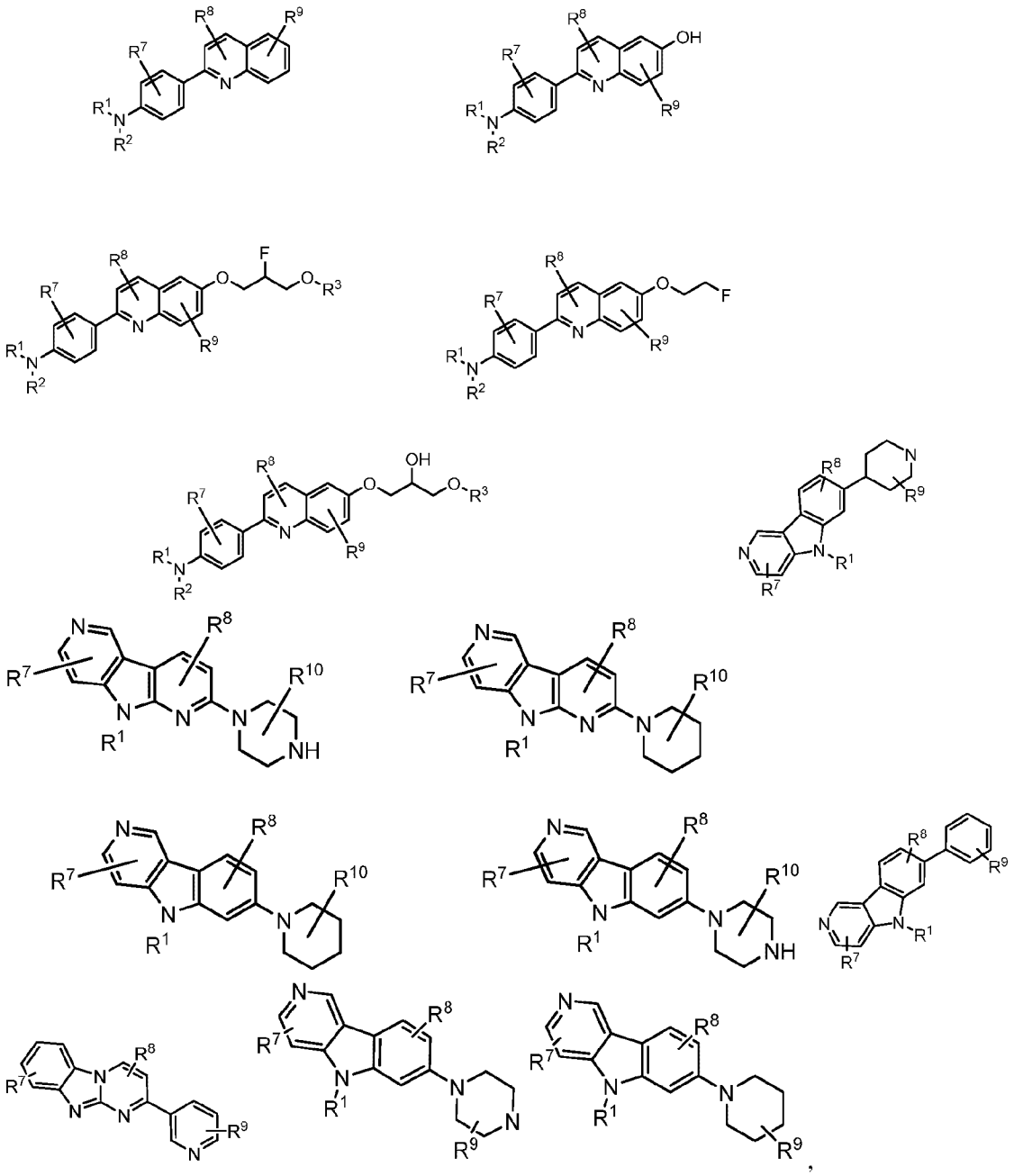
R^6 is 1 to 2 substituents independently selected from H, methyl, ethyl and halogen,

wherein the PTM is coupled to a ULM via L.

[0089] In any of the aspects or embodiments described herein, the PTM is covalently coupled to one or more ULM (VLM or CLM) groups, or a linker to which is attached one or more ULM (VLM or CLM) groups as described herein.

[0090] In certain embodiments, PTM is represented by chemical structure:



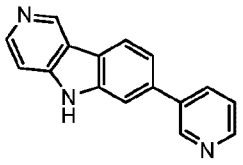
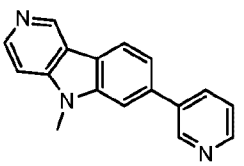
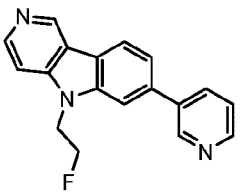
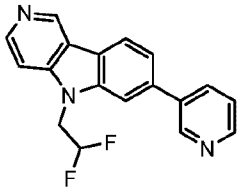
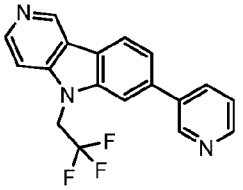
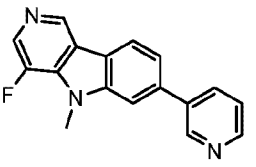
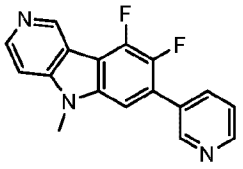
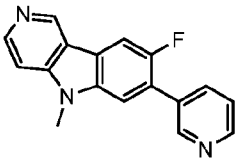
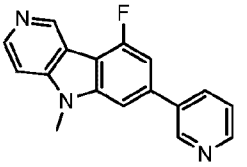
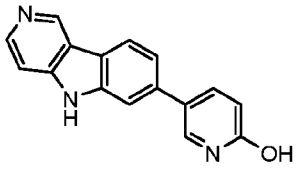
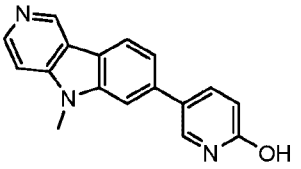
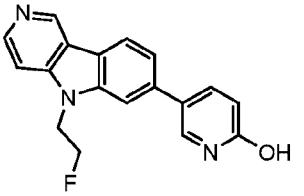
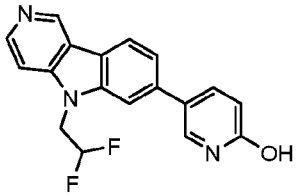
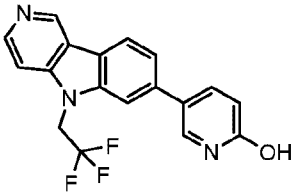
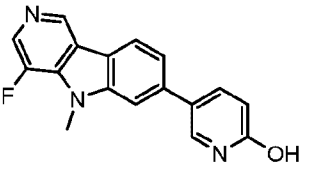
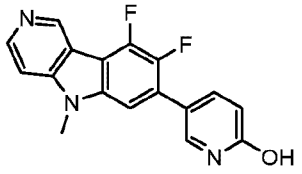
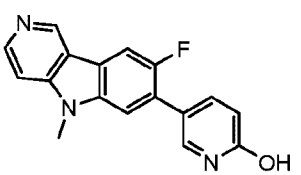
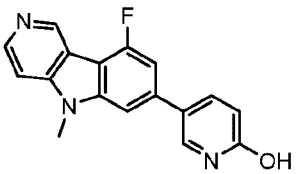


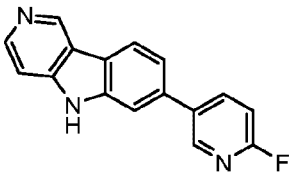
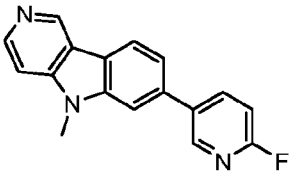
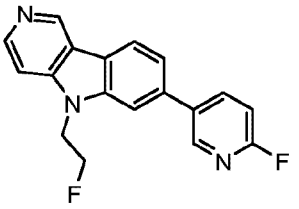
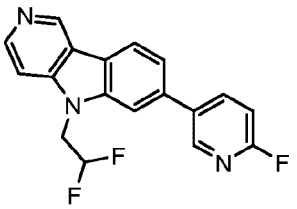
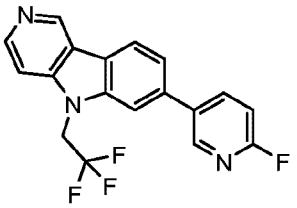
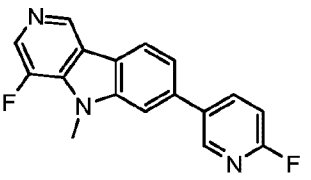
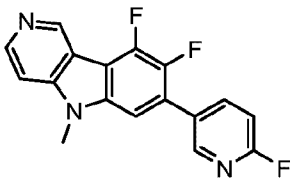
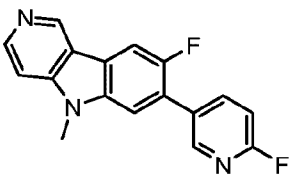
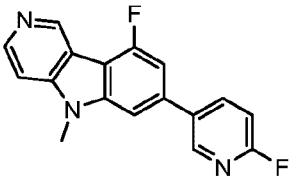
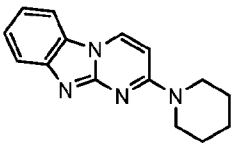
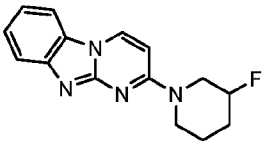
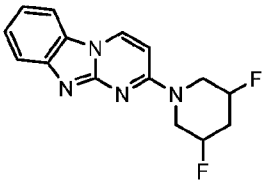
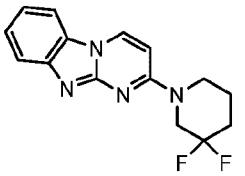
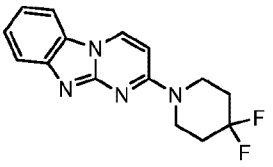
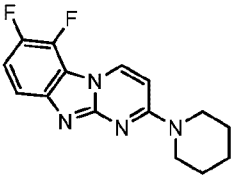
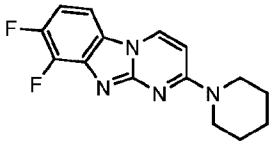
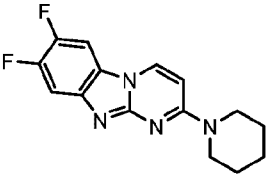
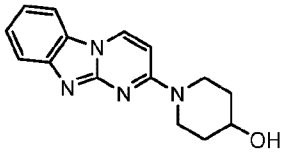
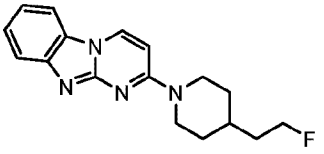
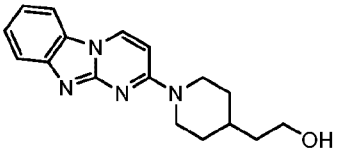
wherein:

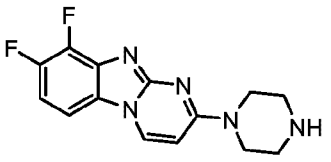
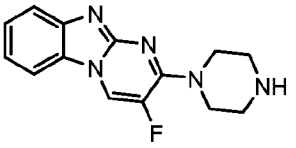
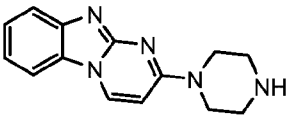
R^1, R^2 and R^3 are independently selected from H, optionally substituted alkyl, methyl, ethyl, 2-fluoroethyl and 2,2,2-trifluoroethyl; and

R^7, R^8 , R^9 and R^{10} are 1 to 8 substituents independently selected from H, optionally substituted alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, dialkylamino, aceylamino, trifluoromethyl or cyano, and wherein the PTM is coupled to a ULM (VLM or CLM) via L.

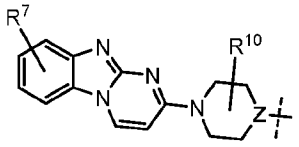
[0091]In certain additional embodiments, PTM is represented by chemical structure:

[0092] In certain embodiments linker attachment point to PTM is as indicated by the dotted line: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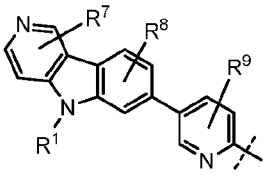
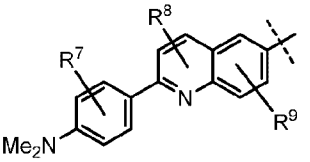
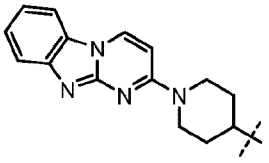
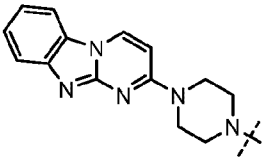
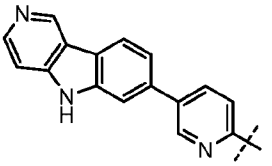
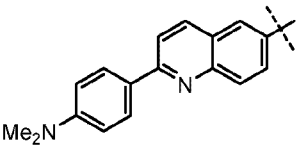
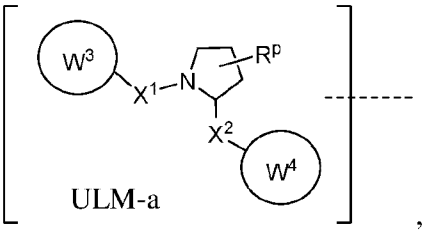







Exemplary VLMs:

[0093] In one aspect ULM is VHL.

[0094] In certain embodiments of the compounds as described herein, ULM is VLM and comprises a chemical structure selected from the group ULM-a:


ULM-a ,

wherein:

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

X^1, X^2 are each independently selected from the group of a bond, O, NR^{Y3}, $CR^{Y3}R^{Y4}$, C=O, C=S, SO, and SO_2;

R^{Y3}, R^{Y4} are each independently selected from the group of H, linear or branched C_{1-6} alkyl, optionally substituted by 1 or more halo, C_{1-6} alkoxyl);

R^P is 1, 2, or 3 groups, each independently selected from the group H, halo, -OH, C_{1-3} alkyl;

W^3 is selected from the group of an optionally substituted –T-$N(R^{1a}R^{1b})$, an optionally substituted –T-$N(R^{1a}R^{1b})X^3$, –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;

X^3 is C=O, R^1 , R^{1a} , R^{1b}

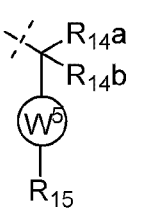
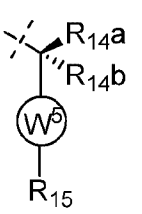
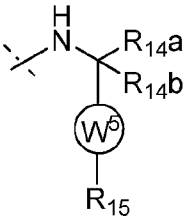
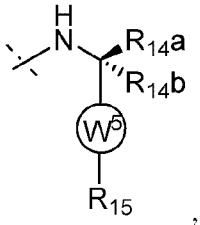
R^1 , R^{1a}, R^{1b} are each independently selected from the group consisting of H, linear or branched C_1-C_6 alkyl group optionally substituted by 1 or more halo or -OH groups, $R^{Y3}C$=O, $R^{Y3}C$=S, $R^{Y3}SO$, $R^{Y3}SO_2$, $N(R^{Y3}R^{Y4})C$=O, $N(R^{Y3}R^{Y4})C$=S, $N(R^{Y3}R^{Y4})SO$, and $N(R^{Y3}R^{Y4})SO_2$;

where T is covalently bonded to X1;

W^4 is an optionally substituted -NR1-T-Aryl, an optionally substituted -NR1-T-Heteroaryl group or an optionally substituted -NR1-T-Heterocycle, where -NR1 is covalently bonded to X2 and R1 is H or CH3, preferably H.

[0095] In any of the embodiments described herein, T is selected from the group of an optionally substituted alkyl, $–(CH_2)_n$- group, wherein each one of the methylene groups is optionally substituted with one or two substituents selected from the group of halogen, methyl, a linear or branched C_1-C_6 alkyl group optionally substituted by 1 or more halogen or -OH groups or an amino acid side chain optionally substituted; and

n is 0 to 6, often 0, 1, 2, or 3, preferably 0 or 1.

[0096] In certain embodiments, W^4 is  ,  ,  or  , wherein $R_{14a,}$ $R_{14b,}$ are each independently selected from the group of H, haloalkyl, or optionally substituted alkyl;

[0097] In any of the aspects or embodiments described herein, W^5 is selected from the group of a phenyl or a 5-10 membered heteroaryl,

R_{15} is selected from the group of 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, or cycloheteroalkyl;

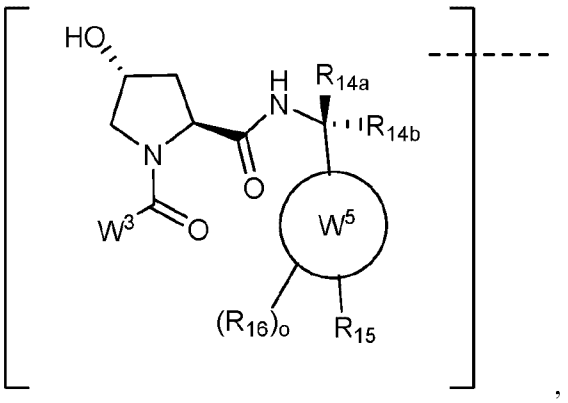
[0098] In additional embodiments, W^4 substituents for use in the present disclosure also include specifically (and without limitation to the specific compound disclosed) the W^4 substituents which are found in the identified compounds disclosed herein. Each of these W^4 substituents may be used in conjunction with any number of W^3 substituents which are also disclosed herein.

[0099] 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, C1-3alkyl.

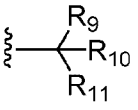
[0100] In any of the embodiments described herein, the W^3, W^4 can independently be covalently coupled to a linker which is attached one or more PTM groups.

and wherein the dashed line indicates the site of attachment of at least one PTM, another ULM (ULM') or a chemical linker moiety coupling at least one PTM or a ULM' or both to ULM.

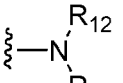
[0101] In certain embodiments, ULM is VHL and is represented by the structure:

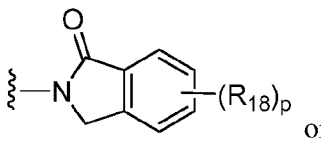
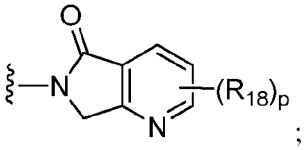


wherein:

W^3 is selected from the group of an optionally substituted aryl, optionally substituted heteroaryl, or  ;

R_9 and R_{10} are 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 selected from the group of an optionally substituted heterocyclic, optionally substituted alkoxy, optionally substituted heteroaryl, optionally substituted aryl,  ,

 or  ;

R_{12} is selected from the group of H or optionally substituted alkyl;

R_{13} is selected from the group of 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}, are each independently selected from the group of H, haloalkyl, or optionally substituted alkyl;

W^5 is selected from the group of a phenyl or a 5-10 membered heteroaryl,

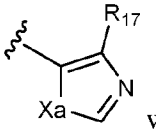
R_{15} is selected from the group of H, halogen, CN, OH, NO_2, N $R_{14a}R_{14b}$, OR_{14a}, $CONR_{14a}R_{14b}$, $NR_{14a}COR_{14b}$, $SO_2NR_{14a}R_{14b}$, NR_{14a} SO_2R_{14b}, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted haloalkoxy; aryl, heteroaryl, cycloalkyl, or cycloheteroalkyl (each independently optionally substituted);

R_{16} is independently selected from the group of H, halo, optionally substituted alkyl, optionally substituted haloalkyl, hydroxy, or optionally substituted haloalkoxy;

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

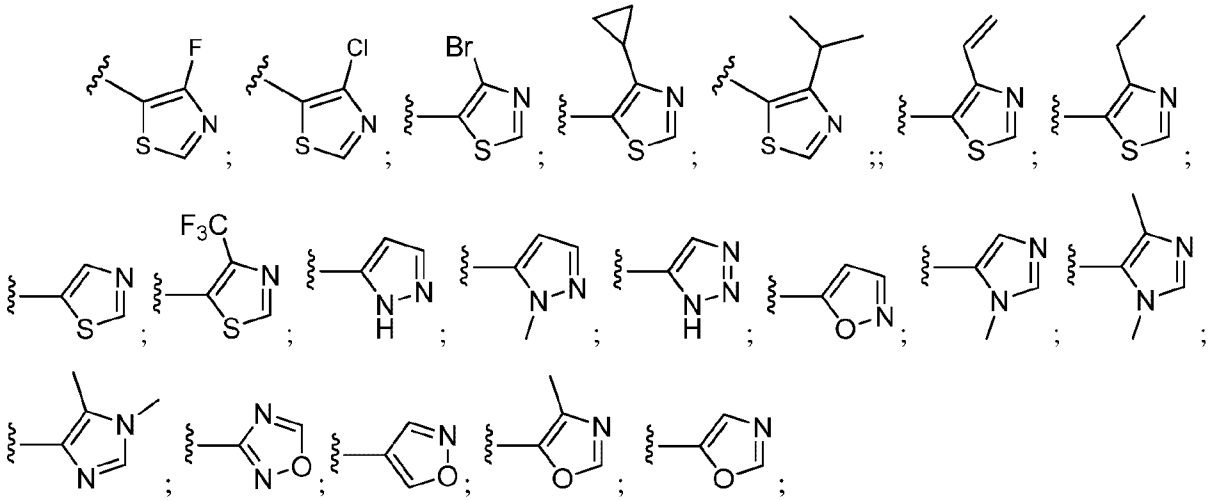
R_{18} is independently selected from the group of halo, optionally substituted alkoxy, cyano, optionally substituted alkyl, haloalkyl, haloalkoxy or a linker; and

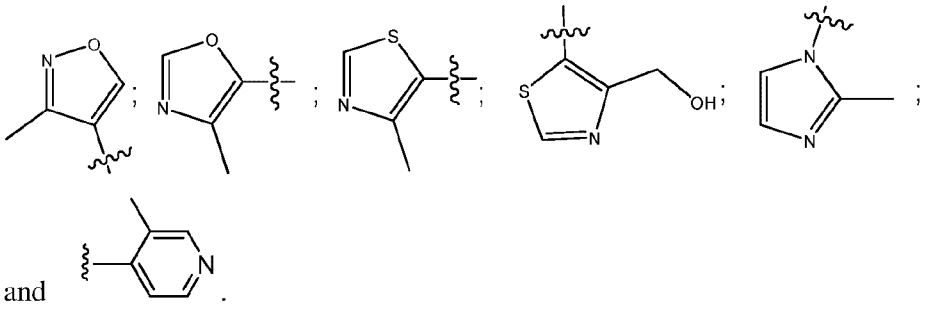
p is 0, 1, 2, 3, or 4, and wherein the dashed line indicates the site of attachment of at least one PTM, another ULM (ULM') or a chemical linker moiety coupling at least one PTM or a ULM' or both to ULM.

[0102] 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 Xa is S or O.

[0103] In certain embodiments, R_{17} is selected from the group methyl, ethyl, isopropyl, and cyclopropyl.

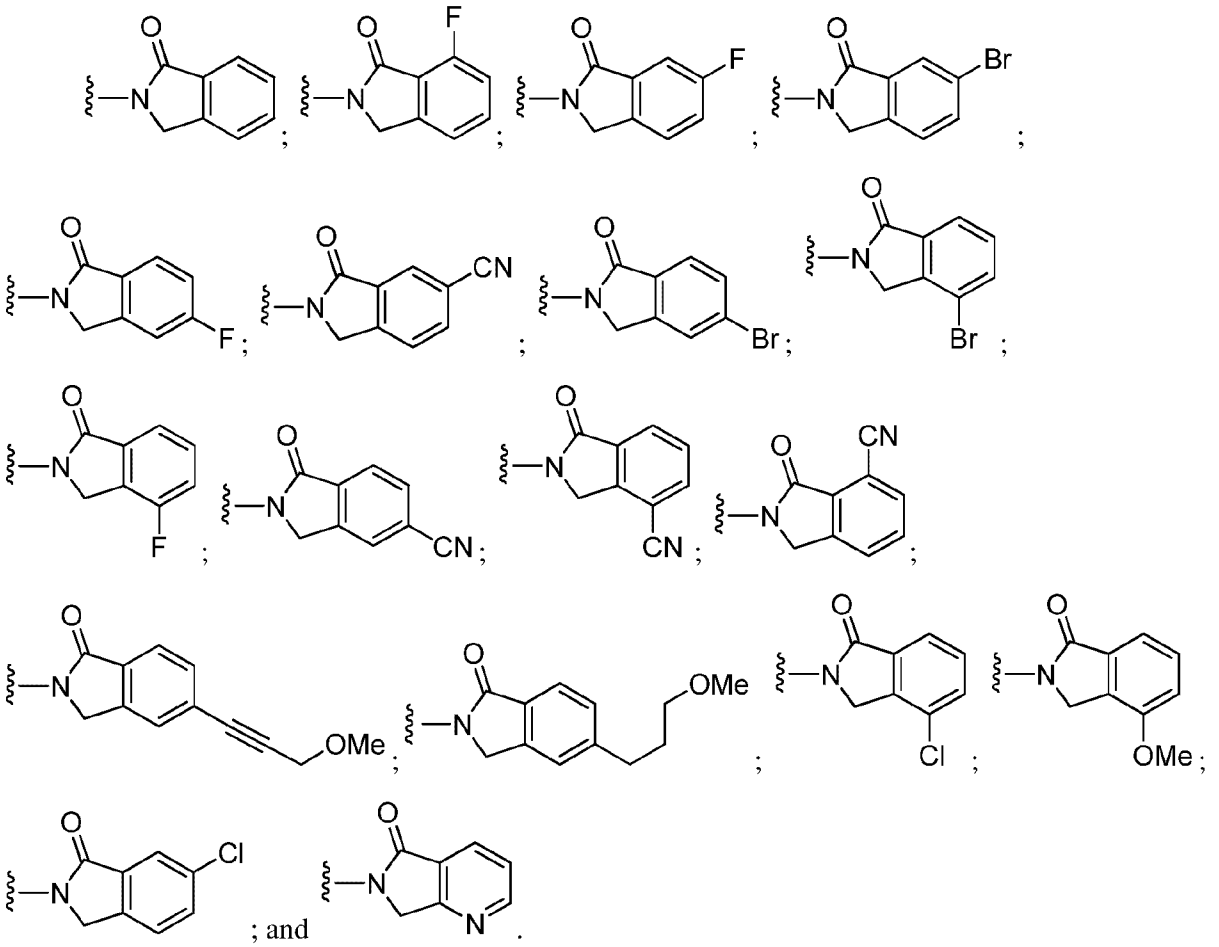
[0104] In certain additional embodiments, R_{15} is selected from the group consisting of:





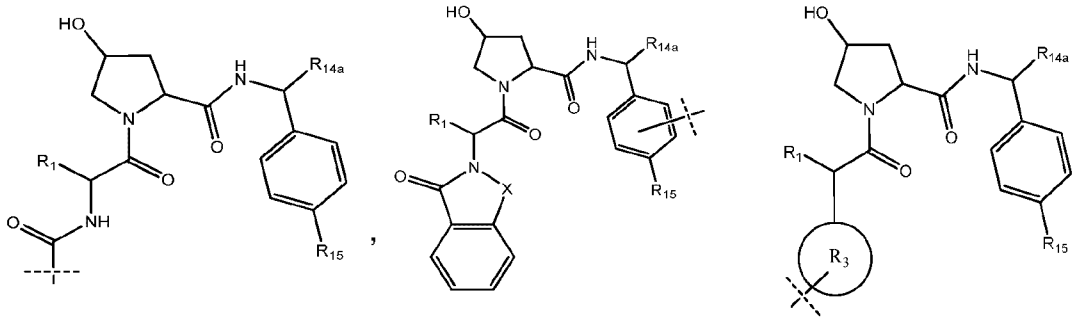
and .

[0105] In certain embodiments, R_{11} is selected from the group consisting of:



; and .

[0106] In certain embodiments, ULM has a chemical structure selected from the group of:



wherein:

R_1 is H, ethyl, isopropyl, tert-butyl, sec-butyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; optionally substituted alkyl, optionally substituted hydroxyalkyl, optionally substituted heteroaryl, or haloalkyl;

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

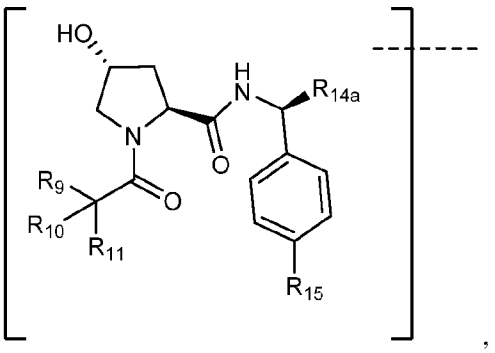
R_{15} is selected from the group consisting of H, halogen, CN, OH, NO_2, optionally substituted heteroaryl, optionally substituted aryl; optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted haloalkoxy, cycloalkyl, or cycloheteroalkyl;

X is C, CH_2, or C=O

R_3 is a bond or an optionally substituted 5 or 6 memebered heteroaryl; and

wherein the dashed line indicates the site of attachment of at least one PTM, another ULM (ULM') or a chemical linker moiety coupling at least one PTM or a ULM' or both to ULM (ULM-a).

[0107] In certain embodiments, ULM comprises a group according to the chemical structure:

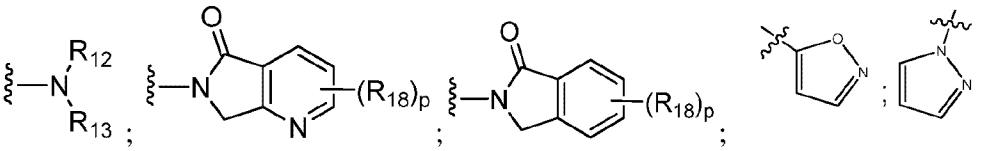


wherein:

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

R_9 is H;

R_{10} is H, ethyl, isopropyl, tert-butyl, sec-butyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl;

R11 is  ;

or optionally substituted heteroaryl;

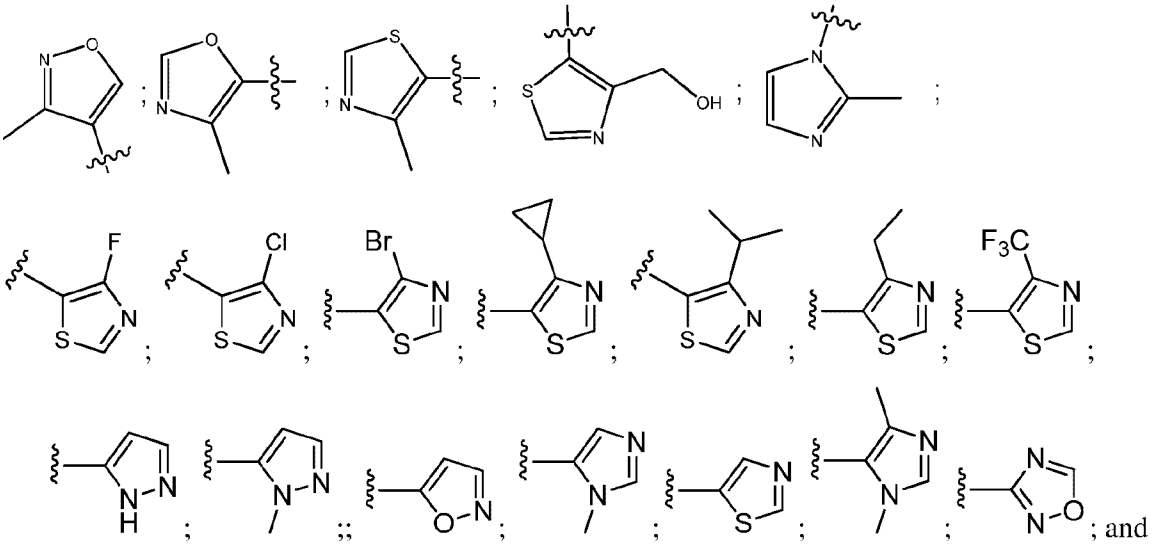
p is 0, 1, 2, 3, or 4;

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

R12 is H, C=O;

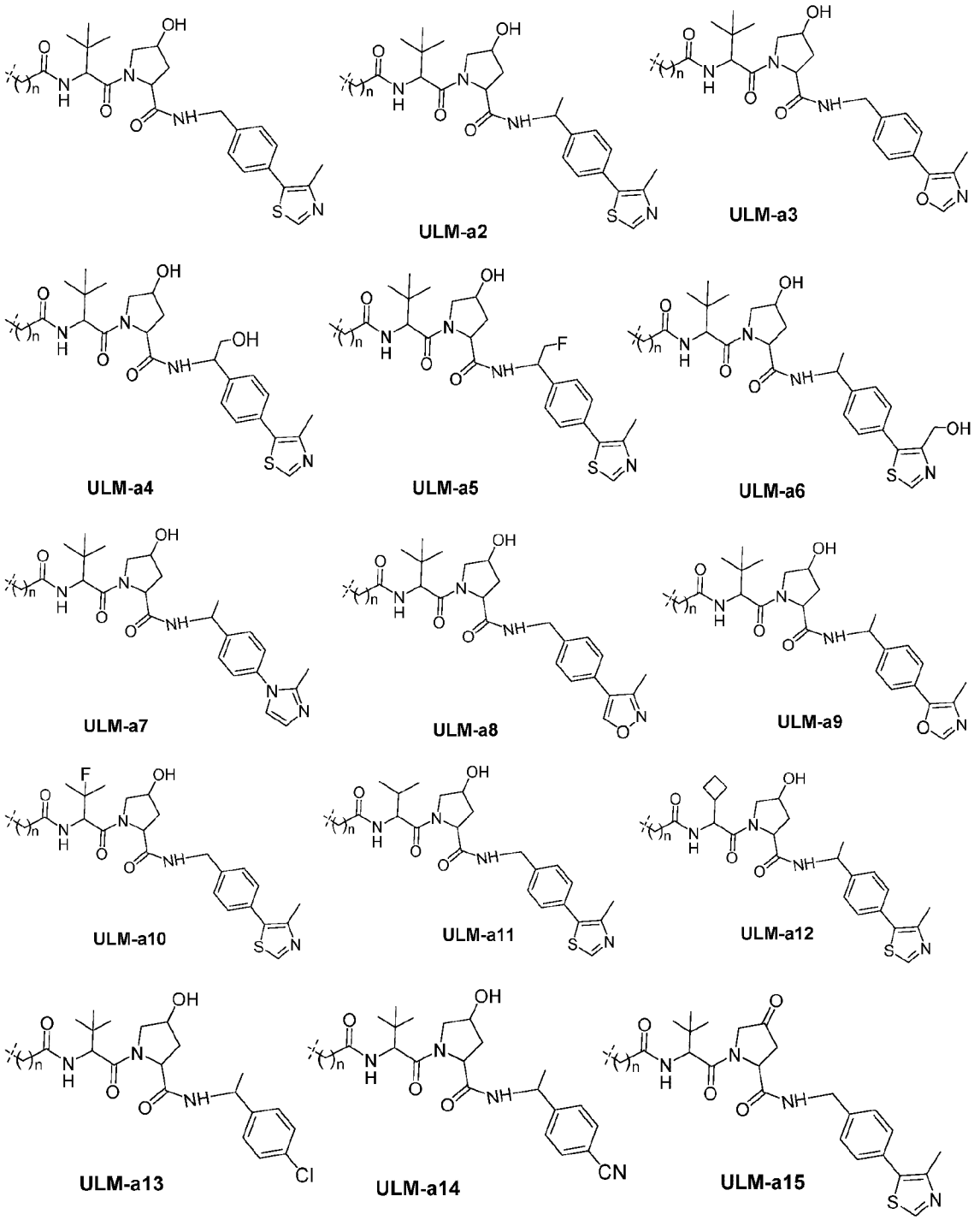
R13 is H, optionally substituted alkyl, optionally substituted alkylcarbonyl, optionally substituted (cycloalkyl)alkylcarbonyl, optionally substituted aralkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted (heterocyclyl)carbonyl, or optionally substituted aralkyl,

R_{15} is selected from the group consisting of H, halogen, Cl, CN, OH, NO_2, optionally substituted heteroaryl, optionally substituted aryl;



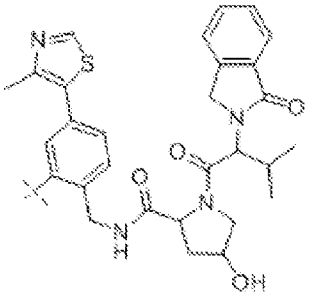
wherein the dashed line indicates the site of attachment of at least one PTM, another ULM (ULM') or a chemical linker moiety coupling at least one PTM or a ULM' or both to ULM.

[0108] In certain embodiments, the ULM is selected from the following structures:

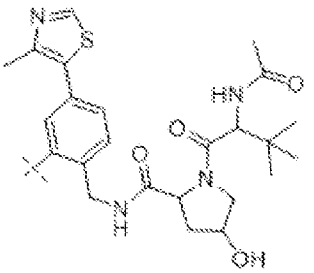


where n is 0 or 1.

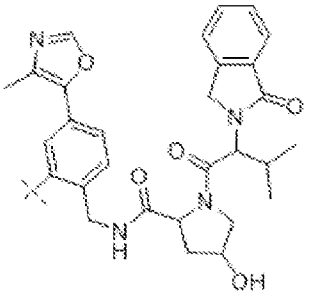
[0109] In certain embodiments, the ULM is selected from the following structures:



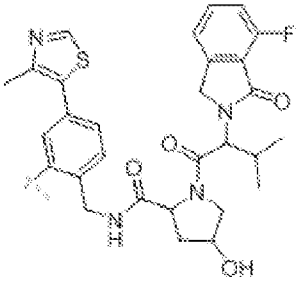
ULM-b1



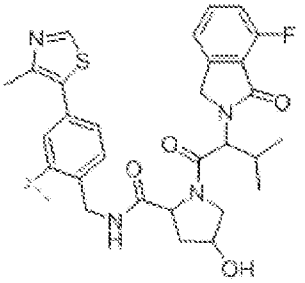
ULM-b2



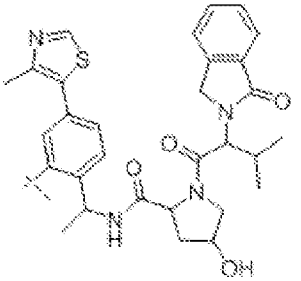
ULM-b3



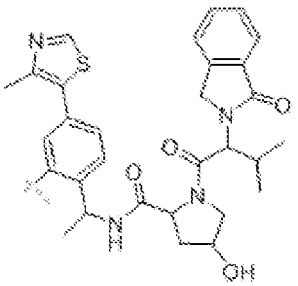
ULM-b4



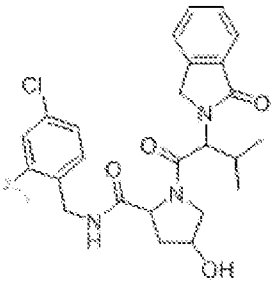
ULM-b5



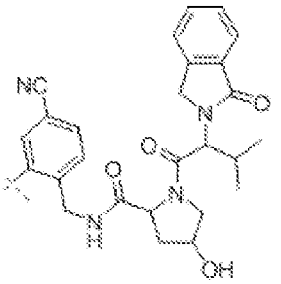
ULM-b6



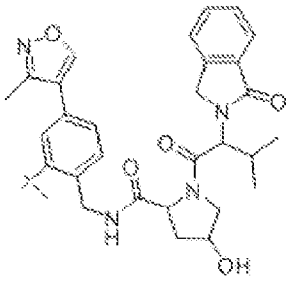
ULM-b7



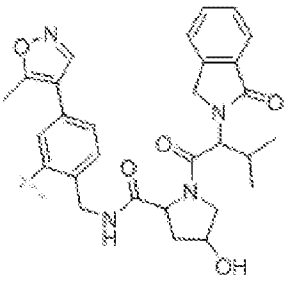
ULM-b8



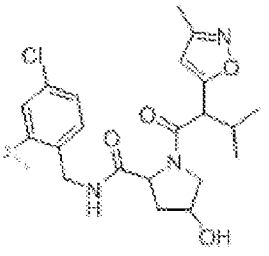
ULM-b9



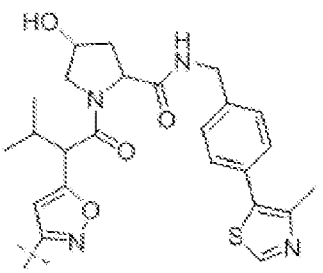
ULM-b7



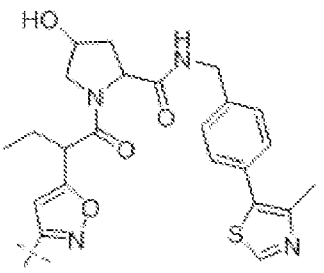
ULM-b8



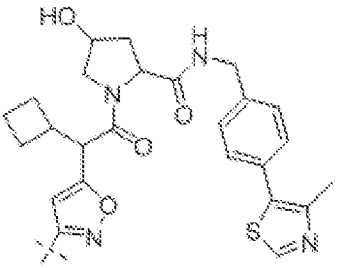
ULM-b9



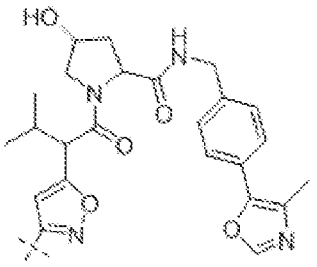
ULM-c1



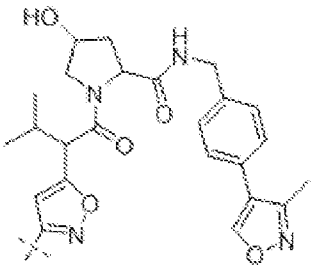
ULM-c2



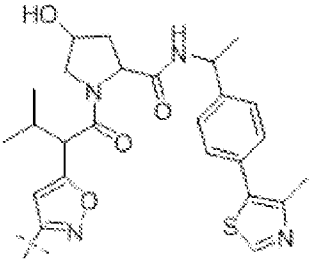
ULM-c3



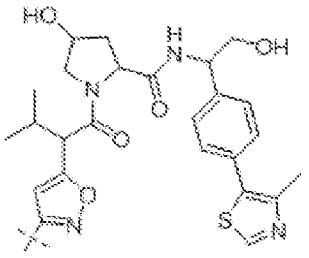
ULM-c4



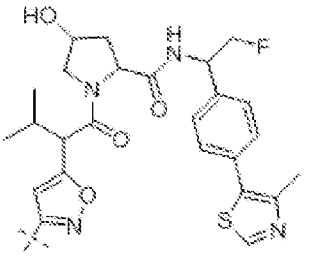
ULM-c5



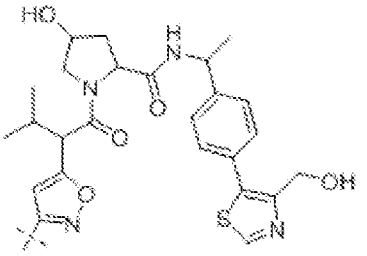
ULM-c6



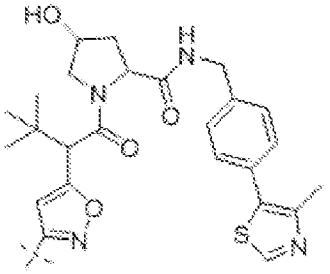
ULM-c7



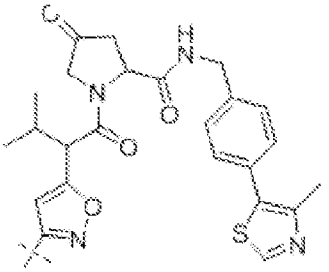
ULM-c8



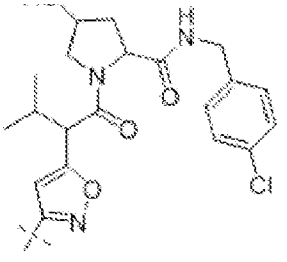
ULM-c9



ULM-c10



ULM-c11



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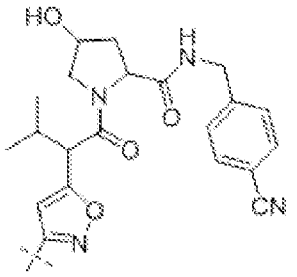
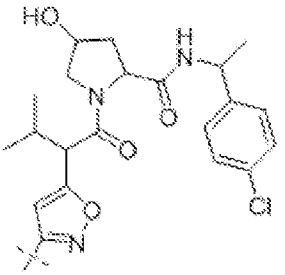


ULM-c13



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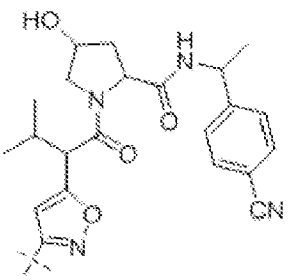
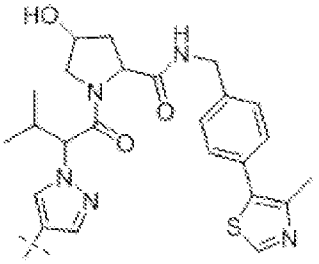
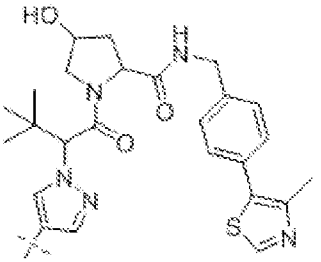


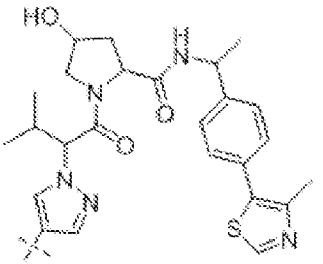
ULM-c15



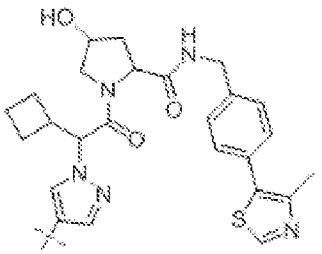
ULM-d1



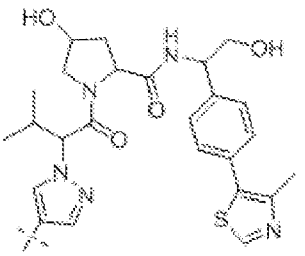
ULM-d2



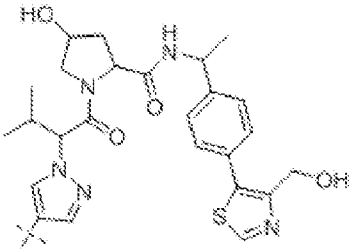
ULM-d3



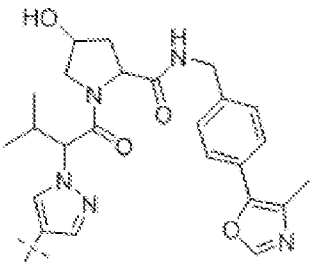
ULM-d4



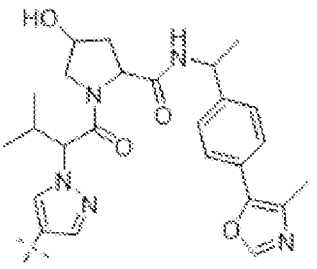
ULM-d5



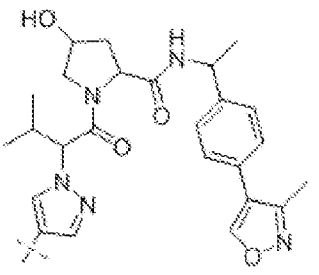
ULM-d6



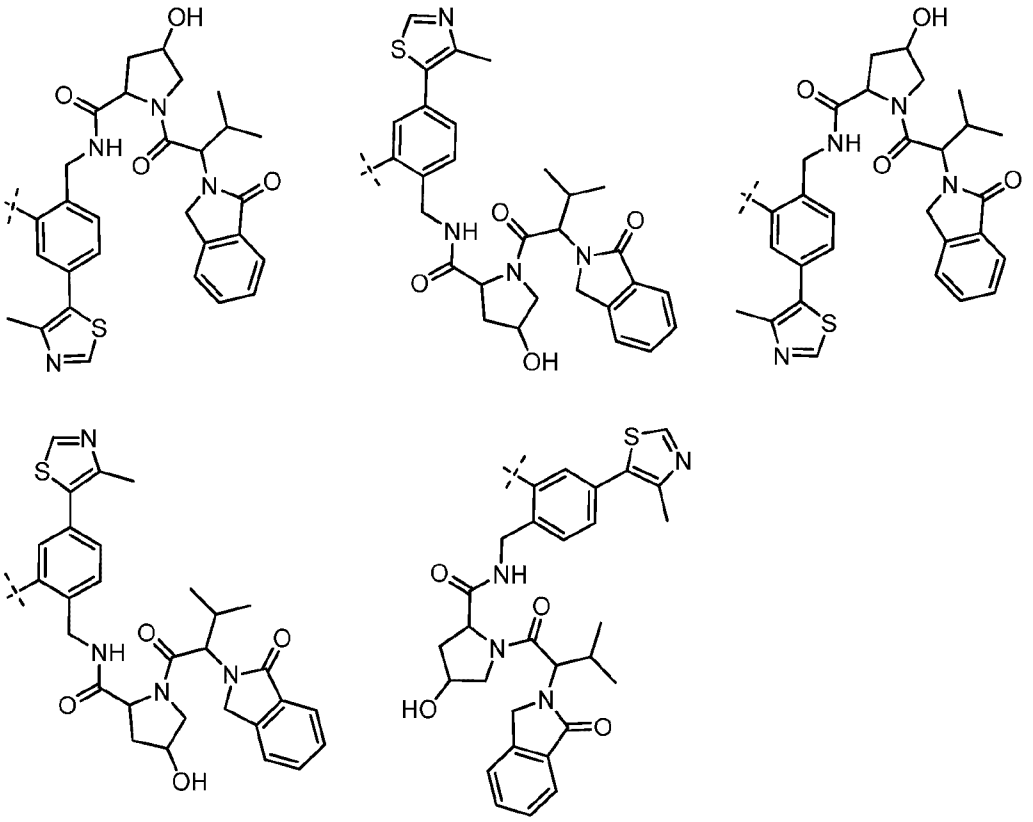
ULM-d7



ULM-d8



ULM-d9

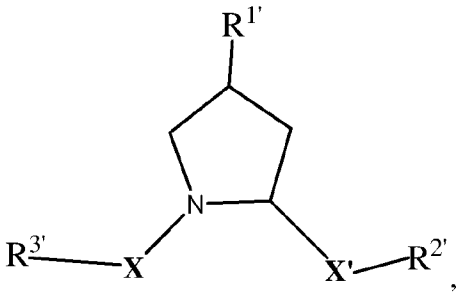


wherein the phenyl ring in ULM-a1 through ULM -a15, ULM -b1 through ULM-b12, ULM-c1 through ULM-c15 and ULM-d1 through ULM-d9 is optionally substituted with fluorine, lower alkyl and alkoxy groups, and wherein the dashed line indicates the site of attachment of at least one PTM, another ULM (ULM') or a chemical linker moiety coupling at least one PTM or a ULM' or both to ULM-a.

[0110] In one embodiment, the phenyl ring in ULM-a1 through ULM-a15, ULM-b1 through ULM-b12, ULM-c1 through ULM-c15 and ULM-d1 through ULM-d9 can be functionalized as the ester to make it a part of the prodrug.

[0111] In certain embodiments, the hydroxyl group on the pyrrolidine ring of ULM-a1 through ULM-a15, ULM-b1 through ULM-b12, ULM-c1 through ULM-c15 and ULM-d1 through ULM-d9, respectively, comprises an ester-linked prodrug moiety.

[0112] In any of the aspects or embodiments described herein, the ULM and where present, ULM', are each independently a group according to the chemical structure:



ULM-g

wherein:

$R^{1'}$ of ULM-g is an optionally substituted C_1-C_6 alkyl group, an optionally substituted -$(CH_2)_nOH$, an optionally substituted -$(CH_2)_nSH$, an optionally substituted $(CH_2)_n$-O-(C_1-C_6)alkyl group, an optionally substituted $(CH_2)_n$-WCOCW-(C_0-C_6)alkyl group containing an epoxide moiety WCOCW where each W is independently H or a C_1-C_3 alkyl group, an optionally substituted -$(CH_2)_nCOOH$, an optionally substituted -$(CH_2)_nC(O)$-(C_1-C_6 alkyl), an optionally substituted -$(CH_2)_nNHC(O)$-R_1, an optionally substituted -$(CH_2)_nC(O)$-NR_1R_2, an optionally substituted -$(CH_2)_nOC(O)$-NR_1R_2, -$(CH_2O)_nH$, an optionally substituted -$(CH_2)_nOC(O)$-(C_1-C_6 alkyl), an optionally substituted -$(CH_2)_nC(O)$-O-(C_1-C_6 alkyl), an optionally substituted -$(CH_2O)_nCOOH$, an optionally substituted -$(OCH_2)_nO$-(C_1-C_6 alkyl), an optionally substituted -$(CH_2O)_nC(O)$-(C_1-C_6 alkyl), an optionally substituted -$(OCH_2)_nNHC(O)$-R_1, an optionally substituted -$(CH_2O)_nC(O)$-NR_1R_2, -$(CH_2CH_2O)_nH$, an optionally substituted -$(CH_2CH_2O)_nCOOH$, an optionally substituted -$(OCH_2CH_2)_nO$-(C_1-C_6 alkyl), an optionally substituted -$(CH_2CH_2O)_nC(O)$-(C_1-C_6 alkyl), an optionally substituted -$(OCH_2CH_2)_nNHC(O)$-R_1, an optionally substituted -$(CH_2CH_2O)_nC(O)$-NR_1R_2,an optionally substituted -SO_2R_S, an optionally substituted $S(O)R_S$, NO_2, CN or halogen (F, Cl, Br, I, preferably F or Cl);

R_1 and R_2 of ULM-g are each independently 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);

R_S of ULM-g is a C_1-C_6 alkyl group, an optionally substituted aryl, heteroaryl or heterocycle group or a -$(CH_2)_mNR_1R_2$ group,;

X and X' of ULM-g are each independently C=O, C=S, -S(O), $S(O)_2$, (preferably X and X' are both C=O);

$R^{2'}$ of ULM-g is an optionally substituted $-(CH_2)_n-(C=O)_u(NR_1)_v(SO_2)_w$alkyl group, an optionally substituted $-(CH_2)_n-(C=O)_u(NR_1)_v(SO_2)_wNR_{1N}R_{2N}$ group, an optionally substituted $-(CH_2)_n-(C=O)_u(NR_1)_v(SO_2)_w$-Aryl, an optionally substituted $-(CH_2)_n-(C=O)_u(NR_1)_v(SO_2)_w$-Heteroaryl, an optionally substituted $-(CH_2)_n-(C=O)_vNR_1(SO_2)_w$-Heterocycle, an optionally substituted $-NR^1-(CH_2)_n-C(O)_u(NR_1)_v(SO_2)_w$-alkyl, an optionally substituted $-NR^1-(CH_2)_n-C(O)_u(NR_1)_v(SO_2)_w-NR_{1N}R_{2N}$, an optionally substituted $-NR^1-(CH_2)_n-C(O)_u(NR_1)_v(SO_2)_w-NR_1C(O)R_{1N}$, an optionally substituted $-NR^1-(CH_2)_n-(C=O)_u(NR_1)_v(SO_2)_w$-Aryl, an optionally substituted $-NR^1-(CH_2)_n-(C=O)_u(NR_1)_v(SO_2)_w$-Heteroaryl or an optionally substituted $-NR^1-(CH_2)_n-(C=O)_vNR_1(SO_2)_w$-Heterocycle, an optionally substituted $-X^{R2'}$-alkyl group; an optionally substituted $-X^{R2'}$- Aryl group; an optionally substituted $-X^{R2'}$- Heteroaryl group; an optionally substituted $-X^{R2'}$- Heterocycle group; an optionally substituted;

$R^{3'}$ of ULM-g is an optionally substituted alkyl, an optionally substituted $-(CH_2)_n-(O)_u(NR_1)_v(SO_2)_w$-alkyl, an optionally substituted $-(CH_2)_n-C(O)_u(NR_1)_v(SO_2)_w-NR_{1N}R_{2N}$, an optionally substituted $-(CH_2)_n-C(O)_u(NR_1)_v(SO_2)_w-NR_1C(O)R_{1N}$, an optionally substituted $-(CH_2)_n-C(O)_u(NR_1)_v(SO_2)_w-C(O)NR_1R_2$, an optionally substituted $-(CH_2)_n-C(O)_u(NR_1)_v(SO_2)_w$-Aryl, an optionally substituted $-(CH_2)_n-C(O)_u(NR_1)_v(SO_2)_w$-Heteroaryl, an optionally substituted $-(CH_2)_n-C(O)_u(NR_1)_v(SO_2)_w$-Heterocycle, an optionally substituted $-NR^1-(CH_2)_n-C(O)_u(NR_1)_v(SO_2)_w$-alkyl, an optionally substituted $-NR^1-(CH_2)_n-C(O)_u(NR_1)_v(SO_2)_w-NR_{1N}R_{2N}$, an optionally substituted $-NR^1-(CH_2)_n-C(O)_u(NR_1)_v(SO_2)_w-NR_1C(O)R_{1N}$, an optionally substituted $-NR^1-(CH_2)_n-C(O)_u(NR_1)_v(SO_2)_w$-Aryl, an optionally substituted $-NR^1-(CH_2)_n-C(O)_u(NR_1)_v(SO_2)_w$-Heteroaryl, an optionally substituted $-NR^1-(CH_2)_n-C(O)_u(NR_1)_v(SO_2)_w$-Heterocycle, an optionally substituted -O-(CH_2)n-$(C=O)_u(NR_1)_v(SO_2)_w$-alkyl, an optionally substituted -O-(CH_2)n-$(C=O)_u(NR_1)_v(SO_2)_w-NR_{1N}R_{2N}$, an optionally substituted -O-(CH_2)n-$(C=O)_u(NR_1)_v(SO_2)_w-NR_1C(O)R_{1N}$, an optionally substituted -O-(CH_2)n-$(C=O)_u(NR_1)_v(SO_2)_w$-Aryl, an optionally substituted -O-$(CH_2)_n-(C=O)_u(NR_1)_v(SO_2)_w$-Heteroaryl or an optionally substituted -O-$(CH_2)_n-(C=O)_u(NR_1)_v(SO_2)_w$-Heterocycle; $-(CH_2)_n-(V)_{n'}-(CH_2)_n-(V)_{n'}$-alkyl group, an optionally substituted $-(CH_2)_n-(V)_{n'}-(CH_2)_n-(V)_{n'}$-Aryl group, an optionally substituted $-(CH_2)_n-(V)_{n'}-(CH_2)_n-(V)_{n'}$-Heteroaryl group, an optionally substituted $-(CH_2)_n-(V)_{n'}-(CH_2)_n-(V)_{n'}$-Heterocycle group, an optionally substituted -$(CH_2)_n$-

$N(R_{1'})(C=O)_{m'}$-$(V)_{n'}$-alkyl group, an optionally substituted -$(CH_2)_n$-$N(R_{1'})(C=O)_{m'}$-$(V)_{n'}$-Aryl group, an optionally substituted -$(CH_2)_n$-$N(R_{1'})(C=O)_{m'}$-$(V)_{n'}$-Heteroaryl group, an optionally substituted -$(CH_2)_n$-$N(R_{1'})(C=O)_{m'}$-$(V)_{n'}$-Heterocycle group, an optionally substituted -$X^{R3'}$- alkyl group; an optionally substituted -$X^{R3'}$- Aryl group; an optionally substituted -$X^{R3'}$- Heteroaryl group; an optionally substituted -$X^{R3'}$- Heterocycle group; an optionally substituted;

R_{1N} and R_{2N} of ULM-g are each independently H, C_1-C_6 alkyl which is optionally substituted with one or two hydroxyl groups and up to three halogen groups or an optionally substituted –$(CH_2)_n$-Aryl, –$(CH_2)_n$-Heteroaryl or –$(CH_2)_n$-Heterocycle group;

V of ULM-g is O, S or NR_1;

R_1 of ULM-g is the same as above;

R^1 and $R_{1'}$ of ULM-g are each independently H or a C_1-C_3 alkyl group;

$X^{R2'}$ and $X^{R3'}$ of ULM-g are each independently an optionally substituted –$CH_2)_n$-, –$CH_2)_n$-$CH(X_v)$=$CH(X_v)$- (cis or trans), –$CH_2)_n$-CH≡CH- , -$(CH_2CH_2O)_n$- or a C_3-C_6 cycloalkyl group, where X_v is H, a halo or a C_1-C_3 alkyl group which is optionally substituted;

each m of ULM-g is independently 0, 1, 2, 3, 4, 5, 6;

each m' of ULM-g is independently 0 or 1;

each n of ULM-g is independently 0, 1, 2, 3, 4, 5, 6;

each n' of ULM-g is independently 0 or 1;

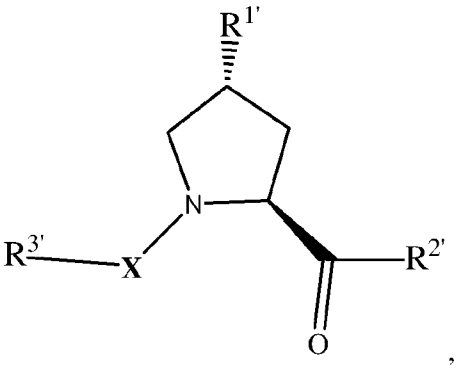
each u of ULM-g is independently 0 or 1;

each v of ULM-g is independently 0 or 1;

each w of ULM-g is independently 0 or 1; and

any one or more of $R^{1'}$, $R^{2'}$, $R^{3'}$, X and X' of ULM-g is optionally modified to be covalently bonded to the PTM group through a linker group when PTM is not ULM', or when PTM is ULM', any one or more of $R^{1'}$, $R^{2'}$, $R^{3'}$, X and X' of each of ULM and ULM' are optionally modified to be covalently bonded to each other directly or through a linker group, or a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof.

[0113] In any of the aspects or embodiments described herein, the ULM and when present, ULM', are each independently a group according to the chemical structure:



ULM-h

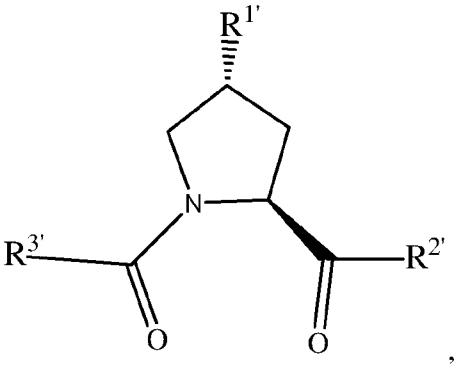
wherein:

each of $R^{1'}$, $R^{2'}$ and $R^{3'}$ of ULM-h are the same as above and X is C=O, C=S, -S(O) group or a $S(O)_2$ group, more preferably a C=O group, and

any one or more of $R^{1'}$, $R^{2'}$ and $R^{3'}$ of ULM-h are optionally modified to bind a linker group to which is further covalently bonded to the PTM group when PTM is not ULM', or when PTM is ULM', any one or more of $R^{1'}$, $R^{2'}$, $R^{3'}$ of each of ULM and ULM' are optionally modified to be covalently bonded to each other directly or through a linker group, or

a pharmaceutically acceptable salt, enantiomer, diastereomer, solvate or polymorph thereof.

[0114] In any of the aspects or embodiments described herein, the ULM, and when present, ULM', are each independently according to the chemical structure:



ULM-i

wherein:

any one or more of $R^{1'}$, $R^{2'}$ and $R^{3'}$ of ULM-I are optionally modified to bind a linker group to which is further covalently bonded to the PTM group when PTM is not ULM', or when PTM is ULM', any one or more of $R^{1'}$, $R^{2'}$, $R^{3'}$ of each of ULM and ULM' are optionally modified to be covalently bonded to each other directly or through a linker group, or

a pharmaceutically acceptable salt, enantiomer, diastereomer, solvate or polymorph thereof.

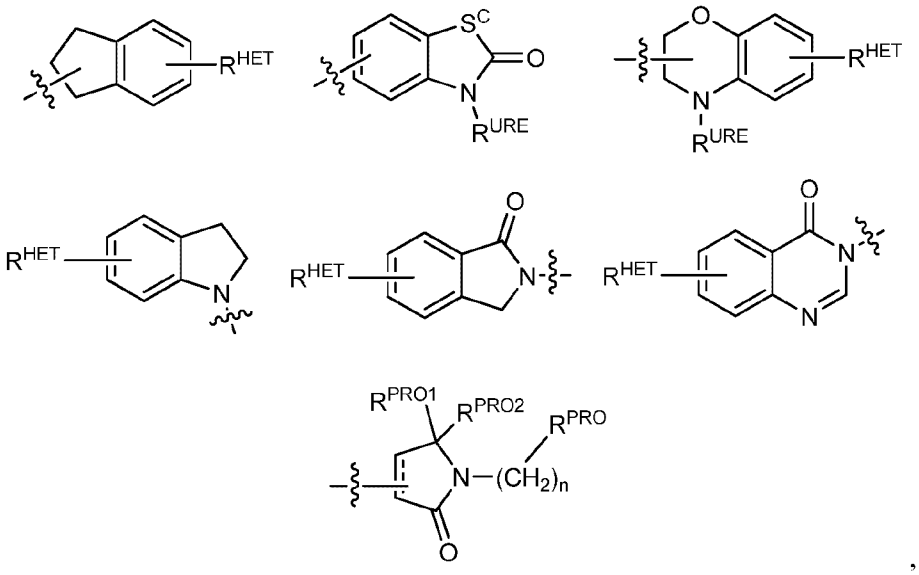
[0115] In further preferred aspects of the invention, $R^{1'}$ of ULM-g through ULM-i is preferably a hydroxyl group or a group which may be metabolized to a hydroxyl or carboxylic group, such that the compound represents a prodrug form of an active compound. Exemplary preferred $R^{1'}$ groups include, for example, -$(CH_2)_nOH$, $(CH_2)_n$-O-(C_1-C_6)alkyl group, -$(CH_2)_nCOOH$, -$(CH_2O)_nH$, an optionally substituted -$(CH_2)_nOC(O)$-(C_1-C_6 alkyl), or an optionally substituted -$(CH_2)_nC(O)$-O-(C_1-C_6 alkyl), wherein n is 0 or 1. Where $R^{1'}$ is or contains a carboxylic acid group, a hydroxyl group or an amine group, the hydroxyl group, carboxylic acid group or amine (each of which may be optionally substituted), may be further chemically modified to provide a covalent link to a linker group to which the PTM group (including a ULM' group) is bonded;

[0116] X and X', where present, of ULM-g and ULM-h are preferably a C=O, C=S, -S(O) group or a $S(O)_2$ group, more preferably a C=O group;

[0117] $R^{2'}$ of ULM-g through ULM-i is preferably an optionally substituted -NR^1-T-Aryl, an optionally substituted -NR^1-T-Heteroaryl group or an optionally substituted -NR^1-T-Heterocycle, where 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_3 alkyl group, 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. 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.

[0118] Preferred Aryl groups for $R^{2'}$ of ULM-g through ULM-i include optionally substituted phenyl or naphthyl groups, preferably phenyl groups, wherein the phenyl or naphthyl group is optionally connected to a PTM group (including a ULM' group) via a linker 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 optionally connected to a PTM group (including a ULM' group) via a linker 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:



wherein:

S^c of ULM-g through ULM-i is CHR^{SS}, NR^{URE}, or O;

R^{HET} of ULM-g through ULM-i 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);

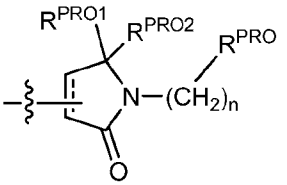
R^{SS} of ULM-g through ULM-i is H, CN, NO_2, halo (preferably F or Cl), optionally substituted C_1-C_6 alkyl (preferably substituted with one or two hydroxyl groups or up to three halo groups), optionally substituted O-(C_1-C_6 alkyl) (preferably substituted with one or two hydroxyl groups or up to 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);

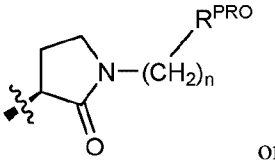
R^{URE} of ULM-g through ULM-i is H, a C_1-C_6 alkyl (preferably H or C_1-C_3 alkyl) or a –C(O)(C_1-C_6 alkyl) each of which groups is optionally substituted with one or two hydroxyl groups or up to three halogen, preferably fluorine groups, or an optionally substituted phenyl group, an optionally substituted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

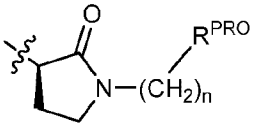
R^{PRO} of ULM-g through ULM-i is H, optionally substituted C_1-C_6 alkyl or an optionally substituted aryl (phenyl or napthyl), heteroaryl or heterocyclic group selected from the group consisting of oxazole, isoxazole, thiazole, isothiazole, imidazole, diazole, oximidazole, pyrrole, pyrollidine, furan,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

R^{PRO1} and $R^{PRO2 \text{ of ULM-g through ULM-i}}$ are each independently H, an optionally subsituted C_1-C_3 alkyl group or together form a keto group; and

each n of ULM-g through ULM-i 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 connected to a PTM group (including a ULM' group) via a linker group.

[0119] In certain preferred aspects,  of ULM-g through ULM-i is a

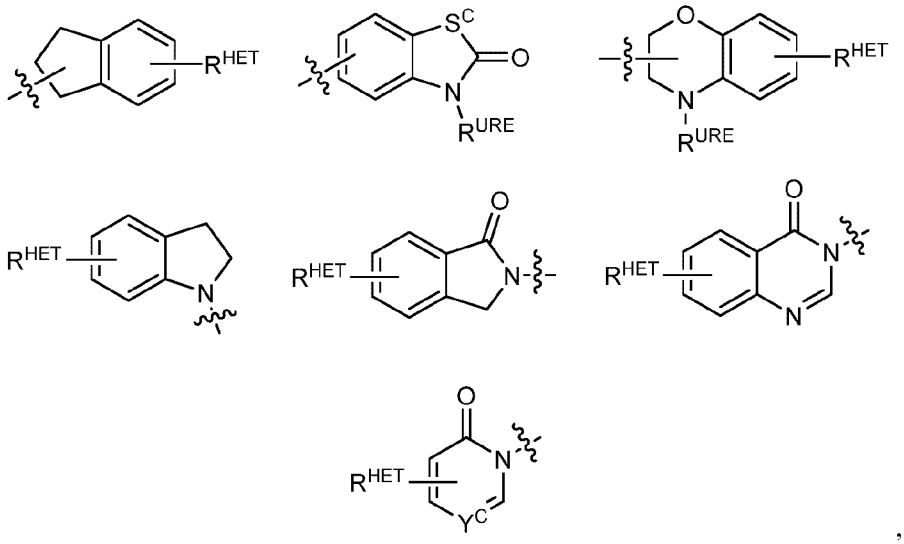


or


group,

where R^{PRO} and n of ULM-g through ULM-i are the same as above.

[0120] Preferred heteroaryl groups for $R^{2'}$ of ULM-g through ULM-i 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:



wherein:

S^c of ULM-g through ULM-i is CHR^{SS}, NR^{URE}, or O;

R^{HET} of ULM-g through ULM-i 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

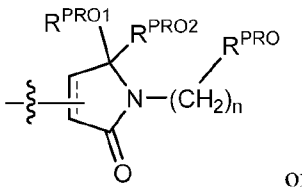
acetylenic group –C≡C-R_a where R_a of ULM-g through ULM-i is H or a C_1-C_6 alkyl group (preferably C_1-C_3 alkyl);

R^{SS} of ULM-g through ULM-i 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);

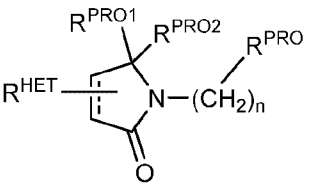
R^{URE} of ULM-g through ULM-i is H, a C_1-C_6 alkyl (preferably H or C_1-C_3 alkyl) or a –C(O)(C_1-C_6 alkyl), each of which groups is optionally substituted with one or two hydroxyl groups or up to three halogen, preferably fluorine groups, or an optionally substituted heterocycle, for example piperidine,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

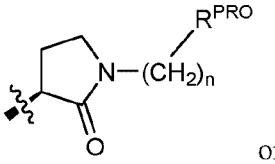
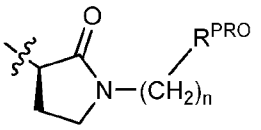
Y^C of ULM-g through ULM-i is N or C-R^{YC}, where R^{YC} is H, OH, CN, NO_2, halo (preferably Cl or F), optionally substituted C_1-C_6 alkyl (preferably substituted with one or two hydroxyl groups or up to three halo groups (e.g. CF_3), optionally substituted O(C_1-C_6 alkyl) (preferably substituted 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 connected to a PTM group (including a ULM' group) via a linker group.

[0121] Preferred heterocycle groups for $R^{2'}$ of ULM-g through ULM-i 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,

wherein:

R^{PRO} of ULM-g through ULM-i is H, optionally substituted C_1-C_6 alkyl or an optionally substituted aryl, heteroaryl or heterocyclic group;

R^{PRO1} and R^{PRO2} of ULM-g through ULM-i are each independently H, an optionally subsituted C_1-C_3 alkyl group or together form a keto group and

each n of ULM-g through ULM-i is independently 0, 1, 2, 3, 4, 5, or 6 (often 0 or 1), each of which groups may be optionally connected to a PTM group (including a ULM' group) via a linker group.

[0122] Preferred $R^{2'}$ substituents of ULM-g through ULM-i also include specifically (and without limitation to the specific compound disclosed) the $R^{2'}$ 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 $R^{2'}$ substituents may be used in conjunction with any number of $R^{3'}$ substituents which are also disclosed herein.

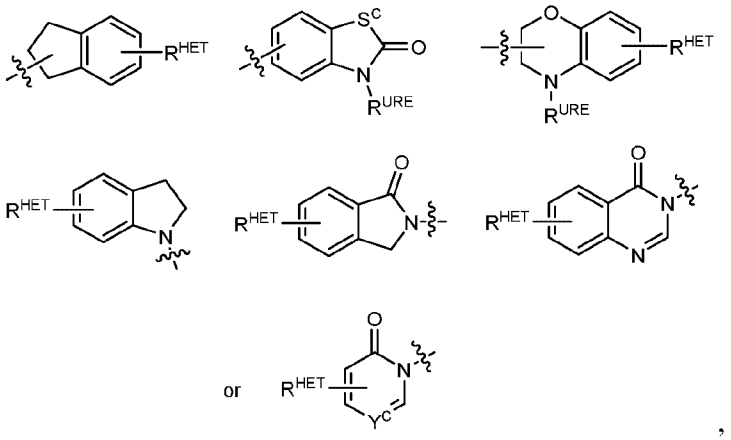
[0123] $R^{3'}$ of ULM-g through ULM-i is preferably an optionally substituted –T-Aryl, an optionally substituted–T-Heteroaryl, an optionally substituted –T-Heterocycle, an optionally substituted-NR^1-T-Aryl, an optionally substituted -NR^1-T-Heteroaryl or an optionally substituted-NR^1-T-Heterocycle, where R^1 is H or a C_1-C_3 alkyl group, preferably H or CH_3, 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_3 alkyl group 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 or 1. 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.

[0124] Preferred aryl groups for $R^{3'}$ of ULM-g through ULM-i include optionally substituted phenyl or naphthyl groups, preferably phenyl groups, wherein the phenyl or naphthyl group is optionally connected to a PTM group (including a ULM' group) via a linker 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 above), a halo (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 PTM 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 connected to a PTM group (including a ULM' group) via a linker group.

[0125] Preferred Heteroaryl groups for $R^{3'}$ of ULM-g through ULM-i 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:



,

wherein:

S^c of ULM-g through ULM-i is CHR^{SS}, NR^{URE}, or O;

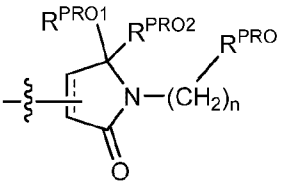
R^{HET} of ULM-g through ULM-i is H, CN, NO_2, halo (preferably Cl or F), optionally substituted C_1-C_6 alkyl (preferably substituted with one or two hydroxyl groups or up to three halo groups (e.g. CF_3), optionally substituted O(C_1-C_6 alkyl) (preferably substituted with one or two hydroxyl groups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

R^{SS} of ULM-g through ULM-i 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);

R^{URE} of ULM-g through ULM-i 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

Y^C of ULM-g through ULM-i 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 connected to a PTM group (including a ULM' group) via a linker group.

[0126] Preferred heterocycle groups for $R^{3'}$ of ULM-g through ULM-i 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:



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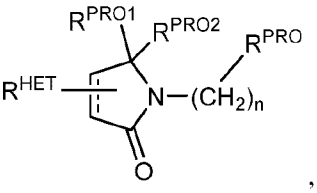
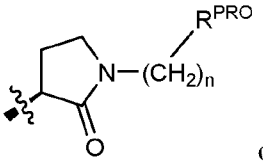


, preferably, a


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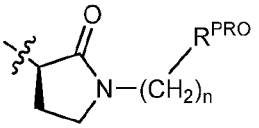


group,

wherein:

R^{PRO} of ULM-g through ULM-i 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;

R^{PRO1} and R^{PRO2} of ULM-g through ULM-i are each independently H, an optionally subsituted C_1-C_3 alkyl group or together form a keto group, and

each n of ULM-g through ULM-i is 0, 1, 2, 3, 4, 5, or 6 (preferably 0 or 1), wherein each of said Heteocycle groups may be optionally connected to a PTM group (including a ULM' group) via a linker group.

[0127] Preferred $R^{3'}$ substituents of ULM-g through ULM-i also include specifically (and without limitation to the specific compound disclosed) the $R^{3'}$ 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 $R^{3'}$ substituents may be used in conjunction with any number of $R^{2'}$ substituents, which are also disclosed herein.

[0128] In certain alternative preferred embodiments, $R^{2'}$ of ULM-g through ULM-i is an optionally substituted -NR_1-$X^{R2'}$-alkyl group, -NR_1-$X^{R2'}$-Aryl group; an optionally substituted -NR_1- $X^{R2'}$-HET, an optionally substituted -NR_1-$X^{R2'}$-Aryl-HET or an optionally substituted -NR_1-$X^{R2'}$-HET-Aryl,

wherein:

R_1 of ULM-g through ULM-i is H or a C_1-C_3 alkyl group (preferably H);

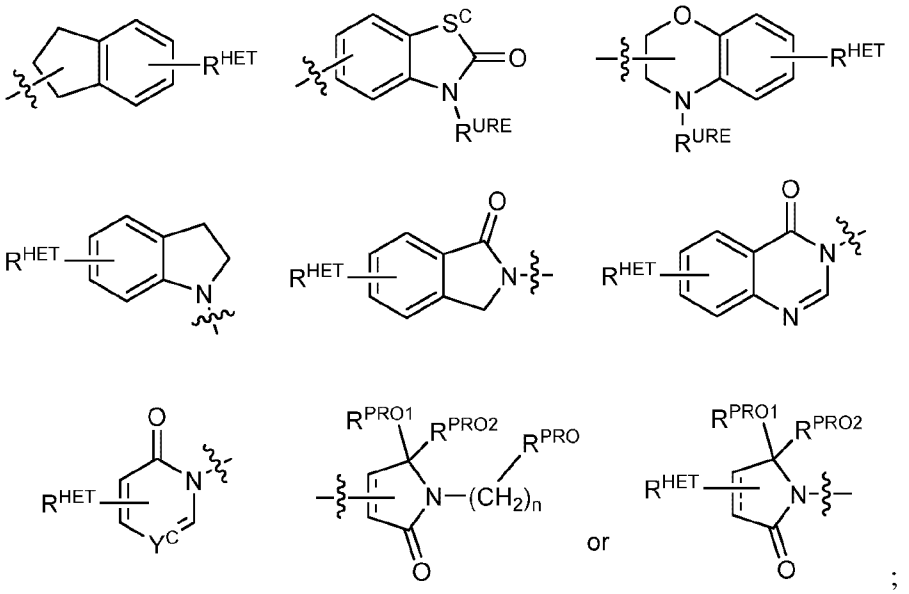
$X^{R2'}$ of ULM-g through ULM-i is an optionally substituted $–CH_2)_n-$, $–CH_2)_n-CH(X_v)=CH(X_v)-$ (cis or trans), $–(CH_2)_n-CH{\equiv}CH-$, $-(CH_2CH_2O)_n-$ or a C_3-C_6 cycloalkyl group; and

X_v of ULM-g through ULM-i is H, a halo or a C_1-C_3 alkyl group which is optionally substituted with one or two hydroxyl groups or up to three halogen groups;

Alkyl of ULM-g through ULM-i is an optionally substituted C1-C_{10} alkyl (preferably a C_1-C_6 alkyl) group (in certain preferred embodiments, the alkyl group is end-capped with a halo group, often a Cl or Br);

Aryl of ULM-g through ULM-i is an optionally substituted phenyl or naphthyl group (preferably, a phenyl group); and

HET of ULM-g through ULM-i is an optionally substituted oxazole, isoxazole, thiazole, isothiazole, imidazole, diazole, oximidazole, pyrrole, pyrollidine, furan, dihydrofuran, tetrahydrofuran, thiene, dihydrothiene, tetrahydrothiene, pyridine, piperidine, piperazine, morpholine, benzofuran, indole, indolizine, azaindolizine, quinoline (when substituted, each preferably substituted with a C_1-C_3 alkyl group, preferably methyl or a halo group, preferably F or Cl) or a group according to the chemical structure:



;

S^c of ULM-g through ULM-i is CHR^{SS}, NR^{URE}, or O;

R^{HET} of ULM-g through ULM-i 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 $–C\equiv C-R_a$ where R_a is H or a C_1-C_6 alkyl group (preferably C_1-C_3 alkyl);

R^{SS} of ULM-g through ULM-i 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);

R^{URE} of ULM-g through ULM-i 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;

Y^C of ULM-g through ULM-i 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);

R^{PRO} of ULM-g through ULM-i 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;

R^{PRO1} and R^{PRO2} of ULM-g through ULM-i are each independently H, an optionally subsituted C_1-C_3 alkyl group or together form a keto group, and

each n of ULM-g through ULM-i is independently 0, 1, 2, 3, 4, 5, or 6 (preferably 0 or 1).

[0129] Each of said groups may be optionally connected to a PTM group (including a ULM' group) via a linker group.

[0130] In certain alternative preferred embodiments of the present invention, $R^{3'}$ of ULM-g through ULM-i is an optionally substituted –$(CH_2)_n$-$(V)_{n'}$-$(CH_2)_n$-$(V)_{n'}$-$R^{S3'}$ group, an optionally substituted-$(CH_2)_n$-$N(R_{1'})(C=O)_{m'}$-$(V)_{n'}$-$R^{S3'}$ group, an optionally substituted -$X^{R3'}$-alkyl group, an optionally substituted -$X^{R3'}$-Aryl group; an optionally substituted -$X^{R3'}$-HET group, an optionally substituted -$X^{R3'}$-Aryl-HET group or an optionally substituted -$X^{R3'}$-HET-Aryl group, wherein:

$R^{S3'}$ is an optionally substituted alkyl group (C_1-C_{10}, preferably C_1-C_6 alkyl), an optionally substituted Aryl group or a HET group;

$R_{1'}$ is H or a C_1-C_3 alkyl group (preferably H);

V is O, S or $NR_{1'}$;

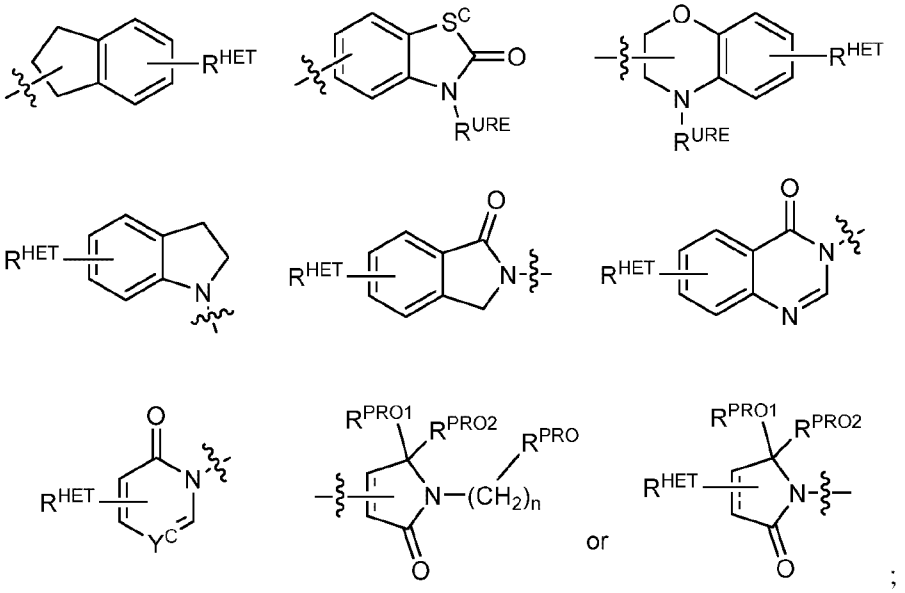
$X^{R3'}$ is –$(CH_2)_n$- , -$(CH_2CH_2O)_n$-, –$CH_2)_n$-$CH(X_v)$=$CH(X_v)$- (cis or trans), –$CH_2)_n$-CH≡CH- , or a C_3-C_6 cycloalkyl group, all optionally substituted;

X_v is H, a halo or a C_1-C_3 alkyl group which is optionally substituted with one or two hydroxyl groups or up to three halogen groups;

Alkyl is an optionally substituted C_1-C_{10} alkyl (preferably a C_1-C_6 alkyl) group (in certain preferred embodiments, the alkyl group is end-capped with a halo group, often a Cl or Br);

Aryl is an optionally substituted phenyl or napthyl group (preferably, a phenyl group); and

HET is an optionally substituted oxazole, isoxazole, thiazole, isothiazole, imidazole, diazole, oximidazole, pyrrole, pyrollidine, furan, dihydrofuran, tetrahydrofuran, thiene, dihydrothiene, tetrahydrothiene, pyridine, piperidine, piperazine, morpholine, benzofuran, indole, indolizine, azaindolizine, quinoline (when substituted, each preferably substituted with a C_1-C_3 alkyl group, preferably methyl or a halo group, preferably F or Cl), or a group according to the chemical structure:



;

S^c of ULM-g through ULM-i is CHR^{SS}, NR^{URE}, or O;

R^{HET} of ULM-g through ULM-i 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);

R^{SS} of ULM-g through ULM-i 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);

R^{URE} of ULM-g through ULM-i is H, a C_1-C_6 alkyl (preferably H or C_1-C_3 alkyl) or a –C(O)(C_0-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;

Y^C of ULM-g through ULM-i 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);

R^{PRO} of ULM-g through ULM-i 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;

R^{PRO1} and R^{PRO2} of ULM-g through ULM-i are each independently H, an optionally subsituted C_1-C_3 alkyl group or together form a keto group;

each n of ULM-g through ULM-i is independently 0, 1, 2, 3, 4, 5, or 6 (preferably 0 or 1);

each m' of ULM-g through ULM-i is 0 or 1; and

each n' of ULM-g through ULM-i is 0 or 1;

wherein each of said compounds, preferably on the alkyl, Aryl or Het groups, is optionally connected to a PTM group (including a ULM' group) via a linker group.

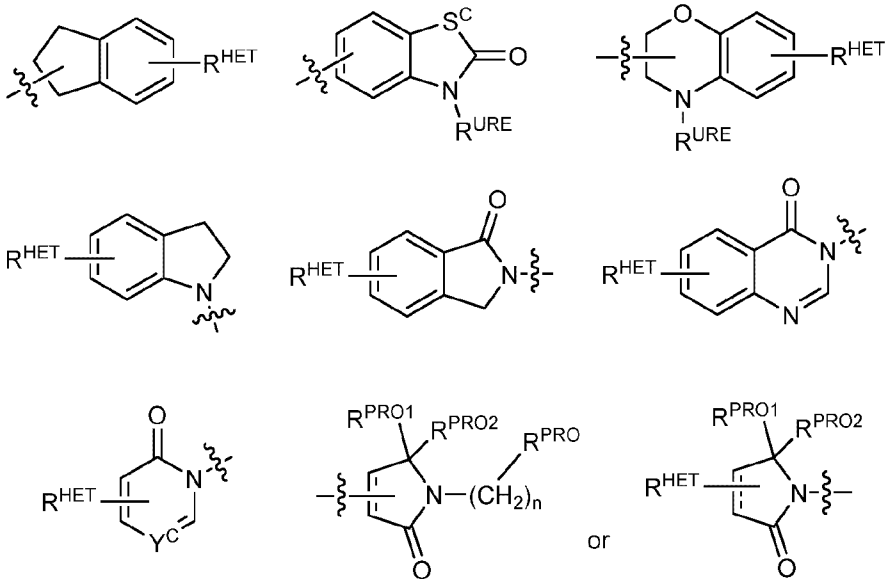
[0131] In alternative embodiments, $R^{3'}$ of ULM-g through ULM-i is –$(CH_2)_n$-Aryl, –$(CH_2CH_2O)_n$-Aryl, –$(CH_2)_n$-HET or –$(CH_2CH_2O)_n$-HET,

wherein:

said Aryl of ULM-g through ULM-i is phenyl which is optionally substituted with one or two substitutents, wherein said substituent(s) is preferably selected from -$(CH_2)_n$OH, C_1-C_6 alkyl which itself is further optionally substituted with CN, halo (up to three halo groups), OH, -$(CH_2)_n$O(C_1-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, or

said Aryl group of ULM-g through ULM-i is substituted with -$(CH_2)_nOH$, -$(CH_2)_n$-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, CN, NO_2, an optionally substituted -$(CH_2)_n$-$(V)_{m'}$-$CH_2)_n$-$(V)_{m'}$-(C_1-C_6)alkyl group, a –$(V)_{m'}$-$(CH_2CH_2O)_n$-R^{PEG} group where V is O, S or $NR_{1'}$, $R_{1'}$ is H or a C_1-C_3 alkyl group (preferably H) and R^{PEG} is H or a C_1-C_6 alkyl group which is optionally substituted (including being optionally substituted with a carboxyl group), or

said Aryl group of ULM-g through ULM-i is optionally substituted with a heterocycle, including a heteroaryl, 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, benzofuran, indole, indolizine, azaindolizine, (when substituted each preferably substituted with a C_1-C_3 alkyl group, preferably methyl or a halo group, preferably F or Cl), or a group according to the chemical structure:



S^c of ULM-g through ULM-i is CHR^{SS}, NR^{URE}, or O;

R^{HET} of ULM-g through ULM-i 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);

R^{SS} of ULM-g through ULM-i 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);

R^{URE} of ULM-g through ULM-i is H, a C_1-C_6 alkyl (preferably H or C_1-C_3 alkyl) or a –C(O)(C_0-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;

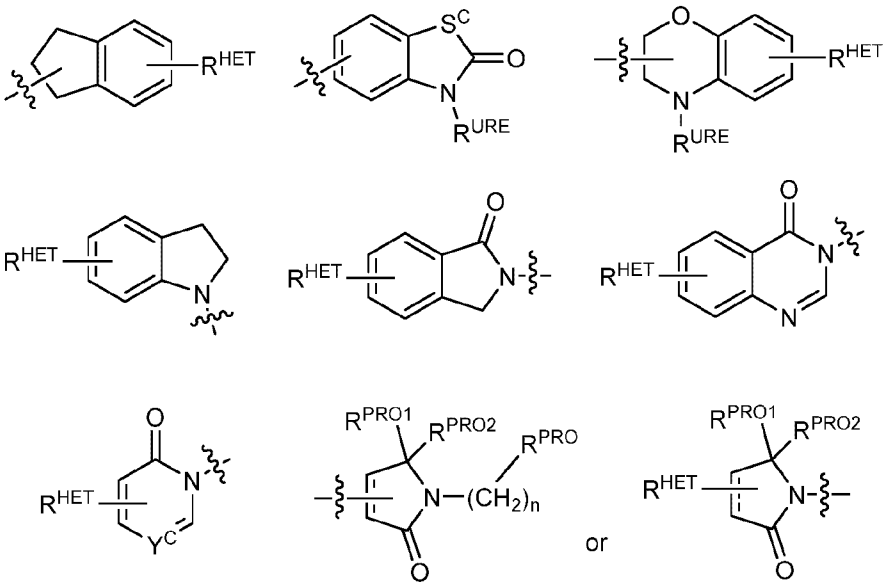
Y^C of ULM-g through ULM-i is N or C-R^{YC}, where R^{YC} is H, OH, CN, NO_2, halo (preferably Cl or F), optionally substituted C_1-C_6 alkyl (preferably substituted with one or two hydroxyl groups or up to three halo groups (e.g. CF_3), optionally substituted O(C_1-C_6 alkyl) (preferably substituted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

R^{PRO} of ULM-g through ULM-i 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;

R^{PRO1} and R^{PRO2} of ULM-g through ULM-i are each independently H, an optionally subsituted C_1-C_3 alkyl group or together form a keto group;

HET of ULM-g through ULM-i is preferably 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, or a group according to the chemical structure:



S^c of ULM-g through ULM-i is CHR^{SS}, NR^{URE}, or O;

R^{HET} of ULM-g through ULM-i 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);

R^{SS} of ULM-g through ULM-i 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);

R^{URE} of ULM-g through ULM-i is H, a C_1-C_6 alkyl (preferably H or C_1-C_3 alkyl) or a –C(O)(C_0-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;

Y^C of ULM-g through ULM-i 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 $-C\equiv C-R_a$ where R_a is H or a C_1-C_6 alkyl group (preferably C_1-C_3 alkyl);

R^{PRO} of ULM-g through ULM-i is H, optionally substituted C_1-C_6 alkyl or an optionally substituted aryl, heteroaryl or heterocyclic group;

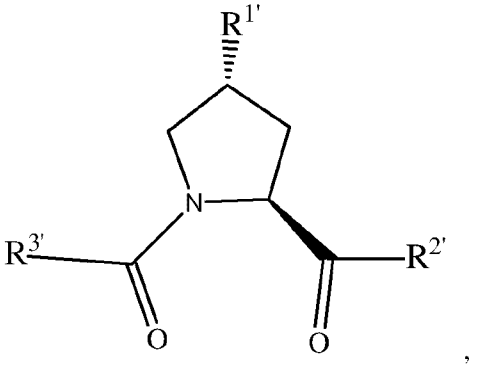
R^{PRO1} and R^{PRO2} of ULM-g through ULM-i are each independently H, an optionally subsituted C_1-C_3 alkyl group or together form a keto group;

each m' of ULM-g through ULM-i is independently 0 or 1; and

each n of ULM-g through ULM-i is independently 0, 1, 2, 3, 4, 5, or 6 (preferably 0 or 1),

wherein each of said compounds, preferably on said Aryl or HET groups, is optionally connected to a PTM group (including a ULM' group) via a linker group.

[0132] In still additional embodiments, preferred compounds include those according to the chemical structure:



ULM-i

wherein:

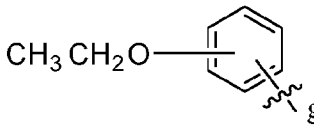
$R^{1'}$ of ULM-i is OH or a group which is metabolized in a patient or subject to OH;

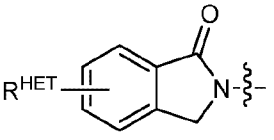
$R^{2'}$ of ULM-i is a $-NH-CH_2$-Aryl-HET (preferably, a phenyl linked directly to a methyl substituted thiazole);

$R^{3'}$ of ULM-i is a $-CHR^{CR3'}$-NH-C(O)-R^{3P1} group or a $-CHR^{CR3'}$-R^{3P2} group;

$R^{CR3'}$ of ULM-i is a C_1-C_4 alkyl group, preferably methyl, isopropyl or tert-butyl;

R^{3P1} of ULM-i is C_1-C_3 alkyl (preferably methyl), an optionally substituted oxetane group (preferably methyl substituted, a $-(CH_2)_nOCH_3$ group where n is 1 or 2 (preferably 2), or a


group (the ethyl ether group is preferably meta-substituted on the phenyl moiety), a morpholino grop (linked to the carbonyl at the 2- or 3-position;

R^{3P2} of ULM-i is a  group;

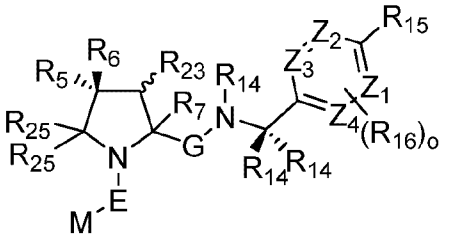
Aryl of ULM-i is phenyl;

HET of ULM-i is an optionally substituted thiazole or isothiazole; and

R^{HET} of ULM-i is H or a halo group (preferably H);

or a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof, wherein each of said compounds is optionally connected to a PTM group (including a ULM' group) via a linker group.

[0133] In certain aspects, bifunctional compounds comprising a ubiquitin E3 ligase binding moiety (ULM), wherein ULM is a group according to the chemical structure:



ULM-j

wherein:

each R_5 and R_6 of ULM-j is independently OH, SH, or optionally substituted alkyl or R_5, R_6, and the carbon atom to which they are attached form a carbonyl;

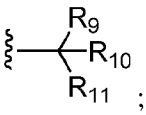
R_7 of ULM-j is H or optionally substituted alkyl;

E of ULM-j is a bond, C=O, or C=S;

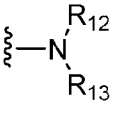
G of ULM-j is a bond, optionally substituted alkyl, -COOH or C=J;

J of ULM-j is O or N-R_8;

R_8 of ULM-j is H, CN, optionally substituted alkyl or optionally substituted alkoxy;

M of ULM-j is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic or  ;

each R_9 and R_{10} of ULM-j is independently H; optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted hydroxyalkyl, optionally substituted thioalkyl, a disulphide linked ULM, 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} of ULM-j is optionally substituted heterocyclic, optionally substituted alkoxy, optionally substituted heteroaryl, optionally substituted aryl, or  ;

R_{12} of ULM-j is H or optionally substituted alkyl;

R_{13} of ULM-j 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; optionally substituted (oxoalkyl)carbamate,

each R_{14} of ULM-j is independently H, haloalkyl, optionally substituted cycloalkyl, optionally substituted alkyl or optionally substituted heterocycloalkyl;

R_{15} of ULM-j is H, optionally substituted heteroaryl, haloalkyl, optionally substituted aryl, optionally substituted alkoxy, or optionally substituted heterocyclyl;

each R_{16} of ULM-j is independently halo, optionally substituted alkyl, optionally substituted haloalkyl, CN, or optionally substituted haloalkoxy;

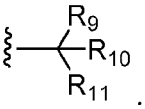
each R_{25} of ULM-j is independently H or optionally substituted alkyl; or both R_{25} groups can be taken together to form an oxo or optionally substituted cycloalkyl group;

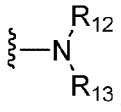
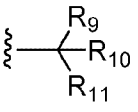
R_{23} of ULM-j is H or OH;

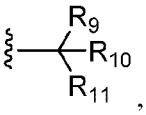
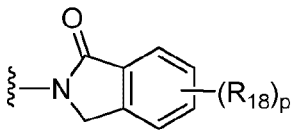
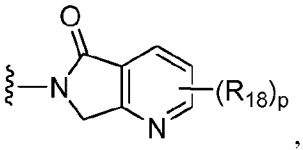
Z_1, Z_2, Z_3, and Z_4 of ULM-j are independently C or N; and

o of ULM-j is 0, 1, 2, 3, or 4, or a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof.

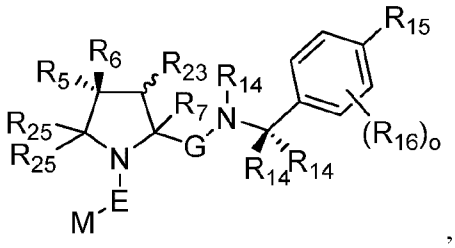
[0134] In certain embodiments, wherein G of ULM-j is C=J, J is O, R_7 is H, each R_{14} is H, and o is 0.

[0135] In certain embodiments, wherein G of ULM-j is C=J, J is O, R_7 is H, each R_{14} is H, R_{15} is optionally substituted heteroaryl, and o is 0. In other instances, E is C=O and M is  .

[0136] In certain embodiments, wherein E of ULM-j is C=O, R_{11} is optionally substituted heterocyclic or  , and M is  .

[0137] In certain embodiments, wherein E of ULM-j is C=O, M is  , and R_{11} is  or  , each R_{18} is independently halo, optionally substituted alkoxy, cyano, optionally substituted alkyl, haloalkyl, or haloalkoxy; and p is 0, 1, 2, 3, or 4.

[0138] In certain embodiments, ULM and where present, ULM', are each independently a group according to the chemical structure:



ULM-k

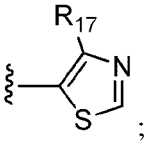
wherein:

G of ULM-k is C=J, J is O;

R_7 of ULM-k is H;

each R_{14} of ULM-k is H;

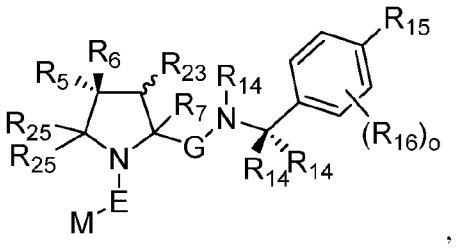
o of ULM-k is 0;

R_{15} of ULM-k is  ; and

R_{17} of ULM-k is H, halo, optionally substituted cycloalkyl, optionally substituted alkyl, optionally substituted alkenyl, and haloalkyl.

[0139] In other instances, R_{17} of ULM-k is alkyl (e.g., methyl) or cycloalkyl (e.g., cyclopropyl).

[0140] In other embodiments, ULM and where present, ULM', are each independently a group according to the chemical structure:



wherein:

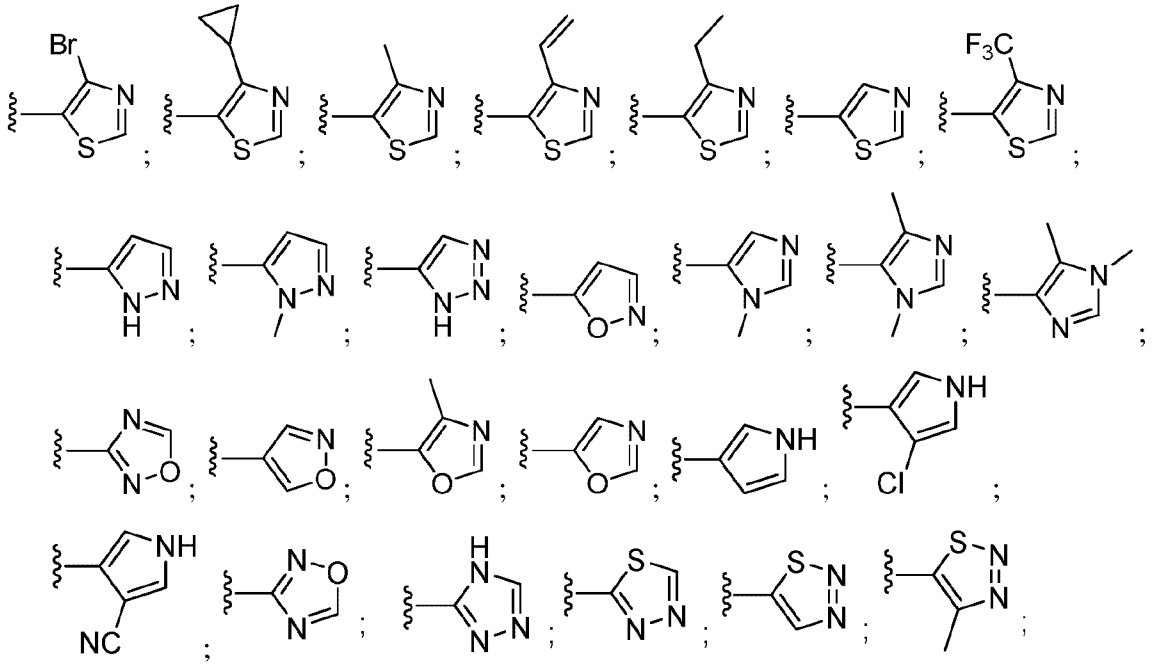
G of ULM-k is C=J, J is O;

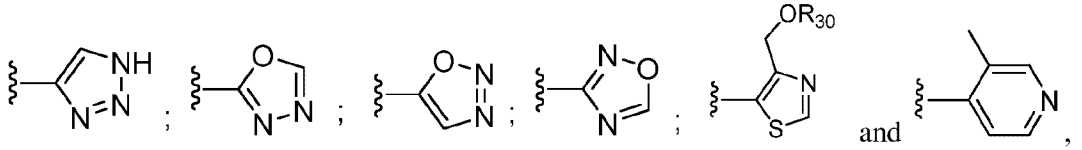
R_7 of ULM-k is H;

each R_{14} of ULM-k is H;

o of ULM-k is 0; and

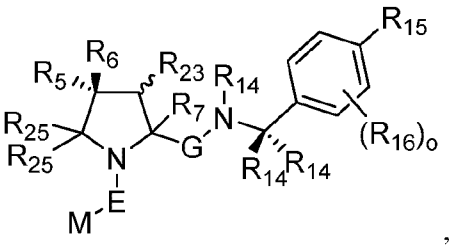
R_{15} of ULM-k is selected from the group consisting of:





wherein R_{30} of ULM-k is H or an optionally substituted alkyl.

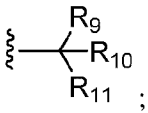
[0141] In other embodiments, ULM and where present, ULM', are each independently a group according to the chemical structure:



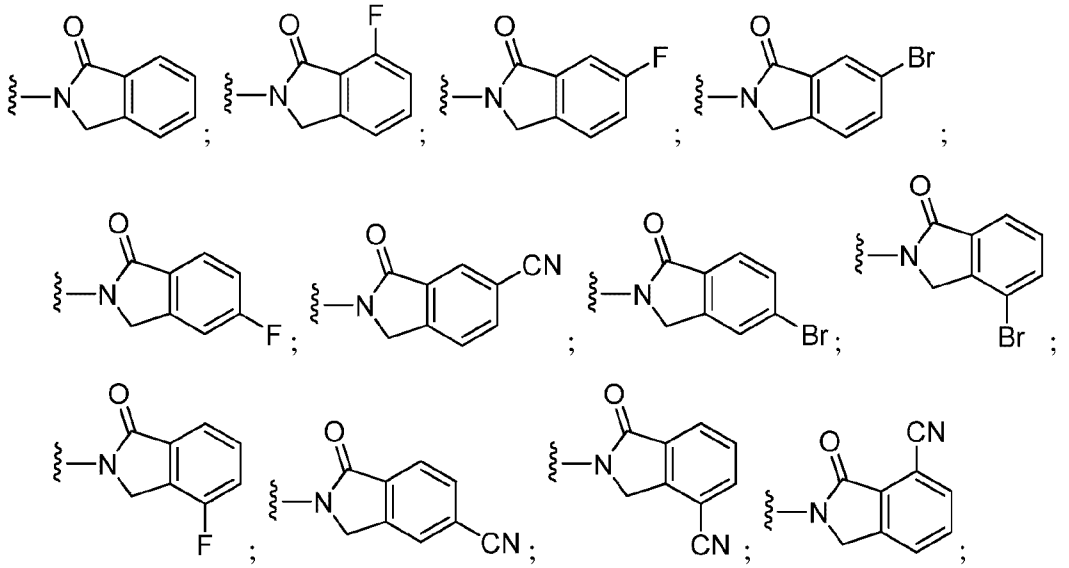
ULM-k

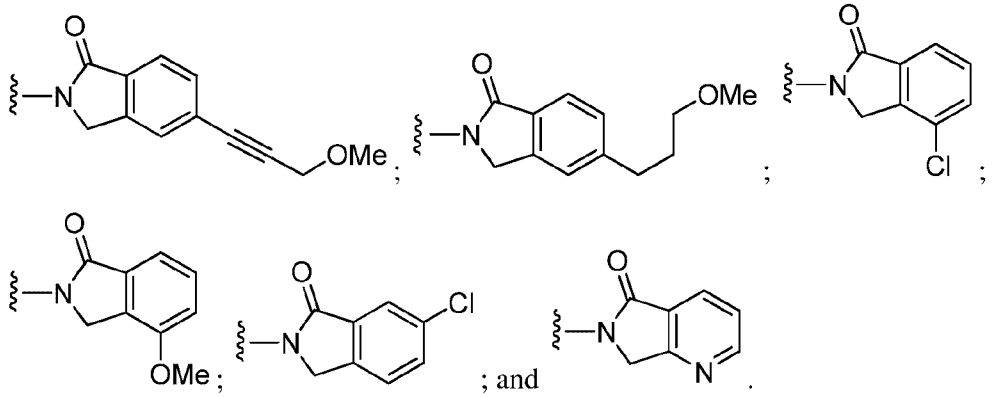
wherein:

E of ULM-k is C=O;

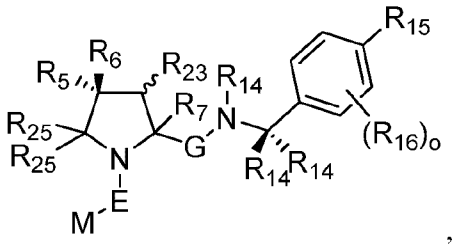
M of ULM-k is  ; and

R_{11} of ULM-k is selected from the group consisting of:





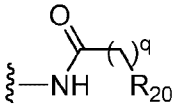
[0142] In still other embodiments, a compound of the chemical structure,

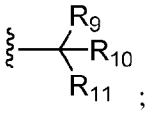


ULM-k

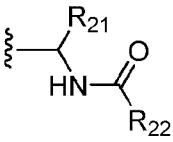
wherein:

E of ULM-k is C=O;

R_{11} of ULM-k is  ; and

M of ULM-k is  ;

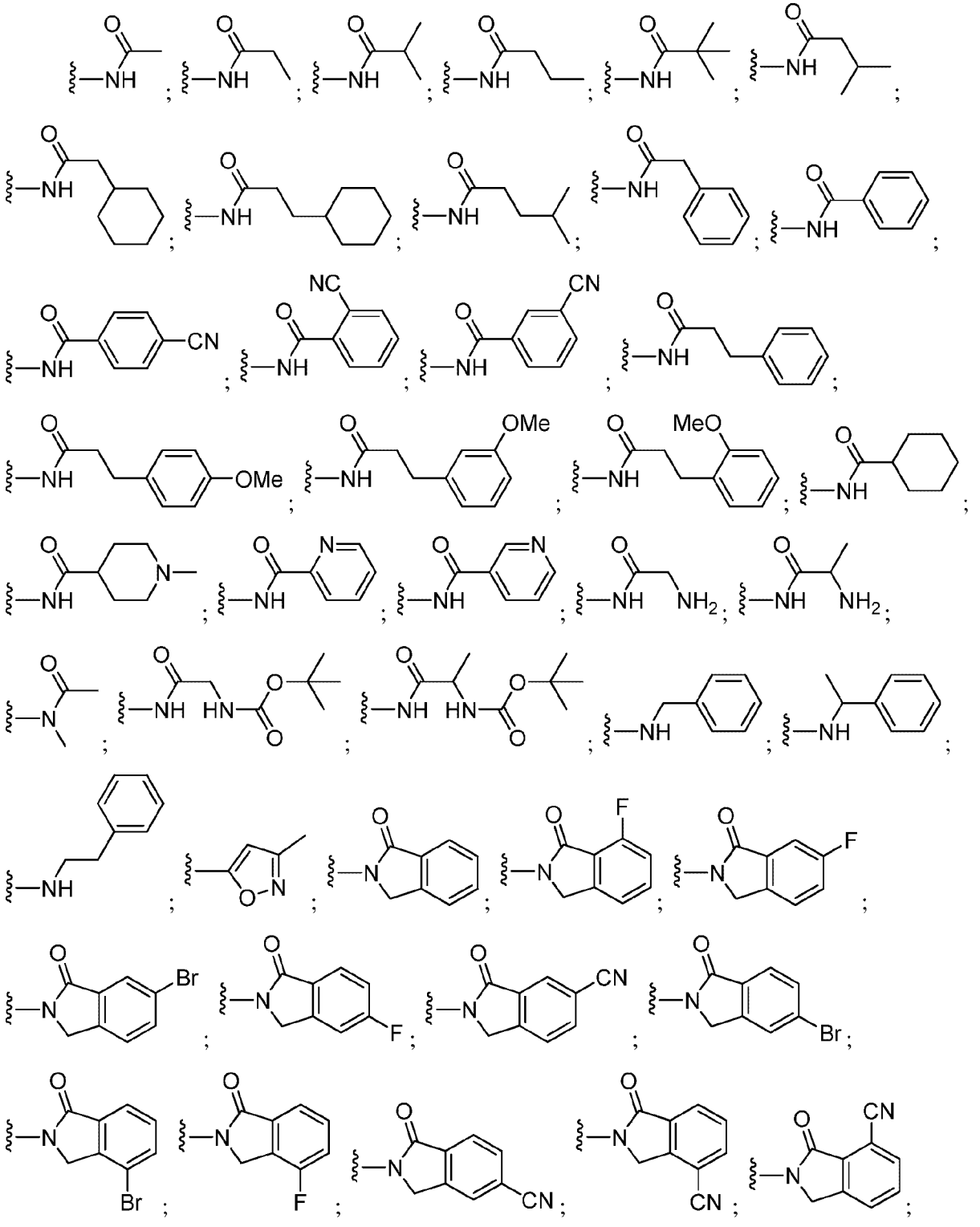
q of ULM-k is 1 or 2;

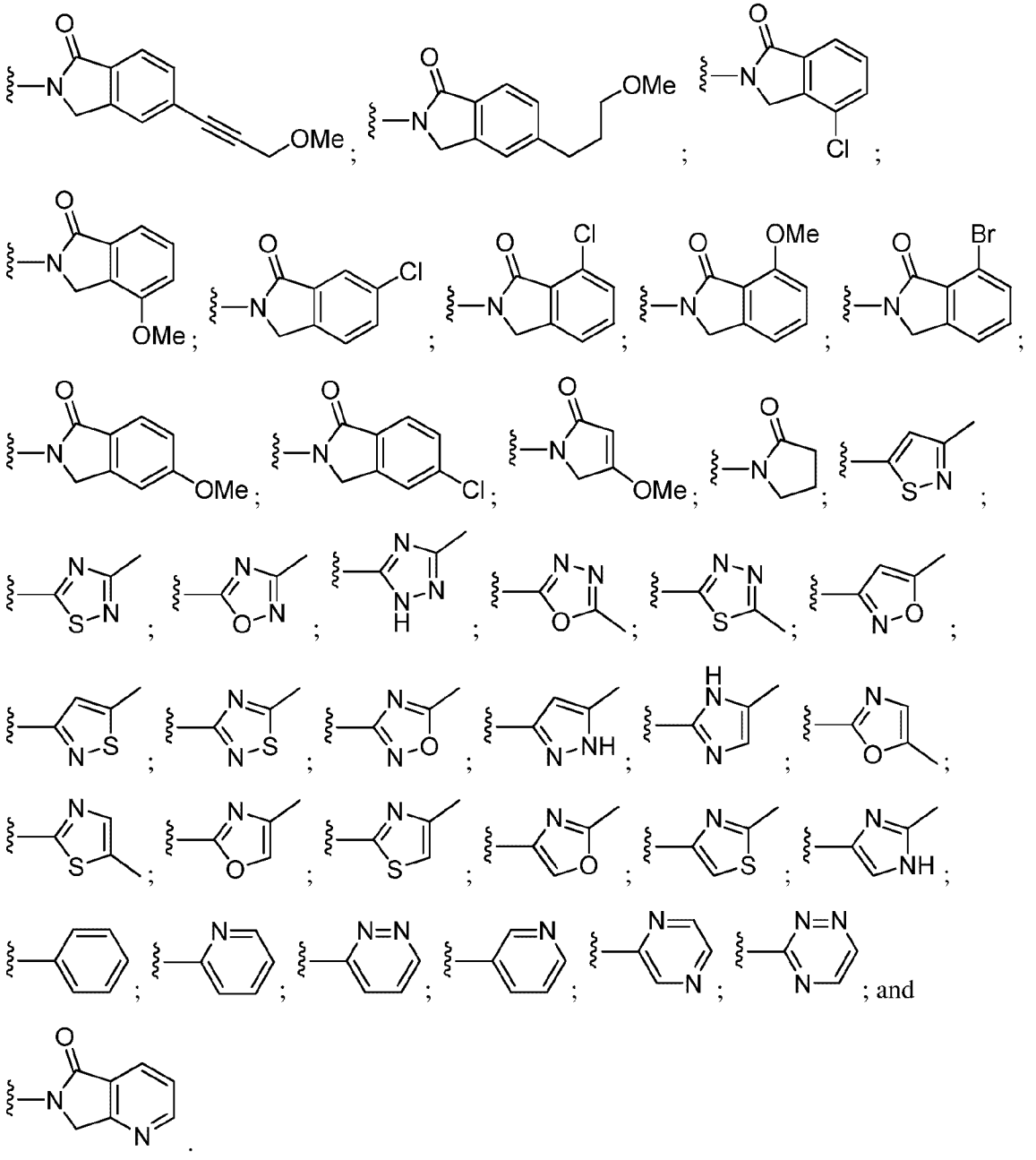
R_{20} of ULM-k is H, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aryl, or  ;

R_{21} of ULM-k is H or optionally substituted alkyl; and

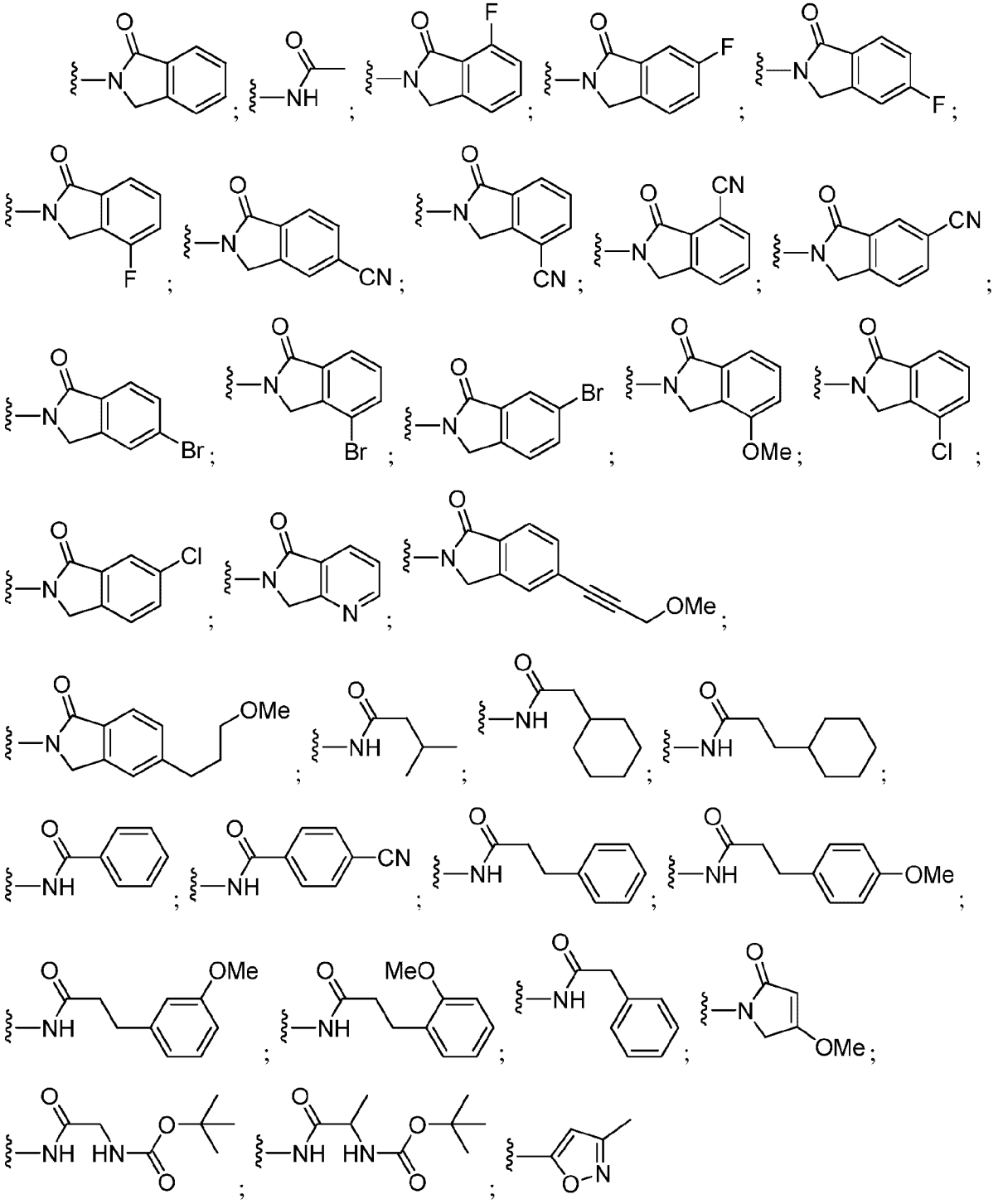
R_{22} of ULM-k is H, optionally substituted alkyl, optionally substituted alkoxy, or haloalkyl.

