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(71) Applicant: **ARVINAS OPERATIONS, INC.** [US/US]; 5 Science Park, New Haven, 06511 (US).

(72) Inventors: **CREW, Andrew P.**; 2 Winterberry Road, Guilford, Connecticut 06437 (US). **CREWS, Craig M.**; 286 Livingston Street, New Haven, Connecticut 06511 (US). **DONG, Hanqing**; 248 Opening Hill Road, Madison, Connecticut 06443 (US). **HORNBERGER, Keith R.**; 182 Wolf Pit Drive, Southbury, Connecticut 06488 (US). **WANG, Jing**; 25 Elm Street, Milford, Connecticut 06460 (US). **QIAN, Yimin**; 5 Camas Court, Plainsboro, New Jersey 08536 (US). **ZIMMERMANN, Kurt**; 5 Skeetfield Point Road, Durham, Connecticut 06422 (US). **BERLIN, Michael**; 14 Hendrick Road, Flemington, New Jersey 08822 (US). **SNYDER, Lawrence B.**; 85 Laurel Ridge Trail, Killingworth, Connecticut 06419 (US).

(74) Agent: **HERREL, Nicholas**; CANTOR COLBURN LLP, 20 Church Street, 22nd Floor, Hartford, Connecticut 06103-3207 (US).

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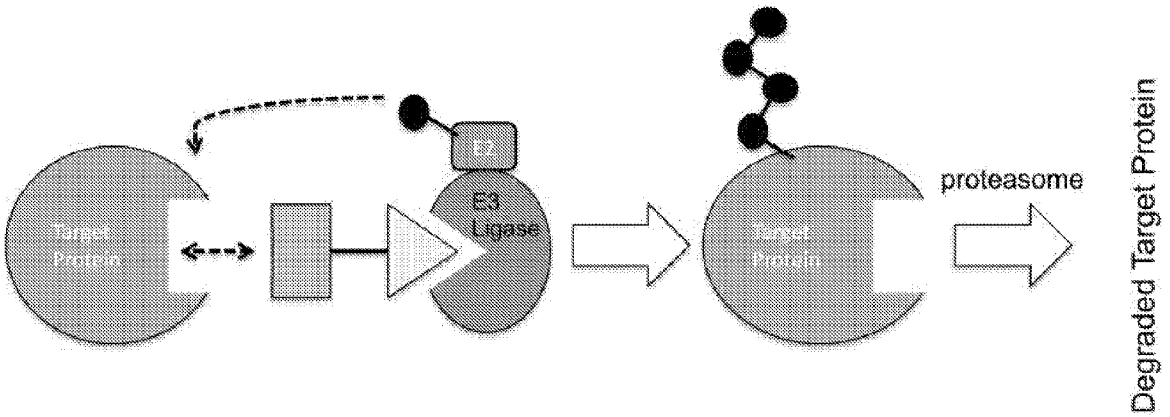
(54) Title: CEREBLON LIGANDS AND BIFUNCTIONAL COMPOUNDS COMPRISING THE SAME

FIG. 1B



(57) Abstract: The description relates to cereblon E3 ligase binding compounds, including bifunctional compounds comprising the same, which find utility as modulators of targeted ubiquitination, especially inhibitors of a variety of polypeptides and other proteins which are degraded and/or otherwise inhibited by bifunctional compounds according to the present disclosure. In particular, the description provides compounds, which contain on one end a ligand which binds to the cereblon E3 ubiquitin ligase and on the other end a moiety which binds a target protein such that the target protein is placed in proximity to the ubiquitin ligase to effect degradation (and inhibition) of that protein. Compounds can be synthesized that exhibit a broad range of pharmacological activities consistent with the degradation/inhibition of targeted polypeptides of nearly any type.

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CEREBLON LIGANDS AND BIFUNCTIONAL COMPOUNDS COMPRISING THE SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present disclosure is an International Application claiming priority to U.S. Non-Provisional Application No. 15/953108, filed 13 April 2018, which is a Continuation-in-Part of U.S. Non-Provisional Application No. 14/686,640, filed 14 April 2015, that claims priority to U.S. Provisional Application No. 61/979,351, filed 14 April 2014, and a Continuation-in-Part of U.S. Non-Provisional Application No. 14/792,414, filed 6 July 2015, that claims priority to U.S. Provisional Application No. 61/979,351, filed 14 April 2014, and U.S. Provisional Application No. 62/171,090, filed 4 June 2015, all of which are incorporated herein by reference in their entirety.

INCORPORATION BY REFERENCE

[0002] U.S. Patent Application Serial No. 15/230,354, filed on August 5, 2016, published as U.S. Patent Application Publication No. 2017/0065719; and U.S. Patent Application Serial No. 15/801,243, filed on 1 November 2017; and U.S. Patent Application 15/206,497 filed 11 July 2016; and U.S. Patent Application 15/209,648 filed 13 July 2016; and U.S. Patent Application Serial No. 15/730,728, filed on October 11, 2017; U.S. Patent Application Serial No. 15/829,541, filed on December 1, 2017; U.S. Patent Application Serial No. 15/881,318, filed on January 26, 2018; and U.S. Patent Application Serial No. 14/686,640, filed on April 14, 2015, published as U.S. Patent Application Publication No. 2015/0291562; and U.S. Patent Application Serial No. 14/792,414, filed on July 6, 2015, published as U.S. Patent Application Publication No. 2016/0058872; and U.S. Patent Application Serial No. 14/371,956, filed on July 11, 2014, published as U.S. Patent Application Publication No. 2014/0356322; and U.S. Patent Application Serial No. 15/074,820, filed on March 18, 2016, published as U.S. Patent Application Publication No. 2016/0272639; and U.S. Patent Application Serial No. 15/885,671, filed on 31 January 2018, are incorporated herein by reference in their entirety. Furthermore, all references cited herein are incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

[0003] The description provides imide-based compounds, including bifunctional compounds comprising the same, and associated methods of use. The bifunctional compounds are useful as modulators of targeted ubiquitination, especially with respect to a variety of polypeptides and other proteins, which are degraded and/or otherwise inhibited by bifunctional compounds according to the present disclosure.

BACKGROUND

[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 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 therapeutic potential is the von Hippel-Lindau (VHL) tumor suppressor. VHL comprises the substrate recognition subunit/E3 ligase complex VCB, which includes elongins B and C, and a complex including Cullin-2 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. We generated the first small molecule ligands of Von Hippel Lindau (VHL) to the substrate recognition subunit of the E3 ligase, VCB, an important target in cancer, chronic anemia and ischemia, and obtained crystal structures 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] Thalidomide, which has been approved for the treatment of a number of immunological indications, has also been approved for the treatment of certain neoplastic diseases, including multiple myeloma. In addition to multiple myeloma, thalidomide and several of its analogs are also currently under investigation for use in treating a variety of other types of cancer. While the precise mechanism of thalidomide's anti-tumor activity is still emerging, it is known to inhibit angiogenesis. Recent literature discussing the biology of the imides includes Lu et al Science 343, 305 (2014) and Krönke et al Science 343, 301 (2014).

[0008] Significantly, thalidomide and its analogs e.g. pomolinamiode and lenalinomide, are known to bind cereblon. These agents bind to cereblon, altering the specificity of the complex to induce the ubiquitination and degradation of Ikaros (IKZF1) and Aiolos (IKZF3), transcription factors essential for multiple myeloma growth. Indeed, higher expression of cereblon has been linked to an increase in efficacy of imide drugs in the treatment of multiple myeloma.

[0009] An ongoing need exists in the art for effective treatments for disease, especially hyperplasias and cancers, such as multiple myeloma. However, non-specific effects, and the inability to target and modulate certain classes of proteins altogether, such as transcription factors, remain as obstacles to the development of effective anti-cancer agents. As such, small molecule therapeutic agents that leverage or potentiate cereblon's substrate specificity and, at the same time, are "tunable" such that a wide range of protein classes can be targetted and modulated with specificity would be very useful as a therapeutic.

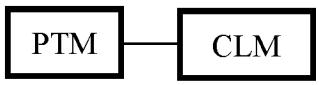
BRIEF SUMMARY OF THE INVENTION

[0010] 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 a variety of polypeptides and other proteins, which are then degraded and/or otherwise inhibited by the bifunctional compounds as described herein. An advantage of the compounds provided herein is that a broad range of pharmacological activities is possible, consistent with the degradation/inhibition of targeted polypeptides from virtually any protein class or family. In addition, the description provides methods of using an effective amount of the compounds as described herein for the treatment or amelioration of a disease condition, such as cancer, e.g., multiple myeloma.

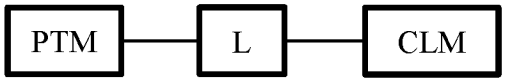
[0011] As such, in one aspect the disclosure provides novel imide-based compounds as described herein.

[0012] In an additional aspect, the disclosure provides bifunctional or PROTAC compounds, which comprise an E3 Ubiquitin Ligase binding moiety (i.e., a ligand for an E3 Ubiquitin Ligase or "ULM" group), and a moiety that binds a target protein (i.e., a protein/polypeptide targeting ligand or "PTM" group) such that the target protein/polypeptide is placed in proximity to the ubiquitin ligase to effect degradation (and inhibition) of that protein. In a preferred embodiment, the ULM is a cereblon E3 Ubiquitin Ligase binding moiety (i.e., a "CLM"). For example, the structure of the bifunctional compound can be depicted as:



[0013] The respective positions of the PTM and CLM moieties as well as their number as illustrated herein is provided by way of example only and is not intended to limit the compounds in any way. 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.

[0014] In certain embodiments, the bifunctional compound further comprises a chemical linker ("L"). In this example, the structure of the bifunctional compound can be depicted as:



where PTM is a protein/polypeptide targeting moiety, L is a linker, and CLM is a cereblon E3 ubiquitin ligase binding moiety.

[0015] In certain preferred embodiments, the E3 Ubiquitin Ligase is cereblon. As such, in certain additional embodiments, the CLM of the bifunctional compound comprises chemistries such as imide, amide, thioamide, thioimide derived moieties. In additional embodiments, the CLM comprises a phthalimido group or an analog or derivative thereof. In still additional embodiments, the CLM comprises a phthalimido-glutarimide group or an analog or derivative thereof. In still other embodiments, the CLM comprises a member of the group consisting of thalidomide, lenalidomide, pomalidomide, and analogs or derivatives thereof.

[0016] In certain embodiments, the compounds as described herein comprise multiple CLMs, multiple PTMs, multiple chemical linkers or a combination thereof.

[0017] In any aspect or embodiment described herein, the ULM (ubiquitination ligase modulator) can be Von Hippel-Lindau E3 ubiquitin ligase (VHL) binding moiety (VLM), or a cereblon E3 ubiquitin ligase binding moiety (CLM), or a mouse double minute 2 homolog (MDM2) E3 ubiquitin ligase binding moiety (MLM), or an IAP E3 ubiquitin ligase binding moiety (i.e., a "ILM"). In any aspect or embodiments described herein, the bifunctional compound includes at least one additional E3 ligase binding moiety selected from the group consisting of VLM, VLM', CLM, CLM', MLM, MLM', ILM, ILM', or a combination thereof. For example, there can be at least 1, 2, 3, 4, or 5 additional E3 ligase binding moieties.

[0018] 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., cancer. 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 CLM and a PTM, preferably linked through a linker moiety, as otherwise described herein, wherein the CLM is coupled to the PTM and wherein the CLM recognizes a ubiquitin pathway protein (e.g., an ubiquitin ligase, preferably an E3 ubiquitin ligase such as, e.g., cereblon) and the PTM recognizes the target protein 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.

[0019] In an additional aspect, the description provides a method for assessing (i.e., determining and/or measuring) a CLM's binding affinity. In certain embodiments, the method comprises providing a test agent or compound of interest, for example, an agent or compound having an imide moiety, e.g., a phthalimido group, phthalimido-glutarimide group, derivatized thalidomide, derivatized lenalidomide or derivatized pomalidomide, and comparing the cereblon binding affinity and/or inhibitory activity of the test agent or compound as compared to an agent or compound known to bind and/or inhibit the activity of cereblon.

[0020] In still another aspect, the description provides methods for treating or emeliorating a disease, disorder or symptom thereof in a subject or a patient, e.g., an animal such as a human, comprising administering to a subject in need thereof a composition comprising an effective amount, e.g., a therapeutically effective amount, of a compound as described herein or salt form thereof, and a pharmaceutically acceptable carrier, wherein the composition is effective for treating or ameliorating the disease or disorder or symptom thereof in the subject.

[0021] In another 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.

[0022] The preceding general areas of utility are given by way of example only and are not intended to be limiting on the scope of the present disclosure and appended claims. Additional objects and advantages associated with the compositions, methods, and processes of the present 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 invention may be utilized in numerous combinations, all of which are expressly contemplated by the present description. These additional advantages objects and embodiments are expressly included within the scope of the present disclosure. The publications and other materials used herein to illuminate the background of the invention, and in particular cases, to provide additional details respecting the practice, are incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] 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 invention. The drawings are only for the purpose of illustrating an embodiment of the invention and are not to be construed as limiting the invention. Further objects, features and advantages of the invention will become apparent from the following detailed description taken in conjunction with the accompanying figures showing illustrative embodiments of the invention, in which:

[0024] **Figure 1A and 1B**. Illustration of general principle for PROTAC function. (**A**) Exemplary PROTACs comprise a protein targeting moiety (PTM; *darkly shaded rectangle*), a ubiquitin ligase binding moiety (ULM; *lightly shaded triangle*), and optionally a linker moiety (L; *black line*) coupling or tethering the PTM to the ULM. (**B**) Illustrates the functional use of the PROTACs as described herein. Briefly, the ULM recognizes and binds to a specific E3 Ubiquitin Ligase, and the PTM binds and recruits a target protein bringing it into close proximity to the E3 Ubiquitin Ligase. Typically, the E3 Ubiquitin Ligase is complexed with an E2 ubiquitin-conjugating protein, and either alone or via the E2 protein catalyzes attachment of ubiquitin (*dark circles*) to a lysine on the target protein via an isopeptide bond. The poly-ubiquitinated protein (*far right*) is then targeted for degration by the proteosomal machinery of the cell.

DETAILED DESCRIPTION

[0025] 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. All publications, patent applications, patents, figures and other references mentioned herein are expressly incorporated by reference in their entirety.

[0026] Presently described are compositions and methods that relate to the surprising and unexpected discovery that an E3 Ubiquitin Ligase protein, e.g., cereblon, ubiquitinates a target protein once it and the target protein are placed in proximity by a bifunctional or chimeric construct that binds the E3 Ubiquitin Ligase protein and the target protein. Accordingly the present disclosure provides such compounds and compositions comprising an E3 Ubiquintin Ligase binding moiety ("ULM") coupled to a protein target binding moiety ("PTM"), which

result in the ubiquitination of a chosen target protein, which leads to degradation of the target protein by the proteasome (*see* **Figures 1A and 1B**). The present disclosure also provides a library of compositions and the use thereof.

[0027] In certain aspects, the present disclosure 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 IAP, VHL, MDM2, 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.

[0028] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The terminology used in the description is for describing particular embodiments only and is not intended to be limiting of the invention.

[0029] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise (such as in the case of a group containing a number of carbon atoms in which case each carbon atom number falling within the range is provided), between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either both of those included limits are also included in the invention.

[0030] The following terms are used to describe the present invention. In instances where a term is not specifically defined herein, that term is given an art-recognized meaning by those of ordinary skill applying that term in context to its use in describing the present invention.

[0031] 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.

[0032] The phrase "and/or," as used herein in the specification and in the claims, should be understood to mean "either or both" of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with "and/or" should be construed in the same fashion, i.e., "one or more" of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the "and/or" clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to "A and/or B", when used in conjunction with open-ended language such as "comprising" can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

[0033] 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."

[0034] 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.

[0035] 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.

[0036] 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.

[0037] The terms "co-administration" and "co-administering" or “combination therapy” refer to both concurrent administration (administration of two or more therapeutic agents at the same time) and time varied administration (administration of one or more therapeutic agents at a time different from that of the administration of an additional therapeutic agent or agents), as long as the therapeutic agents are present in the patient to some extent, preferably at effective amounts, at the same time. In certain preferred aspects, one or more of the present compounds described herein, are coadministered in combination with at least one additional bioactive agent, especially including an anticancer agent. In particularly preferred aspects, the co-administration of compounds results in synergistic activity and/or therapy, including anticancer activity.

[0038] 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 and/or deuterated forms thereof where applicable, in context. Deuterated small molecules contemplated are those in which one or more of the hydrogen atoms contained in the drug molecule have been replaced by deuterium.

[0039] 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. When the bond is shown, both a double bond and single bond are represented or understood within the context of the compound shown and well-known rules for valence interactions.

[0040] 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.

[0041] 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.

[0042] 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.

Compounds and Compositions

[0043] In one aspect, the description provides compounds comprising an E3 Ubiquitin Ligase binding moiety ("ULM") that is a cereblon E3 Ubiquitin Ligase binding moiety ("CLM"). In one embodiment, the CLM is coupled to a chemical linker (L) according to the structure:

(I) L-CLM

wherein L is a chemical linker group and CLM is a cereblon E3 Ubiquitin Ligase binding moiety. The number and/or relative positions of the moieties in the compounds illustrated herein is provided by way of example only. As would be understood by the skilled artisan, compounds as described herein can be synthesized with any desired number and/or relative position of the respective functional moieties.

[0044] The terms ULM and CLM are used in their inclusive sense unless the context indicates otherwise. For example, the term ULM is inclusive of all ULMs, including those that bind cereblon (i.e., CLMs). Further, the term CLM is inclusive of all possible cereblon E3 Ubiquitin Ligase binding moieties.

[0045] In another aspect, the present disclosure provides bifunctional or multifunctional PROTAC compounds useful for regulating protein activity by inducing the degradation of a target protein. In certain embodiments, the compound comprises a CLM coupled, e.g., linked covalently, directly or indirectly, to a moiety that binds a target protein (i.e., protein targeting moiety or "PTM"). In certain embodiments, the CLM and PTM are joined or coupled via a chemical linker (L). The CLM recognizes the cereblon E3 ubiquitin ligase and the PTM recognizes a target protein and the interaction of the respective moieties with their targets

facilitates the degradation of the target protein by placing the target protein in proximity to the ubiquitin ligase protein. An exemplary bifunctional compound can be depicted as:

(II) PTM-CLM

[0046] In certain embodiments, the bifunctional compound further comprises a chemical linker ("L"). For example, the bifunctional compound can be depicted as:

(III) PTM-L-CLM

wherein PTM is a protein/polypeptide targeting moiety, L is a linker, and CLM is a cereblon E3 ligase binding moiety.

[0047] In certain embodiments, the compounds as described herein comprise multiple PTMs (targeting the same or different protein targets), multiple CLMs, one or more ULMs (i.e., moieties that bind specifically to another E3 Ubiquitin Ligase, e.g., VHL) or a combination thereof. In any of the aspects of embodiments described herein, the PTMs, CLMs, and ULMs can be coupled directly or via one or more chemical linkers or a combination thereof. In additional embodiments, where a compound has multiple ULMs, the ULMs can be for the same E3 Ubiquintin Ligase or each respective ULM can bind specifically to a different E3 Ubiquitin Ligase. In still further embodiments, where a compound has multiple PTMs, the PTMs can bind the same target protein or each respective PTM can bind specifically to a different target protein.

[0048] In another embodiment, the description provides a compound which comprises a plurality of CLMs coupled directly or via a chemical linker moiety (L). For example, a compound having two CLMs can be depicted as:

(IV) CLM-CLM or

(V) CLM-L-CLM

[0049] In certain embodiments, where the compound comprises multiple CLMs, the CLMs are identical. In additional embodiments, the compound comprising a plurality of CLMs further comprises at least one PTM coupled to a CLM directly or via a chemical linker (L) or both. In certain additional embodiments, the compound comprising a plurality of CLMs further comprises multiple PTMs. In still additional embodiments, the PTMs are the same or, optionally, different. In still further embodiments, wherein the PTMs are different the respective PTMs may bind the same protein target or bind specifically to a different protein target.

[0050] In additional embodiments, the description provides a compound comprising at least two different CLMs coupled directly or via a chemical linker (L) or both. For example, such a compound having two different CLMs can be depicted as:

(VI) CLM-CLM' or

(VII) CLM-L-CLM'

wherein CLM' indicates a cereblon E3 Ubiquitin Ligase binding moiety that is structurally different from CLM. In certain embodiments, the compound may comprise a plurality of CLMs and/or a plurality of CLM's. In further embodiments, the compound comprising at least two different CLMs, a plurality of CLMs, and/or a plurality of CLM's further comprises at least one PTM coupled to a CLM or a CLM' directly or via a chemical linker or both. In any of the embodiments described herein, a compound comprising at least two different CLMs can further comprise multiple PTMs. In still additional embodiments, the PTMs are the same or, optionally, different. In still further embodiments, wherein the PTMs are different the respective PTMs may bind the same protein target or bind specifically to a different protein target. In still further embodiments, the PTM itself is a ULM or CLM (or ULM' or CLM').

[0051] In a preferred embodiment, the CLM comprises a moiety that is a ligand of the cereblon E3 Ubiquitin Ligase (CRBN). In certain embodiments, the CLM comprises a chemotype from the "imide" class of of molecules. In certain additional embodiments, the CLM comprises a phthalimido group or an analog or derivative thereof. In still additional embodiments, the CLM comprises a phthalimido-glutarimide group or an analog or derivative thereof. In still other embodiments, the CLM comprises a member of the group consisting of thalidomide, lenalidomide, pomalidomide, and analogs or derivatives thereof.

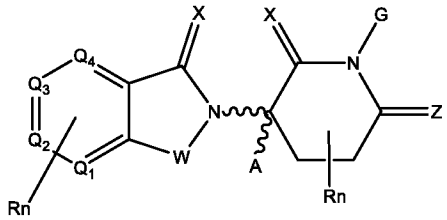
[0052] In additional embodiments, the description provides the compounds as described herein including their enantiomers, diastereomers, solvates and polymorphs, including pharmaceutically acceptable salt forms thereof, e.g., acid and base salt forms.

[0053] **Exemplary Cereblon Binding and/or Inhibiting Compounds**

[0054] In one aspect the description provides compounds useful for binding and/or inhibiting cereblon E3 Ubiquitin Ligase binding moiety. In certain embodiments, the compound has a chemical structure that includes at least one of (e.g., the compound has a chemical structure selected from the group consisting of):

[0055] Neo-imide Compounds

[0056] In one aspect the description provides compounds useful for binding and/or inhibiting cereblon. In certain embodiments, the compound is selected from the group consisting of chemical structures:



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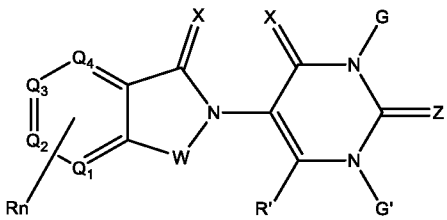

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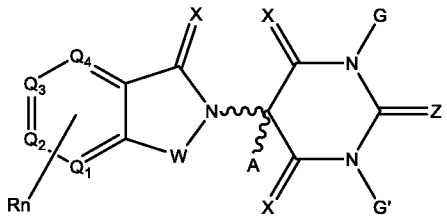

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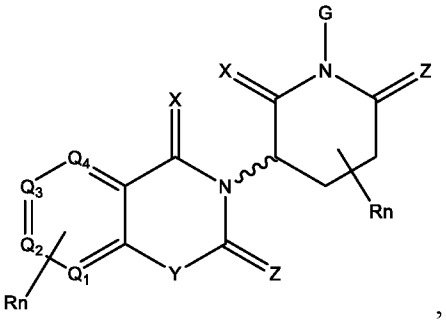

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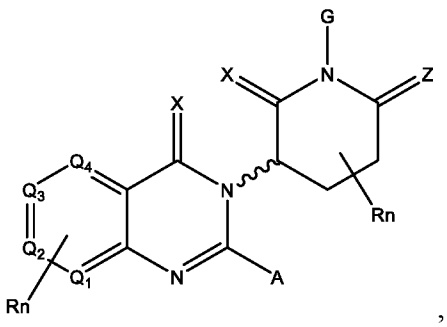
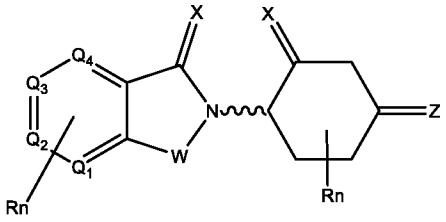
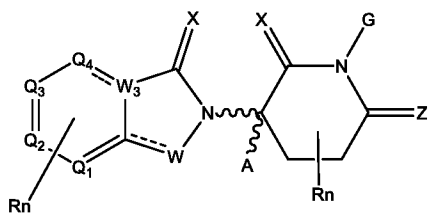


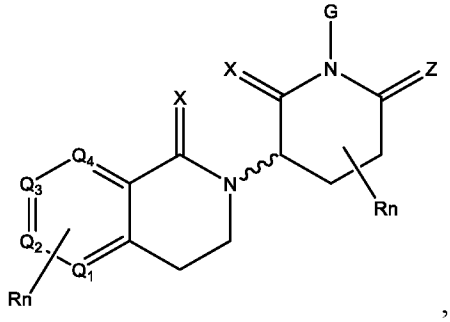
(e)



(f)



(a2)



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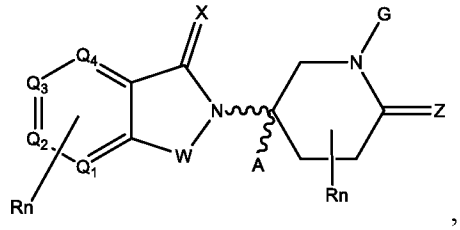


(a3)

wherein:

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

W_3 is selected from C or N;

each X of Formulas (a) through (e) is absent or independently selected from the group O and S;

Y of Formulas (a) through (e) is independently selected from the group CH_2, -C=CR', NH, N-alkyl, N-aryl, N-hetaryl, N-cycloalkyl, N-heterocyclyl, O, and S;

each Z of Formulas (a) through (e) is absent or independently selected from the group O and S, except that both X and Z cannot be absent;

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

Q1 – Q4 of Formulas (a) through (e) represent a carbon C substituted with a group independently selected from R', N or N-oxide;

A of Formulas (a) through (e) is independently selected from the group H, alkyl (linear, branched, optionally substituted), cycloalkyl, Cl and F;

R of Formulas (a) through (e) comprises, but is not limited to: -CONR'R", -OR', -NR'R", -SR', -SO_2R', -SO_2NR'R", -CR'R"-, -CR'NR'R"-, (-CR'O)$_{n'}$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 and -OCF_3

R' and R" of Formulas (a) through (e) are independently selected from a bond, H, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclic, -C(=O)R, heterocyclyl, each of which is optionally substituted;

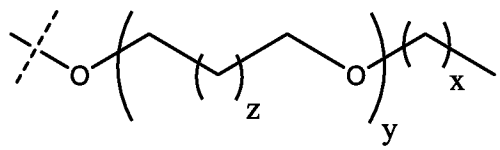
n' of Formulas (a) through (e) is an integer from 1-10 (e.g., 1-4);

〰 of Formulas (a) through (e) represents a bond that may be stereospecific ((R) or (S)) or non-stereospecific;

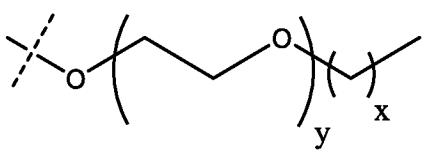
⥱ represents a single bond or a double bond;

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

Rn comprises 1-4 independent functional groups, optionally substituted linear or branched alkyl (e.g., a C1-C6 linear or branched alkyl optionally substituted with one or more halogen, cycloalkyl (e.g., a C3-C6 cycloalkyl), or aryl (e.g., C5-C7 aryl)), optionally substituted aryl (e.g., an optionally substituted C5-C7 aryl), optionally substituted alkyl-aryl (e.g., an alkyl-aryl comprising at least one of an optionally substituted C1-C6 alkyl, an optionally substituted C5-C7 aryl, or combinations thereof), optionally substituted alkoxyl group (e.g., a methoxy, ethoxy, butoxy, propoxy, pentoxy, or hexoxy; wherein the alkoxyl may be substituted with one or more halogen, alkyl, haloalky, fluoroalkyl, cycloalkyl (e.g., a C3-C6 cycloalkyl), or aryl (e.g., C5-C7 aryl)), optionally substituted



(e.g., optionally substituted with one or more halogen, alkyl, haloalky, fluoroalkyl, cycloalkyl (e.g., a C3-C6 cycloalkyl), or aryl (e.g., C5-C7 aryl)), optionally substituted



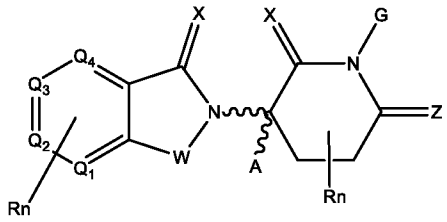
(e.g., optionally

substituted with one or more halogen, alkyl, haloalky, fluoroalkyl, cycloalkyl (e.g., a C3-C6 cycloalkyl), or aryl (e.g., C5-C7 aryl)), or atoms; and

each of x, y, and z are independently 0, 1, 2, 3, 4, 5, or 6,

[0057] **Exemplary CLMs**

[0058] In any of the compounds described herein, the CLM comprises a chemical structure selected from the group:



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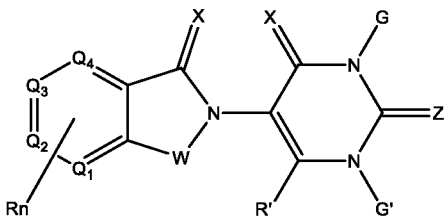

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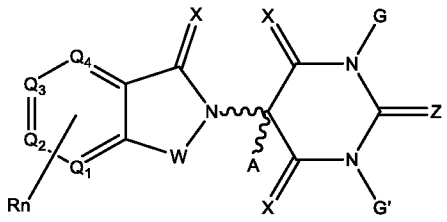

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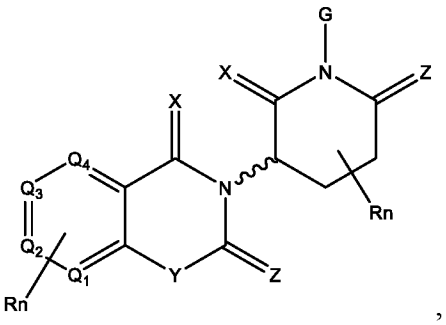

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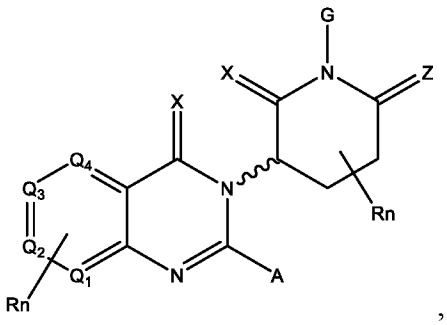
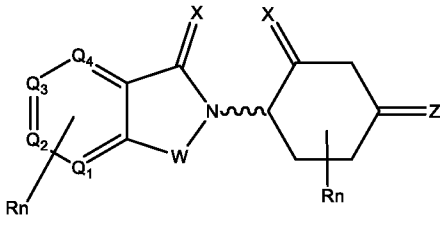


(e)



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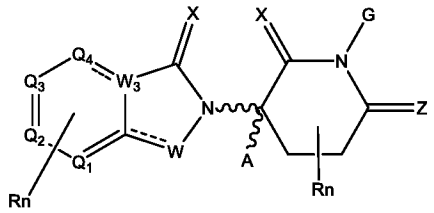

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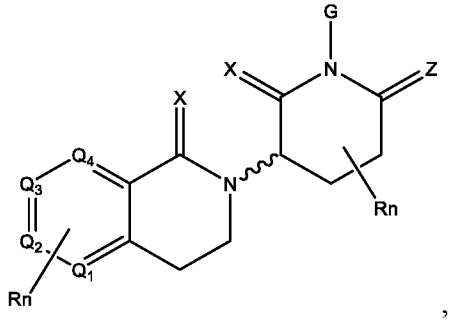

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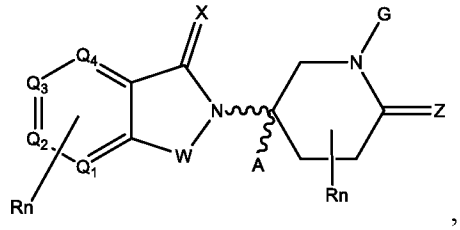

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(a3)

wherein:

W of Formulas (a) through (f) is independently selected from the group CH_2, CHR, C=O, SO_2, NH, N, optionally substituted cyclopropyl group, optionally substituted cyclobutyl group, and N-alkyl;

W_3 is selected from C or N;

each X of Formulas (a) through (f) is absent or independently selected from the group O and S;

Y of Formulas (a) through (f) is independently selected from the group CH2, -C=CR', NH, N-alkyl, N-aryl, N-hetaryl, N-cycloalkyl, N-heterocyclyl, O, and S;

each Z of Formulas (a) through (f) is absent or independently selected from the group O and S, except that both X and Z cannot be absent;

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

Q1 – Q4 of Formulas (a) through (f) represent a carbon C substituted with a group independently selected from R', N or N-oxide;

A of Formulas (a) through (f) is independently selected from the group H, alkyl (linear, branched, optionally substituted), cycloalkyl, Cl and F;

R of Formulas (a) through (f) comprises, but is not limited to: -CONR'R", -OR', -NR'R", -SR', -SO2R', -SO2NR'R", -CR'R"-, -CR'NR'R"-, (-CR'O)$_{n'}$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-NO2)NR'R", -SO2NR'COR", -NO2, -CO2R', -C(C=N-OR')R", -CR'=CR'R", -CCR', -S(C=O)(C=N-R')R", -SF5 and -OCF3

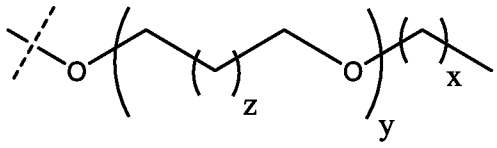
R' and R" of Formulas (a) through (f) are independently selected from a bond, H, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclic, -C(=O)R, heterocyclyl, each of which is optionally substituted;

n' of Formulas (a) through (f) is an integer from 1-10 (e.g., 1-4);

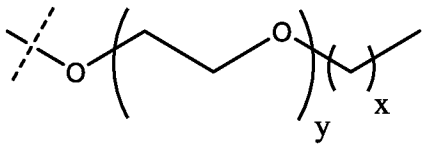
represents a single bond or a double bond;

of Formulas (a) through (f) represents a bond that may be stereospecific ((R) or (S)) or non-stereospecific;

Rn comprises 1-4 independent functional groups, optionally substituted linear or branched alkyl (e.g., a C1-C6 linear or branched alkyl optionally substituted with one or more halogen, cycloalkyl (e.g., a C3-C6 cycloalkyl), or aryl (e.g., C5-C7 aryl)), optionally substituted aryl (e.g., an optionally substituted C5-C7 aryl), optionally substituted alkyl-aryl (e.g., an alkyl-aryl comprising at least one of an optionally substituted C1-C6 alkyl, an optionally substituted C5-C7 aryl, or combinations thereof), optionally substituted alkoxyl group (e.g., a methoxy, ethoxy, butoxy, propoxy, pentoxy, or hexoxy; wherein the alkoxyl may be substituted with one or more halogen, alkyl, haloalky, fluoroalkyl, cycloalkyl (e.g., a C3-C6 cycloalkyl), or aryl (e.g., C5-C7 aryl)), optionally substituted



(e.g., optionally substituted with one or more halogen, alkyl, haloalky, fluoroalkyl, cycloalkyl (e.g., a C3-C6 cycloalkyl), or aryl (e.g., C5-C7 aryl)), optionally substituted



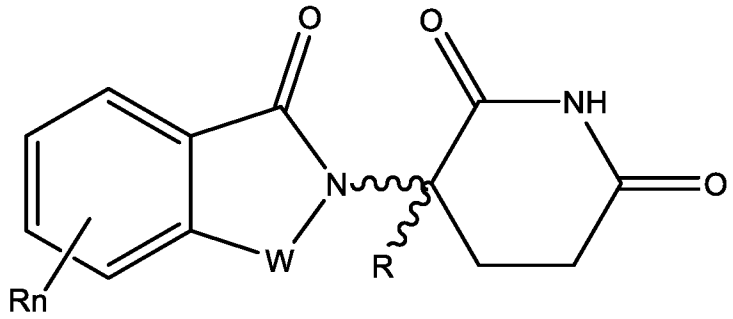
(e.g., optionally

substituted with one or more halogen, alkyl, haloalky, fluoroalkyl, cycloalkyl (e.g., a C3-C6 cycloalkyl), or aryl (e.g., C5-C7 aryl)), or atoms; and

each of x, y, and z are independently 0, 1, 2, 3, 4, 5, or 6.

[0059] In any aspect or embodiment described herein, each of the X and Z of the 6-member monocyclic cyloalkyl or monocyclic heterocycloalkyl of the CLM are each independently absent, O or S, except that both X and Z cannot be absent. In any aspect or embodiment described herein, X on the middle ring is selected from O and S, and each of the X and Z of the 6-member monocyclic cyloalkyl or monocyclic heterocycloalkyl of the CLM are each independently absent, O or S, except that both X and Z cannot be absent.

[0060] In certain embodiments described herein, the CLM or ULM comprises a chemical structure selected from the group:



Formula (g)

wherein:

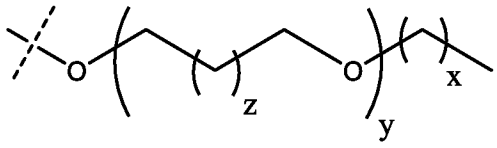
W of Formula (g) is independently selected from the group CH_2, C=O, NH, and N-alkyl;

R of Formula (g) is independently selected from a H, methyl, alkyl (e.g., a or C1-C6 alkyl (linear, branched, optionally substituted));

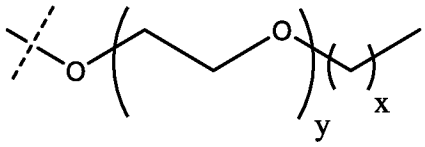
〰 of Formula (g) represents a bond that may be stereospecific ((R) or (S)) or non-stereospecific; and

Rn comprises 1-4 independent functional groups, optionally substituted linear or branched alkyl (e.g., a C1-C6 linear or branched alkyl optionally substituted with one or more halogen, cycloalkyl (e.g., a C3-C6 cycloalkyl), or aryl (e.g., C5-C7 aryl)), optionally substituted aryl (e.g., an optionally substituted C5-C7 aryl), optionally substituted alkyl-aryl (e.g., an alkyl-aryl comprising at least one of an optionally substituted C1-C6 alkyl, an optionally substituted C5-C7 aryl, or combinations thereof), optionally substituted alkoxyl group (e.g., a methoxy, ethoxy, butoxy, propoxy, pentoxy, or hexoxy; wherein

the alkoxyl may be substituted with one or more halogen, alkyl, haloalky, fluoroalkyl, cycloalkyl (e.g., a C3-C6 cycloalkyl), or aryl (e.g., C5-C7 aryl)), optionally substituted



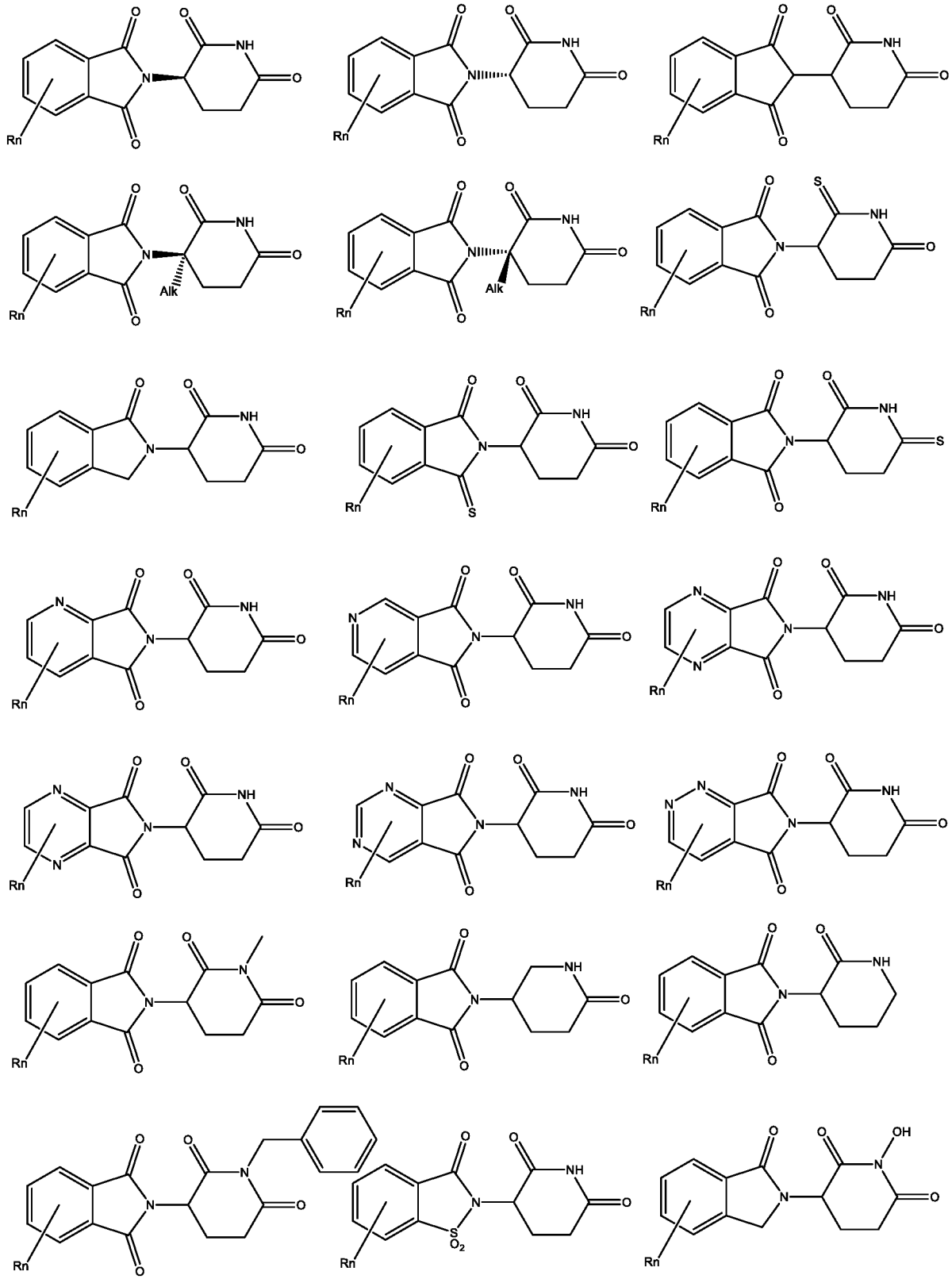
(e.g., optionally substituted with one or more halogen, alkyl, haloalky, fluoroalkyl, cycloalkyl (e.g., a C3-C6 cycloalkyl), or aryl (e.g., C5-C7 aryl)), optionally substituted

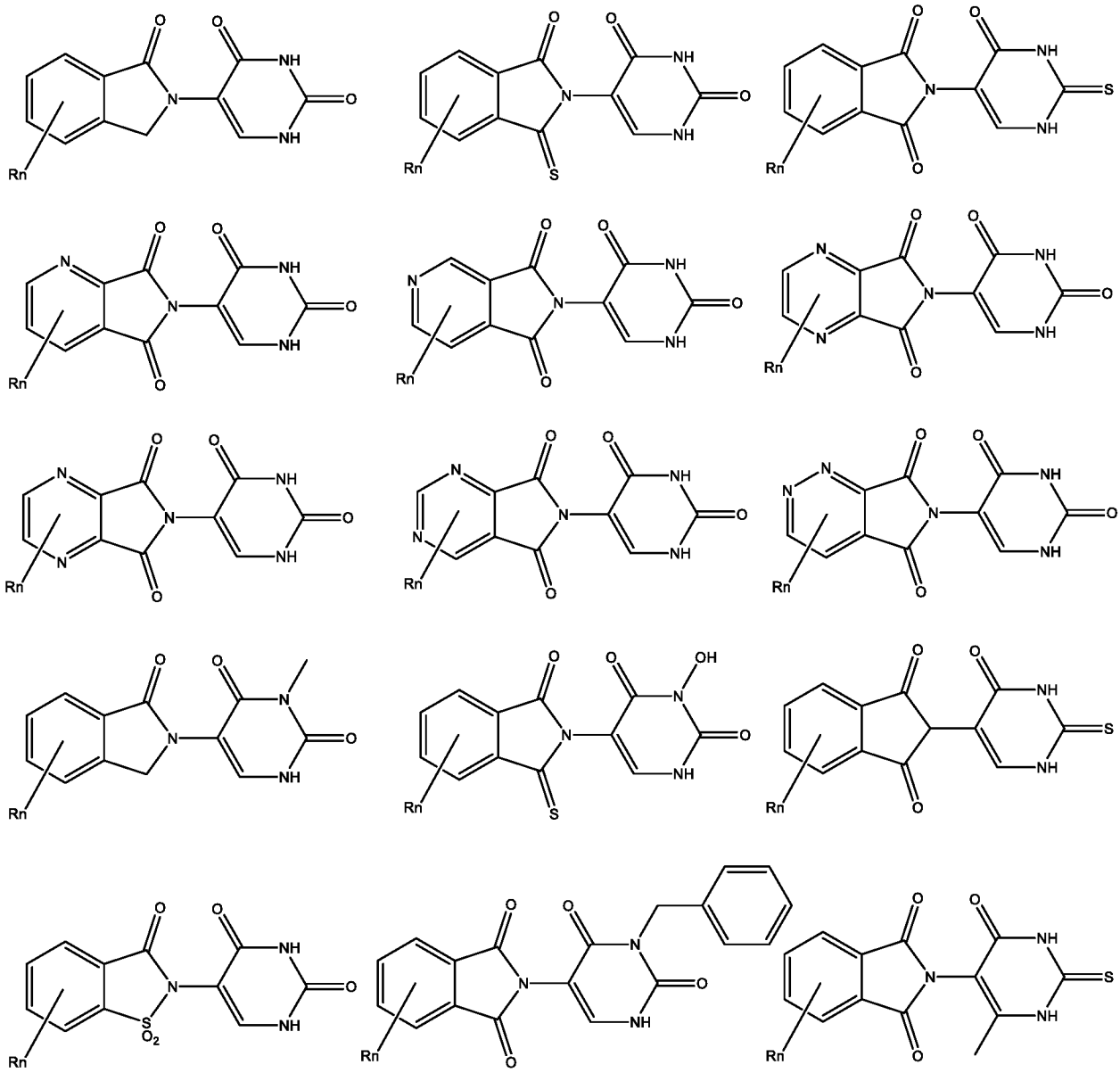


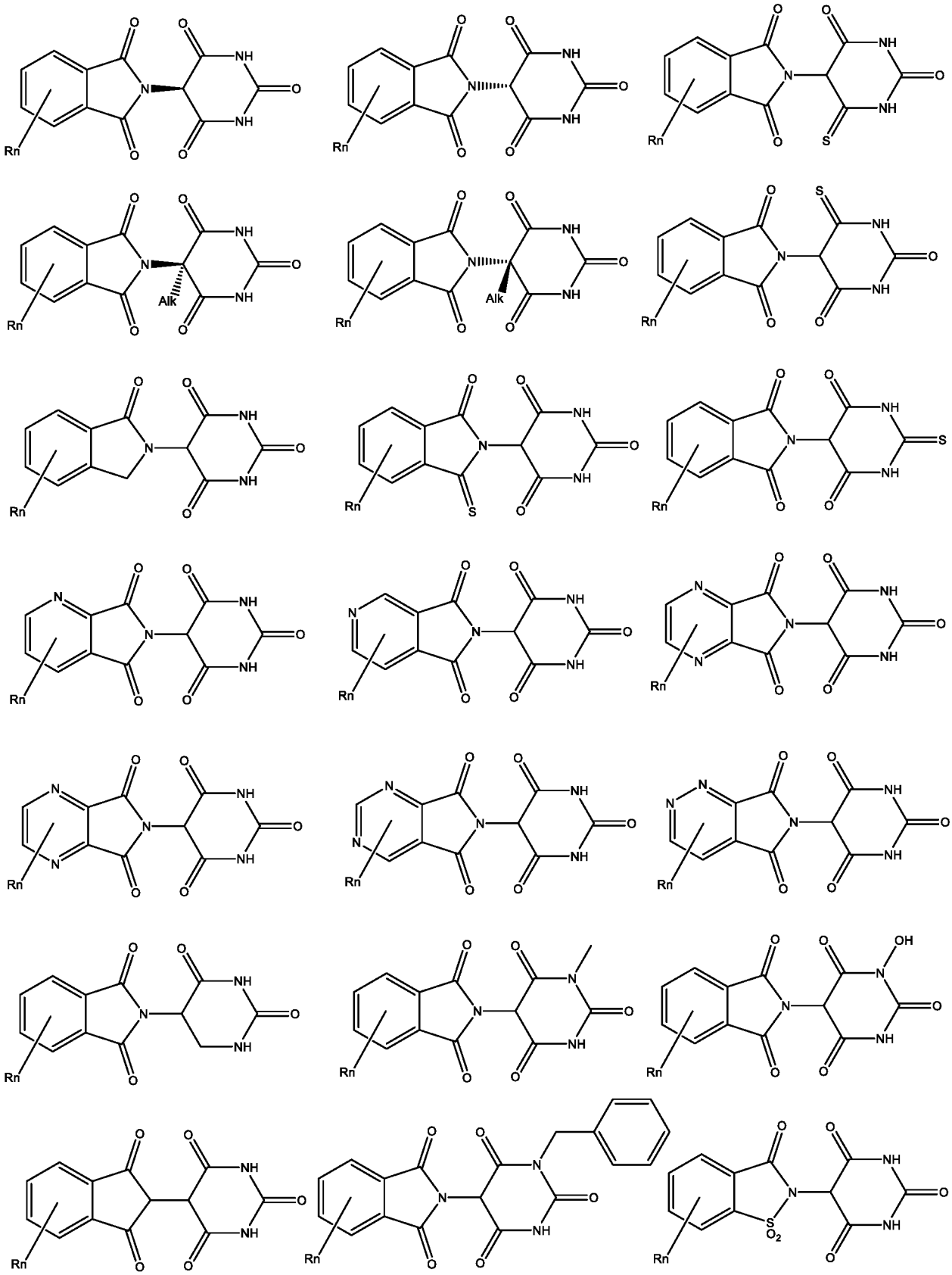
(e.g., optionally substituted with one or more halogen, alkyl, haloalky, fluoroalkyl, cycloalkyl (e.g., a C3-C6 cycloalkyl), or aryl (e.g., C5-C7 aryl)), or atoms.

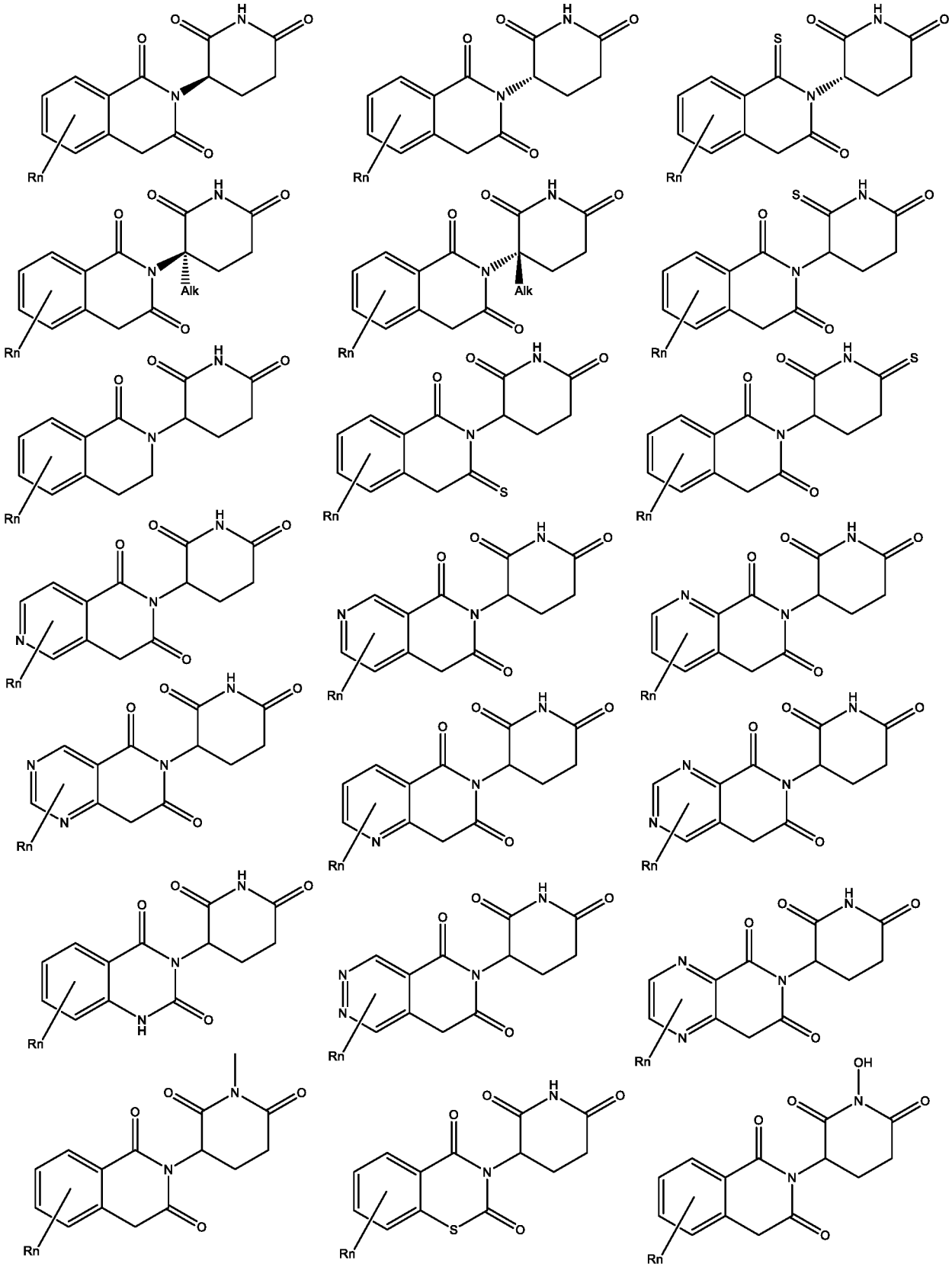
[0061] In any of the embodiments described herein, the W, X, Y, Z, G, G', R, R', R'', Q1-Q4, A, and Rn of Formulas (a) through (g) can independently be covalently coupled to a linker and/or a linker to which is attached one or more PTM, ULM, CLM or CLM' groups.

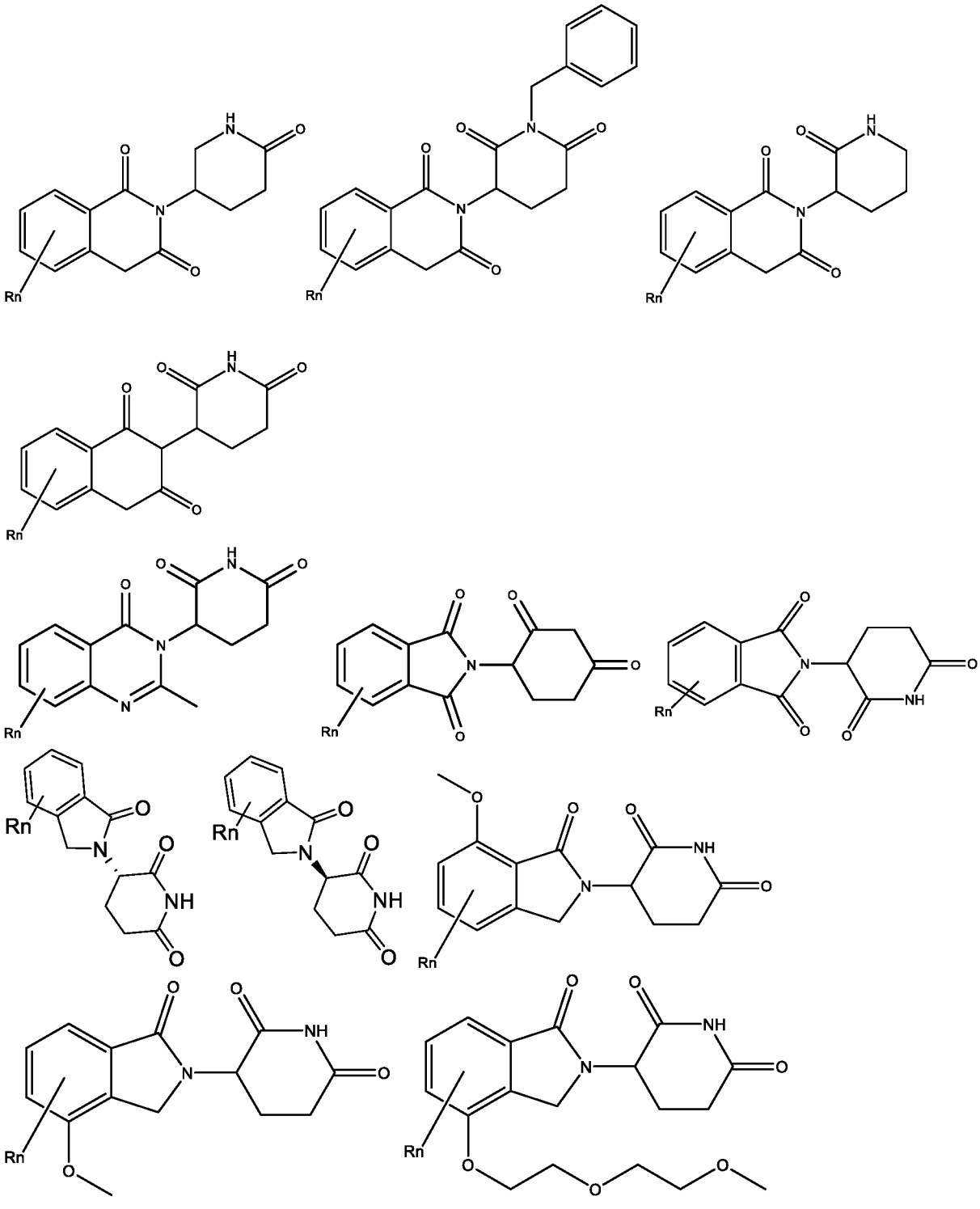
[0062] More specifically, non-limiting examples of CLMs include those shown below as well as those "hybrid" molecules that arise from the combination of 1 or more of the different features shown in the molecules below.

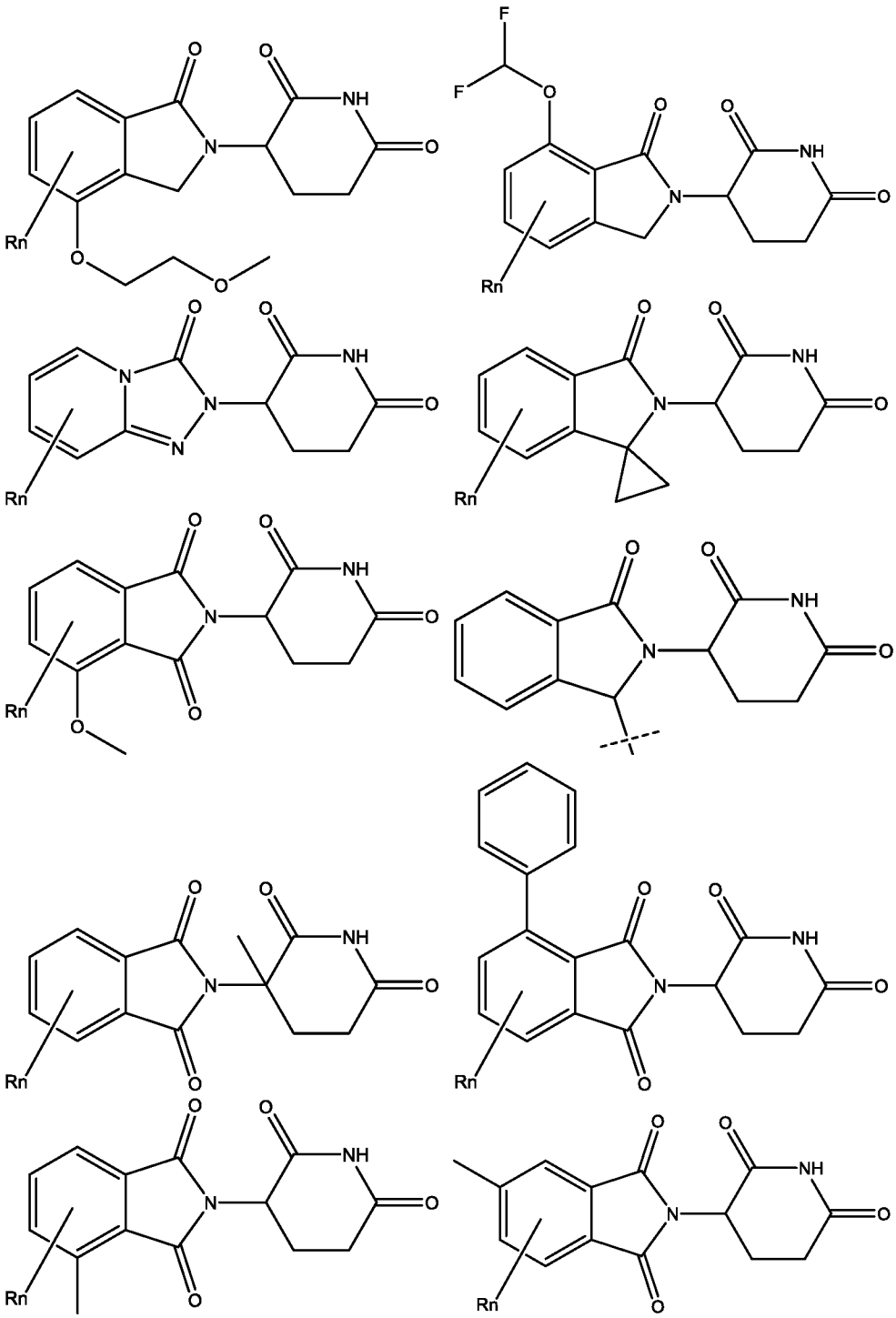


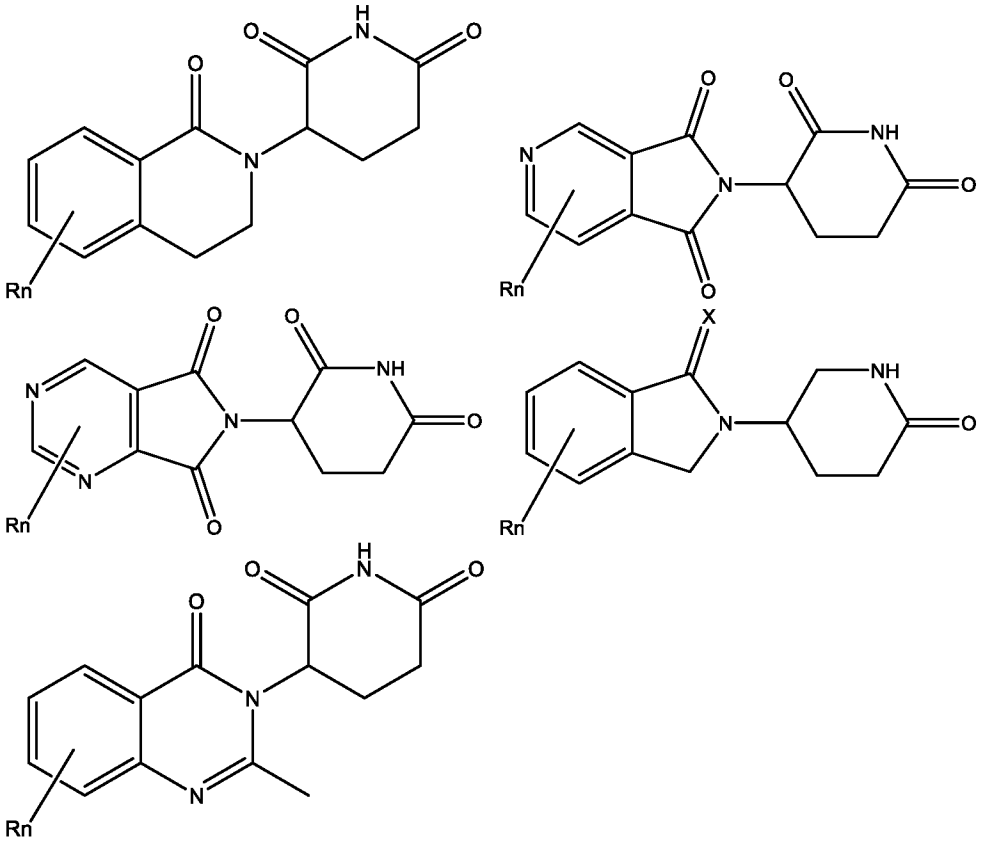


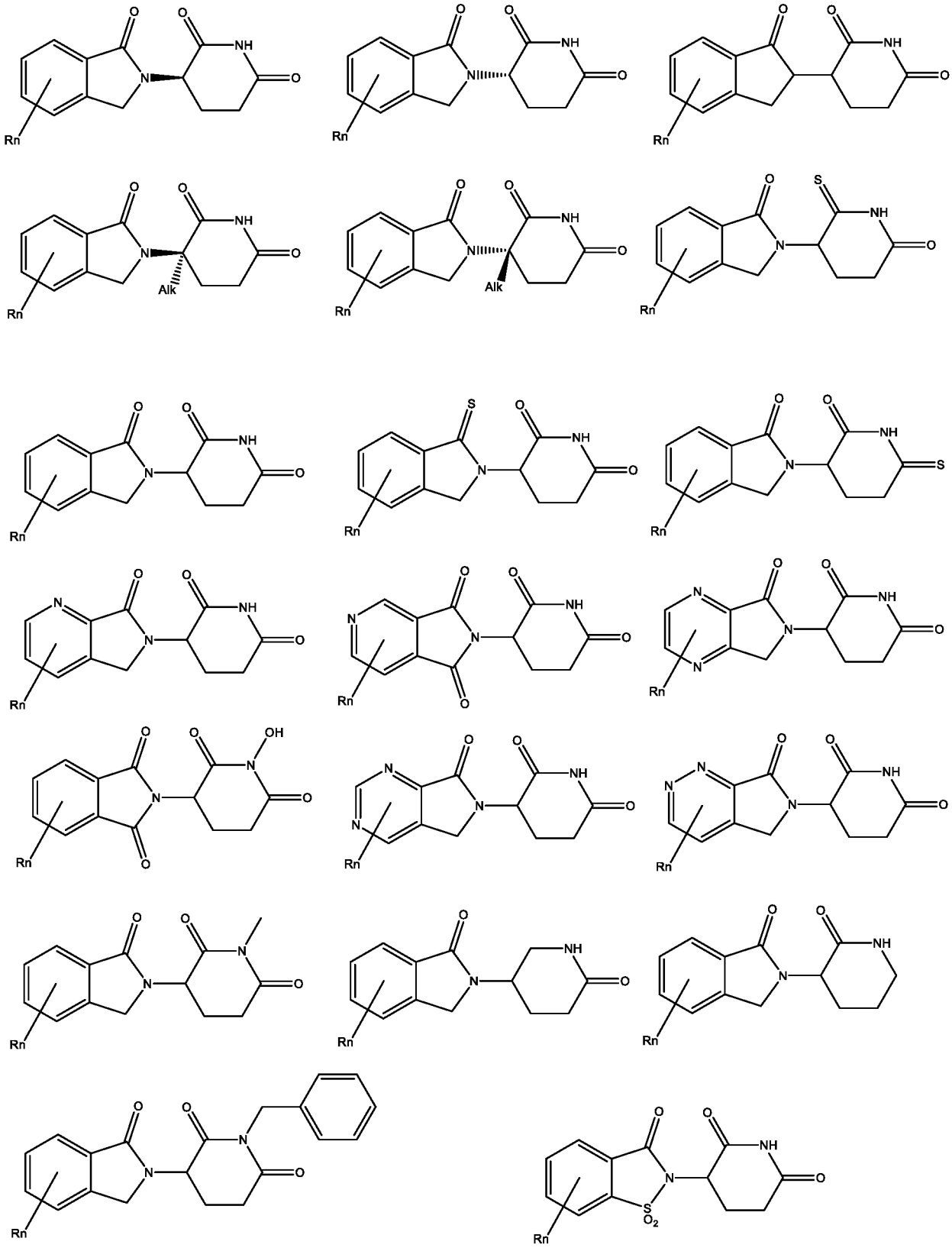


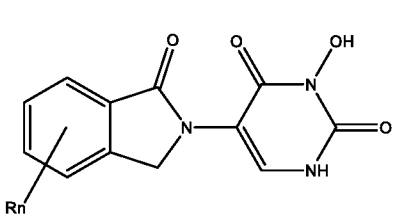
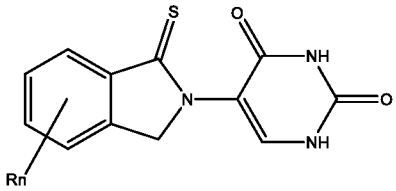
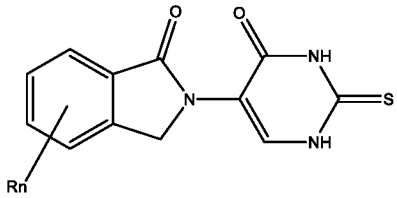
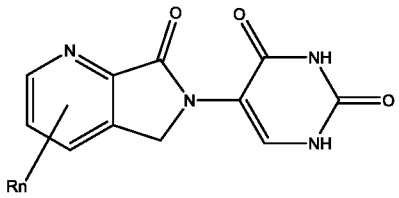
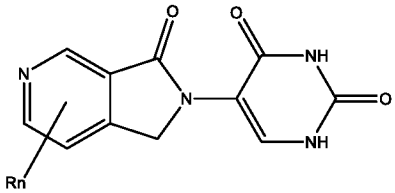
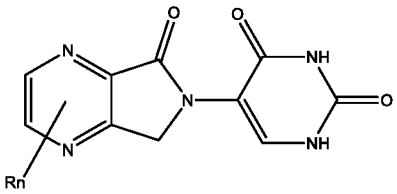
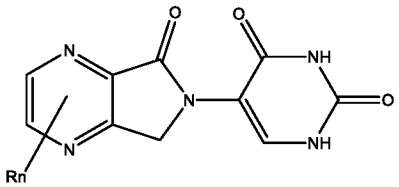
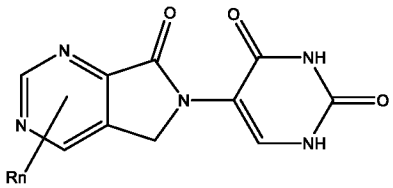
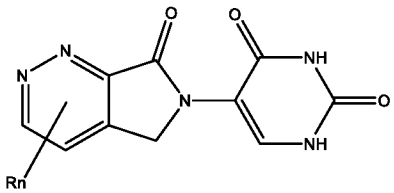
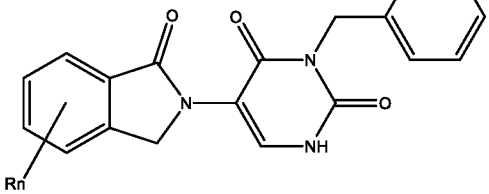
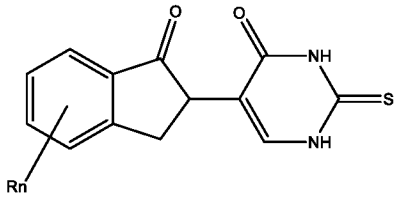
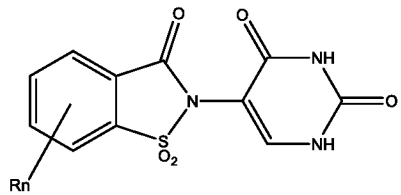
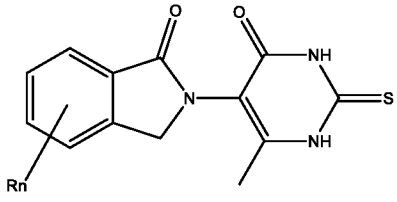


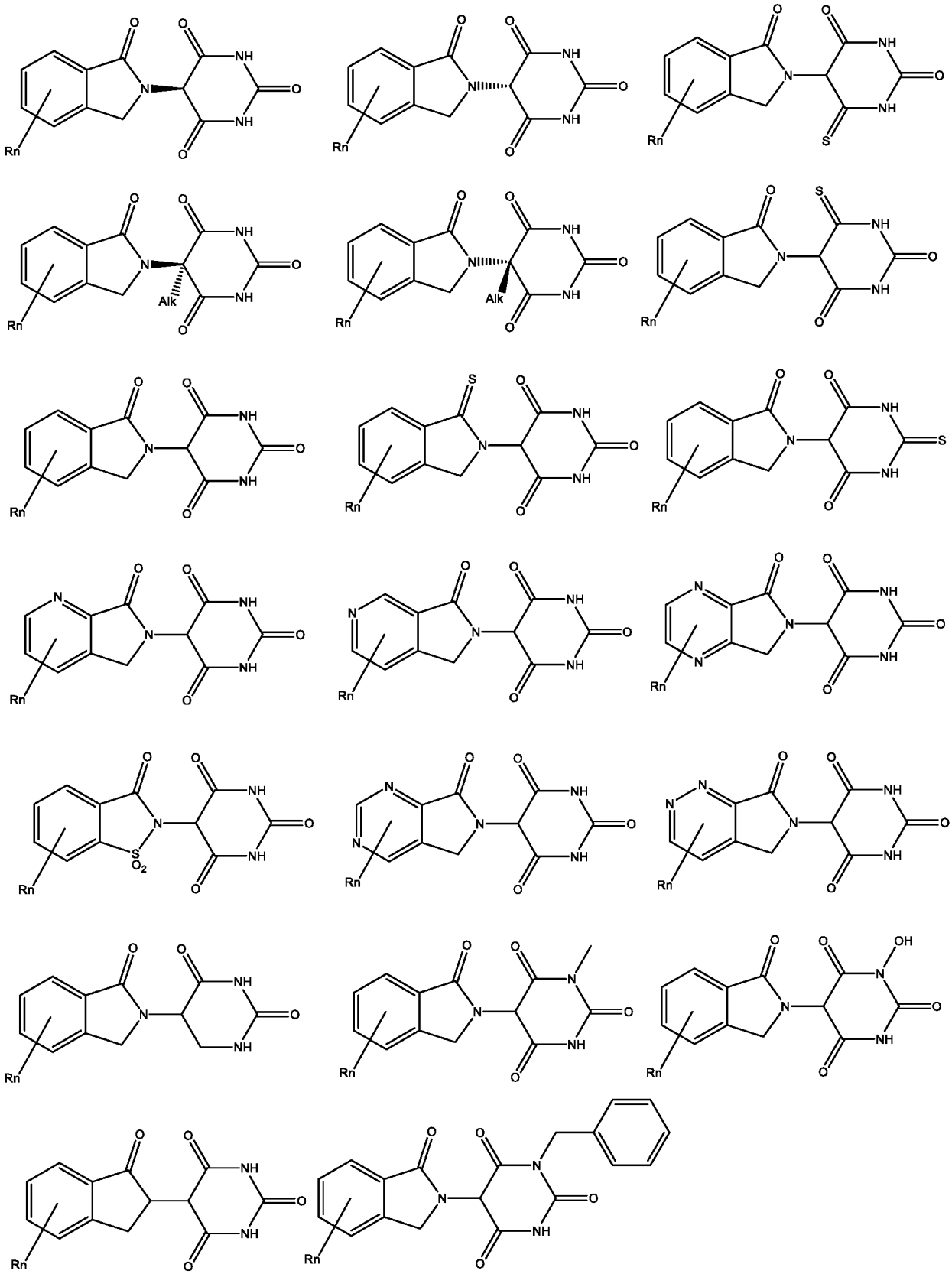


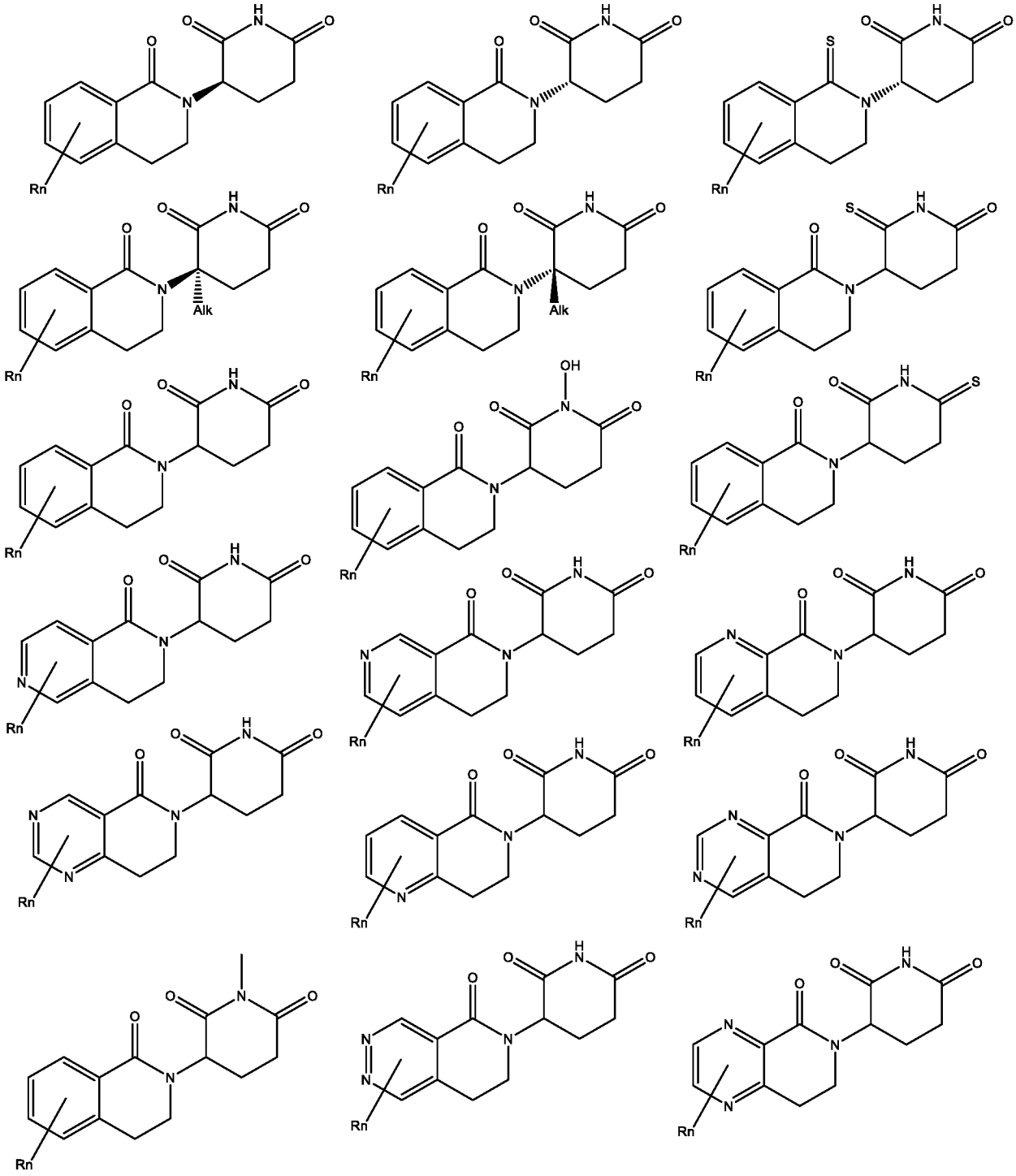


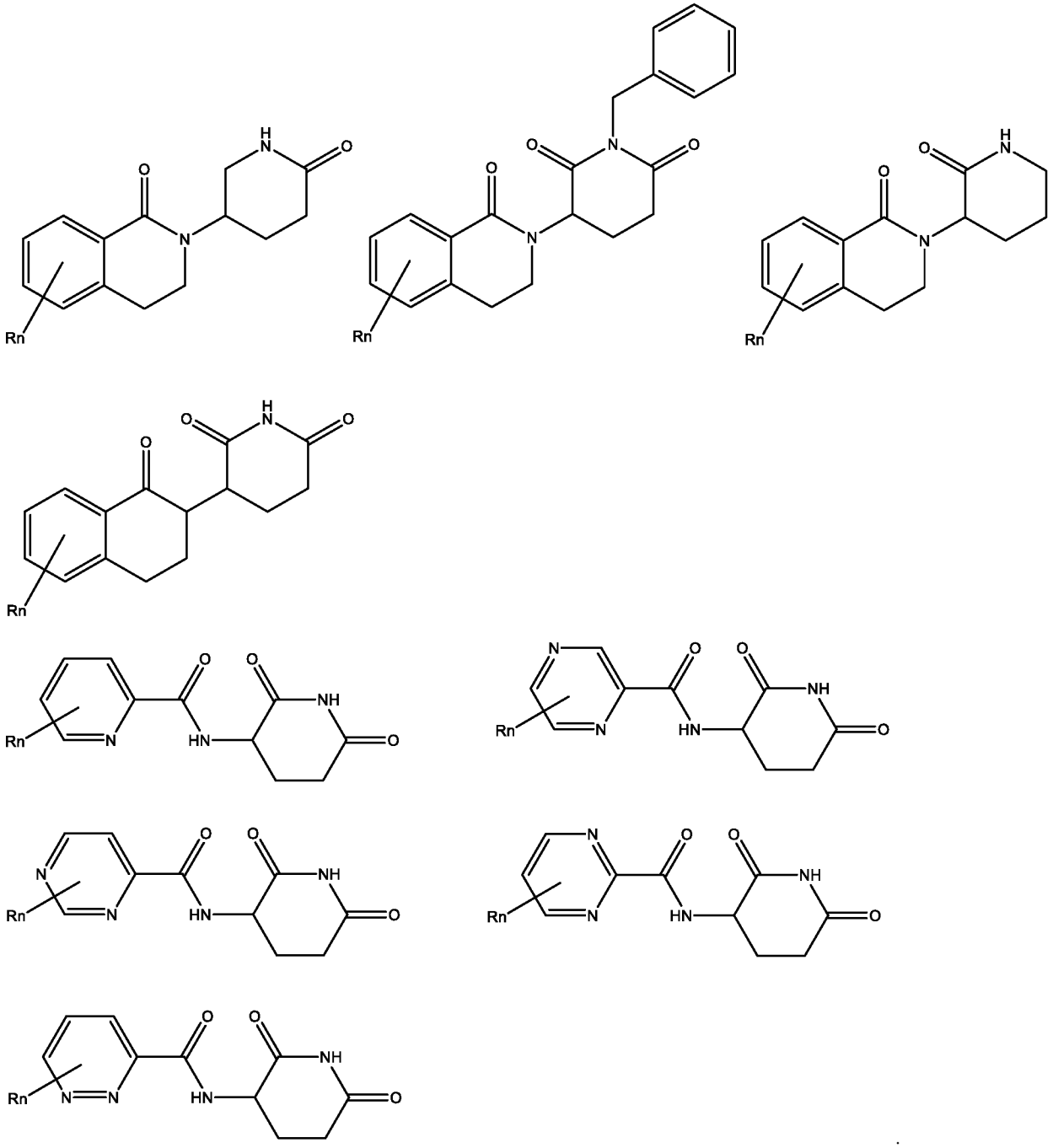










[0063] The term "independently" is used herein to indicate that the variable, which is independently applied, varies independently from application to application.

[0064] The term "alkyl" shall mean within its context a linear, branch-chained or cyclic fully saturated hydrocarbon radical or alkyl group, preferably a C_1-C_{10}, more preferably a C_1-C_6, alternatively a C_1-C_3 alkyl group, which may be optionally substituted. Examples of alkyl groups are methyl, ethyl, n-butyl, sec-butyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl,

isopropyl, 2-methylpropyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclopentylethyl, cyclohexylethyl and cyclohexyl, among others. In certain embodiments, the alkyl group is end-capped with a halogen group (At, Br, Cl, F, or I). In certain preferred embodiments, compounds according to the present disclosure which may be used to covalently bind to dehalogenase enzymes. These compounds generally contain a side chain (often linked through a polyethylene glycol group) which terminates in an alkyl group which has a halogen substituent (often chlorine or bromine) on its distal end which results in covalent binding of the compound containing such a moiety to the protein.

[0065] The term "Alkoxy" refers to an alkyl group singularly bonded to oxygen.

[0066] The term "Alkenyl" refers to linear, branch-chained or cyclic C_2-C_{10} (preferably C_2-C_6) hydrocarbon radicals containing at least one C=C bond.

[0067] The term "Alkynyl" refers to linear, branch-chained or cyclic C_2-C_{10} (preferably C_2-C_6) hydrocarbon radicals containing at least one C≡C bond.

[0068] The term "alkylene" when used, refers to a $-(CH_2)_n-$ group (n is an integer generally from 0-6), which may be optionally substituted. When substituted, the alkylene group preferably is substituted on one or more of the methylene groups with a C_1-C_6 alkyl group (including a cyclopropyl group or a t-butyl group), but may also be substituted with one or more halo groups, preferably from 1 to 3 halo groups or one or two hydroxyl groups, O-(C_1-C_6 alkyl) groups or amino acid sidechains as otherwise disclosed herein. In certain embodiments, an alkylene group may be substituted with a urethane or alkoxy group (or other group) which is further substituted with a polyethylene glycol chain (of from 1 to 10, preferably 1 to 6, often 1 to 4 ethylene glycol units) to which is substituted (preferably, but not exclusively on the distal end of the polyethylene glycol chain) an alkyl chain substituted with a single halogen group, preferably a chlorine group. In still other embodiments, the alkylene (often, a methylene) group, may be substituted with an amino acid sidechain group such as a sidechain group of a natural or unnatural amino acid, for example, alanine, β-alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, glutamine, glycine, phenylalanine, histidine, isoleucine, lysine, leucine, methionine, proline, serine, threonine, valine, tryptophan or tyrosine.

[0069] 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.

[0070] 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 –$SiR_{1sub}R_{2sub}R_{3sub}$ groups where each of R_{1sub} and R_{2sub} is as otherwise described herein and R_{3sub} is H or a C_1-C_6 alkyl group, preferably R_{1sub}, R_{2sub}, R_{3sub} in this context is a C_1-C_3 alkyl group (including an isopropyl or t-butyl group). Each of the above-described groups may be linked directly to the substituted moiety or alternatively, the substituent may be linked to the substituted moiety (preferably in the case of an aryl or heteraryl moiety) through an optionally substituted -$(CH_2)_m$- or alternatively an optionally substituted -$(OCH_2)_m$-, -$(OCH_2CH_2)_m$- or -$(CH_2CH_2O)_m$- group, which may be substituted with any one or more of the above-described substituents.

Alkylene groups -$(CH_2)_m$- or -$(CH_2)_n$- groups or other chains such as ethylene glycol chains, as identified above, may be substituted anywhere on the chain. Preferred substitutents on alkylene groups include halogen or C_1-C_6 (preferably C_1-C_3) alkyl groups, which may be optionally substituted with one or two hydroxyl groups, one or two ether groups (O-C_1-C_6 groups), up to three halo groups (preferably F), or a sidechain 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.

[0071] 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)-$NR_{1sub}R_{2sub}$ or –$N(R_{1sub})$-C(O)-O-R_{1sub}, nitro, cyano and amine (especially including a C_1-C_6 alkylene-$NR_{1sub}R_{2sub}$, 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_{1sub}, -$(CH_2)_n$C(O)-$NR_{1sub}R_{2sub}$, -$(OCH_2)_n$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_{1sub}, -$(CH_2O)_n$C(O)-$NR_{1sub}R_{2sub}$, -$S(O)_2$-R_S, -S(O)-R_S (R_S is C_1-C_6 alkyl or a –$(CH_2)_m$-$NR_{1sub}R_{2sub}$ 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_{1sub} and R_{2sub} 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)-$NR_{1sub}R_{2sub}$ group where R_{1sub} and R_{2sub} 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.

[0072] 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, pyrimidine, phenanthroline, phenacene, oxadiazole, benzimidazole, pyrrolopyridine, pyrrolopyrimidine and pyridopyrimidine; sulfur-containing aromatic heterocycles such as thiophene and benzothiophene; oxygen-containing aromatic

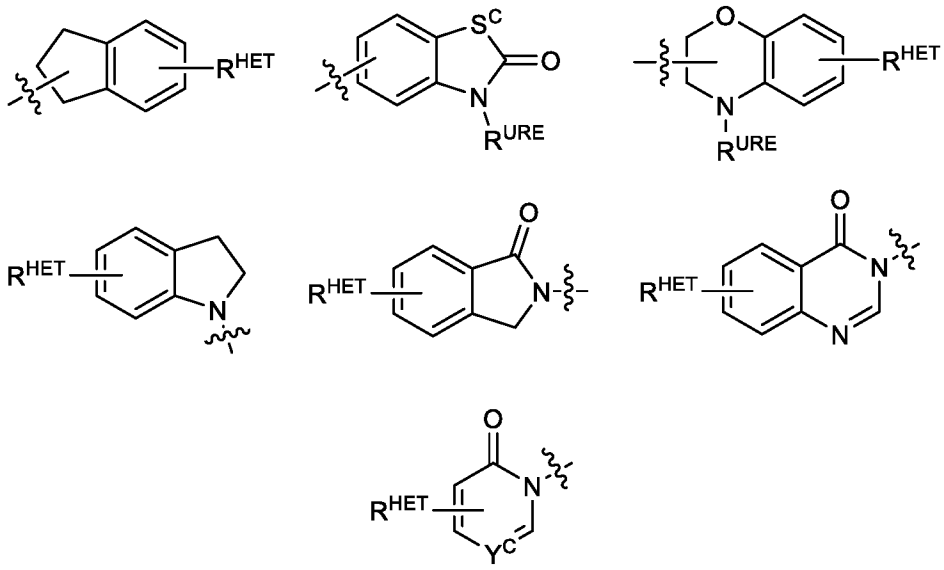
heterocycles such as furan, pyran, cyclopentapyran, benzofuran and isobenzofuran; and aromatic heterocycles comprising 2 or more hetero atoms selected from among nitrogen, sulfur and oxygen, such as thiazole, thiadizole, isothiazole, benzoxazole, benzothiazole, benzothiadiazole, phenothiazine, isoxazole, furazan, phenoxazine, pyrazoloxazole, imidazothiazole, thienofuran, furopyrrole, pyridoxazine, furopyridine, furopyrimidine, thienopyrimidine and oxazole, among others, all of which may be optionally substituted.

[0073] The term "substituted aryl" refers to an aromatic carbocyclic group comprised of at least one aromatic ring or of multiple condensed rings at least one of which being aromatic, wherein the ring(s) are substituted with one or more substituents. For example, an aryl group can comprise a substituent(s) selected from: $-(CH_2)_nOH$, $-(CH_2)_n-O-(C_1-C_6)$alkyl, $-(CH_2)_n-O-(CH_2)_n-(C_1-C_6)$alkyl, $-(CH_2)_n-C(O)(C_0-C_6)$ alkyl, $-(CH_2)_n-C(O)O(C_0-C_6)$alkyl, $-(CH_2)_n-OC(O)(C_0-C_6)$alkyl, amine, mono- or di-(C_1-C_6 alkyl) amine wherein the alkyl group on the amine is optionally substituted with 1 or 2 hydroxyl groups or up to three halo (preferably F, Cl) groups, OH, COOH, C_1-C_6 alkyl, preferably CH_3, CF_3, OMe, OCF_3, NO_2, or CN group (each of which may be substituted in ortho-, meta- and/or para- positions of the phenyl ring, preferably para-), an optionally substituted phenyl group (the phenyl group itself is preferably substituted with a linker group attached to a PTM group, including a ULM group), and/or at least one of F, Cl, OH, COOH, CH_3, CF_3, OMe, OCF_3, NO_2, or CN group (in ortho-, meta- and/or para- positions of the phenyl ring, preferably para-), a naphthyl group, which may be optionally substituted, an optionally substituted heteroaryl, preferably an optionally substituted isoxazole including a methylsubstituted isoxazole, an optionally substituted oxazole including a methylsubstituted oxazole, an optionally substituted thiazole including a methyl substituted thiazole, an optionally substituted isothiazole including a methyl substituted isothiazole, an optionally substituted pyrrole including a methylsubstituted pyrrole, an optionally substituted imidazole including a methylimidazole, an optionally substituted benzimidazole or methoxybenzylimidazole, an optionally substituted oximidazole or methyloximidazole, an optionally substituted diazole group, including a methyldiazole group, an optionally substituted triazole group, including a methylsubstituted triazole group, an optionally substituted pyridine group, including a halo-(preferably, F) or methylsubstitutedpyridine group or an oxapyridine group (where the pyridine group is linked to the phenyl group by an oxygen), an optionally substituted furan, an optionally substituted benzofuran, an optionally substituted dihydrobenzofuran, an optionally substituted

indole, indolizine or azaindolizine (2, 3, or 4-azaindolizine), an optionally substituted quinoline, and combinations thereof.

[0074] "Carboxyl" denotes the group --C(O)OR, where R is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl , whereas these generic substituents have meanings which are identical with definitions of the corresponding groups defined herein.

[0075] The term “heteroaryl”or “hetaryl” can mean but is in no way limited to an optionally substituted quinoline (which may be attached to the pharmacophore or substituted on any carbon atom within the quinoline ring), an optionally substituted indole (including dihydroindole), an optionally substituted indolizine, an optionally substituted azaindolizine (2, 3 or 4-azaindolizine) an optionally substituted benzimidazole, benzodiazole, benzoxofuran, an optionally substituted imidazole, an optionally substituted isoxazole, an optionally substituted oxazole (preferably methyl substituted), an optionally substituted diazole, an optionally substituted triazole, a tetrazole, an optionally substituted benzofuran, an optionally substituted thiophene, an optionally substituted thiazole (preferably methyl and/or thiol substituted), an optionally substituted isothiazole, an optionally substituted triazole (preferably a 1,2,3-triazole substituted with a methyl group, a triisopropylsilyl group, an optionally substituted -$(CH_2)_m$-O-C_1-C_6 alkyl group or an optionally substituted -$(CH_2)_m$-C(O)-O-C_1-C_6 alkyl group), an optionally substituted pyridine (2-, 3, or 4-pyridine) or a group according to the chemical structure:



wherein

S^c is CHR^{SS}, NR^{URE}, or O;

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

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

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

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

[0076] The term "Heterocycle" refers to a cyclic group which contains at least one heteroatom, e.g., N, O 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.