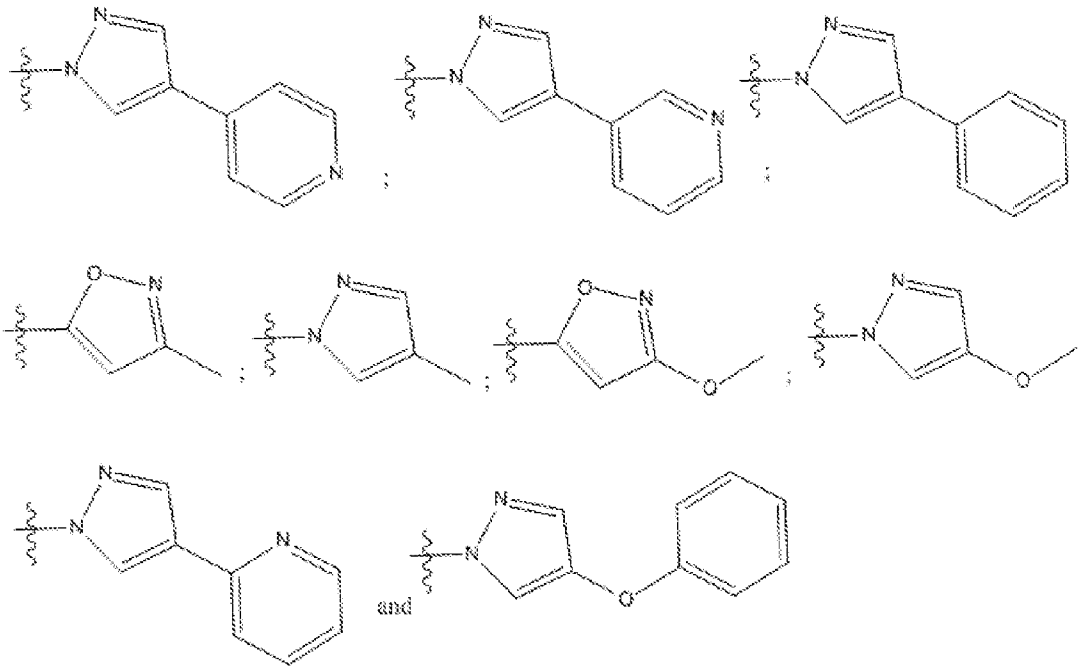
[0143] In any embodiment described herein, R_{11} of ULM-j or ULM-k is selected from the group consisting of:



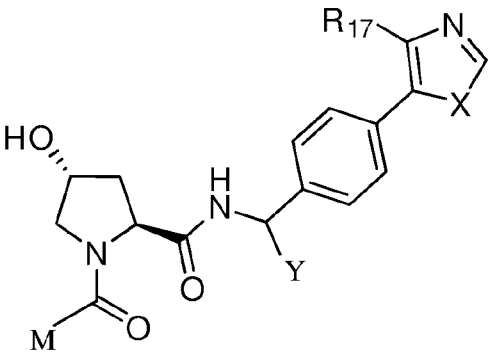


[0144] In certain embodiments, R_{11} of ULM-j or ULM-k is selected from the group consisting of:





[0145] In certain embodiments, ULM (or when present ULM') is a group according to the chemical structure:



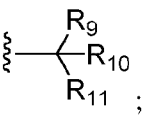
ULM-l

wherein:

X of ULM-l is O or S;

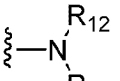
Y of ULM-l is H, methyl or ethyl;

R_{17} of ULM-l is H, methyl, ethyl, hydoxymethyl or cyclopropyl;

M of ULM-l is is optionally substituted aryl, optionally substituted heteroaryl, or  ;

$R_{9\ of\ ULM\text{-}l}$ is H;

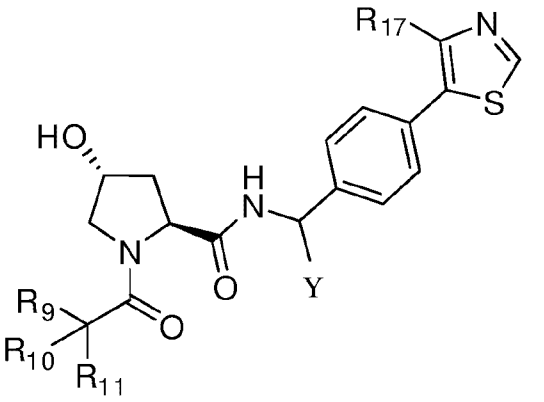
R_{10} of ULM-l is H, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted heteroaryl, optionally substituted aryl, optionally substituted hydroxyalkyl, optionally substituted thioalkyl or cycloalkyl;

R11 of ULM-l is optionally substituted heteroaromatic, optionally substituted heterocyclic, optionally substituted aryl or  ;

R_{12} of ULM-l is H or optionally substituted alkyl; and

R_{13} of ULM-l 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; optionally substituted (oxoalkyl)carbamate.

[0146] In some embodiments, ULM and where present, ULM', are each independently a group according to the chemical structure:



ULM-m

wherein:

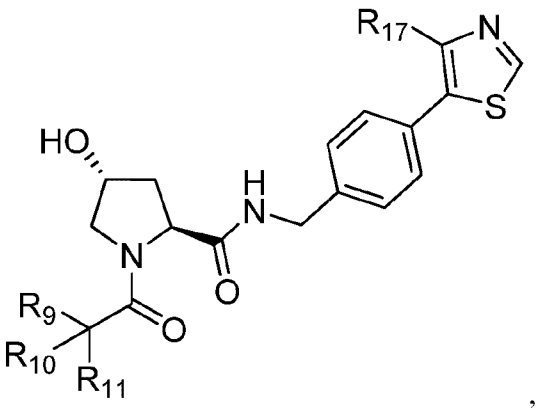
Y of ULM-m is H, methyol or ethyl

R_9 of ULM-m is H;

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

R_{11} of ULM-m is optionally substituted amide, optionally substituted isoindolinone, optionally substituted isooxazole, optionally substituted heterocycles.

[0147] In other preffered embodiments of the invention, ULM and where present, ULM', are each independently a group according to the chemical structure:



ULM-n

wherein:

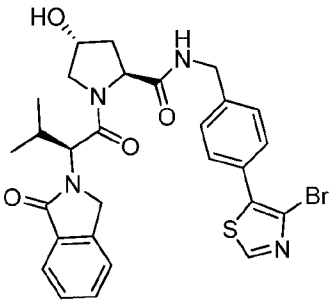
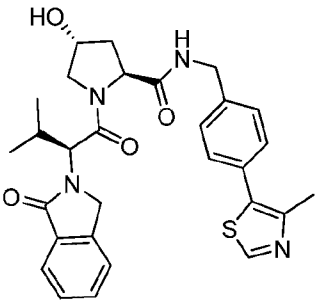
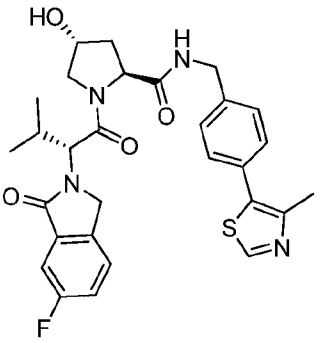
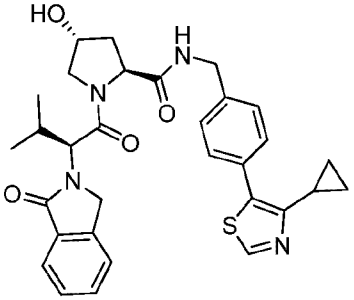
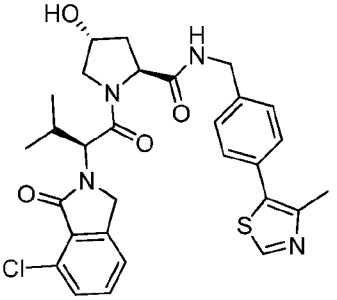
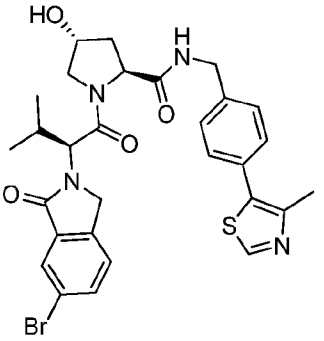
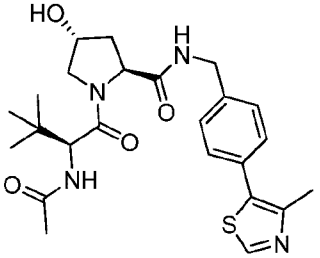
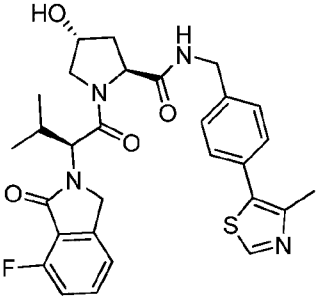
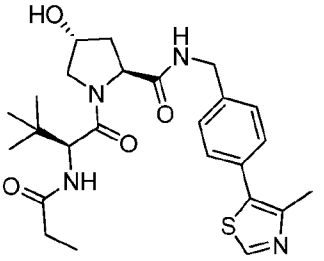
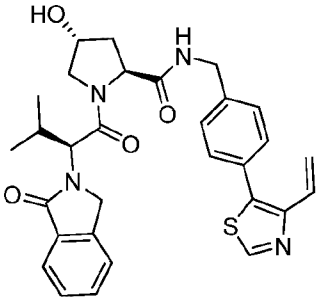
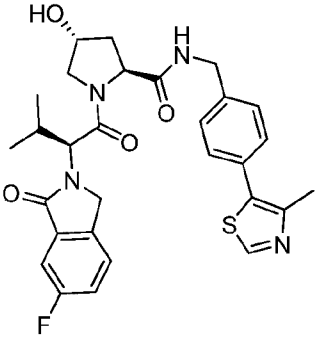
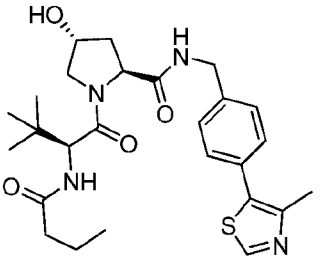
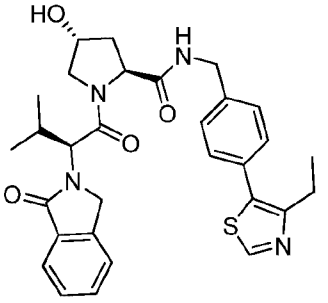
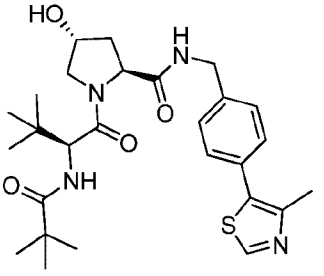
R_{17} of ULM-n is methyl, ethyl, or cyclopropyl; and

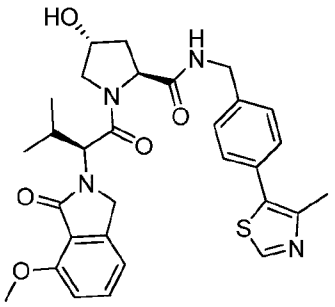
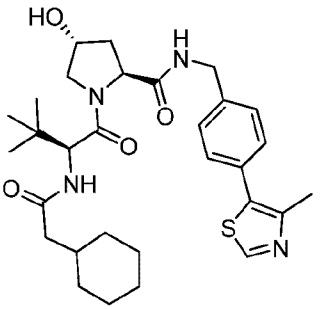
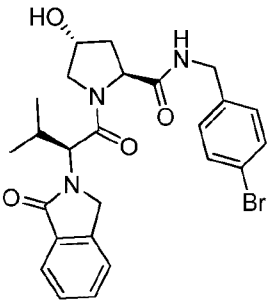
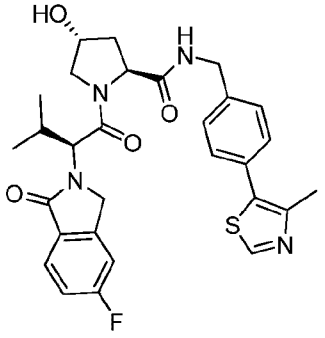
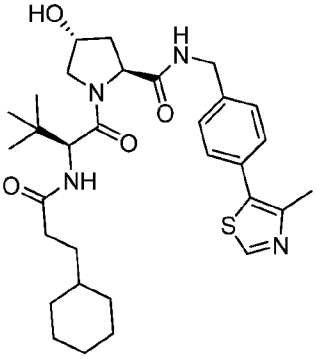
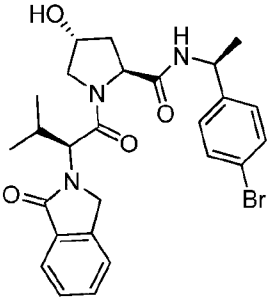
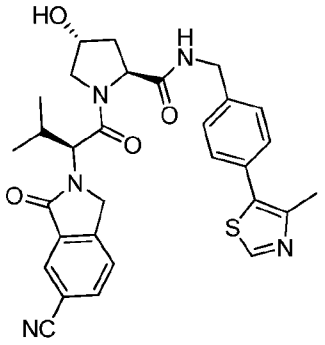
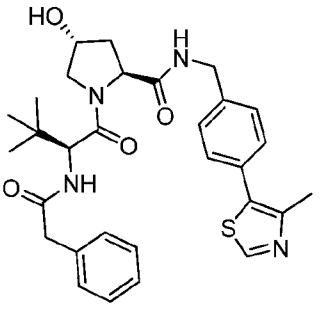
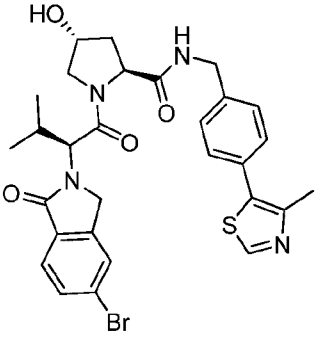
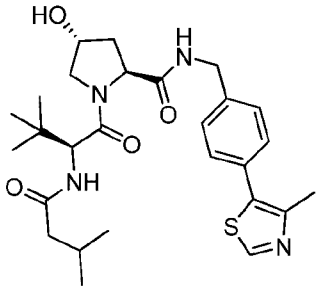
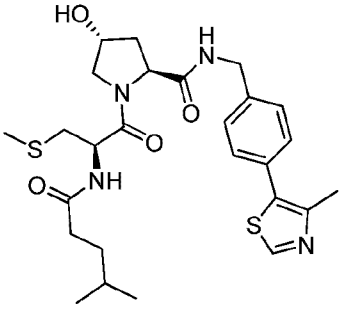
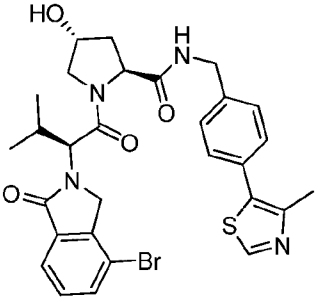
R_9, R_{10}, and R_{11} of ULM-n are as defined above. In other instances, R_9 is H; and

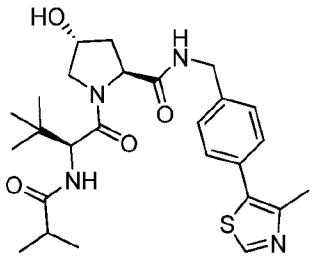
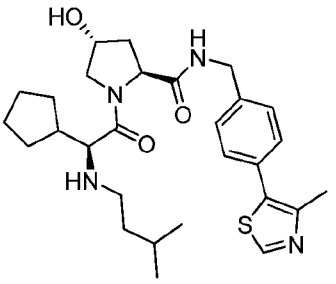
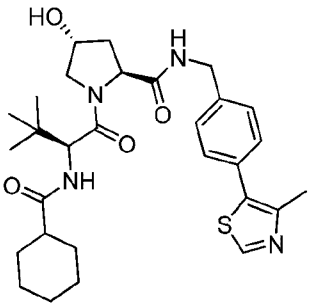
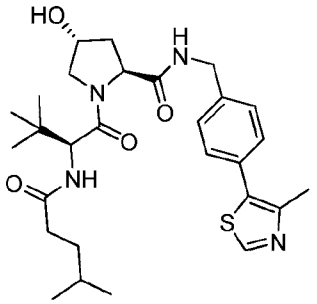
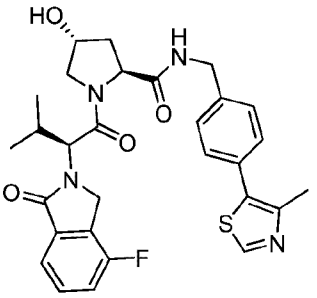
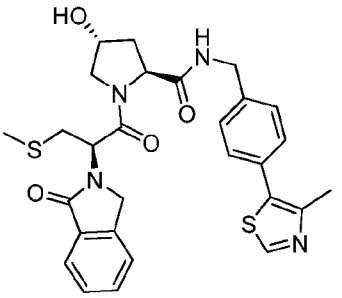
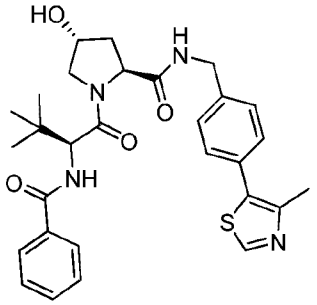
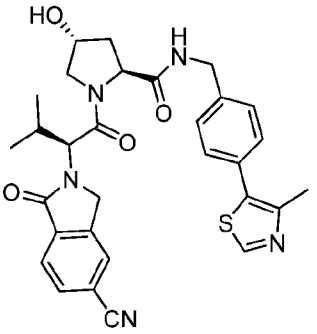
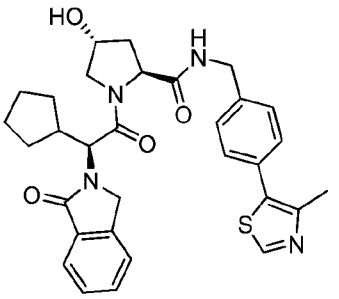
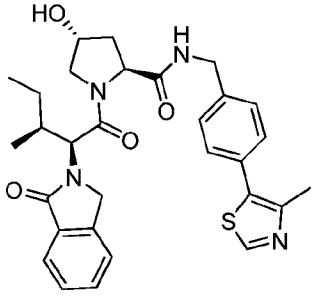
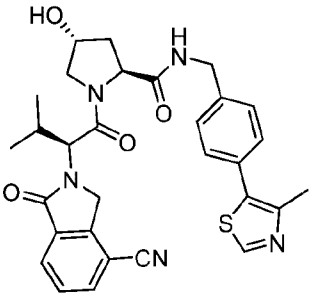
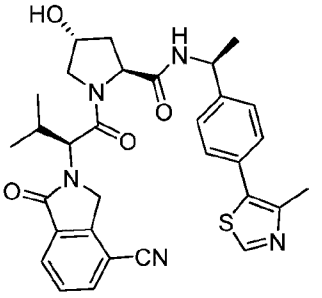
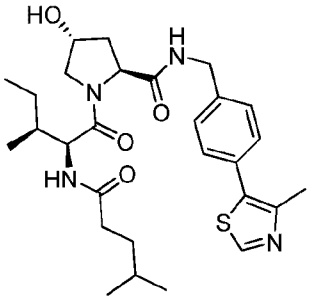
R_{10} of ULM-n is H, alkyl, or or cycloalkyl (preferably, isopropyl, tert-butyl, sec-butyl, cyclopentyl, or cyclohexyl).

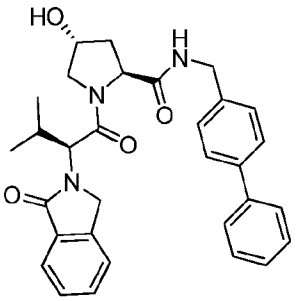
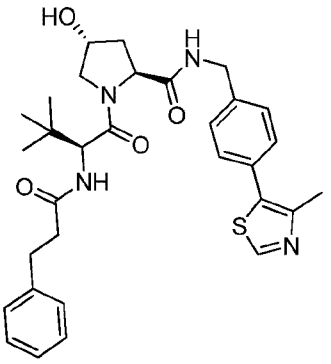
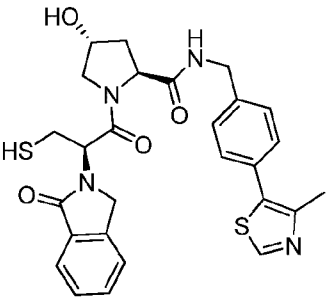
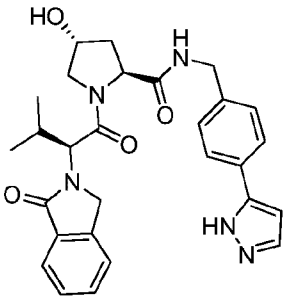
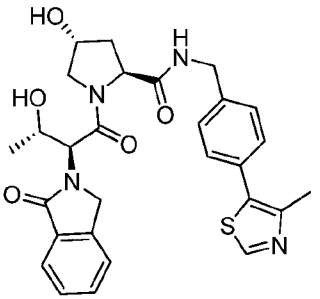
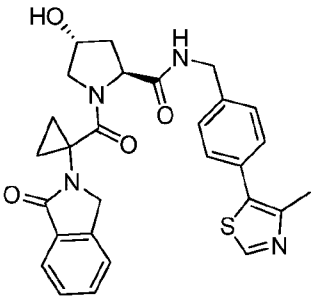
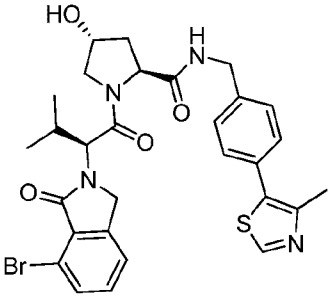
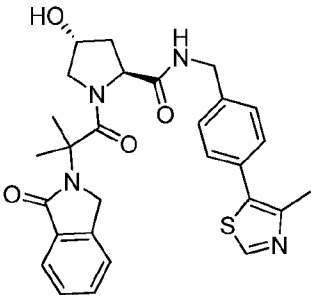
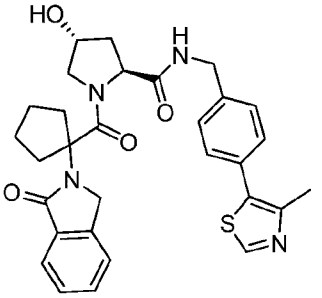
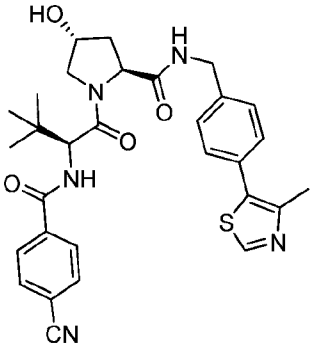
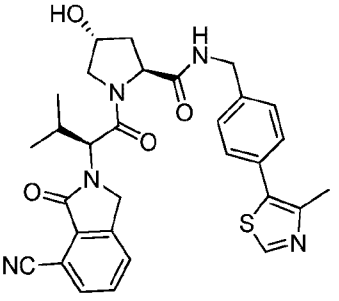
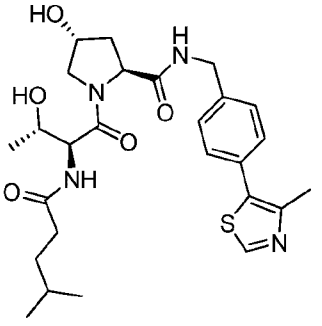
[0148] In any of the aspects or embodiments described herein, the ULM (or when present, ULM') as described herein may be a pharmaceutically acceptable salt, enantiomer, diastereomer, solvate or polymorph thereof. In addition, in any of the aspects or embodiments described herein, the ULM (or when present, ULM') as described herein may be coupled to a PTM directly via a bond or by a chemical linker.

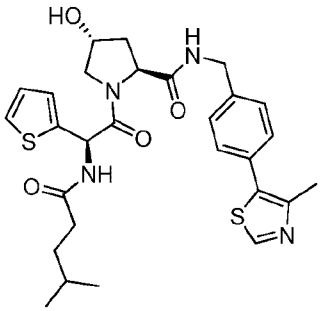
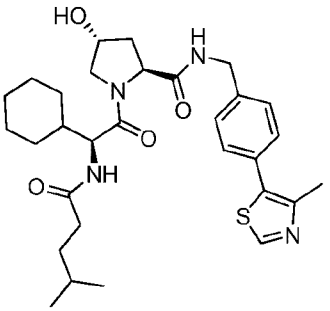
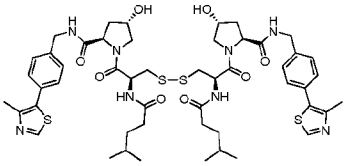
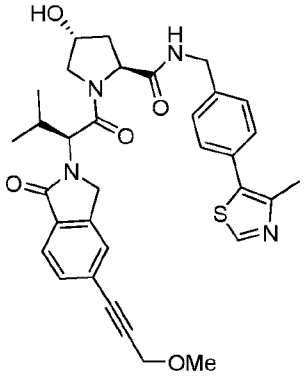
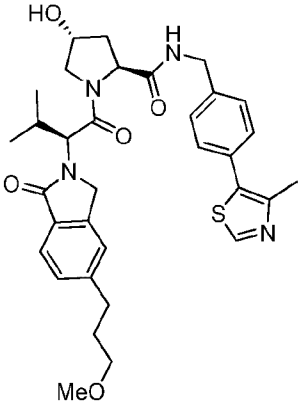
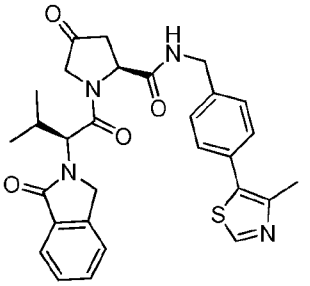
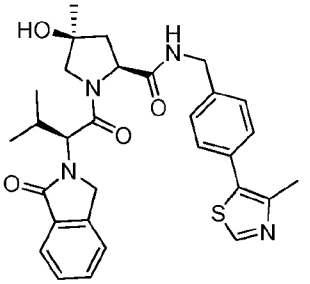
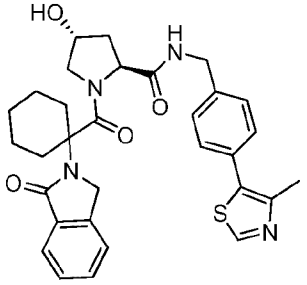
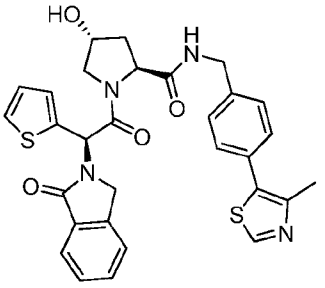
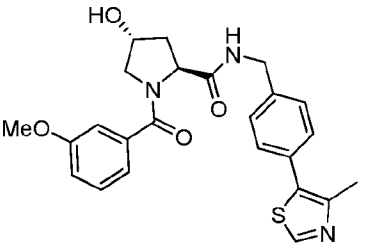
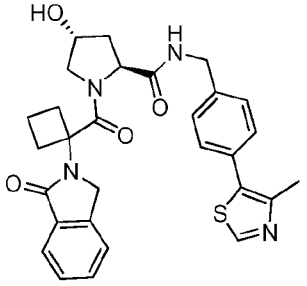
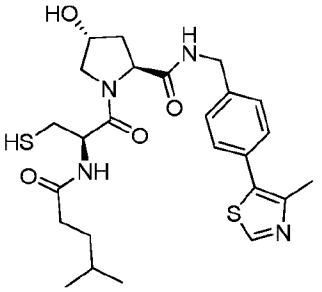
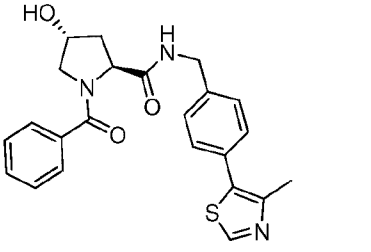
[0149] In certain aspects of the invention, the ULM moiety is selected from the group consisting of:

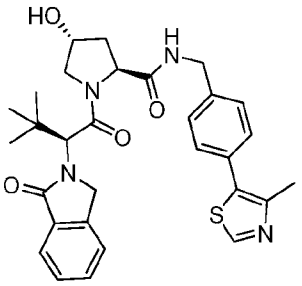
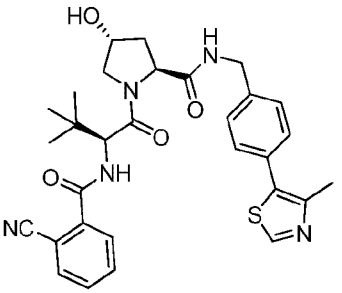
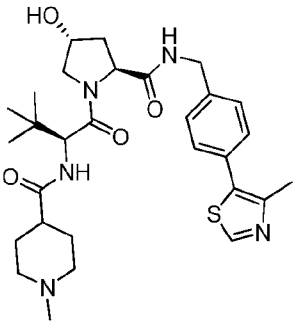
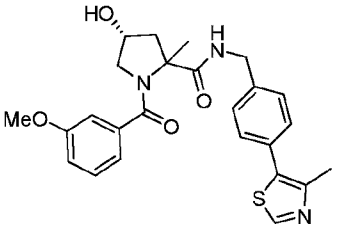
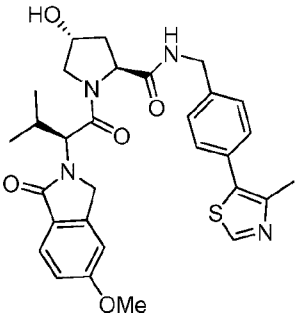
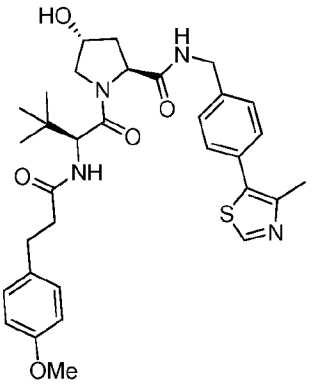
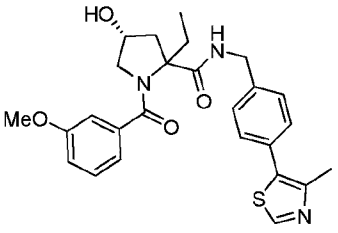
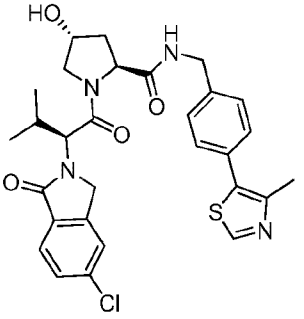
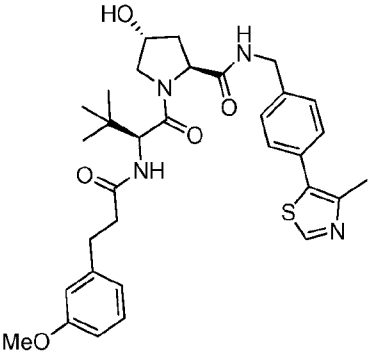
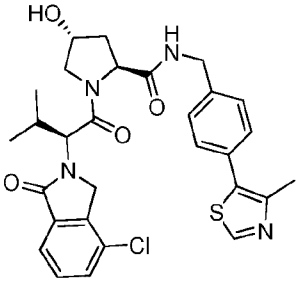
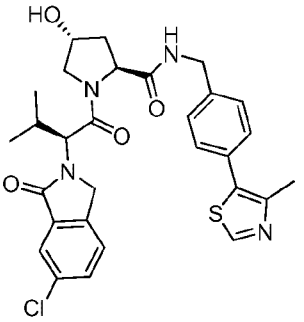
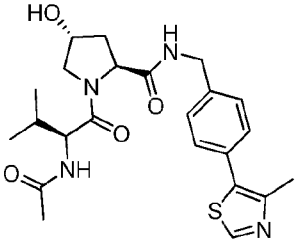
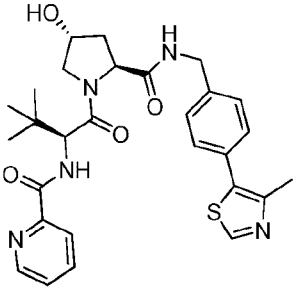















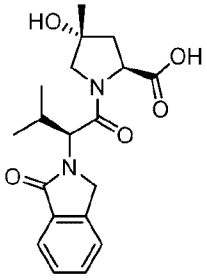
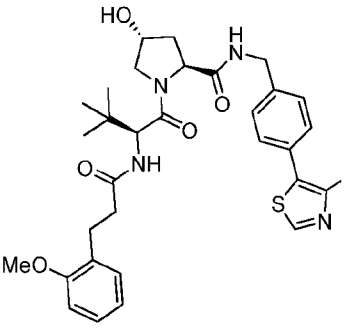
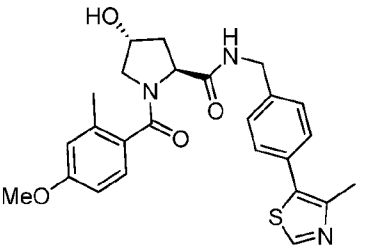
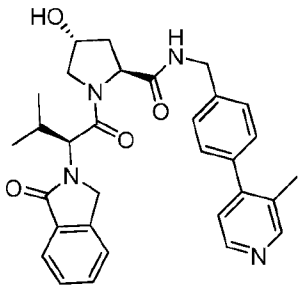
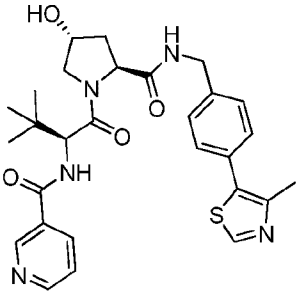
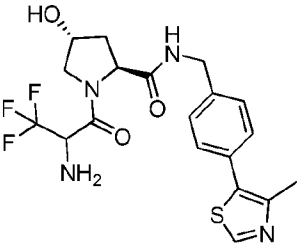
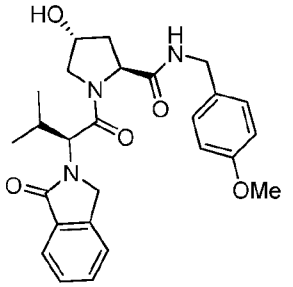
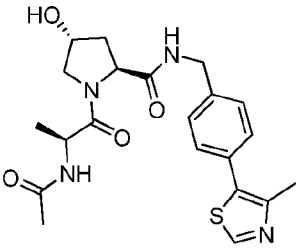
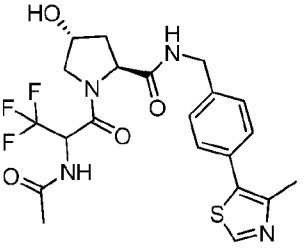
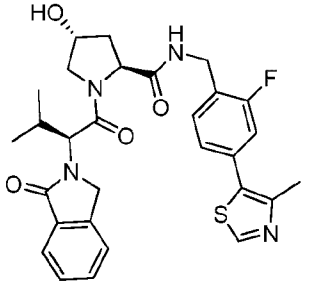
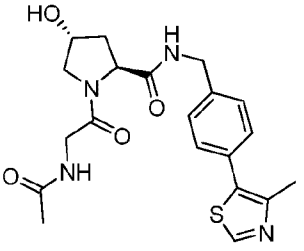
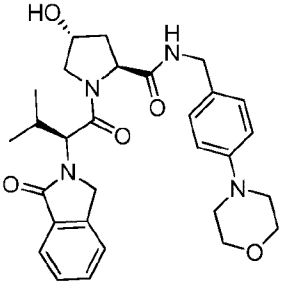
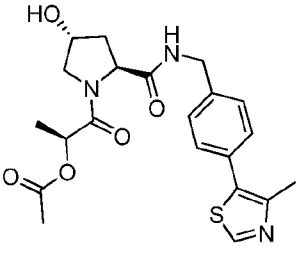
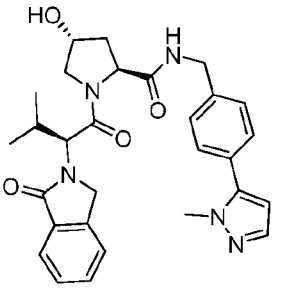













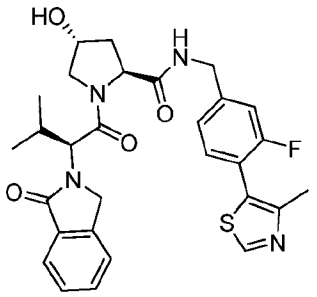
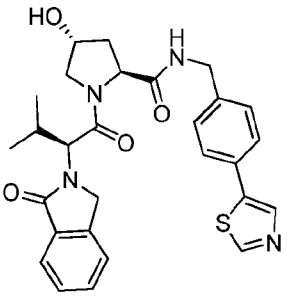
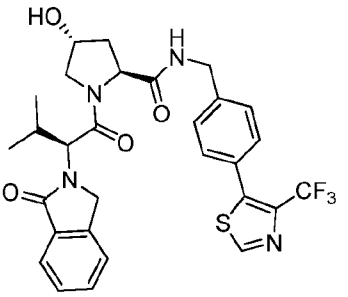
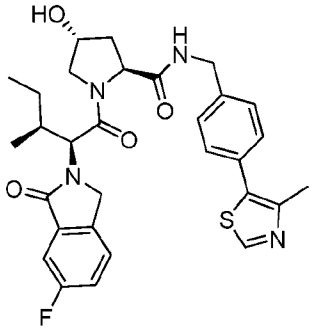
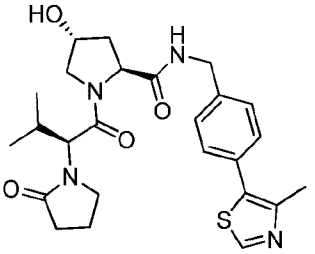
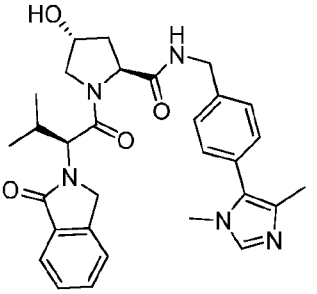
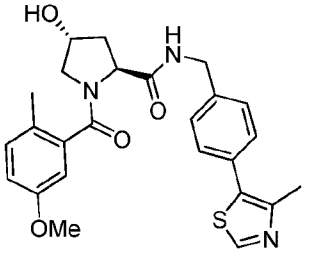
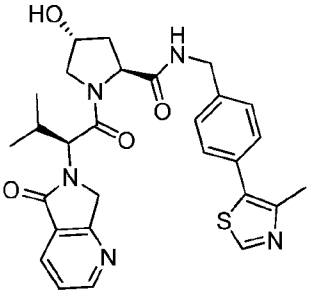
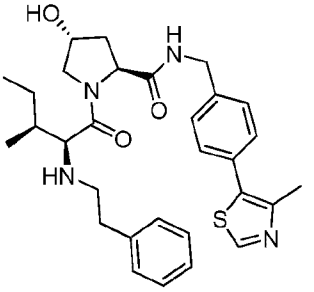
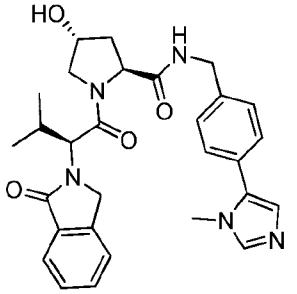
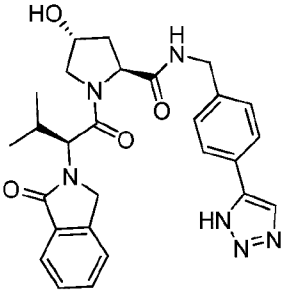
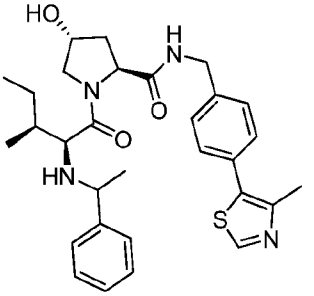
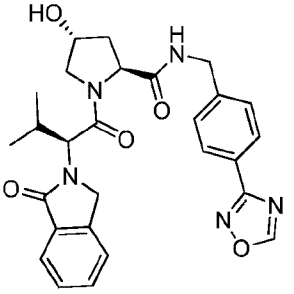














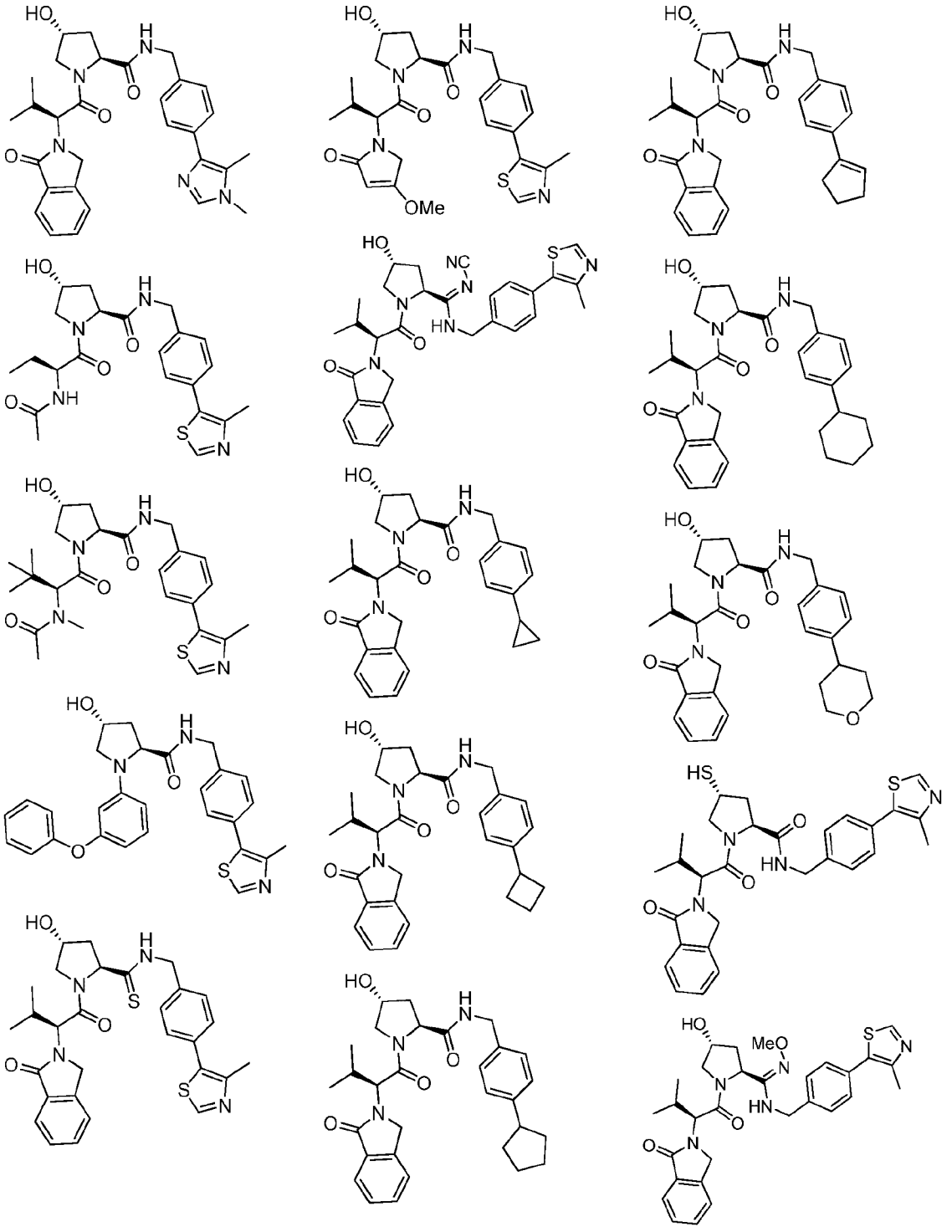













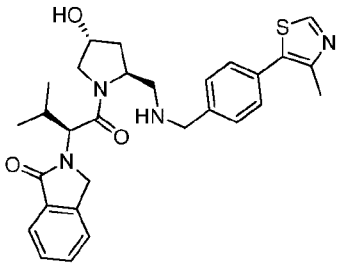
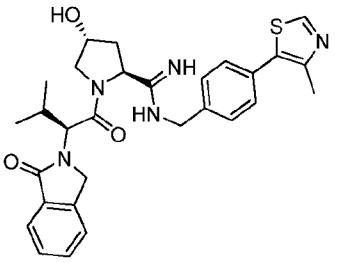
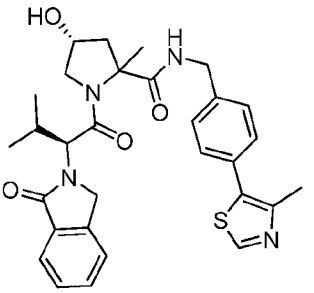
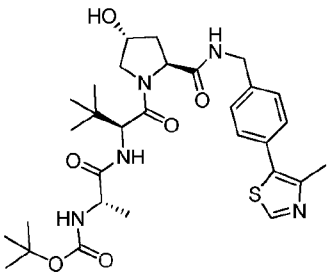
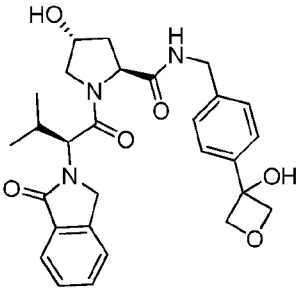
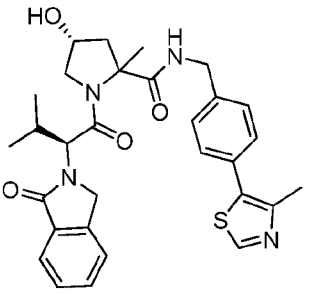
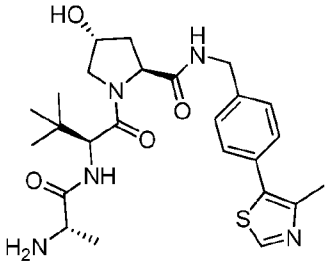
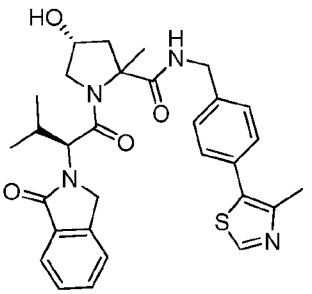
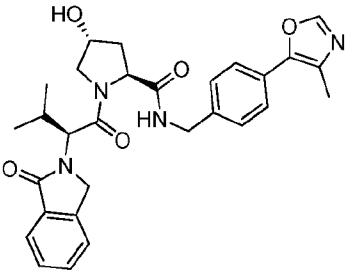
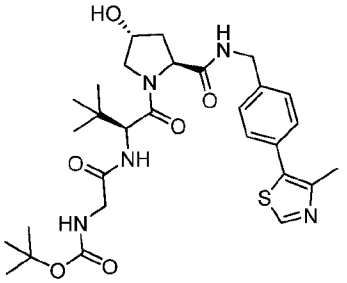
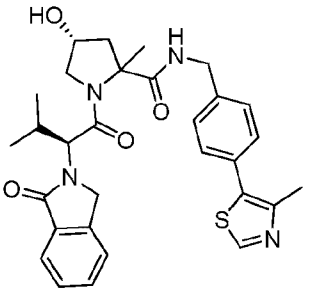
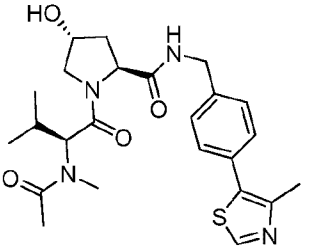
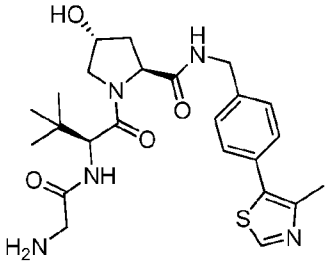
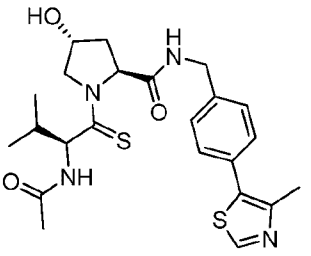
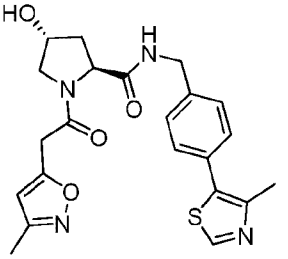














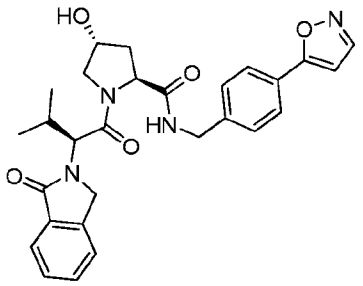
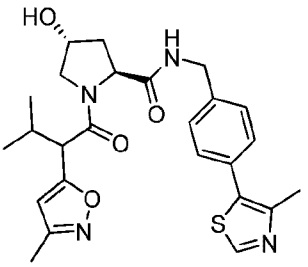
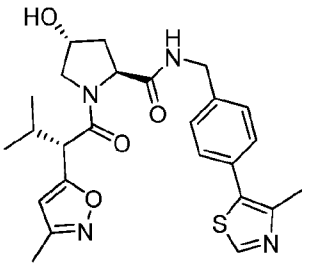
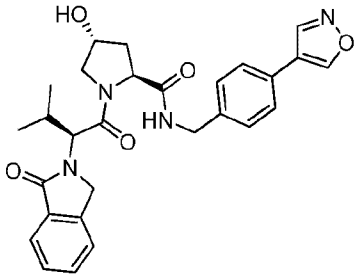
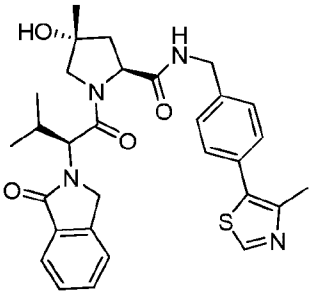
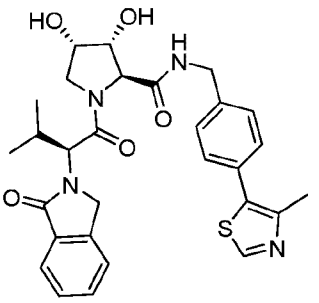
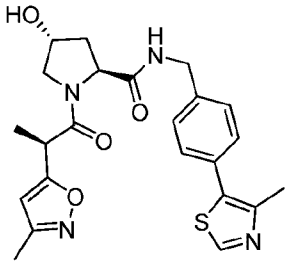
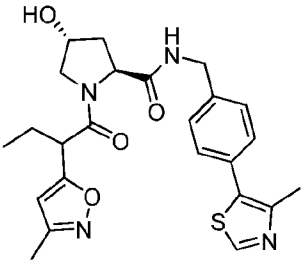
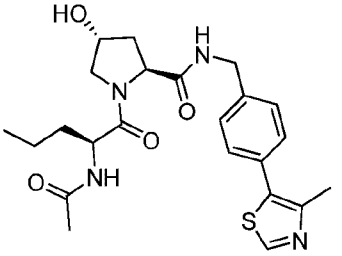
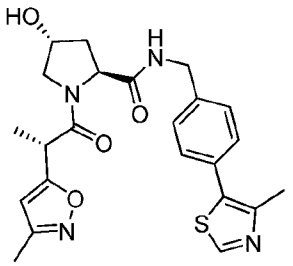
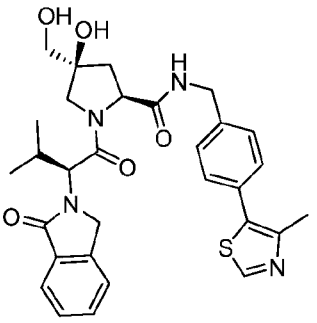
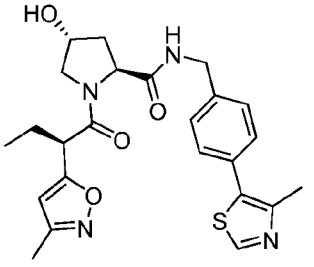
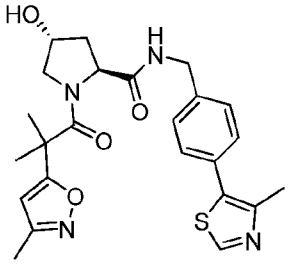
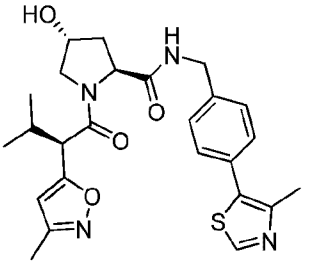
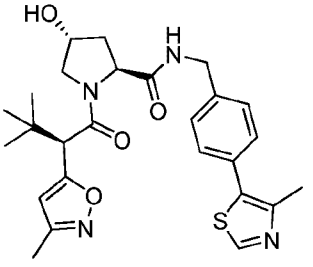














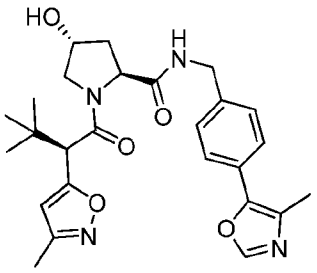
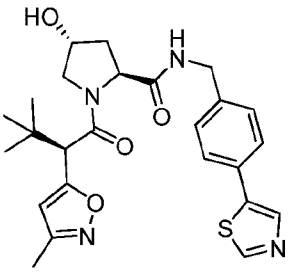
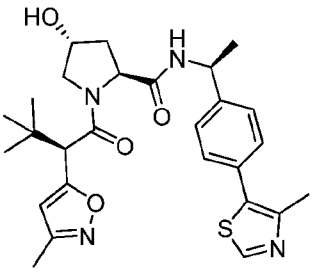
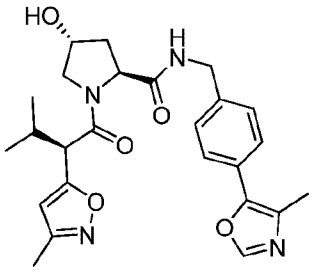
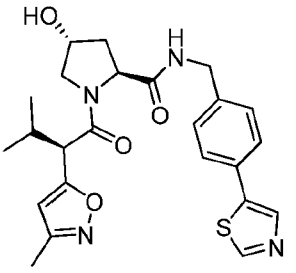
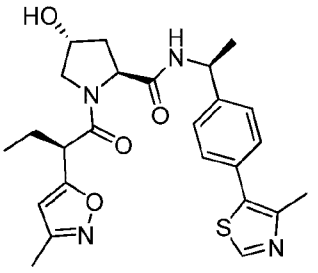
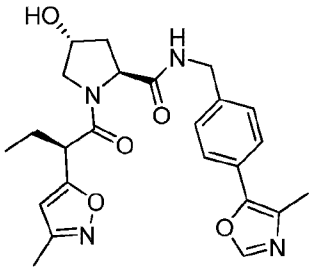
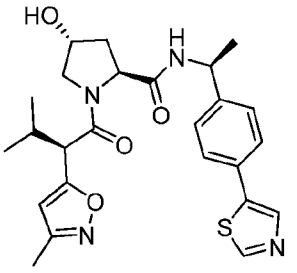
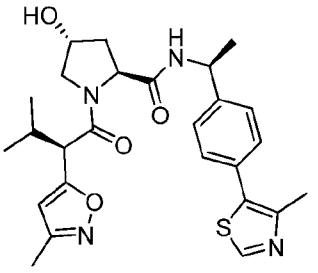
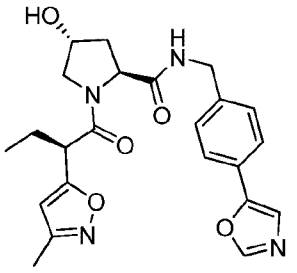
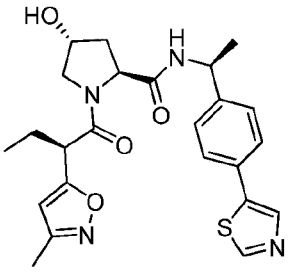
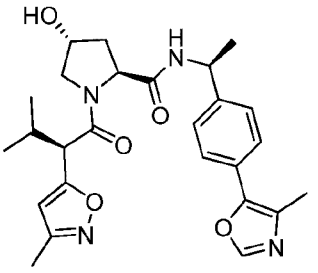
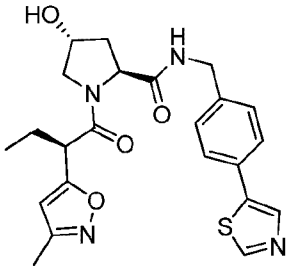
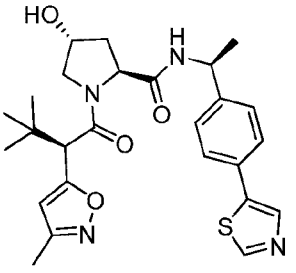
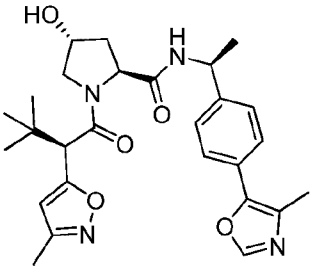















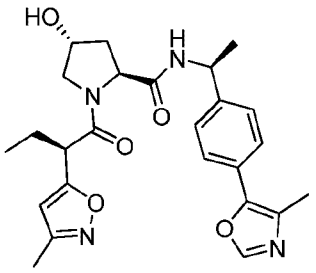
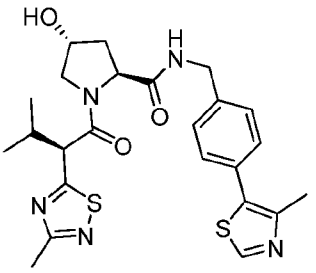
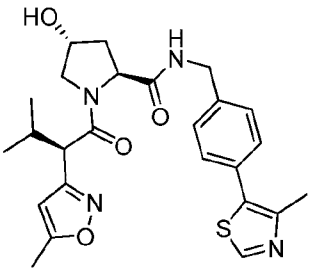
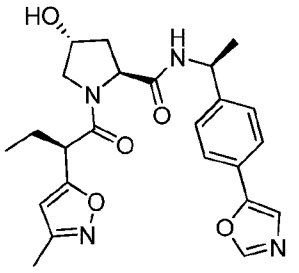
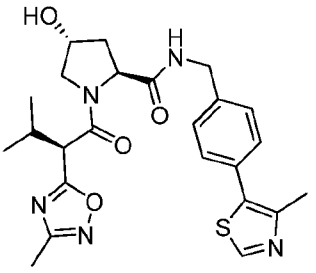
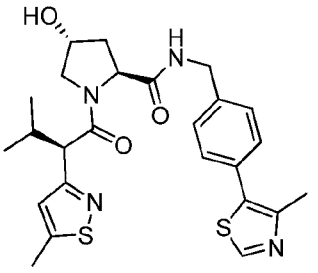
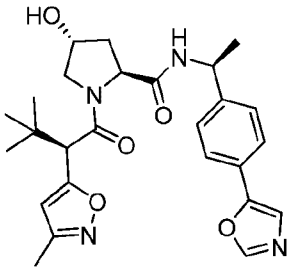
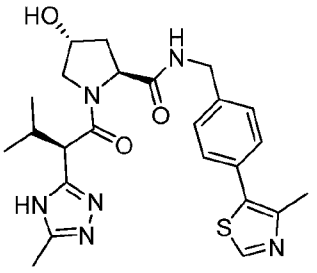
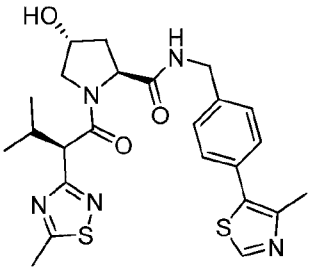
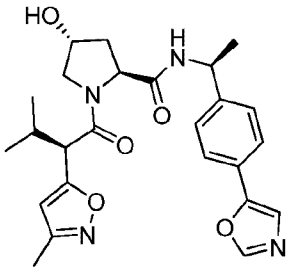
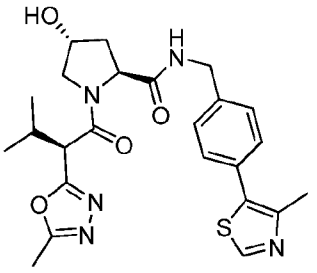
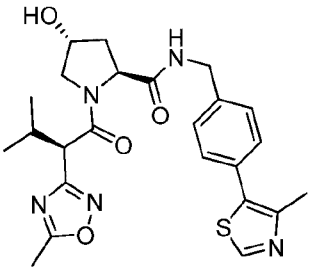
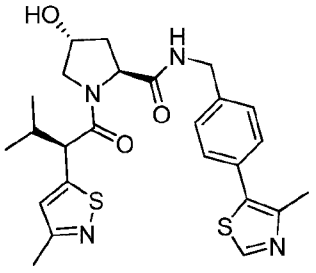
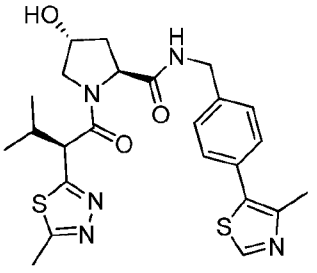
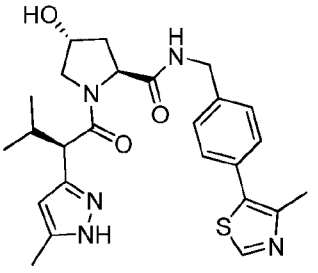














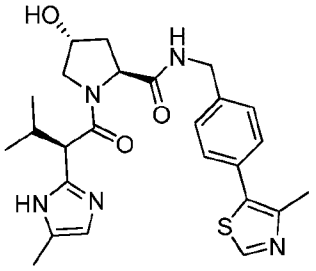
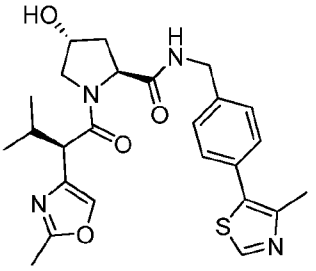
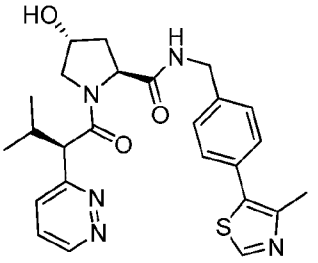
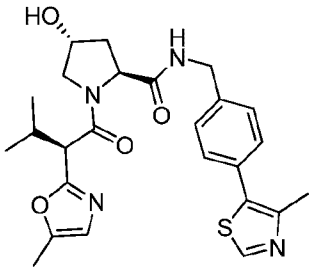
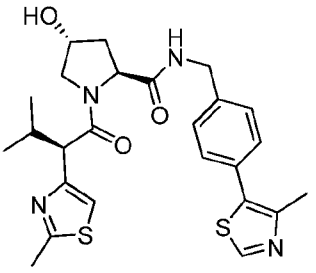
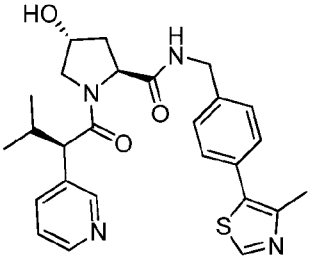
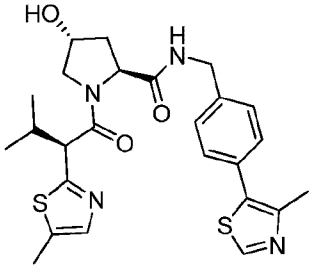
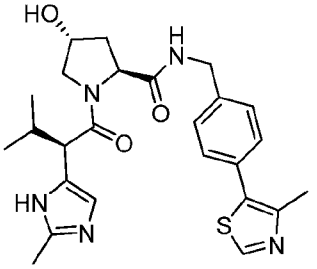
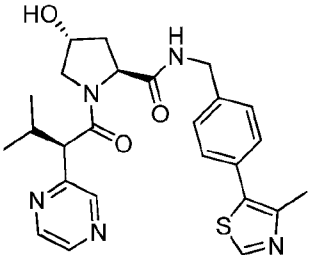
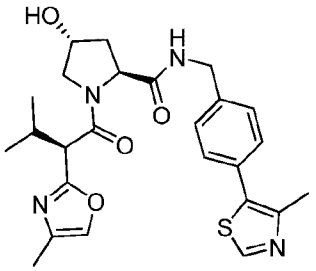
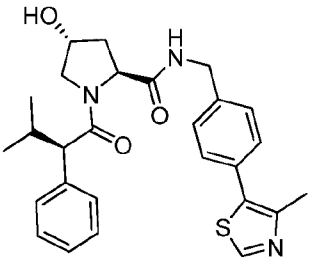
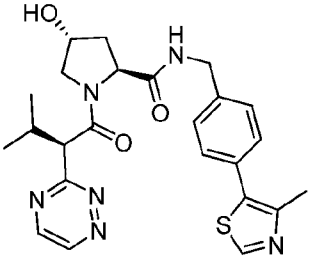
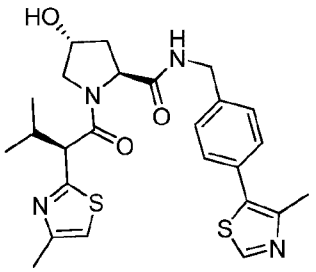
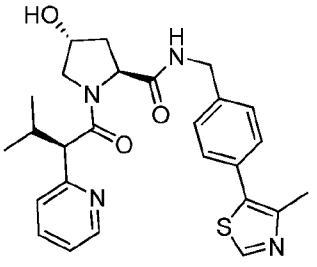


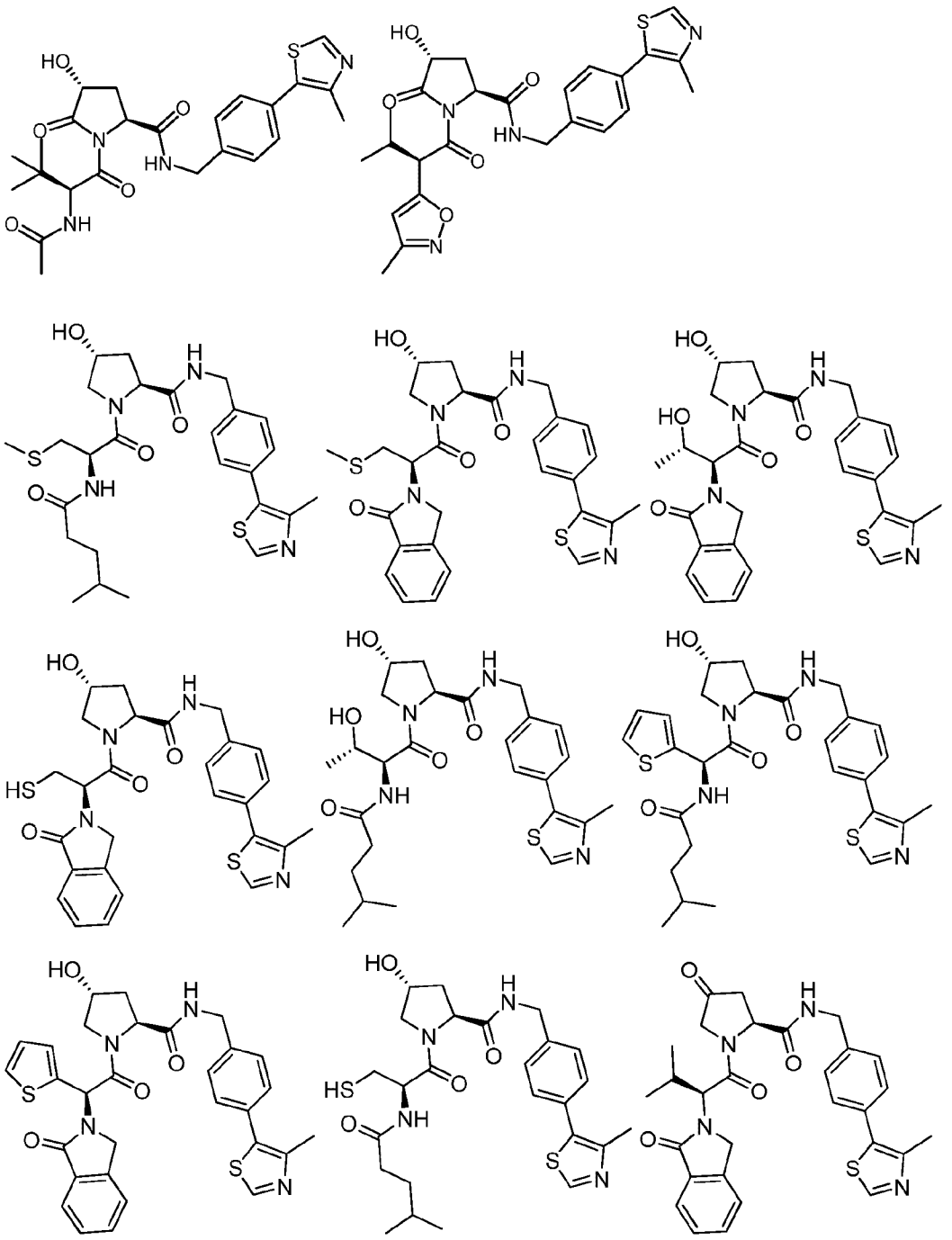
















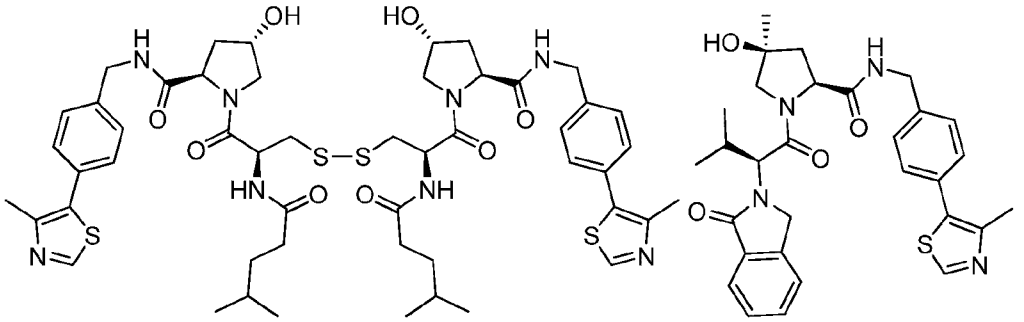
















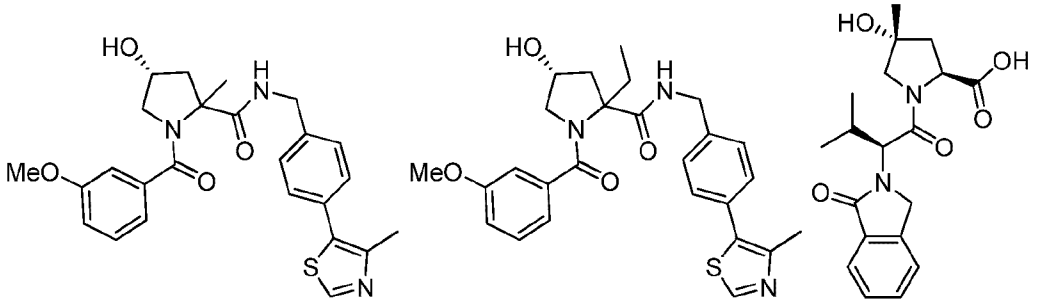
















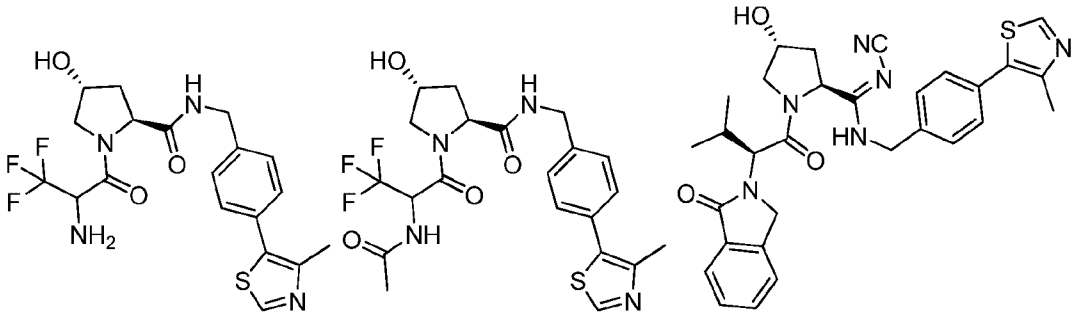
















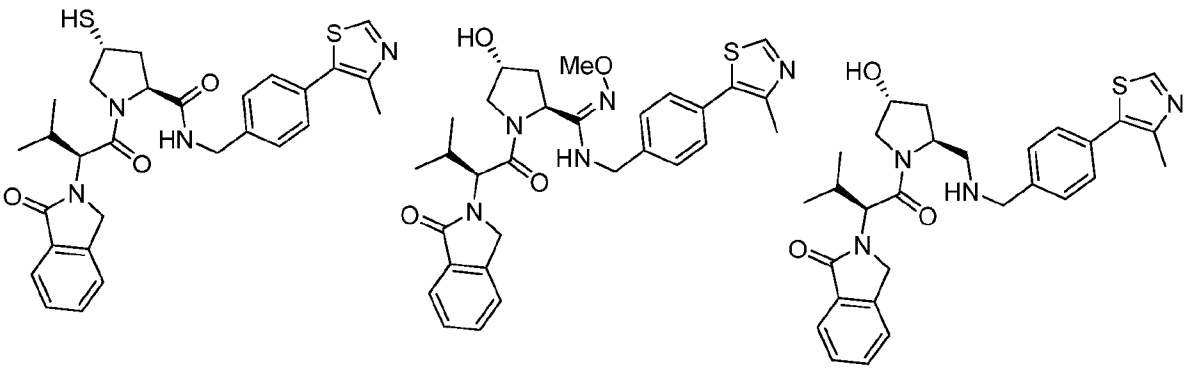















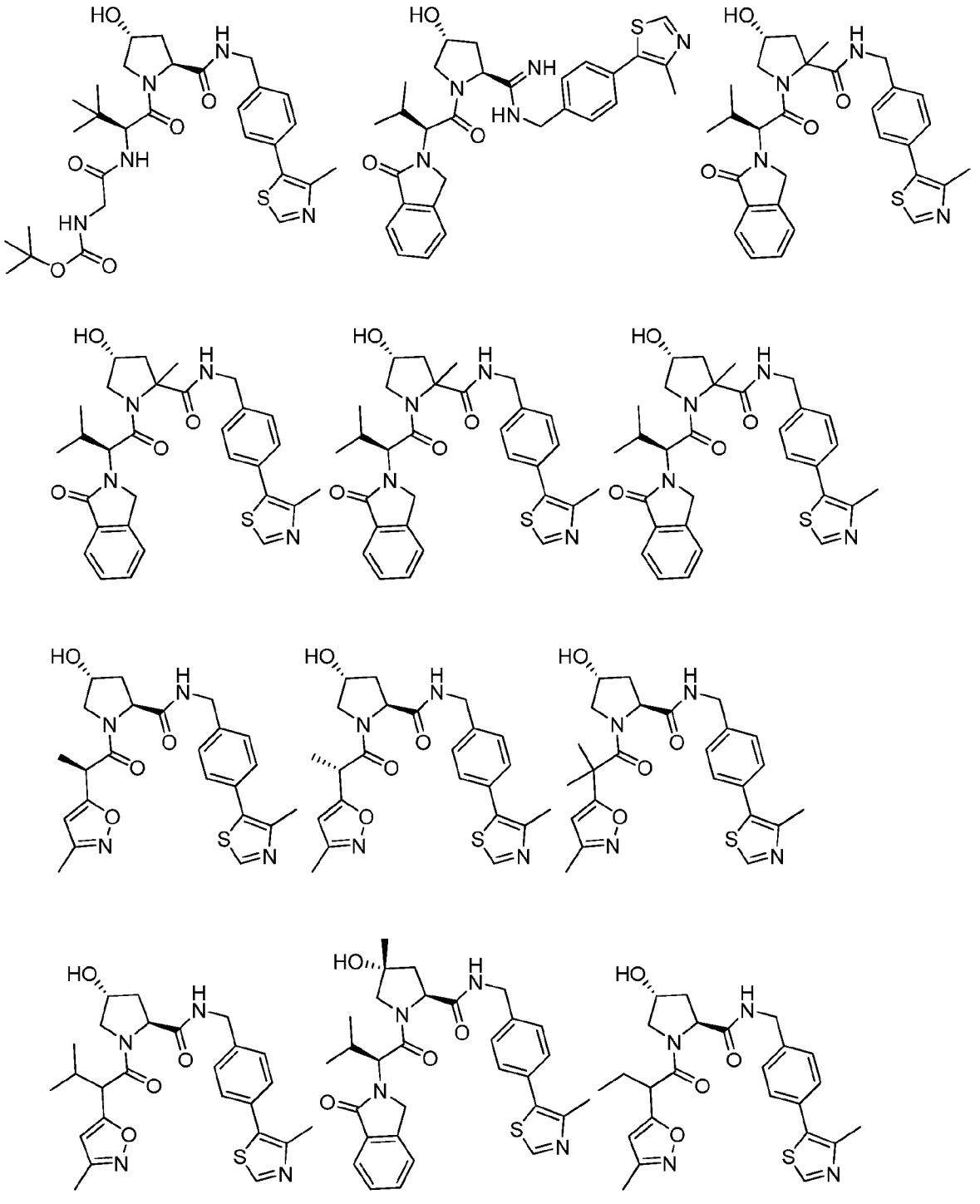


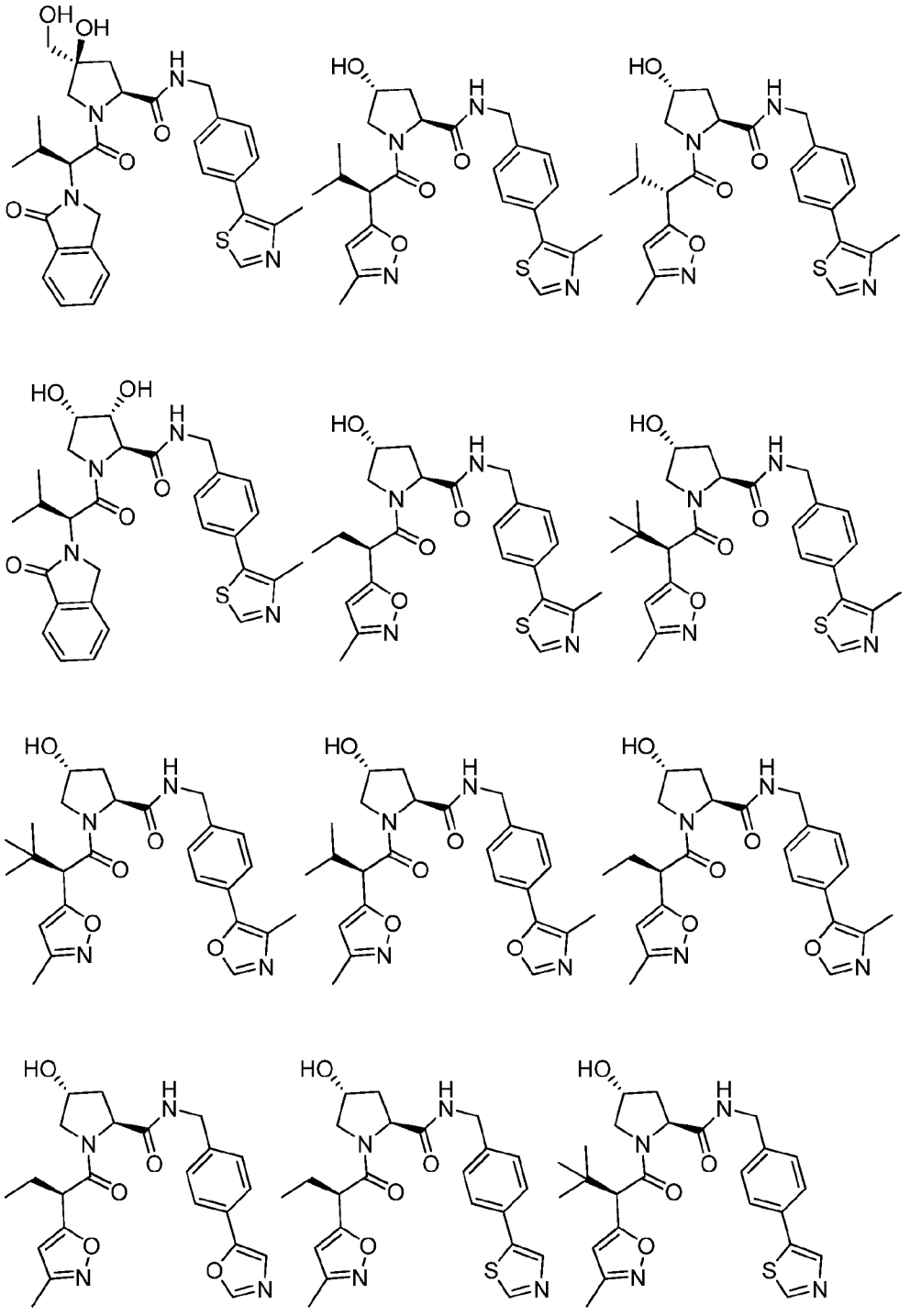


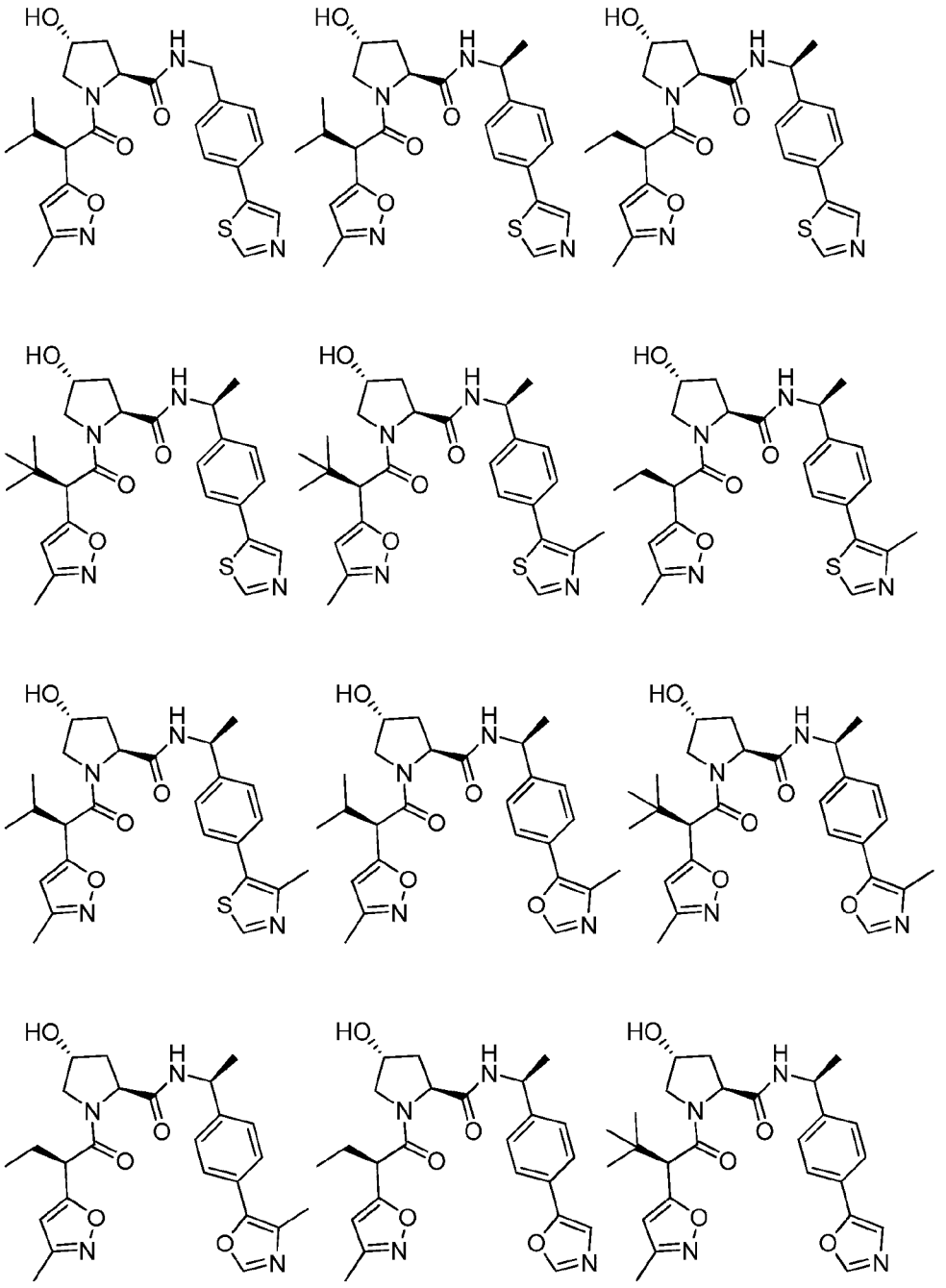


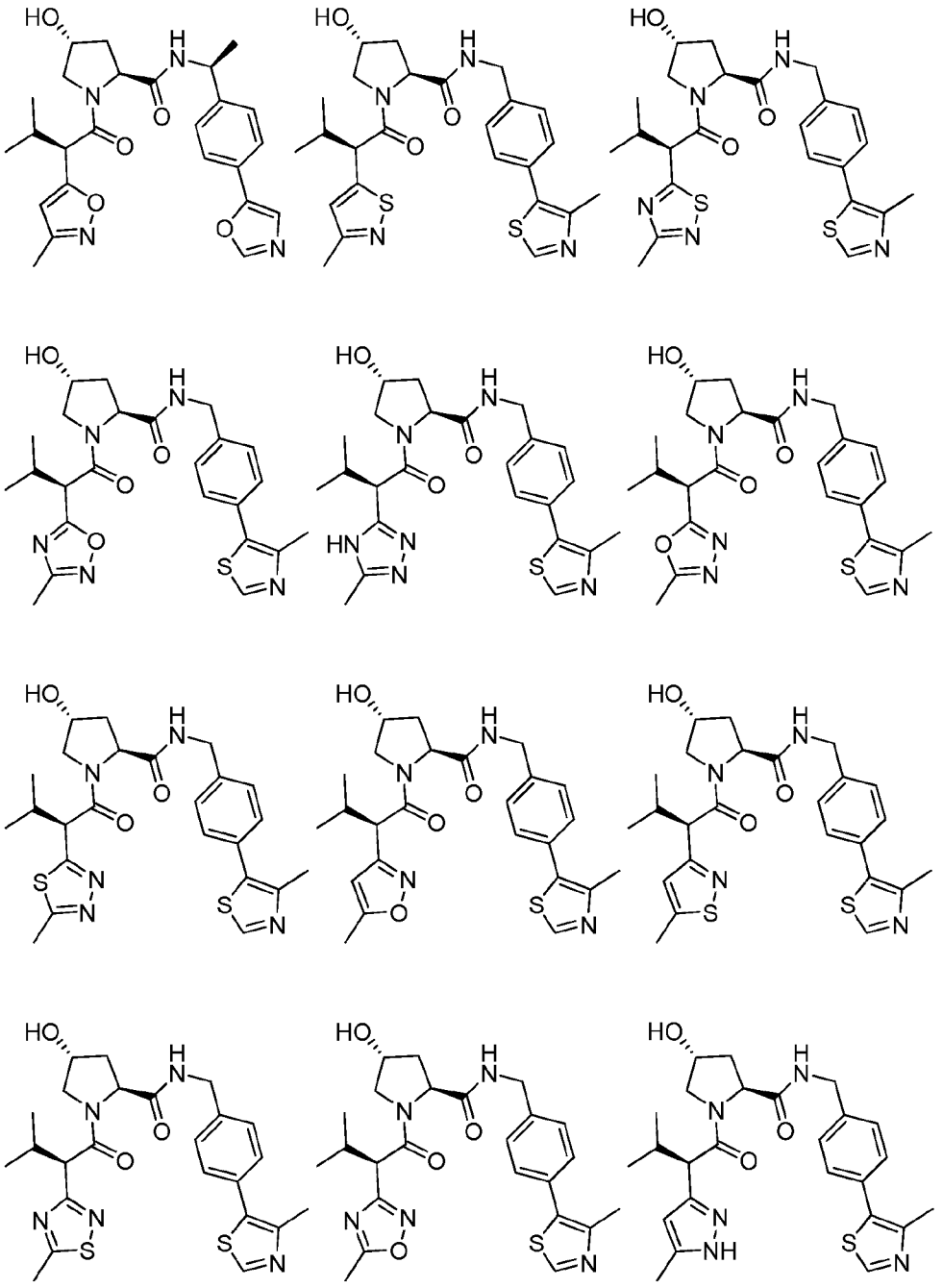


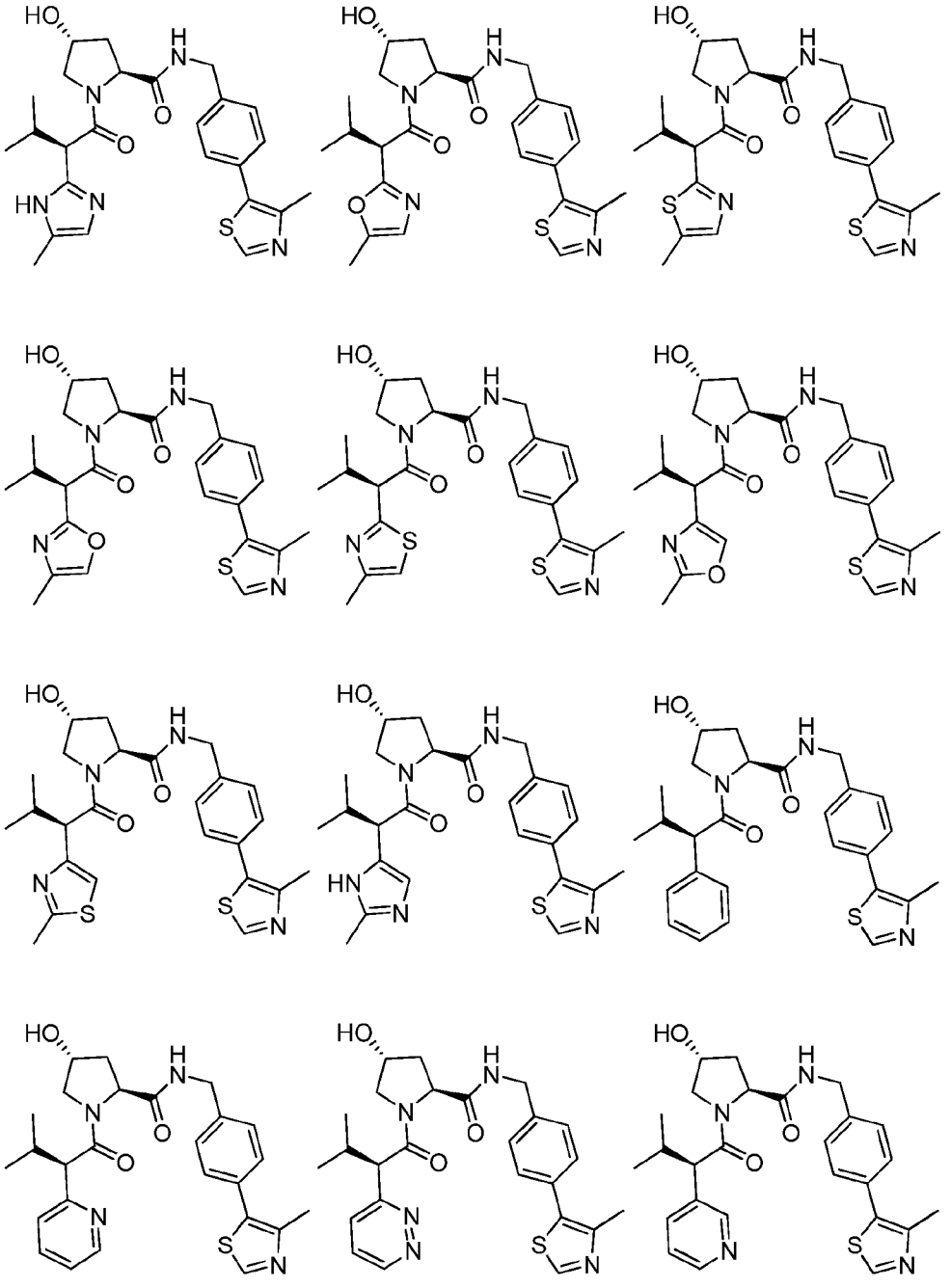


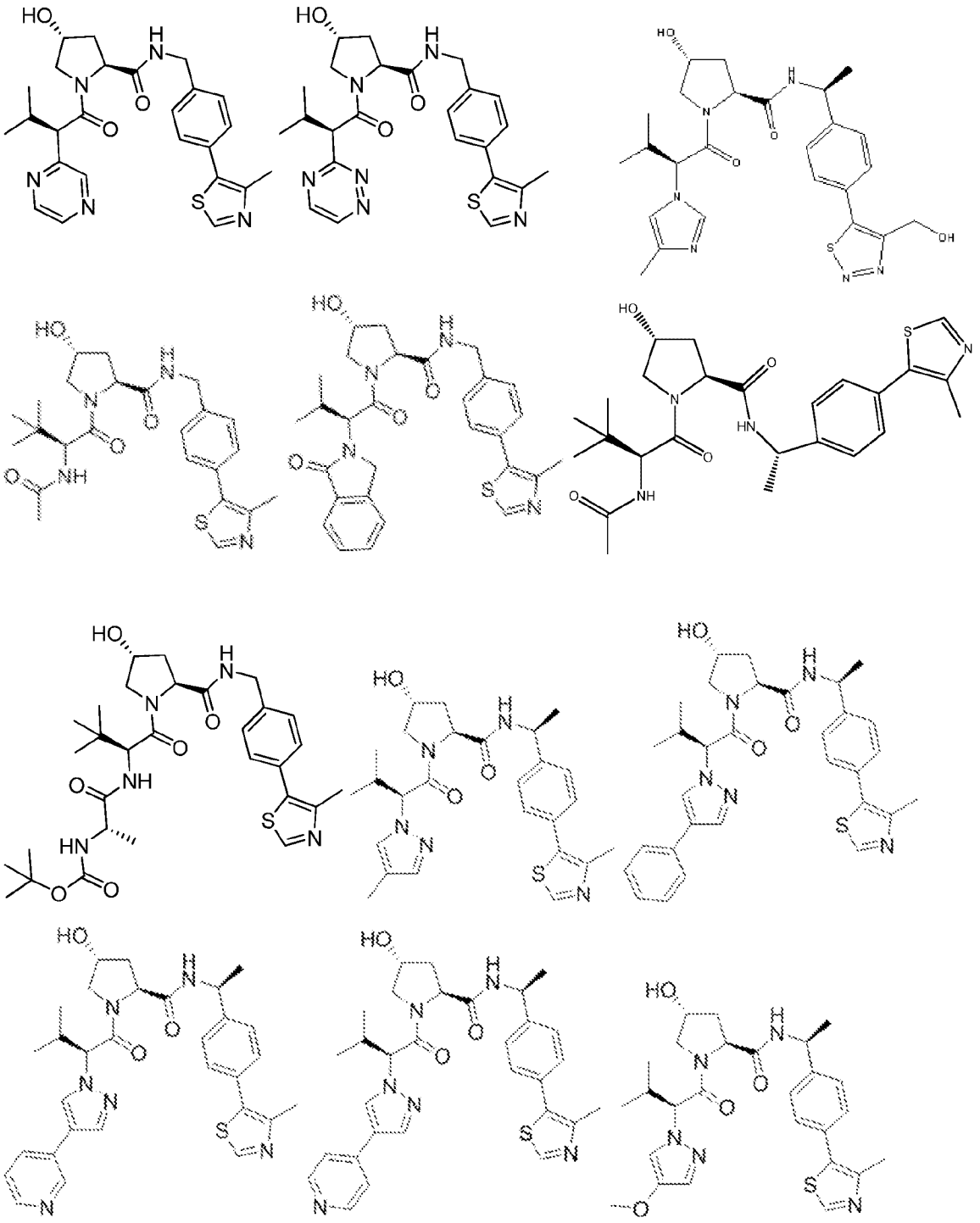


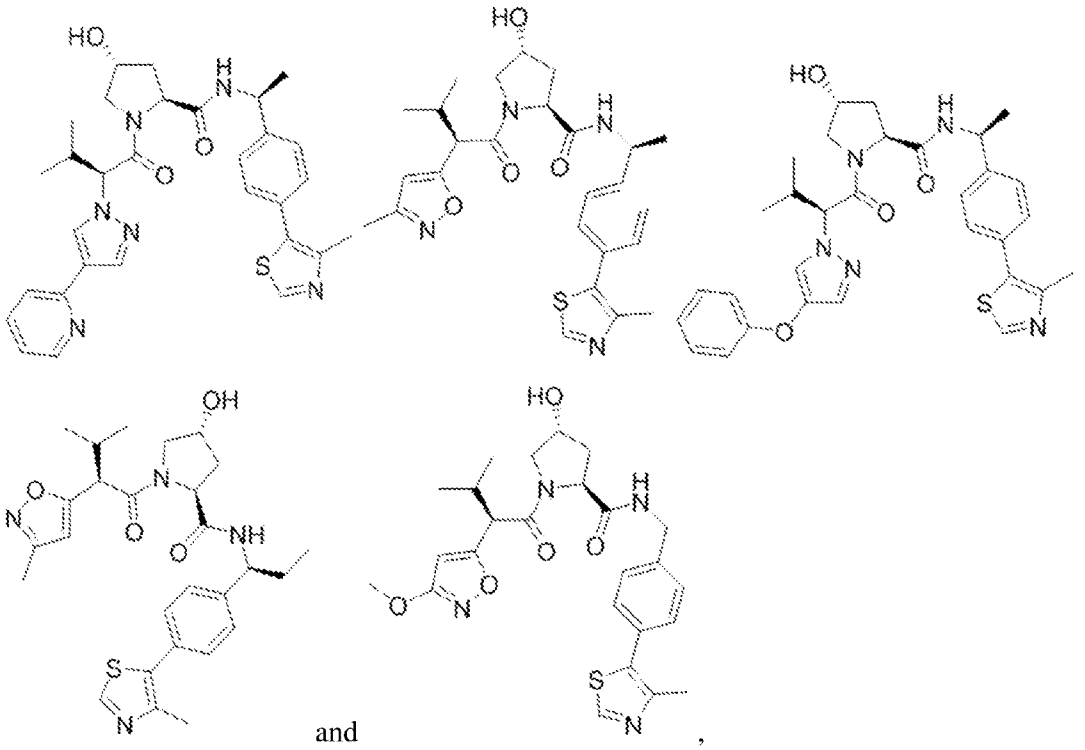












and

wherein the VLM may be connected to a PTM via a linker, as described herein, at any appropriate location, including, e.g., an aryl, heteroary, phenyl, or phenyl of an indole group, optionally via any appropriate functional group, such as an amine, ester, ether, alkyl, or alkoxy.

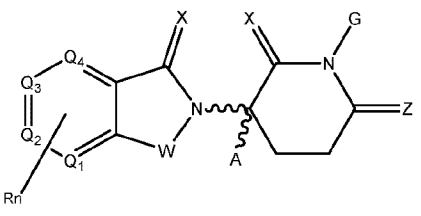
Exemplary CLMs:

[0150] In any aspect or embodiment described herein, the description provides compounds useful for binding and/or inhibiting cereblon (e.g., the ULM is a CLM, the PTM is a CLM, or both the ULM and PTM are CLMs).

[0151] In some embodiments, the ULM is a CLM that is a thalidomide, lenalidomide, pomalidomide, analogs thereof, isosteres thereof, or derivatives thereof.

Neo-imide Compounds

[0152] In certain embodiments, the CLM is selected from the group consisting of chemical structures:



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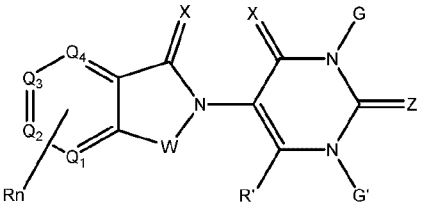

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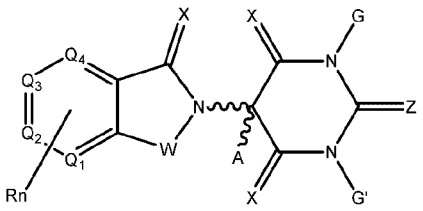
(a) (b)



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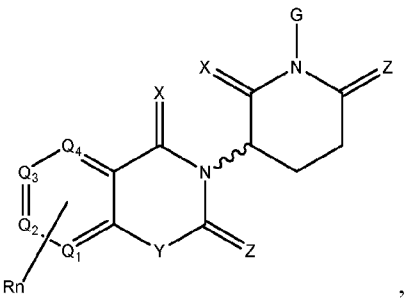

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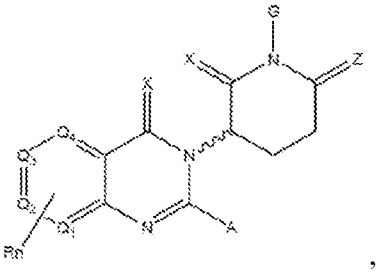
(c) (d)



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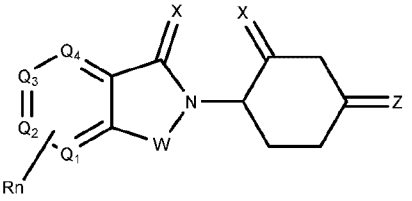


(e) or (f),

wherein:

W is selected from the group consisting of CH_2, CHR, C=O, SO_2, NH, and N-alkyl;

each X is independently selected from the group consisting of O, S, and H_2;

Y is selected from the group consisting of CH_2, -C=CR', NH, N-alkyl, N-aryl, N-hetaryl, N-cycloalkyl, N-heterocyclyl, O, and S;

Z is selected from the group consisting of O, S, and H_2;

G and G' are independently selected from the group consisting of H, alkyl (linear, branched, optionally substituted with R'), OH, R'OCOOR, R'OCONRR",CH_2-heterocyclyl optionally substituted with R', and benzyl optionally substituted with R';

Q_1, Q_2, Q_3, and Q_4 represent a carbon C substituted with a group independently selected from R', N or N-oxide;

A is independently selected from the group H, alkyl, cycloalkyl, Cl and F;

R comprises but is not limited to:-CONR'R", -OR', -NR'R", -SR', -SO_2R', -SO_2NR'R", -CR'R"-, -CR'NR'R"-, -aryl, -hetaryl, -alkyl (linear, branched, optionally substituted), -cycloalkyl, -heterocyclyl, -P(O)(OR')R", -P(O)R'R", -OP(O)(OR')R", -OP(O)R'R", -Cl, -F, -Br, -I, -CF_3, -CN, -NR'SO_2NR'R", -NR'CONR'R",-CONR'COR", -NR'C(=N-

CN)NR'R", -C(=N-CN)NR'R", -NR'C(=N-CN)R", -NR'C(=C-NO_2)NR'R", -SO_2NR'COR", -NO_2, -CO_2R', -C(C=N-OR')R", -CR'=CR'R", -CCR', -S(C=O)(C=N-R')R", -SF_5 or -OCF_3;

R' and R" are independently selected from the group consisting of a bond, H, N, N-oxide, alkyl (linear, branched), cycloalkyl, aryl, heteroaryl, heterocyclic, -C(=O)R, or heterocyclyl, each of which is optionally substituted;

~~~ represents a bond that may be stereospecific ((R) or (S)) or non-stereospecific; and

R_n comprises a functional group or an atom,

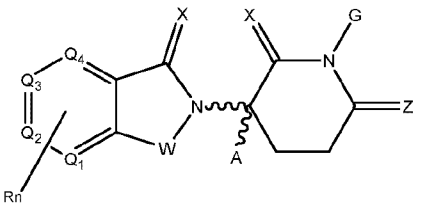
wherein n is an integer from 1-4, and wherein:

when n is 1, R_n is modified to be covalently joined to the linker group (L), and

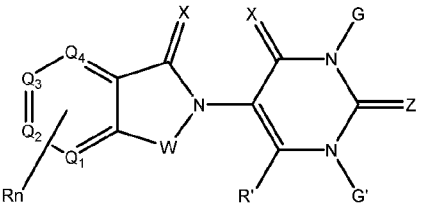
when n is 2, 3, or 4, then one R_n is modified to be covalently joined to the linker group (L), and any other R_n is optionally modified to be covalently joined to a PTM, a CLM, a second CLM having the same chemical structure as the CLM, a CLM', a second linker, or any multiple or combination thereof.

Exemplary CLMs

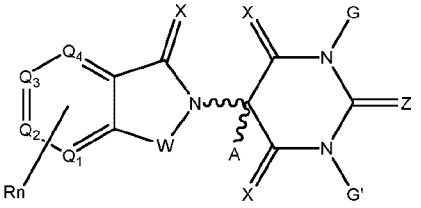
[0153] In any of the compounds described herein, the CLM comprises a chemical structure selected from the group:



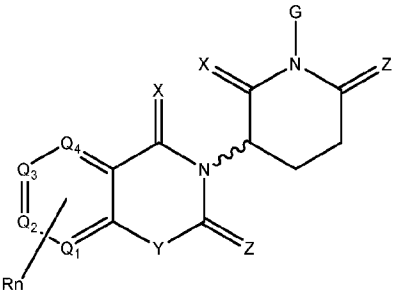
(a)



(b)



(c)



(d)
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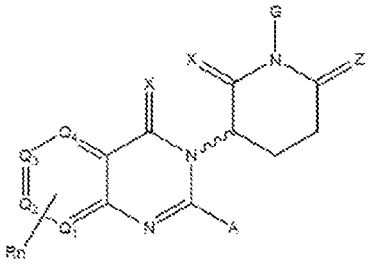
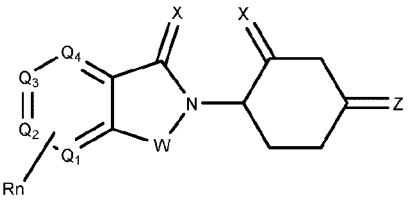


(e) and



(f),

wherein:

W is independently selected from the group CH_2, CHR, C=O, SO_2, NH, and N-alkyl;

X is independently selected from the group O, S and H_2;

Y is independently selected from the group CH_2, -C=CR', NH, N-alkyl, N-aryl, N-hetaryl, N-cycloalkyl, N-heterocyclyl, O, and S;

Z is independently selected from the group O, and S or H_2 except that both X and Z cannot be H2;

G and G' are independently selected from the group H, alkyl (linear, branched, optionally substituted with R'), OH, R'OCOOR, R'OCONRR", CH_2-heterocyclyl optionally substituted with R', and benzyl optionally substituted with R';

Q1 – Q4 represent a carbon C substituted with a group independently selected from R', N or N-oxide;

A is independently selected from the group H, alkyl, cycloalkyl, Cl and F;

R comprises, but is not limited to: -CONR'R", -OR', -NR'R", -SR', -SO_2R', -SO_2NR'R", -CR'R"-, -CR'NR'R"-, -aryl, -hetaryl, -alkyl (linear, branched, optionally substituted), -cycloalkyl, -heterocyclyl, -P(O)(OR')R", -P(O)R'R", -OP(O)(OR')R", -OP(O)R'R", -Cl, -F, -Br, -I, -CF3, -CN, -NR'SO2NR'R", -NR'CONR'R", -CONR'COR", -NR'C(=N-CN)NR'R", -C(=N-CN)NR'R", -NR'C(=N-CN)R", -NR'C(=C-NO_2)NR'R", -SO_2NR'COR", -NO_2, -CO_2R', -C(C=N-OR')R", -CR'=CR'R", -CCR', -S(C=O)(C=N-R')R", -SF_5 or -OCF_3

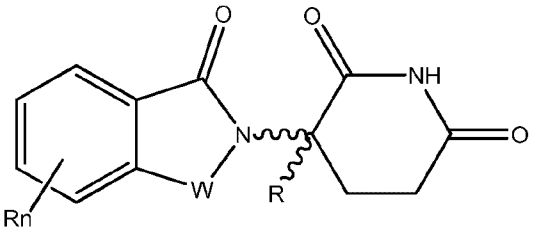
R' and R" are independently selected from the group consisting of a bond, H, N, N-oxide, alkyl (linear, branched), cycloalkyl, aryl, heteroaryl, heterocyclic, -C(=O)R, or heterocyclyl, each of which is optionally substituted;

n is an integer from 1-4;

~~~ represents a bond that may be stereospecific ((R) or (S)) or non-stereospecific; and

Rn comprises 1-4 independent functional groups or atoms, and optionally, one of which is modified to be covalently joined to a ABM, a chemical linker group (L), a ULM, CLM (or CLM') or combination thereof.