[0077] Exemplary heterocyclics include: azetidinyl, benzimidazolyl, 1,4- benzodioxanyl, 1,3-benzodioxolyl, benzoxazolyl, benzothiazolyl, benzothienyl, dihydroimidazolyl, dihydropyranyl, dihydrofuranyl, dioxanyl, dioxolanyl, ethyleneurea, 1,3-dioxolane, 1,3-dioxane, 1,4-dioxane, furyl, homopiperidinyl, imidazolyl, imidazolinyl, imidazolidinyl, indolinyl, indolyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, naphthyridinyl, oxazolidinyl, oxazolyl, pyridone, 2-pyrrolidone, pyridine, piperazinyl, , N-

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

[0078] Heterocyclic groups can be optionally substituted with a member selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxy, carboxyalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, —SO-alkyl, —SO-substituted alkyl, —SOaryl, —SO-heteroaryl, —SO2-alkyl, —SO2-substituted alkyl, —SO2-aryl, oxo (=O), and -SO2-heteroaryl. Such heterocyclic groups can have a single ring or multiple condensed rings. Examples of nitrogen heterocycles and heteroaryls include, but are not limited to, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, morpholino, piperidinyl, tetrahydrofuranyl, and the like as well as N-alkoxy-nitrogen containing heterocycles. The term "heterocyclic" also includes bicyclic groups in which any of the heterocyclic rings is fused to a benzene ring or a cyclohexane ring or another heterocyclic ring (for example, indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, and the like).

[0079] The term “cycloalkyl” can mean but is in no way limited to univalent groups derived from monocyclic or polycyclic alkyl groups or cycloalkanes, as defnied herein, e.g., saturated monocyclic hydrocarbon groups having from three to twenty carbon atoms in the ring, including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. The term "substituted cycloalkyl" can mean but is in no way limited to a monocyclic or polycyclic alkyl group and being substituted by one or more substituents, for example, amino, halogen, alkyl, substituted alkyl, carbyloxy, carbylmercapto, aryl, nitro, mercapto or sulfo,

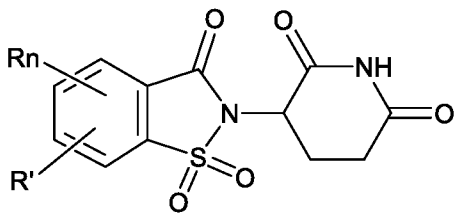
whereas these generic substituent groups have meanings which are identical with definitions of the corresponding groups as defined in this legend.

[0080] 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.

[0081] The term "lower alkyl" refers to methyl, ethyl or propyl

[0082] The term "lower alkoxy" refers to methoxy, ethoxy or propoxy.

[0083] 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:



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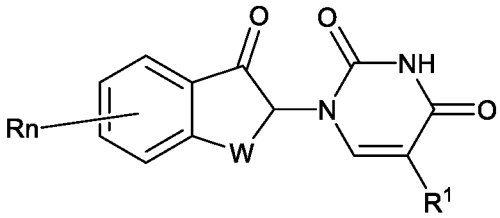

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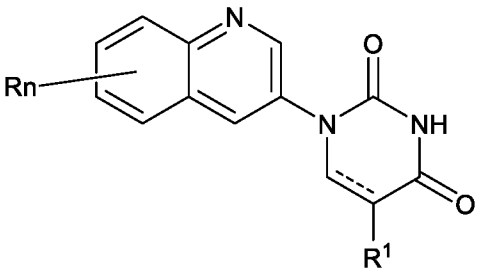

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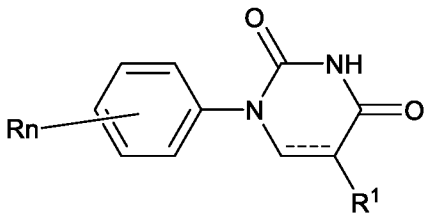

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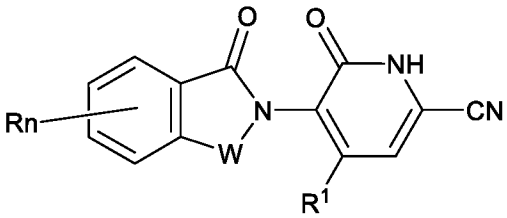

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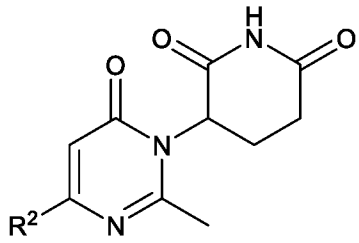

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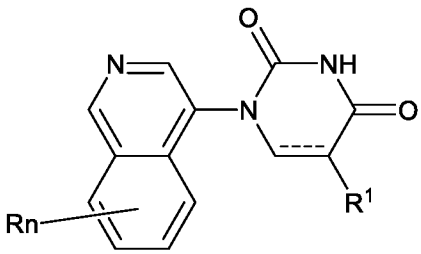

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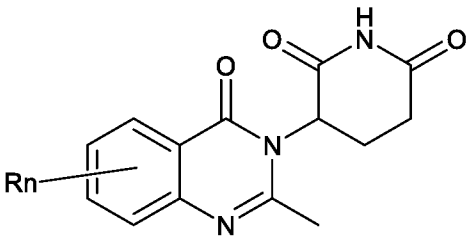

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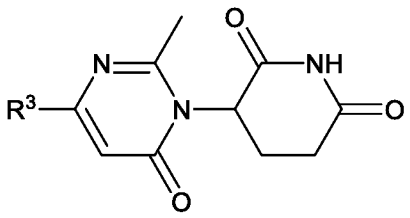

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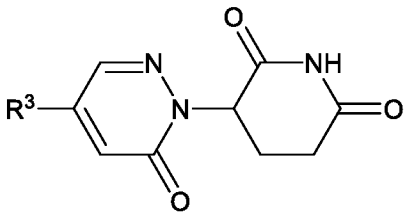

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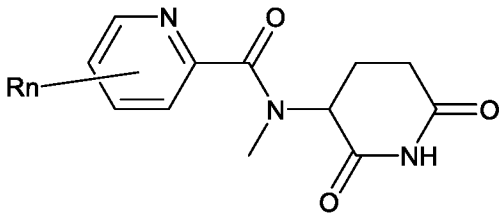

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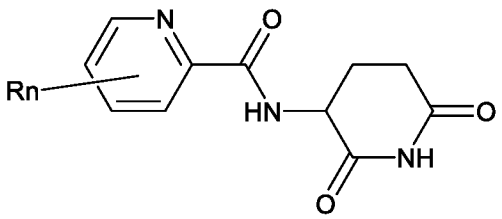

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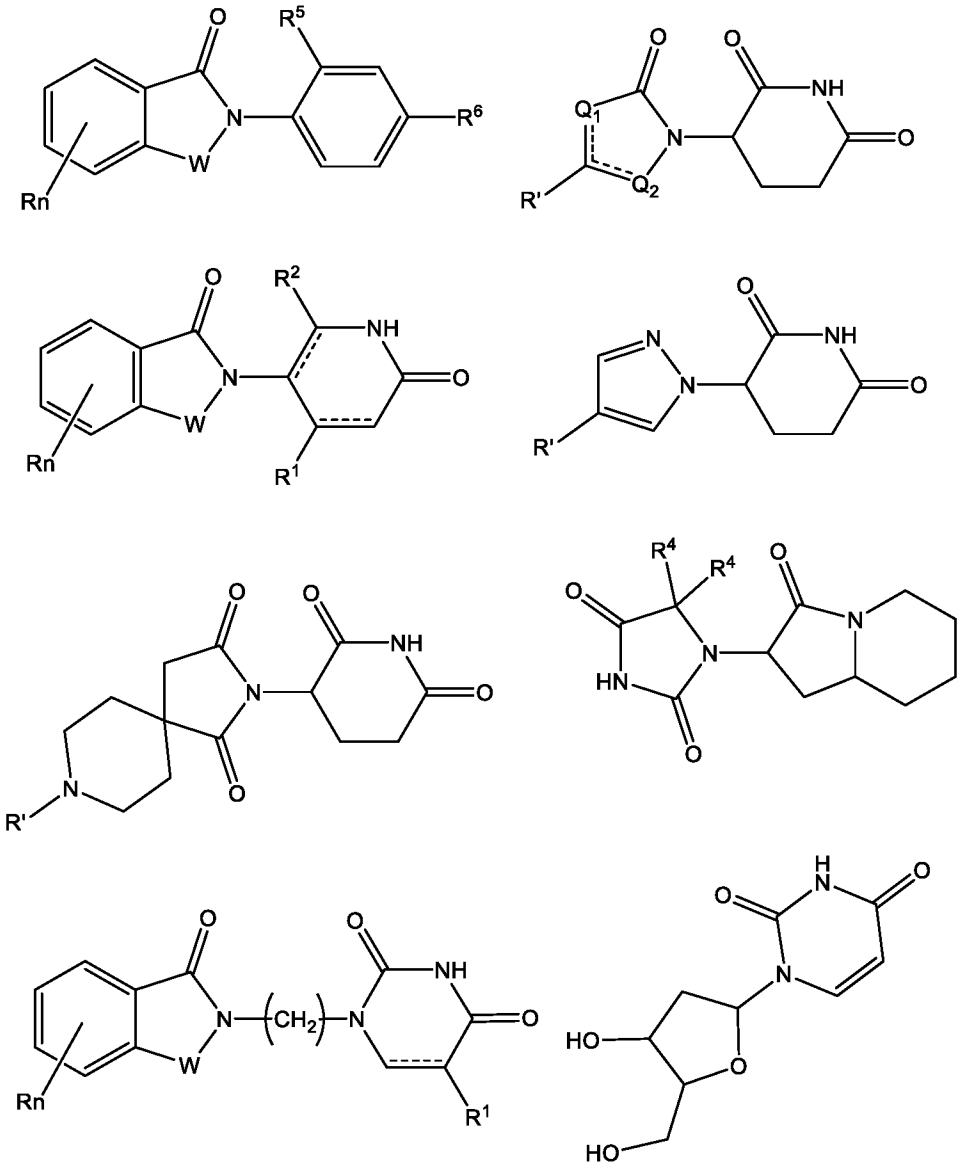


wherein:

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

R^1 is selected from the group absent, H, CH, CN, C1-C3 alkyl;

R^2 is H or a C1-C3 alkyl;

R^3 is selected from H, alkyl, substituted alkyl, alkoxy, substituted alkoxy;

R^4 is methyl or ethyl;

R^5 is H or halo;

R^6 is H or halo;

R of the CLM is H;

R' is H or an attachment point for a PTM, a PTM', a chemical linker group (L), a ULM, a CLM, a CLM',

Q1 and Q2 are each independently C or N substituted with a group independently selected from H or C1-C3 alkyl;

is a single or double bond; and

Rn comprises a functional group or an atom.

[0084] In any of the embodiments described herein, the W, R^1, R^2, Q_1, Q_2, Q_3, Q_4, and Rn 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.

[0085] In any of the embodiments described herein, the R^1, R^2, Q_1, Q_2, Q_3, Q_4, and Rn 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.

[0086] In any of the embodiments described herein, the Q_1, Q_2, Q_3, Q_4, and Rn 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.

[0087] In any aspect or embodiment described herein, R_n 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.

[0088] **Exemplary Linkers**

[0089] In certain embodiments, the compounds as described herein include one or more CLMs chemically linked or coupled to one or more PTMs (e.g., PTM and/or PTM'), ULMs (e.g., ULM, ULM', and/or CLM') via a chemical linker (L). In certain embodiments, the linker group L is a group comprising one or more covalently connected structural units (e.g., $-A^L{}_{1...}(A^L)_q-$ or $-(A^L)_q-$), wherein A_1 is a group coupled to PTM, and Aq is a group coupled to at least one of a ULM, a ULM', a CLM, a CLM', or a combination thereof. In certain embodiments, $A^L{}_1$ links a CLM or CLM' directly to another ULM, PTM, or combination thereof. In other embodiments, $A^L{}_1$ links a CLM or CLM' indirectly to another ULM, PTM, or combination thereof through A_q.

[0090] In any aspect or embodiment described herein, the linker group L is a bond or a chemical linker group represented by the formula $-(A^L)_q-$, wherein A is a chemical moiety and q is an integer from 1-100, and wherein L is covalently bound to the PTM and the ULM, and

provides for sufficient binding of the PTM to the protein target and the ULM to an E3 ubiquitin ligase to result in target protein ubiquitination.

[0091] In certain embodiments, the linker group is $-(A^L)_q-$, wherein

$-(A^L)_q-$ is a group which is connected to at least one of a ULM moiety, a PTM moiety, or a combination thereof;

q of the linker is an integer greater than or equal to 1;

each A^L is independently selected from the group consisting of a bond, $CR^{L1}R^{L2}$, O, S, SO, SO_2, NR^{L3}, SO_2NR^{L3}, $SONR^{L3}$, $CONR^{L3}$, $NR^{L3}CONR^{L4}$, $NR^{L3}SO_2NR^{L4}$, CO, $CR^{L1}=CR^{L2}$, C≡C, $SiR^{L1}R^{L2}$, $P(O)R^{L1}$, $P(O)OR^{L1}$, $NR^{L3}C(=NCN)NR^{L4}$, $NR^{L3}C(=NCN)$, $NR^{L3}C(=CNO_2)NR^{L4}$, C_{3-11}cycloalkyl optionally substituted with 0-6 R^{L1} and/or R^{L2} groups, C_{5-13} spirocycloalkyl optionally substituted with 0-9 R^{L1} and/or R^{L2} groups, C_{3-11}heterocyclyl optionally substituted with 0-6 R^{L1} and/or R^{L2} groups, C_{5-13} spiroheterocycloalkyl optionally substituted with 0-8 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; and

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.

[0092] In certain embodiments, q of the linker is an integer greater than or equal to 0. In certain embodiments, q is an integer greater than or equal to 1.

[0093] In certain embodiments, e.g., where q is greater than 2, A^L_q is a group which is connected to a ULM or ULM' moiety (such as CLM or CLM'), and A^L_1 and A^L_q are connected via structural units of the linker (L).

[0094] In certain embodiments, e.g., where q of the linker is 2, A^L_q is a group which is connected to A^L_1 and to a ULM or a ULM' moiety (such as CLM or CLM').

[0095] In certain embodiments, e.g., where q of the linker is 1, the structure of the linker group L is $-A^L_1-$, and A^L_1 is a group which is connected to a ULM or ULM' moiety (such as CLM or CLM') and a PTM moiety.

[0096] In certain embodiments, the linker (L) comprises a group represented by a general structure selected from the group consisting of:

$-NR(CH_2)_n$-(lower alkyl)-, $-NR(CH_2)_n$-(lower alkoxyl)-, $-NR(CH_2)_n$-(lower alkoxyl)-OCH_2-, $-NR(CH_2)_n$-(lower alkoxyl)-(lower alkyl)-OCH_2-, $-NR(CH_2)_n$-(cycloalkyl)-(lower alkyl)-OCH_2-, $-NR(CH_2)_n$-(hetero cycloalkyl)-, $-NR(CH_2CH_2O)_n$-(lower alkyl)-O-CH_2-, $-NR(CH_2CH_2O)_n$-(hetero cycloalkyl)-O-CH_2-, $-NR(CH_2CH_2O)_n$-Aryl-O-CH_2-, $-NR(CH_2CH_2O)_n$-(hetero aryl)-O-CH_2-, $-NR(CH_2CH_2O)_n$-(cyclo alkyl)-O-(hetero aryl)-O-CH_2-, $-NR(CH_2CH_2O)_n$-(cyclo alkyl)-O-Aryl-O-CH_2-, $-NR(CH_2CH_2O)_n$-(lower alkyl)-NH-Aryl-O-CH_2-, $-NR(CH_2CH_2O)_n$-(lower alkyl)-O-Aryl-CH_2, $-NR(CH_2CH_2O)_n$-cycloalkyl-O-Aryl-, $-NR(CH_2CH_2O)_n$-cycloalkyl-O-(heteroaryl)l-, $-NR(CH_2CH_2)_n$-(cycloalkyl)-O-(heterocycle)-CH_2, $-NR(CH_2CH_2)_n$-(heterocycle)-(heterocycle)-CH_2, -N(R1R2)-(heterocycle)-CH_2; where

n of the linker can be 0 to 10;

R of the linker can be H, lower alkyl;

R1 and R2 of the linker can form a ring with the connecting N.

[0097] In certain embodiments, the A^L group is represented by a general structure selected from the group consisting of:

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

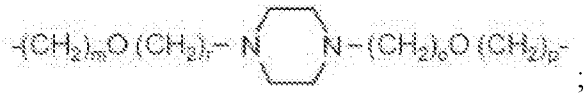
$-O-(CH2)_m-O(CH2)_n-O(CH2)_o-O(CH2)_p-O(CH2)_q-O(CH2)_r-OCH2-$,

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

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

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

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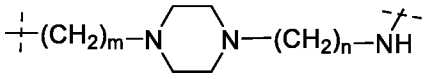
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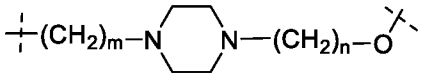
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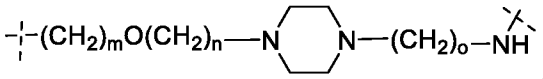
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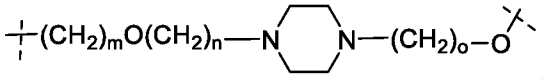
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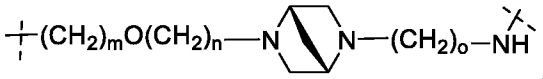
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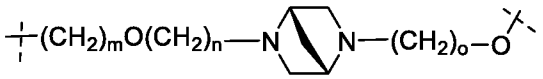

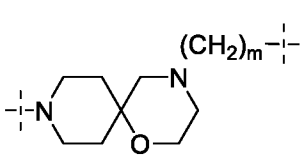
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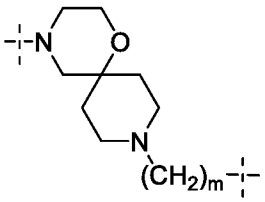
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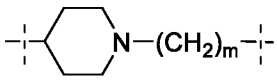
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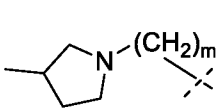
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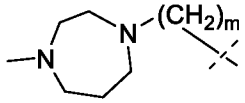

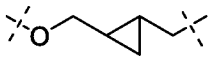
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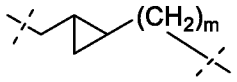
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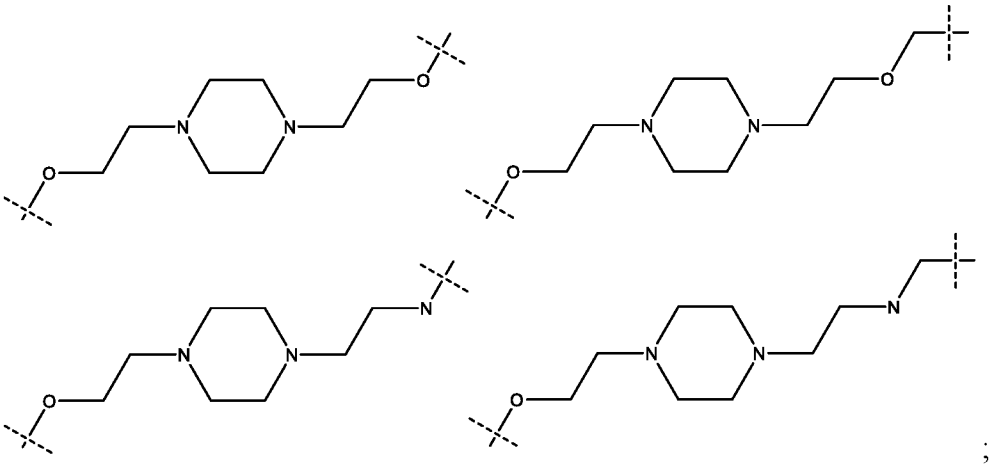
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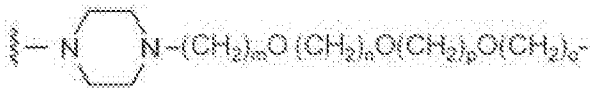
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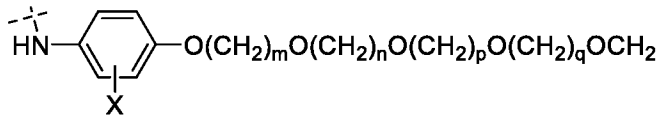
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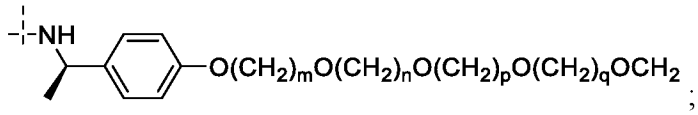
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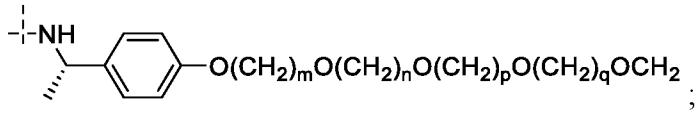
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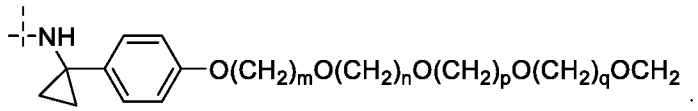
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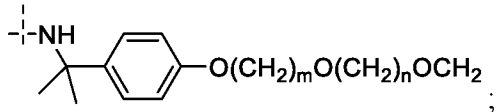
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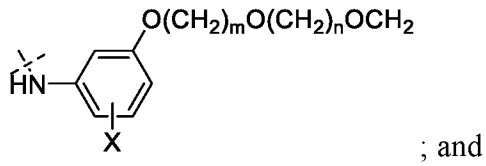
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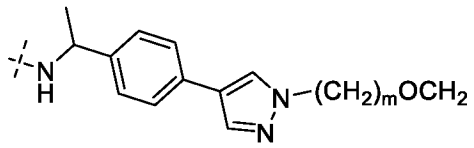
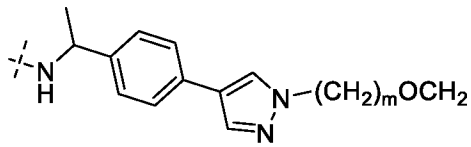

; wherein

m, n, o, p, q, and r of the linker are independently 0, 1, 2, 3, 4, 5, 6; 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20;

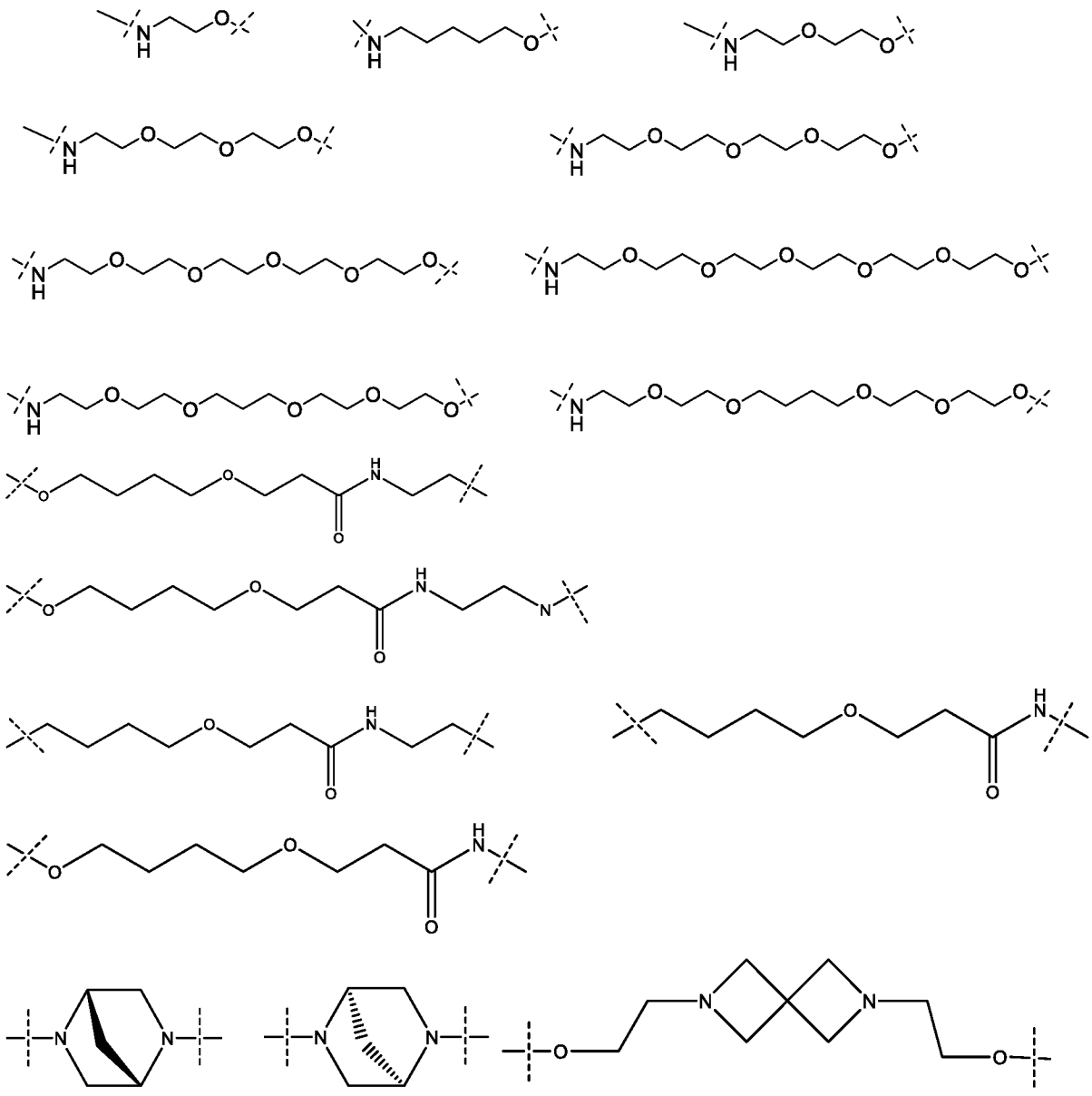
when the number is zero, there is no N-O or O-O bond

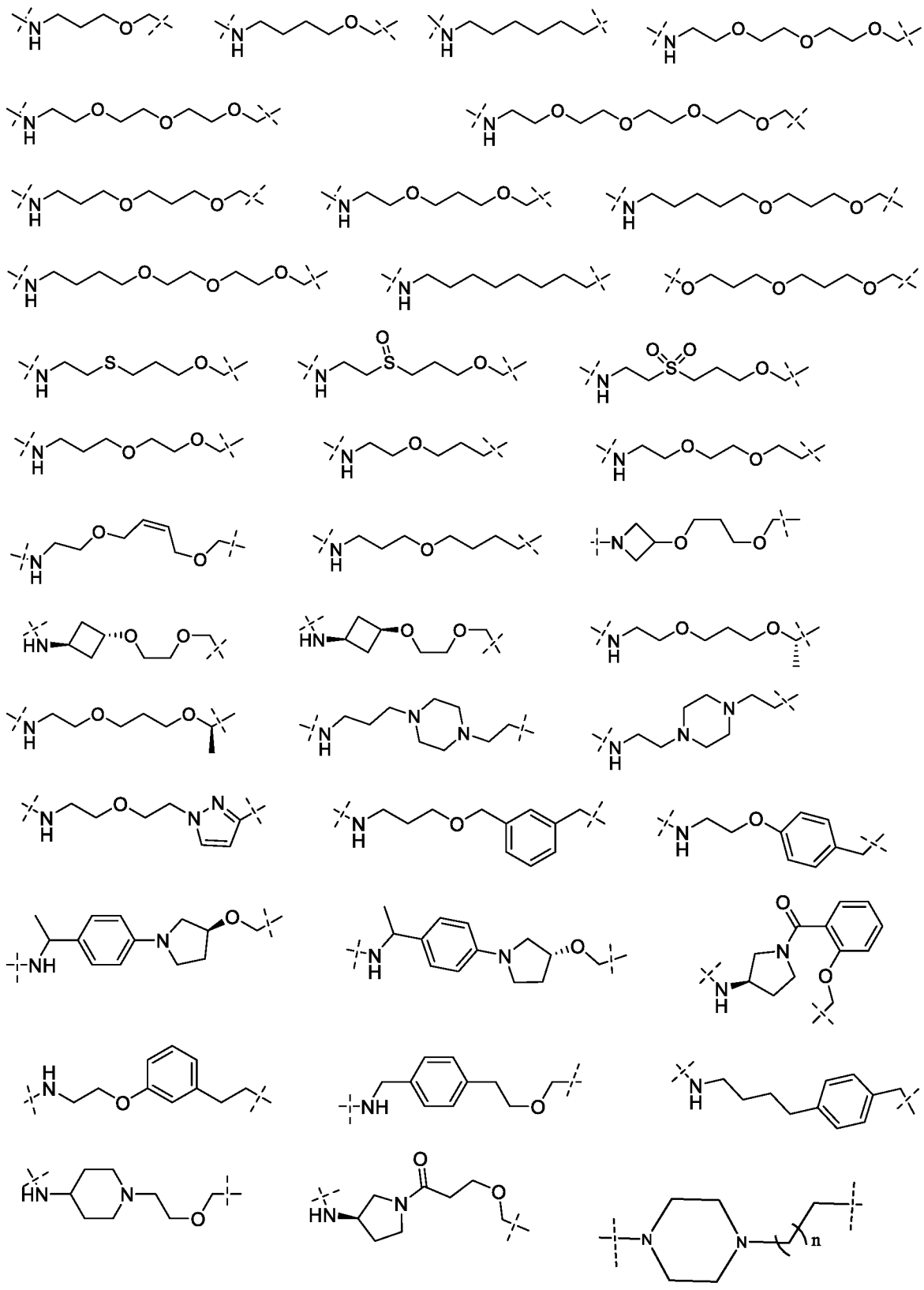
R of the linker is H, methyl and ethyl;

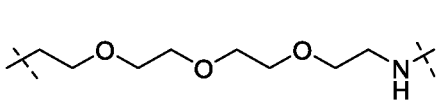
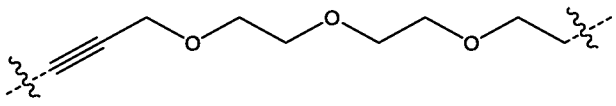
X of the linker is H and F



where m of the linker can be 2, 3, 4, 5;



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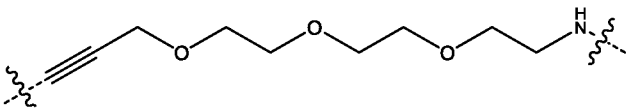
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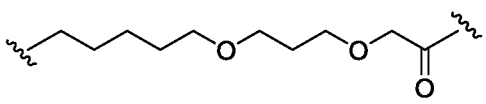
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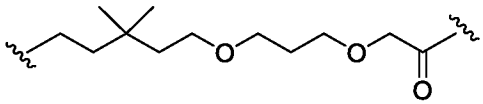
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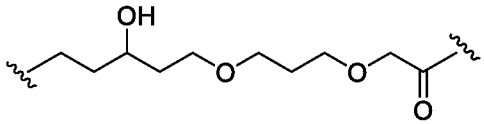
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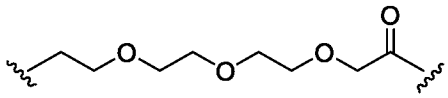
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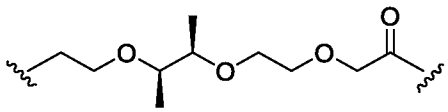
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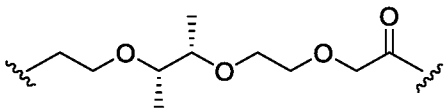
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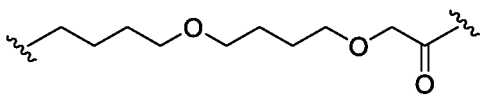
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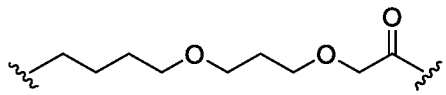
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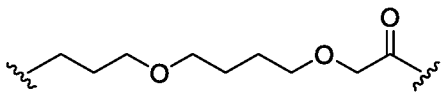
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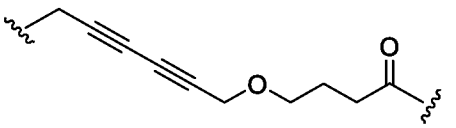
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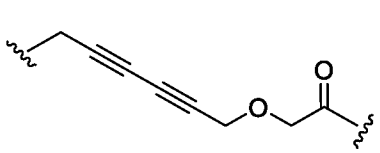
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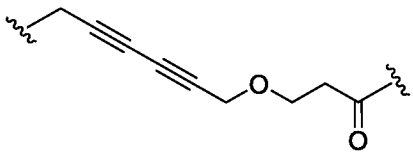
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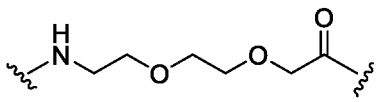
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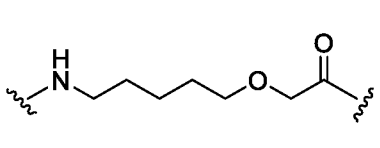
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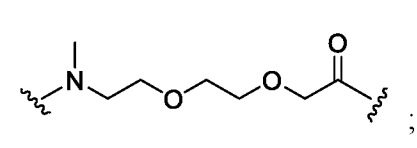
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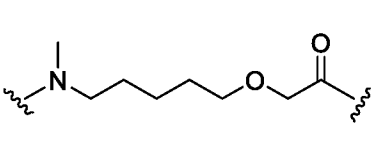
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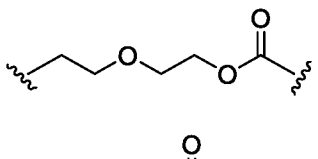
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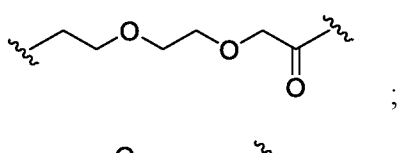
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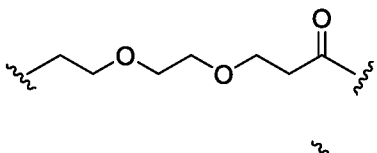
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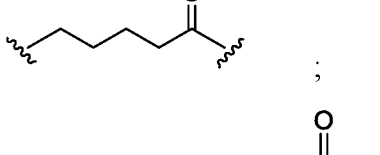
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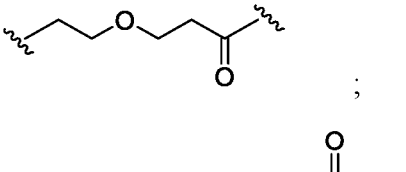
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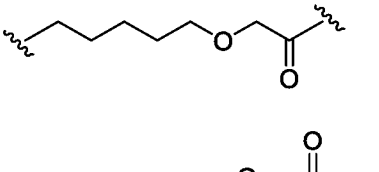
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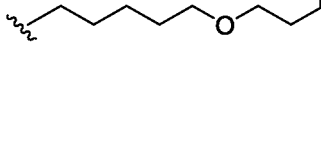
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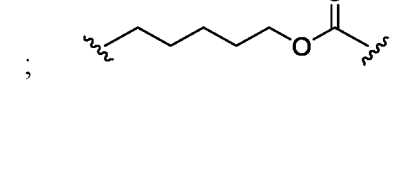
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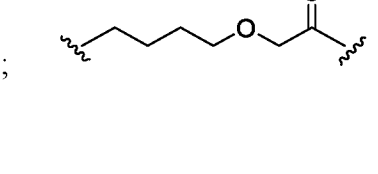
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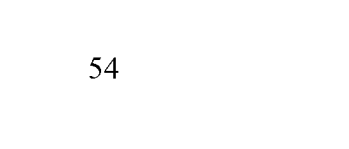
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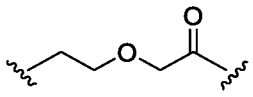
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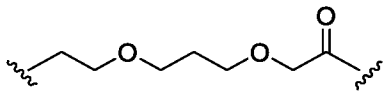
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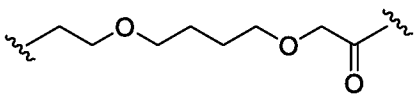
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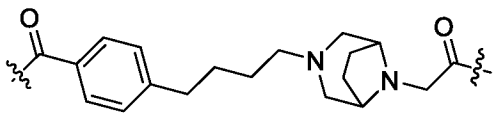
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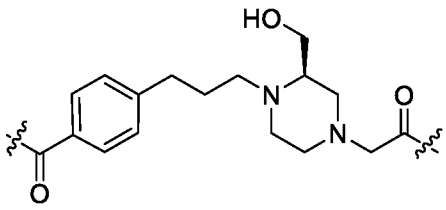
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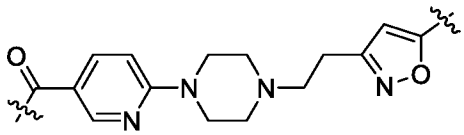
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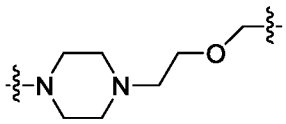
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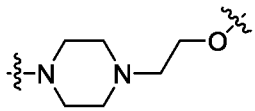
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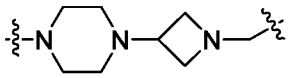
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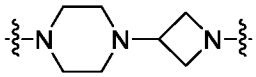
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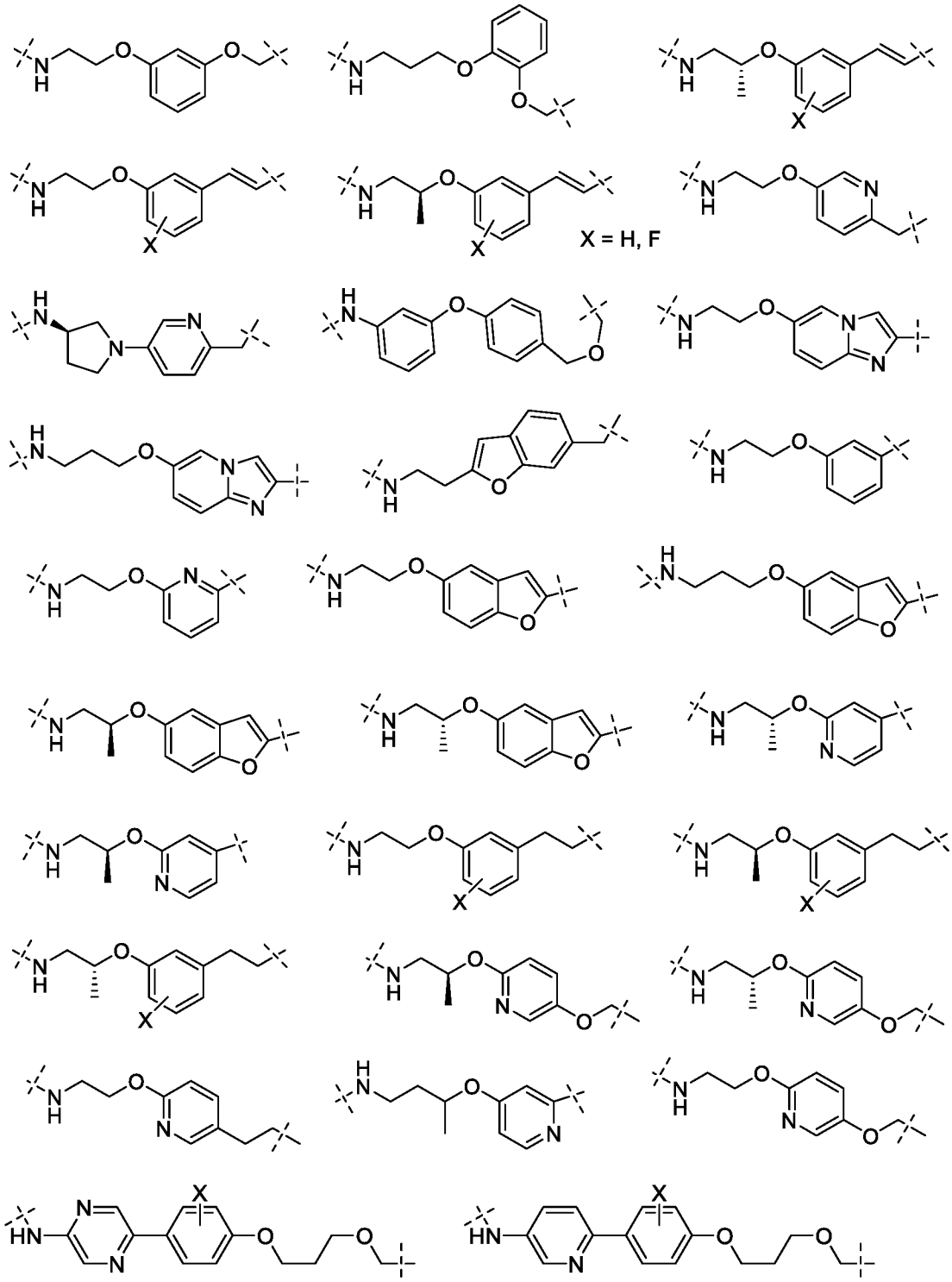
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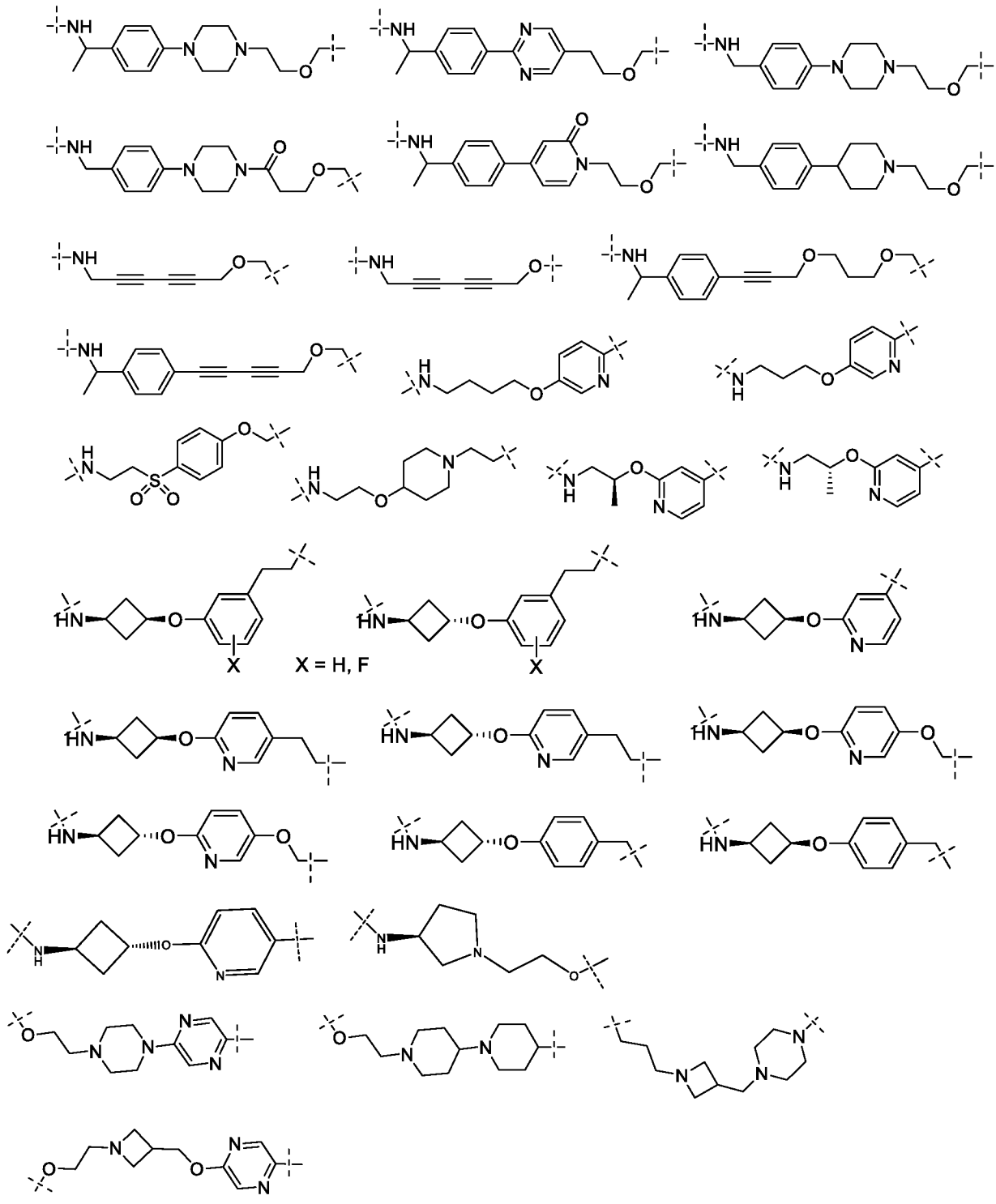
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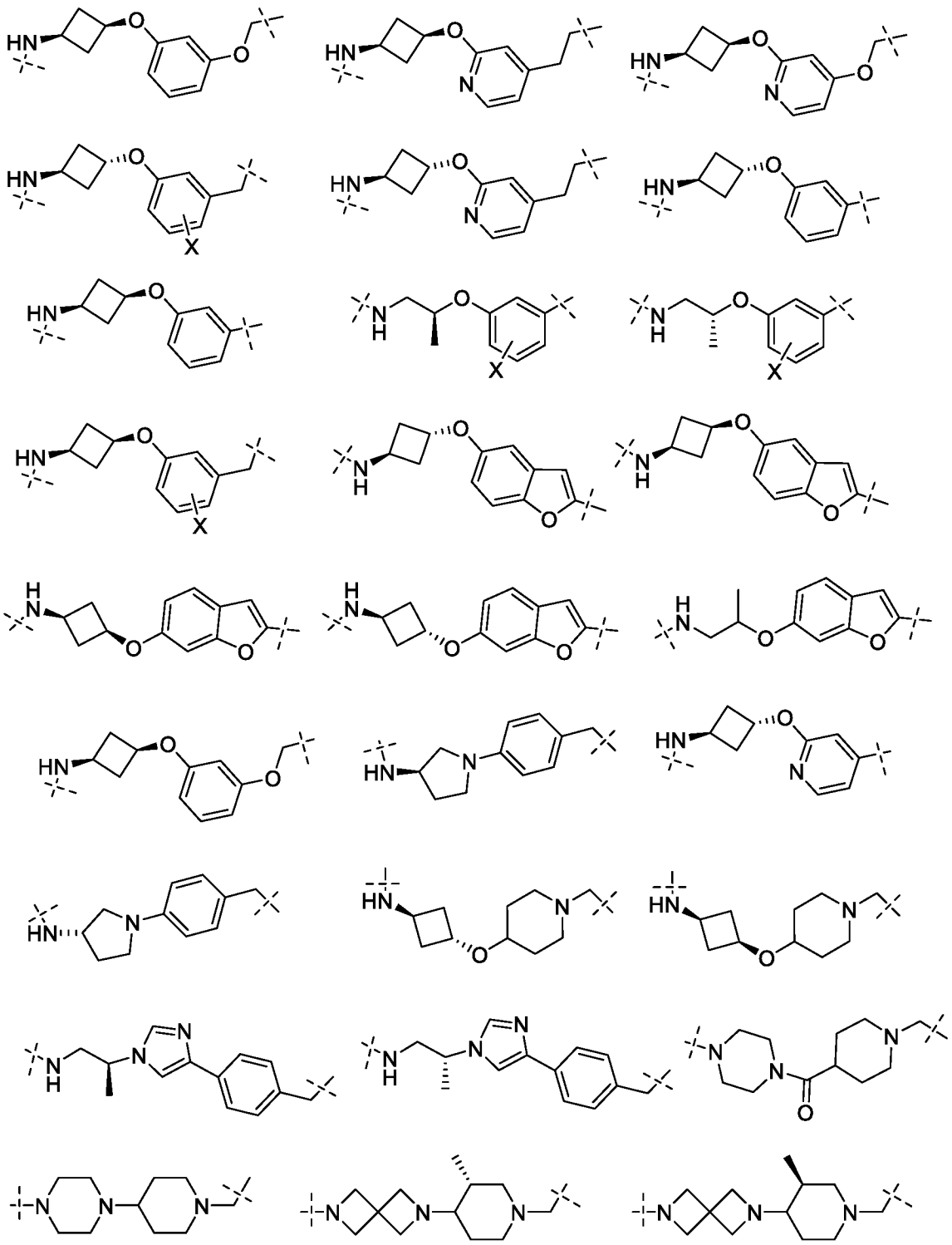
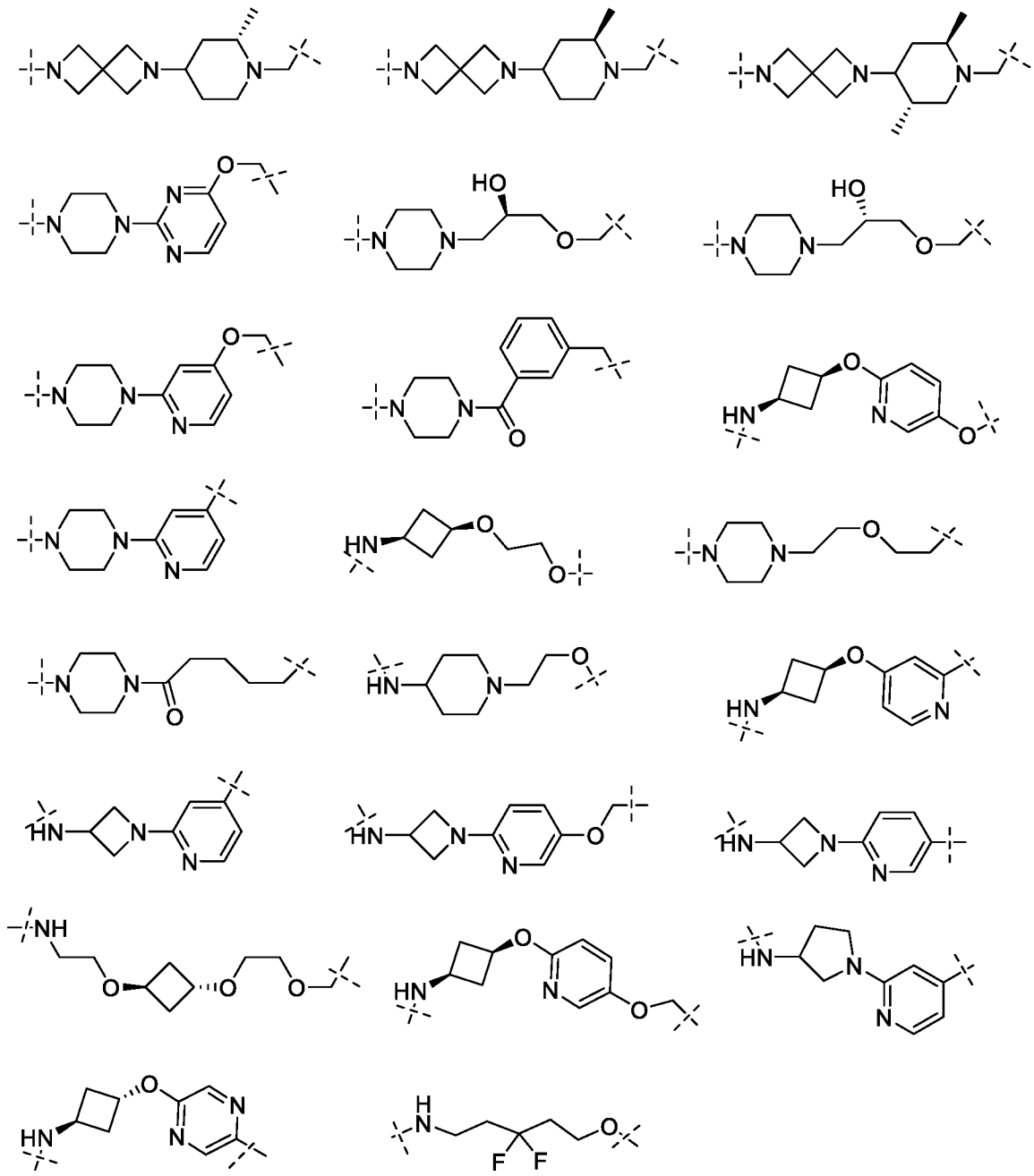
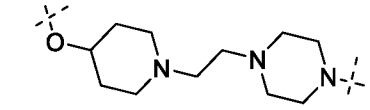
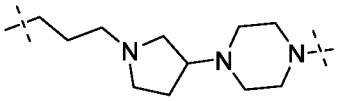
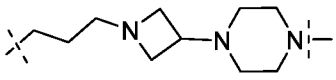
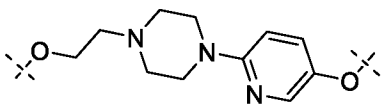
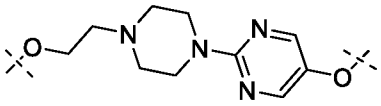
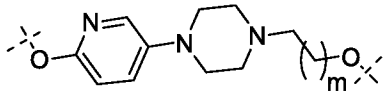
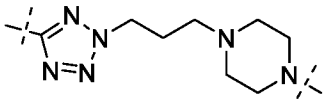
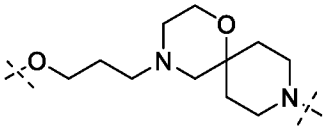
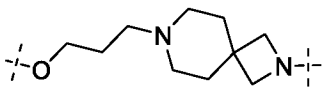
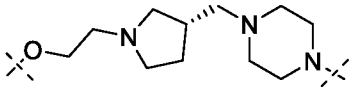
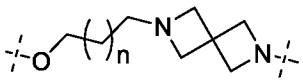
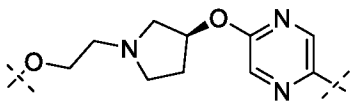
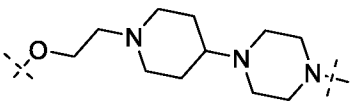
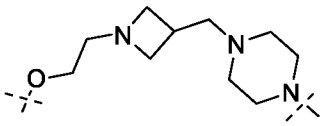
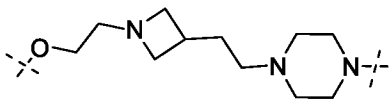
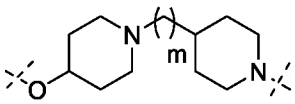
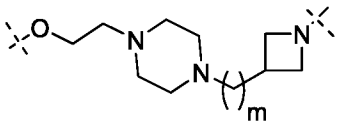
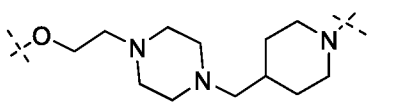
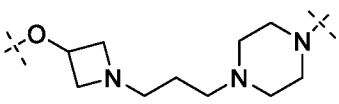
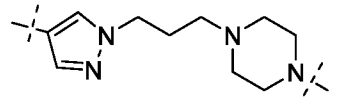
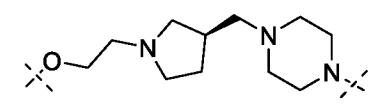
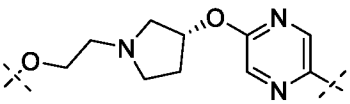
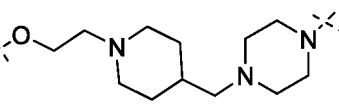
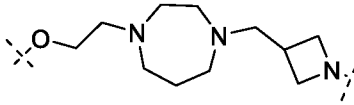
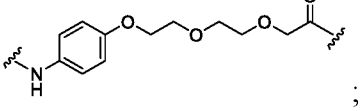
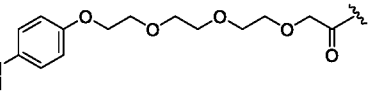
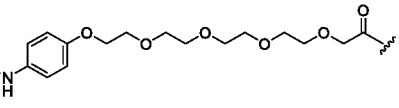
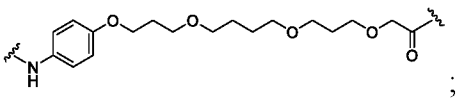
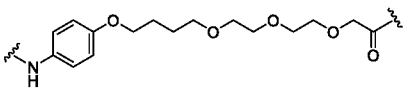
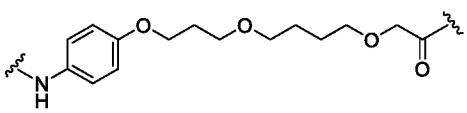
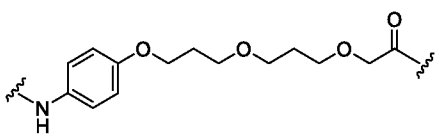


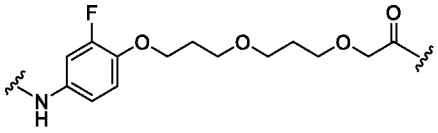


where each n and m of the linker can independently be 0, 1, 2, 3, 4, 5, 6.

[0098] In any aspect or embodiment described herein, the A^L group is selected from the group consisting of: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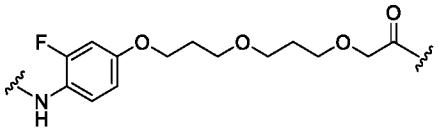
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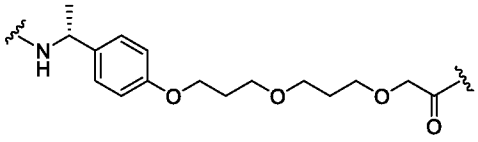
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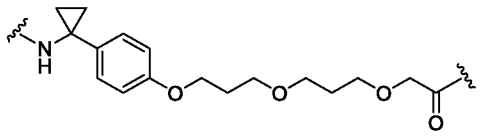
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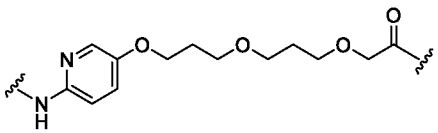
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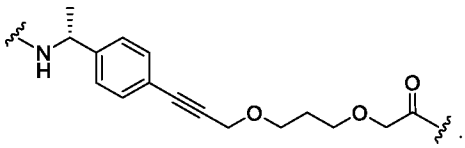
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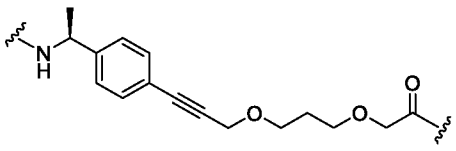
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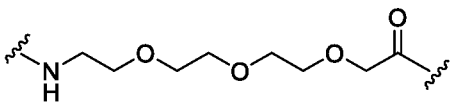
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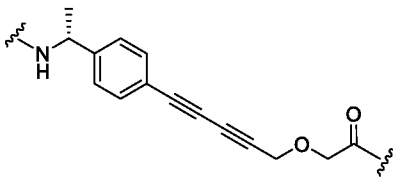
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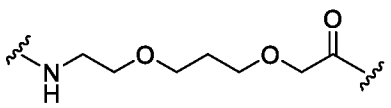
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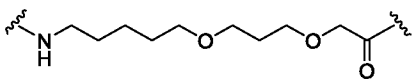
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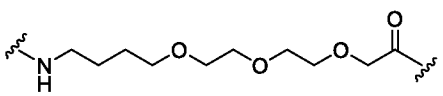
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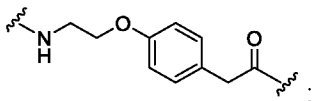
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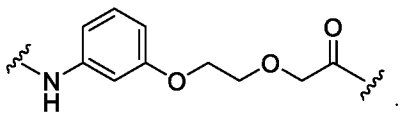
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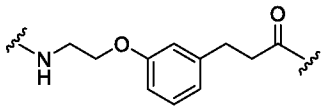
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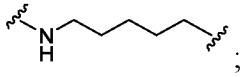
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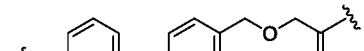
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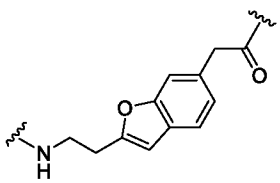
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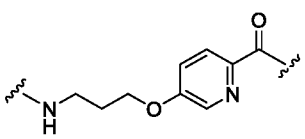
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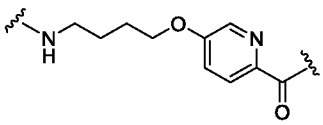
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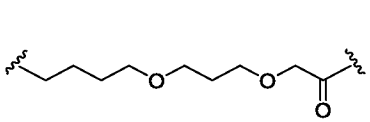
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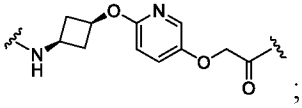
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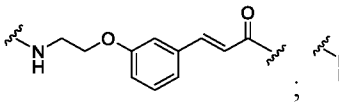
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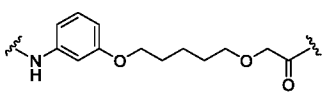
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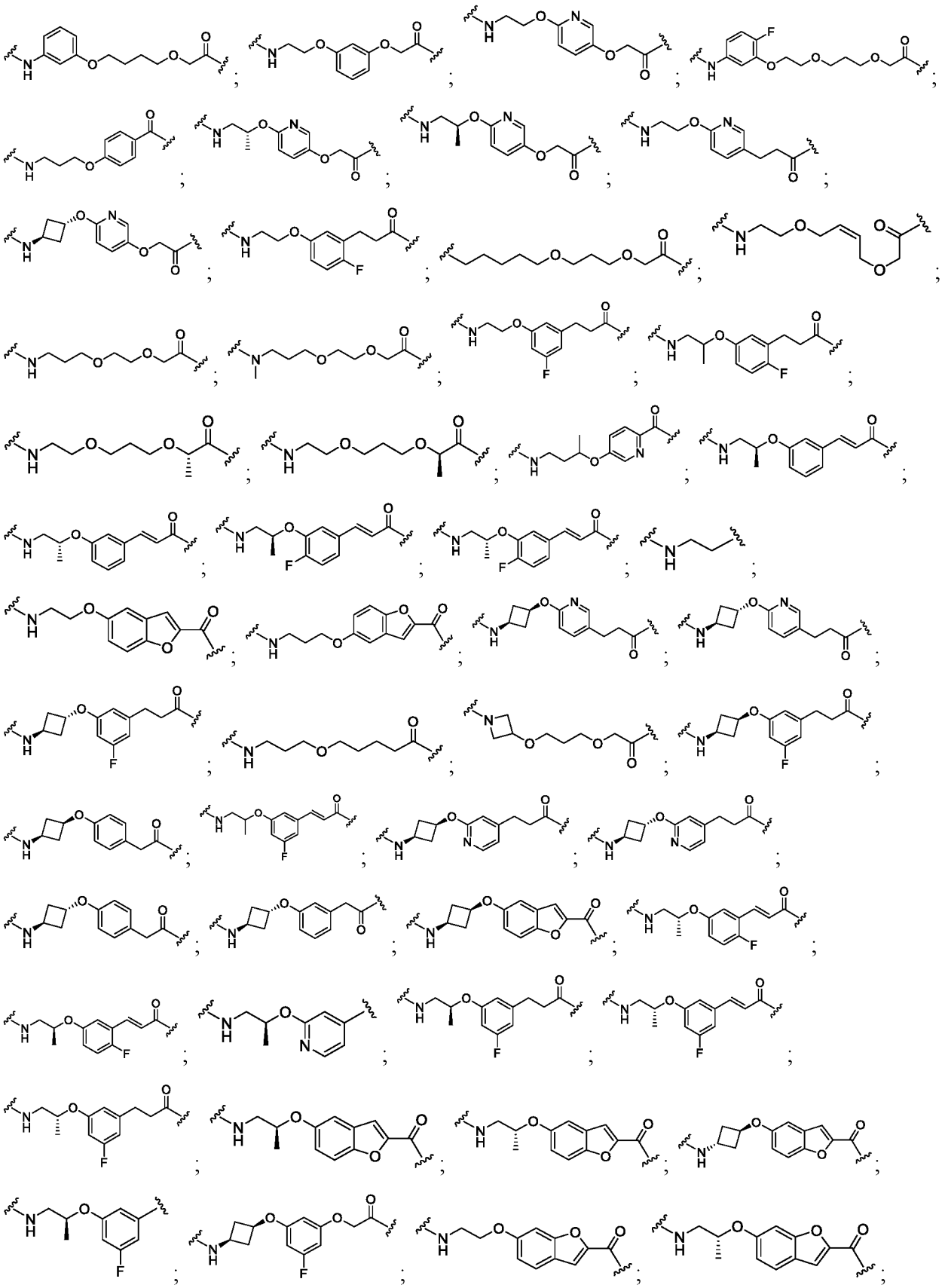
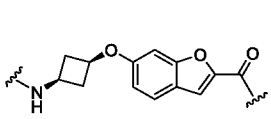
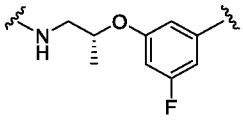
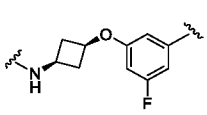
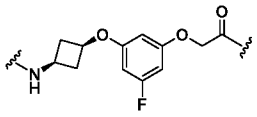
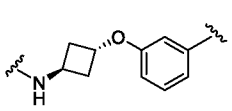
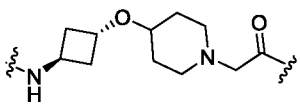
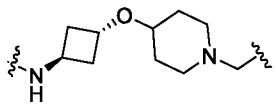
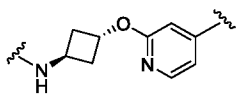
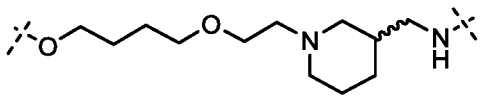
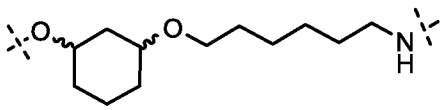


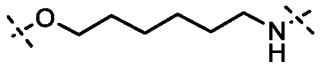
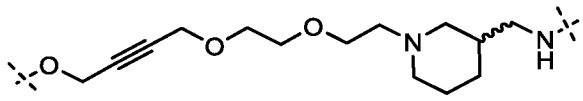
 ;  ;  ;  ;

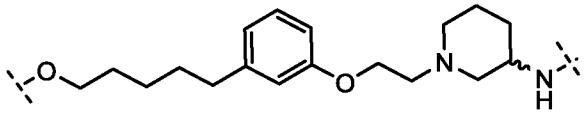
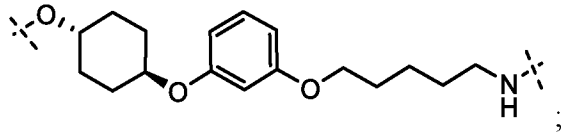
 ;  ;  and  ,

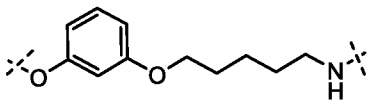
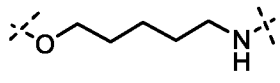
wherein each m and n is independently selected from 0, 1, 2, 3, 4, 5 , or 6.

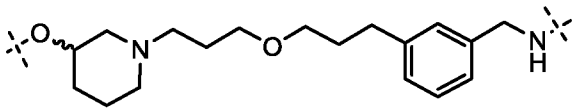
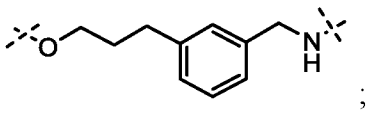
[0099] In any aspect or embodiment described herein, A^L group is selected from the group consisting of:

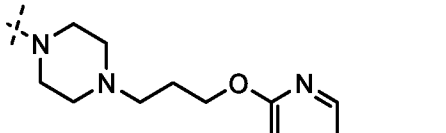
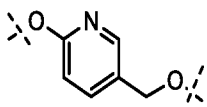
 ;  ;

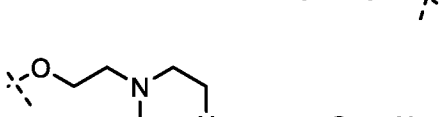
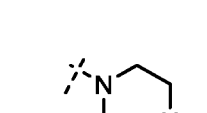
 ; 

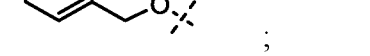
 ;  ;

 ;  ;

 ;  ;

 ; 

 ;  ;

;  ;

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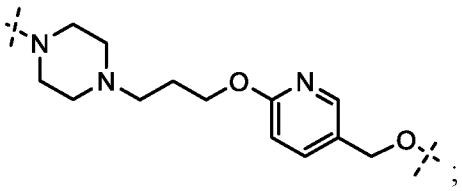
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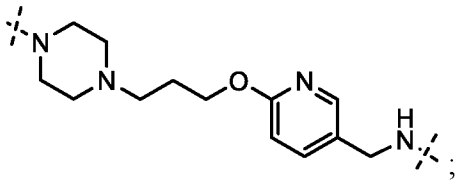
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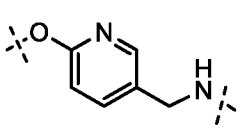
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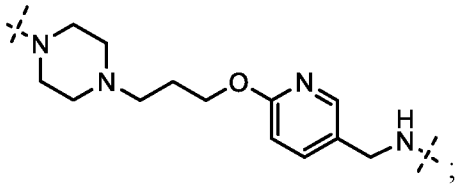
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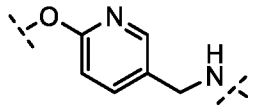
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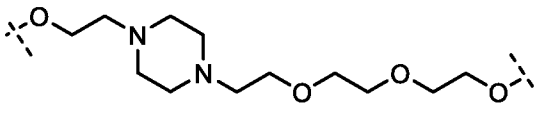
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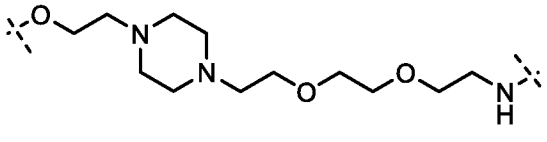
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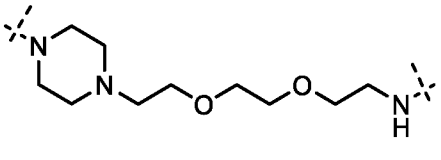
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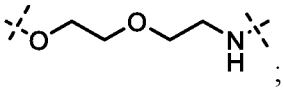
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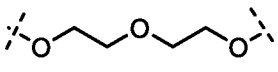
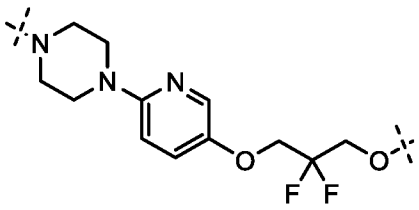
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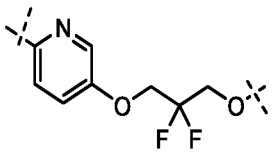
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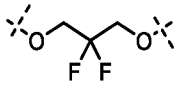
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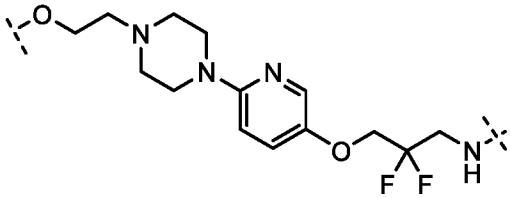
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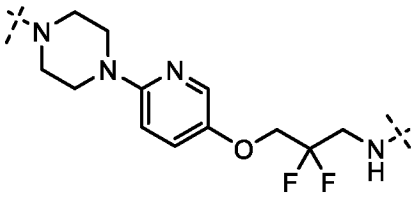
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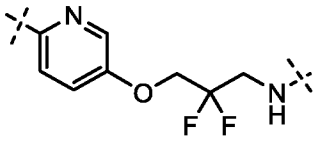
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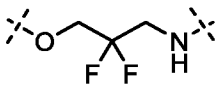
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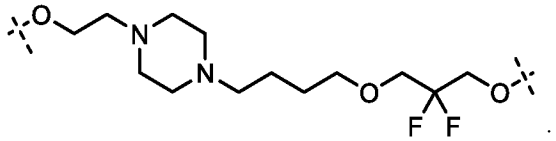
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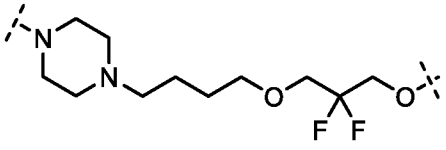
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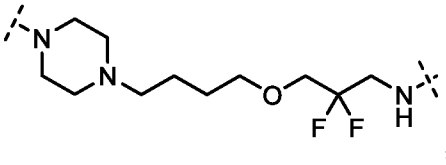
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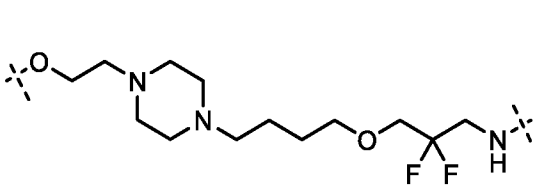
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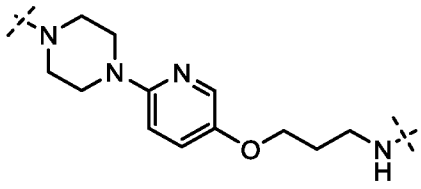
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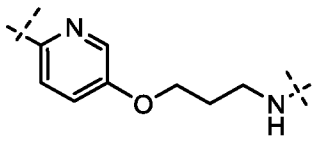
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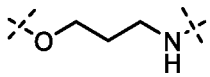
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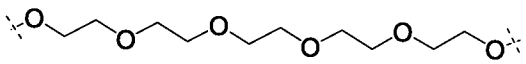
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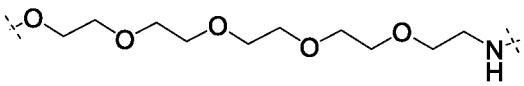
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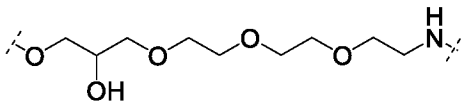
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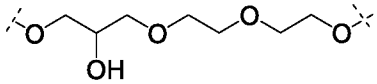
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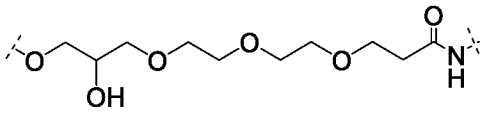
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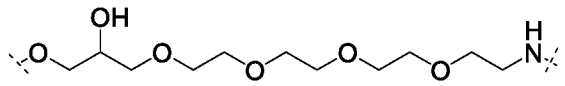
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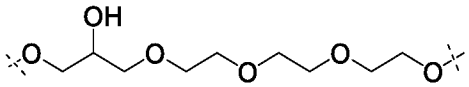
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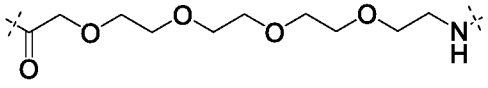
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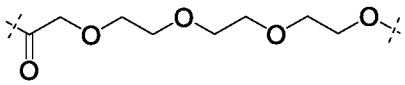
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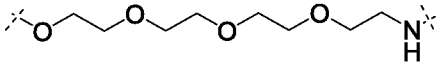
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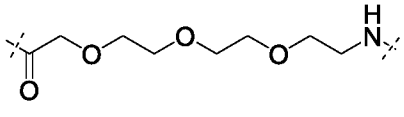
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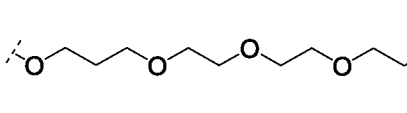
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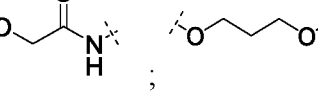
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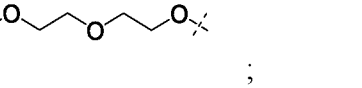
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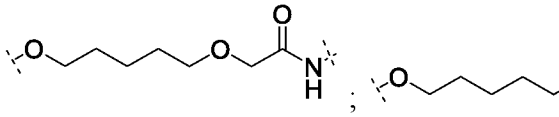
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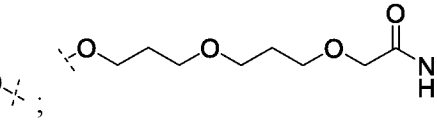
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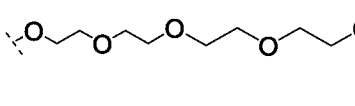
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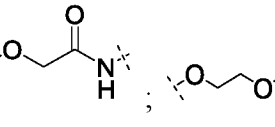
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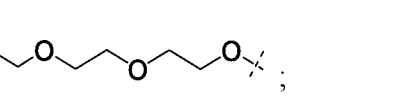
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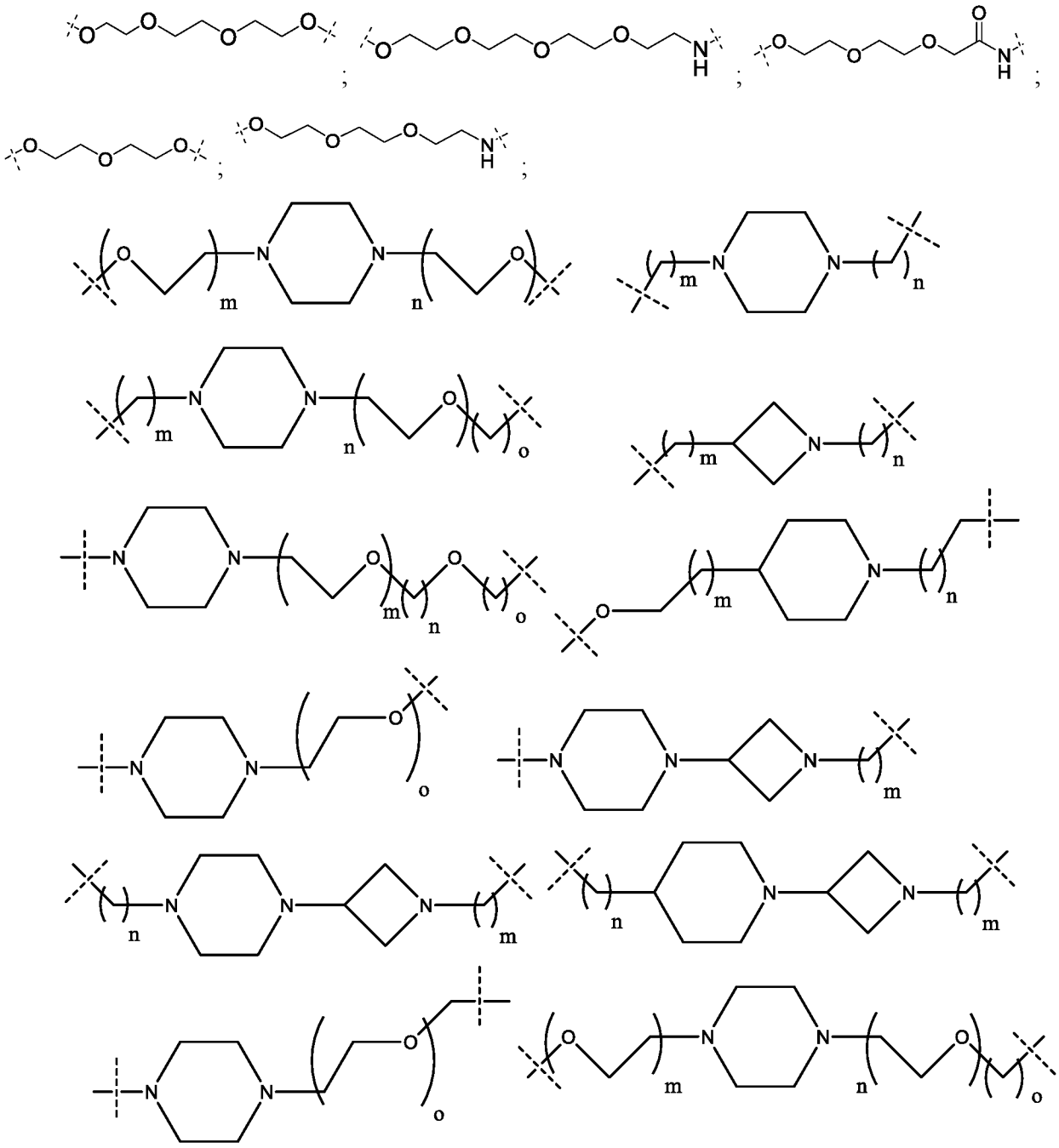
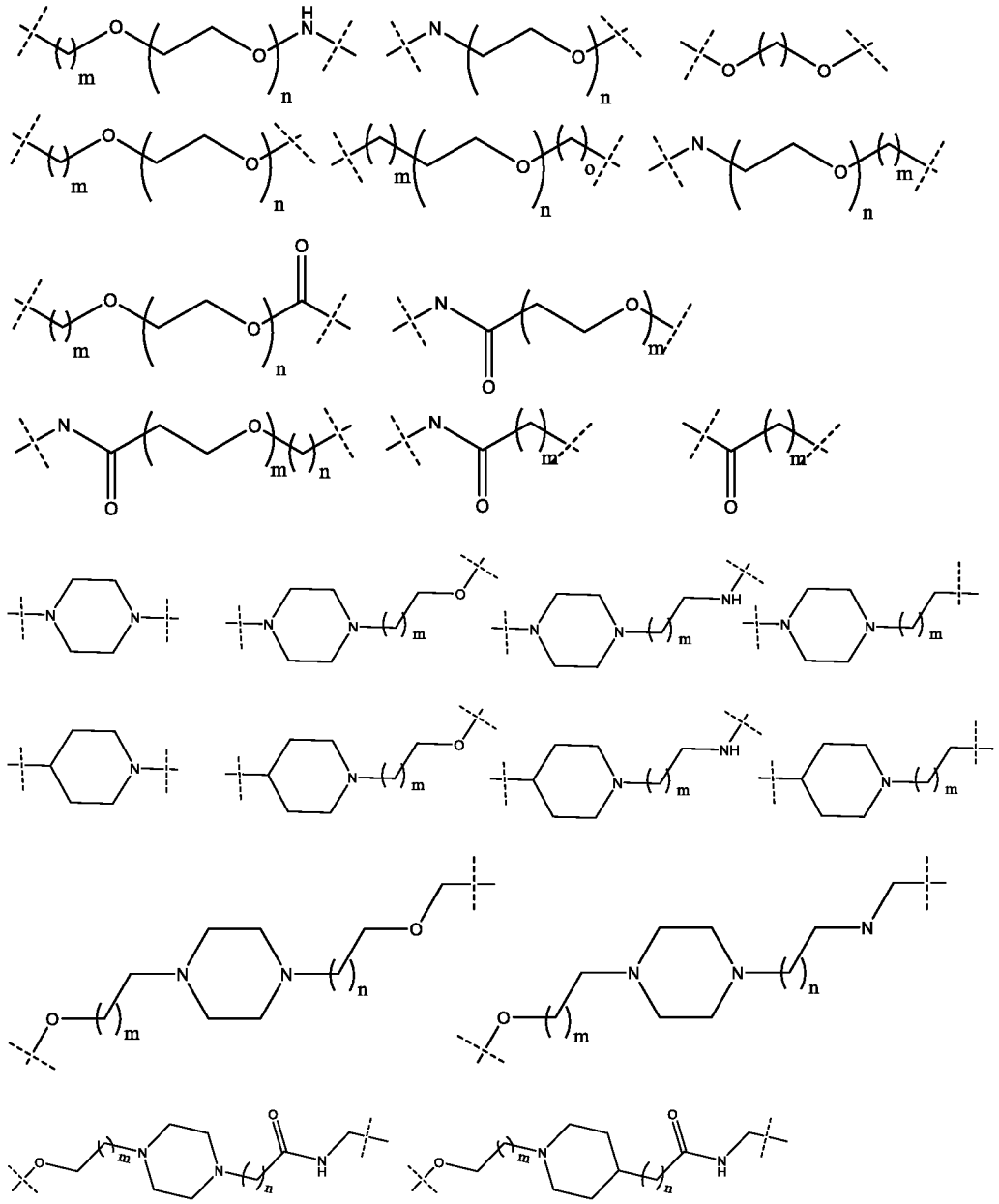
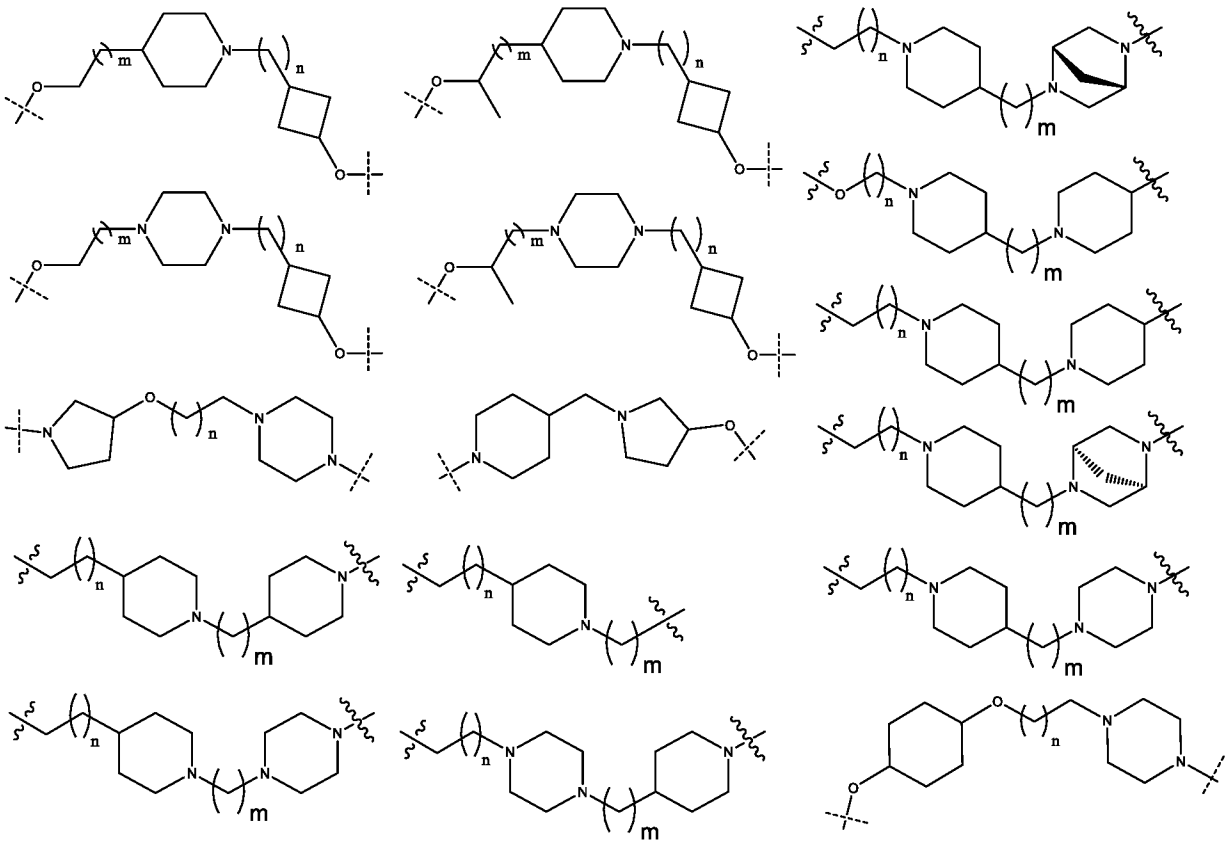
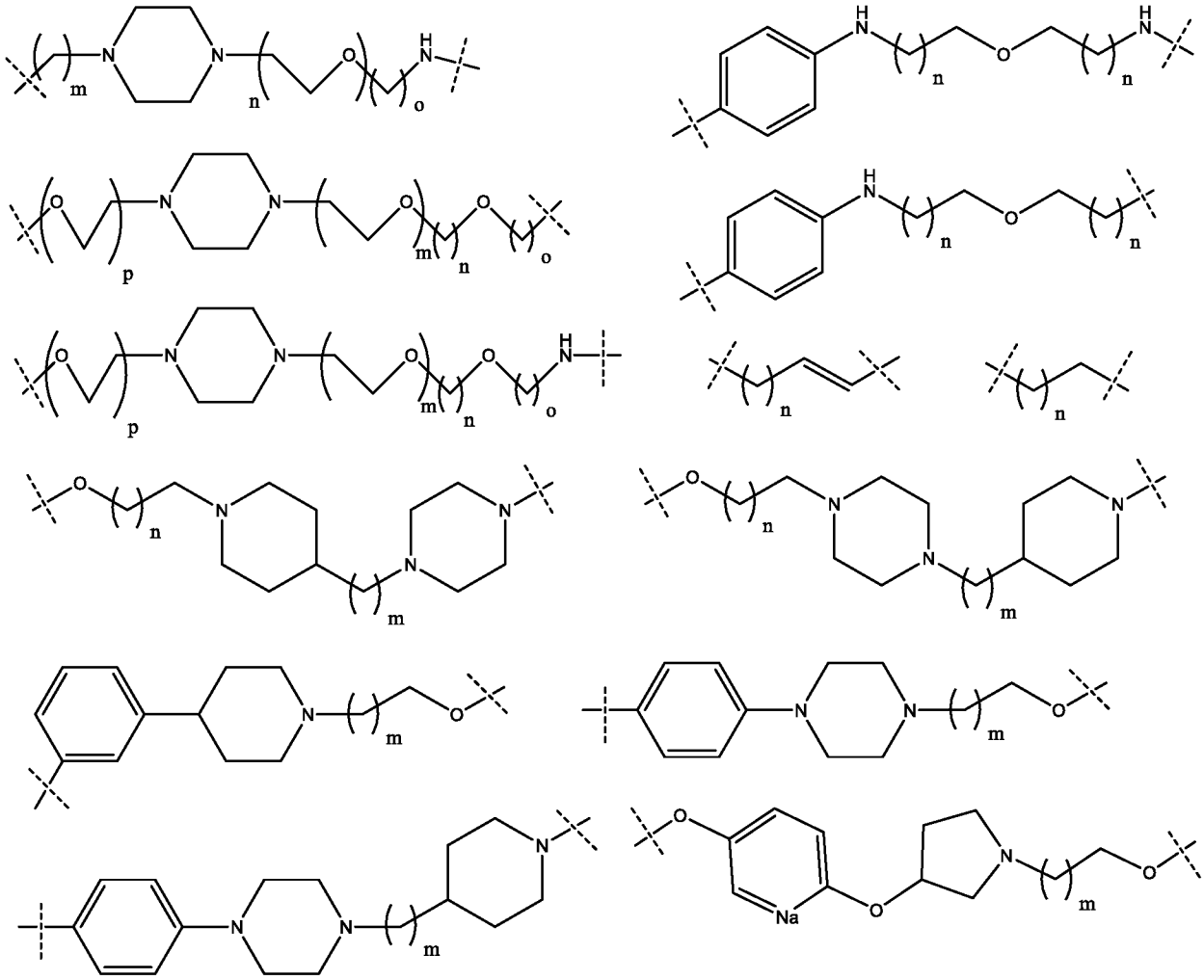
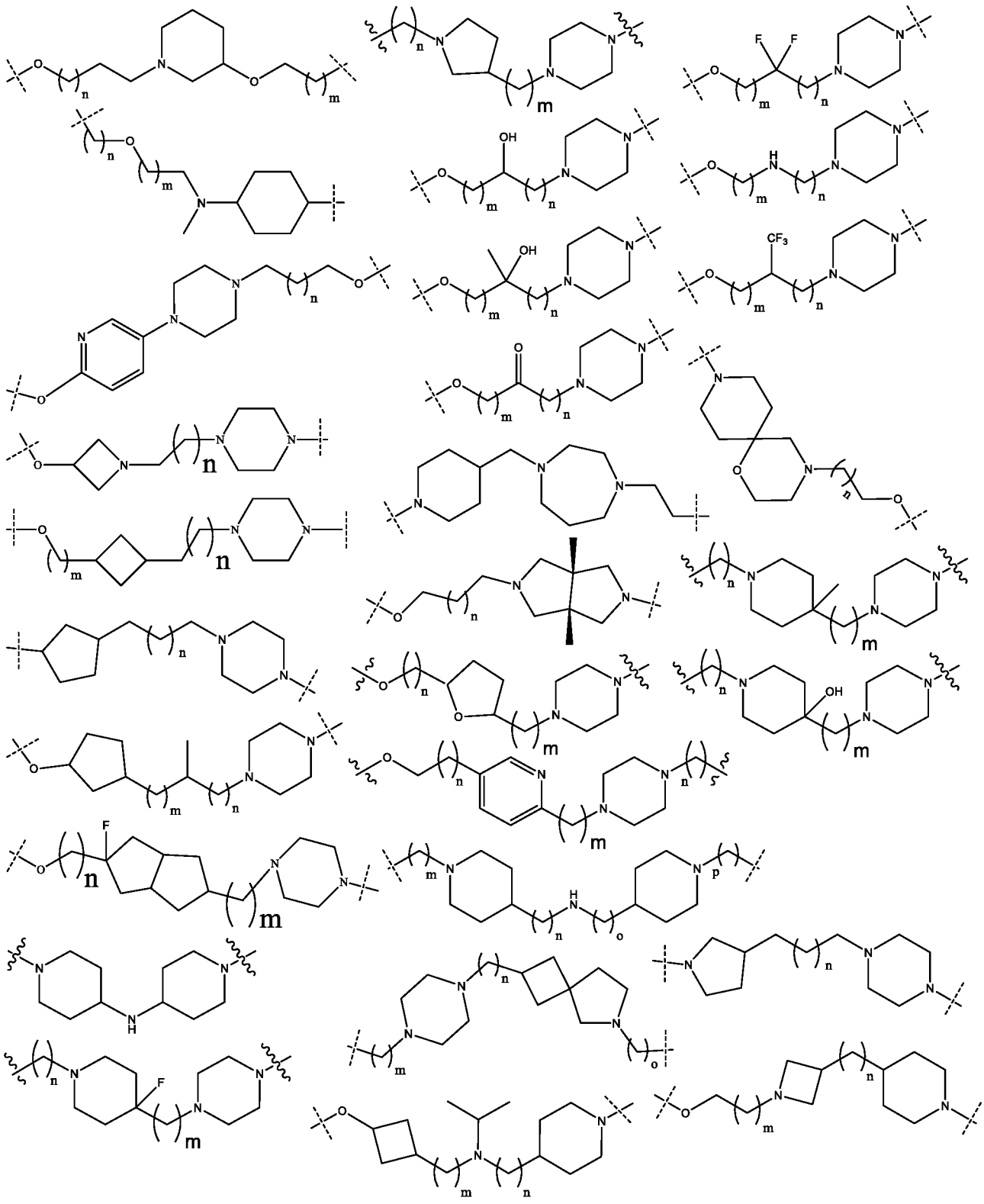
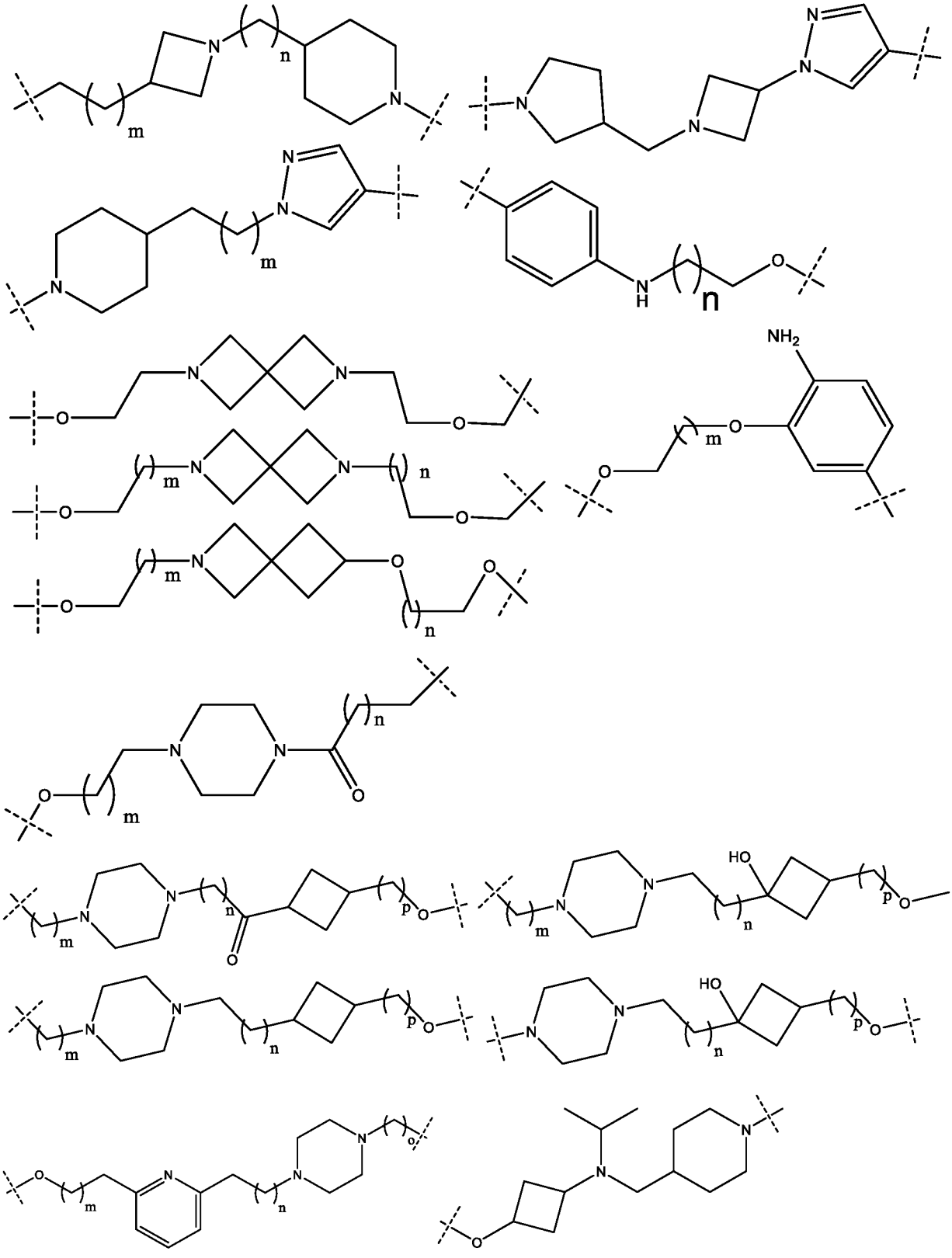


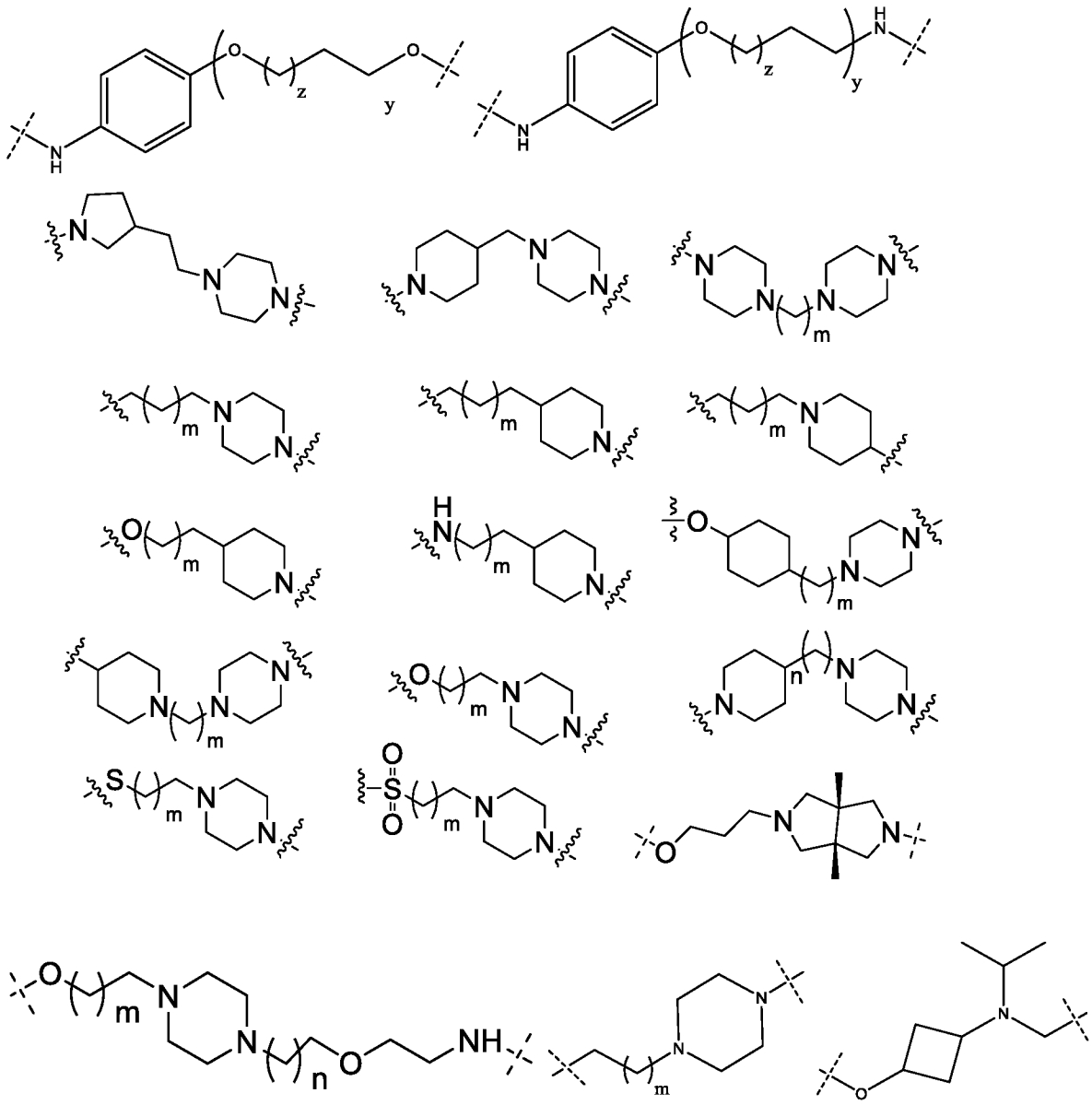


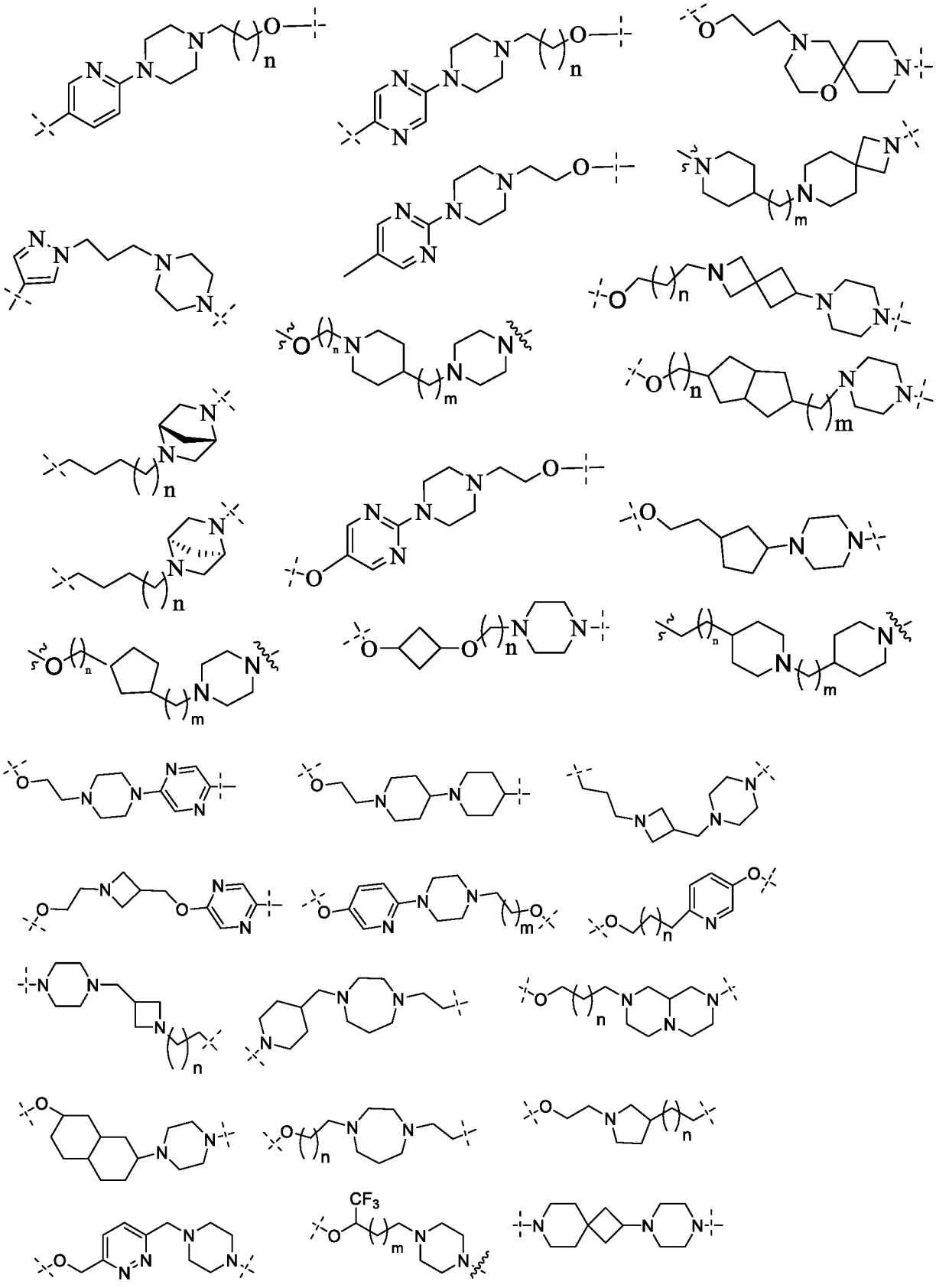


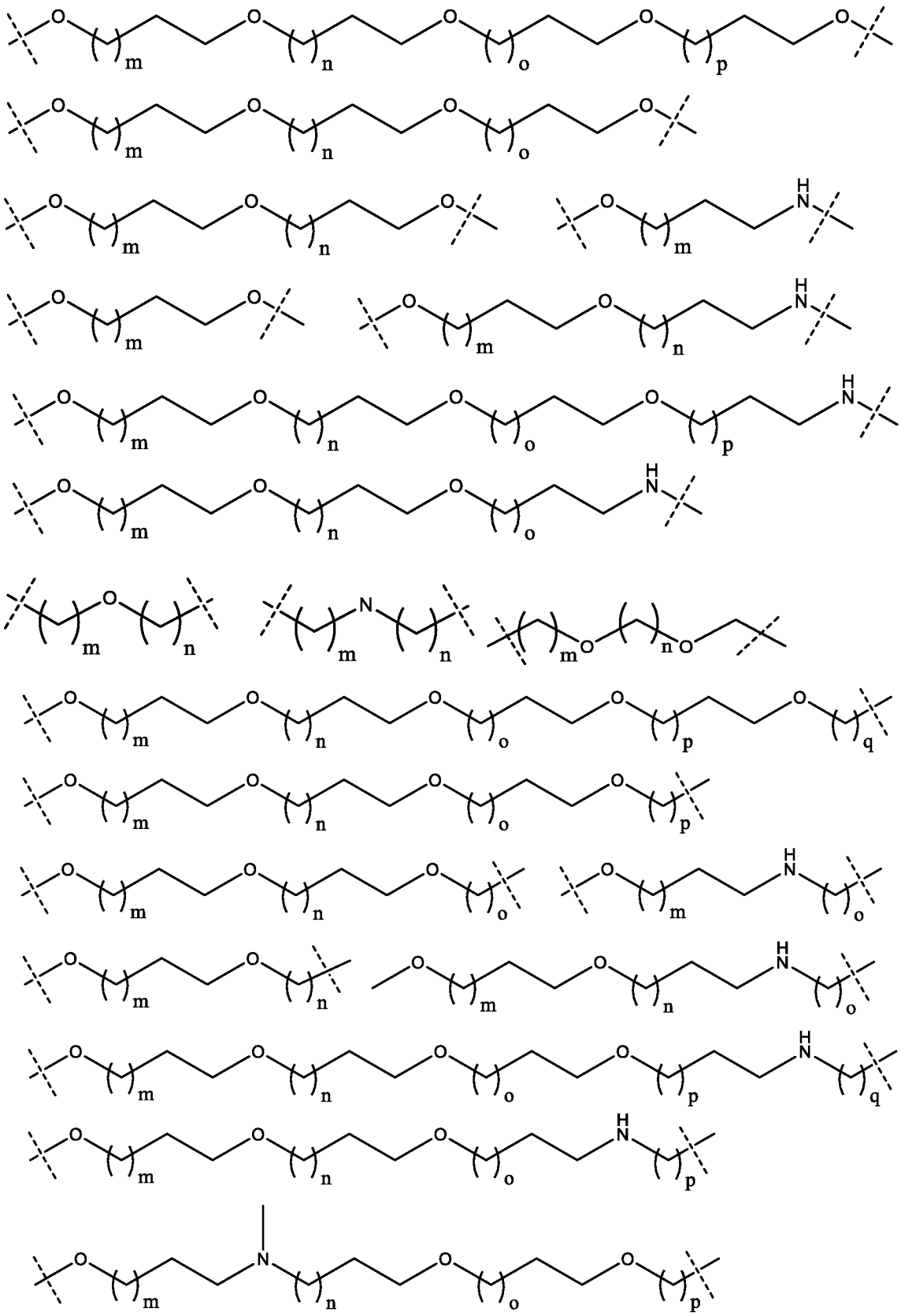


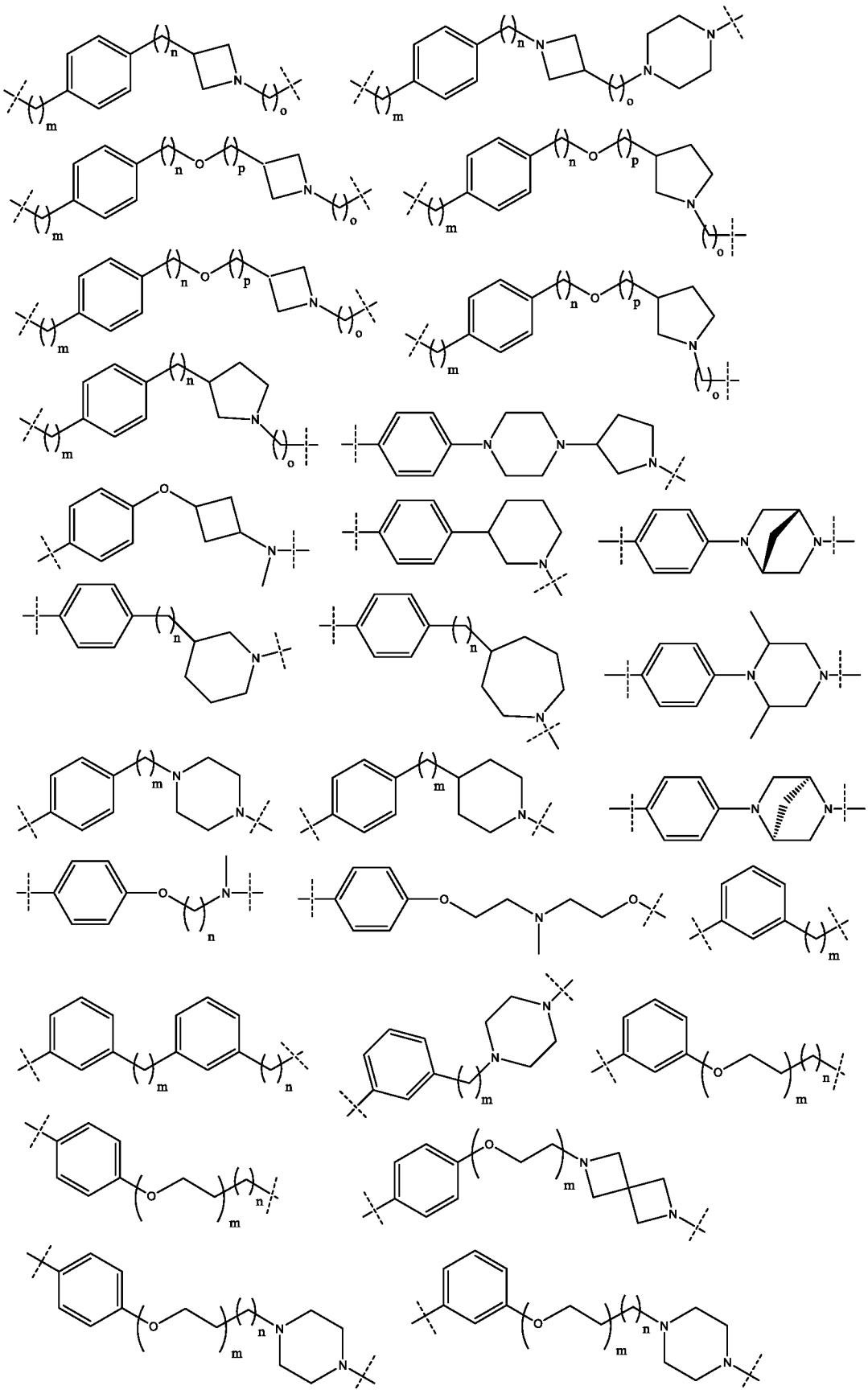


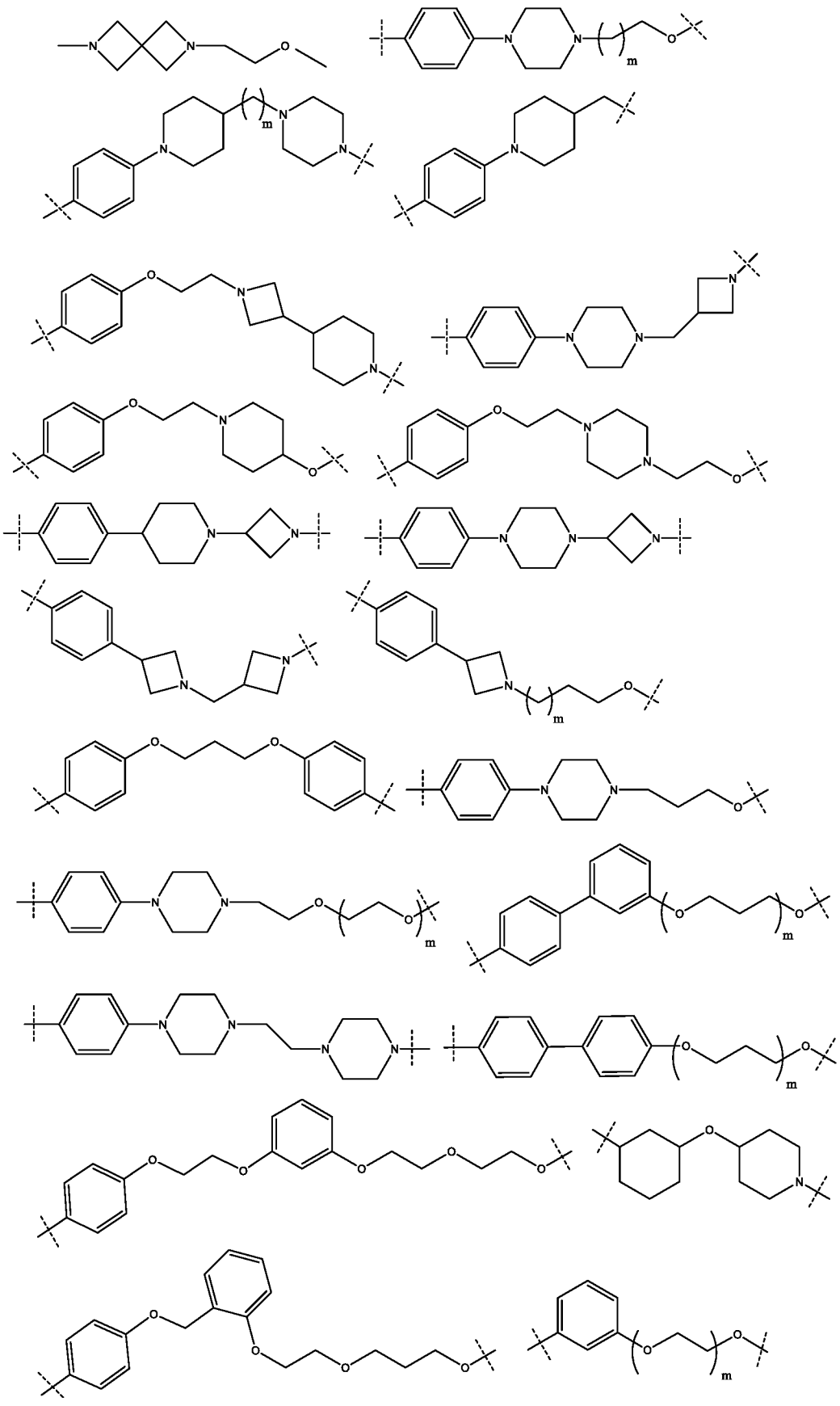


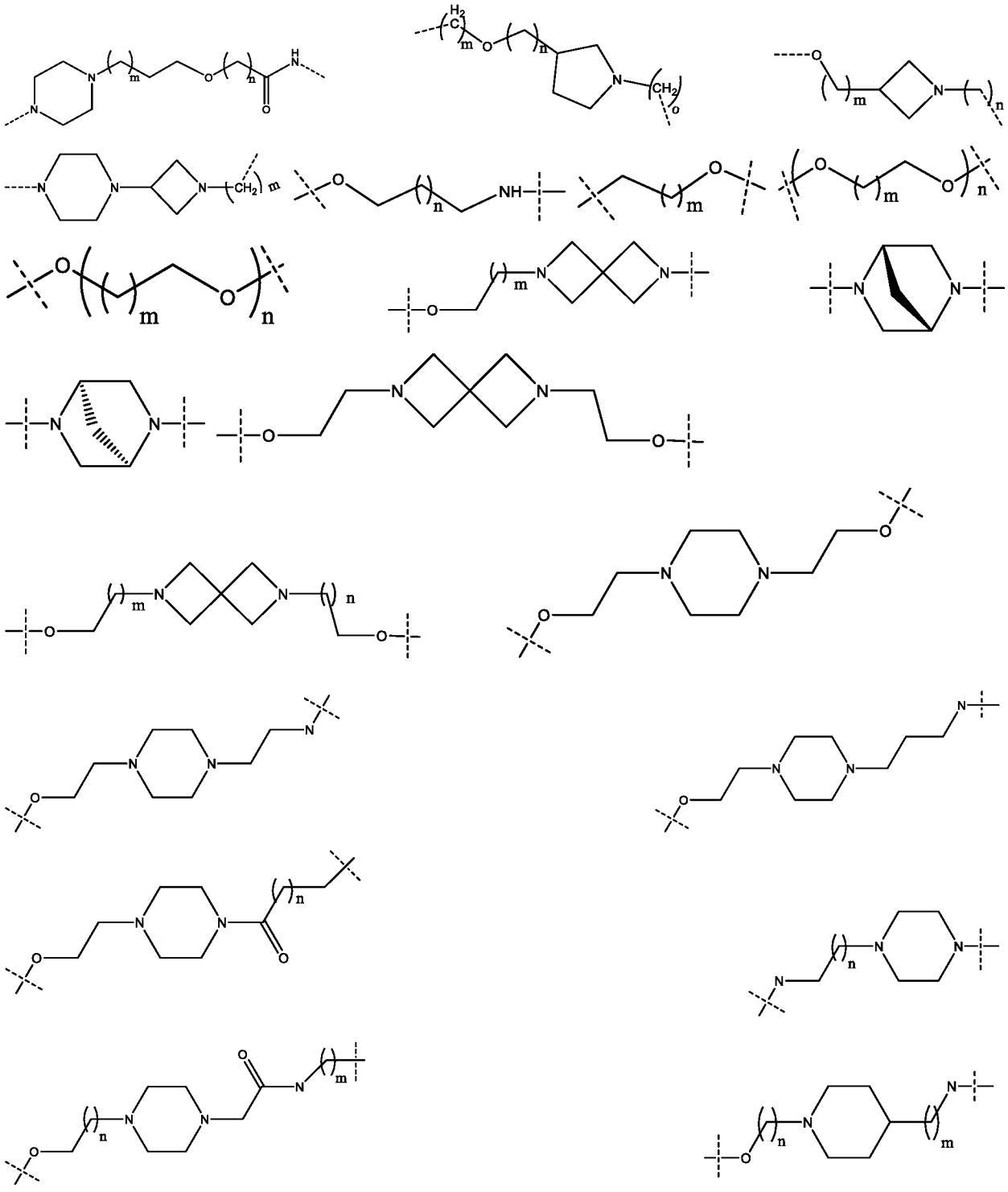


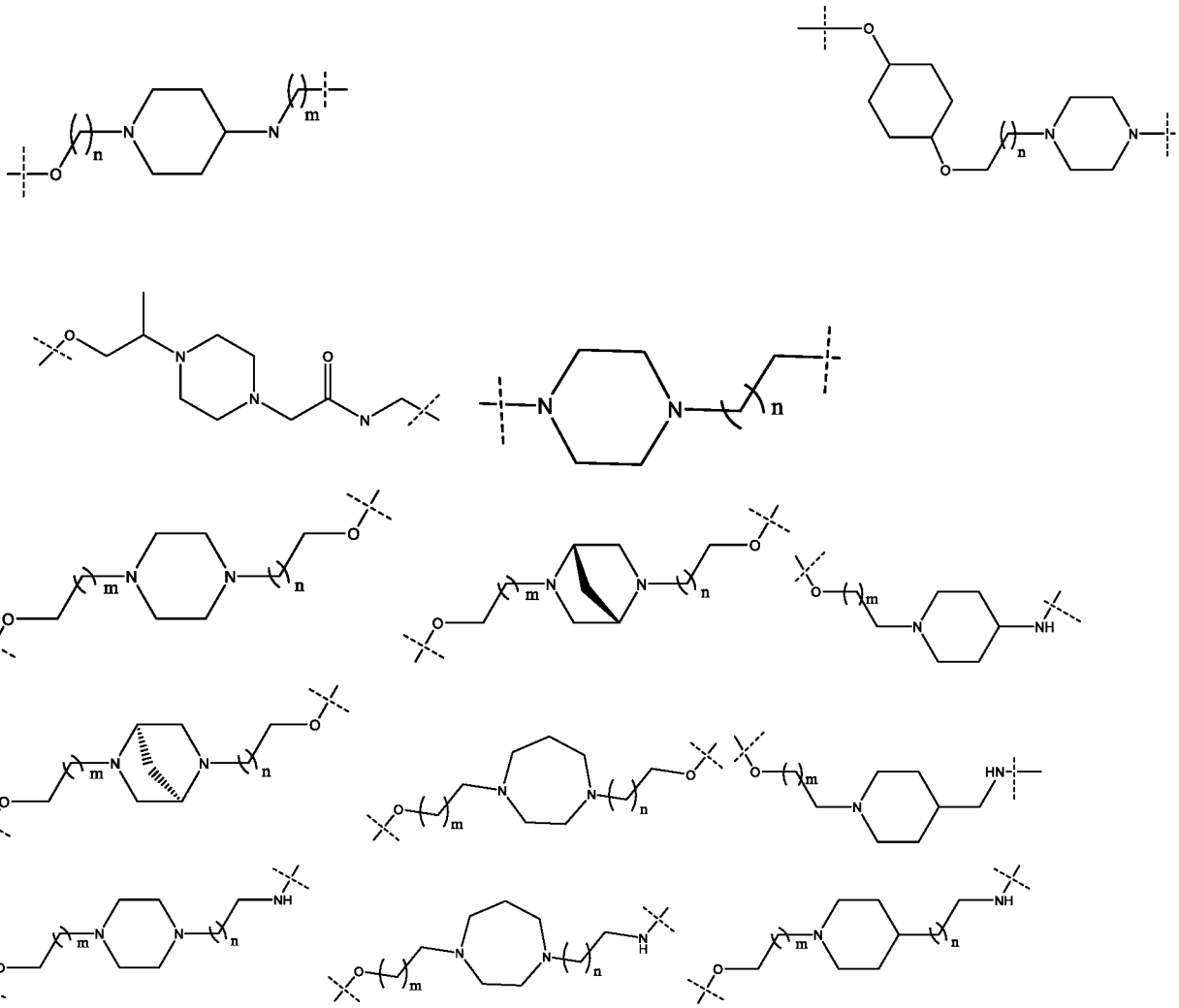


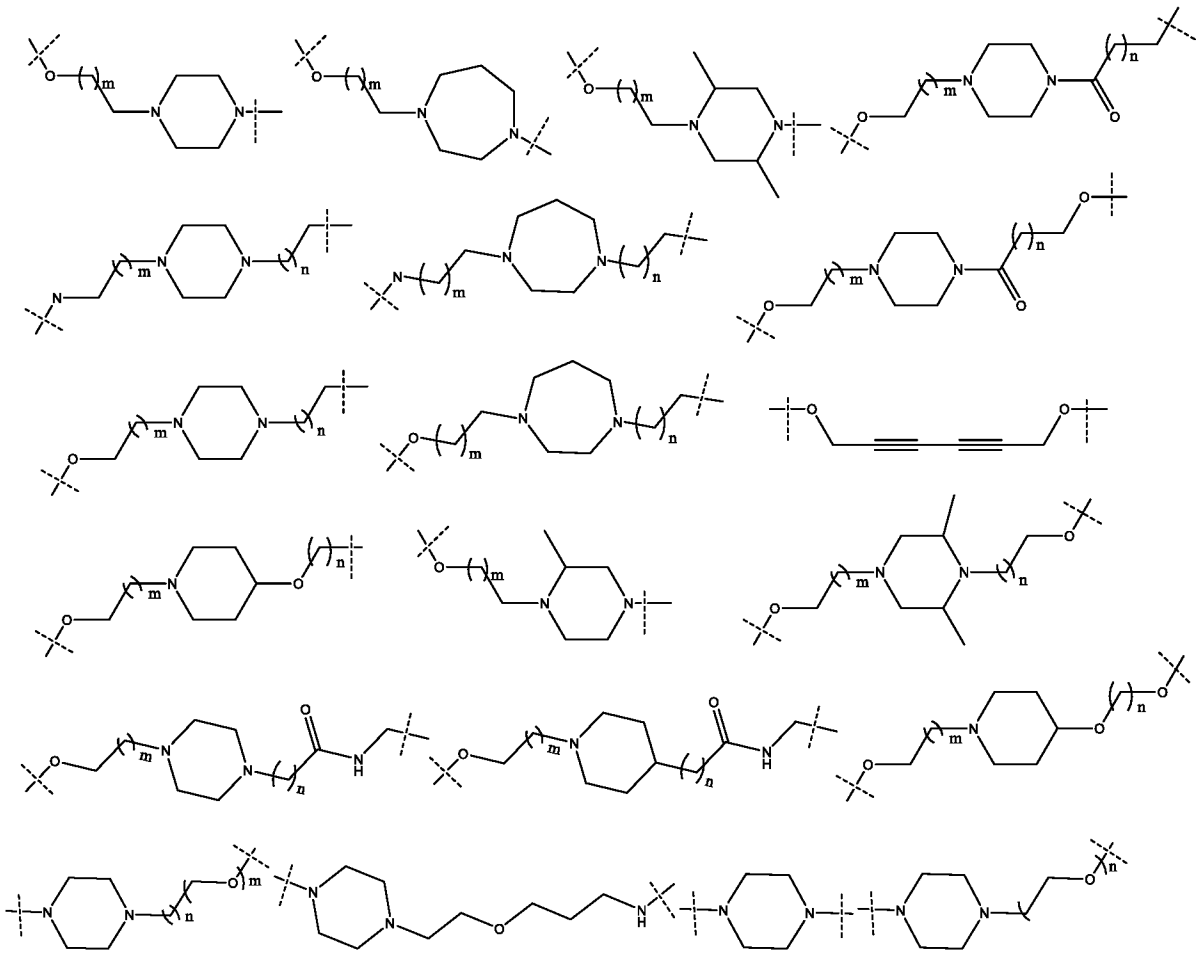


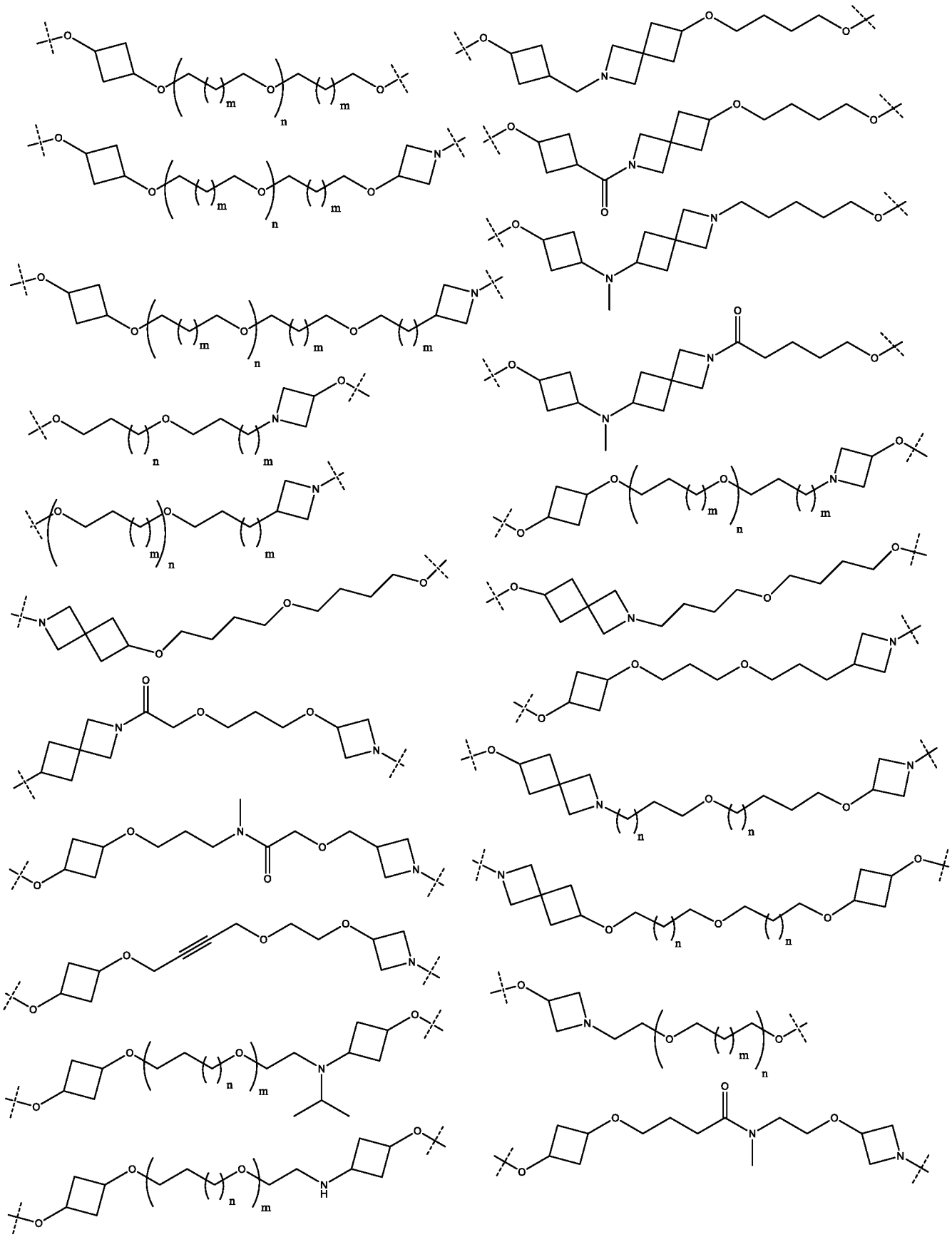


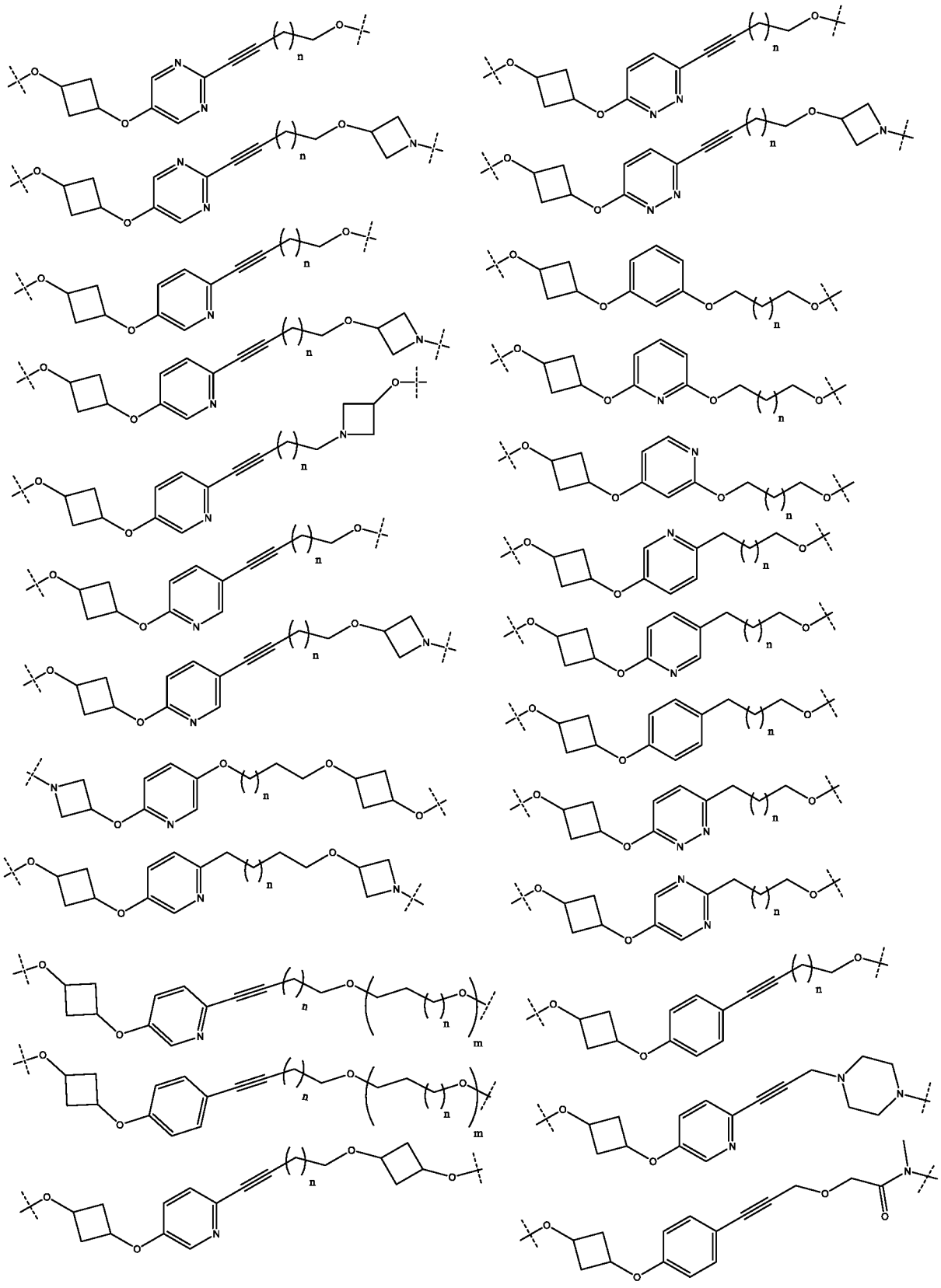


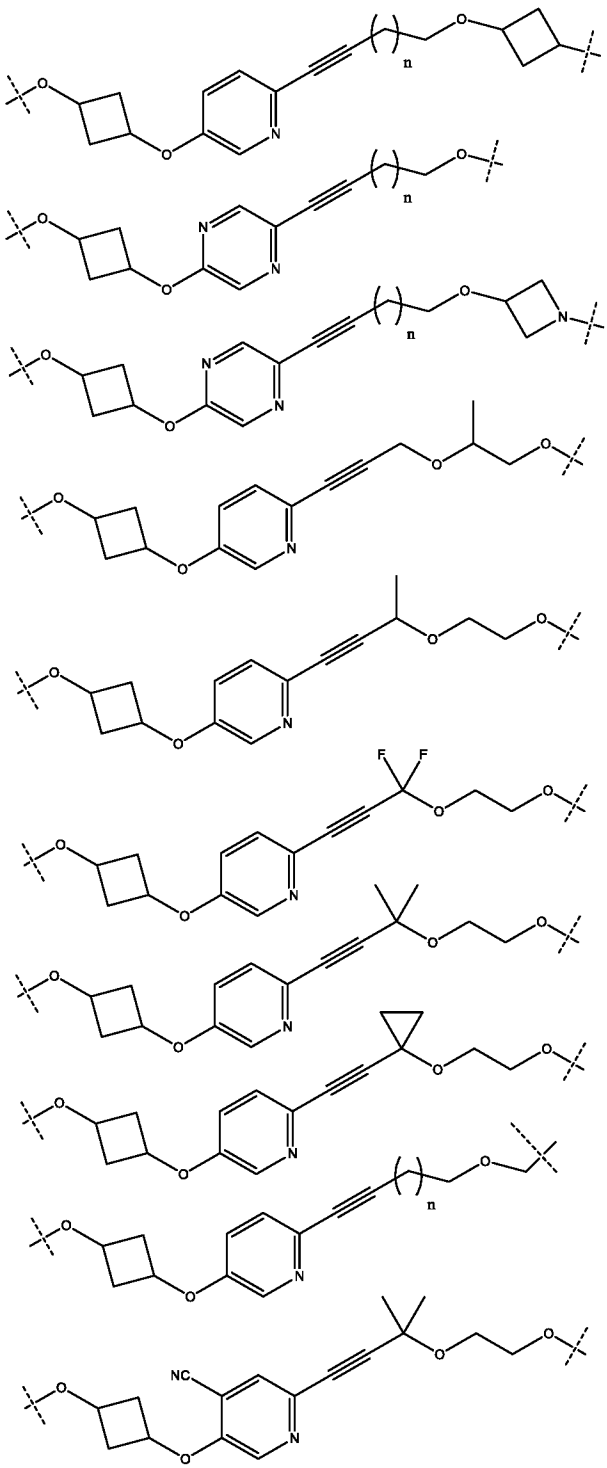


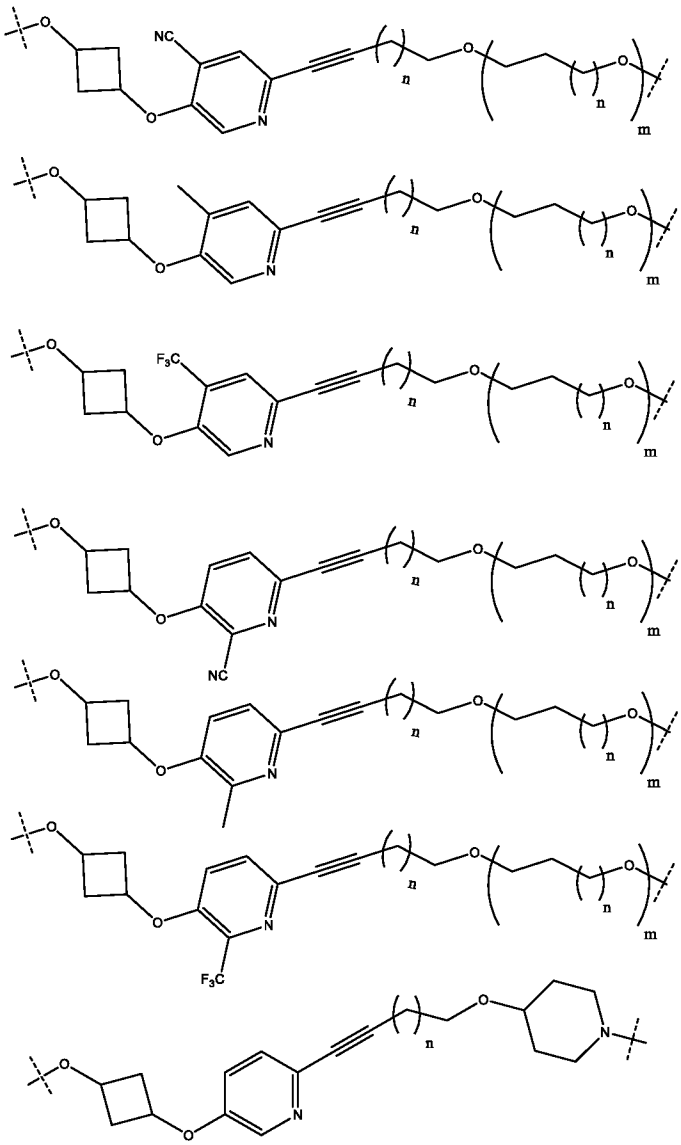


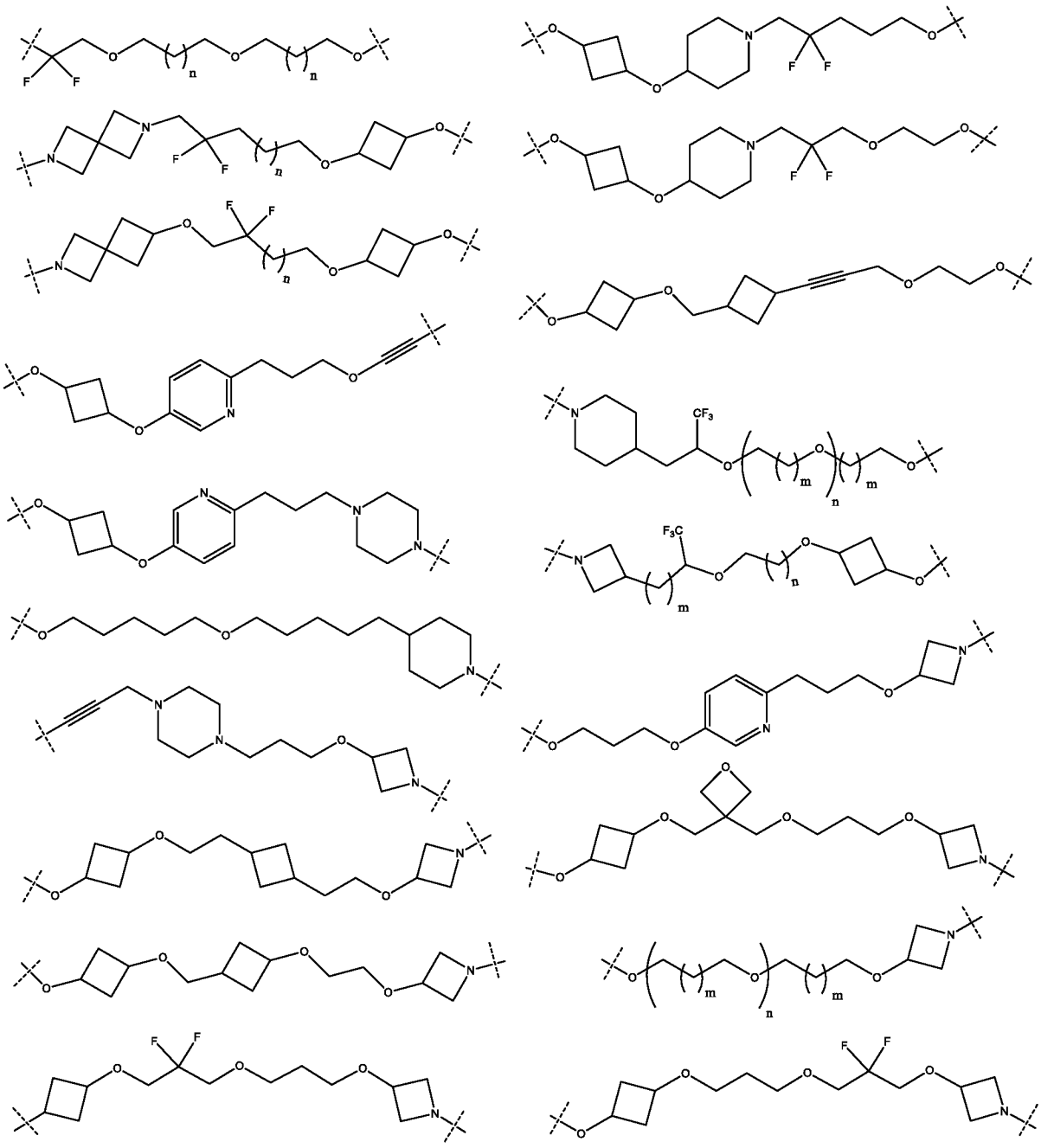


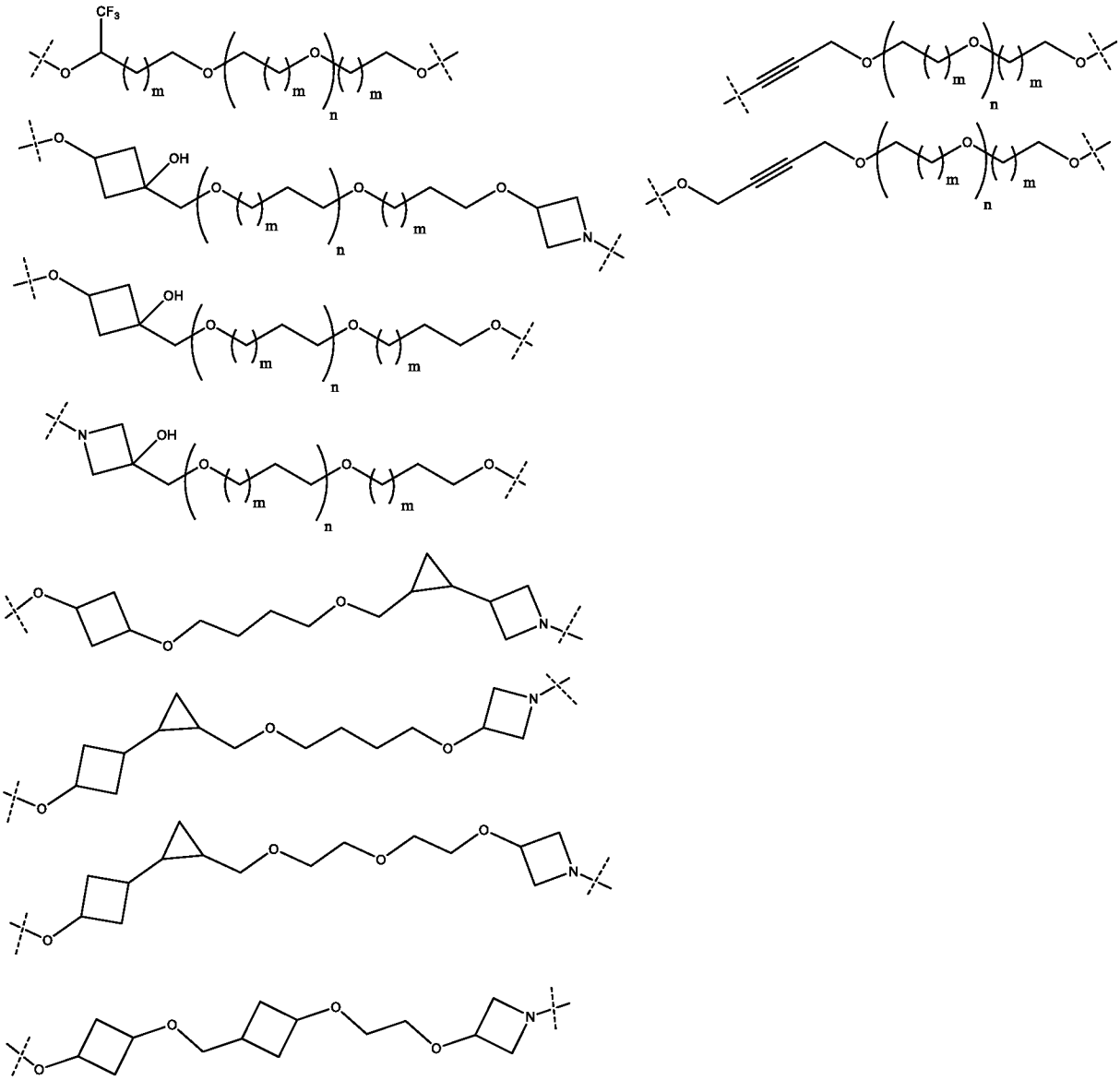


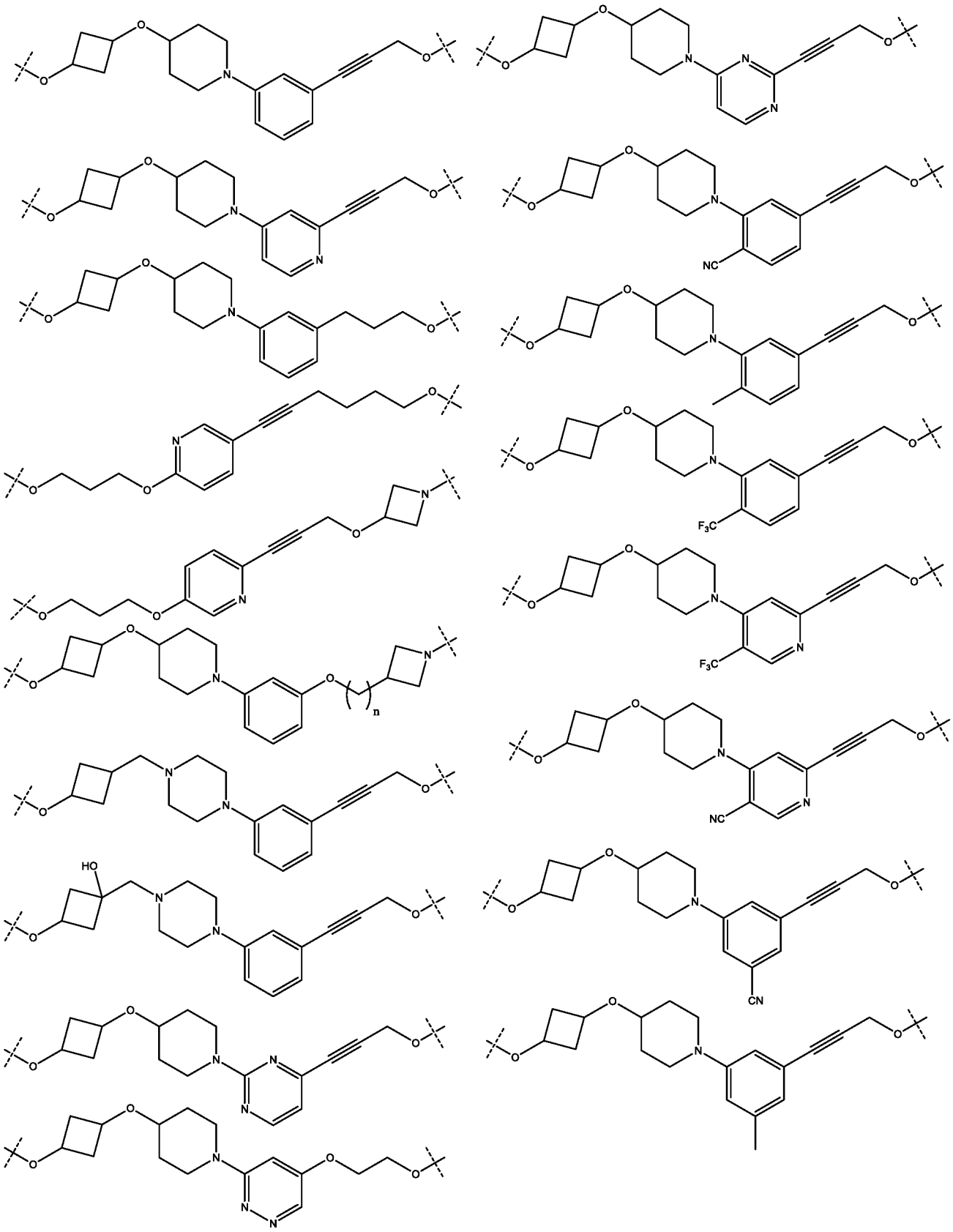


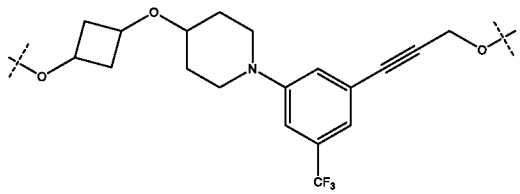
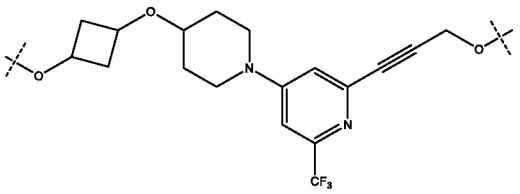
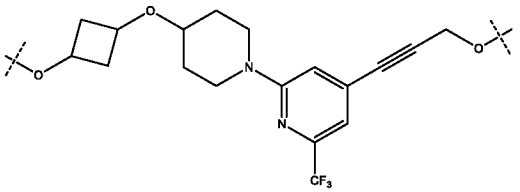


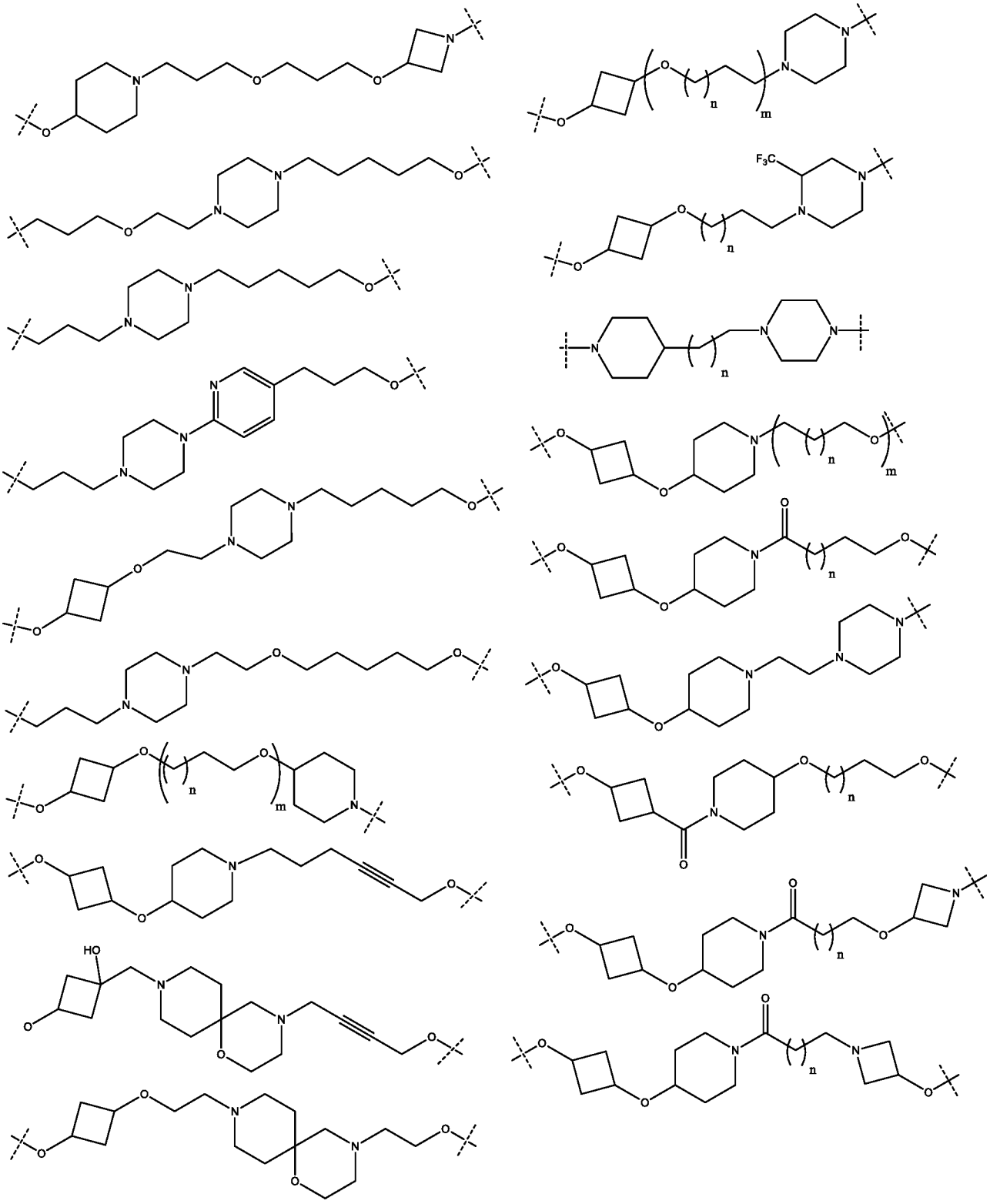


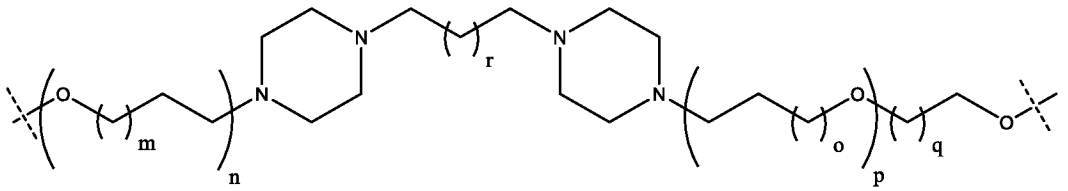


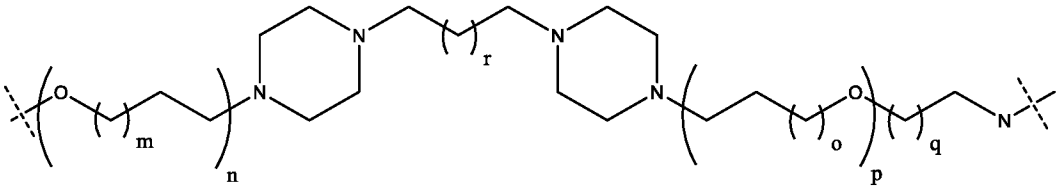


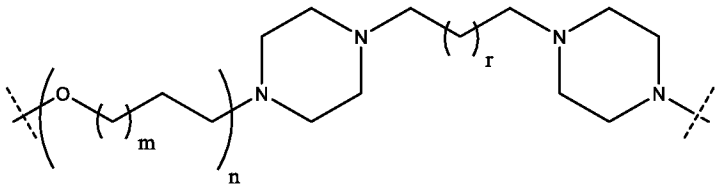


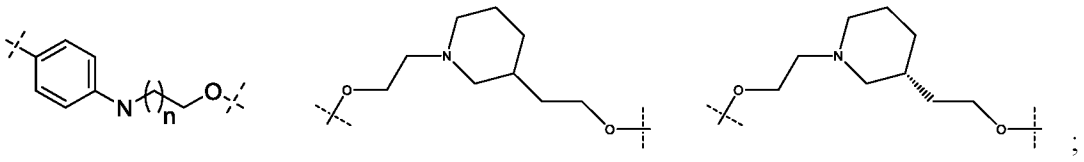




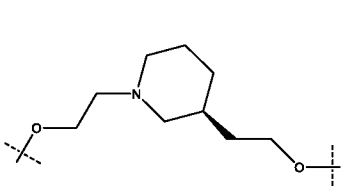


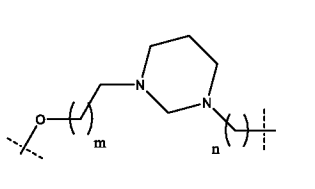


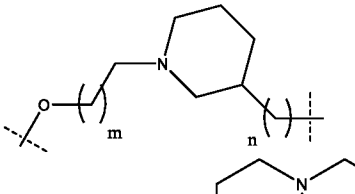


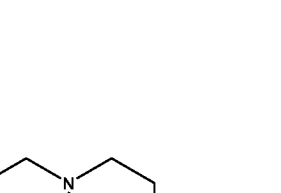


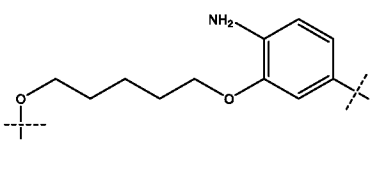


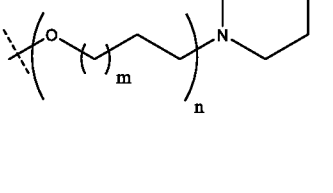


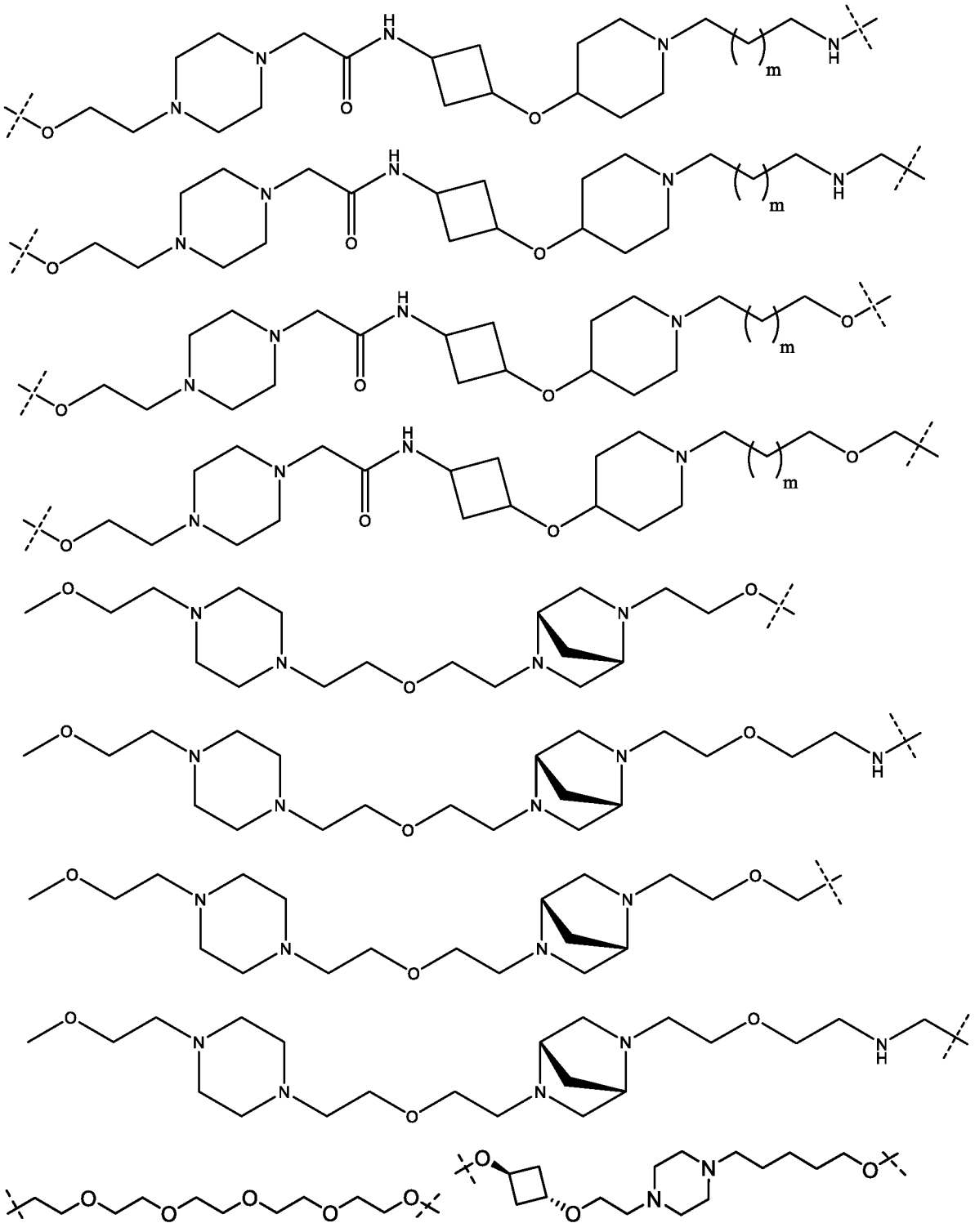


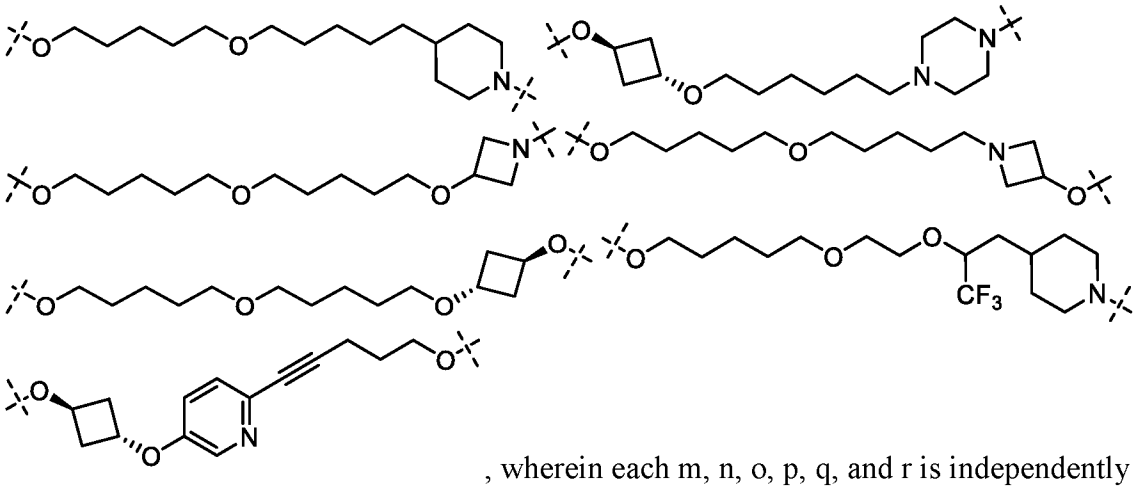






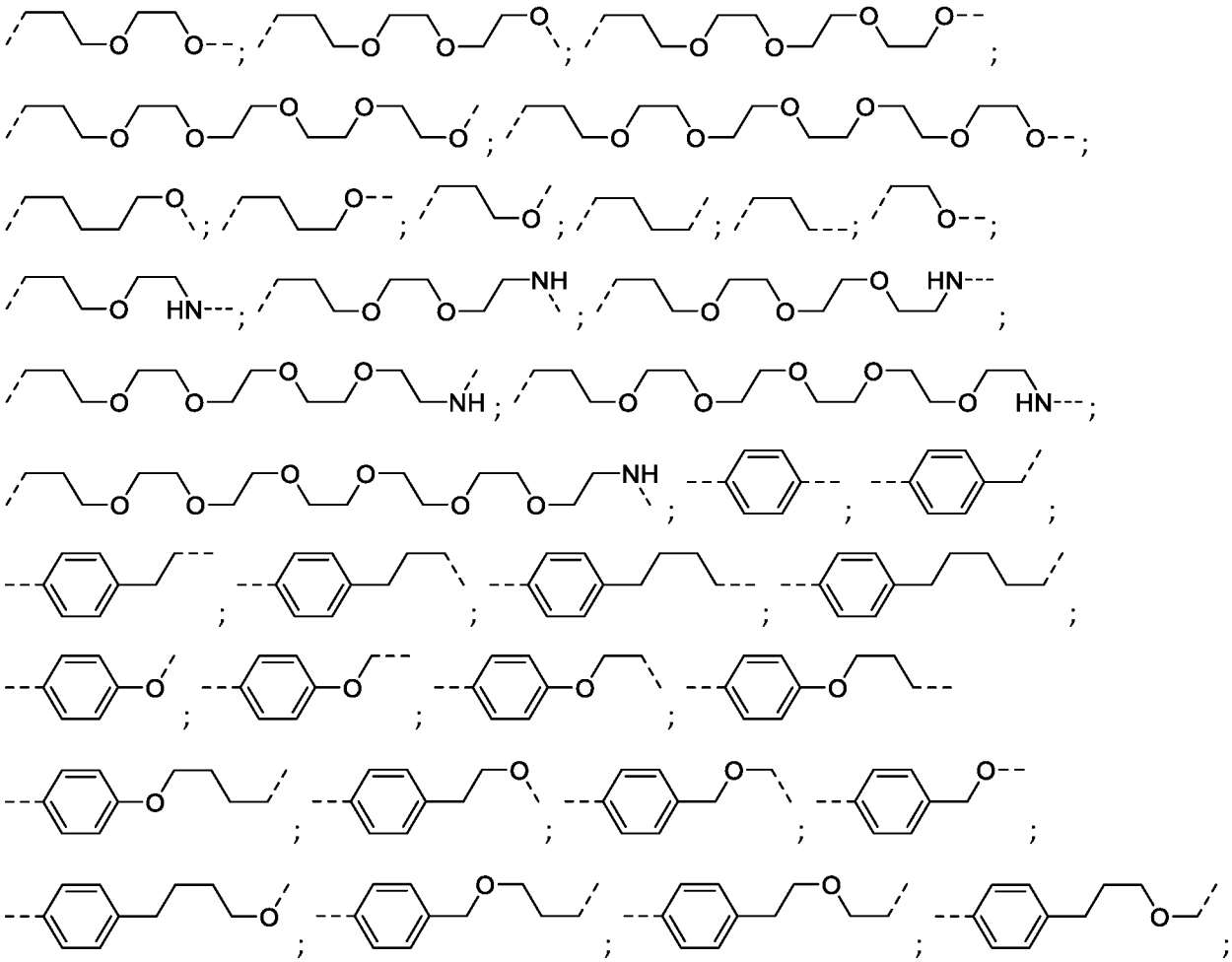


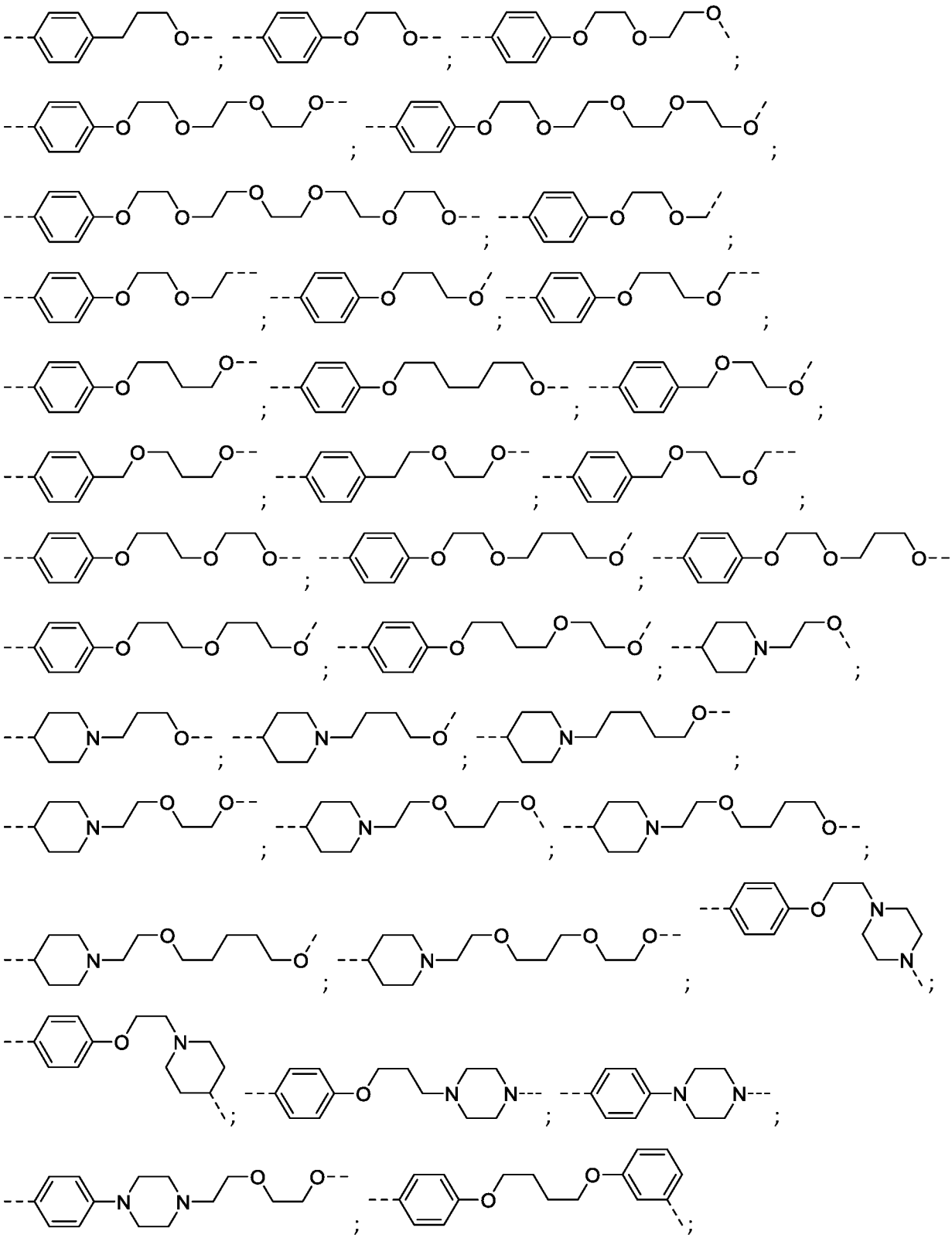


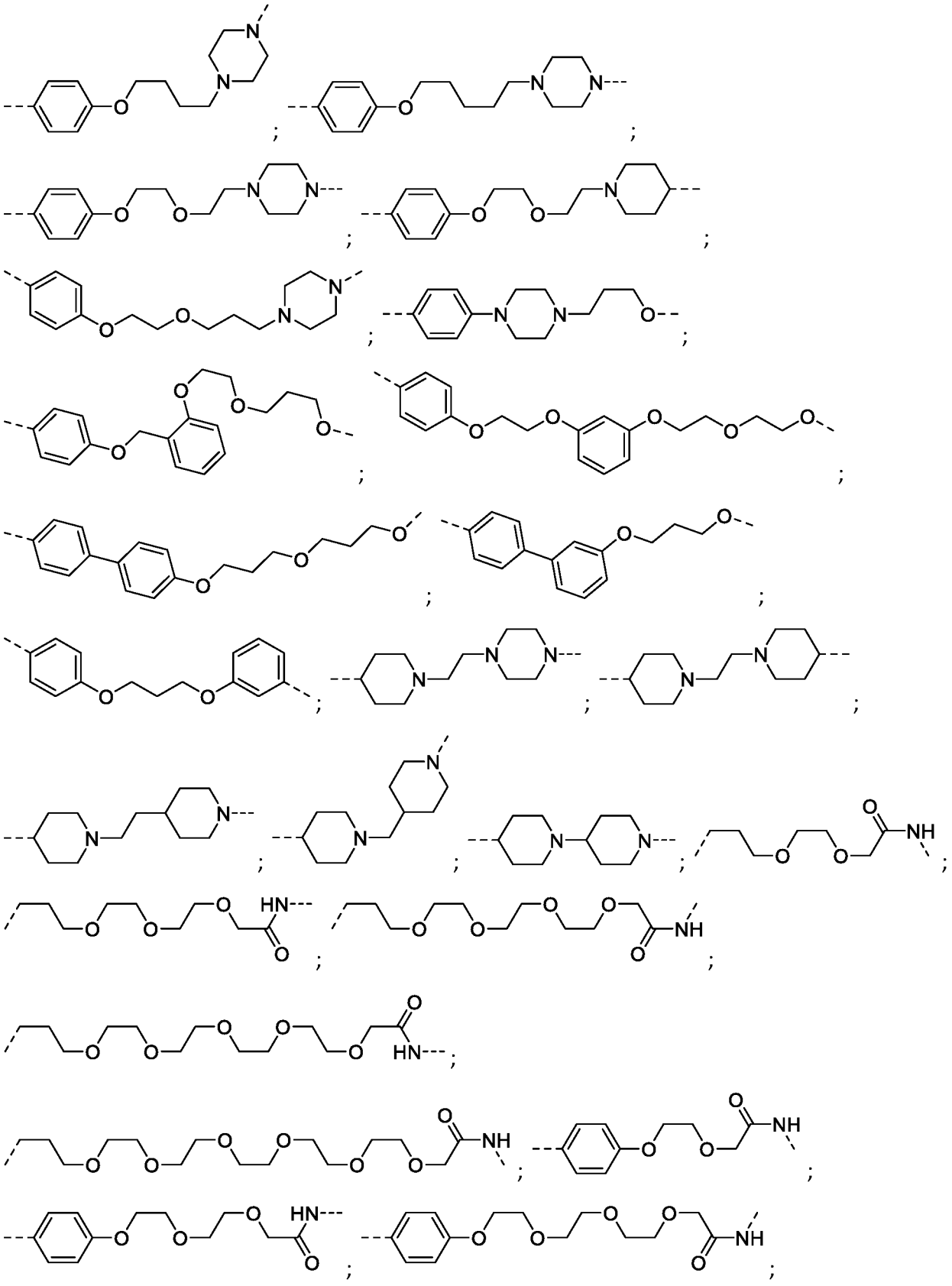


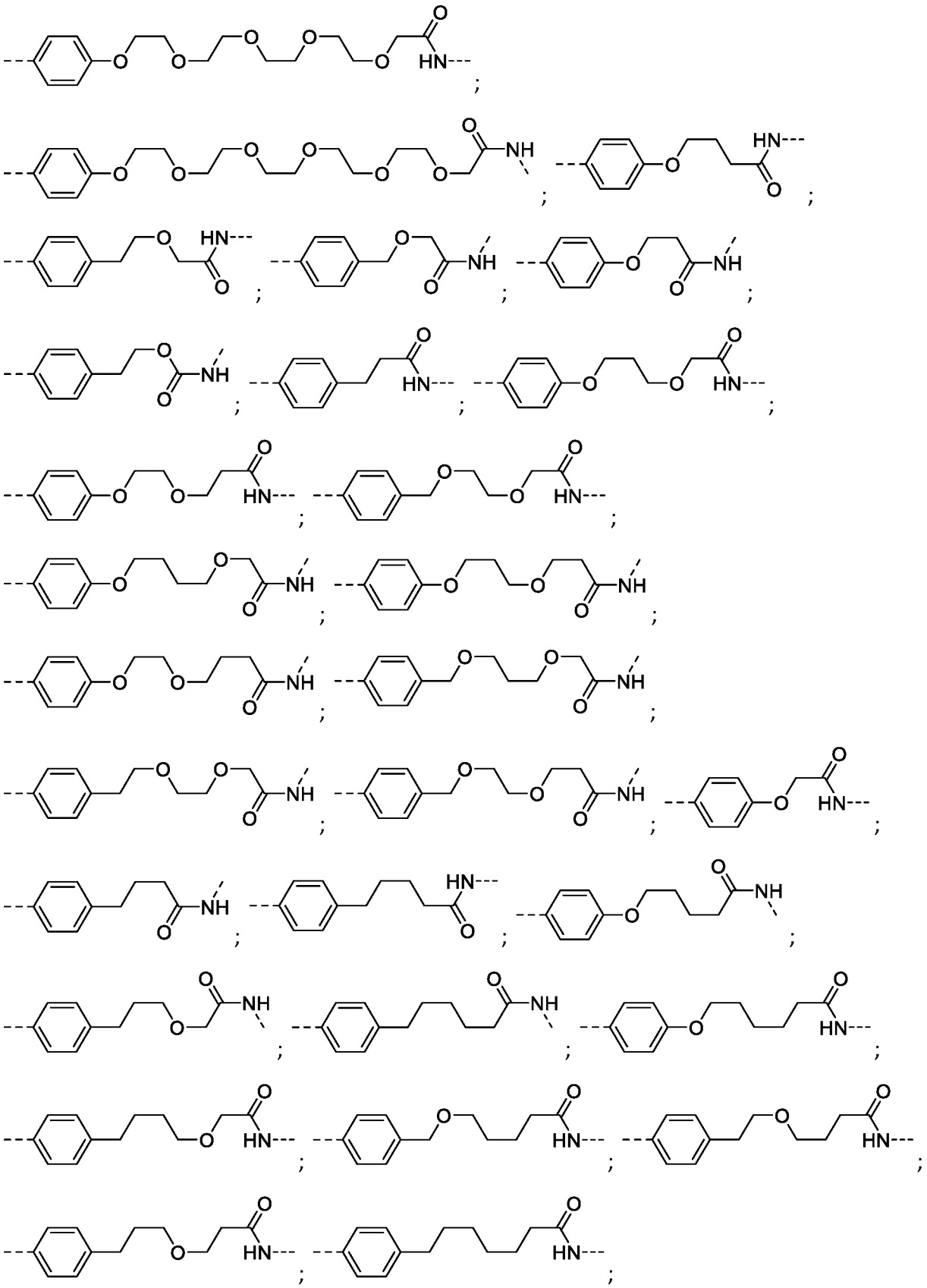
, wherein each m, n, o, p, q, and r is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

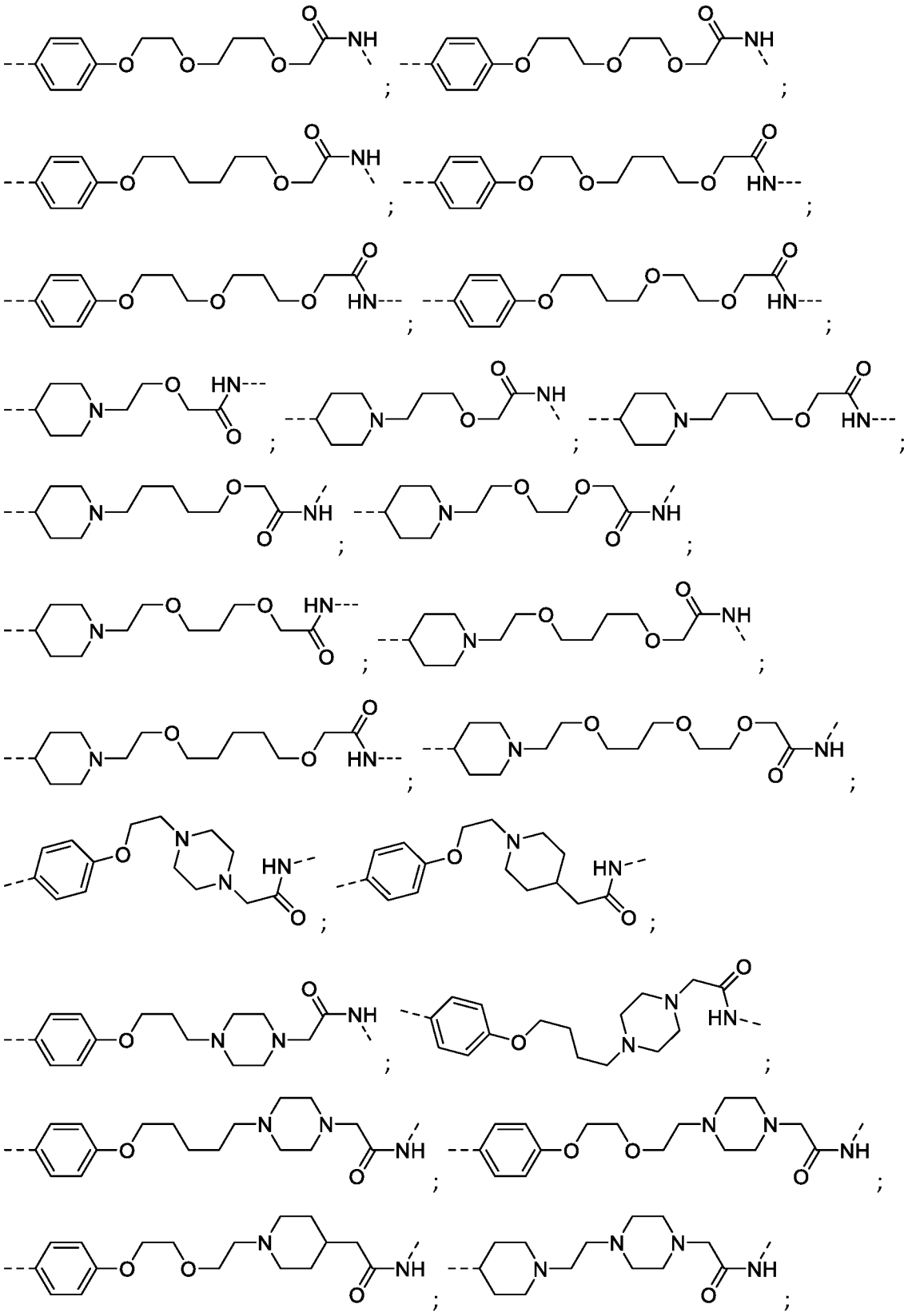
[0100] In any aspect or embodiment described herein, the A^L group is selected from the group consisting of:

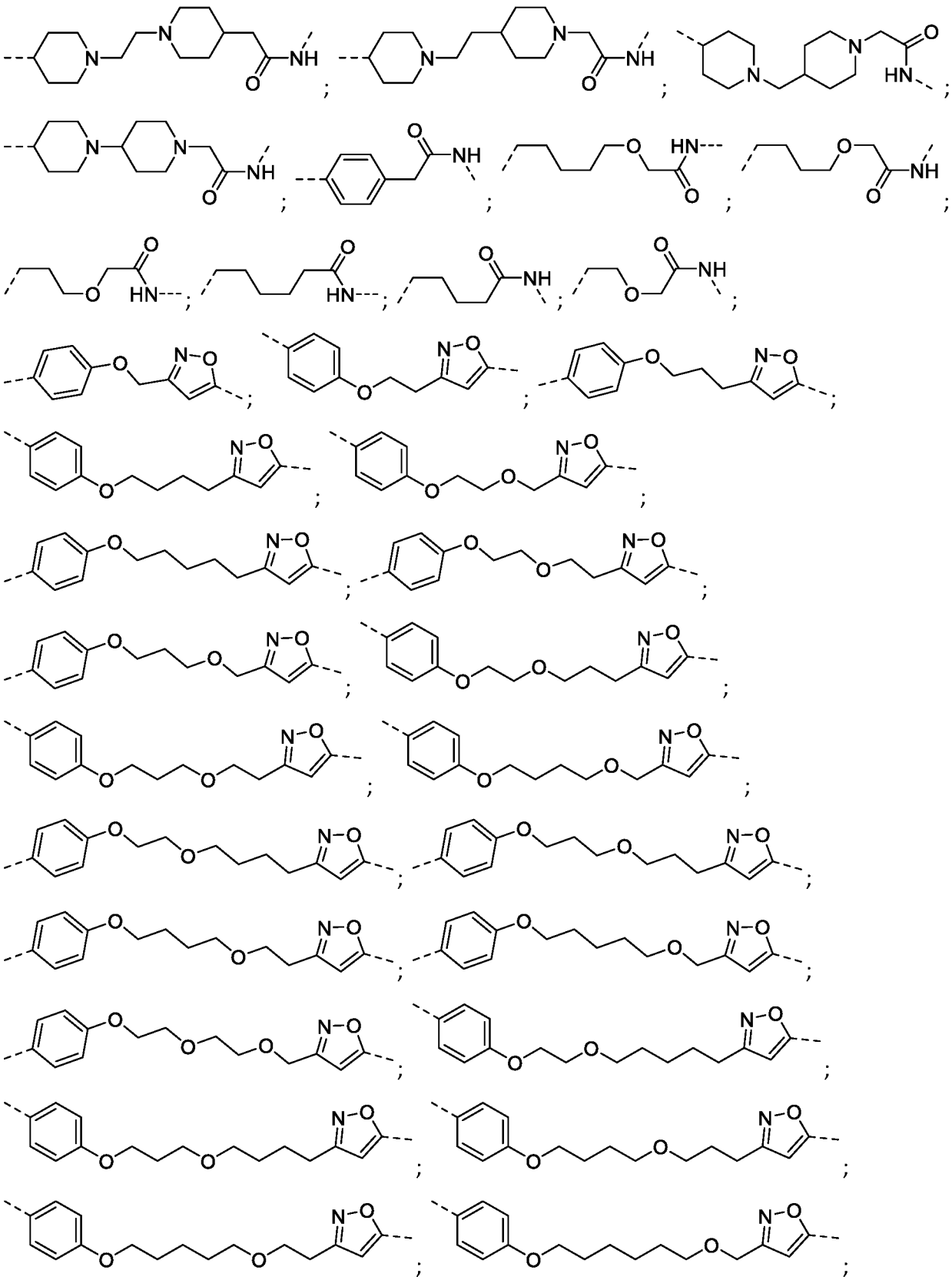


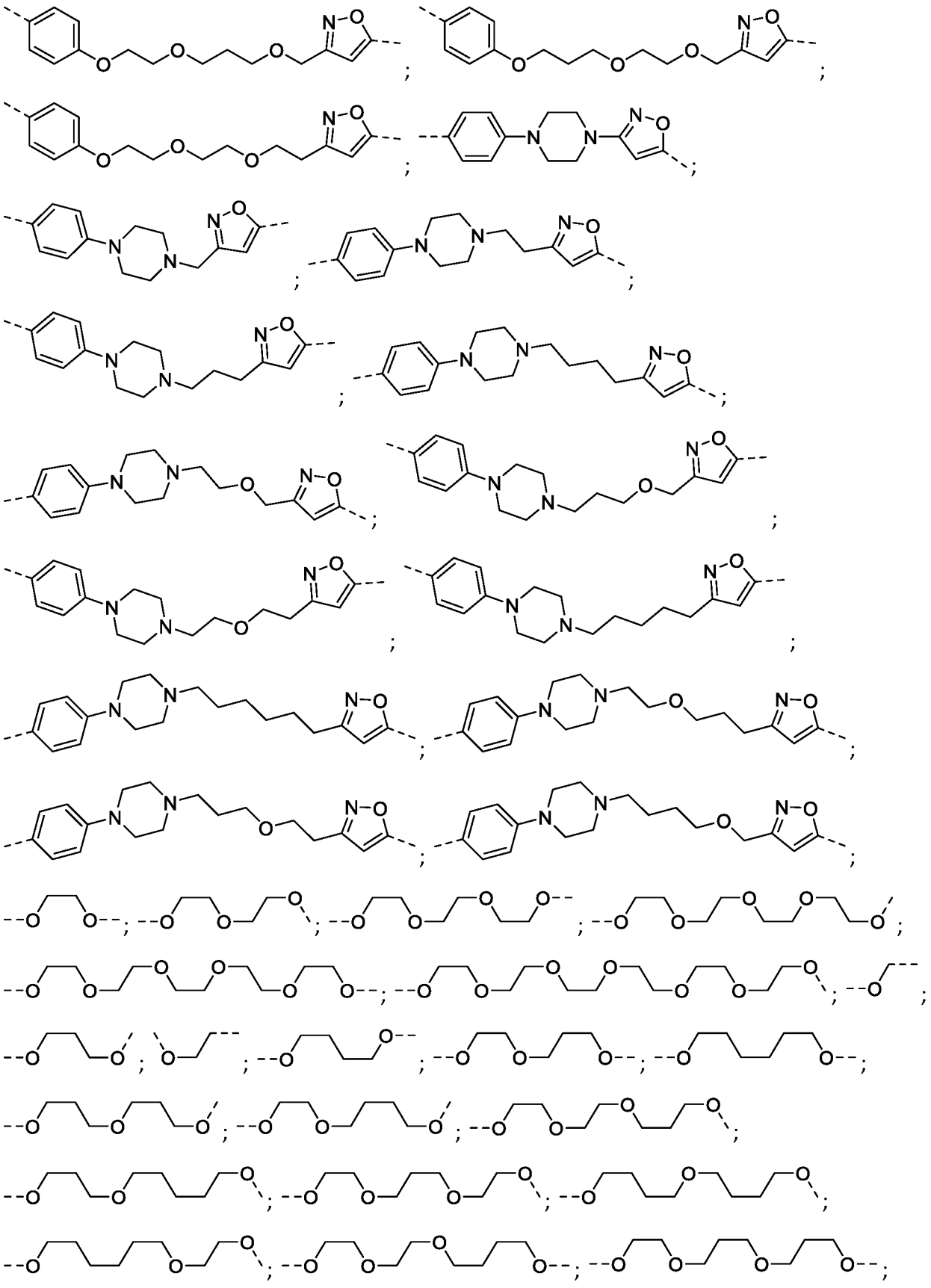


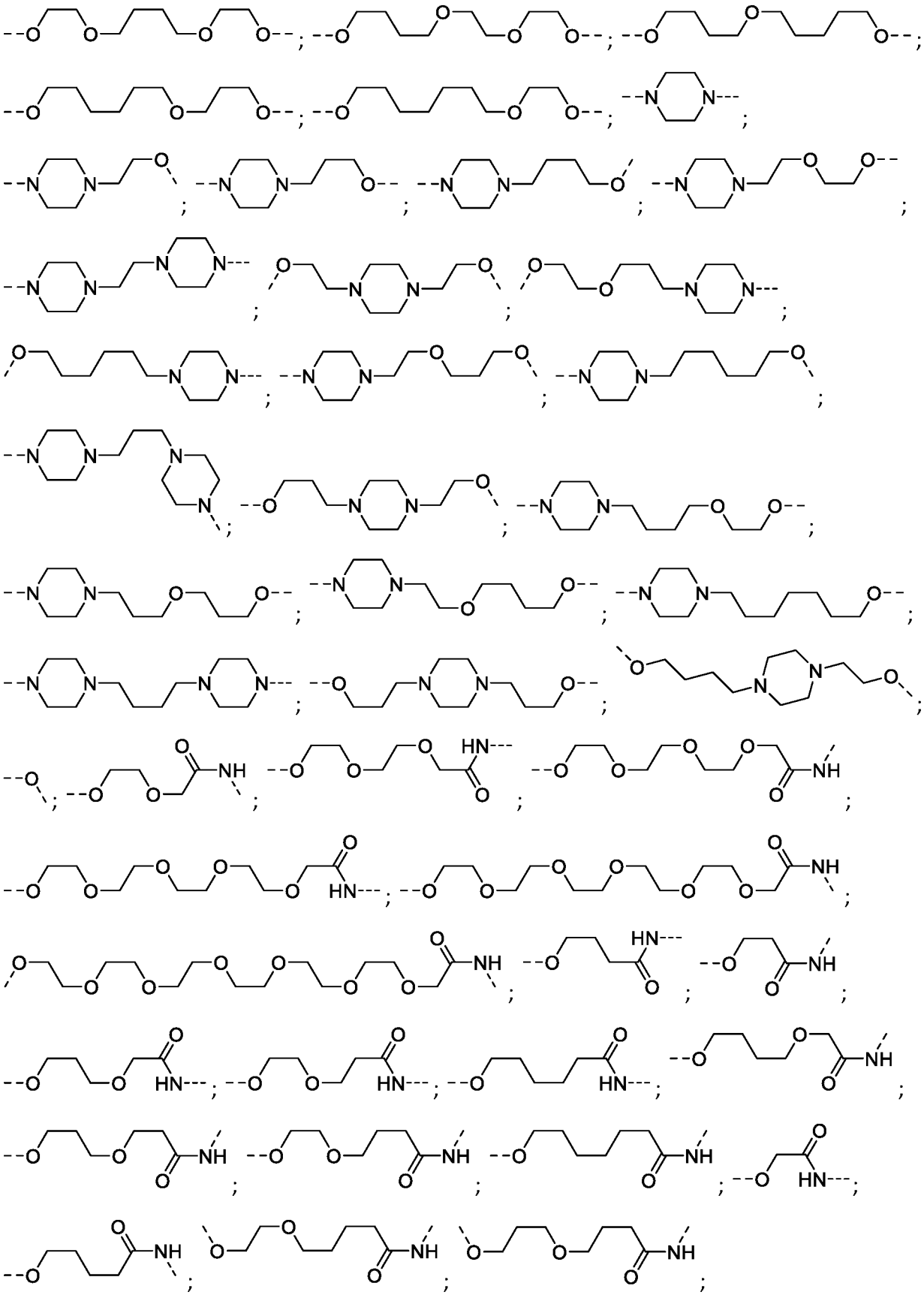


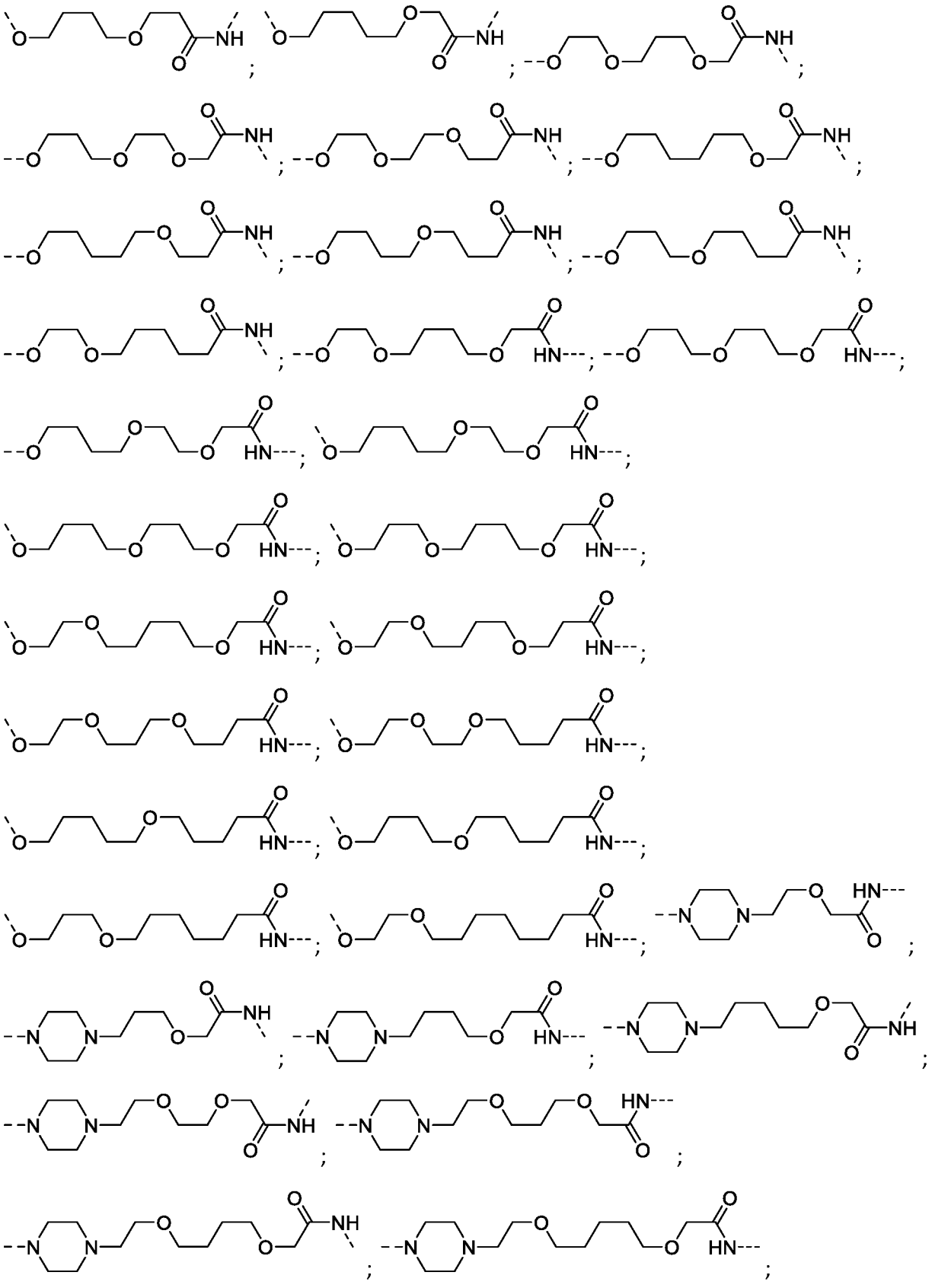


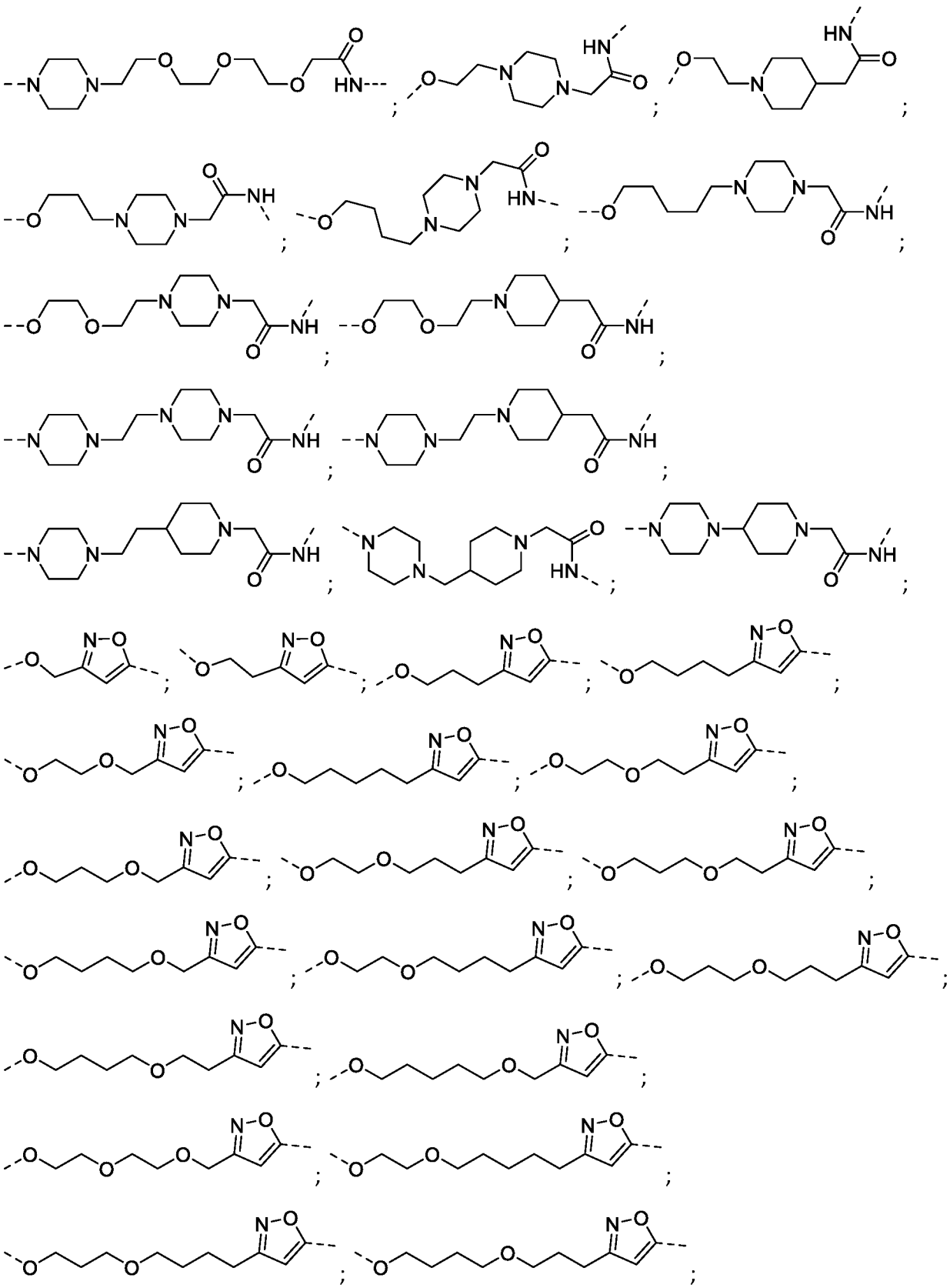


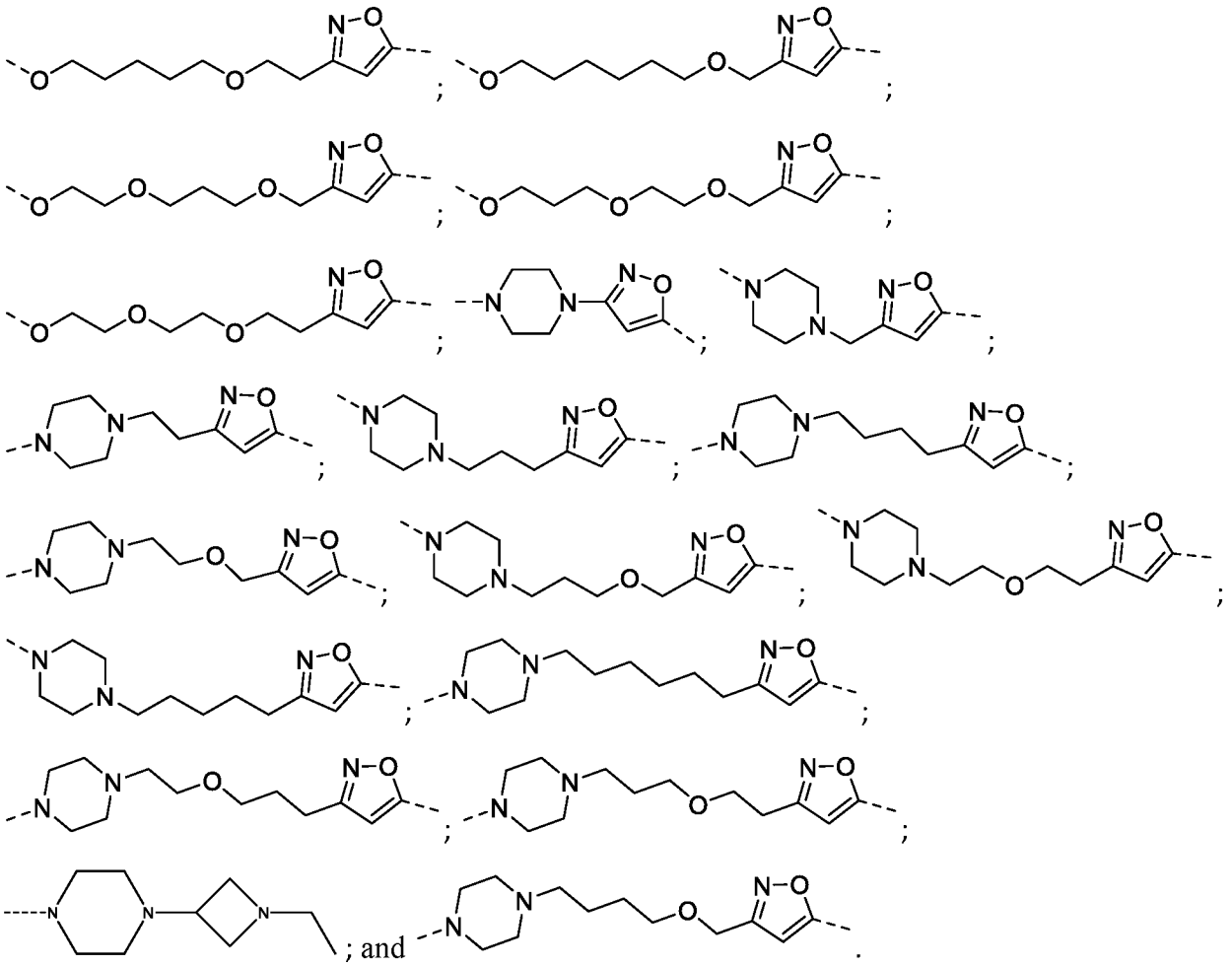




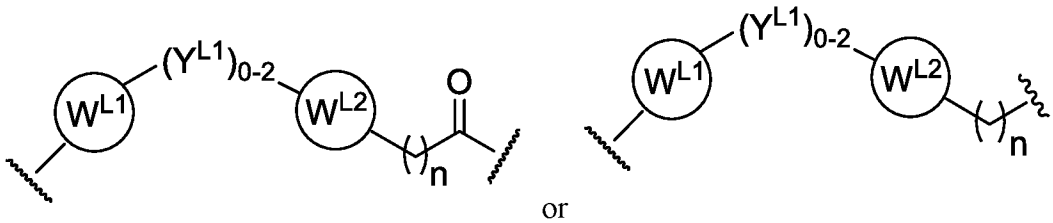








[0101] In additional embodiments, the linker (L) comprises a structure selected from, but not limited to the structure shown below, where a dashed line indicates the attachment point to the PTM or ULM moieties:



wherein:

W^{L1} and W^{L2} are each independently absent, a 4-8 membered ring with 0-4 heteroatoms, optionally substituted with R^Q, each R^Q is independently a H, halo, OH, CN, CF_3, C_1-C_6 alkyl (linear, branched, optionally substituted), C_1-C_6 alkoxy (linear, branched, optionally

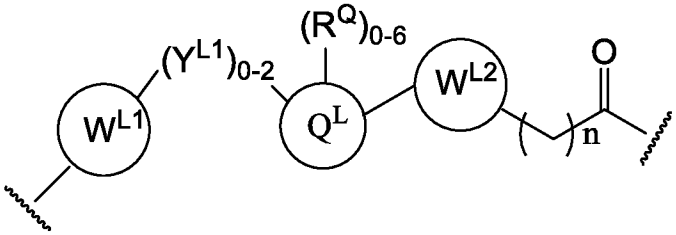
substituted), or 2 R^Q groups taken together with the atom they are attached to, form a 4-8 membered ring system containing 0-4 heteroatoms;

Y^{L1} is each independently a bond, C_1-C_6 alkyl (linear, branched, optionally substituted) and optionally one or more C atoms are replaced with O; or C_1-C_6 alkoxy (linear, branched, optionally substituted);

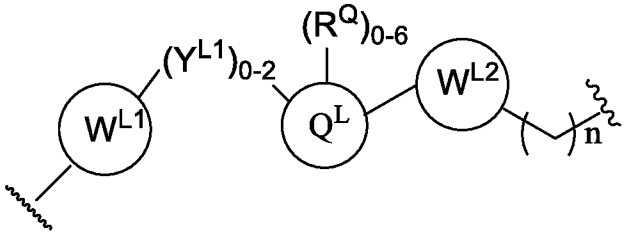
n is 0-10; and

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

[0102] In additional embodiments, the linker (L) comprises a structure selected from, but not limited to the structure shown below, where a dashed line indicates the attachment point to the PTM or ULM moieties:



or



,

wherein:

W^{L1} and W^{L2} are each independently absent, aryl, heteroaryl, cyclic, heterocyclic, C_{1-6} alkyl and optionally one or more C atoms are replaced with O, C_{1-6} alkene and optionally one or more C atoms are replaced with O, C_{1-6} alkyne and optionally one or more C atoms are replaced with O, 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 $\equiv$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.

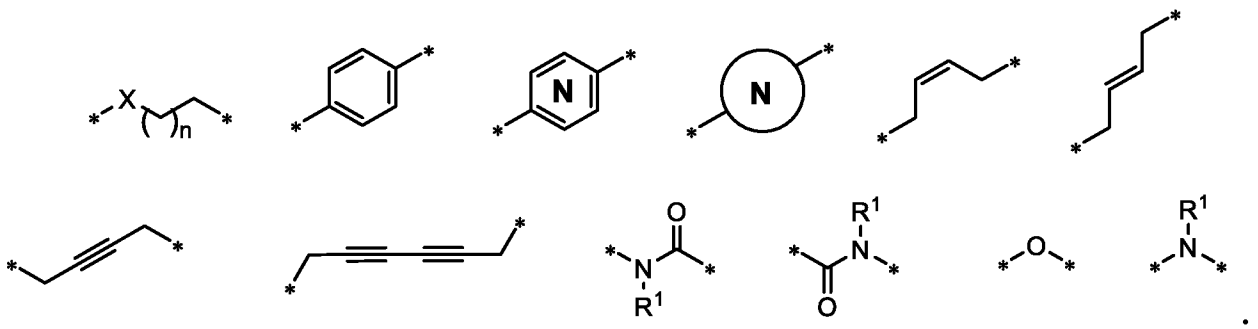
[0103] In additional embodiments, the linker group is optionally substituted (poly)ethyleneglycol having between 1 and about 100 ethylene glycol units, between about 1 and about 50 ethylene glycol units, between 1 and about 25 ethylene glycol units, between about 1 and 10 ethylene glycol units, between 1 and about 8 ethylene glycol units and 1 and 6 ethylene glycol units, between 2 and 4 ethylene glycol units,or optionally substituted alkyl groups interdispersed with optionally substituted, O, N, S, P or Si atoms. In certain embodiments, the linker is substituted with an aryl, phenyl, benzyl, alkyl, alkylene, or heterocycle group. In certain embodiments, the linker may be asymmetric or symmetrical.

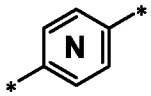
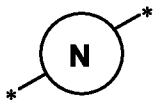
[0104] In any of the embodiments of the compounds described herein, the linker group may be any suitable moiety as described herein. In one embodiment, the linker is a substituted or unsubstituted polyethylene glycol group ranging in size from about 1 to about 12 ethylene glycol units, between 1 and about 10 ethylene glycol units, about 2 about 6 ethylene glycol units, between about 2 and 5 ethylene glycol units, between about 2 and 4 ethylene glycol units.

[0105] In another embodiment, the present disclosure is directed to a compound which comprises a PTM group, which binds to a target protein or polypeptide, which is ubiquitinated by an ubiquitin ligase and is chemically linked directly to the ULM group (such as CLM) or through a linker moiety L, or PTM is alternatively a ULM' group (such as CLM') which is also a ubiquitin ligase binding moiety, which may be the same or different than the ULM group as

described above and is linked directly to the ULM group directly or through the linker moiety; and L is a linker moiety as described above which may be present or absent and which chemically (covalently) links ULM to PTM, or a pharmaceutically acceptable salt, enantiomer, stereoisomer, solvate or polymorph thereof.

[0106] In certain embodiments, the linker group L is a group comprising one or more covalently connected structural units independently selected from the group consisting of:



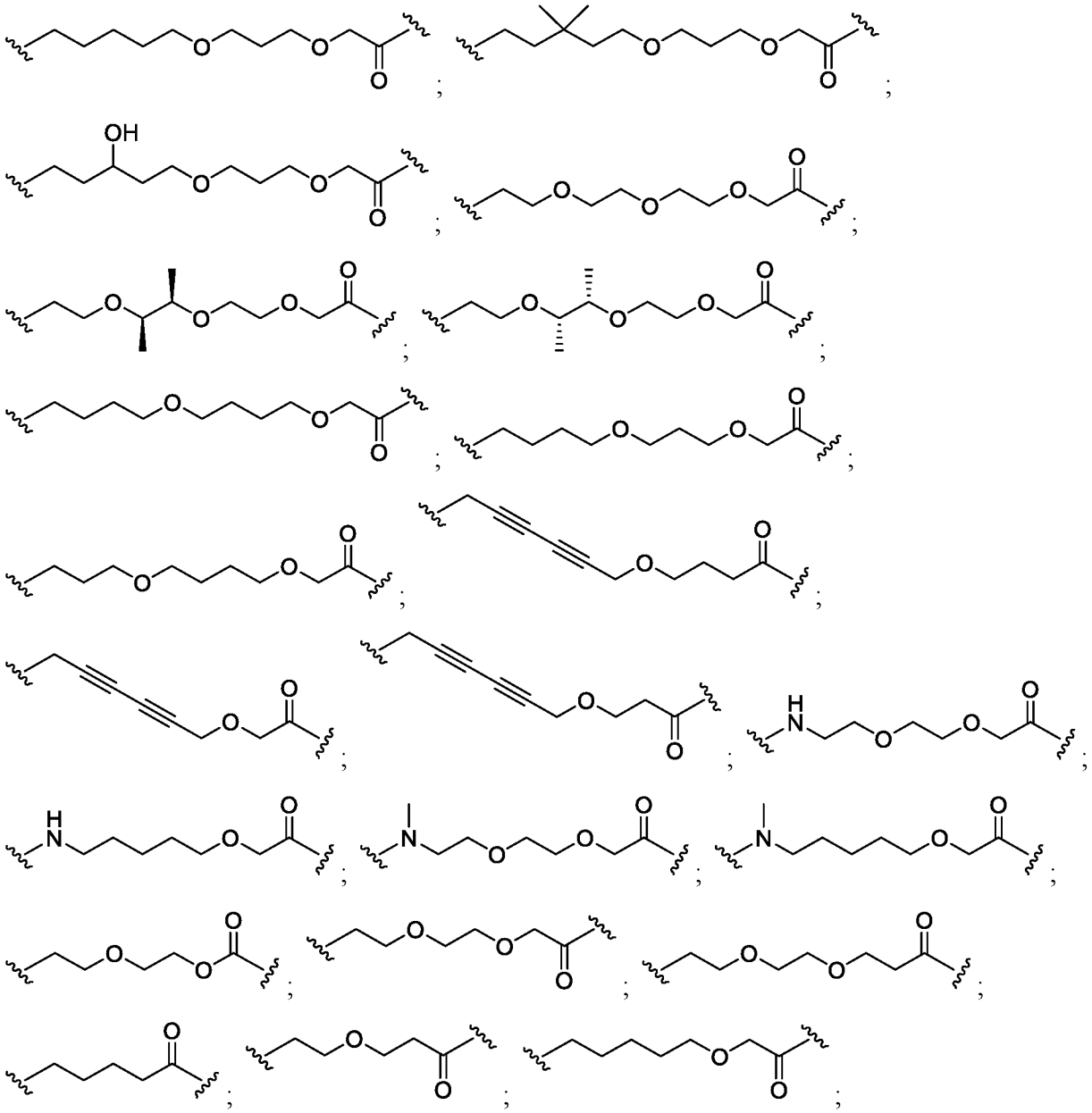
The X is selected from the group consisting of O, N, S, S(O) and SO_2; n is integer from 1 to 5; R^{L1} is hydrogen or alkyl,  is a mono- or bicyclic aryl or heteroaryl optionally substituted with 1–3 substituents selected from alkyl, halogen, haloalkyl, hydroxy, alkoxy or cyano;  is a mono- or bicyclic cycloalkyl or a heterocycloalkyl optionally substituted with 1–3 substituents selected from alkyl, halogen, haloalkyl, hydroxy, alkoxy or cyano; and the phenyl ring fragment can be optionally substituted with 1, 2 or 3 substituents selected from the grou consisting of alkyl, halogen, haloalkyl, hydroxy, alkoxy and cyano. In an embodiment, the linker group L comprises up to 10 covalently connected structural units, as described above.

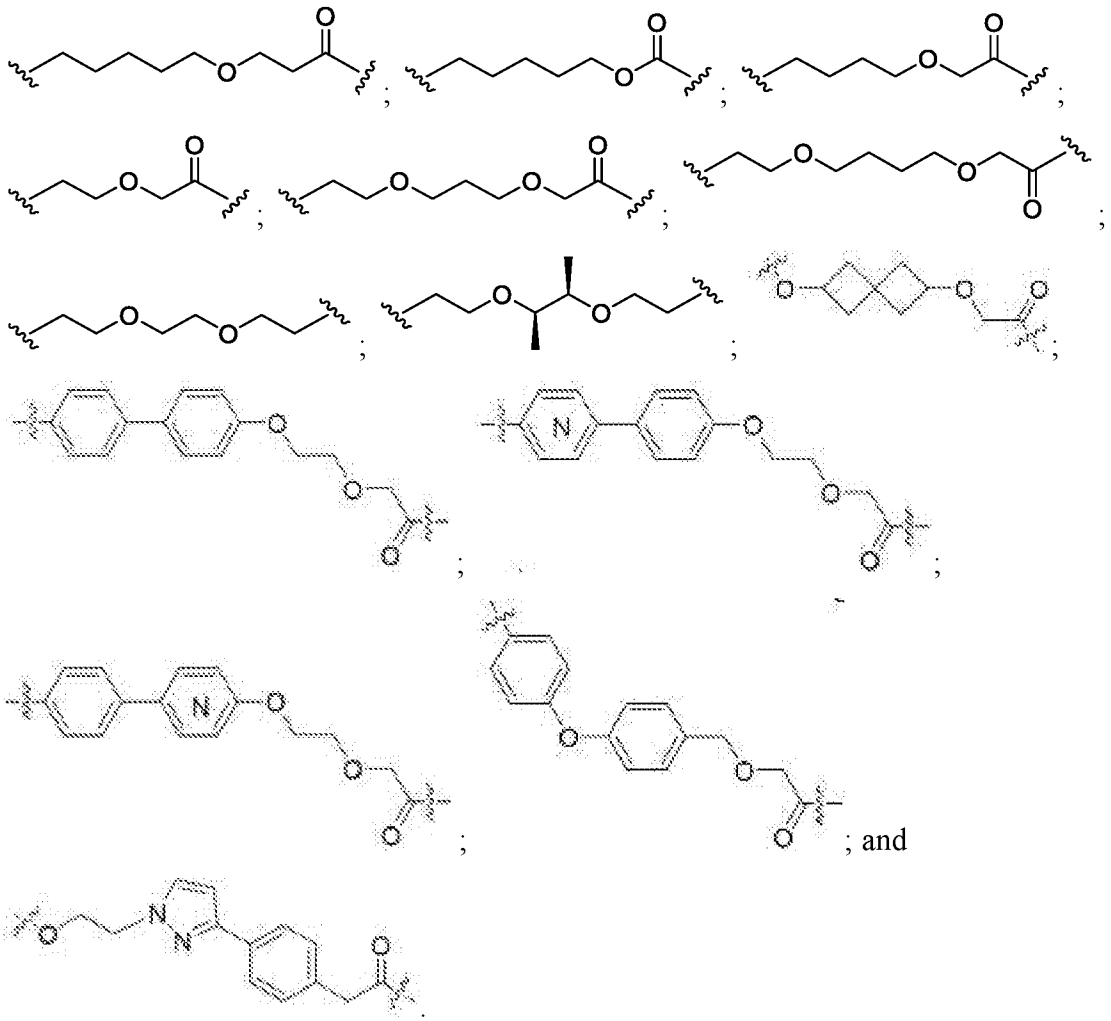
[0107] Although the ULM group and PTM group may be covalently linked to the linker group through any group which is appropriate and stable to the chemistry of the linker, in preferred aspects of the present dislcosure, the linker is independently covalently bonded to the ULM group and the PTM group preferably through an amide, ester, thioester, keto group, carbamate (urethane), carbon or ether, each of which groups may be inserted anywhere on the ULM group and PTM group to provide maximum binding of the ULM group on the ubiquitin ligase and the PTM group on the target protein to be degraded. (It is noted that in certain aspects

where the PTM group is a ULM group, the target protein for degradation may be the ubiquitin ligase itself). In certain preferred aspects, the linker may be linked to an optionally substituted alkyl, alkylene, alkene or alkyne group, an aryl group or a heterocyclic group on the ULM and/or PTM groups.

[0108] In additional embodiments, q is an integer from 1 to 100, 1 to 90, 1 to 80, 1 to 70, 1 to 60, 1 to 50, 1 to 40, 1 to 30, 1 to 20, or 1 to 10.

[0109] In certain embodiments, the linker (L) is selected from the group consisting of:





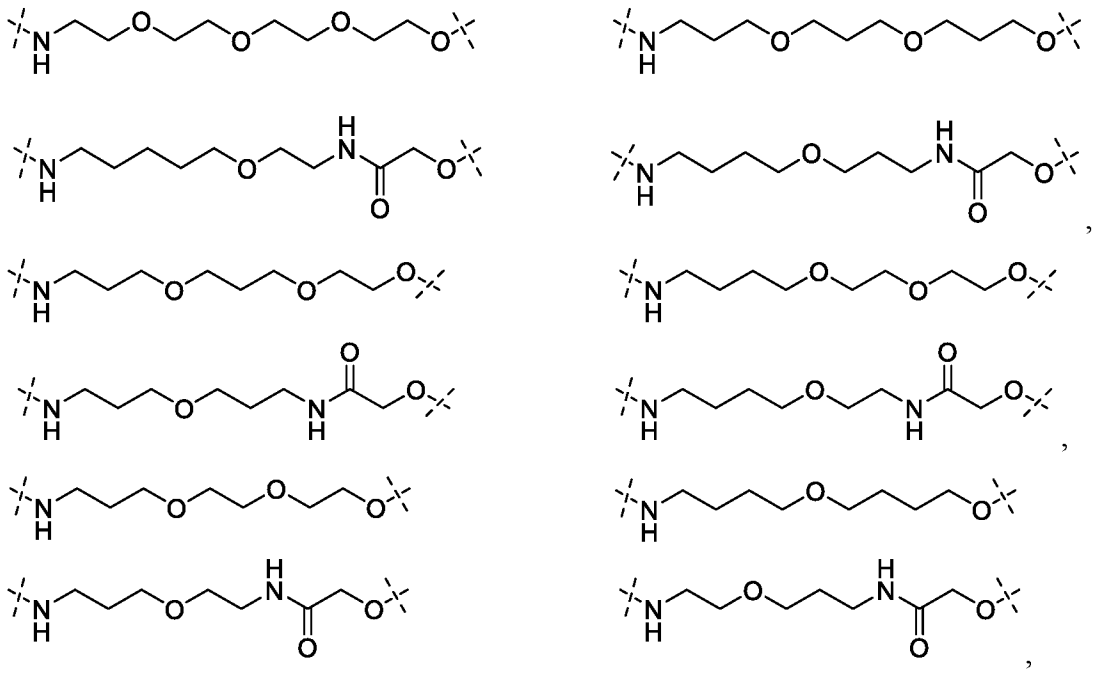
[0110] In additional embodiments, the linker group is optionally substituted (poly)ethyleneglycol having between 1 and about 100 ethylene glycol units, between about 1 and about 50 ethylene glycol units, between 1 and about 25 ethylene glycol units, between about 1 and 10 ethylene glycol units, between 1 and about 8 ethylene glycol units and 1 and 6 ethylene glycol units, between 2 and 4 ethylene glycol units,or optionally substituted alkyl groups interdispersed with optionally substituted, O, N, S, P or Si atoms. In certain embodiments, the linker is substituted with an aryl, phenyl, benzyl, alkyl, alkylene, or heterocycle group. In certain embodiments, the linker may be asymmetric or symmetrical.

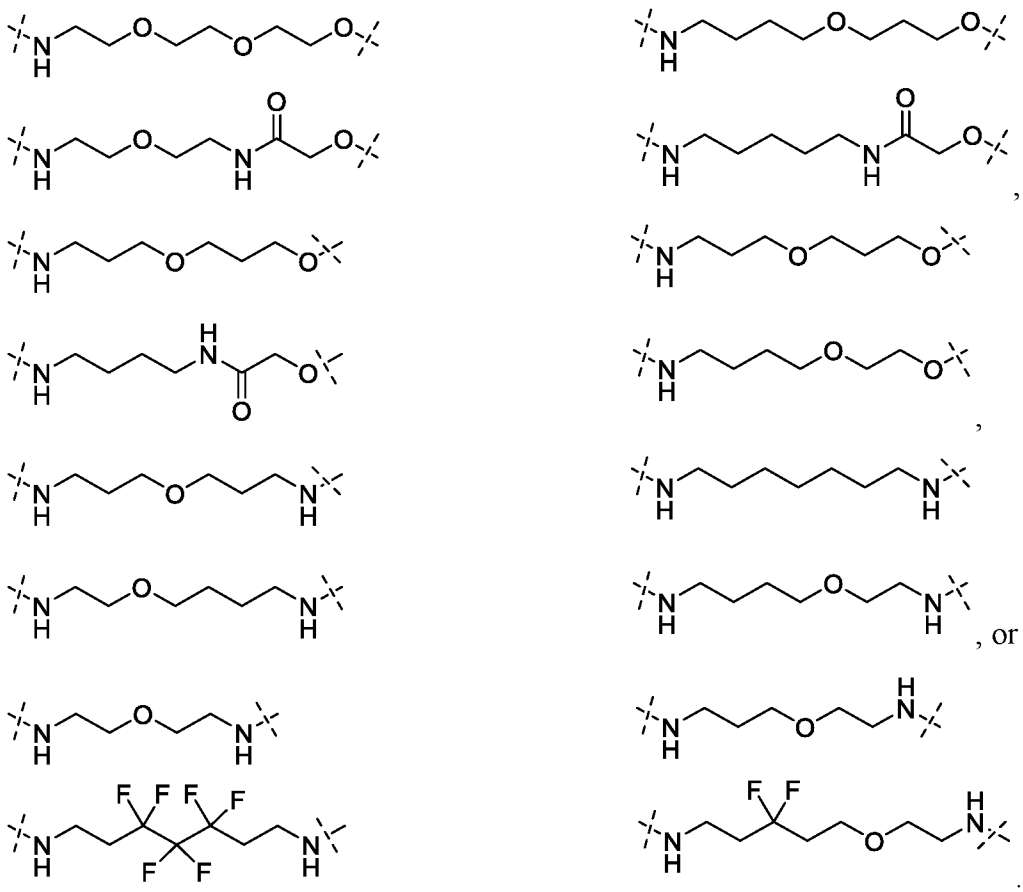
[0111] In any of the embodiments of the compounds described herein, the linker group may be any suitable moiety as described herein. In one embodiment, the linker is a substituted or unsubstituted polyethylene glycol group ranging in size from about 1 to about 12 ethylene glycol

units, between 1 and about 10 ethylene glycol units, about 2 about 6 ethylene glycol units, between about 2 and 5 ethylene glycol units, between about 2 and 4 ethylene glycol units.

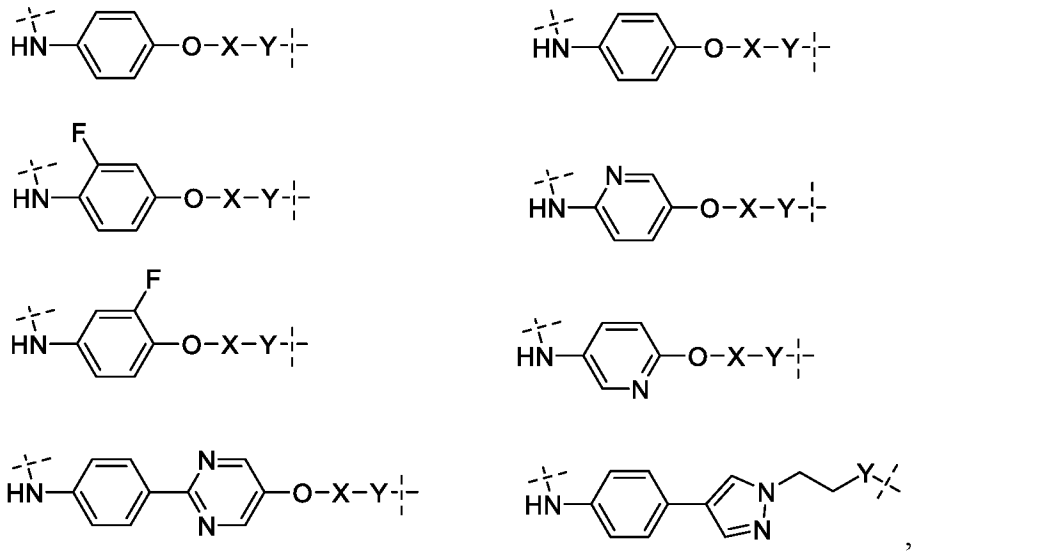
[0112] Although the CLM (or ULM) group and PTM group may be covalently linked to the linker group through any group which is appropriate and stable to the chemistry of the linker, in preferred aspects of the present disclosure, the linker is independently covalently bonded to the CLM group and the PTM group preferably through an amide, ester, thioester, keto group, carbamate (urethane), carbon or ether, each of which groups may be inserted anywhere on the CLM group and PTM group to provide maximum binding of the CLM group on the ubiquitin ligase and the PTM group on the target protein to be degraded. (It is noted that in certain aspects where the PTM group is a ULM group, the target protein for degradation may be the ubiquitin ligase itself). In certain preferred aspects, the linker may be linked to an optionally substituted alkyl, alkylene, alkene or alkyne group, an aryl group or a heterocyclic group on the CLM and/or PTM groups.

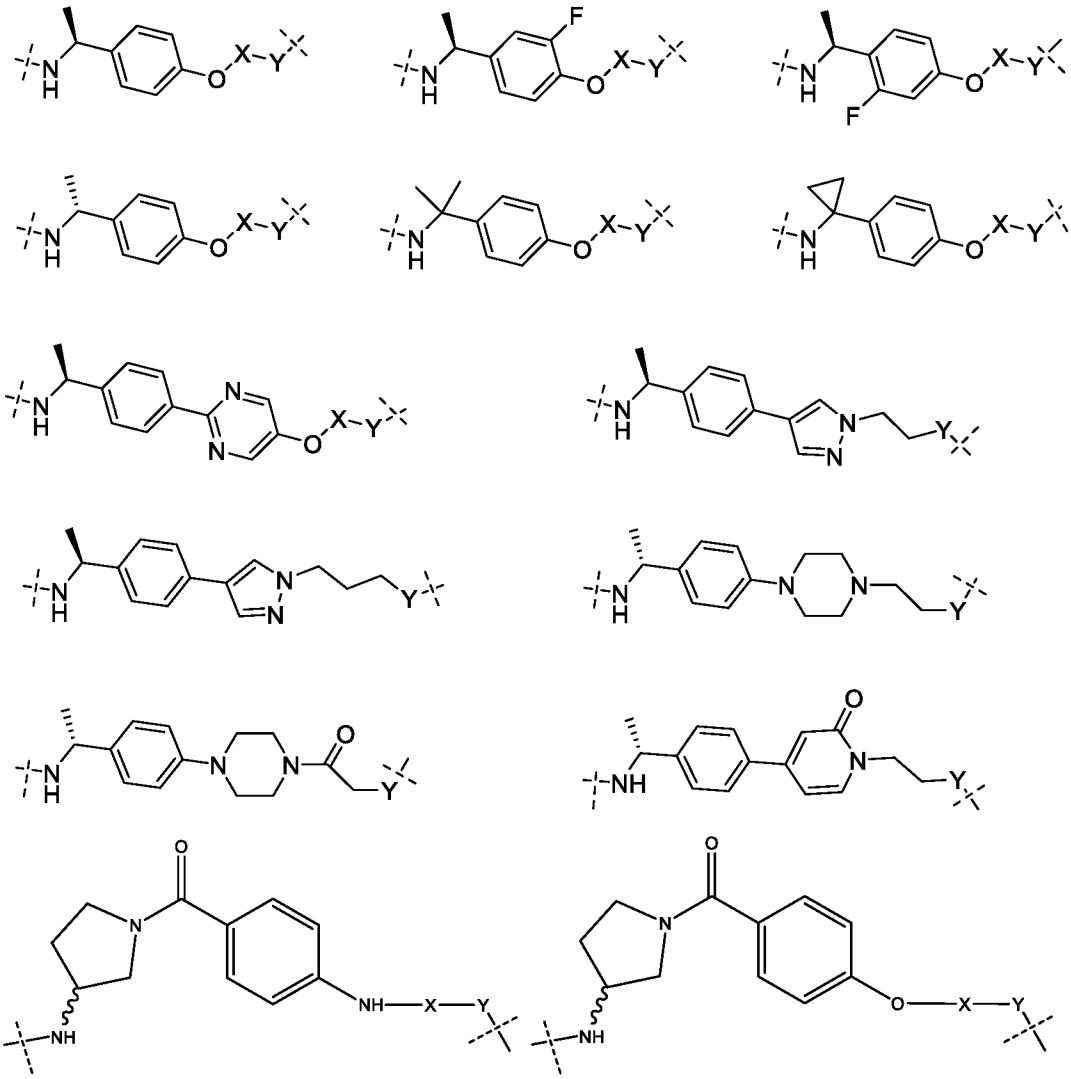
[0113] In certain embodiments, "L" can be linear chains with linear atoms from 4 to 24, the carbon atom in the linear chain can be substituted with oxygen, nitrogen, amide, fluorinated carbon, etc., such as the following:





[0114] In certain embodiments, "L" can be nonlinear chains, and can be aliphatic or aromatic or heteroaromatic cyclic moieties, some examples of "L" include but not be limited to the following:





wherein:

'X" in above structures can be linear chain with atoms ranging from 2 to 14, and the mentioned chain can contain heteroatoms such as oxygen; and

"Y" in above structures can be O, N, $S(O)_n$ (n=0, 1, 2).

[0115] **Exemplary PTMs**

[0116] In preferred aspects of the present disclosure, the PTM group is a group, which binds to target proteins. Targets of the PTM group are numerous in kind and are selected from proteins that are expressed in a cell such that at least a portion of the sequences is found in the cell and may bind to a PTM group. The term "protein" includes oligopeptides and polypeptide sequences of sufficient length that they can bind to a PTM group according to the present disclosure. Any protein in a eukaryotic system or a microbial system, including a virus, bacteria or fungus, as

otherwise described herein, are targets for ubiquitination mediated by the compounds according to the present disclosure. Preferably, the target protein is a eukaryotic protein. In certain aspects, the protein binding moiety is a haloalkane (preferably a C_1-C_{10} alkyl group which is substituted with at least one halo group, preferably a halo group at the distal end of the alkyl group, i.e., away from the linker or CLM group), which may covalently bind to a dehalogenase enzyme in a patient or subject or in a diagnostic assay.

[0117] PTM groups according to the present disclosure include, for example, include any moiety which binds to a protein specifically (binds to a target protein) and includes the following non-limiting examples of small molecule target protein moieties: Hsp90 inhibitors, kinase inhibitors, androgen receptor inhibitors, HDM2 & MDM2 inhibitors, compounds targeting Human BET Bromodomain-containing proteins, HDAC inhibitors, human lysine methyltransferase inhibitors, angiogenesis inhibitors, nuclear hormone receptor compounds, immunosuppressive compounds, and compounds targeting the aryl hydrocarbon receptor (AHR), among numerous others. The compositions described below exemplify some of the members of these nine types of small molecule target protein binding moieties. 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 the ubiquitin ligase binding moiety preferably through a linker in order to present a target protein (to which the protein target moiety is bound) in proximity to the ubiquitin ligase for ubiquitination and degradation.

[0118] Any protein, which can bind to a protein target moiety or PTM group and acted on or degraded by a ubiquitin ligase is a target protein according to the present disclosure. In general, target proteins may include, for example, structural proteins, receptors, enzymes, cell surface proteins, proteins pertinent to the integrated function of a cell, including proteins involved in catalytic activity, aromatase activity, motor activity, helicase activity, metabolic processes (anabolism and catabolism), antioxidant activity, proteolysis, biosynthesis, proteins with kinase activity, oxidoreductase activity, transferase activity, hydrolase activity, lyase activity, isomerase activity, ligase activity, enzyme regulator activity, signal transducer activity, structural molecule activity, binding activity (protein, lipid carbohydrate), receptor activity, cell motility, membrane fusion, cell communication, regulation of biological processes, development, cell differentiation, response to stimulus, behavioral proteins, cell adhesion proteins, proteins involved in cell death,

proteins involved in transport (including protein transporter activity, nuclear transport, ion transporter activity, channel transporter activity, carrier activity, permease activity, secretion activity, electron transporter activity, pathogenesis, chaperone regulator activity, nucleic acid binding activity, transcription regulator activity, extracellular organization and biogenesis activity, translation regulator activity. Proteins of interest can include proteins from eurkaryotes and prokaryotes including humans as targets for drug therapy, other animals, including domesticated animals, microbials for the determination of targets for antibiotics and other antimicrobials and plants, and even viruses, among numerous others.

[0119] In still other embodiments, the PTM group is a haloalkyl group, wherein said alkyl group generally ranges in size from about 1 or 2 carbons to about 12 carbons in length, often about 2 to 10 carbons in length, often about 3 carbons to about 8 carbons in length, more often about 4 carbons to about 6 carbons in length. The haloalkyl groups are generally linear alkyl groups (although branched-chain alkyl groups may also be used) and are end-capped with at least one halogen group, preferably a single halogen group, often a single chloride group. Haloalkyl PT, groups for use in the present disclosure are preferably represented by the chemical structure $-(CH_2)_v$-Halo where v is any integer from 2 to about 12, often about 3 to about 8, more often about 4 to about 6. Halo may be any halogen, but is preferably Cl or Br, more often Cl.

[0120] In another embodiment, the present disclosure provides a library of compounds. The library comprises more than one compound wherein each composition has a formula of A-B, wherein A is a ubiquitin pathway protein binding moiety (preferably, an E3 ubiquitin ligase moiety as otherwise disclosed herein) and B is a protein binding member of a molecular library, wherein A is coupled (preferably, through a linker moiety) to B, and wherein the ubiquitin pathway protein binding moiety recognizes an ubiquitin pathway protein, in particular, an E3 ubiquitin ligase, such as cereblon. In a particular embodiment, the library contains a specific cereblon E3 ubiquitin ligase binding moiety bound to random target protein binding elements (e.g., a chemical compound library). As such, the target protein is not determined in advance and the method can be used to determine the activity of a putative protein binding element and its pharmacological value as a target upon degradation by ubiquitin ligase.

[0121] The present disclosure may be used to treat a number of disease states and/or conditions, including any disease state and/or condition in which proteins are dysregulated and where a patient would benefit from the degradation of proteins.

[0122] 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, additive or excipient, and optionally an additional bioactive agent. 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., cancer (such as prostate cancer) and Kennedy's Disease. In certain additional embodiments, the disease is prostate cancer.

[0123] In alternative aspects, the present disclosure relates to a method for treating a disease state or ameliorating the symptoms of a disease or condition in a subject in need thereof 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, e.g., a therapeutically effective amount, of at least one compound as described hereinabove, optionally in combination with a pharmaceutically acceptable carrier, additive or excipient, and optionally an additional bioactive agent, wherein the composition is effective for treating or ameliorating the disease or disorder or symptom thereof in the subject. The method according to the present disclosure may be used to treat a large number of disease states or conditions including cancer, by virtue of the administration of effective amounts of at least one compound described herein. 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, which leads to a disease state and/or condition.

[0124] In another 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.

[0125] 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 CLM or ULM groups through linker groups L.

[0126] Target proteins which may be bound to the protein target moiety and degraded by the ligase to which the ubiquitin ligase binding moiety is bound include any protein or peptide, including fragments thereof, analogues thereof, and/or homologues thereof. Target proteins include proteins and peptides having any biological function or activity including structural, regulatory, hormonal, enzymatic, genetic, immunological, contractile, storage, transportation, and signal transduction. In certain embodiments, the target proteins include structural proteins, receptors, enzymes, cell surface proteins, proteins pertinent to the integrated function of a cell, including proteins involved in catalytic activity, aromatase activity, motor activity, helicase activity, metabolic processes (anabolism and catabolism), antioxidant activity, proteolysis, biosynthesis, proteins with kinase activity, oxidoreductase activity, transferase activity, hydrolase activity, lyase activity, isomerase activity, ligase activity, enzyme regulator activity, signal transducer activity, structural molecule activity, binding activity (protein, lipid carbohydrate), receptor activity, cell motility, membrane fusion, cell communication, regulation of biological processes, development, cell differentiation, response to stimulus, behavioral proteins, cell adhesion proteins, proteins involved in cell death, proteins involved in transport (including protein transporter activity, nuclear transport, ion transporter activity, channel transporter activity, carrier activity, permease activity, secretion activity, electron transporter activity, pathogenesis, chaperone regulator activity, nucleic acid binding activity, transcription regulator activity, extracellular organization and biogenesis activity, translation regulator activity. Proteins of interest can include proteins from eukaryotes and prokaryotes, including microbes, viruses, fungi and parasites, including humans, microbes, viruses, fungi and parasites, among numerous others, as targets for drug therapy, other animals, including domesticated animals, microbials for the determination of targets for antibiotics and other antimicrobials and plants, and even viruses, among numerous others.

[0127] More specifically, a number of drug targets for human therapeutics represent protein targets to which protein target moiety may be bound and incorporated into compounds according to the present disclosure. These include proteins which may be used to restore function in numerous polygenic diseases, including for example B7.1 and B7, TINFRlm, TNFR2, NADPH oxidase, BclIBax and other partners in the apotosis pathway, C5a receptor, HMG-CoA reductase,

PDE V phosphodiesterase type, PDE IV phosphodiesterase type 4, PDE I, PDEII, PDEIII, squalene cyclase inhibitor, CXCR1, CXCR2, nitric oxide (NO) synthase, cyclo-oxygenase 1, cyclo-oxygenase 2, 5HT receptors, dopamine receptors, G Proteins, i.e., Gq, histamine receptors, 5-lipoxygenase, tryptase serine protease, thymidylate synthase, purine nucleoside phosphorylase, GAPDH trypanosomal, glycogen phosphorylase, Carbonic anhydrase, chemokine receptors, JAW STAT, RXR and similar, HIV 1 protease, HIV 1 integrase, influenza, neuramimidase, hepatitis B reverse transcriptase, sodium channel, multi drug resistance (MDR), protein P-glycoprotein (and MRP), tyrosine kinases, CD23, CD124, tyrosine kinase p56 lck, CD4, CD5, IL-2 receptor, IL-1 receptor, TNF-alphaR, ICAM1, Cat+ channels, VCAM, VLA-4 integrin, selectins, CD40/CD40L, newokinins and receptors, inosine monophosphate dehydrogenase, p38 MAP Kinase, RaslRaflMEWERK pathway, interleukin-1 converting enzyme, caspase, HCV, NS3 protease, HCV NS3 RNA helicase, glycinamide ribonucleotide formyl transferase, rhinovirus 3C protease, herpes simplex virus-1 (HSV-I), protease, cytomegalovirus (CMV) protease, poly (ADP-ribose) polymerase, cyclin dependent kinases, vascular endothelial growth factor, oxytocin receptor, microsomal transfer protein inhibitor, bile acid transport inhibitor, 5 alpha reductase inhibitors, angiotensin 11, glycine receptor, noradrenaline reuptake receptor, endothelin receptors, neuropeptide Y and receptor, estrogen receptors, androgen receptors (AR), adenosine receptors, adenosine kinase and AMP deaminase, purinergic receptors (P2Y1, P2Y2, P2Y4, P2Y6, P2X1-7), farnesyltransferases, geranylgeranyl transferase, TrkA a receptor for NGF, beta-amyloid, tyrosine kinase Flk-IIKDR, vitronectin receptor, integrin receptor, Her-21 neu, telomerase inhibition, cytosolic phospholipaseA2 and EGF receptor tyrosine kinase. Additional protein targets include, for example, ecdysone 20-monooxygenase, ion channel of the GABA gated chloride channel, acetylcholinesterase, voltage-sensitive sodium channel protein, calcium release channel, and chloride channels. Still further target proteins include Acetyl-CoA carboxylase, adenylosuccinate synthetase, protoporphyrinogen oxidase, and enolpyruvylshikimate-phosphate synthase.

[0128] Haloalkane dehalogenase enzymes are another target of specific compounds according to the present disclosure. Compounds according to the present disclosure which contain chloroalkane peptide binding moieties (C_1-C_{12} often about C_2-C_{10} alkyl halo groups) may be used to inhibit and/or degrade haloalkane dehalogenase enzymes which are used in fusion proteins or related dioagnostic proteins as described in PCT/US2012/063401 filed December 6,

2011 and published as WO 2012/078559 on June 14, 2012, the contents of which is incorporated by reference herein.

[0129] These various protein targets 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.

[0130] 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 Hsp90 inhibitors, kinase inhibitors, MDM2 inhibitors, compounds targeting Human BET Bromodomain-containing proteins, HDAC inhibitors, human lysine methyltransferase inhibitors, angiogenesis inhibitors, immunosuppressive compounds, and compounds targeting the aryl hydrocarbon receptor (AHR), among numerous others. The compositions described below exemplify some of the members of these nine types of small molecule target protein.

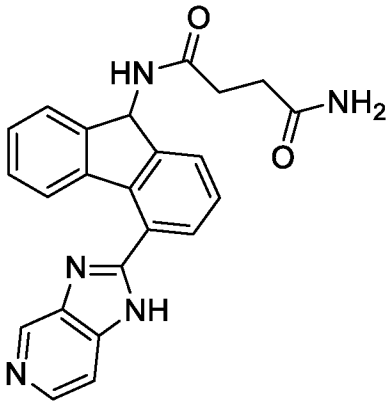
[0131] Exemplary protein target moieties according to the present disclosure include, haloalkane halogenase inhibitors, Hsp90 inhibitors, kinase inhibitors, MDM2 inhibitors, compounds targeting Human BET Bromodomain-containing proteins, HDAC inhibitors, human lysine methyltransferase inhibitors, angiogenesis inhibitors, immunosuppressive compounds, and compounds targeting the aryl hydrocarbon receptor (AHR).

[0132] The compositions described below exemplify some of the members of these types of small molecule target protein binding moieties. 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. References which are cited hereinbelow are incorporated by reference herein in their entirety.

[0133] **I. Heat Shock Protein 90 (HSP90) Inhibitors:**

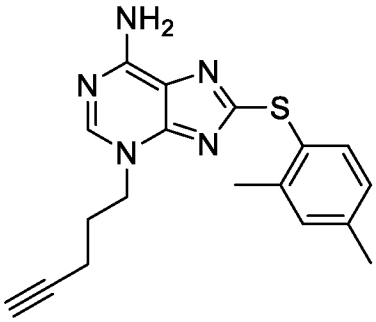
[0134] HSP90 inhibitors as used herein include, but are not limited to:

[0135] **1**. The HSP90 inhibitors identified in Vallee, *et al.*, "Tricyclic Series of Heat Shock Protein 90 (HSP90) Inhibitors Part I: Discovery of Tricyclic Imidazo[4,5-C]Pyridines as Potent Inhibitors of the HSP90 Molecular Chaperone (2011) *J.Med.Chem.* 54: 7206, including YKB (N-[4-(3H-imidazo[4,5-C]Pyridin-2-yl)-9H-Fluoren-9-yl]-succinamide):



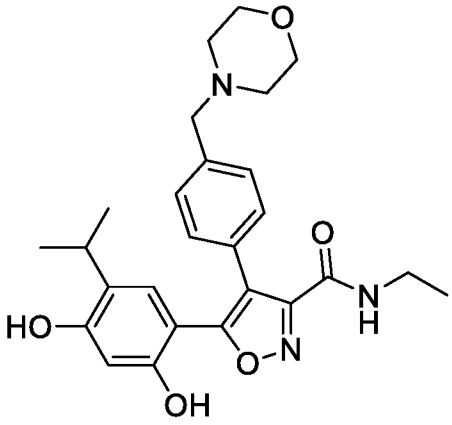
[0136] derivatized where a linker group L or a –(L-CLM) group is attached, for example, via the terminal amide group;

[0137] **2**. The HSP90 inhibitor p54 (modified) (8-[(2,4-dimethylphenyl)sulfanyl]-3]pent-4-yn-1-yl-3H-purin-6-amine):



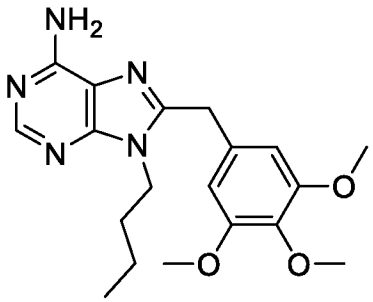
[0138] derivatized where a linker group L or a –(L-CLM) group is attached, for example, via the terminal acetylene group;

[0139] **3**. The HSP90 inhibitors (modified) identified in Brough, *et al.*, "4,5-Diarylisoxazole HSP90 Chaperone Inhibitors: Potential Therapeutic Agents for the Treatment of Cancer", *J.MED.CHEM.* vol: 51, pag:196 (2008), including the compound 2GJ (5-[2,4-dihydroxy-5-(1-methylethyl)phenyl]-n-ethyl-4-[4-(morpholin-4-ylmethyl)phenyl]isoxazole-3-carboxamide) having the structure:



[0140] derivatized, where a linker group L or a –(L-CLM) group is attached, for example, via the amide group (at the amine or at the alkyl group on the amine);

[0141] **4**. The HSP90 inhibitors (modified) identified in Wright, *et al.*, Structure-Activity Relationships in Purine-Based Inhibitor Binding to HSP90 Isoforms, *Chem Biol.* 2004 Jun;11(6):775-85, including the HSP90 inhibitor PU3 having the structure:



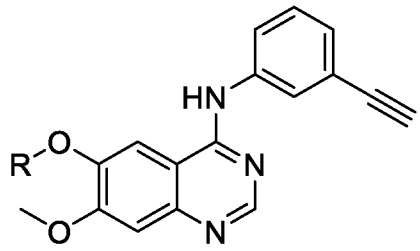
[0142] derivatized where a linker group L or –(L-CLM) is attached, for example, via the butyl group; and

[0143] **5**. The HSP90 inhibitor geldanamycin ((4*E*,6*Z*,8*S*,9*S*,10*E*,12*S*,13*R*,14*S*,16*R*)-13-hydroxy-8,14,19-trimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1] (derivatized) or any of its derivatives (e.g. 17-alkylamino-17-desmethoxygeldanamycin ("17-AAG") or 17-(2-dimethylaminoethyl)amino-17-desmethoxygeldanamycin ("17-DMAG")) (derivatized, where a linker group L or a–(L-CLM) group is attached, for example, via the amide group).

[0144] **II. Kinase and Phosphatase Inhibitors:**

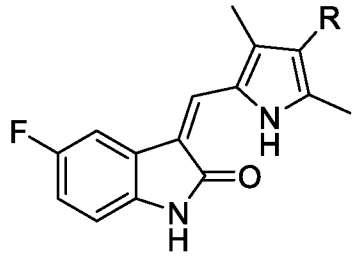
[0145] Kinase inhibitors as used herein include, but are not limited to:

[0146] **1**. Erlotinib Derivative Tyrosine Kinase Inhibitor:

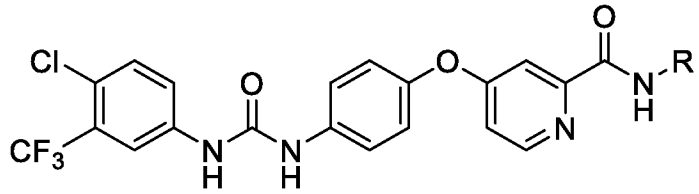


where R is a linker group L or a –(L-CLM) group attached, for example, via the ether group;

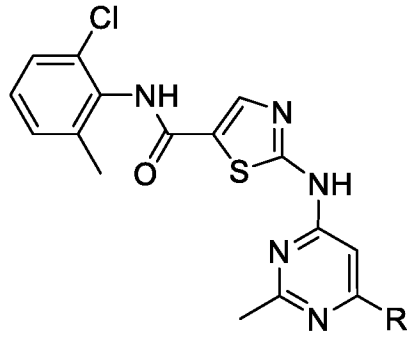
[0147] **2**. The kinase inhibitor sunitinib (derivatized):

[0148]  derivatized where R is a linker group L or a –(L-CLM) group attached, for example, to the pyrrole moiety;

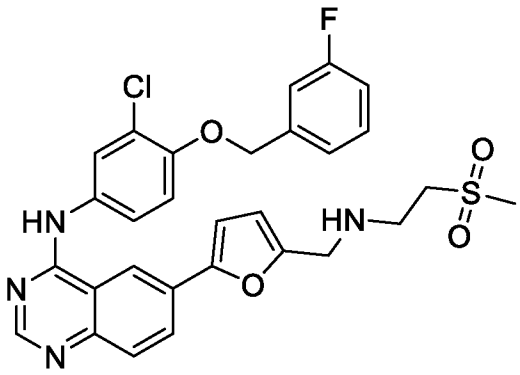
[0149] **3**. Kinase Inhibitor sorafenib (derivatized):

[0150]  derivatized where R is a linker group L or a –(L-CLM) group attached, for example, to the amide moiety;

[0151] **4**. The kinase inhibitor desatinib (derivatized):

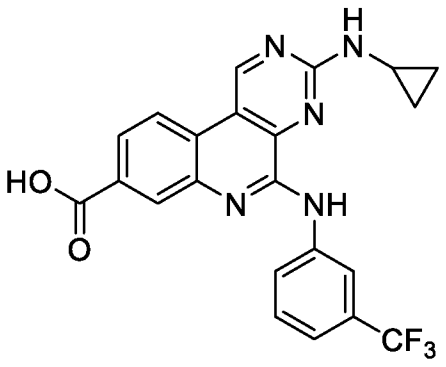
 derivatized where R is a linker group Lor a–(L-CLM) attached, for example, to the pyrimidine;

[0152] **5**. The kinase inhibitor lapatinib (derivatized):



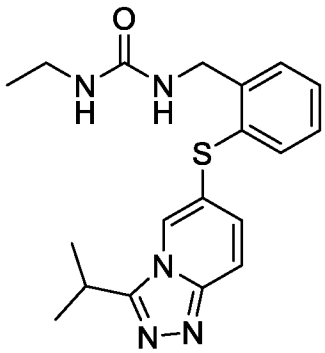
[0153] derivatized where a linker group L or a–(L-CLM) group is attached, for example, via the terminal methyl of the sulfonyl methyl group;

[0154] **6**. The kinase inhibitor U09-CX-5279 (derivatized):

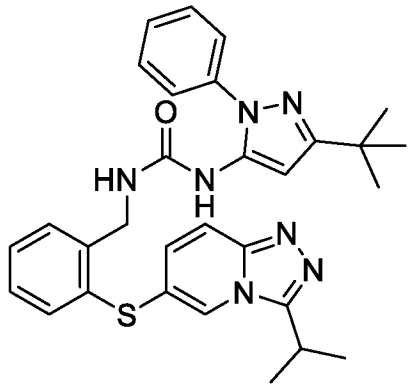


[0155] derivatized where a linker group L or a –(L-CLM) group is attached, for example, via the amine (aniline), carboxylic acid or amine alpha to cyclopropyl group, or cyclopropyl group;

[0156] **7**. The kinase inhibitors identified in Millan, *et al.*, Design and Synthesis of Inhaled P38 Inhibitors for the Treatment of Chronic Obstructive Pulmonary Disease, *J.MED.CHEM.* vol:54, pag:7797 (2011), including the kinase inhibitors Y1W and Y1X (Derivatized) having the structures:

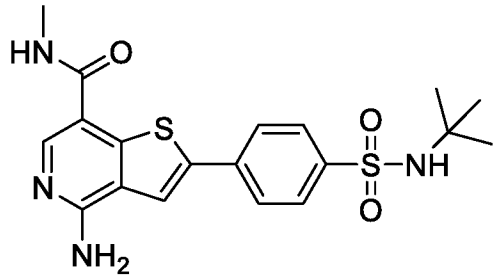


[0157] YIX(1-ethyl-3-(2-{[3-(1-methylethyl)[1,2,4]triazolo[4,3-a]pyridine-6-yl]sulfanyl}benzyl)urea, derivatized where a linker group L or a–(L-CLM) group is attached, for example, via the ^{i}propyl group;

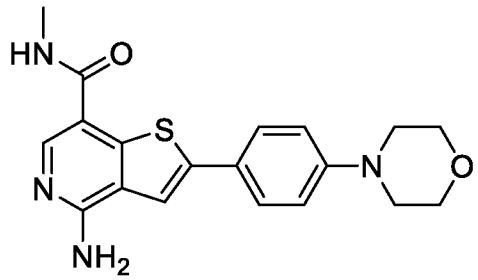


YIW
1-(3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)-3-(2-{[3-(1-methylethyl)[1,2,4]triazolo[4,3-a]pyridin-6-yl]sulfanyl}benzyl)urea
derivatized where a linker group L or a –(L-CLM) group is attached, for example, preferably via either the *i*-propyl group or the *t*-butyl group;

[0158] **8**. The kinase inhibitors identified in Schenkel, *et al.*, Discovery of Potent and Highly Selective Thienopyridine Janus Kinase 2 Inhibitors *J. Med. Chem.*, 2011, *54* (24), pp 8440–8450, including the compounds 6TP and 0TP (Derivatized) having the structures:



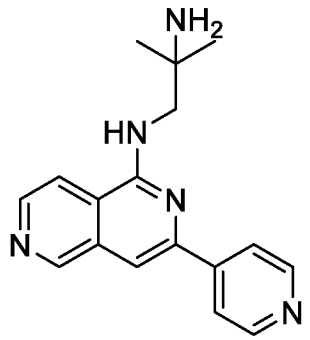
6TP
4-amino-2-[4-(tert-butylsulfamoyl)phenyl]-N-methylthieno[3,2-c]pyridine-7-carboxamide
Thienopyridine 19
derivatized where a linker group L or a –(L-CLM) group is attached, for example, via the terminal methyl group bound to amide moiety;



0TP
4-amino-N-methyl-2-[4-(morpholin-4-yl)phenyl]thieno[3,2-c]pyridine-7-carboxamide
Thienopyridine 8

derivatized where a linker group L or a –(L-CLM)group is attached, for example, via the terminal methyl group bound to the amide moiety;

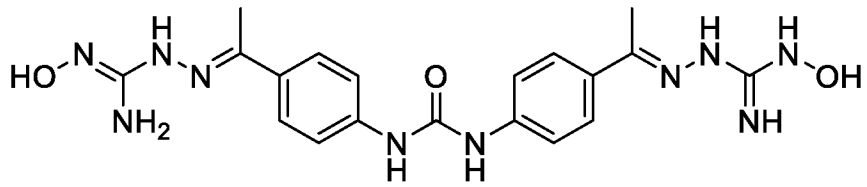
[0159] **9**. The kinase inhibitors identified in Van Eis, *et al.*, "2,6-Naphthyridines as potent and selective inhibitors of the novel protein kinase C isozymes", *Biorg. Med. Chem. Lett.*2011 Dec 15;21(24):7367-72, including the kinase inhibitor 07U having the structure:



07U
2-methyl-N~1~-[3-(pyridin-4-yl)-2,6-naphthyridin-1-yl]propane-1,2-diamine

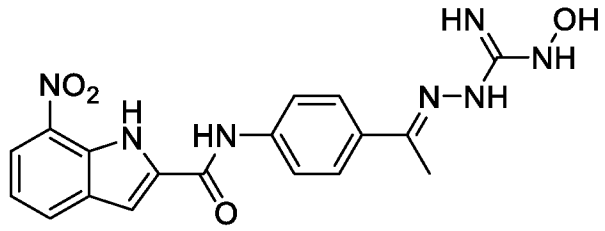
derivatized where a linker group L or a –(L-CLM)group is attached, for example, via the secondary amine or terminal amino group;

[0160] **10**. The kinase inhibitors identified in Lountos, *et al.*, "Structural Characterization of Inhibitor Complexes with Checkpoint Kinase 2 (Chk2), a Drug Target for Cancer Therapy", *J.STRUCT.BIOL.* vol:176, pag:292 (2011), including the kinase inhibitor YCF having the structure:

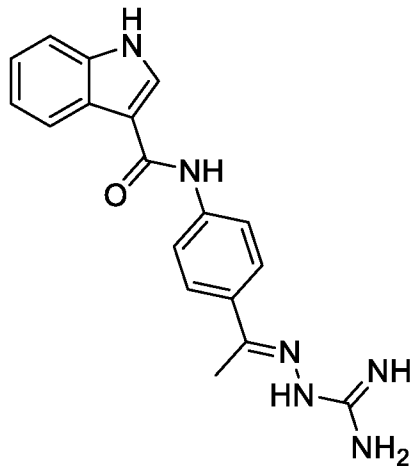


[0161] derivatized where a linker group L or a –(L-CLM) group is attached, for example, via either of the terminal hydroxyl groups;

[0162] **11**. The kinase inhibitors identified in Lountos, *et al.*, "Structural Characterization of Inhibitor Complexes with Checkpoint Kinase 2 (Chk2), a Drug Target for Cancer Therapy", *J.STRUCT.BIOL.* vol:176, pag:292 (2011), including the kinase inhibitors XK9 and NXP (derivatized) having the structures:



XK9
N-{4-[(1E)-N-(N-hydroxycarbamimidoyl)ethanehydrazonoyl]phenyl}-7-nitro-1H-indole-2-carboxamide;



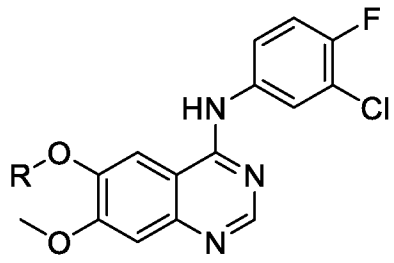
NXP
N-{4-[(1E)-N-CARBAMIMIDOYLETHANEHYDRAZONOYL]PHENYL}-1H-INDOLE-3-CARBOXAMIDE

[0163] derivatized where a linker group L or a –(L-CLM) group is attached, for example, via the terminal hydroxyl group (XK9) or the hydrazone group (NXP);

[0164] **12**. The kinase inhibitor afatinib (derivatized) (*N*-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3*S*)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4(dimethylamino)-2-butenamide) (Derivatized where a linker group L or a –(L-CLM) group is attached, for example, via the aliphatic amine group);

[0165] **13**. The kinase inhibitor fostamatinib (derivatized) ([6-({5-fluoro-2-[(3,4,5-trimethoxyphenyl)amino]pyrimidin-4-yl}amino)-2,2-dimethyl-3-oxo-2,3-dihydro-4H-pyrido[3,2-b]-1,4-oxazin-4-yl]methyl disodium phosphate hexahydrate) (Derivatized where a linker group L or a –(L-CLM) group is attached, for example, via a methoxy group);

[0166] **14**. The kinase inhibitor gefitinib (derivatized) (*N*-(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazolin-4-amine):



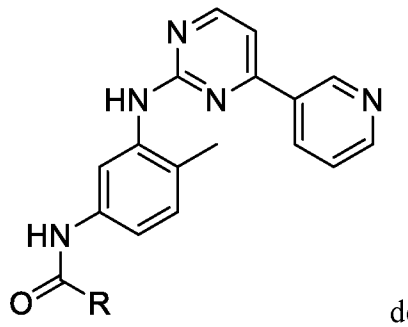
[0167] derivatized where a linker group L or a –(L-CLM) group is attached, for example, via a methoxy or ether group;

[0168] **15**. The kinase inhibitor lenvatinib (derivatized) (4-[3-chloro-4-(cyclopropylcarbamoylamino)phenoxy]-7-methoxy-quinoline-6-carboxamide) (derivatized where a linker group L or a –(L-CLM) group is attached, for example, via the cyclopropyl group);

[0169] **16**. The kinase inhibitor vandetanib (derivatized) (*N*-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine) (derivatized where a linker group L or a –(L-CLM) group is attached, for example, via the methoxy or hydroxyl group);

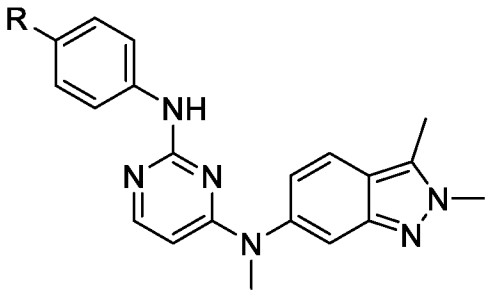
[0170] **17**. The kinase inhibitor vemurafenib (derivatized) (propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide), derivatized where a linker group L or a –(L-CLM) group is attached, for example, via the sulfonyl propyl group;

[0171] **18**. The kinase inhibitor Gleevec (derivatized):



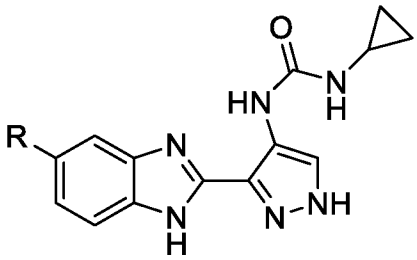
[0172] derivatized where R as a linker group L or a–(L-CLM) group is attached, for example, via the amide group or via the aniline amine group;

[0173] **19**. The kinase inhibitor pazopanib (derivatized) (VEGFR3 inhibitor):



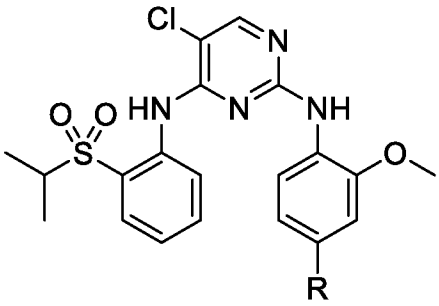
[0174] derivatized where R is a linker group L or a –(L-CLM) group attached, for example, to the phenyl moiety or via the aniline amine group;

[0175] **20**. The kinase inhibitor AT-9283 (Derivatized) Aurora Kinase Inhibitor



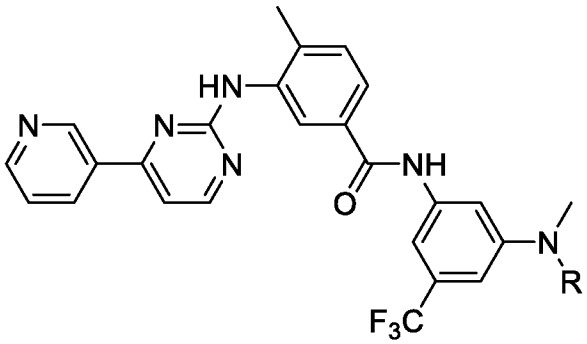
[0176] where R is a linker group L or a –(L-CLM) group attached, for example, to the phenyl moiety);

[0177] **21**. The kinase inhibitor TAE684 (derivatized) ALK inhibitor



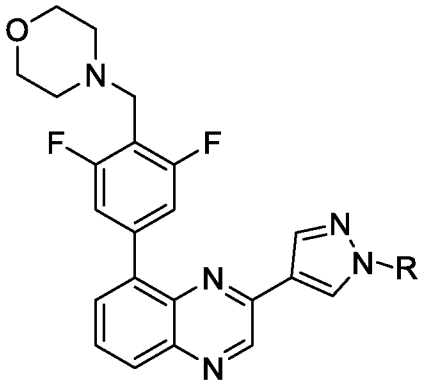
[0178] where R is a linker group L or a –(L-CLM) group attached, for example, to the phenyl moiety);

[0179] **22**. The kinase inhibitor nilotanib (derivatized) Abl inhibitor:



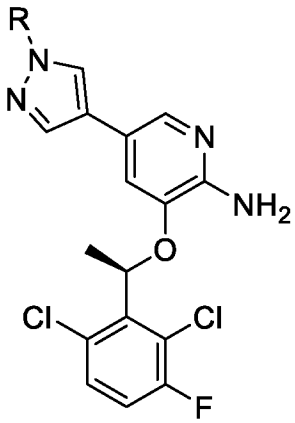
[0180] derivatized where R is a linker group L or a –(L-CLM) group attached, for example, to the phenyl moiety or the aniline amine group;

[0181] **23**. Kinase Inhibitor NVP-BSK805 (derivatized) JAK2 Inhibitor



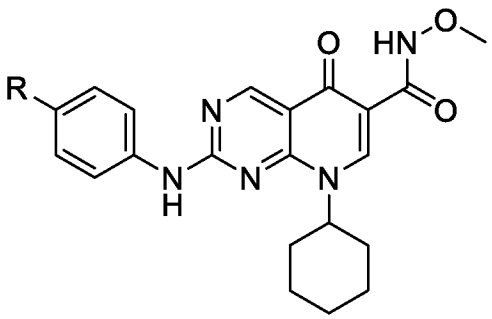
[0182] derivatized where R is a linker group L or a –(L-CLM) group attached, for example, to the phenyl moiety or the diazole group;

[0183] **24**. Kinase Inhibitor crizotinib Derivatized Alk Inhibitor



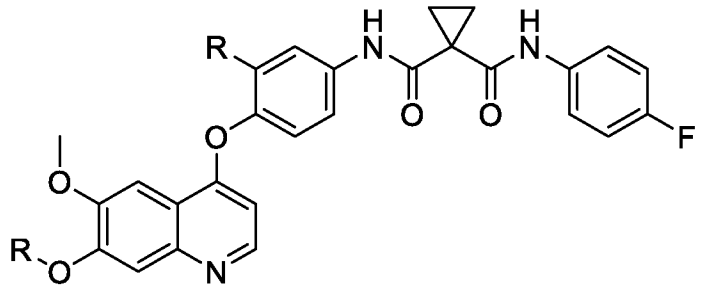
[0184] derivatized where R is a linker group L or a –(L-CLM) group attached, for example, to the phenyl moiety or the diazole group;

[0185] **25**. Kinase Inhibitor JNJ FMS (derivatized) Inhibitor

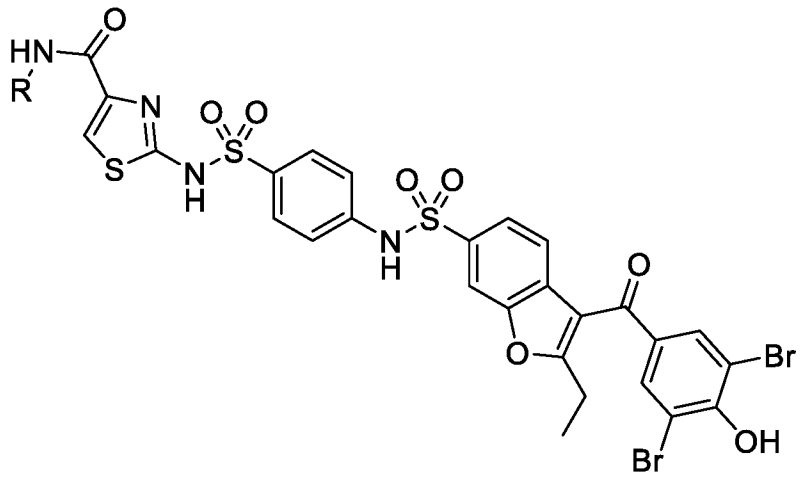


[0186] derivatized where R is a linker group L or a –(L-CLM) group attached, for example, to the phenyl moiety;

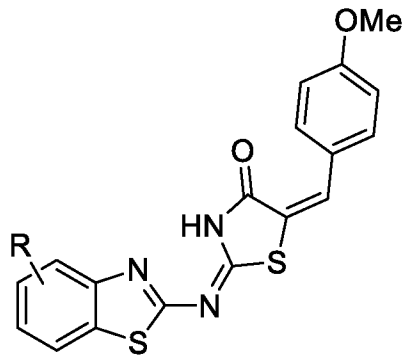
[0187] **26**. The kinase inhibitor foretinib (derivatized) Met Inhibitor

[0188]  derivatized where R is a linker group L or a –(L-CLM)group attached, for example, to the phenyl moiety or a hydroxyl or ether group on the quinoline moiety;

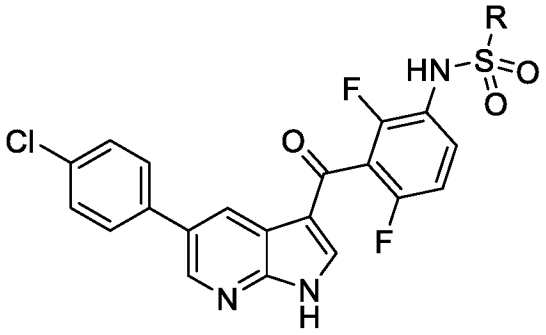
[0189] **27**. The allosteric Protein Tyrosine Phosphatase Inhibitor PTP1B (derivatized):

[0190]  derivatized where a linker group L or a –(L-CLM) group is attached, for example, at R, as indicated;

[0191] **28**. The inhibitor of SHP-2 Domain of Tyrosine Phosphatase (derivatized):

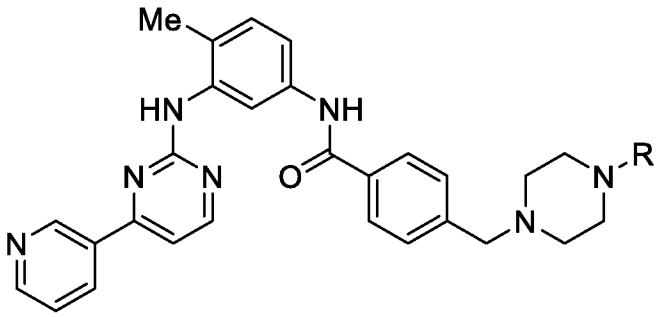
[0192]  derivatized where a linker group L or a –(L-CLM) group is attached, for example, at R;

[0193] **29**. The inhibitor (derivatized) of BRaf ($BRaf^{V600E}$)/MEK:



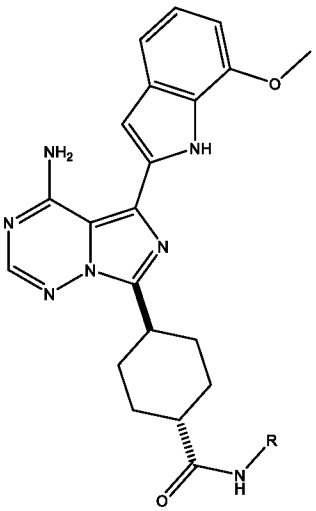
[0194] derivatized where a linker group L or a–(L-CLM) group is attached, for example, at R;

[0195] **30**. Inhibitor (derivatized) of Tyrosine Kinase ABL



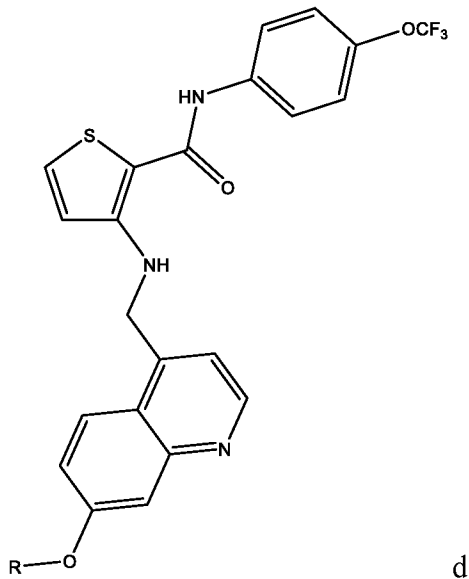
[0196] derivatized where a linker group L or a–(L-CLM) group is attached, for example, at R;

[0197] **31**. The kinase inhibitor OSI-027 (derivatized) mTORC1/2 inhibitor



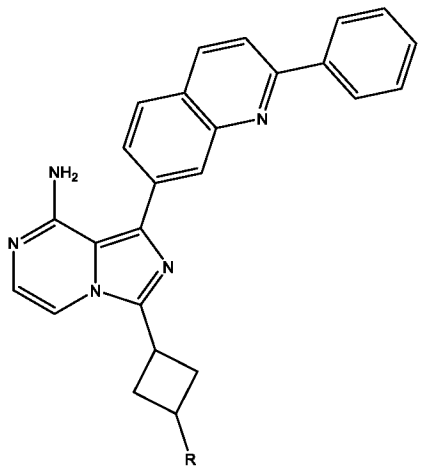
[0198] derivatized where a linker group L or a–(L-CLM) group is attached, for example, at R;

[0199] **32**. The kinase inhibitor OSI-930 (derivatized) c-Kit/KDR inhibitor



[0200] derivatized where a linker group L or a–(L-CLM) group is attached, for example, at R; and

[0201] **33**. The kinase inhibitor OSI-906 (derivatized) IGF1R/IR inhibitor



[0202] derivatized where a linker group L or a–(L-CLM) group is attached, for example, at R.

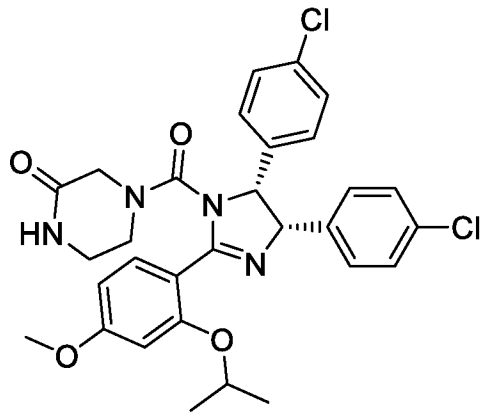
[0203] Wherein, in any of the embodiments described in sections I-XVII, "R" designates a site for attachment of a linker group L or a –(L-CLM)group on the piperazine moiety.

[0204] **III. HDM2/MDM2 Inhibitors:**

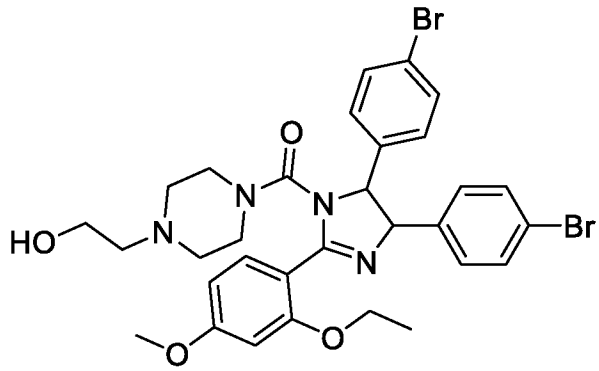
[0205] HDM2/MDM2 inhibitors as used herein include, but are not limited to:

[0206] **1.** The HDM2/MDM2 inhibitors identified in Vassilev, *et al.*, In vivo activation of the p53 pathway by small-molecule antagonists of MDM2, *SCIENCE* vol:303, pag:844-848 (2004), and Schneekloth, *et al.*, Targeted intracellular protein degradation induced by a small molecule: En route to chemical proteomics, *Bioorg. Med. Chem. Lett.* 18 (2008) 5904–5908,

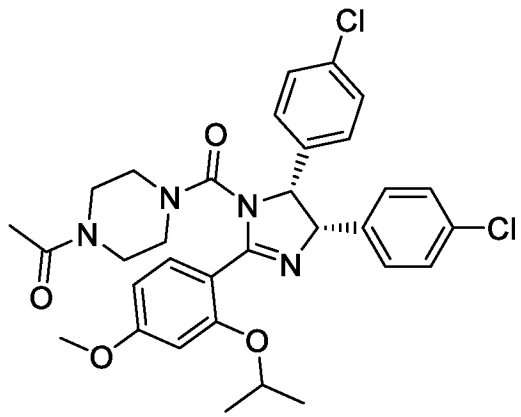
including (or additionally) the compounds nutlin-3, nutlin-2, and nutlin-1 (derivatized) as described below, as well as all derivatives and analogs thereof:



(derivatized where a linker group L or a –(L-CLM)group is attached, for example, at the methoxy group or as a hydroxyl group);

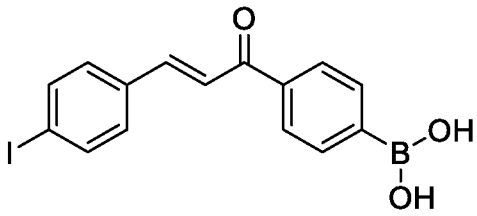


(derivatized where a linker group L or a –(L-CLM) group is attached, for example, at the methoxy group or hydroxyl group);



(derivatized where a linker group L or a –(L-CLM) group is attached, for example, via the methoxy group or as a hydroxyl group); and

[0207] **2.** Trans-4-Iodo-4'-Boranyl-Chalcone

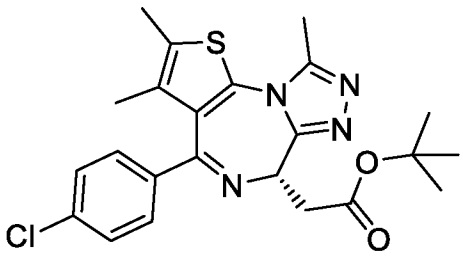


[0208] (derivatized where a linker group L or a a linker group L or a–(L-CLM) group is attached, for example, via a hydroxy group).