[0154] In certain embodiments described herein, the CLM or ULM comprises a chemical structure selected from the group:



wherein:

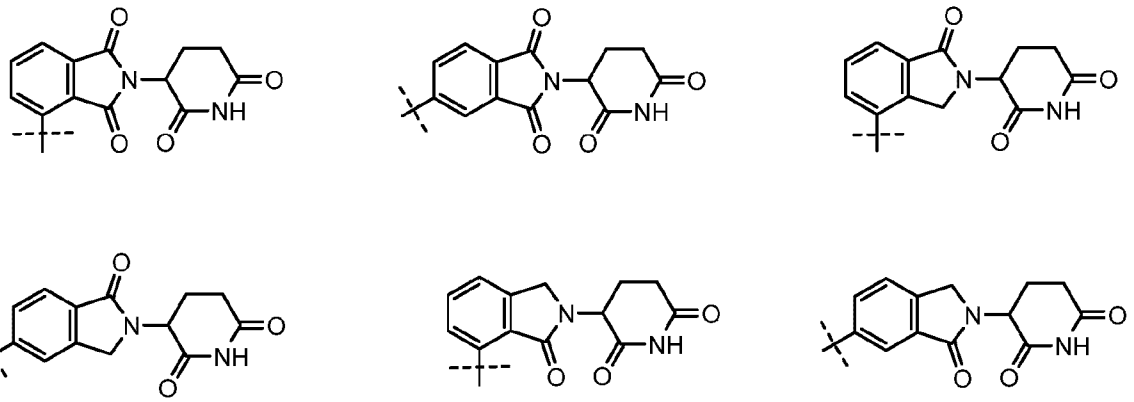
W is independently selected from the group CH_2, C=O, NH, and N-alkyl;

R is independently selected from a H, methyl, alkyl;

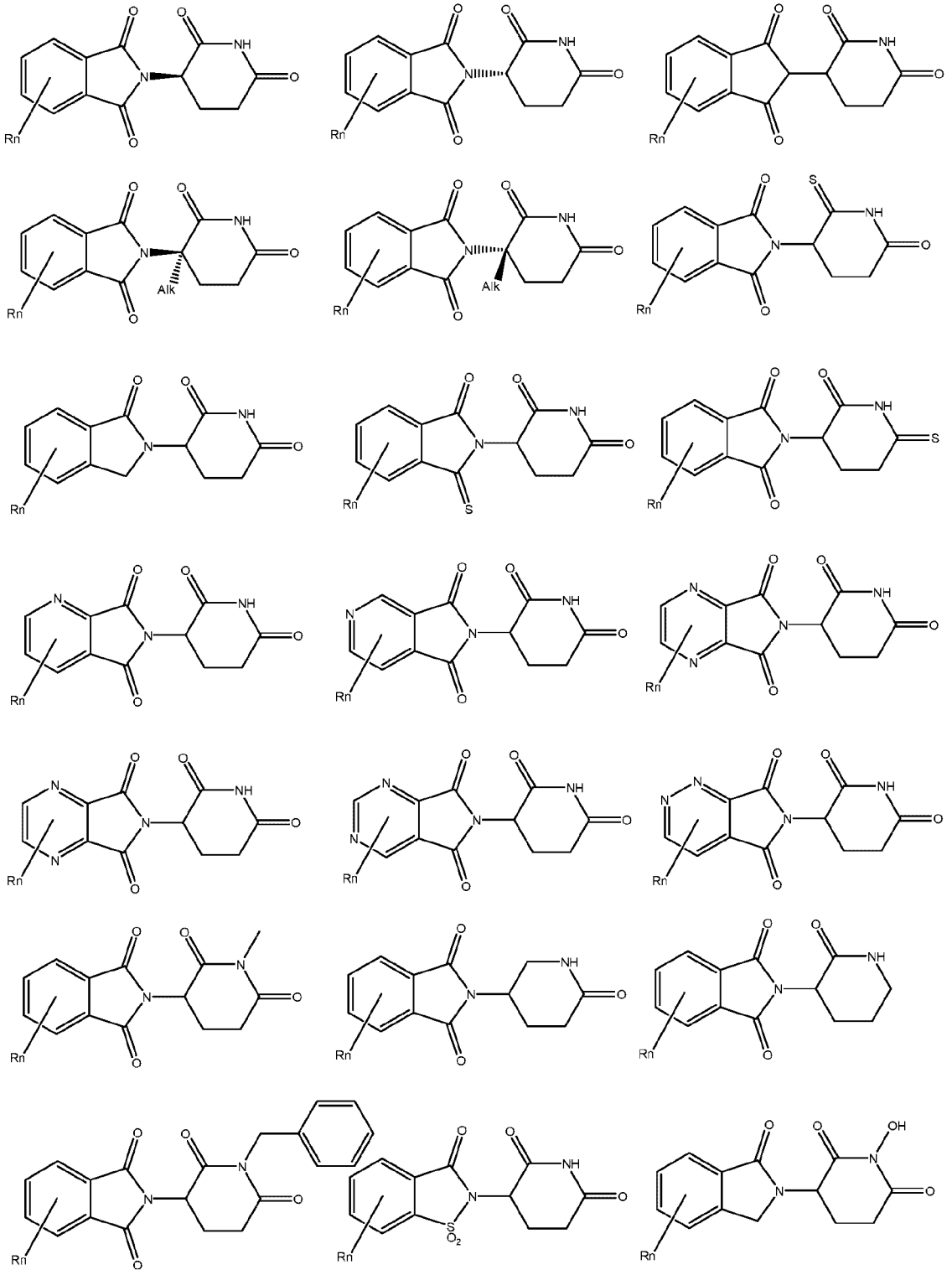
~~~ represents a bond that may be stereospecific ((R) or (S)) or non-stereospecific; and

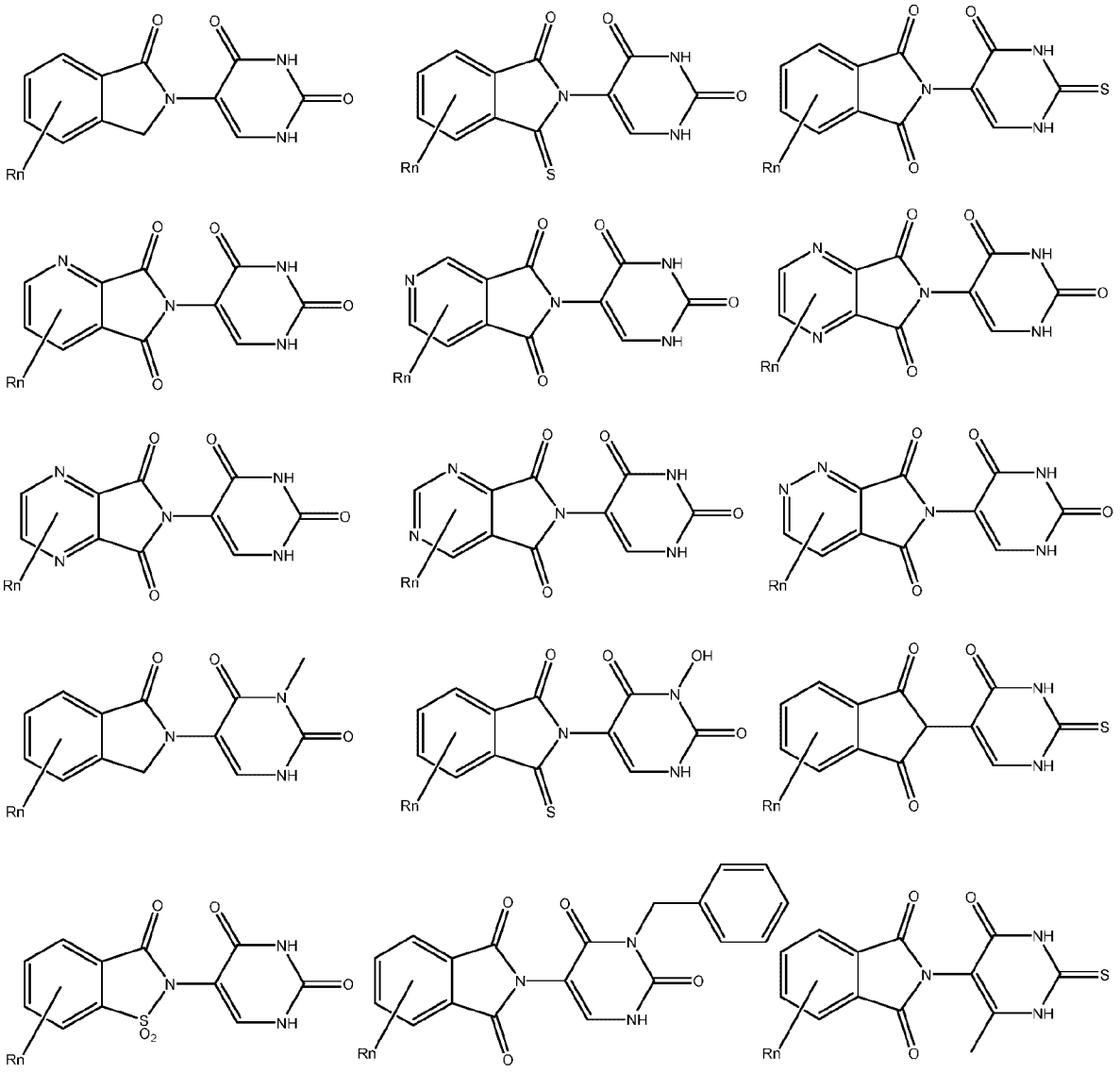
Rn comprises 1-4 independently selected functional groups or atoms, and optionally, one of which is modified to be covalently joined to a PTM, a chemical linker group (L), a CLM (or CLM') or combination thereof.

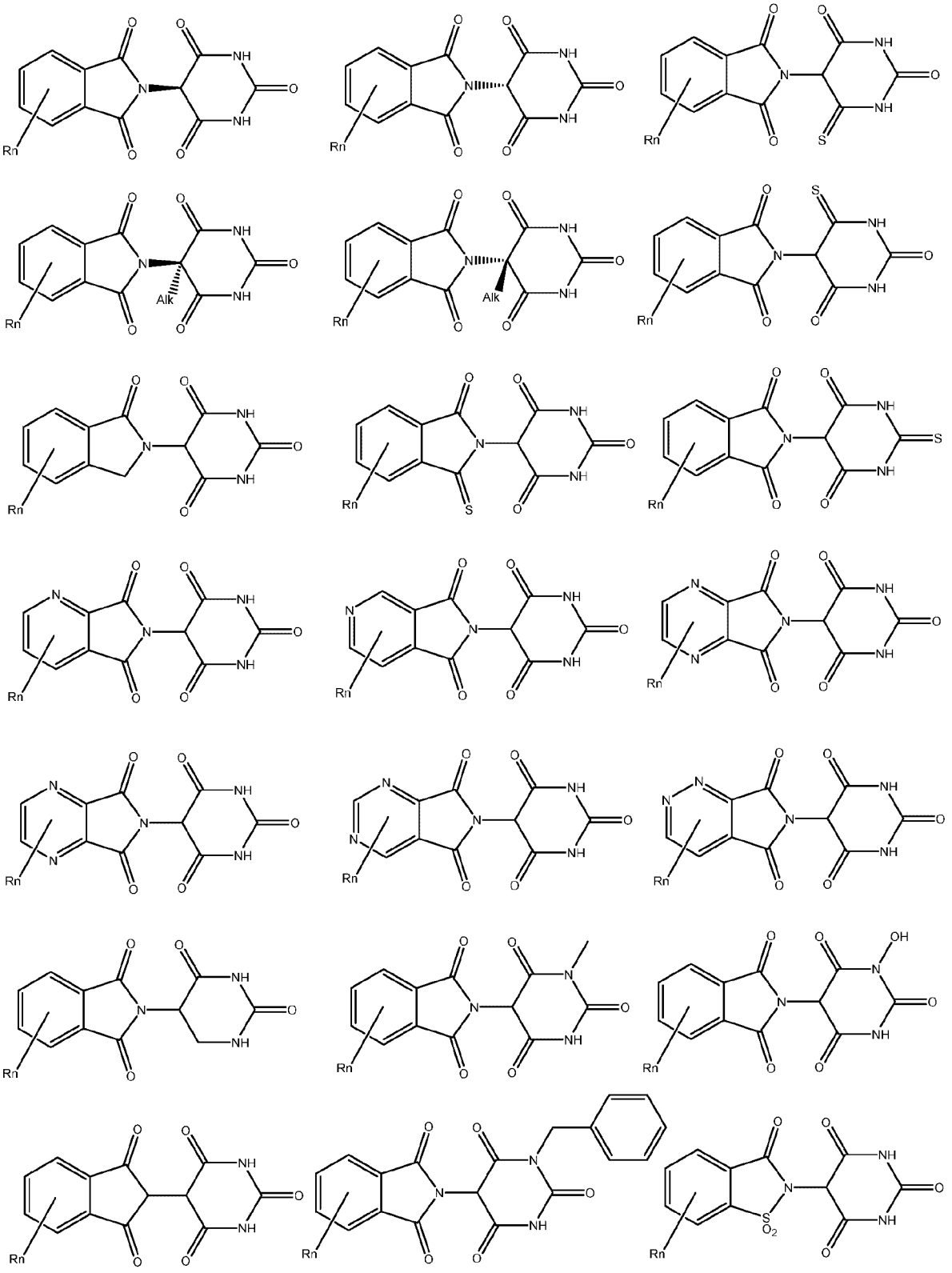
[0155] In some embodiments, the CLM is represented by the following structures with the dashed lines indicating linker attachment points:

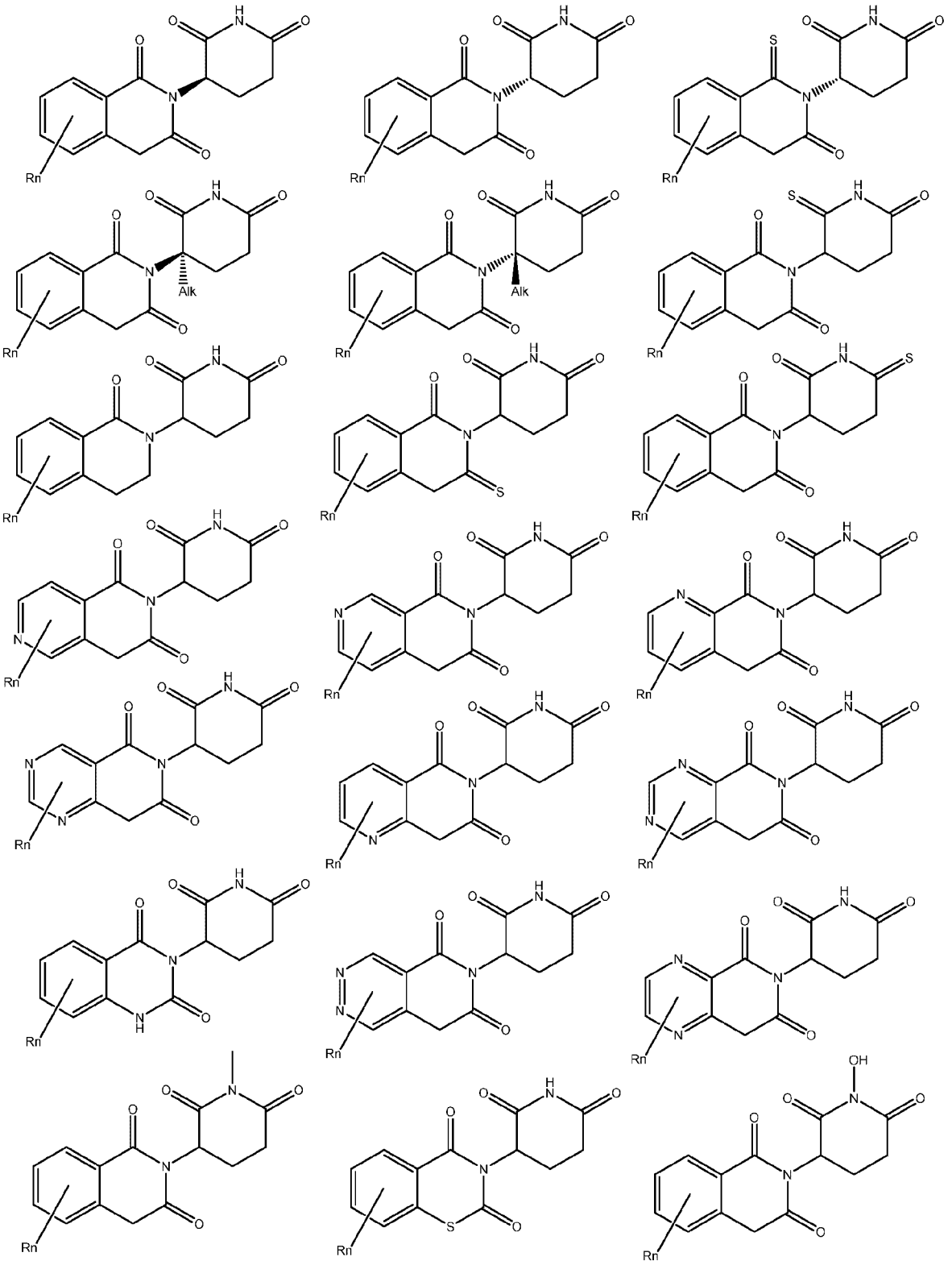


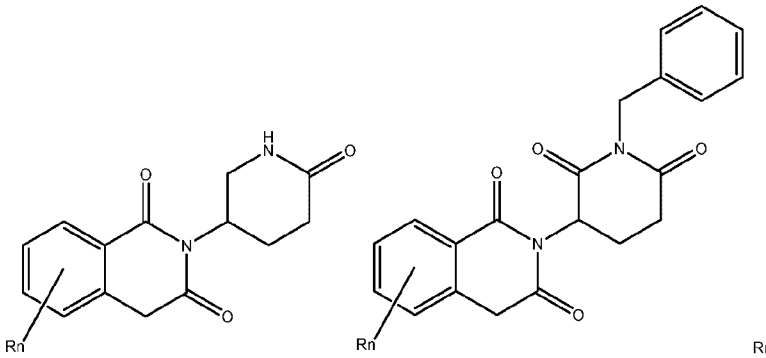
[0156] More specifically, non-limiting examples of CLMs include those shown below as well as those "hybrid" molecules that arise from the combination of 1 or more of the different features shown in the molecules below.

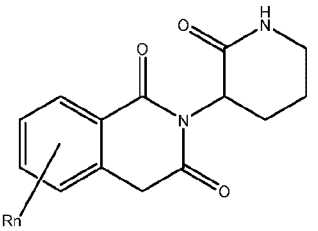
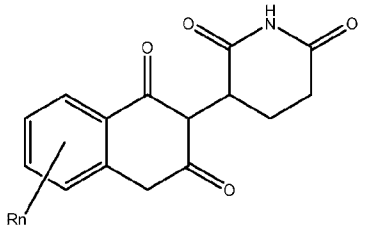
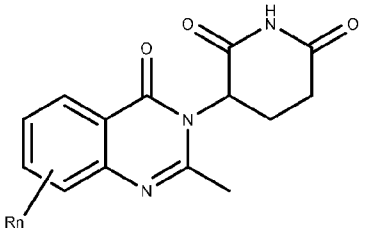
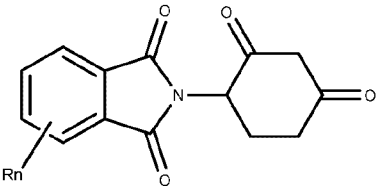
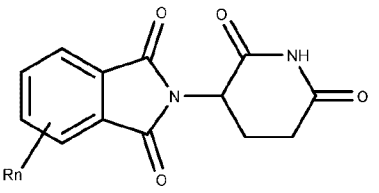


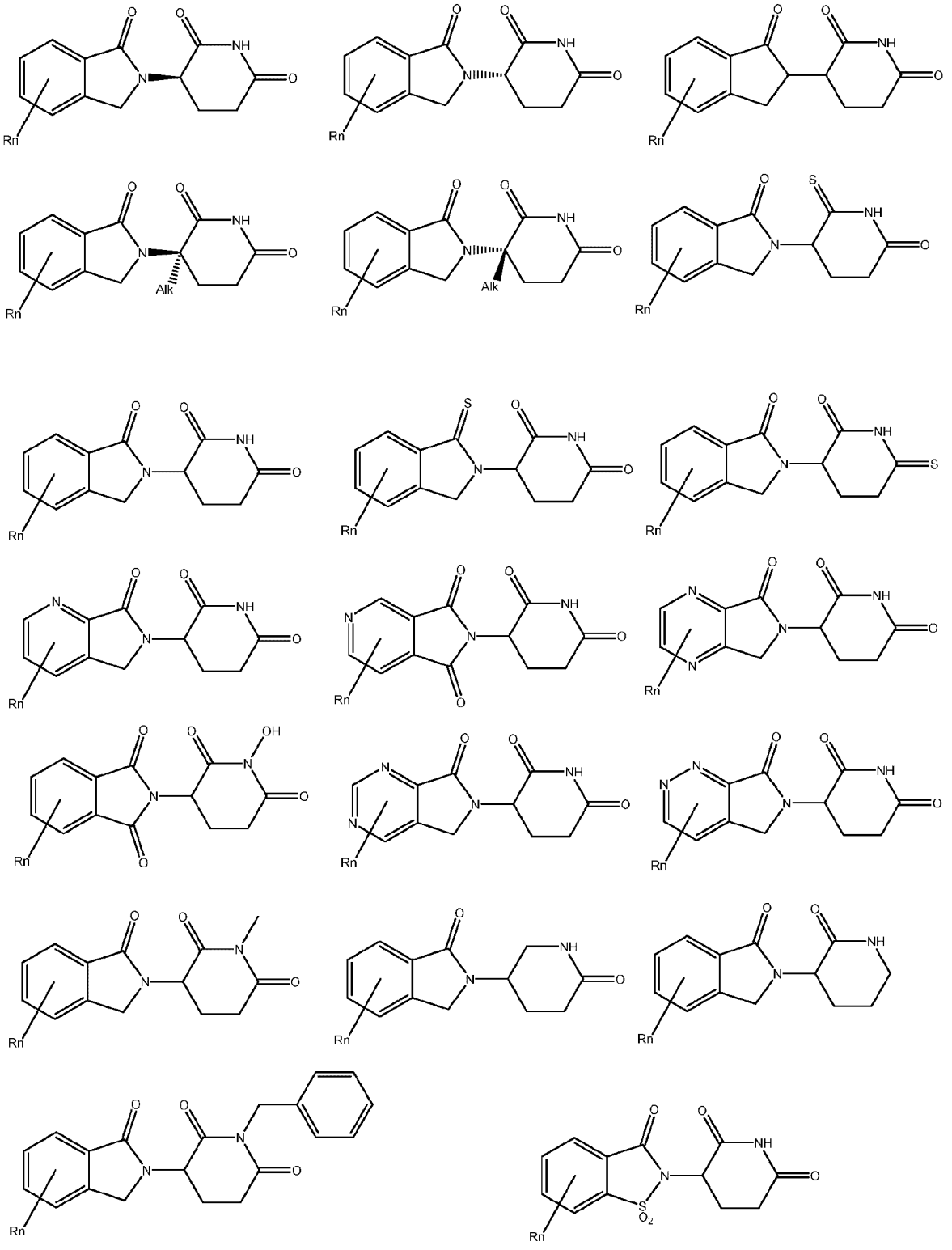


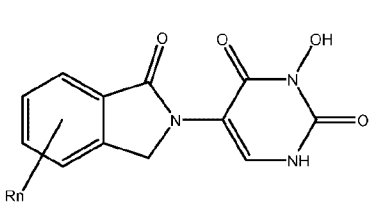
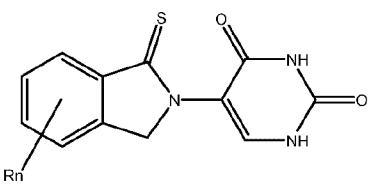
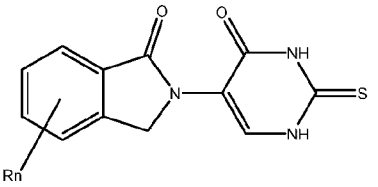
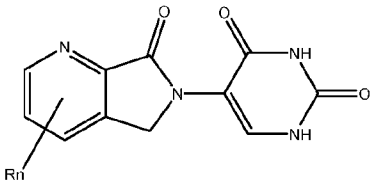
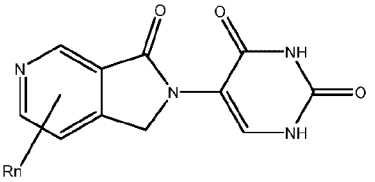
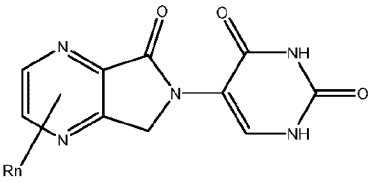
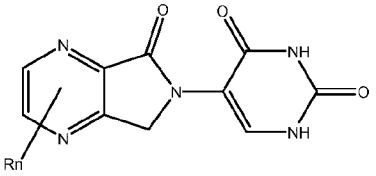
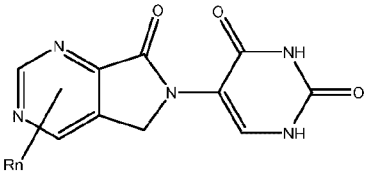
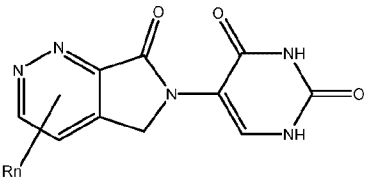
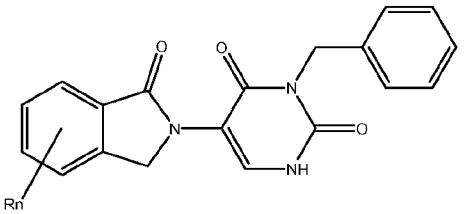
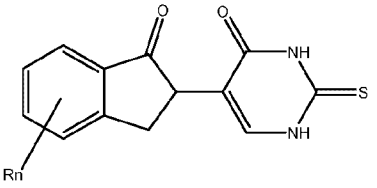
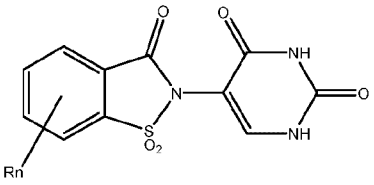
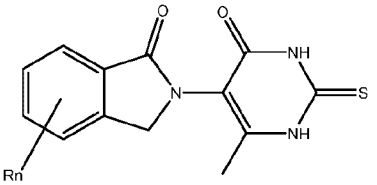


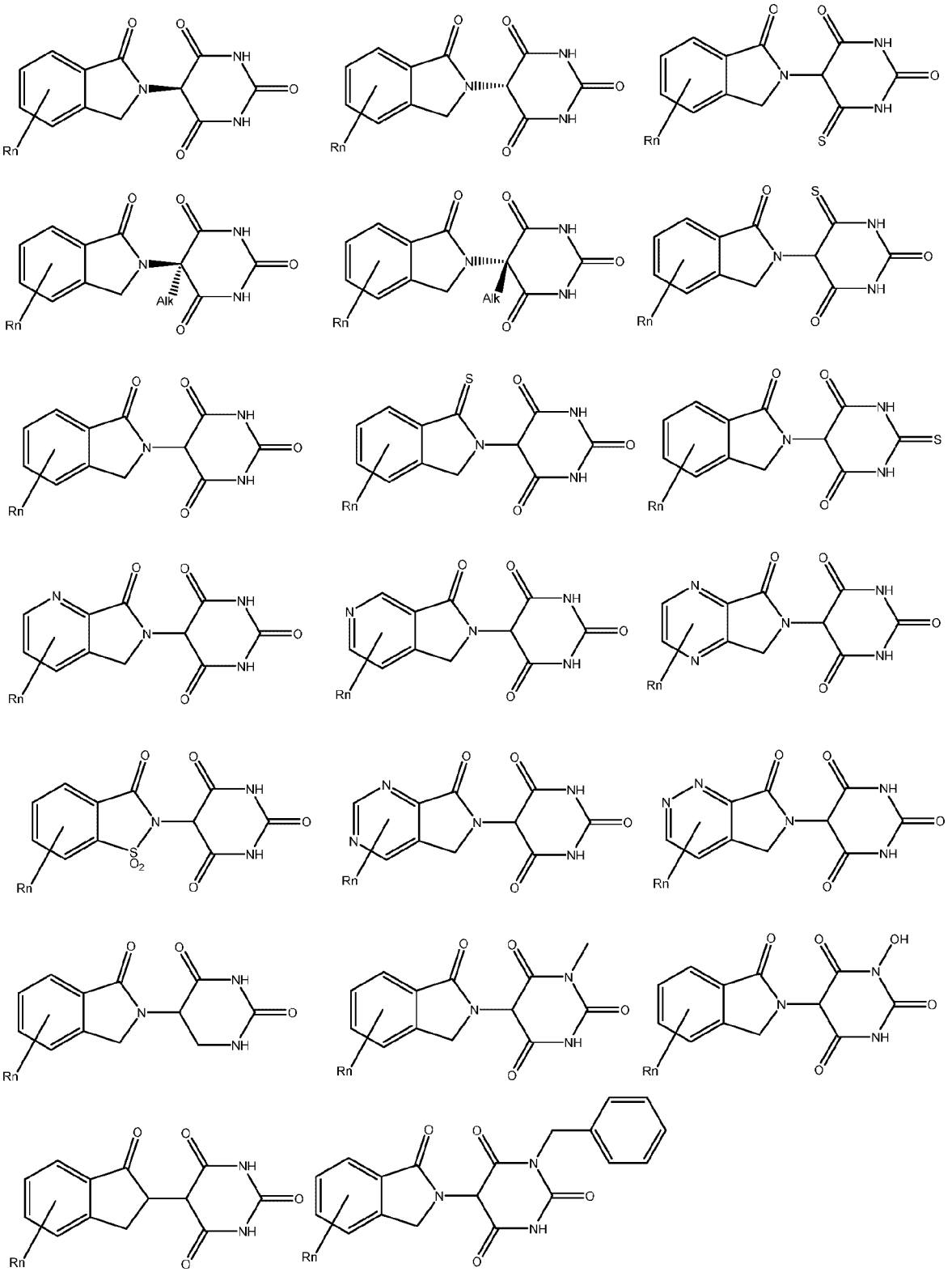


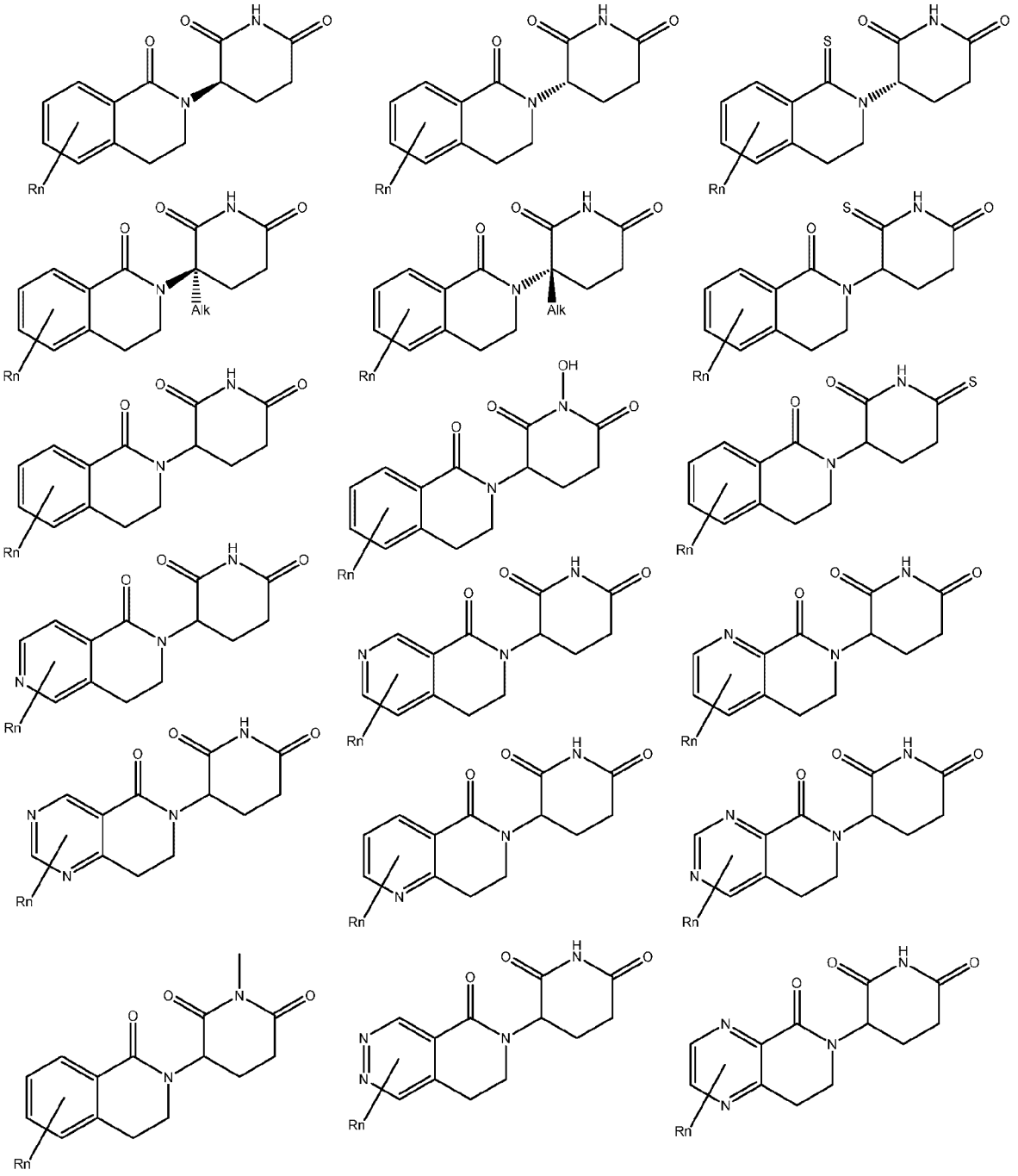


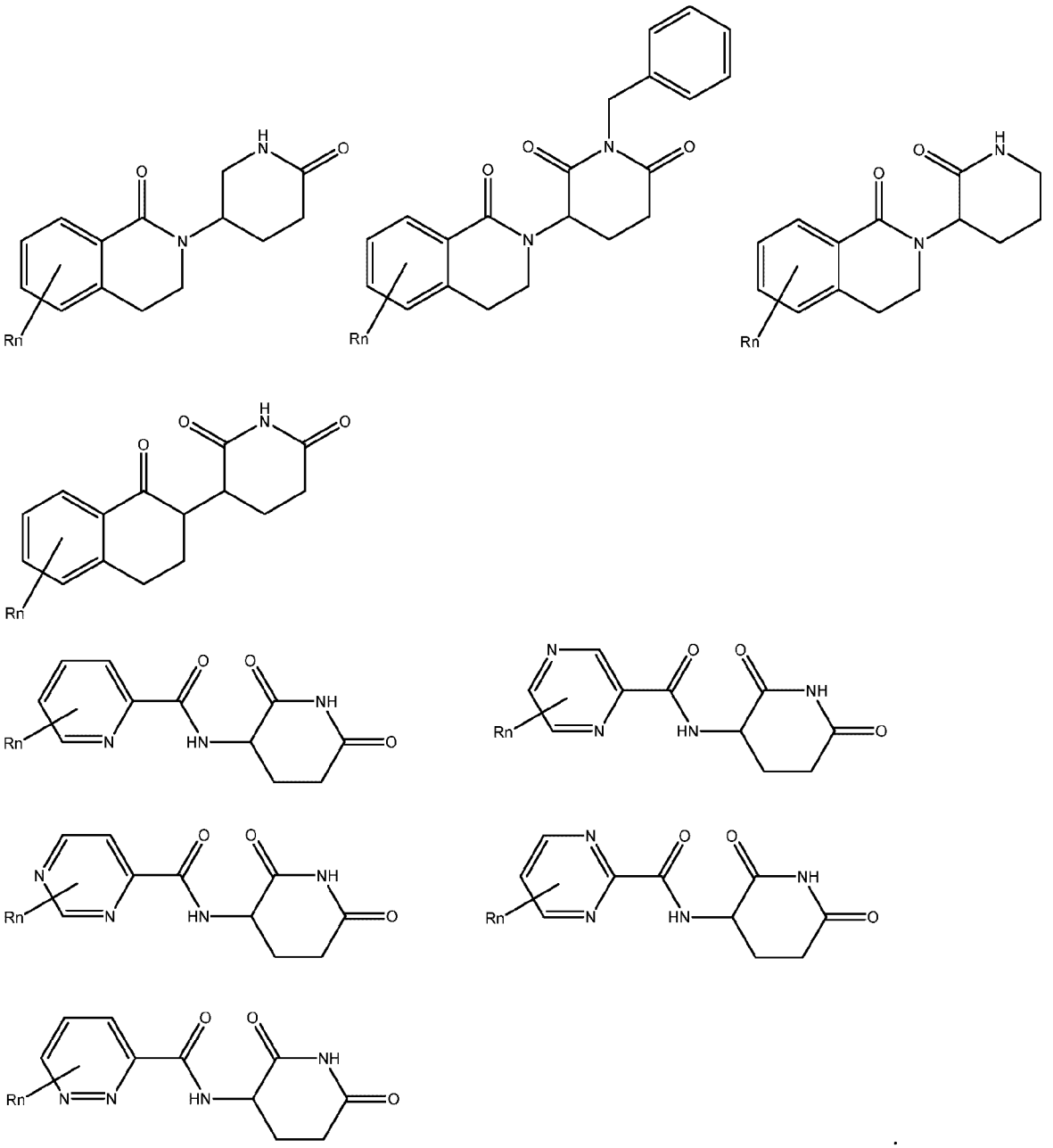








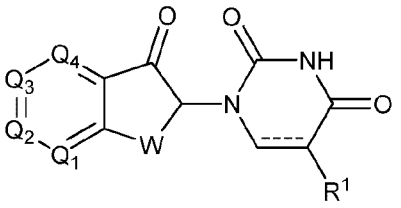




















[0157] In any of the compounds described herein, the CLM comprises a chemical structure selected from the group:



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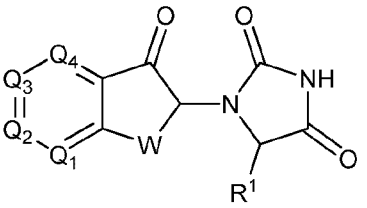

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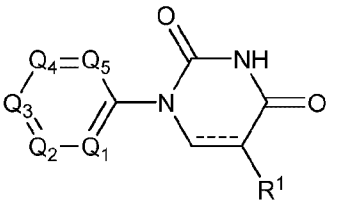

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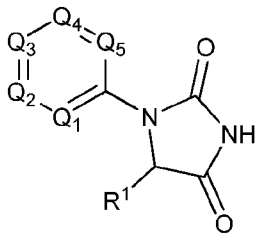

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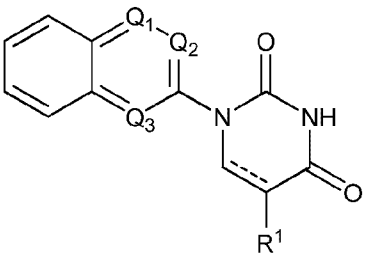

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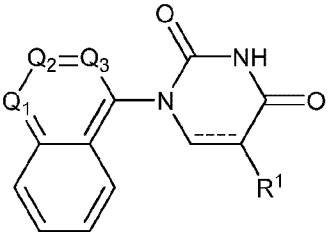

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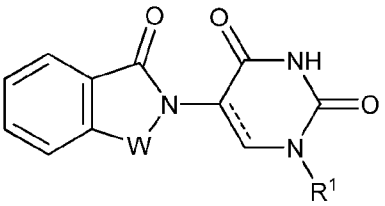

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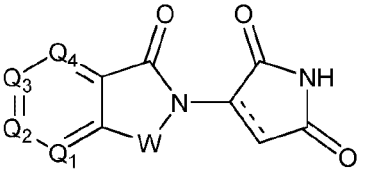

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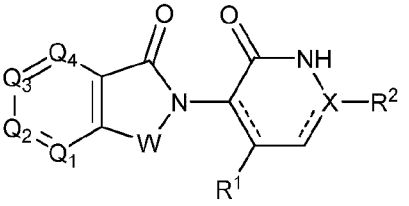

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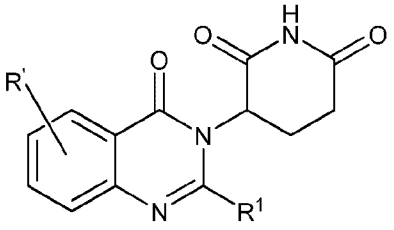

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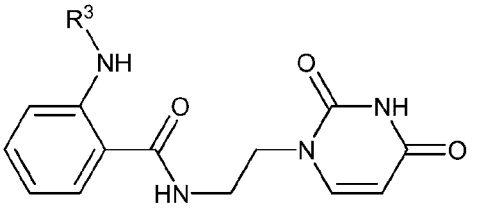

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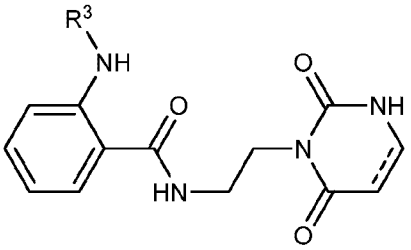

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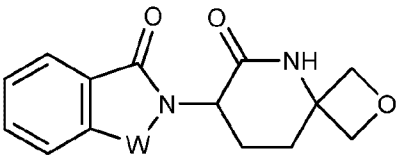

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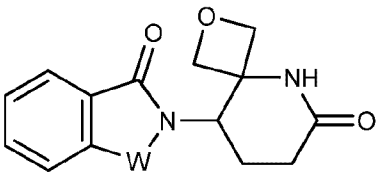

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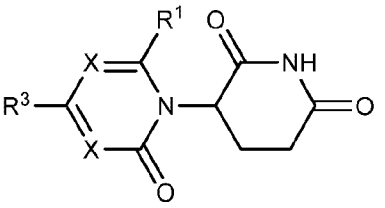

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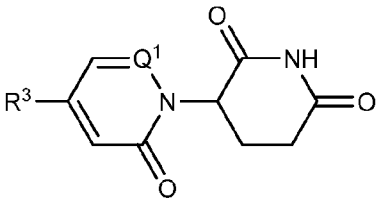

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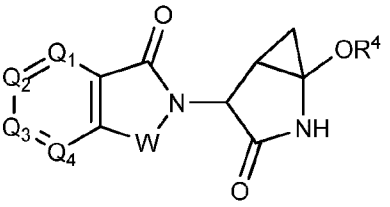

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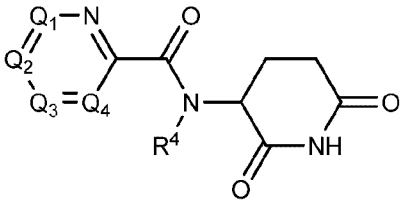
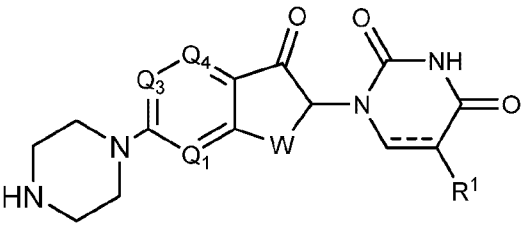


(y)



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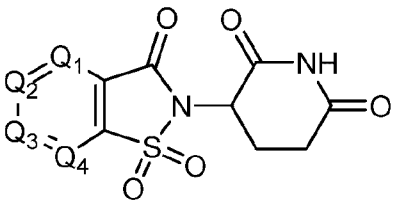

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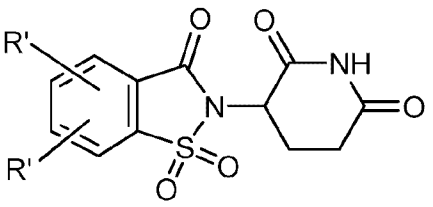


(ab)

wherein:

W of Formulas (h) through (ab) is independently selected from CH_2, CHR, C=O, SO_2, NH, and N-alkyl;

Q_1, Q_2, Q_3, Q_4, Q_5 of Formulas (h) through (ab) are independently represent a carbon C substituted with a group independently selected from R', N or N-oxide;

R^1 of Formulas (h) through (ab) is selected from H, CN, C1-C3 alkyl;

R^2 of Formulas (h) through (ab) is selected from the group H, CN, C1-C3 alkyl, CHF_2, CF_3, CHO;

R^3 of Formulas (h) through (ab) is selected from H, alkyl, substituted alkyl, alkoxy, substituted alkoxy;

R^4 of Formulas (h) through (ab) is selected from H, alkyl, substituted alkyl;

R^5 of Formulas (h) through (ab)is H or lower alkyl;

X of Formulas (h) through (ab) is C, CH or N;

R' of Formulas (h) through (ab) is selected from H, halogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy;

R of Formulas (h) through (ab) is H, OH, lower alkyl, lower alkoxy, cyano, halogenated lower alkoxy, or halogenated lower alkyl

// of Formulas (h) through (ab) is a single or double bond; and

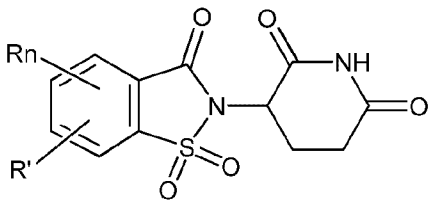
the CLM is covalently joined to a PTM, a chemical linker group (L), a ULM, CLM (or CLM') or combination thereof.

[0158] In any aspect or embodiment described herein, the CLM or CLM' is covalently joined to a PTM, a chemical linker group (L), a ULM, a CLM, a CLM', or a combination thereof via an R group (such as, R, R^1, R^2, R^3, R^4 or R'), W, X, or a Q group (such as, Q_1, Q_2, Q_3, Q_4, or Q_5) of Formulas (h) through (ab).

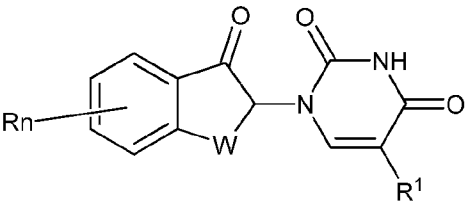
[0159] In any of the embodiments described herein, the CLM or CLM' is covalently joined to a PTM, a chemical linker group (L), a ULM, a CLM, a CLM', or a combination thereof via W, X, R, R^1, R^2, R^3, R^4, R^5, R', Q_1, Q_2, Q_3, Q_4, and Q_5 of Formulas (h) through (ab).

[0160] In any of the embodiments described herein, the W, X, R^1, R^2, R^3, R^4, R', Q_1, Q_2, Q_3, Q_4, and Q_5 of Formulas (h) through (ab) can independently be covalently coupled to a linker and/or a linker to which is attached to one or more PTM, ULM, ULM', CLM or CLM' groups.

[0161] More specifically, non-limiting examples of CLMs include those shown below as well as "hybrid" molecules or compounds that arise from combining 1 or more featrues of the following compounds:



(ac)



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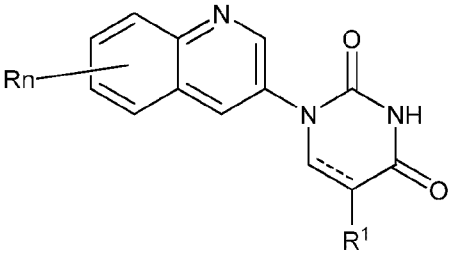

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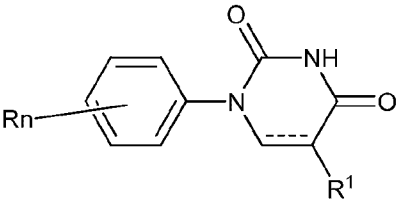
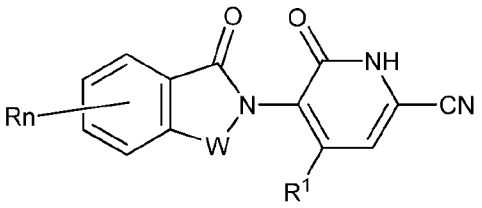


(af)



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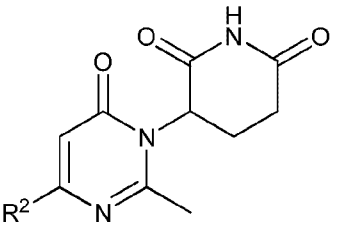

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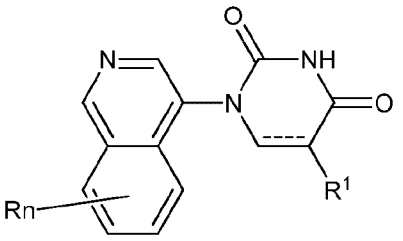

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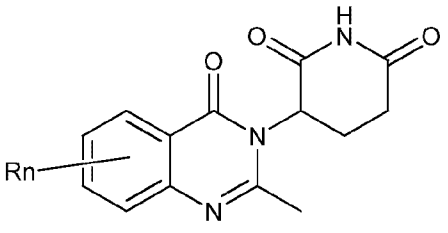

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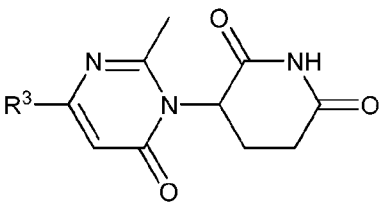

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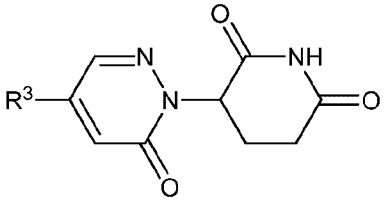

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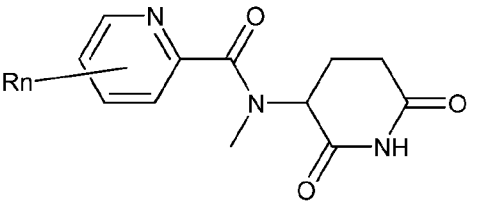

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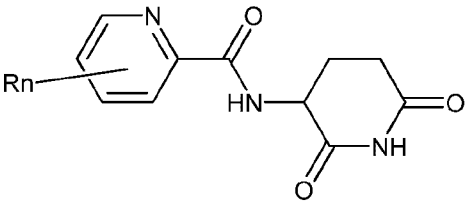


(an)

wherein:

W of Formulas (ac) through (an) is independently selected from the group CH_2, CHR, C=O, SO_2, NH, and N-alkyl;

R^1 of Formulas (ac) through (an) is selected from the group H, CN, C1-C3 alkyl;

R^3 of Formulas (ac) through (an) is selected from H, alkyl, substituted alkyl, alkoxy, substituted alkoxy;

R of Formulas (ac) through (an) is H;

 is a single or double bond; and

Rn of Formulas (ac) through (an) comprises a functional group or an atom.

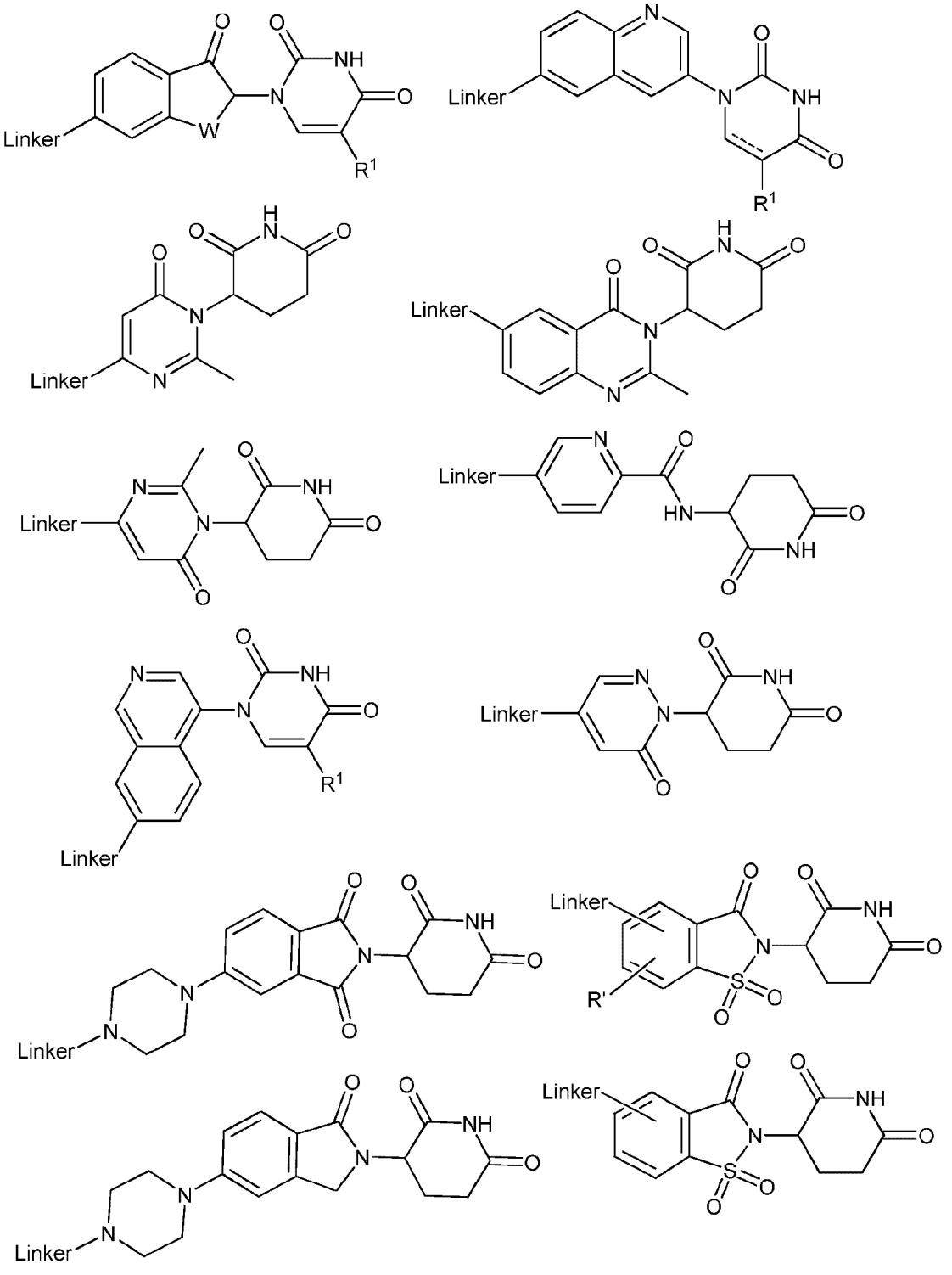
[0162] In any of the embodiments described herein, the W, R^1, R^2, Q_1, Q_2, Q_3, Q_4, and Rn of Formulas (ac) through (an) can independently be covalently coupled to a linker and/or a linker to which is attached one or more PTM, ULM, ULM', CLM or CLM' groups.

[0163] In any of the embodiments described herein, the R^1, R^2, Q_1, Q_2, Q_3, Q_4, and Rn of Formulas (ac) through (an) can independently be covalently coupled to a linker and/or a linker to which is attached one or more PTM, ULM, ULM', CLM or CLM' groups.

[0164] In any of the embodiments described herein, the Q_1, Q_2, Q_3, Q_4, and Rn of Formulas (ac) through (an) can independently be covalently coupled to a linker and/or a linker to which is attached one or more PTM, ULM, ULM', CLM or CLM' groups.

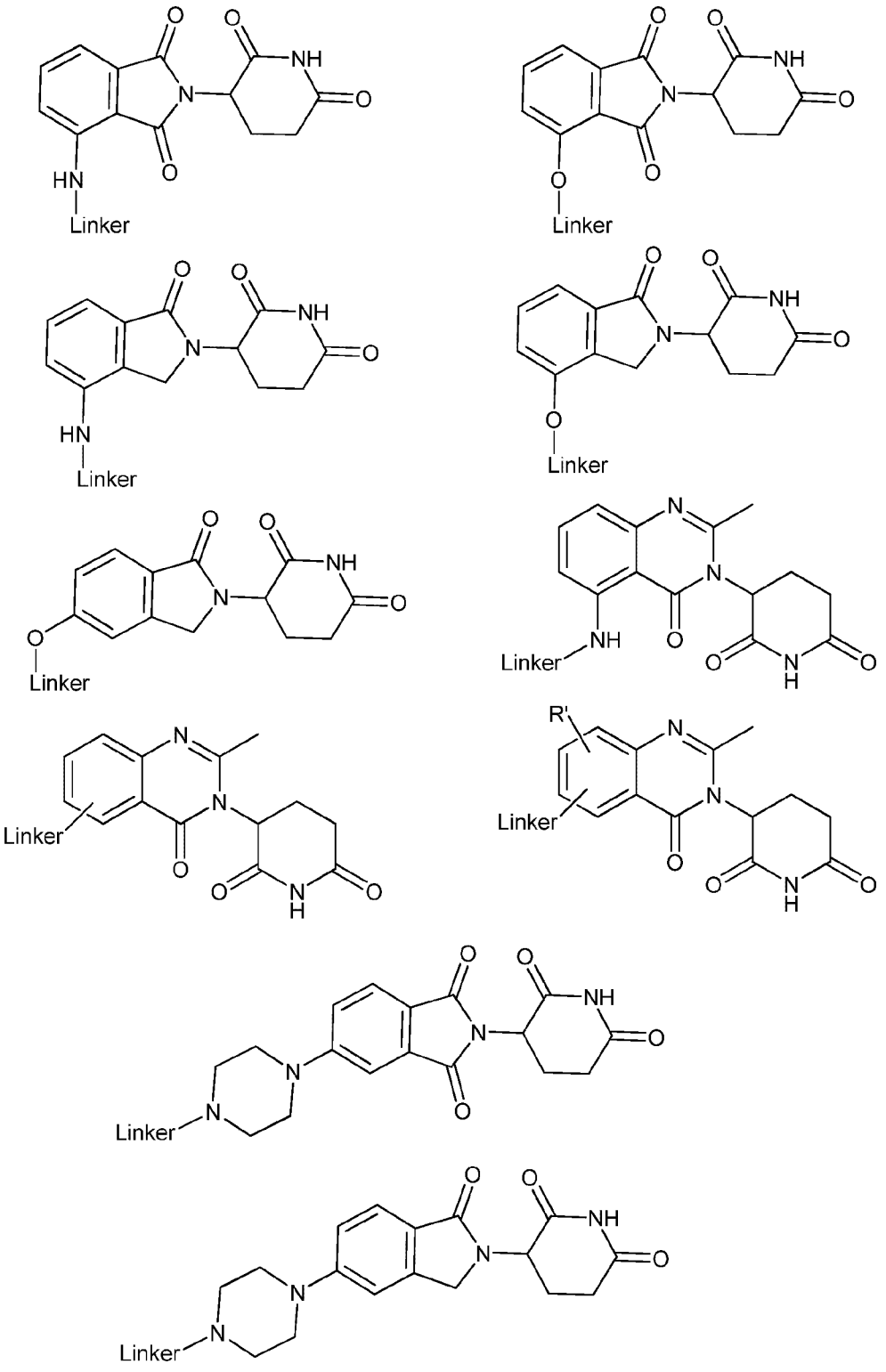
[0165] In any aspect or embodiment described herein, R_n of Formulas (ac) through (an) is modified to be covalently joined to the linker group (L), a PTM, a ULM, a second CLM having the same chemical structure as the CLM, a CLM', a second linker, or any multiple or combination thereof.

[0166] In any aspect or embodiment described herein, the CLM is selected from:



wherein R' is a halogen and R^1 is as described above with regard to Formulas (h) through (ab) or (ac) through (an).

[0167] In certain cases, the CLM can be imides that bind to cereblon E3 ligase. These imides and linker attachment point can be but not limited to the following structures:



, wherein R' is a halogen.

Exemplary Linkers:

[0168] In any of the aspects or embodiments comprising the structure ULM-L-PTM, the linker (L) comprises a chemical structural unit represented by the formula:

$$-(A)_q-,$$

wherein:

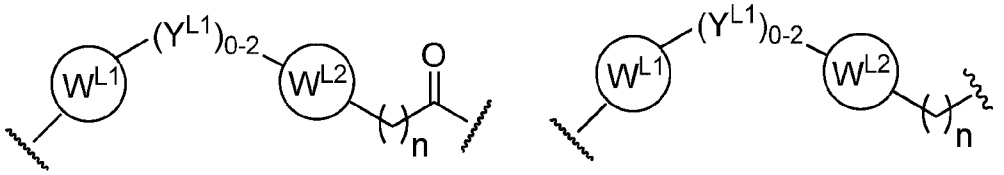
A is a group which is connected to a ULM or PTM moiety; and

q is an integer greater than or equal to 1,

wherein A is 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, where R^{L1} or R^{L2}, each independently are optionally linked to other groups to form cycloalkyl and/or heterocyclyl moiety, optionally substituted with 0-4 R^{L5} groups;

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.

[0169] In any aspect or embodiment described herein, the linker (L) comprises the following chemical structure:



or ,

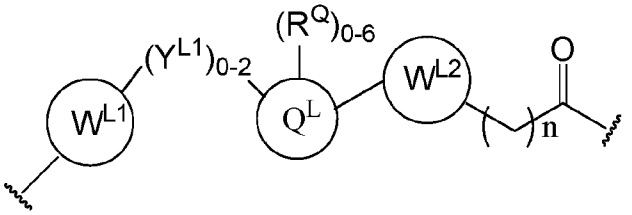
wherein:

W^{L1} and W^{L2} are each independently a 4-8 membered ring with 0-4 heteroatoms, optionally substituted with RQ, each RQ is independently a H, halo, OH, CN, CF3, C1-C6 alkyl (linear, branched, optionally substituted), C1-C6 alkoxy (linear, branched, optionally substituted), or 2 RQ groups taken together with the atom they are attached to, form a 4-8 membered ring system containing 0-4 heteroatoms;

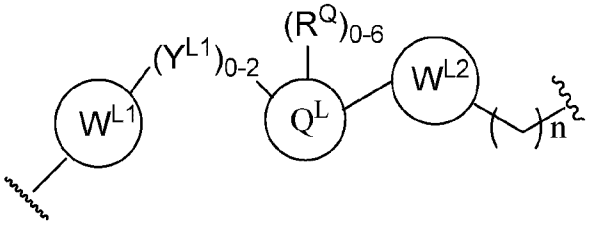
Y^{L1} is each independently a bond, C1-C6 alkyl (linear, branched, optionally substituted) and optionally one or more C atoms are replaced with O; or C1-C6 alkoxy (linear, branched, optionally substituted); and

a dashed line indicates the attachment point to the PTM or ULM moieties.

[0170] In any aspect or embodiment described herein, the linker (L) comprises the following chemical structure:



or



,

wherin:

W^{L1} and W^{L2} are each independently aryl, heteroaryl, cyclic, heterocyclic, C_{1-6} alkyl, bicyclic, biaryl, biheteroaryl,or biheterocyclic, each optionally substituted with R^Q, each R^Q is independently a H, halo, OH, CN, CF_3, hydroxyl, nitro, C≡CH, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkyl (linear, branched, optionally substituted), C_1-C_6 alkoxy (linear, branched, optionally substituted), OC_{1-3}alkyl (optionally substituted by 1 or more –F), OH, NH_2, $NR^{Y1}R^{Y2}$, CN, or 2 R^Q groups taken together with the atom they are attached to, form a 4-8 membered ring system containing 0-4 heteroatoms;

Y^{L1} is each independently a bond, NR^{YL1}, O, S, NR^{YL2}, $CR^{YL1}R^{YL2}$, C=O, C=S, SO, SO_2, C_1-C_6 alkyl (linear, branched, optionally substituted) and optionally one or more C atoms are replaced with O; C_1-C_6 alkoxy (linear, branched, optionally substituted);

Q^L is a 3-6 membered alicyclic or aromatic ring with 0-4 heteroatoms, optionally bridged, 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^{YL1}, R^{YL2} are each independently H, OH, 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);

n is 0-10; and

a dashed line indicates the attachment point to the PTM or ULM moieties.

[0171] In some of the embodiments, linker (L) comprises a group represented by a general structure selected from the group consisting of:

$-N(R)-(CH2)_m-O(CH2)_n-O(CH2)_o-O(CH2)_p-O(CH2)_q-O(CH2)_r-OCH2-$,

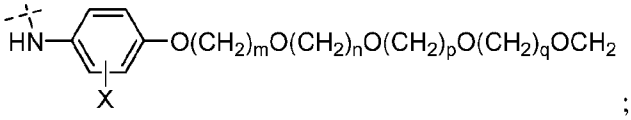
$-O-(CH2)_m-O(CH2)_n-O(CH2)_o-O(CH2)_p-O(CH2)_q-O(CH2)_r-OCH2-$,

$-O-(CH2)_m-O(CH2)_n-O(CH2)_o-O(CH2)_p-O(CH2)_q-O(CH2)_r-O-$;

$-N(R)-(CH2)_m-O(CH2)_n-O(CH2)_o-O(CH2)_p-O(CH2)_q-O(CH2)_r-O-$;

$-(CH2)_m-O(CH2)_n-O(CH2)_o-O(CH2)_p-O(CH2)_q-O(CH2)_r-O-$;

$-(CH2)_m-O(CH2)_n-O(CH2)_o-O(CH2)_p-O(CH2)_q-O(CH2)_r-OCH2-$;



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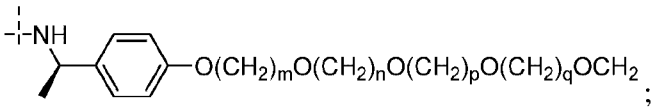

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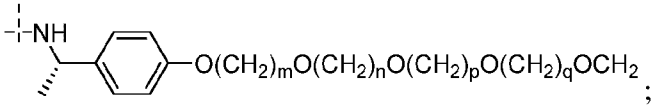

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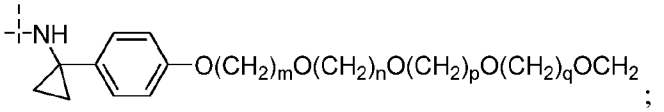

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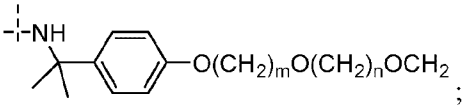
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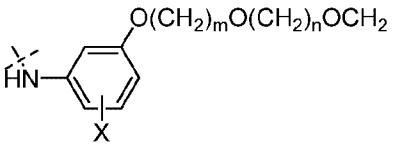
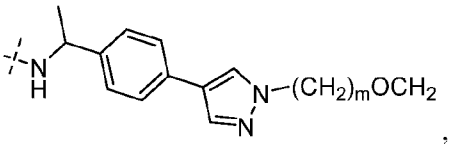
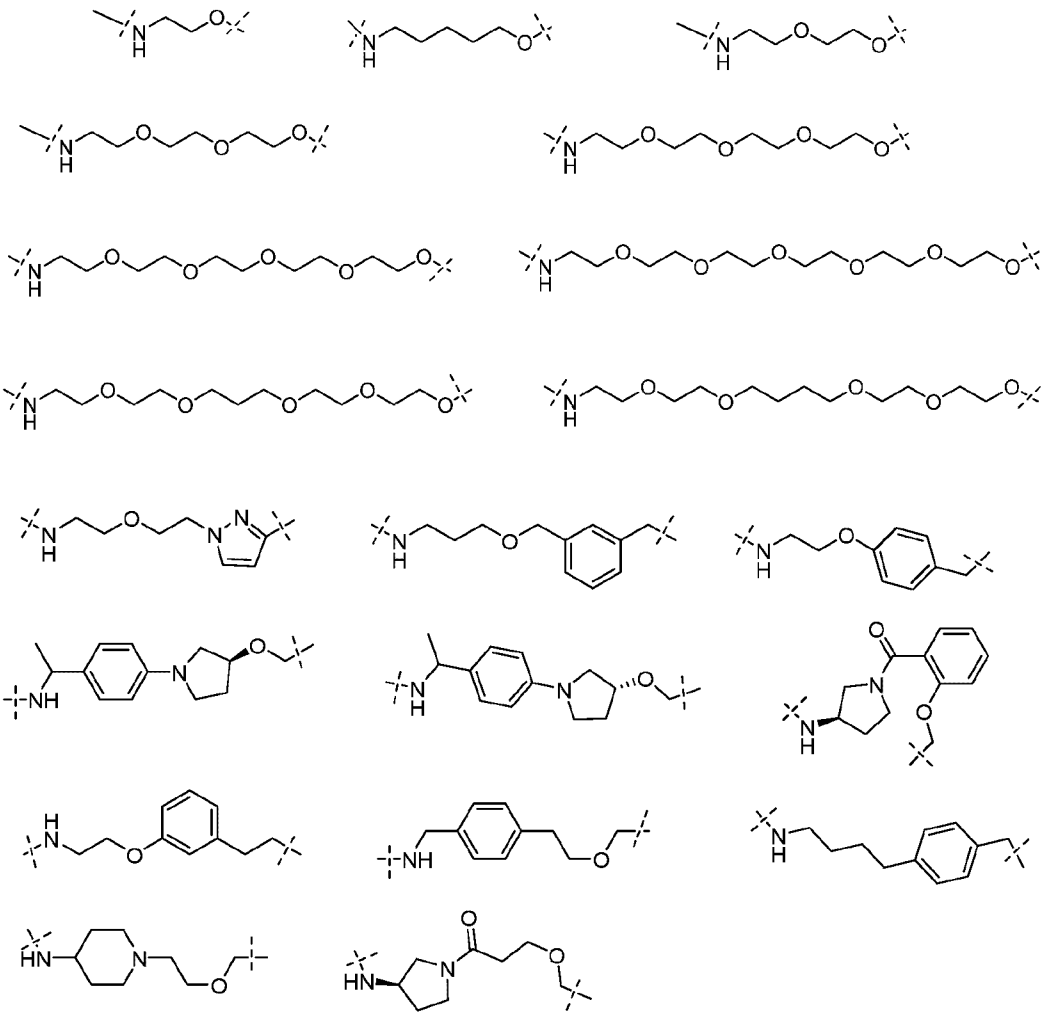
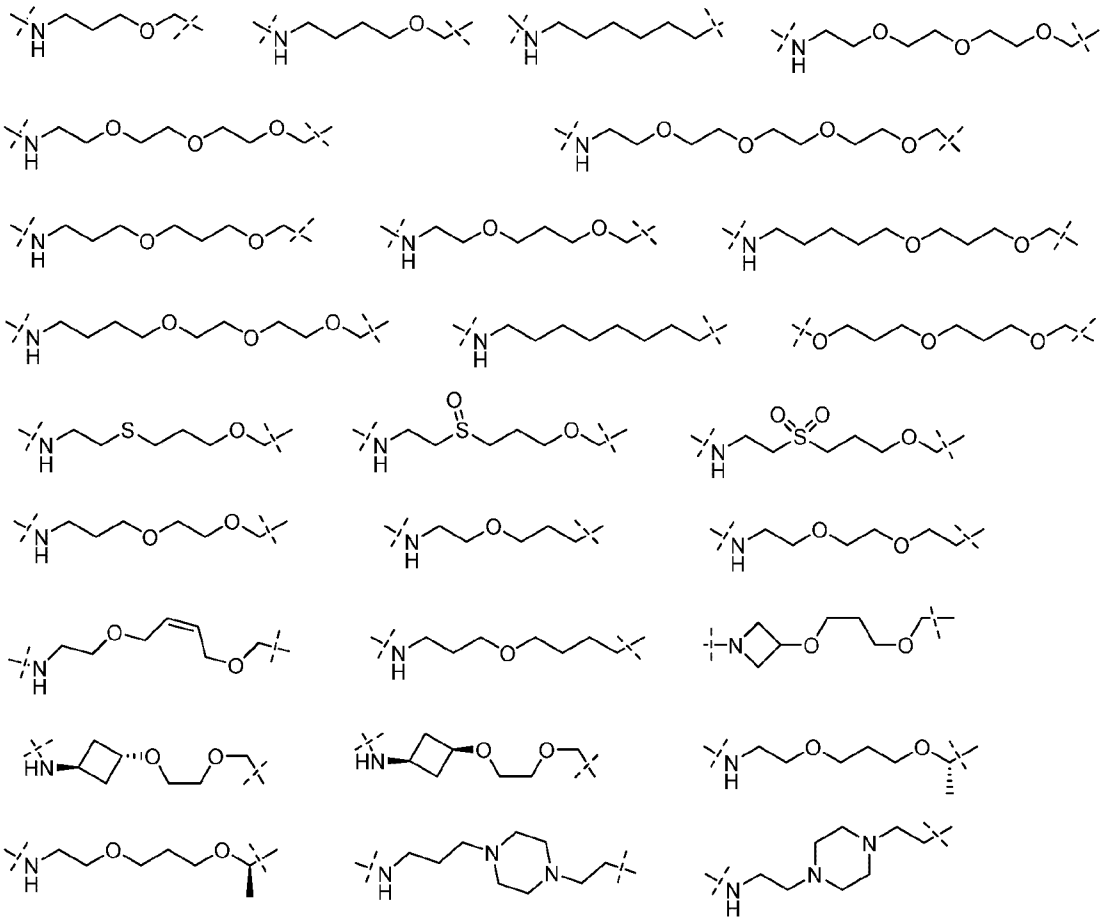
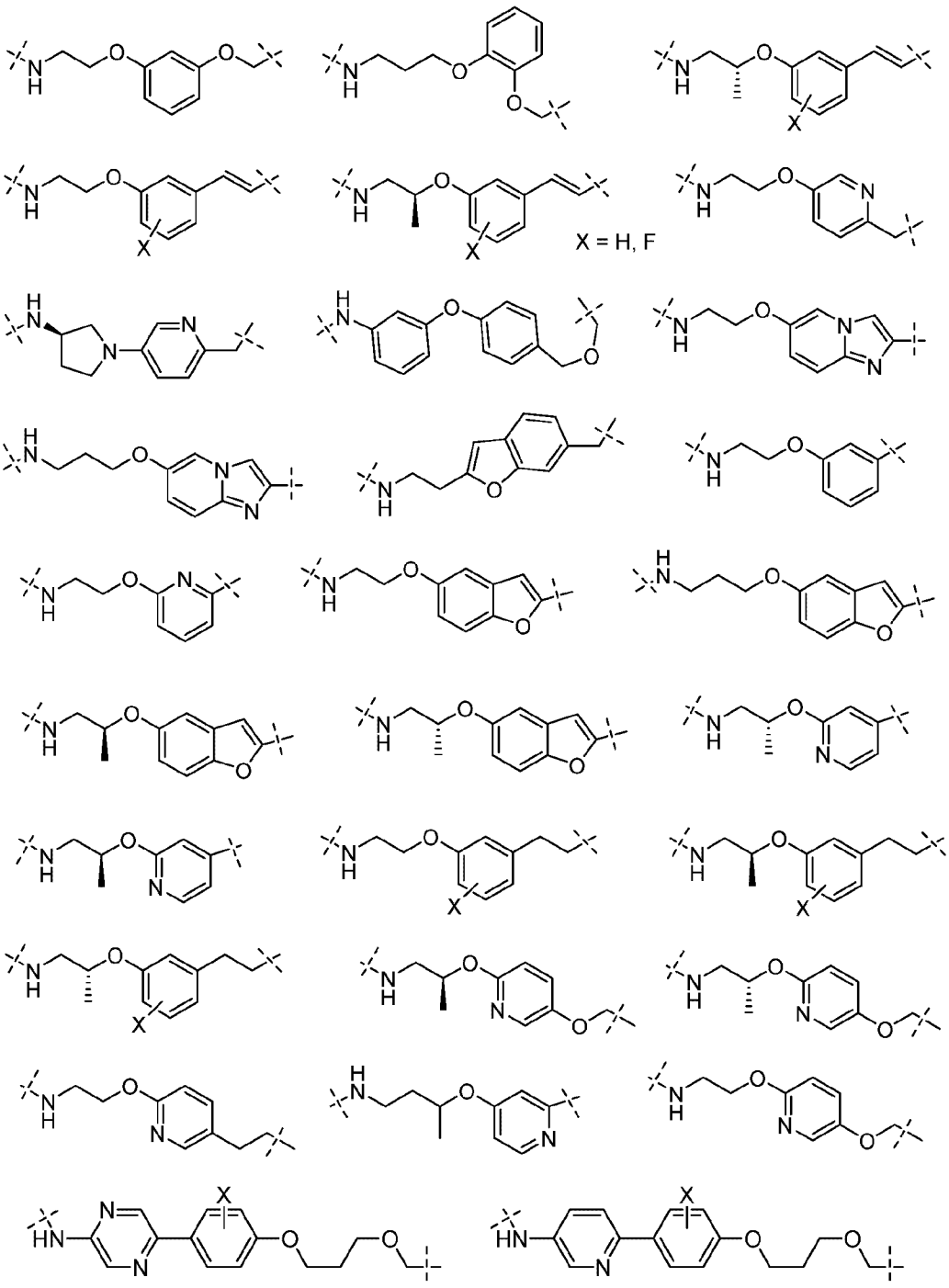
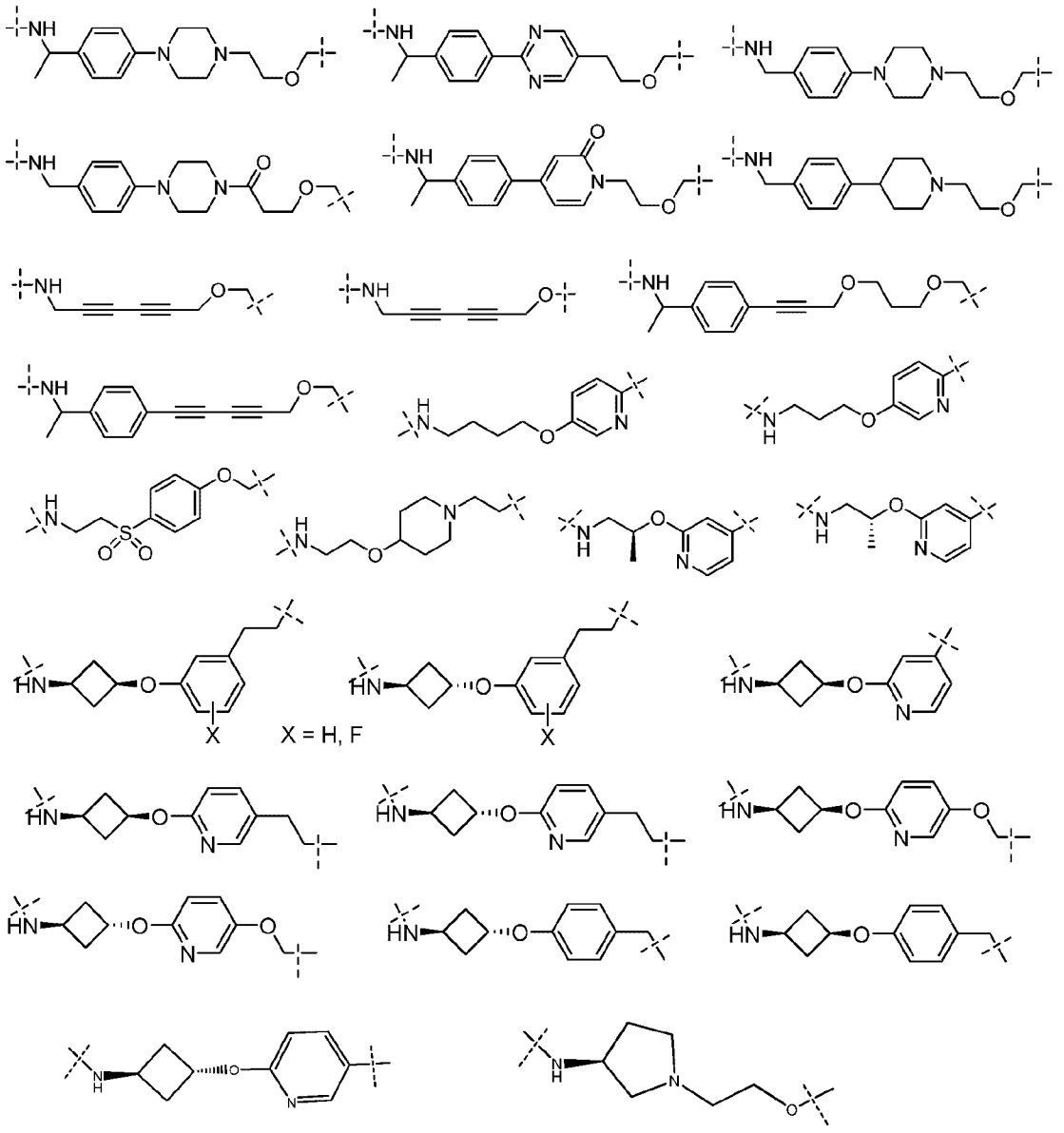

; and

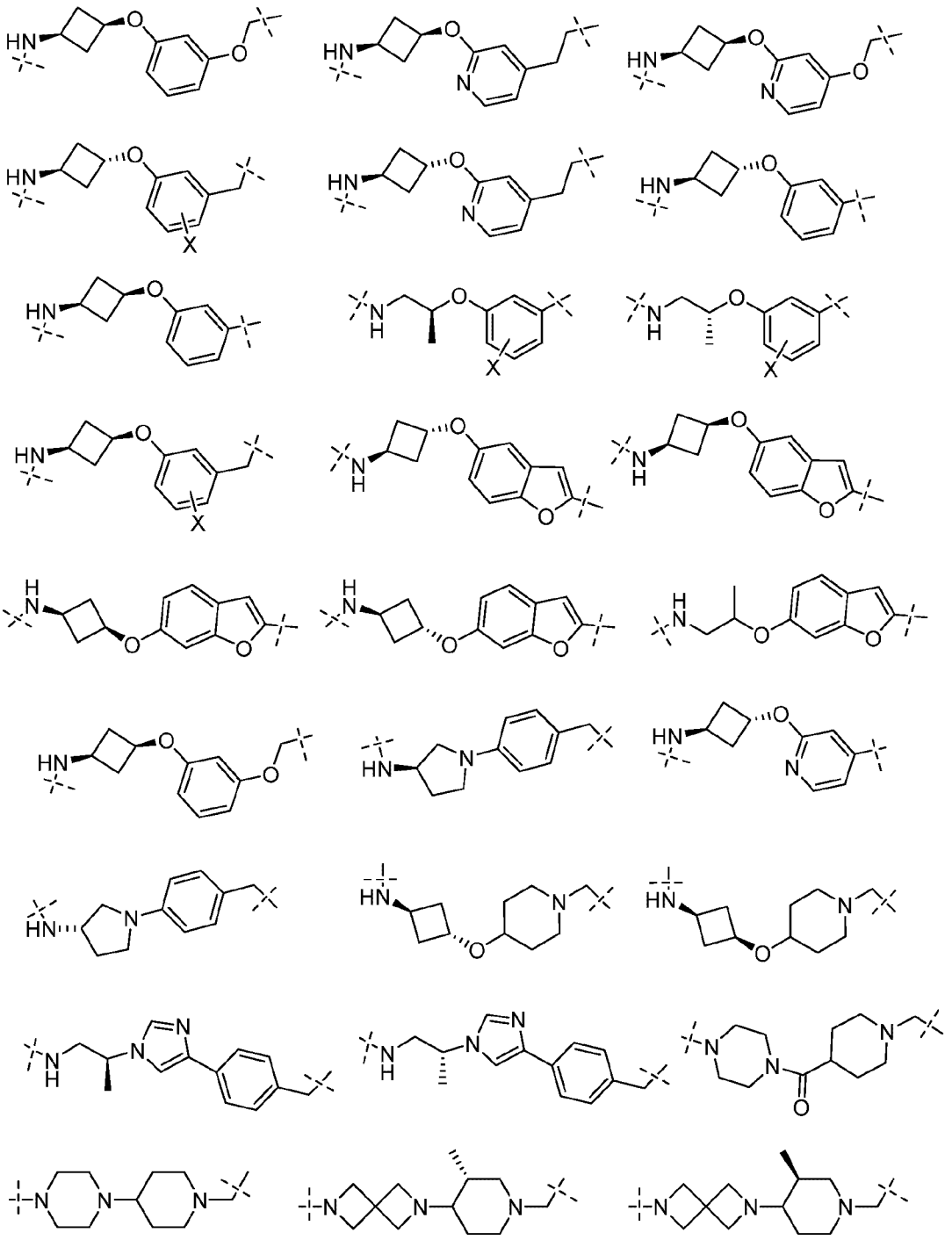

, wherein each m, n, o, p, q, and r, is independently 0, 1, 2, 3, 4, 5, 6 with the proviso that when the number is zero, there is no N-O or O-O bond; R is selected from the group H, methyl or ethyl, and X is selected from the group H or F;

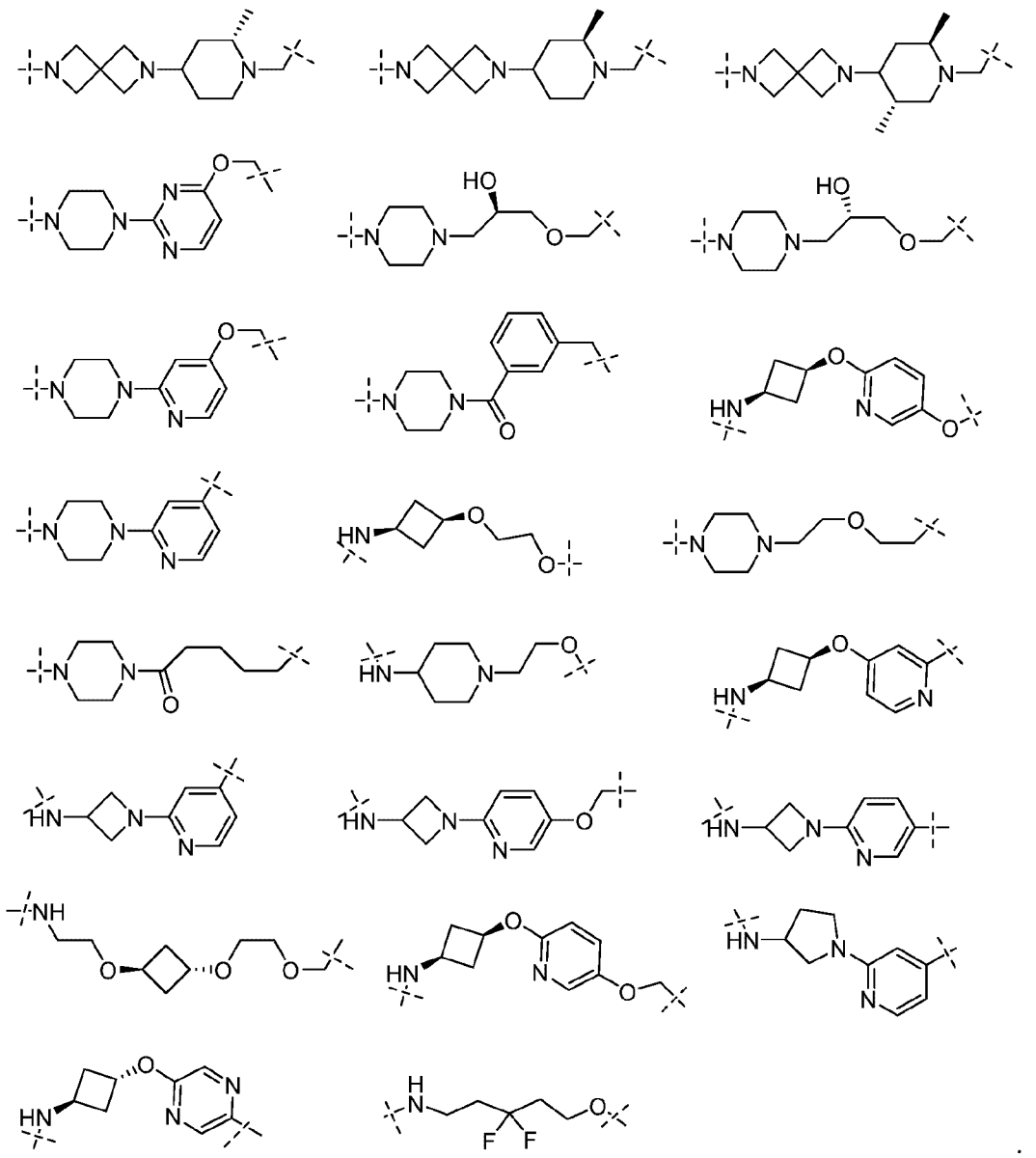




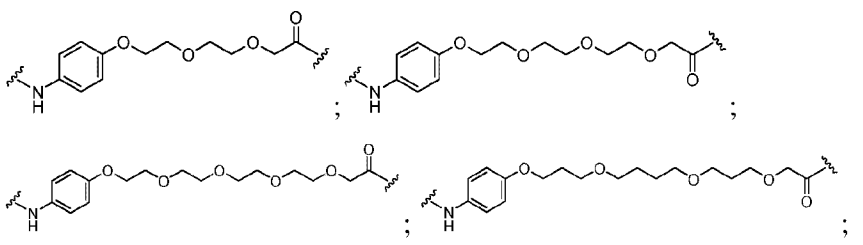

X = H, F

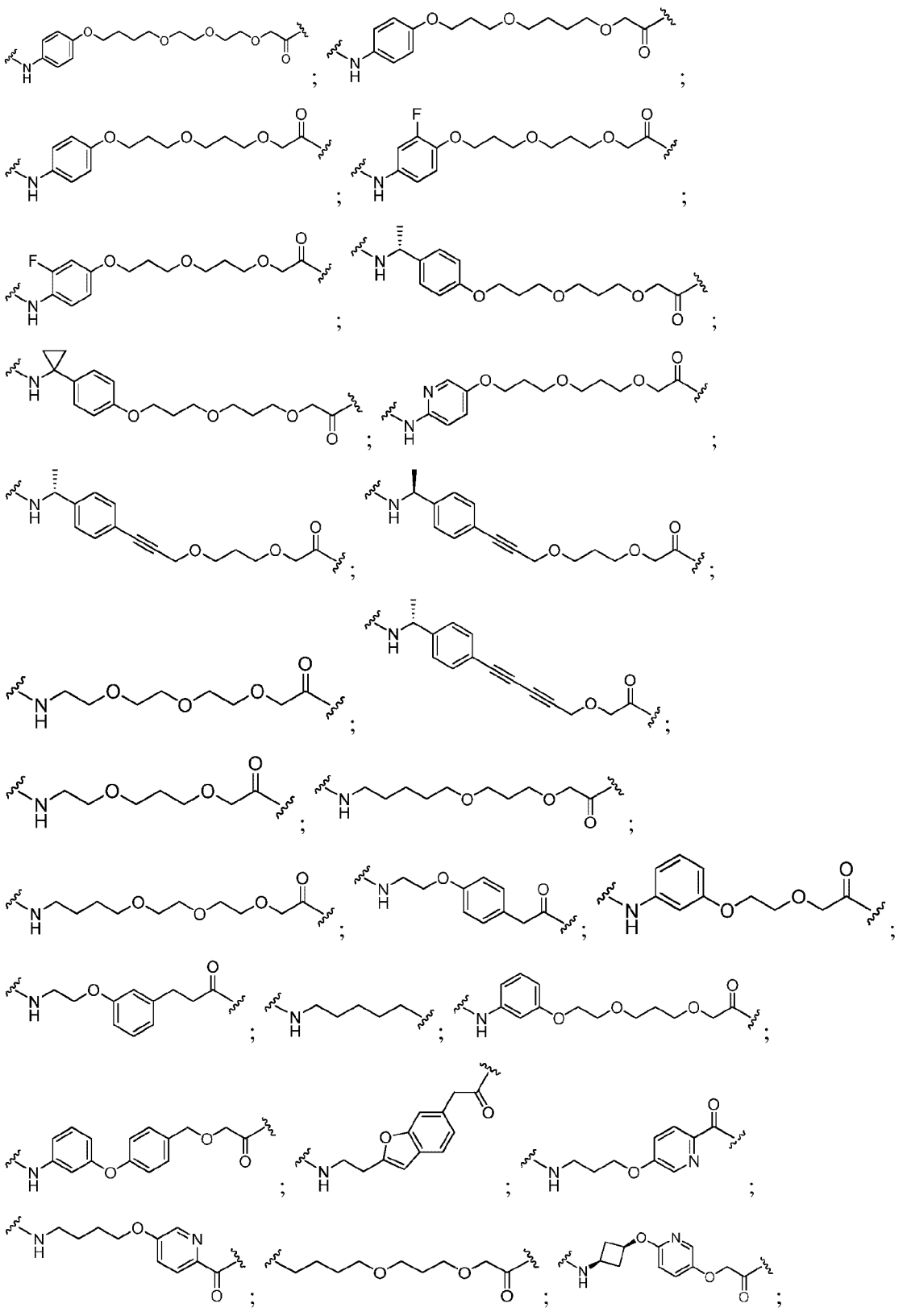

X = H, F

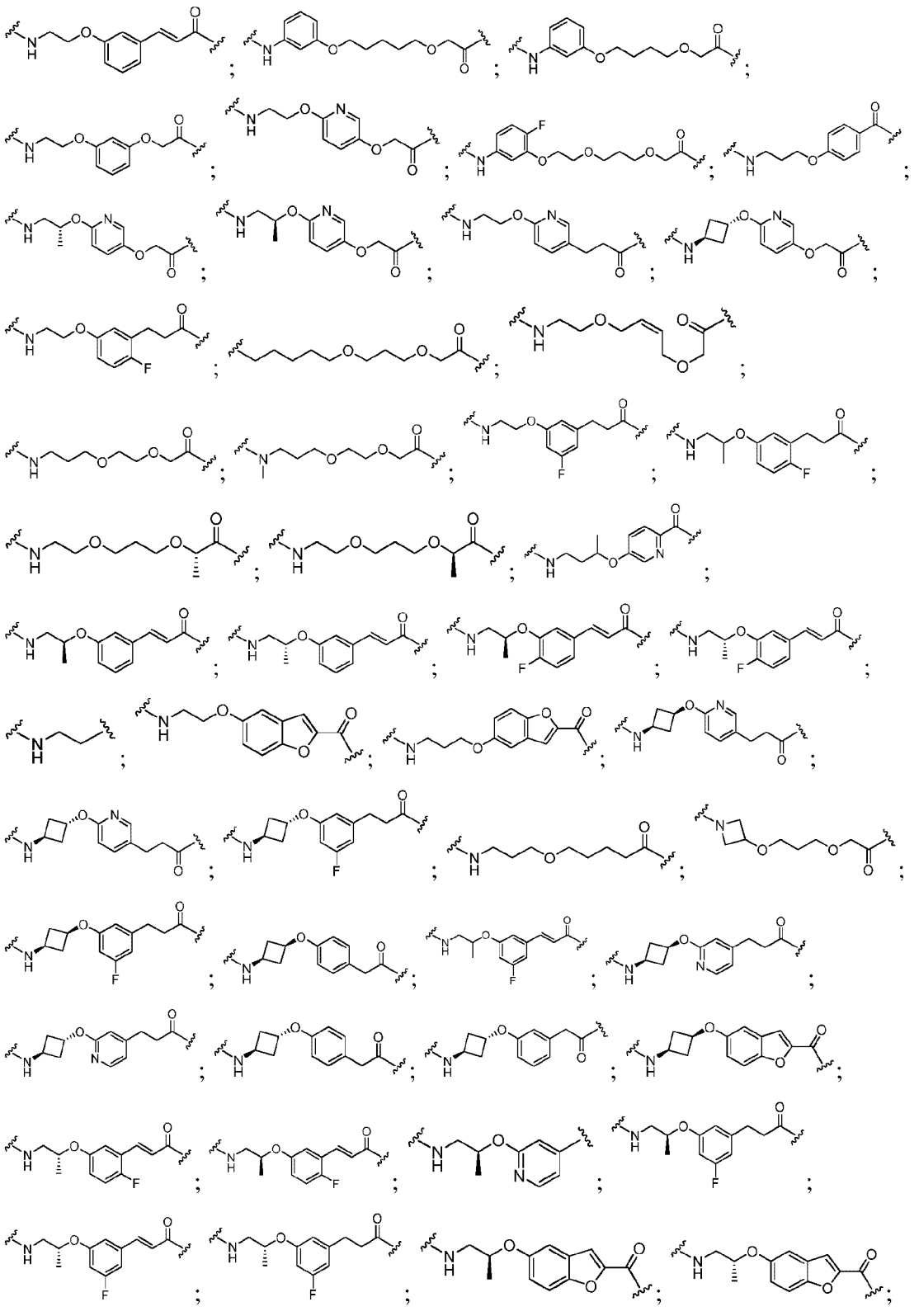


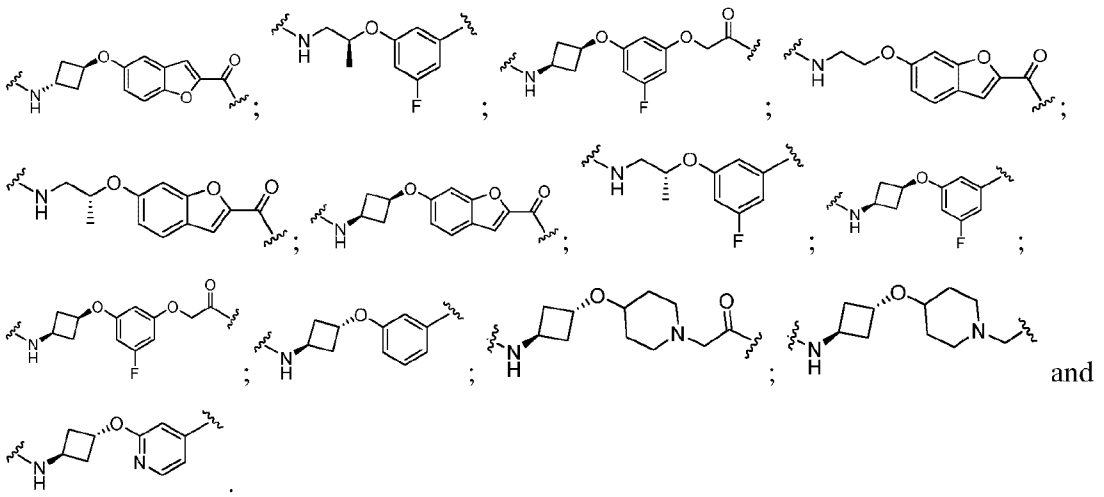


[0172] In some additional embodiments, linker (L) is selected from the group consisting of:



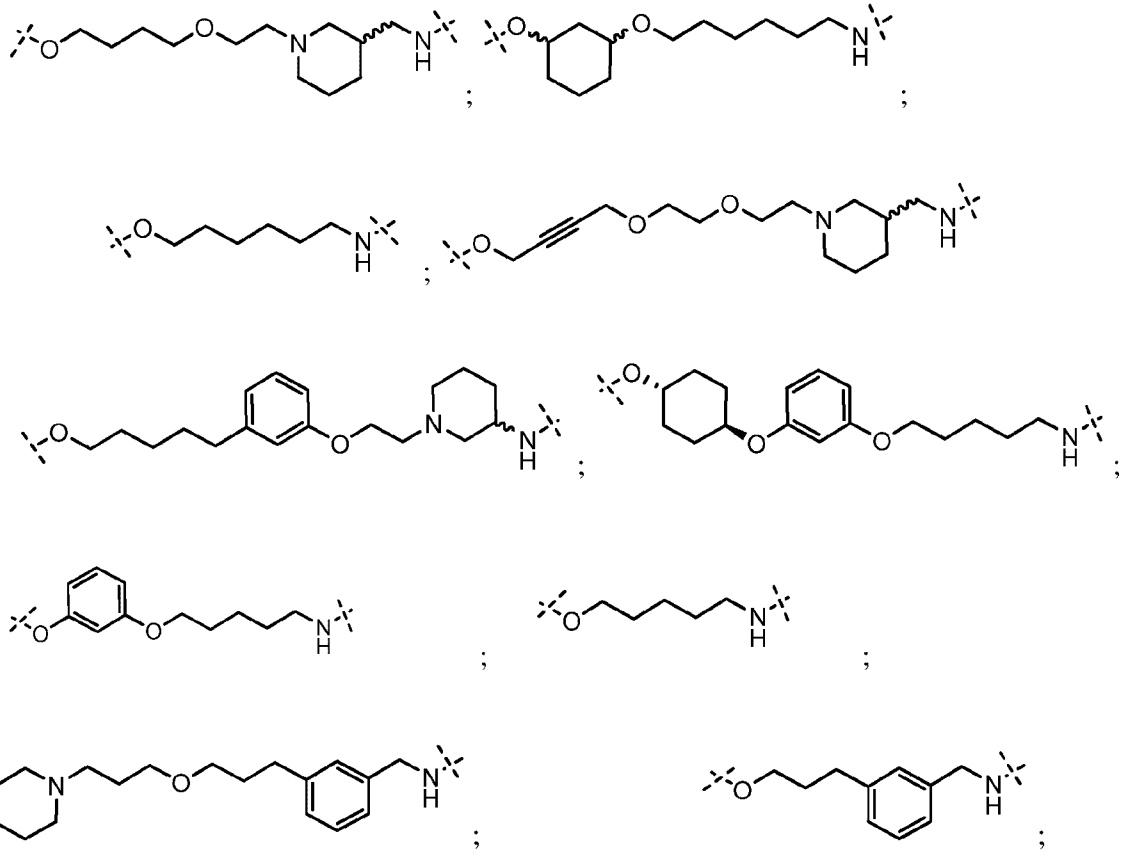


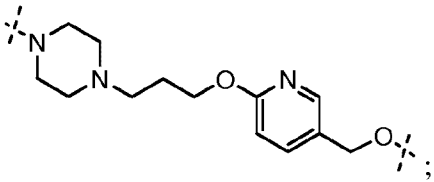
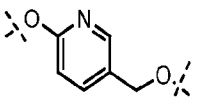
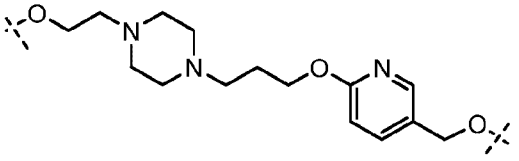


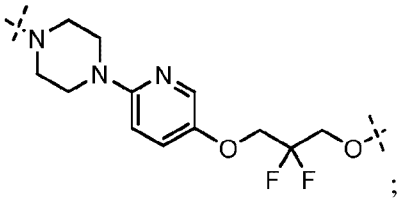
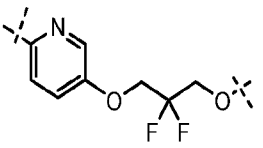
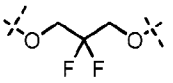


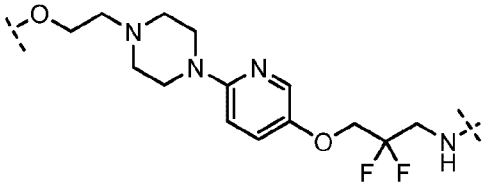
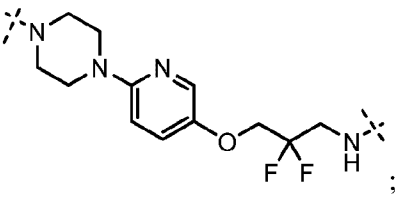
and

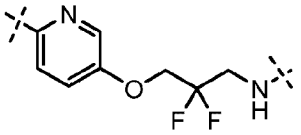
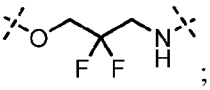
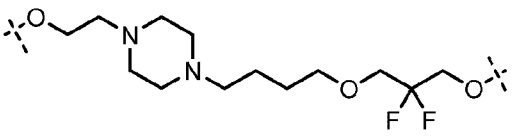
[0173] In some preferred embodiments, linker (L) is selected from the group consisting of:

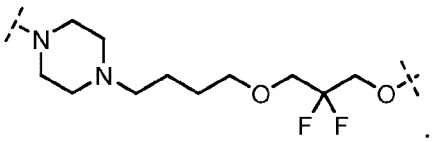
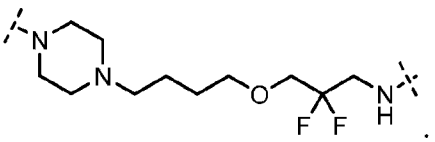


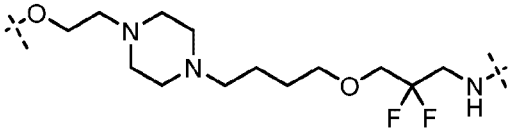
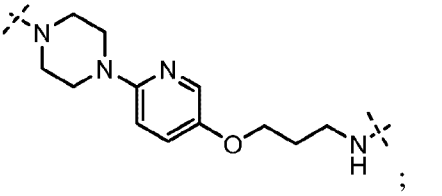
 ;
 ;
 ;

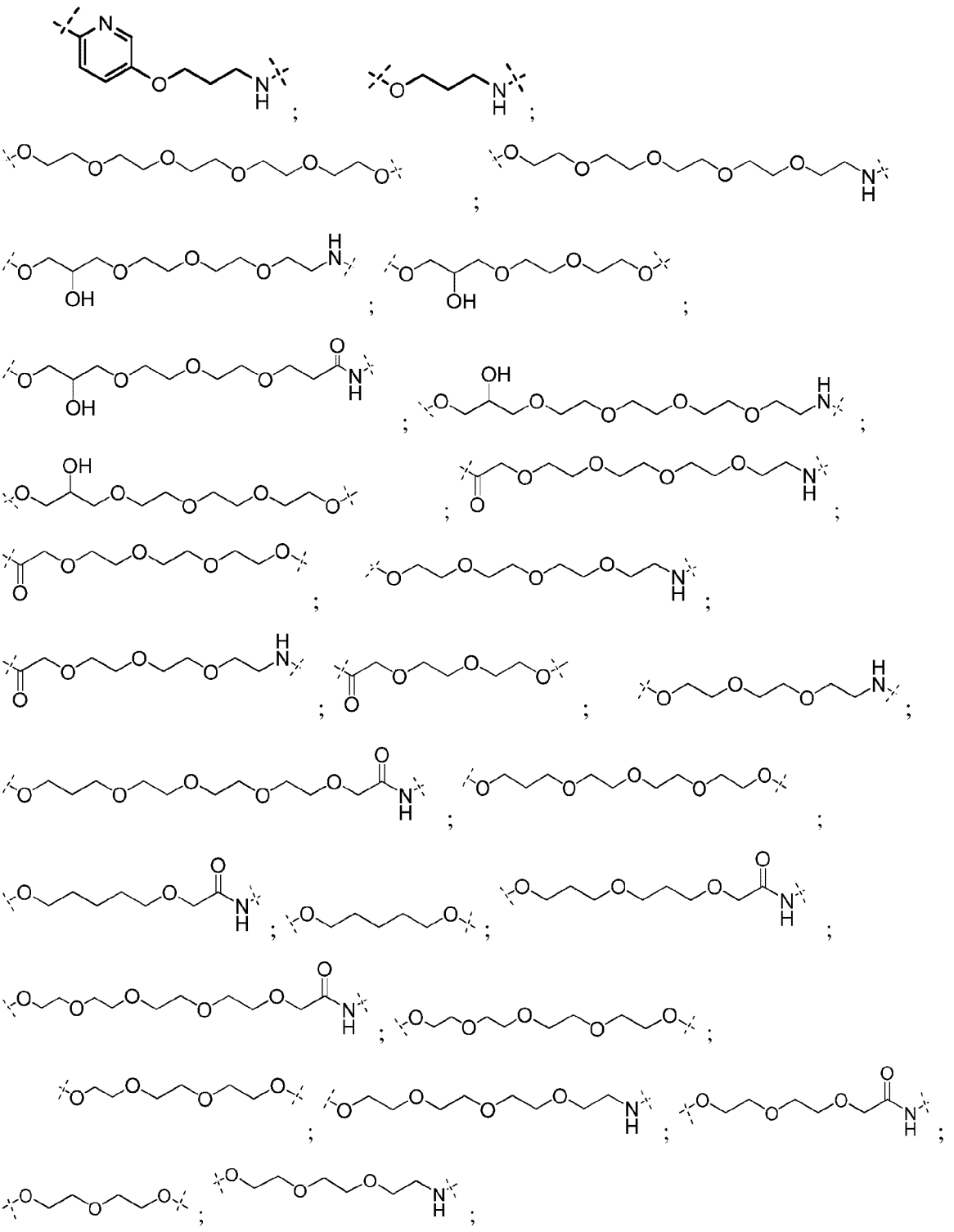
 ;  ;  ;

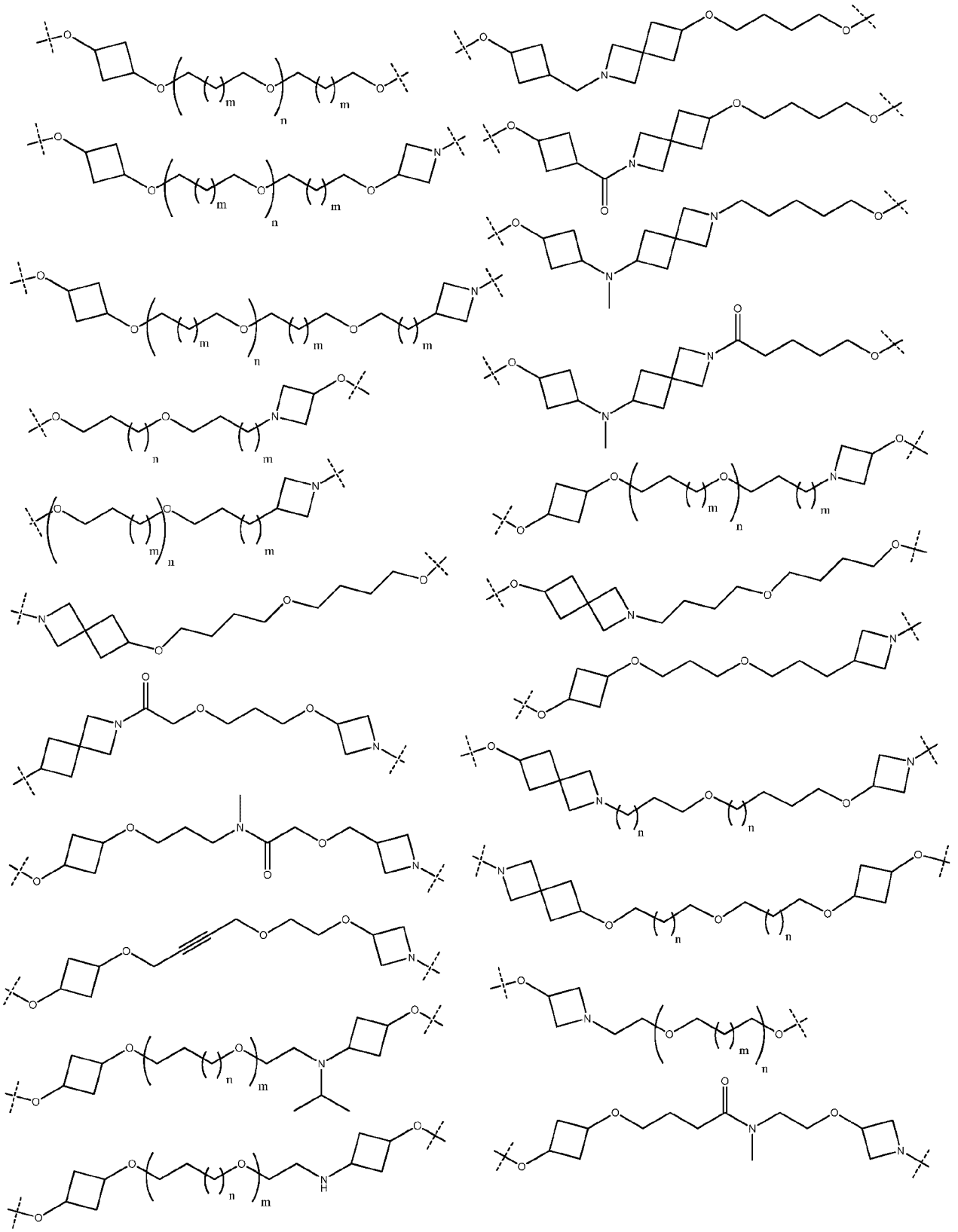
 ;  ;

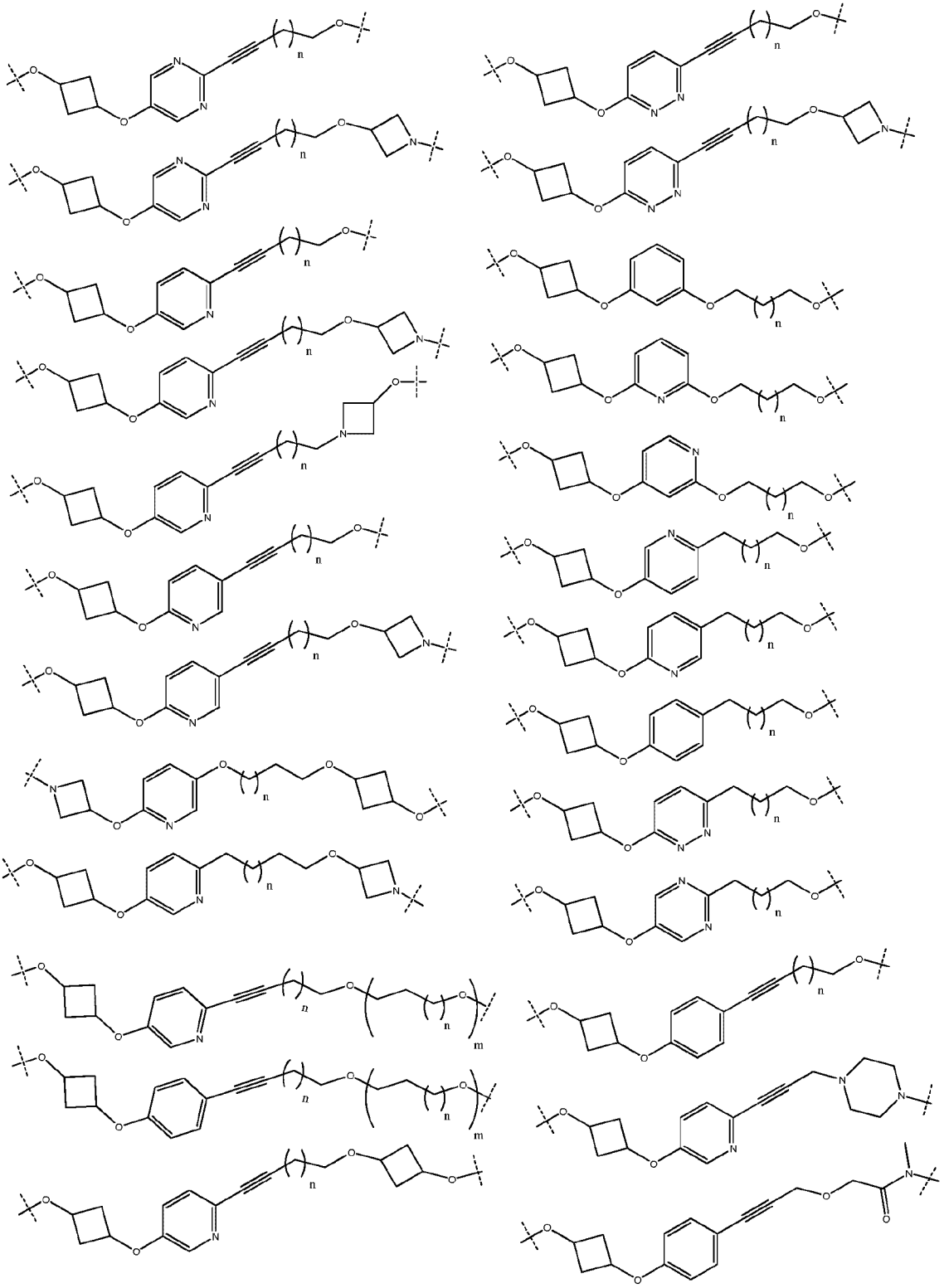
 ;  ;  ;

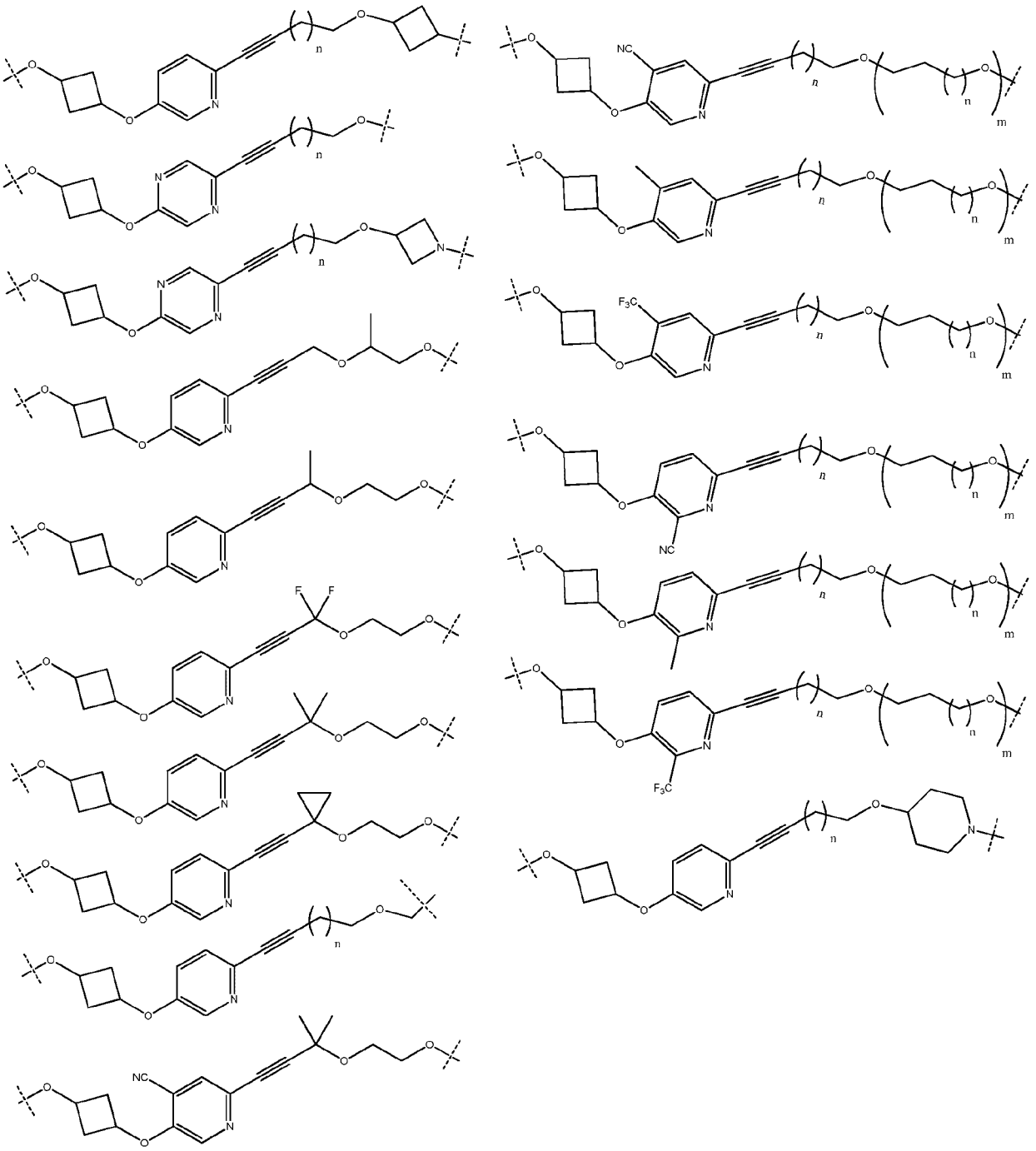
 ;  ;

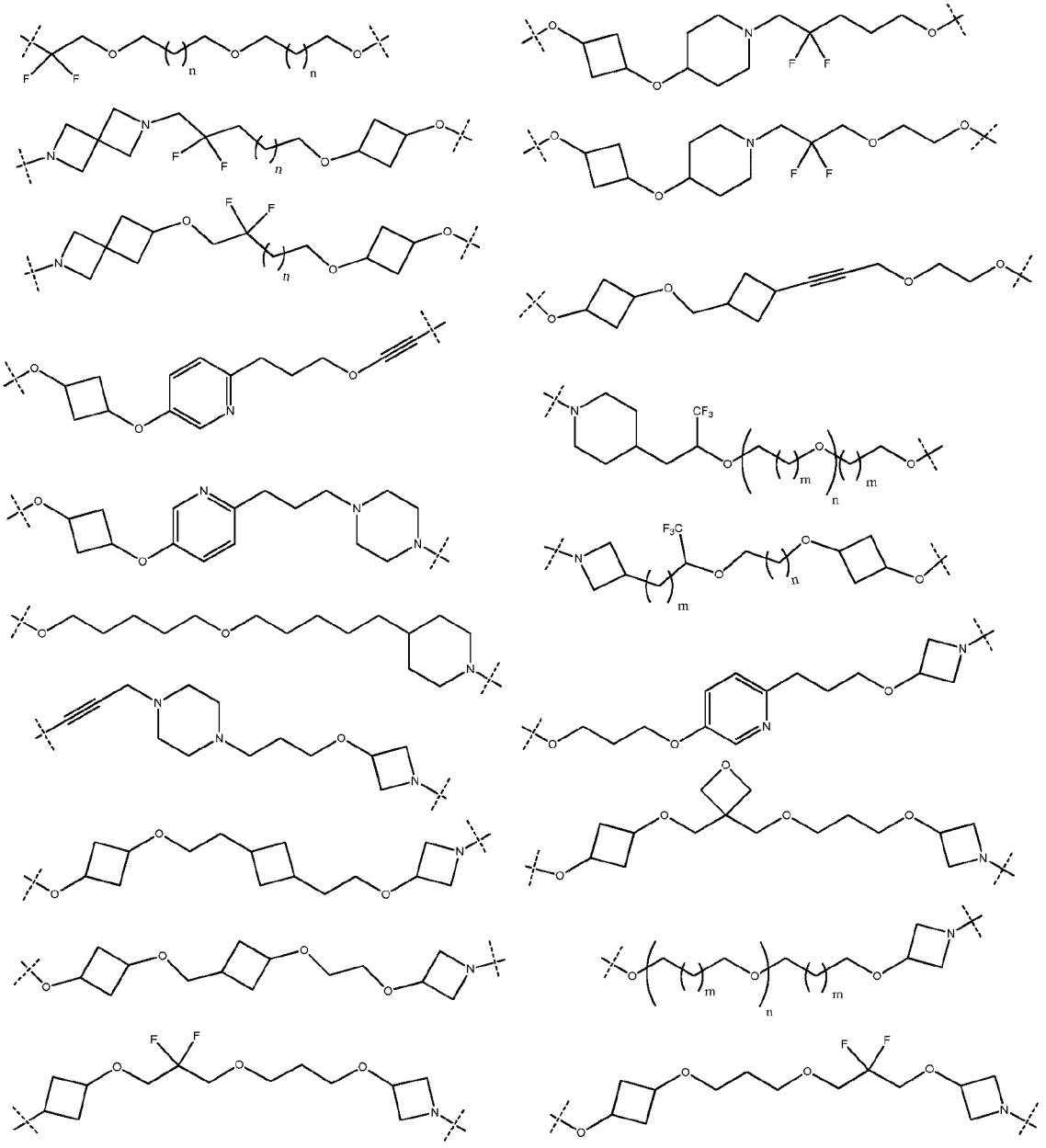
 ;  ;

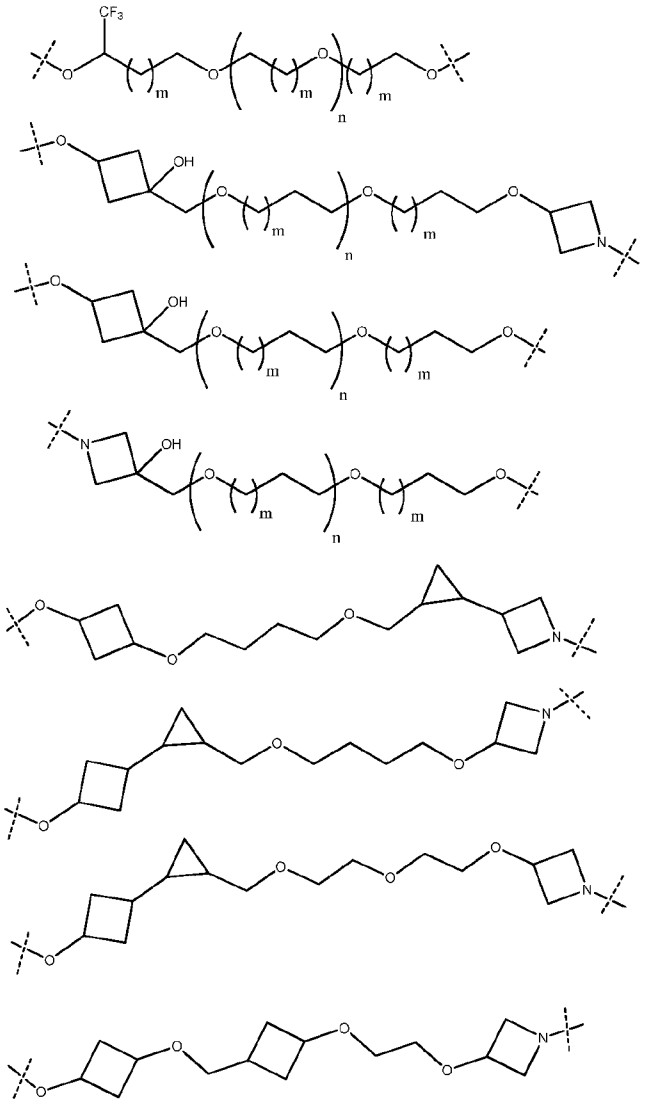


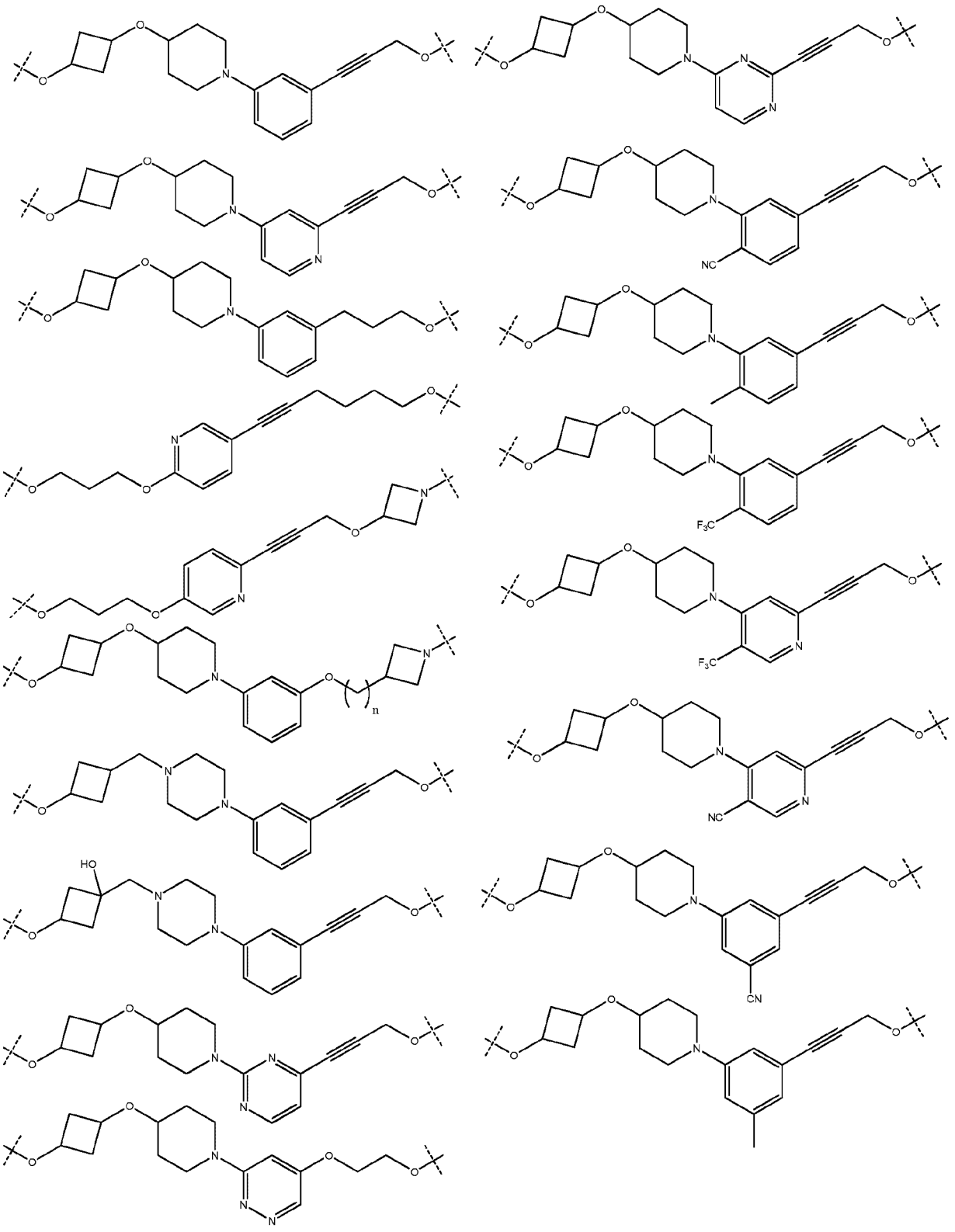


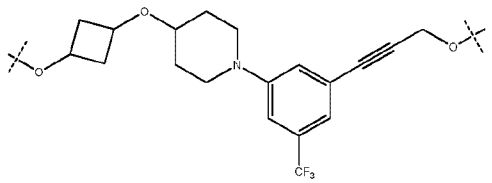
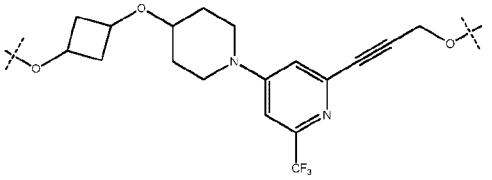
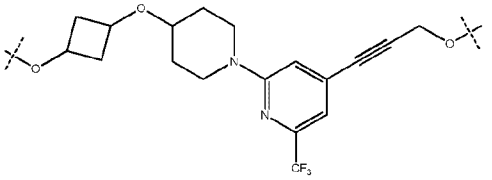
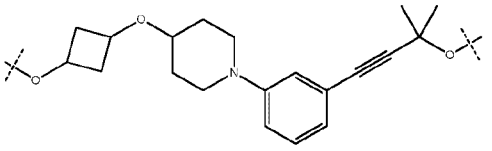
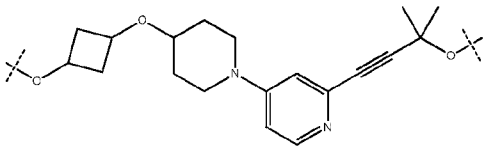
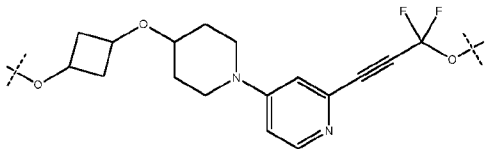
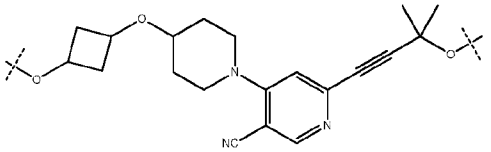
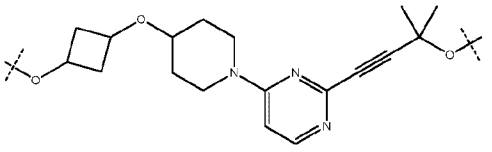


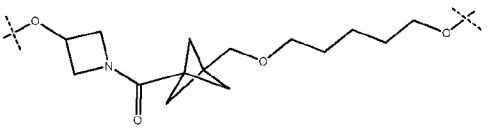


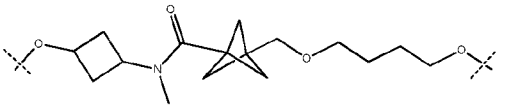
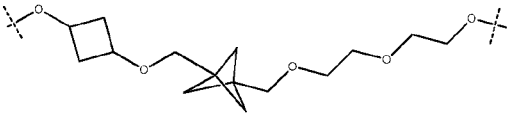


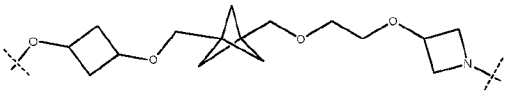


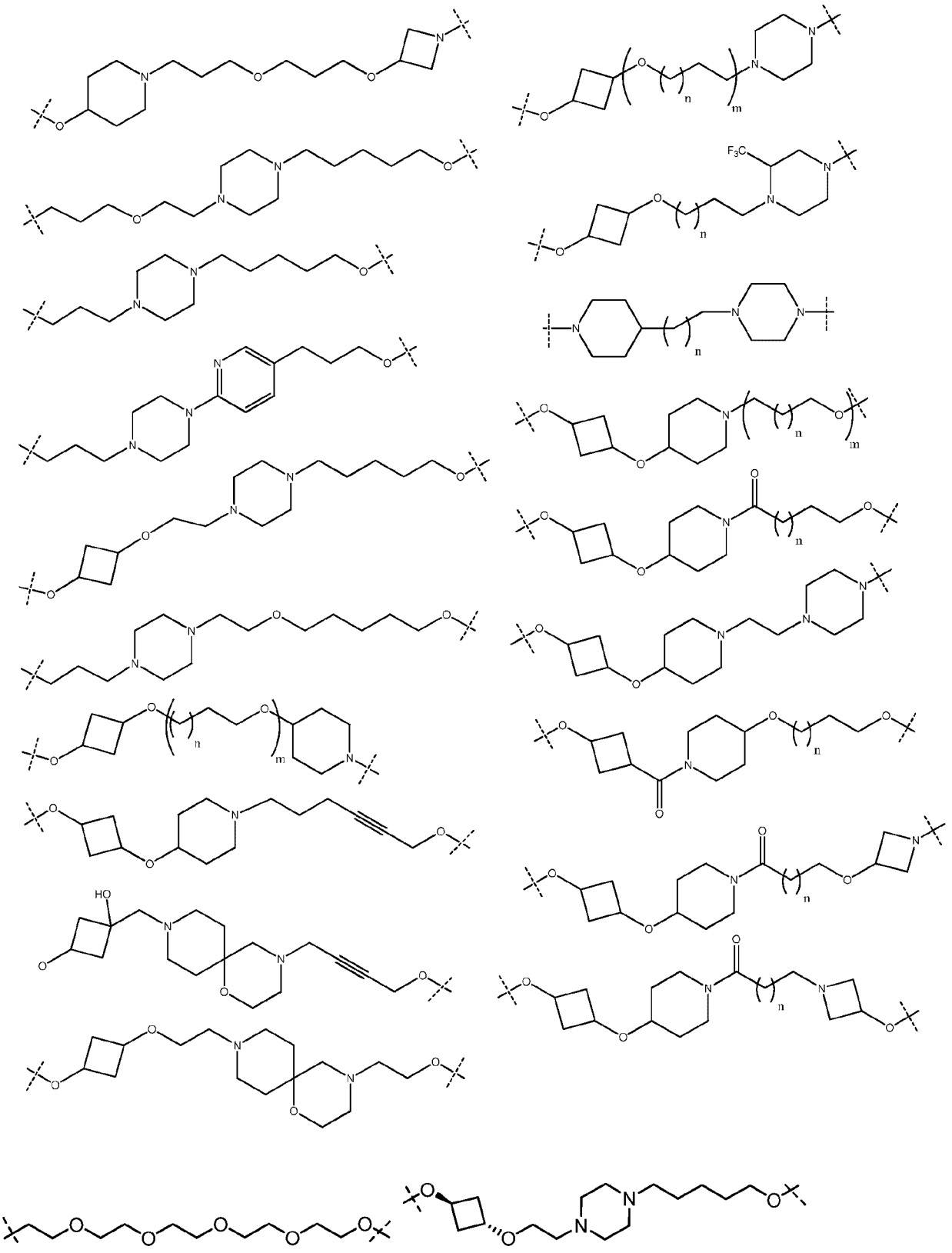


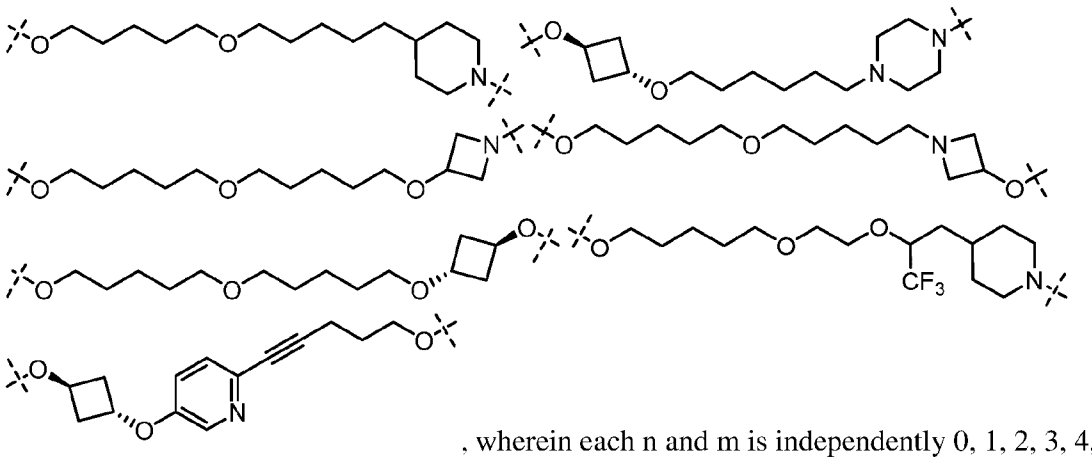

















, wherein each n and m is independently 0, 1, 2, 3, 4, 5, or 6.

[0174] In some embodiments, L is an optionally substituted polyethylenoxy group comprising from 1 to 10 units.

[0175] In some additional embodiments, L is a polyethylene group optionally substituted with aryl or phenyl comprising from 1 to 10 ethylene glycol units.

[0176] In any of the embodiments, the compound comprises multiple ULMs, multiple PTMs, multiple linkers or any combinations thereof.

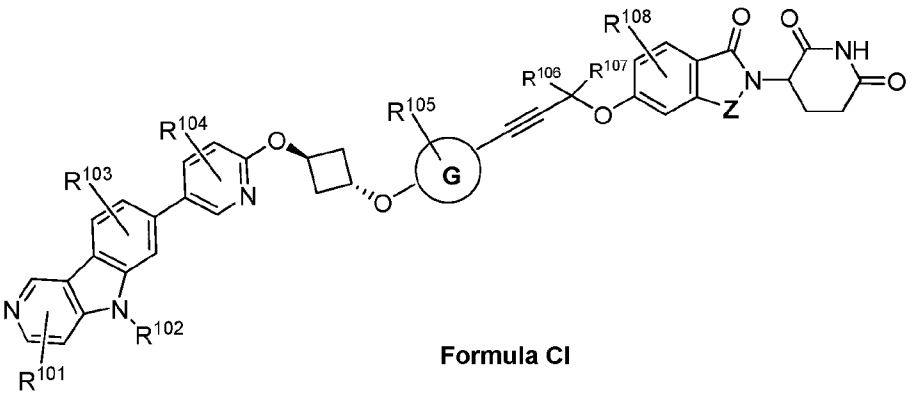
Exemplary Tau-PROTAC Compounds

[0177] As described above, in certain aspects, the description provides bifuctional PROTAC compounds comprising at least one PTM group, a linker, and at least one ULM (VLM or CLM) group as described herein.

[0178] In certain embodiments, the compound is selected from the group consisting of compounds 1-330 (e.g., selected from Table 1 or 2), and salts and polymorphs thereof.

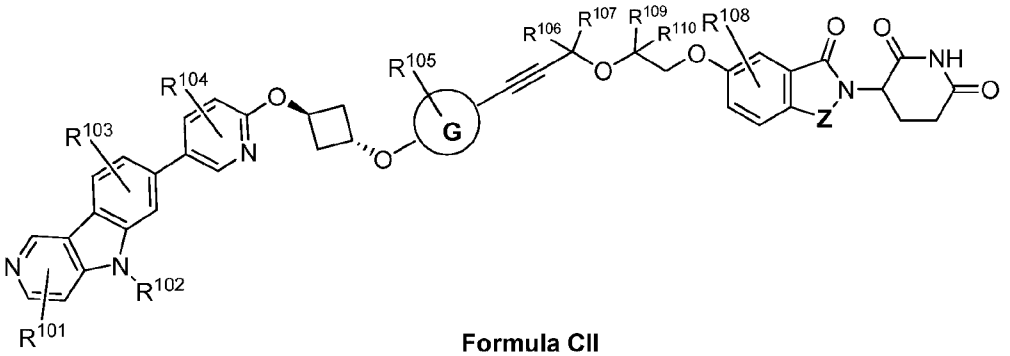
[0179] In certain embodiments, the compound is selected from Table 1 or 2 (i.e., the compound is selected from Compounds 1-330), and salts and polymorphs thereof.

[0180] In any aspect or embodiment described herein, the compound is selected from Formulas CI through CV:



Formula CI

,



Formula CII

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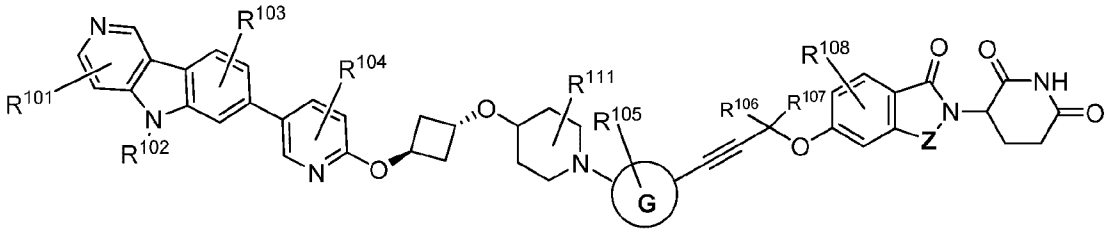

Formula CIII

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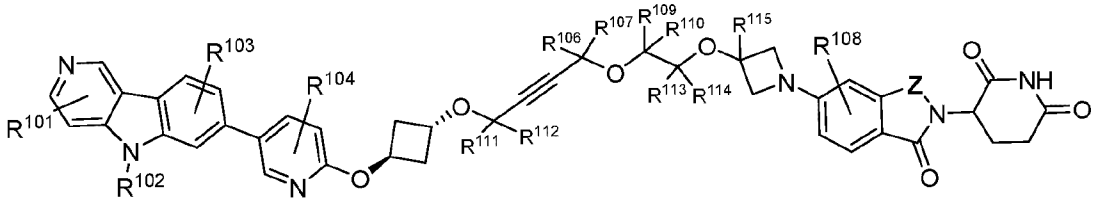
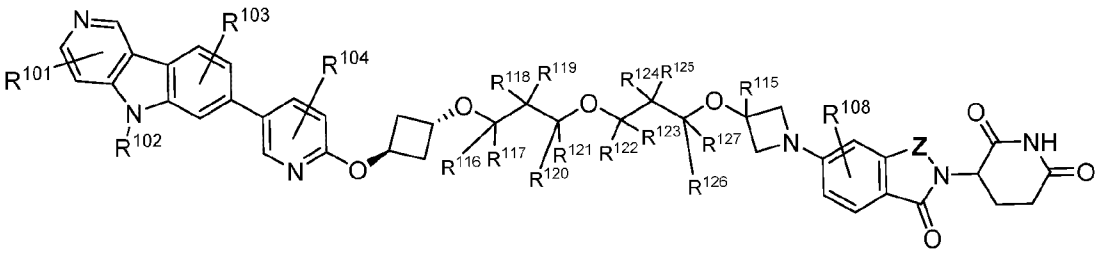


Formula CIV

, or



Formula CV

,

wherein:

R^{101} is 1–2 substituents independently selected from H, alkyl, halogen, haloalkyl or cyano;

R^{102} is selected from H, alkyl, haloalkyl, cycloalkyl or heterocycloalkyl;

R^{103} is 1–2 substituents independently selected from H, alkyl, halogen, haloalkyl or cyano;

R^{104} is 1–2 substituents independently selected from H, alkyl, halogen, haloalkyl or cyano;

R^{105} is 1–2 substituents independently selected from H, alkyl, halogen, haloalkyl or cyano;

R^{106}, R^{107}, R^{109}, R^{110}, R^{111}, R^{112}, R^{113}, R^{114}, R^{116}, R^{117}, R^{120}, R^{121}, R^{126}, R^{127}, R^{122} and R^{123} are each independently selected from H, alkyl, halogen or haloalkyl;

R^{108} is 1–2 substituents independently selected from H, alkyl, halogen, haloalkyl, cyano or methoxy;

R^{115} is selected from H, alkyl and haloalkyl;

R^{118} and R^{119} are independently selected from H, alkyl, halogen or haloalkyl, or R^{118} and R^{119} taken together with the carbon atom to which they are attached represent a 3–6-membered cycloalkyl or heterocycloalkyl ring, such as cyclopropane or an oxetane;

R^{124} and R^{125} are independently selected from H, alkyl, halogen or haloalkyl, or R^{124} and R^{125} taken together with the carbon atom to which they are attached represent a 3–6-membered cycloalkyl or heterocycloalkyl ring, such as cyclopropane or an oxetane;

G is a phenyl or a 5- or 6-membered heteroaryl ring; and

Z is CH_2 or C=O.

[0181] In any aspect or embodiment described herein, at least one of:

R^{101} is H, F or Cl;

R^{102} is H, CH_3, or CF_2H;

R^{103} is H or F;

R^{104} is H, CH_3, F or CN;

R^{105} is H, CN, CH_3 or CF_3;

R^{106} and R^{107} are each independently H, F or CH_3;

R^{108} is H, F or CH_3O;

R^{109} and R^{110} are each independently H or CH_3;

R^{111} and R^{112} are each independently H, F or CH_3;

R^{113} and R^{114} are each independently H or CH_3;

R^{115} is H or CH_3;

R^{116} and R^{117} are each independently H or CH_3;

R^{118} and R^{119} are each independently H, CH_3, F, or R^{118} and R^{119} taken together with the carbon atom to which they are attached represent a cyclopropane or an oxetane ring;

R^{120} and R^{121} are each independently H or CH_3;

R^{122} and R^{123} are each independently H or CH_3;

R^{124} and R^{125} are each independently H, CH_3, F, or R^{124} and R^{125} taken together with the carbon atom to which they are attached represent a cyclopropane or an oxetane ring;

R^{126} and R^{127} are each independently H or CH_3;

A is a pyridine or a pyrimidine;

Z is CH_2 or C=O; or

a combination thereof.

[0182] In any aspect or embodiment described herein, the compound is selected from the group consisting of: (2S,4R)-1-((S)-14-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yloxy)-2-tert-butyl-4-oxo-6,9,12-trioxa-3-azatetradecane)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (1); 4-(2-(2-(2-(2-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yloxy)ethoxy)ethoxy)ethoxy)ethylamino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (2); 4-(2-(2-(2-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yloxy)ethoxy)ethoxy)ethylamino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (3); 4-(14-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yloxy)-3,6,9,12-tetraoxatetradecylamino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (4); (2S,4R)-1-((S)-2-(2-(2-(2-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yloxy)ethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (5); (2S,4R)-1-((S)-17-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yloxy)-2-tert-butyl-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecane)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (6); (2S,4R)-1-((S)-14-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)-2-(tert-butyl)-4-oxo-6,9,12-trioxa-3-azatetradecanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (7);

(2S,4R)-1-((S)-2-tert-butyl-15-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)-4-oxo-6,9,12-trioxa-3-azapentadecane)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (8); (2S,4R)-1-((S)-2-tert-butyl-18-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)-4-oxo-6,9,12,15-tetraoxa-3-azaoctadecane)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (9); (2S,4R)-1-((S)-14-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)-2-(tert-butyl)-4,14-dioxo-6,9,12-trioxa-3-azatetradecanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (10); (2S,4R)-1-((S)-14-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)-2-(tert-butyl)-4-oxo-6,9,12-trioxa-3-azatetradecanoyl)-4-hydroxy-N-(4-(4-methyloxazol-5-yl)benzyl)pyrrolidine-2-carboxamide (11); (2S,4R)-1-((S)-17-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)-2-(tert-butyl)-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-N-(4-(4-methyloxazol-5-yl)benzyl)pyrrolidine-2-carboxamide (12); (2S,4R)-1-((S)-14-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)-2-(tert-butyl)-4,14-dioxo-6,9,12-trioxa-3-azatetradecanoyl)-4-hydroxy-N-(4-(4-methyloxazol-5-yl)benzyl)pyrrolidine-2-carboxamide (13); (2S,4R)-1-((S)-17-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)-2-(tert-butyl)-4,17-dioxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-N-(4-(4-methyloxazol-5-yl)benzyl)pyrrolidine-2-carboxamide (14); (2S,4R)-1-((S)-14-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)-2-(tert-butyl)-4-oxo-6,9,12-trioxa-3-azatetradecanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (15); (2S,4R)-1-((S)-17-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)-2-(tert-butyl)-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (16); (2S,4R)-1-((S)-14-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)-2-(tert-butyl)-4,14-dioxo-6,9,12-trioxa-3-azatetradecanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (17); (2S,4R)-1-((S)-17-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)-2-(tert-butyl)-4,17-dioxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (18); (2S,4R)-1-((S)-14-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)-2-(tert-butyl)-4-oxo-6,9,12-trioxa-3-azatetradecanoyl)-4-hydroxy-N-((S)-1-(4-(4-methyloxazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (19); (2S,4R)-1-((S)-17-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)-2-(tert-butyl)-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-N-((S)-1-(4-(4-methyloxazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (20); (2S,4R)-1-((S)-14-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)-2-(tert-butyl)-4,14-dioxo-

6,9,12-trioxa-3-azatetradecanoyl)-4-hydroxy-N-((S)-1-(4-(4-methyloxazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (21); (2S,4R)-1-((S)-17-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)-2-(tert-butyl)-4,17-dioxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-N-((S)-1-(4-(4-methyloxazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (22); (2S,4R)-1-((S)-17-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)-2-(tert-butyl)-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (23); (2S,4R)-1-((S)-17-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)-2-(tert-butyl)-4,17-dioxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (24); 4-((2-(2-(2-(2-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)ethoxy)ethoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (25); 4-((14-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)-3,6,9,12-tetraoxatetradecyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (26); (2S,4R)-1-((S)-2-(2-(2-(2-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)ethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (27); (2S,4R)-1-((S)-2-(2-(2-(2-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)ethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (28); (2S,4R)-1-((S)-2-tert-butyl-14-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)-4-oxo-6,9,12-trioxa-3-azatetradecane)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (29); (2S,4R)-1-((S)-2-tert-butyl-14-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)-4-oxo-6,9,12-trioxa-3-azatetradecane)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (30); (2S,4R)-1-((S)-2-tert-butyl-17-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecane)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (31); (2S,4R)-1-((S)-2-tert-butyl-17-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecane)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (32); (2S,4R)-1-((S)-2-(2-(4-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)butoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (33); (2S,4R)-1-((S)-2-(2-(4-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)butoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (34); (2S,4R)-1-((S)-2-(2-(3-(3-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)propoxy)propoxy)acetamido)-3,3-

dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (35); (2S,4R)-1-((S)-2-(2-(3-(3-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)propoxy)propoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (36); (2S,4R)-1-((S)-2-(2-(5-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)pentyloxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (37); (2S,4R)-1-((S)-2-(2-(5-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)pentyloxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (38); (2S,4R)-1-((S)-2-tert-butyl-18-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)-4-oxo-6,9,12,15-tetraoxa-3-azaoctadecane)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (39); 4-(15-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)-3,6,9,12-tetraoxapentadecylamino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (40); 4-((2-(2-(2-(2-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)-2-oxoethoxy)ethoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (41); 4-((14-(4-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)piperazin-1-yl)-14-oxo-3,6,9,12-tetraoxatetradecyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (42); (2S,4R)-1-((2S)-2-tert-butyl-15-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)-14-hydroxy-4-oxo-6,9,12-trioxa-3-azapentadecane)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (43); 4-(2-(2-(2-(3-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)propoxy)ethoxy)ethoxy)ethylamino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (44); 4-(15-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)-14-hydroxy-3,6,9,12-tetraoxapentadecylamino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (45); (2S,4R)-1-((2S)-2-tert-butyl-18-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)-17-hydroxy-4-oxo-6,9,12,15-tetraoxa-3-azaoctadecane)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (46); 4-(2-(2-(2-(3-(2-(4-(dimethylamino)phenyl)quinolin-6-yloxy)-2-hydroxypropoxy)ethoxy)ethoxy)ethylamino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (47); 2-(2,6-dioxopiperidin-3-yl)-4-(14-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yloxy)-3,6,9,12-tetraoxatetradecylamino)isoindoline-1,3-dione (48); 3-(4-(14-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yloxy)-3,6,9,12-tetraoxatetradecylamino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (49); 3-(4-(14-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yloxy)-3,6,9,12-tetraoxatetradecyloxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (50); 5-((14-((5-(5H-Pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (51); 5-

((5-(4-(2-(3-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propoxy)ethyl)piperazin-1-yl)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (52); 5-(4-(3-((1s,3s)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)propyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (53); 5-((5-(4-(3-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propyl)piperazin-1-yl)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (54); 5-(3-(6-(4-(3-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propyl)piperazin-1-yl)pyridin-3-yl)propoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (55); 5-((5-(4-(2-((1s,3s)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)ethyl)piperazin-1-yl)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (56); 5-((14-(4-(5H-pyrido[4,3-b]indol-7-yl)piperidin-1-yl)-3,6,9,12-tetraoxatetradecyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (57); 5-((5-(2-(4-(3-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propyl)piperazin-1-yl)ethoxy)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (58); 5-((5-(4-(2-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)ethyl)piperazin-1-yl)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (59); 5-(4-(3-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)propyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (60); 2-(2,6-dioxopiperidin-3-yl)-5-((5-(4-(3-(5-(5-(2,2,2-trifluoroethyl)-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propyl)piperazin-1-yl)pentyl)oxy)isoindoline-1,3-dione (61); 3-(5-((5-(4-(3-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propyl)piperazin-1-yl)pentyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (62); 2-(2,6-dioxopiperidin-3-yl)-5-((5-(4-(3-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)-3-(trifluoromethyl)pyridin-2-yl)propyl)piperazin-1-yl)pentyl)oxy)isoindoline-1,3-dione (63); 5-(4-(3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)propyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (64); 5-((5-(4-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (65); 5-(4-(2-(4-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)ethyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (66); 2-(2,6-dioxopiperidin-3-yl)-5-((14-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)isoindoline-1,3-dione (67); 2-(2,6-dioxopiperidin-3-yl)-5-(4-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pentyl)piperazin-1-yl)isoindoline-1,3-dione (68); 2-(2,6-dioxopiperidin-3-yl)-5-((14-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)-4-(trifluoromethyl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)isoindoline-1,3-dione (69); 2-(2,6-dioxopiperidin-3-yl)-5-(2-(2-(2-(2-

((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)ethoxy)ethoxy)ethoxy)isoindoline-1,3-dione (70); 2-(2,6-dioxopiperidin-3-yl)-5-((15-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)-3,6,9,12-tetraoxapentadec-14-yn-1-yl)oxy)isoindoline-1,3-dione (71); 5-((14-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)-2-(2,6-dioxopiperidin-3-yl)-4,6,7-trifluoroisoindoline-1,3-dione (72); [5-((3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione] (73); 2-(2,6-dioxopiperidin-3-yl)-5-((15-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)-3,6,9,12-tetraoxapentadecyl)oxy)isoindoline-1,3-dione (74); 2-(2,6-dioxopiperidin-3-yl)-5-(4-(5-((5-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)pentyl)oxy)pentyl)piperidin-1-yl)isoindoline-1,3-dione (75); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(3-(4-(3-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)prop-2-yn-1-yl)piperazin-1-yl)propoxy)azetidin-1-yl)isoindoline-1,3-dione (76); 5-(3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)propoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (77); 2-(2,6-dioxopiperidin-3-yl)-5-(4-(6-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)hexyl)piperazin-1-yl)isoindoline-1,3-dione (78); 2-(2,6-dioxopiperidin-3-yl)-5-(3-((5-((5-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)pentyl)oxy)pentyl)oxy)azetidin-1-yl)isoindoline-1,3-dione (79); 2-(2,6-dioxopiperidin-3-yl)-5-((1-(5-((5-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)pentyl)oxy)pentyl)azetidin-3-yl)oxy)isoindoline-1,3-dione (80); 5-((14-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)-2-(2,6-dioxopiperidin-3-yl)-6-fluoroisoindoline-1,3-dione (81); 2-(2,6-dioxopiperidin-3-yl)-5-((5-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)pentyl)oxy)isoindoline-1,3-dione (82); 5-((5-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (83); 2-(2,6-dioxopiperidin-3-yl)-5-((6-(3-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)phenoxy)hexyl)oxy)isoindoline-1,3-dione (84); 2-(2,6-dioxopiperidin-3-yl)-5-((1r,3r)-3-((5-((5-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)pentyl)oxy)pentyl)oxy)cyclobutoxy)isoindoline-1,3-dione (85); 4-((14-(4-(5H-pyrido[4,3-b]indol-7-yl)phenoxy)-3,6,9,12-tetraoxatetradecyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (86); 6-((14-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)-2-(2,6-dioxopiperidin-3-yl)-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (87);

2-(2,6-dioxopiperidin-3-yl)-5-((14-((5-(5-(2,2,2-trifluoroethyl)-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)isoindoline-1,3-dione (88); 2-(2,6-dioxopiperidin-3-yl)-5-(4-(3,3,3-trifluoro-2-(2-((5-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)pentyl)oxy)ethoxy)propyl)piperidin-1-yl)isoindoline-1,3-dione (89); 2-(2,6-dioxopiperidin-3-yl)-5-(4-(4-((4-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)but-2-yn-1-yl)oxy)butoxy)butoxy)isoindoline-1,3-dione (90); 2-(2,6-dioxopiperidin-3-yl)-5-(4-(8-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)octyl)piperazin-1-yl)isoindoline-1,3-dione (91); 5-((14-((3-chloro-5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (92); 5-((6-((5-(2,2-difluoro-2-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)ethoxy)pentyl)oxy)hexyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (93); 2-(2,6-dioxopiperidin-3-yl)-5-((5-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)pent-4-yn-1-yl)oxy)isoindoline-1,3-dione (94); 2-(2,6-dioxopiperidin-3-yl)-5-((5-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)pentyl)oxy)isoindoline-1,3-dione (95); 2-(2,6-dioxopiperidin-3-yl)-5-(4-(6-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)hexyl)-3-(trifluoromethyl)piperazin-1-yl)isoindoline-1,3-dione (96); 2-(2,6-dioxopiperidin-3-yl)-5-((6-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)hex-5-yn-1-yl)oxy)isoindoline-1,3-dione (97); 2-(2,6-dioxopiperidin-3-yl)-5-((6-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)hexyl)oxy)isoindoline-1,3-dione (98); 2-(2,6-dioxopiperidin-3-yl)-5-((1-(3-(3-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)propoxy)propyl)azetidin-3-yl)oxy)isoindoline-1,3-dione (99); 2-(2,6-dioxopiperidin-3-yl)-5-(6-(4-(4-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)butoxy)butoxy)-2-azaspiro[3.3]heptan-2-yl)isoindoline-1,3-dione (100); 5-((1-(3-(3-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclobutoxy)propoxy)propyl)azetidin-3-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (101); 2-(2,6-dioxopiperidin-3-yl)-5-((6-(6-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-3-yl)hex-5-yn-1-yl)oxy)isoindoline-1,3-dione (102); 5-((14-((5-(8,9-difluoro-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (103); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(3-(3-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-

yl)oxy)cyclobutoxy)propoxy)propoxy)azetidin-1-yl)isoindoline-1,3-dione (104); 2-(2,6-dioxopiperidin-3-yl)-5-((1-(3-(3-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclobutoxy)propoxy)propyl)azetidin-3-yl)oxy)isoindoline-1,3-dione (105); 2-(2,6-dioxopiperidin-3-yl)-5-((5-((5-(3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)azetidin-1-yl)pentyl)oxy)pentyl)oxy)isoindoline-1,3-dione (106); 2-(2,6-dioxopiperidin-3-yl)-5-(4-(4-(6-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)butoxy)butoxy)isoindoline-1,3-dione (107); 2-(2,6-dioxopiperidin-3-yl)-5-((6-((6-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)oxy)hexyl)oxy)isoindoline-1,3-dione (108); 2-(2,6-dioxopiperidin-3-yl)-5-((6-((4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)oxy)hexyl)oxy)isoindoline-1,3-dione (109); 2-(2,6-dioxopiperidin-3-yl)-5-((6-(6-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-3-yl)hexyl)oxy)isoindoline-1,3-dione (110); 2-(2,6-dioxopiperidin-3-yl)-5-(3-((3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)azetidin-1-yl)isoindoline-1,3-dione (111); 5-((14-((5-(8,9-difluoro-5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (112); 5-((14-((4-chloro-5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (113); 2-(2,6-dioxopiperidin-3-yl)-5-((5-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)butoxy)pentyl)oxy)isoindoline-1,3-dione (114); 2-(2,6-dioxopiperidin-3-yl)-5-((5-((5-((1-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)azetidin-3-yl)oxy)pentyl)oxy)pentyl)oxy)isoindoline-1,3-dione (115); 2-(2,6-dioxopiperidin-3-yl)-5-((2-(4-(4-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)butoxy)butyl)-2-azaspiro[3.3]heptan-6-yl)oxy)isoindoline-1,3-dione (116); 2-(2,6-dioxopiperidin-3-yl)-5-((3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)isoindoline-1,3-dione (117); 2-(2,6-dioxopiperidin-3-yl)-5-(3-((3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)azetidin-1-yl)isoindoline-1,3-dione (118); (2S,4R)-1-((S)-17-((5-(5H-pyrido[4,3-b]indol-7-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)-2-(tert-butyl)-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (119); (2S,4R)-1-((S)-2-(2-(2-((5-(5H-pyrido[4,3-

b]indol-7-yl)pyridin-2-yl)oxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (120); (2S,4R)-1-((S)-20-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-2-(tert-butyl)-4-oxo-6,9,12,15,18-pentaoxa-3-azaicosanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (121); (2S,4R)-1-((S)-23-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-2-(tert-butyl)-4-oxo-6,9,12,15,18,21-hexaoxa-3-azatricosanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (122); 2-(2,6-dioxopiperidin-3-yl)-5-((5-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)pentyl)oxy)isoindoline-1,3-dione (123); 2-(2,6-dioxopiperidin-3-yl)-5-((6-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)phenyl)hex-5-yn-1-yl)oxy)isoindoline-1,3-dione (124); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(3-(3-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclobutoxy)propoxy)propoxy)azetidin-1-yl)isoindoline-1,3-dione (125); 2-(2,6-dioxopiperidin-3-yl)-5-((5-(6-(methyl((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutyl)amino)-2-azaspiro[3.3]heptan-2-yl)pentyl)oxy)isoindoline-1,3-dione (126); 3-(5-(4-((1-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (127); 3-(5-(4-(2-(1-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)piperidin-4-yl)ethyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (128); 2-(2,6-dioxopiperidin-3-yl)-5-((1,1,1-trifluoro-6-(2-(2-(2-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)ethoxy)ethoxy)ethoxy)hexan-2-yl)oxy)isoindoline-1,3-dione (129); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(3-(3-(4-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)piperidin-1-yl)propoxy)propoxy)azetidin-1-yl)isoindoline-1,3-dione (130); 2-(2,6-dioxopiperidin-3-yl)-5-((17-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12,15-pentaoxaheptadecyl)oxy)isoindoline-1,3-dione (131); 2-(2,6-dioxopiperidin-3-yl)-5-((20-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12,15,18-hexaoxaicosyl)oxy)isoindoline-1,3-dione (132); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(6-((5-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)pentyl)oxy)hexyl)azetidin-1-yl)isoindoline-1,3-dione (133); 2-(2,6-dioxopiperidin-3-yl)-5-((6-(6-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridazin-3-yl)hex-5-yn-1-yl)oxy)isoindoline-1,3-dione (134); 2-(2,6-dioxopiperidin-3-yl)-5-(4-((2-(((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutyl)methyl)-2-azaspiro[3.3]heptan-6-yl)oxy)butoxy)isoindoline-1,3-dione (135); 2-(2,6-dioxopiperidin-3-yl)-5-(4-((2-((1s,3s)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-

7-yl)pyridin-2-yl)oxy)cyclobutane-1-carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)butoxy)isoindoline-1,3-dione (136); 2-(2,6-dioxopiperidin-3-yl)-5-((5-(6-(methyl((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutyl)amino)-2-azaspiro[3.3]heptan-2-yl)-5-oxopentyl)oxy)isoindoline-1,3-dione (137); 5-((14-((5-(5-(difluoromethyl)-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (138); 2-(2,6-dioxopiperidin-3-yl)-5-((14-((3-fluoro-5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)isoindoline-1,3-dione (139); 2-(2,6-dioxopiperidin-3-yl)-5-((14-((3-methyl-5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)isoindoline-1,3-dione (140); 2-(2,6-dioxopiperidin-3-yl)-5-((6-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyrimidin-2-yl)hex-5-yn-1-yl)oxy)isoindoline-1,3-dione (141); 2-(2,6-dioxopiperidin-3-yl)-5-((1-(3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)azetidin-3-yl)oxy)isoindoline-1,3-dione (142); 2-(2,6-dioxopiperidin-3-yl)-5-((14-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)-6-(trifluoromethyl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)isoindoline-1,3-dione (143); 2-(2,6-dioxopiperidin-3-yl)-5-(6-(6-((1s,3s)-3-(5-(5-methyl -5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yloxy)cyclobutoxy) pyridin-3-yl)hex-5-ynyloxy)isoindoline-1,3-dione (144); 2-(2,6-dioxopiperidin-3-yl)-5-(6-(6-((1s,3s)-3-(5-(5- methyl-5H-pyrido[4,3-b]indol-7-yl) pyridin-2-yloxy)cyclobutoxy) pyridin-3-yl)hexyloxy)isoindoline-1,3-dione (145); 2-(2,6-dioxopiperidin-3-yl)-5-((6-(6-(3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)propoxy)pyridin-3-yl)hex-5-yn-1-yl)oxy)isoindoline-1,3-dione (146); 2-(2,6-dioxopiperidin-3-yl)-5-((6-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)phenyl)hexyl)oxy)isoindoline-1,3-dione (147); 5-(3-(3-(3-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)cyclobutoxy)propoxy)propoxy)azetidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (148); 2-(2,6-dioxopiperidin-3-yl)-5-((6-(6-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridazin-3-yl)hexyl)oxy)isoindoline-1,3-dione] (149); 5-(6-(2,2-difluoro-5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pentyl)-2,6-diazaspiro[3.3]heptan-2-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (150); 2-(2,6-dioxopiperidin-3-yl)-5-((6-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyrimidin-2-yl)hexyl)oxy)isoindoline-1,3-dione (151); 2-(2,6-dioxopiperidin-3-yl)-5-((1-(3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-

b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)azetidin-3-yl)oxy)isoindoline-1,3-dione (152); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(3,3,3-trifluoro-2-((5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pentyl)oxy)propyl)azetidin-1-yl)isoindoline-1,3-dione (153); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(2,2,2-trifluoro-1-((6-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)hexyl)oxy)ethyl)azetidin-1-yl)isoindoline-1,3-dione (154); 2-(2,6-dioxopiperidin-3-yl)-5-(3-((5-(2-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)ethoxy)pyridin-2-yl)oxy)azetidin-1-yl)isoindoline-1,3-dione (155); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)propoxy)azetidin-1-yl)isoindoline-1,3-dione (156); 2-(2,6-dioxopiperidin-3-yl)-5-(4-((2-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutane-1-carbonyl)-2-azaspiro[3.3]heptan-6-yl)oxy)butoxy)isoindoline-1,3-dione (157); 2-(2,6-dioxopiperidin-3-yl)-5-(2-((6-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)pyridazin-4-yl)oxy)ethoxy)isoindoline-1,3-dione (158); 2-(2,6-dioxopiperidin-3-yl)-5-(3-((3-(5-((1s,3s)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)azetidin-1-yl)isoindoline-1,3-dione (159); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(3-(5-((1s,3s)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)propoxy)azetidin-1-yl)isoindoline-1,3-dione (160); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(2-(2-(2-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)ethoxy)ethoxy)ethoxy)azetidin-1-yl)isoindoline-1,3-dione (161); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(4-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)butoxy)butoxy)azetidin-1-yl)isoindoline-1,3-dione (162); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(2-(2-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)ethoxy)ethoxy)azetidin-1-yl)isoindoline-1,3-dione (163); 5-(6-(4-((1r,3r)-3-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yloxy)cyclobutoxy)piperidin-1-yl)-6-oxohexyloxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (164); 5-((5-((1-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutane-1-carbonyl)piperidin-4-yl)oxy)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (165); 5-((5-((1-((1s,3s)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutane-1-carbonyl)piperidin-4-yl)oxy)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (166); 2-(2,6-dioxopiperidin-3-yl)-5-(3-((3-(5-(3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)propoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)azetidin-1-yl)isoindoline-1,3-dione (167); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(3-(5-(3-((5-(5-

methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)propoxy)pyridin-2-yl)propoxy)azetidin-1-yl)isoindoline-1,3-dione (168); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(3-((3-(((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)methyl)oxetan-3-yl)methoxy)propoxy)azetidin-1-yl)isoindoline-1,3-dione (169); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(3-(3-((1s,3s)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)propoxy)propoxy)azetidin-1-yl)isoindoline-1,3-dione (170); 5-((4,4-difluoro-5-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (171); 5-((6-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)hex-5-yn-1-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (172); 5-(2-((3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)ethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (173); 2-(2,6-dioxopiperidin-3-yl)-5-(4-((3-(((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)methyl)bicyclo[1.1.1]pentan-1-yl)methoxy)butoxy)isoindoline-1,3-dione (174); 2-(2,6-dioxopiperidin-3-yl)-5-((5-((3-(3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)azetidine-1-carbonyl)bicyclo[1.1.1]pentan-1-yl)methoxy)pentyl)oxy)isoindoline-1,3-dione (175); 5-(3-(3-(3-((1r,3r)-3-((5-(8,9-difluoro-5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)propoxy)propoxy)azetidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (176); 3-(5-(3-(3-(3-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)propoxy)propoxy)azetidin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (177); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(((6-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)hexyl)oxy)methyl)azetidin-1-yl)isoindoline-1,3-dione (178); 2-(2,6-dioxopiperidin-3-yl)-5-(2-((3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)ethoxy)isoindoline-1,3-dione (179); 3-(5-((3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (180); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(2-((5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pentyl)oxy)ethyl)azetidin-1-yl)isoindoline-1,3-dione (181); 5-(3-(3-(3-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)propoxy)propoxy)azetidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (182); 5-((3-(5-((1s,3s)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-

dione (183); 2-(2,6-dioxopiperidin-3-yl)-5-((7-(3-(3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)azetidine-1-carbonyl)bicyclo[1.1.1]pentan-1-yl)heptyl)oxy)isoindoline-1,3-dione (184); (2S,4R)-N-(2-(2-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-4-hydroxy-1-((S)-3-methyl-2-(1-oxoisoindolin-2-yl)butanoyl)pyrrolidine-2-carboxamide (185); (2S,4R)-N-(2-(2-(2-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-4-hydroxy-1-((S)-3-methyl-2-(1-oxoisoindolin-2-yl)butanoyl)pyrrolidine-2-carboxamide (186); (2S,4R)-N-(2-(2-(2-(2-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)ethoxy)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-4-hydroxy-1-((S)-3-methyl-2-(1-oxoisoindolin-2-yl)butanoyl)pyrrolidine-2-carboxamide (187); 5-(2-((3-(4-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)phenyl)prop-2-yn-1-yl)oxy)ethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (188); 5-((3-(4-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)phenyl)prop-2-yn-1-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (189); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(2-(2-(2-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)ethoxy)ethoxy)ethyl)azetidin-1-yl)isoindoline-1,3-dione (190); 2-(2,6-dioxopiperidin-3-yl)-5-(3-((3-(2-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)ethoxy)propoxy)methyl)azetidin-1-yl)isoindoline-1,3-dione (191); 2-(2,6-dioxopiperidin-3-yl)-5-(3-((2-(2-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)ethoxy)ethoxy)methyl)azetidin-1-yl)isoindoline-1,3-dione (192); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(3-(2-(6-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)-2-oxoethoxy)propoxy)azetidin-1-yl)isoindoline-1,3-dione (193); 5-(3-((3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)azetidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (194); 5-((14-((5-(4-chloro-5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (195); (2S,4R)-N-(2-(2-(2-(2-(2-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-4-hydroxy-1-((S)-3-methyl-2-(1-oxoisoindolin-2-yl)butanoyl)pyrrolidine-2-carboxamide (196); 5-(6-((2,2-difluoro-5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pentyl)oxy)-2-azaspiro[3.3]heptan-2-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (197); 2-(2,6-dioxopiperidin-3-yl)-5-((3-(3-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)phenyl)prop-2-yn-1-yl)oxy)isoindoline-1,3-dione (198); 3-((4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-

yl)oxy)butoxy)methyl)-N-methyl-N-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutyl)bicyclo[1.1.1]pentane-1-carboxamide (199); 2-(2,6-dioxopiperidin-3-yl)-5-(3-((7-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)heptyl)oxy)azetidin-1-yl)isoindoline-1,3-dione (200); (2S,4R)-N-(2-((14-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-4-hydroxy-1-((S)-3-methyl-2-(1-oxoisoindolin-2-yl)butanoyl)pyrrolidine-2-carboxamide (201); 2-((1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)azetidin-3-yl)methoxy)-N-methyl-N-(3-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)propyl)acetamide (202); 2-((14-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)-5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)nicotinonitrile (203); 5-((3-(5-((1r,3r)-3-((5-(8,9-difluoro-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (204); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(3-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)phenyl)propoxy)isoindoline-1,3-dione (205); 2-(2,6-dioxopiperidin-3-yl)-5-(3-((2-(2-(2-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)ethoxy)ethoxy)ethoxy)methyl)azetidin-1-yl)isoindoline-1,3-dione (206); 5-((14-((5-(benzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (207); 2-(2,6-dioxopiperidin-3-yl)-5-(2-(2-(2-(2-((1-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)azetidin-3-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)isoindoline-1,3-dione (208); 2-(2,6-dioxopiperidin-3-yl)-5-(2-(2-((3-(((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)methyl)bicyclo[1.1.1]pentan-1-yl)methoxy)ethoxy)ethoxy)isoindoline-1,3-dione (209); 2-(2,6-dioxopiperidin-3-yl)-5-((15-(4-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)piperazin-1-yl)-3,6,9,12-tetraoxapentadecyl)oxy)isoindoline-1,3-dione (210); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(3-(2-(6-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-2-azaspiro[3.3]heptan-2-yl)ethoxy)propoxy)azetidin-1-yl)isoindoline-1,3-dione (211); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(2-((4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)but-2-yn-1-yl)oxy)ethoxy)azetidin-1-yl)isoindoline-1,3-dione (212); 2-(2,6-dioxopiperidin-3-yl)-5-(6-(2-(2-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)ethoxy)ethoxy)-2-azaspiro[3.3]heptan-2-yl)isoindoline-1,3-dione (213); 2-(2,6-dioxopiperidin-3-yl)-5-(4-(3-(3-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-

2-yl)oxy)cyclobutoxy)propoxy)propyl)piperazin-1-yl)isoindoline-1,3-dione (214); 2-(2,6-dioxopiperidin-3-yl)-5-((1R,3r)-3-(isopropyl(2-(3-((1r,3R)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)propoxy)ethyl)amino)cyclobutoxy)isoindoline-1,3-dione (215); 2-(2,6-dioxopiperidin-3-yl)-5-(4-(2-(3-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)propoxy)ethoxy)piperidin-1-yl)isoindoline-1,3-dione (216); 2-(2,6-dioxopiperidin-3-yl)-5-((1R,3r)-3-((2-(3-((1r,3R)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)propoxy)ethyl)amino)cyclobutoxy)isoindoline-1,3-dione (217); 2-(2,6-dioxopiperidin-3-yl)-5-((14-((5-(4-fluoro-5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)isoindoline-1,3-dione (218); 3-(5-((3-(5-((1r,3r)-3-((5-(8,9-difluoro-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (219); 3-(5-(2-((3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)ethoxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (220); 3-(5-(3-((3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)azetidin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (221); 3-(5-((3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyrimidin-2-yl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (222); 3-(5-((3-(6-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-3-yl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (223); 3-(5-(3-(3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)propoxy)prop-1-yn-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (224); 3-(5-(3-((3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)propyl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (225); 3-(5-((3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)-4,6-difluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (226); 3-(5-((1R,3r)-3-((3-(5-((1r,3R)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)cyclobutoxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (227); 3-(5-(4-(3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (228); 2-((3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-N-methylacetamide (229); 3-(5-((1R,3r)-3-((3-(5-((1r,3R)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-

yl)oxy)cyclobutyl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (230); 3-(5-((3-(6-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridazin-3-yl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (231); 3-(5-((3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyrazin-2-yl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (232); 3-(5-(2-((3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)ethoxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (233); 3-(5-((3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (234); 2-((1r,3r)-3-((6-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)ethoxy)prop-1-yn-1-yl)pyridin-3-yl)oxy)cyclobutoxy)-5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)nicotinonitrile (235); 5-(2-((3-(5-((1r,3r)-3-((5-(5-(difluoromethyl)-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)ethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (236); 2-(2,6-dioxopiperidin-3-yl)-5-(2-((3-(5-((1r,3r)-3-((3-methyl-5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)ethoxy)isoindoline-1,3-dione (237); 2-((1r,3r)-3-((6-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)oxy)ethoxy)prop-1-yn-1-yl)pyridin-3-yl)oxy)cyclobutoxy)-5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)nicotinonitrile (238); 3-(5-(2-((3-(5-((1r,3r)-3-((5-(5-(difluoromethyl)-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)ethoxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (239); 3-(5-(2-((3-(5-((1r,3r)-3-((3-methyl-5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)ethoxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (240); 3-(5-((3-(3-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)phenyl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (241); 2-(2,6-dioxopiperidin-3-yl)-5-((3-(4-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)pyridin-2-yl)prop-2-yn-1-yl)oxy)isoindoline-1,3-dione (242); 3-(5-((3-(4-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)pyridin-2-yl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (243); 2-(2,6-dioxopiperidin-3-yl)-5-((3-(4-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)pyrimidin-2-yl)prop-2-yn-1-yl)oxy)isoindoline-1,3-dione (244); 3-(5-((3-(4-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)pyrimidin-2-yl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (245); 2-(2,6-dioxopiperidin-3-yl)-5-((3-(2-(4-

((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)pyrimidin-4-yl)prop-2-yn-1-yl)oxy)isoindoline-1,3-dione (246); 3-(5-((3-(2-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)pyrimidin-4-yl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (247); 2-(2,6-dioxopiperidin-3-yl)-5-(2-(3-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)propoxy)ethoxy)isoindoline-1,3-dione (248); 3-(5-(2-(3-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)propoxy)ethoxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (249); 2-(2,6-dioxopiperidin-3-yl)-5-((6-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)hex-2-yn-1-yl)oxy)isoindoline-1,3-dione (250); 3-(5-((6-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)hex-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (251); 2-(2,6-dioxopiperidin-3-yl)-5-(2-(2-(2-(2-(3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)azetidin-1-yl)ethoxy)ethoxy)ethoxy)ethoxy)isoindoline-1,3-dione (252); N-(2-((1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)azetidin-3-yl)oxy)ethyl)-N-methyl-4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)butanamide (253); 2-(2,6-dioxopiperidin-3-yl)-5-((1-(2-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)-2-oxoethyl)azetidin-3-yl)oxy)isoindoline-1,3-dione (254); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(2-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)-2-oxoethoxy)azetidin-1-yl)isoindoline-1,3-dione (255); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(3-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)phenoxy)azetidin-1-yl)isoindoline-1,3-dione (256); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(3-(3-(((1s,3s)-1-hydroxy-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutyl)methoxy)propoxy)propoxy)azetidin-1-yl)isoindoline-1,3-dione (257); 2-(2,6-dioxopiperidin-3-yl)-5-(2-(9-(2-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)ethoxy)isoindoline-1,3-dione (258); 2-(2,6-dioxopiperidin-3-yl)-5-((4-(9-(((1s,3s)-1-hydroxy-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutyl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)but-2-yn-1-yl)oxy)isoindoline-1,3-dione (259); 2-(2,6-dioxopiperidin-3-yl)-5-((3-(3-(4-(((1s,3s)-1-hydroxy-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutyl)methyl)piperazin-1-yl)phenyl)prop-2-yn-1-yl)oxy)isoindoline-1,3-dione (260); 2-(2,6-dioxopiperidin-3-yl)-5-((3-(3-(4-(((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-

yl)pyridin-2-yl)oxy)cyclobutyl)methyl)piperazin-1-yl)phenyl)prop-2-yn-1-yl)oxy)isoindoline-1,3-dione (261); 2-(2,6-dioxopiperidin-3-yl)-5-(2-(3-(3-(((1s,3s)-1-hydroxy-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutyl)methoxy)propoxy)propoxy)ethoxy)isoindoline-1,3-dione (262); 2-(2,6-dioxopiperidin-3-yl)-5-(2-(3-(3-((3-hydroxy-1-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)azetidin-3-yl)methoxy)propoxy)propoxy)ethoxy)isoindoline-1,3-dione (263); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(3-(3-((5'-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)-3'H-spiro[cyclobutane-1,2'-furo[2,3-b]pyridin]-3-yl)oxy)propoxy)propoxy)azetidin-1-yl)isoindoline-1,3-dione (264); 5-((14-((5-(6,8-difluoro-5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (265); 2-(2,6-dioxopiperidin-3-yl)-5-((14-((1-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)piperidin-4-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)isoindoline-1,3-dione (266); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(2-((1R,3r)-3-(2-((1r,3R)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)ethyl)cyclobutyl)ethoxy)azetidin-1-yl)isoindoline-1,3-dione (267); 2-(2,6-dioxopiperidin-3-yl)-5-(3-((1S,2R)-2-((4-((1r,3R)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)butoxy)methyl)cyclopropyl)azetidin-1-yl)isoindoline-1,3-dione (268); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(4-(((1R,2R)-2-((1r,3R)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutyl)cyclopropyl)methoxy)butoxy)azetidin-1-yl)isoindoline-1,3-dione (269); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(2-(2-(((1R,2R)-2-((1r,3R)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutyl)cyclopropyl)methoxy)ethoxy)ethoxy)azetidin-1-yl)isoindoline-1,3-dione (270); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(2-((1R,3r)-3-(((1r,3R)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)methyl)cyclobutoxy)ethoxy)azetidin-1-yl)isoindoline-1,3-dione (271); 5-(3-(3-(2,2-difluoro-3-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)propoxy)propoxy)azetidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (272); 5-(3-(2,2-difluoro-3-(3-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)propoxy)propoxy)azetidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (273); 2-(2,6-dioxopiperidin-3-yl)-5-(2-((3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)propoxy)isoindoline-1,3-dione (274); 2-(2,6-dioxopiperidin-3-yl)-5-(2-((4-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)but-3-yn-2-yl)oxy)ethoxy)isoindoline-1,3-dione (275); 5-(2-((1,1-difluoro-3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-

2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)ethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (276); 3-(5-((4-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)but-3-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (277); 3-(5-(((3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)methyl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (278); 3-(5-(3-((4-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)but-3-yn-1-yl)oxy)azetidin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (279); 5-(3-((4-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)but-3-yn-1-yl)oxy)azetidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (280); 5-(3-((5-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)pent-4-yn-1-yl)oxy)azetidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (281); 3-(5-(3-((5-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)pent-4-yn-1-yl)oxy)azetidin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (282); 2-(2,6-dioxopiperidin-3-yl)-5-((1-(4-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)but-3-yn-1-yl)azetidin-3-yl)oxy)isoindoline-1,3-dione (283); 3-(5-((1-(4-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)but-3-yn-1-yl)azetidin-3-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (284); 5-(2-(2,2-difluoro-3-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)propoxy)ethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (285); 2-((1r,3r)-3-((6-(3-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)oxy)prop-1-yn-1-yl)pyridin-3-yl)oxy)cyclobutoxy)-5-(5H-pyrido[4,3-b]indol-7-yl)nicotinonitrile (286); 3-(5-((3-(5-((1r,3r)-3-((3-methyl-5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (287); 3-(5-((3-(5-((1r,3r)-3-((5-(4-chloro-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (288); 3-(5-((3-(5-((1r,3r)-3-((5-(4-fluoro-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (289); 3-(5-((3-(5-((1r,3r)-3-((5-(5-(difluoromethyl)-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (290); 2-(2,6-dioxopiperidin-3-yl)-5-(2-((3-(3-(((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)methyl)bicyclo[1.1.1]pentan-1-yl)prop-2-yn-1-yl)oxy)ethoxy)isoindoline-1,3-dione (291); 2-(2,6-dioxopiperidin-3-yl)-5-(2-((3-((1R,3r)-3-

(((1r,3R)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)methyl)cyclobutyl)prop-2-yn-1-yl)oxy)ethoxy)isoindoline-1,3-dione (292); 3-(5-(4-((3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)piperidin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (293); 6-(2-((3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)ethoxy)-2-(2,6-dioxopiperidin-3-yl)-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (294); 2-(2,6-dioxopiperidin-3-yl)-5-(3-(2-((3-(((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)methyl)bicyclo[1.1.1]pentan-1-yl)methoxy)ethoxy)azetidin-1-yl)isoindoline-1,3-dione (295); 2-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)ethoxy)prop-1-yn-1-yl)-5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)isonicotinonitrile (296); 2-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)oxy)ethoxy)prop-1-yn-1-yl)-5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)isonicotinonitrile (297); 2-(2,6-dioxopiperidin-3-yl)-5-(2-((3-(4-methyl-5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)ethoxy)isoindoline-1,3-dione (298); 3-(5-(2-((3-(4-methyl-5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)ethoxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (299); 3-(5-(2-((3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)-4-(trifluoromethyl)pyridin-2-yl)prop-2-yn-1-yl)oxy)ethoxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (300); 2-(2,6-dioxopiperidin-3-yl)-5-(2-((3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)-4-(trifluoromethyl)pyridin-2-yl)prop-2-yn-1-yl)oxy)ethoxy)isoindoline-1,3-dione (301); 6-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)ethoxy)prop-1-yn-1-yl)-3-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)picolinonitrile (302); 6-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)oxy)ethoxy)prop-1-yn-1-yl)-3-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)picolinonitrile (303); 2-(2,6-dioxopiperidin-3-yl)-5-(2-((3-(6-methyl-5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)ethoxy)isoindoline-1,3-dione (304); 3-(5-(2-((3-(6-methyl-5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)ethoxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (305); 2-(2,6-dioxopiperidin-3-yl)-5-(2-((3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)-6-(trifluoromethyl)pyridin-2-yl)prop-2-yn-1-

yl)oxy)ethoxy)isoindoline-1,3-dione (306); 3-(5-(2-((3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)-6-(trifluoromethyl)pyridin-2-yl)prop-2-yn-1-yl)oxy)ethoxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (307); 2-(2,6-dioxopiperidin-3-yl)-5-(2-((2-methyl-4-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)but-3-yn-2-yl)oxy)ethoxy)isoindoline-1,3-dione (308); 3-(5-(2-((2-methyl-4-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)but-3-yn-2-yl)oxy)ethoxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (309); 3-(5-(2-(1-((5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)ethynyl)cyclopropoxy)ethoxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (310); 2-(2,6-dioxopiperidin-3-yl)-5-(2-(1-((5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)ethynyl)cyclopropoxy)ethoxy)isoindoline-1,3-dione (311); 4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)prop-1-yn-1-yl)-2-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)benzonitrile (312); 4-(3-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)oxy)prop-1-yn-1-yl)-2-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)benzonitrile (313); 3-(5-((3-(4-methyl-3-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)phenyl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (314); 3-(5-((3-(3-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)-4-(trifluoromethyl)phenyl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (315); 3-(5-((3-(4-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)-5-(trifluoromethyl)pyridin-2-yl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (316); 6-(3-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)oxy)prop-1-yn-1-yl)-4-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)nicotinonitrile (317); 3-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)prop-1-yn-1-yl)-5-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)benzonitrile (318); 3-(3-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)oxy)prop-1-yn-1-yl)-5-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)benzonitrile (319); 3-(5-((3-(3-methyl-5-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)phenyl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (320); 3-(5-((3-(3-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)-

5-(trifluoromethyl)phenyl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (321); 3-(5-((3-(4-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)-6-(trifluoromethyl)pyridin-2-yl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (322); 3-(5-((3-(2-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)-6-(trifluoromethyl)pyridin-4-yl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (323); 2-(2,6-dioxopiperidin-3-yl)-5-((2-methyl-4-(3-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)phenyl)but-3-yn-2-yl)oxy)isoindoline-1,3-dione (324); 3-(5-((2-methyl-4-(3-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)phenyl)but-3-yn-2-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (325); 3-(5-((2-methyl-4-(4-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)pyridin-2-yl)but-3-yn-2-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (326); 3-(5-((1,1-difluoro-3-(4-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)pyridin-2-yl)prop-2-yn-1-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (327); 3-(5-((2-methyl-4-(4-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)pyrimidin-2-yl)but-3-yn-2-yl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (328); 6-(3-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)oxy)-3-methylbut-1-yn-1-yl)-4-(4-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)piperidin-1-yl)nicotinonitrile (329); 2-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)oxy)ethoxy)-3-methylbut-1-yn-1-yl)-5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)isonicotinonitrile (330).

[0183] 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 disclosure.

[0184] 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 disclosure.

[0185] The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds useful in this disclosure 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.

[0186] Pharmaceutically acceptable base addition salts may also be used to produce pharmaceutically acceptable salt forms of the compounds or derivatives according to the present disclosure. 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.

Compositions:

[0187] In another aspect, the description provides compositions comprising compounds as described herein, including salts 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 pharmaceutically acceptable carrier.

[0188] The amount of compound in a pharmaceutical composition of the instant disclosure 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 present disclosure, 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.

[0189] The compositions of the present disclosure 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.

[0190] In any of the aspects or embodiments described herein, the PTM, ULM or both have an affinity (IC_{50}) for their respective target protein of less than about 500 μM, 450 μM, 400 μM, 350 μM, 300 μM, 250 μM, 200 μM, 150 μM, 100 μM, 50 μM, 10 μM, 0.10 μM, 0.01 μM, 0.001 μM, 0.1 nM, 0.01 nM, 0.001 nM or less. The determination of the IC_{50} can be performed using methods well known to those of skill in the art in view of the present disclosure.

[0191] In any of the aspects or embodiments, the compounds as described herein effectuate the ubquitination of a target protein at sufficient levels or amounts to effectuate or induce degradation of the target protein.

[0192] 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.

[0193] 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.

[0194] 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.

[0195] 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.

[0196] If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

[0197] 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.

[0198] 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. 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 is 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.

Modes of Administration

[0199] 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.

[0200] 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.

[0201] 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

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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.

[0202] 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.

[0203] 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.

[0204] 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.

[0205] 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.

[0206] 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.

[0207] 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.

[0208] The pharmaceutical compositions of the disclosure 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 disclosure 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 disclosure, 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.

[0209] 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.

[0210] 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.

[0211] The pharmaceutical compositions of this disclosure 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.

[0212] 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.

[0213] 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.

[0214] 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.

Co-administration

[0215] 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.

[0216] The term "co-administration" 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 disclosure 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 co-administered compounds or compositions are found in the subject at a given time. In certain preferred aspects of the present disclosure, one or more of the present compounds described above, are co-administered in combination with at least one additional bioactive agent, especially including an anticancer agent. In particularly preferred aspects of the disclosure, the co-administration of compounds results in synergistic therapeutic, including anticancer therapy.

[0217] 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.

[0218] Pharmaceutical compositions comprising combinations of an effective amount of at least one bifunctional compound according to the present disclosure, 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 disclosure.

[0219] 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 assist in effecting an intended therapy, for example, P-gp

inhibitors or agents that have pharmacological activity similar to that for which the present compounds are used or administered and include for example, anti-neurodegenerative agents.

[0220] The term "P-gp" is used to describe "permeability glycoprotein" or P-glycoprotein (ABCB1) which was discovered in 1976 in rodent cells. The presence of "endogenous or physiological" P-gp is a potential problem to achieving targeted exposure with therapeutic agents. P-gp is expressed at barrier tissue to sanctuary sites (e.g., blood-brain barrier) and at secretory/absorptive tissues (e.g., gastrointestinal tract) (Cordon-Cardo et al., 1989, 1990). The protein acts as a cellular defender and influences the overall pharmacokinetic profile of numerous drugs by actively pumping them out of the intracellular environment (effluxing) thereby reducing drug penetration of the barrier tissues. In particular, P-gp efflux reduces drug permeability across the gastrointestinal tract membranes and may lead to reduced systemic exposure of the drug. P-gp efflux also reduces drug access across the blood-brain barrier. P-gp inhibitors could indirectly contribute to efficacy by increasing PROTAC exposure, particularly CNS exposure

[0221] The term "additional anti-neurodegenerative agent" is used to describe an anti-neurodegenerative agent, which may be combined with PROTAC compounds according to the present description to treat neurodenerative diseases.

[0222] In certain embodiments, the PROTAC(s) are used along with P-gp inhibitors.

[0223] In certain additional embodiments, the P-gp inhibitors are selected from the group consisting of, but not limited to, Amiodarone, Azithromycin, Captopril, Clarithromycin, Cyclosporine, Piperine, Quercetin, Quinidine, Quinine, Reserpine, Ritonavir, Tariquidar, Elacridar and Verapamil.

Methods of Treatment

[0224] 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 degradation of the protein in the subject. In certain embodiments, the protein is Tau protein.

[0225] In certain embodiments, the description provides a method for regulating protein activity of Tau protein by degenerating Tau aggregates in a patient in need comprising administering to said patient an amount of a compound as described herein to a patient.

[0226] In still additional embodiments, the description provides a method of treating a disease state or condition in a patient wherein dysregulated protein activity (Tau aggregation and accumulation) 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 Tau.

[0227] 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 neurological and neurodegenerative diseases, which may be treated using compounds according to the present disclosure are set forth hereinabove.

[0228] In another aspect, the disclosure provides methods of modulating Tau 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 a compound as described herein to a subject, wherein the compound or composition comprising the same is effective in modulating Tau protein ubquitination and degradation of the protein in the subject.

[0229] In another aspect, the disclosure provides methods of treating or ameliorating a symptom of a disease related to Tau accumulation or aggregation 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 Tau aggregation in the subject.

[0230] In certain embodiments, the disease or disorder is a neurological disorder including but not limited to Absence of the Septum Pellucidum, Acquired Epileptiform Aphasia, Acute Disseminated Encephalomyelitis, ADHD, Adie's Pupil, Adie's Syndrome, Adreno-leukodystrophy, Agenesis of the Corpus Callosum, Agnosia, Aicardi Syndrome, AIDS-Neurological Complications, Alexander Disease, Alpers' Disease, Alternating Hemiplegia, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Anencephaly, Aneurysm, Angelman Syndrome, Angiomatosis, Anoxia, Aphasia, Apraxia, Arachnoid Cysts, Arachnoiditis, Arnold-Chiari Malformation, Arteriovenous Malformation, Asperger Syndrome, Ataxia, Ataxia, Telangiectasia, Ataxias and

Cerebellar/Spinocerebellar Degeneration, Attention Deficit-Hyperactivity Disorder, Autism, Autonomic Dysfunction, Back Pain, Barth Syndrome Batten Disease, Becker's Myotonia, Behcet's Disease, Bell's Palsy, Benign Essential Blepharospasm, Benign Focal Amyotrophy, Benign Intracranial Hypertension, Bernhardt-Roth Syndrome, Binswanger's Disease, Blepharospasm, Bloch-Sulzberger Syndrome, Brachial Plexus Birth Injuries, Brachial Plexus Injuries, Bradbury-Eggleston Syndrome, Brain and Spinal Tumors, Brain Aneurysm, Brain Injury, Brown-Sequard Syndrome, Bulbospinal Muscular Atrophy, Canavan Disease, Carpal Tunnel Syndrome Causalgia, Cavernomas, Cavernous Angioma, Cavernous Malformation, Central Cervical Cord Syndrome, Central Cord Syndrome, Central Pain Syndrome, Cephalic Disorders, Cerebellar Degeneration, Cerebellar Hypoplasia, Cerebral Aneurysm, Cerebral Arteriosclerosis, Cerebral Atrophy, Cerebral Beriberi, Cerebral Gigantism, Cerebral Hypoxia, Cerebral Patsy, Cerebro-Oculo-Facio-Skeletal Syndrome, Charcot-Marie-Tooth Disease, Chiari Malformation, Chorea, Choreoacanthocytosis, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Chronic Orthostatic Intolerance, Chronic Pain Cockayne Syndrome Type II, Coffin Lowry Syndrome, COFS, Colpocephaly, Coma and Persistent Vegetative State, Complex Regional Pain Syndrome, Congenital Facial Diplegia, Congenital Myasthenia, Congenital Myopathy, Congenital Vascular Cavernous, Malformations, Corticobasal Degeneration, Cranial Arteritis, Craniosynostosis, Creutzfeldt-Jakob Disease, Cumulative Trauma Disorders, Cushing's Syndrome, Cytomegalic Inclusion Body Disease, Cytomegalovirus Infection, Dancing Eyes-Dancing Feet Syndrome, Dandy-Walker Syndrome, Dawson Disease, De Morsier's Syndrome, Deep Brain Stimulation for Parkinson's Disease, Dejerine-Klumpke Palsy, Dementia, Dementia—Multi-Infarct, Dementia—Semantic, Dementia—Subcortical, Dementia With Lewy Bodies, Dentate Cerebellar Ataxia, Dentatorubral Atrophy, Dermatomyositis, Developmental Dyspraxia, Devic's Syndrome, Diabetic Neuropathy, Diffuse Sclerosis, Dysautonomia, Dysgraphia, Dyslexia, Dysphagia, Dyspraxia, Dyssynergia Cerebellaris, Myoclonica, Dyssynergia Cerebellaris Progressiva, Dystonias, Early Infantile Epileptic, Encephalopathy, Empty Sella Syndrome, Encephalitis Lethargica, Encephaloceles, Encephalopathy, Encephalotrigeminal Angiomatosis, Epilepsy, Erb-Duchenne and Dejerine-Klumpke Palsies, Erb's Palsy, Fabry's Disease, Fahr's Syndrome, Fainting, Familial Dysautonomia, Familial Hemangioma, Familial Idiopathic Basal Ganglia, Calcification, Familial Periodic Paralyses, Familial Spastic Paralysis, Febrile Seizures, Fisher Syndrome, Floppy Infant Syndrome, Friedreich's Ataxia, Frontotemporal, Dementia, Gaucher's Disease, Gerstmann's Syndrome, Gerstmann-Straussler-Scheinker, Disease, Giant Cell Arteritis, Giant Cell Inclusion Disease,

Globoid Cell Leukodystrophy, Glossopharyngeal Neuralgia, Guillain-Barre Syndrome, Hallervorden-Spatz Disease, Head Injury, Headache, Hemicrania Continua, Hemifacial Spasm, Hemiplegia Alterans, Hereditary Neuropathies, Hereditary Spastic Paraplegia, Heredopathia Atactica Polyneuritiformis, Herpes Zoster, Herpes Zoster Oticus, Hirayama Syndrome, Holmes-Adie syndrome, Holoprosencephaly, HTLV-1 Associated, Myelopathy, Huntington's Disease, Hydranencephaly, Hydrocephalus, Hydrocephalus—Normal Pressure, Hydromyelia, Hyperactivity, Hypercortisolism, Hypersomnia, Hypertonia, Hypotonia,—Infantile, Hypoxia, Immune-Mediated Encephalomyelitis, Inclusion Body Myositis, Incontinentia Pigmenti, Infantile Hypotonia, Infantile Neuroaxonal Dystrophy, Infantile Phytanic Acid Storage Disease, Infantile Refsum Disease, Infantile Spasms, Inflammatory Myopathy, Iniencephaly, Intestinal Lipodystrophy, Intracranial Cysts, Intracranial Hypertension, Isaac's Syndrome, Joubert Syndrome, Kearns-Sayre Syndrome, Kennedy's Disease, Kinsbourne syndrome, Kleine-Levin Syndrome, Klippel-Feil Syndrome, Klippel-Trenaunay Syndrome (KTS), Klüver-Bucy Syndrome, Korsakoff's Amnesic Syndrome, Krabbe Disease, Kugelberg-Welander Disease, Kuru, Lambert-Eaton Myasthenic Syndrome, Landau-Kleffner Syndrome, Lateral Femoral, Cutaneous Nerve Entrapment, Lateral Medullary Syndrome, Learning Disabilities, Leigh's Disease, Lennox-Gastaut Syndrome, Lesch-Nyhan Syndrome, Leukodystrophy, Levine-Critchley Syndrome, Lewy Body Dementia, Lipid Storage Diseases, Lissencephaly, Locked-In Syndrome, Lou Gehrig's Disease, Lupus—Neurological, Sequelae, Lyme Disease—Neurological Complications, Machado-Joseph Disease, Macrencephaly, Mania, Megalencephaly, Melkersson-Rosenthal Syndrome, Meningitis, Meningitis and Encephalitis, Menkes Disease, Meralgia Paresthetica, Metachromatic, Leukodystrophy, Microcephaly, Migraine, Miller Fisher Syndrome, Mini-Strokes, Mitochondrial Myopathies, Mobius Syndrome, Monomelic Amyotrophy, Motor Neuron Diseases, Moyamoya Disease, Mucolipidoses, Mucopolysaccharidoses, Multifocal Motor Neuropathy, Multi-Infarct Dementia, Multiple Sclerosis, Multiple System Atrophy, Multiple System Atrophy with Orthostatic Hypotension, Muscular Dystrophy, Myasthenia—Congenital, Myasthenia Gravis, Myelinoclastic Diffuse Sclerosis, Myoclonic Encephalopathy of Infants, Myoclonus, Myopathy, Myopathy—Congenital, Myopathy-Thyrotoxic, Myotonia, Myotonia Congenita, Narcolepsy, Neuroacanthocytosis, Neurodegeneration with Brain Iron Accumulation, Neurofibromatosis, Neuroleptic Malignant Syndrome, Neurological Complications of AIDS, Neurological Complications Of Lyme Disease, Neurological Consequences of Cytomegalovirus Infection, Neurological Manifestations of Pompe Disease, Neurological Sequelae Of Lupus, Neuromyelitis

Optica, Neuromyotonia, Neuronal Ceroid, Lipofuscinosis, Neuronal Migration Disorders, Neuropathy—Hereditary, Neurosarcoidosis, Neurotoxicity, Nevus Cavernosus, Niemann-Pick Disease, Normal Pressure Hydrocephalus, Occipital Neuralgia, Obesity, Occult Spinal Dysraphism Sequence, Ohtahara Syndrome, Olivopontocerebellar Atrophy, Opsoclonus Myoclonus, Orthostatic Hypotension, O'Sullivan-McLeod Syndrome, Overuse Syndrome, Pain—Chronic, Paine, Pantothenate Kinase-Associated Neurodegeneration, Paraneoplastic Syndromes, Paresthesia, Parkinson's Disease, Paroxysmal Choreoathetosis, Paroxysmal Hemicrania, Parry-Romberg, Pelizaeus-Merzbacher Disease, Pena Shokeir II Syndrome, Perineural Cysts, Periodic Paralyses, Peripheral Neuropathy, Periventricular Leukomalacia, Persistent Vegetative State, Pervasive Developmental Disorders, Phytanic Acid Storage Disease, Pick's Disease, Pinched Nerve, Piriformis Syndrome, Pituitary Tumors, Polymyositis, Pompe Disease, Porencephaly, Postherpetic Neuralgia, Postinfectious Encephalomyelitis, Post-Polio Syndrome, Postural Hypotension, Postural Orthostatic, Tachycardia Syndrome, Postural Tachycardia Syndrome, Primary Dentatum Atrophy, Primary Lateral Sclerosis, Primary Progressive Aphasia, Prion Diseases, Progressive Hemifacial Atrophy, Progressive Locomotor Ataxia, Progressive Multifocal, Leukoencephalopathy, Progressive Sclerosing Poliodystrophy, Progressive Supranuclear, Palsy, Prosopagnosia, Pseudotumor Cerebri, Ramsay Hunt Syndrome I (formerly known as), Ramsay Hunt Syndrome II (formerly known as), Rasmussen's Encephalitis, Reflex Sympathetic Dystrophy Syndrome, Refsum Disease, Refsum Disease—Infantile, Repetitive Motion Disorders, Repetitive Stress Injuries, Restless Legs Syndrome, Retrovirus-Associated Myelopathy, Rett Syndrome, Reye's Syndrome, Riley-Day Syndrome, Sacral Nerve Root Cysts, Saint Vitus Dance, Salivary Gland Disease, Sandhoff Disease, Schilder's Disease, Schizencephaly, Seitelberger Disease, Seizure Disorder, Semantic Dementia, Septo-Optic Dysplasia, Shaken Baby Syndrome, Shingles Shy-Drager Syndrome, Sjogren's Syndrome, Sleep Apnea, Sleeping Sickness, Sotos Syndrome, Spasticity, Spina Bifida, Spinal Cord Infarction, Spinal Cord Injury, Spinal Cord Tumors, Spinal Muscular Atrophy, Spinocerebellar Atrophy, Spinocerebellar, Degeneration, Steele-Richardson-Olszewski Syndrome, Stiff-Person Syndrome, Striatonigral Degeneration, Stroke, Sturge-Weber Syndrome, Subacute Sclerosing Panencephalitis, Subcortical Arteriosclerotic Encephalopathy, SUNCT Headache Swallowing Disorders, Sydenham Chorea, Syncope, Syphilitic Spinal Sclerosis, Syringohydromyelia, Syringomyelia, Systemic Lupus Erythematosus, Tabes Dorsalis Tardive Dyskinesia, Tarlov Cysts, Tay-Sachs Disease, Temporal Arteritis, Tethered Spinal Cord Syndrome, Thomsen's Myotonia, Thoracic Outlet Syndrome, Thyrotoxic Myopathy, Tic Douloureux, Todd's

Paralysis, Tourette Syndrome, Transient Ischemic Attack, Transmissible Spongiform Encephalopathies, Transverse Myelitis, Traumatic Brain Injury, Tremor, Trigeminal Neuralgia, Tropical Spastic Paraparesis, Tuberous Sclerosis, Vascular Erectile Tumor, Vasculitis including Temporal Arteritis, Von Economo's Disease, Von Hippel-Lindau Disease (VHL), Von Recklinghausen's Disease, Wallenberg's Syndrome, Werdnig-Hoffman Disease, Wernicke-Korsakoff Syndrome, West Syndrome, Whiplash, Whipple's Disease, Williams Syndrome, Wilson's Disease, X-Linked Spinal and Bulbar Muscular Atrophy, or Zellweger Syndrome.

[0231] In certain embodiments, the disease or disorder is at least one of Huntington's disease, muscular dystrophy, Parkinson's disease, Alzheimer's disease, Batten disease, Injuries to the spinal cord and brain, Seizure disorders, epilepsy, brain tumors, meningitis, autoimmune diseases such as multiple sclerosis, Neurofibromatosis, Depression, Amyotrophic Lateral Sclerosis, Arteriovenous Malformation, Brain Aneurysm, Dural Arteriovenous Fistulae, Headache, Memory Disorders, Peripheral Neuropathy, Post-Herpetic Neuralgia, Spinal Cord Tumor and Stroke.

[0232] In certain embodiments, the disease or disorder is Alzheimer's disease.

[0233] In another aspect, the disclosure provides methods of treating or ameliorating a symptom of a disease related to Tau accumulation or aggregation 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 amount 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 Tau accumulation or aggregation in the subject by Tau degradation/inhibition.

[0234] In certain embodiments, the disease to be treated is Neurological disorder. In a preferred embodiment, the subject is a human.

[0235] In certain additional embodiments, the additional bioactive agent is an anti-neurodegenerative agent.

[0236] In alternative aspects, the present disclosure 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 disclosure may be used to treat a large number of neurological disease states or conditions, by virtue of the administration of effective amounts of at least one compound described herein.

[0237] 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 disclosure.

Kits

[0238] 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 disclosure. In addition, the kits of the present disclosure may preferably contain instructions, which describe a suitable use. Such kits can be conveniently used, e.g., in clinical settings, to treat patients with Neurological disorders.

Examples

[0239] The PROTAC compounds of the instant disclosure are effective in Tau degradation. Exemplary compounds are presented in Tables 1 and 2 with in vitro data of some selected compounds in Tables 2 and 3 showing degradation of tau protein. *In vivo* studies showing degradation of tau protein are illustrated in Figure 1.

General Methods of Chemical Synthesis

[0240] The synthesis of the claimed chimeric compounds can be carried out according to the general synthetic procedures known in literature. Synthetic routes shown in the schemes in the present disclosure are described as one of the methods that can be used to obtain the desired compounds. Other methods can also be used for those skilled in the art of synthesis. The ULM and PTM described in schemes only represent one of many ULMs and PTMs in this application.

LC-MS method for purity analysis (quality control)

[0241] LCMS Method:

Instrumentations: 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.

The solvents employed are:

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

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

The gradient employed are as follows:

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

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.

[0242] Abbreviations:

ACN: acetonitrile

Boc_2O: di-tert-butyl dicarbonate

DCM: dichloromethane.

DIPEA: *N*,*N*-diisopropylethylamine

DMA: N,N-dimethylacetamide

DMF: *N*,*N*-dimethylformamide

EA: ethyl acetate

HATU: 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

HPLC: high-performance liquid chromatography

LC-MS: liquid chromatography-mass spectrometry

Min: minutes

MTBE: methyl tert-butyl ether

PE: petroleum ether

RT: room temperature

SPB: sodium perborate

tBu: tert-butyl

TBACl: tetra-butyl ammonium chloride

TFA: trifluoroacetic acid

THF: tetrahydrofuran

TLC: thin layer chromatography

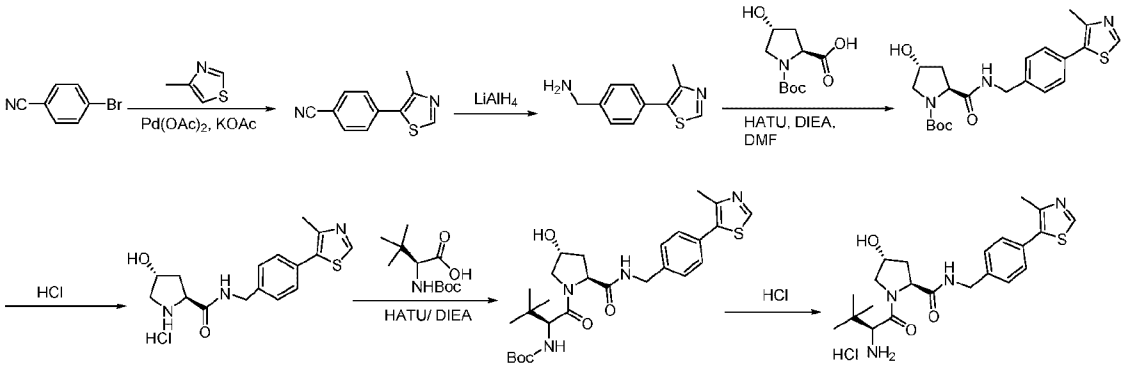
TMS: trimethylsilyl

t_R: retention rime

TsCl: p-toluene sulfonyl chloride

[0243] Intermediates of ubiquitin E3 ligase targeting moiety (ULM) and protein targeting moiety (PTM)

[0244] Intermediate 1: (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)



Step 1: Preparation of 4-(4-methyl-1,3-thiazol-5-yl)benzonitrile

[0245] To a stirred solution of 4-bromobenzonitrile (20 g, 109.88 mmol) in DMA (250 mL) under a nitrogen atmosphere was added 4-methyl-1,3-thiazole (21.88 g, 220.67 mmol), palladium (II) acetate (743 mg, 3.31 mmol) and potassium acetate (21.66 g, 220.71 mmol) at room temperature. The resulting mixture was heated to 150 °C and stirred at this temperature for 5 hours, at which time LC-MS indicated completion of the reaction. The mixture was cooled to room temperature, diluted with 1 L of water and extracted with ethyl acetate (300 mL x 3). The organic layers were combined, washed with brine (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 column chromatography (eluent: ethyl acetate/petroleum ether, v: v = 1:5) to give the titled compound (yield: 91%) as a white solid.

Step 2: Preparation of of [4-(4-methyl-1,3-thiazol-5-yl)phenyl]methanamine

[0246] To a stirred solution of 4-(4-methyl-1,3-thiazol-5-yl)benzonitrile (35 g, 174.77 mmol) in tetrahydrofuran (1000 mL) was added $LiAlH_4$ (20 g, 526.32 mmol) in portions at 0°C in 10 minutes under a nitrogen atmosphere. The resulting mixture was then stirred at 60 °C for 3 hours, at which time LC-MS indicated completion of reaction. The mixture was cooled to 0°C, then quenched by the addition of 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 brine (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 column chromatography (eluent: dichloromethane/methanol (v:v = 10:1)) to give the titled compound (yield: 56%) as a yellow oil.

Step 3: Preparation of tert-butyl (2S,4R)-4-hydroxy-2-([[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]carbamoyl)pyrrolidine-1-carboxylate

[0247] To a stirred solution of (2S,4R)-1-[(tert-butoxy)carbonyl]-4-hydroxypyrrolidine-2-carboxylic acid (2.7 g, 11.68 mmol) in N,N-dimethylformamide (20 mL) was added DIPEA (2.52 g, 19.50 mmol), HATU (4.47 g, 11.76 mmol) and [4-(4-methyl-1,3-thiazol-5-yl)phenyl]methanamine (2 g, 9.79 mmol) at room temperature. The resulting mixture was stirred at room temperature overnight, at which time LC-MS indicated completion of reaction. The reaction mixture was diluted with 20 mL of water and extracted with ethyl acetate (50 mL x 3). The organic layers were combined, washed with brine (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 column chromatography (eluent: dichloromethane/methanol (v:v = 20:1)) to give the titled compound (yield: 56%) as a yellow solid.

Step 4: Preparation of (2S,4R)-4-hydroxy-N-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride

[0248] To 1L round bottom flask containing tert-butyl (2S,4R)-4-hydroxy-2-([[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]carbamoyl)pyrrolidine-1-carboxylate (45 g, 107.78 mmol) in dioxane was added hydrogen chloride in dioxane (4N, 300 mL). The resulting solution was stirred for 2 hours at room temperature. The solids were collected by filtration to give the titled product (yield: 98%) as a yellow solid.

Step 5: Preparation 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

[0249] To a stirred solution of (2S)-2-{[(tert-butoxy)carbonyl]amino}-3,3-dimethylbutanoic acid (15.7 g, 68.0 mmol) in N,N-dimethylformamide (500 mL) was added DIPEA (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 (20.0 g, 56.5 mmol) at room temperature.

[0250] The resulting solution was stirred at room temperature for 16 hours, 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 the title compound (yield: 51%) as a yellow solid.

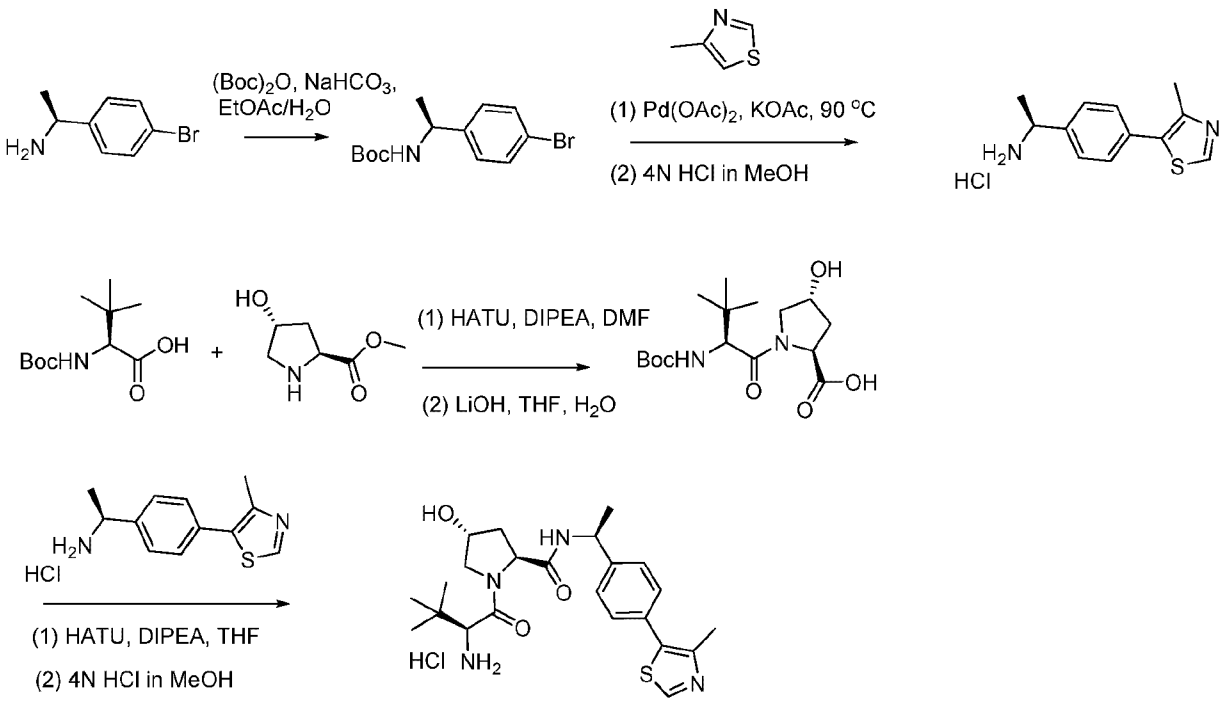
Step 6: Synthesis of (2S, 4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride (**ULM-1**)

[0251] 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 (12 g, 22.61 mmol) in dioxane (20 mL) was added a solution of hydrogen chloride in dioxane (4N, 80 mL) at room temperature. The resulting solution was stirred at room temperature for 2 hours, at which time LC-MS indicated completion of reaction. Precipitated solids were collected by filtration to give the titled product (yield: 48%) as a yellow solid.

[0252] d: 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.

Intermediate 2: (*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 (ULM-2)



Step 1: Preparation of (*S*)-*tert*-butyl -1-(4-bromophenyl)-ethyl carbamate

[0253] To a mixture of (*S*)-1-(4-bromophenyl)ethanamine (3.98 g, 19.9 mmol) and $NaHCO_3$ (1.24 g, 14.8 mmol) in H_2O (10 mL) and ethyl acetate (10 mL) was added $(Boc)_2O$ (5.20 g, 23.8 mmol) at 5°C. The reaction was continued to react for 2 hours. TLC showed reaction was complete. The reaction mixture was filtered. The solid was collected and suspended in a mixture of hexane (10 mL) and H_2O (10 mL) for 0.5 hours. The mixture was filtered and the solid was collected and dried in oven at 50°C to afford the title compound as white solid (5.9 g, 98.7%).

^{1}HNMR (400 MHz, DMSO-d_6): δ 1.28 (d, J = 7.2 Hz, 3H), 1.36 (s, 9H), 4.55-4.60 (m, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.39 (br, 1H), 7.49 (d, J = 8.4 Hz, 2H).

Step 2: Preparation of (*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethanamine hydrochloride

[0254] A mixture of (*S*)-*tert*-butyl -1-(4-bromophenyl)-ethyl carbamate (4.0 g, 13.3 mmol), 4-methylthiazole (2.64 g, 26.6 mmol), palladium (II) acetate (29.6 mg, 0.13 mmol) and potassium acetate (2.61 g, 26.6 mmol) in DMF(10 mL) was stirred at 90°C under N_2 for 18 hours. After cooling to ambient temperature, the reaction mixture was filtered. To the filtrate was added H_2O (50 mL) and the resulting mixture was stirred at ambient temperature for 4 hours. The reaction mixture was filtered. The solid was collected by filtration and dried in oven at 50°C to afford (*S*)-*tert*-butyl 1-(4-(4-methylthiazol-5-yl)phenyl)ethylcarbamate (3.48 g, 82.3%) as gray solid.

^{1}HNMR (400 MHz, DMSO-d_6): δ 1.33 (d, J = 7.2 Hz, 3H), 1.38 (s, 9H), 2.46 (s, 3H), 4.64-4.68 (m, 1H), 7.23 (br d, 0.5H), 7.39 (d, J = 8 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.50 (br d, 0.5H), 8.99 (s, 1H); LC-MS $[M+1]^+$: 319.5

[0255] This solid material (1.9 g, 6.0 mmol) was dissolved in 4N hydrochloride in methanol (5 mL, 20 mmol, prepared from acetyl chloride and methanol) and the mixture was stirred at ambient temperature for 3h then concentrated and triturated with ether. The mixture was filtered and the solid was collected and dried in oven at 60°C to afford (*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethanamine hydrochloride (1.3 g , 85%) as a light green solid.

^{1}HNMR (400 MHz, DMSO-d6): δ 1.56 (d, J = 6.8 Hz, 3H), 2.48 (s, 3H), 4.41-4.47 (m, 1H), 7.57 (d, J = 8.4Hz, 2H), 7.67 (d, J = 8.4 Hz), 8.75 (s, 3H), 9.17 (s, 1H); LC-MS $[M+1]^+$: 219.2

Step 3: Preparation of (*2S, 4R*)-1-{(*S*)-2-[(*tert*-butoxycarbonyl)amino]-3,3-dimethylbutanoyl}-4-hydroxypyrrolidine-2-carboxylic acid

[0256] HATU (2.15 g, 5.7 mmol) was added to a solution of (*S*)-2-(*tert*-butoxycarbonyl)amino-3,3-dimethylbutanoic acid (1.25 g, 5.4 mol), (*2S,4R*)-methyl 4-hydroxypyrrolidine-2-carboxylate hydrochloride (0.98 g, 5.4 mmol) and DIPEA (2.43 g, 18.9 mmol) in DMF (10 mL) at 0°C under nitrogen. The mixture was stirred at ambient temperature for 18 hours. TLC showed the reaction complete. The reaction mixture was quenched with water (30 mL) and extracted with ethyl acetate (15 mL X 4). The combined organic layer was washed with the 5% citric acid (10 mL x 2), saturated $NaHCO_3$ solution (10 mL x 2), brine (10 mL x 2) and dried over Na_2SO_4. The organic solution was filtered and concentrated to afford (*2S, 4R*)-methyl 1-{(*S*)-2-[(*tert*-butoxycarbonyl)amino]-3,3-dimethylbutanoyl}-4-hydroxypyrrolidine-2-carboxylate as pale yellow oil (1.93 g, 100% yield). This crude product (1.93 g) and lithium hydroxide hydrate (2.2 g, 54 mmol) were taken into THF (20 mL) and H_2O (10 mL). The resulting mixture was stirred at ambient temperature for 18 hours. THF was removed by concentration. The residue was diluted with ice-water (10 mL) and slowly adjusted to pH 2-3 with 3N HCl. The resulting suspension was filtered, washed with H_2O (6 mL × 2). The solid was collected by filtration and dried in oven at 50°C to afford the title compound as a white solid (1.4 g, 75% for two steps).

^{1}HNMR (400 MHz, DMSO-d_6): δ 6.50 (d, J = 9.6 Hz, 1H), 5.19 (br s, 1H), 4.32 (br s, 1H), 4.25 (t, J = 8.4 Hz, 1H), 4.16 (d, J = 9.2 Hz, 1H), 3.57-3.66 (m, 2H), 2.08-2.13 (m, 1H), 1.85-1.91 (m, 1H), 1.38 (s, 9H), 0.94 (s, 9H).

Step 4: Preparation of (*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 (**ULM-2**)

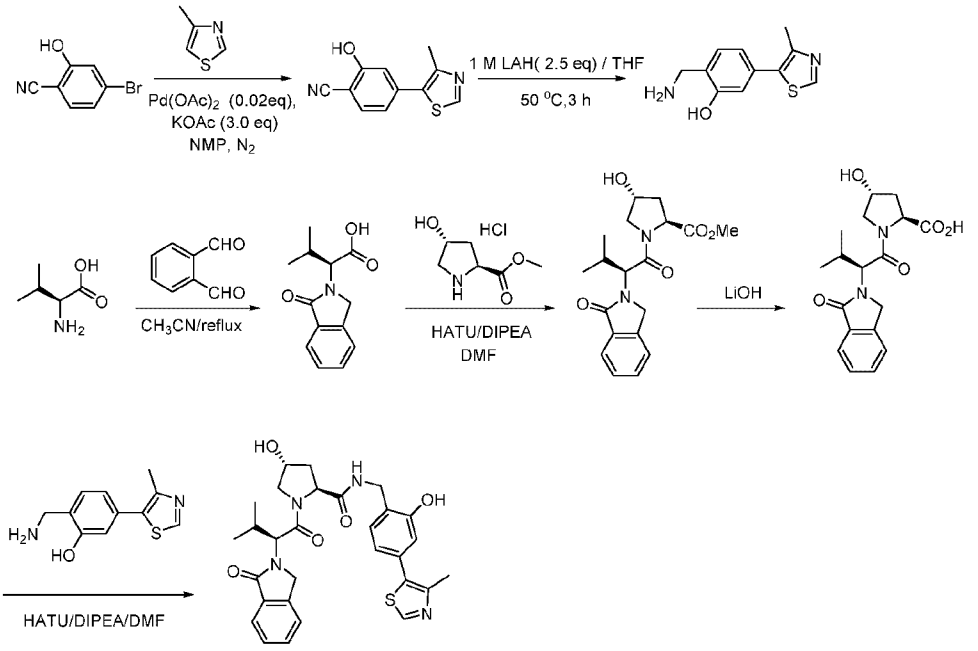
[0257] HATU (1.6 g, 4.2 mmol) was added to a stirred solution containing (*2S, 4R*)-1-{(*S*)-2-[(*tert*-butoxycarbonyl)amino]-3,3-dimethylbutanoyl}-4-hydroxypyrrolidine-2-carboxylic acid (1.21 g, 3.5 mmol), (*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethanamine hydrochloride (0.9 g, 3.5 mmol), and DIPEA (1.36 g, 10.5 mmol) in anhydrous THF (15 mL) at 0°C. The resulting mixture was allowed to warm up to ambient temperature and continued to stir for 2 hours. TLC showed reaction completed. THF was removed by concentration. To the residue was added water (15 mL) and the resulting mixture was stirred for 4 hours. The resulting mixture was filtered. The solid was collected and dried in oven at 50°C to give a white solid. This solid was taken into methanol (10 mL) and activated carbon (150 mg) was added. The resulting mixture was heated at 80°C and stirred for 1h. The mixture was filtered while it was hot. Water (5 mL) was added to the filtrate at 80°C. The resulting mixture was cooled to ambient temperature and continued to stir for 18 hours. The suspension was filtered. The solid was collected and dried in oven at 50°C to afford *tert*-butyl-{(*S*)-1-[(*2S,4R*)-4-hydroxy]-2-[(*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)-ethylcarbamoyl]pyrrolidin-1-yl}-3,3-dimethyl-1-oxobutan-2-yl-carbamate (1.41 g, 74.2%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.42 (s, 9H), 1.47 (d, *J* = 7.2 Hz, 3H), 2.04-2.10 (m, 1H), 2.53 (s, 3H), 2.58-2.64 (m, 1H), 3.23 (s, 1H), 3.58 (dd, *J* = 11.2 Hz, 3.2 Hz, 1H), 4.11 (d, *J* = 11.6 Hz, 1H), 4.22 (d, *J* = 9.2 Hz, 1H), 4.51 (br, 1H), 4.79 (t, *J* = 8.0 Hz, 1H), 5.04-5.11 (m, 1H), 5.22 (d, *J* = 8.8 Hz, 1H), 7.36-7.42 (m, 4H), 7.61 (d, *J* = 7.6 Hz 1H), 8.68 (s, 1H).

[0258] This solid (1.04 g, 1.9 mmol) was dissolved in 4N hydrogen chloride in methanol (3.0 mL) and the mixture was stirred at ambient temperature for 3 hours. TLC showed reaction complete. The reaction mixture was concentrated to remove all volatiles under reduced pressure to give a light yellow solid. The solid was added to TBME (5 mL) and the resulting mixture was stirred at ambient temperature for 4 hours. The reaction mixture was filtered and the solid was collected and dried in oven at 50°C to afford the title compound (0.92 g, 100%).

^{1}H NMR (400 MHz, DMSO-d6): δ 1.03 (s, 9H), 1.38 (d, *J* = 7.2 Hz, 3H), 1.72-1.79 (m, 1H), 2.09-2.14 (m, 1H), 2.49 (s, 3H), 3.48-3.52 (m, 1H), 3.75-3.79 (m, 1H), 3.88-3.90 (m, 1H), 4.31 (br, 1H), 4.56 (t, *J* = 8.4 Hz, 1H), 4.89-4.95 (m, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 8.20 (br, 3H), 8.67 (d, *J* = 7.6 Hz, 1H), 9.22 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d6): δ 170.7, 167.1, 153.0, 146.5, 145.7, 132.5, 129.4, 129.3, 126.9, 69.4, 59.3, 58.5, 56.9, 48.3, 38.4, 34.8, 26.6, 23.0, 15.7; LC-MS $[M+1]^+$: 445.6

Intermediate 3: (2S,4R)-4-hydroxy-N-(2-hydroxy-4- (4-methylthiazol-5-yl)benzyl)-1-((S)-3-methyl-2-(1-oxoisoindolin-2-yl)butanoyl)pyrrolidine-2-carboxamide (ULM-3)



Step 1: Preparation of 2-hydroxy-4-(4-methylthiazol-5-yl) benzonitrile

[0259] A mixture of 4-bromo-2-hydroxybenzonitrile (15 g, 76 mmol), 4-methylthiazole (14 mL, 152 mmol), KOAc (14.9 g, 152 mmol) and $Pd(OAc)_2$ (0.34g, 1.52 mmol) in dry NMP (125 mL) was stirred at 110 °C for 6 hours under nitrogen atmosphere. TLC showed the reaction was complete. The mixture was first cooled to room temperature, then partitioned between EtOAc and water. The combined organic fraction was filtered and the filtrate was washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was dissolved in toluene (100 mL) and re-evaporated to afford the crude product. The crude product was treated with cold MeOH (80 mL). The resulting precipitate was collected by filtration, washed with MeOH (20 mL), and dried under vacuum to afford the title compound as a light yellow solid (10.5 g, 64 %).

LC/MS: 217.2 $[M+1]^+$.

^{1}HNMR (400 MHz, DMSO-d6): δ2.49(s, 3H), 7.07(dd, J=8.0, 1.6Hz, 1H), 7.13(d, J=1.6Hz, 1H), 7.70(d, J=8.0 Hz,1H), 9.07(s, 1H), 11.34 (s, 1H).

Step 2: Preparation of 2-(aminomethyl)-5-(4-methylthiazol-5-yl)phenol

[0260] To a solution of 2-hydroxy-4-(4-methylthiazol-5-yl)benzonitrile (2.9 g, 13.41 mmol) in dry THF (150 mL), was added $LiAlH_4$ (1.5 g, 40.23 mmol) in portions at 0 °C. The resulting mixture was stirred at 50 °C for 3h under nitrogen atmosphere. TLC showed the reaction was complete. The mixture was cooled in ice-water bath then $Na_2SO_4 \cdot 10H_2O$ (5 g) was added carefully and stirred at this temperature for 1h. The mixture was filtered and the filter cake was washed with

10% MeOH in DCM for four times. The combined filtrates were concentrated to afford the crude 2-(aminomethyl)-5-(4-methylthiazol-5-yl)phenol as a light yellow solid (2.0 g, 68%). It was used in next step without further purification.

LCMS: 221.2$[M+H]^+$.

^{1}HNMR (400MHz, DMSO-d6): δ2.43 (s, 3H), 3.54 (br, 2H), 6.11 (d, J=7.2Hz ,1H), 6.40 (d, J=11.6Hz, 1H), 6.83 (d, J=7.6Hz, 1H), 8.81 (s, 1H).

Step 3: Preparation of (S)-3-methyl-2-(1-oxoisoindolin-2-yl) butanoic acid

[0261] L-Valine (4.37 g, 37.3 mmol) was added to a solution of phthalic dicarboxaldehyde (5.0 g, 37.3 mmol) in acetonitrile (350 mL). The resulting mixture was refluxed for 5 hours. The reaction mixture was filtered whilst hot and the filtrate was cooled to room temperature slowly. The resulting precipitate was filtered and dried to afford (S)-3-methyl-2-(1-oxoisoindolin-2-yl)butanoic acid as a white solid (6.45 g, 74 %).

^{1}HNMR (400 MHz, DMSO-d6): δ 0.85(d, J=6.8Hz, 3H), 1.0(d, J=6.8Hz, 3H), 2.25-2.34(m, 1H), 4.51(d, J=4.4Hz, 1H), 4.54(d, J=3.6Hz, 1H), 4.64(d, J=18.0Hz,1H), 7.48-7.54(m, 1H), 7.63 (d, J=3.6 Hz, 2H), 7.72(d, J=7.6Hz, 1H), 13.01(br, 1H).

Step 4: Preparation of (2S,4R)-methyl 4-hydroxy-1-((S)- 3-methyl-2-(1-oxoisoindolin-2-yl)butanoyl)pyrrolidine-2-carboxylate

[0262] To a solution containing 4-hydroxy-L-proline methyl ester hydrochloride (1.0 g, 5.52 mmol), (S)-3-methyl-2-(1-oxoisoindolin-2-yl)butanoic acid (1.16 g, 4.97 mmol), and DIPEA (2.58 g, 20 mmol) in dry DMF (15 mL) was added HATU (3.8 g, 10 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 hours. The mixture was partitioned between EtOAc and water. The organic phase was washed with water, brine and dried over anhydrous Na_2SO_4. The residue was purified by silica gel chromatography using 30-50% EtOAc in hexane as eluent to afford the title compound as a light yellow solid (1.21g, 67.6%).

LCMS: 361.3$[M+1]^+$.

Step 5: Preparation of (2S,4R)-4-hydroxy-1-((S)-3-methyl-2 -(1-oxoisoindolin-2-yl)butanoyl)pyrrolidine-2-carboxylic acid