[0209] **IV. Compounds Targeting Human BET Bromodomain-containing proteins:**

[0210] In certain embodiments, "PTM" can be ligands binding to Bromo- and Extra-terminal (BET) proteins BRD2, BRD3 and BRD4. Compounds targeting Human BET Bromodomain-containing proteins include, but are not limited to the compounds associated with the targets as described below, where "R" or "linker" designates a site for linker group L or a–(L-CLM) group attachment, for example:

[0211] **1.** JQ1, Filippakopoulos et al. Selective inhibition of BET bromodomains. *Nature* (2010):



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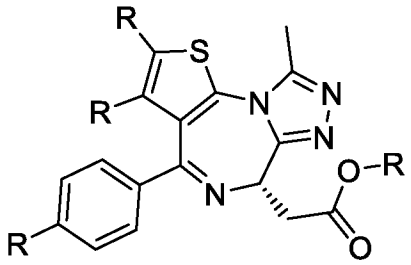

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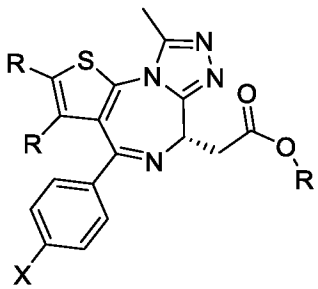
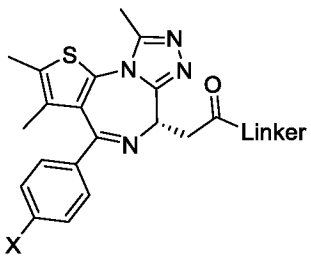


X = Cl, Br, F, H, bond, or a chemical moiety coupling the CLM to the PTM

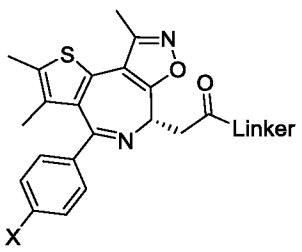
R = H, a lower alkyl, a bond, or a chemcial moiety coupling the CLM to the PTM

,



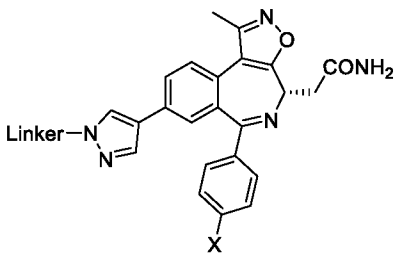
X = Cl, Br, F, H

,



X = Cl, Br, F, H

,



X = Cl, Br, F, H

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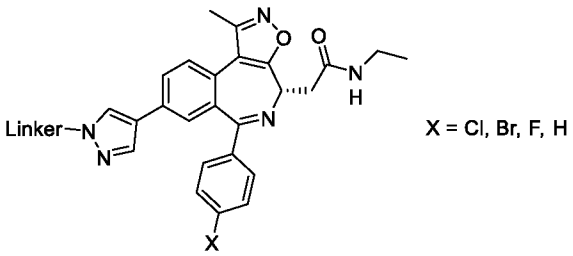

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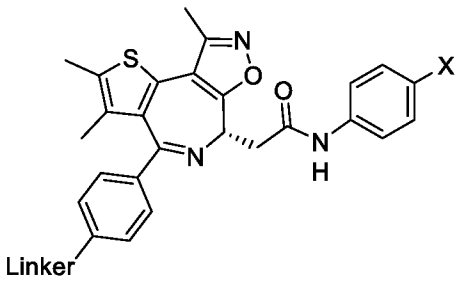
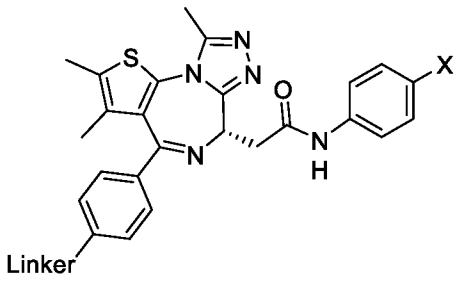
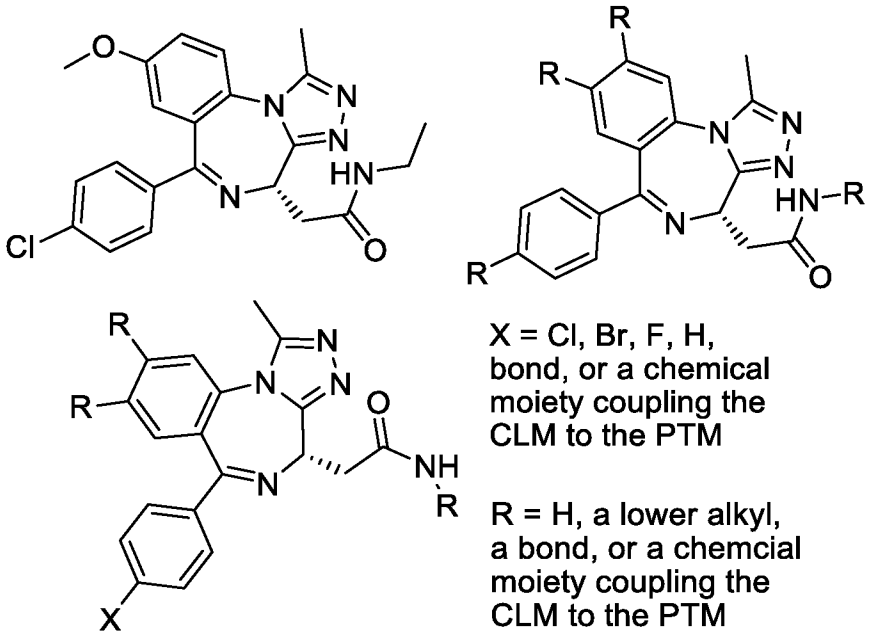


, or

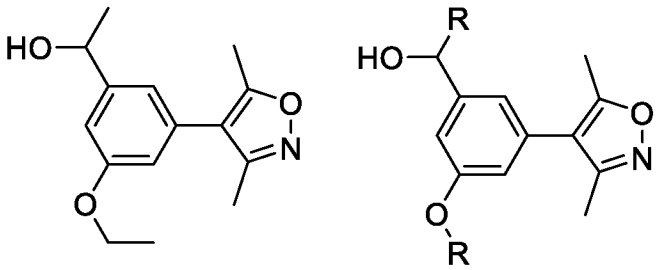


X = H, F .

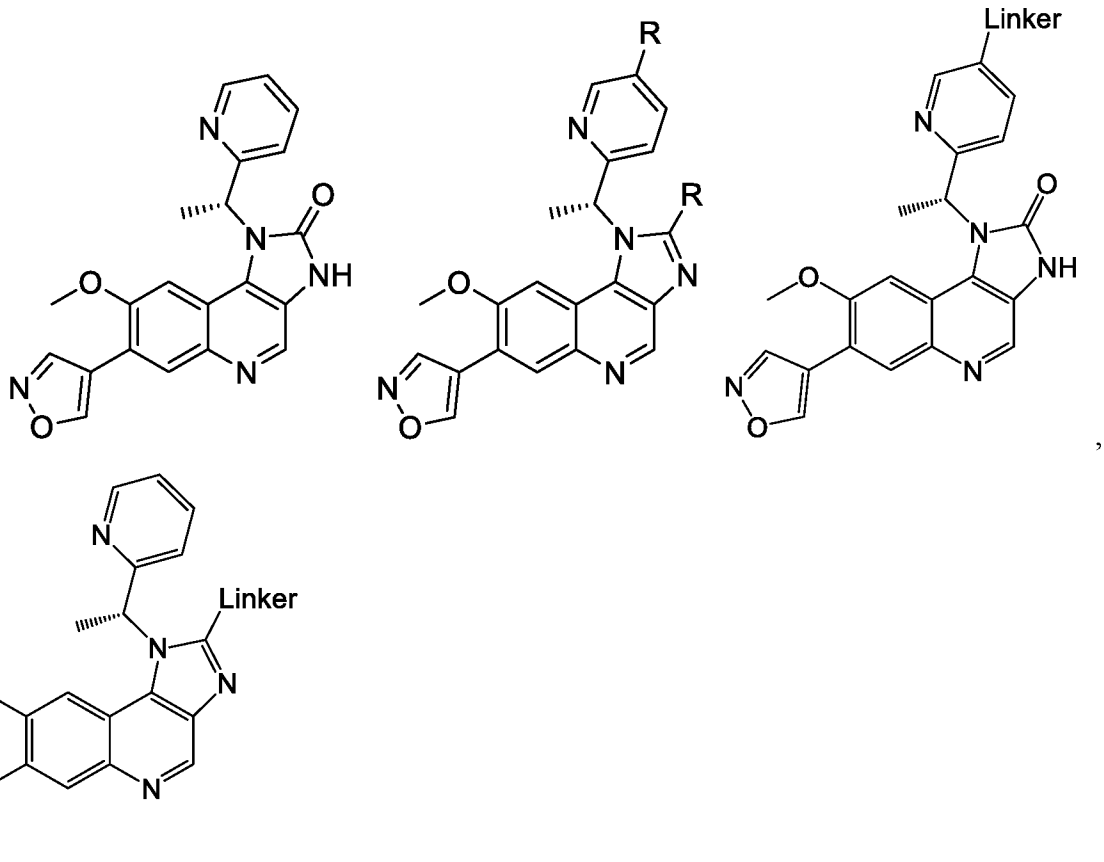
[0212] **2.** I-BET, Nicodeme et al. Supression of Inflammation by a Synthetic Histone Mimic. *Nature* (2010). Chung et al. Discovery and Characterization of Small Molecule Inhibitors of the BET Family Bromodomains. J. Med Chem. (2011):



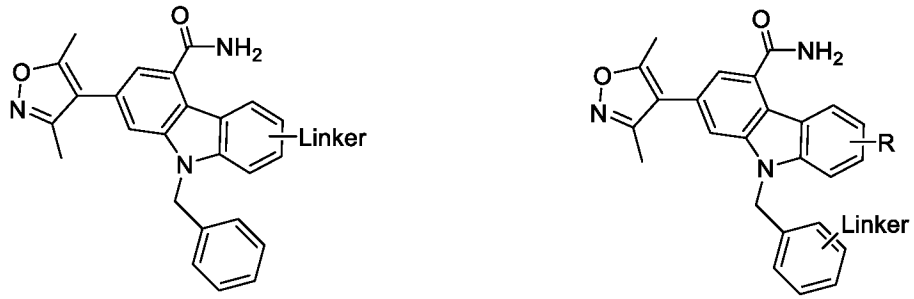
[0213] **3.** Compounds described in Hewings et al. 3,5-Dimethylisoxazoles Act as Acetyl-lysine Bromodomain Ligands. J. Med. Chem. (2011) 54 6761-6770.



[0214] **4.** I-BET151, Dawson et al. Inhibition of BET Recruitment to Chromatin as an Efective Treatment for MLL-fusion Leukemia. Nature (2011):

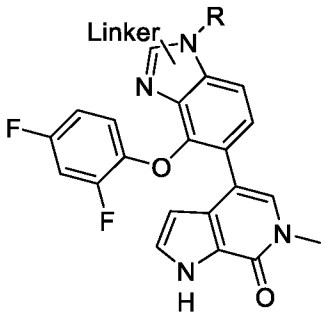
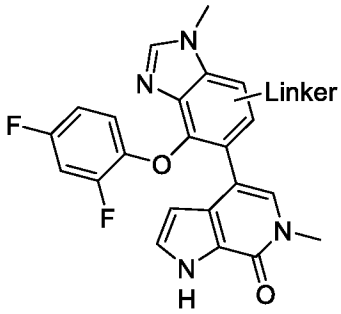


[0215] **5.** Carbazole type (US 2015/0256700)



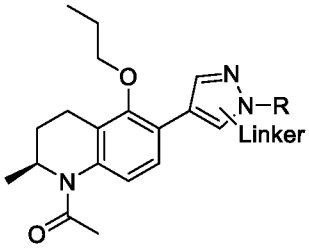
[0216]

[0217] **6.** Pyrrolopyridone type (US 2015/0148342)

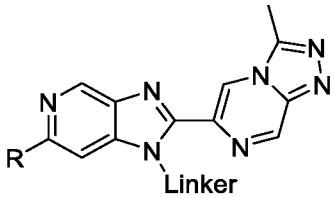
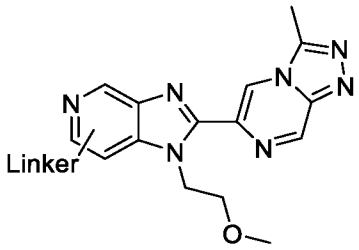
[0218]

[0219] **7.** Tetrahydroquinoline type (WO 2015/074064)



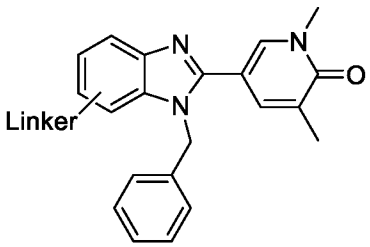
[0220]

[0221] **8.** Triazolopyrazine type (WO 2015/067770)

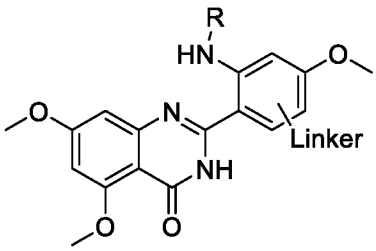
[0222]

[0223] **9.** Pyridone type (WO 2015/022332)



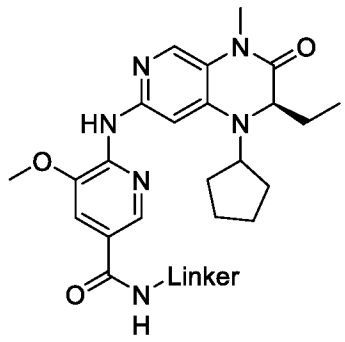
[0224]

[0225] **10.** Quinazolinone type (WO 2015/015318)



[0226]

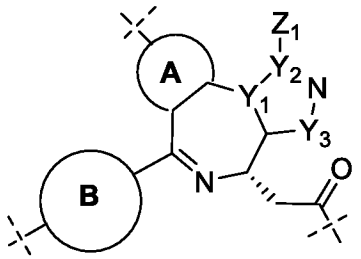
[0227] **11.** Dihydropyridopyrazinone type (WO 2015/011084)



[0228]

[0229] (Where R or L or linker, in each instance, designates a site for attachment, for example, of a linker group L or a –(L-CLM) group).

[0230] In any aspect or embodiment described herein, the claimed structure the PTM may be composed of tricyclic diazepine or tricyclic azepine as a BET/BRD4 targeting moiety (PTM-a), where the dashed lines indicate the linker connection trajectory and three sites are defined to which linkers may be attached:



PTM-a

,

wherein:

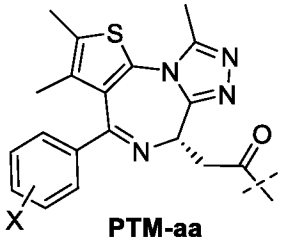
A and B are independently an aromatic ring, a heteroaromatic ring, a 5-membered carbocyclic, a 6-membered carbocyclic, a 5-membered heterocyclic, a 6-membered heterocyclic, a thiophene, a pyrrole, a pyrazole, a pyridine, a pyrimidine, a pyrazine, optionally substituted by alkyl, aloxy, halogen, nitrile or another aromatic or heteroaromatic ring, where A is fused to the central azepine (Y1=C) or diazepine (Y1 = N) moiety;

Y1, Y2, and Y3 and Y4 can be carbon, nitrogen or oxygen for to form a fused 5-membered aromatic ring as triazole or isoxazole; and

Z1 is methyl, or lower alkyl group.

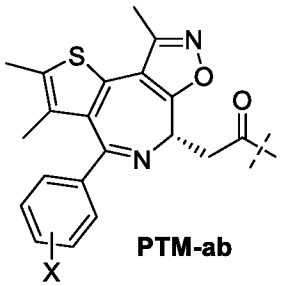
[0231] The fragment of PTM-a as BET/BRD4 targeting moiety is described in the literature (WO 2016/069578; WO2014/001356; WO2016/050821; WO 2015/195863; WO 2014/128111).

[0232] In any aspect or embodiment described herein comprising the structure CLM-L-PTM-a, PTM-a can be represented by the following general structures, where dashed line indicates a possible linker connection point. In structure PTM-aa through PTM-ai, the substitution pattern of X and Y can be mono- or bis-substitution.



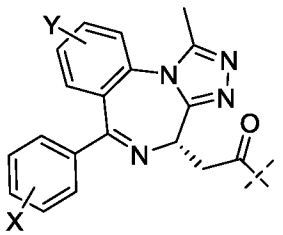
PTM-aa

X = Cl, F, Br, H, CN, methyl, acetylene, methoxy



PTM-ab

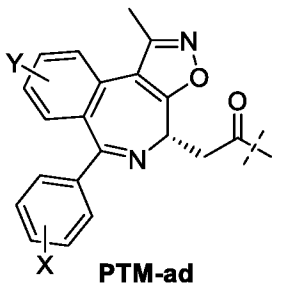
X = Cl, F, Br, H, CN, methyl, acetylene, methoxy



PTM-ac

X = Cl, F, Br, H, CN, methyl, methoxy, acetylene

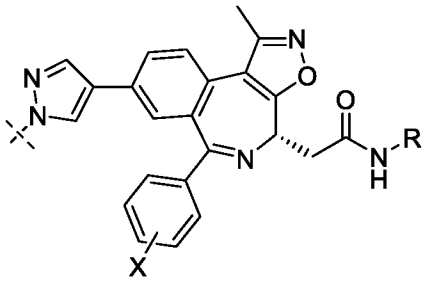
Y: mono- or di-substitution, Y = Me, OMe, N-methypyrazole/imidazole



PTM-ad

X = Cl, F, Br, H, CN, methyl, methoxy, acetylene

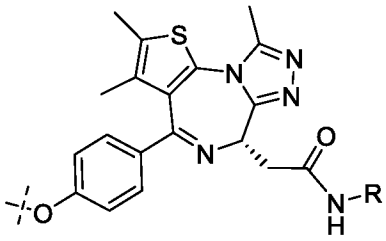
Y: mono- or di-substitution, Y = Me, OMe, N-methylpyrazole/imidazole



PTM-ae

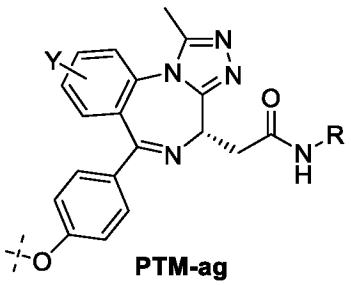
X = Cl, F, Br, H, CN, methyl, methoxy, acetylene

R = lower alkyl, aryl, substituted aryl



PTM-af

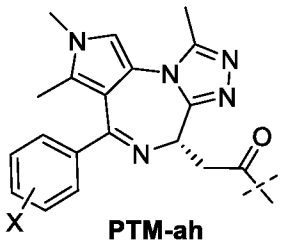
R = lower alkyl, aryl, substituted aryl



PTM-ag

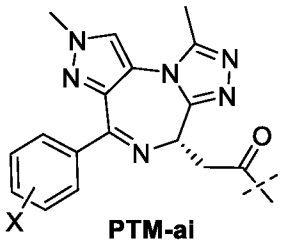
Y: mono- or di-substitution, Y = Me, OMe, N-methylpyrazole/imidazole

R = lower alkyl, aryl, substituted aryl



PTM-ah

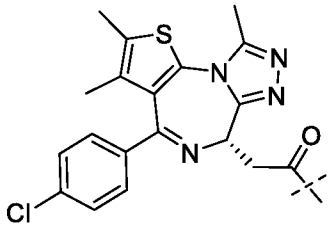
X = Cl, F, Br, H, CN, methyl, acetylene, methoxy



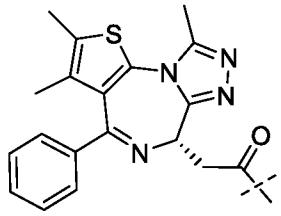
PTM-ai

X = Cl, F, Br, H, CN, methyl, acetylene, methoxy

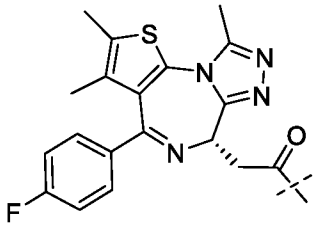
[0233] In any aspect or embodiment described herein, the structures of PTM-a as the BET/BRD4 targeting moiety includes, wherein the dashed line indicates the connection point between the BET/BRD4 targeting moiety and the linkers:



PTM-a1



PTM-a2



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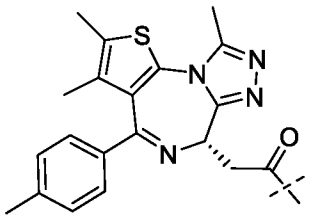

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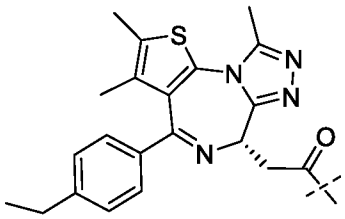

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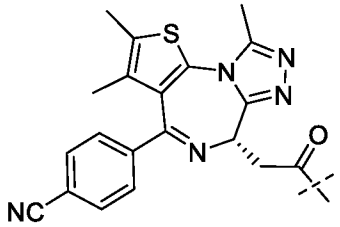

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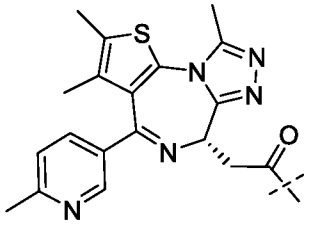

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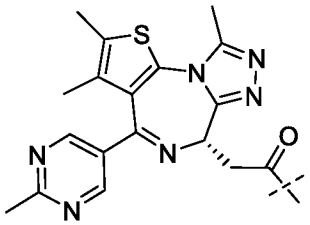

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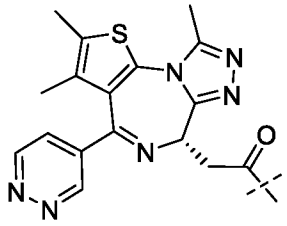

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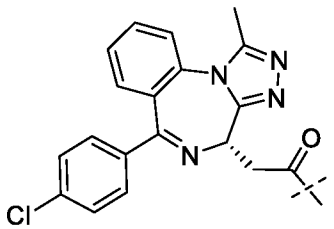

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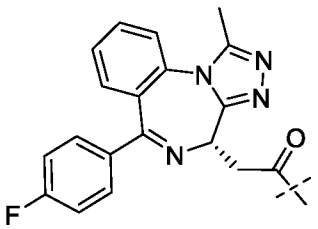

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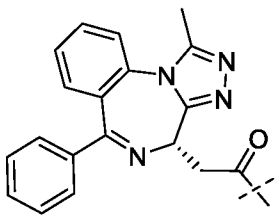

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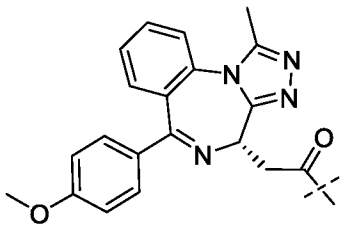

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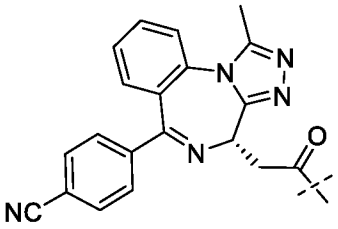

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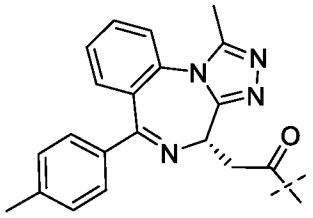

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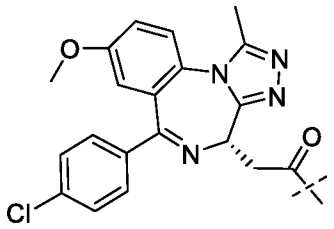

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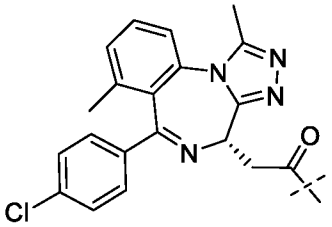

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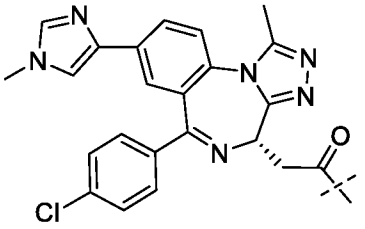

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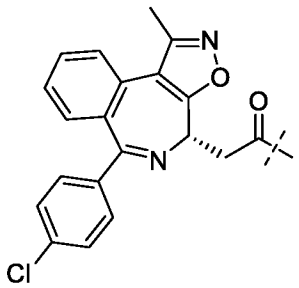

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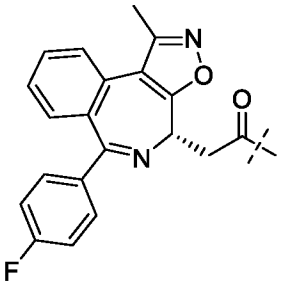

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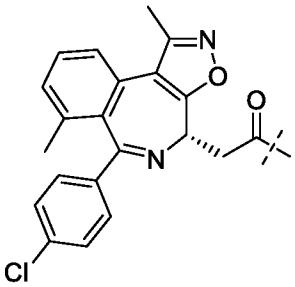

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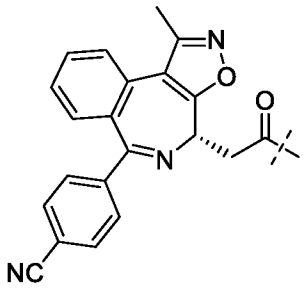

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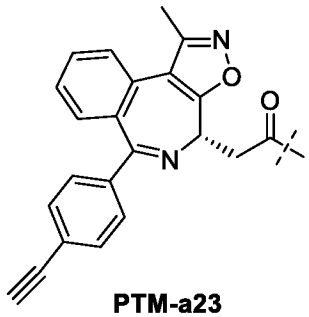

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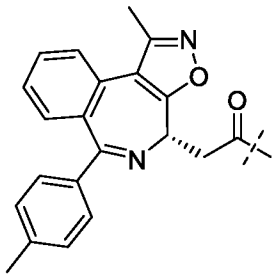

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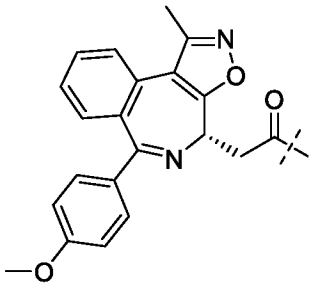

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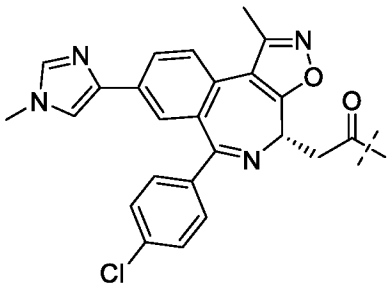

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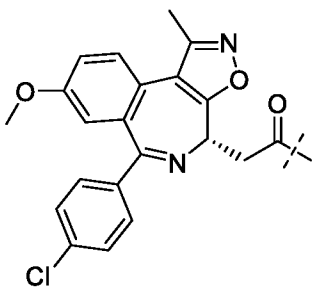

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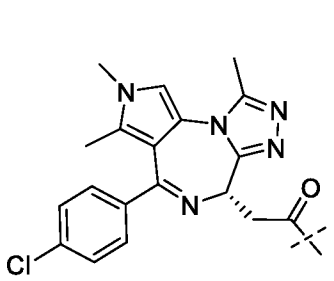

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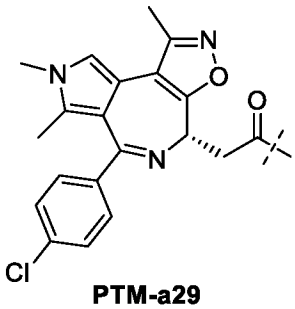

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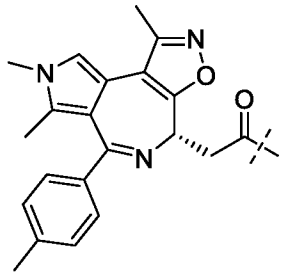

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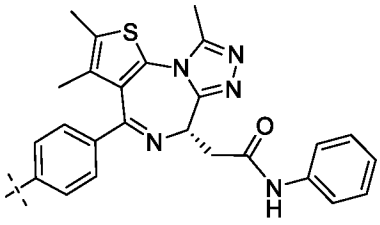

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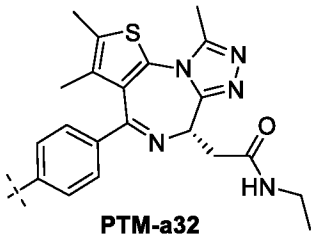

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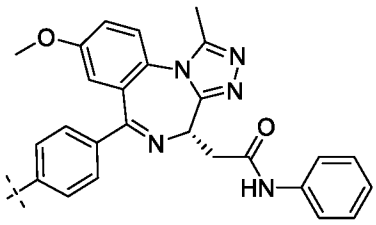

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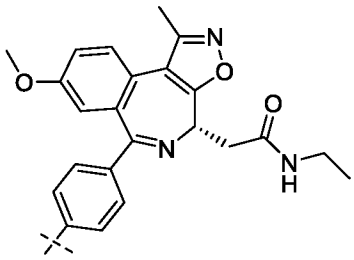

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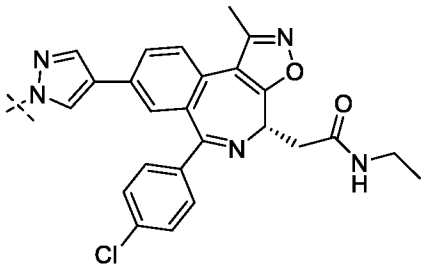

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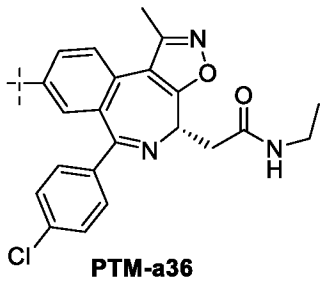
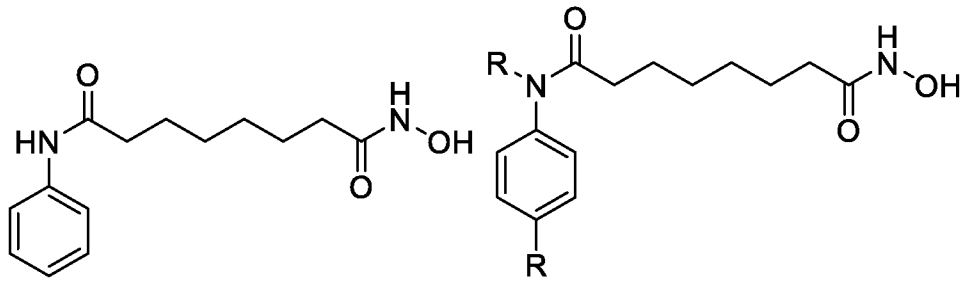


PTM-a36

[0234] **V. HDAC Inhibitors:**

[0235] HDAC Inhibitors (derivatized) include, but are not limited to:

[0236] **1.** Finnin, M. S. et al. Structures of Histone Deacetylase Homologue Bound to the TSA and SAHA Inhibitors. Nature 40, 188-193 (1999).



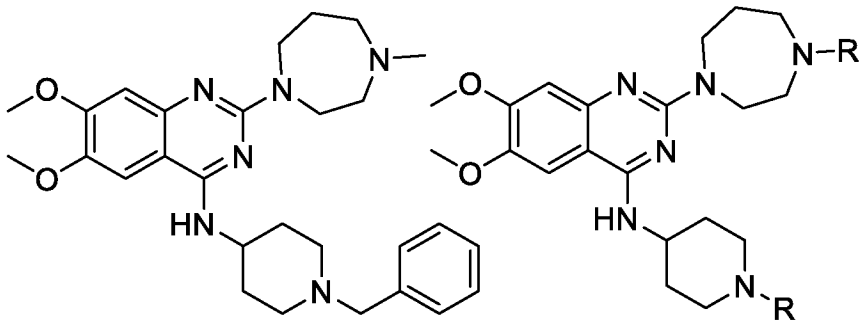
(Derivatized where "R" designates a site for attachment, for example, of a linker group L or a –(L-CLM) group); and

[0237] **2.** Compounds as defined by formula (I) of PCT WO0222577 ("DEACETYLASE INHIBITORS") (Derivatized where a linker group L or a –(L-CLM) group is attached, for example, via the hydroxyl group);

[0238] **VI. Human Lysine Methyltransferase Inhibitors:**

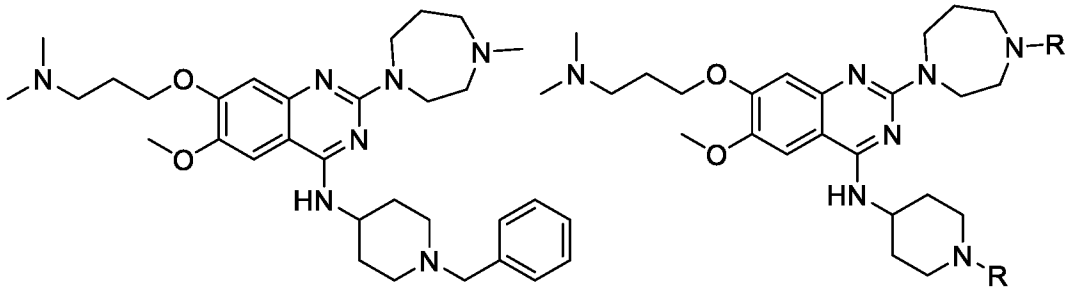
[0239] Human Lysine Methyltransferase inhibitors include, but are not limited to:

[0240] **1.** Chang et al. Structural Basis for G9a-Like protein Lysine Methyltransferase Inhibition by BIX-1294. Nat. Struct. Biol. (2009) 16(3) 312.



[0241] (Derivatized where "R" designates a site for attachment, for example, of a linker group L or a –(L-CLM) group);

[0242] **2.** Liu, F. et al Discovery of a 2,4-Diamino-7-aminoalkoxyquinazoline as a Potent and Selective Inhibitor of Histone Methyltransferase G9a. J. Med. Chem. (2009) 52(24) 7950.



[0243] (Derivatized where "R" designates a potential site for attachment, for example, of a linker group L or a –(L-CLM) group);

[0244] **3.** Azacitidine (derivatized) (4-amino-1-β-D-ribofuranosyl-1,3,5-triazin-2(1*H*)-one) (Derivatized where a linker group L or a –(L-CLM) group is attached, for example, via the hydroxy or amino groups); and

[0245] **4.** Decitabine (derivatized) (4-amino-1-(2-deoxy-b-D-erythro-pentofuranosyl)-1, 3, 5-triazin-2(1*H*)-one) (Derivatized where a linker group L or a –(L-CLM) group is attached, for example, via either of the hydroxy groups or at the amino group).

[0246] **VII. Angiogenesis Inhibitors:**

[0247] Angiogenesis inhibitors include, but are not limited to:

[0248] **1.** GA-1 (derivatized) and derivatives and analogs thereof, having the structure(s) and binding to linkers as described in Sakamoto, *et al.*, Development of Protacs to target cancer-promoting proteins for ubiquitination and degradation, *Mol Cell Proteomics* 2003 Dec;2(12):1350-8;

[0249] **2.** Estradiol (derivatized), which may be bound to a linker group L or a –(L-CLM) group as is generally described in Rodriguez-Gonzalez, *et al.*, Targeting steroid hormone receptors for ubiquitination and degradation in breast and prostate cancer, *Oncogene* (2008) 27, 7201–7211;

[0250] **3.** Estradiol, testosterone (derivatized) and related derivatives, including but not limited to DHT and derivatives and analogs thereof, having the structure(s) and binding to a linker group L or a –(L-CLM) group as generally described in Sakamoto, *et al.*, Development of Protacs to target cancer-promoting proteins for ubiquitination and degradation, *Mol Cell Proteomics* 2003 Dec; 2(12):1350-8; and

[0251] **4.** Ovalicin, fumagillin (derivatized), and derivatives and analogs thereof, having the structure(s) and binding to a linker group L or a –(L-CLM) group as is generally described in Sakamoto, et al., Protacs: chimeric molecules that target proteins to the Skp1-Cullin-F box complex for ubiquitination and degradation *Proc Natl Acad Sci USA*. 2001 Jul 17;98(15):8554-9 and United States Patent No. 7,208,157.

[0252] **VIII. Immunosuppressive Compounds:**

[0253] Immunosuppressive compounds include, but are not limited to:

[0254] **1.** AP21998 (derivatized), having the structure(s) and binding to a linker group L or a –(L-CLM) group as is generally described in Schneekloth, *et al.*, Chemical Genetic Control of Protein Levels: Selective in Vivo Targeted Degradation, *J. AM. CHEM. SOC.* 2004, 126, 3748-3754;

[0255] **2.** Glucocorticoids (e.g., hydrocortisone, prednisone, prednisolone, and methylprednisolone) (Derivatized where a linker group L or a –(L-CLM) group is to bound, e.g. to any of the hydroxyls) and beclometasone dipropionate (Derivatized where a linker group or a –(L-CLM) is bound, e.g. to a proprionate);

[0256] **3.** Methotrexate (Derivatized where a linker group or a –(L-CLM) group can be bound, e.g. to either of the terminal hydroxyls);

[0257] **4.** Ciclosporin (Derivatized where a linker group or a –(L-CLM) group can be bound, e.g. at any of the butyl groups);

[0258] **5.** Tacrolimus (FK-506) and rapamycin (Derivatized where a linker group L or a –(L-CLM) group can be bound, e.g. at one of the methoxy groups); and

[0259] **6.** Actinomycins (Derivatized where a linker group L or a –(L-CLM) group can be bound, e.g. at one of the isopropyl groups).

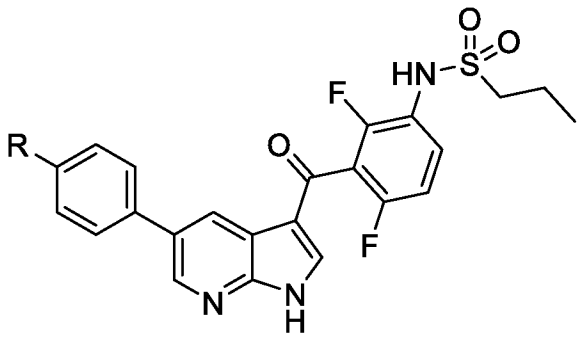
[0260] **IX. Compounds targeting the aryl hydrocarbon receptor (AHR):**

[0261] Compounds targeting the aryl hydrocarbon receptor (AHR) include, but are not limited to:

[0262] **1**. Apigenin (Derivatized in a way which binds to a linker group L or a –(L-CLM) group as is generally illustrated in Lee, et al., Targeted Degradation of the Aryl Hydrocarbon Receptor by the PROTAC Approach: A Useful Chemical Genetic Tool, ChemBioChem Volume 8, Issue 17, pages 2058–2062, November 23, 2007); and

[0263] **2.** SR1 and LGC006 (derivatized such that a linker group L or a –(L-CLM) is bound), as described in Boitano, *et al.*, Aryl Hydrocarbon Receptor Antagonists Promote the Expansion of Human Hematopoietic Stem Cells, *Science* 10 September 2010: Vol. 329 no. 5997 pp. 1345-1348.

[0264] **X. Compounds targeting RAF Receptor (Kinase):**

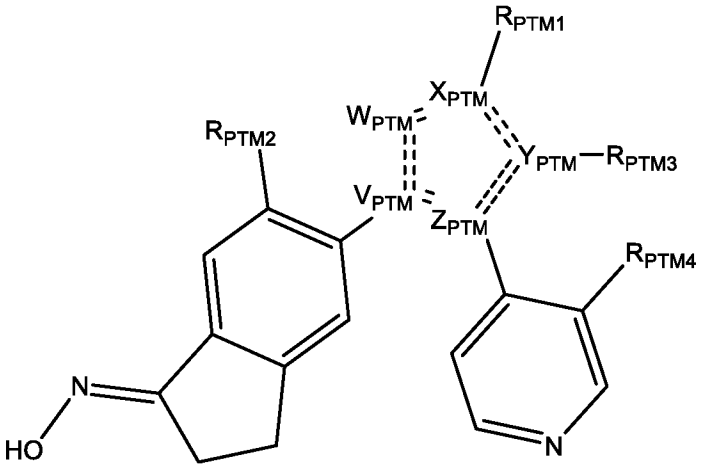


[0265] PLX4032

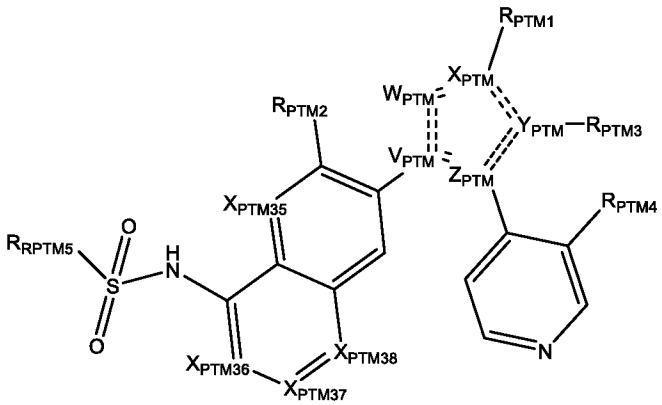
[0266] (Derivatized where "R" designates a site for linker group L or –(L-CLM) group attachment, for example).

[0267] Any protein, which can bind to a protein target moiety or PTM group and acted on or degraded by an ubiquitin ligase (e.g., RAF) is a target protein according to the present disclosure.

[0268] In any aspect or embodiment described herein, the PTM targets and/or binds RAF (i.e., a Raf or BRaf targeting moiety). For example, in any aspect or embodiment described herein, the PTM may comprise a chemical group selected from the group of chemical structures consisting of PTM-Ia or PTM-Ib:



PTM-Ia or



PTM-Ib ,

wherein:

double dotted bonds are aromaric bonds;

V_{PTM}, W_{PTM}, X_{PTM}, Y_{PTM}, Z_{PTM} is one of the following combinations: C, CH, N, N, C; C, N, N, CH, C; C, O, C, CH, C; C, S, C, CH, C; C, CH, C, O, C; C, CH, C, S, C; C, CH, N, CH, C; N, CH, C, CH, C; C, CH, C, CH, N; N, N, C, CH, C; N, CH, C, N, C; C, CH, C, N, N; C, N, C, CH, N; C, N, C, N, C; and C, N, N, N, C;

X_{PTM35}, X_{PTM36}, X_{PTM37}, and X_{PTM38} are independently selected from CH and N;

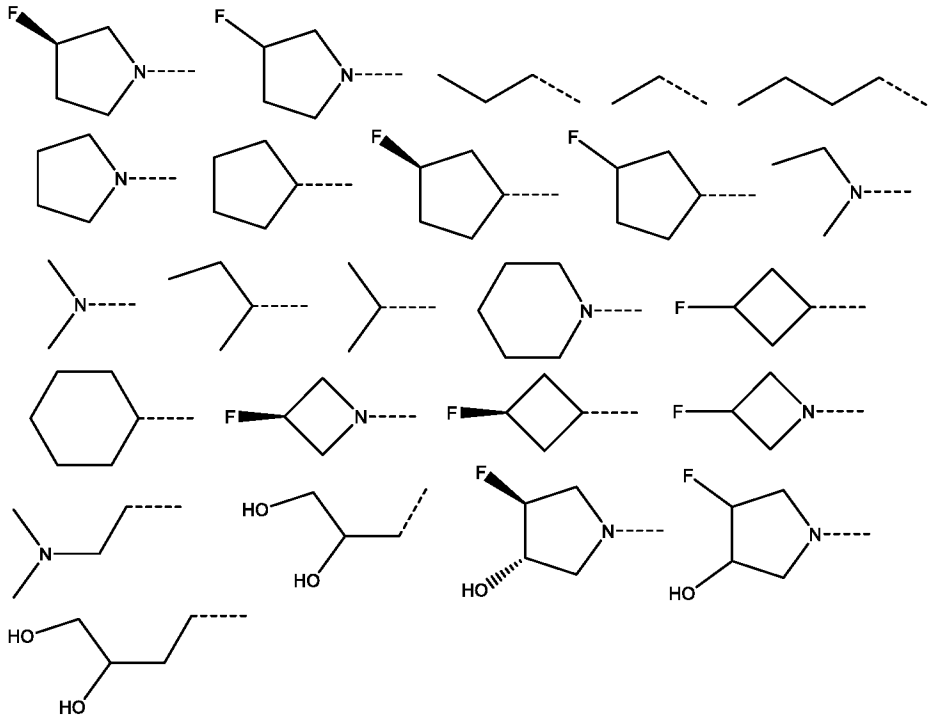
R_{PTM1} is covalently joined to a ULM, a chemical linker group (L), a CLM, an ILM, a VLM, MLM, a ULM', a CLM', a ILM', a VLM', a MLM', or combination thereof;

R_{PTM2} is hydrogen, halogen, aryl, methyl, ethyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

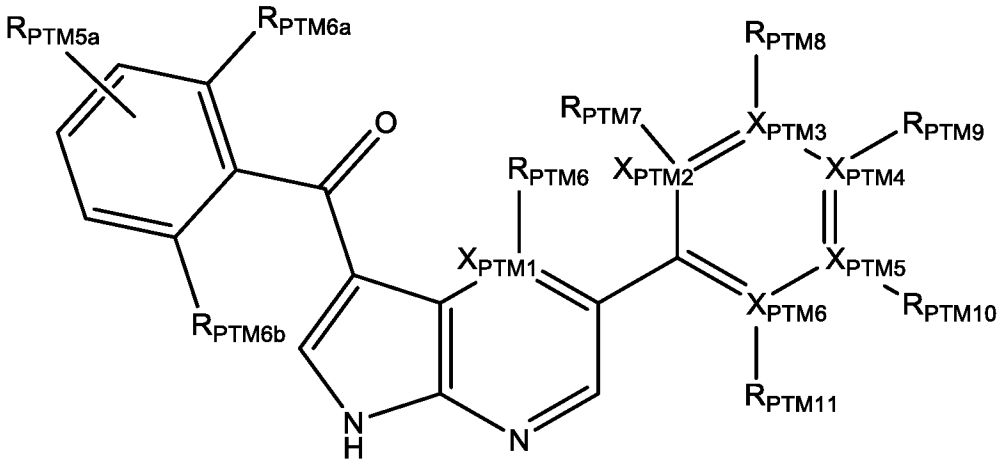
R_{PTM3} is absent, hydrogen, aryl, methyl, ethyl, other alkyl, cyclic alkyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

R_{PTM4} is hydrogen, halogen, aryl, methyl, ethyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle; and

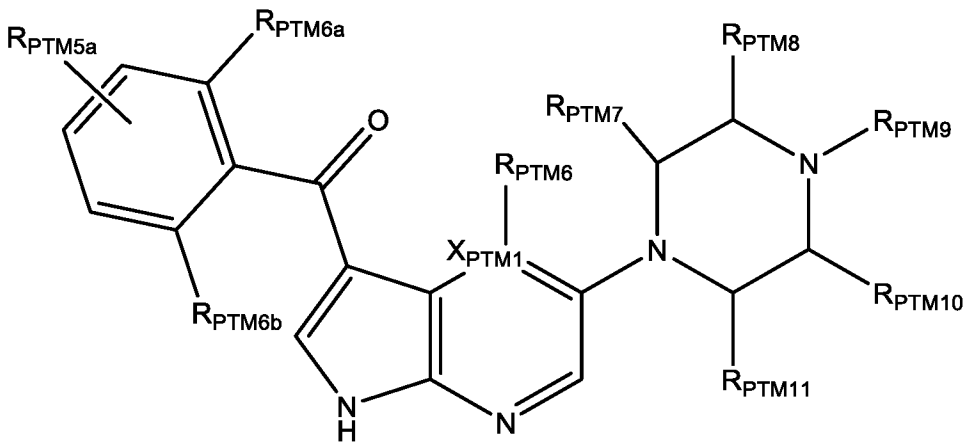
R_{PTM5} is selected from the group consisting of



[0269] In any aspect or embodiment described herein, the PTM may comprise a chemical group selected from the group of chemical structures consisting of PTM-IIa or PTM-IIb:



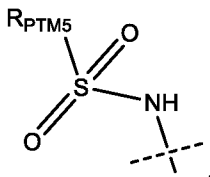
PTM-IIa or



PTM-IIb ,

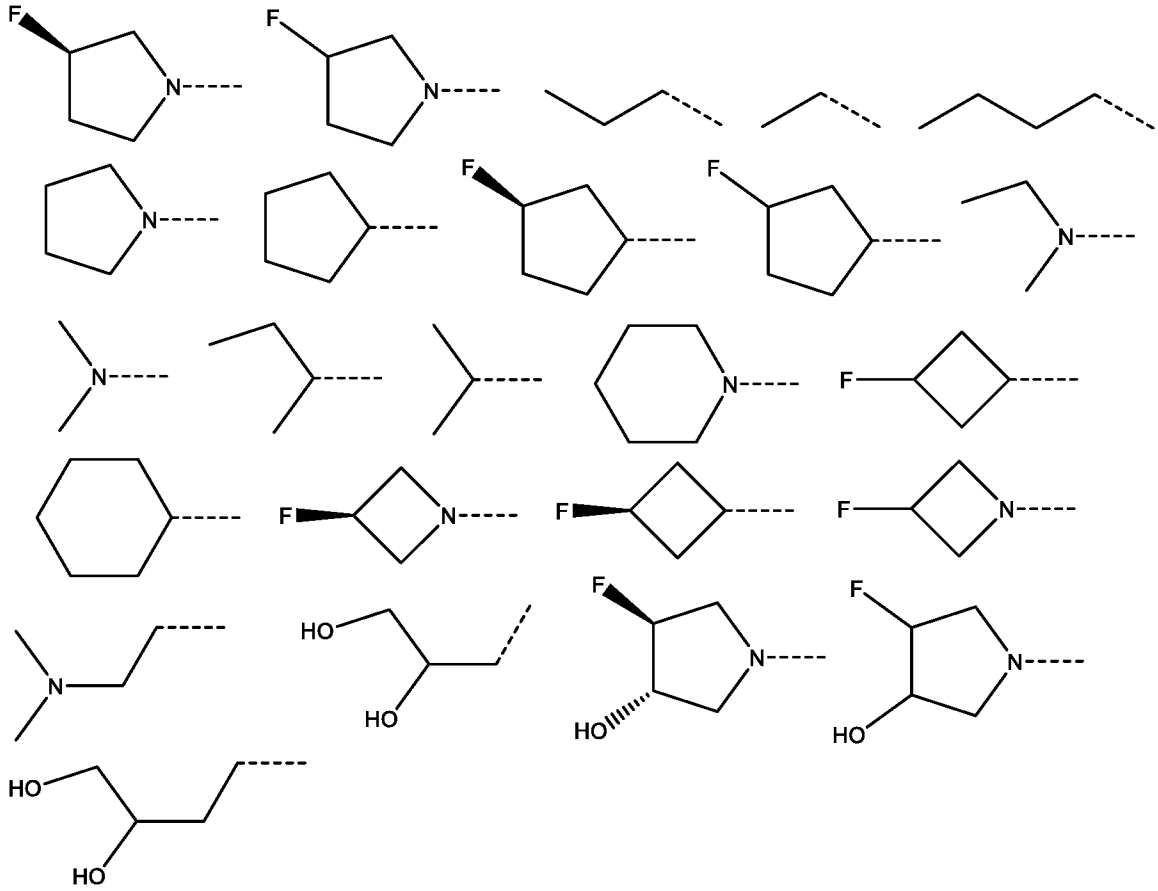
wherein:

X_{PTM1}, X_{PTM2}, X_{PTM3}, X_{PTM4}, X_{PTM5}, and X_{PTM6} are independently selected from CH or N;

R_{PTM5a} is selected from the group consisting of: bond, optionally substituted amine, optionally substituted amide (e.g., optionally substituted with an alkyl, methyl, ethyl, propyl, or butyl group), H, 

, , -NHC(O)R_{PTM5};

R_{PTM5} is selected from the group consisting of



R_{PTM6a} and R_{PTM6b} are each independently selected from hydrogen, halogen, or optionally substituted C_1-C_6 alkyl (linear, branched, optionally substituted);

R_{PTM6} is absent, hydrogen, halogen, aryl, methyl, ethyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

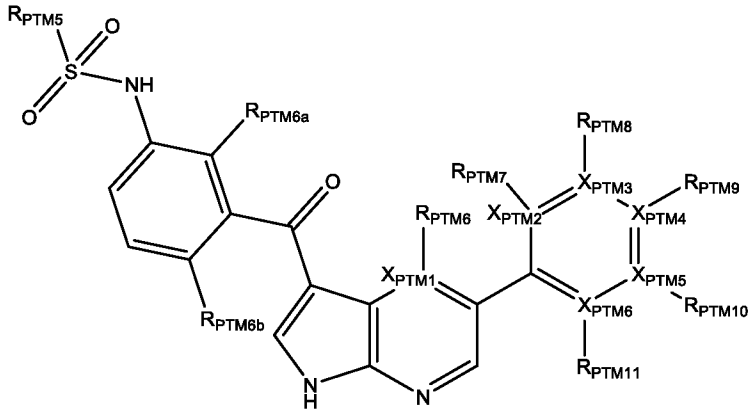
R_{PTM7} is absent, hydrogen, halogen, aryl, methyl, ethyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O or NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

R_{PTM8}, R_{PTM9} or R_{PTM10} are independently selected from the group consisting of absent, hydrogen, halogen, aryl, heteroaryl, alkyl, cycloalkyl, heterocycle, methyl, ethyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

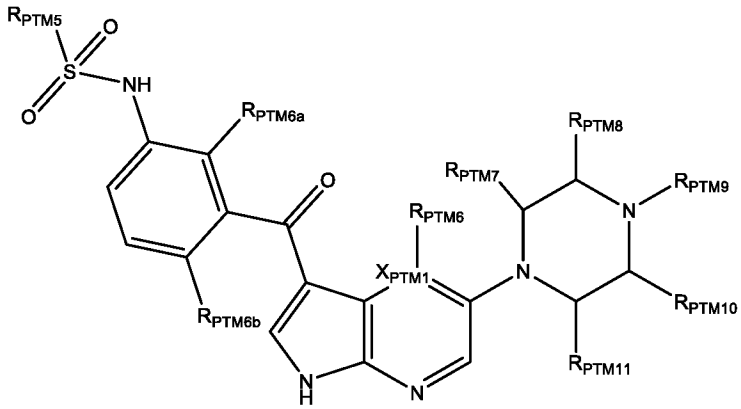
R_{PTM11} is absent, hydrogen, halogen, methyl, ethyl, OCH_3, NH CH_3 or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O or NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle; and

at least one of R_{PTM8}, R_{PTM9} or R_{PTM10} is modified to be covalently joined to a ULM, a chemical linker group (L), a CLM, an ILM, a VLM, MLM, a ULM', a CLM', a ILM', a VLM', a MLM', or combination thereof.

[0270] In certain embodiments, the PTM may comprise a chemical group selected from the group of chemical structures consisting of:



or



,

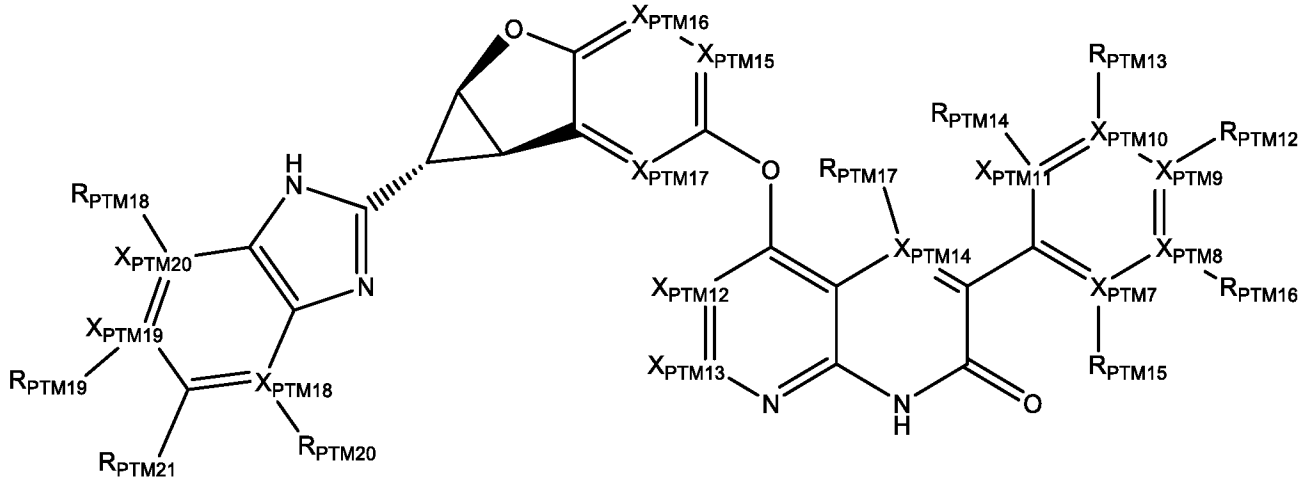
wherein R_{PTM5}, R_{PTM6a}, R_{PTM6b}, R_{PTM6}, R_{PTM7}, R_{PTM8}, R_{PTM9}, R_{PTM10}, R_{PTM11} are as described herein.

[0271] In some embodiments, when R_{PTM9} is the covalently joined position, R_{PTM7} and R_{PTM8} can be connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM7} and R_{PTM8} are attached.

[0272] In other embodiments, when R_{PTM8} is the covalently joined position, R_{PTM9} and R_{PTM10} can be connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM9} and R_{PTM10} are attached.

[0273] In further embodiments, when R_{PTM10} is the covalently joined position, R_{PTM8} and R_{PTM9} can be connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM8} and R_{PTM9} are attached.

[0274] In any aspect or embodiment described herein, the PTM may comprise a chemical group selected from the group of chemical structures consisting of PTM-III:



PTM-III

wherein:

X_{PTM7}, X_{PTM8}, X_{PTM9}, X_{PTM10}, X_{PTM11}, X_{PTM12}, X_{PTM13}, X_{PTM14}, X_{PTM15}, X_{PTM16}, X_{PTM17}, X_{PTM18}, X_{PTM19}, X_{PTM20} are independently CH or N;

R_{PTM12}, R_{PTM13}, R_{PTM14}, R_{PTM15}, R_{PTM16}, R_{PTM17}, R_{PTM18}, R_{PTM19} are independently selected from the group consisting of absent, hydrogen, halogen, aryl, heteroaryl, cycloalkyl, heterocycle, methyl, ethyl, other alkyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

R_{PTM20} is a small group containing less than four non-hydrogen atoms;

R_{PTM21} is selected from the group consisting of trifluoromethyl, chloro, bromo, fluoro, methyl, ethyl, propyl, isopropyl, *tert*-butyl, butyl, iso-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, OCH_3, $NHCH_3$, dimethylamino or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O or NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle; and

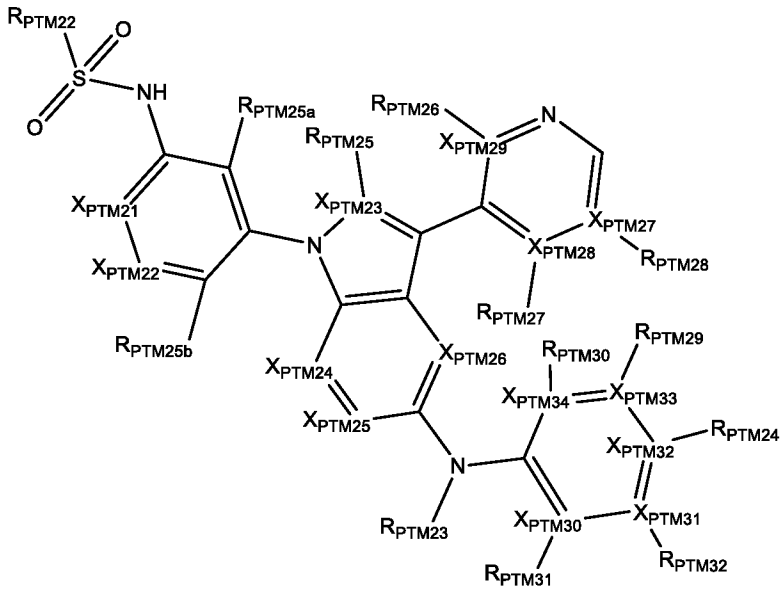
at least one of R_{PTM12}, R_{PTM13} and R_{PTM16} is modified to be covalently joined to a ULM, a chemical linker group (L), a CLM, an ILM, a VLM, MLM, a ULM', a CLM', a ILM', a VLM', a MLM', or combination thereof.

[0275] In some embodiments, when R_{PTM12} is the covalently joined position, R_{PTM13} and R_{PTM14} can be connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM13} and R_{PTM14} are attached; and/or R_{PTM15} and R_{PTM16} can be connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM15} and R_{PTM16} are attached.

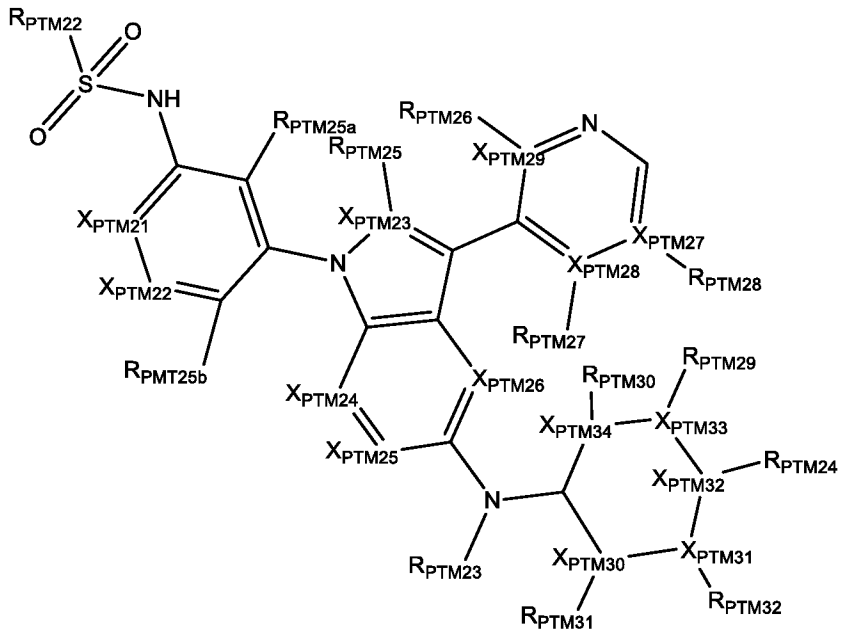
[0276] In other embodiments, when R_{PTM13} is the covalently joined position, R_{PTM12} and R_{PTM16} can be connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM12} and R_{PTM16} are attached; and/or R_{PTM15} and R_{PTM16} can be connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM15} and R_{PTM16} are attached.

[0277] In further embodiments, when R_{PTM16} is the covalently joined position, R_{PTM12} and R_{PTM13} can be connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM12} and R_{PTM13} are attached; and/or R_{PTM13} and R_{PTM14} can be connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM13} and R_{PTM14} are attached.

[0278] In any aspect or embodiment described herein, the PTM may comprise a chemical group selected from the group of chemical structures consisting of PTM-IVa or PTM-IVb:



PTM-IVa or

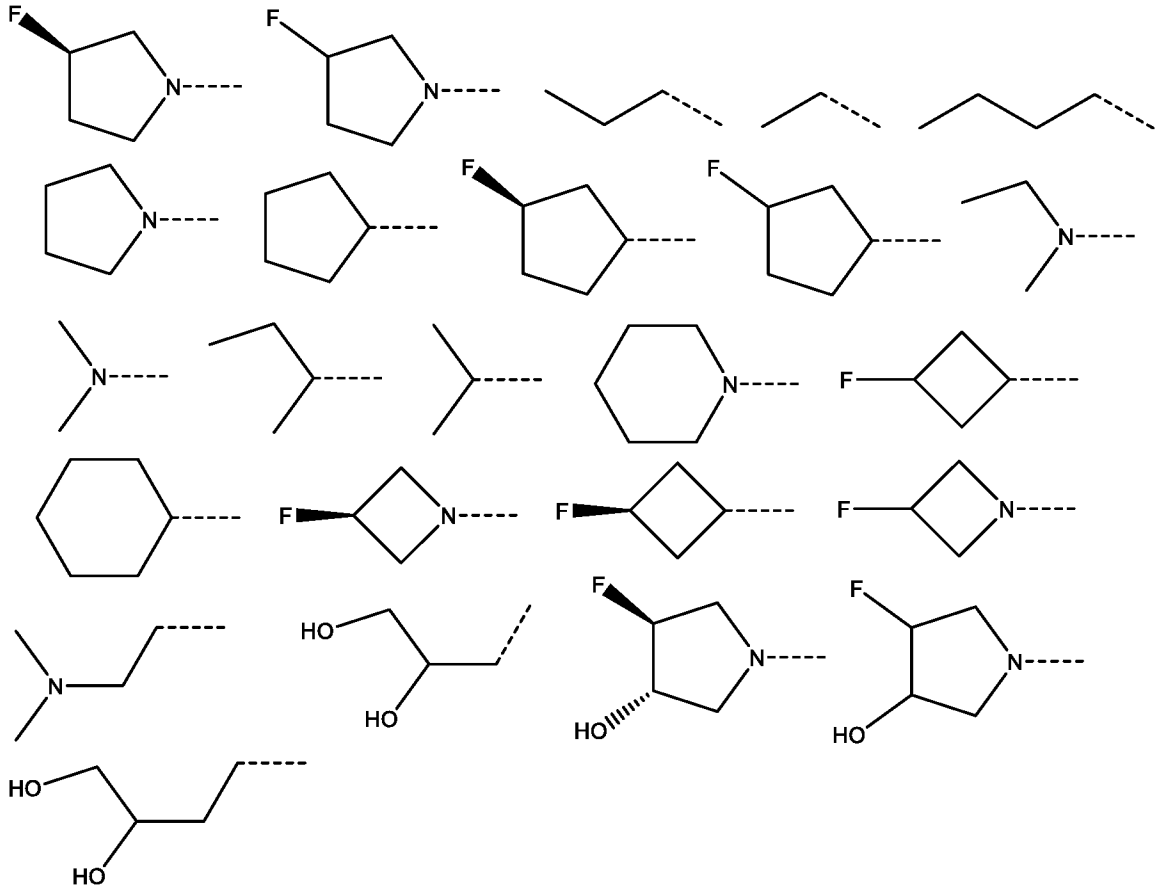


PTM-IVb ,

wherein:

X_{PTM21}, X_{PTM22}, X_{PTM23}, X_{PTM24}, X_{PTM25}, X_{PTM26}, X_{PTM27}, X_{PTM28}, X_{PTM29}, X_{PTM30}, X_{PTM31}, X_{PTM32}, X_{PTM33}, X_{PTM34} are independently CH or N;

R_{PTM22} is selected from the group consisting of



R_{PTM25a} and R_{PTM25b} are each independently selected from hydrogen, halogen, or C_1-C_6 alkyl (linear, branched, optionally substituted);

R_{PTM23}, R_{PTM24}, R_{PTM28}, R_{PTM29}, R_{PTM30}, R_{PTM31}, R_{PTM32} are independently selected from the group consisting of absent, bond, hydrogen, halogen, aryl (optionally substituted), heteroaryl (optionally substituted), cycloalkyl (optionally substituted), heterocycle (optionally substituted), methyl, ethyl (optionally substituted), other alkyl (linear, branched, optionally substituted), OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl (linear, branched, optionally substituted), cyclic alkyl (optionally substituted), aryl (optionally substituted)or heterocycle (optionally substituted); and

R_{PTM25} is absent, hydrogen, halogen, C_1-C_6 alkyl (linear, branched, optionally substituted), OCH3, $NHCH_3$ or SCH_3;

R_{PTM26} is absent, hydrogen, halogen, C_1-C_6 alkyl (linear, branched, optionally substituted), OCH3, $NHCH_3$ or SCH_3;

R_{PTM27} is selected from the group consisting of absent, hydrogen, halogen, C_1-C_6 alkyl (linear, branched, optionally substituted), OCH_3, $NHCH_3$ or SCH_3; and

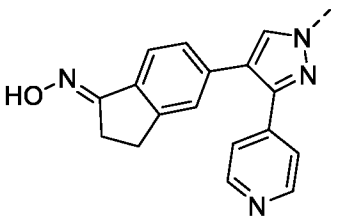
at least one of R_{PTM24}, R_{PTM29}, R_{PTM32} is modified to be covalently joined to a ULM, a chemical linker group (L), a CLM, an ILM, a VLM, MLM, a ULM', a CLM', a ILM', a VLM', a MLM', or combination thereof.

[0279] In some embodiments, when R_{PTM24} is the covalently joined position, R_{PTM31} and R_{PTM32} can be connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM31} and R_{PTM32} are attached; or R_{PTM29} and R_{PTM30} can be connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM29} and R_{PTM30} are attached.

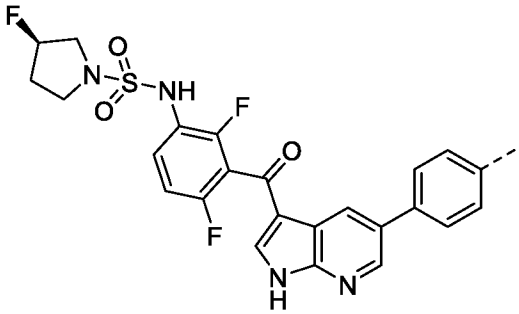
[0280] In other embodiments, when R_{PTM29} is the covalently joined position, R_{PTM24} and R_{PTM32} can be connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM24} and R_{PTM32} are attached; and/or R_{PTM31} and R_{PTM32} can be connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM31} and R_{PTM32} are attached.

[0281] In further embodiments, when R_{PTM32} is the covalently joined position, R_{PTM24} and R_{PTM29} can be connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM24} and R_{PTM29} are attached; and/or R_{PTM29} and R_{PTM30} can be connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM29} and R_{PTM30} are attached.

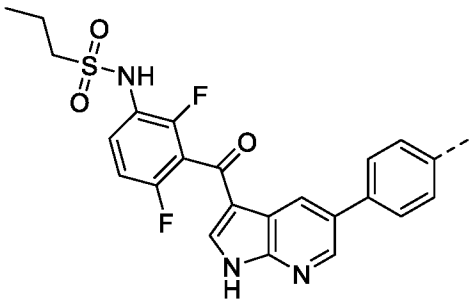
[0282] In any aspect or embodiments described herein, the PTM is selected from the group consisting of chemical structures PTM-1, PTM-2, PTM-3, PTM-4, PTM-5, PTM-6, PTM-7, and PTM-8:



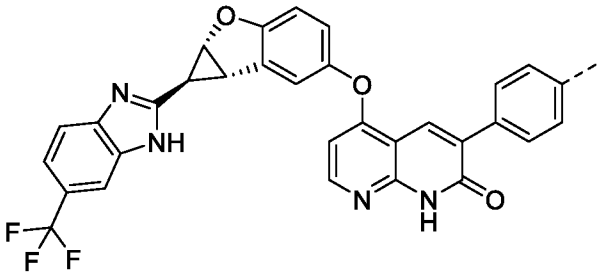
PTM-1



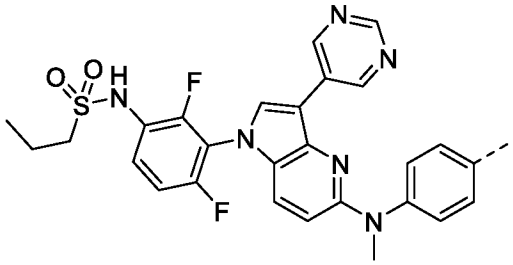
PTM-2



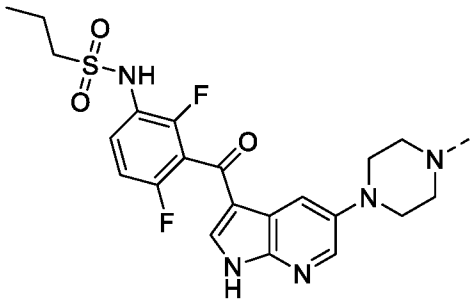
PTM-3



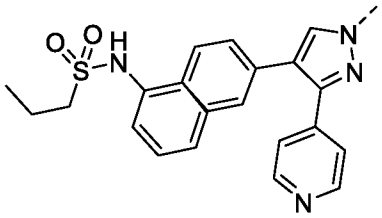
PTM-4



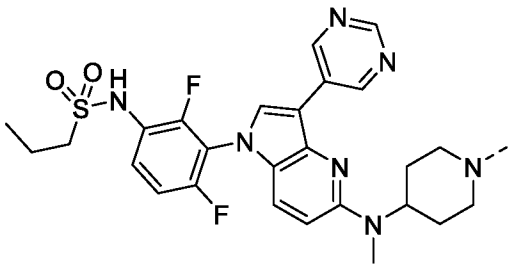
PTM-5



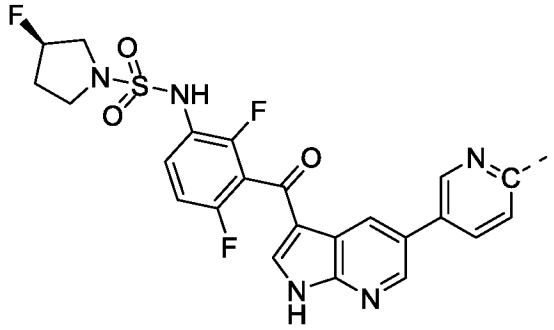
PTM-6



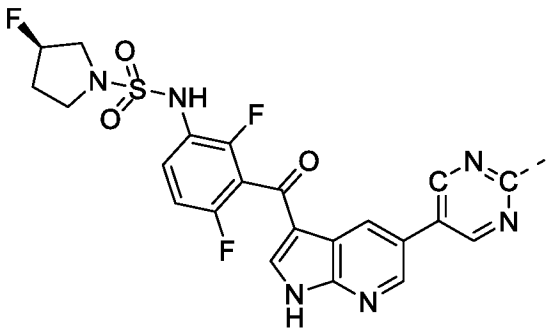
PTM-7



PTM-8

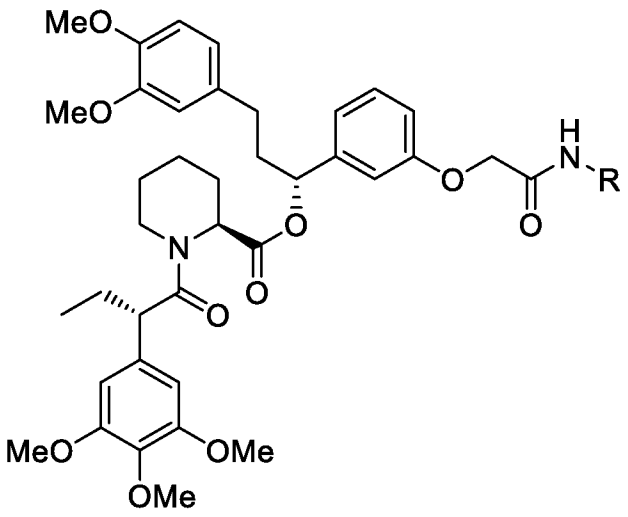


PTM-9



PTM-10

[0283] **XI. Compounds Targeting FKBP:**

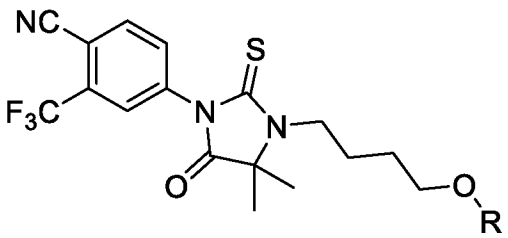


[0284]

[0285] (Derivatized where "R" designates a site for a linker group L or a –(L-CLM) group attachment, for example).

[0286] **XII. Compounds Targeting Androgen Receptor (AR)**

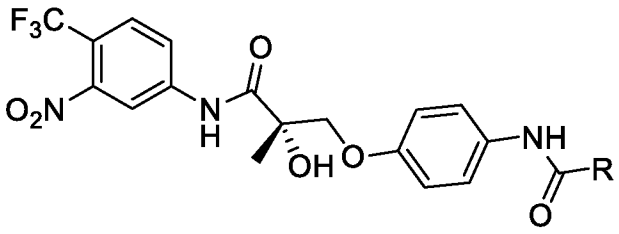
[0287] **1.** RU59063 Ligand (derivatized) of Androgen Rceptor



[0288]

[0289] (Derivatized where "R" designates a site for a linker group L or a –(L-CLM) group attachment, for example).

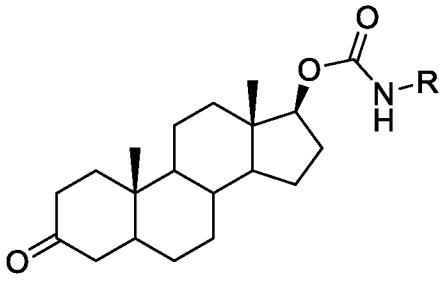
[0290] **2.** SARM Ligand (derivatized) of Androgen Receptor



[0291]

[0292] (Derivatized where "R" designates a site for a linker group L or a–(L-CLM) group attachment, for example).

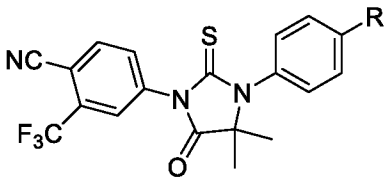
[0293] **3.** Androgen Receptor Ligand DHT (derivatized)



[0294]

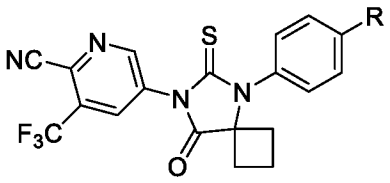
[0295] (Derivatized where "R" designates a site for a linker group L or –(L-CLM) group attachment, for example).

[0296] **4.** MDV3100 Ligand (derivatized)



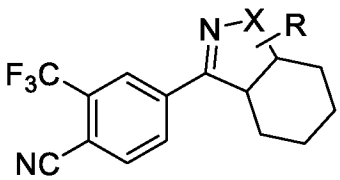
[0297]

[0298] **5.** ARN-509 Ligand (derivatized)



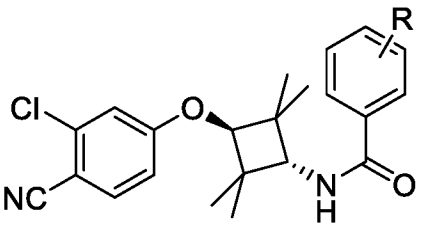
[0299]

[0300] **6.** Hexahydrobenzisoxazoles



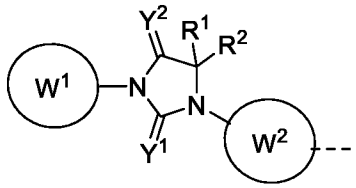
[0301]

[0302] **7.** Tetramethylcyclobutanes

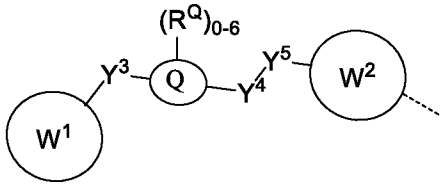
[0303] 

[0304] 8. In any aspect or embodiment described herein, the PTM is a chemical moiety that binds to the androgen receptor (AR). Various androgen receptor binding compounds have been described in literature, including various androgen derivatives such as testosterone, dihydrotestosterone, and metribolone (also known as methyltrienolone or R1881), and non-steroidal compounds such as bicalutamide, enzalutamide, some of which are described above. Those of ordinary skill in the art would appreciate that these androgen receptor binding compounds could be potentially used as an androgen binding moiety (ABM) in a PROTAC compound. Such literature includes, but not limited to, G. F. Allan et. al, *Nuclear Receptor Signaling*, 2003, 1, e009; R. H. Bradbury et. al, *Bioorganic & Medicinal Chemistry Letters*, 2011 5442–5445; C. Guo et. al, *Bioorganic & Medicinal Chemistry Letters*, 2012 2572-2578; P. K. Poutiainen et. al, *J. Med. Chem.* 2012, 55, 6316 − 6327 A. Pepe et. al, *J. Med. Chem.* 2013, 56, 8280 – 8297; M. E. Jung et al, *J. Med. Chem.* 2010, 53, 2779–2796, which are incorporated by reference herein

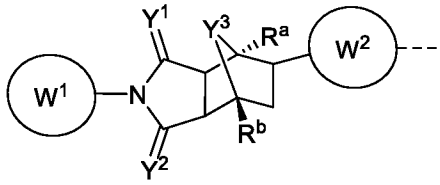
[0305] In any aspect or embodiment described herein, the ABM comprises a structure selected from, but not limited to the structures shown below, wherein a dashed line indicates the attachment point of a linker moiety or a ULM, such as a CLM:



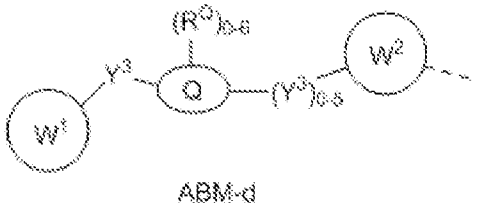
ABM-a ;



ABM-b ;



ABM-c ; and



ABM-d ,

wherein:

W^1 is aryl, heteroaryl, bicyclic, or biheterocyclic, each independently substituted by 1 or more H, halo, hydroxyl, nitro, CN, C≡CH, C_{1-6} alkyl (linear, branched, optionally substituted; for example, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), C_{1-6} alkoxyl (linear, branched, optionally substituted; for example, optionally substituted by 1 or more halo), C_{2-6} alkenyl, C_{2-6} alkynyl, or CF_3;

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

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

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

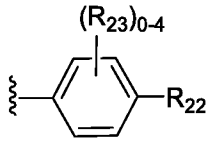
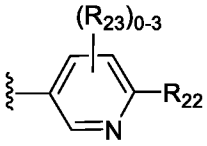
R^1, R^2, R^a, R^b, R^{Y1}, R^{Y2} are each independently H, C_{1-6} alkyl (linear, branched, optionally substituted; for example, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), halogen, C_{1-6} alkoxy, cyclic, heterocyclic , or R^1, R^2 together with the atom they are attached to, form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

W^2 is a bond, C_{1-6} alkyl, C_{1-6} heteroalkyl, O, aryl, heteroaryl, alicyclic, heterocyclic, biheterocyclic, biaryl, or biheteroaryl, each optionally substituted by 1-10 R^{W2};

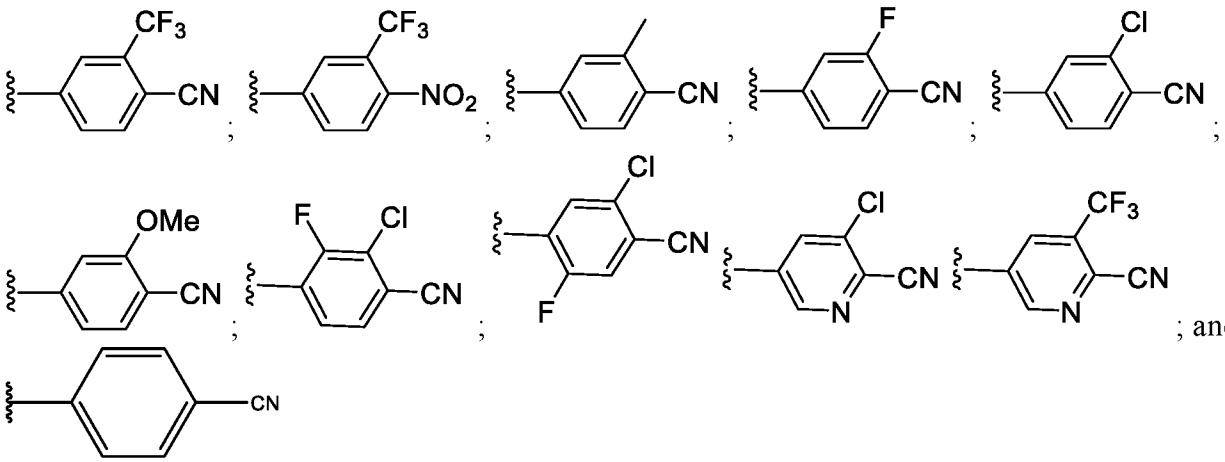
each R^{W2} is independently H, halo, C_{1-6} alkyl (linear, branched, optionally substituted; for example, optionally substituted by 1 or more F), $-OR^{W2A}$, C_{3-6} cycloalkyl, C_{4-6} cycloheteroalkyl, C_{1-6} alicyclic (optionally substituted), heterocyclic (optionally substituted), aryl (optionally substituted), or heteroaryl (optionally substituted), bicyclic hereoaryl or aryl, OC_{1-3}alkyl (optionally substituted), OH, NH_2, $NR^{Y1}R^{Y2}$, CN; and

R^{W2A} is H, C_{1-6} alkyl (linear, branched), or C_{1-6} heteroalkyl (linear, branched), each optionally substituted by a cycloalkyl, cycloheteroalkyl, aryl, heterocyclic, heteroaryl, halo, or OC_{1-3}alkyl.

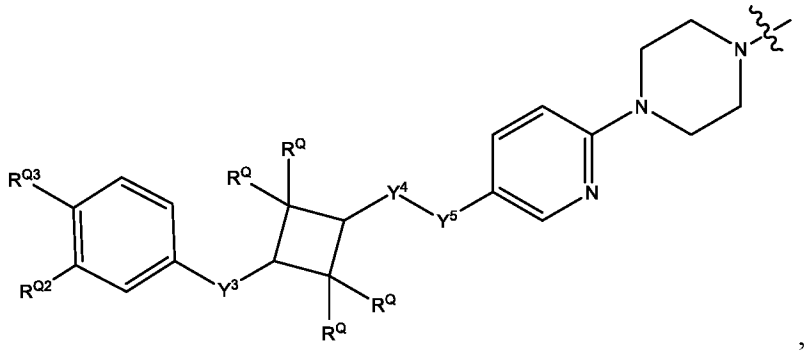
[0306] In any aspect or embodiment described herein, the W^2 is covalently coupled to one or more ULM or CLM groups, or a linker to which is attached one or more ULM or CLM groups as described herein.

[0307] In any aspect or embodiment described herein, W^1 is  or  , wherein each R_{22} is independently halo, H, optionally substituted alkyl, haloalkyl, cyano, or nitro; and each R_{23} is independently H, halo, CF_3, optionally substituted alkyl, alkoxy,haloalkyl, cyano, or nitro.

[0308] In any aspect or embodiment described herein, W^1 is selected from the group consisting of:


; and

[0309] In any aspect or embodiment described herein, the ABM comprises a structure selected from the following structures shown below, where a ~~~ indicates tha attachment point of a linker or a ULM:



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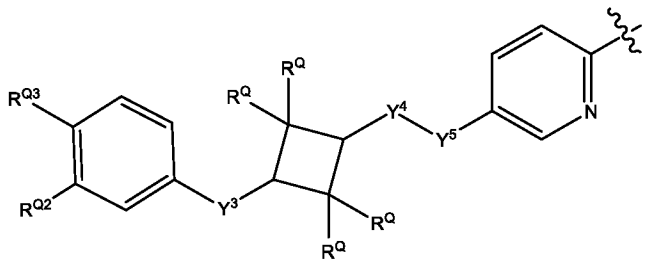
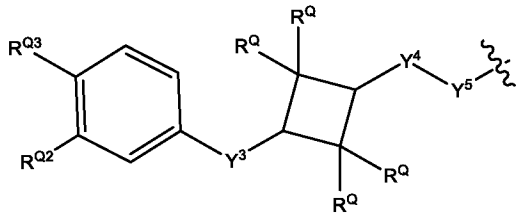


, and



,

wherein:

R^{Q2} is a H, halogen, CH_3 or CF_3;

R^{Q3} is H, halo, hydroxyl, nitro, CN, C≡CH, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), C_{1-6} alkoxyl (linear, branched, optionally substituted by 1 or more halo), C_{2-6} alkenyl, C_{2-6} alkynyl, or CF_3;

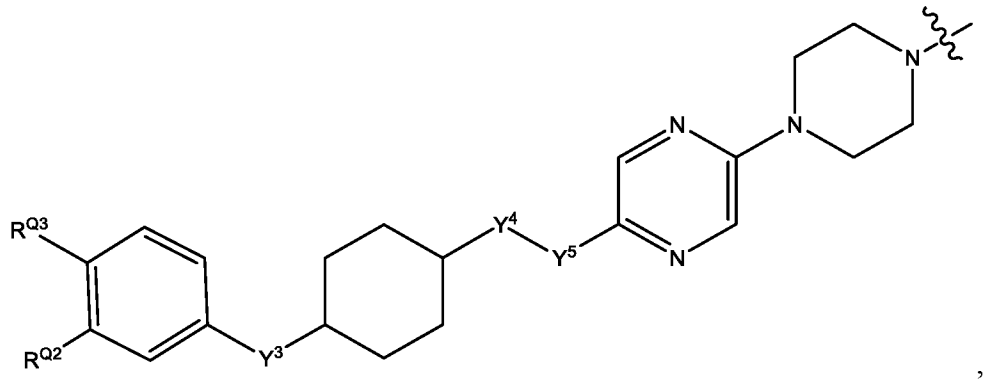
Y^3, Y^4, Y^5 are each independently a bond, O, NR^{Y2}, $CR^{Y1}R^{Y2}$, C=O, heteroaryl, or aryl;

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

R^Q each independently is H, C_1-C_6 alkyl (linear, branched, optionally substituted by 1 or more halo, or C_{1-6} alkoxyl), or two R^Q together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms.

[0310] In any aspect or embodiment described herein, each R^Q is independently H or CH_3. In another embodiment R^{Q3} is CN.

[0311] In any aspect or embodiment described herein, the ABM comprises a structure selected from the following structures shown below, where a indicates the attachment point of a linker or a ULM:



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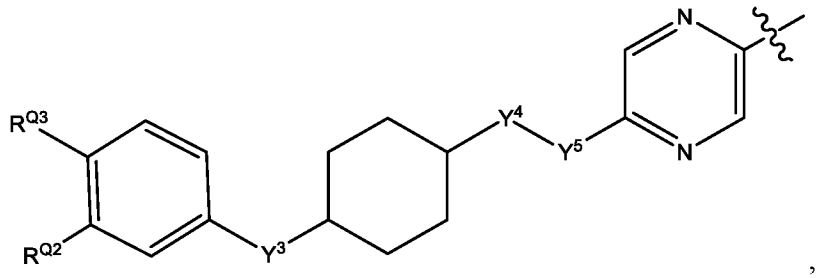

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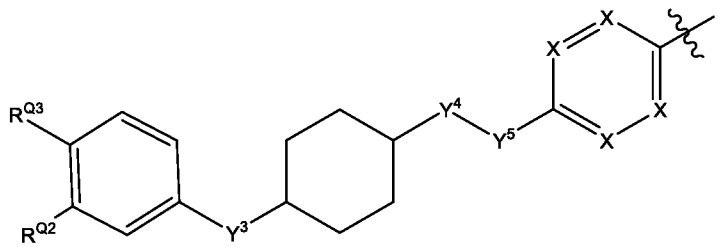
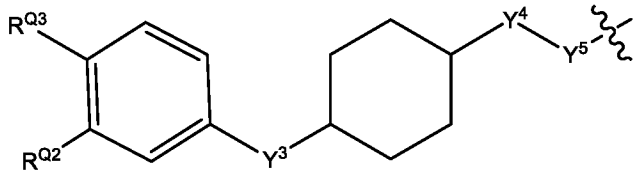


, and



,

wherein:

R^{Q2} is a H, halogen, CN, CH_3 or CF_3; and

R^{Q3} is H, halo, hydroxyl, nitro, CN, C≡CH, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), C_{1-6} alkoxyl (linear, branched, optionally substituted by 1 or more halo), C_{2-6} alkenyl, C_{2-6} alkynyl, or CF_3; .

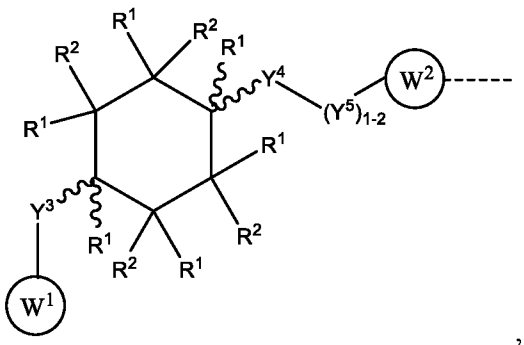
Y^3, Y^4, Y^5 are each independently a bond, O, NR^{Y2}, $CR^{Y1}R^{Y2}$, C=O, heteroaryl, or aryl; and

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

X is N or C.

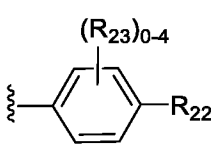
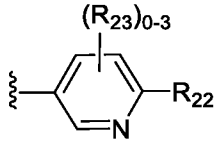
[0312] In any aspect or embodiment described herein, R^{Q3} is a CN.

[0313] In any aspect or embodiment described herein, the ABM comprises a structure shown below, where a dashed line indicates the attachment point of a linker moiety or a ULM or a CLM:



,

wherein:

W^1 is  or  ;

each R_{22} is independently H or -CN;

each R_{23} is independently H, halo, C_1-C_6 alkyl (linear, branched, optionally substituted), C_1-C_6 alkoxy, or $-CF_3$;

Y^3 is a bond or O;

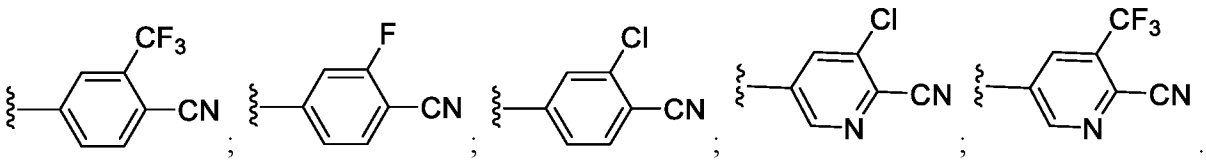
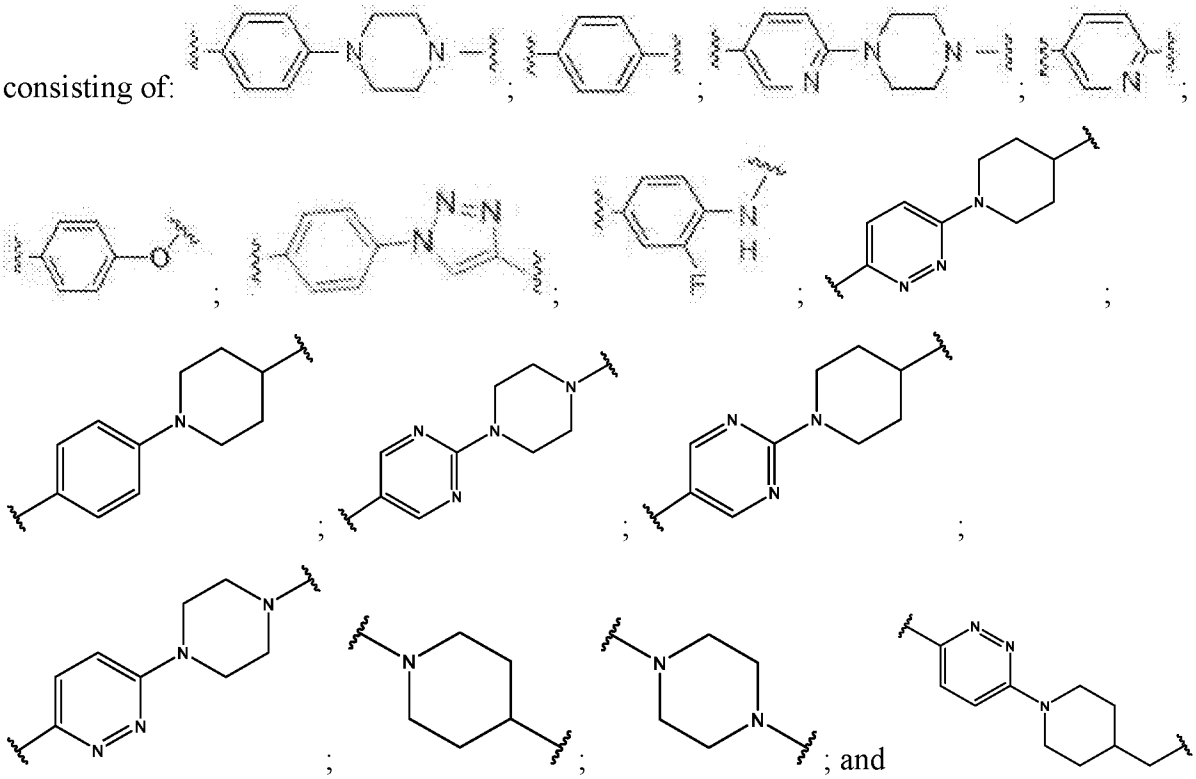
Y^4 is a bond or NH;

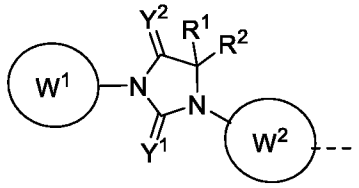
Y^5 is a bond, C=O, C_1-C_6 heteroaryl, or C_1-C_6 aryl;

R^1, R^2, are each independently H, or C_1-C_6 alkyl (linear or branched, optionally substituted; for example, optionally substituted by 1 or more halo, or C_{1-6} alkoxyl);

W^2 is a bond, C_{1-6} aryl, C_{1-6} heteroaryl, C_{1-6} alicyclic, or C_{1-6} heterocyclic, biheterocyclic, biaryl, or biheteroaryl, each optionally substituted by 1-10 R^{W2}; and

each R^{W2} is independently H, or halo; and

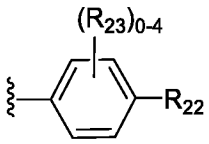
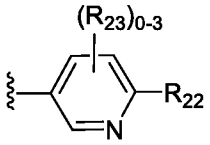
~~~ represents a bond that may be stereospecific ((R) or (S)) or non-stereospecific.

[0314] In any aspect or embodiment described herein, the W^2 is covalently coupled to one or more ULM or CLM groups, or a linker to which is attached one or more ULM or CLM groups as described herein.

[0315] In any aspect or embodiment described herein, W^1 is selected from the group consisting of:



[0316] In any aspect or embodiment described herein, W^2 is selected from the group consisting of:



[0317] In any aspect or embodiment described herein, the ABM comprises a structure selected from, but not limited to the structures shown below, where a dashed line indicates the attachment point of a linker moiety or a ULM:
~~~



ABM-a

,

wherein:

W^1 is  or  ;

each R_{22} is independently H or -CN;

each R_{23} is independently H, halo, or $–CF_3$;

Y^1, Y^2 are each independently O or S;

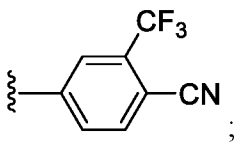
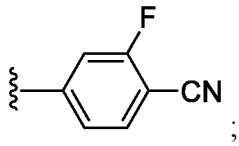
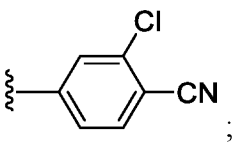
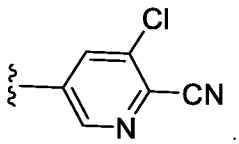
R^1, R^2, are each independently H or a methyl group;

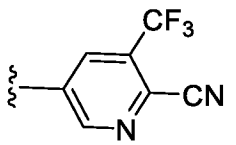
W^2 is a bond, C_{1-6} aryl, or heteroaryl, each optionally substituted by 1, 2 or 3 R^{W2}; and

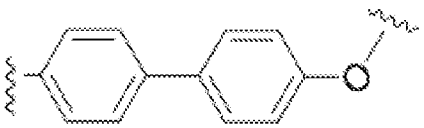
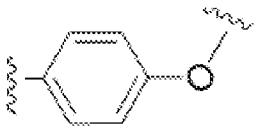
each R^{W2} is independently H, halo, C_{1-6} alkyl (optionally substituted by 1 or more F), OC_{1-3}alkyl (optionally substituted by 1 or more –F).

[0318] In any of the embodiments described herein, the W^2 is covalently coupled to one or more ULM or CLM groups, or a linker to which is attached one or more ULM or CLM groups as described herein.

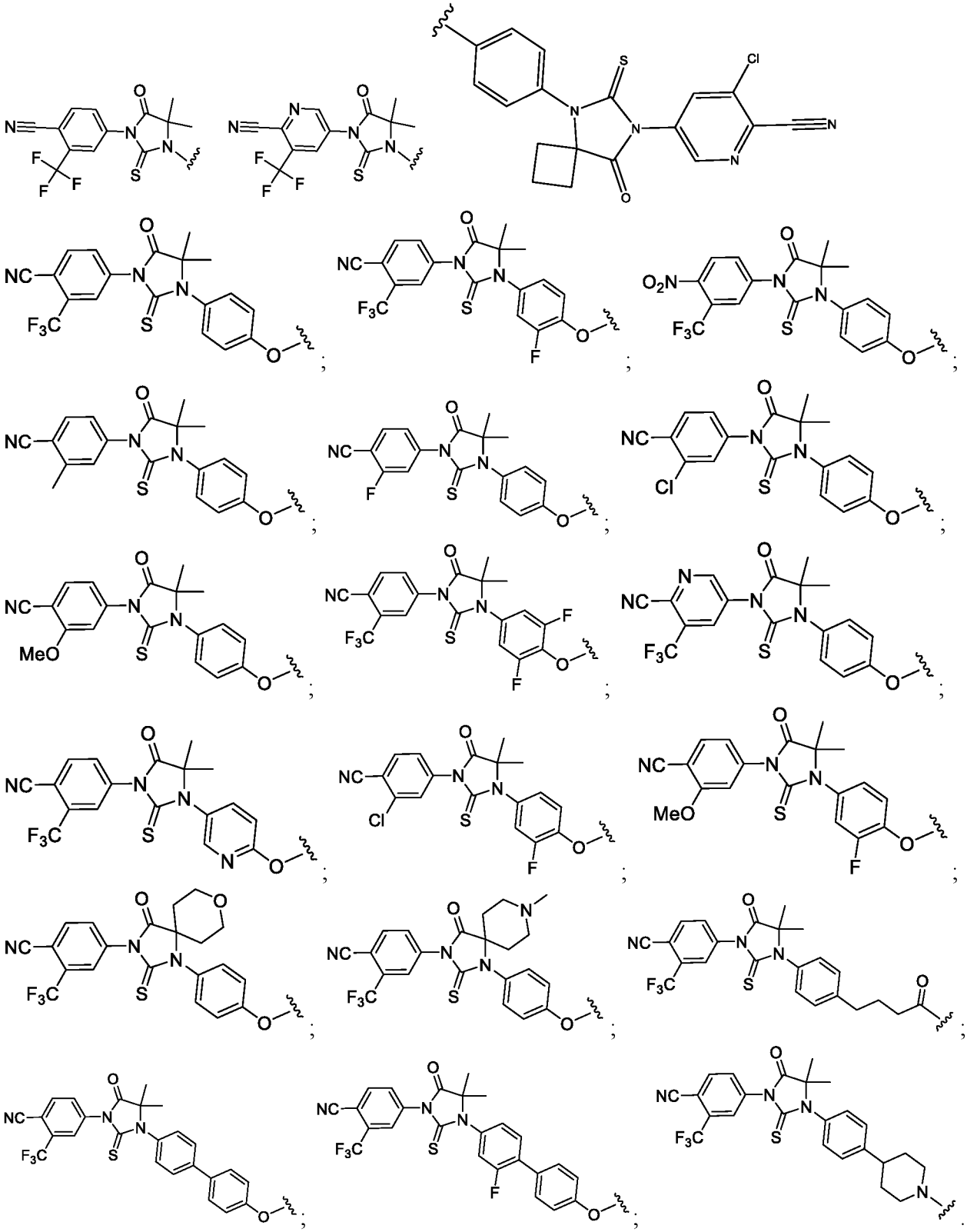
[0319] In certain additional embodiments, W^1 is selected from the group consisting of:

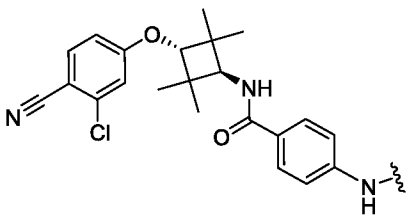
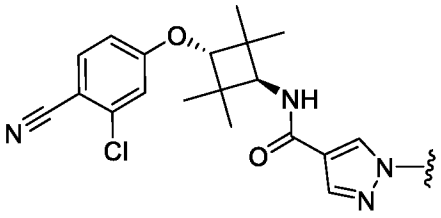
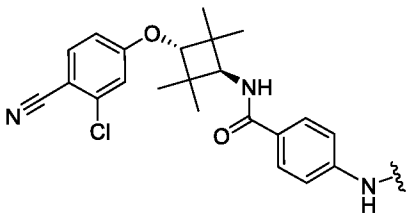
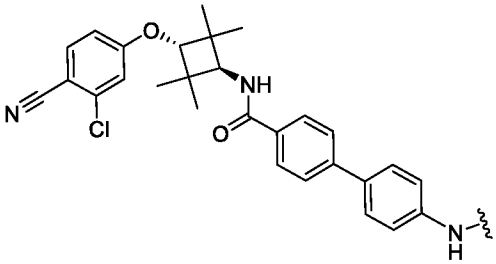
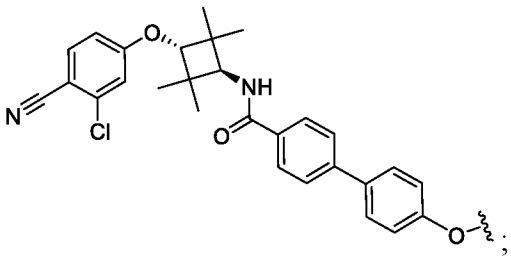
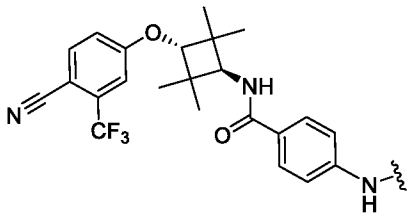
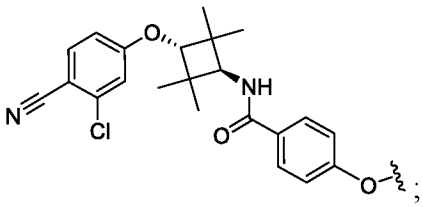
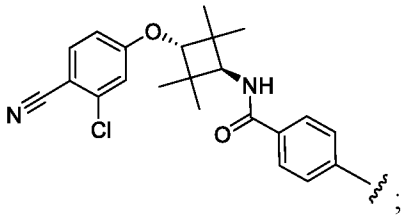
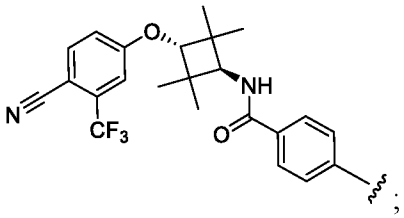
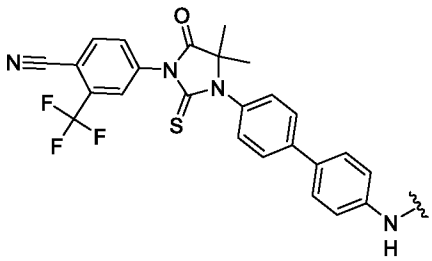
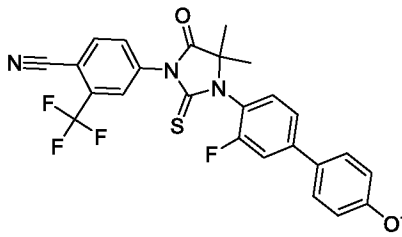
 ;  ;  ;  ; and

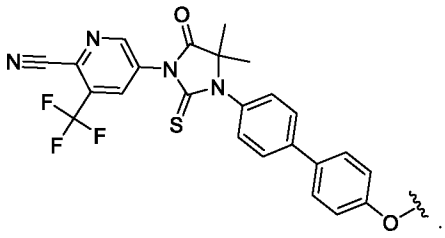
 .

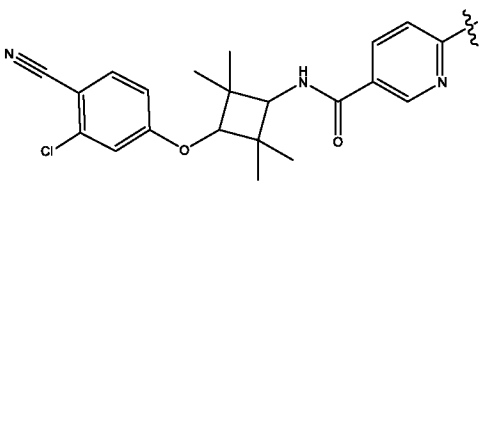
[0320] In any aspect or embodiment described herein, W2 is selected from the group consisting of:  and  .

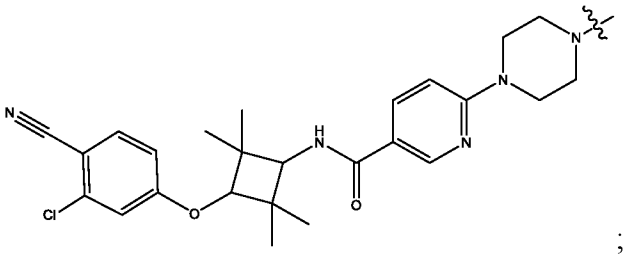
[0321] In any aspect or embodiment described herein, ABM is selected from the group consisting of:





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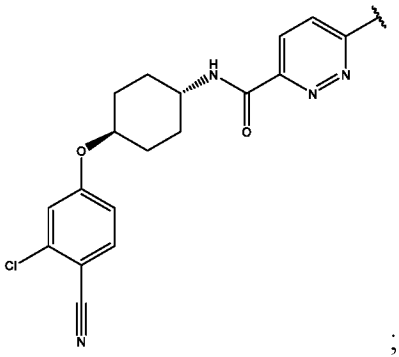
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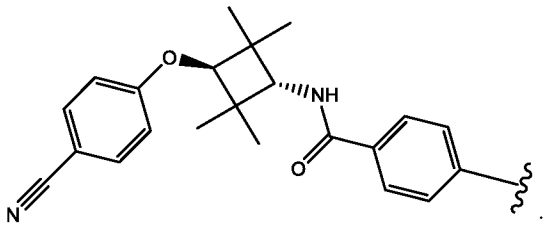
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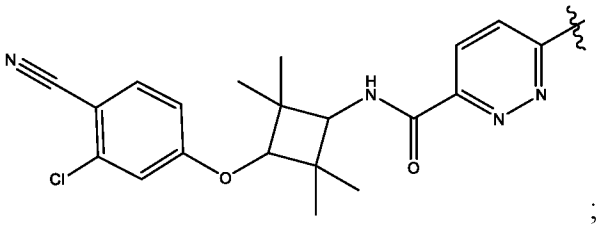
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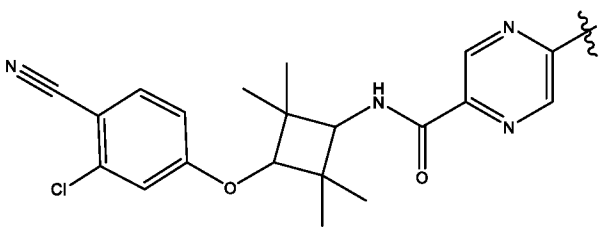
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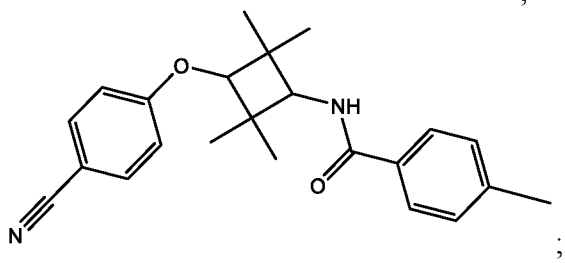
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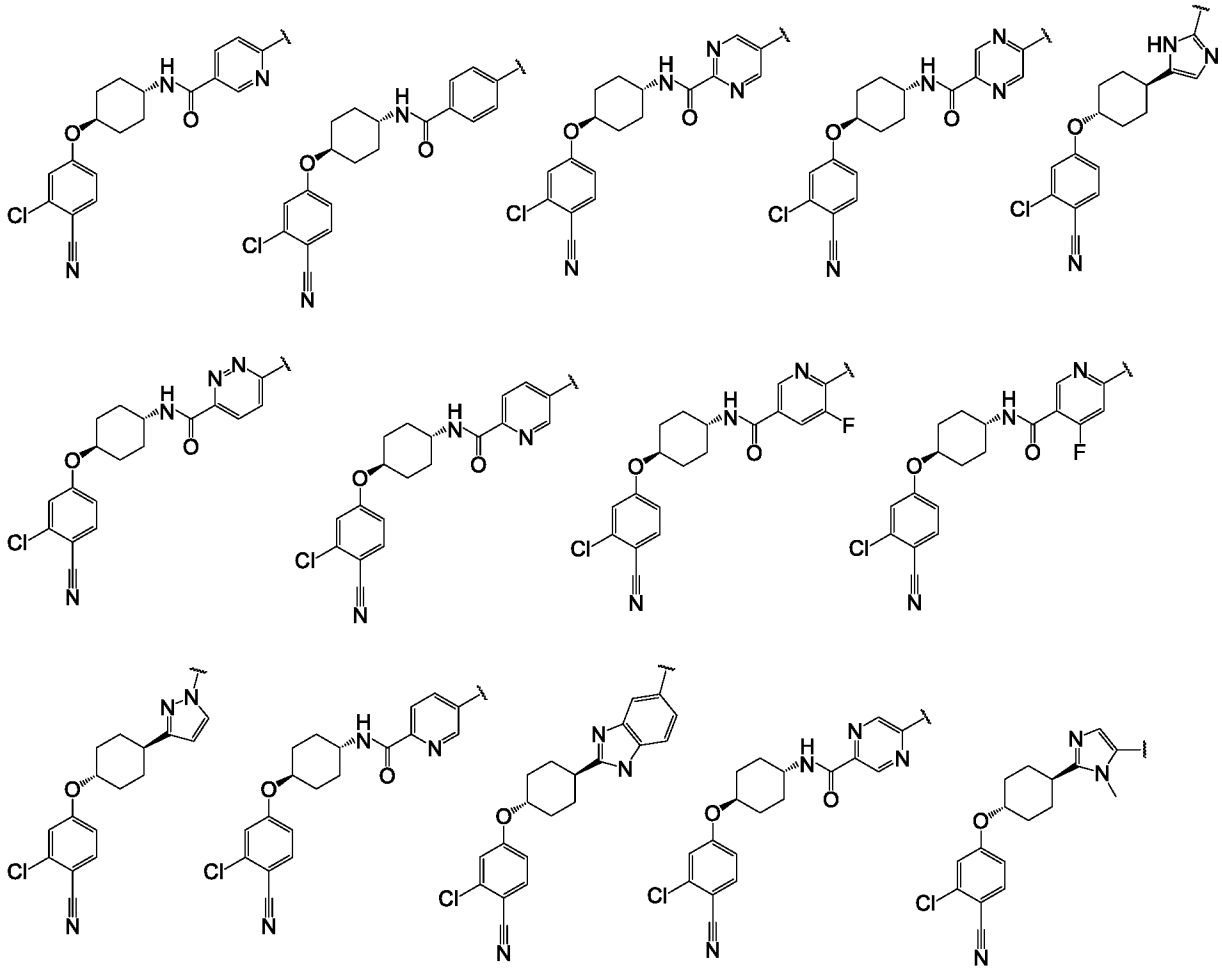
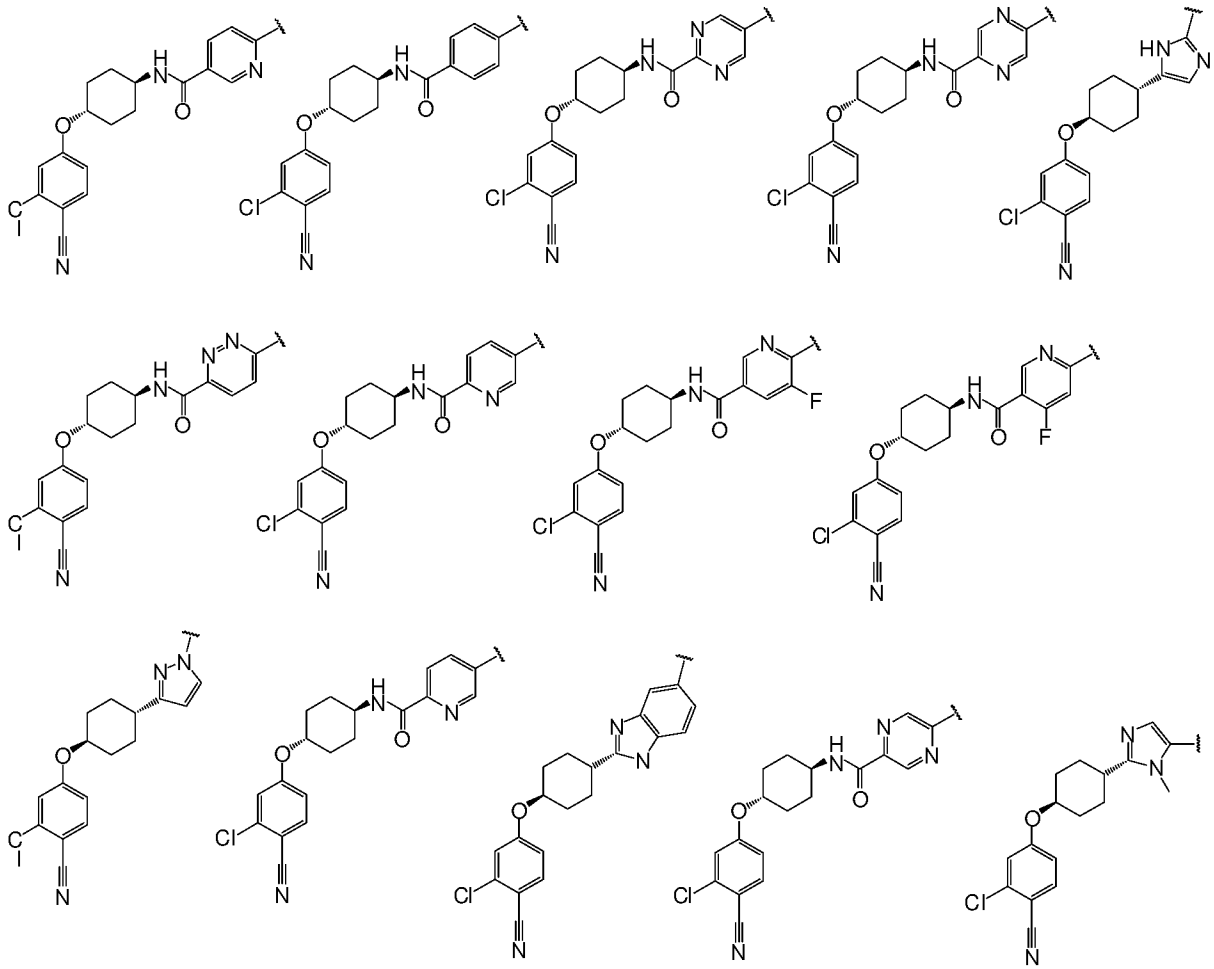




[0322] In any aspect or embodiment described herein, the ABM comprises the structure:

ABM-b

wherein:

W^1 is aryl, or heteroaryl, each independently substituted by 1 or more H, halo, hydroxyl, nitro, CN, C≡CH, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), C_{1-6} alkoxyl (linear, branched, optionally substituted by 1 or more halo), C_{2-6} alkenyl, C_{2-6} alkynyl, or CF_3;

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

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

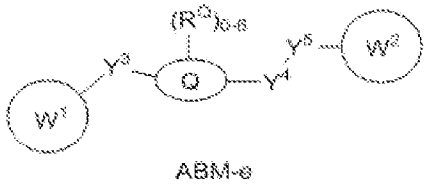
R^{Y1}, R^{Y2} are each independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl);

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

each R^{W2} is independently H, halo, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more F), C_{1-6} heteroalkyl (linear, branched, optionally substituted), -OR^{W2A} OC_{1-3}alkyl (optionally substituted by 1 or more –F), C_{3-6} cycloalkyl, C_{4-6} cycloheteroalkyl (optionally substituted), C_{1-6} alkyl (optionally substituted), C_{1-6} alicyclic (optionally substituted), heterocyclic (optionally substituted), aryl (optionally substituted), heteroaryl (optionally substituted), bicyclic hereoaryl (optionally substituted), bicyclic aryl, OH, NH_2, $NR^{Y1}R^{Y2}$, or CN; and

R^{W2A} is H, C_{1-6} alkyl (linear, branched), or C_{1-6} heteroalkyl (linear, branched), each optionally substituted by a cycloalkyl, cycloheteroalkyl, aryl, heterocyclic, heteroaryl, halo, or OC_{1-3}alkyl.

[0323] In any aspect or embodiment described herein, the description provides an androgen receptor bindingcompound comprising a structure of:



ABM-e ,

wherein:

W^1 is aryl, heteroaryl, , bicyclic, or biheterocyclic, each independently substituted by 1 or more H, halo, hydroxyl, nitro, CN, C≡CH, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), C_{1-6} alkoxyl (linear, branched, optionally substituted by 1 or more halo), C_{2-6} alkenyl, C_{2-6} alkynyl, or CF_3;

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

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

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

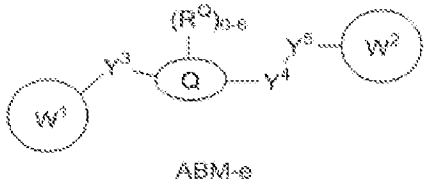
R^1, R^2, R^a, R^b, R^{Y1}, R^{Y2} are each independently H, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or R^1, R^2 together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

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

each R^{W2} is independently H, halo, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more F), C_{1-6} heteroalkyl (linear, branched, optionally substituted), $-OR^{W2A}$, OC_{1-3}alkyl (optionally substituted by 1 or more –F), C_{3-6} cycloalkyl, C_{4-6} cycloheteroalkyl, C_{1-6} alkyl (optionally substituted), C_{1-6} alicyclic (optionally substituted), heterocyclic (optionally substituted), aryl (optionally substituted), or heteroaryl (optionally substituted), bicyclic hereoaryl or aryl, OH, NH_2, $NR^{Y1}R^{Y2}$, CN; and

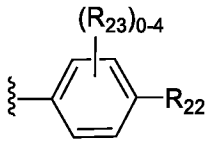
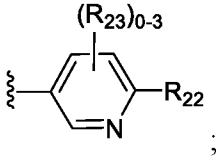
R^{W2A} is H, C_{1-6} alkyl (linear, branched), or C_{1-6} heteroalkyl (linear, branched), each optionally substituted by a cycloalkyl, cycloheteroalkyl, aryl, heterocyclic, heteroaryl, halo, or OC_{1-3}alkyl.

[0324] In any aspect or embodiment described herein, an androgen receptor binding moiety has a structure of:



ABM-e ,

wherein:

W^1 is  or  ;

each R_{22} is independently H or -CN;

each R_{23} is independently H, halo, or $-CF_3$;

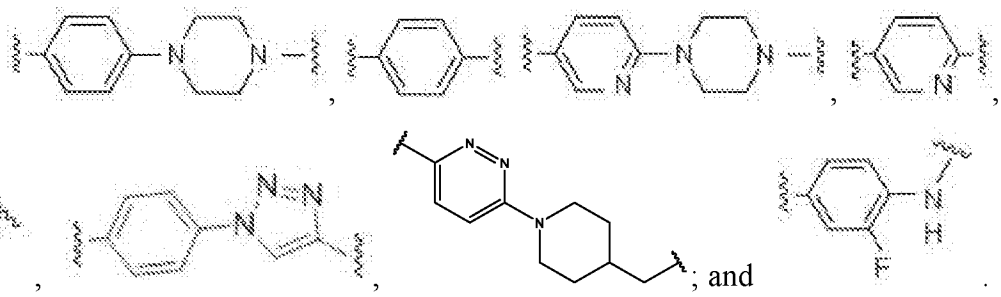
Y^3 is a bond or O;

Q is a 4 member ring, optionally substituted with 0-4 R^Q, each R^Q is independently H or methyl;

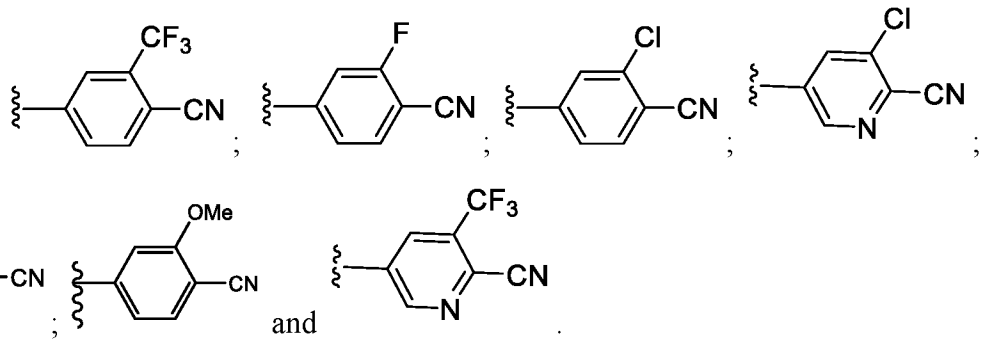
Y4 is a bond or NH;

Y5 is a bond, a C=O, or a C=S; and

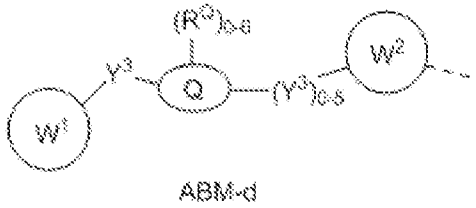
each W^2 is independently a bond, C1-6 aryl or heteroaryl, each optionally substituted by 1, 2 or 3 R^{W2}, each R^{W2} is independently H, halo, a 6 member alicyclic ring with 1 or 2 heteroatoms or a 5 member aromatic ring with 1 or 2 or 3 heteroatoms.

[0325] In any aspect or embodiment described herein, W^2 is selected from the group consisting of: 

[0326] In any aspect or embodiment described herein, the W^2 is covalently coupled to one or more ULM or CLM groups, or a linker to which is attached one or more ULM or CLM groups as described herein.

[0327] In any aspect or embodiment described herein, W^1 is selected from the group consisting of: 

[0328] In any aspect or embodiment described herein, an androgen binding moiety has a structure of:



ABM-d

,

wherein:

W^1 is aryl, independently substituted by 1 or more halo, CN;

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

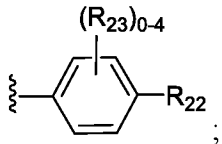
Q is a 5 membered aromatic ring with 1 or 2 heteroatoms;

R^{Y1}, R^{Y2} are each independently H, C_{1-6} alkyl (linear, branched);

W^2 is a bond, aryl, or heteroaryl, each optionally substituted by 1, 2 or 3 R^{W2}; and

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

[0329] In any aspect or embodiment described herein, the W^2 is covalently coupled to one or more ULM or CLM groups, or a linker to which is attached one or more ULM or CLM groups as described herein.

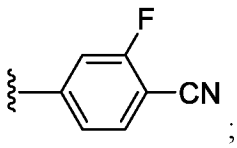
[0330] In any aspect or embodiment described herein, W^1 is 

;

wherein each R_{22} is independently halo or CN; and

each R_{23} is independently H or halo.

[0331] In any aspect or embodiment described herein, W^1 is selected from the group consisting of:



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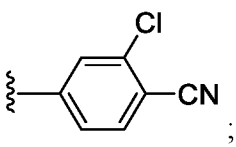

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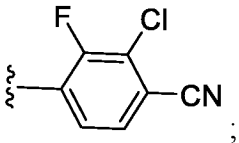
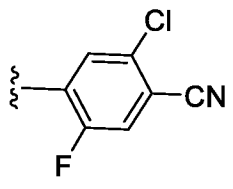


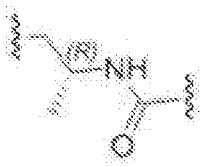
; and


.

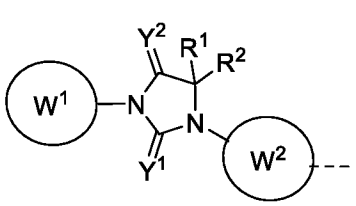
[0332] In any aspect or embodiment described herein, Q is

.

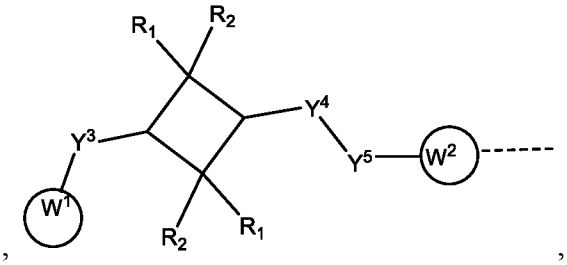
[0333] In any aspect or embodiment described herein, W^2 is .

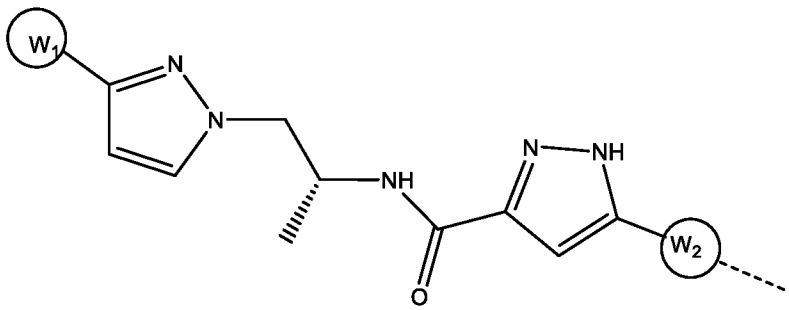
[0334] In any aspect or embodiment described herein, $(Y^3)_{0-5}$ is  .

[0335] In any aspect or embodiment described herein, the ABM comprises a structure selected from, but not limited to the structures shown below, where a dashed line indicates the attachment point of a linker moiety or a ULM, such as a CLM:

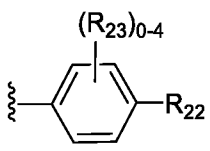
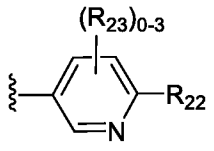


ABM-a





wherein:

W^1 is  or  ;

each R_{22} is independently H or -CN;

each R_{23} is independently H, halo, or $–CF_3$;

Y^1, Y^2 are each independently O or S;

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

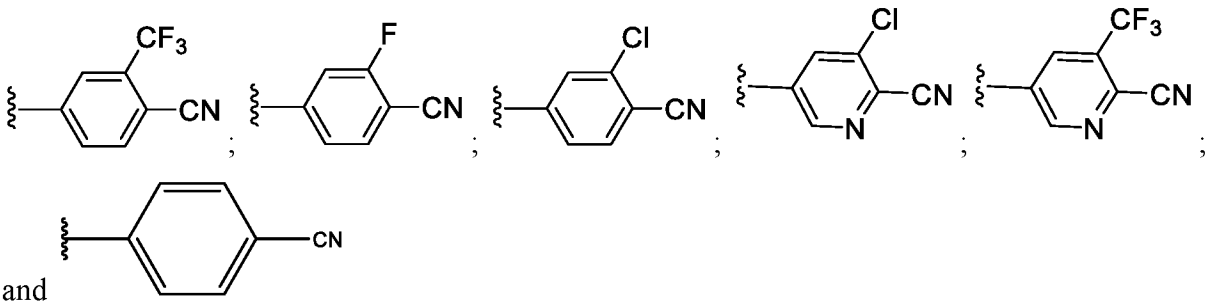
R^1, R^2, are each independently H or a methyl group;

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

each R^{W2} is independently H, halo, C_{1-6} alkyl (optionally substituted by 1 or more F), C_{3-6} cycloalkyl, C_{4-6} cycloheteroalkyl, OC_{1-3}alkyl (optionally substituted by 1 or more –F).

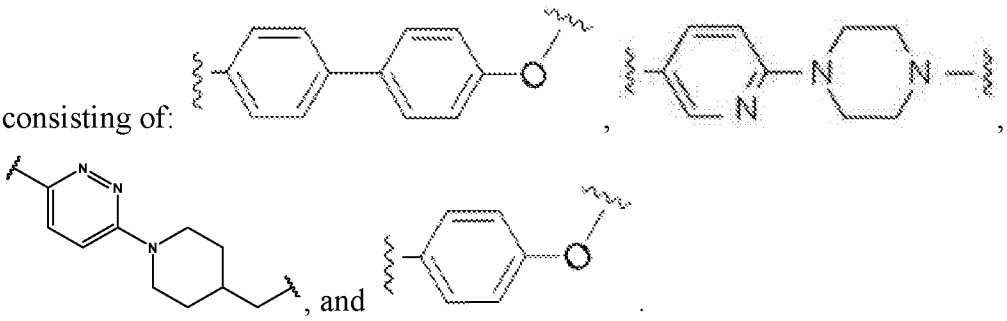
[0336] In any aspect or embodiment described herein, the W^2 is covalently coupled to one or more ULM or CLM groups, or a linker to which is attached one or more ULM or CLM groups as described herein.

[0337] In any aspect or embodiment described herein, W^1 is selected from the group consisting of:

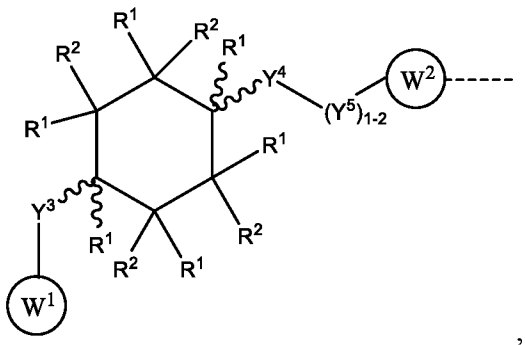


and

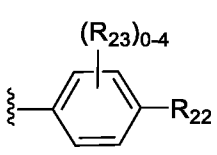
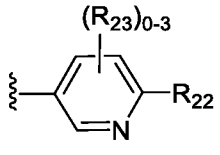
[0338] In any aspect or embodiment described herein, W2 is selected from the group consisting of:



[0339] In any aspect or embodiment described herein, the ABM comprises a structure shown below, where a dashed line indicates the attachment point of a linker moiety or a ULM or a CLM:



wherein:

W^1 is  or  ;

each R_{22} is independently H or -CN;

each R_{23} is independently H, halo, or $–CF_3$;

Y^3 is a bond or O;

Y^4 is a bond or NH;

Y^5 is a bond, C=O, C_1-C_6 heteroaryl, or C_1-C_6 aryl;

R^1, R^2, are each independently H, or C_1-C_6 alkyl (linear or branched, optionally substituted by 1 or more halo, or C_{1-6} alkoxyl);

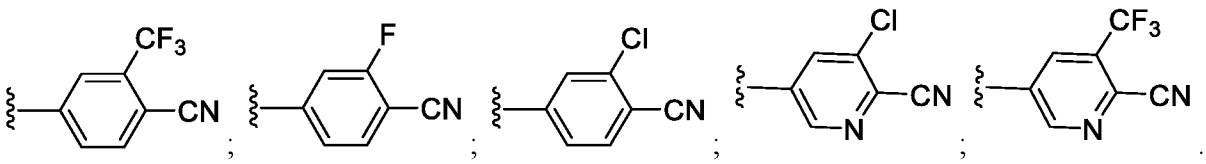
W^2 is a bond, C_{1-6} aryl, C_{1-6} heteroaryl, C_{1-6} alicyclic, or C_{1-6} heterocyclic, each optionally substituted by 1-10 R^{W2}; and

each R^{W2} is independently H, or halo; and

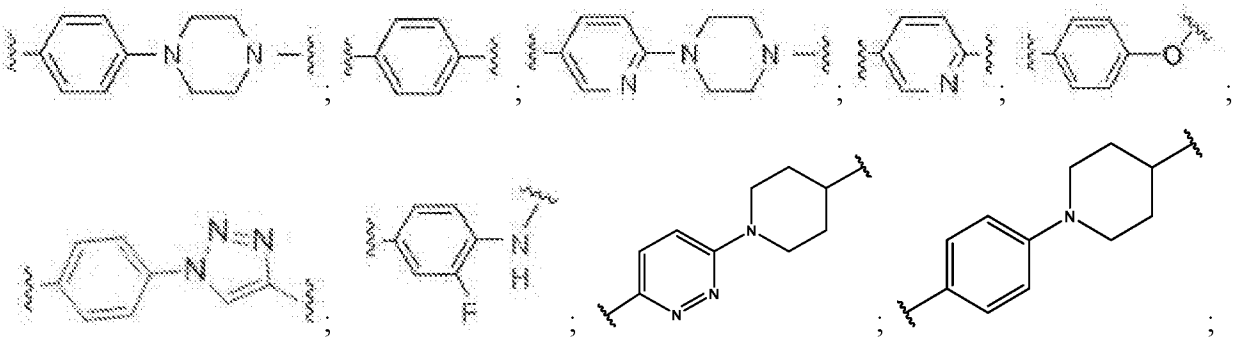
[0340] ~~~ represents a bond that may be stereospecific ((R) or (S)) or non-stereospecific.

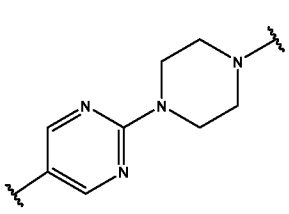
[0341] In any of the embodiments described herein, the W^2 is covalently coupled to one or more ULM or CLM groups, or a linker to which is attached one or more ULM or CLM groups as described herein.

[0342] In certain additional embodiments, W^1 is selected from the group consisting of:



[0343] In certain additional embodiments, W^2 is selected from the group consisting of:

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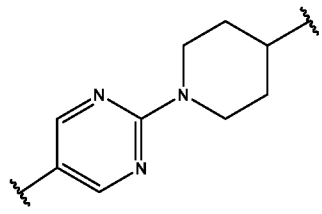
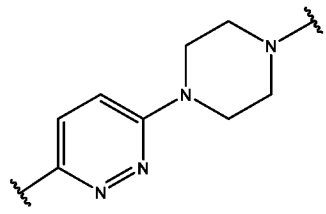

;

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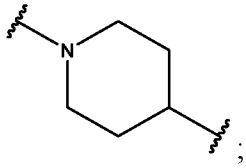
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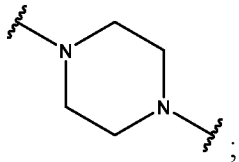
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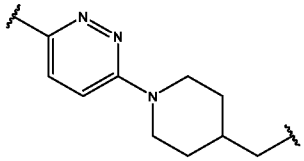
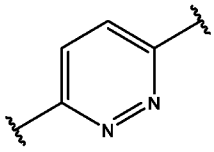

; and

.

[0344] In certain embodiments, the androgen receptor binding compound of ABM is selected from the group consisting of:

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

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

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

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

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

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

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

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

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

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

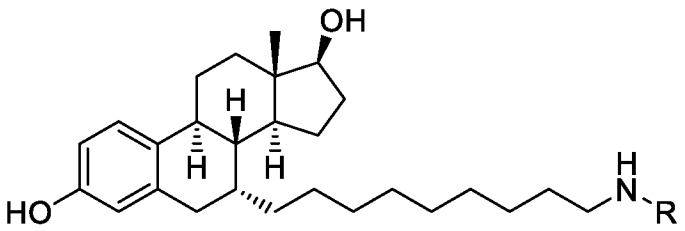
trans 4-[(5-Hydroxypentyl)amino]-N-[3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide; and

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

N-((1r,3r)-3-(4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-methylbenzamide.

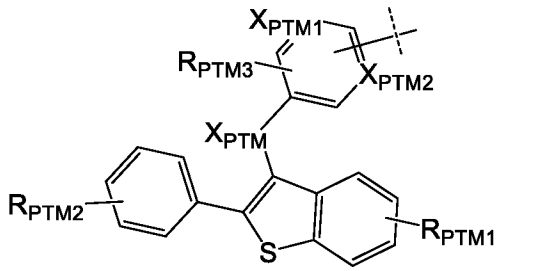
[0345] **XIII. Compounds Targeting Estrogen Receptor (ER) ICI-182780**

[0346] **1.** Estrogen Receptor Ligand

[0347] 

[0348] (Derivatized where "R" designates a site for linker group L or –(L-CLM) group attachment).

[0349] In any embodiment or aspect described herein, the PTM may be represented by the Formula PTM-I:



PTM-I

wherein:

X_{PTM} is O or C=O;

each of X_{PTM1} and X_{PTM2} is independently selected from N or CH;

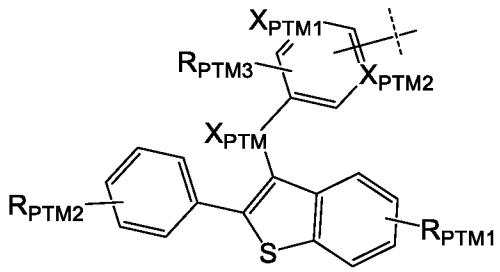
R_{PTM1} is independently selected from OH, O(CO)R_{PTM}, O-lower alkyl, wherein R_{PTM} is an alkyl or aryl group in the ester;

at least one R_{PTM2}, each independently selected from H, OH, halogen, CN, CF_3, SO_2-alkyl, O-lower alkyl;

at least one R_{PTM3}, each independently selected from H, halogen; and

the dashed line indicates the site of attachment of at least one linker, CLM, CLM', PTM, PTM', or a combination thereof.

[0350] In any embodiment or aspect described herein, the PTM may be represented by the Formula PTM-I:



,

PTM-I

wherein:

X_{PTM} is O or C=O;

each of X_{PTM1} and X_{PTM2} is independently selected from N or CH;

R_{PTM1} is independently selected from OH, O(CO)R_{PTM}, O-lower alkyl, wherein R_{PTM} is an alkyl or aryl group in the ester;

each R_{PTM2} is independently selected from H, OH, halogen, CN, CF_3, SO_2-alkyl, O-lower alkyl;

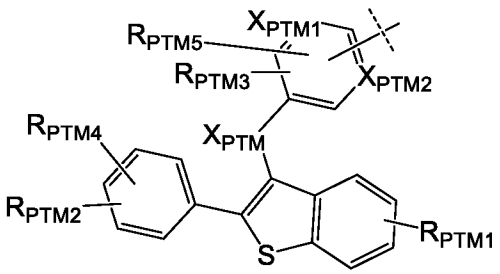
each R_{PTM3} is independently selected from H, halogen;

the PTM-I comprises as least one R_{PTM2}, at least one R_{PTM3}, or a combination thereof on the respective rings; and

the dashed line indicates the site of attachment of at least one linker, CLM, CLM', PTM, PTM', or a combination thereof.

[0351] In any embodiment or aspect described herein, PTM-I has at least one of: two R_{PTM2}, two R_{PTM3}, or a combination thereof.

[0352] In any embodiment or aspect described herein, the PTM may be represented by the Formula PTM-II:



,

PTM-II

wherein:

X_{PTM} is O or C=O;

each of X_{PTM1} and X_{PTM2} is independently selected from N or CH;

R_{PTM1} is independently selected from OH, $O(CO)R_{PTM}$, O-lower alkyl, wherein R_{PTM} is an alkyl or aryl group in the ester;

R_{PTM2} and R_{PTM4} are independently selected from H, OH, halogen, CN, CF_3, SO_2-alkyl, O-lower alkyl;

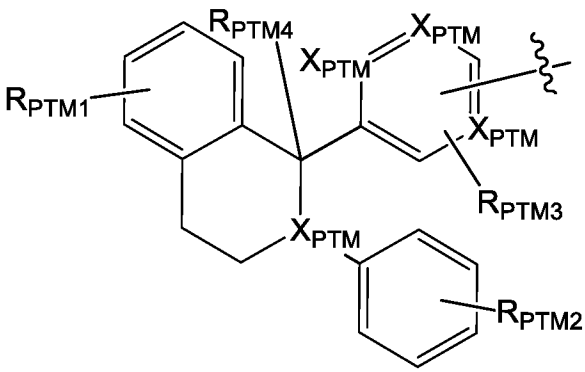
R_{PTM3} and R_{PTM5} are independently selected from H, halogen; and

the dashed line indicates the site of attachment of at least one linker, CLM, CLM', PTM, PTM', or a combination thereof.

[0353] In aspect or embodiment described herein, $O(CO)R_{PTM}$ functions as a prodrug of the corresponding phenol in Formula PTM-I or PTM-II.

[0354] In any embodiment or aspect described herein, the O-lower alkyl of PTM-I or PTM-II an alkyl chain with carbon number 1 to 3.

[0355] In aspect or embodiment described herein, the present disclosure provides a compound or PTM of Formula (I_{PTM}):



,

Formula (I_{PMT})

wherein:

each X_{PTM} is independently CH, N;

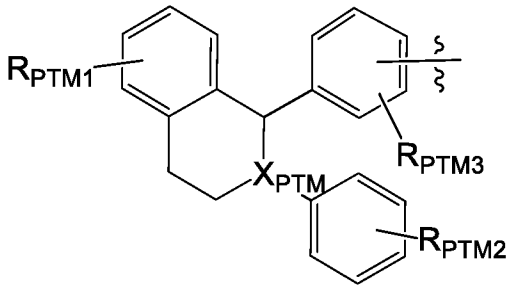
indicates the site of attachment of at least one linker, CLM, CLM', PTM, PTM', or a combination thereof;

each R_{PTM1} is independently OH, halogen, $O(CO)R_{PTM}$, where R_{PTM} is alkyl or cycloalkyl group with 1 to 6 carbons or aryl groups, substitution can be mono-, di- or tri-substituted;

each R_{PTM2} is independently H, halogen, CN, CF_3, alkoxy, substitution can be mono- or di-substitution; and

each R_{PTM3} is independently H, halogen, substitution can be mono- or di-substitution.

[0356] In any aspect or embodiment described herein, the PTM is represented by the Formula (II_{PTM}):



Formula (II_{PMT})

wherein:

X_{PTM} is CH, N;

indicates the site of attachment of at least one linker, CLM, CLM', PTM, PTM', ULM, an ILM, a VLM, MLM, a ULM', a ILM', a VLM', a MLM', or a combination thereof;

each R_{PTM1} is independently OH, halogen (e.g., F);

each R_{PTM2} is independently H, halogen (e.g., F), CF_3, substitution can be mono- or di-substitution; and

each R_{PTM3} is independently halogen (e.g. F), substitution can be mono- or di-substitution.

[0357] In certain embodiments, at least one of:

X_{PTM} of Formula (II_{PTM}) is CH;

R_{PTM1} of Formula (II_{PTM}) is OH;

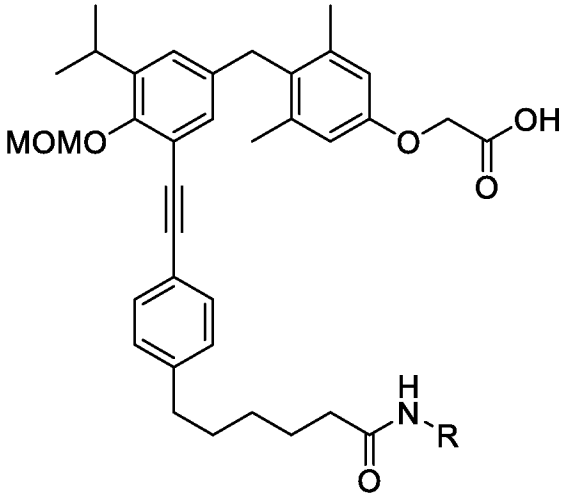
R_{PTM2} of Formula (II_{PTM})is H;

each R_{PTM3} of Formula (II_{PTM}) is independently H or F; or

a combination thereof.

[0358] **XIV. Compounds Targeting Thyroid Hormone Receptor (TR)**

[0359] **1.** Thyroid Hormone Receptor Ligand (derivatized)

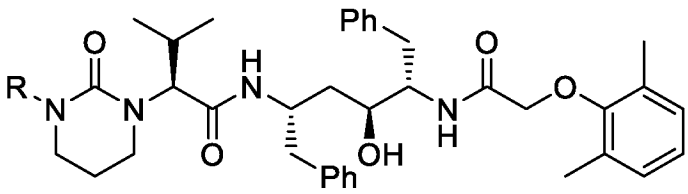


[0360]

[0361] (Derivatized where "R" designates a site for linker group L or –(L-CLM) group attachment and MOMO indicates a methoxymethoxy group).

[0362] **XV. Compounds targeting HIV Protease**

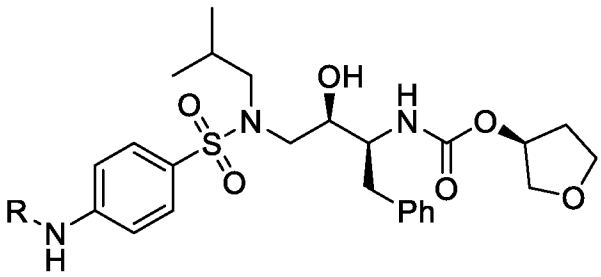
[0363] **1.** Inhibitor of HIV Protease (derivatized)



[0364]

[0365] (Derivatized where "R" designates a site for linker group L or–(L-CLM) group attachment). See, *J. Med. Chem.* **2010**, 53, 521-538.

[0366] **2.** Inhibitor of HIV Protease

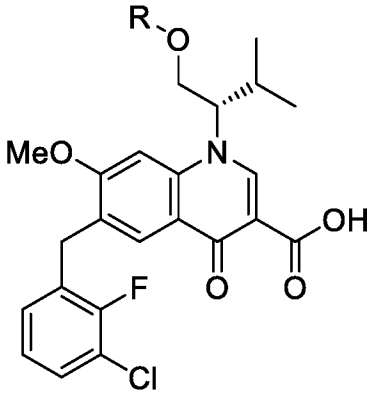


[0367]

[0368] (Derivatized where "R" designates a potential site for linker group L or –(L-CLM) group attachment). See, *J. Med. Chem.* **2010**, 53, 521-538.

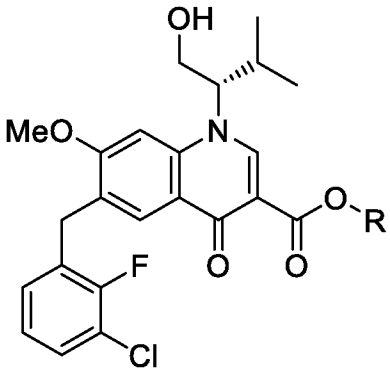
[0369] **XVI. Compounds targeting HIV Integrase**

[0370] **1**. Inhibitor of HIV Integrase (derivatized)

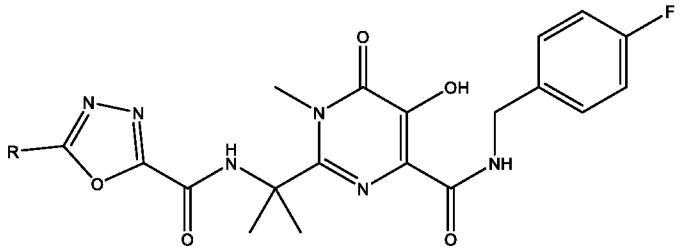
[0371] 

[0372] (Derivatized where "R" designates a site for linker group L or –(L-CLM) group attachment). See, *J. Med. Chem.* **2010**, 53, 6466.

[0373] **2**. Inhibitor of HIV Integrase (derivatized)

[0374] 

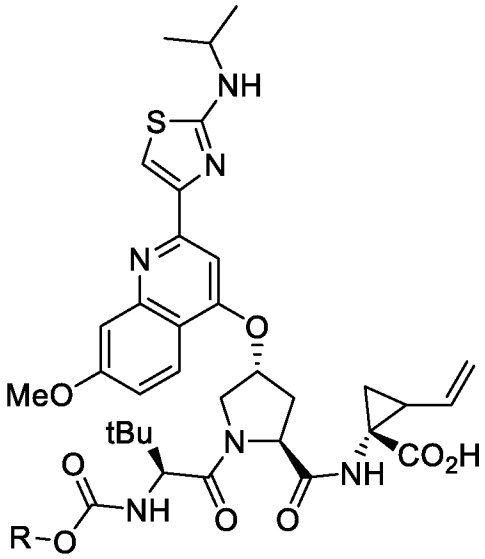
[0375] **3.** Inhibitor of HIV integrase Isetntress (derivatized)

[0376] 

[0377] (Derivatized where "R" designates a site for linker group L or –(L-CLM) group attachment). See, *J. Med. Chem.* **2010**, 53, 6466.

[0378] **XVII. Compounds targeting HCV Protease**

[0379] **1.** Inhibitors of HCV Protease (derivatized)

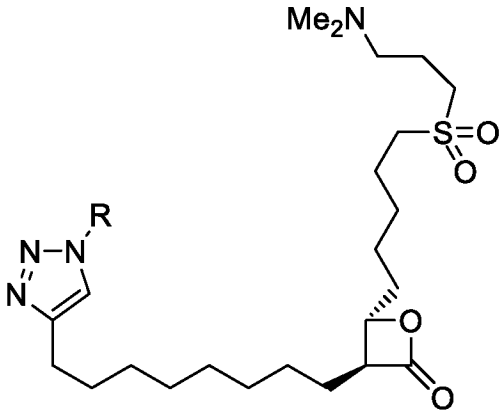


[0380]

[0381] (Derivatized where "R" designates a site for linker group L or –(L-CLM) group attachment).

[0382] **XVIII. Compounds targeting Acyl-protein Thioesterase-1 and -2 (APT1 and APT2)**

[0383] **1.** Inhibitor of APT1 and APT2 (derivatized)



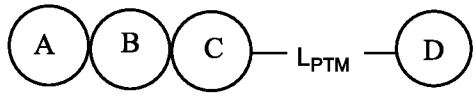
[0384]

[0385] (Derivatized where "R" designates a site for linker group L or –(L-CLM) group attachment). See, *Angew. Chem. Int. Ed.* **2011**, 50, 9838 –9842, where L is a linker group as otherwise described herein and said CLM group is as otherwise described herein such that –(L-CLM) binds the CLM group to a PTMgroup as otherwise described herein.

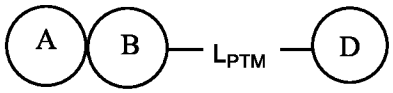
[0386] **VIV. Compound targeting Tau Protein**

[0387] In any aspect or embodiment described herein, the PTM may include a Tau protein binding moieties. For example, the PTM may be represented by Formula I, Formula II, Formula

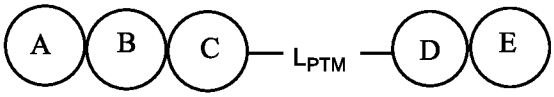
III, Formula IV, Formula V, Formula VI, Formula, VII, Formula, VIII, Formula IX, Formula X, or Formula XI:



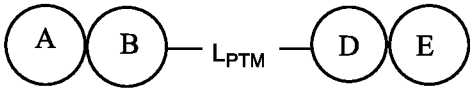
I



II



III



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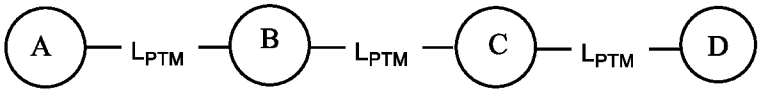
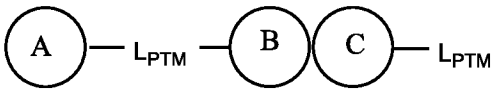
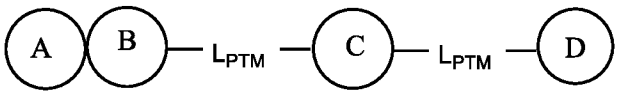


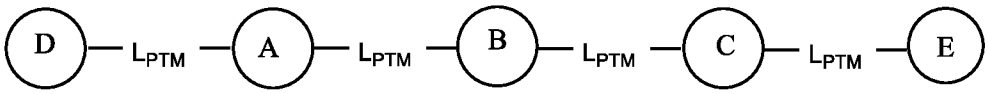
V



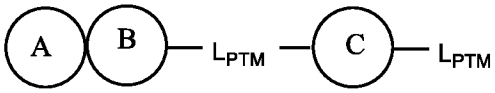
VI



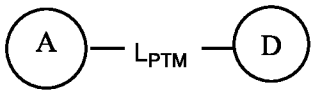
VII



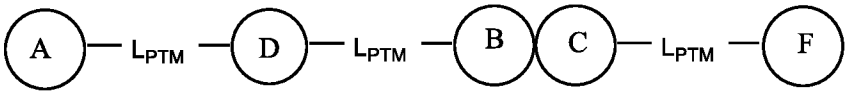
VIII



IX



X



XI

,

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.

[0388] In any aspect or embodiment described herein, 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.

[0389] In any aspect or embodiment described herein, 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;

[0390] In any aspect or embodiment described herein, 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.

[0391] In any aspect or embodiment described herein, 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;

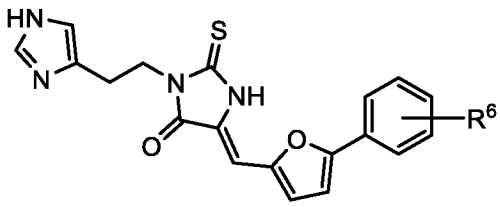
L_{PTM} is a bond; and

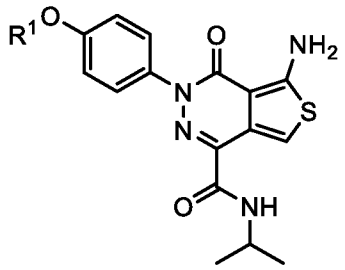
D is a 6-membered heteroaryl or a 6-membered heterocycloalkyl ring;

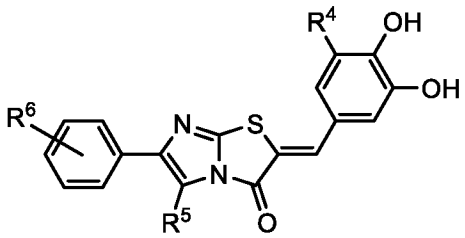
wherein each A, B, C and D is optionally independently substituted with alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, dialkylamino or cyano, and wherein a nitrogen atom of any of the A, B, C and D rings is not directly connected to a heteroatom or to a carbon atom, to which another heteroatom is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

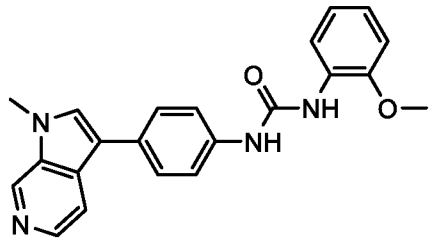
[0392] In any aspect or embodiment described herein, the PTM has the chemical structure of Formula III or IV, wherein A, B and C are 5- or 6- membered fused aryl or heteroaryl rings, L_{PTM} is selected from a bond or an alkyl, and D and E are 5- or 6-membered fused aryl or heteroaryl rings, wherein A, B, C, D and E are optionally substituted with alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, alkylamino, dialkylamino or cyano.

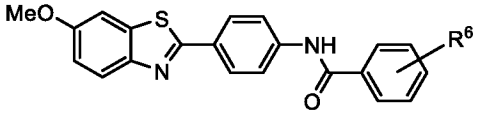
[0393] In any aspect or embodiment described herein, the PTM is represented by following chemical structure:

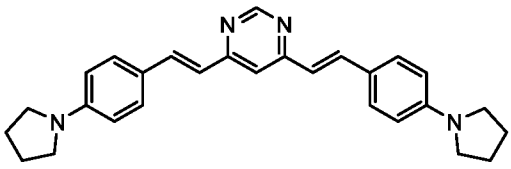


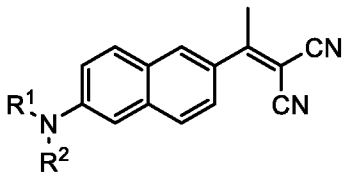


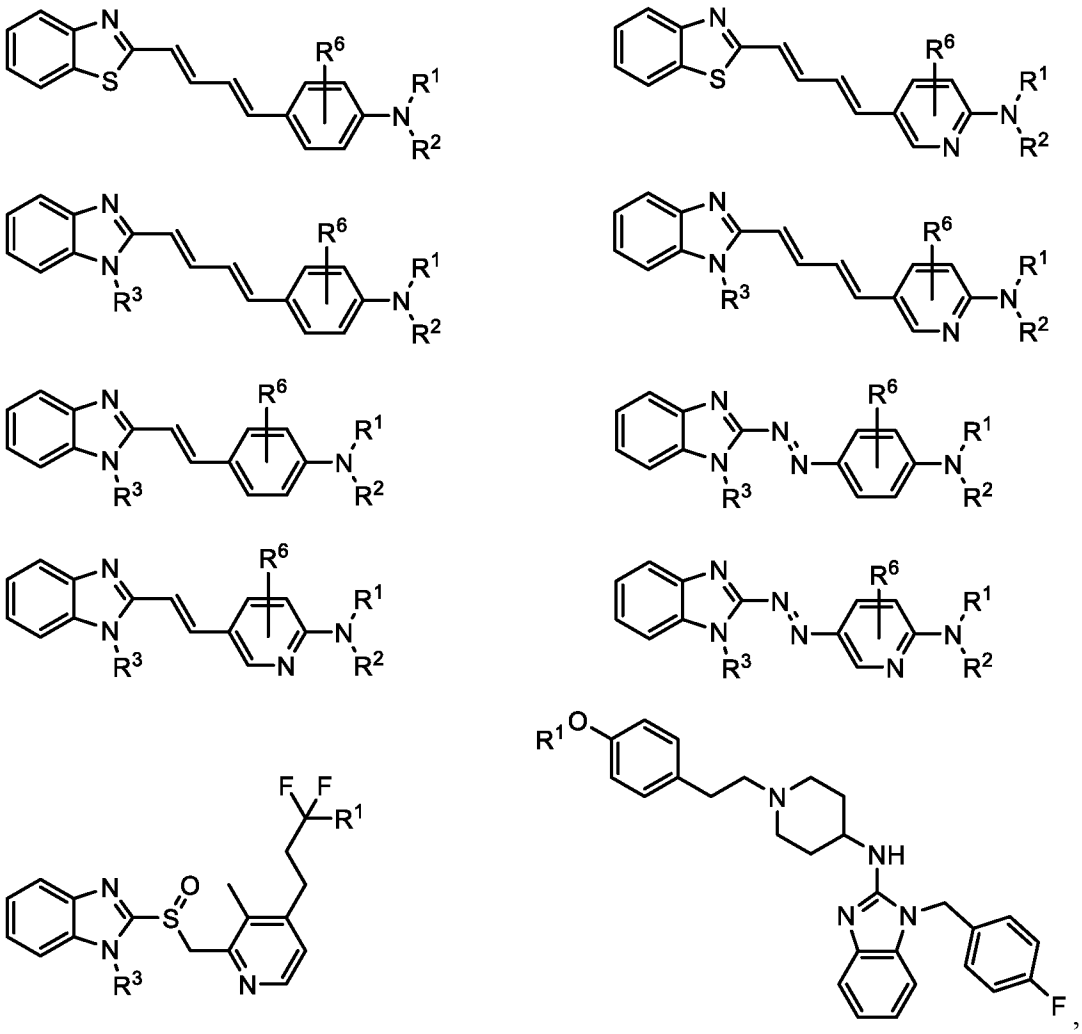












wherein:

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

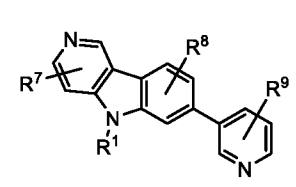
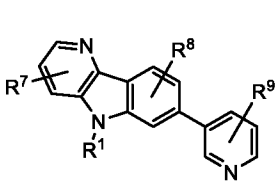
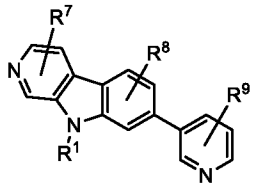
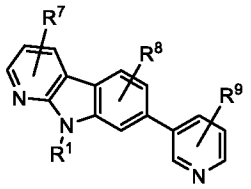
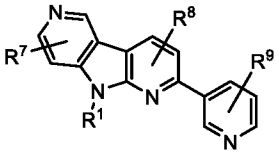
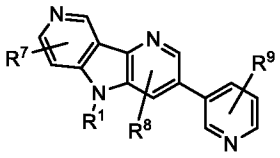
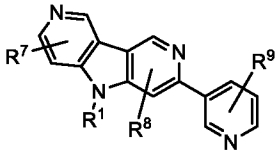
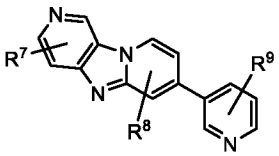
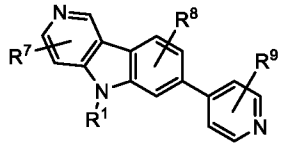
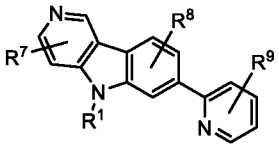
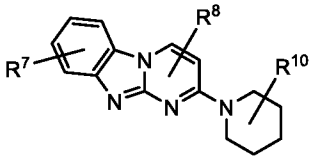
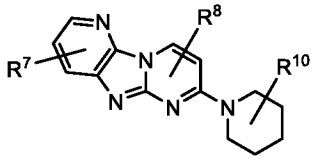
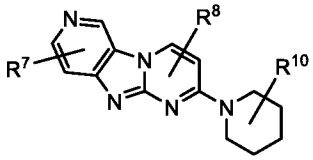
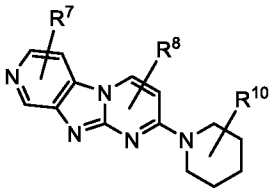
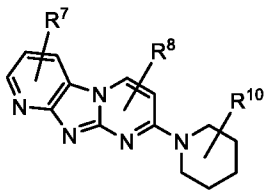
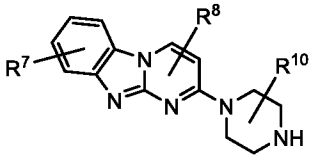
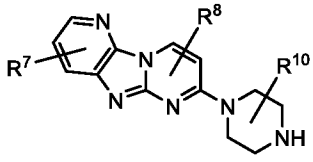
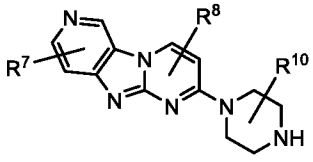
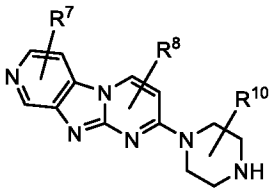
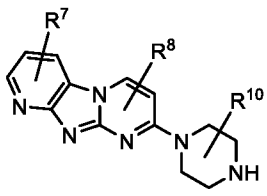
R^4 and R^5 are independently selected from H, methyl, ethyl and halogen; and

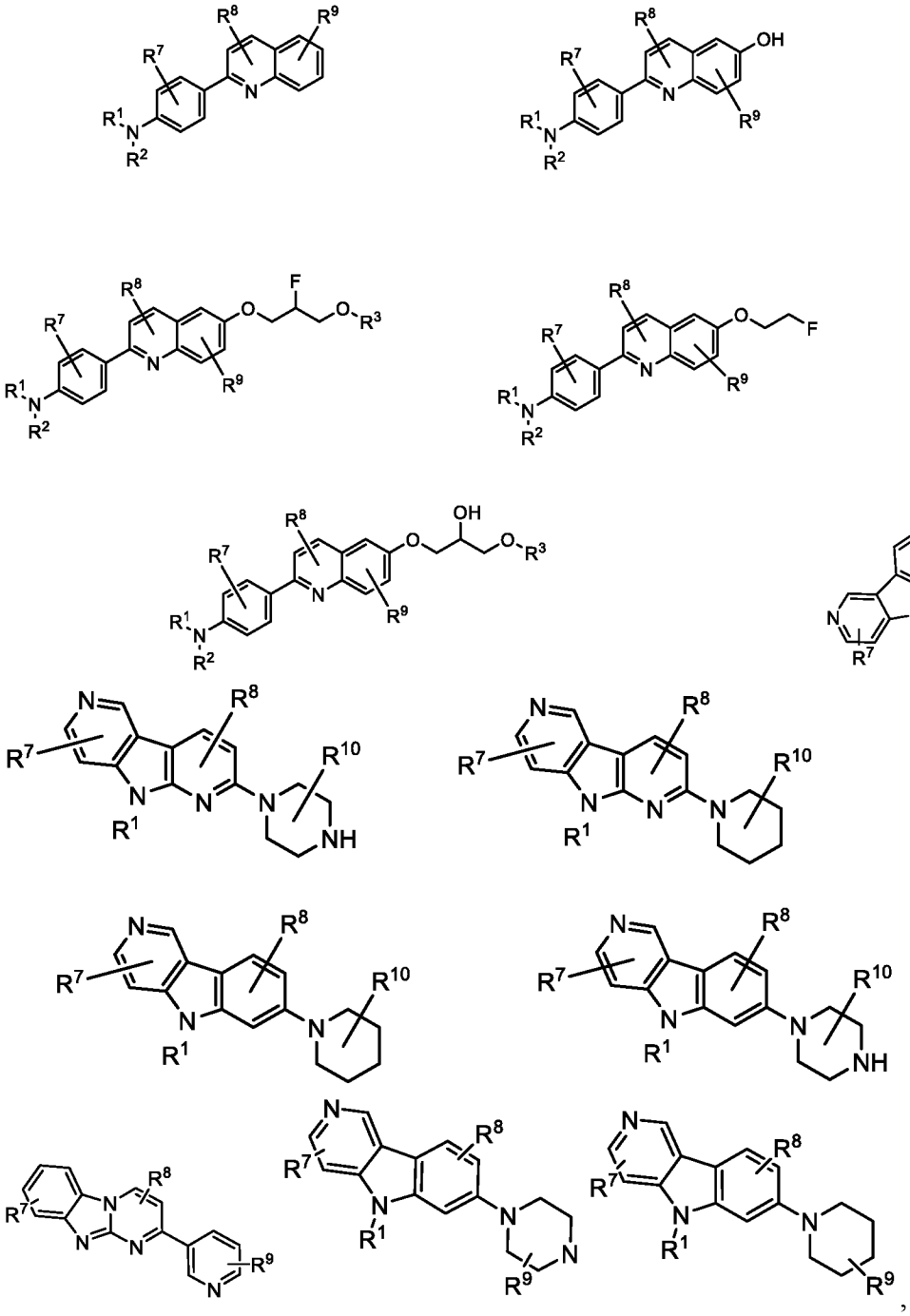
R^6 is 1 to 2 substituents independently selected from H, methyl, ethyl and halogen,

wherein the PTM is coupled to a ULM via L.

[0394] 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.

[0395] In any aspect or embodiment described herein, PTM is represented by chemical structure:



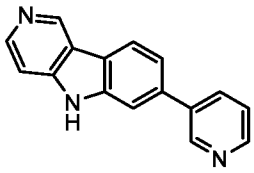
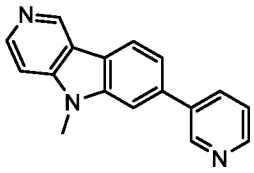
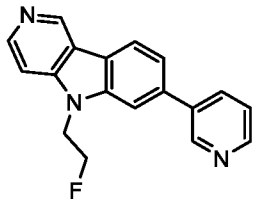
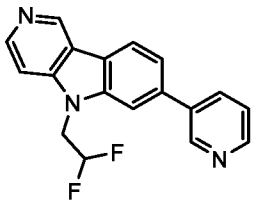
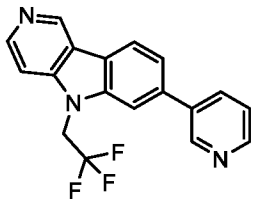
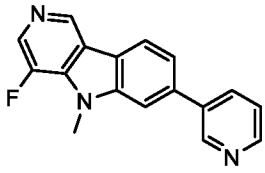
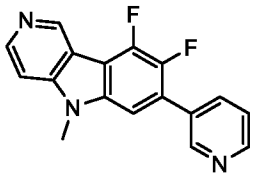
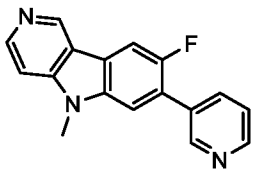
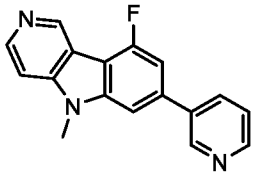
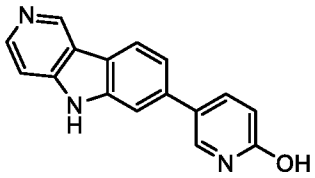
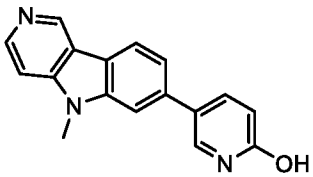
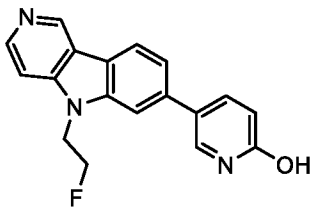
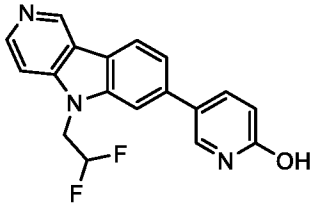
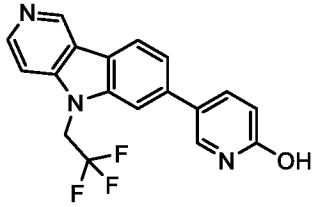
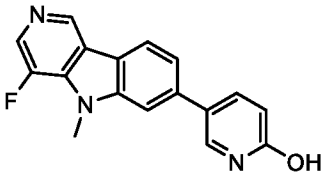
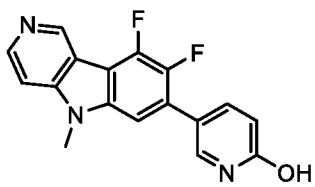
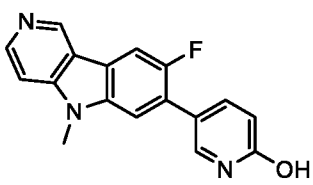
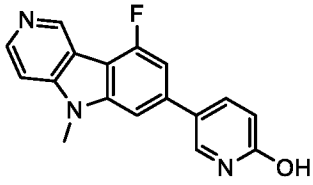
wherein:

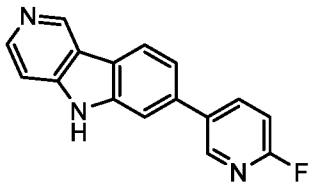
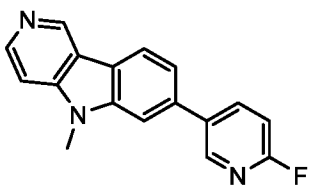
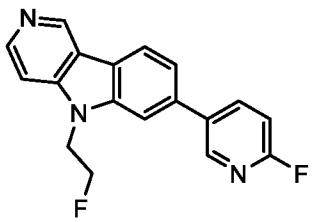
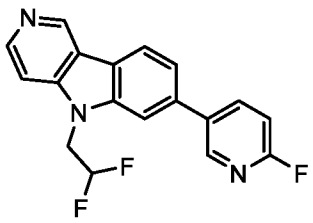
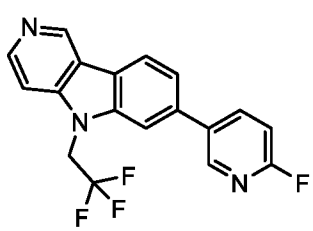
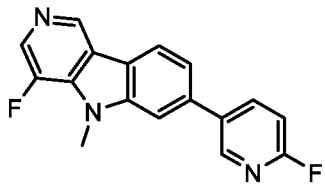
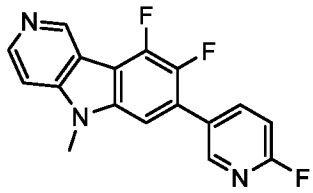
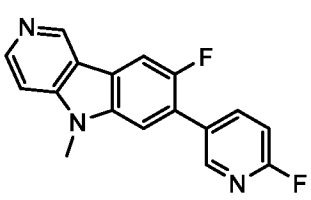
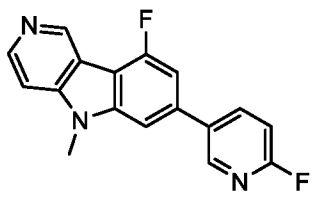
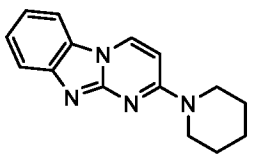
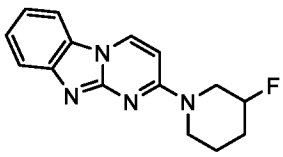
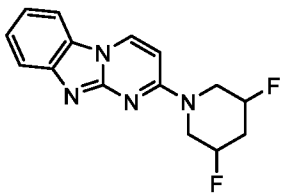
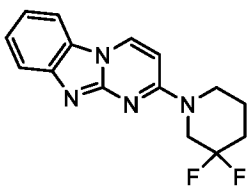
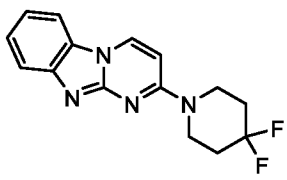
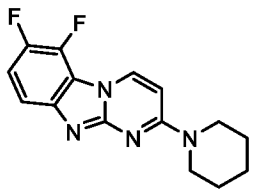
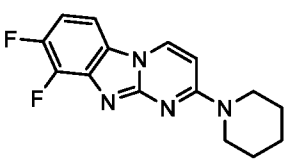
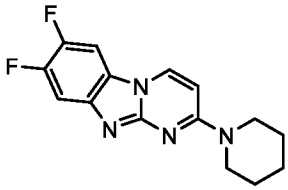
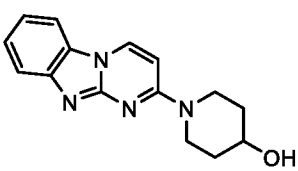
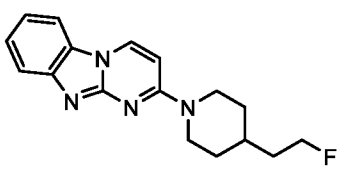
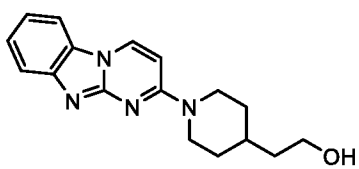
R^1, R^2 and R^3 are independently selected from H, optionally substituted alkyl, methyl, ethyl, 2-fluoroethyl and 2,2,2-trifluoroethyl; and

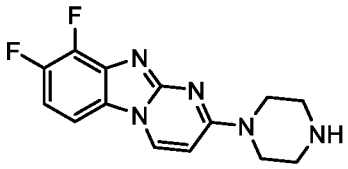
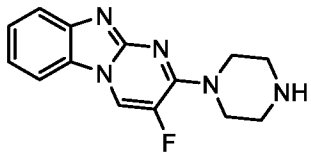
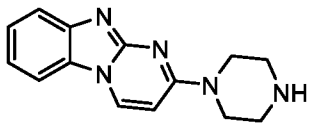
R^7, R^8 , R^9 and R^{10} are 1 to 8 substituents independently selected from H, optionally substituted alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, dialkylamino, aceylamino,

trifluoromethyl or cyano, and wherein the PTM is coupled to a ULM (VLM or CLM) via L.

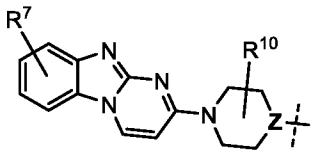
[0396] In any aspect or embodiment described herein, PTM is represented by chemical structure:

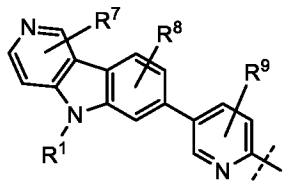
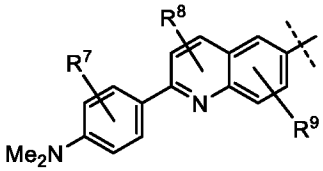
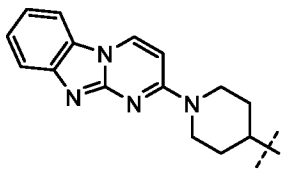
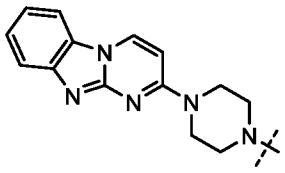
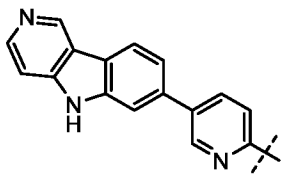
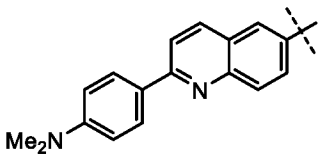





















[0397] In any aspect or embodiment described herein, the linker attachment point to PTM is as indicated by the dotted line:



Z = N, CH

[0398] **Therapeutic Compositions**

[0399] Pharmaceutical compositions comprising combinations of an effective amount of at least one bifunctional compound as described herein, 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.

[0400] The present disclosure includes, where applicable, the compositions comprising the pharmaceutically acceptable salts, in particular, acid or base addition salts of compounds as described herein. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds useful according to this aspect 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.

[0401] 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.

[0402] The compounds as described herein may, in accordance with the disclosure, be administered in single or divided doses by the oral, parenteral or topical routes. Administration of the active compound may range from continuous (intravenous drip) to several oral administrations per day (for example, Q.I.D.) and may include oral, topical, parenteral, intramuscular, intravenous, sub-cutaneous, transdermal (which may include a penetration enhancement agent), buccal, sublingual and suppository administration, among other routes of administration. Enteric coated oral tablets may also be used to enhance bioavailability of the compounds from an oral route of administration. The most effective dosage form will depend upon the pharmacokinetics of the particular agent chosen as well as the severity of disease in the patient. Administration of compounds according to the present disclosure as sprays, mists, or aerosols for intra-nasal, intra-tracheal or pulmonary administration may also be used. The present disclosure therefore also is directed to pharmaceutical compositions comprising an effective amount of compound as described herein, optionally in combination with a pharmaceutically acceptable carrier, additive or excipient. Compounds according to the present disclosureion 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.

[0403] The compositions as described herein 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.

[0404] The compositions as described herein may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously.

[0405] 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.

[0406] 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.

[0407] 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.

[0408] The pharmaceutical compositions as described herein 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.

[0409] For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. In certain preferred aspects of the invention, the compounds may be coated onto a stent which is to be surgically implanted into a patient in order to inhibit or reduce the likelihood of occlusion occurring in the stent in the patient.

[0410] 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.

[0411] 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.

[0412] The pharmaceutical compositions as described herein 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.

[0413] The amount of compound in a pharmaceutical composition as described herein 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. Preferably, the compositions should be formulated to contain between about 0.05 milligram to about 750 milligrams or more, more preferably about 1 milligram to about 600 milligrams, and even more preferably about 10 milligrams to about 500 milligrams of active ingredient, alone or in combination with at least one other compound according to the present disclosure.

[0414] 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.

[0415] A patient or subject in need of therapy using compounds according to the methods described herein can be treated by administering to the patient (subject) an effective amount of the compound according to the present disclosure including pharmaceutically acceptable salts, solvates or polymorphs, thereof optionally in a pharmaceutically acceptable carrier or diluent, either alone, or in combination with other known erythopoiesis stimulating agents as otherwise identified herein.

[0416] These 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, or by aerosol form.

[0417] 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.

[0418] 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.

[0419] 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.

[0420] 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.

[0421] 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 can be included as part of the composition.

[0422] 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.

[0423] 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.

[0424] The active compound or pharmaceutically acceptable salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as erythropoietin stimulating agents, including EPO and darbapoietin alfa, among others. In certain preferred aspects of the invention, one or more compounds according to the present disclosure are coadministered with another bioactive agent, such as an erythropoietin stimulating agent or a would healing agent, including an antibiotic, as otherwise described herein.

[0425] 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.

[0426] If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

[0427] 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.

[0428] Liposomal suspensions may also be pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound are then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

[0429] **Therapeutic Methods**

[0430] 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.

[0431] The terms “treat”, “treating”, and “treatment”, etc., as used herein, refer to any action providing a benefit to a patient for which the present compounds may be administered, including the treatment of any disease state or condition which is modulated through the protein to which the present compounds bind. Disease states or conditions, including cancer, which may be treated using compounds according to the present disclosure are set forth hereinabove.

[0432] The description provides therapeutic compositions as described herein for effectuating the degradation of proteins of interest for the treatment or amelioration of a disease, e.g., cancer. In certain additional embodiments, the disease is multiple myeloma. As such, in another aspect, the description 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, e.g., a CLM and a PTM, preferably linked through a linker moiety, as otherwise described herein, wherein the CLM is coupled to the PTM and wherein the CLM recognizes a ubiquitin pathway protein (e.g., an ubiquitin ligase, preferably an E3 ubiquitin ligase such as, e.g., cereblon) and the PTM recognizes the target protein 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 cell, e.g., cell of a patient. In certain embodiments, the method comprises administering an effective amount of a compound as described herein, optionally including a pharamaceutically acceptable excipient, carrier, adjuvant, another bioactive agent or combination thereof.

[0433] In additional embodiments, the description provides methods for treating or emeliorating a disease, disorder or symptom thereof in a subject or a patient, e.g., an animal such as a human, comprising administering to a subject in need thereof a composition comprising an effective amount, e.g., a therapeutically effective amount, of a compound as described herein or salt form thereof, and a pharmaceutically acceptable excipient, carrier, adjuvant, another bioactive agent or combination thereof, wherein the composition is effective for treating or ameliorating the disease or disorder or symptom thereof in the subject.

[0434] In another 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.

[0435] In another embodiment, the present disclosure is directed to a method of treating a human patient in need for a disease state or condition modulated through a protein 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, which leads to a disease state and/or condition

[0436] 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 one or more proteins 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.

[0437] Disease states of conditions which may be treated using compounds according to the present disclosure include, for example, asthma, autoimmune diseases such as multiple sclerosis, various cancers, ciliopathies, cleft palate, diabetes, heart disease, hypertension, inflammatory bowel disease, mental retardation, mood disorder, obesity, refractive error, infertility, Angelman syndrome, Canavan disease, Coeliac disease, Charcot–Marie–Tooth disease, Cystic fibrosis, Duchenne muscular dystrophy, Haemochromatosis, Haemophilia, Klinefelter's syndrome, Neurofibromatosis, Phenylketonuria, Polycystic kidney disease, (PKD1) or 4 (PKD2) Prader–Willi syndrome, Sickle-cell disease, Tay–Sachs disease, Turner syndrome.

[0438] Further disease states or conditions which may be treated by compounds according to the present disclosure include Alzheimer's disease, Amyotrophic lateral sclerosis (Lou Gehrig's disease), Anorexia nervosa, Anxiety disorder, Atherosclerosis, Attention deficit hyperactivity disorder, Autism, Bipolar disorder, Chronic fatigue syndrome, Chronic obstructive pulmonary disease, Crohn's disease, Coronary heart disease, Dementia, Depression, Diabetes mellitus type 1, Diabetes mellitus type 2, Epilepsy, Guillain–Barré syndrome, Irritable bowel syndrome, Lupus, Metabolic syndrome, Multiple sclerosis, Myocardial infarction, Obesity, Obsessive–compulsive disorder, Panic disorder, Parkinson's disease, Psoriasis, Rheumatoid arthritis, Sarcoidosis, Schizophrenia, Stroke, Thromboangiitis obliterans, Tourette syndrome, Vasculitis.

[0439] Still additional disease states or conditions which can be treated by compounds according to the present disclosure include aceruloplasminemia, Achondrogenesis type II, achondroplasia, Acrocephaly, Gaucher disease type 2, acute intermittent porphyria, Canavan disease, Adenomatous Polyposis Coli, ALA dehydratase deficiency, adenylosuccinate lyase deficiency, Adrenogenital syndrome, Adrenoleukodystrophy, ALA-D porphyria, ALA

dehydratase deficiency, Alkaptonuria, Alexander disease, Alkaptonuric ochronosis, alpha 1-antitrypsin deficiency, alpha-1 proteinase inhibitor, emphysema, amyotrophic lateral sclerosis Alström syndrome, Alexander disease, Amelogenesis imperfecta, ALA dehydratase deficiency, Anderson-Fabry disease, androgen insensitivity syndrome, Anemia Angiokeratoma Corporis Diffusum, Angiomatosis retinae (von Hippel–Lindau disease) Apert syndrome, Arachnodactyly (Marfan syndrome), Stickler syndrome, Arthrochalasis multiplex congenital (Ehlers–Danlos syndrome#arthrochalasia type) ataxia telangiectasia, Rett syndrome, primary pulmonary hypertension, Sandhoff disease, neurofibromatosis type II, Beare-Stevenson cutis gyrata syndrome, Mediterranean fever, familial, Benjamin syndrome, beta-thalassemia, Bilateral Acoustic Neurofibromatosis (neurofibromatosis type II), factor V Leiden thrombophilia, Bloch-Sulzberger syndrome (incontinentia pigmenti), Bloom syndrome, X-linked sideroblastic anemia, Bonnevie-Ullrich syndrome (Turner syndrome), Bourneville disease (tuberous sclerosis), prion disease, Birt–Hogg–Dubé syndrome, Brittle bone disease (osteogenesis imperfecta), Broad Thumb-Hallux syndrome (Rubinstein-Taybi syndrome), Bronze Diabetes/Bronzed Cirrhosis (hemochromatosis), Bulbospinal muscular atrophy (Kennedy's disease), Burger-Grutz syndrome (lipoprotein lipase deficiency), CGD Chronic granulomatous disorder, Campomelic dysplasia, biotinidase deficiency, Cardiomyopathy (Noonan syndrome), Cri du chat, CAVD (congenital absence of the vas deferens), Caylor cardiofacial syndrome (CBAVD), CEP (congenital erythropoietic porphyria), cystic fibrosis, congenital hypothyroidism, Chondrodystrophy syndrome (achondroplasia), otospondylomegaepiphyseal dysplasia, Lesch-Nyhan syndrome, galactosemia, Ehlers–Danlos syndrome, Thanatophoric dysplasia, Coffin-Lowry syndrome, Cockayne syndrome, (familial adenomatous polyposis), Congenital erythropoietic porphyria, Congenital heart disease, Methemoglobinemia/Congenital methaemoglobinaemia, achondroplasia, X-linked sideroblastic anemia, Connective tissue disease, Conotruncal anomaly face syndrome, Cooley's Anemia (beta-thalassemia), Copper storage disease (Wilson's disease), Copper transport disease (Menkes disease), hereditary coproporphyria, Cowden syndrome, Craniofacial dysarthrosis (Crouzon syndrome), Creutzfeldt-Jakob disease (prion disease), Cockayne syndrome, Cowden syndrome, Curschmann-Batten-Steinert syndrome (myotonic dystrophy), Beare-Stevenson cutis gyrata syndrome, primary hyperoxaluria, spondyloepimetaphyseal dysplasia (Strudwick type), muscular dystrophy, Duchenne and Becker types (DBMD), Usher syndrome, Degenerative nerve diseases including de Grouchy syndrome

and Dejerine-Sottas syndrome, developmental disabilities, distal spinal muscular atrophy, type V, androgen insensitivity syndrome, Diffuse Globoid Body Sclerosis (Krabbe disease), Di George's syndrome, Dihydrotestosterone receptor deficiency, androgen insensitivity syndrome, Down syndrome, Dwarfism, erythropoietic protoporphyria Erythroid 5-aminolevulinate synthetase deficiency, Erythropoietic porphyria, erythropoietic protoporphyria, erythropoietic uroporphyria, Friedreich's ataxia,, familial paroxysmal polyserositis, porphyria cutanea tarda, familial pressure sensitive neuropathy, primary pulmonary hypertension (PPH), Fibrocystic disease of the pancreas, fragile X syndrome, galactosemia, genetic brain disorders, Giant cell hepatitis (Neonatal hemochromatosis), Gronblad-Strandberg syndrome (pseudoxanthoma elasticum), Gunther disease (congenital erythropoietic porphyria), haemochromatosis, Hallgren syndrome, sickle cell anemia, hemophilia, hepatoerythropoietic porphyria (HEP), Hippel-Lindau disease (von Hippel-Lindau disease), Huntington's disease, Hutchinson-Gilford progeria syndrome (progeria), Hyperandrogenism, Hypochondroplasia, Hypochromic anemia, Immune system disorders, including X-linked severe combined immunodeficiency, Insley-Astley syndrome, Kennedy's syndrome, Jackson-Weiss syndrome, Joubert syndrome, Lesch-Nyhan syndrome, Jackson-Weiss syndrome, Kidney diseases, including hyperoxaluria, Klinefelter's syndrome, Kniest dysplasia, Lacunar dementia,Langer-Saldino achondrogenesis, ataxia telangiectasia, Lynch syndrome, Lysyl-hydroxylase deficiency, Machado-Joseph disease, Metabolic disorders, including Kniest dysplasia, Marfan syndrome, Movement disorders, Mowat-Wilson syndrome, cystic fibrosis, Muenke syndrome, Multiple neurofibromatosis, Nance-Insley syndrome, Nance-Sweeney chondrodysplasia, Niemann–Pick disease, Noack syndrome (Pfeiffer syndrome), Osler-Weber-Rendu disease, Peutz-Jeghers syndrome, Polycystic kidney disease, polyostotic fibrous dysplasia (McCune–Albright syndrome), Peutz-Jeghers syndrome, Prader-Labhart-Willi syndrome, hemochromatosis, primary hyperuricemia syndrome (Lesch-Nyhan syndrome), primary pulmonary hypertension, primary senile degenerative dementia, prion disease, progeria (Hutchinson Gilford Progeria Syndrome), progressive chorea, chronic hereditary (Huntington) (Huntington's disease), progressive muscular atrophy, spinal muscular atrophy, propionic acidemia, protoporphyria, proximal myotonic dystrophy, pulmonary arterial hypertension, PXE (pseudoxanthoma elasticum), Rb (retinoblastoma), Recklinghausen disease (neurofibromatosis type I), Recurrent polyserositis, Retinal disorders, Retinoblastoma, Rett syndrome, RFALS type 3, Ricker syndrome, Riley-Day syndrome, Roussy-Levy syndrome, severe achondroplasia with

developmental delay and acanthosis nigricans (SADDAN), Li-Fraumeni syndrome, sarcoma, breast, leukemia, and adrenal gland (SBLA) syndrome, sclerosis tuberose (tuberous sclerosis), SDAT, SED congenital (spondyloepiphyseal dysplasia congenita), SED Strudwick (spondyloepimetaphyseal dysplasia, Strudwick type), SEDc (spondyloepiphyseal dysplasia congenita) SEMD, Strudwick type (spondyloepimetaphyseal dysplasia, Strudwick type), Shprintzen syndrome, Skin pigmentation disorders, Smith-Lemli-Opitz syndrome, South-African genetic porphyria (variegate porphyria), infantile-onset ascending hereditary spastic paralysis, Speech and communication disorders, sphingolipidosis, Tay-Sachs disease, spinocerebellar ataxia, Stickler syndrome, stroke, androgen insensitivity syndrome, tetrahydrobiopterin deficiency, beta-thalassemia, Thyroid disease, Tomaculous neuropathy (hereditary neuropathy with liability to pressure palsies), Treacher Collins syndrome, Triplo X syndrome (triple X syndrome), Trisomy 21 (Down syndrome), Trisomy X, VHL syndrome (von Hippel-Lindau disease), Vision impairment and blindness (Alström syndrome), Vrolik disease, Waardenburg syndrome, Warburg Sjo Fledelius Syndrome, Weissenbacher-Zweymüller syndrome, Wolf–Hirschhorn syndrome, Wolff Periodic disease, Weissenbacher-Zweymüller syndrome and Xeroderma pigmentosum, among others.