[0263] A mixture containing (2S,4R)-methyl 4-hydroxy-1-((S)- 3-methyl-2-(1-oxoisoindolin-2-yl)butanoyl)pyrrolidine-2-carboxylate (1.2 g, 3.33 mmol), $LiOH{\cdot}H_2O$ (559 mg, 13.32 mmol) in THF (20 mL) and H_2O (10 mL) was stirred at room temperature for 2 hours. TLC showed the reaction was complete. The reaction mixture was acidified with 1N HCl to pH 1-2, and extracted

with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford the title compound as a light yellow solid (1.05 g, 91% yield).

^{1}HNMR (400MHz, $CDCl_3$): δ0.91 (d, J=6.4Hz, 3H), 1.05 (d, J=6.8Hz, 3 H), 2.30 (dd, J=8.4,2.8 Hz, 2H), 2.44-2.50 (m, 1H), 3.75 (dd, J=11.2, 3.2 Hz, 1H),4.42 (d, J=17.6Hz, 1H), 4.50-4.55 (m, 2H), 4.66 (t, J=8.4Hz, 1H), 4.75 (d, J=17.6Hz, 1H), 4.83 (d, J=11.2Hz, 1H), 7.42-7.45 (m, 2H), 7.51-7.56 (m, 1H), 7.78 (d, J=7.6 Hz, 1H).

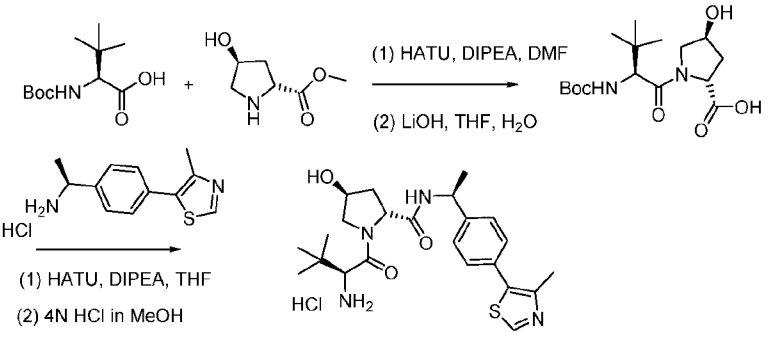
Step 6: Preparation of (2S,4R)-4-hydroxy-N-(2-hydroxy-4- (4-methylthiazol-5-yl)benzyl)-1-((S)-3-methyl-2-(1-oxoisoindolin-2-yl)butanoyl)pyrrolidine-2-carboxamide

[0264] To a solution containing (2S,4R)-4-hydroxy-1-((S)-3-methyl-2-(1-oxoisoindolin-2-yl)butanoyl)pyrrolidine-2-carboxylic acid (1.0 g, 2.89 mmol), 2-(aminomethyl)-5-(4-methylthiazol-5-yl)phenol (954 mg, 4.33 mmol), and DIPEA (1.5 g, 11.55 mmol) in DMF (20 mL) was added HATU (2.2 g, 5.77 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 1h. TLC showed the reaction was complete. The mixture was partitioned between EtOAc and water. The organic phase was washed with water, brine and dried over anhydrous Na_2SO_4. The residue was purified by silica gel column chromatography using 2-5% MeOH in DCM to afford the title compound as a light yellow solid (650 mg, 43% yield).

LCMS: 549.2$[M+H]^+$

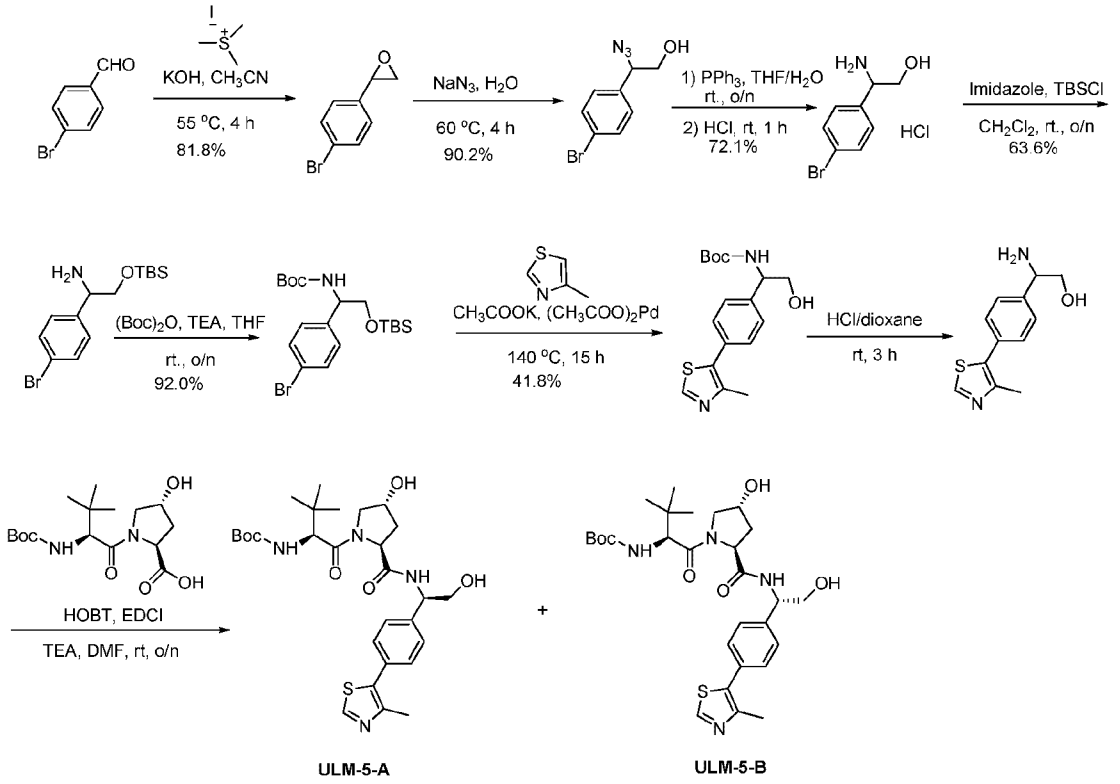
^{1}HNMR (400MHz, $CDCl_3$): δ0.80 (d,J=6.8Hz, 3H), 0.88 (d, J=6.8Hz ,3 H), 1.96-2.01 (m, 1H), 2.34-2.40 (m, 1H), 2.47-2.53 (m, 4H), 3.61 (dd, J=11.6, 3.6 Hz ,1H), 4.29-4.37 (m, 2H), 4.38-4.41 (m, 1H), 4.47-4.50 (m, 2H), 4.64-4.69 (m, 2H), 4.72 (s, 1H), 6.90 (dd, J=8.0, 2.0 Hz,1H), 7.01 (d, J=2,0Hz, 1H), 7.14 (d, J=8.0Hz, 1H), 7.39-7.44 (m, 2H), 7.51-7.54 (m, 1H), 7.76 (d, J=7.6Hz , 1H), 8.03 (t, J=6.4Hz , 1H), 8.66 (s, 1H),9.27 (br, 1H).

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



[0265] This compound was synthesized using the same method as descried in the preparation of **ULM-2** using (*2R,4S*)-methyl 4-hydroxypyrrolidine-2-carboxylate hydrochloride. ^{1}HNMR (400 MHz, CD_3OD): δ 1.14 (s, 9H), 1.55 (d, *J* = 6.8 Hz, 3H), 2.00-2.05 (m, 1H), 2.51-2.58 (m, 1H), 2.65 (s, 3H), 3.77-3.81 (m, 1H), 3.88-3.92 (m, 1H), 4.06 (br, 1H), 4.41-4.46 (m, 1H), 4.56-4.60 (m, 1H), 5.07-5.12 (m, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 10.02 (s, 1H). LC-MS $[M+H]^+$: 445.3

Intermediate 5 and Intermediate 6: *tert*-butyl-N-[(2S)-1-[(2S,4R)-4-hydroxy-2- {[(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]carbamoyl}pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate (ULM-5-A) and *tert*-butyl N-[(2S)-1-[(2S,4R)-4-hydroxy-2-{[(1S)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]carbamoyl}pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate (ULM-5-B)



Step 1: The synthesis of 2-(4-bromophenyl)oxirane

[0266] A mixture of 4-bromobenzaldehyde (2.52 g, 13.6 mmol), trimethylsulfonium iodide (2.87 g, 14.1 mmol), water (0.65 mL, 36.1 mmol) and potassium hydroxide (1.56 g, 27.7 mmol) in acetonitrile (20 mL) was warmed to 55 °C for 4 hours. The resulting solution was partitioned

between water and diethyl ether, and the organic layer was washed with water, diluted hydrochloric acid, and brine, and dried over sodium sulfate. Crude product of 2-(4-bromophenyl)oxirane (2.20 g, 81.8% yield) was obtained by removal of organic solvent under reduced pressure, which was used for next reaction without purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (1H, q, J = 2.8 Hz), 3.14 (1H, dd, J = 4.0 Hz, 5.2 Hz), 3.82 (1H, dd, J = 2.4 Hz, 4.0 Hz), 7.15 (2H, d, J = 8.4 Hz), 7.47 (2H, d, J = 8.8 Hz).

Step 2: The synthesis of 2-azido-2-(4-bromophenyl)ethanol

[0267] To a stirred suspension of 2-(4-bromophenyl)oxirane (5.0 g, 25.3 mmol) in distilled water (70 mL) was added the sodium azide (3.28 g, 50.5 mmol), the resulting mixture was stirred at 60 °C for 4 hour and was monitored by TLC. After reaction completion, the mixture was extracted with EtOAc, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give 2-azido-2-(4-bromophenyl)ethanol (5.5 g, 90.2 %) as pale yellow oils. The crude product was used for next step directly.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94 (1H, s), 3.63-3.66 (2H, m), 4.57 (1H, dd, J = 5.2 Hz, 7.6 Hz), 7.15 (2H, d, J = 8.4 Hz), 7.46 (2H, d, J = 8.4 Hz).

Step 3: The synthesis of 2-amino-2-(4-bromophenyl)ethanol hydrochloride

[0268] To a solution of 2-azido-2-(4-bromophenyl)ethanol (2.0 g, 8.30 mmol) in tetrahydrofuran (20.0 mL) and water (5.00 mL) was added triphenylphosphine (4.35 g, 16.6 mmol). The reaction mixture was stirred at room temperature overnight and the solvent was removed *in vacuo*. The residue was dissolved in HCl/ dioxane (4M, 10.0 mL) and stirred at room temperature for 1 hour. After being concentrated, the solid was washed with dichloromethane to give 2-amino-2-(4-bromophenyl)ethanol hydrochloride (1.5 g, 72.1 % yield) as white solids.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (2H, s), 4.28 (1H, s), 5.55 (1H, s), 7.47 (2H, d, J = 8.4 Hz), 7.63 (2H, d, J = 8.4 Hz), 8.61 (3H, s); LC/MS 216.2 $[M+H]^+$.

Step 4: The synthesis of 1-(4-bromophenyl)-2-(tert-butyldimethylsilyloxy)ethanamine

[0269] To a solution of 2-amino-2-(4-bromophenyl)ethanol hydrochloride (1.80 g, 7.17 mmol) in dichloromethane (50 mL) was added imidazole (1.95 g, 2.87 mmol) and tert-butyldimethylsilyl chloride (TBSCl) (1.63 g, 10.8 mmol) ar room temperature. The reaction mixture was stirred at room temperature overnight and then quenched with water. The aqueous phase was extracted with dichloromethane (30 mL x 3), the combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give crude compound. The crude product was

purified by silica gel column chromatography (petroether/ethyl acetate = 5:1) to give 1-(4-bromophenyl)-2-(tert-butyldimethylsilyloxy)ethanamine (1.50 g, 63.6%) as white solids.

LC/MS: 330.1 $[M+H]^+$;

Step 5: The synthesis of tert-butyl 1-(4-bromophenyl)-2-(tert-butyldimethylsilyloxy)ethylcarbamate

[0270] To a solution of 1-(4-bromophenyl)-2-(tert-butyldimethylsilyloxy)ethanamine (1.50 g, 4.56 mmol) in tetrahydrofuran (20 mL) was added triethylamine (0.69 g, 6.84 mmol) and di-tert-butyl dicarbonate (1.49 g, 6.84 mmol). The reaction mixture was stirred at room temperature overnight and then quenched with water. The aqueous phase was extracted with ethyl acetate (50 mL x 3) and washed with brine. The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give crude compound. The crude product was purified by silica gel column chromatography (petroether/ethyl acetate = 100:1) to give tert-butyl 1-(4-bromophenyl)-2-(tert-butyldimethylsilyloxy)ethylcarbamate (1.80 g, 92.0%) as pale yellow oils.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (6H, d, J = 9.6 Hz), 0.86 (9H, s), 1.42 (9H, s), 3.65-3.70 (2H, m), 4.60-4.63 (1H, m), 7.34 (2H, d, J = 8.0 Hz), 7.39 (1H, d, J =8.8 Hz), 7.56 (2H, d, J = 8.4 Hz).

Step 6: The synthesis of tert-butyl 2-hydroxy-1-(4-(4-methylthiazol-5-yl)phenyl)-ethylcarbamate

[0271] A mixture of *tert*-butyl 1-(4-bromophenyl)-2-(*tert*-butyldimethylsilyloxy)ethylcarbamate (4.0 g, 9.32 mmol), 4-methylthiazole (1.85 g, 18.6 mmol), potassium acetate (1.82 g, 18.6 mmol), palladium (II) acetate (0.11 g, 0.47 mmol) were dissolved in dimethylacetamide and stirred under argon. The mixture was heated to 140 °C and stirred for 15 hours, then diluted with water. The aqueous phase was extracted with ethyl acetate (50 mL x 3) and washed with brine. The combined organic layer was dried over sodium sulfate, filtered and concentrated under vacuum to give crude compound which was purified by silica gel column chromatography (petroether/ethyl acetate = 100:1) to give *tert*-butyl 2-hydroxy-1-(4-(4-methylthiazol-5-yl)phenyl) ethylcarbamate (1.30 g, 41.8%) as pale yellow solids.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (9H, s), 2.46 (3H, s), 3.52 (2H, t, J =6.0 Hz), 4.55-4.58 (1H, m), 4.84 (1H, t, J =6.0 Hz), 7.30 (1H, d, J =8.0 Hz), 7.38-7.45 (4H, m), 8.99 (1H, s); LC/MS 335.2 $[M+H]^+$; Rt = 1.859 min

Step 7: The synthesis of 2-amino-2-(4-(4-methylthiazol-5-yl)phenyl)ethanol hydrochloride

[0272] The tert-butyl 2-hydroxy-1-(4-(4-methylthiazol-5-yl)phenyl)ethylcarbamate (300 mg, 0.536 mmol) was dissolved in hydrochloric acid/dioxane (5 mL, 4M). The resulting reaction mixture was stirred at room temperature for 3 hours. The solvent was concentrated *in vacuo* to give 2-amino-2-(4-(4-methylthiazol-5-yl)phenyl)ethanol hydrochloride as white solids, which was used for the next step without further purification.

Step 8: The synthesis of *tert*-butyl N-[(2S)-1-[(2S,4R)-4-hydroxy-2-{[(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]carbamoyl}pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate (**ULM-5-A**) and *tert*-butyl N-[(2S)-1-[(2S,4R)-4-hydroxy-2-{[(1S)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]carbamoyl}pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate (**ULM-5-B**)

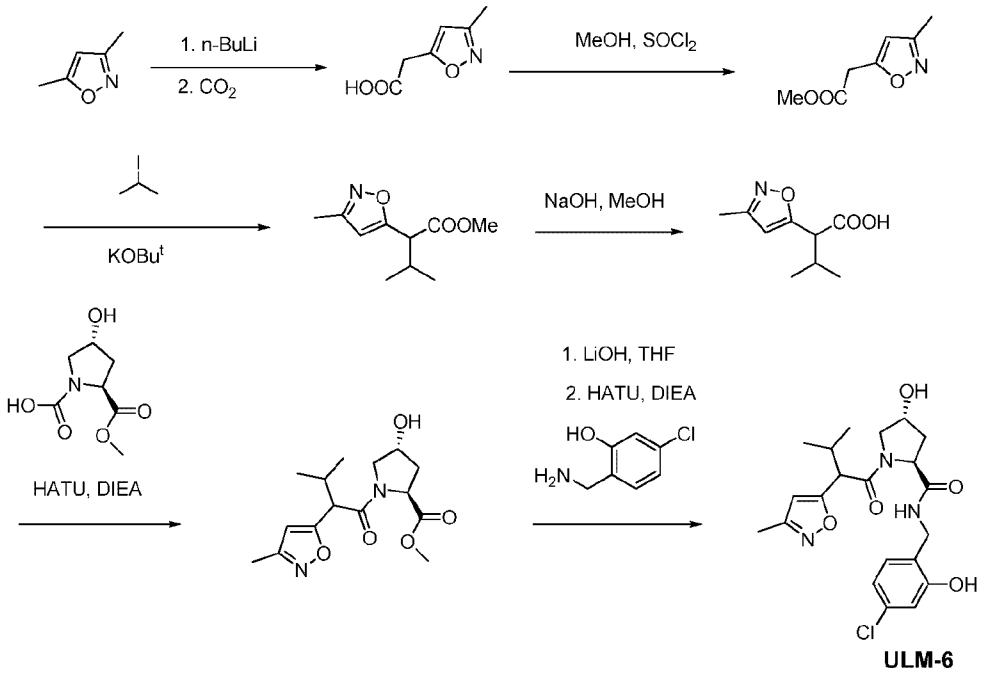
[0273] A solution of 2-amino-2-(4-(4-methylthiazol-5-yl)phenyl)ethanol hydrochloride (1000 mg, 3.70 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI) (995 mg, 5.19 mmol), 1-hydroxybenzotriazole (HOBT) (695 mg, 5.19 mmol) , (2S,4R)-1-((S)-2-(tert-butoxycarbonylamino)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxylic acid (1273 mg, 3.70 mmol) and triethylamine (747 mg, 7.40 mmol) in *N*,*N*-dimethylformamide (50 mL) was stirred at room temperature overnight under agron, and then water (80 mL) was added to the mixture. The aqueous layer was extracted with ethyl acetate (50 mL x 5). The combined organic layer was washed with brine (50 mL x 3), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was purified by preparative TLC (dichloromethyl/methanol = 15:1) to give tert-butyl (S)-1-((2S,4R)-4-hydroxy-2-((R)-2-hydroxy-1-(4-(4-methylthiazol-5-yl)phenyl)ethylcarbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (700 mg) as pale yellow oils and tert-butyl (S)-1-((2S,4R)-4-hydroxy-2-((S)-2-hydroxy-1-(4-(4-methylthiazol-5-yl)phenyl) ethyl carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (500 mg) as pale yellow oils.

[0274] **ULM-5-A**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (9H, s), 1.39 (9H, s), 1.77-1.83 (1H, m), 2.01-2.06 (1H, m), 2.46 (3H, s), 3.54-3.60 (4H, m), 4.13-4.19 (1H, m), 4.29-4.36 (1H, m), 4.50 (1H, t, J = 8.0 Hz), 4.78 (1H, t, J = 5.6 Hz), 4.81-4.88 (1H, m), 5.12-5.16 (1H, m), 6.46 (1H, d, J = 9.2 Hz), 7.36-7.46 (4H, m), 8.41 (1H, d, J = 8.0 Hz), 8.99 (1H, s); LC/MS 561.2 $[M+H]^+$; Rt = 1.897 min

[0275] **ULM-5-B**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (9H, s), 1.38 (9H, s), 1.92-2.06 (2H, m), 2.45 (3H, s), 3.56-3.69 (4H, m), 4.06-4.14 (1H, m), 4.36 (1H, s), 4.56 (1H, t, J = 7.6 Hz), 4.76-

4.81 (1H, m), 4.87 (1H, t, J = 5.6 Hz), 5.146 (1H, d, J = 2.8 Hz), 6.47 (1H, d, J = 8.8 Hz), 7.37 (2H, d, J = 8.0 Hz), 7.51 (2H, d, J = 8.0 Hz), 8.37 (1H, d, J = 7.6 Hz), 8.98 (1H, s); LC/MS 561.2 $[M+H]^+$; Rt = 1.887 min

Intermediate7: (2S,4R)-N-[(4-chloro-2-hydroxyphenyl)methyl]-4-hydroxy-1-[3-methyl-2-(3-methyl-1,2-oxazol-5-yl)butanoyl]pyrrolidine-2-carboxamide (ULM-6)



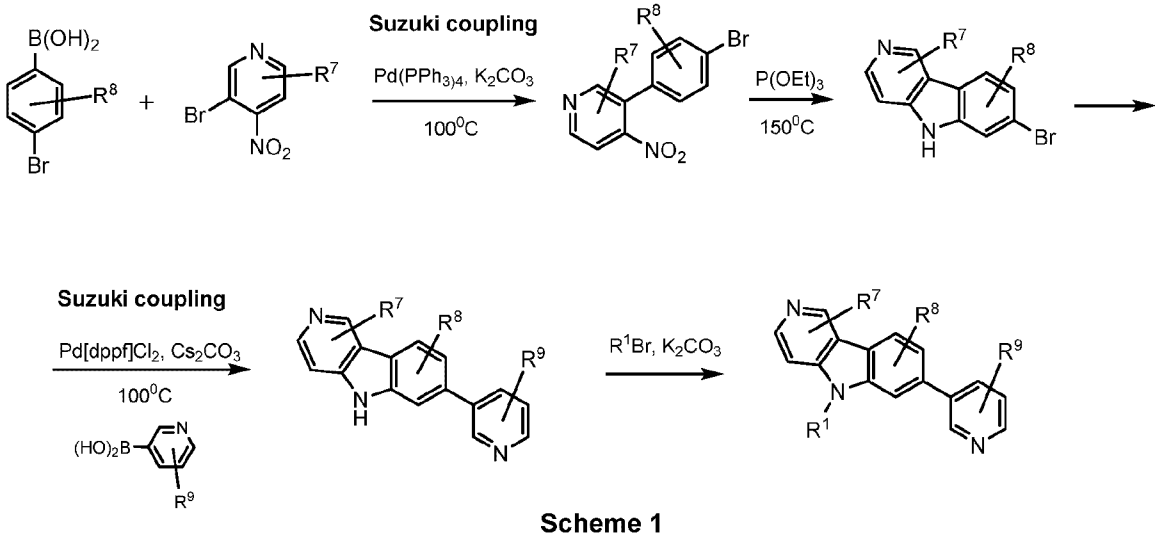
[0276] This key intermediate was prepared using the synthetic route above. The required 3-methylisoxazole-5-acetic acid was prepared according to the literature (J. Org. Chem. 66, 6595-6603, 2001). The alkylation with 2-iodopropane has been described in the literature. The desired ULM-6 was prepared using the same synthetic method as described in the preparation of intermediate ULM-3.

[0277] ^{1}H NMR (400 MHz, $CDCl_3$) : δ 9.33 (s, 0.5H), 9.20 (s, 0.5H), 8.07(t, J = 6.4 Hz, 0.5H), 7.83(t, J = 6.0 Hz, 0.5H), 6.99(dd, J = 2.4, 8.0 Hz, 1H), 6.89-6.90(m, 1H), 6.76-6.78 (m, 1H), 6.02(s, 0.5H), 5.99(s, 0.5H), 5.80-5.83(m, 0.5H), 4.35(q, J = 6.4 Hz, 1.5), 4.16-4.25(m, 2H), 3.72-3.76(m, 0.5H), 3.61(d, J = 9.2 Hz, 1.0H), 3.51-3.55(m, 1.5H), 2.30-2.46(m, 2.5H), 2.26(s, 1.5H), 2.24(s, 1.5H), 1.95-2.05(m, 1H), 1.01(d, J = 6.8 Hz, 1.5H), 0.82-0.87(m, 4.5H); LC-MS 436.1 $[M+1]^+$; Rt =3.57 min.

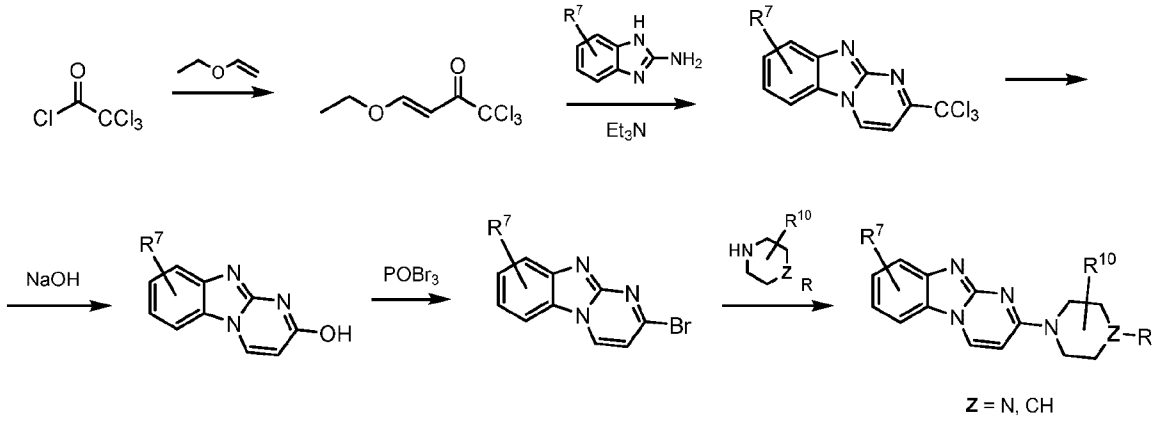
PTM Synthesis:

[0278] Preferred PTM embodiments of the current disclosure can be prepared according to the synthetic routes in schemes 1–3 below. These routes can be modified and adapted to the synthesis of the particular PTM embodiment using general methods known to those skilled in the art.

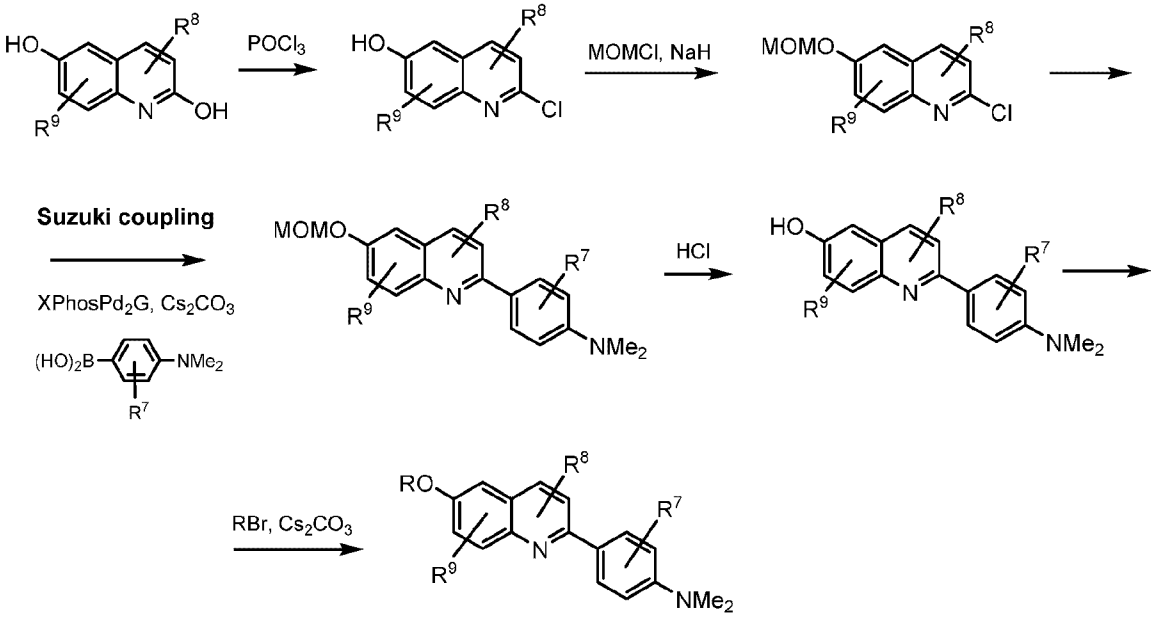
[0279]



Scheme 1



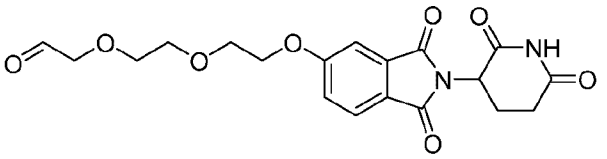
Scheme 2



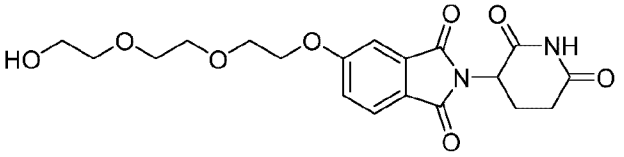
Scheme 3

Exemplary PROTAC Synthesis:

[0280] Intermediate 1



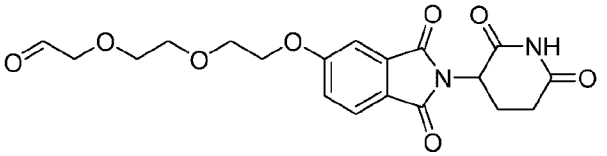
[0281] Step 1: 2-(2,6-dioxopiperidin-3-yl)-5-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)isoindoline-1,3-dione



[0282] To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione (500 mg, 1.82 mmol) in DMF (10 mL) were added K_2CO_3 (756 mg, 5.47 mmol) and 2-(2-(2-hydroxyethoxy)ethoxy)ethyl 4-methyl-benzenesulfonate (832 mg, 2.73 mmol) at 25°C. The resulting solution was stirred at 70 °C for 5 hours. After cooling to room temperature, the reaction was quenched with H_2O (10 mL), and the mixture was extracted with EtOAc (10 mL x 2). The

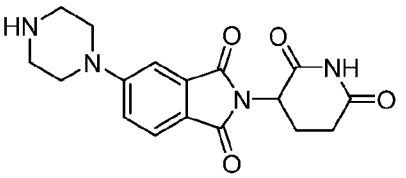
combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified with silica gel column to afford the desired product (95 mg, 13% yield).

[0283] Step 2: 2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)ethoxy)ethoxy)acetaldehyde



[0284] To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)isoindoline-1,3-dione (95 mg, 0.23 mmol) in CH_3CN (5 mL) was added IBX (130 mg, 0.46 mmol) at 25°C. The reaction was stirred at 80 °C for 2 hours. After cooling to room temperature, the mixture was filtered through Celite, and the filtrate was concentrated to afford crude intermediate **1**, 2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)ethoxy)ethoxy)acetaldehyde, (90 mg), which was used without further purification.

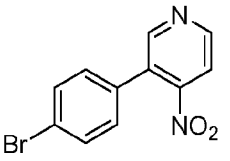
[0285] **Intermediate 2**



[0286] To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindoline-1,3-dione (10 g, 36.2 mmol) in NMP (70 mL) was added tert-butyl piperazine-1-carboxylate (13.47 g, 72.5 mmol) and DIPEA (18.6 g, 14.5 mmol). The resulting mixture was stirred at 90°C for 16 hours. After cooling to room temperature, the reaction was quenched with water (100 mL), and the mixture was extracted with ErOAc (300 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE / EA = 100~2/1) to afford the desired product, 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindoline-1,3-dione (14 g, 31.67 mmol, 87.5 % yield) as a light yellow solid.

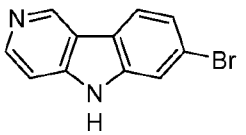
[0287] **Synthetic Scheme for Exemplary Compound 51**

[0288] Step 1: 3-(4-bromophenyl)-4-nitropyridine



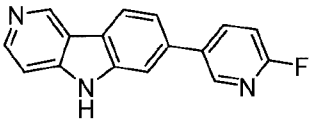
[0289] To a stirred solution of 3-bromo-4-nitropyridine (100 g, 492.6 mmol), (4-bromophenyl)boronic acid (98.6 g, 492.6 mmol), and potassium carbonate (203.9 g, 1.47 mol) in toluene (1000 ml)-water (100 ml) was added tetrakis(triphenylphosphine)palladium (14.8 g, 12.8 mmol) at room temperature under nitrogen atmosphere; the mixture was degassed with nitrogen three times. The resulting mixture was stirred at 50°C overnight. TLC showed the reaction was complete. The solid was removed through filtration and washed with ethyl acetate (100 ml x 3). The organic layer was collected and the aqueous layer was extracted with ethyl acetate (100 ml x 2). The combined organic layers were washed with brine (400 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by silica gel pad (eluted with 10-33 % ethyl acetate in hexane) to afford 3-(4-bromophenyl)-4-nitropyridine (89 g, yield 65%) as yellow solid.

[0290] Step 2: 7-bromo-5H-pyrido[4,3-b]indole



[0291] A mixture of 3-(4-bromophenyl)-4-nitropyridine (20.0 g, 71.7 mmol) in triethyl phosphate (400 ml) was stirred at 110°C for 2 hours under nitrogen atmosphere. TLC showed the reaction was complete. The volatiles were evaporated under reduced pressure to give a residue which was purified by recrystallization (methanol) to afford 7-bromo-5H-pyrido[4,3-b]indole (11.0 g, yield 62%) as brown solid.

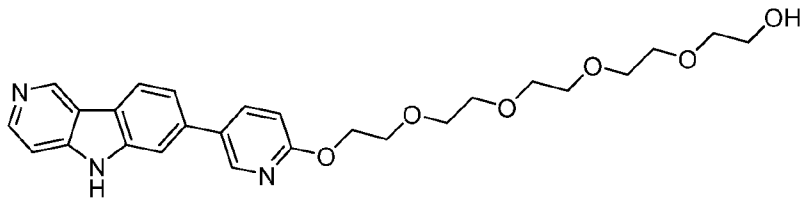
[0292] Step 3: 7-(6-Fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole



[0293] A mixture of 7-bromo-5H-pyrido[4,3-b]indole (400mg, 1.63 mmol), (6-fluoropyridin-3-yl)boronic acid (344mg, 2.44 mmol), $PdCl_2(dppf)$ (120mg, 0.163 mmol), tBu_3PHBF_4 (95mg, 0.326 mmol) and Cs_2CO_3(1.1 g, 3.26 mmol) in dioxane/ water (20mL, 20:1) was heated to 90°C for 4 hours under N_2. The solid was filtered and the filtrate was evaporated. The residue was

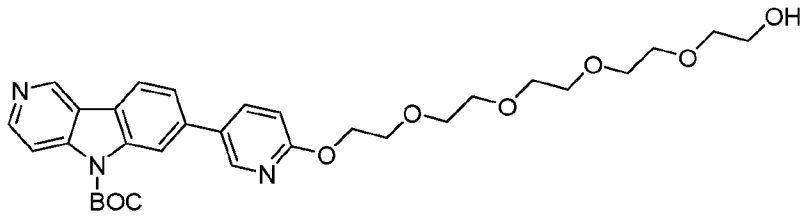
purified by chromatography (silica gel, 200-300 mesh, CH_2Cl_2 : MeOH =30:1) to afford 7-(6-Fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole (250mg, 59% yield).

[0294] Step 4: 14-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecan-1-ol



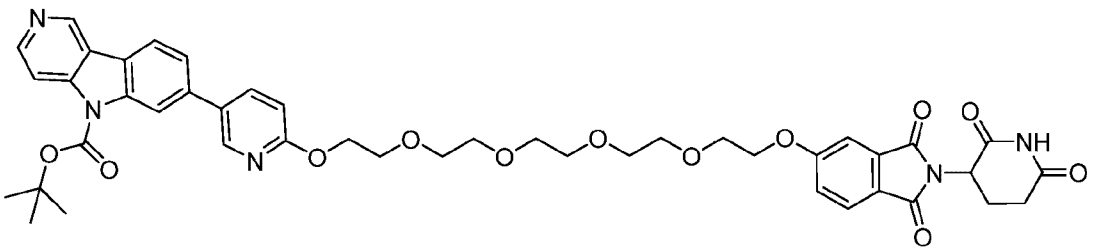
[0295] To a solution of 3,6,9,12-tetraoxatetradecane-1,14-diol (270mg, 1.13 mmol) in THF (10 mL) was added NaH (45 mg, 60%, 1.13 mmol) at 0°C. After stirring at 20°C for 1 hour, a solution of 7-(6-Fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole (150 mg, 0.57 mmol) in DMF (2.0 mL) was added. The resulting solution was stirred at 80°C for 4 hours. After cooling to room temperature, the reaction was diluted with EA (30 mL), and the mixture was washed with brine. The organic phase was evaporated under reduced pressure. The residue was purified by silica gel column chromatography on silica gel (DCM/MeOH= 4/1) to afford the desired product (200 mg.72.89%yield) as a colorless oil.

[0296] Step 5: tert-butyl 7-(6-((14-hydroxy-3,6,9,12-tetraoxatetradecyl)oxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole-5-carboxylate



[0297] To a solution of 14-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecan-1-ol (150 mg, 0.31 mmol) in DCM (10 mL) were added NEt_3 (94.5 mg, 0.93 mmol) and Boc_2O (102.0 mg, 0.47 mmol). The resulting solution was stirred at ambient temperature for 12 hours. The solvent was removed under vacuum. The residue was diluted with EA (30 mL), and the mixture was washed with brine. The organic phase was dried over anhydrous sodium sulfate, and concentrated *in vacuo* to afford the desired product (120 mg, 66% yield), which was used in the next step without further purification.

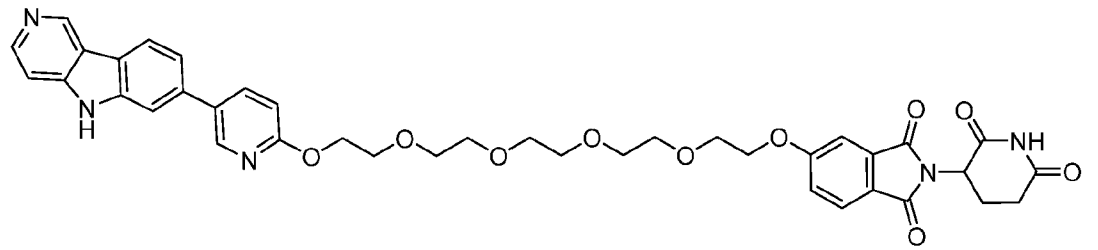
[0298] Step 6: tert-butyl 7-(6-((14-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole-5-carboxylate



[0299] To a solution of tert-butyl 7-(6-((14-hydroxy-3,6,9,12-tetraoxatetradecyl)oxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole-5-carboxylate (120 mg, 0.31 mmol) and NEt_3 (93.9 mg, 0.93 mmol) in DCM (10 mL) was added MsCl (38.9 mg, 0.34 mmol) at 0°C. After stirring at 30°C for 1 hour, the solvent was removed. The residue was diluted with EA (30 mL), and washed with brine. The organic phase was concentrated to give the intermediate mesylate.

[0300] To the stirred solution of mesylate (100 mg, 0.15 mmol) in dry DMF (10 mL) were added 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione (45.6 mg, 0.17mmol) and K_2CO_3 (31.4 mg, 0.23 mmol). The resulting mixture was stirred at 68 °C for 4 hours. The mixture was diluted by EtOAc (40 mL), washed with brine twice, and dried over anhydrous sodium sulfate. The organic phase was evaporated under reduced pressure. The residue was purified by prep-TLC (DCM/MeOH=20/1) to afford the desired product as a yellow solid (15 mg, 23.6% yield).

[0301] Step 7: 5-((14-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione



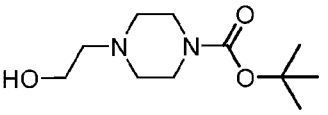
[0302] To a solution of tert-butyl 7-(6-((14-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)-3,6,9,12-tetraoxatetradecyl)oxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole-5-carboxylate (30 mg, 0.036 mmol) in DCM (2 mL) was added TFA (5 mL). The mixture was stirred at ambient temperature for 4 hours. The mixture was evaporated under reduced pressure. The residue was purified by prep-HPLC to afford the title compound as a white solid (10 mg, 38%yield). ^1H NMR (400 MHz, $CDCl_3$): δ 12.34 – 12.48 (m, 1H), 9.19 – 9.29 (m, 1H), 8.80 (s, 1H), 8.29 – 8.42 (m, 1H), 8.02 – 8.14 (m, 1H), 7.95 (s, 1H), 7.69 – 7.81 (m, 1H), 7.60 (s, 2H), 7.17 (s, 1H), 7.09 (s,

1H), 6.62 (s, 1H), 4.97 (s, 1H), 4.43 (s, 2H), 4.14 (s, 2H), 3.88 (d, J = 24.1 Hz, 3H), 3.78 (d, J = 8.2 Hz, 3H), 3.69 (d, J = 10.0 Hz, 6H), 2.80 (m, 4H), 1.99 – 2.29 (m, 4H). $(M+H)^+$ 738.3.

[0303] Using procedures analogous to those for **Compound 51**, **Compound 50** was also prepared.

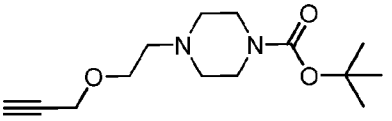
[0304] **Synthetic Scheme for Exemplary Compound 52**

[0305] Step 1: tert-butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate



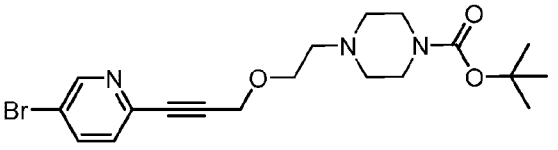
[0306] The solution of 2-(piperazin-1-yl)ethanol (5 g, 38.5 mmol) and TEA(12 g, 115 mmol) was stirred in DCM at 0°C, Boc_2O was added, then the mixture was stirred at 10 °C overnight. Water was added. Then the mixture was extracted with DCM, dried and concentrated, and filtered through a silica gel pad to get 8.1 g product (92% yield).

[0307] Step 2: tert-butyl 4-(2-(prop-2-yn-1-yloxy)ethyl)piperazine-1-carboxylate



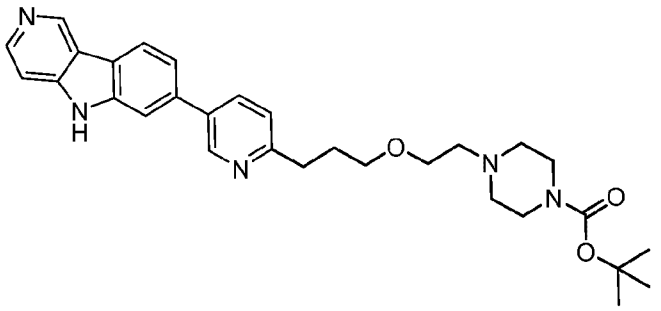
[0308] The solution of tert-butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (3 g, 13 mmol) in THF was stirred at 0°C. NaH (624 mg, 15.6 mmol) was added, then, the mixture was stirred at room temperature for 1 hour. 3-bromoprop-1-yne (1.85 g, 15.6 mmol) was added, and stirring was continued at 70 °C overnight. Then the mixture was cooled to room temperature. Water was added, then the mixture was extracted with EA, dried with Na_2SO_4 and concentrated. Filtered through a silica gel pad (EA) to get 1.5 g product (43% yield).

[0309] Step 3: tert-butyl 4-(2-((3-(5-bromopyridin-2-yl)prop-2-yn-1-yl)oxy)ethyl)piperazine-1-carboxylate



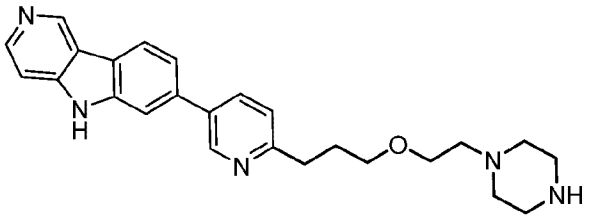
[0310] tert-butyl 4-(2-(prop-2-yn-1-yloxy)ethyl)piperazine-1-carboxylate (500 mg, 1.86 mmol), 2,5-dibromopyridine (442 mg, 1.86 mmol), $Pd(PPh_3)_2Cl_2$(10%), CuI (11%), DIPEA and CH_3CN were stirred at 5 °C overnight, and EA was added. The mixture was washed by water, concentrated. Then filtered through a silica gel (EA) to get 450 mg product (57% yield).

[0311] Step 4: tert-butyl 4-(2-(3-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propoxy)ethyl)piperazine-1-carboxylate



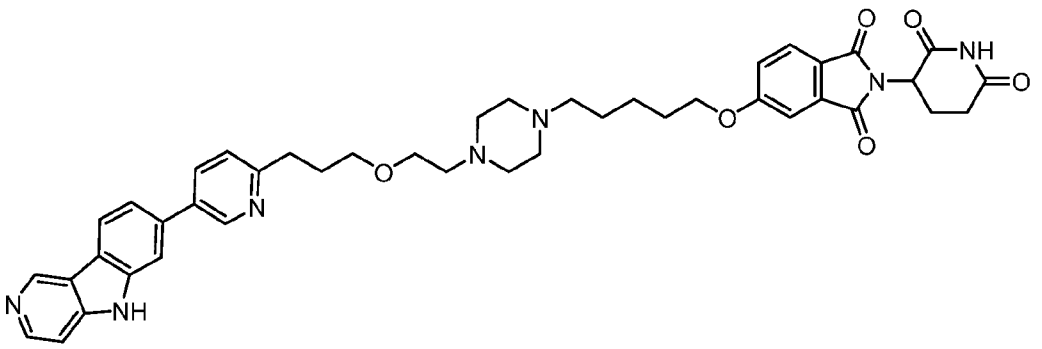
[0312] 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5H-pyrido[4,3-b]indole-5-carboxylate [prepared by using procedure analogous to that of step 1 of Exemplary Compound 63] (300 mg, 0.76 mmol), Pd(aMphose)Cl_2 (50 mg, 10%), and CsF (450 mg, 2.96 mmol) was stirred in CH_3CN/H_2O (10:1) at 120°C in the microwave for 40 minutes. The mixture was cooled to room temperature, and EA was added. The organic layer was washed by water, then filtered through a silica gel pad (DCM:MeOH=20:1) to get 100 mg tert-butyl 4-(2-(3-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)prop-2-ynyloxy)ethyl)piperazine-1-carboxylate. The crude product was dissolved in MeOH, Pd/C was added, and the mixture was stirred at 30 °C under 2Mpa of H_2 for 2 hours, filtered and concentrated to produce 100 mg of product (26% yield).

[0313] Step 5: 7-(6-(3-(2-(piperazin-1-yl)ethoxy)propyl)pyridin-3-yl)-5H-pyrido[4,3-b]indole



[0314] tert-butyl 4-(2-(3-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propoxy)ethyl)piperazine-1-carboxylate (100 mg, 0.2 mmol) in HCl/dioxane solution (2 mL) was stirred at 5°C for 1 hour. Concentrated to obtain 100 mg of crude product.

[0315] Step 6: 5-((5-(4-(2-(3-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propoxy)ethyl)piperazin-1-yl)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione

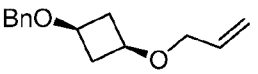


[0316] 5-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yloxy)pentanal (86 mg, 0.24 mmol), $NaBH_4CN$ (55 mg, 0.48 mmol) and CH_3COOH (cat.) was stirred in MeOH at 5°C for 3 hours. Then DCM added. The organic layer was washed by water, concentrated, and filtered through silica gel pad (DCM:MeOH=8:1) to afford 11 mg of product.

[0317] ^{1}HNMR (400 MHz, MeOD): δ 9.25 (s, 1H), 8.79 (s, 1H), 8.37-8.39 (d, *J*=8 Hz, 1H), 8.28-8.30 (d, *J*=8 Hz, 1H), 8.11-8.13 (d, *J*=8 Hz, 1H), 7.80 (s, 1H), 7.75-7.77 (d, *J*=8 Hz, 1H), 7.60 (s, 1H), 7.49-7.51 (d, *J*=8 Hz, 1H), 7.43-7.45 (d, *J*=8 Hz, 1H), 7.33 (s, 1H), 5.07-5.09 (m, 1H), 4.06-4.09 (m, 2H), 3.57-3.60 (m, 2H), 3.51-3.54 (m, 2H), 2.93-2.95 (m, 2H), 2.91-2.93 (m, 1H), 2.59-2.75 (m, 12H), 2.37-2.41 (m, 2H), 2.04-2.06 (m, 3H), 1.78-1.80 (m, 2H), 1.46-1.55 (m, 5H). $(M+H)^+$ 758.3.

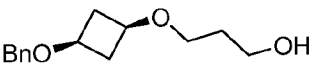
[0318] **Synthetic Scheme for Exemplary Compound 53**

[0319] Step 1: (((1s,3s)-3-(allyloxy)cyclobutoxy)methyl)benzene



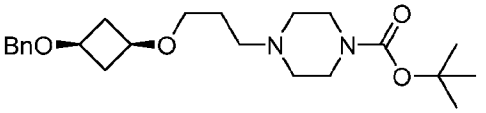
[0320] To a solution of (1s, 3s)-3-(benzyloxy)cyclobutanol (1.0 g, 5.61 mmol) in DMF (10 mL) was added NaH (60%, 0.336 g, 8.4 mmol) at 0 °C. After stirring for 30 min, 3-bromoprop-1-ene was added dropwise at room temperature. The resulting solution was stirred at room temperature for 3 hours. After it was quenched with saturated solution NH_4Cl (20 mL), the mixture was extracted with EtOAc (20 mL x 2). The combined organic layers were dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column with PE/EA= 10~1: as eluent to afford the desired product (1.0 g, 82%) as a colorless oil.

[0321] Step 2: 3-((1s,3s)-3-(benzyloxy)cyclobutoxy)propan-1-ol



[0322] To a solution of (((1s,3s)-3-(allyloxy)cyclobutoxy)methyl)benzene (1.0 g, 4.58 mmol) in THF (20 mL) was added dicyclohexylborane in THF (1.0 M, 9.0 mL) at 0 °C. After it was stirred at room temperature for 4 hours, NaOH (37%, 3.0 mL) and H_2O_2 (30%, 3.0 mL) were added to the mixture at 0°C. The resulting solution was stirred at room temperature overnight. The reaction was quenched with $Na_2S_2O_3$ (20 mL). The mixture was taken up in DCM. The organic phase was dried with Na_2SO_4 and concentrated under vacuum. The residue was purified on silica gel column with PE/EA= 2:1 as eluent to afford the desired product (1.0 g, 100%) as a colorless oil.

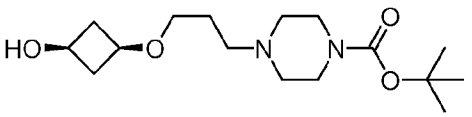
[0323] Step 3: tert-butyl 4-(3-((1s,3s)-3-(benzyloxy)cyclobutoxy)propyl)piperazine-1-carboxylate



[0324] To a solution of 3-((1s,3s)-3-(benzyloxy)cyclobutoxy)propan-1-ol (1.0 g, 4.58 mmol) and TEA (2.0 g, 19.8 mmol) in DCM (10 mL) was added MsCl (0.97 g, 9.2 mmol) at 0 °C. After stirring at room temperature for 2 hours, the reaction was quenched with saturated solution of sodium bicarbonate (20 mL), and the mixture was extracted DCM (20 mL x 2). The combined organic layers were dried with Na_2SO_4, and concentrated under vacuum to afford the desired product (1.1 g, crude), which was used in the next reaction without further purification.

[0325] To a solution of the above intermediate (1.1 g, crude) in DMF (10 mL) was added tert-butyl piperazine-1-carboxylate (1.60 g, 9.2 mmol). The resulting solution was heated to 90°C for 4 hours. After cooling to room temperature, the reaction was quenched with water (20 mL) and the mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by silica gel column with PE / EA = 2:1 as eluent to afford the desired product (980 mg, 58%) as a colorless oil.

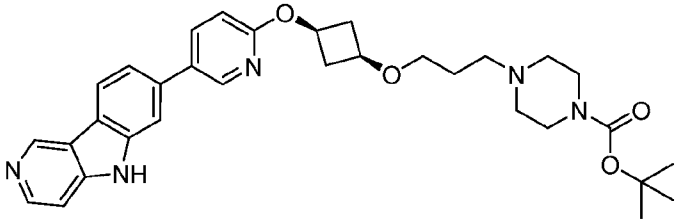
[0326] Step 4: tert-butyl 4-(3-((1s,3s)-3-hydroxycyclobutoxy)propyl)piperazine-1-carboxylate



[0327] A mixture of tert-butyl 4-(3-((1s,3s)-3-(benzyloxy)cyclobutoxy)propyl)piperazine-1-carboxylate (980 mg, 2.42 mmol) and $Pd(OH)_2/C$ (300 mg, 20%) in CH_3OH (10 mL) was stirred at room temperature overnight under H_2 at 1 atm. The mixture was filtered through Celite, and the

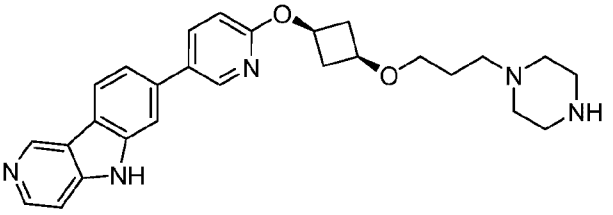
filtrate was concentrated to afford the desired product (700 mg, crude) which was used in the next reaction without further purification.

[0328] Step 5: tert-butyl 4-(3-((1s,3s)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)propyl)piperazine-1-carboxylate



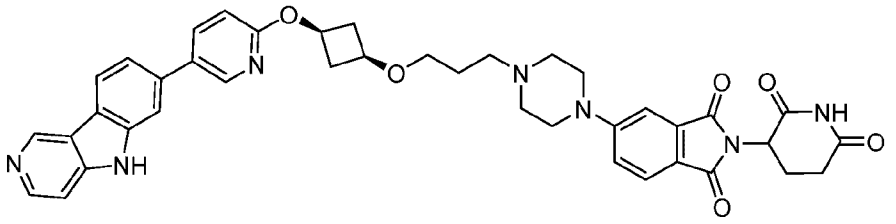
[0329] To a solution of tert-butyl 4-(3-((1s,3s)-3-hydroxycyclobutoxy)propyl)piperazine-1-carboxylate (180 mg, 0.57 mmol) and 7-(6-Fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole (100 mg, 0.379 mmol) in NMP (10 mL) was added NaH (60%, 100 mg, 2.5 mmol) at room temperature. The resulting solution was heated to 90°C for 2 hours. After cooling to room temperature, the reaction was quenched with saturated solution of NH_4Cl (20 mL), and the mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by prep-TLC with DCM/CH_3OH (15 : 1) to afford the desired product (120 mg, 0.21 mmol) as a brown solid.

[0330] Step 6: 7-(6-((1s,3s)-3-(3-(piperazin-1-yl)propoxy)cyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole



[0331] A mixture of tert-butyl 4-(3-((1s,3s)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)propyl)piperazine-1-carboxylate (120 mg, 0.21 mmol) in CH_3OH (2.0 mL) and HCl in 1,4-dioxane (4.0 mL) was stirred at room temperature for 2 hours. The solvent was removed under vacuum to afford the desired product (100 mg, crude), which was used in the next reaction without further purification.

[0332] Step 7: 5-(4-(3-((1s,3s)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)propyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione

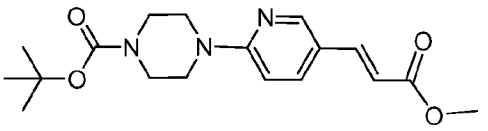


[0333] To a mixture of 7-(6-((1s,3s)-3-(3-(piperazin-1-yl)propoxy)cyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole (80 mg, crude) and DIEA (300 mg, 2.36 mmol) in NMP (2.0 mL) was added 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindoline-1,3-dione (100 mg, 0.36 mmol). The mixture was microwave heated at 130°C for 45 minutes. After cooling to room temperature, the reaction was taken up with EtOAc (100 mL). The mixture was washed with brine (20 mL x 3). The organic phase was dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by prep-TLC with DCM/CH_3OH/NH_3H_2O (15:1:0.1) to afford the title product (16.0 mg, 13%) as a yellow solid.

[0334] ^1H NMR (400 MHz, $CDCl_3$): δ 9.34 (s, 1H), 8.55 (d, *J* = 5.6 Hz, 1H), 8.44 (m, 2H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.87-7.92 (m, 3H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.60 (s, 1H), 7.48-7.50 (m, 1H), 7.38 (d, *J* = 5.6 Hz, 1H), 7.06 (m, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.93-4.94 (m, 2H), 3.75 (m, 2H), 3.42-3.49 (m, 6H), 2.72-2.98 (m, 5H), 2.61 (s, 4H), 2.53 (t, *J* = 7.2 Hz, 2H), 2.15-2.18 (m, 2H), 1.81 (t, *J* = 6.8 Hz, 2H). $(M+H)^+$ 714.3

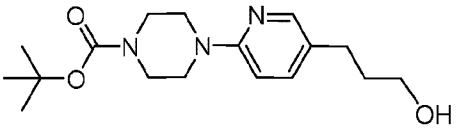
[0335] **Synthetic Scheme for Exemplary Compound 55**

[0336] Step 1: tert-butyl I-4-(5-(3-methoxy-3-oxoprop-1-en-1-yl)pyridin-2-yl)piperazine-1-carboxylate



[0337] To a solution of tert-butyl 4-(5-formylpyridin-2-yl)piperazine-1-carboxylate (1.0 g, 3.44 mmol) and methyl 2-(dimethoxyphosphoryl)acetate (750 mg, 4.12 mmol) in THF (15 ml) was added DBU (1.57 g, 10.3 mmol). The reaction mixture was stirred at room temperature overnight. After it was quenched with water H_2O (10 mL), the mixture was extracted with ethyl acetate (50 mL). The organic phase was washed with brine, and dried over Na_2SO_4. It was filtered, and concentrated under vacuum. The residue was broken with petroleum ether to afford the desired product (800 mg, 2.3 mmol, yield: 66.9 %) as a pale solid.

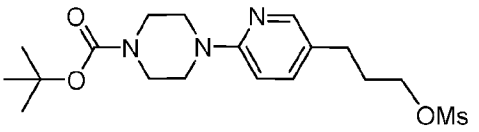
[0338] Step 2: tert-butyl 4-(5-(3-hydroxypropyl)pyridin-2-yl)piperazine-1-carboxylate



[0339] To a solution of tert-butyl I-4-(5-(3-methoxy-3-oxoprop-1-en-1-yl)pyridin-2-yl)piperazine-1-carboxylate

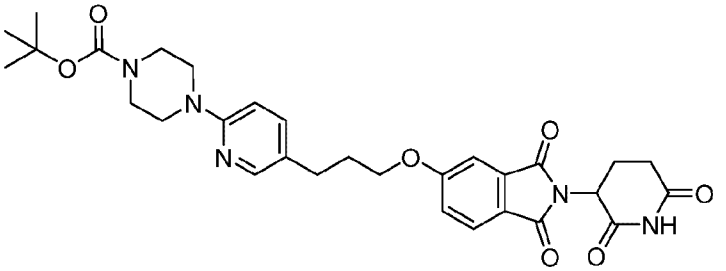
[0340] (800 mg, 2.3 mmol) in CH_3OH (8 mL) and THF (35 mL) was added $NaBH_4$ (874 mg, 23.0 mmol). The mixture was heated to 80°C for 3 hours. After cooling to room temperature, the reaction was quenched with 2N NH_4Cl, and the mixture was extracted with EtOAc (80 mL X 3). The combined organic layers were washed with brine, and dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by silica gel column (EA: PE =1:1) to give the desired compound (420 mg, 1.31 mmol, yield: 57.0 %) as a yellow oil.

[0341] Step 3: tert-butyl 4-(5-(3-((methylsulfonyl)oxy)propyl)pyridin-2-yl)piperazine-1-carboxylate



[0342] To a solution of tert-butyl 4-(5-(3-hydroxypropyl)pyridin-2-yl)piperazine-1-carboxylate (50 mg, 0.16 mmol) and Et_3N (48 mg, 0.48 mmol) in DCM (2 mL) was added MsCl (27 mg, 0.23 mmol). The reaction was stirred at room temperature for 1 hour. After it was quenched with water H_2O (30 mL), the mixture was extracted with DCM (20 mL). The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum to give the crude desired compound (64 mg) as a yellow oil which was used in the next reaction without further purification.

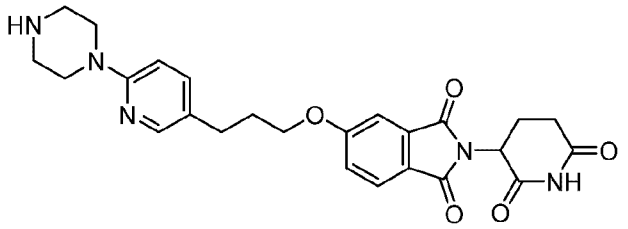
[0343] Step 4: tert-butyl 4-(5-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)propyl)pyridin-2-yl)piperazine-1-carboxylate



[0344] To a solution of tert-butyl 4-(5-(3-((methylsulfonyl)oxy)propyl)pyridin-2-yl)piperazine-1-carboxylate (64 mg, 0.16 mmol) and 2-(2,6-dioxopiperidin-3-yl)-5-

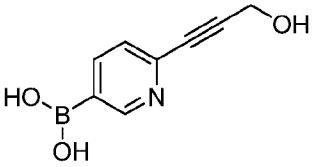
hydroxyisoindoline-1,3-dione (66 mg, 0.24 mmol) in DMF (5 ML) was added K_2CO_3 (55 mg, 0.40 mmol). The reaction mixture was stirred at 90°C for 2 hours. After cooling to room temperature, the reaction was quenched water (5 mL), and the mixture was extracted with dichloromethane (30 mL). The organic phase was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column (MeOH:DCM=1:100–1:20) to give the title product (30 mg, 0.052 mmol, yield: 32 %).

[0345] Step 5: 2-(2,6-dioxopiperidin-3-yl)-5-(3-(6-(piperazin-1-yl)pyridin-3-yl)propoxy)isoindoline-1,3-dione



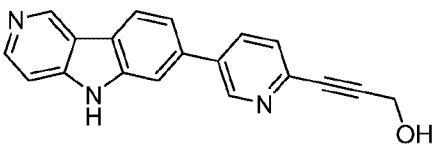
[0346] To a solution of tert-butyl 4-(5-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)propyl)pyridin-2-yl)piperazine-1-carboxylate (200 mg, 0.39 mmol) in dioxane (10 mL) was added 6N HCl in dioxane (2 mL, 12.0 mmol). The reaction mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure to give the crude title product (200mg) as a yellow solid.

[0347] Step 6: (6-(3-Hydroxyprop-1-yn-1-yl)pyridin-3-yl)boronic acid



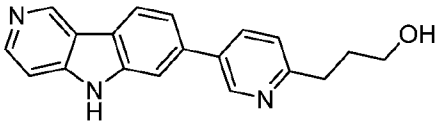
[0348] To a solution of (6-bromopyridin-3-yl)boronic acid (1.0 g, 4.95 mmol) and prop-2-yn-1-ol (830 mg, 14.8 mmol) in THF (30 mL) were added $PdCl_2(PPh_3)_2$ (350 mg, 0.50 mmol), $^iPr_2NH$ (2 g, 19.8 mmol) and CuI (95mg, 0.5 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was filtered through Celite, and to the filtrate was added 1N NaOH (10 mL). The mixture was extracted with DCM. The pH was adjusted to around 6 with 2N HCl. The aqueous solution was extracted with ethyl acetate. The combined EtOAc layers were dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure to give the desired compound (500mg, 2.82 mmol, yield 57%) as a pale solid.

[0349] Step 7: 3-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)prop-2-yn-1-ol



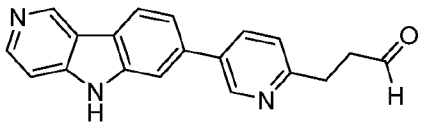
[0350] To the mixture of 7-bromo-5H-pyrido[4,3-b]indole (50 mg, 0.20 mmol) and (6-(3-Hydroxyprop-1-yn-1-yl)pyridin-3-yl)boronic acid (53 mg, 0.30 mmol) in dioxane (10 mL) and water (1.0 mL) were added $PdCl_2(dppf)$ (29 mg, 0.04 mmol), Cs_2CO_3 (130 mg, 0.40 mmol) and $^tBu_3PHBF_4$ (23 mg, 0.08 mmol). The mixture was stirred at 100°C for 3 hours under N_2 atmosphere. After cooling to room temperature, the reaction was quenched with water (3 mL), and the mixture was extracted with EtOAc (20 ml x 3). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on silica gel column (MeOH: DCM =1:20–1:10) to give the desired compound (30 mg, 0.10 mmol, yield: 50.0 %) as a yellow solid.

[0351] Step 8: 3-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propan-1-ol



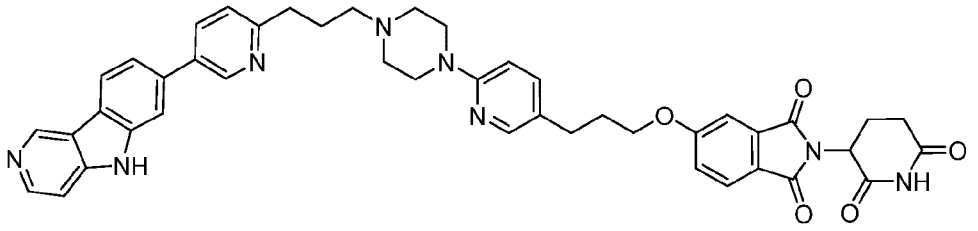
[0352] To a solution of 3-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)prop-2-yn-1-ol (30 mg, 0.10 mmol) in MeOH (2 mL) was added $Pd(OH)_2/C$ (20%, 10 mg) and cat. Conc. HCl (0.1 mL). The reaction was stirred at room temperature for 2 hours under H_2 atmosphere. The mixture was filtered through Celite, and the filtrate was concentrated to give the crude desired compound (30 mg) as a yellow oil.

[0353] Step 9: 3-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propanal



[0354] A solution of 3-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propan-1-ol (100 mg, 0.33 mmol) in DMSO (4 mL) was mixed with IBX (231 mg, 0.82 mmol). The reaction mixture was stirred at 25°C for 2 hours. The reaction was quenched with saturated $Na_2S_2O_3$ (2 mL) and saturated $NaHCO_3$ (2 mL). The mixture was extracted with dichloromethane (30 mL). The organic phase was washed with water and brine. It was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude title product (60 mg) as a yellow oil.

[0355] Step 10: 5-(3-(6-(4-(3-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propyl)piperazin-1-yl)pyridin-3-yl)propoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione

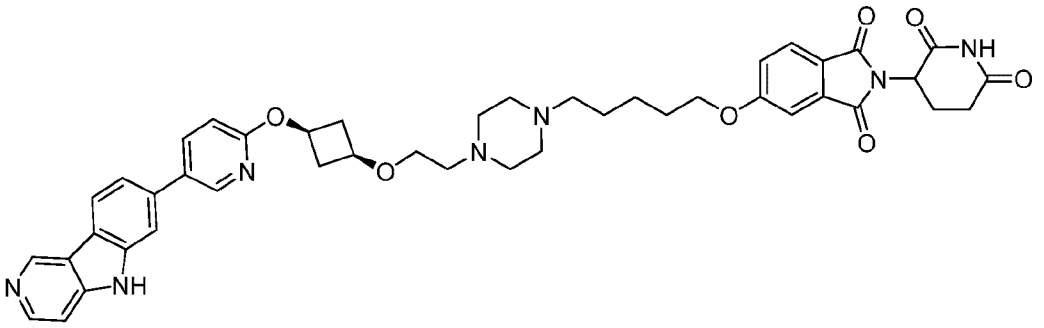


[0356] To a solution of 3-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propanal (100 mg, crude) in MeOH (10 mL) were added 2-(2,6-dioxopiperidin-3-yl)-5-(3-(6-(piperazin-1-yl)pyridin-3-yl)propoxy)isoindoline-1,3-dione (100 mg, 0.21 mmol) and $NaBH_3CN$ (41 mg, 0.66 mmol). The reaction mixture was stirred at room temperature for 1 hour. The mixture was diluted with water (6 ml) and extracted with DCM (20 mL x 2). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC to give the desired product (15 mg, 0.02 mmol) as a white solid.

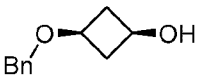
[0357] ^1H NMR (400 MHz, MeOD): δ 9.62 (s, 1H), 9.03 (s, 1H), 8.58 (d, J = 6.8 Hz, 1H), 8.52 (d, J = 8.0 Hz, 1H), 8.31-8.40 (m, 1H), 8.08 (s, 1H), 7.87-7.99 (m, 2H), 7.78-7.87 (m, 3H), 7.68-7.72 (m, 1H), 7.26-7.30 (m, 2H), 7.10-7.14 (m, 1H), 5.08-5.12 (m, 1H), 4.17 (t, J = 6.0 Hz, 2H), 3.81-3.92 (m, 4H), 3.50-3.60 (m, 4H), 3.30-3.40 (m, 2H), 3.10-3.18 (m, 2H), 2.71-2.86 (m, 5H), 2.30-2.33 (m, 2H), 2.10-2.16 (m, 3H). $(M+H)^+$ 763.3

[0358] **Synthetic Scheme for Exemplary Compound 56**

[0359] 5-((5-(4-(2-((1s,3s)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)ethyl)piperazin-1-yl)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione

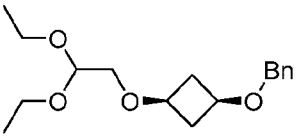


[0360] Step 1: (1s,3s)-3-(benzyloxy)cyclobutan-1-ol



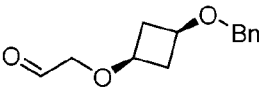
[0361] To a solution of 3-(benzyloxy)cyclobutanone (10.0 g, 56.75 mmol) in EtOH (100 mL) was added $NaBH_4$ (4.3 g, 68.1 mmol) at 0°C. The mixture was stirred at 10°C for 2 hours. After the reaction was quenched with 10% NH_4Cl, the mixture was extracted with ethyl acetate (200 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to give crude the desired product (9.5 g) as a colorless oil, which was used in the next step without further purification.

[0362] Step 2: (((1s,3s)-3-(2,2-diethoxyethoxy)cyclobutoxy)methyl)benzene



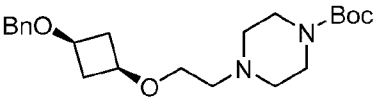
[0363] To a solution of (1s,3s)-3-(benzyloxy)cyclobutan-1-ol (300 mg, crude, 1.69 mmol) in THF (10 mL) was added NaH (168 mg, 4.22 mmol, 60%). After stirring at 5°C for 0.5 hours, 2-bromo-1,1-diethoxyethane (333 mg, 3.38 mmol) was added. The resulting mixture was stirred at 70 °C for 18 hours. After cooling to room temperature, the reaction was diluted with water (50 mL), and the mixture was extracted with EA. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography (silica gel, PE:EA (50:1, v:v)) to afford the desired compound (220 mg) as a yellow solid.

[0364] Step 3: 2-((1s,3s)-3-(benzyloxy)cyclobutoxy)acetaldehyde



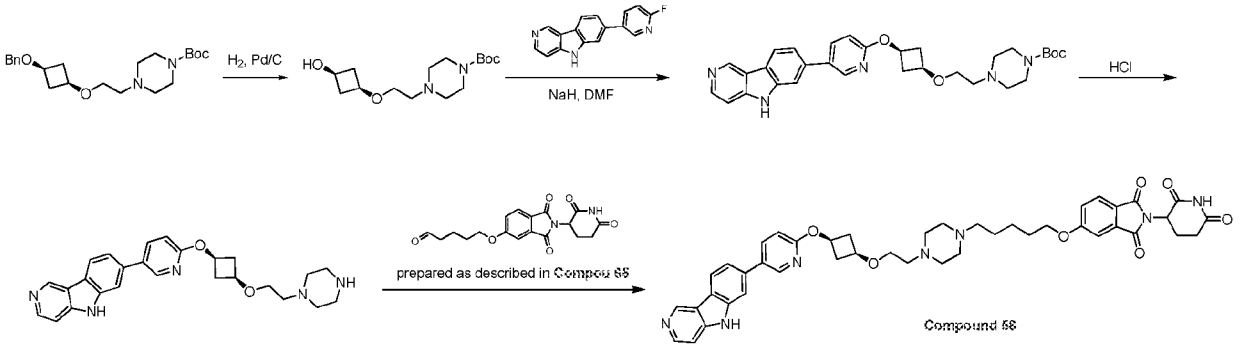
[0365] To a solution of (((1s,3s)-3-(2,2-diethoxyethoxy)cyclobutoxy)methyl)benzene (220 mg, 0.74 mmol) in CH_3CN (5 mL) was added HCl (2 mL, 2.5 mol/L in H_2O). The resulting mixture was stirred at 70 °C for 2 hours. TLC (PE : EA = 3:1, Rf = 0.5) showed that starting material was consumed. The mixture was diluted with water (50 mL) and extracted with EA. The organic phase was washed with $NaHCO_3$, brine. The solution was dried over $MgSO_4$ and concentrated to afford the desired compound (170 mg, crude) as a yellow oil, which was used in the next step without further purification.

[0366] Step 4: tert-butyl 4-(2-((1s,3s)-3-(benzyloxy)cyclobutoxy)ethyl)piperazine-1-carboxylate



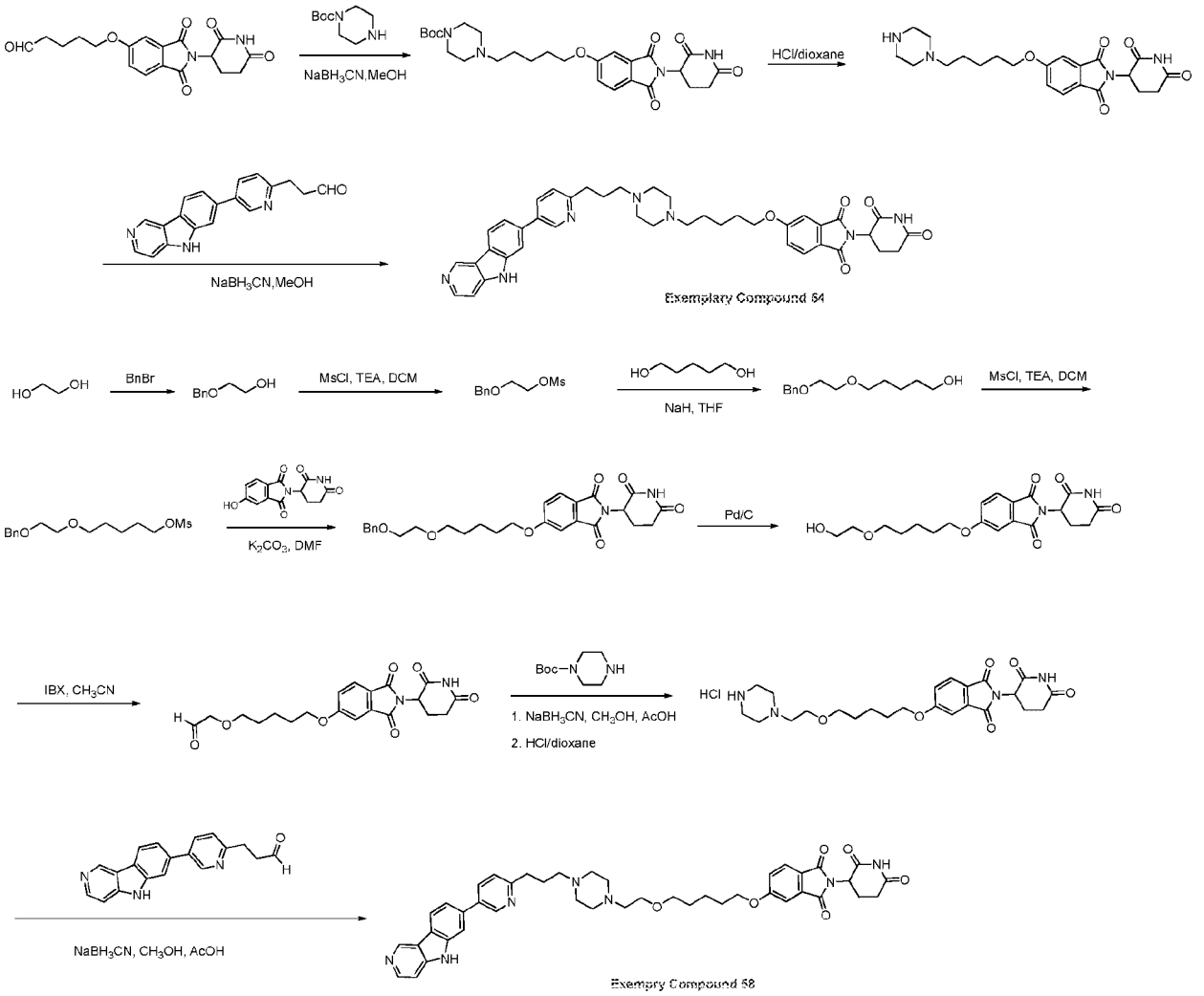
[0367] To a solution of 2-((1s,3s)-3-(benzyloxy)cyclobutoxy)acetaldehyde (170 mg, crude, 0.772 mmol) in MeOH (10 mL) were added tert-butyl piperazine-1-carboxylate (215 mg, 1.16 mmol), AcOH (1 drop) and $NaBH_3CN$ (97 mg, 154 mmol). The resulting mixture was stirred at 10 °C for 18 hours. The reaction mixture was diluted with water (50 mL) and the mixture was extracted with EA. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography (silica gel, PE:EA (1:1, v:v)) to afford the desired compound (280 mg) as a colorless oil.

[0368] Tert-Butyl 4-(2-((1s,3s)-3-(benzyloxy)cyclobutoxy)ethyl)piperazine-1-carboxylate was converted to the title compound, 5-((5-(4-(2-((1s,3s)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)ethyl)piperazin-1-yl)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione, according to the scheme below using procedures described above for **Exemplary Compound 42** and **Exemplary Compound 53**.



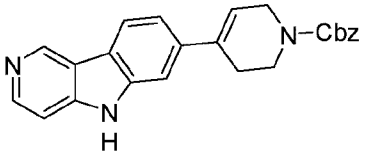
[0369] **Exemplary Compound 56**: ^1H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.89 (s, 1H), 8.53 (s, 1H), 8.42 (s, 1H), 8.18 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 6.2 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.62 (s, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.42 (s, 1H), 7.29 (d, J = 11.5 Hz, 1H), 7.17 (d, J = 6.5 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 5.34 (s, 2H), 5.00 – 4.87 (m, 1H), 4.07 (s, 2H), 3.75 (s, 1H), 3.57 (s, 1H), 3.04 – 2.49 (m, 10H), 2.20 (m, 4H), 2.01 (s, 4H), 1.85 (s, 3H), 1.75 – 1.55 (m, 3H), 1.52 (s, 2H).

[0370] **Exemplary Compound 54** and **Exemplary Compound 58** were prepared according to the schemes below and using procedures analogous to those described above.



[0371] Synthetic Scheme for Exemplary Compound 57

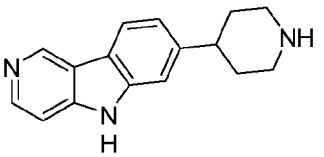
[0372] Step 1: Benzyl 4-(5H-pyrido[4,3-b]indol-7-yl)-3,6-dihydropyridine-1(2H)-carboxylate



[0373] A mixture of 7-bromo-5H-pyrido[4,3-b]indole (492mg, 2 mmol), benzyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (755 mg, 2.2 mmol), Pd(aMphose)Cl_2 (146 mg, 0.2 mmol) and CsF (1.2 g, 8 mmol) in dioxane/H_2O (20 mL/2mL) was stirred at 90°C for 16 hours. After cooling to room temperature, the reaction was quenched by the addition of water (30 mL). The mixture was extracted with ethyl acetate (20 mL x 3). The

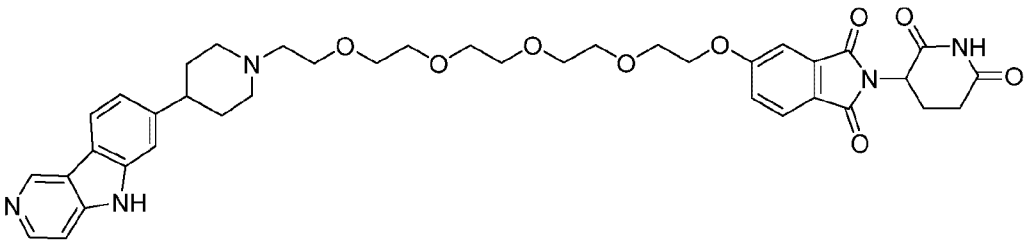
combined organic layers were washed with brine (20 mL x 2), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column eluting with dichloromethane/methanol to afford 260 mg (0.68 mmol, 34%) of the desired product.

[0374] Step 2: 7-(piperidin-4-yl)-5H-pyrido[4,3-b]indole



[0375] To a solution of benzyl 4-(5H-pyrido[4,3-b]indol-7-yl)-3,6-dihydropyridine-1(2H)-carboxylate (130 mg, 0.34 mmol) and one drop conc. HCl in CH_3OH (10 mL) was added Pd/C (13 mg, 10%) at room temperature. The resulting solution was stirred at room temperature overnight under 1 atm of H_2. Then the solid was filtered off and the filtrate was concentrated under vacuum to afford crude product (80 mg), which was used in the next reaction without further purification.

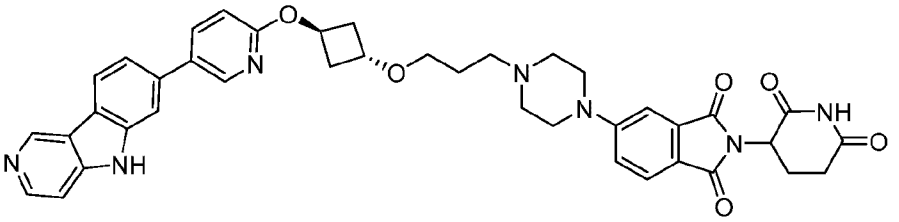
[0376] Step 3: 5-((14-(4-(5H-pyrido[4,3-b]indol-7-yl)piperidin-1-yl)-3,6,9,12-tetraoxatetradecyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione



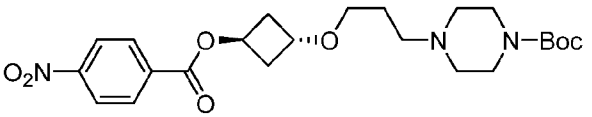
[0377] To a solution of 7-(piperidin-4-yl)-5H-pyrido[4,3-b]indole (80 mg, 0.32 mmol) and 14-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)-3,6,9,12-tetraoxatetradecanal (175 mg, 0.36 mmol) [prepared as described for intermediate **101** above] in CH_3OH (10 mL) were added $NaBH_3CN$ (40 mg, 0.64 mmol) and one drop of CH_3COOH at room temperature. After stirring for 2 hours, the reaction was quenched by the addition of water (20 mL). The resulting solution was extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by prep-TLC with DCM/CH_3OH (10:1) to afford the desired product (18 mg, 0.025 mmol, 8%). ^1H NMR (400 MHz, CD_3OD): δ 9.30 (s, 1H), 8.42-8.60 (m, 2H), 8.19 (d, J=8.0 Hz, 1H), 7.60-7.65 (m, 2H), 7.52 (s, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.19 (s, 1H), 7.12-7.14 (m, 1H), 5.07-5.10 (m, 1H), 4.12 (t, J = 4.0 Hz, 2H), 3.66-3.86 (m, 18H), 3.37 (s, 2H), 3.15-3.20 (m, 3H), 2.71-2.76 (m, 3H), 2.09-2.22 (m, 5H). $(M+H)^+$ 728.3.

[0378] **Sythetic Scheme for Exemplary Compound 60**

[0379] 5-(4-(3-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)propyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione

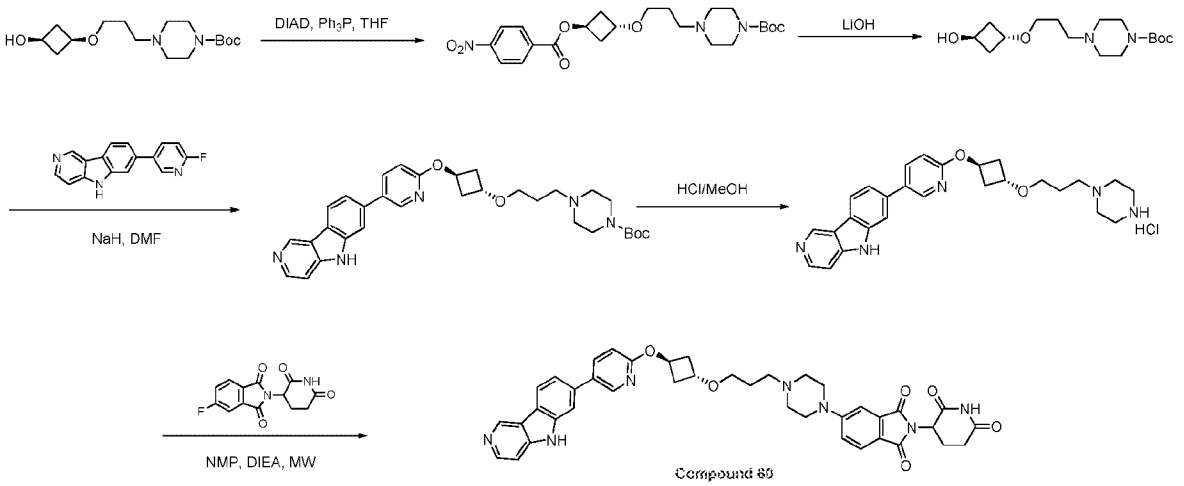


[0380] Step 1: tert-butyl 4-(3-((1r,3r)-3-((4-nitrobenzoyl)oxy)cyclobutoxy)propyl)piperazine-1-carboxylate



[0381] To a solution of tert-butyl-4-(3-((1s,3s)-3-hydroxycyclobutoxy)propyl)piperazine- 1-carboxylate (530 mg, 1.68 mmol), triphenylphosphine (1.32 g, 5.06 mmol) and 4-nitrobenzoic acid (310 mg, 1.85 mmol) in THF (10 mL) was added DIAD (1.02 g, 5.06 mmol) dropwise at room temperature under N_2. After stirring at room temperature for 3 hours, it was quenched with water (20 mL), and the mixture was extracted with EtOAc (20 mL x 2). The combined organic layers were concentrated under vacuum. The residue was purified by silica gel column with PE/EA from 2:1 to 1:1 as eluent to afford the desired product (350 mg, 45%) as a semi-solid.

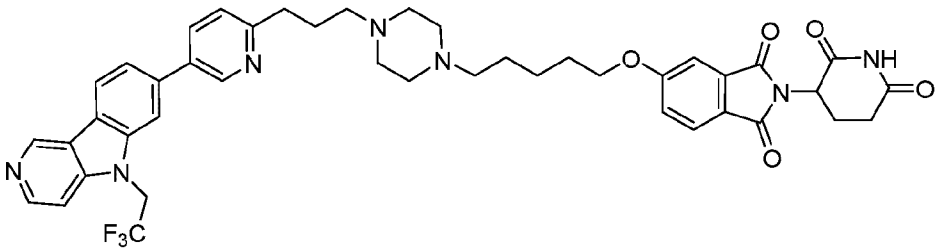
[0382] Tert-butyl 4-(3-((1r,3r)-3-((4-nitrobenzoyl)oxy)cyclobutoxy)propyl)piperazine-1-carboxylate was converted to the title compound, 5-(4-(3-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)propyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione, according to the following scheme and using procedures described above for **Exemplary Compound 53**.



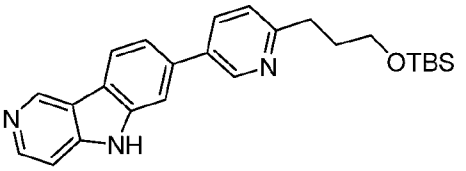
[0383] **Compound 60**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.07 (s, 1H), 9.76 (s, 1H), 8.67 (d, J = 6.0 Hz, 1H), 8.60 (s, 1H), 8.52 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 8.80-8.02 (m, 2H), 7.77 (t, J = 8.4 Hz, 2H), 7.50 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 8.8 Hz, 1H), 5.36 (m, 1H), 5.07-5.11 (m, 1H), 4.24 (br, 3H), 3.62 (br, 9H), 3.55 (s, 3H), 3.17-.3.25 (m, 6H), 2.86-2.93 (m, 1H), 2.38-2.62 (m, 4H), 1.97-2.04 (m, 1H). $(M+H)^+$ 714.3.

[0384] **Synthetic Scheme for Exemplary Compound 61**

[0385] 2-(2,6-dioxopiperidin-3-yl)-5-((5-(4-(3-(5-(5-(2,2,2-trifluoroethyl)-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propyl)piperazin-1-yl)pentyl)oxy)isoindoline-1,3-dione



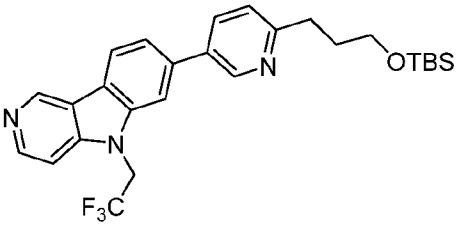
[0386] Step 1: 7-(6-(3-((tert-butyldimethylsilyl)oxy)propyl)pyridin-3-yl)-5H-pyrido[4,3-b]indole



[0387] To a solution of 3-(5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propan-1-ol (prepared as described for **Compound 55**; 100 mg, 0.33 mmol) in DCM (5 mL) were added imidazole (44.8 mg, 0.66 mmol) and TBSCl (59.6 mg, 0.40 mmol). The resulting solution was stirred at 40°C for 3

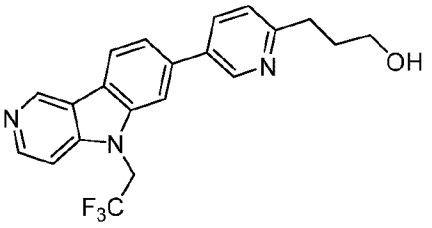
hours. The solvent was removed under reduced pressure. The residue was diluted with EA (30 mL), the mixture was washed with brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (DCM/MeOH= 20/1, 0.2% Net_3) to afford the title product (100 mg.73% yield).

[0388] Step 2: 7-(6-(3-((tert-butyldimethylsilyl)oxy)propyl)pyridin-3-yl)-5-(2,2,2-trifluoroethyl)-5H-pyrido[4,3-b]indole



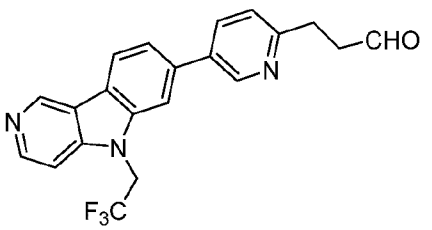
[0389] To a solution of 7-(6-(3-((tert-butyldimethylsilyl)oxy)propyl)pyridin-3-yl)-5H-pyrido[4,3-b]indole (60 mg, 0.14 mmol) in DMF(5 mL) was added NaH (8.6 mg, 0.22mmol) at 5°C. After stirring for 20 min, a solution of CF_3CH_2Otf (66.6 mg, 0.29 mmol) in DMF(1 mL) was added dropwise. The mixture was stirred for another 1 hour, and the reaction was diluted by EtOAc (40 mL), washed with brine, dried over anhydrous sodium sulfate. The filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (DCM/MeOH=40:1, 0.2% $NH_3 \cdot H_2O$) to afford the title product (55 mg, 92%).

[0390] Step 3: 3-(5-(5-(2,2,2-trifluoroethyl)-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propan-1-ol



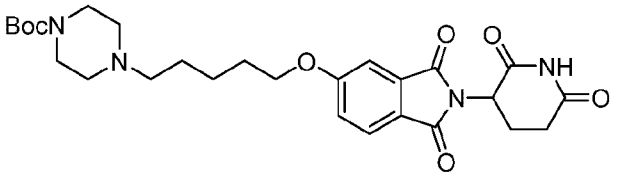
[0391] To a solution of 7-(6-(3-((tert-butyldimethylsilyl)oxy)propyl)pyridin-3-yl)-5-(2,2,2-trifluoroethyl)-5H-pyrido[4,3-b]indole (110 mg, 0.22 mmol) in CH_3OH(2 mL) was added HCl/Dioxane (6 N, 3 mL). The resulting solution was stirred at 5°C for 1 hour. Then it was diluted with EtOAc (40 mL), and the mixture was washed with sat. $NaHCO_3$(a.q.) and brine, and dried over anhydrous sodium sulfate. The organic phase was evaporated under reduced pressure to afford crude title product (84.9 mg) which was used in the next reaction without further purification.

[0392] Step 4: 3-(5-(5-(2,2,2-trifluoroethyl)-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propanal



[0393] To a solution of 3-(5-(5-(2,2,2-trifluoroethyl)-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propan-1-ol (90 mg, 0.23 mmol) in DMSO (2 mL) was added IBX (130.9 mg, 0.47 mL). The resulting mixture was stirred at 40 °C for 2 hours. The mixture was quenched by sat. $Na_2S_2O_3$ a.q. (5 mL) and sat. $NaHCO_3$ a.q. (5 mL). The mixture was extracted with EtOAc (20 mL x 5). The combined organic layer was dried over anhydrous sodium sulfate, concentrated under vacuum to afford crude desired product (89.5 mg) which was used in the next reaction without further purification.

[0394] Step 5: tert-butyl 4-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)pentyl)piperazine-1-carboxylate



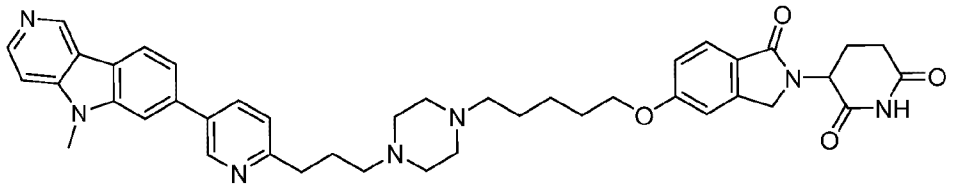
[0395] To a solution of 5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)pentanal (150 mg, 0.42 mmol) [prepared according to the procedures described above] in MeOH (5 mL) were added *tert*-butyl piperazine-1-carboxylate (77.9 mg, 0.42 mmol) and $NaBH_3CN$ (52.6 mg, 0.84 mmol). The resulting solution was stirred at 40°C for 2 hours. The solvent was evaporated under reduced pressure. The residue was diluted with EA (30 mL), and the mixture was washed with brine. The organic phase was dried over anhydrous sodium sulfate, filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM/MeOH= 60/1) to afford the desired product (200 mg, 90%yield).

[0396] Using BOC-deprotection and reductive amination procedures analogous to those described above, compounds of the steps 4 and 5 were converted into the final compound, 2-(2,6-dioxopiperidin-3-yl)-5-((5-(4-(3-(5-(5-(2,2,2-trifluoroethyl)-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propyl)piperazin-1-yl)pentyl)oxy)isoindoline-1,3-dione.

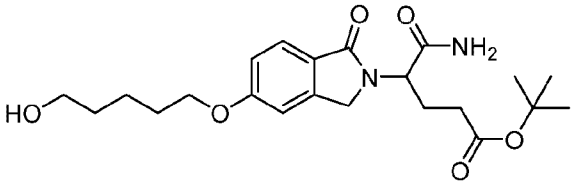
[0397] ^{1}H NMR (400 MHz, CD_3OD) δ 9.35 (s, 1H), 8.89 (s, 1H), 8.55 (d, J = 5.8 Hz, 1H), 8.40 (d, J = 8.0 Hz, 1H), 8.17 – 8.22 (m, 1H), 8.05 (s, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.74 (d, J = 5.6 Hz, 1H), 7.51 (d, J = 8.2 Hz, 1H), 7.40 (s, 1H), 7.33 (s, 1H), 5.40 (d, J = 9.1 Hz, 2H), 5.08 – 5.16 (m, 1H), 4.95 (s, 4H), 4.59 (s, 2H), 4.18 (t, J = 6.2 Hz, 1H), 2.91 – 3.00 (m, 2H), 2.58 – 2.91 (m, 9H), 2.12 – 2.18 (m, 1H), 2.06 (s, 2H), 1.89 (s, 2H), 1.69 (s, 2H), 1.57 (s, 2H). $(M+H)^+$ 796.3.

[0398] **Synthetic Scheme for Exemplary Compound 62**

[0399] 3-(5-((5-(4-(3-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propyl)piperazin-1-yl)pentyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione

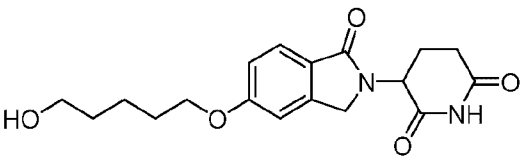


[0400] Step 1: tert-butyl 5-amino-4-(5-((5-hydroxypentyl)oxy)-1-oxoisoindolin-2-yl)-5-oxopentanoate



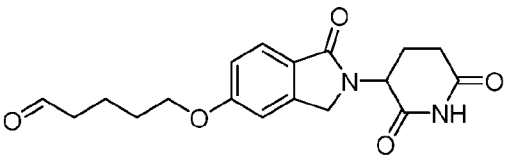
[0401] To a solution of tert-butyl 5-amino-4-(5-hydroxy-1-oxoisoindolin-2-yl)-5-oxopentanoate (500.0 mg, 1.0 eq), pentane-1,5-diol (187 mg, 1.2 eq) and PPh3 (590.0 mg, 1.5eq) in anhydrous tetrahydrofuran (50 mL) was added DIAD (455 mg, 2.25mmol, 1.5 eq). The resulting solution was stirred at room temperature for 16 hours. Then the reaction was quenched by the addition of water (100 mL). The resulting solution was extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (10:1) to afford the desired product (560 mg. 1.33mmol, 89%).

[0402] Step 2: 3-(5-((5-hydroxypentyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione



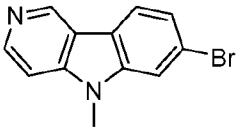
[0403] To a solution of tert-butyl 5-amino-4-(5-((5-hydroxypentyl)oxy)-1-oxoisoindolin-2-yl)-5-oxopentanoate (560 mg, 1.0 eq) in MeCN (20 mL) was added p-TsA (253 mg, 3.0 eq) at room temperature. The resulting solution was stirred at 90°C for 6 hours. Then the reaction was cooled to room temperature and quenched by the addition of water (10 mL). The resulting solution was extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with brine (10 mL x 2), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (10:1) to afford the desired product (190 mg, 0.55 mmol, 46%).

[0404] Step 3: 5-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)oxy)pentanal



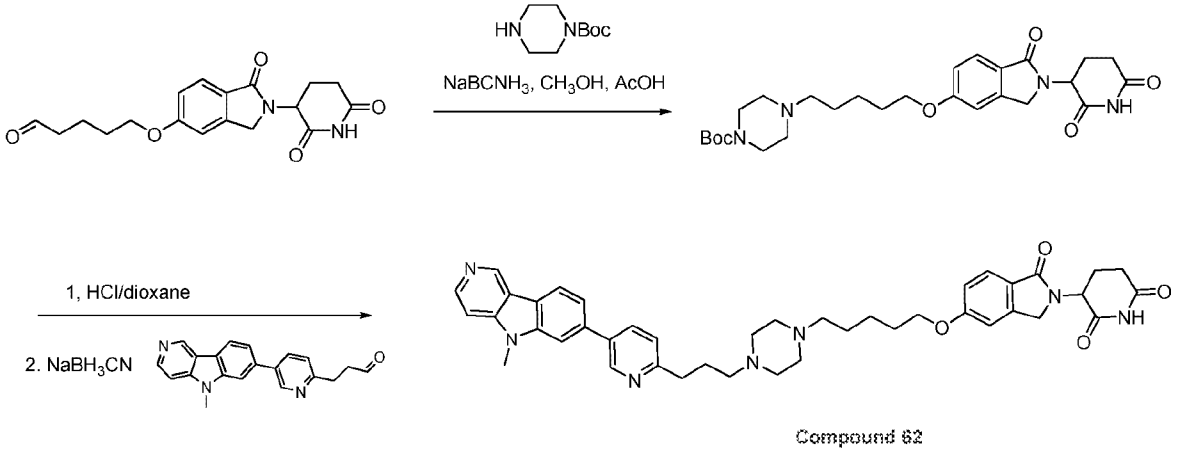
[0405] To a solution of 3-(5-((5-hydroxypentyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (190 mg, 1.0 equiv) in DCM (20 mL) was added IBX (100 mg, 2eq) at room temperature. The resulting solution was stirred at room temperature for 2 hours. Then the solid was filtered off and the filtrate was concentrated under vacuum to afford crude product (190 mg) which was used into next reaction without further purification.

[0406] Step 4: 7-bromo-5-methyl-5H-pyrido[4,3-b]indole]



[0407] To a solution of 7-bromo-5H-pyrido[4,3-b]indole (8.0 g, 32.4 mmol) in N,N-dimethylformamide (50 ml) was added sodium hydride (1.4 g, 35.6 mmol, 60% in mineral oil) at 0°C, and the reaction mixture was stirred at 0°C for 30 minutes. To the resulting mixture was added iodomethane (4.6 g, 32.4 mmol) at 0°C, and the reaction mixture was allowed to warm up to room temperature and stirred overnight. TLC showed the reaction was complete. The reaction mixture was quenched with water (30 ml) at 0°C, and extracted with ethyl acetate (50 ml x 2). The combined organic layers were washed with water (80 ml) then brine (90 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluted with 20-40% ethyl acetate in hexane) to afford 7-bromo-5-methyl-5H-pyrido[4,3-b]indole (6.0 g, yield 71%) as brown solid.

[0408] Using procedures described above for the **Exemplary Compound 61**, 5-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)oxy)pentanal was converted into the title compound, 3-(5-((5-(4-(3-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)propyl)piperazin-1-yl)pentyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione according to the scheme below.

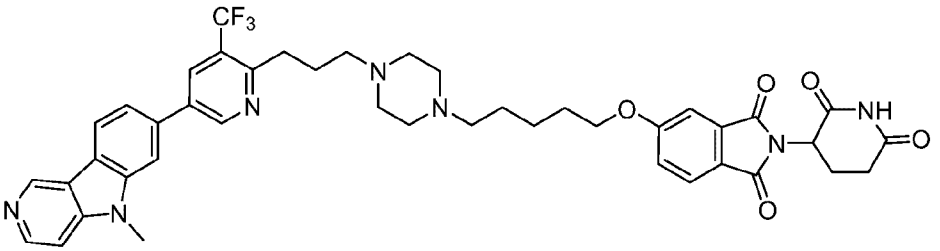


Compound 62

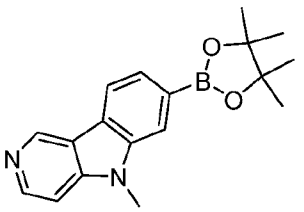
[0409] **Exemplary Compound 62**: ^{1}HNMR(400 MHz, MeOD): δ 9.27 (s, 1H), 8.86 (d, J=2.0 Hz, 1H), 8.46 (d, J=6.0 Hz, 1H), 8.33 (d, J=8.0 Hz, 1H), 8.16 (d, J=2.4 Hz, 1H), 7.90 (s, 1H), 7.59-7.70 (m, 3H), 7.47 (d, J=6.0 Hz, 1H), 7.03-7.09 (m, 2H), 5.06-5.12 (m, 1H), 4.42 (d, J=5.6 Hz, 2H), 4.07 (t, J=6.4 Hz, 2H), 3.99 (s, 3H), 2.89-2.96 (m, 3H), 2.51-2.75 (m, 13H), 2.12-2.24 (m, 1H), 2.01-2.03 (m, 3H), 1.82-1.84 (m, 2H), 1.52-1.63 (m, 6H). $(M+H)^+$ 714.3.

[0410] **Exemplary Compound 63**

[0411] 2-(2,6-dioxopiperidin-3-yl)-5-((5-(4-(3-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)-3-(trifluoromethyl)pyridin-2-yl)propyl)piperazin-1-yl)pentyl)oxy)isoindoline-1,3-dione

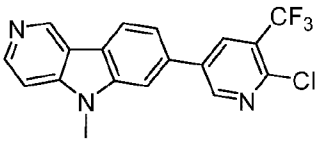


[0412] Step 1: 5-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5H-pyrido[4,3-b]indole



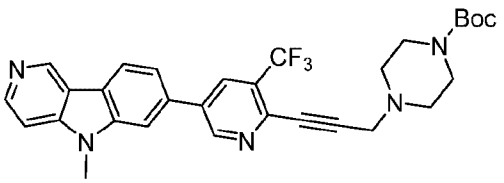
[0413] To a solution of 7-bromo-5-methyl-5H-pyrido[4,3-b]indole (150 mg, 0.577 mmol) in dioxane were added KOAc (114 mg, 1.15 mmol), $Pd(dppf)Cl_2$ (35 mg, 0.05 mmol), and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (294 mg, 1.15 mmol) subsequently. The resulting solution was heated to 100°C overnight under N_2. After cooling to room temperature, the reaction was quenched with water, the mixture was extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL). The organic phase was dried over Na_2SO_4, concentrated under vacuum to afford crude desired product (180 mg, crude), which was used into next reaction without further purification.

[0414] Step 2: 7-(6-chloro-5-(trifluoromethyl)pyridin-3-yl)-5-methyl-5H-pyrido[4,3-b]indole



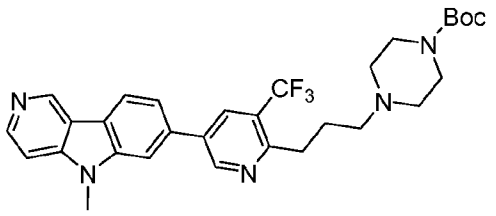
[0415] To a mixture of 5-bromo-2-chloro-3-trifluoromethylpyridine (135 mg, 0.7 mmol) and 5-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5H-pyrido[4,3-b]indole (180 mg, 0.58 mmol) in dioxane/H_2O (*v/v*=10/1, 10 mL) were added $Pd(dppf)_2Cl_2$ (20 mg, 10%) and CsF (180 mg, 1.16 mmol). The mixture was stirred at 80°C overnight. The solution was quenched with water. The mixture was extracted with ethyl acetate (20 mL), and the combined organic layers were washed with brine (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford the desired product (170 mg, 95% yield).

[0416] Step 3: tert-butyl 4-(3-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)-3-(trifluoromethyl)pyridin-2-yl)prop-2-yn-1-yl)piperazine-1-carboxylate



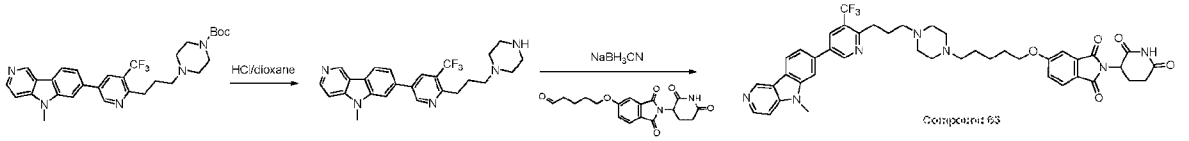
[0417] To a mixture of 7-(6-chloro-5-(trifluoromethyl)pyridin-3-yl)-5-methyl-5H-pyrido[4,3-b]indole (170 mg, 0.58 mmol) and tert-butyl 4-(prop-2-ynyl)piperazine-1-carboxylate (156 mg, 0.69 mmol) in DMF (10 mL) were added $Pd(PPh_3)_2Cl_2$ (17 mg, 10%), Cs_2CO_3 (378 mg, 1.16 mmol), DBU (30 mg, 0.116 mmol) and t-Bu_3P (25 mg, 0.116 mmol). The mixture was microwave-heated at 150°C for 10 minutes. The reaction mixture was quenched with water. The mixture was extracted with ethyl acetate (20 mL). The combined organic layers were washed with brine (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford the desired product (200 mg).

[0418] Step 4: tert-butyl 4-(3-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)-3-(trifluoromethyl)pyridin-2-yl)propyl)piperazine-1-carboxylate



[0419] To a solution of tert-butyl 4-(3-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)-3-(trifluoromethyl)pyridin-2-yl)prop-2-yn-1-yl)piperazine-1-carboxylate (200 mg) in ethanol was added Pd/C (20 mg). The mixture was stirred at 30°C under H_2 atmosphere (3Mpa) for 8 hours. The mixture was filtered through Celite, and the filtrate was concentrated under vacuum. The residue was purified by prep-HPLC to afford the desired product (25 mg).

[0420] Using BOC-deprotection and reductive amination procedures described above tert-butyl 4-(3-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)-3-(trifluoromethyl)pyridin-2-yl)propyl)piperazine-1-carboxylate was converted into the title compound, 2-(2,6-dioxopiperidin-3-yl)-5-((5-(4-(3-(5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)-3-(trifluoromethyl)pyridin-2-yl)propyl)piperazin-1-yl)pentyl)oxy)isoindoline-1,3-dione according to the scheme below.

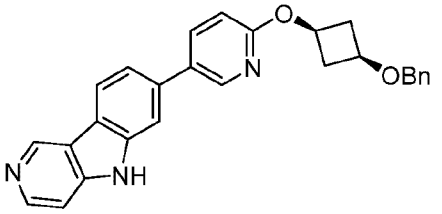


[0421] **Exemplary Compound 63**: ^1H NMR (400 MHz, CD_3OD): δ 9.25 (s, 1H), 8.45 (s, 1H), 8.23(d, J = 7.6 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.66 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.35 (s, 2H), 7.26-7.28 (m, 1H), 6.06 (s, 1H), 5.72 (s, 1H), 5.06–5.08 (m, 1H), 4.30

(d, J = 6.4 Hz, 1H), 4.11–4.15 (m, 2H), 3.90–3.94 (m, 4H), 3.70–3.74 (m, 2H), 3.03–3.06 (m, 2H), 2.82–2.88 (m, 4H), 2.71–2.75 (m, 6H), 2.51–2.55 (m, 3H), 2.05–2.25 (m, 2H), 1.82–1.86 (m, 2H), 1.61–1.63 (m, 2H), 1.51–1.52 (m, 2H). $(M+H)^+$ 796.2.

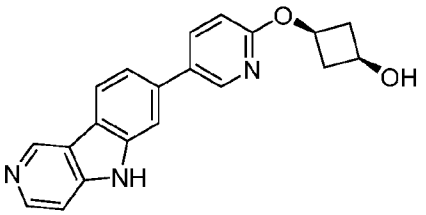
[0422] **Exemplary Compound 73**

[0423] Step 1: 7-(6-((1s,3s)-3-(benzyloxy)cyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole



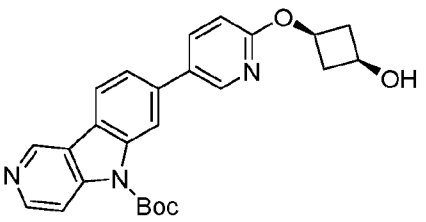
[0424] To a solution of 7-(6-fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole (1.1 g, 4.18 mmol) and (1s,3s)-3-(benzyloxy)cyclobutanol (745 mg, 4.18 mmol) in 1-methylpyrrolidin-2-one (2 ml) was added sodium hydride (60% in mineral oil) (334 mg, 8.35 mmol) at 0°C. The mixture was stirred at room temperature for 2 hours. TLC showed the reaction was complete. The mixture was partitioned between ethyl acetate (20 ml) and water (20 ml). The organic layer was collected, washed with brine (30 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluted with 2-5% methanol in dichloromethane) to afford 7-(6-((1s,3s)-3-(benzyloxy)cyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole (1.42 g, 82%) as white solid.

[0425] Step 2: (1s,3s)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutan-1-ol



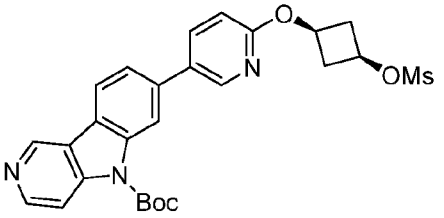
[0426] A mixture of 7-(6-((1s,3s)-3-(benzyloxy)cyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole (1.42 g, 3.37 mmol) and palladium on carbon (10%, 150 mg) in methanol (30 ml)-tetrahydrofuran (10 ml) was stirred at 50°C for 2 hours under hydrogen atmosphere (hydrogen balloon). TLC showed the reaction was complete. Palladium on carbon was removed through filtration and washed with methanol (10 ml x 2). The combined filtrate was concentrated under reduced pressure to afford (1s,3s)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutanol (1.57 g, crude) as white solid.

[0427] Step 3: tert-butyl 7-(6-((1s,3s)-3-hydroxycyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole-5-carboxylate



[0428] To a suspension of (1s,3s)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutanol (1.57 g, 4.27 mmol) and sodium carbonate (1.1 g, 10.69 mmol) in tetrahydrofuran (20 ml)-water (5 ml) was added di-tert-butyl carbonate (1.2 g, 5.55 mmol) at room temperature. The mixture was stirred at room temperature for 17 hours. TLC showed the reaction was complete. The mixture was concentrated and the residue was partitioned between ethyl acetate (20 ml) and water (30 ml). The organic layer was collected, washed with brine (20 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluted with 1-2% methanol in dichloromethane) to afford tert-butyl 7-(6-((1s,3s)-3-hydroxycyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole-5-carboxylate (1.1 g, two steps 73%) as white solid.

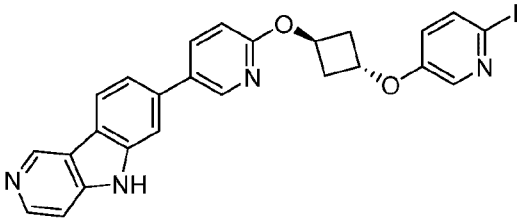
[0429] Step 4: tert-butyl 7-(6-((1s,3s)-3-((methylsulfonyl)oxy)cyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole-5-carboxylate



[0430] To a suspension of tert-butyl 7-(6-((1s,3s)-3-hydroxycyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole-5-carboxylate (500 mg, 1.16 mmol) and triethylamine (352 mg, 3.47 mmol) in dichloromethane (10 ml) was added methanesulfonyl chloride (530 mg, 4.63 mmol) at 0°C. The resulting mixture was allowed to warm up to room temperature and stirred at room temperature for 5 hours. TLC showed the reaction was completed. The mixture was diluted with dichloromethane (10 ml) and washed with water (10 ml). The organic layer was washed with brine (20 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford tert-butyl 7-(6-

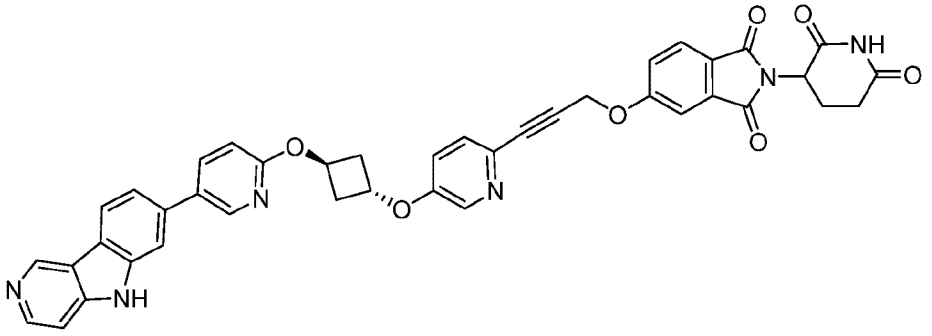
((1s,3s)-3-hydroxycyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole-5-carboxylate (700 mg, crude) which was used in next step without further purification.

[0431] Step 5: 7-(6-((1r,3r)-3-((6-iodopyridin-3-yl)oxy)cyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole



[0432] A mixture of tert-butyl 7-(6-((1s,3s)-3-hydroxycyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole-5-carboxylate (350 mg, 0.69 mmol), 6-iodopyridin-3-ol (155 mg, 0.69 mmol) and cesium carbonate (452 mg, 1.39 mmol) in dry N,N-dimethylformamide (4 ml) was stirred at 90°C for 12 hours. TLC showed the reaction was complete. The mixture was partitioned between ethyl acetate (30 ml) and water (40 ml). The organic layer was collected, washed with brine (30 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluted with 1-2% methanol in dichloromethane) to afford 7-(6-((1r,3r)-3-((6-iodopyridin-3-yl)oxy)cyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole (250 mg, 68%) as light yellow solid.

[0433] Step 6: [5-((3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione]



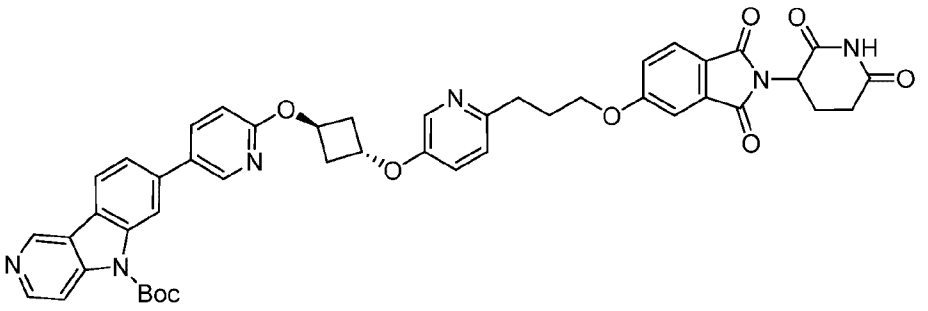
[0434] To a stirred solution of 7-(6-((1r,3r)-3-((6-iodopyridin-3-yl)oxy)cyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole (150 mg, 0.24 mmol), 2-(2,6-dioxopiperidin-3-yl)-5-(prop-2-yn-1-yloxy)isoindoline-1,3-dione (111 mg, 0.35 mmol) [prepared using procedure of step 1 from **Exemplary Compound 180**] and triethylamine (121 mg, 1.20 mmol) in N,N-dimethylformamide

(2 ml) were added Bis(triphenylphosphine)palladium(II) chloride (8 mg, 0.01 mmol) and cuprous iodide (2 mg, 0.01 mmol) at room temperature under nitrogen atmosphere; the mixture was degassed with nitrogen three times. The resulting mixture was stirred at 65°C under nitrogen overnight. TLC showed the reaction was complete. The mixture was partitioned between water (30 ml) and ethyl acetate (30 ml). The organic layer was collected and 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 column chromatography (eluted with 2% methanol in dichloromethane) to afford 5-((3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (45 mg, yield 26%) as white solid.

[0435] ^{1}H NMR (400 MHz, DMSOd-6): δ 2.04-2.07 (m, 1H), 2.57-2.77 (m, 6H), 2.86-2.93 (m, 1H), 5.10-5.14 (m, 2H), 5.32 (s, 2H), 5.39-5.48 (m, 1H), 6.97 (d, J = 8.0 Hz, 1H), 7.32-7.33 (m, 1H), 7.46-7.58 (m, 5H), 7.77 (s, 1H), 7.90 (d, J = 7.2 Hz ,1H), 8.14 (d, J = 7.2 Hz, 1H), 8.25(s, 1H), 8.30 (d, J = 7.6 Hz ,1H), 8.43 (s, 1H), 8.56 (s, 1H), 9.36 (s, 1H), 11.12 (s, 1H), 11.82 (s, 1H). $(M+H)^+$ 719.4.

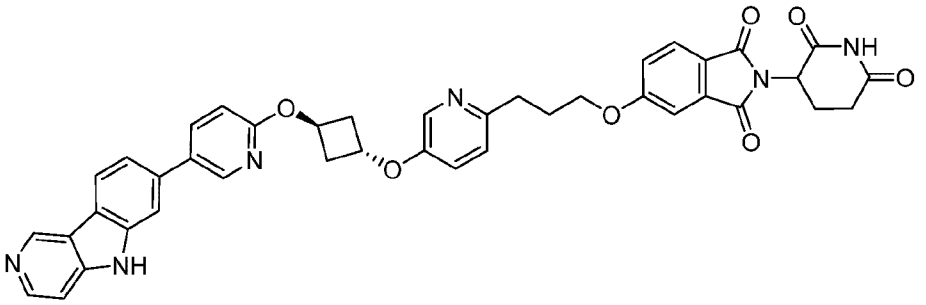
[0436] **Synthetic Scheme for Exemplary Compound 77**

[0437] Step 1: tert-butyl 7-(6-((1r,3r)-3-((6-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)propyl)pyridin-3-yl)oxy)cyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole-5-carboxylate



[0438] To a solution of tert-butyl 7-(6-((1r,3r)-3-((6-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)prop-1-yn-1-yl)pyridin-3-yl)oxy)cyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole-5-carboxylate (15 mg) in MeOH was added Pd/C. The solution was stirred at 30°C for 2 hours under H_2 (2 Mpa). The mixture was filtered through Celite, and the filtrate was concentrated under vacuum. The residue was purified by silica gel to afford the desired product (6 mg).

[0439] Step 2: 5-(3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)propoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione

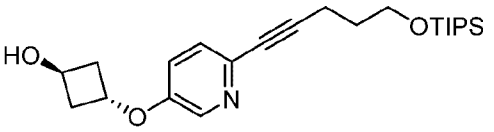


[0440] A solution of tert-butyl 7-(6-((1r,3r)-3-((6-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)propyl)238pyridin-3-yl)oxy)cyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole-5-carboxylate (6 mg) in DCM/TFA (2 mL/1 mL) was stirred at room tempereature for 4 hours. The solvent was removed under vacuum to afford 5-(3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)propoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (5.5 mg).

[0441] ^{1}H NMR (400 MHz, CD_3OD): δ 9.56 (s,1H), 8.54–8.56 (m, 2H), 8.45 (d, J = 8.4 Hz, 1H), 8.37 (d, J = 2.4 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.8 Hz, 2H), 7.81 (d, J = 8.4 Hz, 1H), 7.79 (s, 1H), 7.76–7.78 (d, J = 8 Hz, 1H), 7.29 (s, 1H), 7.21(d, J = 8.0 Hz, 1H), 6.98(d, J = 8.0 Hz, 1H), 5.48–5.52 (m, 1H), 5.32–5.34 (m, 1H), 5.18–5.22 (m, 1H), 5.06–5.10 (m, 1H), 4.25–4.28 (m, 2H), 3.21–3.23 (m, 3H), 2.78–2.81 (m, 5H), 2.67–2.70 (m, 2H), 2.30–2.33 (m, 2H), 2.17–2.19 (m, 1H), 1.97–2.07 (m, 3H). $(M+H)^+$ 723.5.

[0442] **Synthetic Scheme for Exemplary Compound 94**

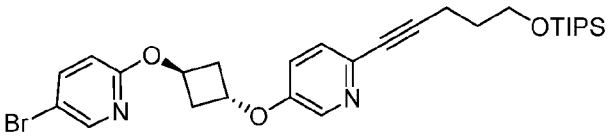
[0443] Step 1: (1r,3r)-3-((6-(5-((triisopropylsilyl)oxy)pent-1-yn-1-yl)pyridin-3-yl)oxy)cyclobutan-1-ol



[0444] To a solution of (1r,3r)-3-((6-bromopyridin-3-yl)oxy)cyclobutan-1-ol (530 mg, 2.17 mmol) in dry THF (10 mL) was added triisopropyl(pent-4-yn-1-yloxy)silane (626 mg, 2.61 mmol), TEA (1.1 g, 10.86 mmol), CuI (45 mg, 0.24 mmol) and $Pd(PPh_3)_2Cl_2$ (110 mg, 4.34 mmol) at 25°C under N_2. The resulting solution was stirred at 45°C for 16 hours. The reaction was diluted with H_2O (10 mL). The resulting mixture was extracted with EtOAc (10 mL x 2). The combined

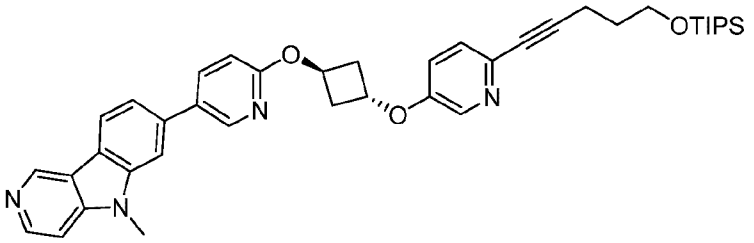
organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified with silica gel column to afford the desired product (1r,3r)-3-((6-(5-((triisopropylsilyl)oxy)pent-1-yn-1-yl)pyridin-3-yl)oxy)cyclobutan-1-ol (600 mg, 68% yield) as a colorless oil.

[0445] Step 2: 5-bromo-2-((1r,3r)-3-((6-(5-((triisopropylsilyl)oxy)pent-1-yn-1-yl)pyridin-3-yl)oxy)cyclobutoxy)pyridine



[0446] To a solution of (1r,3r)-3-((6-(5-((triisopropylsilyl)oxy)pent-1-yn-1-yl)pyridin-3-yl) oxy)cyclobutan-1-ol (300 mg, 0.74 mmol) in DMF (5 mL) was added NaH (45 mg, 1.11 mmol) at 0°C. The reaction was stirred at 0 °C for 0.5 hours, and 5-bromo-2-fluoropyridine (144 mg, 0.82 mmol) was added dropwise at 0 °C. The reaction was stirred at 20 °C for 2 hours. The reaction was diluted with a solution of H_2O (10 mL). The resulting mixture was extracted with EtOAc (10 mL x 2), the combined organic layers were dried over anhydrous sodium sulfate and concentration. The residue was purified with silica gel column to afford the desired product 5-bromo-2-((1r,3r)-3-((6-(5-((triisopropylsilyl)oxy)pent-1-yn-1-yl)pyridin-3-yl)oxy)cyclobutoxy)pyridine (240 mg, 58% yield) as a white solid.

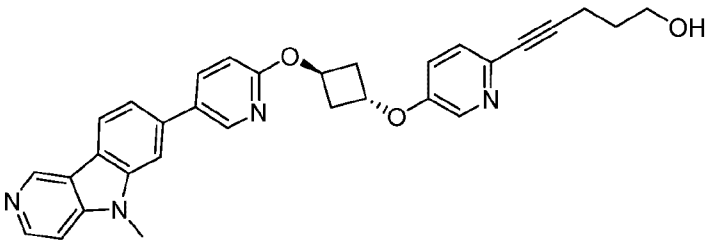
[0447] Step 3: 5-methyl-7-(6-((1r,3r)-3-((6-(5-((triisopropylsilyl)oxy)pent-1-yn-1-yl)pyridin-3-yl)oxy)cyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole



[0448] To a solution of 5-bromo-2-((1r,3r)-3-((6-(5-((triisopropylsilyl)oxy)pent-1-yn-1-yl) pyridin-3-yl)oxy)cyclobutoxy)pyridine (180 mg, 0.32 mmol) in 1,4-dioxane (5 ml) and H_2O (1 mL) was added 5-methyl-7-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan -2-yl)pyridin-3-yl)-5H-pyrido[4,3-b]indole (119 mg, 0.39 mmol), CsF (147 mg, 0.96 mmol) and Pd(aMphos)Cl_2 (34 mg, 0.06 mmol) at 15 °C under N_2. The resulting mixture was stirred at 80 °C for 5 hours. The mixture was quenched with H_2O (20 mL), extracted with EtOAc (10 mL x 2). Then the combined organic layers were washed with brine (20 mL x 2), dried over anhydrous sodium sulfate and concentrated.

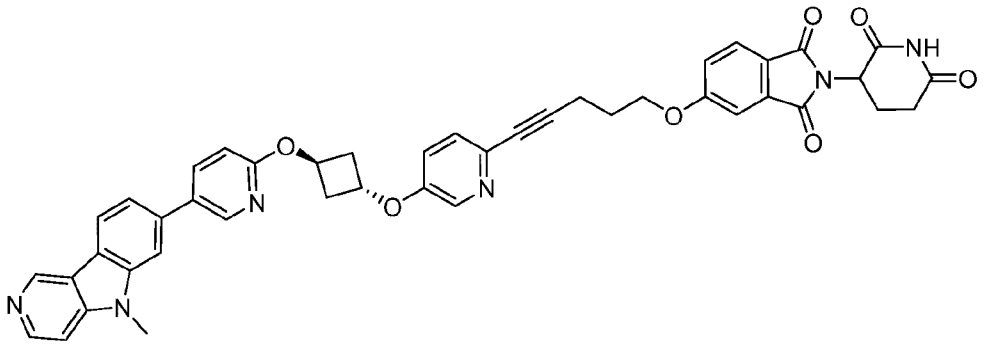
The residue was purified with silica gel column to afford the desired product 5-methyl-7-(6-((1r,3r)-3-((6-(5-((triisopropylsilyl)oxy)pent-1-yn-1-yl)pyridin-3-yl)oxy)cyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole (80 mg, 38% yield).

[0449] Step 4: 5-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)pent-4-yn-1-ol



[0450] To a solution of 5-methyl-7-(6-((1r,3r)-3-((6-(5-((triisopropylsilyl)oxy)pent-1-yn-1-yl)pyridin-3-yl)oxy)cyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole (90 mg, 0.14 mmol) in dry THF (10 mL) was added 1 M TBAF in THF (1 mL, 0.7 mmol) under N_2 at 15 °C. The mixture was stirred at 40 °C for 1 hour under N_2 balloon. The mixture was concentrated. The residue was purified with prep-TLC to afford the desired product 5-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)pent-4-yn-1-ol (30 mg, 43% yield) as a white solid.

[0451] Step 5: 2-(2,6-dioxopiperidin-3-yl)-5-((5-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)pent-4-yn-1-yl)oxy)isoindoline-1,3-dione



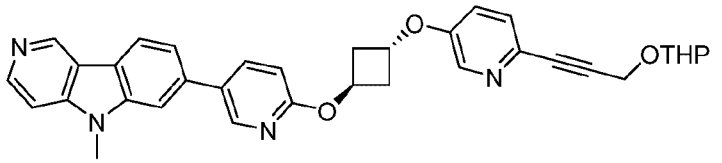
[0452] To a solution of 5-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin- 2-yl)oxy)cyclobutoxy)pyridin-2-yl)pent-4-yn-1-ol (25 mg, 0.05 mmol) in dry THF (2 mL) was added 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione (20 mg, 0.07 mmol), PPh_3 (40 mg, 0.14 mmol) at 15 °C under N_2. DIAD (32 mg, 0.14 mmol) was added to the mixture at 40°C under N_2. The resulting mixture was stirred at 40°C for 0.5 hours. Cooled the mixture to 20 °C and quenched with H_2O (10 mL), extracted with EtOAc (10 mL x 2). Then the combined organic

layers were washed with brine (20 mL x 5), dried over anhydrous sodium sulfate and concentrated. The residue was purified with prep-TLC to afford the desired product 2-(2,6-dioxopiperidin-3-yl)-5-((5-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)pent-4-yn-1-yl)oxy)isoindoline-1,3-dione (22 mg, 58% yield) as a white solid.

[0453] ^{1}HNMR (400 MHz, DMSO-d_6): δ: 11.04(s, 1H), 9.29(s, 1H), 8.58(d, J = 2.0 Hz, 1H), 8.43(d, J = 5.6 Hz, 1H), 8.25(d, J = 8.0 Hz, 1H), 8.12-8.16(m, 2H), 7.92(s, 1H), 7.78(d, J = 7.6 Hz, 1H), 7.56(d, J = 6.0 Hz, 2H), 7.40(s, 1H), 7.33(d, J = 8.4 Hz, 2H), 7.20-7.22(m, 1H), 6.92(d, J = 4.4 Hz, 1H), 5.37(s, 1H), 5.01-5.37(m, 2H), 4.25(t, J = 6.0 Hz, 2H), 3.89(s, 3H), 2.43-2.65(m, 9H), 1.98(t, J = 6.4 Hz, 3H). $(M+H)^+$ 761.5.

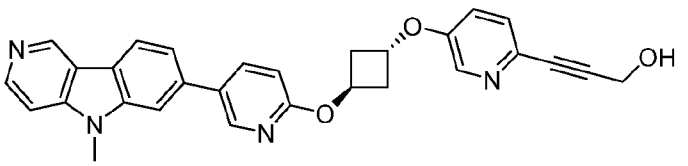
[0454] **Synthetic Scheme for Exemplary Compound 117**

[0455] Step 1: 5-methyl-7-(6-((1r,3r)-3-((6-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridin-3-yl)oxy)cyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole



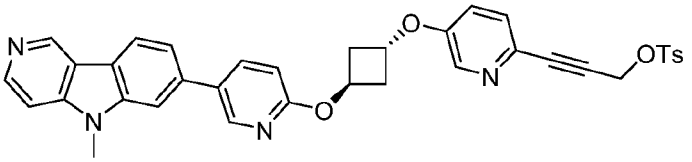
[0456] A mixture of (1s,3s)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutyl methanesulfonate (480mg, 1.1mmol) [prepared using procedure described in step 4 of **Exemplary Compound 73**], 6-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridin-3-ol (256 mg, 1.1 mmol) and cesium carbonate (715 mg, 2.2 mmol) in N,N-dimethylformamide (15 ml) was stirred at 70°C for 16 hours. TLC showed the reaction was complete. The reaction mixture was partitioned between water (20 ml) and ethyl acetate (40 ml). The organic layer was collected, washed with brine (50 ml), dried over sodium sulfate and evaporated under reduced pressure to give a crude residue which was purified by silica gel flash column chromatography (eluted with 0-30% ethyl acetate in hexane) to afford 5-methyl-7-(6-((1r,3r)-3-((6-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridin-3-yl)oxy)cyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole (350 mg, yield 57%) as white solid.

[0457] Step 2: 3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-ol



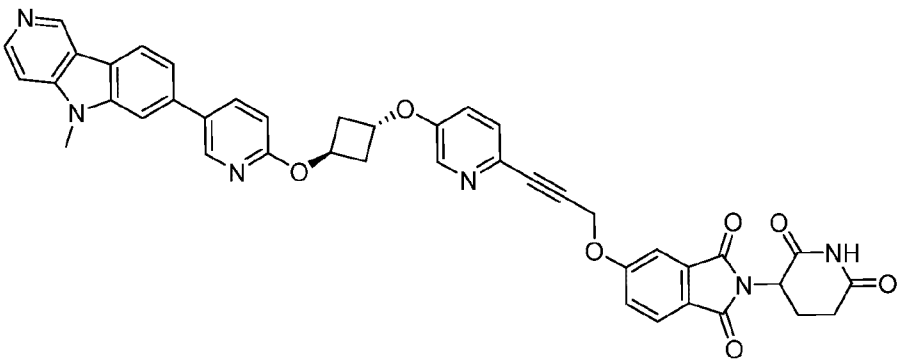
[0458] To the solution of 5-methyl-7-(6-((1r,3r)-3-((6-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridin-3-yl)oxy)cyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole (350mg, 0.62mmol) in tetrahydrofuran (10 ml) was added aqueous hydrogen chloride (5 ml, 2M), and the reaction mixture was stirred at room temperature for 1 hours. TLC showed the reaction was complete. The reaction mixture was quenched with aqueous sodium bicarbonate solution (20ml), and the reaction mixture was extracted with ethyl acetate (20 ml). The organic layer was collected, and the aqueous layer was extracted with ethyl acetate (10 ml x 2). The combined organic layers were washed with brine (10 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give 3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-ol (270 mg, crude) as white solid which was used in the next step without purification.

[0459] Step 3: 3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate



[0460] A mixture of 3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-ol (200 mg, crude), triethylamine (127 mg, 1.26 mmol) and 4-methyl-benzenesulfonyl chloride (120 mg, 0.63 mmol) in dichloromethane (10 ml) was stirred at room temperature for 1 hour. The reaction mixture was quenched with water (20 ml), extracted with dichloromethane (30ml). The organic layer was washed with brine (20 ml), dried over sodium sulfate and evaporated under reduced pressure to give a crude residue which was purified by silica gel flash column chromatography (eluted with 5% methanol in dichloromethane) to afford 3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate (130 mg, yield 49%) as white solid.

[0461] Step 4: 2-(2,6-dioxopiperidin-3-yl)-5-((3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)isoindoline-1,3-dione



[0462] To a solution of 3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate(130 mg, 0.21 mmol), potassium carbonate (85 mg, 0.62 mmol) and 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione (57 mg, 0.21 mmol) in N,N-dimethylformamide (10 ml) was added potassium iodide (35 mg, 0.21 mmol) under nitrogen atmosphere. The resulting mixture was warmed to 50°C and stirred for 16 hours. TLC showed the reaction was complete. The reaction mixture was partitioned between water (20 ml) and ethyl acetate (20 ml).The organic layer was collected, washed with brine (10 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the crude product which was purified by silica gel flash column chromatography (eluted with 8% methanol in dichloromethane) to afford 2-(2,6-dioxopiperidin-3-yl)-5-((3-(5-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)isoindoline-1,3-dione (21.3 mg, yield 14%) as yellow solid.

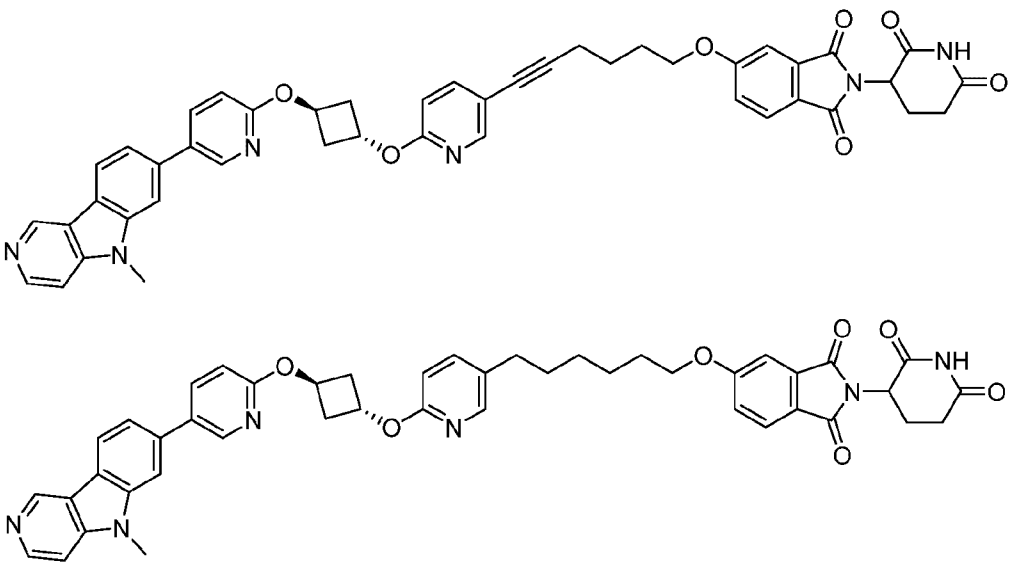
[0463] ^{1}H NMR (400 MHz,CD_3OD):δ 1.92-1.94 (m, 1H), 2.02-2.10 (m, 2H), 2.62-2.65 (m, 5H), 3.90 (s, 3H), 4.97-5.02 (m, 2H), 5.10 (s, 2H), 5.37 (t, J = 6 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 7.20-7.22 (m, 1H), 7.34-7.41 (m, 2H), 7.45 (d, J = 2.0 Hz, 1H), 7.50-7.56 (m, 2H), 7.75-7.77 (m, 2H), 8.02-8.06 (m, 2H), 8.21 (d, J = 8.0 Hz, 1H), 8.37 (d, J = 6.0 Hz, 1H), 8.42 (d, J = 2.4 Hz, 1H), 9.18 (s, 1H). $(M+H)^+$ 733.4.

[0464] Using procedures analogous to those described above for **Compound 83** (method of **Compound 94**), **Compound 95**, **Compound 97** (method of **Compound 94**), **Compound 98**, **Compound 183** (method of **Compound 73**), **Compound 204** (combination of methods of **Compound 73** and **Compound 176**) were prepared.

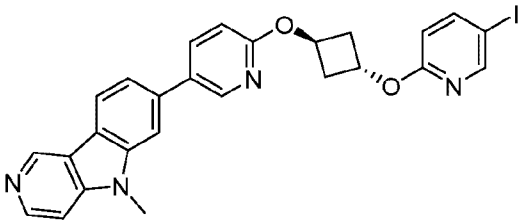
[0465] **Synthetic Scheme for Exemplary Compound 102** and **Exemplary Compound 110**

[0466] 2-(2,6-dioxopiperidin-3-yl)-5-((6-(6-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-3-yl)hex-5-yn-1-yl)oxy)isoindoline-1,3-dione

(**Exemplary Compound 102**) and 2-(2,6-dioxopiperidin-3-yl)-5-((6-(6-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-3-yl)hexyl)oxy)isoindoline-1,3-dione (**Exemplary Compound 110**)



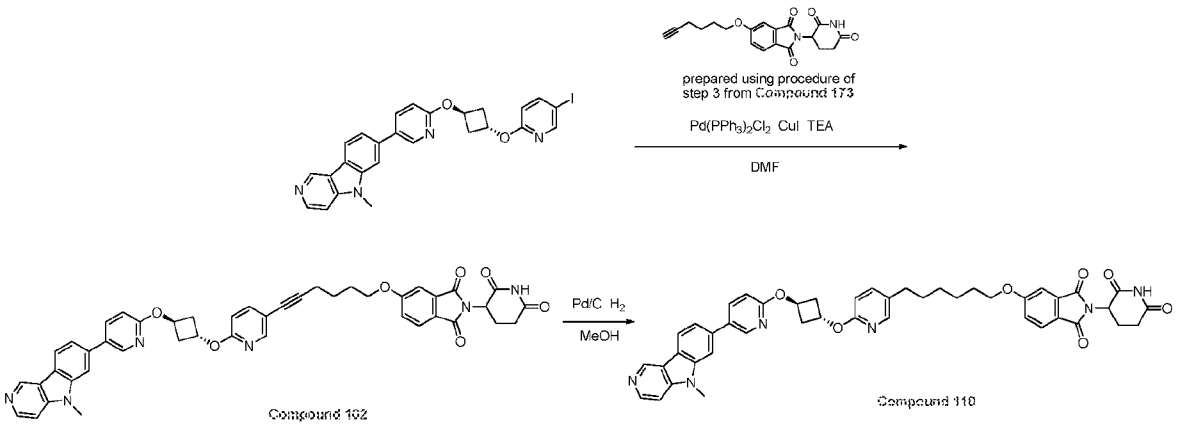
[0467] Step 1: 7-(6-((1r,3r)-3-((5-iodopyridin-2-yl)oxy)cyclobutoxy)pyridin-3-yl)-5-methyl-5H-pyrido[4,3-b]indole



[0468] To a solution of (1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutanol (100 mg, 0.29 mmol) [prepared by using procedures analogous to the ones described for steps 1 and 2 for **Compound 73**] in 1-methylpyrrolidin-2-one (5 ml) was added sodium hydride (60% in mineral oil) (58 mg, 1.45 mmol) at 0°C, and the reaction mixture was stirred for 1 hour. Then to the reaction mixture 2-fluoro-5-iodopyridine (65 mg, 0.29 mmol) was added, and the mixture was stirred at room temperature for 2 hours. TLC showed the reaction complete. The reaction was quenched with water (10 ml) at 0°C, extracted with ethyl acetate (20 ml x 2). The combined organic layers were washed with water (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 (eluted with 5% methanol in dichloromethane) to

afford 7-(6-((1r,3r)-3-((5-iodopyridin-2-yl)oxy)cyclobutoxy)pyridin-3-yl)-5-methyl-5H-pyrido[4,3-b]indole (100 mg, yield 63%) as a white solid.

[0469] Using procedures described for **Compound 73**, 7-(6-((1r,3r)-3-((5-iodopyridin-2-yl)oxy)cyclobutoxy)pyridin-3-yl)-5-methyl-5H-pyrido[4,3-b]indole was converted to the title compounds, 2-(2,6-dioxopiperidin-3-yl)-5-((6-(6-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-3-yl)hex-5-yn-1-yl)oxy)isoindoline-1,3-dione (**Compound 102**) and 2-(2,6-dioxopiperidin-3-yl)-5-((6-(6-((1r,3r)-3-((5-(5-methyl-5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-3-yl)hexyl)oxy)isoindoline-1,3-dione (**Compound 110**) according to the scheme below.

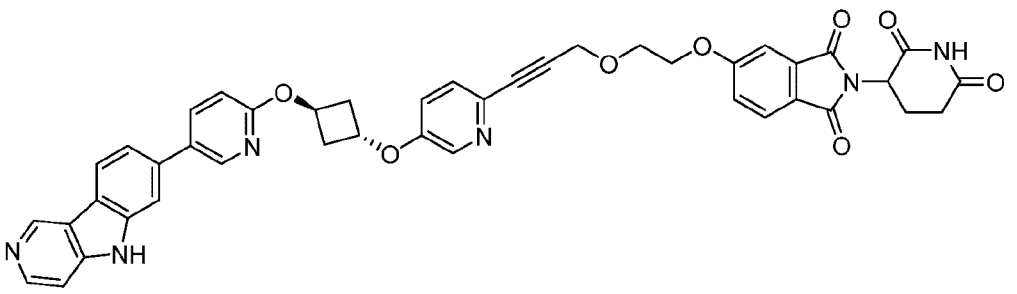


[0470] **Compound 102**: ^{1}HNMR (400 MHz, DMSO-d_6): δ 1.73 (d, J = 7.2 Hz, 2H), 1.91 (d, J = 7.2 Hz, 2H), 2.01-2.08 (m, 1H), 2.51-2.67 (m, 8H), 2.83-2.94 (m, 1H), 3.96 (s, 3H), 4.24 (t, J = 6.0 Hz, 2H), 5.12 (dd, J = 12.8, 5.2 Hz, 1H), 5.31-5.52 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 8.6 Hz, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.44 (s, 1H), 7.75-7.58 (m, 3H), 7.82 (d, J = 8.2 Hz, 1H), 7.99 (s, 1H), 8.10-8.28 (m, 2H), 8.33 (d, J = 8.2 Hz, 1H), 8.52 (s, 1H), 8.64 (d, J = 1.6 Hz, 1H), 9.40 (s, 1H),11.11 (s, 1H). $(M+H)^+$ 775.5

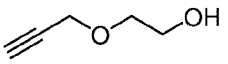
[0471] **Compound 110**: ^{1}H NMR (400 MHz,DMSO-d_6): δ 1.36 (d, J = 7.6 Hz, 2H), 1.45 (d, J = 6.8 Hz, 2H), 1.52-1.61 (m, 2H), 1.70-1.80 (m, 2H), 1.98-2.02 (m, 3H), 2.54-2.70 (m, 6H), 2.89 (t, J = 16.6 Hz, 1H), 3.96 (s, 3H), 4.16 (d, J = 5.0 Hz, 2H), 5.12 (dd, J = 12.8, 4.4 Hz, 1H), 5.36-5.43 (m, 2H), 6.77 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H),7.34 (d, J = 8.8 Hz, 1H), 7.42 (s, 1H),7.60-7.64 (m, 3H), 7.83 (d, J = 8.0 Hz, 1H), 7.97 (dd, J = 14.0, 6.4 Hz, 2H), 8.33 (d, J = 8.4 Hz, 1H), 8.21 (d, J = 8.0 Hz, 1H), 8.50 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 9.37 (s, 1H), 11.11 (s, 1H). $(M+H)^+$ 779.5

[0472] **Synthetic Scheme for Exemplary Compound 173**

[0473] 5-(2-((3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)ethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione

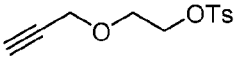


[0474] Step 1: 2-(prop-2-yn-1-yloxy)ethan-1-ol



[0475] To a stirred mixture of sodium hydride (60% in mineral oil, 115 mg, 2.8 mmol) in anhydrous N,N-dimethylformamide (20 ml) at 0°C was added ethane-1,2-diol (3.9 g, 63 mmol) and stirred at 0°C for 0.5 hour. To the resulting mixture was added 3-bromoprop-1-yne (5.0 g, 42 mmol) at 0°C and stirred at 50°C overnight. TLC showed the reaction was complete. The reaction mixture was quenched with ice water (20 ml) and partitioned between ethyl acetate (80 ml) and water (100 ml). The organic layer was collected, and the aqueous layer was extracted with ethyl acetate (50 ml x 2). The combined organic layers were washed with brine (80 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluted with 0-20 % ethyl acetate in hexane) to afford 2-(prop-2-yn-1-yloxy)ethanol (3.4 g, yield 80%) as colorless oil.

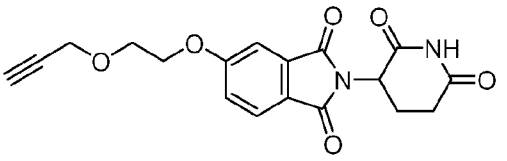
[0476] Step 2: 2-(prop-2-yn-1-yloxy)ethyl 4-methylbenzenesulfonate



[0477] To a stirred solution of 2-(prop-2-yn-1-yloxy)ethanol (1 g, 10 mmol), triethylamine (3 g, 3 mmol) and N,N-dimethylpyridin-4-amine (20 mg, 1 mmol), in dichloromethane (20 ml) was added p-toluenesulfonic acid 2.9 g, 15 mmol) at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane (20 ml), washed with brine (50 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude residue. It was purified by silica

gel flash column chromatography (eluent 10-20 % ethyl acetate in hexane) to afford 2-(prop-2-yn-1-yloxy)ethyl 4-methylbenzenesulfonate (700 mg, yield: 40%) as light yellow oil.

[0478] Step 3: 2-(2,6-dioxopiperidin-3-yl)-5-(2-(prop-2-yn-1-yloxy)ethoxy)isoindoline-1,3-dione



[0479] To a stirred solution of 2-(prop-2-yn-1-yloxy)ethyl 4-methylbenzenesulfonate (700 mg, 2.8 mmol) and potassium carbonate (1.1 g, 8.3 mmol) in N,N-dimethylformamide (15 ml) was added 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione (755 mg, 2.8 mmol) at room temperature. The resulting mixture was stirred at 50°C overnight. TLC showed the reaction was complete. The mixture solution was cooled to room temperature. The reaction mixture was partitioned between ethyl acetate (20 ml) and water (30 ml); the organic layer was collected and the aqueous layer was extracted with ethyl acetate (20 ml x 2). The combined organic layers were washed with brine (30 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluted with 0-50 % ethyl acetate in hexane) to afford 2-(2,6-dioxopiperidin-3-yl)-5-(2-(prop-2-yn-1-yloxy)ethoxy)isoindoline-1,3-dione (290 mg, yield 30%) as light yellow solid.

[0480] 2-(2,6-dioxopiperidin-3-yl)-5-(2-(prop-2-yn-1-yloxy)ethoxy)isoindoline-1,3-dione was reacted with 7-(6-((1r,3r)-3-((6-iodopyridin-3-yl)oxy)cyclobutoxy)pyridin-3-yl)-5H-pyrido[4,3-b]indole using procedure described for **Compound 73** to produce the title compound, 5-(2-((3-(5-((1r,3r)-3-((5-(5H-pyrido[4,3-b]indol-7-yl)pyridin-2-yl)oxy)cyclobutoxy)pyridin-2-yl)prop-2-yn-1-yl)oxy)ethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione.

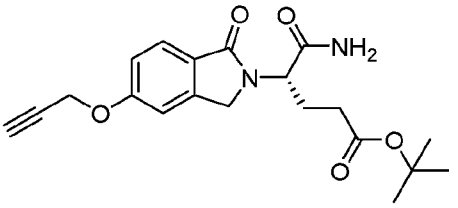
[0481] ^{1}H NMR (400 MHz, DMSO-*d6*): δ 2.02-2.08 (m, 1H), 2.52-2.76 (m, 6H), 2.85-2.93 (m, 1H), 3.89-3.95 (m, 2H), 4.37-4.42 (m, 2H), 4.49 (s, 2H), 5.06-5.14 (m, 2H), 5.40-5.47 (m, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 7.30-7.33 (m, 1H), 7.38-7.40 (m, 1H), 7.46-7.48 (m, 2H), 7.62-7.64 (m, 2H), 7.82-7.84 (m, 2H), 8.14-8.17 (m, 1H), 8.24 (d, *J* = 2.8 Hz, 1H), 8.36-8.38 (m, 1H), 8.49 (d, *J* = 6 Hz, 1H), 8.58 (d, *J* = 2.0 Hz, 1H), 9.47 (s, 1H), 11.11 (s, 1H), 12.14-12.28 (m, 1H). $(M+H)^+$ 763.5.

[0482] Using procedures analogous to those described above **Compounds 110** (method of **Compound 102**), **124**, **144** (method of **Compound 102**), **145**, **146**, **147** (method of **Compound**

94), **172** (method of **Compound 73**), **179** (method of **Compound 173**), **188** (method of **Compound 173**), **189** (method of **Compound 73**) were prepared.

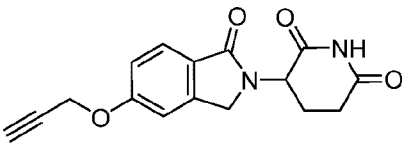
[0483] Synthetic Scheme for Exemplary Compound 180

[0484] Step 1: tert-butyl (S)-5-amino-5-oxo-4-(1-oxo-5-(prop-2-yn-1-yloxy)isoindolin-2-yl)pentanoate



[0485] To a stirred solution of (S)-tert-butyl 5-amino-4-(5-hydroxy-1-oxoisoindolin-2-yl)-5-oxopentanoate (450 mg, 1.35 mmol), and 3-bromoprop-1-yne (192 mg, 1.62 mmol) in N,N-dimethylformamide (4 ml) was added potassium carbonate (372 mg, 2.69 mmol) and potassium iodide (22.4 mg, 0.135 mmol), and the mixture was stirred at 50°C overnight under nitrogen. LCMS showed formation of desired product. The mixture was partitioned between ethyl acetate (50 ml) and water (30 ml). The organic layer was washed with brine (30 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluted with 50% ethyl acetate in hexane and added 5% methanol) to afford (S)-tert-butyl 5-amino-5-oxo-4-(1-oxo-5-(prop-2-yn-1-yloxy)isoindolin-2-yl)pentanoate (489 mg, yield 97%) as colorless oil.

[0486] Step 2: 3-(1-oxo-5-(prop-2-yn-1-yloxy)isoindolin-2-yl)piperidine-2,6-dione



[0487] To a stirred solution of (S)-tert-butyl 5-amino-5-oxo-4-(1-oxo-5-(prop-2-yn-1-yloxy)isoindolin-2-yl)pentanoate (325 mg, 0.873 mmol) in anhydrous tetrahydrofuran (20 ml) was added dropwise potassium tert-butoxide (1N, in THF) (107.7 mg, 0.96 mmol) at 0°C under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 20 minutes. LCMS showed formation of desired product. The reaction mixture was quenched with water (20 ml), and extracted with ethyl acetate (50 ml). The organic layer was collected, washed with water (20 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluted with 50% ethyl

DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.

CECI EST LE TOME __1___ DE __2 __

NOTE: Pour les tomes additionels, veillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1___ OF __2___

NOTE: For additional volumes please contact the Canadian Patent Office.

Claims:

1. A bifunctional compound having the chemical structure:

ULM—L—PTM,

or a pharmaceutically acceptable salt thereof,

wherein:

(a) the L is a chemical linking moiety represented by the formula :-$(A^L)_q$-, wherein:

$(A^L)_q$ is a group that is coupled to the ULM and the PTM;

q is an integer greater than or equal to 1;

each A^L is selected from $CR^{L1}R^{L2}$, 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, C_{3-11}cycloalkyl optionally substituted with 1-6 R^{L1} and/or R^{L2} groups, C_{3-11}heterocyclyl optionally substituted with 1-6 R^{L1} and/or R^{L2} groups, aryl optionally substituted with 1-6 R^{L1} and/or R^{L2} groups, and heteroaryl optionally substituted with 1-6 R^{L1} and/or R^{L2} groups, where R^{L1} or R^{L2}, each independently are optionally linked to other groups to form cycloalkyl and/or heterocyclyl moiety, optionally substituted with 1-4 R^{L5} groups; and

R^{L1}, R^{L2}, R^{L3}, R^{L4} and R^{L5} are, each independently, H, halogen, 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_{3-8}cycloalkyl, SC_{3-8}cycloalkyl, NHC_{3-8}cycloalkyl, $N(C_{3-8}cycloalkyl)_2$, $N(C_{3-8}cycloalkyl)(C_{1-8}alkyl)$, OH, NH_2, SH, SO_2C_{1-8}alkyl, 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($C_{1-8}alkyl)_2$, COC_{1-8}alkyl, CO_2H, CN, CF_3, CHF_2, CH_2F, NO_2, 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 $SO_2N(C_{1-8}alkyl)_2$, or NH SO_2NH_2;

(b) the ULM is:

(i) represented by the structure:

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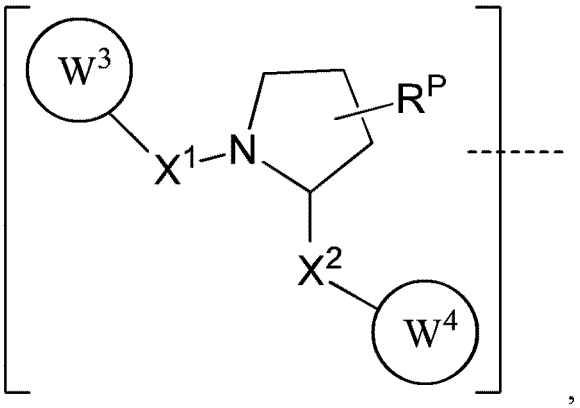

wherein:

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

R^{Y3} and R^{Y4} are each independently selected from: H; and linear or branched C_{1-6} alkyl, optionally substituted by 1 or more halo or C_{1-6} alkoxyl;

R^P is 1, 2, or 3 groups, each independently selected from H, halogen, -OH, and C_{1-3} alkyl;

W^3 is selected from the group of an optionally substituted –T-$N(R^{1a}R^{1b})$, an optionally substituted –T-$N(R^{1a}R^{1b})X^3$, –T-aryl, an optionally substituted –T-heteroaryl, an optionally substituted –T-heterocyclyl, an optionally substituted -NR^1-T-aryl, an optionally substituted -NR^1-T-heteroaryl, and an optionally substituted -NR^1-T-heterocyclyl;

X^3 is C=O, R^1, R^{1a}, or R^{1b};

R^1, R^{1a}, and R^{1b} are each independently selected from: H; linear or branched C_1-C_6 alkyl group optionally substituted by 1 or more halogen or -OH groups; $R^{Y3}C$=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; $N(R^{Y3}R^{Y4})SO$; and $N(R^{Y3}R^{Y4})SO_2$;

T is selected from an optionally substituted alkyl, $–(CH_2)_n$- group, wherein each one of the methylene groups is optionally substituted with one or two substituents selected from halogen, methyl, a linear or branched C_1-C_6 alkyl group optionally substituted by 1 or more halogen or -OH groups, and an amino acid side chain optionally substituted;

n is 0, 1, 2, 3, 4, 5, or 6;

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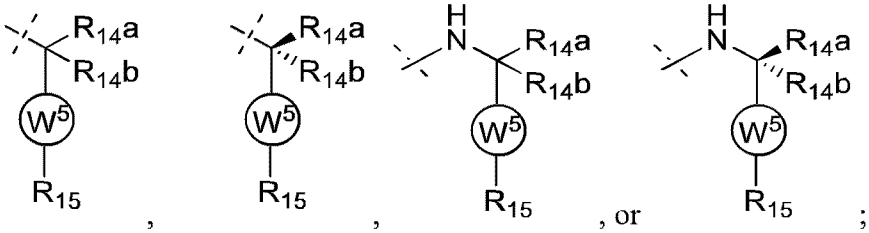
W^4 is  , or ;

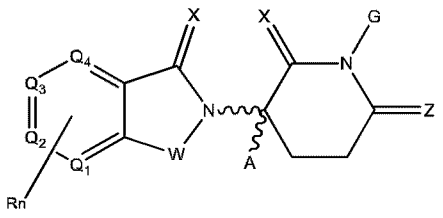
R_{14a} and R_{14b}, are each independently selected from H, haloalkyl, and optionally substituted alkyl;

W^5 is selected from a phenyl and a 5-10 membered heteroaryl; and

R_{15} is selected from 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, and heterocycloalkyl, and

is the site of attachment of the ULM to the L; or

(ii) represented by the chemical structure:



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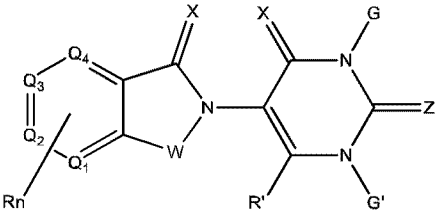

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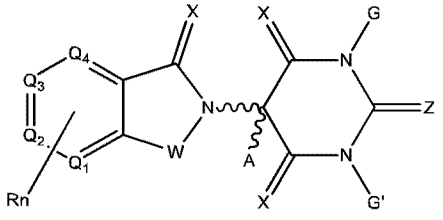

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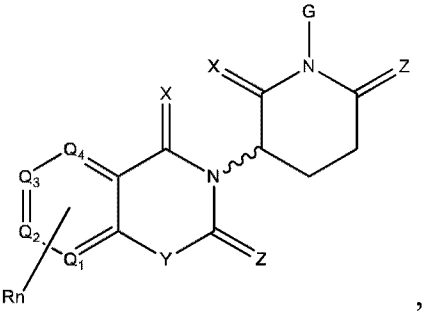

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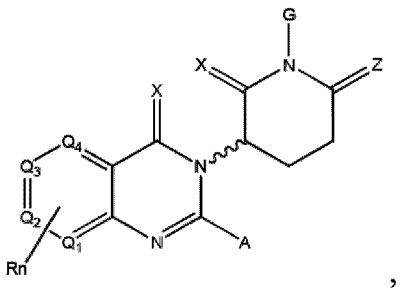

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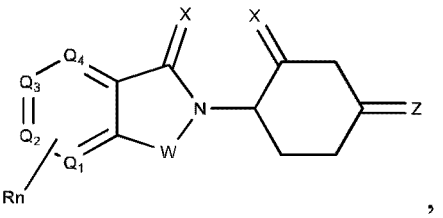

,

(e) or (f),

wherein:

W is selected from CH_2, CHR, C=O, SO_2, NH, and N-alkyl;

each X is independently selected from absent, O, and S;

Y is selected from CH_2, -C=CR', NH, N-alkyl, N-aryl, N-hetaryl, N-cycloalkyl, N-heterocyclyl, O, and S;

Z is selected from absent, O, and S;

G and G' are independently selected from: H; linear or branched alkyl optionally substituted with R'; OH; R'OCOOR; R'OCONRR"; CH_2-heterocyclyl optionally substituted with R'; and benzyl optionally substituted with R';

each of Q_1, Q_2, Q_3,or Q_4 are independently N or C independently substituted with H or R;

A is selected from H, alkyl, cycloalkyl, Cl, and F;

n is 1, 2, 3, or 4;

R is -CONR'R", -OR', -NR'R", -SR', -SO_2R', -SO_2NR'R", -CR'R"-, -CR'NR'R"-, -aryl, -heteroaryl, - optionally substituted linear or branched alkyl, -cycloalkyl, -heterocyclyl, -P(O)(OR')R", -P(O)R'R", -OP(O)(OR')R", -OP(O)R'R", -Cl, -F, -Br, -I, -CF_3, -CN, -NR'SO_2NR'R", -NR'CONR'R", -CONR'COR", -NR'C(=N-CN)NR'R", -C(=N-CN)NR'R", -NR'C(=N-CN)R", -NR'C(=C-NO_2)NR'R", -SO_2NR'COR", -NO_2, -CO_2R', -C(C=N-OR')R", -CR'=CR'R", -CCR', -S(C=O)(C=N-R')R", -SF_5 or -OCF_3, wherein one R is covalently joined to the L;

R' and R" are independently selected from a bond, H, N-oxide, linear or branched alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocyclyl; and

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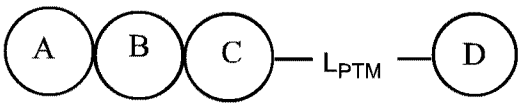
〰 represents a bond that is stereospecific or non-stereospecific;

(c) the PTM is represented by a formula I:



(I),

wherein:

rings A, B, C, and D are independently selected from an optionally substituted 5- or 6-membered aryl, an optionally substituted 5- or 6-membered heteroaryl, an optionally substituted 4- to 7-membered cycloalkyl, and an optionally substituted 4- to 7-membered heterocycloalkyl, where contact between circles indicates ring fusion;

L_{PTM} is selected from a bond, an alkyl, an alkenyl and an alkynyl, optionally interrupted by one or more rings, or one or more functional groups selected from the groups -O-, -S-, -NR^1_{PTM}-, -N=N-, -S(O)-, -SO_2-, -C(O)-, -NHC(O)-, -C(O)NH-, -$NHSO_2$-, -NHC(O)NH-, -NHC(O)O-, and -OC(O)NH-, wherein the functional group is optionally located at either end of the L_{PTM}; and

R^1_{PTM} is H or alkyl.

2. The compound of claim 1, wherein

at least one of the A ring, the B ring, and the C ring is selected from a 5- or 6-membered aryl and a 5- or 6-membered heteroaryl, each optionally substituted with 1–8 substituents, each substituent independently selected from alkyl, alkenyl, haloalkyl, halogen, hydroxyl, alkoxy, fluoroalkoxy, amino, alkylamino, dialkylamino, acylamino, trifluoromethyl and cyano, wherein said alkyl and alkenyl groups are further optionally substituted.

3. The compound of claim 1, wherein rings A, B, C, and D are each a 5- or 6-membered aryl or a 5- or 6-membered heteroaryl, each optionally substituted with 1–8 substituents, each substituent independently selected from alkyl, alkenyl, haloalkyl, halogen, hydroxyl, alkoxy, fluoroalkoxy, amino, alkylamino, dialkylamino, acylamino, trifluoromethyl and cyano, wherein the said alkyl and alkenyl groups are further optionally substituted.

4. The compound of claim 1, wherein:

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A, B and C rings are each independently a 5- or 6- membered aryl or a 5- or 6- membered heteroaryl;

L_{PTM} is a bond or alkyl; and

D ring is selected from 6-membered aryl, 6-membered heteroaryl and 6-membered heterocycloalkyl,

wherein A, B, C and D rings are optionally substituted with alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, trifluoromethyl or cyano.

5. The compound of claim 1; wherein:

the A and the C rings are each independently a phenyl or a 6-membered heteroaryl;

the B ring is a 5-membered heteroaryl;

L_{PTM} is a bond; and

the D ring is a 6-membered heteroaryl or a 6-membered heterocycloalkyl,

wherein each of the A, B, C and D rings is optionally substituted, each substituent independently selected from alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, dialkylamino, trifluoromethyl, or cyano, and wherein a nitrogen atom of any of the A, B, C and D rings is not directly connected to a heteroatom or to a carbon atom, to which another heteroatom is directly attached.

6. The compound of claim 1, wherein the PTM is represented by a chemical structure selected from:

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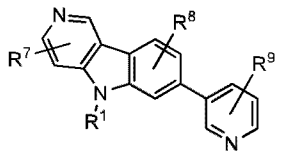
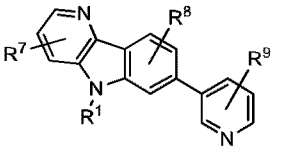
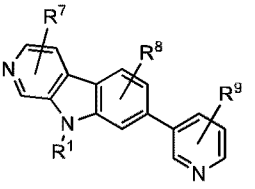
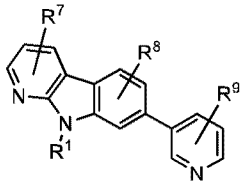
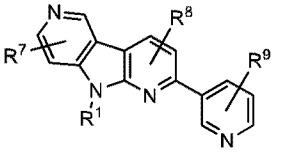
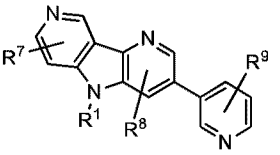
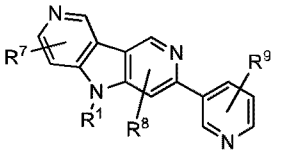
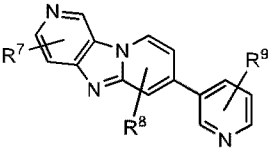
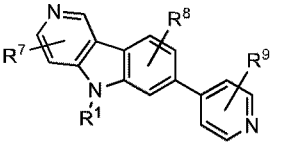
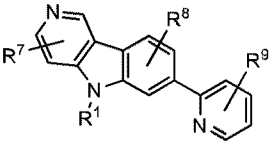
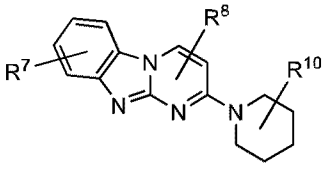
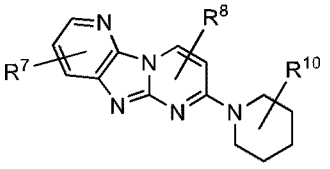
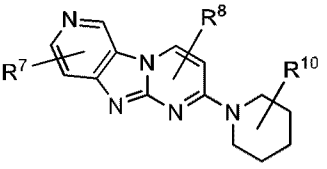
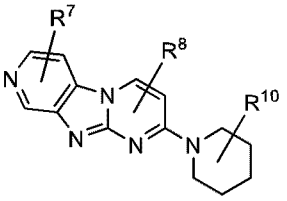
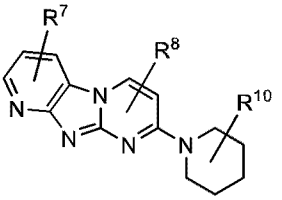

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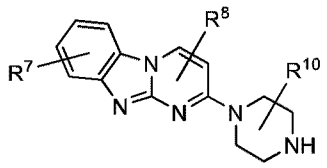
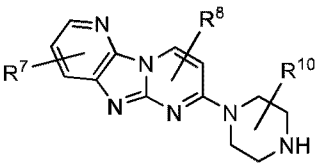
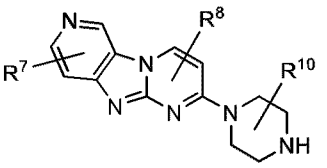
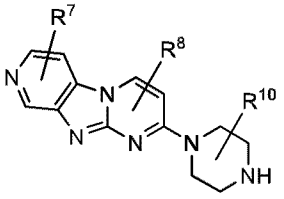
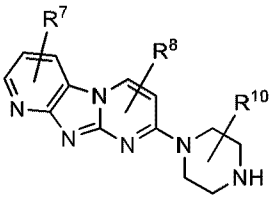
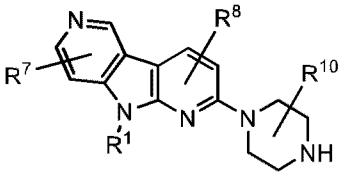
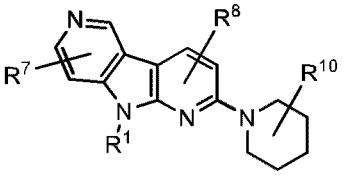
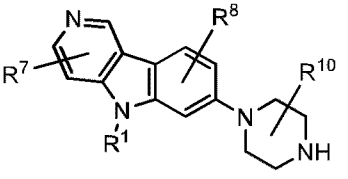
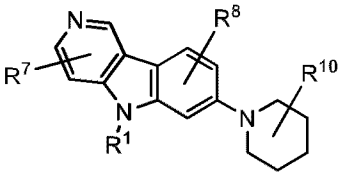
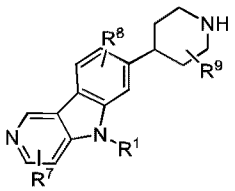
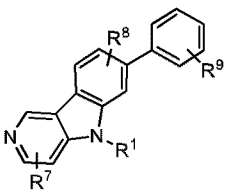
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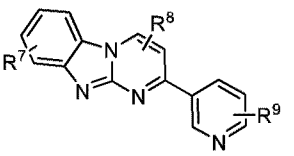
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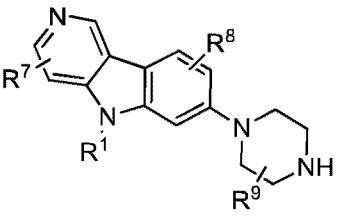
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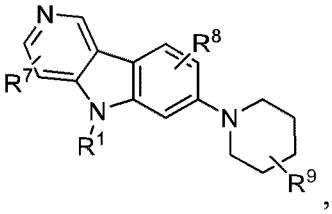
,

wherein:

R^1 is independently selected from H, optionally substituted alkyl, methyl, ethyl, 2-fluoroethyl and 2,2,2-trifluoroethyl; and

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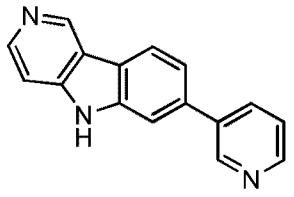
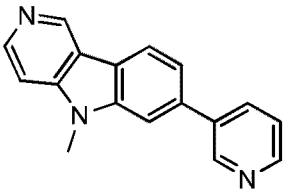
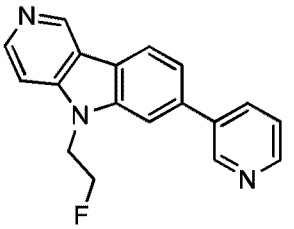
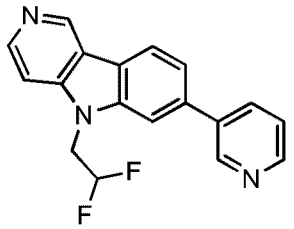
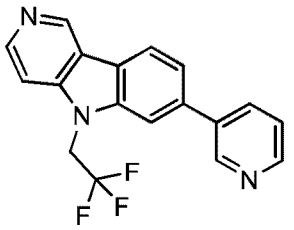
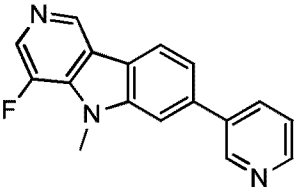
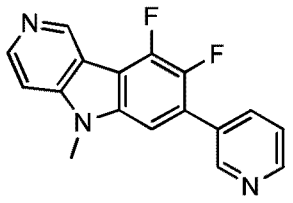
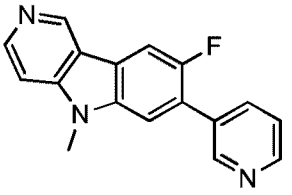
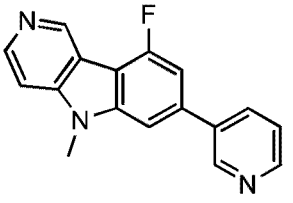
R^7, R^8, R^9 and R^{10} are 1 to 8 substituents independently selected from H, optionally substituted alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, dialkylamino, acetylamino, trifluoromethyl, and cyano.

7. The compound of any one of claims 1, 2, and 6, wherein the PTM is represented by a chemical structure selected from:

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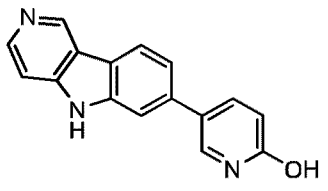
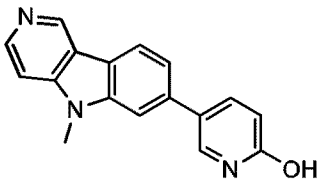
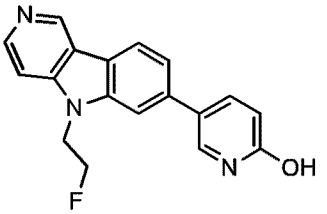
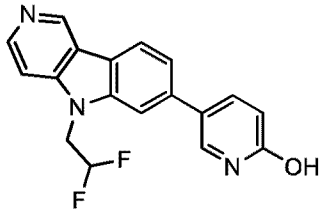
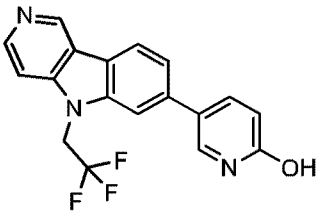
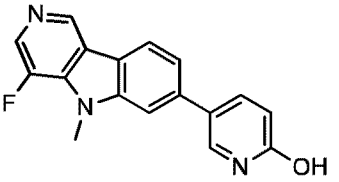
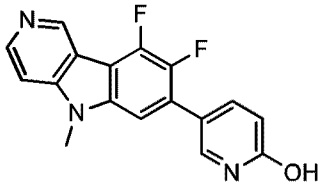
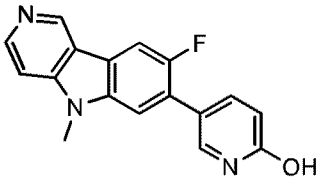
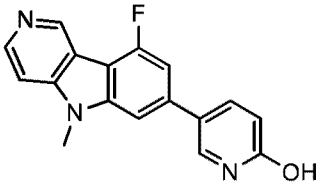

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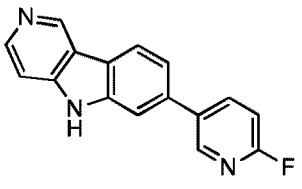
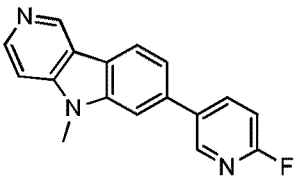
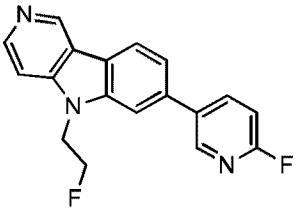
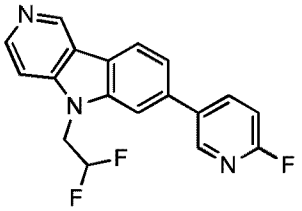
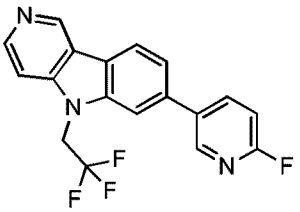
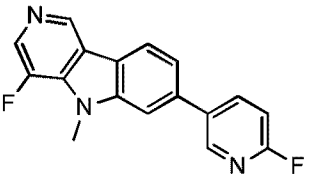
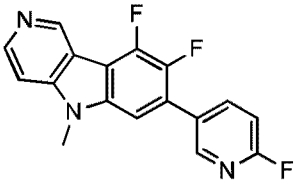
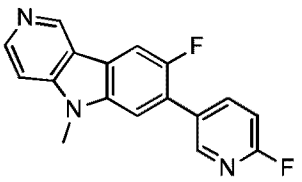
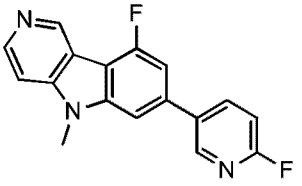
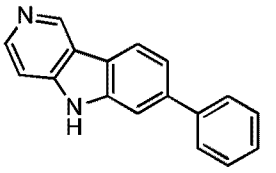

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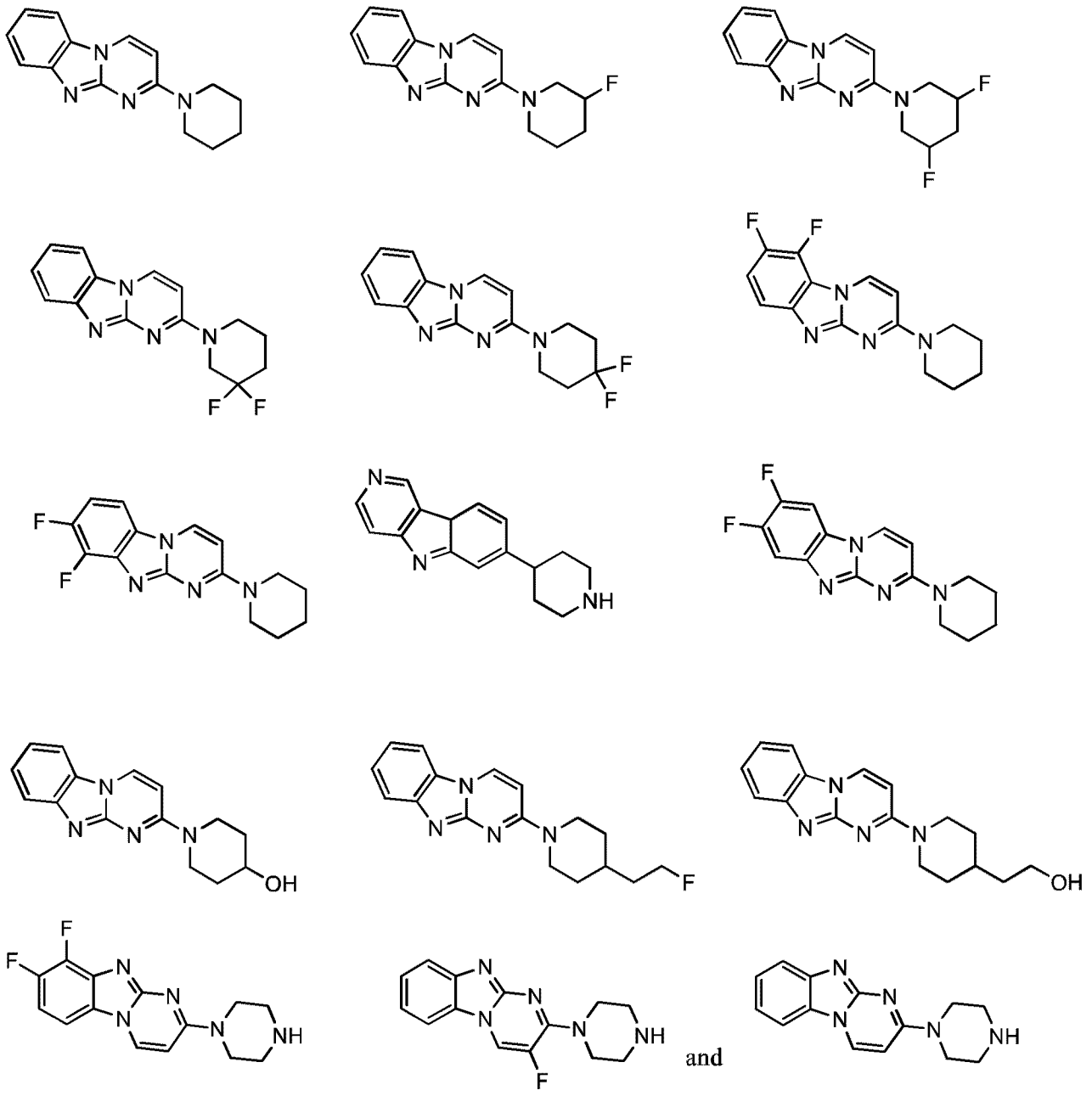

and

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8. The compound of any one of claims 1-7, wherein the ULM is represented by the structure:

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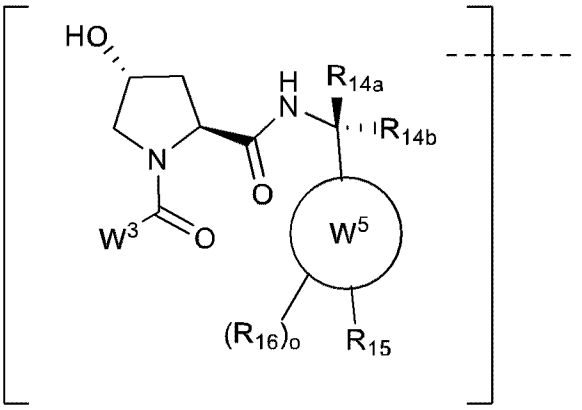
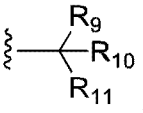
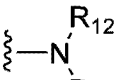
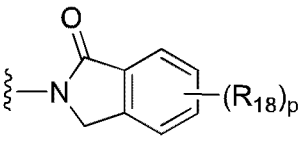
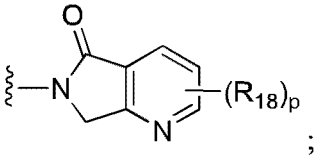


wherein:

W^3 is selected from an optionally substituted aryl, optionally substituted heteroaryl, and  ;

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

R_{11} is selected from an optionally substituted heterocyclic, optionally substituted alkoxy, optionally substituted heteroaryl, optionally substituted aryl,  ,  and  ;

R_{12} is H or optionally substituted alkyl;

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

R_{14a} and R_{14b}, are each independently selected from H, haloalkyl, and optionally substituted alkyl;

W^5 is selected from a phenyl and a 5-10 membered heteroaryl;

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R_{15} is selected from 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, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

each R_{16} is independently selected from H, halogen, optionally substituted alkyl, optionally substituted haloalkyl, hydroxy, and optionally substituted haloalkoxy;

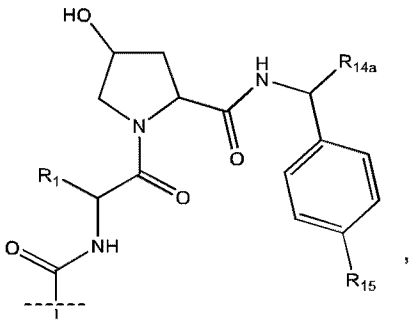
o is 0, 1, 2, 3, or 4;

each R_{18} is independently selected from halogen, optionally substituted alkoxy, cyano, optionally substituted alkyl, haloalkyl, and haloalkoxy;

p is 0, 1, 2, 3, or 4; and

indicates the site of attachment of the ULM to the L.

9. The compound of any one of the claims 1-7, wherein the ULM has a chemical structure selected from: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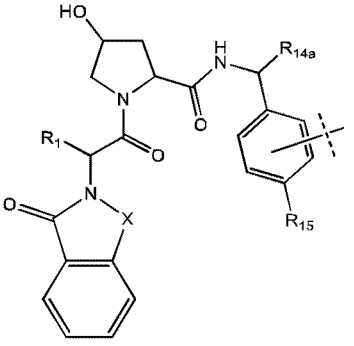
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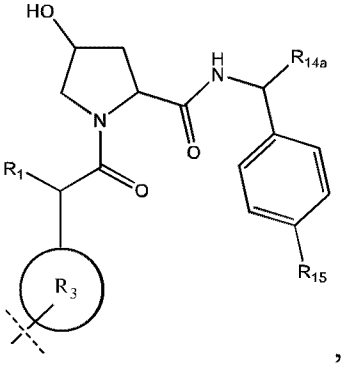
and ,

wherein:

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R_1 is H, ethyl, isopropyl, tert-butyl, sec-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl; optionally substituted alkyl, optionally substituted hydroxyalkyl, optionally substituted heteroaryl, or haloalkyl;

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

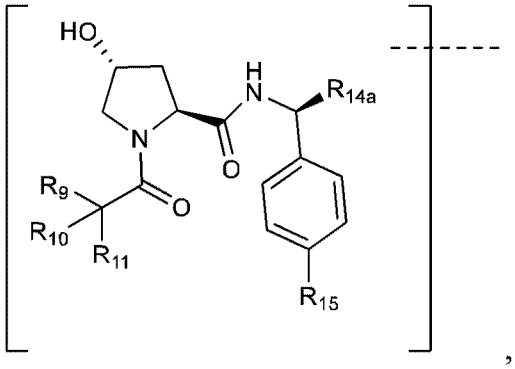
R_{15} is selected from H, halogen, CN, OH, NO_2, optionally substituted heteroaryl, optionally substituted aryl; optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted haloalkoxy, cycloalkyl, and cycloheteroalkyl;

X is CH_2, or C=O;

R_3 is a bond or an optionally substituted 5 or 6 membered heteroaryl; and

indicates the site of attachment of the ULM to L.

10. The compound of any one of claims 1-7, wherein the ULM is represented by the chemical structure:

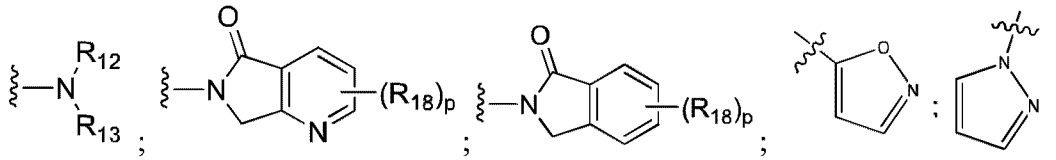


, wherein:

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

R_9 is H;

R_{10} is H, ethyl, isopropyl, tert-butyl, sec-butyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl;

R_{11} is 

or optionally substituted heteroaryl;

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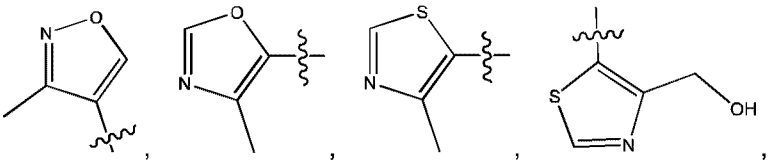
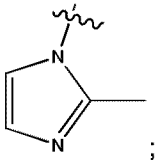
p is 0, 1, 2, 3, or 4;

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

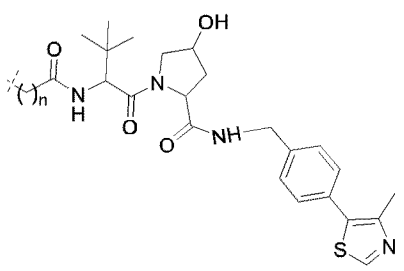
R_{12} is H, or C=O;

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;

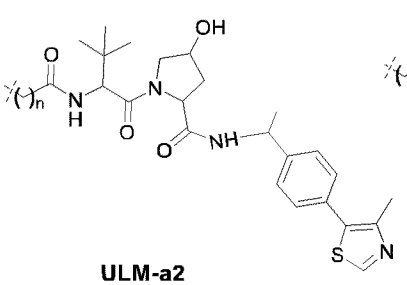
R_{15} is selected from H, halogen, Cl, CN, OH, NO_2, optionally substituted heteroaryl, optionally substituted aryl,  , and  ; and

indicates the site of attachment of the ULM to L.

11. The compound of any one of claims 1-7, wherein the ULM is selected from:



ULM-a2



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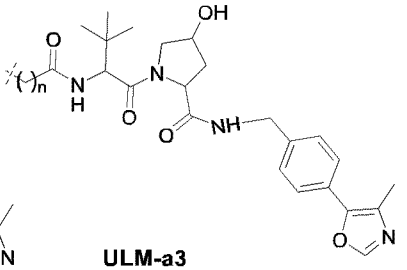
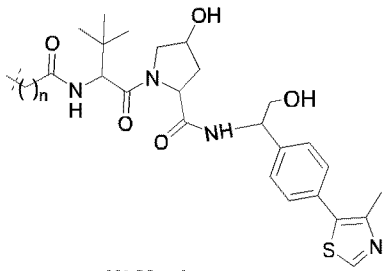
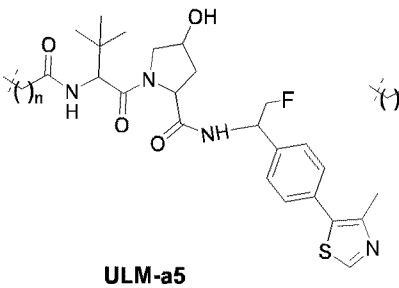
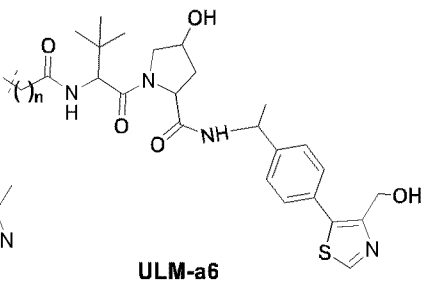




ULM-a4



ULM-a5



ULM-a6

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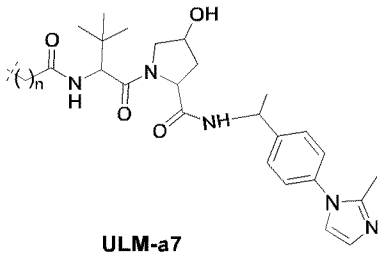

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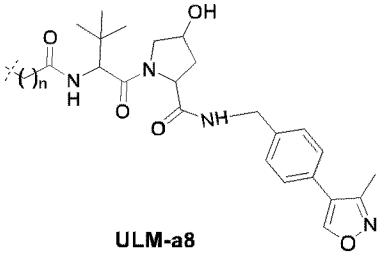

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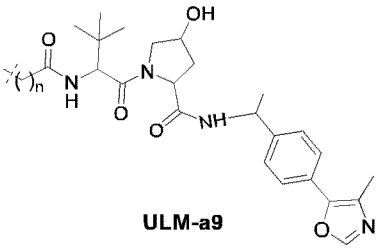

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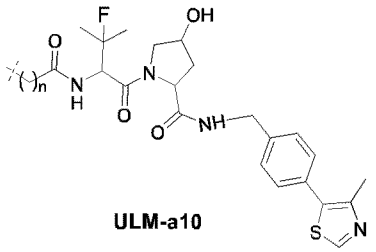

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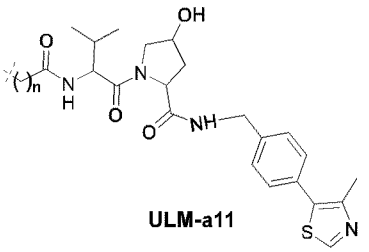

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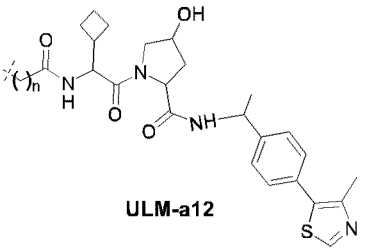

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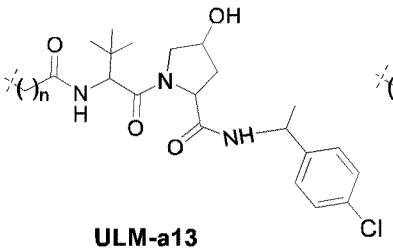

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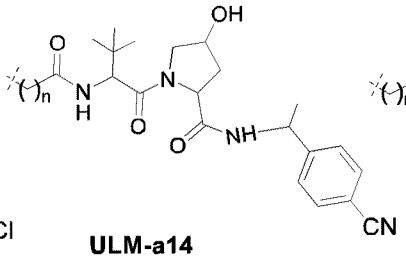

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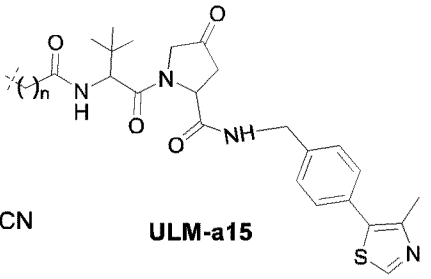

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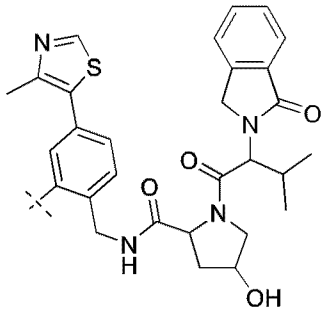

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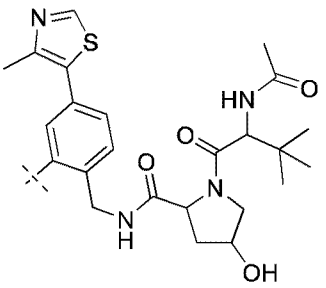
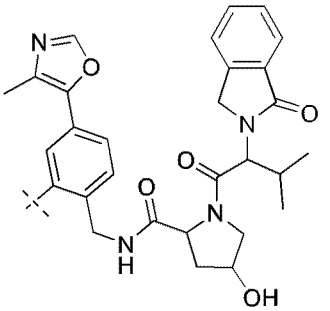


ULM-b2



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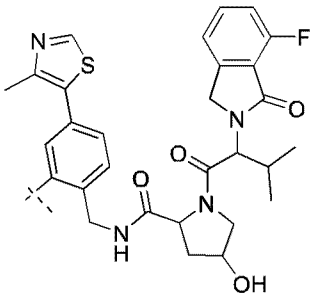

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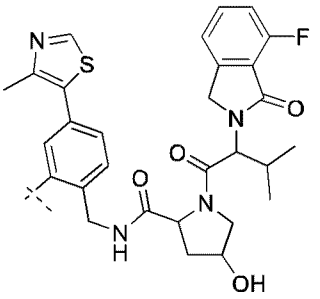

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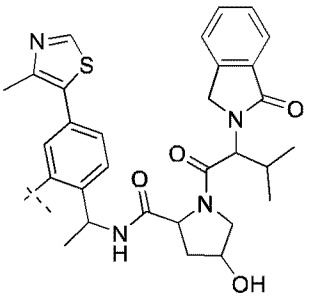

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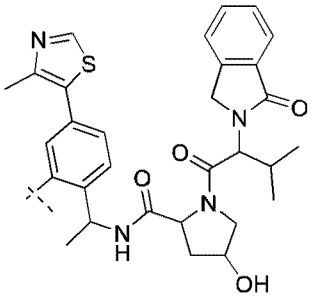

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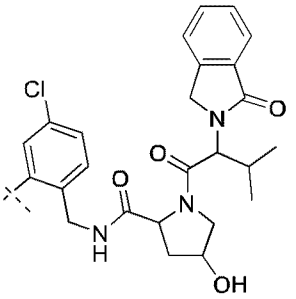

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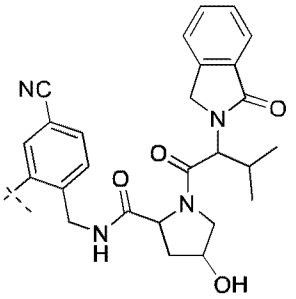

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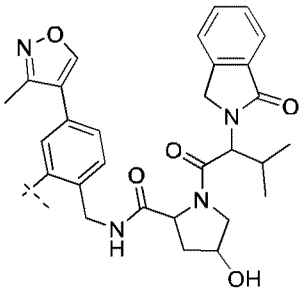

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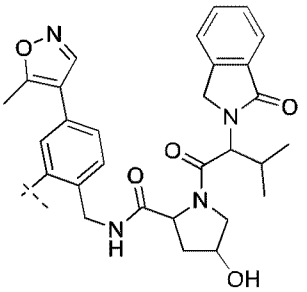

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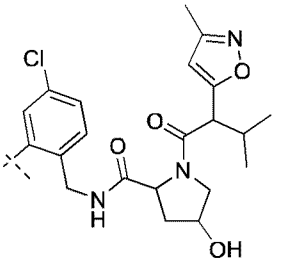

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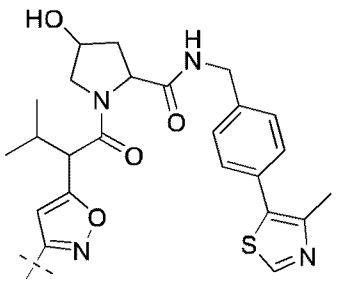
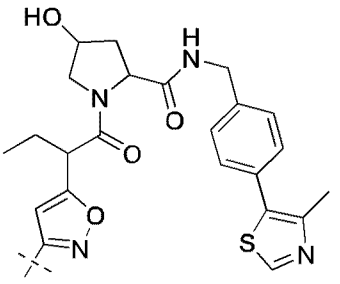


ULM-c1



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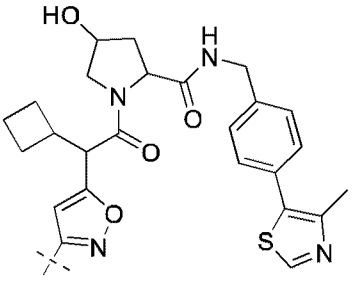

ULM-c3

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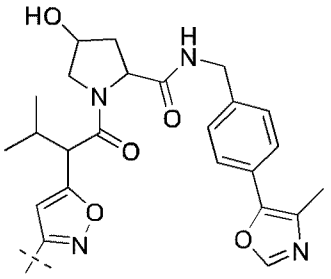

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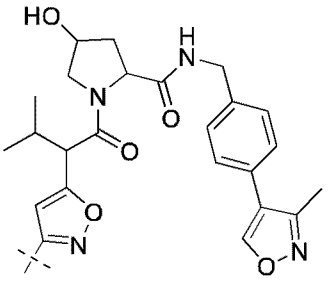

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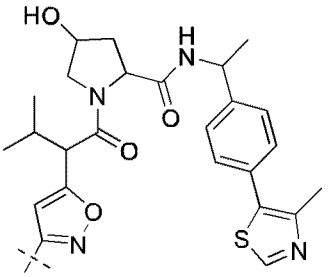

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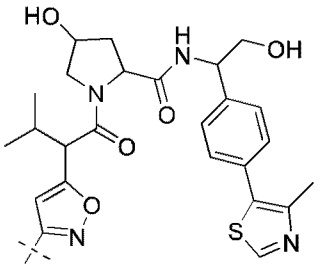

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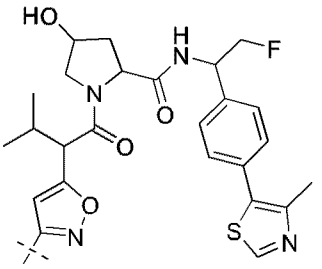

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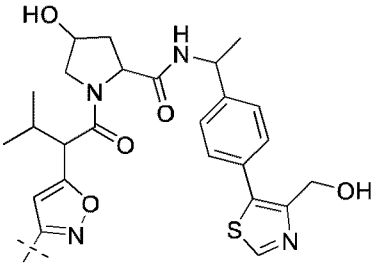

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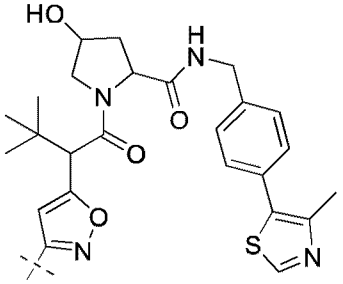

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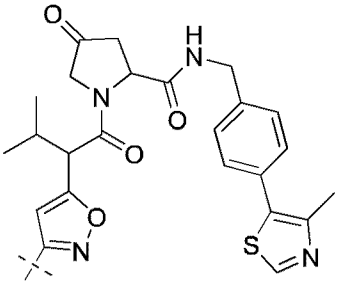
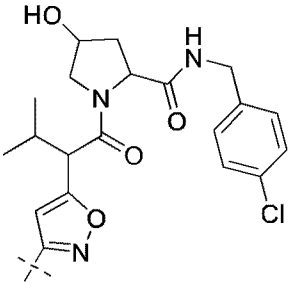


ULM-c11



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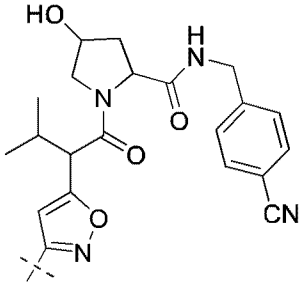

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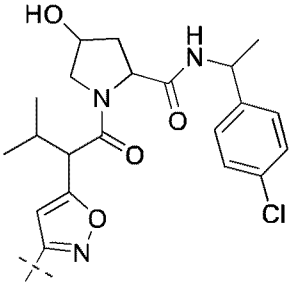

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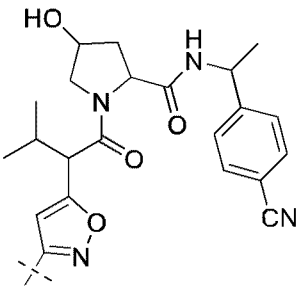

ULM-c15

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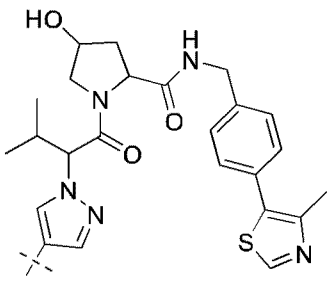
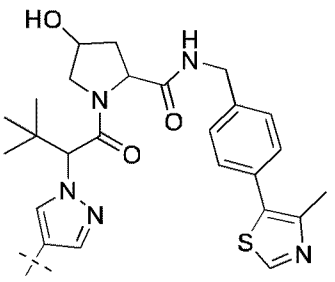
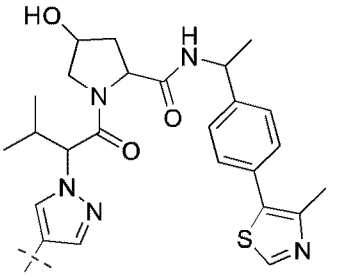


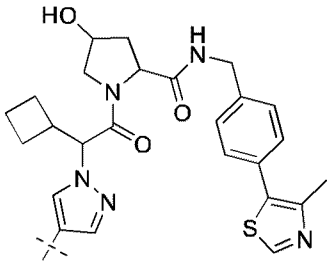
ULM-d1



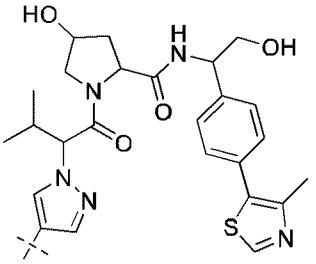
ULM-d2



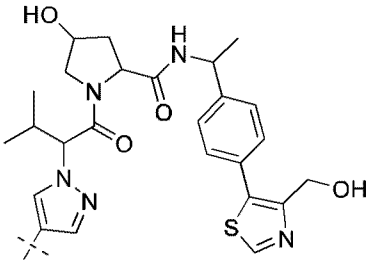
ULM-d3



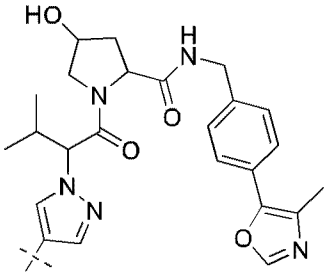
ULM-d4



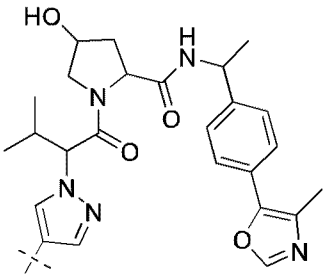
ULM-d5



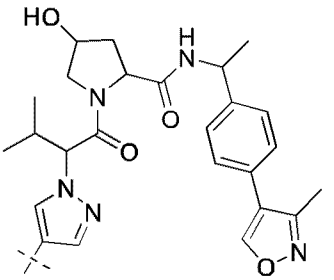
ULM-d6



ULM-d7



ULM-d8



ULM-d9

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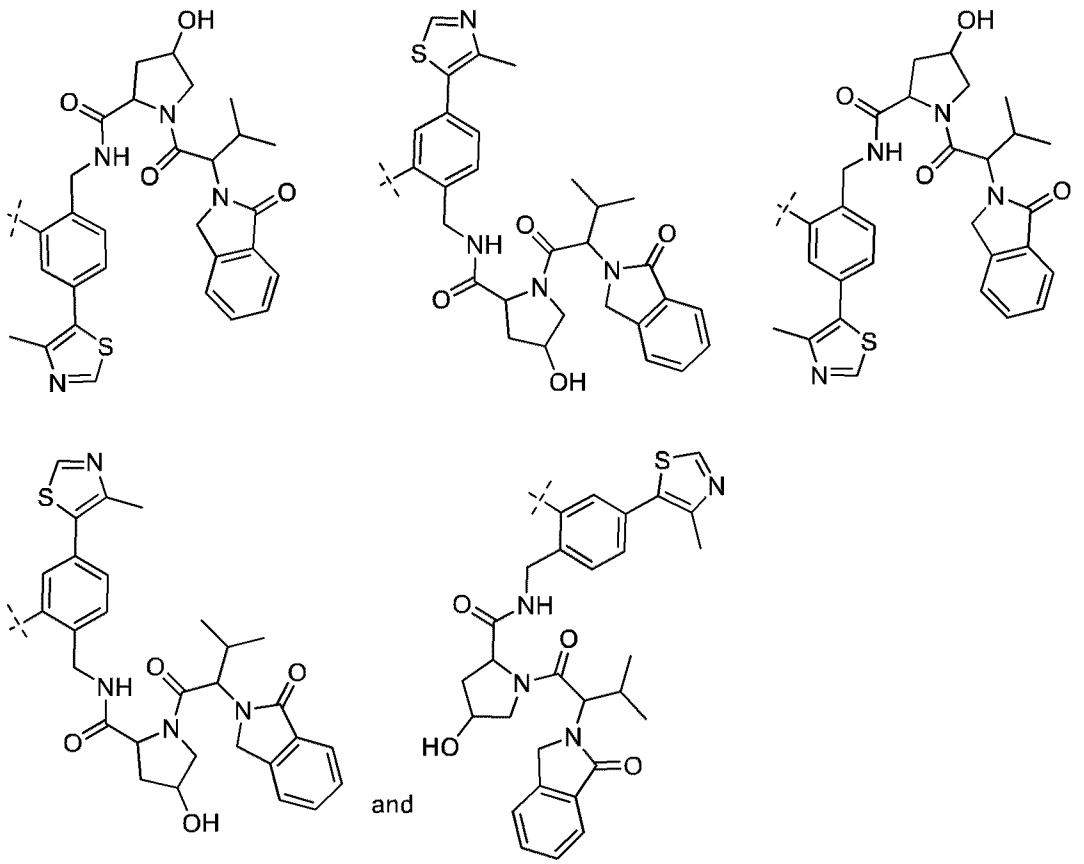
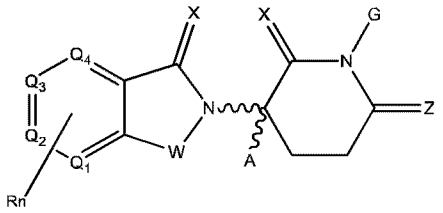


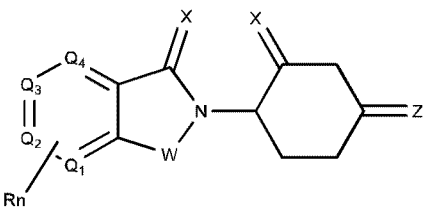
wherein the phenyl ring in ULM-a1 through ULM -a15, ULM -b1 through ULM-b12, ULM-c1 through ULM-c15 and ULM-d1 through ULM-d9 is optionally substituted with fluorine, lower alkyl and alkoxy groups, and wherein the indicates the site of attachment of the ULM to L.

12. The compound of any one of claims 1-7, wherein the ULM represented by:



(a)

or



(f) .

13. The compound of any one of claims 1-7, wherein the ULM has a chemical structure represented by:

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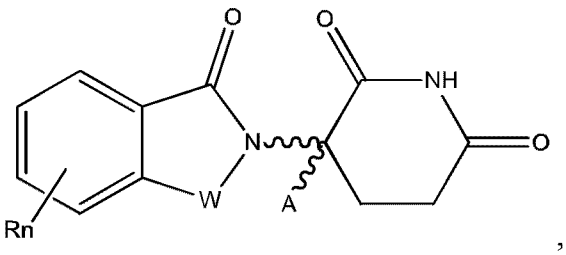


wherein:

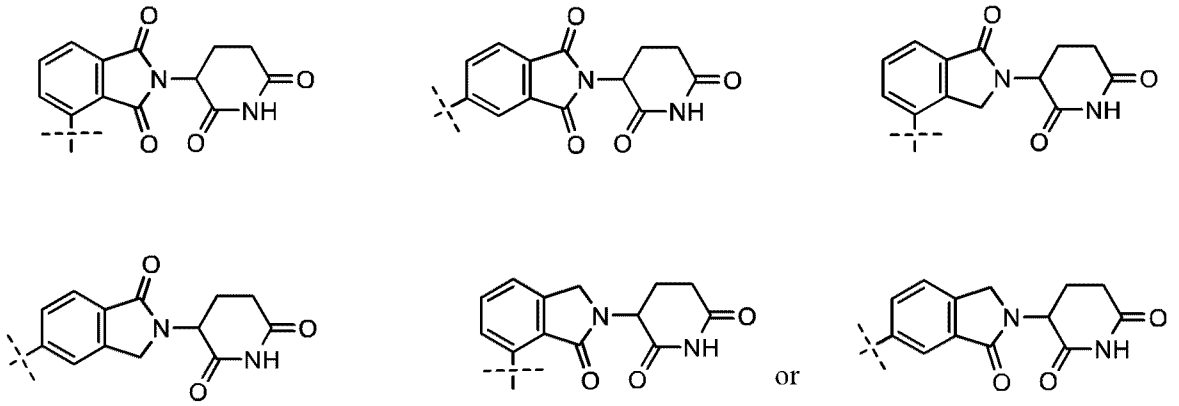
W is independently selected from the group CH_2, C=O, NH, and N-alkyl;

A is independently selected from a H, methyl, and alkyl;

n is 1, 2, 3, or 4, wherein one R is covalently joined to L; and