[0440] The term "neoplasia" or “cancer” is used throughout the specification to refer to the pathological process that results in the formation and growth of a cancerous or malignant neoplasm, i.e., abnormal tissue that grows by cellular proliferation, often more rapidly than normal and continues to grow after the stimuli that initiated the new growth cease. Malignant neoplasms show partial or complete lack of structural organization and functional coordination with the normal tissue and most invade surrounding tissues, metastasize to several sites, and are likely to recur after attempted removal and to cause the death of the patient unless adequately treated. As used herein, the term neoplasia is used to describe all cancerous disease states and embraces or encompasses the pathological process associated with malignant hematogenous, ascitic and solid tumors. Exemplary cancers which may be treated by the present compounds either alone or in combination with at least one additional anti-cancer agent include squamous-cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinomas, and renal cell carcinomas, cancer of the bladder, bowel, breast, cervix, colon, esophagus, head, kidney, liver, lung, neck, ovary, pancreas, prostate, and stomach; leukemias; benign and malignant lymphomas, particularly Burkitt's lymphoma and Non-Hodgkin's lymphoma; benign and malignant

melanomas; myeloproliferative diseases; sarcomas, including Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma, synovial sarcoma, gliomas, astrocytomas, oligodendrogliomas, ependymomas, gliobastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors, meningiomas, meningeal sarcomas, neurofibromas, and Schwannomas; bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, esophageal cancer, pancreatic cancer, stomach cancer, liver cancer, colon cancer, melanoma; carcinosarcoma, Hodgkin's disease, Wilms' tumor and teratocarcinomas. Additional cancers which may be treated using compounds according to the present disclosure include, for example, T-lineage Acute lymphoblastic Leukemia (T-ALL), T-lineage lymphoblastic Lymphoma (T-LL), Peripheral T-cell lymphoma, Adult T-cell Leukemia, Pre-B ALL, Pre-B Lymphomas, Large B-cell Lymphoma, Burkitts Lymphoma, B-cell ALL, Philadelphia chromosome positive ALL and Philadelphia chromosome positive CML.

[0441] 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 present compounds as an agent with biological activity to assist in effecting an intended therapy, inhibition and/or prevention/prophylaxis for which the present compounds are used. Preferred bioactive agents for use herein include those agents which have pharmacological activity similar to that for which the present compounds are used or administered and include for example, anti-cancer agents, antiviral agents, especially including anti-HIV agents and anti-HCV agents, antimicrobial agents, antifungal agents, etc.

[0442] The term “additional anti-cancer agent” is used to describe an anti-cancer agent, which may be combined with compounds according to the present disclosure to treat cancer. These agents include, for example, everolimus, trabectedin, abraxane, TLK 286, AV-299, DN-101, pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, a FLT-3 inhibitor, a VEGFR inhibitor, an EGFR TK inhibitor, an aurora kinase inhibitor, a PIK-1 modulator, a Bcl-2 inhibitor, an HDAC inhbitor, a c-MET inhibitor, a PARP inhibitor, a Cdk inhibitor, an EGFR TK inhibitor, an IGFR-TK inhibitor, an anti-HGF antibody, a PI3 kinase inhibitor, an AKT inhibitor, an mTORC1/2 inhibitor, a JAK/STAT inhibitor, a checkpoint-1 or 2 inhibitor, a focal adhesion kinase inhibitor, a Map

kinase kinase (mek) inhibitor, a VEGF trap antibody, pemetrexed, erlotinib, dasatanib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab, zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111, 131-I-TM-601, ALT-110, BIO 140, CC 8490, cilengitide, gimatecan, IL13-PE38QQR, INO 1001, IPdR$_1$ KRX-0402, lucanthone, LY317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311, romidepsin, ADS-100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, liposomal doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709, seliciclib; PD0325901, AZD-6244, capecitabine, L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H- pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate, camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrazole, exemestane, letrozole, DES(diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11, CHIR-258); 3-[5-(methylsulfonylpiperadinemethyl)- indolyl-quinolone, vatalanib, AG-013736, AVE-0005, goserelin acetate, leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714; TAK-165, HKI-272, erlotinib, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-166, GW-572016, Ionafarnib, BMS-214662, tipifarnib; amifostine, NVP-LAQ824, suberoyl analide hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib, KRN951 , aminoglutethimide, arnsacrine, anagrelide, L-asparaginase, Bacillus Calmette-Guerin (BCG) vaccine, adriamycin, bleomycin, buserelin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, diethylstilbestrol, epirubicin, fludarabine, fludrocortisone, fluoxymesterone, flutamide, gleevec, gemcitabine, hydroxyurea, idarubicin, ifosfamide, imatinib, leuprolide, levamisole, lomustine, mechlorethamine, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, octreotide, oxaliplatin, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, teniposide, testosterone, thalidomide, thioguanine, thiotepa, tretinoin, vindesine, 13-cis-retinoic acid, phenylalanine mustard, uracil mustard, estramustine, altretamine, floxuridine, 5-deooxyuridine, cytosine arabinoside, 6-mecaptopurine, deoxycoformycin, calcitriol, valrubicin, mithramycin, vinblastine, vinorelbine, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291 , squalamine, endostatin, SU5416, SU6668, EMD121974,

interleukin-12, IM862, angiostatin, vitaxin, droloxifene, idoxyfene, spironolactone, finasteride, cimitidine, trastuzumab, denileukin diftitox,gefitinib, bortezimib, paclitaxel, cremophor-free paclitaxel, docetaxel, epithilone B, BMS- 247550, BMS-310705, droloxifene, 4-hydroxytamoxifen, pipendoxifene, ERA-923, arzoxifene, fulvestrant, acolbifene, lasofoxifene, idoxifene, TSE-424, HMR- 3339, ZK186619, topotecan, PTK787/ZK 222584, VX-745, PD 184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-23573, RAD001, ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684, LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, erythropoietin, granulocyte colony-stimulating factor, zolendronate, prednisone, cetuximab, granulocyte macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-2a, pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L-asparaginase, lenalidomide, gemtuzumab, hydrocortisone, interleukin-11, dexrazoxane, alemtuzumab, all-transretinoic acid, ketoconazole, interleukin-2, megestrol, immune globulin, nitrogen mustard, methylprednisolone, ibritgumomab tiuxetan, androgens, decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, cortisone, editronate, mitotane, cyclosporine, liposomal daunorubicin, Edwina-asparaginase, strontium 89, casopitant, netupitant, an NK-1 receptor antagonist, palonosetron, aprepitant, diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone, methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, erythropoietin, epoetin alfa, darbepoetin alfa and mixtures thereof.

[0443] The term “anti-HIV agent” or “additional anti-HIV agent” includes, for example, nucleoside reverse transcriptase inhibitors (NRTI), other non-nucloeoside reverse transcriptase inhibitors (i.e., those which are not representative of the present disclosure), protease inhibitors, fusion inhibitors, among others, exemplary compounds of which may include, for example, 3TC (Lamivudine), AZT (Zidovudine), (-)-FTC, ddI (Didanosine), ddC (zalcitabine), abacavir (ABC), tenofovir (PMPA), D-D4FC (Reverset), D4T (Stavudine), Racivir, L-FddC, L-FD4C, NVP (Nevirapine), DLV (Delavirdine), EFV (Efavirenz), SQVM (Saquinavir mesylate), RTV (Ritonavir), IDV (Indinavir), SQV (Saquinavir), NFV (Nelfinavir), APV (Amprenavir), LPV (Lopinavir), fusion inhibitors such as T20, among others, fuseon and mixtures thereof, including anti-HIV compounds presently in clinical trials or in development.

[0444] Other anti-HIV agents which may be used in coadministration with compounds according to the present disclosure include, for example, other NNRTI's (i.e., other than the NNRTI's according to the present disclosure) may be selected from the group consisting of nevirapine (BI-R6-587), delavirdine (U-90152S/T), efavirenz (DMP-266), UC-781 (N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2methyl3-furancarbothiamide), etravirine (TMC125), Trovirdine (Ly300046.HCl), MKC-442 (emivirine, coactinon), HI-236, HI-240, HI-280, HI-281, rilpivirine (TMC-278), MSC-127, HBY 097, DMP266, Baicalin (TJN-151) ADAM-II (Methyl 3',3'-dichloro-4',4"-dimethoxy-5',5"-bis(methoxycarbonyl)-6,6-diphenylhexenoate), Methyl 3-Bromo-5-(1-5-bromo-4-methoxy-3-(methoxycarbonyl)phenyl)hept-1-enyl)-2-methoxybenzoate (Alkenyldiarylmethane analog, Adam analog), (5-chloro-3-(phenylsulfinyl)-2'-indolecarboxamide), AAP-BHAP (U-104489 or PNU-104489), Capravirine (AG-1549, S-1153), atevirdine (U-87201E), aurin tricarboxylic acid (SD-095345), 1-[(6-cyano-2-indolyl)carbonyl]-4-[3-(isopropylamino)-2-pyridinyl]piperazine, 1-[5-[[N-(methyl)methylsulfonylamino]-2-indolylcarbonyl-4-[3-(isopropylamino)-2-pyridinyl]piperazine, 1-[3-(Ethylamino)-2-[pyridinyl]-4-[(5-hydroxy-2-indolyl)carbonyl]piperazine, 1-[(6-Formyl-2-indolyl)carbonyl]-4-[3-(isopropylamino)-2-pyridinyl]piperazine, 1-[[5-(Methylsulfonyloxy)-2-indoyly)carbonyl]-4-[3-(isopropylamino)-2-pyridinyl]piperazine, U88204E, Bis(2-nitrophenyl)sulfone (NSC 633001), Calanolide A (NSC675451), Calanolide B, 6-Benzyl-5-methyl-2-(cyclohexyloxy)pyrimidin-4-one (DABO-546), DPC 961, E-EBU, E-EBU-dm, E-EPSeU, E-EPU, Foscarnet (Foscavir), HEPT (1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymine), HEPT-M (1-[(2-Hydroxyethoxy)methyl]-6-(3-methylphenyl)thio)thymine), HEPT-S (1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)-2-thiothymine), Inophyllum P, L-737,126, Michellamine A (NSC650898), Michellamine B (NSC649324), Michellamine F, 6-(3,5-Dimethylbenzyl)-1-[(2-hydroxyethoxy)methyl]-5-isopropyluracil, 6-(3,5-Dimethylbenzyl)-1-(ethyoxymethyl)-5-isopropyluracil, NPPS, E-BPTU (NSC 648400), Oltipraz (4-Methyl-5-(pyrazinyl)-3H-1,2-dithiole-3-thione), N-{2-(2-Chloro-6-fluorophenethyl]-N'-(2-thiazolyl)thiourea (PETT Cl, F derivative), N-{2-(2,6-Difluorophenethyl]-N'-[2-(5-bromopyridyl)]thiourea {PETT derivative), N-{2-(2,6-Difluorophenethyl]-N'-[2-(5-methylpyridyl)]thiourea {PETT Pyridyl derivative), N-[2-(3-Fluorofuranyl)ethyl]-N'-[2-(5-chloropyridyl)]thiourea, N-[2-(2-Fluoro-6-ethoxyphenethyl)]-N'-[2-(5-bromopyridyl)]thiourea, N-(2-Phenethyl)-N'-(2-thiazolyl)thiourea (LY-73497), L-697,639, L-697,593, L-697,661, 3-[2-

(4,7-Difluorobenzoxazol-2-yl)ethyl}-5-ethyl-6-methyl(pypridin-2(1H)-thione (2-Pyridinone Derivative), 3-[[(2-Methoxy-5,6-dimethyl-3-pyridyl)methyl]amine]-5-ethyl-6-methyl(pypridin-2(1H)-thione, R82150, R82913, R87232, R88703, R89439 (Loviride), R90385, S-2720, Suramin Sodium, TBZ (Thiazolobenzimidazole, NSC 625487), Thiazoloisoindol-5-one, (+)(R)-9b-(3,5-Dimethylphenyl-2,3-dihydrothiazolo[2,3-a]isoindol-5(9bH)-one, Tivirapine (R86183), UC-38 and UC-84, among others.

[0445] 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.

[0446] 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.

[0447] **General Synthetic Approach**

[0448] The synthetic realization and optimization of the bifunctional molecules as described herein may be approached in a step-wise or modular fashion. For example, identification of compounds that bind to the target molecules can involve high or medium throughput screening campaigns if no suitable ligands are immediately available. It is not unusual for initial ligands to require iterative design and optimization cycles to improve suboptimal aspects as identified by data from suitable in vitro and pharmacological and/or ADMET assays. Part of the optimization/SAR campaign would be to probe positions of the ligand that are tolerant of substitution and that might be suitable places on which to attach the linker chemistry previously referred to herein. Where crystallographic or NMR structural data are available, these can be used to focus such a synthetic effort.

[0449] In a very analogous way one can identify and optimize ligands for an E3 Ligase, i.e. ULMs/CLMs.

[0450] With PTMs and ULMs (e.g. CLMs) in hand one skilled in the art can use known synthetic methods for their combination with or without a linker moiety. Linker moieties can be synthesized with a range of compositions, lengths and flexibility and functionalized such that the PTM and ULM groups can be attached sequentially to distal ends of the linker. Thus a library of bifunctional molecules can be realized and profiled in in vitro and in vivo pharmacological and ADMET/PK studies. As with the PTM and ULM groups, the final bifunctional molecules can be subject to iterative design and optimization cycles in order to identify molecules with desirable properties.

[0451] **Abbreviations:**

ACN: acetonitrile

AcOH, acetic acid

ADDP: 1,1'-(azodicarbonyl)dipiperidine

aq., aqueous

BAST: *N,N*-bis(2-methoxyethyl)aminosulfur trifluoride

BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene

Boc, tert-butoxycarbonyl

Boc_2O, di-tert-butyl decarbonate

BOP, (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate

BPO: benzoyl peroxide

Cbz: Carbonylbezyloxy

$CDCl_3$, deuteriochloroform

CD3OD, deuteriomethanol

CH_3CN, acetonitrile

CH_3OH, methanol

CsF, cesium fluoride

Cs_2CO_3, cesium carbonate

$Cu(OAc)_2$, copper (II) acetate

Cy_2NMe, dicyclohexylmethylamine

DAST: diethylaminosulfur trifluoride

DBE: 1,2-dibromoethane

DCM: dichloromethane

DEAD: diethyl azodicarboxylate

DIAD: diisopropyl azodicarboxylate

DIBAL: disiobutylaluminium hydride

DIEA or DIPEA: diisopropylethylamine

DMA: *N,N*-dimethylacetamide

DMAP, N,N-dimethylaminopyridine

DMF: *N,N*-dimethylformamide

DMP: Dess-Martin periodinane

DMSO, dimethylsulfoxide

DMSO-d_6, hexadeuterodimethyl sulfoxide

EA: ethyl acetate

EDCI: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

Et_2NH, diethylamine

EtOAc or EA, ethyl acetate

HCl, hydrochloric acid

H_2O, water

HBTU: N,N,N'N'-tetramethyl-O-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate

HMDS: bis9trimethylsilyl)amine

HMPA: hexamethylphosphoramide

HPLC, high performance liquid chromatography

IBX, 2-iodoxybenzoic acid

KOAc, potassium acetate

LCMS, liquid chromatography / mass spectrometry

LDA: lithium diisopropylamide

LiOH, lithium hydroxide

MCPBA: meta-chloroperoxybenzoic acid

MeOH, methanol

MsCl: methanesulfonyl chloride

M.W: microwave

N_2, nitrogen

NaH, sodium hydride

$NaBH_3CN$, sodium cyanoborohydride

$NaBH(OAc)_3$, sodium triacetoxyborohydride

NaCl, sodium chloride

$NaHCO_3$, sodium bicarbonate

NaI, sodium iodide

Na_2SO_4, sodium sulfate

NBS: *N*-bromosuccinimide

n-BuLi, n-butyllithium

NH_3, ammonia

NH_4Cl, ammonium chloride

$NH_2OH{\cdot}HCl$, hydroxylamine hydrochloride

NMP, N-methylpyrrolidone

NMR, nuclear magnetic resonance

O_2, oxygen

PCC: pyridinium chlorochromate

Pd-118 or $Pd(dtpf)Cl_2$: 1,1'-bis(di-tert-butylphosphino)ferrocene dichloropalladium

$Pd(aMPhos)Cl_2$, bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II)

$Pd_2(dba)_3$: Tris(dibenzylideneacetone)dipalladium

$Pd(dppf)Cl_2$: 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium

$Pd(dba)_2$: bis(dibenzylideneacetone)palladium

$Pd(OH)_2$, palladium hydroxide

$Pd(PPh_3)_4$, tetrakis(triphenylphosphine)palladium(0)

PE, petroleum ether

Ph_3P, triphenylphosphine

PPTS: pyridium p-tolunesulfonate

PTSA: p-toluenesulfonic acid

Py, pyridine

PyBOP, (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

rt, room temperature

RuPhos-Pd-G3: XPhos-Pd-G3: [(2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)] palladium(II) methanesulfonate

RuPhos-Pd-G2: Chloro[(2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)] palladium(II)

SFC: supercritical fluid chromatography

TBAF, tetra-n-butylammonium fluoride

TBDPSCl, tert-butyldiphenylsilyl chloride

TBS, tert-butyldimethylsilyl

tBuOK, potassium tert-butoxide

$[tBu_3PH]BF_4$, tri-tert-butyl phosphonium tetrafluoroborate

t-BuXPhos-Pd-G3: [(2-di-*tert*-butylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)] palladium(II) methanesulfonate

TEA: trimethylamine

TFA: trifluoroacetic acid

TLC: thin layer chromatography

TMP: 2,2,6,6-tetramethylpiperidine

TEMPO: 2,2,6,6-tetramethylpiperidine-N-oxide

TMSOTf, trimethylsilyl trifluoromethanesulfonate

TosCl or TsCl: p-toluenesulfonyl chloride

TsCl, p-toluenesufonyl chloride

TsOH: p-toluenesulfonic acid

XantPhos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

XPhos: 2-dicyclohexylphosphino-2’4’6’-triisopropylbiphenyl

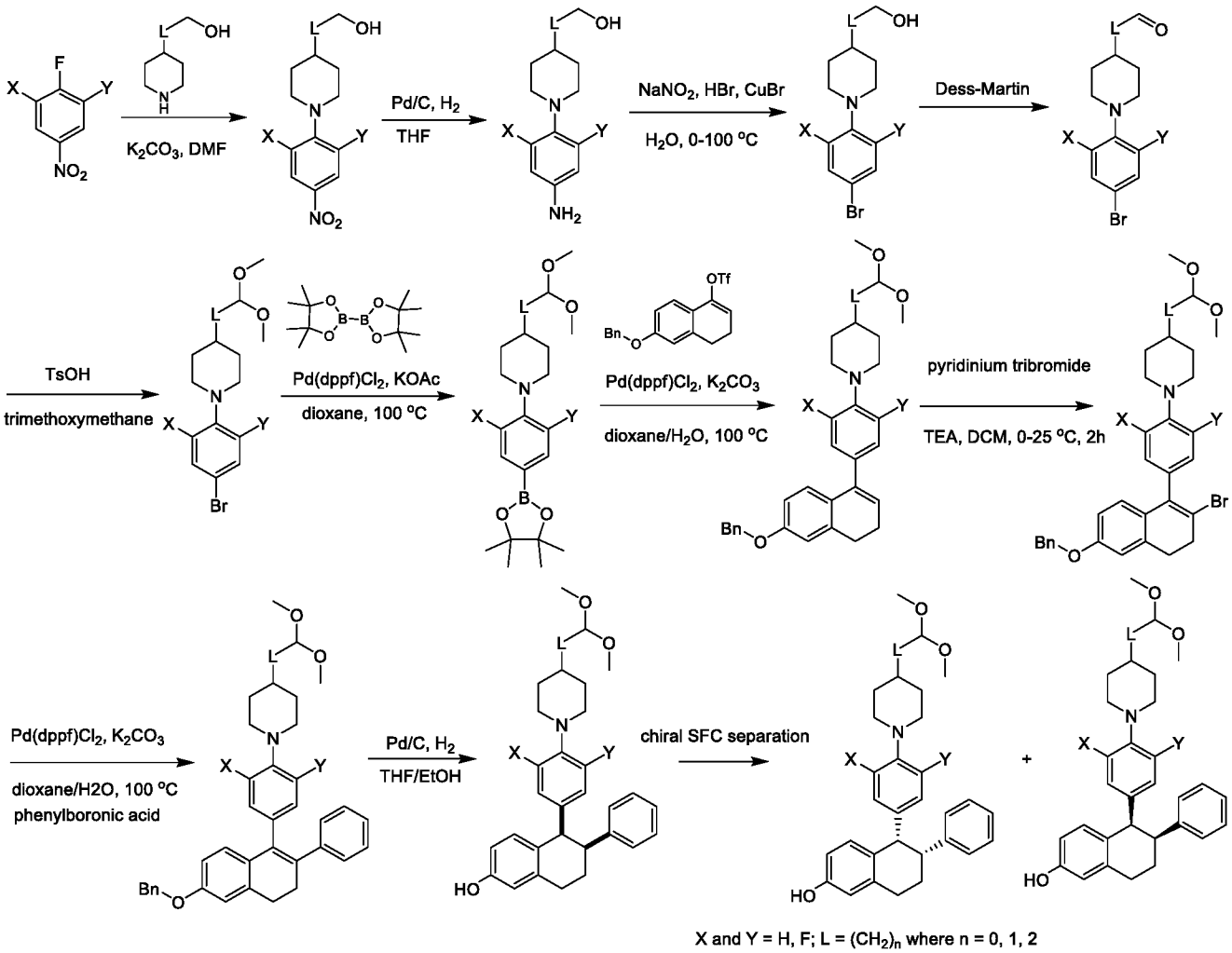
XPhos-Pd-G3: [(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)] palladium(II) methanesulfonate

12354-85-7: bis(pentamethylcyclopentadienylrhodium dichloride)

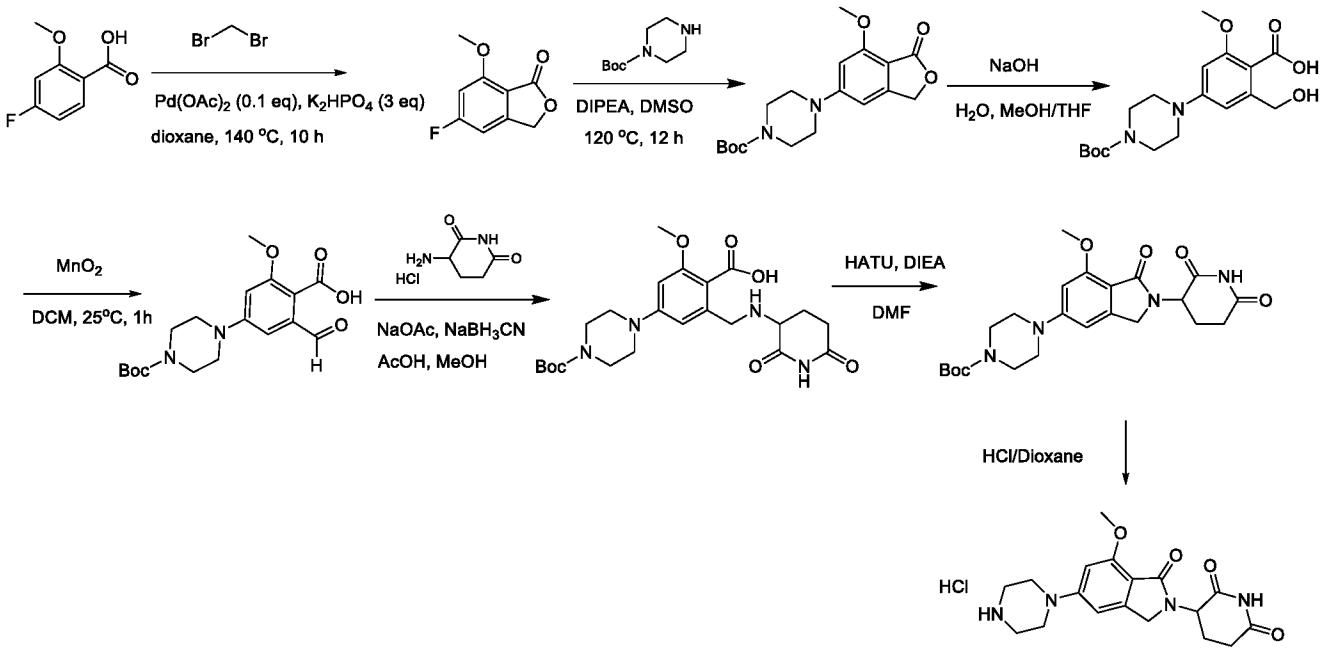
[0452] **A. Exemplary Synthetic Schemes for Exemplary Estrogen Receptor Binding Moiety Based Compounds**

[0453] Synthetic scheme A-1, A-2 through A-5, A-6, and A-7 described the routes used in the preparation of CRBN ligands, as well as CRBN ligands with partial linker moieties connected.

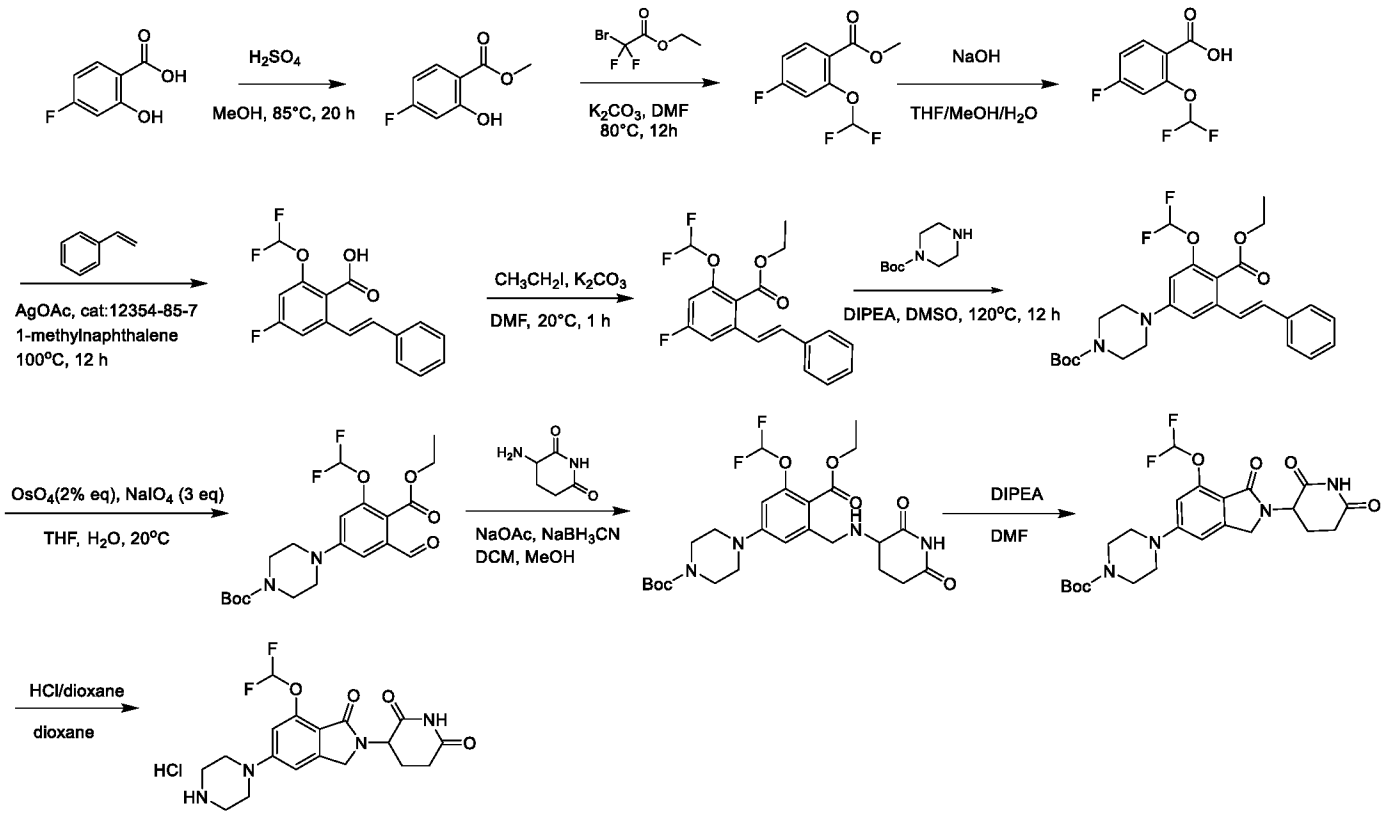
[0454] General synthetic scheme A-1 to prepare intermediate.



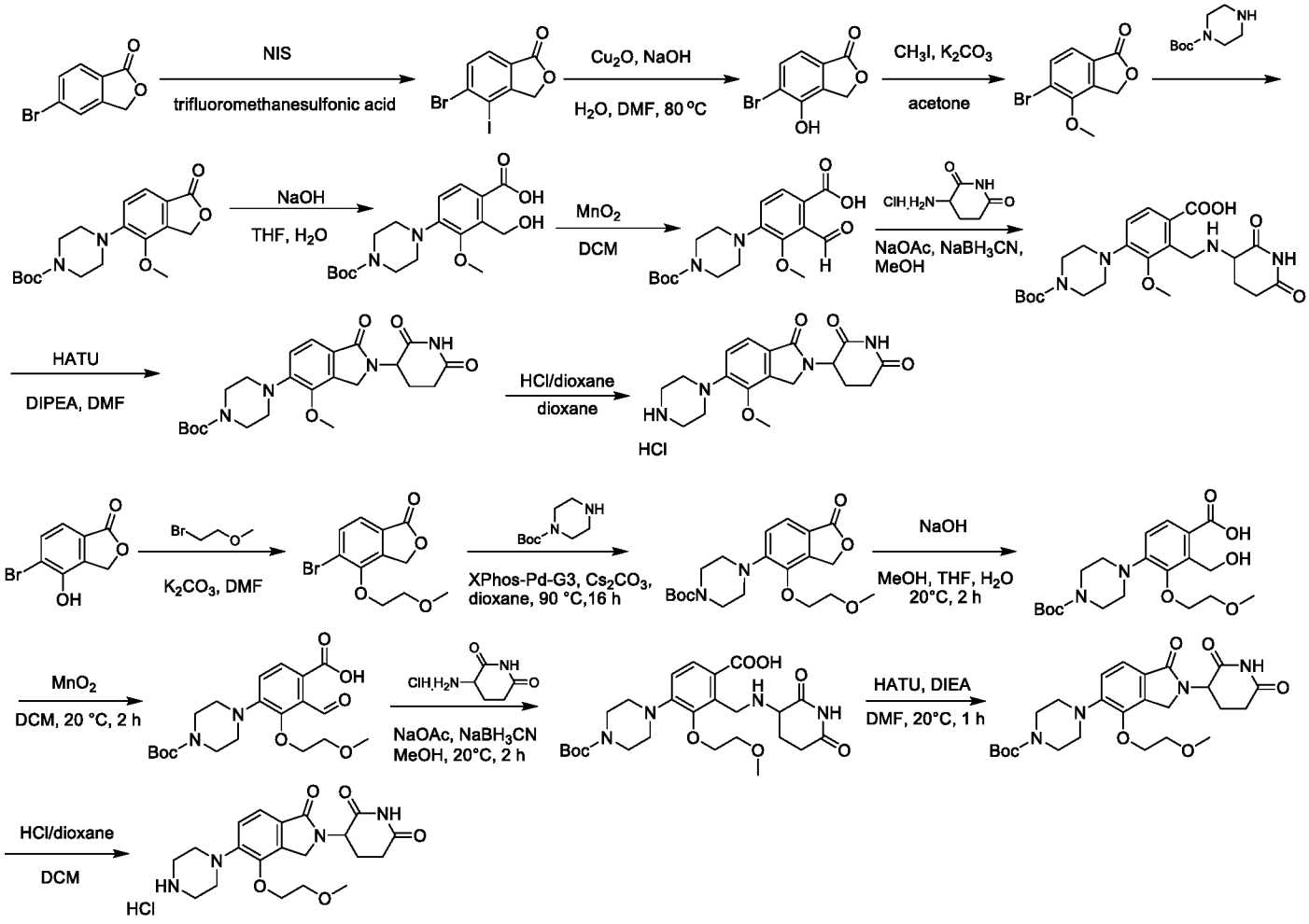
[0455] General synthetic scheme A-2 to prepare intermediate.



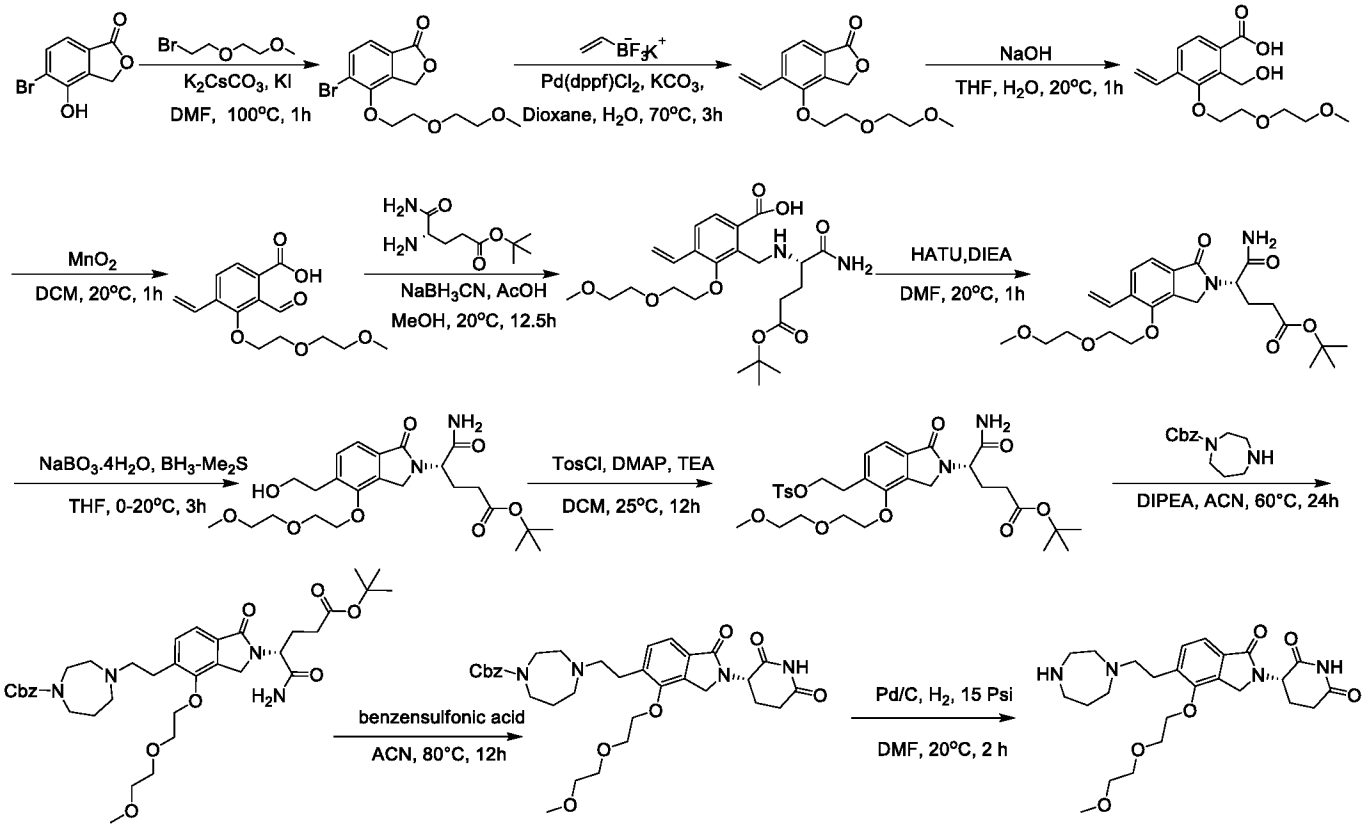
[0456] General synthetic scheme A-3 to prepare intermediate.



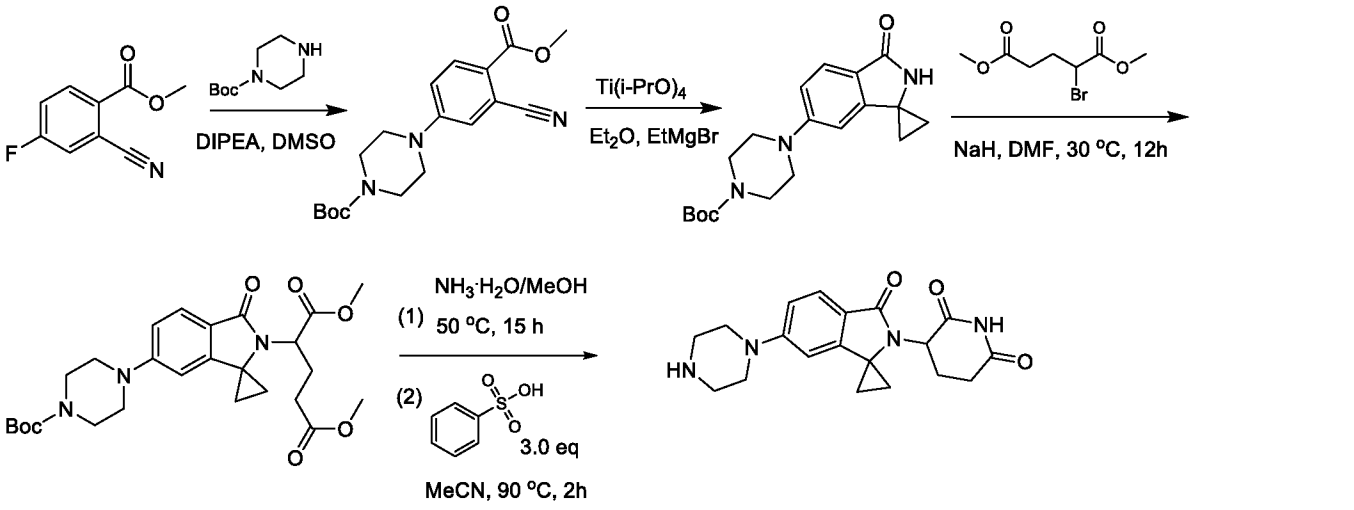
[0457] General synthetic scheme A-4 to prepare intermediate.



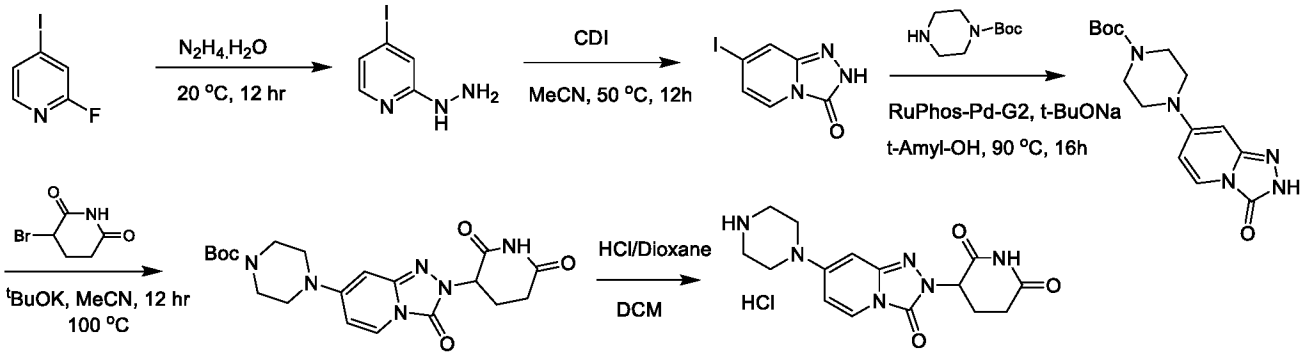
[0458] General synthetic scheme A-5 to prepare intermediate.



[0459] General synthetic scheme A-6 to prepare intermediate.

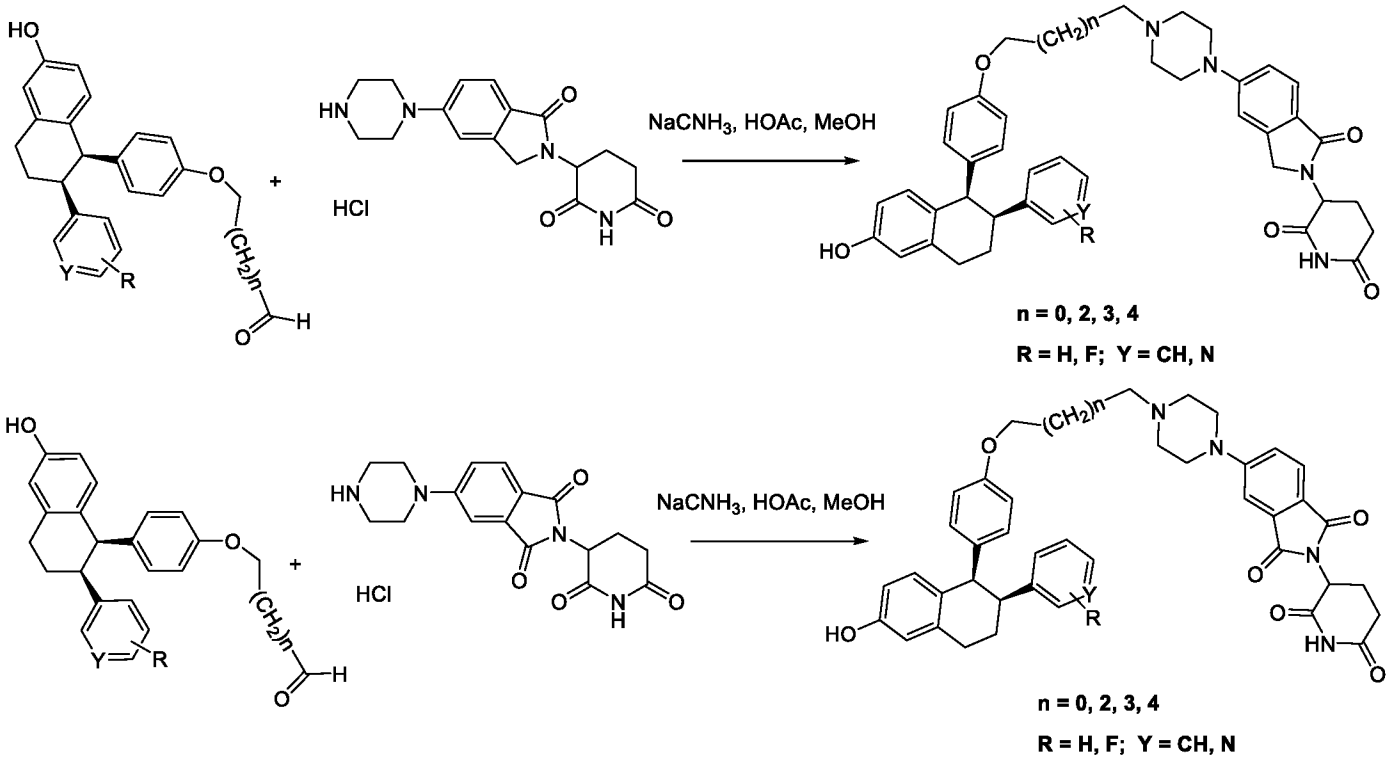


[0460] General synthetic scheme A-7 to prepare intermediate.

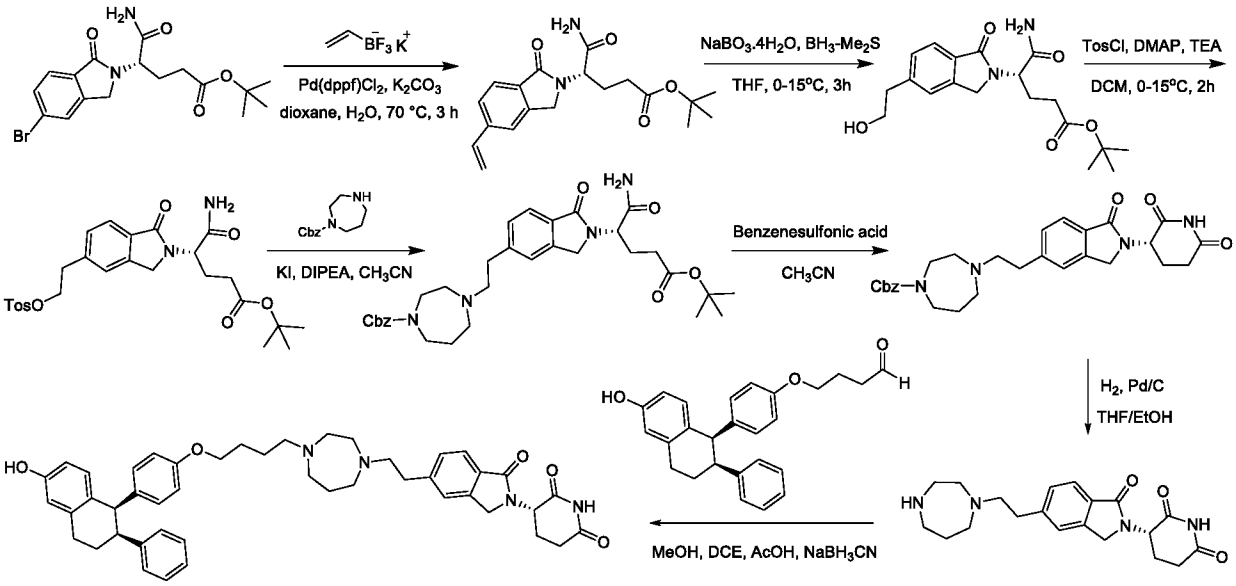


[0461] Synthetic schemes A-8, A-9, A-10, A-11, A-12, A-13, A-14, A-15, A-16, and A-17, described the routes used in the preparation of representative chimeric compounds claimed in this application.

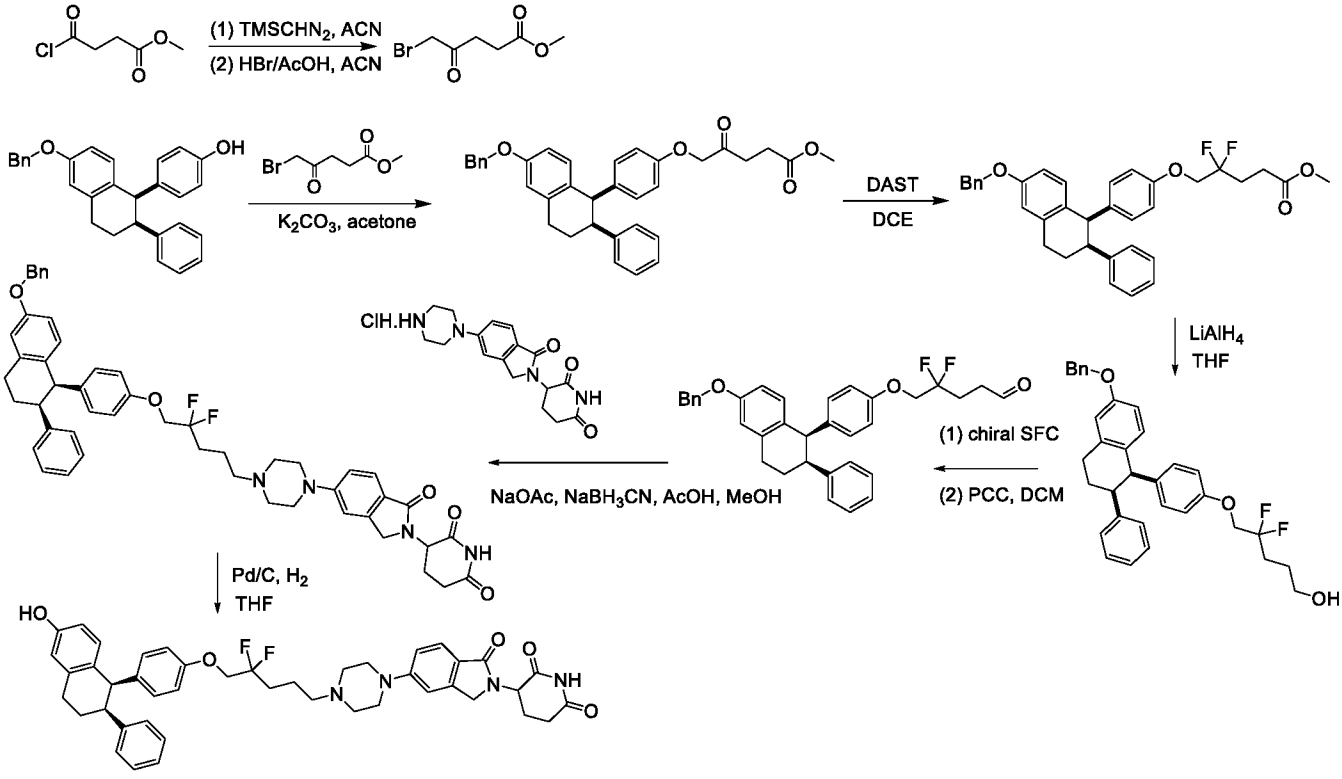
[0462] General synthetic scheme A-8 to prepare claimed compounds.



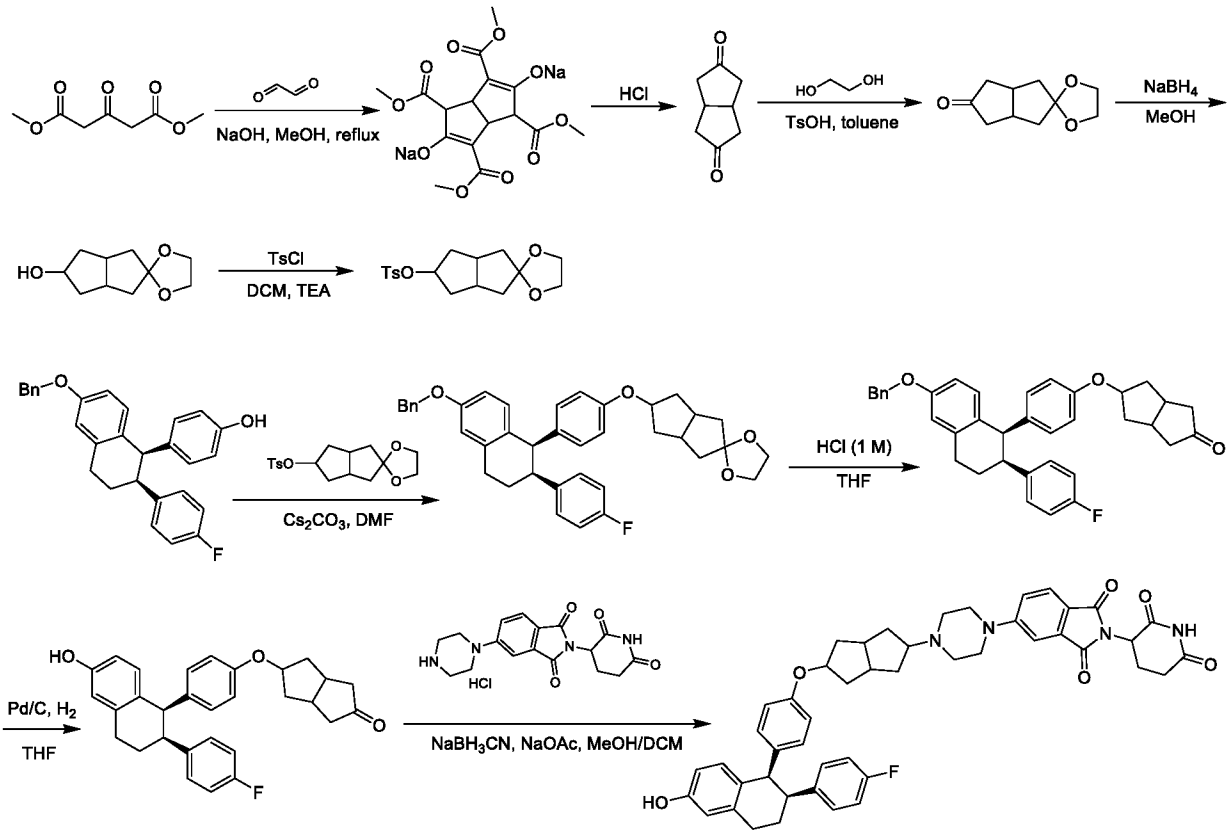
[0463] General synthetic scheme A-9 to prepare claimed compounds.



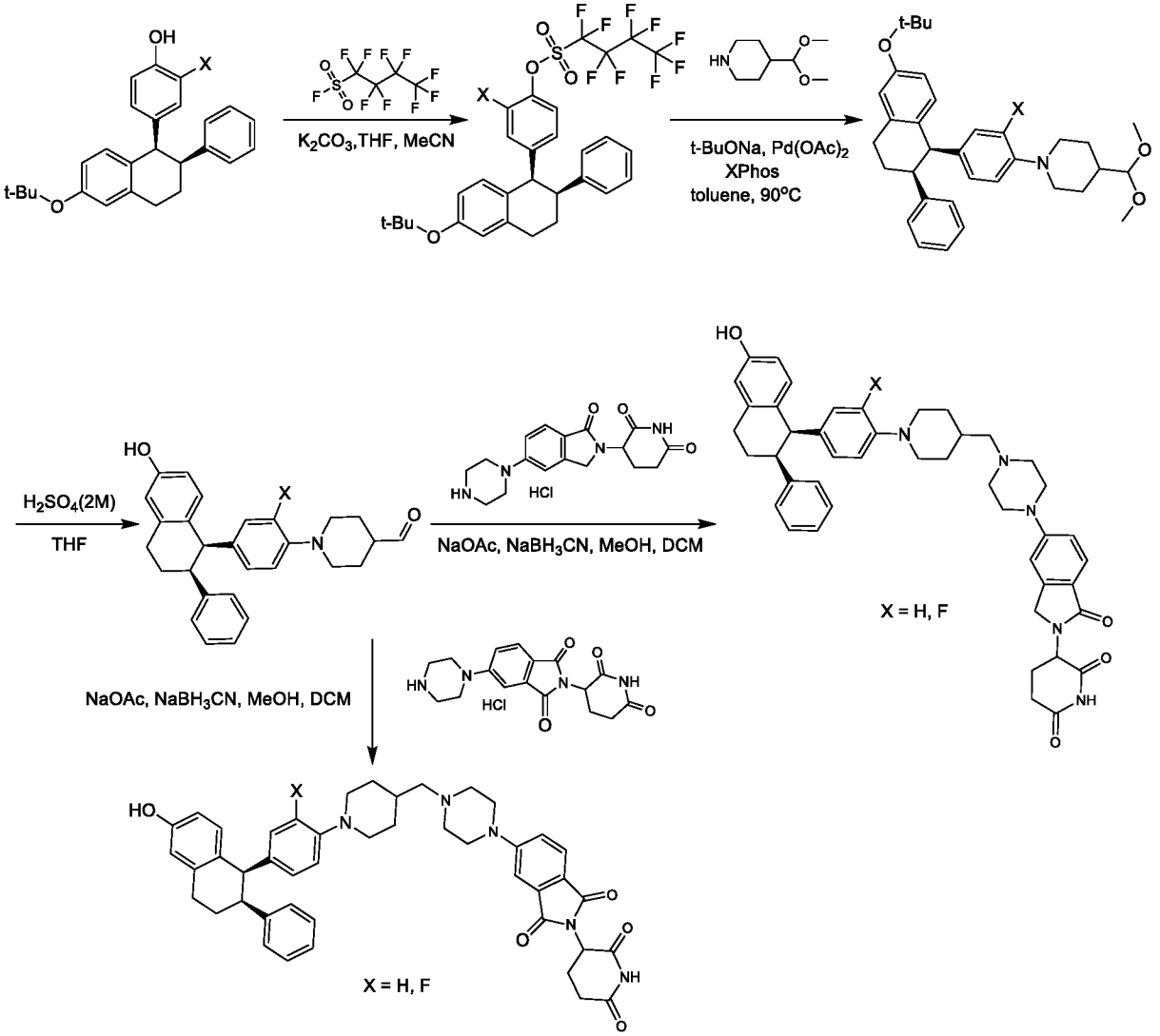
[0464] General synthetic scheme A-10 to prepare claimed compounds.



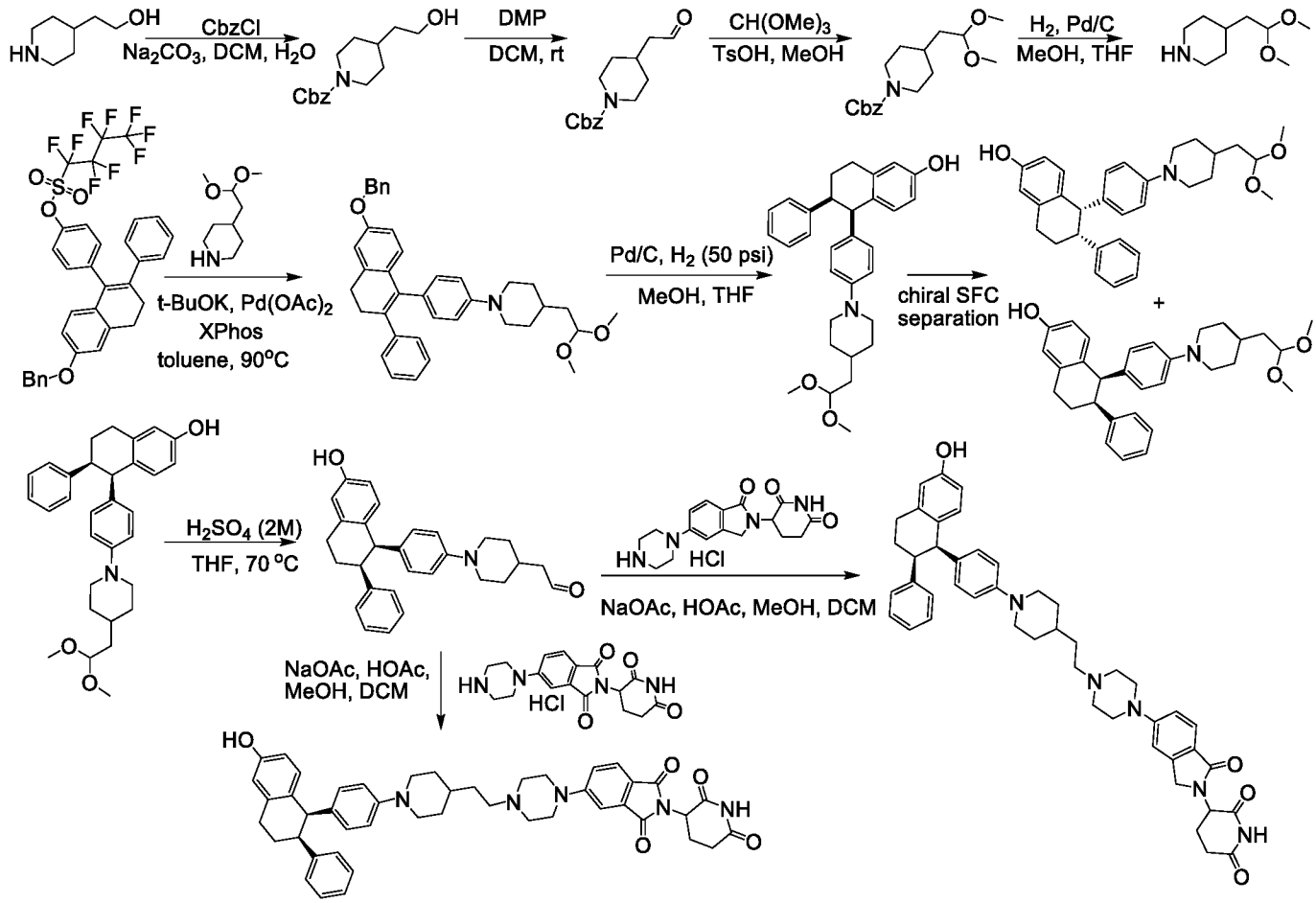
[0465] General synthetic scheme A-11 to prepare claimed compounds.


NaOH, MeOH, reflux
HCl
TsOH, toluene
NaBH4
MeOH
TsCl
DCM, TEA
Cs2CO3, DMF
HCl (1 M)
THF
Pd/C, H2
THF
NaBH3CN, NaOAc, MeOH/DCM

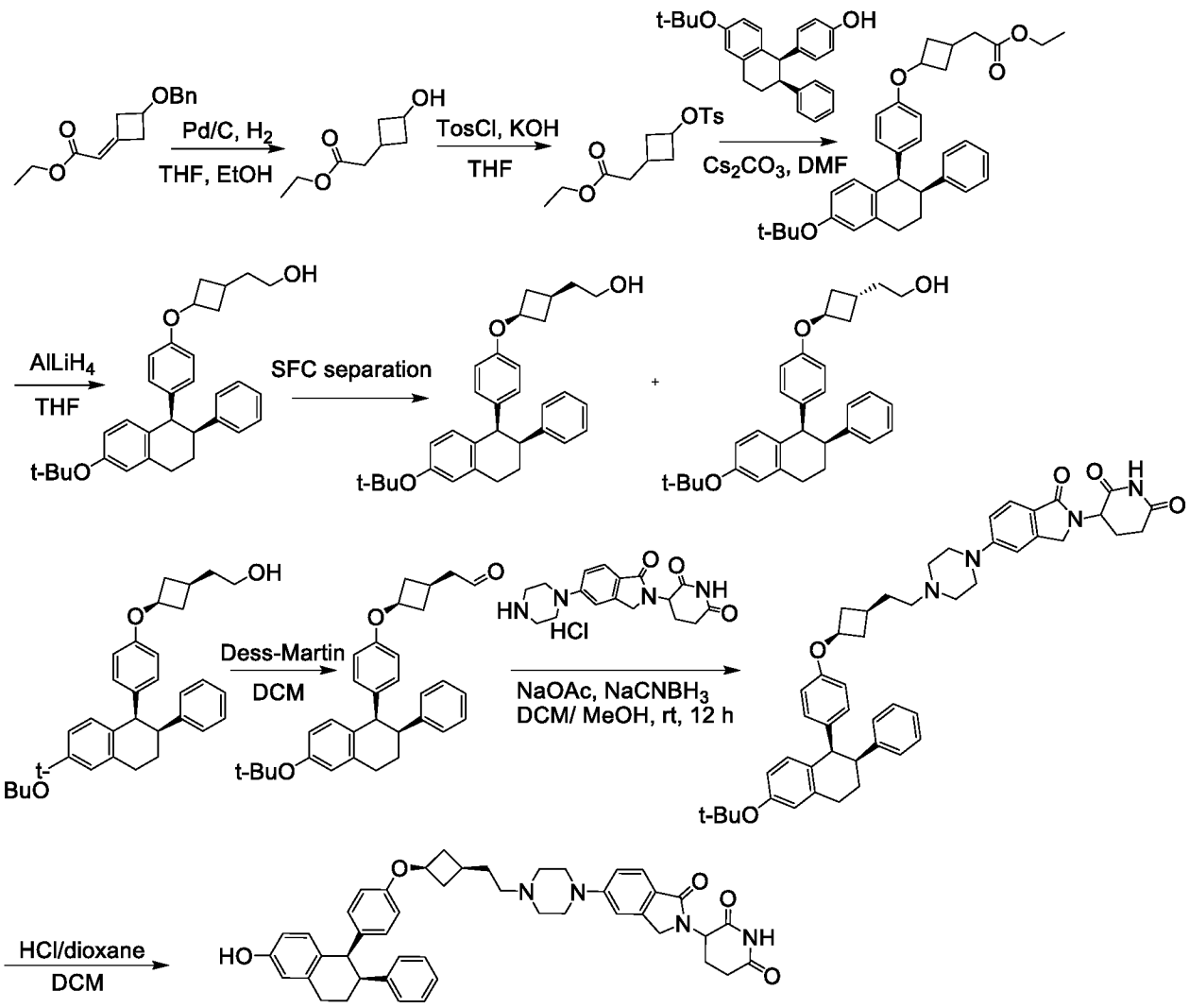
[0466] General synthetic scheme A-12 to prepare claimed compounds.



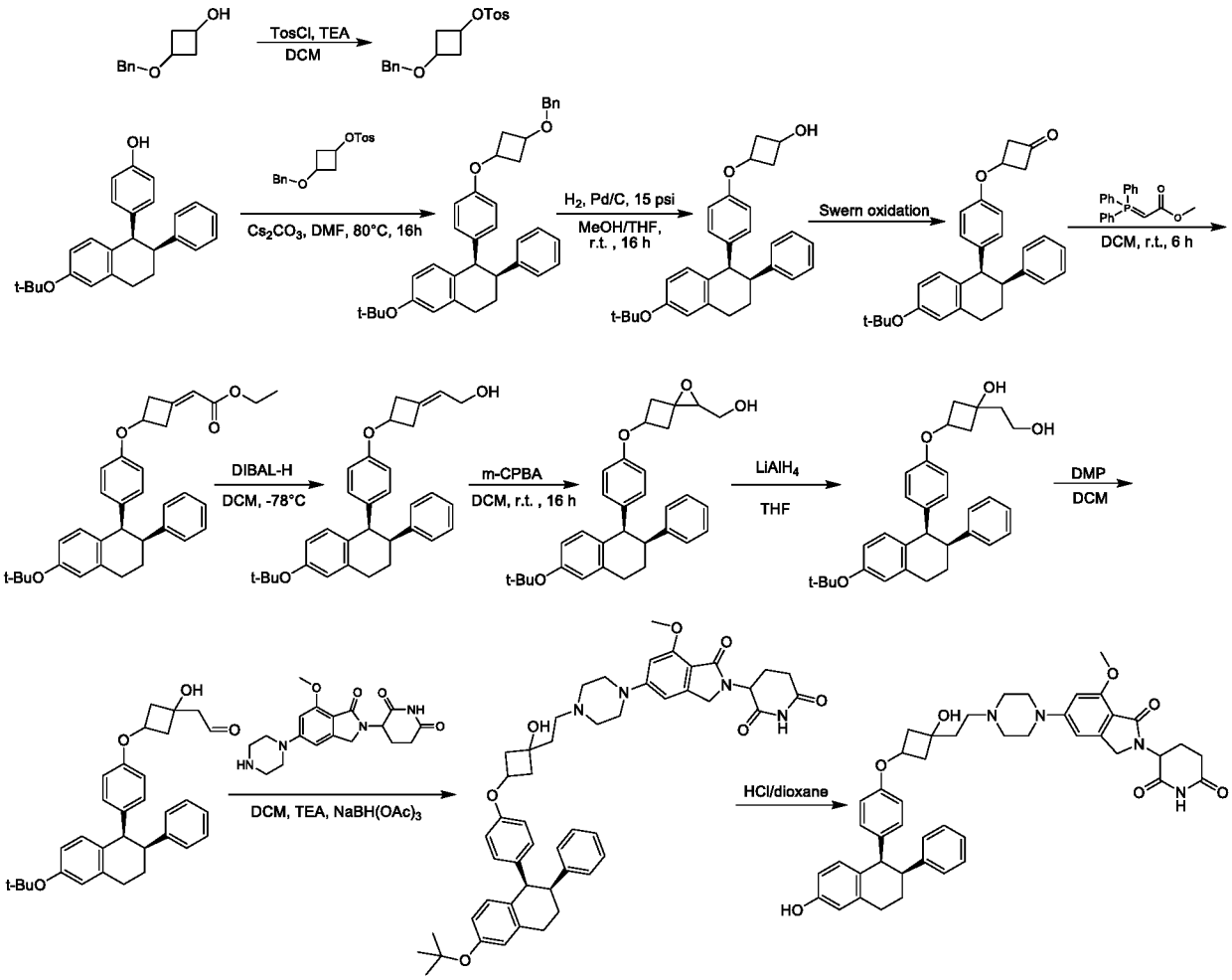
[0467] General synthetic scheme A-13 to prepare claimed compounds.



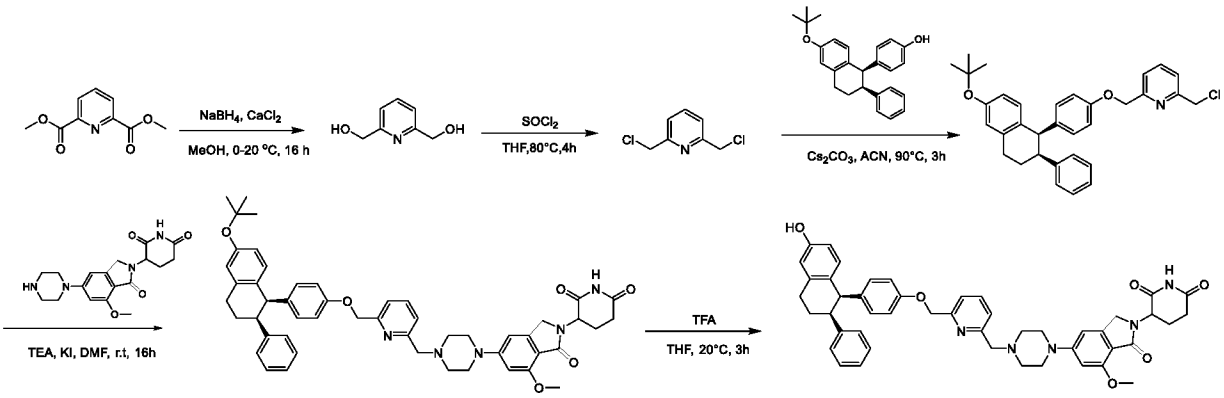
[0468] General synthetic scheme A-14 to prepare claimed compounds.



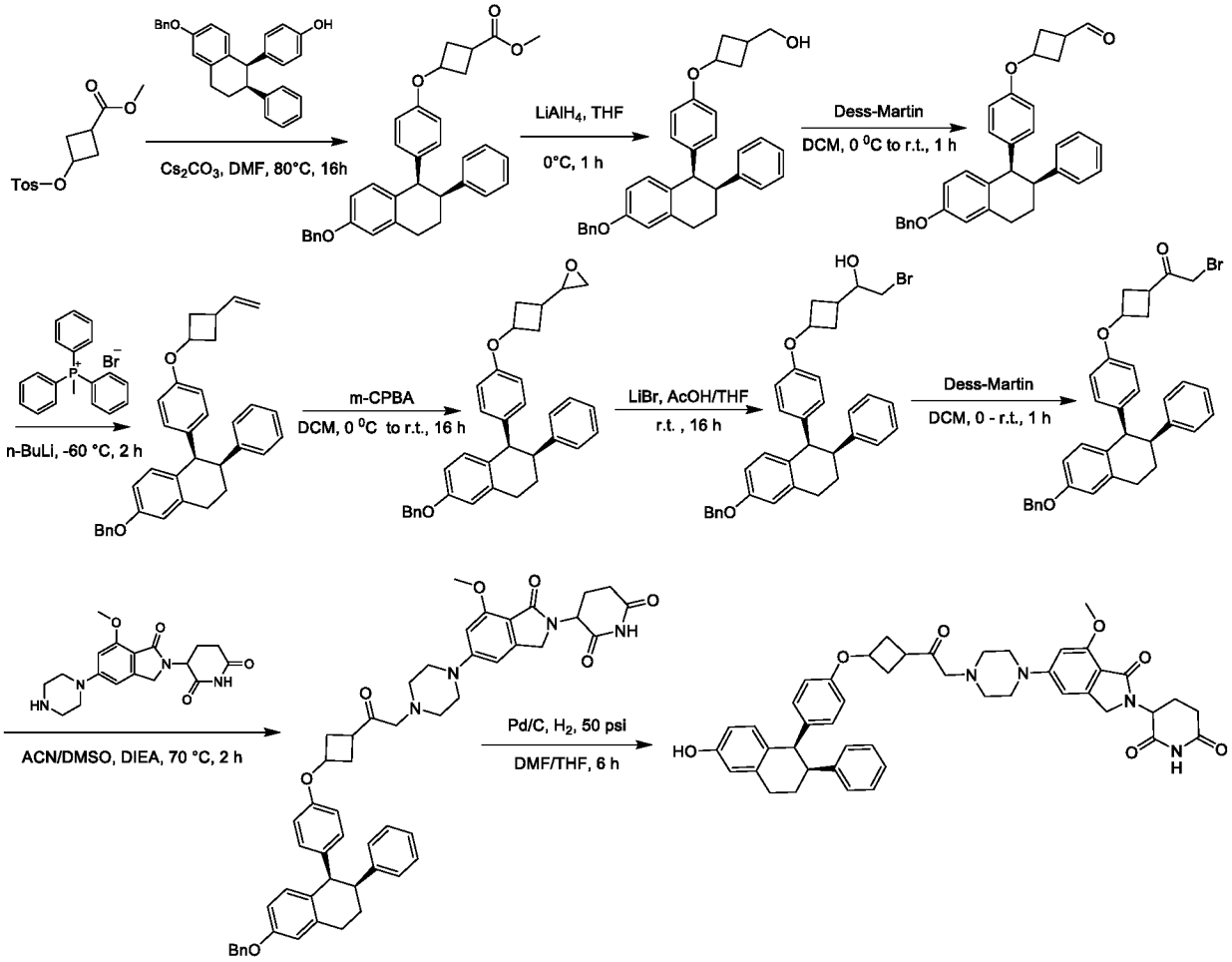
[0469] General synthetic scheme A-15 to prepare claimed compounds.



[0470] General synthetic scheme A-16 to prepare claimed compounds.



[0471] General synthetic scheme A-17 to prepare claimed compounds.



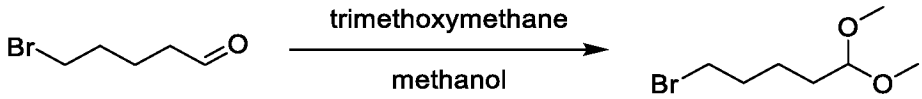
[0472] Exemplary Synthesis of Exemplary Compound 2: 3-{5-[4-(5-{4-[(1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl]phenoxy}pentyl)piperazin-1-yl]-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione

[0473] Step 1: Preparation of 5-bromopentanal

[0474] To a solution of oxalyl dichloride (9.12 g, 72 mmol, 6 mL, 4.00 *eq*) in dichloromethane (50 mL) was added a solution of dimethylsulfoxide (5.61 g, 72 mmol, 4.00 *eq*) in dichloromethane (10 mL) at -70 °C over 30 min, and then 5-bromopentan-1-ol (3.00 g, 18 mmol, 1.00 *eq*) was added at below -60 °C. The resulting mixture was stirred at -70 °C for 1 hr. Thin-layer chromatography (petroleum ether: ethyl acetate = 10:1) showed the reaction was complete. Triethylamine (14.54 g, 144 mmol, 20 mL, 8.00 *eq*) was added into the mixture and

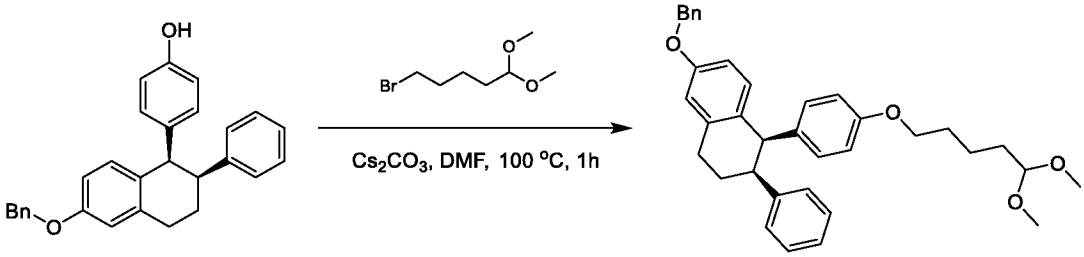
the reaction was stirred at -60 °C for 30 min. The mixture was poured into water (20 mL) and stirred for 1 min. The aqueous phase was extracted with dichloromethane (20 mL x 3). The combined organic phase was washed with brine (20 mL x 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was directly used for the next step without further purification. 5-bromopentanal (2.80 g, 17 mmol, 94% yield) was obtained as a colorless oil.

[0475] Step 2: Preparation of 5-bromo-1,1-dimethoxypentane



[0476] To a solution of 5-bromopentanal (2.80 g, 16.97 mmol, 1.00 *eq*) in methanol (50 mL) was added trimethoxymethane (9.00 g, 85 mmol, 9 mL, 5.00 *eq*) and 4-methylbenzenesulfonic acid hydrate (161 mg, 0.85 mmol, 0.05 *eq*) at 25 °C. The resulting mixture was stirred at 25 °C for 16 hr. Thin-layer chromatography (petroleum ether: ethyl acetate =10:1) showed a major new spot. The mixture was poured into water (40 mL) and stirred for 1 min. The aqueous phase was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (20 mL x 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate =15:1). 5-Bromo-1,1-dimethoxy-pentane (3.50 g, 16.58 mmol, 97% yield) was obtain as a colorless oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 4.37 (t, *J*=5.6 Hz, 1H), 3.41 (s, 2H), 3.33 (s, 6H), 1.95 - 1.84 (m, 2H), 1.67 - 1.59 (m, 2H), 1.54 - 1.45 (m, 2H).

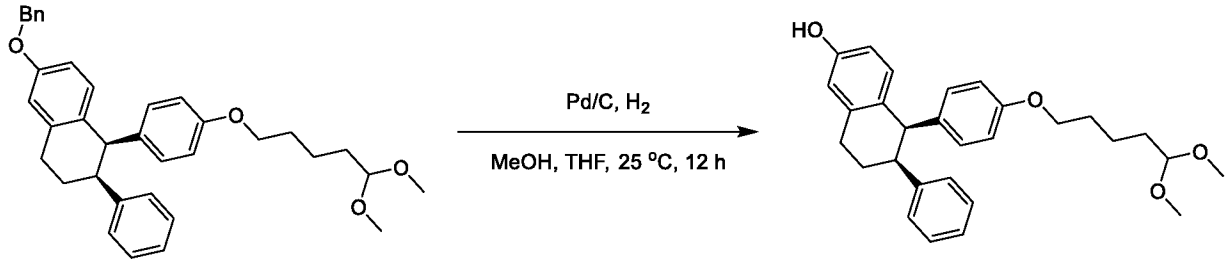
[0477] Step 3: Preparation of (1R,2S)-6-benzyloxy-1-[4-(5,5-dimethoxypentoxy)phenyl]-2-phenyl-tetralin



[0478] To a solution of 4-[(1R,2S)-6-benzyloxy-2-phenyl-tetralin-1-yl]phenol (500 mg, 1.23 mmol, 1.00 *eq*) in dimethylformamide (5 mL) was added cesium carbonate (1.2 g, 3.69 mmol, 3.00 *eq*) and 5-bromo-1,1-dimethoxy-pentane (390 mg, 1.84 mmol, 1.50 *eq*). The mixture was stirred at 100 °C for 1 hour. The reaction mixture was diluted with water (30 mL) and extracted

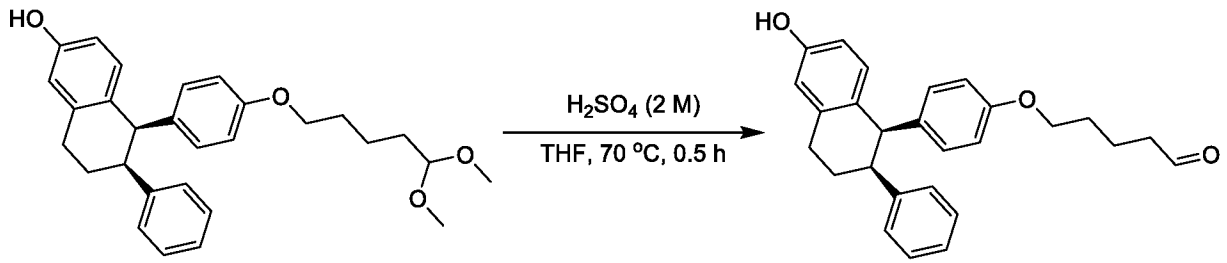
with ethyl acetate (15 mL x 2). The combined organic phase was washed with saturated brine (15 mL x 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 50:1 to 10:1) to give (1R,2S)-6-benzyloxy-1-[4-(5,5-dimethoxypentoxy)phenyl]-2-phenyl-tetralin (500 mg, 0.93 mmol, 76% yield) as a white solid. LC/MS (ESI) *m/z*: 559.2 $[M+23]^+$, ^1H NMR (400MHz, $CDCl_3$) δ 7.49 - 7.45 (m, 2H), 7.44 - 7.38 (m, 2H), 7.37 - 7.31 (m, 1H), 7.21 - 7.13 (m, 3H), 6.90 - 6.85 (m, 2H), 6.82 (dd, *J*=2.0, 7.2 Hz, 2H), 6.76 (dd, *J*=2.4, 8.4 Hz, 1H), 6.53 (d, *J*=8.8 Hz, 2H), 6.32 (d, *J*=8.8 Hz, 2H), 5.07 (s, 2H), 4.38 (t, *J*=5.6 Hz, 1H), 4.25 (d, *J*=4.8 Hz, 1H), 3.84 (t, *J*=6.4 Hz, 2H), 3.41 - 3.28 (m, 7H), 3.17 - 2.99 (m, 2H), 2.28 - 2.13 (m, 1H), 1.87 - 1.71 (m, 3H), 1.69 - 1.60 (m, 2H), 1.54 - 1.42 (m, 2H).

[0479] Step 4: Preparation of (1R,2S)-1-[4-(5,5-dimethoxypentoxy)phenyl]- 2-phenyl-tetralin-6-ol



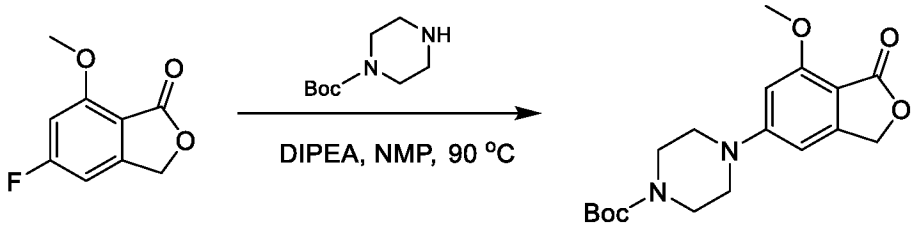
[0480] To a solution of (1R,2S)-6-benzyloxy-1-[4-(5,5-dimethoxypentoxy)phenyl]-2-phenyl-tetralin (500 mg, 0.93 mmol, 1.00 *eq*) in methanol (20 mL) and tetrahydrofuran (20 mL) was added palladium on carbon (200 mg, 10% purity) under nitrogen atmosphere. The suspension was degassed and purged with hydrogen 3 times. The mixture was stirred under hydrogen (15 psi) at 25 °C for 12 h. The reaction mixture was filtered and the filter was concentrated to give (1R,2S)-1-[4-(5,5-dimethoxypentoxy)phenyl]-2-phenyl-tetralin-6-ol (420 mg, crude) as a white solid. LC/MS (ESI) *m/z*: 469.1 $[M+23]^+$.

[0481] Step 5: Preparation of 5-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl] phenoxy]pentanal



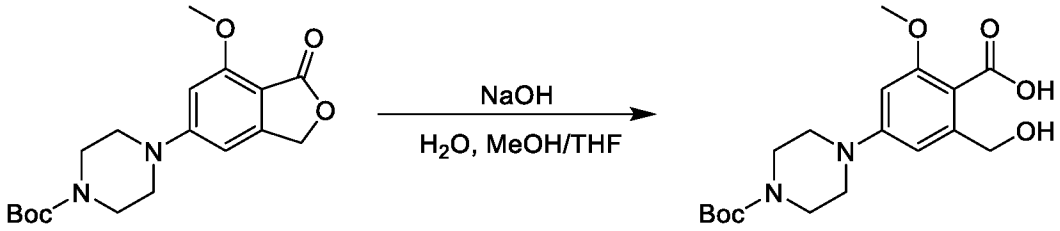
[0482] To a solution of (1R,2S)-1-[4-(5,5-dimethoxypentoxy)phenyl]-2-phenyl-tetralin-6-ol (420 mg, 0.94 mmol, 1.00 *eq*) in tetrahydrofuran (75 mL) was added sulfuric acid (2 M in water, 18 mL, 40.00 *eq*). The mixture was stirred at 70 °C for 0.5 h. Thin layer chromatography (petroleum ether: ethyl acetate = 3:1) showed the reaction was completed and a new spot formed. The reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic phase was washed with saturated sodium bicarbonate (15 mL) and saturated brine (20 mL x 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum to give 5-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenoxy] pentanal (370 mg, 0.92 mmol, 98% yield) as a white solid.

[0483] Step 6: Preparation of tert-butyl 4-(7-methoxy-1-oxo-1,3-dihydroisobenzofuran-5-yl)piperazine-1-carboxylate



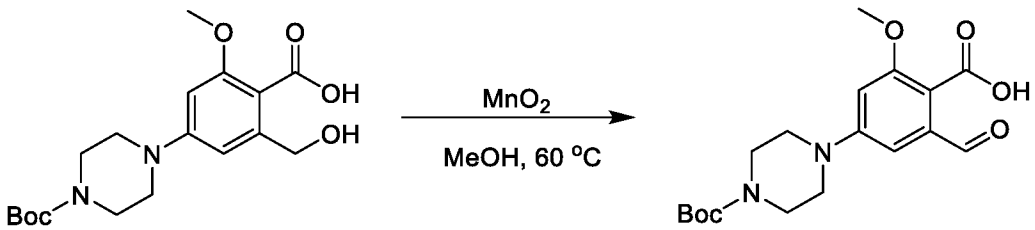
[0484] To a mixture of 5-fluoro-7-methoxy-3H-isobenzofuran-1-one (1 g, 5.49 mmol, 1 *eq*) and tert-butyl piperazine-1-carboxylate (2.05 g, 10.98 mmol, 2 *eq*) in 1-methylpyrrolidin-2-one (6 mL) was added N-ethyl-N-isopropylpropan-2-amine (2.84 g, 21.96 mmol, 3.83 mL, 4 *eq*) in one portion. The mixture was stirred at 100 °C for 12 hours. TLC (ethyl acetate/petroleum ether = 1/1, R_f = 0.1) indicated a new spot formed. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (40 mL × 2). The combined organic layers were washed with water (15 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 10/1 to 1:1). Tert-butyl 4-(7-methoxy-1-oxo-3H-isobenzofuran-5-yl)piperazine-1-carboxylate (1 g, 2.87 mmol, 52% yield) was obtained as a yellow solid. LC/MS (ESI) *m/z*: 349.3 $[M+1]^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.38 (s, 1H), 6.30 (s, 1H), 5.13 (s, 2H), 3.99 (s, 3H), 3.62-3.59 (m, 4H), 3.42-3.35 (m, 4H), 1.48 (s, 9H).

[0485] Step 7: Preparation of 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-(hydroxymethyl)-6-methoxybenzoic acid



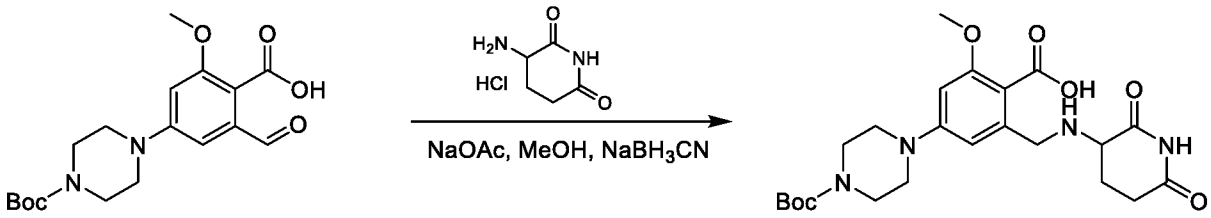
[0486] To a mixture of tert-butyl 4-(7-methoxy-1-oxo-3H-isobenzofuran-5-yl)piperazine-1-carboxylate (1 g, 2.87 mmol, 1 *eq*) in methyl alcohol (10 mL) and tetrahydrofuran (10 mL) was added the solution of sodium hydroxide (459 mg, 11.48 mmol, 4 *eq*) in water (2 mL). The mixture was stirred at 20 °C for 1 h. TLC (ethyl acetate/petroleum ether = 1/1, $R_f = 0$) indicated a new spot formed. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with water (20 mL) and extracted with ethyl acetate (30 mL × 2). The aqueous phase was adjusted to pH value to 4 ~ 5 with hydrochloric acid (1.5 N), then filtered and the solid was collected. The solid was used for the next step without further purification. 4-(4-Tert-butoxycarbonylpiperazin-1-yl)-2-(hydroxymethyl)-6-methoxy-benzoic acid (700 mg, 1.68 mmol, 58% yield, 88% purity) was obtained as a white solid. LC/MS (ESI) *m/z*: 367.3 $[M+1]^+$.

[0487] Step 8: Preparation of 4-(4-(tert-butoxycarbonyl)piperazin-1-yl) -2-formyl-6-methoxybenzoic acid



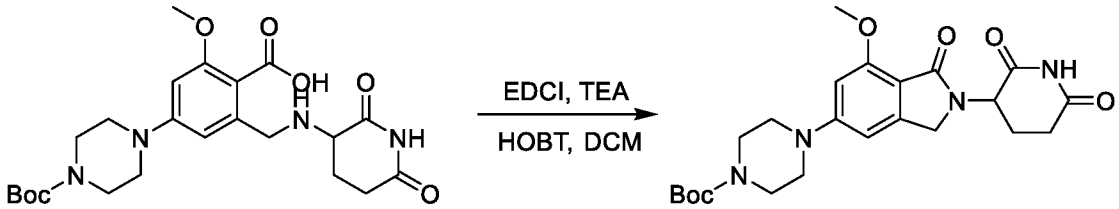
[0488] To a mixture of 4-(4-tert-butoxycarbonylpiperazin-1-yl)-2-(hydroxymethyl)-6-methoxy-benzoic acid (650 mg, 1.77 mmol, 1 *eq*) and in methyl alcohol (20 mL) was added manganese dioxide (1.54 g, 17.74 mmol, 10 *eq*) in one portion at 20 °C under nitrogen. The mixture was stirred at 50 °C for 12 hours. LC/MS showed the reaction was completed and desired product was formed. The reaction mixture was filtered and the solution was concentrated under vacuum. The reaction was used for the next step without further purification. 4-(4-Tert-butoxycarbonylpiperazin-1-yl)-2-formyl-6-methoxy-benzoic acid (600 mg, 1.65 mmol, 92% yield) was obtained as a yellow solid. LC/MS (ESI) *m/z*: 365.3 $[M+1]^+$.

[0489] Step 9: Preparation of 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-(((2,6-dioxopiperidin-3-yl)amino)methyl)-6-methoxybenzoic acid



[0490] To a mixture of 4-(4-tert-butoxycarbonylpiperazin-1-yl)-2-formyl-6-methoxy-benzoic acid (600 mg, 1.65 mmol, 1 *eq*) and 3-aminopiperidine-2,6-dione (407 mg, 2.47 mmol, 1.5 *eq*, HCl) in methyl alcohol (10 mL) was added sodium acetate (203 mg, 2.47 mmol, 1.5 *eq*) and sodium cyanoborohydride (310 mg, 4.94 mmol, 3 *eq*) in one portion at 20 °C. The mixture was stirred at 20 °C for 2 h. LC/MS showed the reaction was completed and desired product was formed. The reaction mixture was concentrated under vacuum. The residue was purified by reverse phase flash silica gel chromatography (120 g SepaFlash silica gel column, eluent of 0~60% acetonitrile in water with a flow rate of 30 mL/min). 4-(4-Tert-butoxycarbonylpiperazin-1-yl)-2-[[(2,6-dioxo-3-piperidyl)amino]methyl]-6-methoxy-benzoic acid (300 mg, 0.63 mmol, 38% yield) was obtained as a white solid. LC/MS (ESI) *m/z*: 477.4 $[M+1]^+$.