~~~ represents a bond that is stereospecific or non-stereospecific.

14. The compound of any one of claims 1-7, wherein the ULM has a chemical structure represented by:



wherein indicates attachment points to the chemical linking moiety (L).

15. The compound of any one of claims 1-14, wherein:

each A^L is selected from $CR^{L1}R^{L2}$, O, SO_2, NR^{L3}, $CONR^{L3}$, $NR^{L3}CONR^{L4}$, $NR^{L3}SO_2NR^{L4}$, CO, $CR^{L1}=CR^{L2}$, C≡C, C_{3-11}cycloalkyl optionally substituted with 1-6 R^{L1} and/or R^{L2} groups, C_{3-11}heteocyclyl optionally substituted with 1-6 R^{L1} and/or R^{L2} groups, aryl optionally substituted with 1-6 R^{L1} and/or R^{L2} groups, and heteroaryl optionally substituted with 1-6 R^{L1} and/or R^{L2} groups, where R^{L1} or R^{L2}, each independently are optionally linked to other groups to form cycloalkyl and/or heterocyclyl moiety, optionally substituted with 1-4 R^{L5} groups; and

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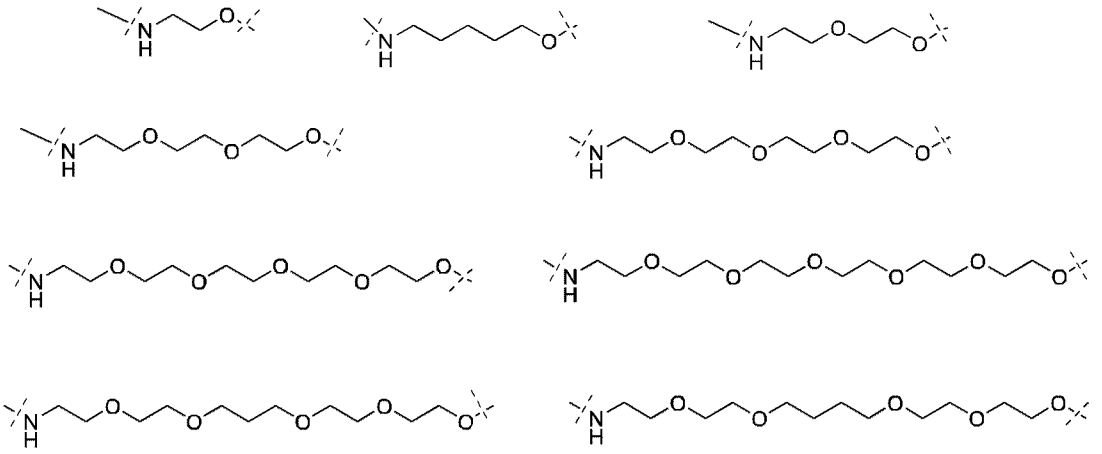
R^{L1}, R^{L2}, R^{L3}, R^{L4} and R^{L5} are, each independently, H, halogen, C_{1-8}alkyl, OC_{1-8}alkyl, NHC_{1-8}alkyl, $N(C_{1-8}alkyl)_2$, C_{3-11}cycloalkyl, aryl, heteroaryl, C_{3-11}heterocyclyl, OC_{3-8}cycloalkyl, OH, NH_2, CN, CF_3, CHF_2, CH_2F, or NO_2CONHC_{1-8}alkyl, .

16. The compound according to any one of claims 1-14, wherein L is a group represented by a structure selected from:



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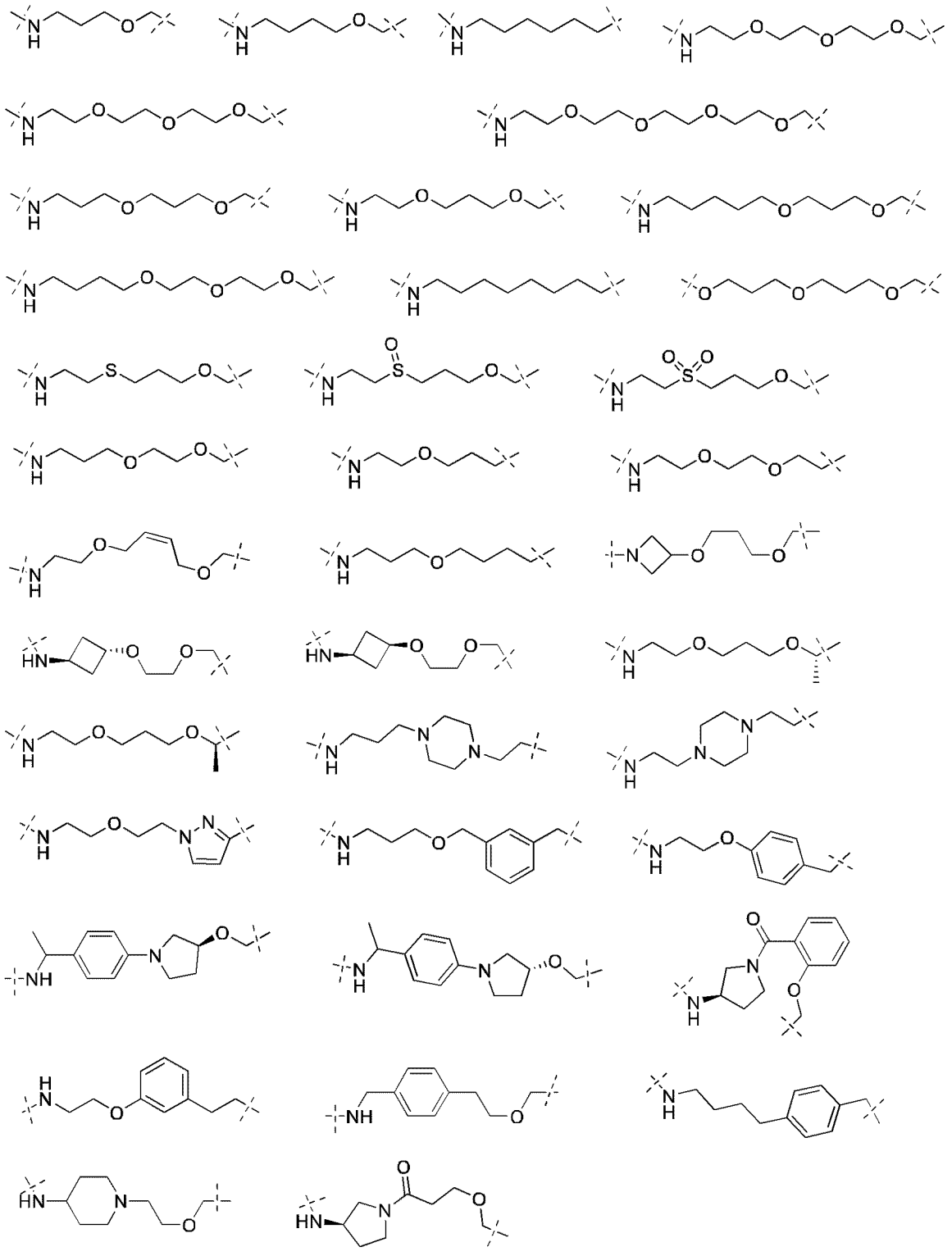

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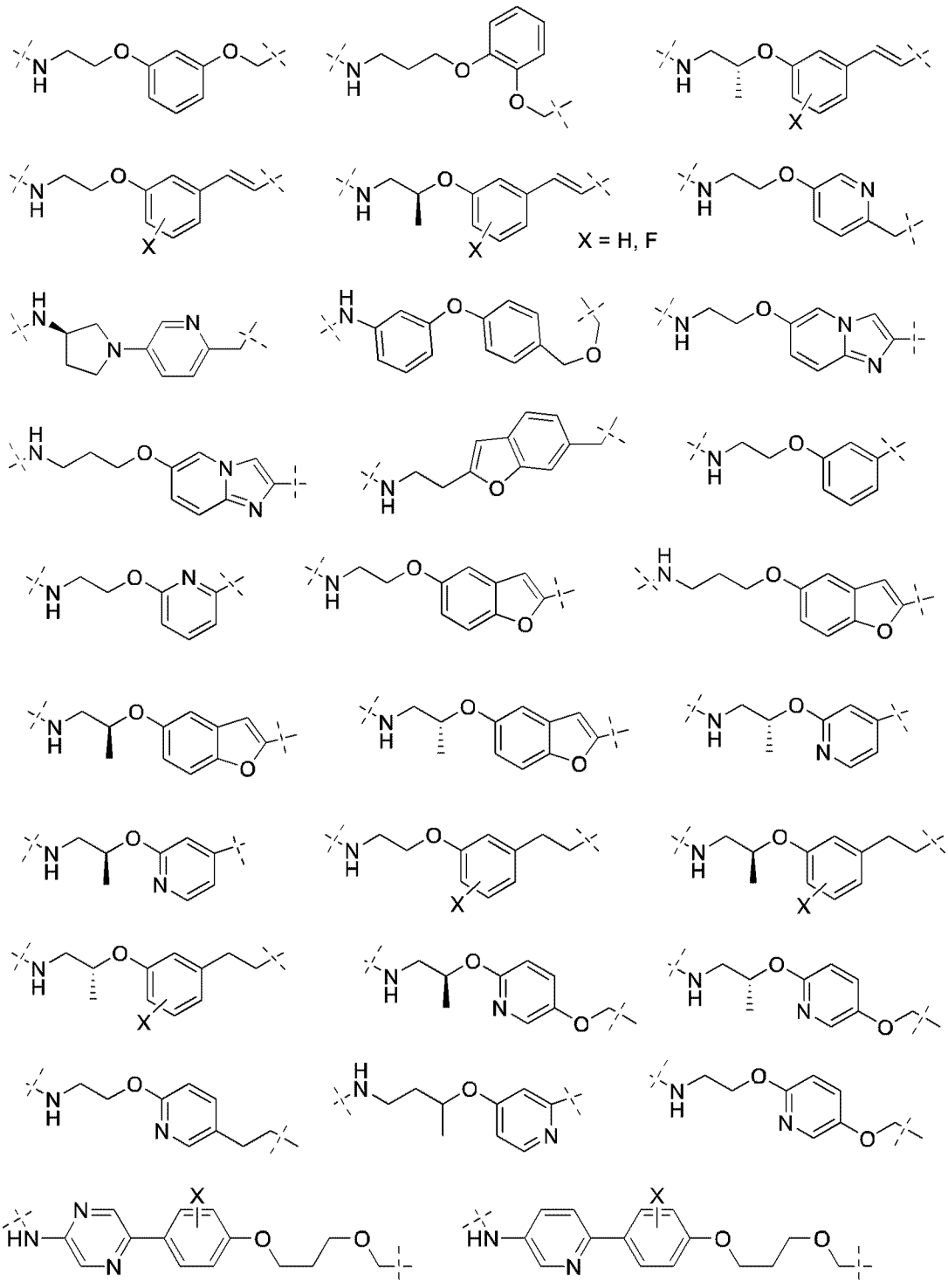

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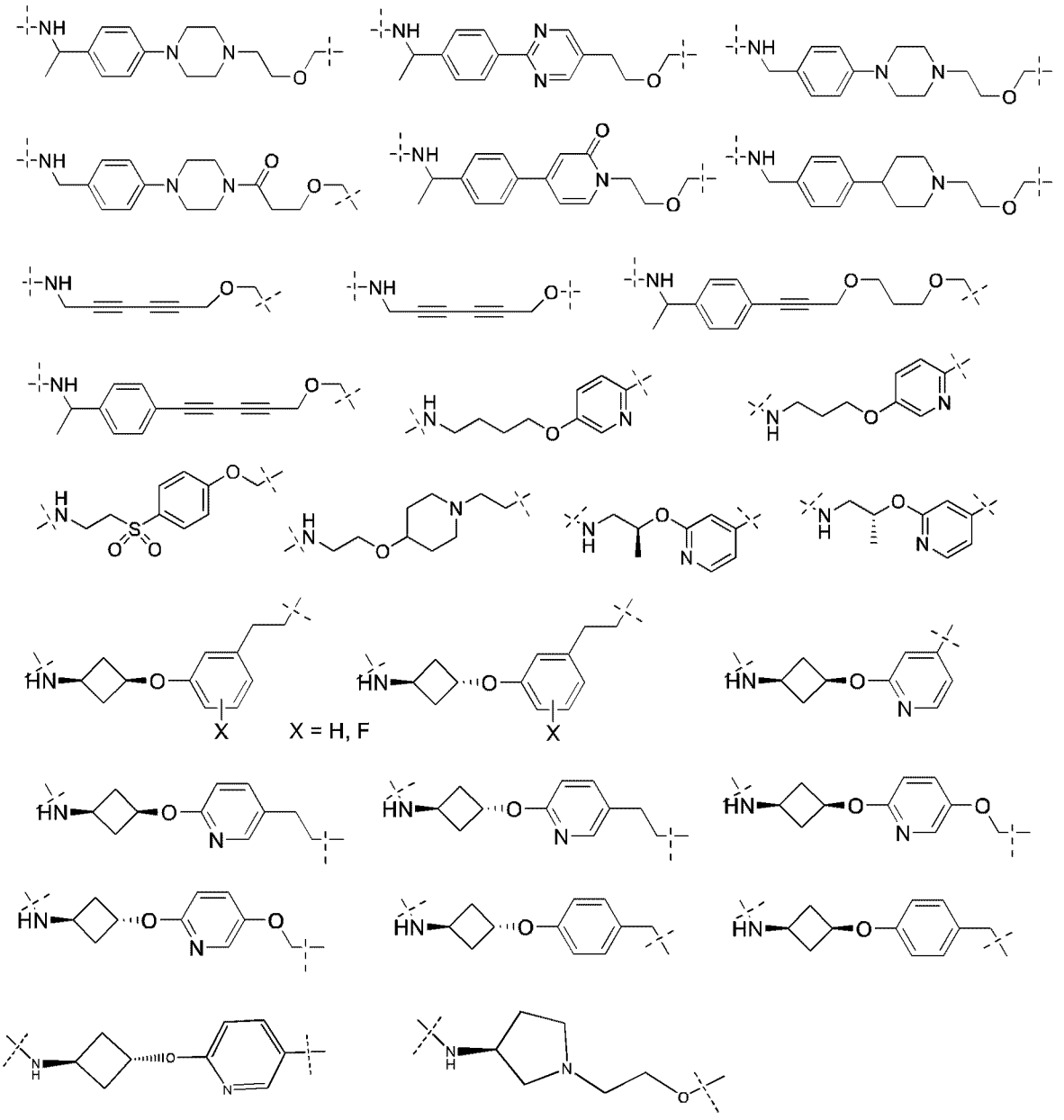

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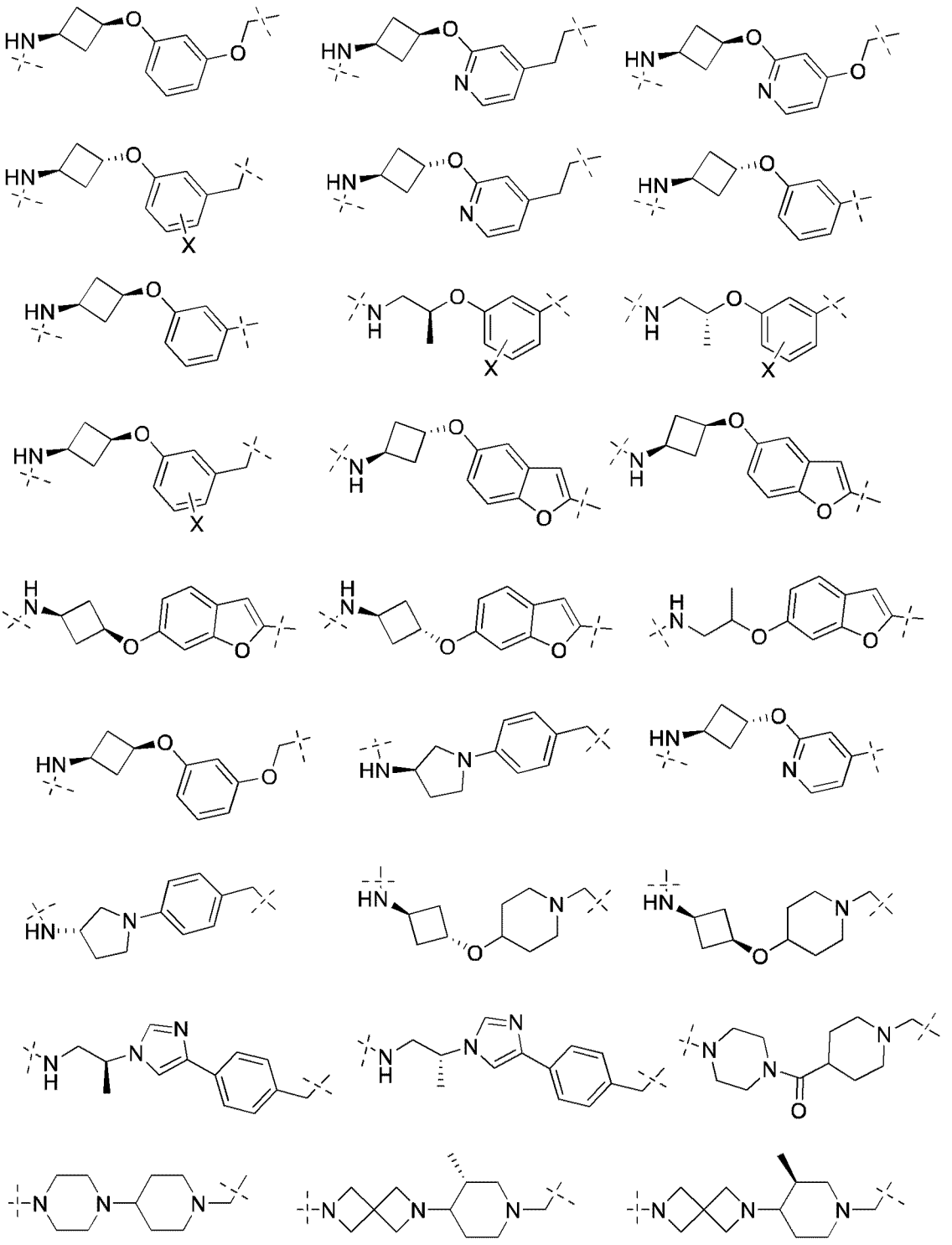

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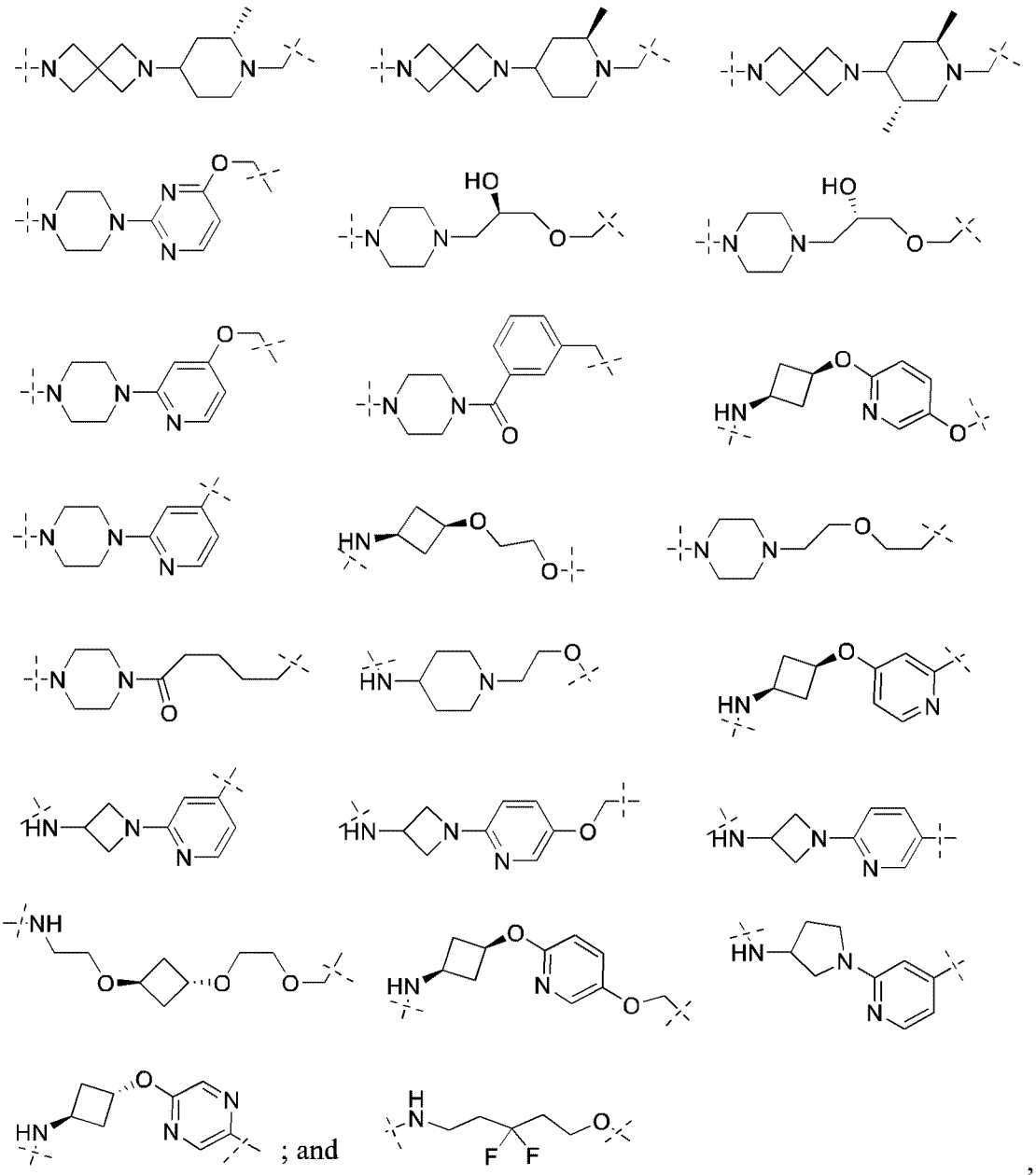

; and

,

-N(R)-$(CH_2)_m$-O$(CH_2)_n$-O$(CH_2)_o$-O$(CH_2)_p$-O$(CH_2)_q$-O$(CH_2)_r$-OCH2-,

-O-$(CH_2)_m$-O$(CH_2)_n$-O$(CH_2)_o$-O$(CH_2)_p$-O$(CH_2)_q$-O$(CH_2)_r$-OCH2-,

-O-$(CH_2)_m$-O$(CH_2)_n$-O$(CH_2)_o$-O$(CH_2)_p$-O$(CH_2)_q$-O$(CH_2)_r$-O-;

-N(R)-$(CH_2)_m$-O$(CH_2)_n$-O$(CH_2)_o$-O$(CH_2)_p$-O$(CH_2)_q$-O$(CH_2)_r$-O-;

-$(CH_2)_m$-O$(CH_2)_n$-O$(CH_2)_o$-O$(CH_2)_p$-O$(CH_2)_q$-O$(CH_2)_r$-O-;

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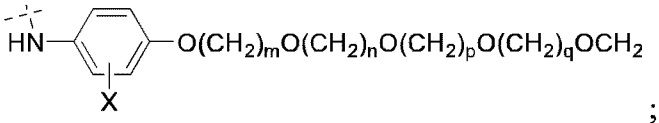
-$(CH2)_m$-$O(CH2)_n$-$O(CH2)_o$-$O(CH2)_p$-$O(CH2)_q$-$O(CH2)_r$-$OCH2$-;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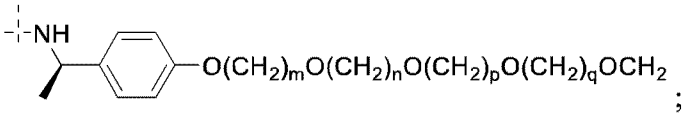
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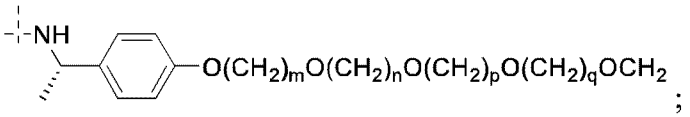
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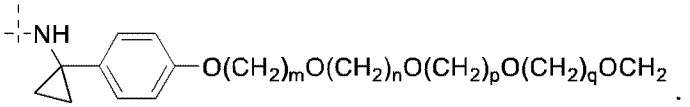
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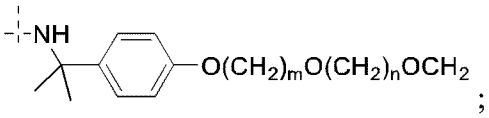
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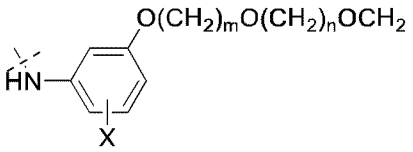
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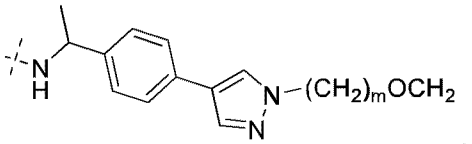
,

wherein:

R of L is selected from H, methyl, and ethyl;

X of L is H or F; and

m, n, o, p, q, and r of L is independently 0, 1, 2, 3, 4, 5, or 6, with the proviso that when m, n, o, p, q, or r is 0, there is no N-O or O-O bond.

17. The compound of any one of claims 1-14, wherein L is selected from:

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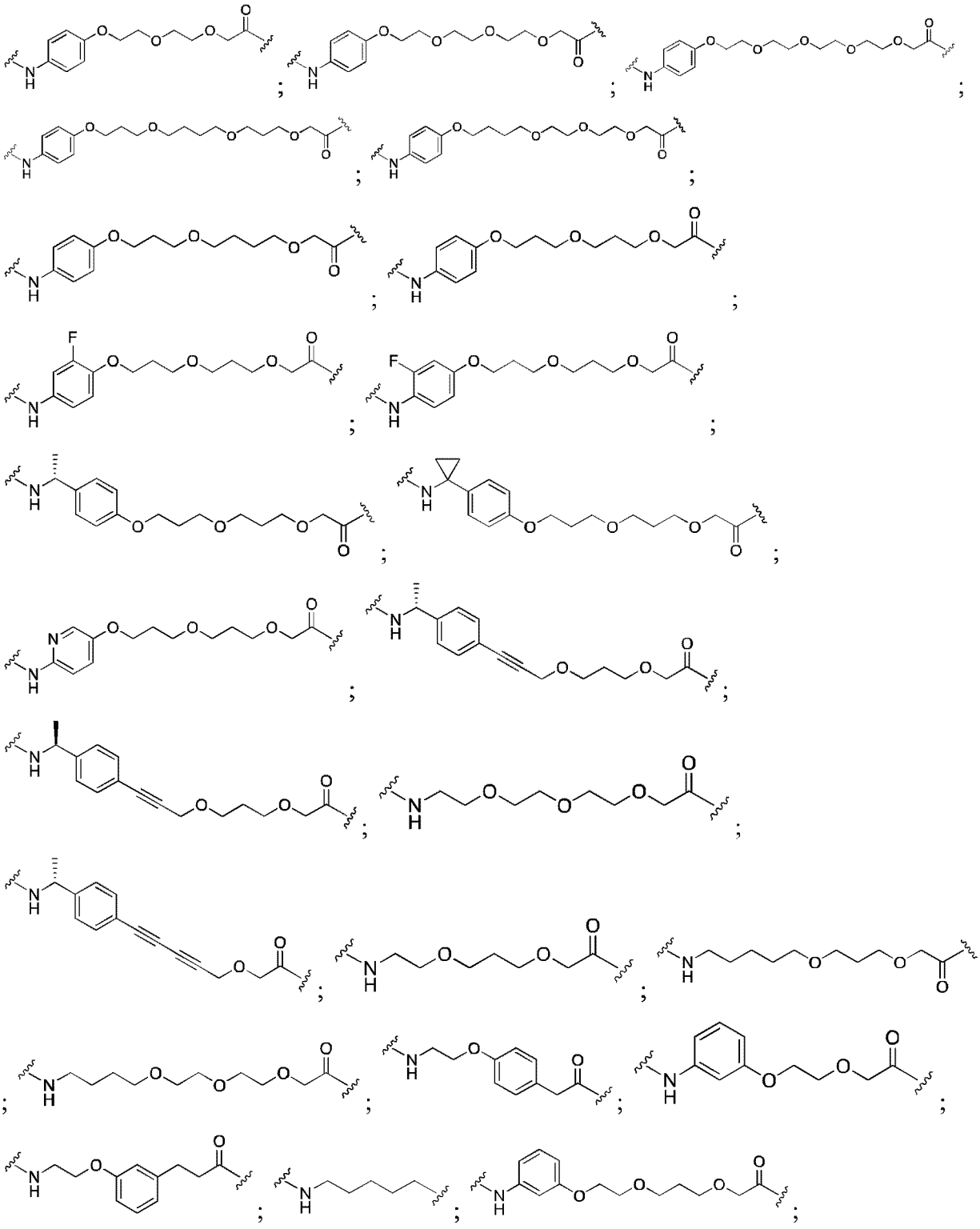

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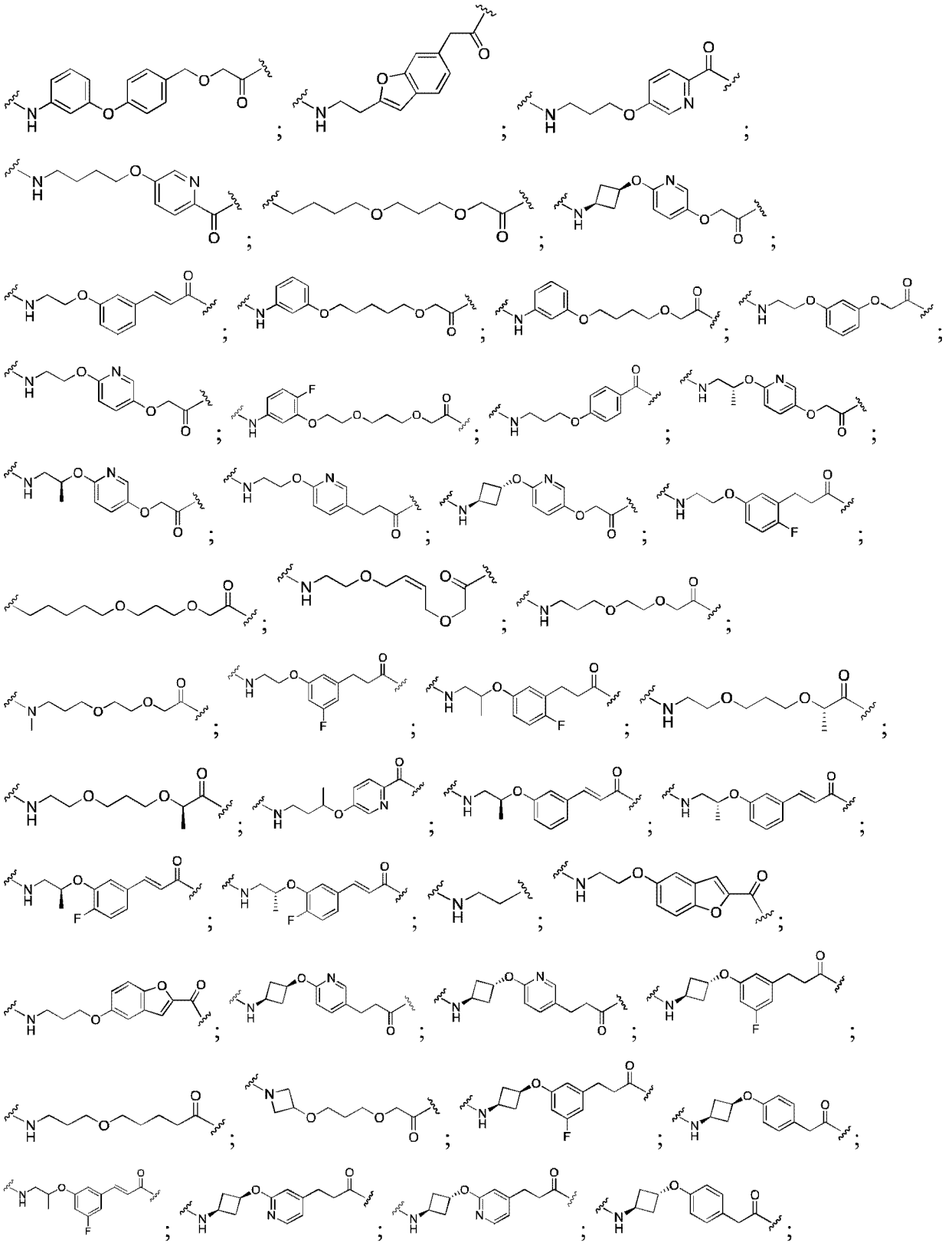

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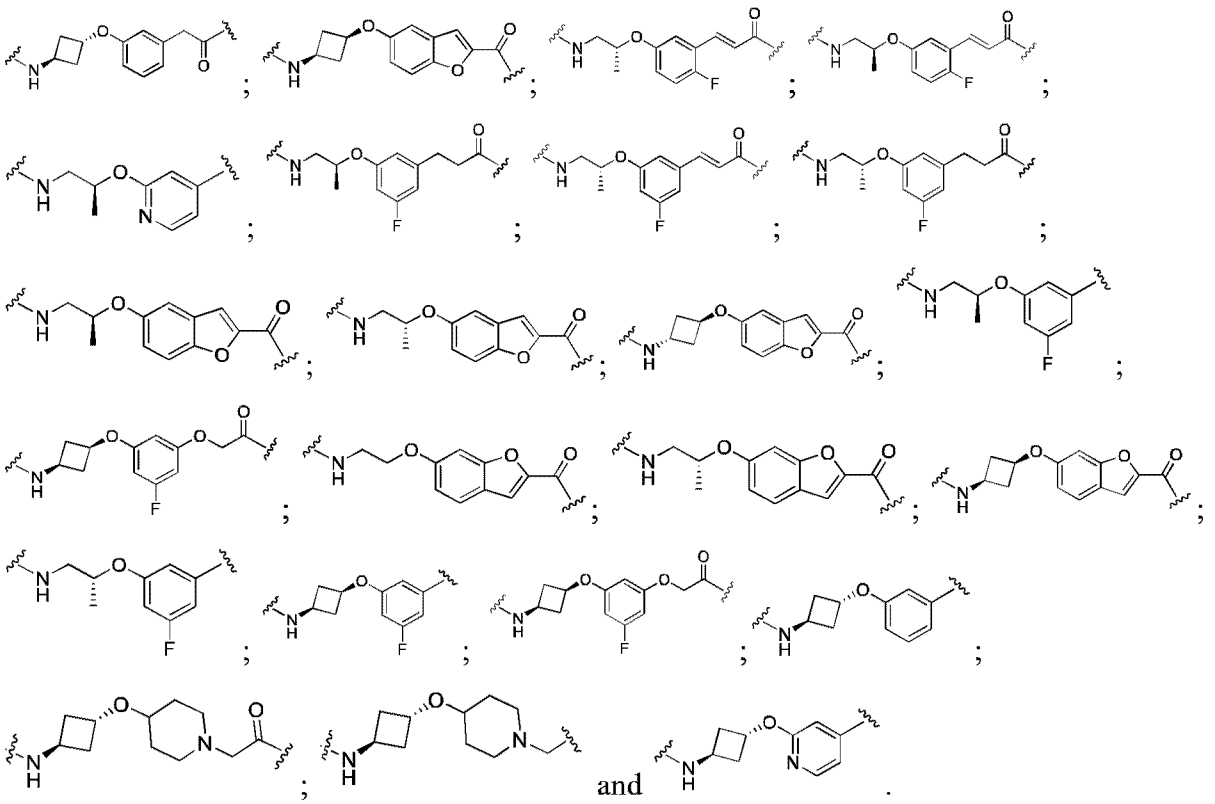
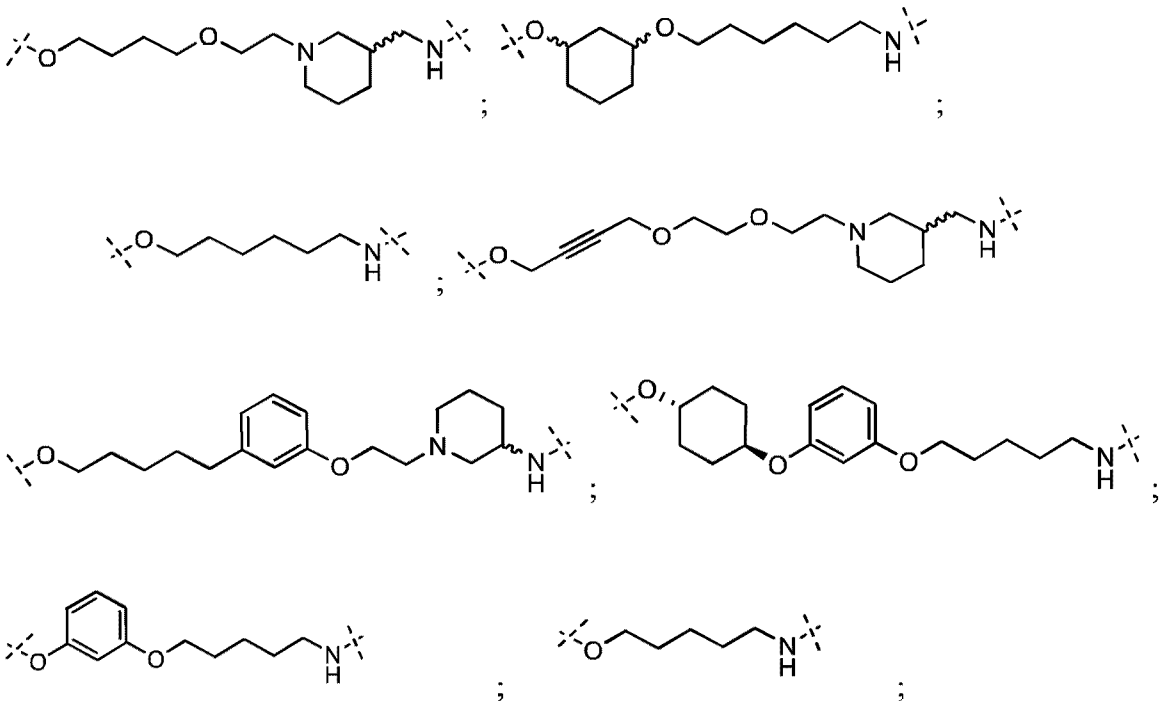


and

18. The compound of any one of claims 1-14, wherein L is selected from:



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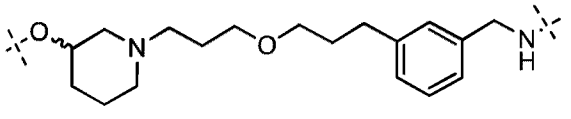
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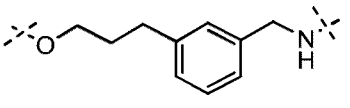
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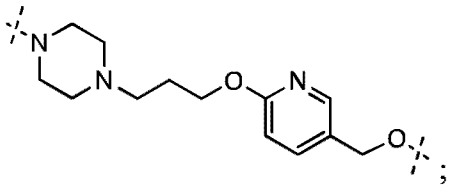
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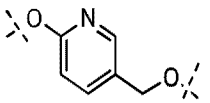
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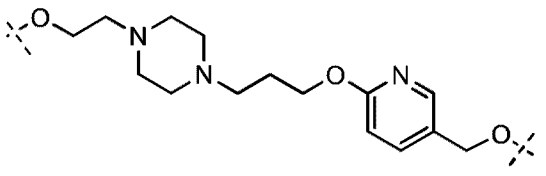
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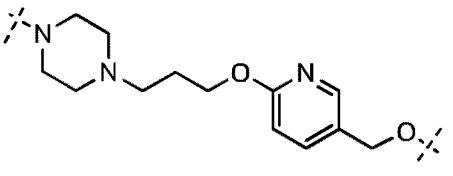
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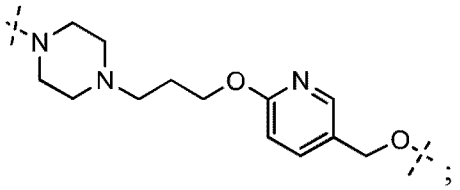
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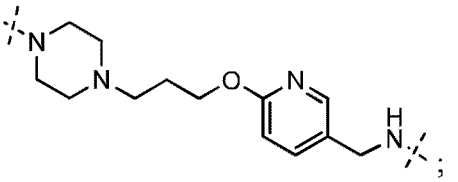
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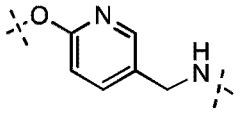
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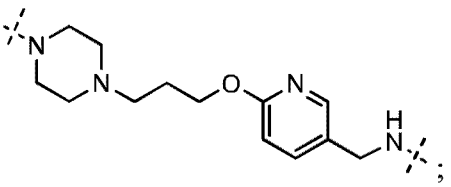
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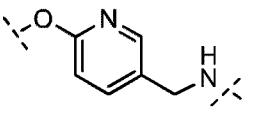
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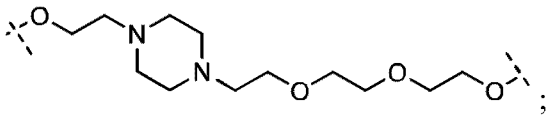
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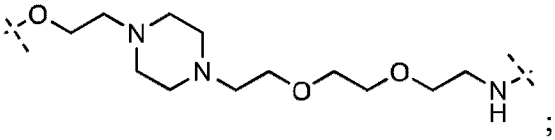
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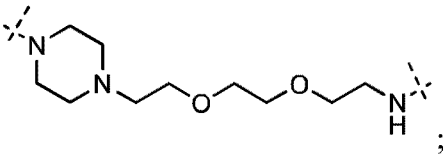
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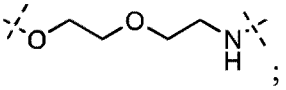
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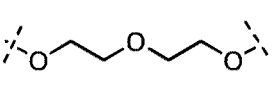

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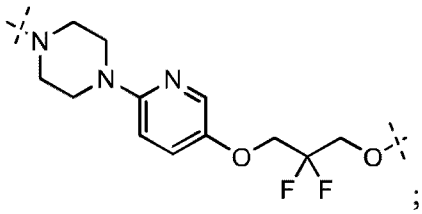
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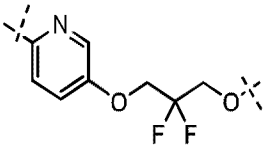
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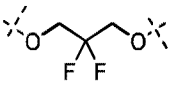
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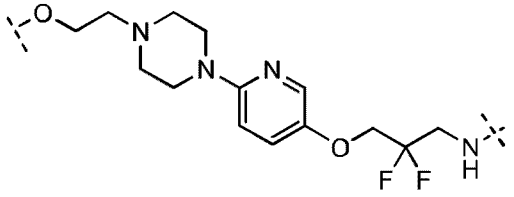
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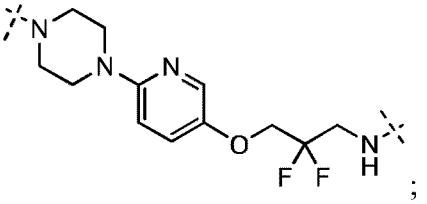
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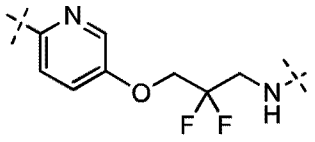
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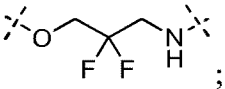
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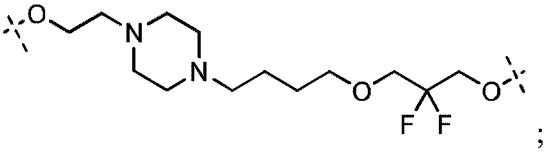
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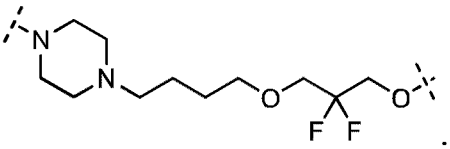
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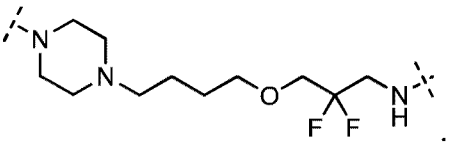
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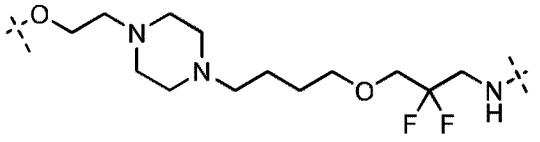
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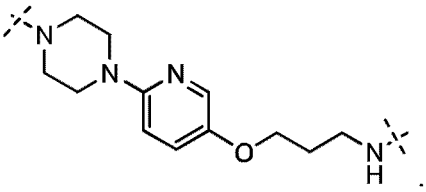
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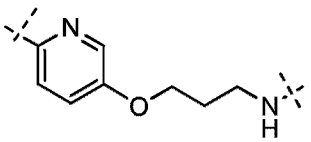
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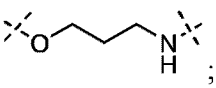
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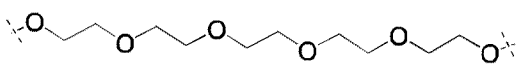
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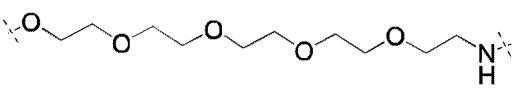
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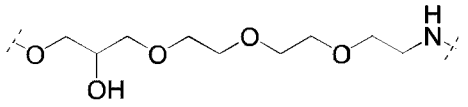
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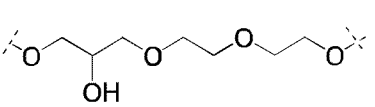
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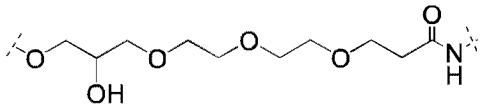
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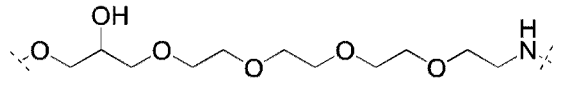
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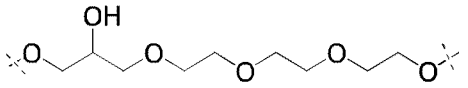
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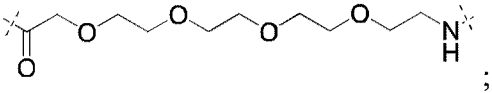
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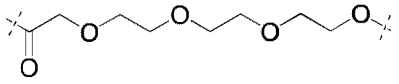
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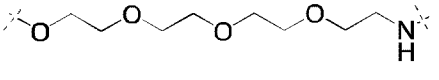
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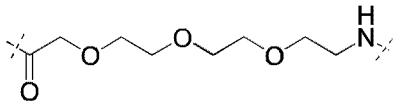
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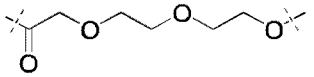
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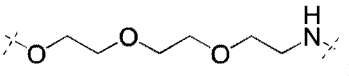
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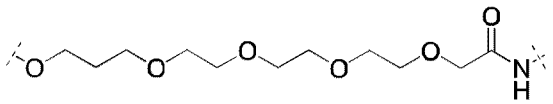
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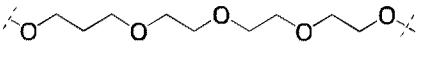
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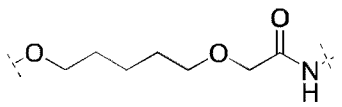
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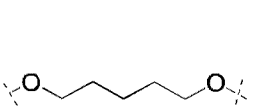
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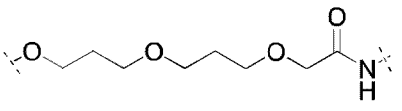
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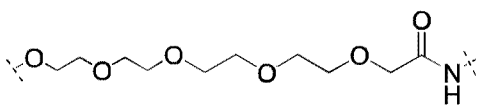
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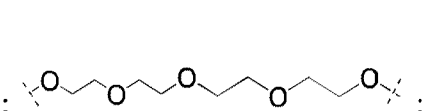
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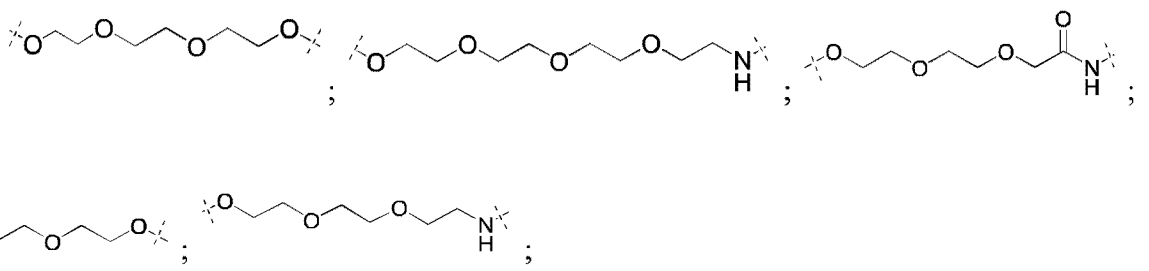

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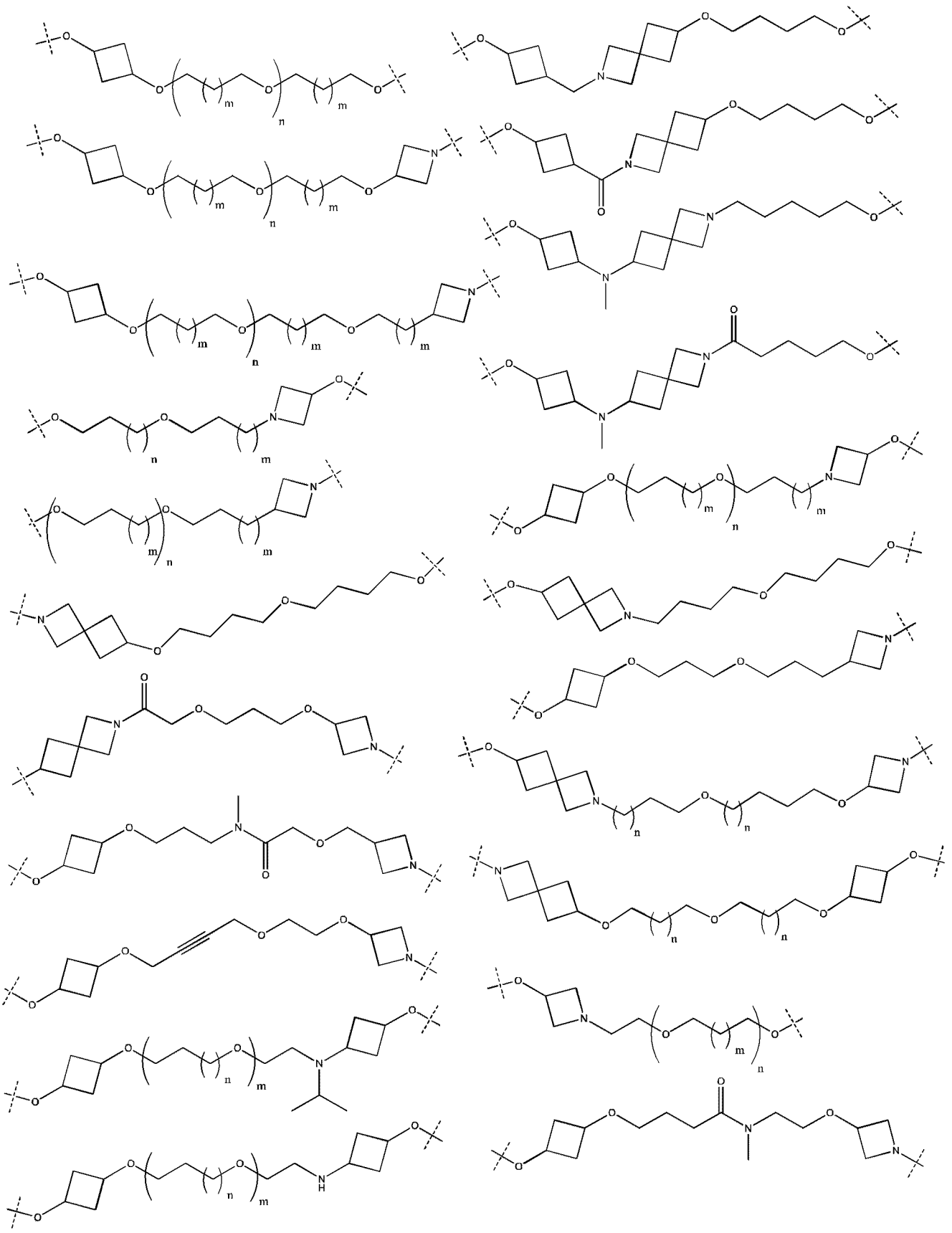

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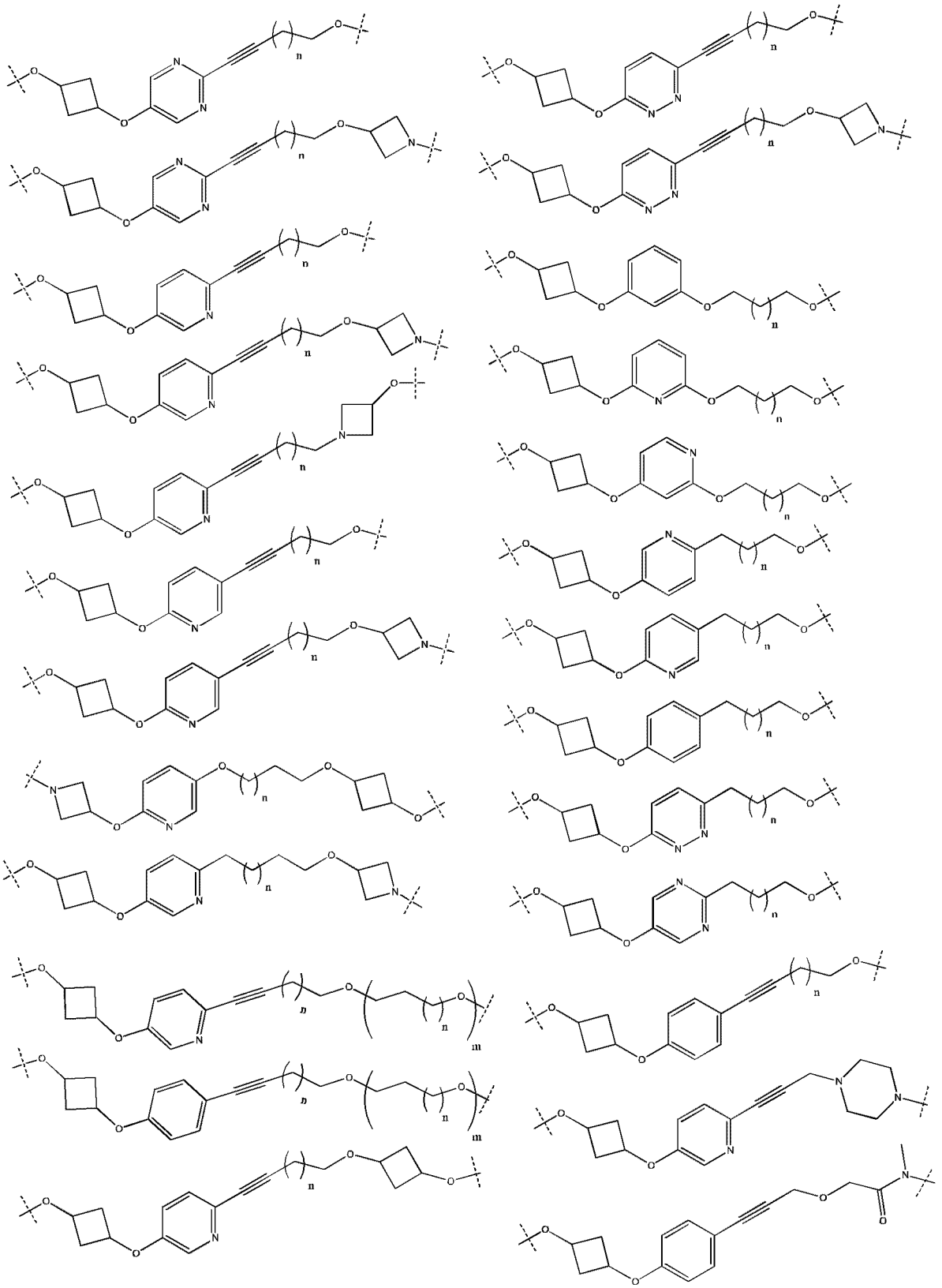

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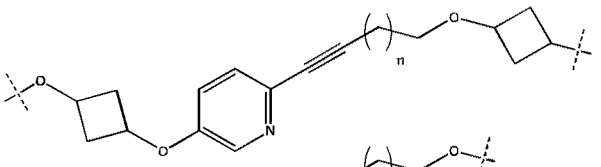

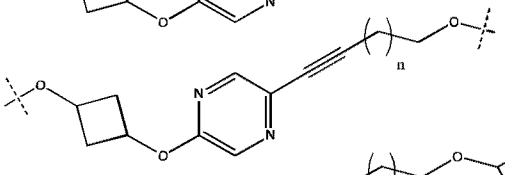

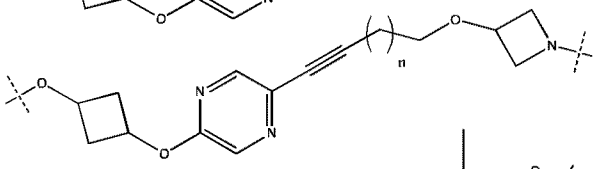

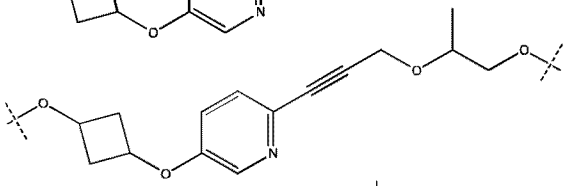

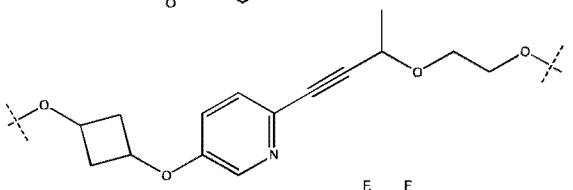

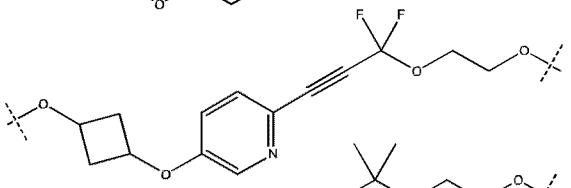

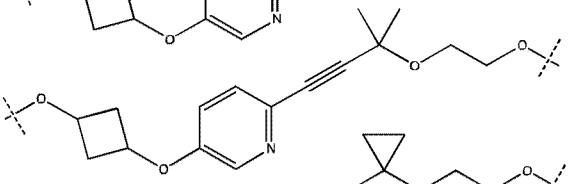

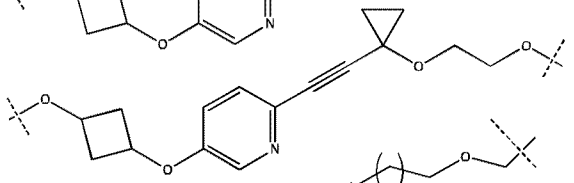

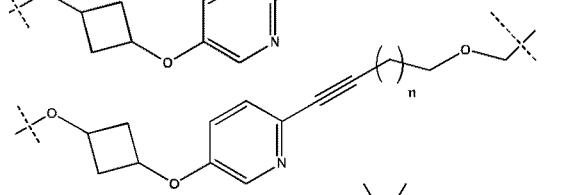

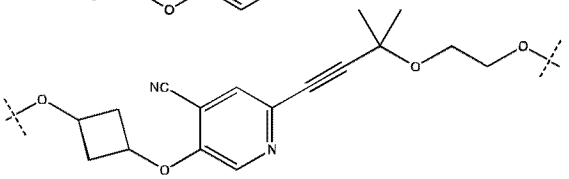

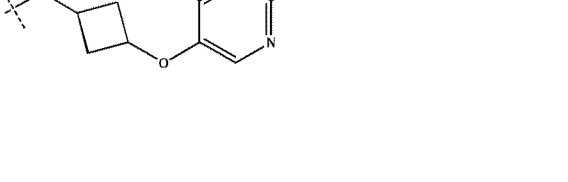

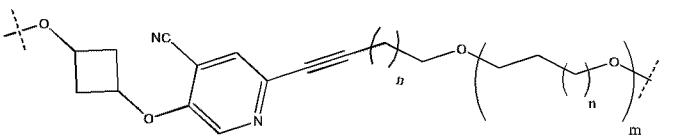

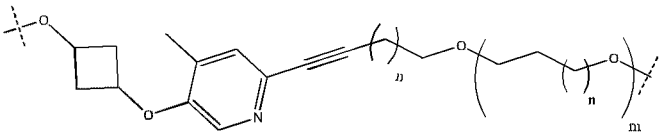

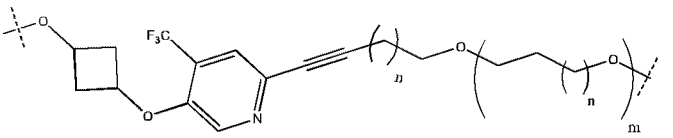

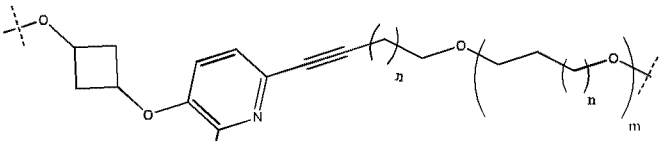

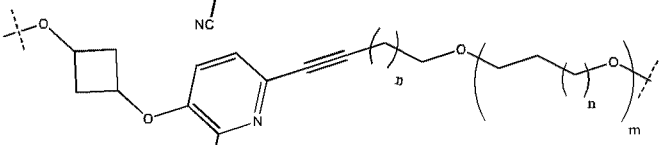

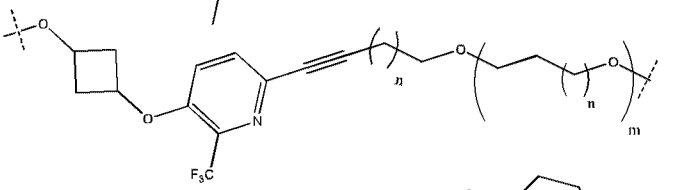

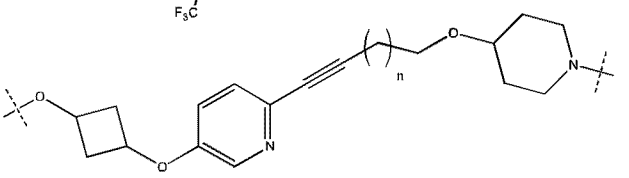

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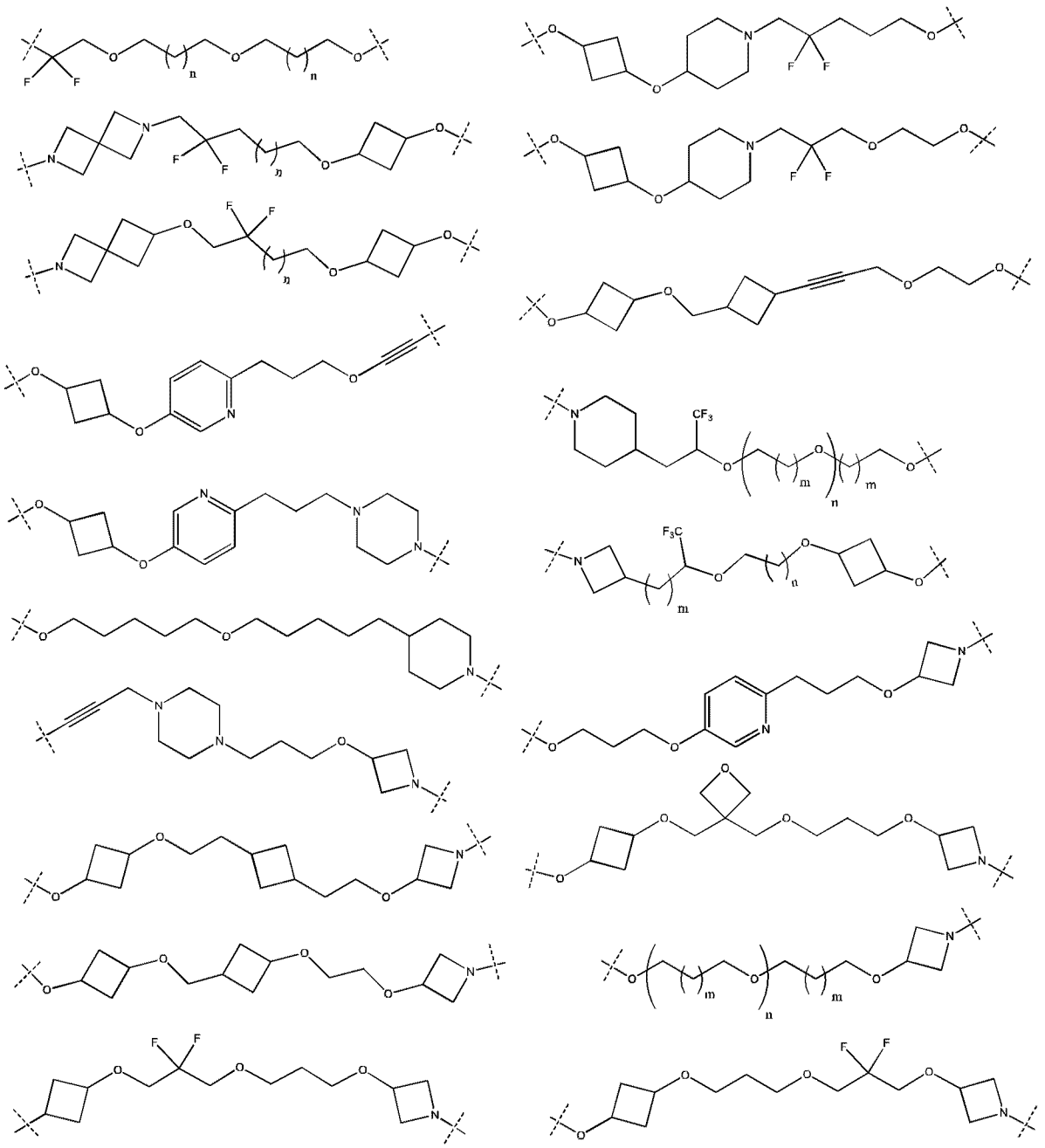

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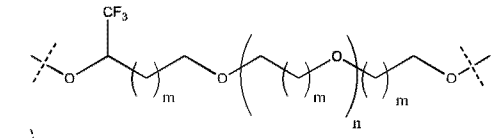

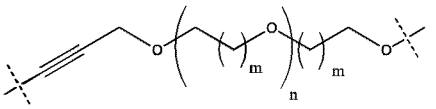

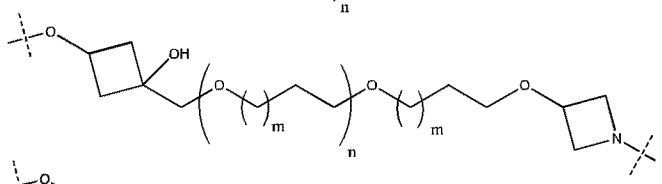

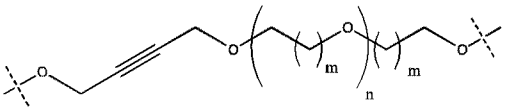

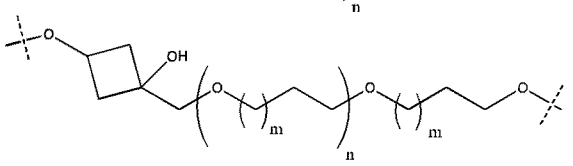

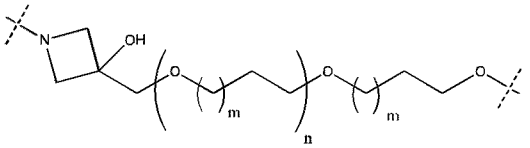

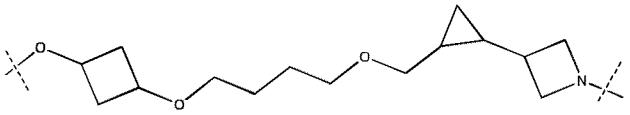

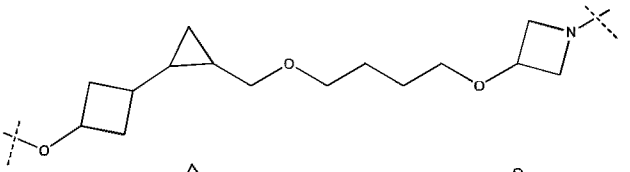

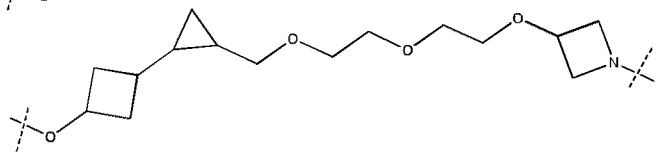

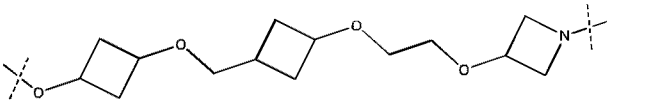

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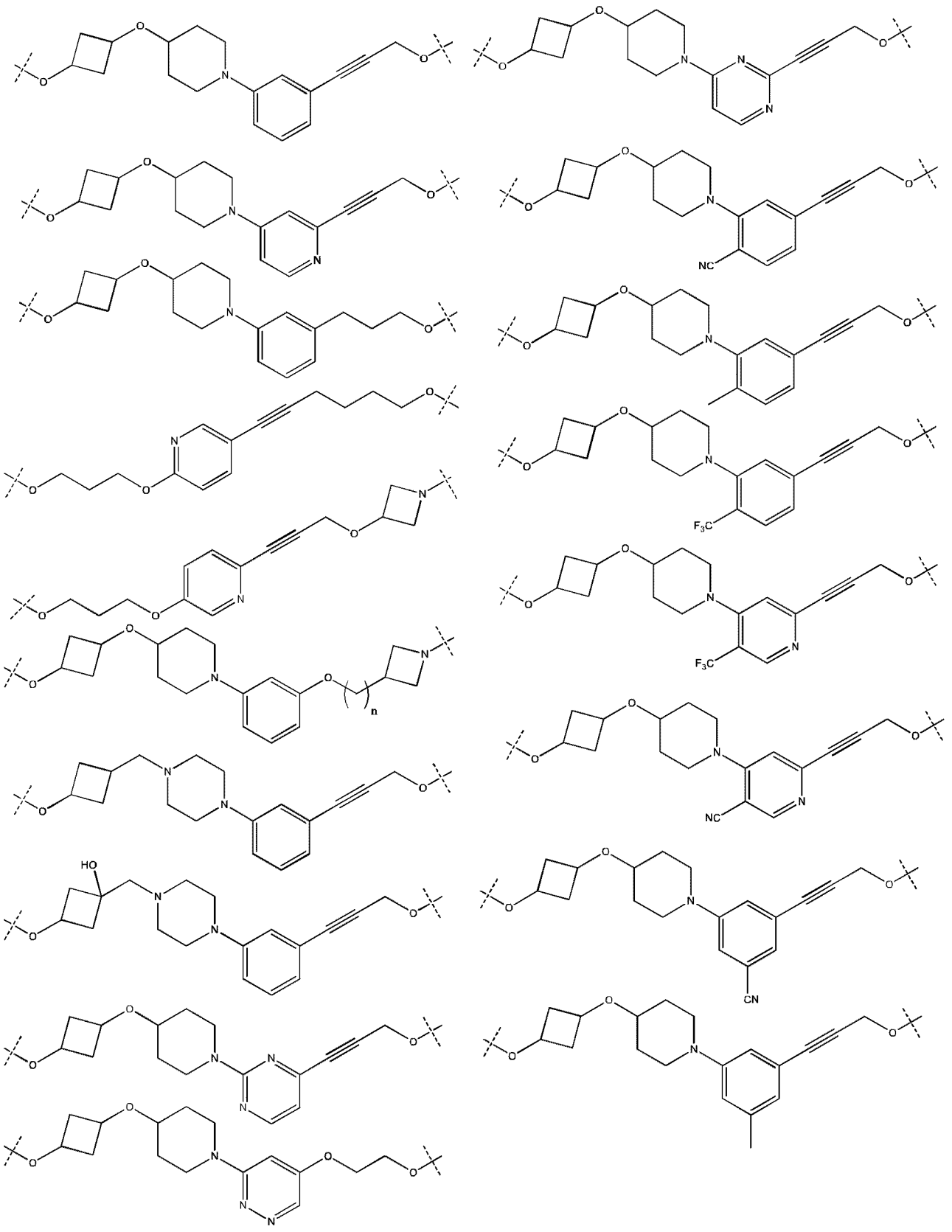

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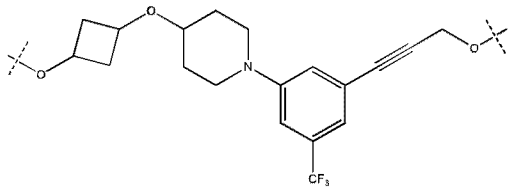
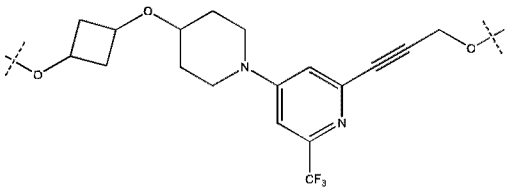
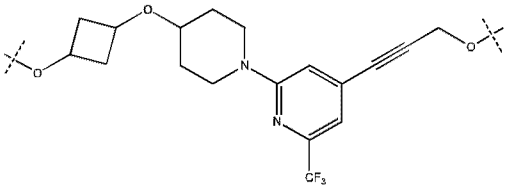
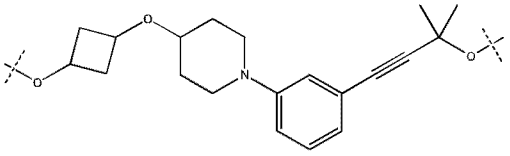
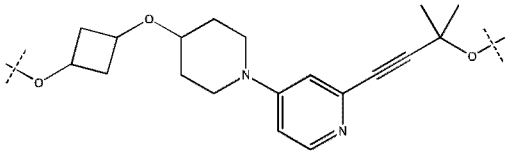
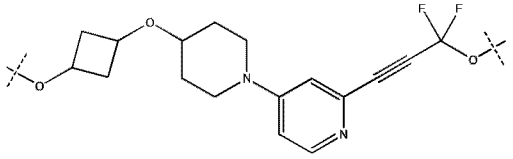
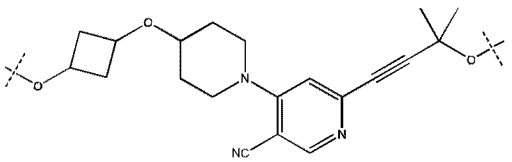
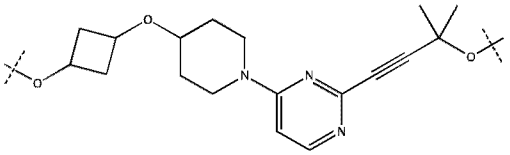

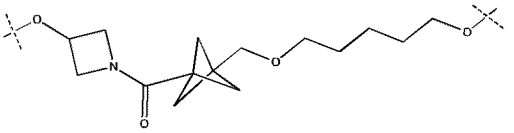
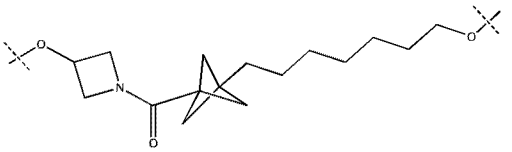
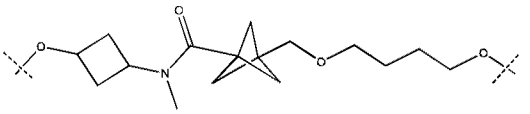
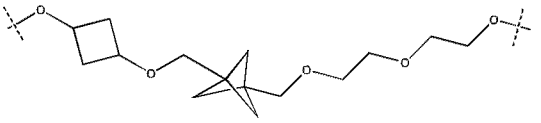
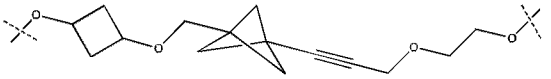
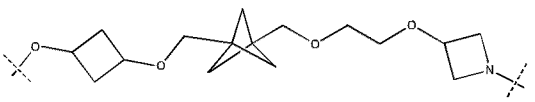

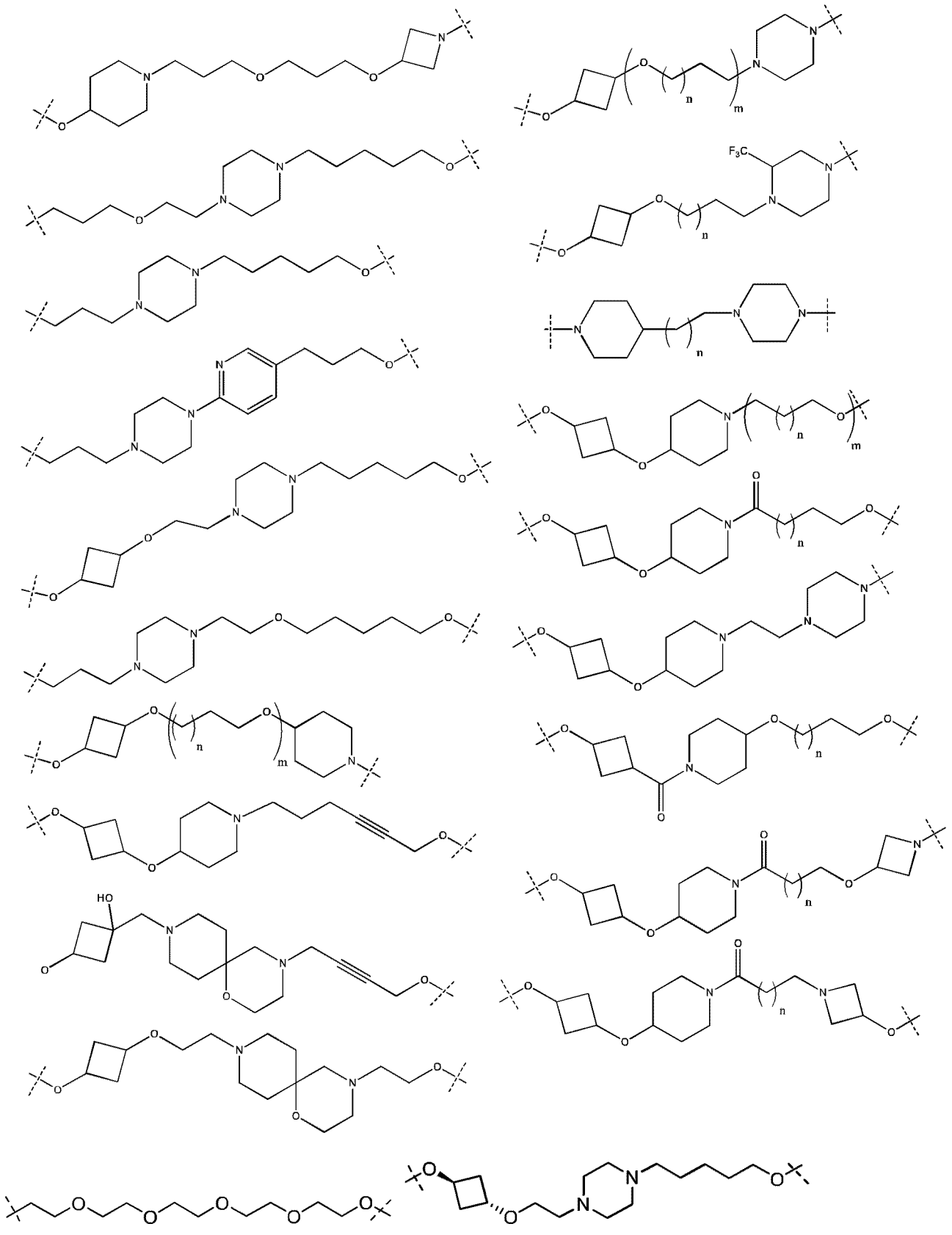

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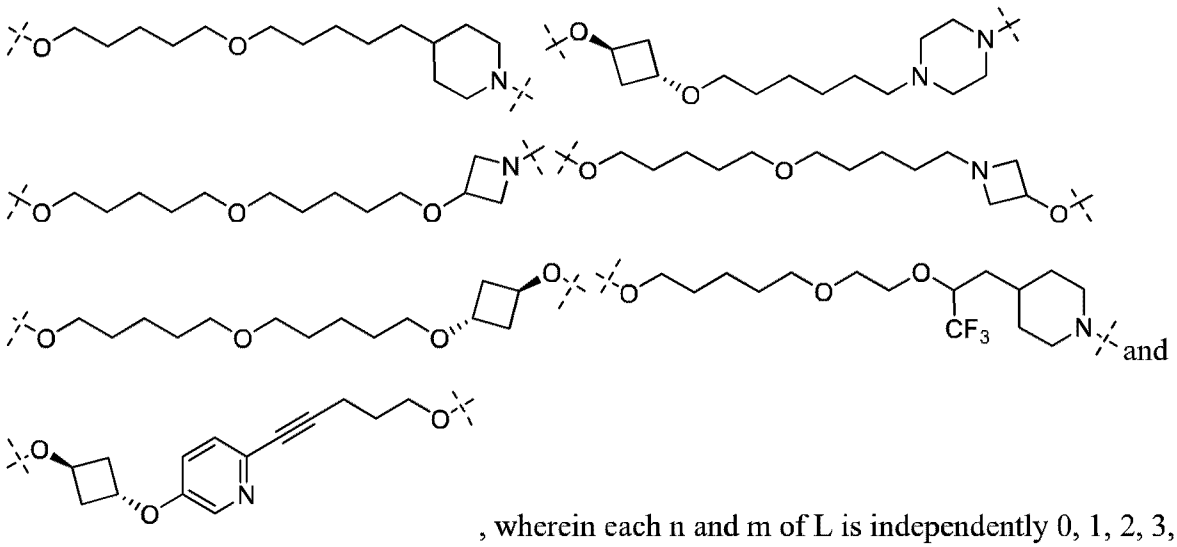
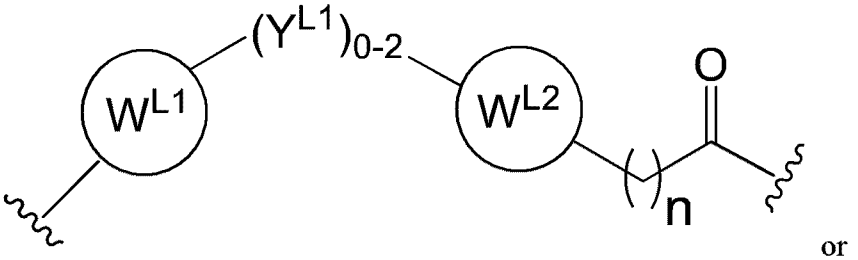
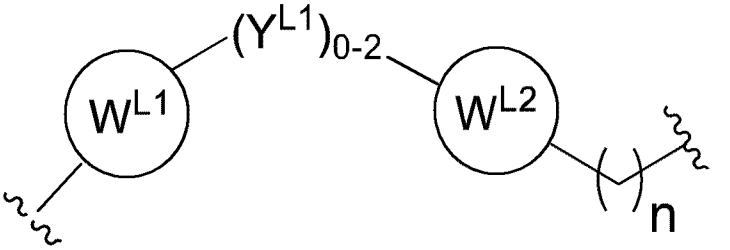


, wherein each n and m of L is independently 0, 1, 2, 3, 4, 5, or 6.

19. The compound of any one of claims 1-14, wherein L is:



or



,

wherein:

W^{L1} and W^{L2} are each independently a 4-8 membered ring with 0-4 heteroatoms, optionally substituted with RQ, each RQ is independently a halogen, OH, CN, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, or 2 RQ groups taken together with the atom to which they are attached form a 4-8 membered ring system containing 0-4 heteroatoms;

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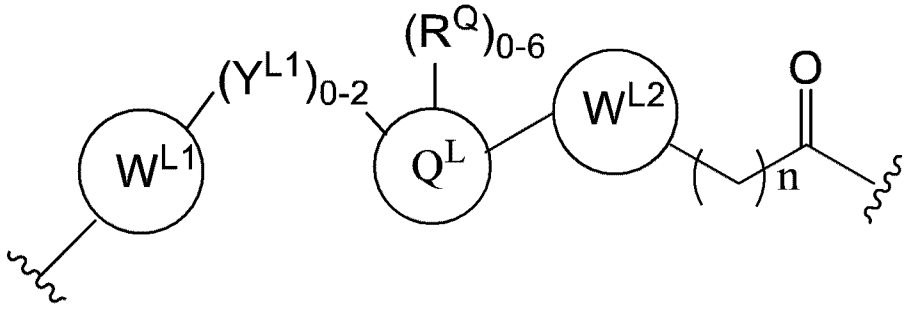
each Y^{L1} is independently a bond, optionally substituted linear or branched C_{1-6} alkoxy, or optionally substituted linear or branched C_{1-6}-alkyl and optionally one or more C atoms are replaced with O;

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

indicates the attachment point of the L to the PTM or the ULM.

20. The compound of any one of claims 1-14, wherein L is:



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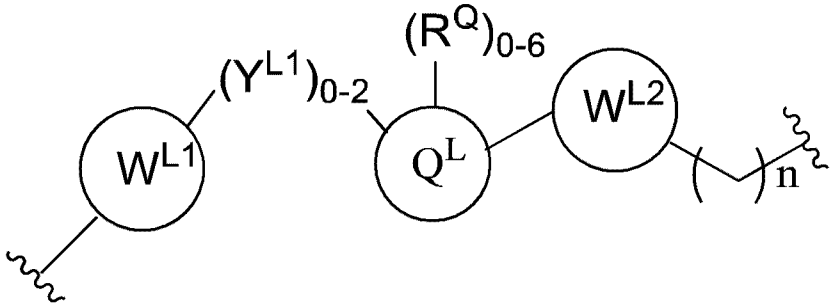

,

wherein:

W^{L1} and W^{L2} are each independently aryl, heteroaryl, cyclic, heterocyclic, C_{1-6} alkyl, bicyclic, biaryl, biheteroaryl, or biheterocyclic, each optionally substituted with RQ, each RQ is independently a halogen, OH, NH_2, CN, CF_3, hydroxyl, nitro, C≡CH, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkyl, C_{1-6} alkoxy, OC_{1-3}alkyl optionally substituted by 1 or more –F, or 2 RQ groups taken together with the atom to which they are attached form a 4-8 membered ring system containing 0-4 heteroatoms;

each Y^{L1} is independently a bond, O, S, NR^{YL2}, $CR^{YL1}R^{YL2}$, C=O, C_{1-6} alkoxy, or C_{1-6} alkyl and optionally one or more C atoms are replaced with O;

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

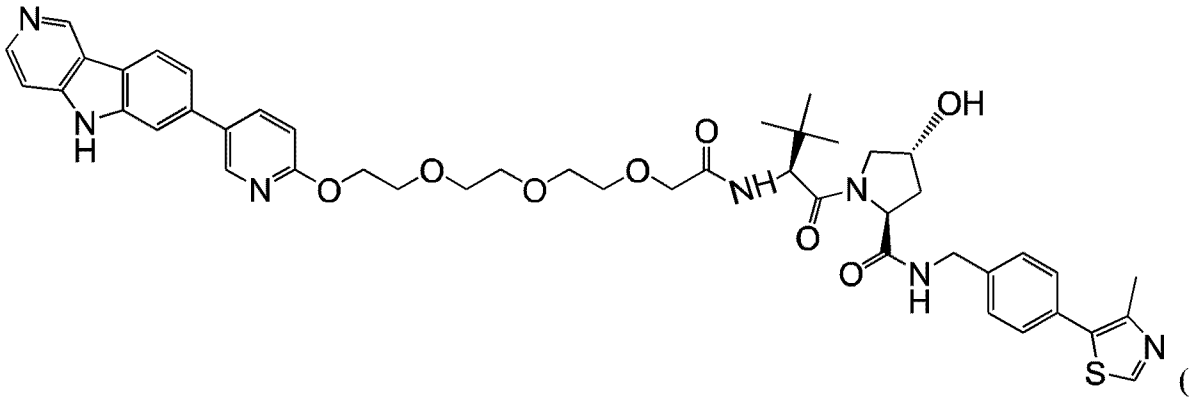
R^{YL1} and R^{YL2} are each independently: H; OH; C_{1-6} alkyl optionally substituted by 1 or more halogen or C_{1-6} alkoxyl; or R^{YL1}, R^{YL2} together with the atom to which they are attached form a 3-8 membered ring system containing 0-2 heteroatoms;

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

indicates the attachment point of the L to the PTM or the ULM.

21. The compound of any one of claims 1-14, wherein the L is a polyethylenoxy group comprising from 1 to 10 ethylene glycol units optionally substituted with aryl or phenyl.

22. The bifunctional compound of claim 1, wherein the compound is selected from:



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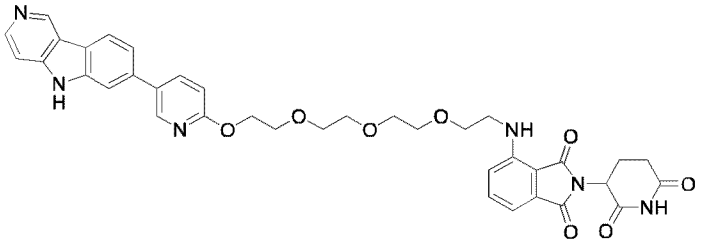

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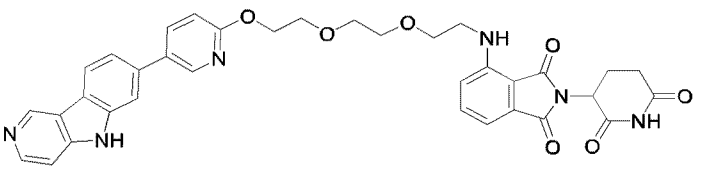

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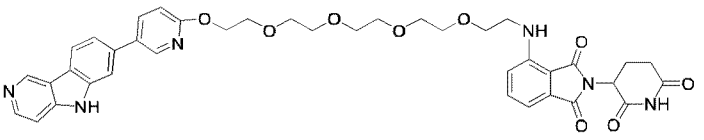

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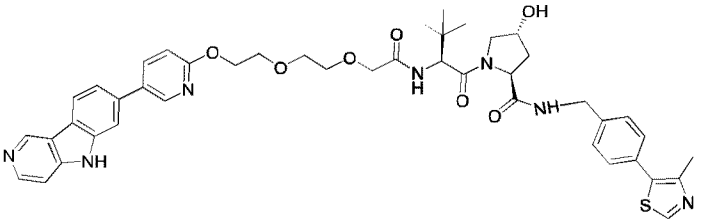

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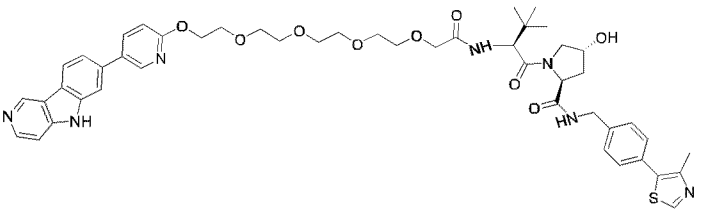

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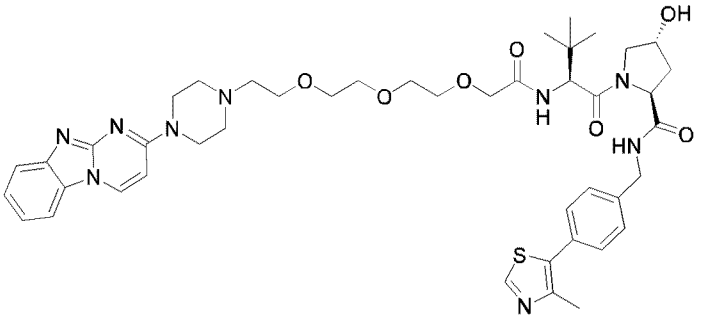

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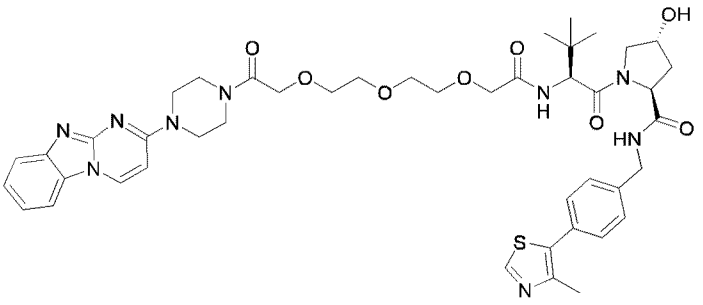

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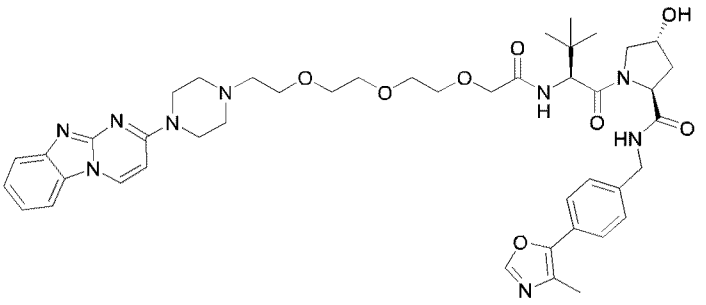

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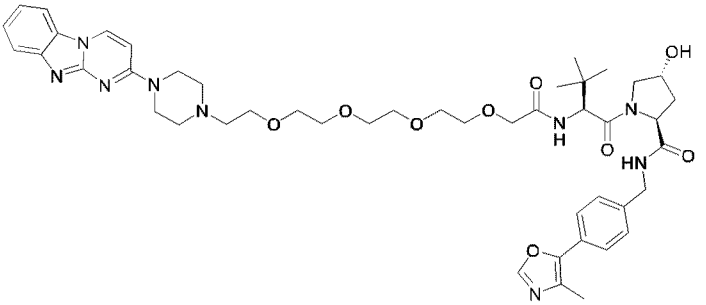

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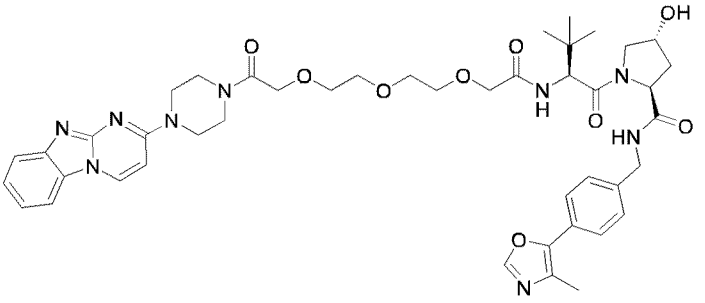

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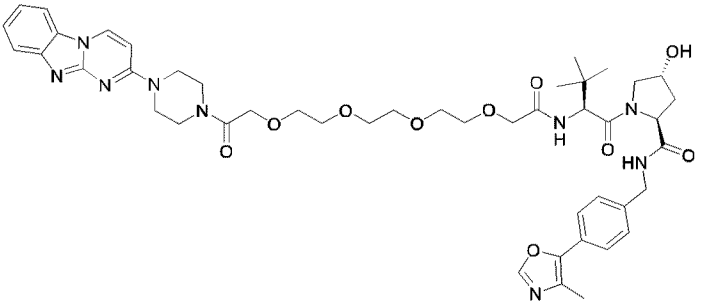

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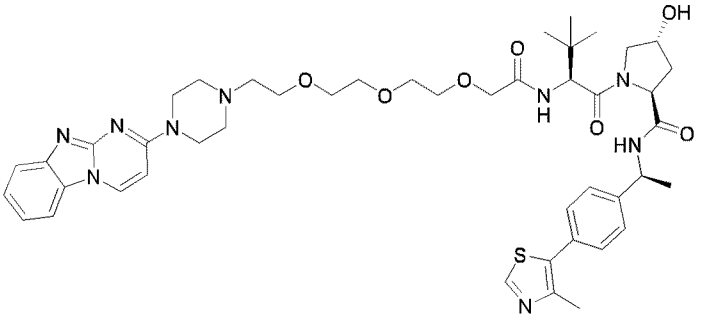

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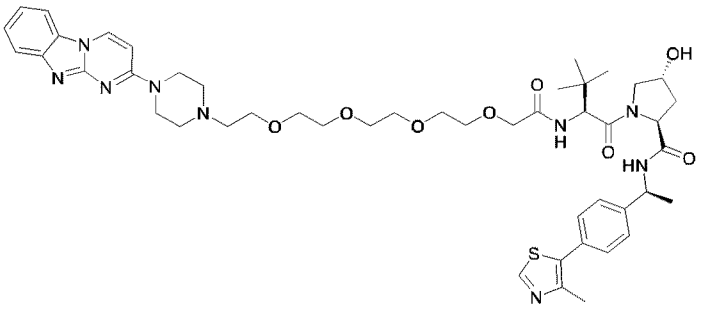

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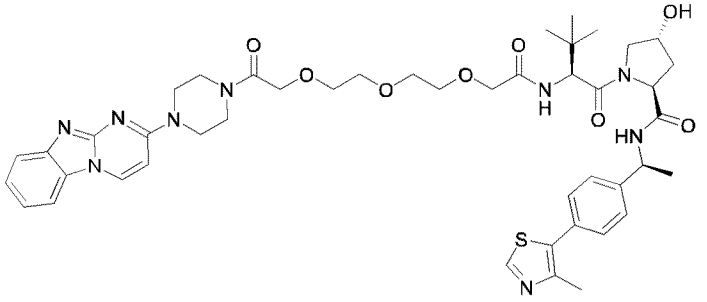

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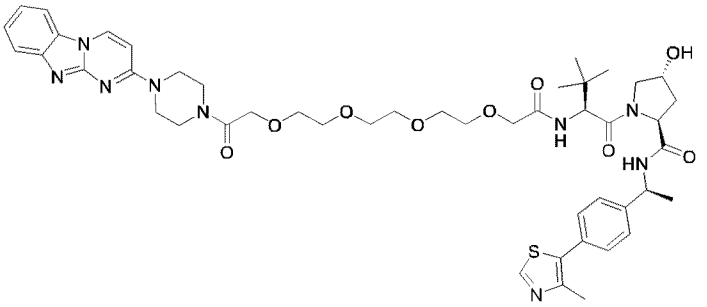

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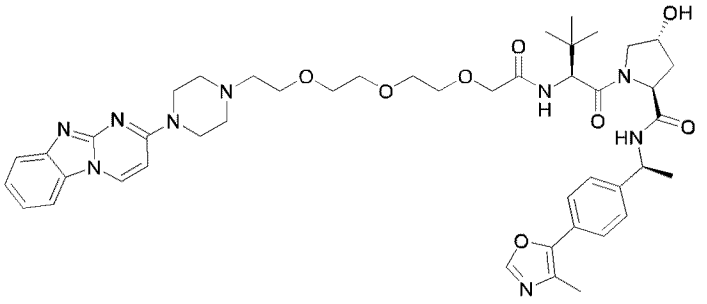

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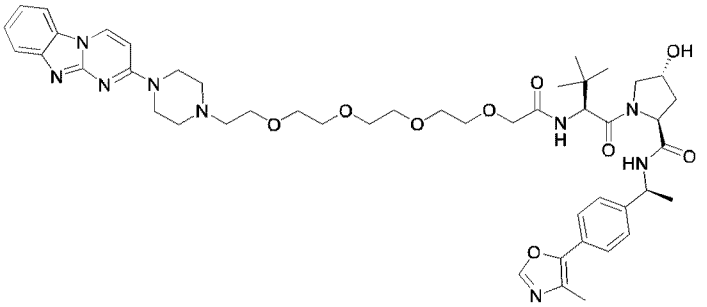

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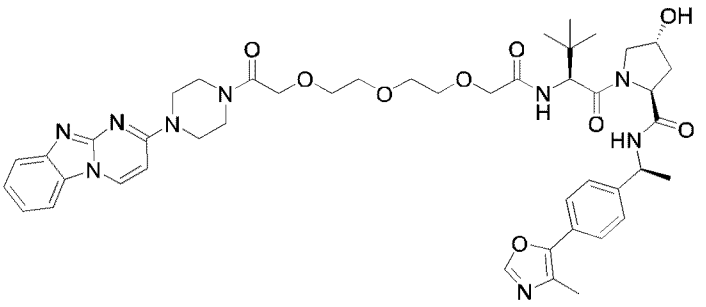

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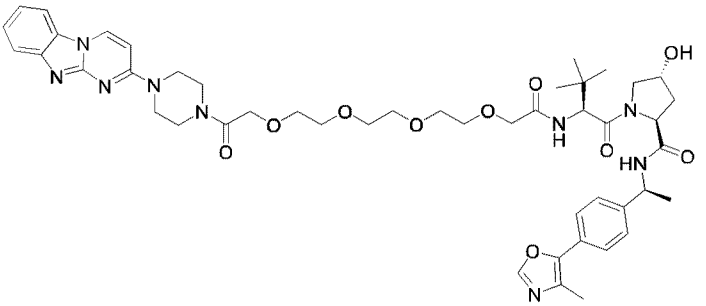

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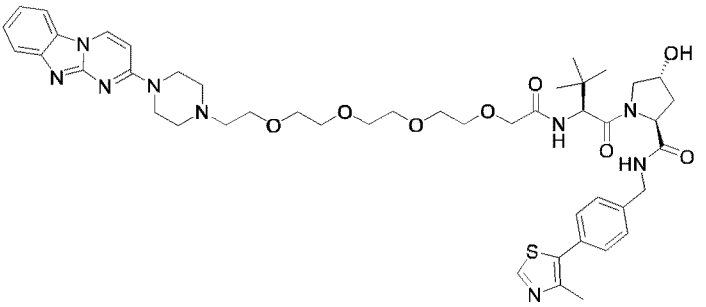

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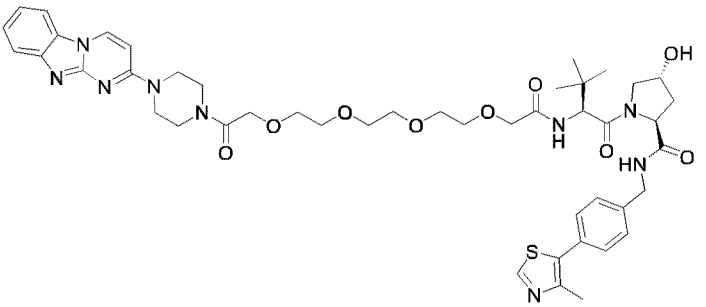

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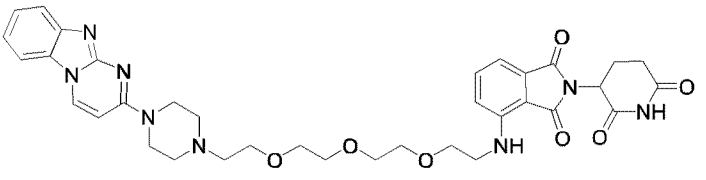

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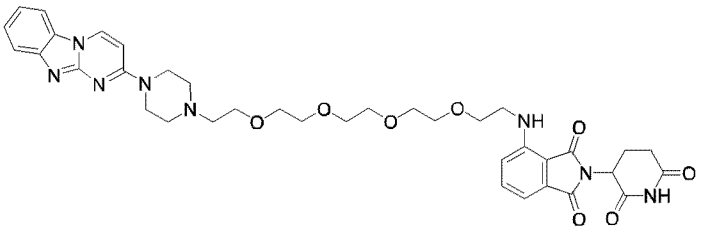

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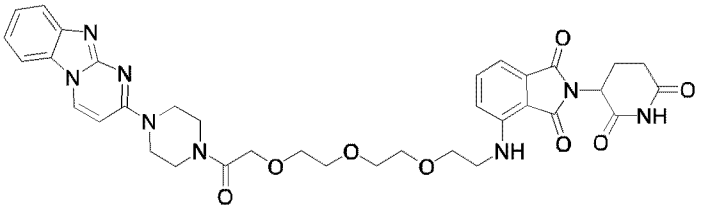

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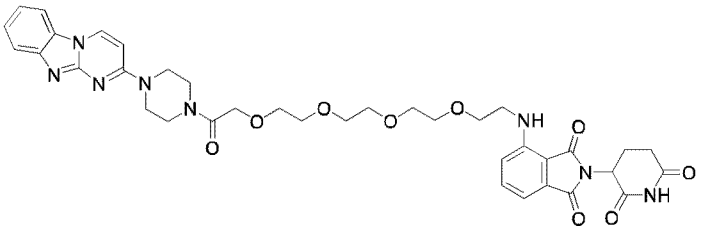

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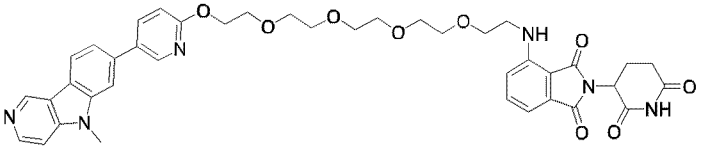

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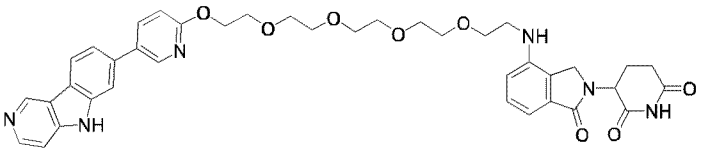

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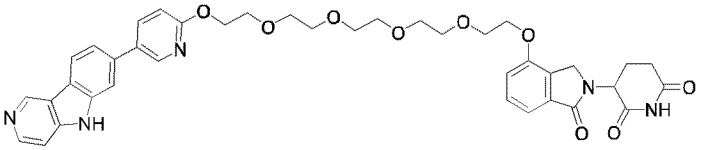

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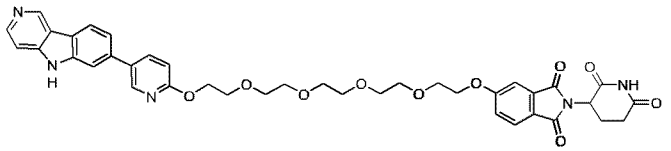

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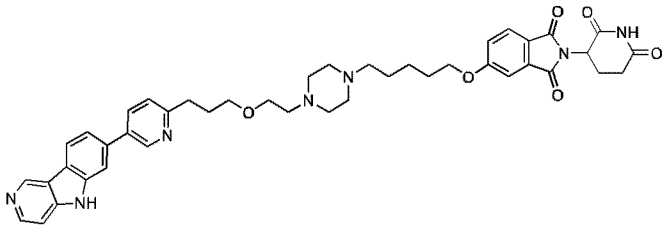

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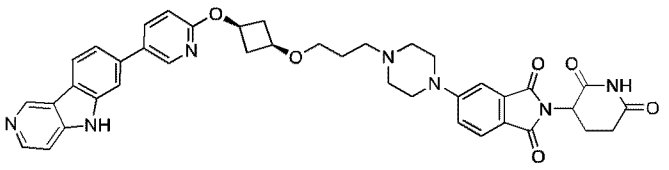

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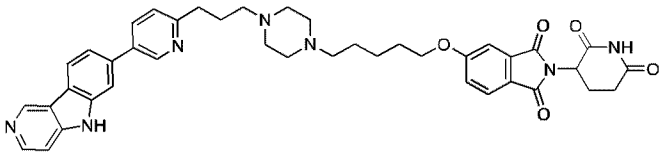

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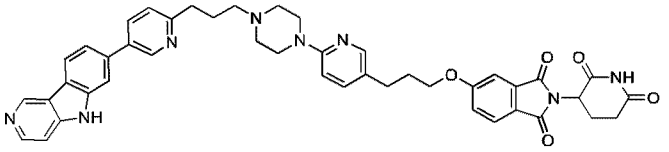

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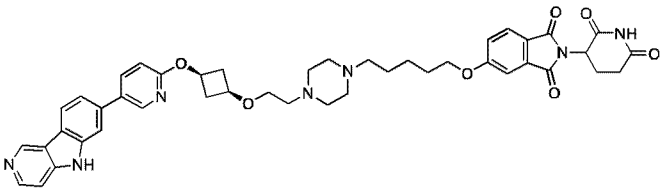

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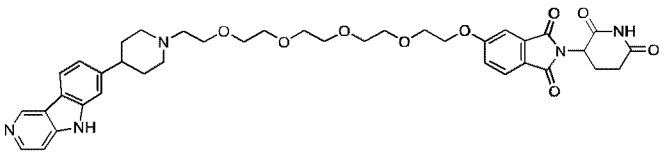

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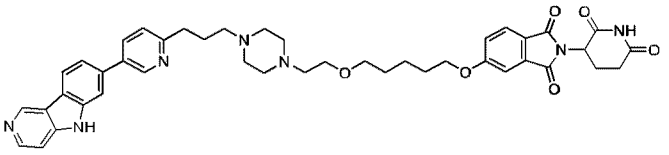

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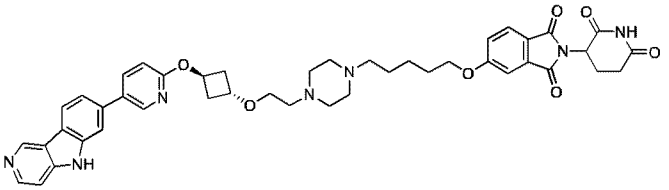

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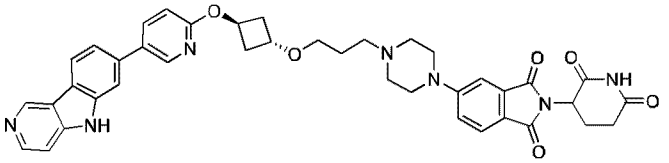

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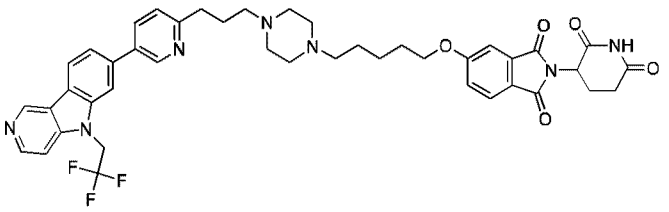

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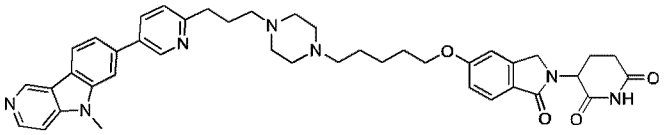

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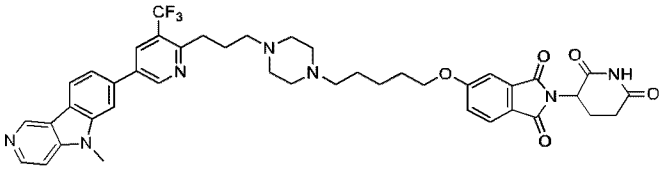

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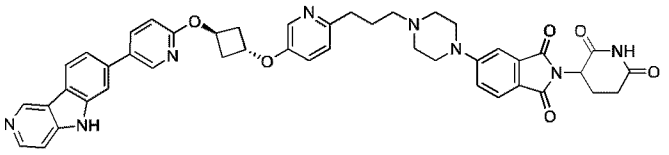

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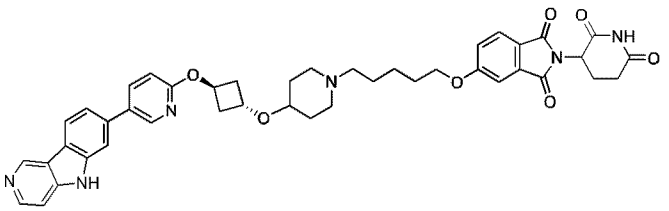

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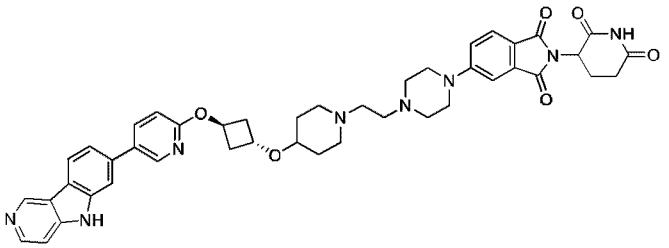

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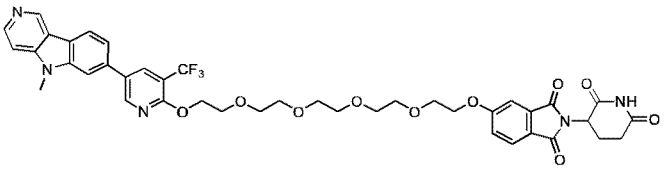

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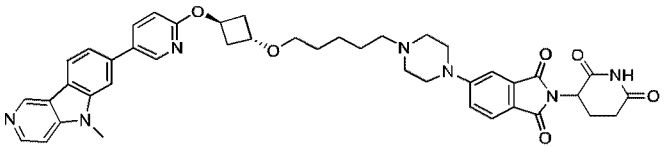

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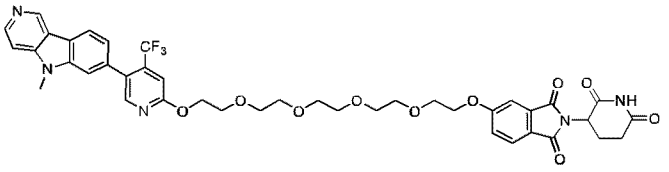

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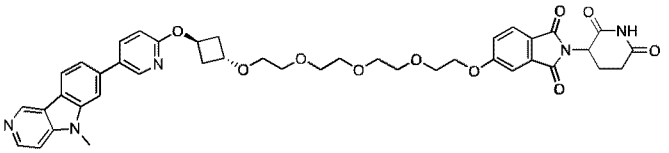

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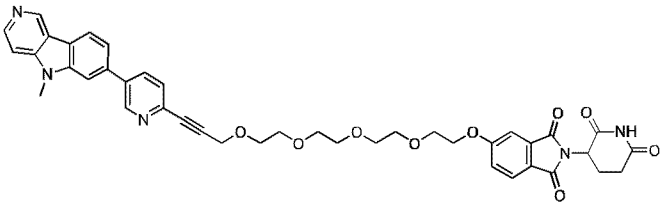

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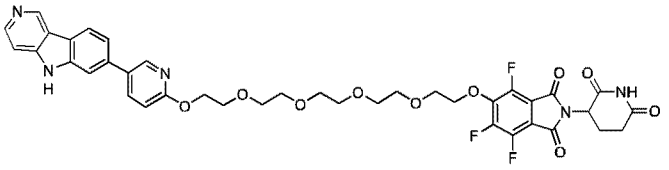

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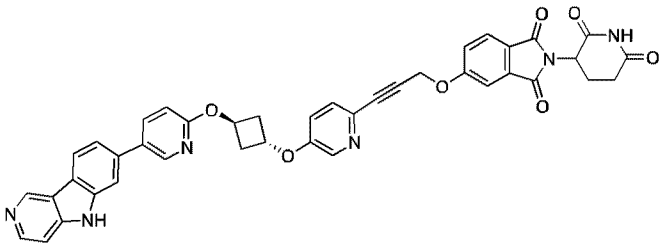

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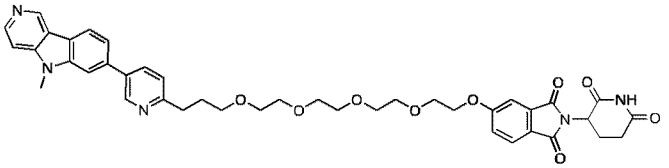

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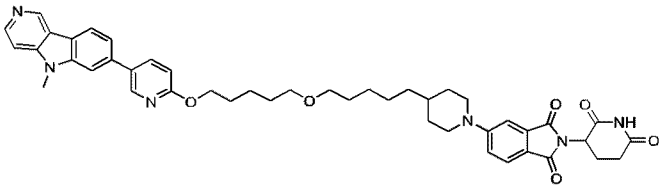

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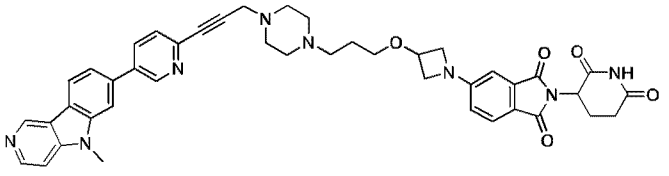

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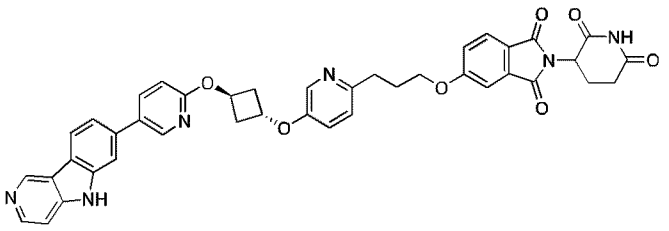

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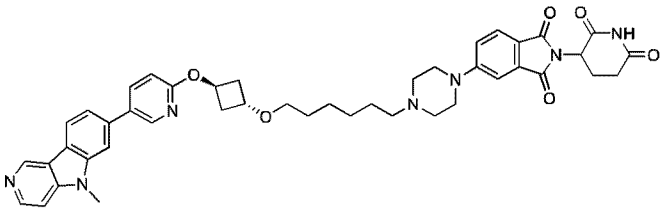

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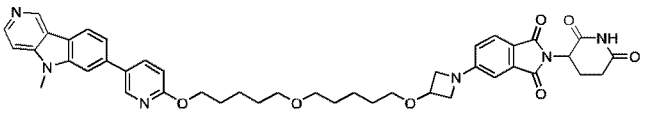

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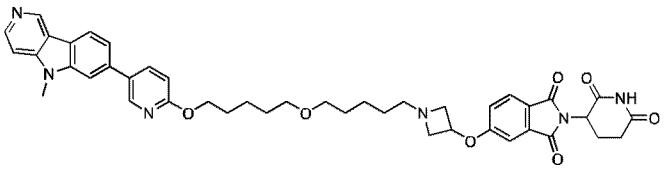

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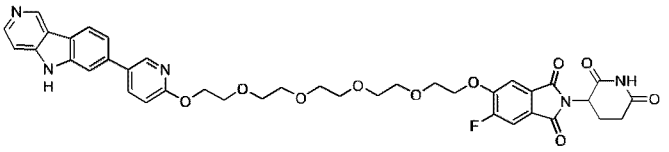

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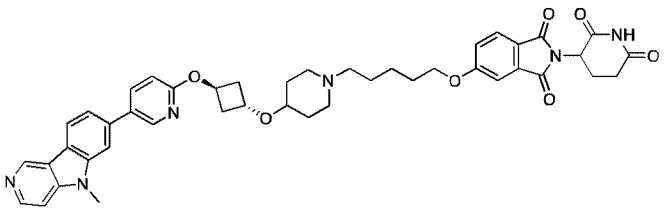

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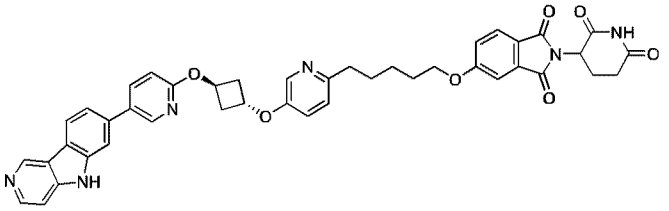

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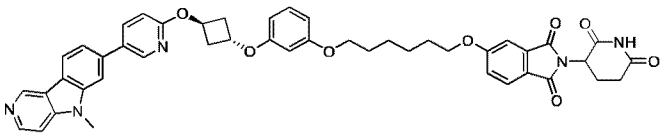

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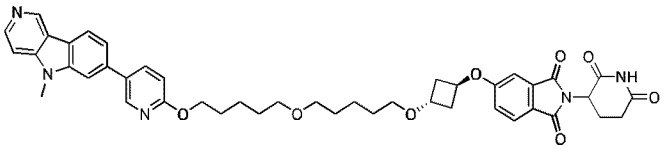

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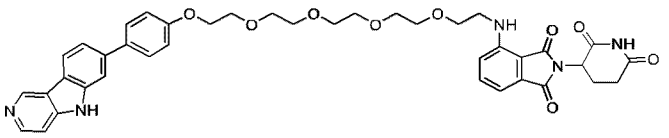

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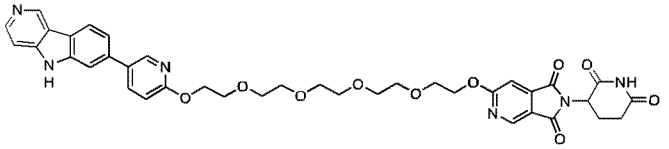

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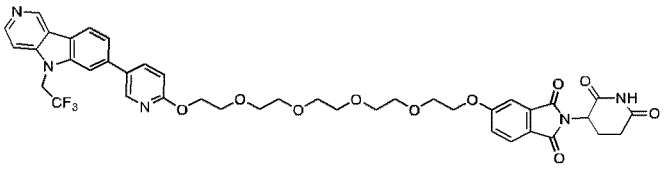

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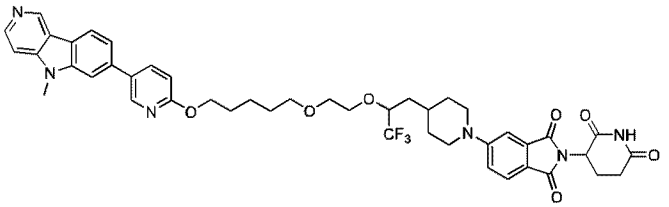

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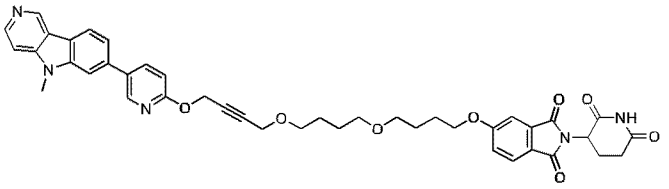

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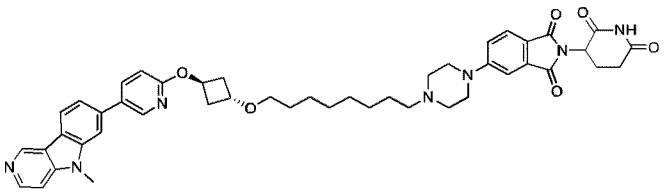

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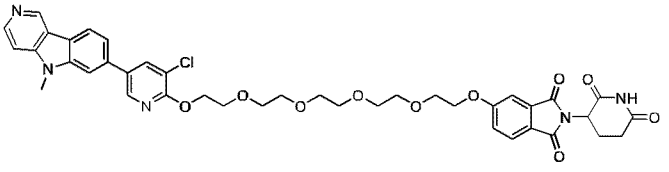

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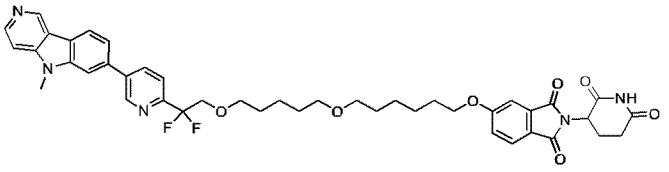

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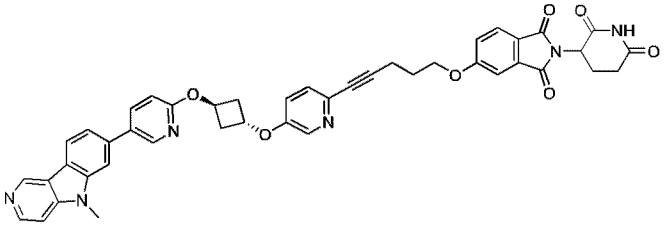

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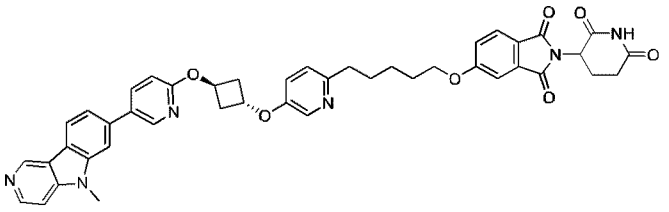

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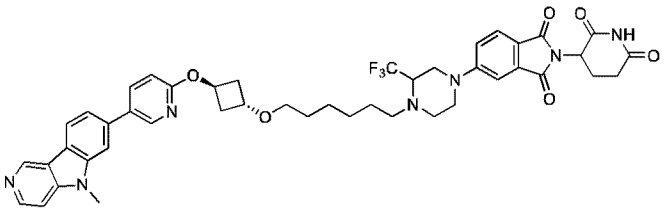

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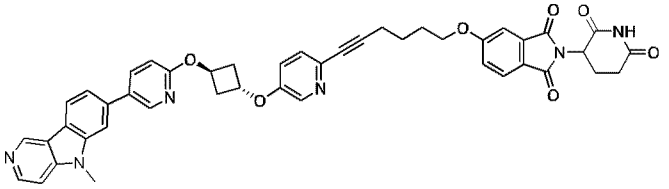

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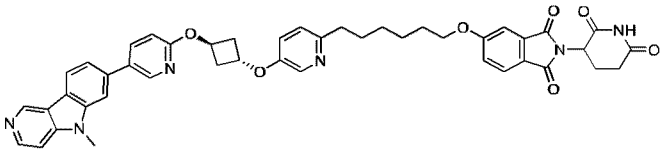

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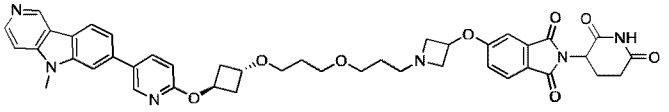

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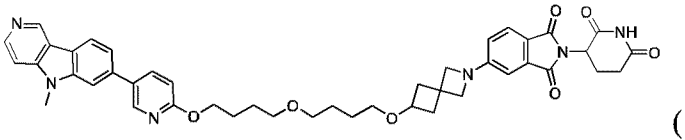

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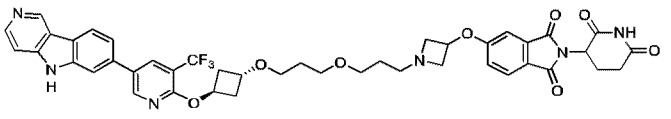

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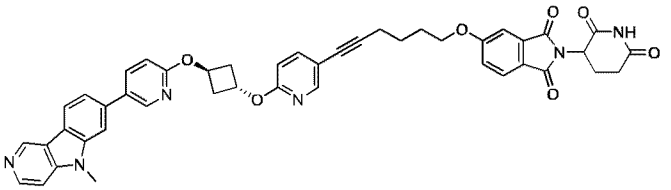

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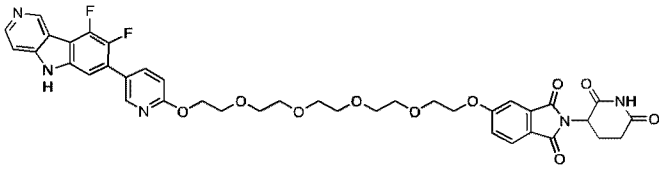

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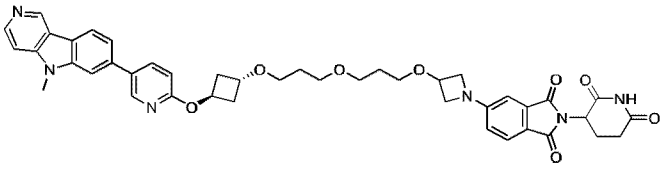

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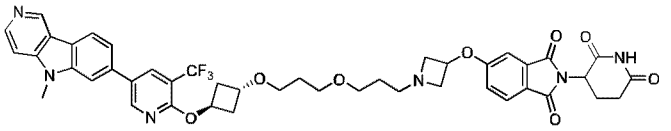

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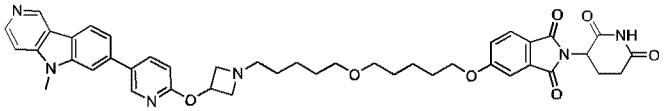

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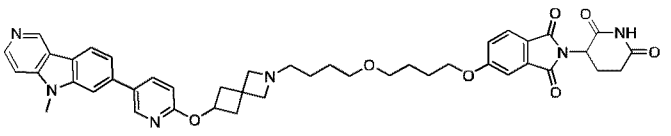

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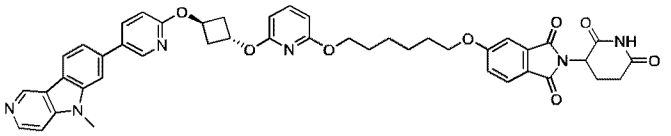

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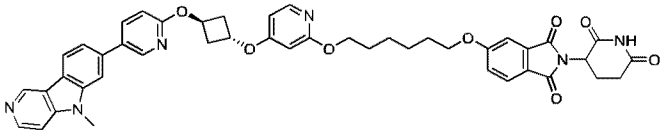

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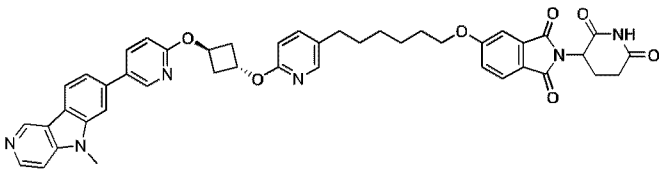

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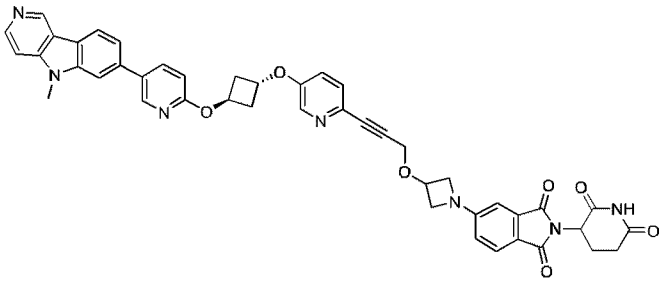

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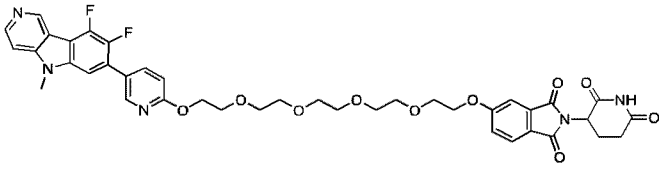

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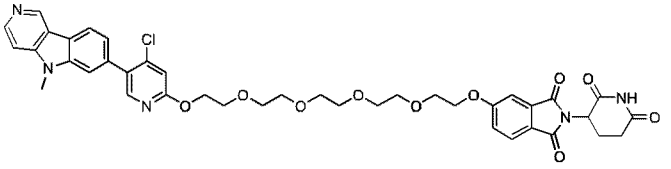

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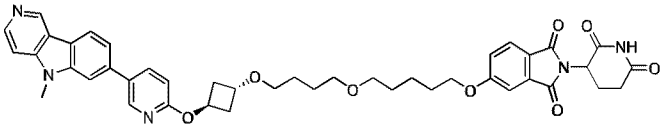

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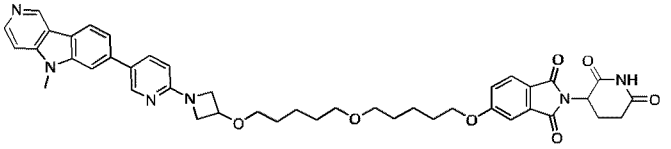

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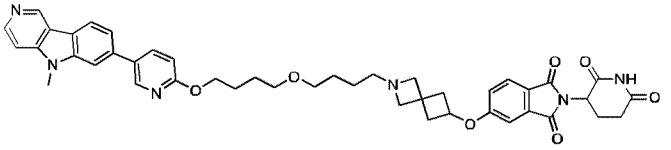

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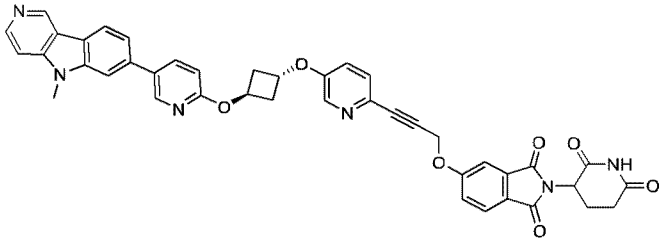

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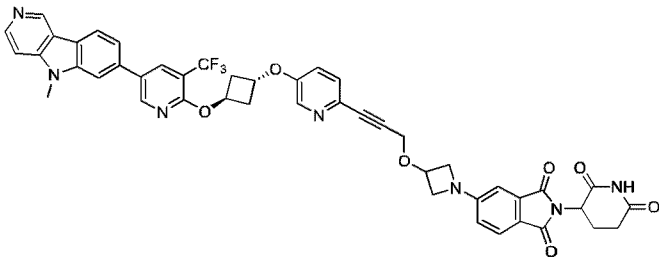

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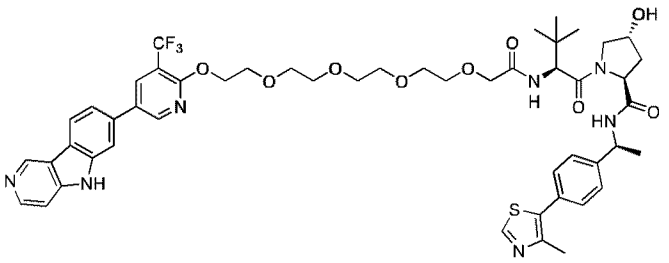

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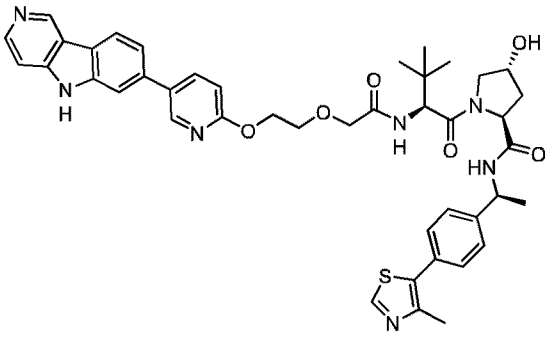

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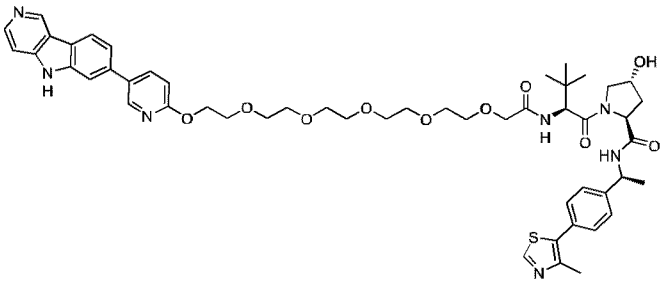

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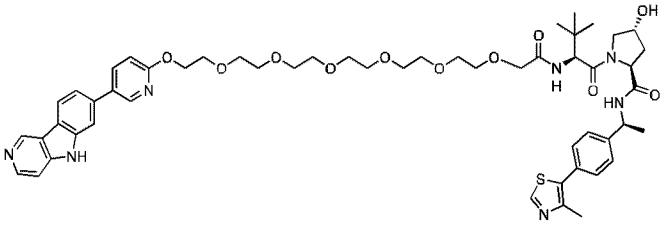

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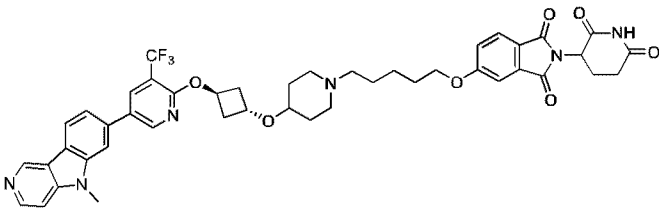

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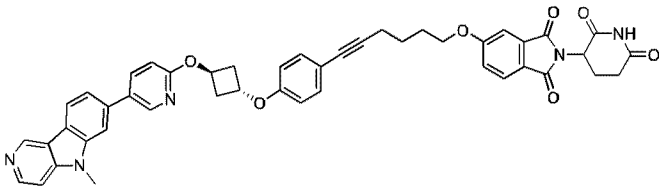

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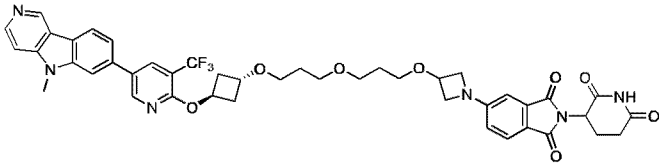

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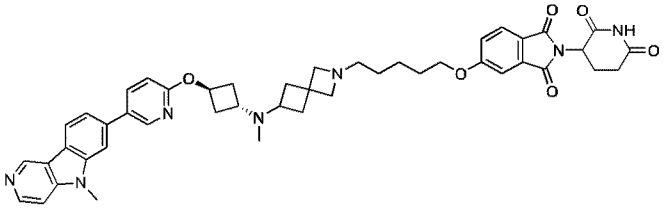

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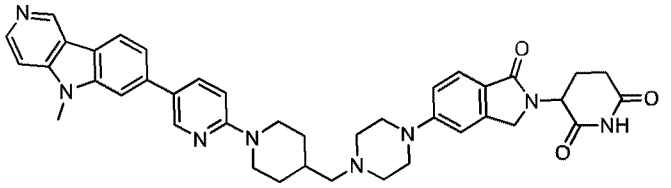

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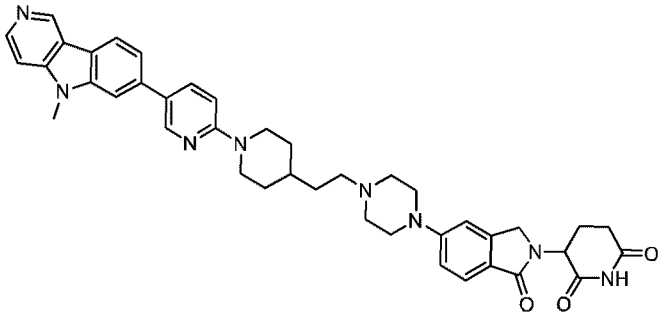

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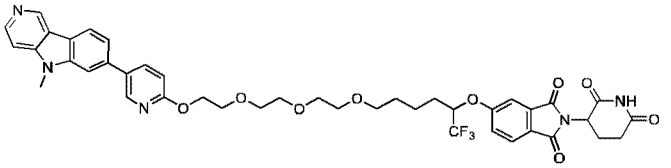

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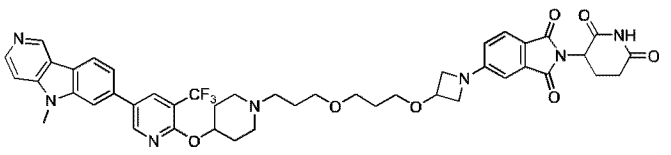

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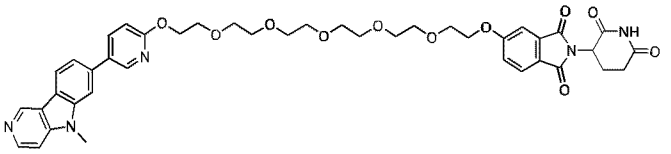

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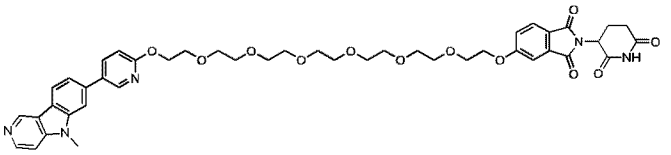

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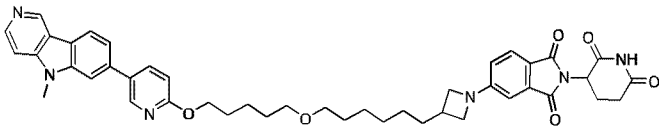

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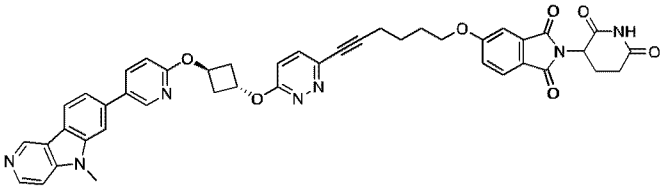

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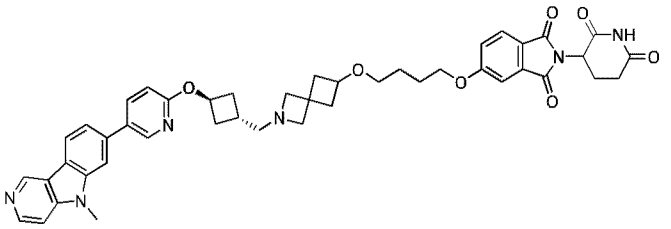

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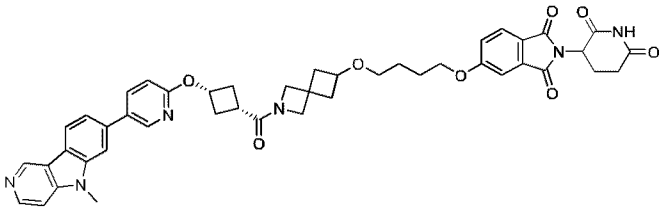

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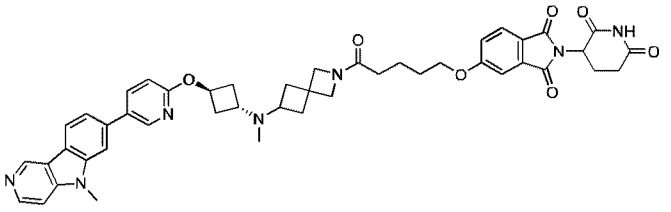

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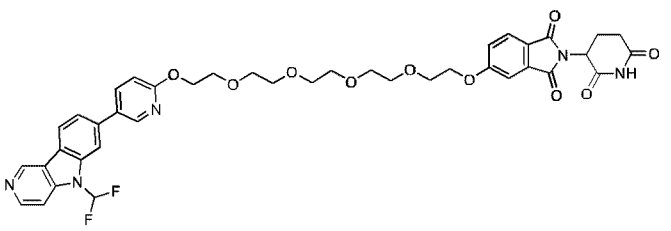

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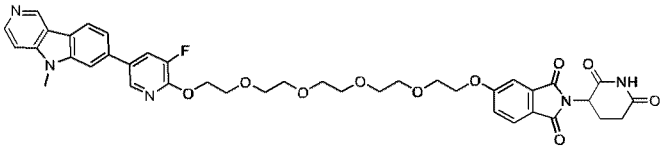

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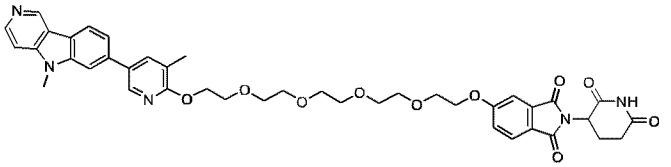

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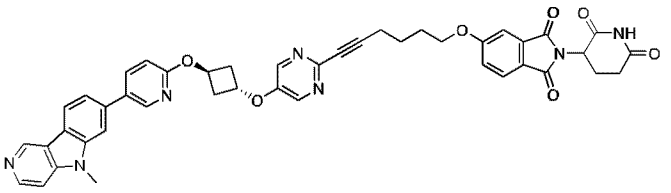

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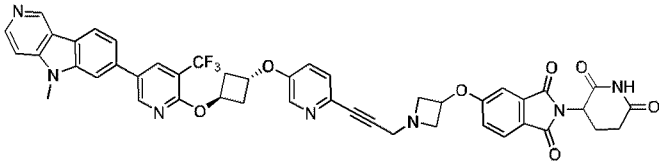

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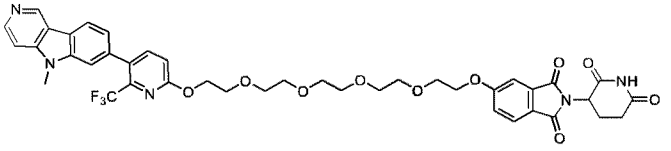

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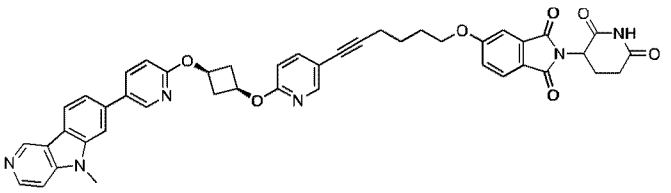

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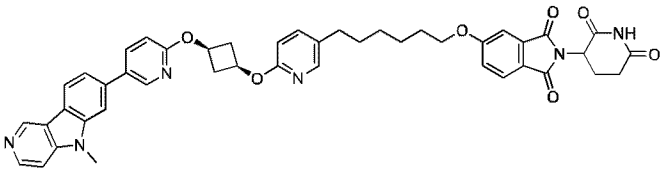

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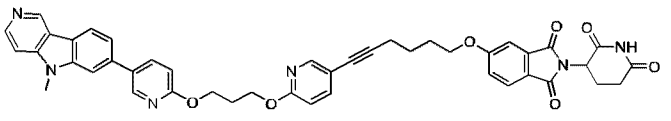

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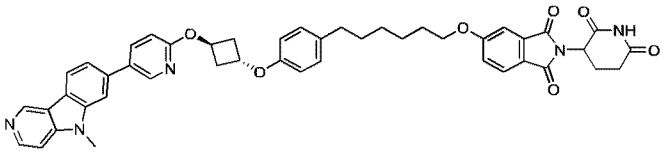

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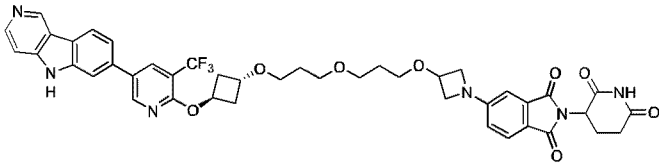

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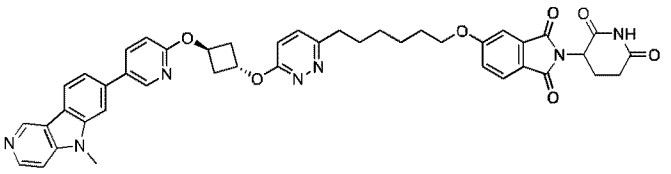

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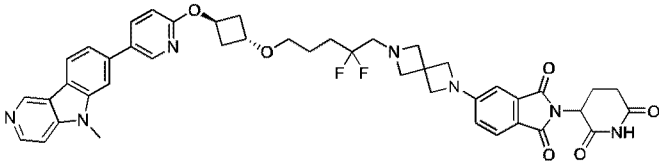

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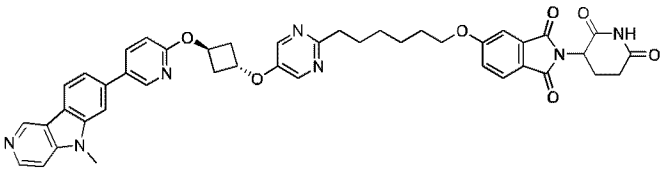

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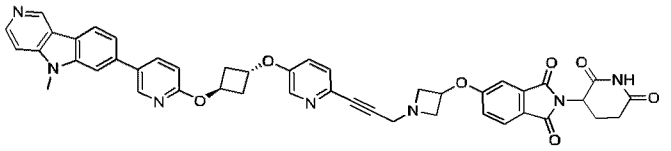

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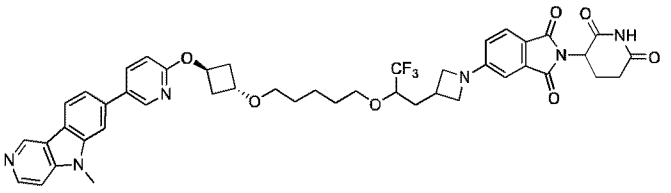

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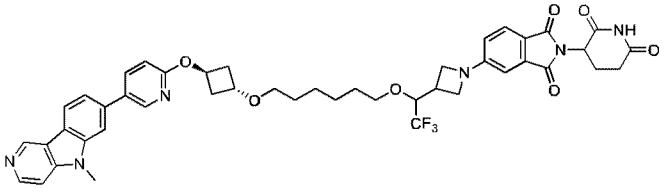

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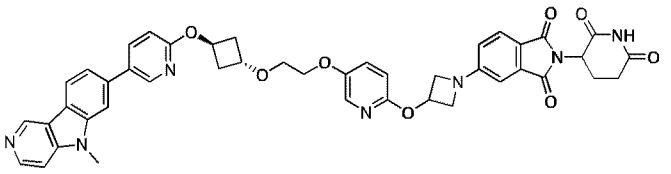

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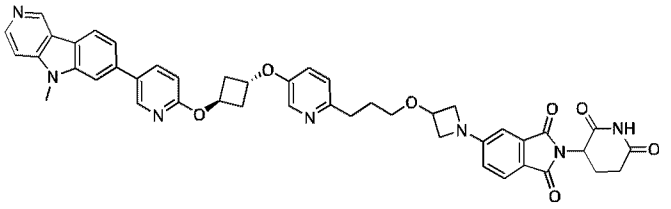

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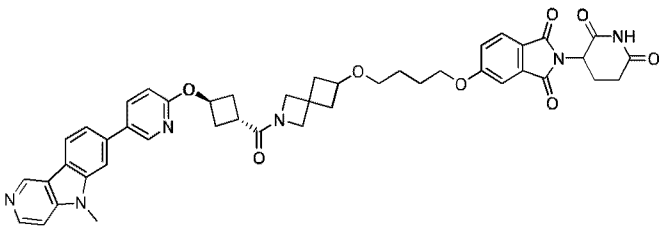

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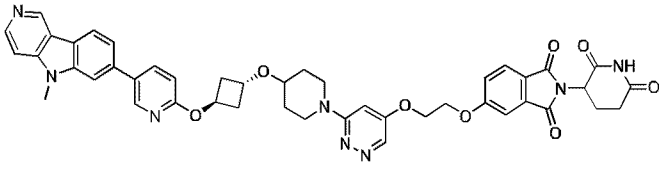

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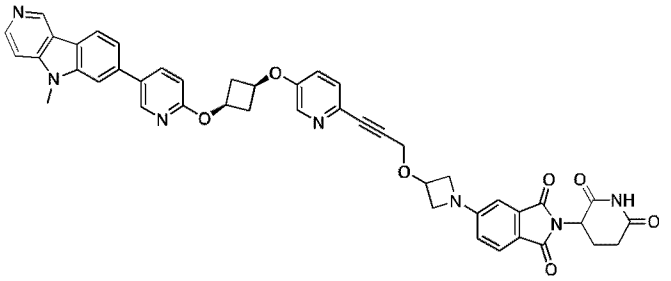

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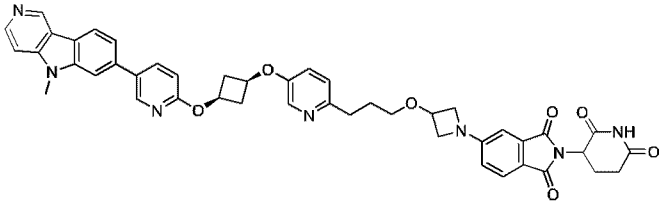

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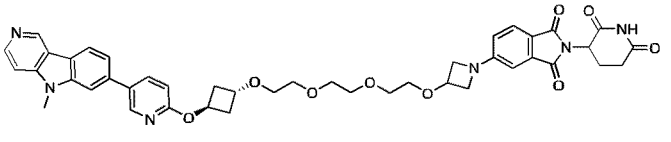

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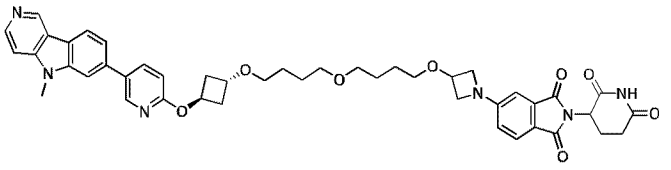

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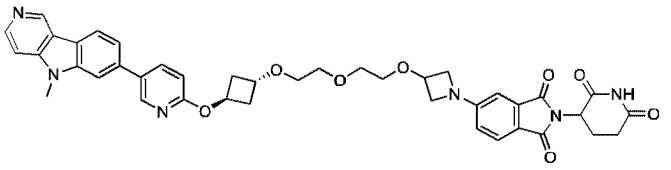

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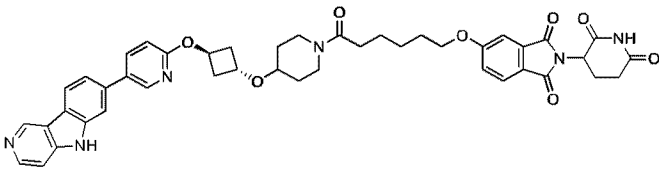

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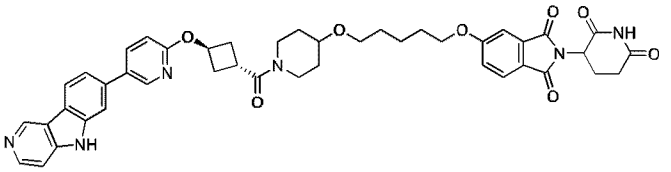

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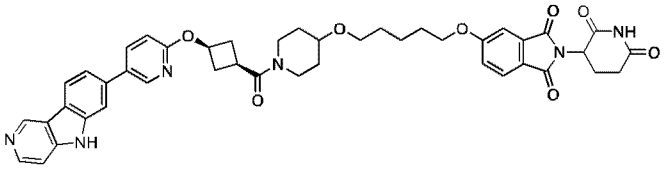

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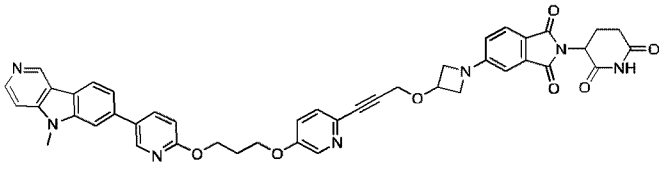

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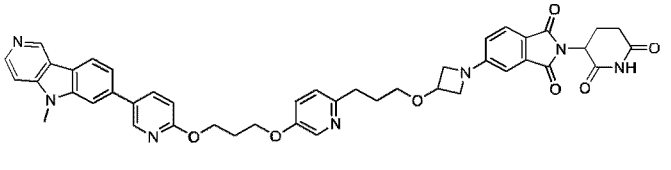

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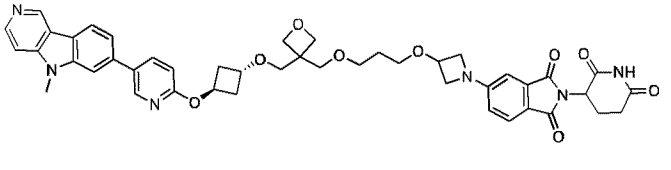

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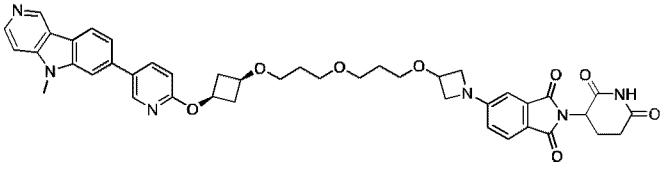

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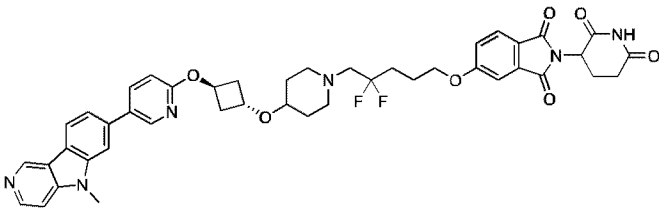

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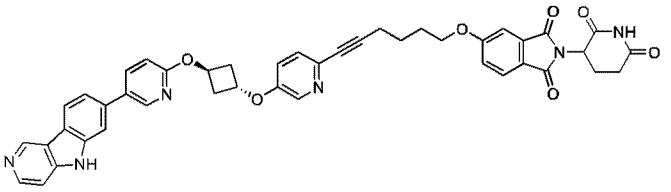

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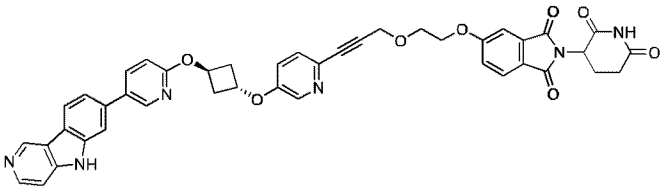

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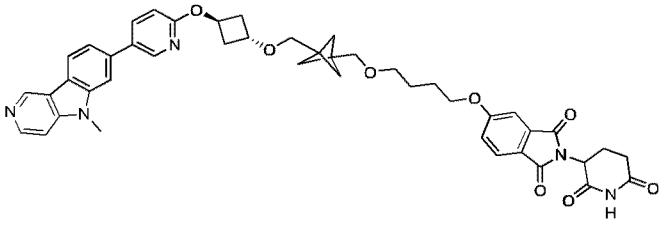

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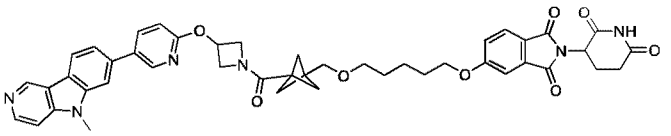

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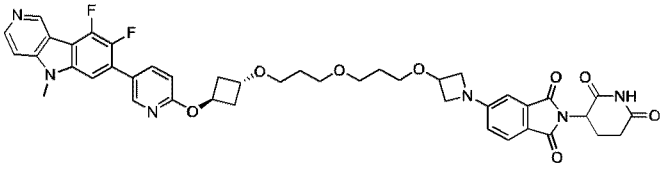

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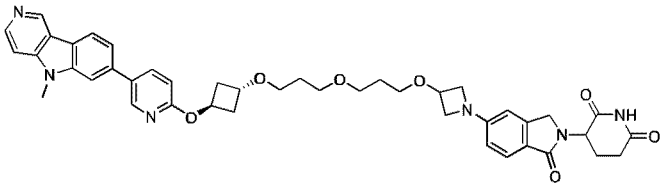

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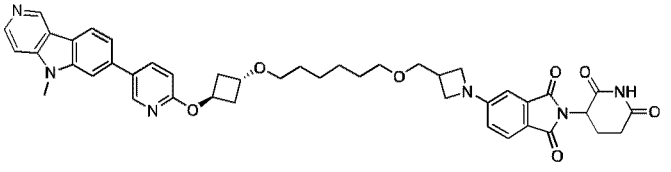

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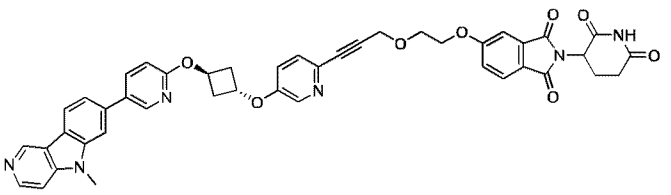

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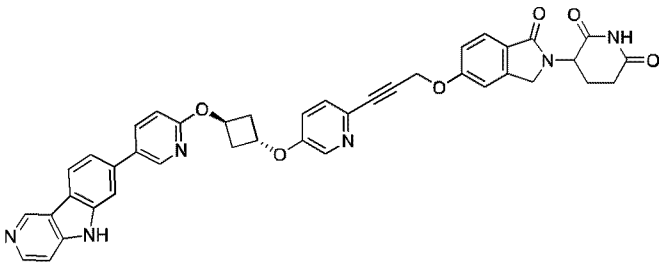

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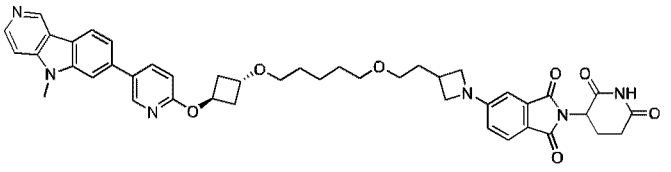

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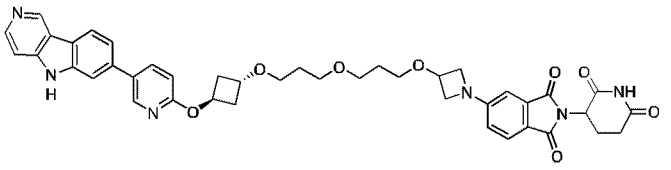

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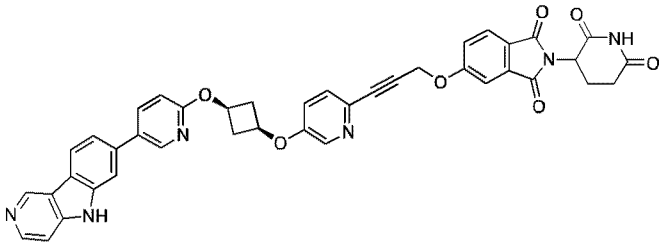

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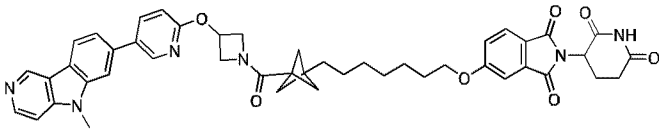

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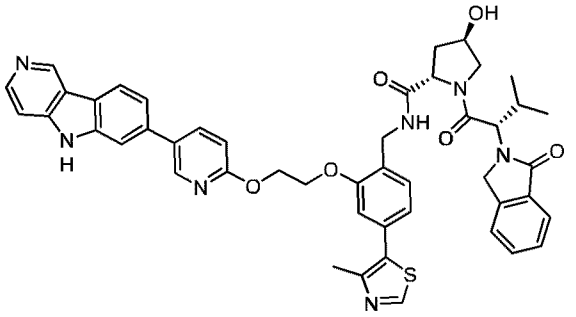

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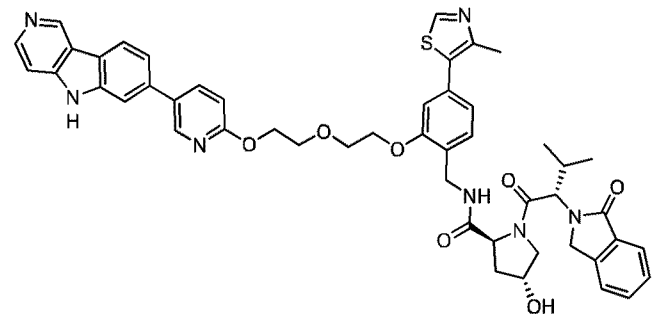

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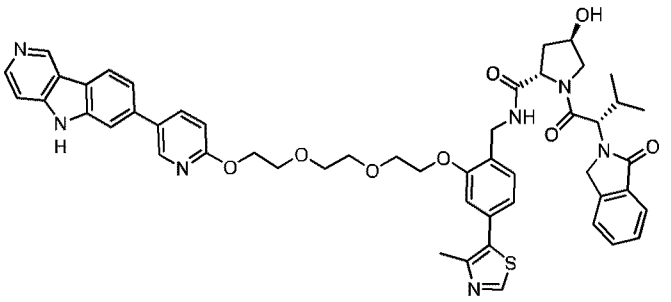

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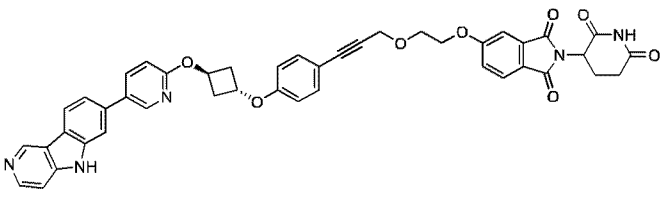

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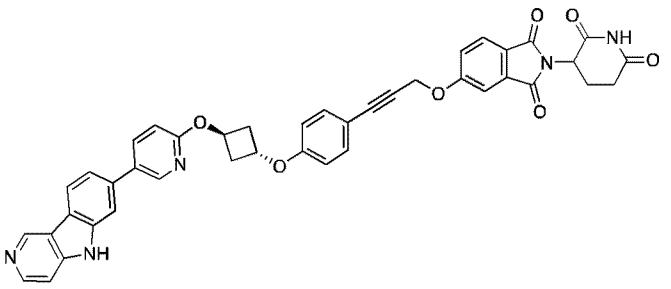

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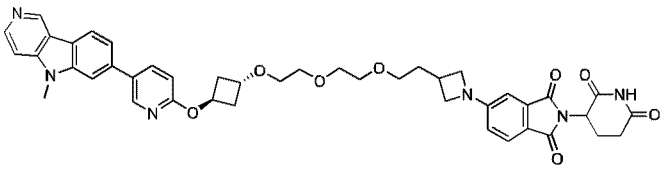

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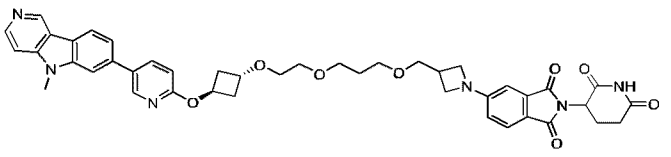

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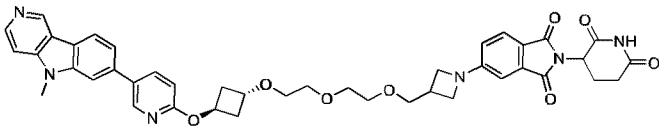

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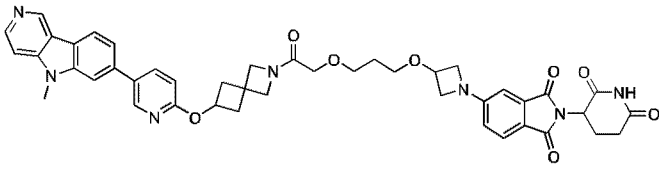

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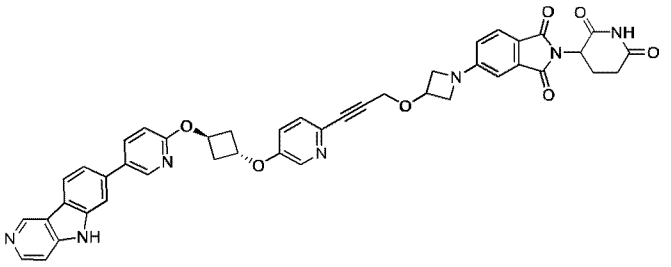

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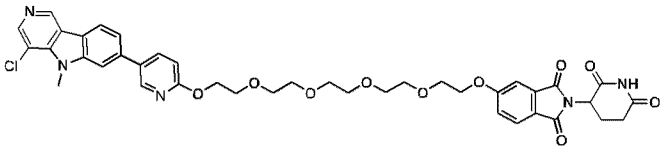

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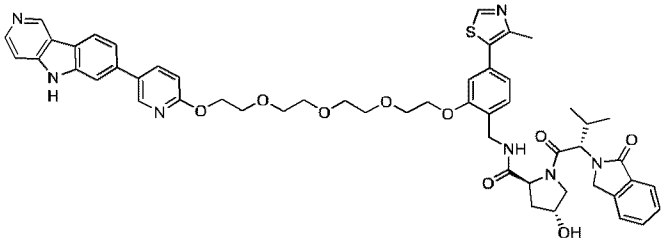

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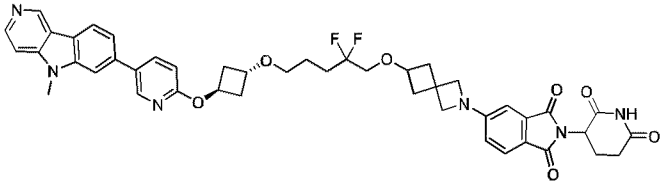

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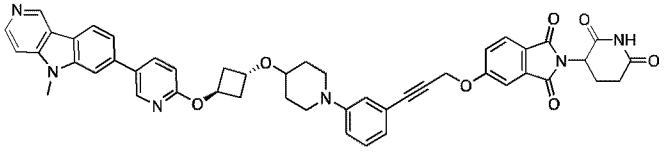

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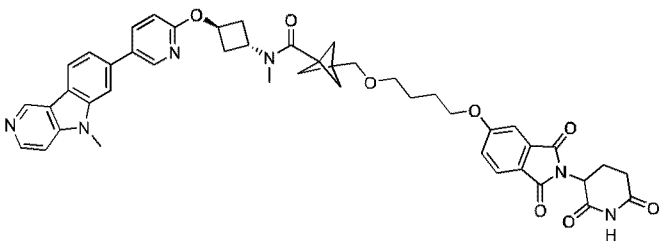

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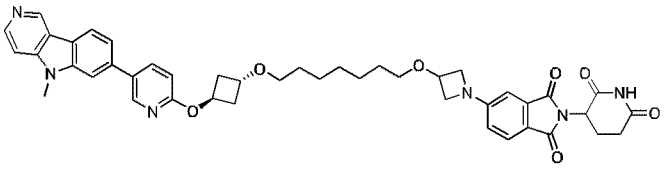

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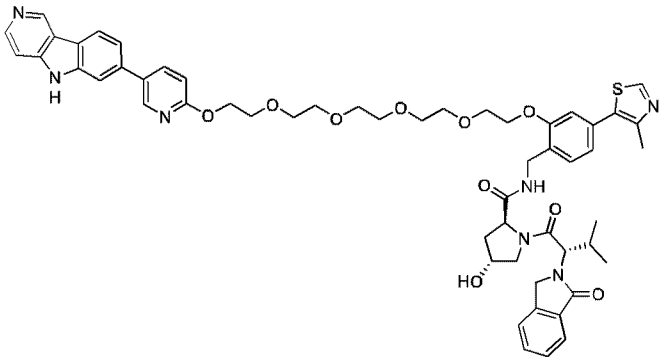

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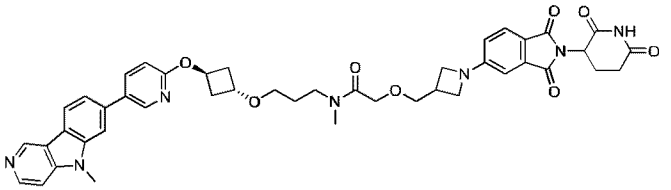

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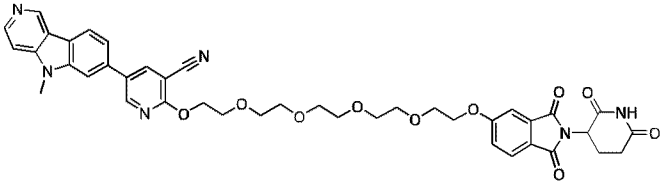

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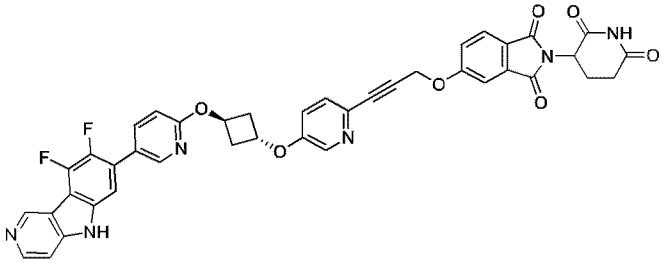

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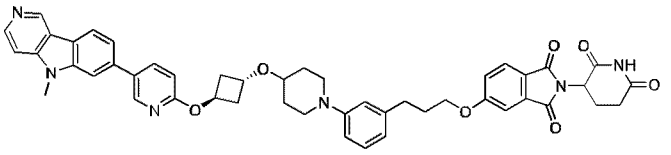

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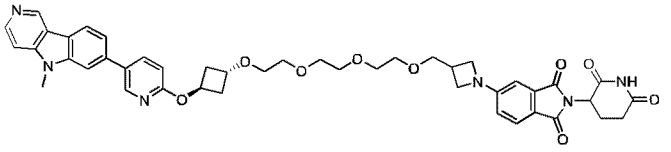

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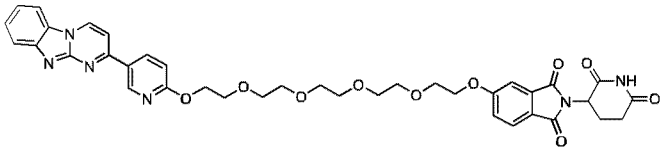

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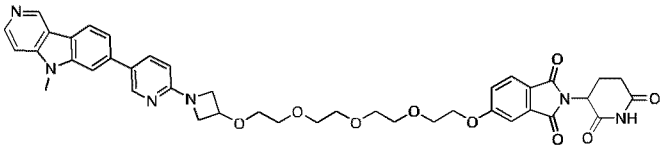

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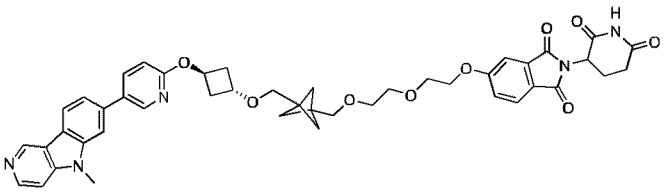

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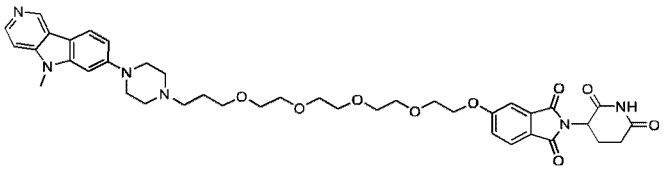

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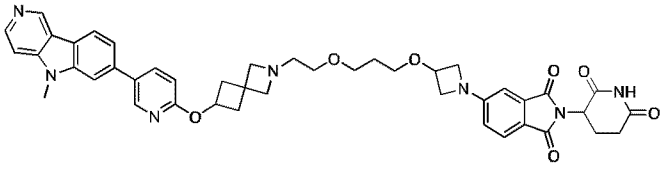

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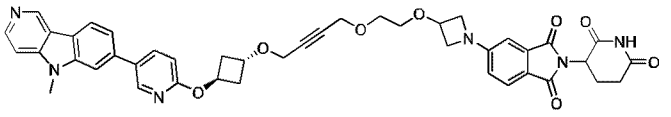

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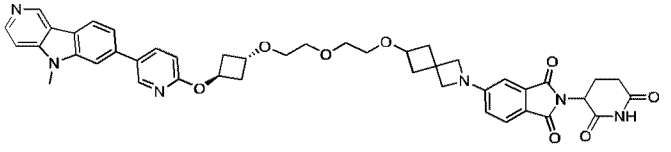

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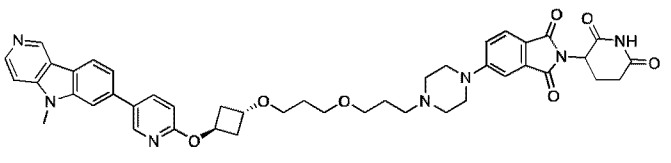

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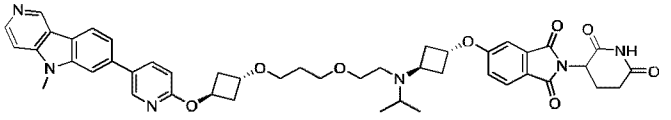

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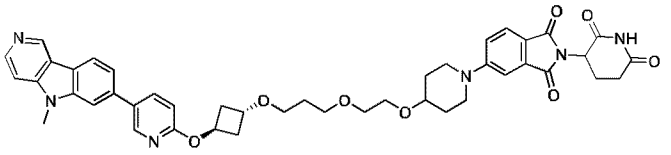

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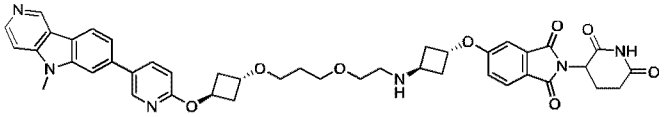

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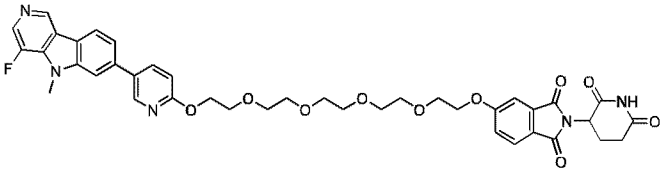

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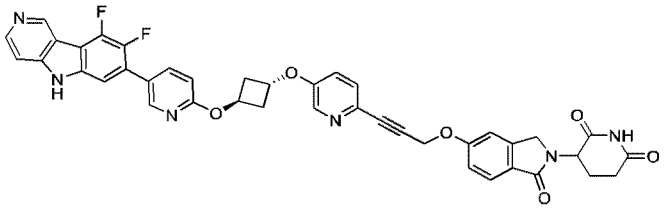

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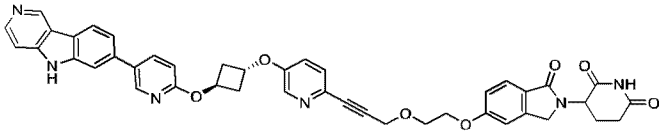

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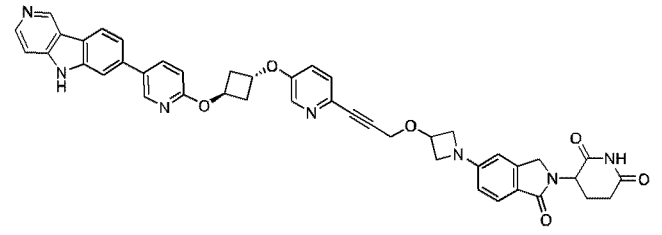

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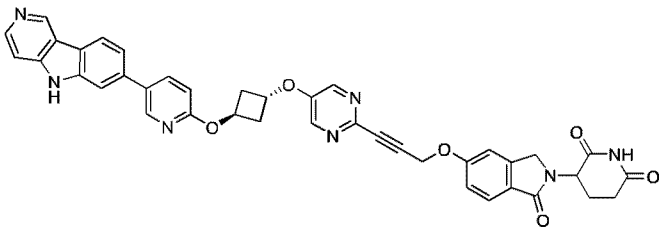

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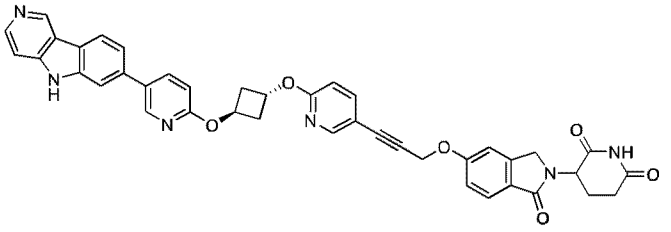

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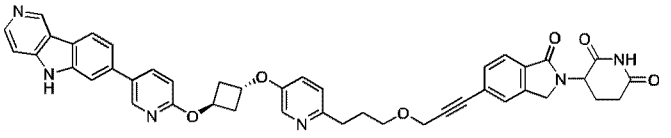

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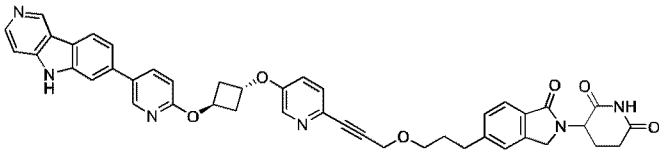

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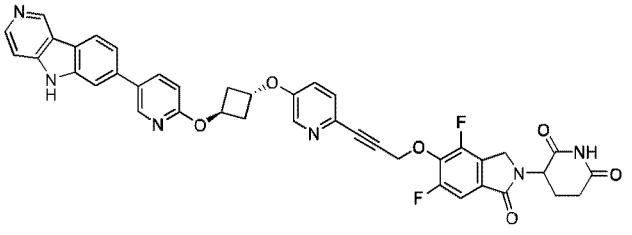

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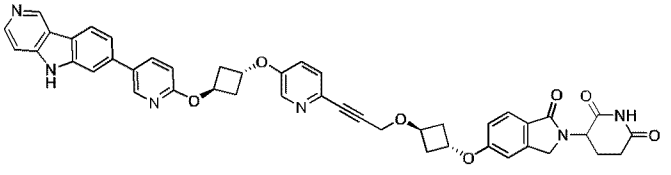

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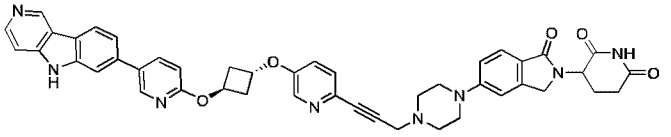

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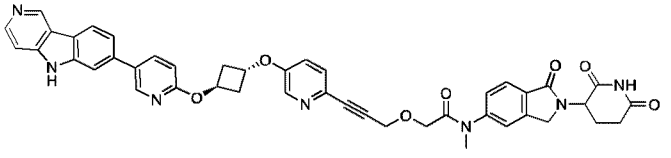

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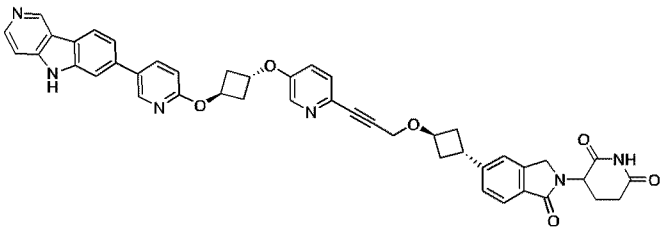

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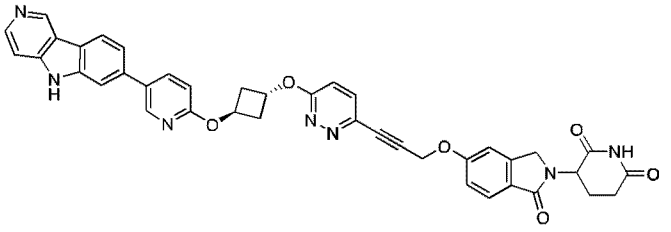

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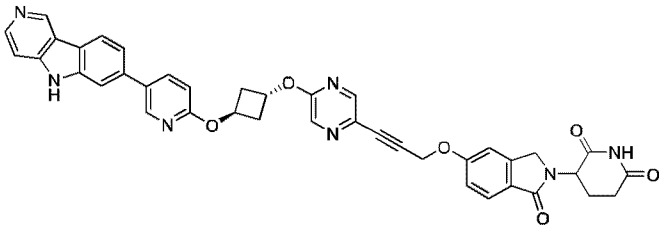

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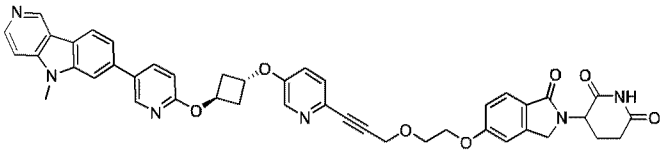

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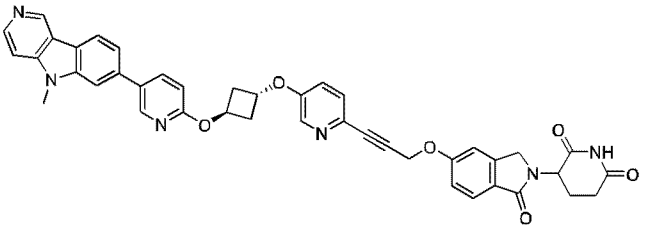

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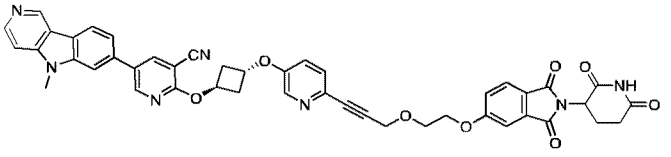

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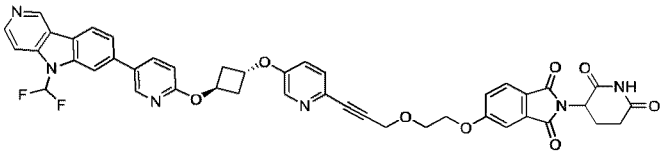

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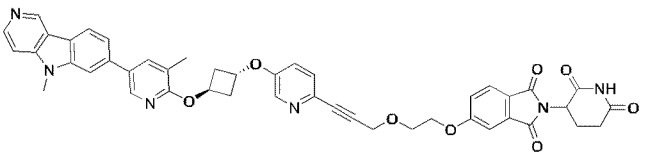

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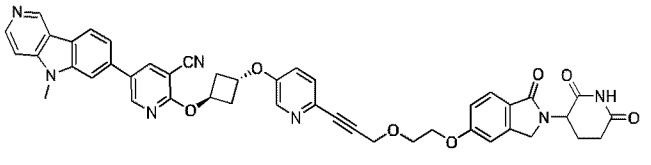
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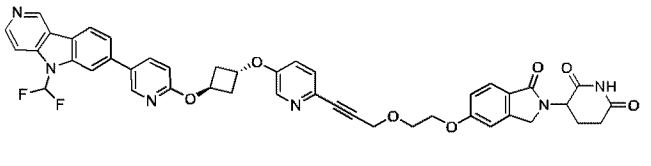
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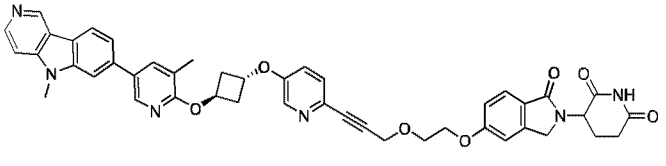
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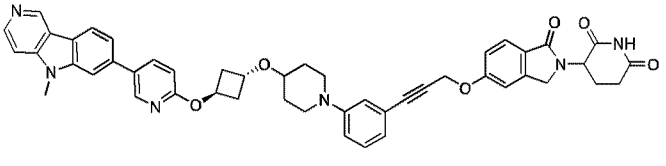
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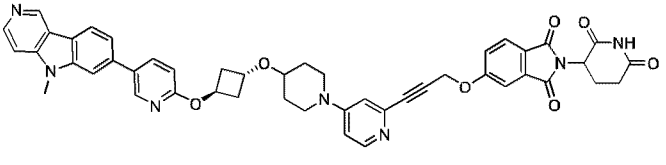
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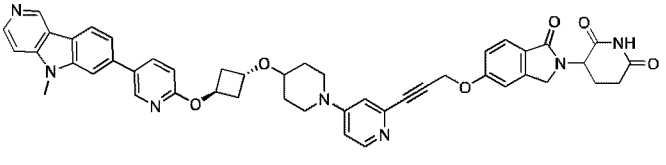
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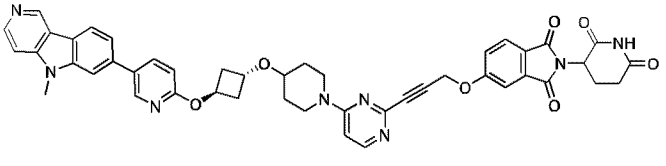
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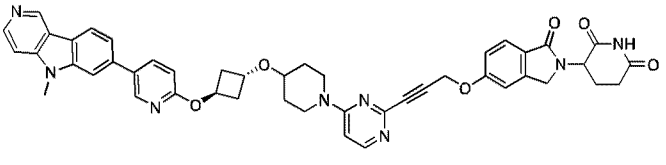
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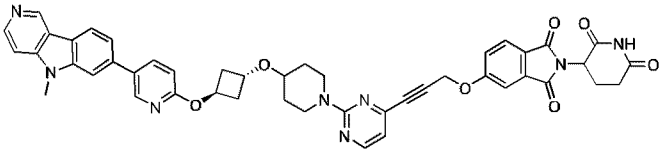
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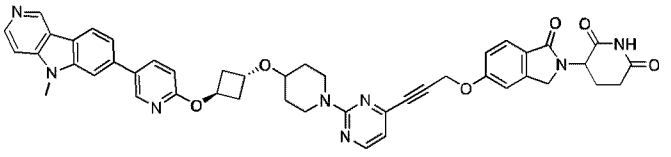

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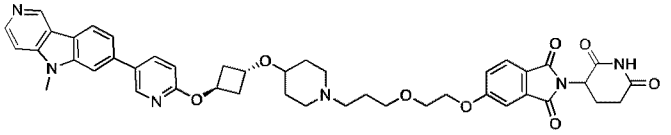

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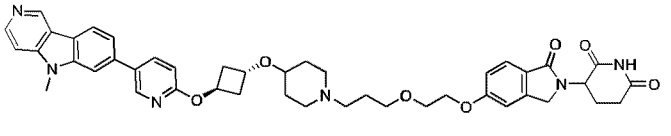

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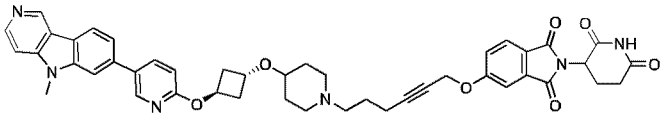

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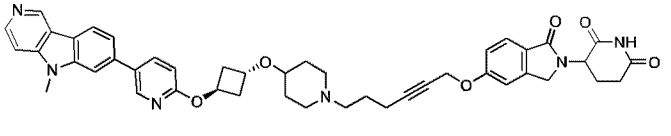

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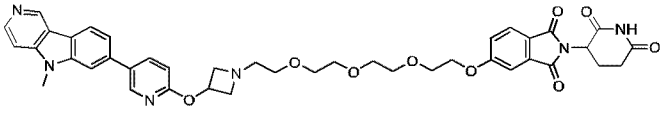

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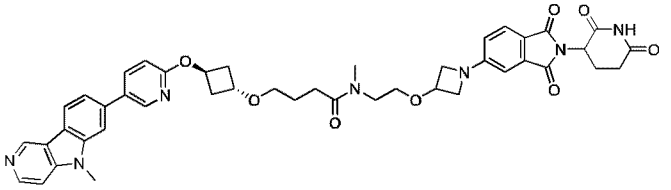

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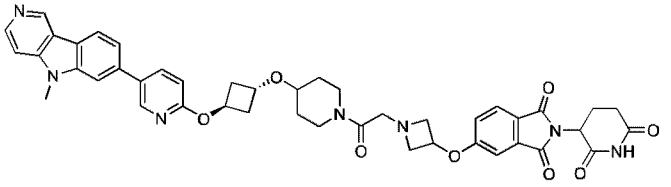

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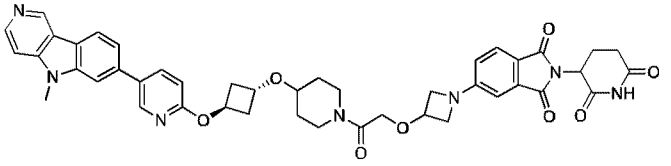

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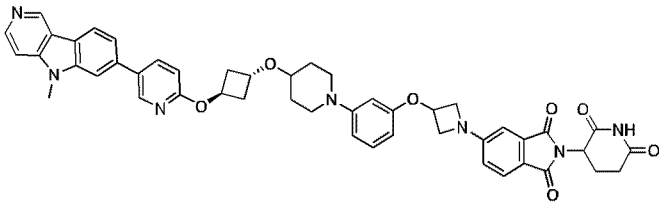

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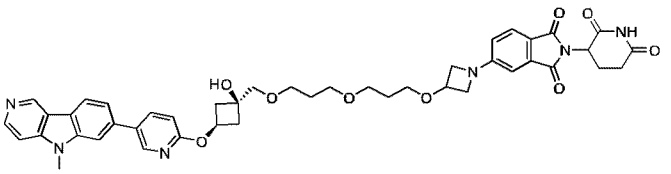

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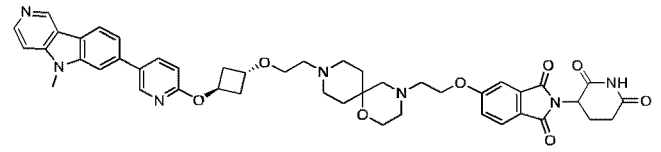

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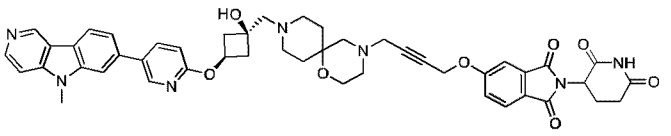

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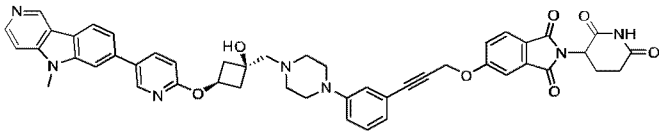

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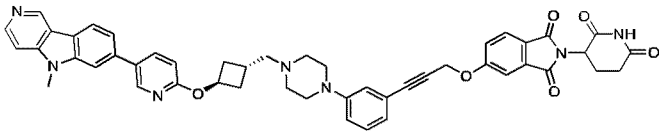

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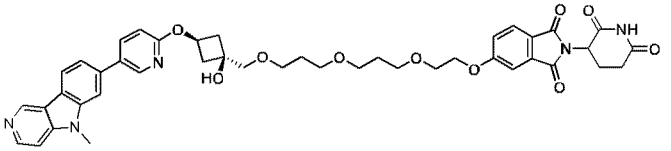

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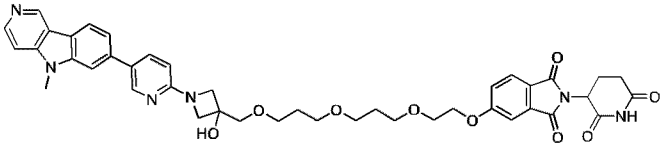

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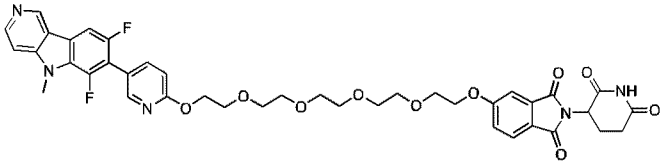

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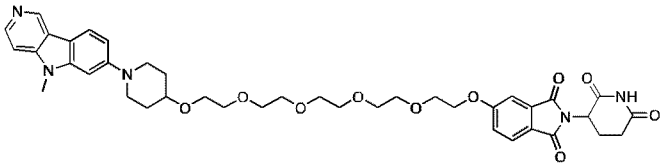

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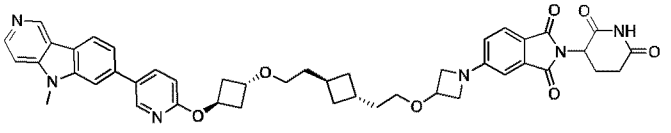

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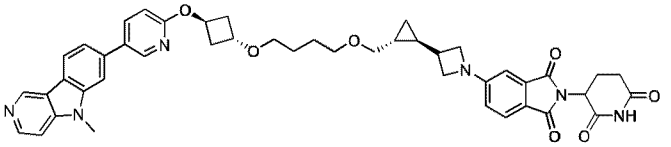

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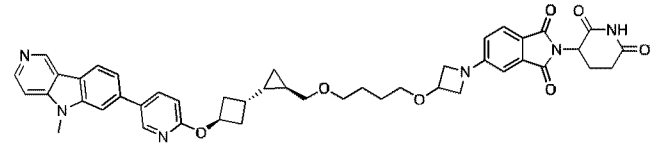

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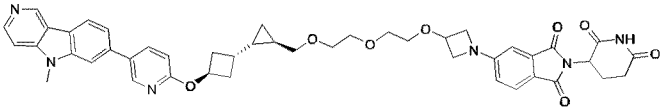

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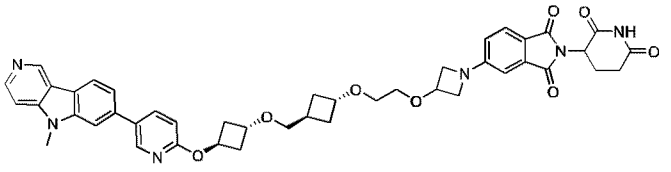

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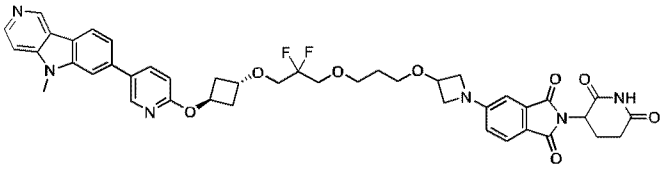

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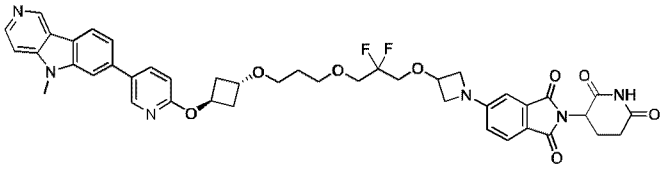

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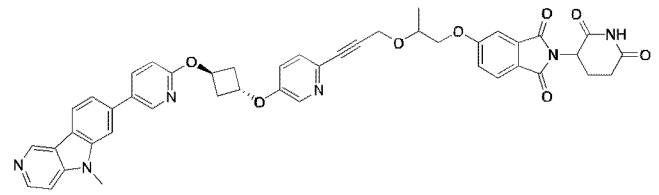

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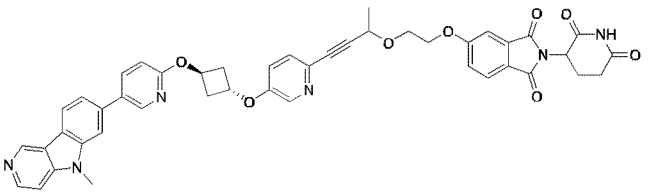

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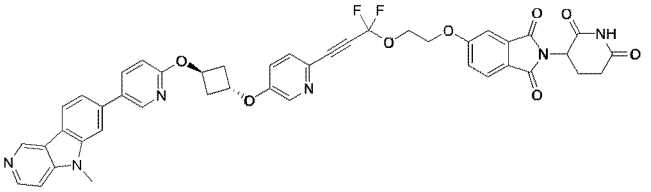

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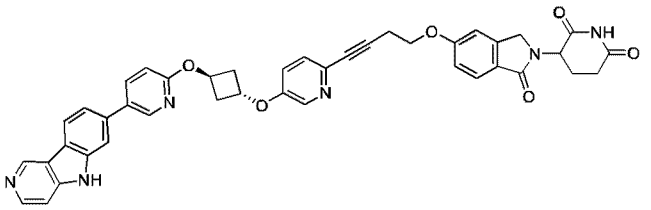

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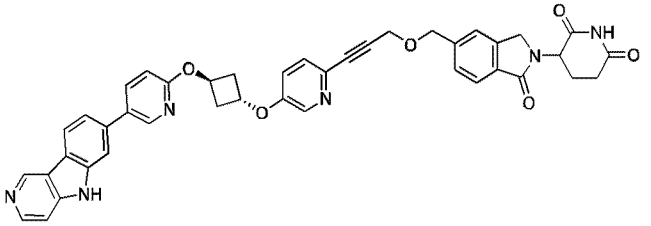

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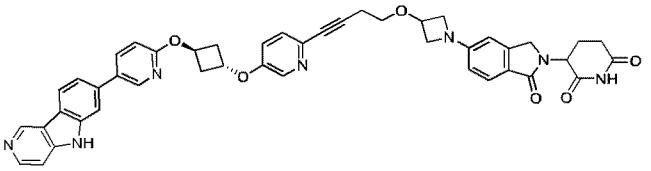

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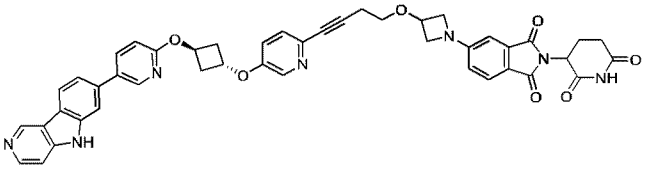

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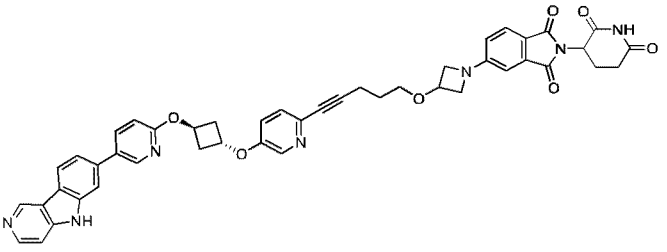

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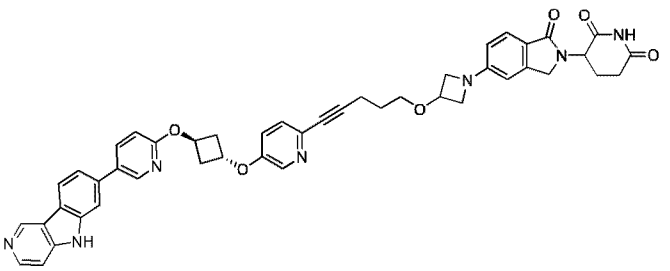

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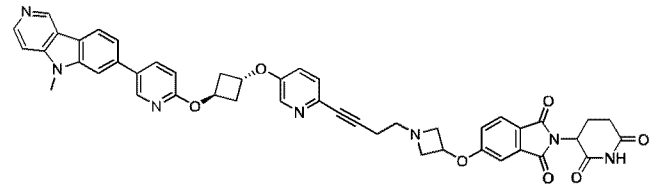

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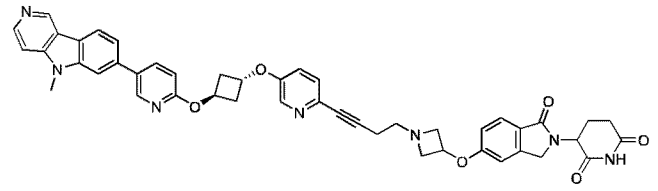

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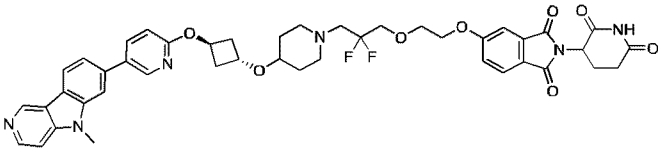

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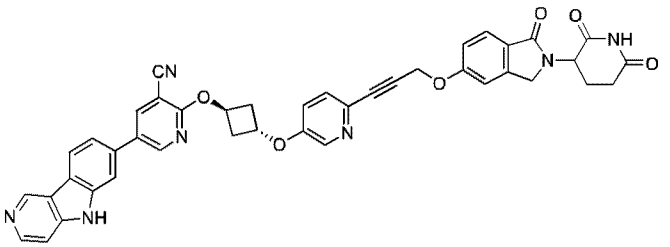

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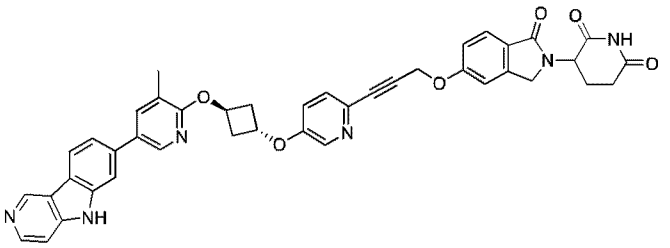

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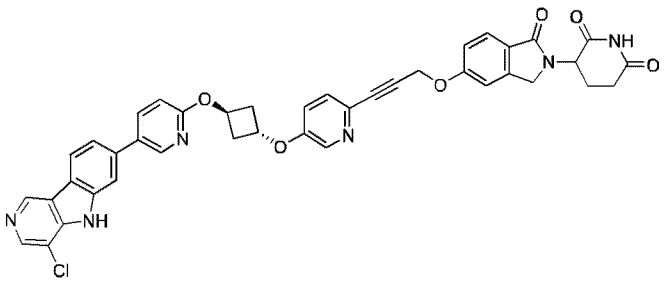

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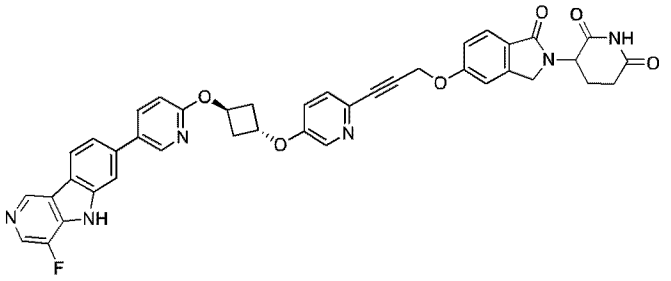

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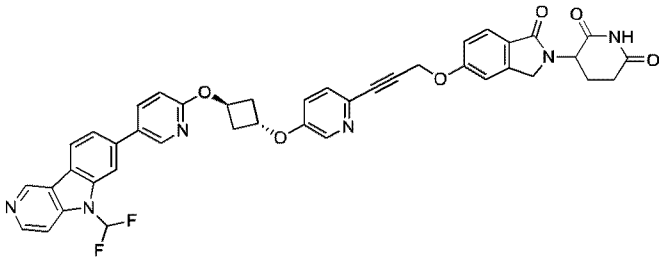

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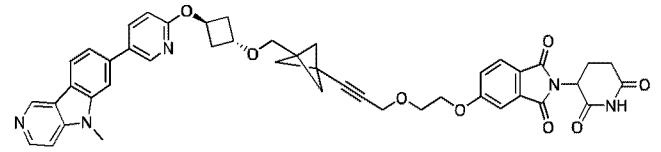

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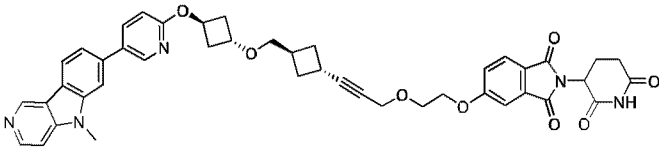

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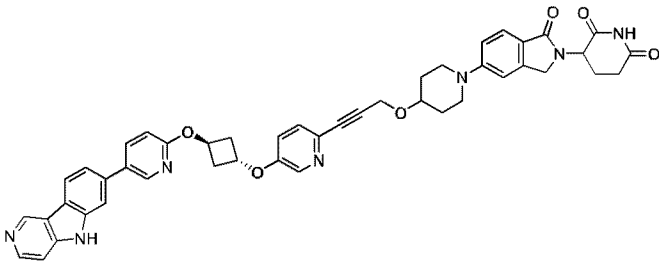

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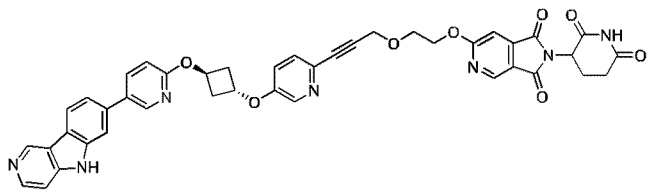

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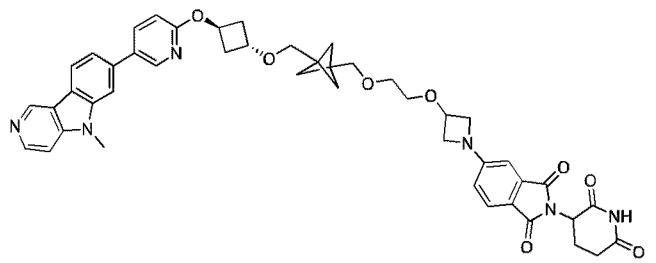

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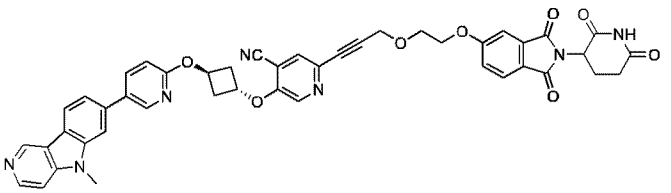

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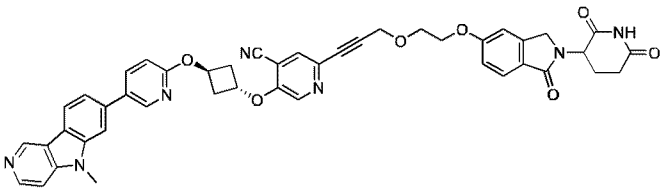

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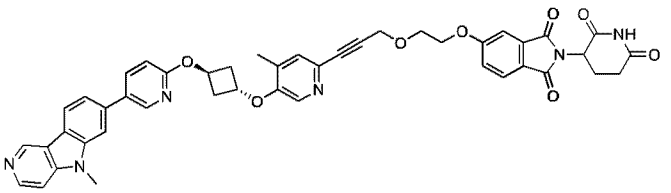

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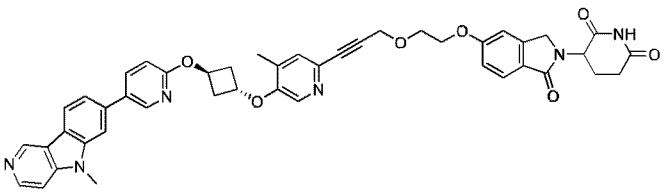

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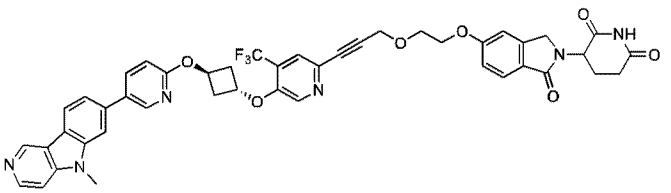

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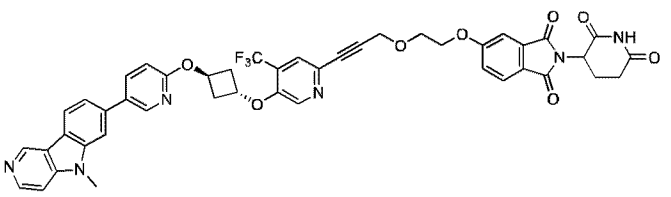

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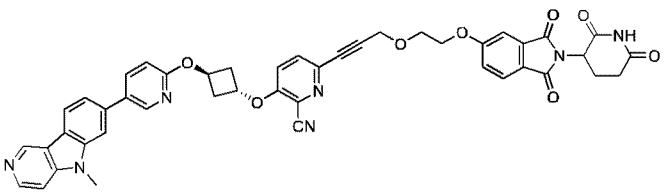

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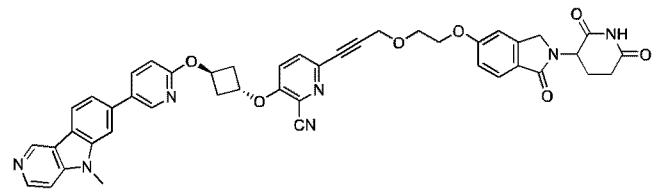

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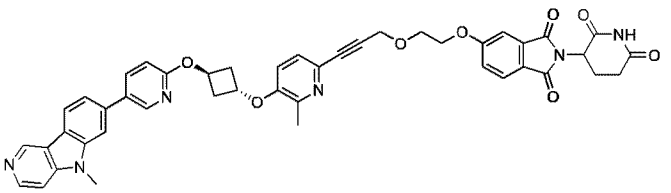

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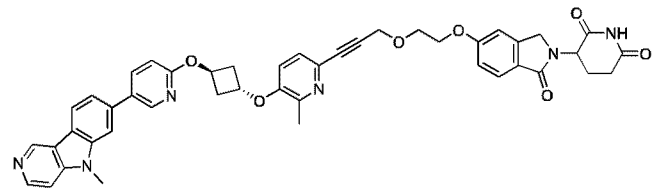

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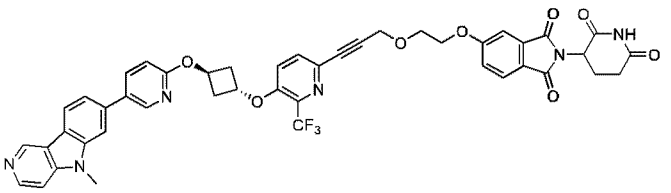

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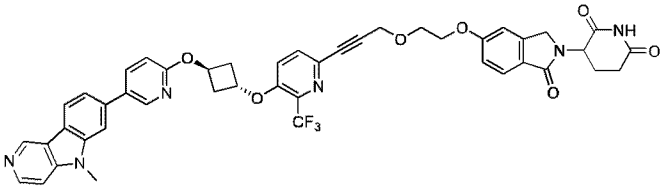

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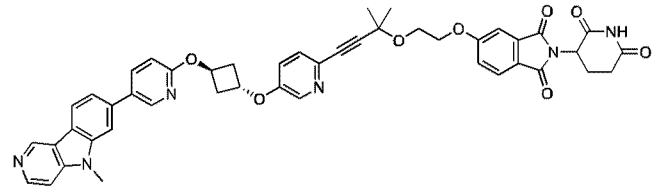

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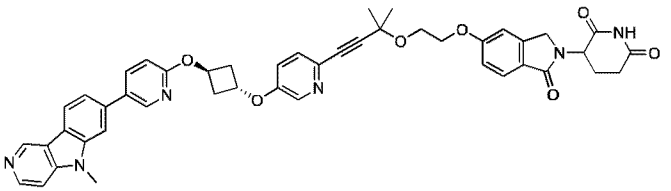

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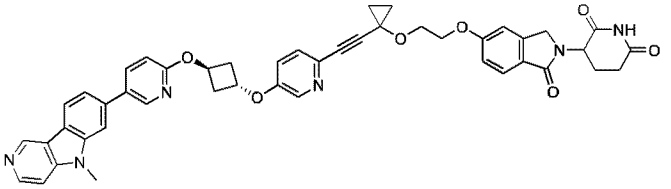

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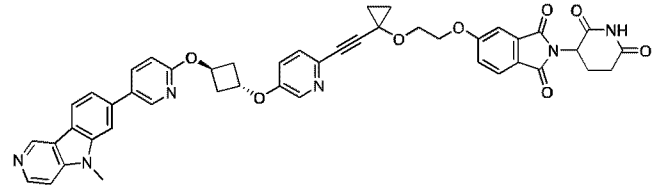

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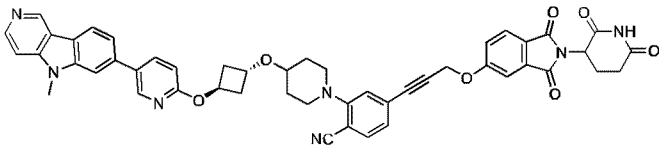

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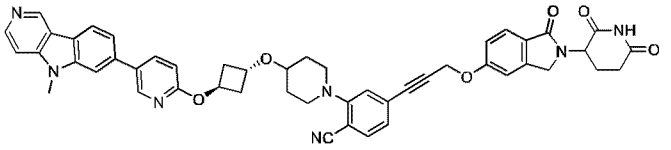

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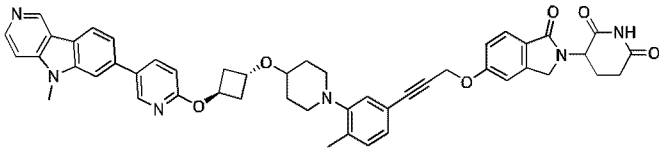

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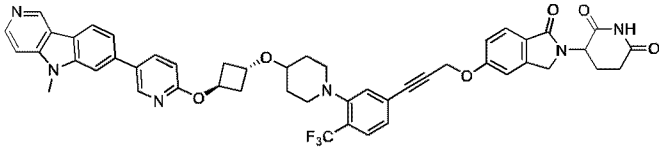

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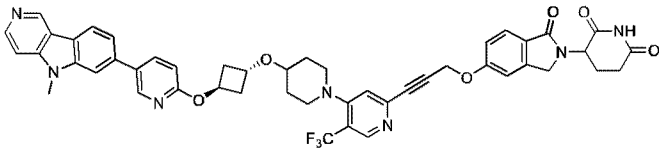

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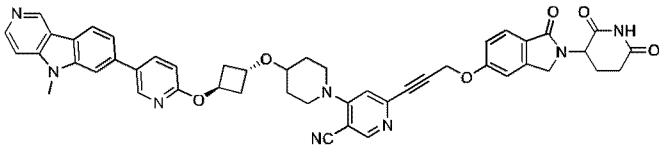

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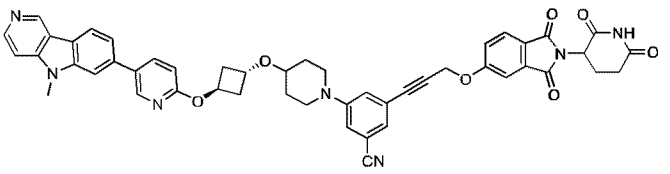

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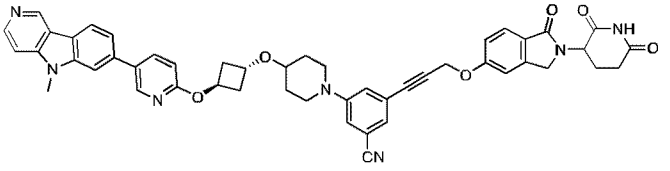

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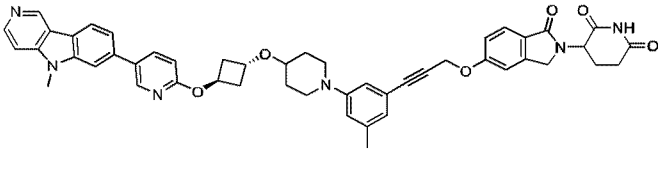

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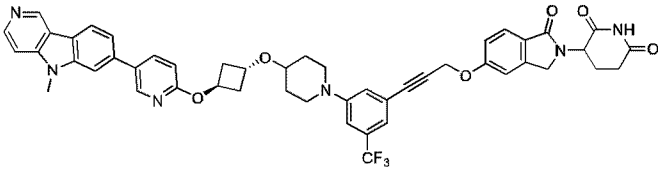

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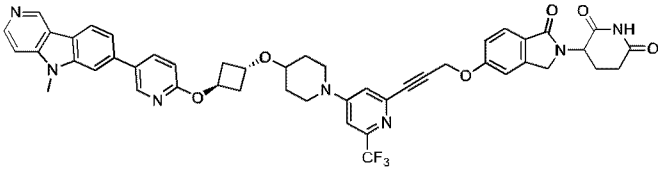

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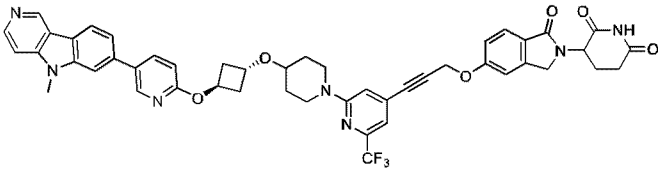

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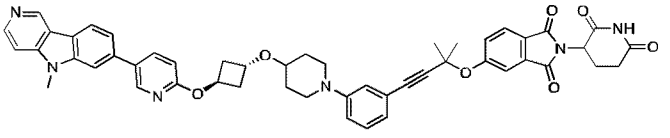

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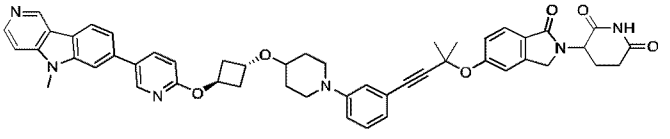

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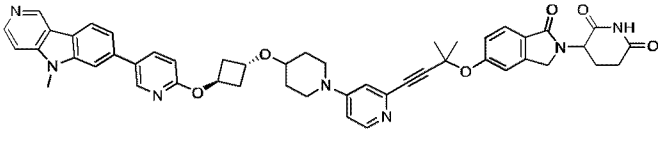

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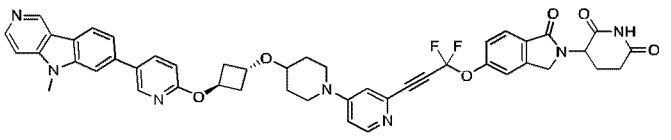

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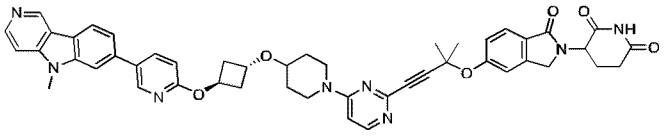

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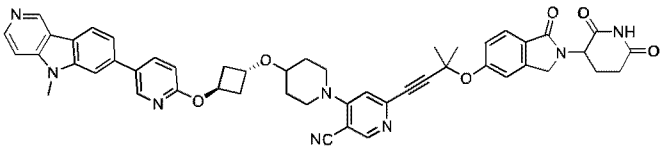

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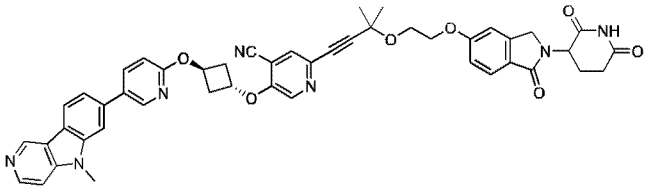
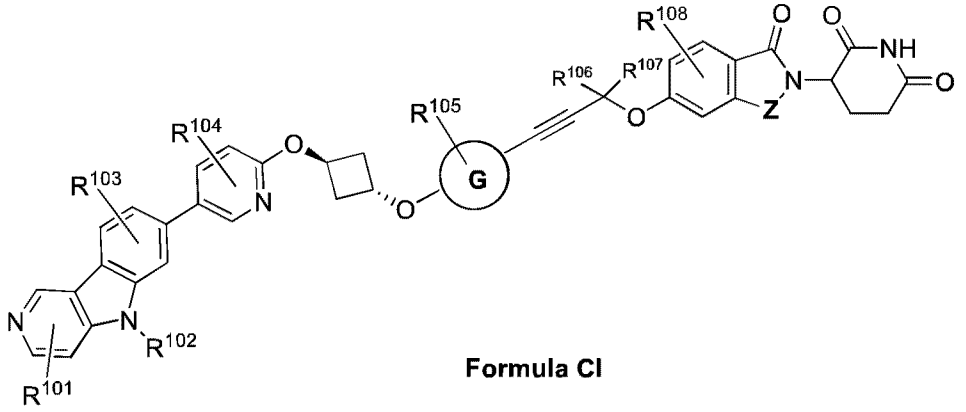


(330),

or a pharmaceutically acceptable salt thereof.

23. The compound of claim 1, wherein the compound has a chemical structure selected from Formulas CI through CV:



Formula CI

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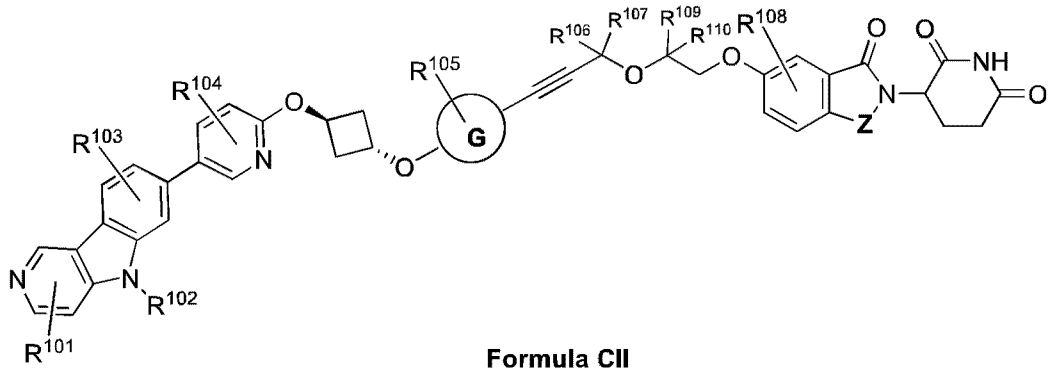

Formula CII

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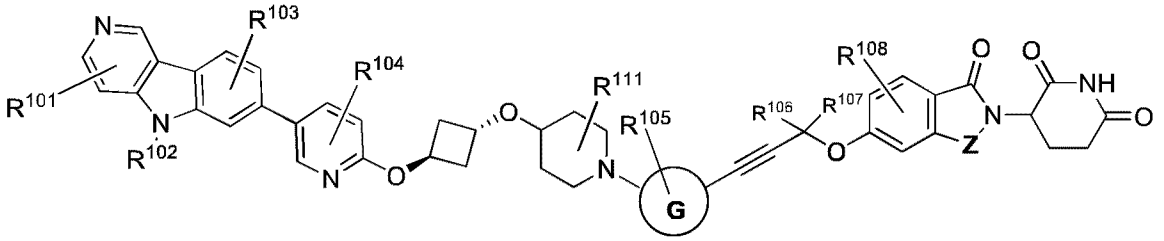

Formula CIII

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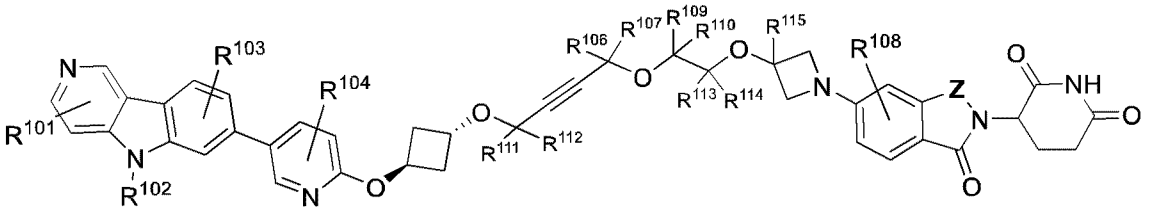
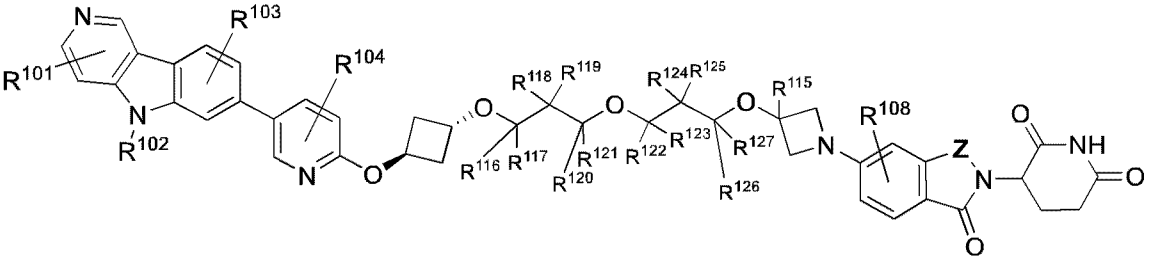


Formula CIV

,

and



Formula CV

,

wherein:

R^{101} is 1–2 substituents independently selected from H, alkyl, halogen, haloalkyl, and cyano;

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R^{102} is selected from H, alkyl, haloalkyl, cycloalkyl, and heterocycloalkyl;

R^{103} is 1–2 substituents independently selected from H, alkyl, halogen, haloalkyl, and cyano;

R^{104} is 1–2 substituents independently selected from H, alkyl, halogen, haloalkyl, and cyano;

R^{105} is 1–2 substituents independently selected from H, alkyl, halogen, haloalkyl, and cyano;

R^{106}, R^{107}, R^{109}, R^{110}, R^{111}, R^{112}, R^{113}, R^{114}, R^{116}, R^{117}, R^{120}, R^{121}, R^{126}, R^{127}, R^{122}, and R^{123} are each independently selected from H, alkyl, halogen, and haloalkyl;

R^{108} is 1–2 substituents independently selected from H, alkyl, halogen, haloalkyl, cyano, and methoxy;

R^{115} is selected from H, alkyl, and haloalkyl;

R^{118} and R^{119} are independently selected from H, alkyl, halogen, and haloalkyl, or R^{118} and R^{119} taken together with the carbon atom to which they are attached represent a 3–6-membered cycloalkyl or heterocycloalkyl ring;

R^{124} and R^{125} are independently selected from H, alkyl, halogen, and haloalkyl, or R^{124} and R^{125} taken together with the carbon atom to which they are attached represent a 3–6-membered cycloalkyl or heterocycloalkyl ring;

G is a phenyl or a 5- or 6-membered heteroaryl ring; and

Z is CH_2 or C=O.

24. A composition comprising a bifunctional compound of any one of claims 1-23 and a pharmaceutically acceptable carrier.

25. The composition of claim 24, wherein the composition further comprises an additional bioactive agent.

26. The composition of claim 25, wherein the additional bioactive agent is an anti-neurodegenerative agent.

27. The composition of claim 26, wherein the additional bioactive agent is a P-gp inhibitor.

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28. The composition of claim 27, wherein the P-gp inhibitor is Amiodarone, Azithromycin, Captopril, Clarithromycin, Cyclosporine, Piperine, Quercetin, Quinidine, Quinine, Reserpine, Ritonavir, Tariquidar, Elacridar or Verapamil.

29. Use of a compound of any one of claims 1-23 to treat a Tau-related disease or disorder associated with Tau accumulation and aggregation.

30. The use of claim 29, wherein the disease or disorder is a neurodegenerative disease.

31. The use of claim 29 or 30, wherein the disease or disorder is Acquired Epileptiform Aphasia, Acute Disseminated Encephalomyelitis, ADHD, Adie's Pupil, Adie's Syndrome, Adrenoleukodystrophy, Agenesis of the Corpus Callosum, Agnosia, Aicardi Syndrome, AIDS—Neurological Complications, Alexander Disease, Alpers' Disease, Alternating Hemiplegia, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Anencephaly, Aneurysm, Angelman Syndrome, Angiomatosis, Anoxia, Aphasia, Apraxia, Arachnoid Cysts, Arachnoiditis, Arnold-Chiari Malformation, Arteriovenous Malformation, Asperger Syndrome, Ataxia, Ataxia, Telangiectasia, Ataxias and Cerebellar/Spinocerebellar Degeneration, Attention Deficit-Hyperactivity Disorder, Autism, Autonomic Dysfunction, Back Pain, Barth Syndrome Batten Disease, Becker's Myotonia, Behcet's Disease, Bell's Palsy, Benign Essential Blepharospasm, Benign Focal Amyotrophy, Benign Intracranial Hypertension, Bernhardt-Roth Syndrome, Binswanger's Disease, Blepharospasm, Bloch-Sulzberger Syndrome, Brachial Plexus Birth Injuries, Brachial Plexus Injuries, Bradbury-Eggleston Syndrome, Brain and Spinal Tumors, Brain Aneurysm, Brain Injury, Brown-Sequard Syndrome, Bulbospinal Muscular Atrophy, Canavan Disease, Carpal Tunnel Syndrome Causalgia, Cavernomas, Cavernous Angioma, Cavernous Malformation, Central Cervical Cord Syndrome, Central Cord Syndrome, Central Pain Syndrome, Cephalic Disorders, Cerebellar Degeneration, Cerebellar Hypoplasia, Cerebral Aneurysm, Cerebral Arteriosclerosis, Cerebral Atrophy, Cerebral Beriberi, Cerebral Gigantism, Cerebral Hypoxia, Cerebral Patsy, Cerebro-Oculo-Facio-Skeletal Syndrome, Charcot-Marie-Tooth Disease, Chiari Malformation, Chorea, Choreoacanthocytosis, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Chronic Orthostatic Intolerance, Chronic Pain Cockayne Syndrome Type II, Coffin Lowry Syndrome, COFS, Colpocephaly, Coma and Persistent

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Vegetative State, Complex Regional Pain Syndrome, Congenital Facial Diplegia, Congenital Myasthenia, Congenital Myopathy, Congenital Vascular Cavernous, Malformations, Corticobasal Degeneration, Cranial Arteritis, Craniosynostosis, Creutzfeldt-Jakob Disease, Cumulative Trauma Disorders, Cushing's Syndrome, Cytomegalic Inclusion Body Disease, Cytomegalovirus Infection, Dancing Eyes-Dancing Feet Syndrome, Dandy-Walker Syndrome, Dawson Disease, De Morsier's Syndrome, Deep Brain Stimulation for Parkinson's Disease, Dejerine-Klumpke Palsy, Dementia, Dementia—Multi-Infarct, Dementia—Semantic, Dementia—Subcortical, Dementia With Lewy Bodies, Dentate Cerebellar Ataxia, Dentatorubral Atrophy, Dermatomyositis, Developmental Dyspraxia, Devic's Syndrome, Diabetic Neuropathy, Diffuse Sclerosis, Dysautonomia, Dysgraphia, Dyslexia, Dysphagia, Dyspraxia, Dyssynergia Cerebellaris, Myoclonica, Dyssynergia Cerebellaris Progressiva, Dystonias, Early Infantile Epileptic, Encephalopathy, Empty Sella Syndrome, Encephalitis Lethargica, Encephaloceles, Encephalopathy, Encephalotrigeminal Angiomatosis, Epilepsy, Erb-Duchenne and Dejerine-Klumpke Palsies, Erb's Palsy, Fabry's Disease, Fahr's Syndrome, Fainting, Familial Dysautonomia, Familial Hemangioma, Familial Idiopathic Basal Ganglia, Calcification, Familial Periodic Paralyses, Familial Spastic Paralysis, Febrile Seizures, Fisher Syndrome, Floppy Infant Syndrome, Friedreich's Ataxia, Frontotemporal, Dementia, Gaucher's Disease, Gerstmann's Syndrome, Gerstmann-Straussler-Scheinker, Disease, Giant Cell Arteritis, Giant Cell Inclusion Disease, Globoid Cell Leukodystrophy, Glossopharyngeal Neuralgia, Guillain-Barre Syndrome, Hallervorden-Spatz Disease, Head Injury, Headache, Hemicrania Continua, Hemifacial Spasm, Hemiplegia Alterans, Hereditary Neuropathies, Hereditary Spastic Paraplegia, Heredopathia Atactica Polyneuritiformis, Herpes Zoster, Herpes Zoster Oticus, Hirayama Syndrome, Holmes-Adie syndrome, Holoprosencephaly, HTLV-1 Associated, Myelopathy, Huntington's Disease, Hydranencephaly, Hydrocephalus, Hydrocephalus—Normal Pressure, Hydromyelia, Hyperactivity, Hypercortisolism, Hypersomnia, Hypertonia, Hypotonia,—Infantile, Hypoxia, Immune-Mediated Encephalomyelitis, Inclusion Body Myositis, Incontinentia Pigmenti, Infantile Hypotonia, Infantile Neuroaxonal Dystrophy, Infantile Phytanic Acid Storage Disease, Infantile Refsum Disease, Infantile Spasms, Inflammatory Myopathy, Iniencephaly, Intestinal Lipodystrophy, Intracranial Cysts, Intracranial Hypertension, Isaac's Syndrome, Joubert Syndrome, Kearns-Sayre Syndrome, Kennedy's Disease, Kinsbourne syndrome, Kleine-Levin Syndrome, Klippel-Feil Syndrome, Klippel-Trenaunay Syndrome (KTS), Klüver-Bucy

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Syndrome, Korsakoff's Amnesic Syndrome, Krabbe Disease, Kugelberg-Welander Disease, Kuru, Lambert-Eaton Myasthenic Syndrome, Landau-Kleffner Syndrome, Lateral Femoral, Cutaneous Nerve Entrapment, Lateral Medullary Syndrome, Learning Disabilities, Leigh's Disease, Lennox-Gastaut Syndrome, Lesch-Nyhan Syndrome, Leukodystrophy, Levine-Critchley Syndrome, Lewy Body Dementia, Lipid Storage Diseases, Lissencephaly, Locked-In Syndrome, Lou Gehrig's Disease, Lupus—Neurological, Sequelae, Lyme Disease—Neurological Complications, Machado-Joseph Disease, Macrencephaly, Mania, Megalencephaly, Melkersson-Rosenthal Syndrome, Meningitis, Meningitis and Encephalitis, Menkes Disease, Meralgia Paresthetica, Metachromatic, Leukodystrophy, Microcephaly, Migraine, Miller Fisher Syndrome, Mini-Strokes, Mitochondrial Myopathies, Mobius Syndrome, Monomelic Amyotrophy, Motor Neuron Diseases, Moyamoya Disease, Mucolipidoses, Mucopolysaccharidoses, Multifocal Motor Neuropathy, Multi-Infarct Dementia, Multiple Sclerosis, Multiple System Atrophy, Multiple System Atrophy with Orthostatic Hypotension, Muscular Dystrophy, Myasthenia—Congenital, Myasthenia Gravis, Myelinoclastic Diffuse Sclerosis, Myoclonic Encephalopathy of Infants, Myoclonus, Myopathy, Myopathy—Congenital, Myopathy-Thyrotoxic, Myotonia, Myotonia Congenita, Narcolepsy, Neuroacanthocytosis, Neurodegeneration with Brain Iron Accumulation, Neurofibromatosis, Neuroleptic Malignant Syndrome, Neurological Complications of AIDS, Neurological Complications Of Lyme Disease, Neurological Consequences of Cytomegalovirus Infection, Neurological Manifestations of Pompe Disease, Neurological Sequelae Of Lupus, Neuromyelitis Optica, Neuromyotonia, Neuronal Ceroid, Lipofuscinosis, Neuronal Migration Disorders, Neuropathy—Hereditary, Neurosarcoidosis, Neurotoxicity, Nevus Cavernosus, Niemann-Pick Disease, Normal Pressure Hydrocephalus, Occipital Neuralgia, Obesity, Occult Spinal Dysraphism Sequence, Ohtahara Syndrome, Olivopontocerebellar Atrophy, Opsoclonus Myoclonus, Orthostatic Hypotension, O'Sullivan-McLeod Syndrome, Overuse Syndrome, Pain—Chronic, Paine, Pantothenate Kinase-Associated Neurodegeneration, Paraneoplastic Syndromes, Paresthesia, Parkinson's Disease, Paroxysmal Choreoathetosis, Paroxysmal Hemicrania, Parry-Romberg, Pelizaeus-Merzbacher Disease, Pena Shokeir II Syndrome, Perineural Cysts, Periodic Paralyses, Peripheral Neuropathy, Periventricular Leukomalacia, Persistent Vegetative State, Pervasive Developmental Disorders, Phytanic Acid Storage Disease, Pick's Disease, Pinched Nerve, Piriformis Syndrome, Pituitary Tumors, Polymyositis, Pompe

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Disease, Porencephaly, Postherpetic Neuralgia, Postinfectious Encephalomyelitis, Post-Polio Syndrome, Postural Hypotension, Postural Orthostatic, Tachycardia Syndrome, Postural Tachycardia Syndrome, Primary Dentatum Atrophy, Primary Lateral Sclerosis, Primary Progressive Aphasia, Prion Diseases, Progressive Hemifacial Atrophy, Progressive Locomotor Ataxia, Progressive Multifocal, Leukoencephalopathy, Progressive Sclerosing Poliodystrophy, Progressive Supranuclear, Palsy, Prosopagnosia, Pseudotumor Cerebri, Ramsay Hunt Syndrome I (formerly known as), Ramsay Hunt Syndrome II (formerly known as), Rasmussen's Encephalitis, Reflex Sympathetic Dystrophy Syndrome, Refsum Disease, Refsum Disease—Infantile, Repetitive Motion Disorders, Repetitive Stress Injuries, Restless Legs Syndrome, Retrovirus-Associated Myelopathy, Rett Syndrome, Reye's Syndrome, Riley-Day Syndrome, Sacral Nerve Root Cysts, Saint Vitus Dance, Salivary Gland Disease, Sandhoff Disease, Schilder's Disease, Schizencephaly, Seitelberger Disease, Seizure Disorder, Semantic Dementia, Septo-Optic Dysplasia, Shaken Baby Syndrome, Shingles Shy-Drager Syndrome, Sjogren's Syndrome, Sleep Apnea, Sleeping Sickness, Sotos Syndrome, Spasticity, Spina Bifida, Spinal Cord Infarction, Spinal Cord Injury, Spinal Cord Tumors, Spinal Muscular Atrophy, Spinocerebellar Atrophy, Spinocerebellar, Degeneration, Steele-Richardson-Olszewski Syndrome, Stiff-Person Syndrome, Striatonigral Degeneration, Stroke, Sturge-Weber Syndrome, Subacute Sclerosing Panencephalitis, Subcortical Arteriosclerotic Encephalopathy, SUNCT Headache Swallowing Disorders, Sydenham Chorea, Syncope, Syphilitic Spinal Sclerosis, Syringohydromyelia, Syringomyelia, Systemic Lupus Erythematosus, Tabes Dorsalis Tardive Dyskinesia, Tarlov Cysts, Tay-Sachs Disease, Temporal Arteritis, Tethered Spinal Cord Syndrome, Thomsen's Myotonia, Thoracic Outlet Syndrome, Thyrotoxic Myopathy, Tic Douloureux, Todd's Paralysis, Tourette Syndrome, Transient Ischemic Attack, Transmissible Spongiform Encephalopathies, Transverse Myelitis, Traumatic Brain Injury, Tremor, Trigeminal Neuralgia, Tropical Spastic Paraparesis, Tuberous Sclerosis, Vascular Erectile Tumor, Vasculitis including Temporal Arteritis, Von Economo's Disease, Von Hippel-Lindau Disease (VHL), Von Recklinghausen's Disease, Wallenberg's Syndrome, Werdnig-Hoffman Disease, Wernicke-Korsakoff Syndrome, West Syndrome, Whiplash, Whipple's Disease, Williams Syndrome, Wilson's Disease, X-Linked Spinal and Bulbar Muscular Atrophy, or Zellweger Syndrome.

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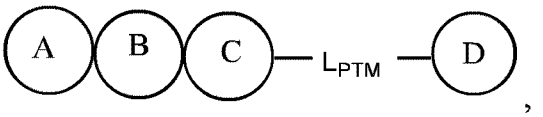
32. The use of claim 29, wherein the disease or disorder is a neurological disorder with at least one of Huntington's disease, muscular dystrophy, Parkinson's disease, Alzheimer's disease, Batten disease, Injuries to the spinal cord and brain, Seizure disorders, epilepsy, brain tumors, meningitis, autoimmune diseases such as multiple sclerosis, neurofibromatosis, Depression, Amyotrophic Lateral Sclerosis, Arteriovenous Malformation, Brain Aneurysm, Dural Arteriovenous Fistulae, Headache, Memory Disorders, Peripheral Neuropathy, Post-Herpetic Neuralgia, Spinal Cord Tumor and Stroke.

33. The use of claim 29, wherein the disease or disorder is Alzheimer's disease.

34. The use of claim 29 or 30, wherein the disease or disorder is Huntington's disease.

35. A compound having the chemical structure:



,

or a pharmaceutically acceptable salt thereof,

wherein:

rings A, B, C, and D are independently selected from a 5- or 6-membered aryl, a 5- or 6-membered heteroaryl, a 4- to 7-membered cycloalkyl, and a 4- to 7-membered heterocycloalkyl, where contact between circles indicates ring fusion, and rings A, B, C, and D are each optionally substituted with 1–8 substituents independently selected from alkyl, alkenyl, haloalkyl, halogen, hydroxyl, alkoxy, fluoroalkoxy, amino, alkylamino, dialkylamino, acylamino, trifluoromethyl, and cyano;

L_{PTM} is selected from a bond, an alkyl, an alkenyl, and an alkynyl, optionally interrupted by one or more functional groups selected from -O-, -S-, -NR^1_{PTM}-, -N=N-, -S(O)-, -SO_2-, -C(O)-, -NHC(O)-, -C(O)NH-, -$NHSO_2$-, -NHC(O)NH-, -NHC(O)O-, and -OC(O)NH-, wherein the functional group is optionally located at either end of the L_{PTM}; and

R^1_{PTM} is H or alkyl.

36. The compound of claim 35, wherein one or more of ring A, ring B, and ring C is optionally substituted 5- or 6-membered aryl or optionally substituted 5- or 6-membered heteroaryl.

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37. The compound of claim 35, wherein:

rings A, B and C are each independently optionally substituted 5- or 6- membered aryl or optionally substituted 5- or 6-membered heteroaryl;

L_{PTM} is selected from a bond or an alkyl; and

ring D is optionally substituted 6-membered aryl, optionally substituted 6-membered heteroaryl or optionally substituted 6-membered heterocycloalkyl,

wherein the optional substituents of rings A, B, C, and D are independently selected from alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, trifluoromethyl, and cyano.

38. The compound of claim 35, wherein:

rings A and C are each independently optionally substituted phenyl or optionally substituted 6-membered heteroaryl;

ring B is optionally substituted 5-membered heteroaryl;

L_{PTM} is a bond; and

ring D is optionally substituted 6-membered heteroaryl or optionally substituted 6-membered heterocycloalkyl,

wherein the optional substituents of rings A, B, C, and D are independently selected from alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, dialkylamino, trifluoromethyl, and cyano, provided that a nitrogen atom of any of the A, B, C, and D rings is not directly connected to a heteroatom or to a carbon atom, to which another heteroatom is directly attached.

39. The compound of claim 35, wherein the compound is represented by a chemical structure selected from:

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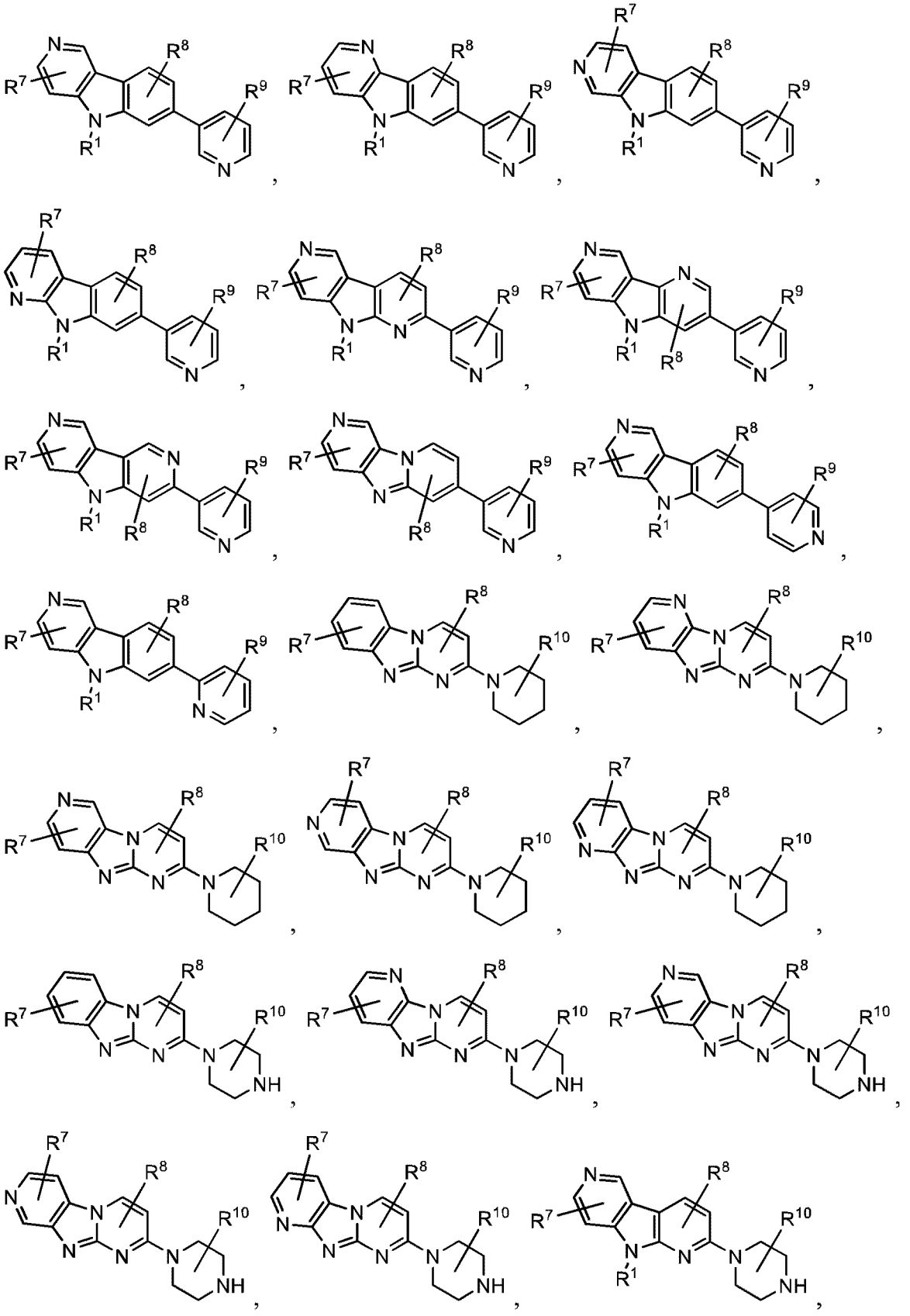

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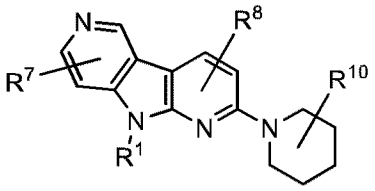
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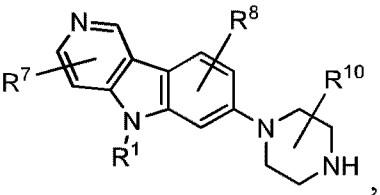
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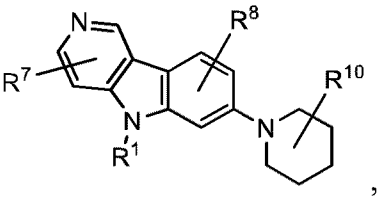
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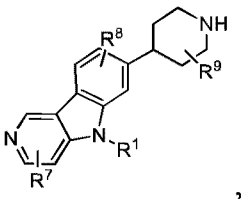
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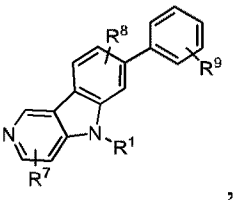
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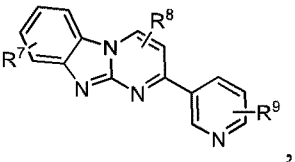
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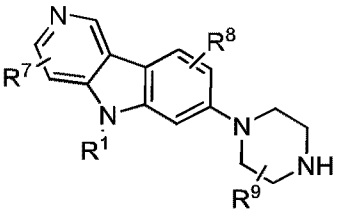
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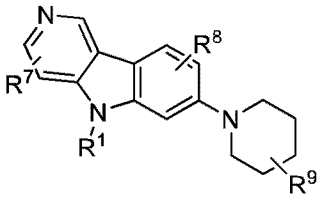

and ,

wherein:

R^1 is H, alkyl, or haloalkyl;

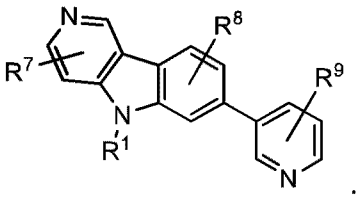
R^7 is 1 to 8 substituents, each independently selected from H, alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, dialkylamino, acetylamino, and cyano;

R^8 is 1 to 8 substituents, each independently selected from H, alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, dialkylamino, acetylamino, and cyano;

R^9 1 to 8 substituents, each independently selected from H, alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, dialkylamino, acetylamino, and cyano; and

R^{10} is 1 to 8 substituents, each independently selected from H, alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, dialkylamino, acetylamino, and cyano.

40. The compound of claim 39, wherein the compound is represented by the chemical structure: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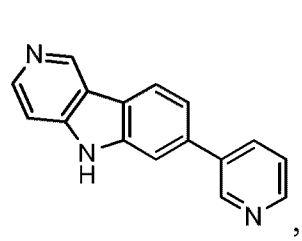
41. The compound of claim 39 or 40, wherein R^1 is H, methyl, ethyl, 2-fluoroethyl, or 2,2,2-trifluoroethyl.

42. The compound of claim 35, wherein the compound is selected from: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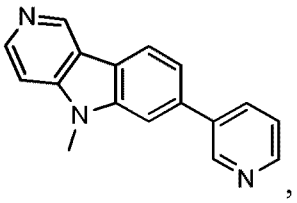
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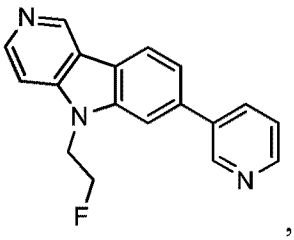
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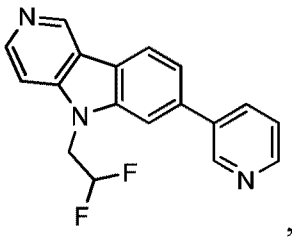
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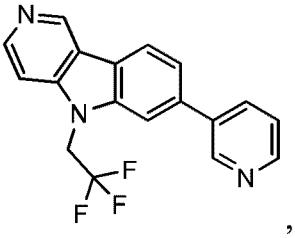
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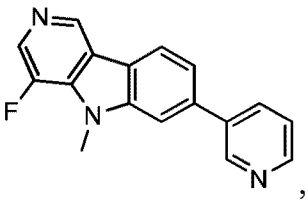
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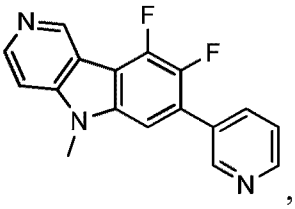
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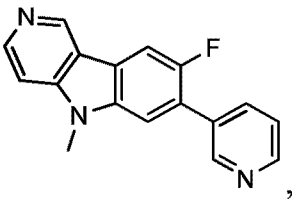
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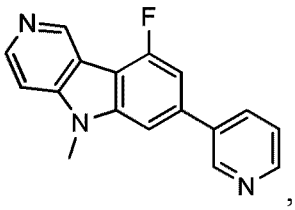
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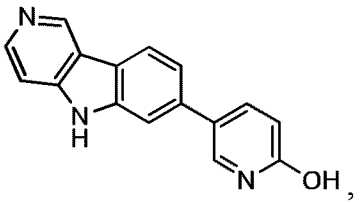
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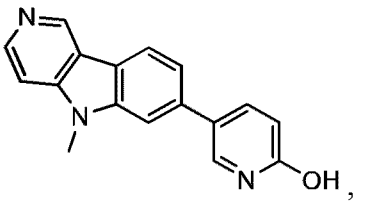
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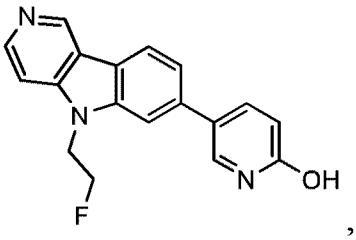
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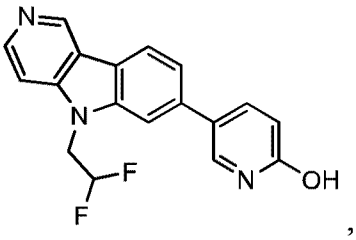
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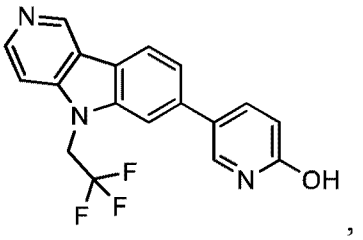
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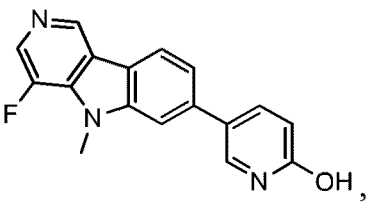
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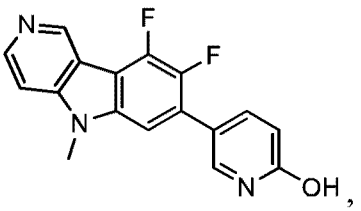
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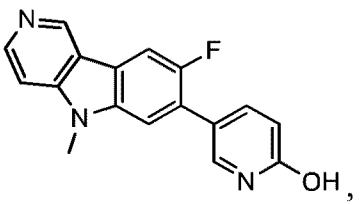
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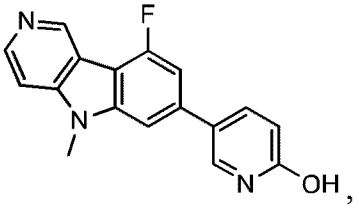
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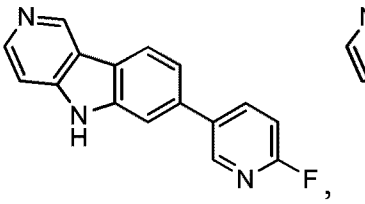
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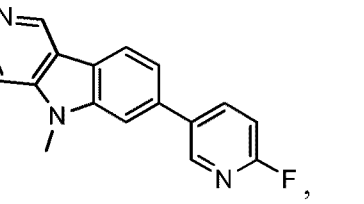
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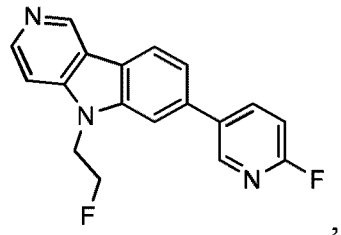
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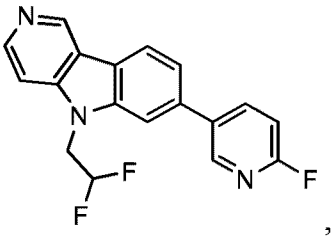
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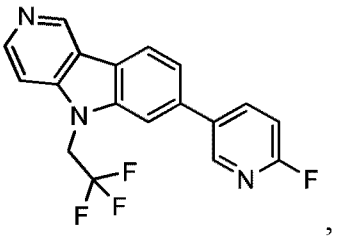
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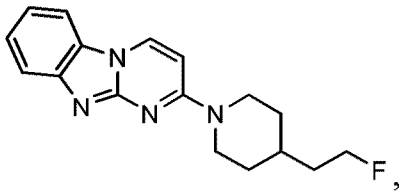
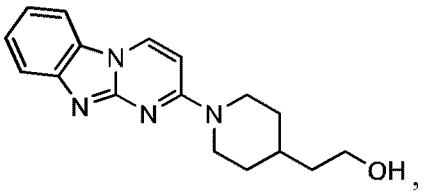
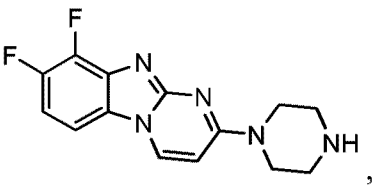
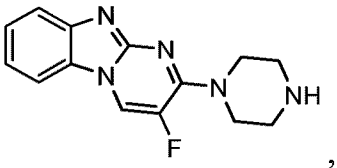
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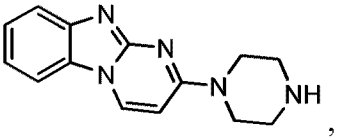
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or a pharmaceutically acceptable salt thereof.

43. A composition comprising a compound of any one of claims 36-42 and a pharmaceutically acceptable carrier.

44. The composition of claim 43, wherein the composition further comprises an additional bioactive agent.

45. The composition of claim 44, wherein the additional bioactive agent is an anti-neurodegenerative agent.

46. The composition of claim 44, wherein the additional bioactive agent is a P-gp inhibitor.

47. The composition of claim 46, wherein the P-gp inhibitor is Amiodarone, Azithromycin, Captopril, Clarithromycin, Cyclosporine, Piperine, Quercetin, Quinidine, Quinine, Reserpine, Ritonavir, Tariquidar, Elacridar or Verapamil.

48. Use of a compound of any one of claims 35-42 to treat a Tau-related disease or disorder associated with Tau accumulation and aggregation.

49. The use of claim 48, wherein the disease or disorder is a neurodegenerative disease.

50. The use of claim 48 of 49, wherein the disease or disorder is Acquired Epileptiform Aphasia, Acute Disseminated Encephalomyelitis, ADHD, Adie's Pupil, Adie's Syndrome,

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Adrenoleukodystrophy, Agenesis of the Corpus Callosum, Agnosia, Aicardi Syndrome, AIDS—Neurological Complications, Alexander Disease, Alpers' Disease, Alternating Hemiplegia, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Anencephaly, Aneurysm, Angelman Syndrome, Angiomatosis, Anoxia, Aphasia, Apraxia, Arachnoid Cysts, Arachnoiditis, Arnold-Chiari Malformation, Arteriovenous Malformation, Asperger Syndrome, Ataxia, Ataxia, Telangiectasia, Ataxias and Cerebellar/Spinocerebellar Degeneration, Attention Deficit-Hyperactivity Disorder, Autism, Autonomic Dysfunction, Back Pain, Barth Syndrome Batten Disease, Becker's Myotonia, Behcet's Disease, Bell's Palsy, Benign Essential Blepharospasm, Benign Focal Amyotrophy, Benign Intracranial Hypertension, Bernhardt-Roth Syndrome, Binswanger's Disease, Blepharospasm, Bloch-Sulzberger Syndrome, Brachial Plexus Birth Injuries, Brachial Plexus Injuries, Bradbury-Eggleston Syndrome, Brain and Spinal Tumors, Brain Aneurysm, Brain Injury, Brown-Sequard Syndrome, Bulbospinal Muscular Atrophy, Canavan Disease, Carpal Tunnel Syndrome Causalgia, Cavernomas, Cavernous Angioma, Cavernous Malformation, Central Cervical Cord Syndrome, Central Cord Syndrome, Central Pain Syndrome, Cephalic Disorders, Cerebellar Degeneration, Cerebellar Hypoplasia, Cerebral Aneurysm, Cerebral Arteriosclerosis, Cerebral Atrophy, Cerebral Beriberi, Cerebral Gigantism, Cerebral Hypoxia, Cerebral Patsy, Cerebro-Oculo-Facio-Skeletal Syndrome, Charcot-Marie-Tooth Disease, Chiari Malformation, Chorea, Choreoacanthocytosis, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Chronic Orthostatic Intolerance, Chronic Pain Cockayne Syndrome Type II, Coffin Lowry Syndrome, COFS, Colpocephaly, Coma and Persistent Vegetative State, Complex Regional Pain Syndrome, Congenital Facial Diplegia, Congenital Myasthenia, Congenital Myopathy, Congenital Vascular Cavernous, Malformations, Corticobasal Degeneration, Cranial Arteritis, Craniosynostosis, Creutzfeldt-Jakob Disease, Cumulative Trauma Disorders, Cushing's Syndrome, Cytomegalic Inclusion Body Disease, Cytomegalovirus Infection, Dancing Eyes-Dancing Feet Syndrome, Dandy-Walker Syndrome, Dawson Disease, De Morsier's Syndrome, Deep Brain Stimulation for Parkinson's Disease, Dejerine-Klumpke Palsy, Dementia, Dementia—Multi-Infarct, Dementia—Semantic, Dementia—Subcortical, Dementia With Lewy Bodies, Dentate Cerebellar Ataxia, Dentatorubral Atrophy, Dermatomyositis, Developmental Dyspraxia, Devic's Syndrome, Diabetic Neuropathy, Diffuse Sclerosis, Dysautonomia, Dysgraphia, Dyslexia, Dysphagia, Dyspraxia, Dyssynergia Cerebellaris, Myoclonica, Dyssynergia Cerebellaris Progressiva, Dystonias, Early Infantile

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Epileptic, Encephalopathy, Empty Sella Syndrome, Encephalitis Lethargica, Encephaloceles, Encephalopathy, Encephalotrigeminal Angiomatosis, Epilepsy, Erb-Duchenne and Dejerine-Klumpke Palsies, Erb's Palsy, Fabry's Disease, Fahr's Syndrome, Fainting, Familial Dysautonomia, Familial Hemangioma, Familial Idiopathic Basal Ganglia, Calcification, Familial Periodic Paralyses, Familial Spastic Paralysis, Febrile Seizures, Fisher Syndrome, Floppy Infant Syndrome, Friedreich's Ataxia, Frontotemporal, Dementia, Gaucher's Disease, Gerstmann's Syndrome, Gerstmann-Straussler-Scheinker, Disease, Giant Cell Arteritis, Giant Cell Inclusion Disease, Globoid Cell Leukodystrophy, Glossopharyngeal Neuralgia, Guillain-Barre Syndrome, Hallervorden-Spatz Disease, Head Injury, Headache, Hemicrania Continua, Hemifacial Spasm, Hemiplegia Alterans, Hereditary Neuropathies, Hereditary Spastic Paraplegia, Heredopathia Atactica Polyneuritiformis, Herpes Zoster, Herpes Zoster Oticus, Hirayama Syndrome, Holmes-Adie syndrome, Holoprosencephaly, HTLV-1 Associated, Myelopathy, Huntington's Disease, Hydranencephaly, Hydrocephalus, Hydrocephalus—Normal Pressure, Hydromyelia, Hyperactivity, Hypercortisolism, Hypersomnia, Hypertonia, Hypotonia,—Infantile, Hypoxia, Immune-Mediated Encephalomyelitis, Inclusion Body Myositis, Incontinentia Pigmenti, Infantile Hypotonia, Infantile Neuroaxonal Dystrophy, Infantile Phytanic Acid Storage Disease, Infantile Refsum Disease, Infantile Spasms, Inflammatory Myopathy, Iniencephaly, Intestinal Lipodystrophy, Intracranial Cysts, Intracranial Hypertension, Isaac's Syndrome, Joubert Syndrome, Kearns-Sayre Syndrome, Kennedy's Disease, Kinsbourne syndrome, Kleine-Levin Syndrome, Klippel-Feil Syndrome, Klippel-Trenaunay Syndrome (KTS), Klüver-Bucy Syndrome, Korsakoff's Amnesic Syndrome, Krabbe Disease, Kugelberg-Welander Disease, Kuru, Lambert-Eaton Myasthenic Syndrome, Landau-Kleffner Syndrome, Lateral Femoral, Cutaneous Nerve Entrapment, Lateral Medullary Syndrome, Learning Disabilities, Leigh's Disease, Lennox-Gastaut Syndrome, Lesch-Nyhan Syndrome, Leukodystrophy, Levine-Critchley Syndrome, Lewy Body Dementia, Lipid Storage Diseases, Lissencephaly, Locked-In Syndrome, Lou Gehrig's Disease, Lupus—Neurological, Sequelae, Lyme Disease—Neurological Complications, Machado-Joseph Disease, Macrencephaly, Mania, Megalencephaly, Melkersson-Rosenthal Syndrome, Meningitis, Meningitis and Encephalitis, Menkes Disease, Meralgia Paresthetica, Metachromatic, Leukodystrophy, Microcephaly, Migraine, Miller Fisher Syndrome, Mini-Strokes, Mitochondrial Myopathies, Mobius Syndrome, Monomelic Amyotrophy, Motor Neuron Diseases, Moyamoya Disease, Mucolipidoses,

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Mucopolysaccharidoses, Multifocal Motor Neuropathy, Multi-Infarct Dementia, Multiple Sclerosis, Multiple System Atrophy, Multiple System Atrophy with Orthostatic Hypotension, Muscular Dystrophy, Myasthenia—Congenital, Myasthenia Gravis, Myelinoclastic Diffuse Sclerosis, Myoclonic Encephalopathy of Infants, Myoclonus, Myopathy, Myopathy—Congenital, Myopathy-Thyrotoxic, Myotonia, Myotonia Congenita, Narcolepsy, Neuroacanthocytosis, Neurodegeneration with Brain Iron Accumulation, Neurofibromatosis, Neuroleptic Malignant Syndrome, Neurological Complications of AIDS, Neurological Complications Of Lyme Disease, Neurological Consequences of Cytomegalovirus Infection, Neurological Manifestations of Pompe Disease, Neurological Sequelae Of Lupus, Neuromyelitis Optica, Neuromyotonia, Neuronal Ceroid, Lipofuscinosis, Neuronal Migration Disorders, Neuropathy—Hereditary, Neurosarcoidosis, Neurotoxicity, Nevus Cavernosus, Niemann-Pick Disease, Normal Pressure Hydrocephalus, Occipital Neuralgia, Obesity, Occult Spinal Dysraphism Sequence, Ohtahara Syndrome, Olivopontocerebellar Atrophy, Opsoclonus Myoclonus, Orthostatic Hypotension, O'Sullivan-McLeod Syndrome, Overuse Syndrome, Pain—Chronic, Paine, Pantothenate Kinase-Associated Neurodegeneration, Paraneoplastic Syndromes, Paresthesia, Parkinson's Disease, Paroxysmal Choreoathetosis, Paroxysmal Hemicrania, Parry-Romberg, Pelizaeus-Merzbacher Disease, Pena Shokeir II Syndrome, Perineural Cysts, Periodic Paralyses, Peripheral Neuropathy, Periventricular Leukomalacia, Persistent Vegetative State, Pervasive Developmental Disorders, Phytanic Acid Storage Disease, Pick's Disease, Pinched Nerve, Piriformis Syndrome, Pituitary Tumors, Polymyositis, Pompe Disease, Porencephaly, Postherpetic Neuralgia, Postinfectious Encephalomyelitis, Post-Polio Syndrome, Postural Hypotension, Postural Orthostatic, Tachycardia Syndrome, Postural Tachycardia Syndrome, Primary Dentatum Atrophy, Primary Lateral Sclerosis, Primary Progressive Aphasia, Prion Diseases, Progressive Hemifacial Atrophy, Progressive Locomotor Ataxia, Progressive Multifocal, Leukoencephalopathy, Progressive Sclerosing Poliodystrophy, Progressive Supranuclear, Palsy, Prosopagnosia, Pseudotumor Cerebri, Ramsay Hunt Syndrome I (formerly known as), Ramsay Hunt Syndrome II (formerly known as), Rasmussen's Encephalitis, Reflex Sympathetic Dystrophy Syndrome, Refsum Disease, Refsum Disease—Infantile, Repetitive Motion Disorders, Repetitive Stress Injuries, Restless Legs Syndrome, Retrovirus-Associated Myelopathy, Rett Syndrome, Reye's Syndrome, Riley-Day Syndrome, Sacral Nerve Root Cysts, Saint Vitus Dance, Salivary Gland Disease, Sandhoff Disease,

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Schilder's Disease, Schizencephaly, Seitelberger Disease, Seizure Disorder, Semantic Dementia, Septo-Optic Dysplasia, Shaken Baby Syndrome, Shingles Shy-Drager Syndrome, Sjogren's Syndrome, Sleep Apnea, Sleeping Sickness, Sotos Syndrome, Spasticity, Spina Bifida, Spinal Cord Infarction, Spinal Cord Injury, Spinal Cord Tumors, Spinal Muscular Atrophy, Spinocerebellar Atrophy, Spinocerebellar, Degeneration, Steele-Richardson-Olszewski Syndrome, Stiff-Person Syndrome, Striatonigral Degeneration, Stroke, Sturge-Weber Syndrome, Subacute Sclerosing Panencephalitis, Subcortical Arteriosclerotic Encephalopathy, SUNCT Headache Swallowing Disorders, Sydenham Chorea, Syncope, Syphilitic Spinal Sclerosis, Syringohydromyelia, Syringomyelia, Systemic Lupus Erythematosus, Tabes Dorsalis Tardive Dyskinesia, Tarlov Cysts, Tay-Sachs Disease, Temporal Arteritis, Tethered Spinal Cord Syndrome, Thomsen's Myotonia, Thoracic Outlet Syndrome, Thyrotoxic Myopathy, Tic Douloureux, Todd's Paralysis, Tourette Syndrome, Transient Ischemic Attack, Transmissible Spongiform Encephalopathies, Transverse Myelitis, Traumatic Brain Injury, Tremor, Trigeminal Neuralgia, Tropical Spastic Paraparesis, Tuberous Sclerosis, Vascular Erectile Tumor, Vasculitis including Temporal Arteritis, Von Economo's Disease, Von Hippel-Lindau Disease (VHL), Von Recklinghausen's Disease, Wallenberg's Syndrome, Werdnig-Hoffman Disease, Wernicke-Korsakoff Syndrome, West Syndrome, Whiplash, Whipple's Disease, Williams Syndrome, Wilson's Disease, X-Linked Spinal and Bulbar Muscular Atrophy, or Zellweger Syndrome.

51. The use of any one of claims 48-50, wherein the disease or disorder is at least one neurological disorder selected from Huntington's disease, muscular dystrophy, Parkinson's disease, Alzheimer's disease, Batten disease, Injuries to the spinal cord and brain, Seizure disorders, epilepsy, brain tumors, meningitis, autoimmune diseases such as multiple sclerosis, neurofibromatosis, Depression, Amyotrophic Lateral Sclerosis, Arteriovenous Malformation, Brain Aneurysm, Dural Arteriovenous Fistulae, Headache, Memory Disorders, Peripheral Neuropathy, Post-Herpetic Neuralgia, Spinal Cord Tumor, and Stroke.

52. The use of any one of claims 48-50, wherein the disease or disorder is Alzheimer's disease.

53. The use of any one of claims 48-50, wherein the disease or disorder is Huntington's disease.

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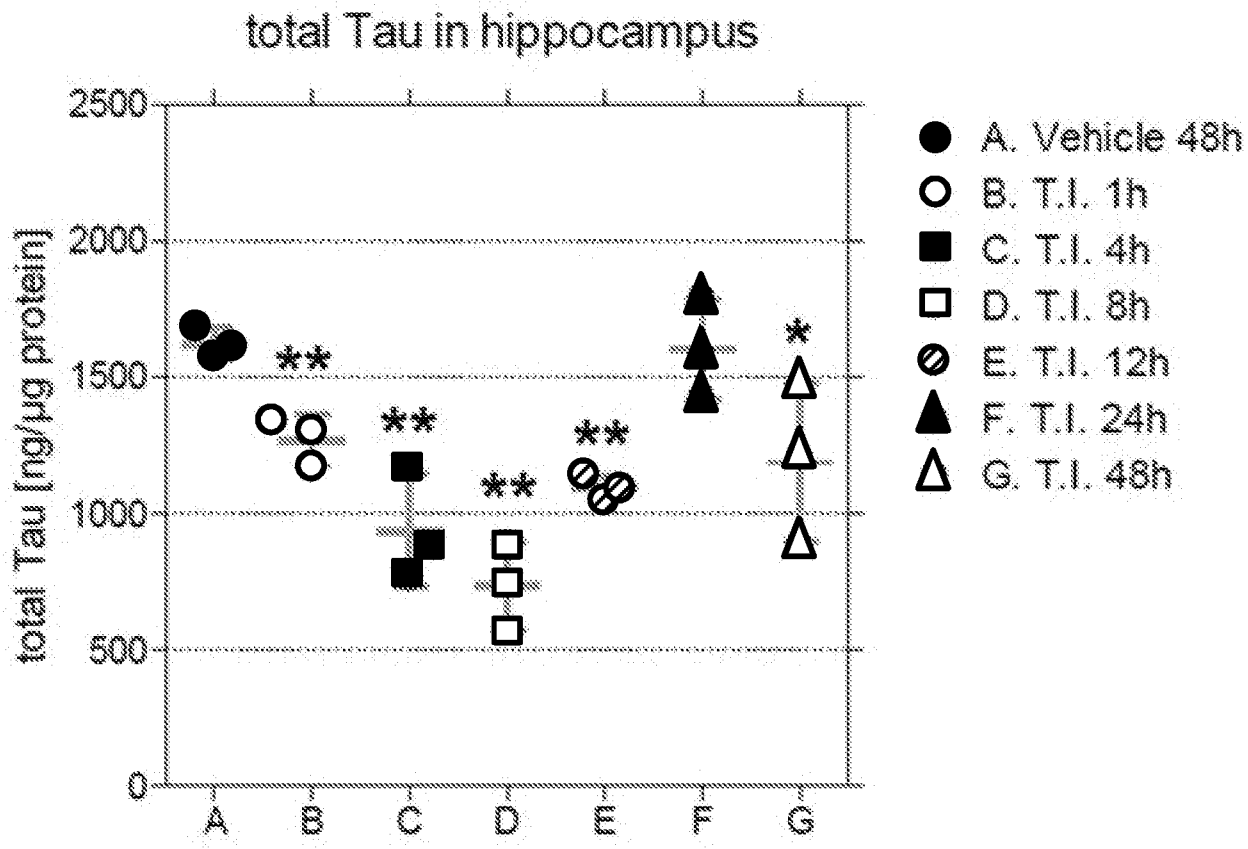
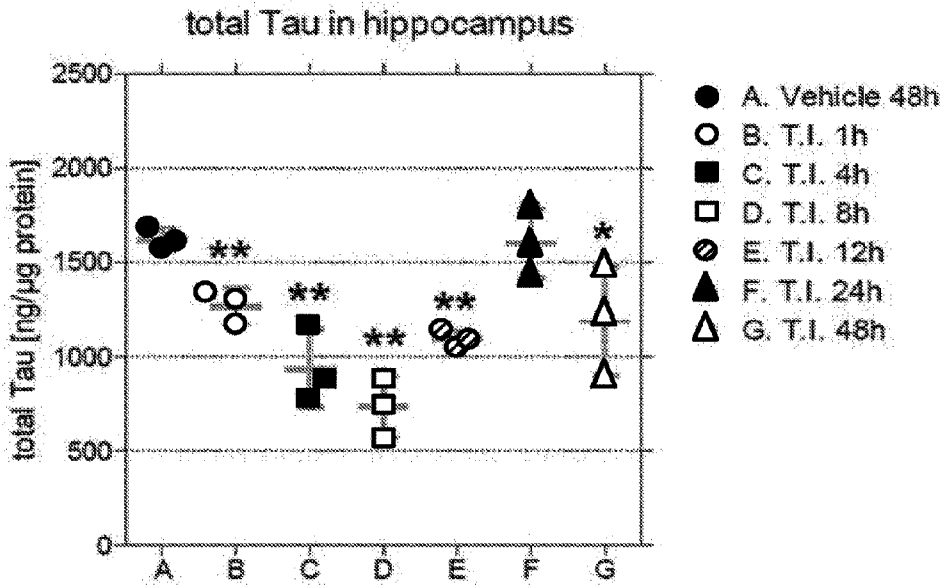
FIG. 1


total Tau in hippocampus
total Tau [ng/µg protein]
2500
2000
1500
1000
500
0
A
B
C
D
E
F
G
**
**
**
**
*
A. Vehicle 48h
B. T.I. 1h
C. T.I. 4h
D. T.I. 8h
E. T.I. 12h
F. T.I. 24h
G. T.I. 48h


total Tau in hippocampus
total Tau [ng/µg protein]
2500
2000
1500
1000
500
0
A
B
C
D
E
F
G
**
**
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*
A. Vehicle 48h
B. T.I. 1h
C. T.I. 4h
D. T.I. 8h
E. T.I. 12h
F. T.I. 24h
G. T.I. 48h