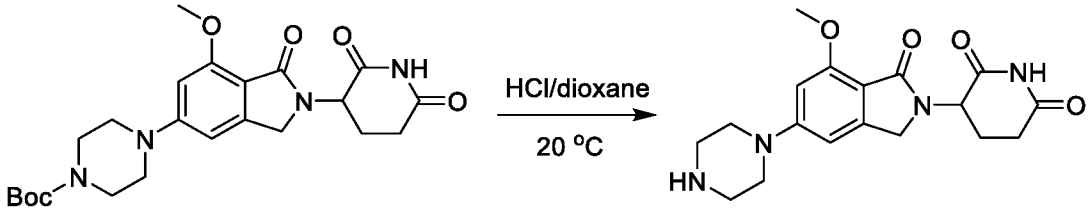
[0491] Step 10: Preparation of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1-oxoisoindolin-5-yl)piperazine-1-carboxylate



[0492] To a mixture of 4-(4-tert-butoxycarbonylpiperazin-1-yl)-2-[[(2,6-dioxo-3-piperidyl)amino]methyl]-6-methoxy-benzoic acid (300 mg, 0.63 mmol, 1 *eq*) in dichloromethane (10 mL) was added N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (181 mg, 0.94 mmol, 1.5 *eq*), N-hydroxybenzotrizole (128 mg, 0.94 mmol, 1.5 *eq*), and triethylamine (191 mg, 1.89 mmol, 3 *eq*). The mixture was stirred at 20 °C for 1 h. LC/MS showed the reaction was completed and desired product was formed. The reaction mixture was quenched by addition of water (15 mL), and then extracted with dichloromethane (40 mL × 2). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (dichloromethane: methyl

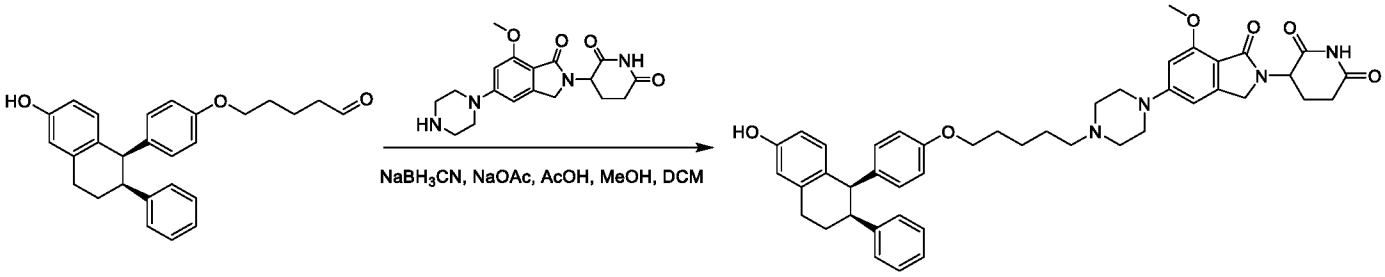
alcohol = 10:1, R_f = 0.60). Tert-butyl 4-[2-(2,6-dioxo-3-piperidyl)-7-methoxy-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (260 mg, 0.57 mmol, 90% yield) was obtained as a white solid. LC/MS (ESI) *m/z*: 459.4 $[M+1]^+$.

[0493] Step 11: Preparation of 3-(7-methoxy-1-oxo-5-(piperazin-1-yl)isoindolin-2-yl) piperidine-2,6-dione



[0494] To a mixture of tert-butyl 4-[2-(2,6-dioxo-3-piperidyl)-7-methoxy-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate (300 mg, 0.65 mmol, 1 *eq*) in dioxane (10 mL) was added hydrogen chloride/dioxane (4 M, 17 mL, 105.81 *eq*) in one portion. The mixture was stirred at 20 °C for 2 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was used for the next step without further purification. 3-(7-Methoxy-1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (216 mg, 0.55 mmol, 83% yield, HCl salt) was obtained as a white solid. LC/MS (ESI) *m/z*: 359.2 $[M+1]^+$; ^{1}H-NMR (400MHz, MeOD) *δ:* 6.72 (s, 1H), 6.60 (s, 1H), 5.08-5.04 (m, 1H), 4.36-4.35 (m, 2H), 3.92 (s, 3H), 3.66-3.65 (m, 5H), 3.38-3.35 (m, 4H), 2.89-2.78 (m, 1H), 2.77-2.67 (m, 1H), 2.45-2.42 (m, 1H), 2.14-2.14 (m, 1H).

[0495] Step 12: Preparation of 3-{5-[4-(5-{4-[(1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl]phenoxy}pentyl)piperazin-1-yl]-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione (**Exemplary Compound 2**)

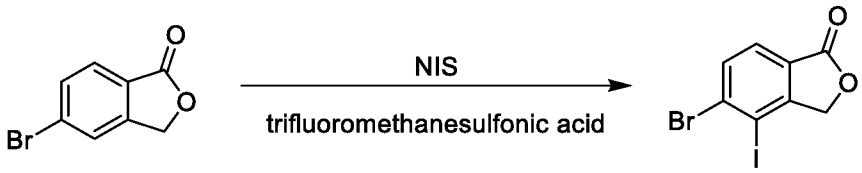


[0496] To a mixture of 3-(7-methoxy-1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione hydrochloride (89 mg, 0.23 mmol) in methyl alcohol (5 mL) and dichloromethane (1 mL) was added sodium acetate (102 mg, 1.25 mmol, 5 *eq*) in one portion at 20 °C. The mixture was stirred at 20 °C for 1 h, then 5-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenoxy]pentanal

(100 mg, 0.25 mmol, 1 *eq*) was added to the reaction mixture and stirred for 1 h. Sodium cyanoborohydride (31 mg, 0.50 mmol, 2 *eq*) and acetic acid (0.05 mL) was added to the reaction mixture. The resulting solution was stirred at 20 °C for 5 h. LC/MS showed the reaction was completed and desired product was formed. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by preparative HPLC (column: Phenomenex Synergi C18 150 × 25 × 10 um; mobile phase: [water(0.05%HCl)-acetonitrile]; B%: 35%-55%, 7.8 min). 3-[5-[4-[5-[4-[(1R,2S)-6-Hydroxy-2-phenyl-tetralin-1-yl]phenoxy]pentyl]piperazin-1-yl]-7-methoxy-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (109.9 mg, 0.14 mmol, 56% yield, 100% purity, HCl salt) was obtained as a white solid. LC/MS (ESI) *m/z*: 743.7 $[M+1]^+$; ^{1}H-NMR (400MHz, DMSO-*d*6) δ 10.93 (s, 1H), 10.56-10.43 (m, 1H), 9.18-9.13 (m, 1H), 7.16-7.13 (m, 3H), 6.84-6.83 (d, J = 6.4Hz, 2H), 6.69 (s, 1H), 6.62-6.61 (m, 2H), 6.55-6.52 (m, 3H), 6.28-6.26 (d, J = 8.4Hz, 2H), 4.99-4.97 (m, 1H), 4.29-4.25 (m, 1H), 4.23-4.18 (m, 1H), 4.17-4.15 (m, 1H), 4.06-4.00 (m, 2H), 3.85-3.83 (m, 5H), 3.56-3.53 (m, 1H), 3.34-3.33 (m, 4H), 3.10-3.02 (m, 4H), 3.00-2.85 (m, 2H), 2.60-2.58 (m, 3H), 2.16-2.08 (m, 1H), 1.91-1.88 (m, 1H), 1.76-1.69 (m, 5H), 1.43-1.41 (m, 2H).

[0497] Exemplary Synthesis of Exemplary Compound 3: 3-[5-[4-[5-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl] phenoxy]pentyl]piperazin-1-yl]-4-methoxy-1-oxo-isoindolin-2-yl]piperidine-2,6-dione

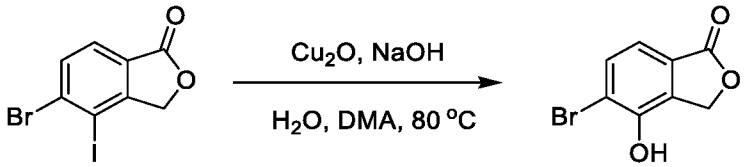
[0498] Step 1: Preparation of 5-bromo-4-iodo-3H-isobenzofuran-1-one



[0499] To a solution of 5-bromo-3H-isobenzofuran-1-one (50 g, 234.71 mmol, 1 *eq*) in trifluoromethanesulfonic acid (680 g, 4.53 mol, 400 mL, 19.30 *eq*) was added 1-iodopyrrolidine-2,5-dione (55.45 g, 246.45 mmol, 1.05 *eq*) at 0 °C in portions. The mixture was allowed to warm to 15 °C and held for 16 h. TLC (petroleum ether: ethyl acetate = 5:1) showed no starting material remained and two new spots (R_f = 0.4, 0.5) formed. The reaction mixture was poured into ice-water (1 L) and yellow solid precipitated. The mixture was filtered and the filter cake was washed with water. The filter cake was dissolved in ethyl acetate (500 mL) and the resulting orange solution was dried over sodium sulfate. The mixture was filtered and the filtrate was concentrated to afford a yellow solid. The residue was triturated with ethyl acetate (50 mL),

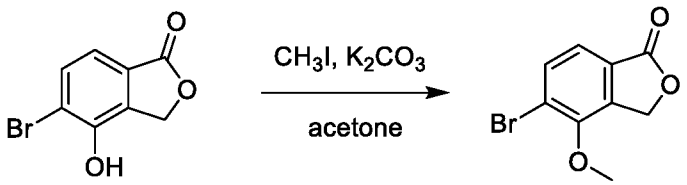
filtered and washed with ethyl acetate (10 mL x 2). 5-Bromo-4-iodo-3H-isobenzofuran-1-one (40 g, 118.02 mmol, 50% yield) was obtained as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.83 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 5.10 (s, 2H).

[0500] Step 2: Preparation of 5-bromo-4-hydroxy-3H-isobenzofuran-1-one



[0501] To a mixture of 5-bromo-4-iodo-3H-isobenzofuran-1-one (40 g, 118.02 mmol, 1 *eq*), sodium hydroxide (23.60 g, 590.10 mmol, 5 *eq*) in water (400 mL) and N,N-dimethylacetamide (200 mL) was added cuprous oxide (3.38 g, 23.60 mmol, 2.4 mL, 0.2 *eq*). The reaction mixture was heated to 80 °C and held for 16 h. TLC (petroleum ether : ethyl acetate = 1:1, R_f = 0.3) showed the reaction was completed. The reaction mixture was poured into 1N hydrochloride solution (400 mL) and extracted with ethyl acetate (400 mL x 2). The combined organic layers were concentrated and dissolved in ethyl acetate (500 mL), washed with saturated aqueous sodium bicarbonate (150 mL), brine (150 mL) and then dried over sodium sulfate. The mixture was filtered and the filtrate was concentrated to afford a residue. The residue was triturated with ethyl acetate (20 mL), filtered and washed with ethyl acetate (10 mL) to give a solid. The filtrate was further concentrated and triturated with ethyl acetate. 5-Bromo-4-hydroxy-3H-isobenzofuran-1-one (14.5 g, 60.15 mmol, 50% yield, 95% purity) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO) δ 10.90 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 5.35 (s, 2H).

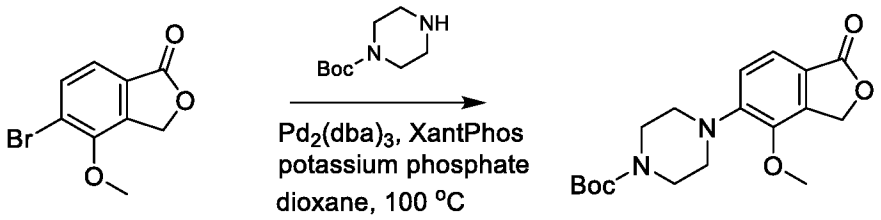
[0502] Step 3: Preparation of 5-bromo-4-methoxy-3H-isobenzofuran-1-one



[0503] To a mixture of 5-bromo-4-hydroxy-3H-isobenzofuran-1-one (3 g, 13.10 mmol, 1 *eq*) in acetone (20 mL) was added iodomethane (17.5 g, 123.29 mmol, 7.7 mL, 9.41 *eq*) and potassium carbonate (5.43 g, 39.30 mmol, 3 *eq*). The mixture was stirred at 20 °C for 15 h. TLC (ethyl acetate: petroleum ether = 1:3, R_f = 0.37) indicated reaction was completed. The reaction mixture was quenched by addition of water (10 mL), and then extracted with ethyl acetate (20

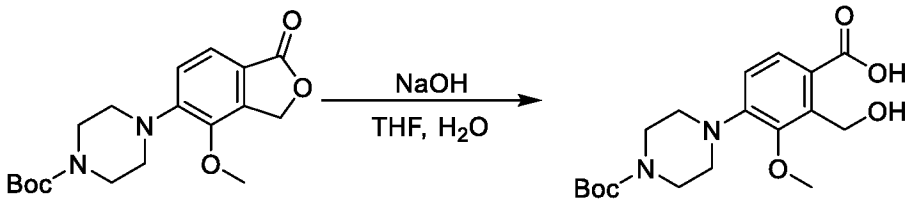
mL x 2). The combined organic layers were washed with saturated sodium bicarbonate (10 mL x 2), dried over sodium sulfate, filtered and concentrated under reduced pressure. 5-Bromo-4-methoxy-3H-isobenzofuran-1-one (2.9 g, 11.93 mmol, 91% yield) was obtained as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 5.44 (s, 2H), 4.00 (s, 3H).

[0504] Step 4: Preparation of tert-butyl 4-(4-methoxy-1-oxo-3H-isobenzofuran -5-yl) piperazine-1-carboxylate



[0505] A vial was charged with 5-bromo-4-methoxy-3H-isobenzofuran-1-one (500 mg, 2.06 mmol, 1 *eq*), tert-butyl piperazine-1-carboxylate (383 mg, 2.06 mmol, 1 *eq*), tris(dibenzylideneacetone)dipalladium(0) (188 mg, 0.20 mmol, 0.1 *eq*), XantPhos (119 mg, 0.20 mmol, 0.1 *eq*), potassium phosphate (873 mg, 4.11 mmol, 2 *eq*) and dioxane (5 mL). The mixture was purged with nitrogen and heated to 100 °C for 16 h. TLC (ethyl acetate: petroleum ether = 1:3) showed reaction was complete. The mixture was diluted with ethyl acetate (30 mL) and washed with water (30 mL). The aqueous layer was extracted with ethyl acetate (15 mL x 3). The organic layer was washed with brine (30 mL) and dried over sodium sulfate. The crude was purified by silica gel chromatography (ethyl acetate : petroleum ether = 1:20 to 1:6). Tert-butyl 4-(4-methoxy-1-oxo-3H-isobenzofuran-5-yl)piperazine-1-carboxylate (700 mg, 2.01 mmol, 97% yield) was obtained as a yellow solid. LC/MS (ESI) *m/z*: 349.2 $[M+1]^+$.

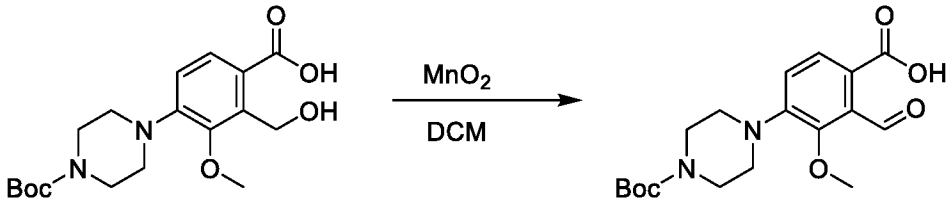
[0506] Step 5: Preparation of 4-(4-tert-butoxycarbonylpiperazin-1-yl)-2- (hydroxylmethyl)-3-methoxy-benzoic acid



[0507] To a solution of tert-butyl 4-(4-methoxy-1-oxo-3H-isobenzofuran-5-yl)piperazine-1-carboxylate (700 mg, 2.01 mmol, 1 *eq*) in tetrahydrofuran (4 mL) and water (4 mL) was added sodium hydroxide (401 mg, 10.05 mmol, 5 *eq*). The mixture was stirred at 20 °C for 16 h. TLC

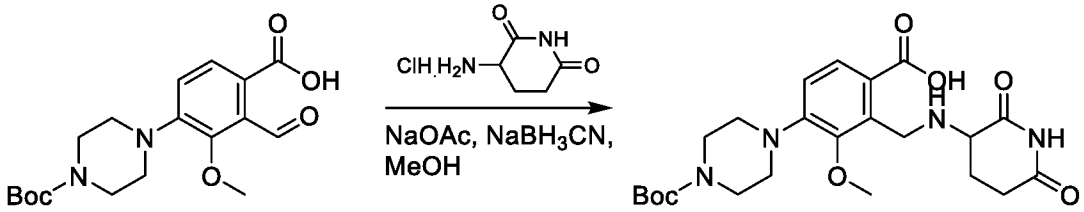
(ethyl acetate: petroleum ether = 1:2) showed reaction was complete. The mixture was adjusted to pH = 4 with aqueous hydrochloric acid (1 M) and extracted with ethyl acetate (10 ml x 3). The organic layer was washed with brine (20 mL) and dried over sodium sulfate. The crude material was not further purified. 4-(4-Tert-butoxycarbonylpiperazin-1-yl)-2-(hydroxymethyl) -3-methoxy-benzoic acid (700 mg, crude) was obtained as a yellow solid.

[0508] Step 6: Preparation of 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2- formyl-3-methoxybenzoic acid



[0509] To a solution of 4-(4-tert-butoxycarbonylpiperazin-1-yl)-2-(hydroxymethyl)-3-methoxy -benzoic acid (700 mg, 1.91 mmol, 1 *eq*) in dichloromethane (10 mL) was added manganese dioxide (2.49 g, 28.66 mmol, 15 *eq*). The mixture was stirred at 20 °C for 1 h. TLC (dichloromethane: methanol = 20:1) showed reaction was complete. The mixture was diluted with dichloromethane (10 mL) and filtered through a pad of Celite. The filtrate was concentrated in vacuum. The crude product was purified by silica gel column chromatography (dichloromethane: methanol = 100:1to 60:1). 4-(4-(Tert-butoxycarbonyl)piperazin-1-yl)-2-formyl-3-methoxybenzoic acid (300 mg, 0.82 mmol, 43% yield) was obtained as a pale yellow solid.

[0510] Step 7: Preparation of 4-(4-tert-butoxycarbonylpiperazin-1-yl)-2 -[[(2,6-dioxo -3-piperidyl)amino]methyl]-3-methoxy-benzoic acid



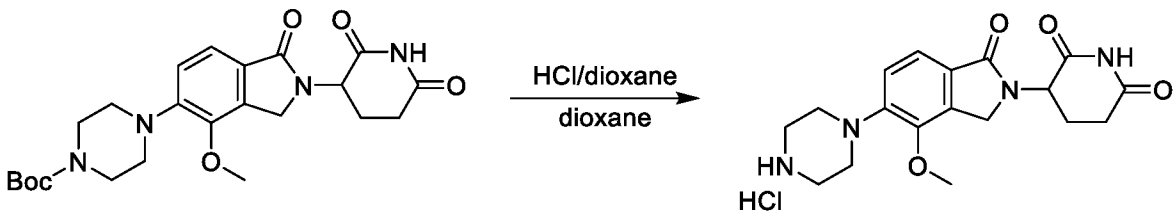
[0511] To a mixture of 3-aminopiperidine-2,6-dione (135 mg, 0.82 mmol, 1 *eq*, HCl salt) in methanol (2 mL) and dichloromethane (4 mL) was added sodium acetate (270 mg, 3.29 mmol, 4 *eq*). The mixture was stirred at 20 °C for 10 min, then 4-(4-tert-butoxycarbonylpiperazin-1-yl) -2-formyl-3-methoxy-benzoic acid (300 mg, 0.82 mmol, 1 *eq*) was added and the mixture was stirred for 10 min. Sodium cyanoborohydride (103 mg, 1.65 mmol, 2 *eq*) was added and the

mixture was further stirred for 40 min. LCMS showed reaction was complete. The mixture was adjusted to pH = 4-5 with aqueous hydrochloric acid solution (1 M) and extracted with ethyl acetate (10 mL x 3). The organic layer was dried over sodium sulfate. The crude product was not further purified. 4-(4-Tert-butoxycarbonylpiperazin-1-yl)-2-[[(2,6-dioxo-3-piperidyl)amino]methyl]-3-methoxy-benzoic acid (400 mg, crude) was obtained as a white solid. LC/MS (ESI) *m/z*: 477.1 $[M+1]^+$.

[0512] Step 8: Preparation of tert-butyl 4-[2-(2,6-dioxo-3-piperidyl)-4-methoxy-1-oxo-isoindolin-5-yl]piperazine-1-carboxylate

[0513] To a solution of 4-(4-tert-butoxycarbonylpiperazin-1-yl)-2-[[(2,6-dioxo-3-piperidyl)amino] methyl]-3-methoxy-benzoic acid (400 mg, 0.84 mmol, 1 *eq*) in dimethylformamide (5 mL) was added o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (383 mg, 1.01 mmol, 1.2 *eq*). The solution was stirred for 10min, then N,N-diisopropylethylamine (325 mg, 2.52 mmol, 3 *eq*) was added. The solution was stirred at 20 °C for 20 min. LCMS showed reaction was complete. The solution was diluted with ethyl acetate (40 mL) and washed with water (30 mL x 5) and brine (40 mL). The organic layer was dried over sodium sulfate. Tert-butyl 4-[2-(2,6-dioxo-3-piperidyl)-4-methoxy-1-oxo-isoindolin-5-yl] piperazine-1-carbo xylate (400 mg, crude) was obtained as a pale yellow solid. LC/MS (ESI) *m/z*: 459.1 $[M+1]^+$.

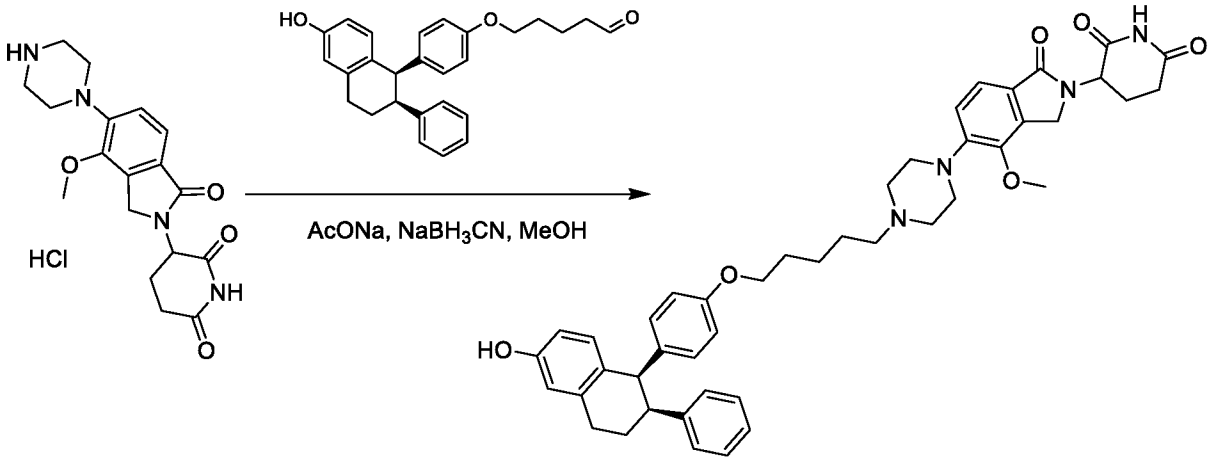
[0514] Step 9: Preparation of 3-(4-methoxy-1-oxo-5-piperazin-1-yl-isoindolin -2-yl) piperidine-2,6-dione



[0515] To a mixture of tert-butyl 4-[2-(2,6-dioxo-3-piperidyl)-4-methoxy-1-oxo–isoindolin-5-yl] piperazine-1-carboxylate (400 mg, 0.87 mmol, 1 *eq*) in dioxane (2 mL) was added hydrochloric acid in dioxane (4 M, 4 mL, 18.34 *eq*). The mixture was stirred at 20 °C for 10 min

and solvent was removed under vacuum. 3-(4-Methoxy-1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (350 mg, crude, HCl salt) was obtained as a white solid. LC/MS (ESI) *m/z*: 359.1 $[M+1]^+$.

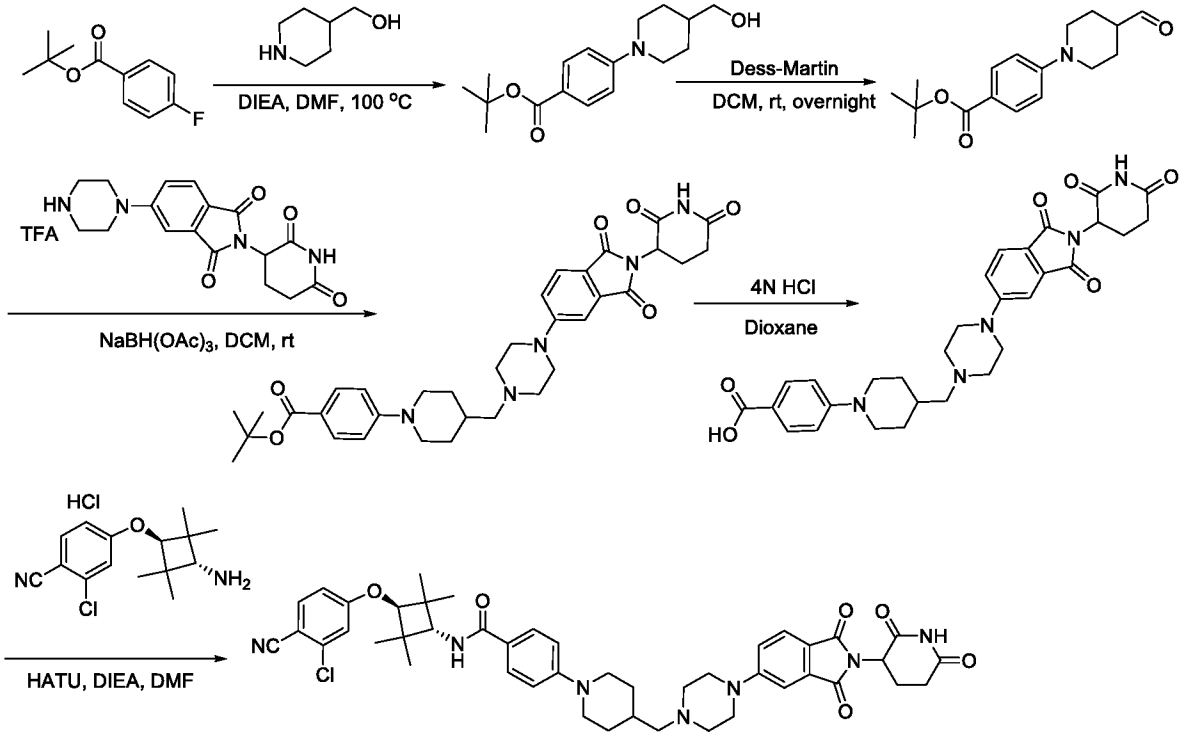
[0516] Step 10: Preparation of 3-[5-[4-[5-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl] phenoxy]pentyl]piperazin-1-yl]-4-methoxy-1-oxo-isoindolin-2-yl]piperidine -2,6-dione (**Exemplary Compound 3**)



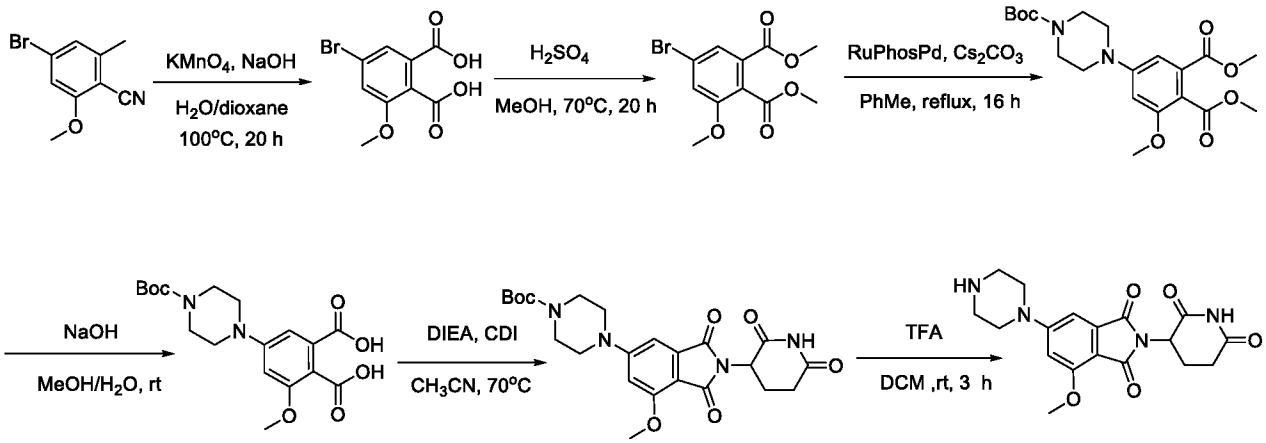
[0517] To a mixture of 3-(4-methoxy-1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (100 mg, 0.25 mmol, 1 *eq*, HCl salt) in dichloromethane (4 mL) and methanol (1 mL) was added sodium acetate (83 mg, 1.01 mmol, 4 *eq*). The mixture was stirred at 20 °C for 10 min. Then 5-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenoxy]pentanal (101 mg, 0.25 mmol, 1.00 *eq*) was added and the mixture was stirred for 10 min. Sodium cyanoborohydride (31 mg, 0.51 mmol, 2 *eq*) was added to the mixture and stirring was kept for 40 min. LCMS and TLC (dichloromethane: methanol = 10:1) showed reaction was complete. Solvent was removed under vacuum. The crude product was purified by prep-TLC (dichloromethane: methanol = 10:1). 3-[5-[4-[5-[4-[(1R,2S)-6-Hydroxy-2-phenyl-tetralin-1-yl]phenoxy]pentyl]piperazin-1-yl]-4-methoxy-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (55 mg, 0.07 mmol, 29% yield, 99% purity) was obtained as a white solid. LC/MS (ESI) *m/z*: 743.3 $[M+1]^+$; ^{1}H-NMR (400MHz, DMSO-*d*6) δ 10.96 (s, 1H), 9.12 (s, 1H), 7.39 (d, *J*=8.0 Hz, 1H), 7.25 - 6.98 (m, 4H), 6.83 (d, *J*=6.8 Hz, 2H), 6.72 - 6.43 (m, 5H), 6.26 (d, *J*=8.6 Hz, 2H), 5.06 (dd, *J*=5.0, 13.2 Hz, 1H), 4.56 - 4.11 (m, 3H), 3.94 - 3.70 (m, 5H), 3.30 - 3.25 (m, 1H), 3.21 - 2.77 (m, 8H), 2.64-2.55 (m, 5H), 2.46 - 2.26 (m, 2H), 2.16 - 1.94 (m, 2H), 1.80 - 1.22 (m, 7H).

[0518] B. Exemplary Synthetic Schemes for Exemplary Androgen Receptor Binding Moiety Based Compounds

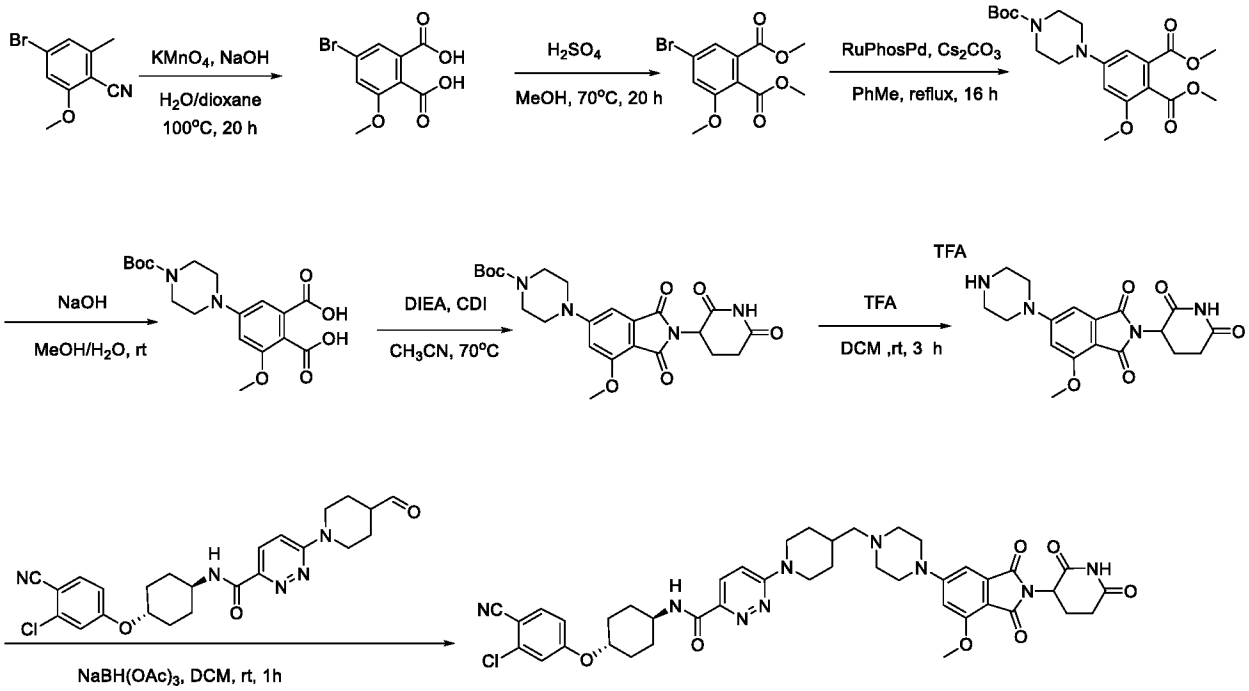
[0519] General Synthetic Scheme B-1



[0520] General Synthetic Scheme B-2



[0521] Exemplary Synthetic Scheme for Exemplary Compound 32:



[0522] **1. Synthesis of 5-bromo-3-methoxybenzene-1,2-dicarboxylic acid**

[0523] Into a 100-mL round-bottom flask, was placed 4-bromo-2-methoxy-6-methylbenzonitrile (800 mg, 3.54 mmol, 1.00 equiv), water (10 mL), sodium hydroxide (708 mg, 17.70 mmol, 5.00 equiv), $KMnO_4$ (1.12 g, 7.09 mmol, 2.00 equiv). The resulting solution was stirred for 16 h at 100°C in an oil bath. The solids were filtered out. The pH value of the solution was adjusted to 3 with hydrogen chloride (2 mol/L). The resulting solution was extracted with dichloromethane (15 mL x 3) and the aqueous layers combined. The resulting solution was extracted with ethyl acetate / methanol = 10:1 (15 mL x 3) and the organic layers combined and dried in an oven under reduced pressure, concentrated under vacuum. This resulted in 330 mg (34%) of 5-bromo-3-methoxybenzene-1,2-dicarboxylic acid as a white solid.

[0524] **2. Synthesis of 1,2-dimethyl 5-bromo-3-methoxybenzene-1,2-dicarboxylate**

[0525] Into a 100-mL round-bottom flask, was placed 5-bromo-3-methoxybenzene-1,2-dicarboxylic acid (330 mg, 1.20 mmol, 1.00 equiv), methanol (20 mL), sulfuric acid (5 mL). The resulting solution was stirred for 16 h at 70°C in an oil bath. The resulting solution was diluted with water (40 mL). The pH value of the solution was adjusted to 8 with sodium carbonate. The resulting solution was extracted with ethyl acetate (30 mL x 3) and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was

applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). This resulted in 340 mg (93%) of 1,2-dimethyl 5-bromo-3-methoxybenzene-1,2-dicarboxylate as a white solid.

[0526] LC-MS (ES+): m/z 302.85 [MH+], t_R = 0.906 min (2.0 minute run).

[0527] 3. Synthesis of 1,2-dimethyl-5-[4-[(tert-butoxy)carbonyl]piperazin-1-yl]-3-methoxybenzene-1,2-dicarboxylate

[0528] Into a 100-mL round-bottom flask, was placed 1,2-dimethyl 5-bromo-3-methoxybenzene-1,2-dicarboxylate (300 mg, 0.99 mmol, 1.00 equiv), tert-butyl piperazine-1-carboxylate (277 mg, 1.49 mmol, 1.50 equiv), RuphosPd (39 mg, 0.05 mmol, 0.05 equiv), Cs_2CO_3 (978 mg, 3.00 mmol, 3.00 equiv), toluene (15 mL). The resulting solution was stirred for 12 h at 100°C in an oil bath. The resulting solution was diluted with water (30 mL). The resulting solution was extracted with ethyl acetate (30 mL x 3) and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/ethyl acetate (10:1). This resulted in 340 mg (84%) of 1,2-dimethyl 5-[4-[(tert-butoxy)carbonyl]piperazin-1-yl]-3-methoxybenzene-1,2-dicarboxylate as light yellow oil.

[0529] LC-MS (ES+): m/z 409.05 [MH+], t_R = 0.963 min (2.0 minute run).

[0530] 4. Synthesis of 5-[4-[(tert-butoxy)carbonyl]piperazin-1-yl]-3-methoxybenzene-1,2-dicarboxylic acid

[0531] Into a 100-mL round-bottom flask, was placed 1,2-dimethyl 5-[4-[(tert-butoxy)carbonyl]piperazin-1-yl]-3-methoxybenzene-1,2-dicarboxylate (340 mg, 0.83 mmol, 1.00 equiv), methanol/H_2O/THF (8 mL), sodiumol (100 mg, 2.50 mmol, 3.00 equiv). The resulting solution was stirred for 12 h at 25°C The resulting solution was diluted with water (30 mL). The pH value of the solution was adjusted to 8 with hydrogen chloride (2 mol/L). citric acid monohydrate was employed to adjust the pH to 3. The resulting solution was extracted with ethyl acetate (30 mL x 3) and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 300 mg (95%) of 5-[4-[(tert-butoxy)carbonyl]piperazin-1-yl]-3-methoxybenzene-1,2-dicarboxylic acid as colorless oil.

[0532] LC-MS (ES+): m/z 306.95 [MH+], t_R = 0.853 min (2.0 minute run).

[0533] 5. Synthesis of tert-butyl-4-[2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]piperazine-1-carboxylate

[0534] Into a 100-mL round-bottom flask, was placed tert-butyl 4-(7-methoxy-1,3-dioxo-1,3-dihydro-2-benzofuran-5-yl)piperazine-1-carboxylate (260 mg, 0.72 mmol, 1.00 equiv), 3-aminopiperidine-2,6-dione hydrochloride (153.6 mg, 0.93 mmol, 1.30 equiv), pyridine (10 mL). The resulting solution was stirred for 4 h at 120°C in an oil bath. The resulting solution was diluted with water (30 mL). The resulting solution was extracted with ethyl acetate (30 mL x 3) and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (100:1). This resulted in 280 mg (83%) of tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]piperazine-1-carboxylate as a yellow solid.

[0535] LC-MS (ES+): m/z 417.05 [MH+], t_R = 0.852 min (2.0 minute run).

[0536] 6. Synthesis of 2-(2,6-dioxopiperidin-3-yl)-4-methoxy-6-(piperazin-1-yl)isoindoline-1,3-dione

[0537] Into a 50-mL round-bottom flask, was placed tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]piperazine-1-carboxylate (270 mg, 0.57 mmol, 1 equiv), dichloromethane (6 mL, 0.07 mmol, 0.124 equiv), TFA (2 mL, 0.02 mmol, 0.031 equiv). The resulting solution was stirred for 2 hr at 25 °C. The resulting mixture was concentrated to give 2-(2,6-dioxopiperidin-3-yl)-4-methoxy-6-(piperazin-1-yl)isoindoline-1,3-dione as a brown oil.

[0538] LC-MS (ES+): m/z 373.05 [MH+], t_R = 0.155 min (2.0 minute run).

[0539] 7. Synthesis of 6-[4-([4-[2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl]methyl)piperidin-1-yl]-N-[(1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl]pyridazine-3-carboxamide

[0540] Into a 100-mL round-bottom flask, was placed 2,2,2-trifluoroacetaldehyde; 2-(2,6-dioxopiperidin-3-yl)-4-methoxy-6-(piperazin-1-yl)-2,3-dihydro-1H-isoindole-1,3-dione (130 mg, 0.28 mmol, 1.078 equiv), dichloromethane (10 mL, 0.12 mmol), 6-(4-formylpiperidin-1-yl)-N-[(1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl]pyridazine-3-carboxamide (120 mg, 0.26 mmol, 1 equiv), $NaBH(OAc)_3$ (163.4 mg, 0.77 mmol, 3.006 equiv). The resulting solution was stirred for 2 hr at 25°C. The resulting solution was diluted with dichloromethane (30 mL). The resulting mixture was washed with H_2O (30 mL x 3). The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/ethyl acetate

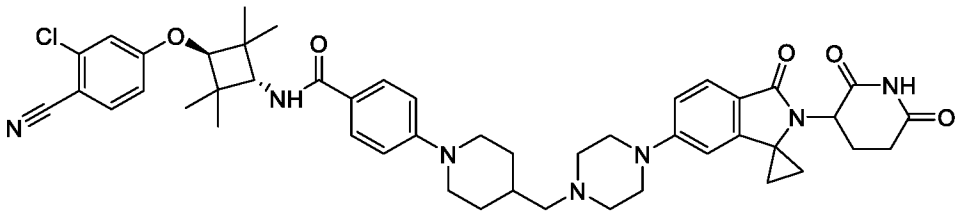
(3:1). The crude product was purified by Prep-HPLC with the following conditions: Column, XBridge Prep C18 OBD Column, 5um,19*150mm; mobile phase, Water (10 mmol/L NH_4HCO_3) and acetonitrile (43% Phase B up to 65% in 8 min); Detector, uv. This resulted in 70 mg (33.11%) of 6-[4-([4-[2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl]methyl)piperidin-1-yl]-N-[(1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl]pyridazine-3-carboxamide as a yellow solid.

[0541] 1H NMR (400 MHz, DMSO-*d6*) δ 11.04 (s, 1H), 8.57 (d, *J* = 8.4Hz, 1H), 7.87–7.79 (m, 2H), 7.39–7.32 (m, 2H), 7.15–7.12 (m, 1H), 6.96 (s, 1H), 6.68 (s, 1H), 5.04–4.98 (m, 1H), 4.50–4.47 (m, 3H), 4.93–3.85 (m, 4H), 3.35-3.33 (m, 5H), 3.07 – 2.81 (m, 3H), 2.51 (s, 3H), 2.27 –22.1 (m, 2H), 2.09 –2.01 (m, 2H), 2.00 – 1.49 (m, 11H), 1.23 – 1.11(m, 3H); LC-MS (ES+): m/z 824.25/826.25 [MH+], t_R = 182 min (3.0 minute run).

[0542] Chemical Formula: $C_{42}H_{46}ClN_9O_7$ [823.32/825.32]

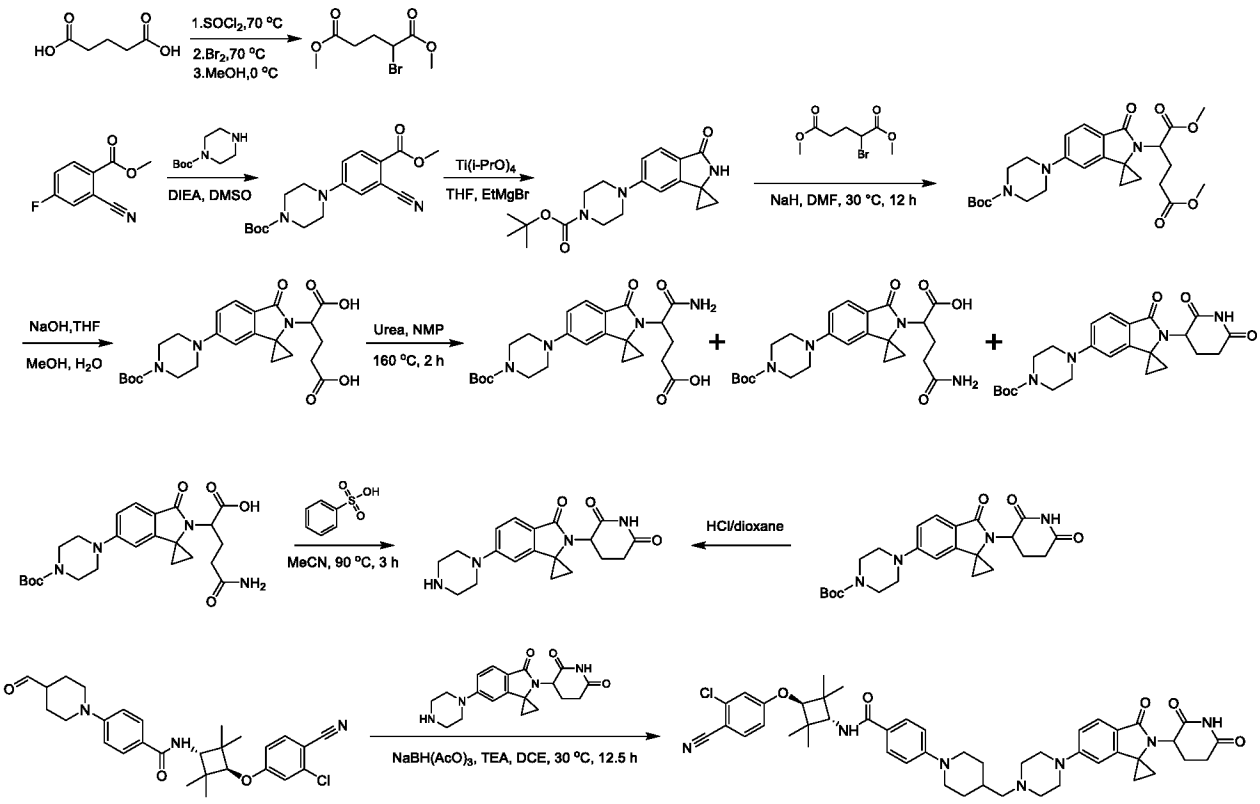
[0543] Total H count from HNMR data: 46.

[0544] **Exemplary Synthesis of Exemplary Compound 34**

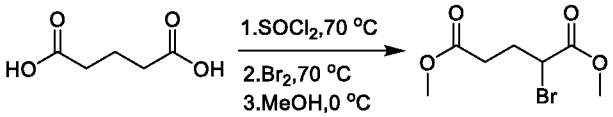


rac-N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((4-(2'-(2,6-dioxopiperidin-3-yl)-3'-oxospiro[cyclopropane-1,1'-isoindolin]-6'-yl)piperazin-1-yl)methyl)piperidin-1-yl)benzamide

[0545] **Synthetic scheme:**



[0546] Step 1: Synthesis of dimethyl 2-bromopentanedioate



[0547] To a solution of glutaric acid (30 g, 227.07 mmol, 1 *eq*) in chloroform (90 mL) was added thionyl chloride (59 g, 499.56 mmol, 36 mL, 2.2 *eq*). The mixture was stirred at 70 °C for 1 h. Liquid bromine (36.29 g, 227.07 mmol, 1 *eq*) was added into the mixture dropwise. The mixture was stirred at 70 °C for 12 h. The mixture was cooled to 0 °C and methanol (58 g, 1.82 mol, 73 mL, 8 *eq*) was added into the mixture drop wise at 0 °C. LCMS detected the desired product. The mixture was extracted with ethyl acetate (150 mL x 3) and washed with saturated aqueous sodium bicarbonate (200 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified with Flash C18 column chromatography (acetonitrile: water = 1:0 to 1:1). Dimethyl 2-bromopentanedioate (4g+20 g (crude), 16.73 mmol, 7% yield) was obtained as a yellow oil.

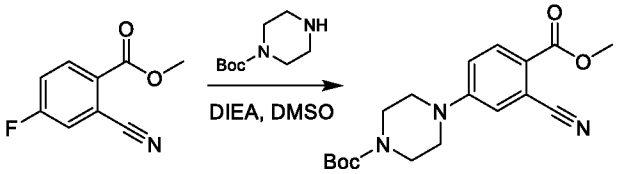
[0548] LCMS: MS (ESI) *m/z*: 241.0 $[M+1]^+$.

[0549] Chemical Formula: $C_7H_{11}BrO_4$, Molecular Weight: 239.06

[0550] **^{1}H NMR:** (400 MHz, $DCCl_3$) *δ:* 4.39 - 4.36 (m, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 2.56 - 2.49 (m, 2H), 2.44 - 2.34 (m, 1H), 2.33 - 2.23 (m, 1H).

[0551] Total H count from HNMR data: 11.

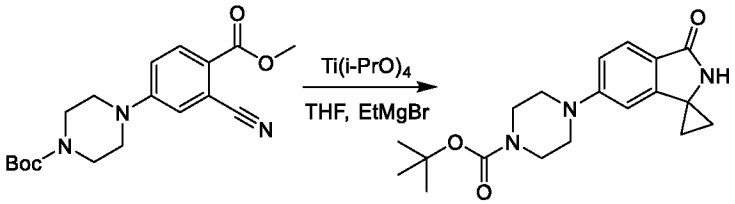
[0552] **Step 2: Synthesis of tert-butyl 4-(3-cyano-4-(methoxycarbonyl) phenyl)piperazine-1-carboxylate**



[0553] To a solution of methyl 2-cyano-4-fluoro-benzoate (10 g, 55.82 mmol, 1 *eq*), tert-butyl piperazine-1-carboxylate (12.48 g, 66.98 mmol, 1.2 *eq*) in dimethylsulfoxide (100 mL) was added diisopropylethylamine (28.86 g, 223.28 mmol, 4 *eq*). The reaction mixture was stirred at 120 °C for 12 h. Thin layer chromatography (petroleum ether: Ethyl acetate = 3:1) showed methyl 2-cyano-4-fluoro-benzoate was consumed, and desired product was detected. The mixture was poured into water (50 mL), and filtered. The filtrate was dried under vacuum. The residue was purified with silica gel column chromatography (petroleum ether: ethyl acetate = 10:1 to 3:1). Tert-butyl 4-(3-cyano-4-methoxycarbonyl-phenyl)piperazine-1- carboxylate (18 g, 52.11 mmol, 93% yield) was obtained as a yellow solid.

[0554] Chemical Formula: $C_{18}H_{23}N_3O_4$, Molecular Weight: 345.39

[0555] **Step 3: Synthesis of tert-butyl 4-(1'-oxospiro[cyclopropane-1,3'-isoindoline]-5'-yl)piperazine-1-carboxylate**



[0556] To a solution of tert-butyl 4-(3-cyano-4-methoxycarbonyl-phenyl)piperazine-1-carboxylate (18 g, 52.11 mmol, 1 *eq*) in tetrahydrofuran (200 mL) was added tetraisopropyl titanate (17.77 g, 62.54 mmol, 1.2 *eq*) and a solution of ethyl magnesium bromide in tetrahydrofuran (2 M, 52.11 mL, 2 *eq*) at 0 °C. The mixture was stirred at 25 °C for 1 h. Thin layer chromatography (petroleum ether: ethyl acetate = 1:1) showed tert-butyl 4-(3-cyano-4-methoxycarbony l-phenyl)piperazine-1-carboxylate was consumed, and desired product was detected. The mixture was added into saturated aqueous ammonuim chloride (150 mL). The

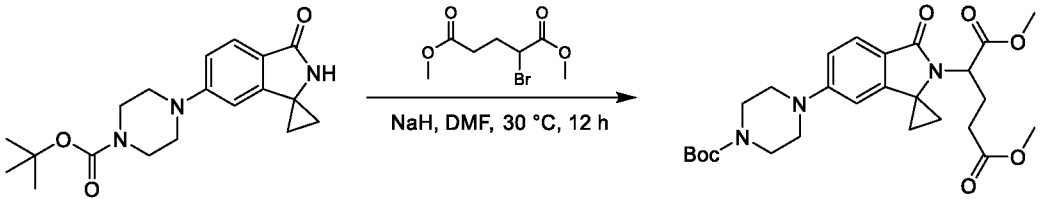
mixture was extracted with ethyl acetate (100 mL x 3). The organic layer was dried over sodium sulfate and concentrated. The residue was triturated with ethyl acetate (30 mL) and filtered. Tert-butyl 4-(1'-oxospiro[cyclopropane-1,3'-isoindoline]-5'-yl)piperazine-1-carboxylate (6 g, 17.47 mmol, 33% yield) was obtained as a yellow solid.

[0557] Chemical Formula: $C_{19}H_{25}O_3N_3$, Molecular Weight: 343.42

[0558] **^{1}H NMR:** (400 MHz, $CDCl_3$) *δ:* 7.75 – 7.73 (d, *J*=8.8 Hz, 1H), 6.97 – 6.95 (d, *J*=8.8 Hz, 1H), 6.94 – 6.85 (m, 1H), 6.41 (s, 1H), 3.61 - 3.58 (t, *J*=4.8 Hz, 4H), 3.28 - 3.25 (t, *J*=4.8 Hz, 4H), 1.56 (s, 2H), 1.49 (s, 9H), 1.38 – 1.36 (m, 2H).

[0559] Total H count from HNMR data: 25.

[0560] **Step 4: Synthesis of dimethyl 2-[6'-(4-tert-butoxycarbonylpiperazin-1-yl)-3'-oxo-spiro[cyclopropane-1,1'-isoindoline]-2'-yl]pentanedioate**

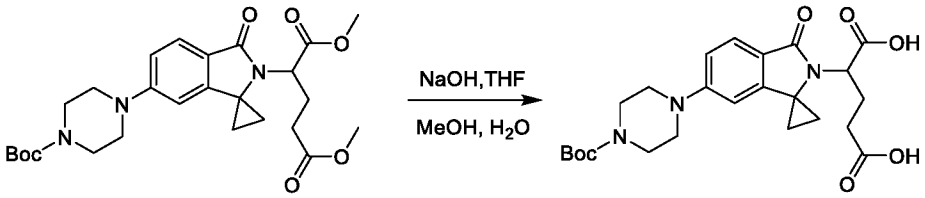


[0561] 20 batches in parallel:

[0562] To a solution of tert-butyl 4-(1'-oxospiro[cyclopropane-1,3'-isoindoline]-5'-yl)piperazine-1- carboxylate (100 mg, 0.29 mmol, 1 *eq*) and dimethyl 2-bromopentanedioate (104 mg, 0.44 mmol, 1.5 *eq*) in dimethylformamide (2 mL) was added sodium hydride (35 mg, 0.88 mmol, 60% in mineral oil, 3 *eq*). The mixture was stirred at 30 °C for 12 h. Thin layer cromatography (petroleum ether: ethyl acetate = 1:1) showed 30% of the tert-butyl 4-(1'-oxospiro[cyclopropane-1,3'-isoindoline]-5'-yl)piperazine-1-carboxylate was consumed. The 20 reaction mixtures were poured into 50 mL of brine, and extracted with ethyl acetate (30 mL x 2), the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ ethyl acetate=3/1 to 1/1). Dimethyl 2-[6'-(4-tert-butoxycarbonylpiperazin-1-yl)-3'-oxo-spiro[cyclopropane-1,1'-isoindoline]-2'-yl]pentanedioate (200 mg, 0.40 mmol, 10% yield corrected for recovered starting material) was obtained as a yellow oil. Also isolated was tert-butyl 4-(1'-oxospiro[cyclopropane-1,3'-isoindoline]-5'-yl)piperazine-1-carboxylate (675 mg).

[0563] Chemical Formula: $C_{26}H_{35}N_3O_7$, Molecular Weight: 501.57

[0564] Step 5: Synthesis of 2-[6'-(4-tert-butoxycarbonylpiperazin-1-yl)-3'-oxo-spiro[cyclopropane-1,1'-isoindoline]-2'-yl]pentanedioic acid

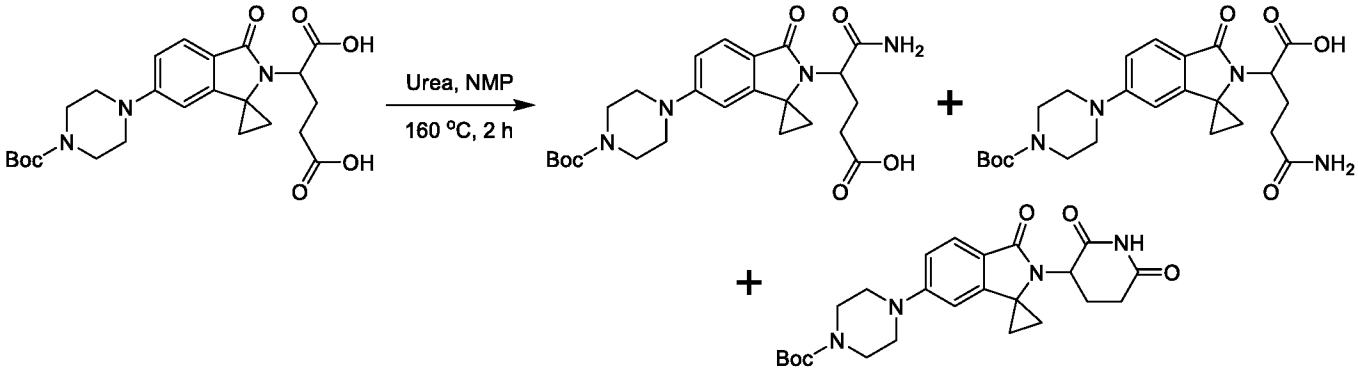


[0565] To a solution of dimethyl 2-[6'-(4-tert-butoxycarbonylpiperazin-1-yl)-3'-oxo-spiro [cyclopropane-1,1'-isoindoline]-2'-yl]pentanedioate (800 mg, 1.59 mmol, 1 *eq*) in tetrahydrofuran (5 mL) and methanol (5 mL) was added a solution of sodium hydroxide (255 mg, 6.38 mmol, 4 *eq*) in water (3 mL). The mixture was stirred at 25 °C for 2 hr. LCMS showed the reaction was completed and desired MS was detected. The mixture together with the other batch was poured into 20 mL water, and adjusted the pH to 3.0 with 2.0 N hydrochloride acid, then extracted with ethyl acetate (30 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, then concentrated in vacuum. 2-[6'-(4-tert-butoxycarbonylpiperazin-1-yl)-3'-oxo-spiro[cyclopropane-1,1'-isoindoline]-2'-yl]pentanedioic acid (740 mg, 1.56 mmol, 97% yield) as an off-white solid was obtained, which was directly used for the next step without further purification.

[0566] LCMS: MS (ESI) *m/z*: 474.3[M+1] $^{+}$.

[0567] Chemical Formula: $C_{24}H_{31}N_3O_7$, Molecular Weight: 473.52

[0568] Step 6: Synthesis of 5-amino-4-[6'-(4-tert-butoxycarbonylpiperazin-1-yl)-3'-oxo-spiro[cyclopropane-1,1'-isoindoline]-2'-yl]-5-oxo-pentanoic acid; 5-amino-2-[6'-(4-tert-butoxycarbonylpiperazin-1-yl)-3'-oxo-spiro[cyclopropane-1,1'-isoindoline]-2'-yl]-5-oxo-pentanoic acid and tert-butyl 4-[2'-(2,6-dioxo-3-piperidyl)-1'-oxo-spiro[cyclopropane-1,3'-isoindoline]-5'-yl]piperazine-1-carboxylate



[0569] A mixture of 2-[6'-(4-tert-butoxycarbonylpiperazin-1-yl)-3'-oxo-spiro[cyclopropane-1,1'-isoindoline]-2'-yl]pentanedioic acid (400 mg, 0.85 mmol, 1 *eq*) and urea (253 mg, 4.22 mmol, 5 *eq*) in 1-methyl-2-pyrrolidinone (4 mL) was heated to 160 °C and stirred at 160 °C for 2 hours. LCMS showed two peaks with desired MS signals. The mixture together with the other batch was filtered. The filtrate was further purified by Semi-preparative reverse phase HPLC (column: Boston Green ODS 150*30 5 um; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 35%-45%, 10 min). 2 isomeric mono-amides 5-amino-4-[6'-(4-tert-butoxycarbonylpiperazin-1-yl)-3'-oxo-spiro[cyclopropane-1,1'-isoindoline]-2'-yl]-5-oxo-pentanoic acid and 5-amino-2-[6'-(4-tert-butoxycarbonylpiperazin-1-yl)-3'-oxo-spiro[cyclopropane-1,1'-isoindoline]-2'-yl]-5-oxo-pentanoic acid were obtained (170 mg, 0.36 mmol, 42% yield and 90 mg, 0.19 mmol, 22% yield respectively. It was not conclusively established which of the 2 isomeres corresponds to which structure.) Also isolated was tert-butyl 4-[2'-(2,6-dioxo-3-piperidyl)-1'-oxo-spiro[cyclopropane -1,3'-isoindoline]-5'-yl]piperazine-1-carboxylate (90 mg, 0.20 mmol, 23% yield) as an off-white solid.

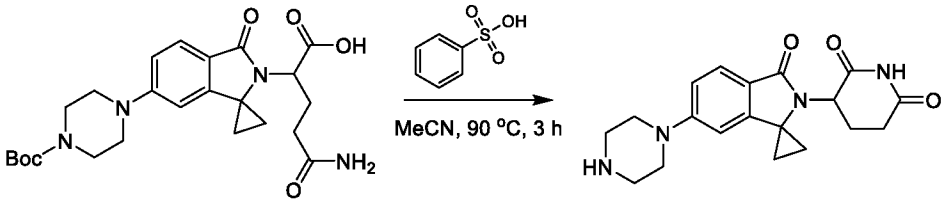
[0570] **LCMS:** mono-amide product 1: MS (ESI) *m/z*: 473.1[M+1] $^+$, Mono-amide product 2: MS (ESI) *m/z*: 473.1[M+1] $^+$, Imide product 3: MS (ESI) *m/z*: 455.1[M+1] $^+$.

[0571] Chemical Formula mono-amide product 1: $C_{24}H_{32}N_4O_6$, Molecular Weight: 472.53.

[0572] Chemical Formula mono-amide product 2: $C_{24}H_{32}N_4O_6$, Molecular Weight: 472.53.

[0573] Chemical Formula Imide product: $C_{24}H_{30}N_4O_5$, Molecular Weight: 454.52.

[0574] **Step 7a: Synthesis of 3-(3'-oxo-6'-piperazin-1-yl-spiro[cyclopropane -1,1'-isoindoline]-2'-yl)piperidine-2,6-dione from the mono-amide product 1 of step 6**

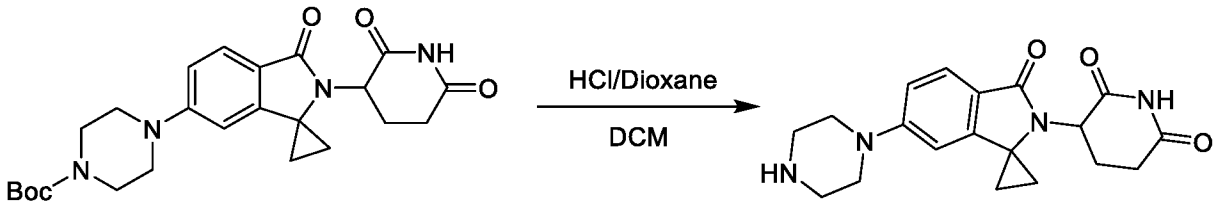


[0575] To a mixture of 5-amino-2-[6'-(4-tert-butoxycarbonylpiperazin-1-yl)-3'-oxo-spiro [cyclopropane-1,1'-isoindoline]-2'-yl]-5-oxo-pentanoic acid (190 mg, 0.40 mmol, 1 *eq*, the first eluting mono-amide product from above) in acetonitrile (15 mL) was added benzenesulfonic acid (114 mg, 0.72 mmol, 1.80 *eq*) in one portion at 25 °C under nitrogen atmosphere. The mixture was stirred at 90 °C for 3 hours. LCMS showed the product was the main peak. The mixture was concentrated in vacuum. The residue was purified by Semi-preparative reverse phase HPLC (column: Boston Green ODS 150*30 5 um; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 1%-27%, 10 min). The product 3-(3'-oxo-6'-piperazin-1-yl-spiro[cyclopropane-1,1'-isoindoline]- 2'-yl)piperidine-2,6-dione (55 mg, 0.14 mmol, 34% yield, benzene sulfonate) was obtained as a brown solid.

[0576] **LCMS:** EW4875-628-P1B, MS (ESI) *m/z*: 355.1[M+1] $^{+}$.

[0577] Chemical Formula: $C_{19}H_{22}N_4O_3$, Molecular Weight: 354.40.

[0578] **Step 7b: Synthesis of 3-(3'-oxo-6'-piperazin-1-yl-spiro[cyclopropane -1,1'-isoindoline]-2'-yl)piperidine-2,6-dione from the imide product of step 6**

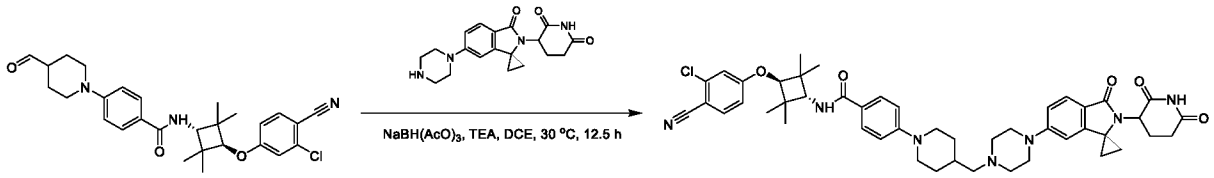


[0579] To a mixture of tert-butyl 4-[2'-(2,6-dioxo-3-piperidyl)-1'-oxo-spiro[cyclopropane -1,3'-isoindoline]-5'-yl]piperazine-1-carboxylate (90 mg, 0.20 mmol, 1 *eq*) in dichloromethane (5 mL) was added hydrochloric acid (4 M in dioxane, 2.5 mL, 50 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 1 hour. LCMS showed the product was the main peak. The mixture was concentrated in vacuum. The crude solid The product 3-(3'-oxo-6'-piperazin-1-yl-spiro[cyclopropane-1,1'-isoindoline]-2'-yl)piperidine-2,6-dione (70 mg, 0.18 mmol, 90% yield, hydrochloride) was obtained as a brown solid, which was directly used into the next step without further purification.

[0580] **LCMS:** MS (ESI) *m/z*: 355.1[M+1] $^{+}$.

[0581] Chemical Formula: $C_{19}H_{22}N_4O_3$, Molecular Weight: 354.40

[0582] **Step 8: Synthesis of N-[3-(3-chloro-4-cyano-phenoxy)-2,2,4,4-tetramethyl-cyclobutyl]-4-[4-[[4-[2'-(2,6-dioxo-3-piperidyl)-1'-oxo-spiro[cyclopropane-1,3'-isoindoline]-5'-yl]piperazin-1-yl]methyl]-1-piperidyl]benzamide**



[0583] To a solution of N-[3-(3-chloro-4-cyano-phenoxy)-2,2,4,4-tetramethyl-cyclobutyl]-4-(4- formyl-1-piperidyl)benzamide (63 mg, 0.12 mmol, 1 *eq*) in 1,2-dichloroethane (3 mL) was added triethylamine (38 mg, 0.38 mmol, 3 *eq*) and 3-(3'-oxo-6'-piperazin-1-yl-spiro[cyclopropane-1,1'-isoindoline]-2'-yl)piperidine-2,6-dione (50 mg, 0.12 mmol, 1 *eq*, hydrochloride). The mixture was stirred at 30°C for 30 min. Sodium triacetoxyborohydride (54 mg, 0.25 mmol, 2 *eq*) was added, then the mixture was stirred at 30°C for 12 hours. LCMS showed the reaction was completed and desired MS can be detected. The reaction mixture was concentrated under reduced pressure to remove solution. The residue was purified by Semi-preparative reverse phase HPLC (column: Phenomenex Synergi C18 150*25*10um;mobile phase: [water(0.225%FA)-ACN];B%: 40%-70%,10min) to give N-[3-(3-chloro-4-cyano-phenoxy)-2,2,4,4-tetramethyl-cyclobutyl]-4-[4-[[4-[2'-(2,6-dioxo-3-piperidyl)-1'-oxo-spiro[cyclopropane-1,3'-isoindoline]-5'-yl]piperazin-1-yl]methyl]-1-piperidyl]benzamide (17.8 mg, 0.02 mmol, 16% yield, 98% purity) as a white solid.

[0584] **LCMS:** MS (ESI) *m/z*: 932.3 $[M+1]^+$.

[0585] **^{1}H NMR:** (400MHz, DMSO-d_6) *δ:* 10.88 (s, 1H), 8.22 (s, 1H), 7.91 (d, *J*=8.8 Hz, 1H), 7.74 (d, *J*=8.8 Hz, 2H), 7.53 - 7.45 (m, 2H), 7.21 (d, *J*=2.4 Hz, 1H), 6.99 (dd, *J*=9.2, 17.6 Hz, 4H), 6.73 (s, 1H), 4.33 (s, 1H), 4.06 (d, *J*=9.2 Hz, 1H), 3.86 (d, *J*=12.4 Hz, 3H), 3.32 - 3.29 (m, 9H), 2.80 (t, *J*=12.0 Hz, 3H), 2.59 - 2.54 (m, 4H), 2.22 (d, *J*=6.8 Hz, 2H), 1.81 (d, *J*=10.3 Hz, 4H), 1.55 - 1.47 (m, 2H), 1.45 - 1.31 (m, 2H), 1.25 - 1.17 (s, 8H), 1.13 (s, 6H).

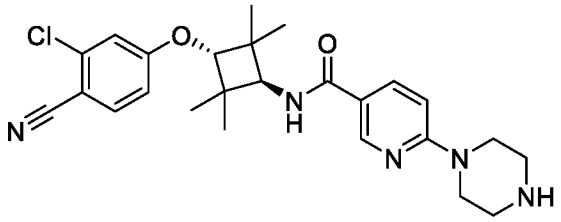
[0586] Chemical Formula: $C_{47}H_{54}ClN_7O_5$, Molecular Weight: 832.43.

[0587] Total H count from HNMR data: 54.

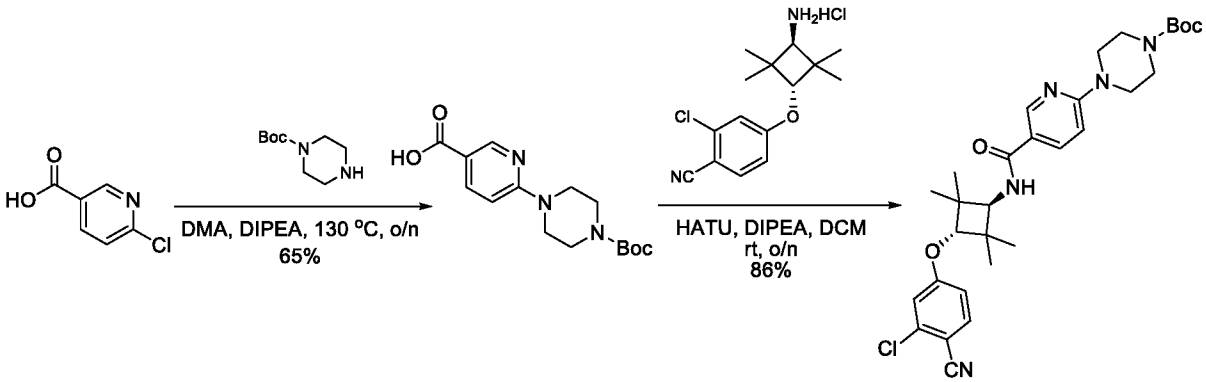
[0588] **C. Exemplary Synthetic Schemes for Exemplary Androgen Receptor Binding Moiety Based Compounds that are Imide Isosteres**

[0589] General Synthetic Scheme C-1

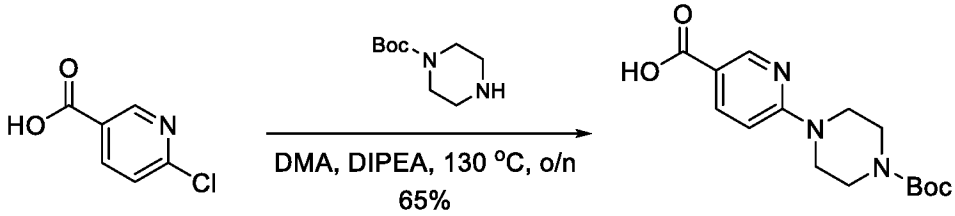
[0590] **Synthesis of building block N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(piperazin-1-yl)nicotinamide**



[0591] **Synthetic Scheme**



[0592] **Step 1:** Synthesis of 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)nicotinic acid



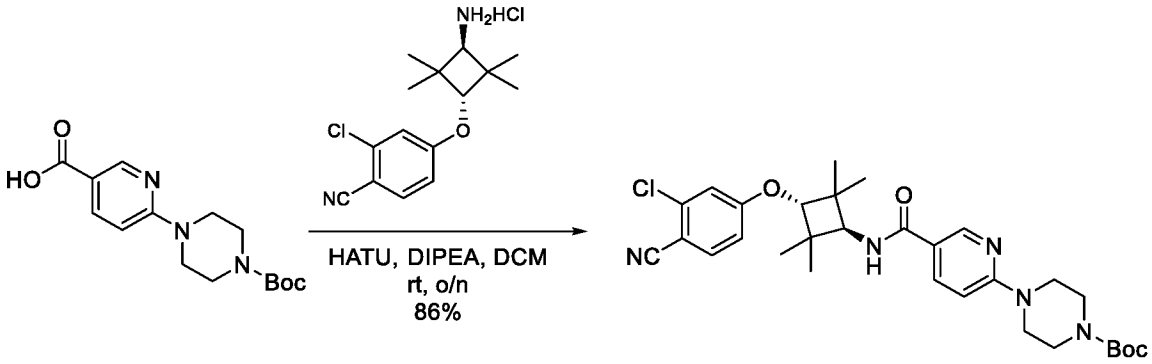
[0593] 6-Chloronicotinic acid (1.6 g, 10.0 mmol) was dissolved in N,N-dimethylacetamide (15 mL), and tert-butyl piperazine-1-carboxylate (1.9 g, 10.0 mmol) and ethyldiisopropylamine (2.6 g, 20 mmol) were added thereto, followed by stirring at 130° C overnight. The reaction mixture was concentrated under reduced pressure, and to the obtained residue was added a 1 M aqueous NaOH solution (10 mL), followed by washing with $CHCl_3$ (50 mL). The pH of the aqueous layer was adjusted to around 6 to 7 by the addition of 1 M hydrochloric acid, followed

by extraction with $CHCl_3$ (50 mL x 3). The organic layer was dried over anhydrous sodium sulfate and the solvent was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 10/1) to give 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)nicotinic acid (2.0 g, 65 % yield) as a white solid.

[0594] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (50 mm*4.6 mm*3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100% [CH_3CN] in 1.6 min, then under this condition for 1.4 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 0.7 min). Purity is 83.17%, Rt = 1.312 min; MS Calcd.: 307.15; MS Found: 308.2 $[M+H]^+$.

[0595] Chemical Formula: $C_{15}H_{21}N_3O_4$, Molecular Weight: 307.34.

[0596] Step 2: Synthesis of tert-butyl 4-(5-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutylcarbamoyl)pyridin-2-yl)piperazine-1-carboxylate



[0597] A mixture of 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)nicotinic acid (614 mg, 2.0 mmol), 4-((1r,3r)-3-amino-2,2,4,4-tetramethylcyclobutoxy)-2-chlorobenzonitrile hydrochloride (630 mg, 2.0 mmol), 2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (1.1 g, 3.0 mmol) and ethyldiisopropylamine (516 mg, 4.0 mmol) in dichloromethane (20 mL) was stirred at room temperature overnight. Water (50 mL) was added and extracted with dichloromethane (50 mL x 3). Combined organic layers were washed by brine (50 mL x 2), dried over anhydrous sodium sulfate. The solvent was concentrated to give the residue, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/1) to give tert-butyl 4-(5-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutylcarbamoyl)pyridin-2-yl)piperazine-1-carboxylate (977 mg, 86 % yield) as a white solid.

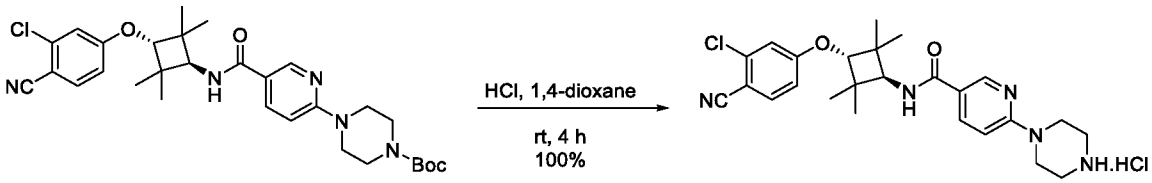
[0598] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (50 mm*4.6 mm*3.5 µm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100% [CH_3CN] in 1.6 min, then under this condition for 1.4 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 0.7 min). Purity is 88.26%, Rt = 2.161 min; MS Calcd.: 567.26; MS Found: 568.3 $[M+H]^+$.

[0599] ^1H NMR (400 MHz, DMSO-d_6) δ1.12 (6H, s), 1.22 (6H, s), 1.43 (9H, s), 3.42-3.44 (4H, m), 3.60-3.63 (4H, m), 4.02-4.07 (1H, m), 4.31 (1H, s), 6.88 (1H, d, J = 8.8 Hz), 7.00 (1H, dd, J = 8.4, 2.4 Hz), 7.21 (1H, d, J = 2.4 Hz), 7.65 (1H, d, J = 9.2 Hz), 7.91 (1H, d, J = 8.8 Hz), 7.99 (1H, dd, J = 8.8, 2.4 Hz), 8.64 (1 H, d, J = 2.4 Hz).

[0600] Chemical Formula: $C_{30}H_{38}ClN_5O_4$, Molecular Weight: 568.11.

[0601] Total H count from HNMR data: 38.

[0602] Step 3: Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(piperazin-1-yl)nicotinamide hydrochloride



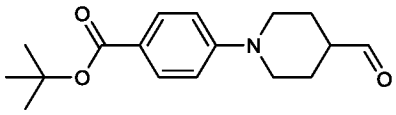
[0603] A mixture of tert-butyl 4-(5-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl carbamoyl)pyridin-2-yl)piperazine-1-carboxylate (405 mg, 0.7 mmol) in HCl/1,4-dioxane (10 mL) was stirred at room temperature for 4 h. The solvent was removed in vacuum to give N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(piperazin-1-yl)nicotinamide hydrochloride (353 mg, 100 % yield) as a white solid.

[0604] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (50 mm*4.6 mm*3.5 µm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100% [CH_3CN] in 1.6 min, then under this condition for 1.4 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 0.7 min). Rt = 1.791 min; MS Calcd.:467.21; MS Found: 468.3 $[M+H]^+$.

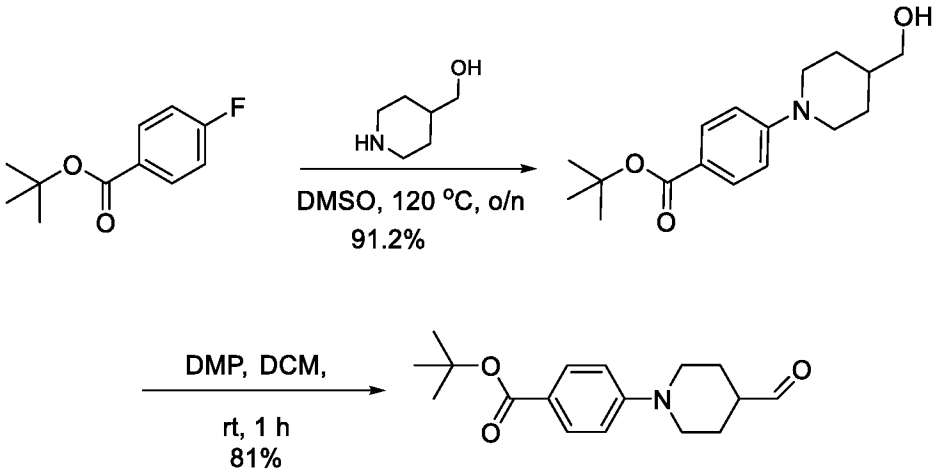
[0605] Chemical Formula: $C_{25}H_{31}Cl_2N_5O_2$, Molecular Weight: 504.45

[0606] General Synthetic Scheme C-2

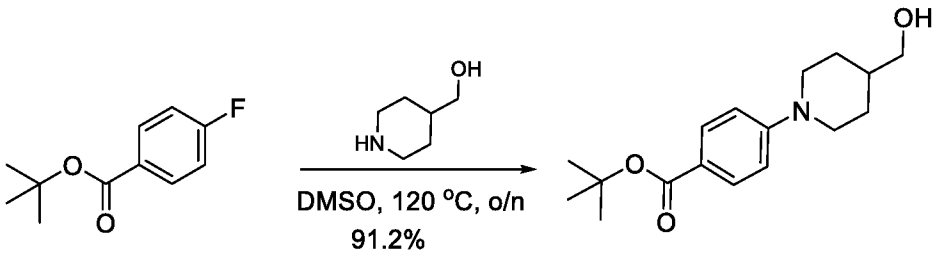
[0607] **Synthesis of building block tert-butyl 4-(4-formylpiperidin-1-yl)benzoate**



[0608] Synthetic scheme:



[0609] Step 1: Synthesis of tert-butyl 4-(4-(hydroxymethyl)piperidin-1-yl)benzoate



[0610] To a solution of tert-butyl 4-fluorobenzoate (23 g, 0.12 mmol) in DMSO (100 mL) was added piperidin-4-ylmethanol (40.5 g, 0.35 mmol). The mixture was heated to 120 °C overnight under nitrogen. After cooling to room temperature, water (50 mL) was added to the reaction mixture, and extracted with ethyl acetate (20 mL x 3). The organic layer was washed with brine (15 mL x 3). The combined organic phases were dried over anhydrous sodium sulfate and concentrated *in vacuo*, and purified by CC (PE/EA = 10:1) to give compound tert-butyl 4-(4-(hydroxymethyl)piperidin-1-yl)benzoate (31g, 91.2%) as a white solid.

[0611] LCMS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (50 mm x 4.6 mm x 3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 90% [(total 10mM $AcONH_4$) water/CH_3CN=900/100 (v/v)] and 10% [(total 10mM $AcONH_4$) water/CH_3CN=100/900 (v/v)] to 10% [(total 10mM $AcONH_4$) water /CH_3CN=900/100 (v/v)] and 90% [(total 10mM $AcONH_4$) water/CH_3CN=100/900 (v/v)] in 1.6 min, then under this

condition for 2.4 min, finally changed to 90% [(total 10mM $AcONH_4$) water/CH_3CN=900/100 (v/v)] and 10% [(total 10mM $AcONH_4$) water/CH_3CN=100/900 (v/v)] in 0.1 min and under this condition for 0.7 min). Purity is 99.57%, Rt = 2.035 min.; MS Calcd.: 291.2; MS Found: 292.2 [M+H]+.

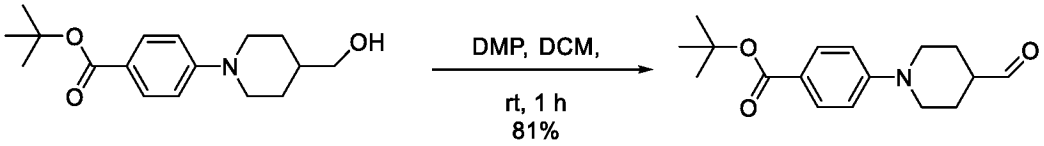
[0612] HPLC (Agilent HPLC 1200, Column: Waters X-Bridge C18 (150 mm x 4.6 mm x 3.5 μm); Column Temperature: 40 °C; Flow Rate: 1.0 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100% [CH_3CN] in 10 min, then under this condition for 5 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 5 min). Purity is 93.27%, Rt = 9.542 min.

[0613] ^1H NMR (400 MHz, $CDCl_3$) δ 1.29-1.40 (2H, m), 1.49 (1H, d, J = 5.4 Hz), 1.57 (9H, s), 1.70-1.75 (1H, m), 1.82 (2H, d, J = 12.8 Hz), 2.80-2.87 (2H, m), 3.53 (2H, t, J = 5.8 Hz), 3.87-3.90 (2H, m), 6.85 (2H, d, J = 9.2 Hz), 7.84 (2H, d, J = 9.2 Hz).

[0614] Chemical Formula: $C_{17}H_{25}NO_3$, Molecular Weight: 291.39.

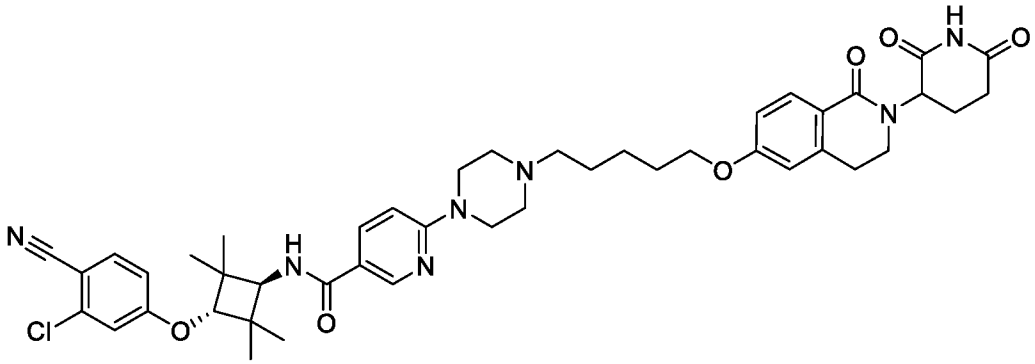
[0615] Total H count from HNMR data: 25.

[0616] Step 2: Synthesis of tert-butyl 4-(4-formylpiperidin-1-yl)benzoate



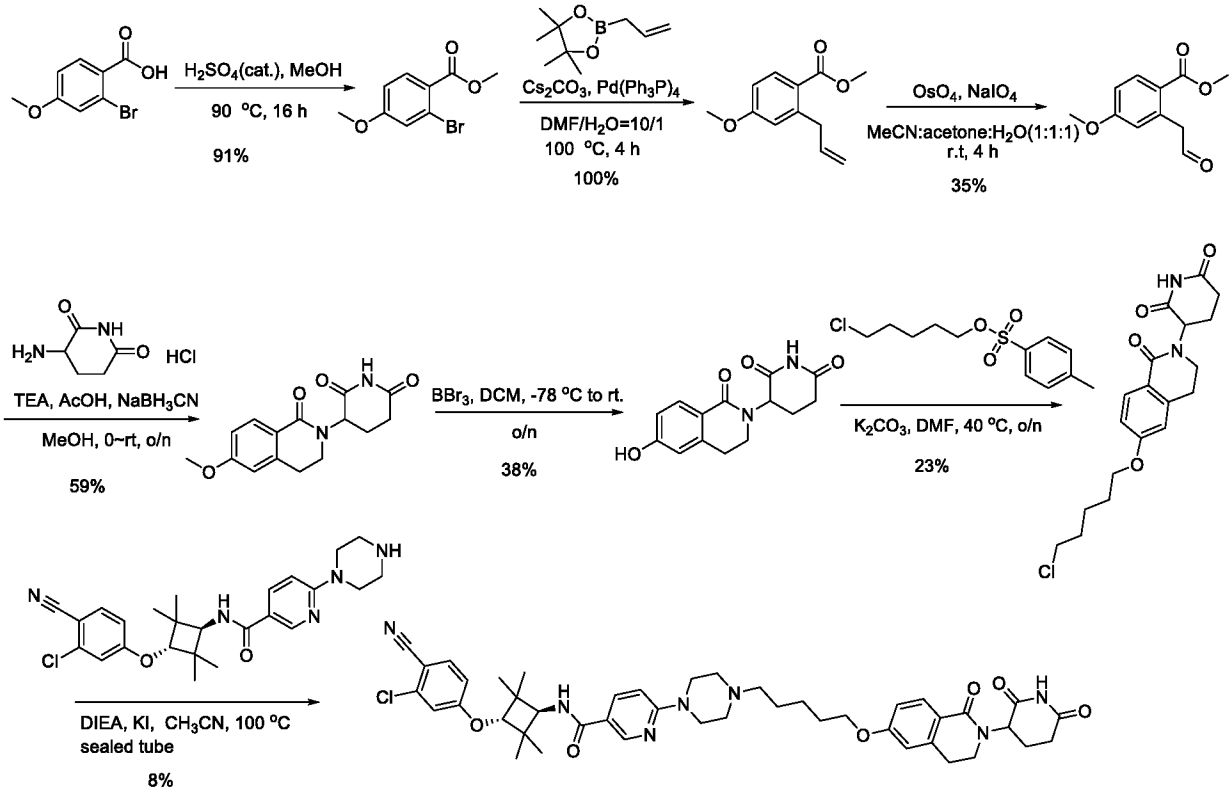
[0617] To a solution of tert-butyl 4-(4-(hydroxymethyl)piperidin-1-yl)benzoate (300 mg, 1.03 mmol) in dichloromethane (20 mL) was added Dess-Martin periodinane (1.31 g, 3.09 mmol) slowly at 0 °C. The reaction mixture was stirred at room temperature for 1 h. Then filtered, and concentrated *in vacuo* to give compound tert-butyl 4-(4-formylpiperidin-1-yl)benzoate (240 mg, 81%) as a pale yellow solid.

[0618] **Exemplary Synthesis of Exemplary Compound 46**

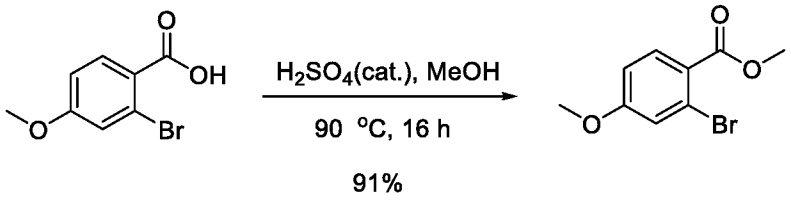


N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(5-((2-(2,6-dioxopiperidin-3-yl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy)pentyl)piperazin-1-yl)nicotinamide

[0619] Synthetic Scheme



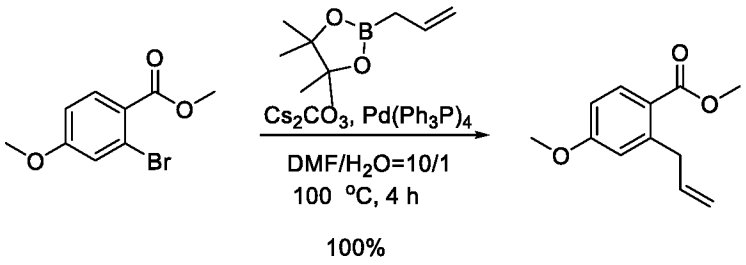
[0620] Step 1: Synthesis of methyl 2-bromo-4-methoxybenzoate



[0621] To a solution of 2-bromo-4-methoxybenzoic acid (5.0 g, 21.7 mmol) in methanol (50 mL) was added 98% sulfuric acid (0.5 ml). The reaction mixture was heated to 90 °C for 16 h under nitrogen gas, and concentraction under reduced pressure. After cooling to room temperature, sodium bicarbonate (2.0 M) was added to adjust PH=8. Thus was extracted with ethyl acetate (50 mL x 3). The organic layer was washed with brine (30 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give 2-bromo-4-methoxybenzoate (4.8 g, 91%) as yellow oil.

[0622] Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (50 mm x 4.6 mm x 3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 90% [(total 10mM $AcONH_4$) water/CH_3CN=900/100 (v/v)] and 10% [(total 10mM $AcONH_4$) water/CH_3CN=100/900 (v/v)] to 10% [(total 10mM $AcONH_4$) water /CH_3CN=900/100 (v/v)] and 90% [(total 10mM $AcONH_4$) water/CH_3CN=100/900 (v/v)] in 1.6 min, then under this condition for 2.4 min, finally changed to 90% [(total 10mM $AcONH_4$) water/CH_3CN=900/100 (v/v)] and 10% [(total 10mM $AcONH_4$) water/CH_3CN=100/900 (v/v)] in 0.1 min and under this condition for 0.7 min. Purity is 98.94%, Rt = 2.609 min; MS Calcd.: 243.97; MS Found: 245.0 $[M+H]^+$.

[0623] Step 2: Synthesis of methyl 2-allyl-4-methoxybenzoate

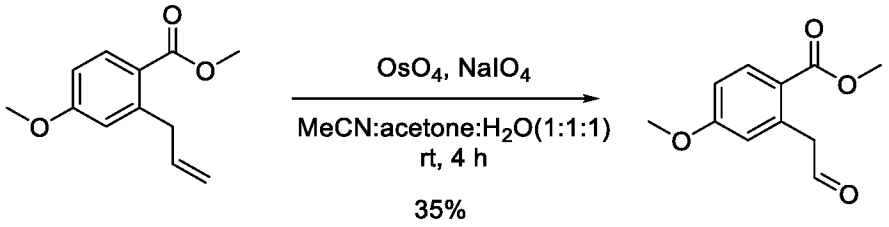


[0624] To a solution of methyl 2-bromo-4-methoxybenzoate (3.0 g, 12.3 mmol), cesium carbonate (12.0 g, 36.9 mmol), 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.98 g, 18.5

mmol) in *N*,N-dimethylformamide /water (30.0 mL/3.0 mL) was added tetrakis(triphenylphosphine)palladium (1.42 g, 1.23 mmol) under nitrogen atmosphere. The reaction mixture was heated to 100 °C and stirred for 4 h. The resulting reaction was concentrated under reduced pressure, and then water (10 mL) was added. The mixture was extracted with ethyl acetate (50 mL x 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography column (petroether/ethyl acetate = 4:1) to give the methyl 2-allyl-4-methoxybenzoate (2.6 g, 100%) as yellow oil.

[0625] Agilent LCMS 1200-6110, Column: Waters X-Bridge C18 (50 mm x 4.6 mm x 3.5 μm); Column Temperature: 40 °C; Flow Rate: 1.5 mL/min; Mobile Phase: from 95% [water + 0.05% TFA] and 5% [CH_3CN + 0.05% TFA] to 0% [water + 0.05% TFA] and 100% [CH_3CN + 0.05 % TFA] in 1.5 min, then under this condition for 0.5 min, finally changed to 95% [water + 0.05% TFA] and 5% [CH_3CN + 0.05% TFA] in 0.1 min and under this condition for 0.5 min. Purity is 96.85%, Rt = 1.293 min; MS Calcd.: 206.09; MS Found:207.3 $[M+H]^+$.

[0626] Step 3: Synthesis of methyl 4-methoxy-2-(2-oxoethyl)benzoate

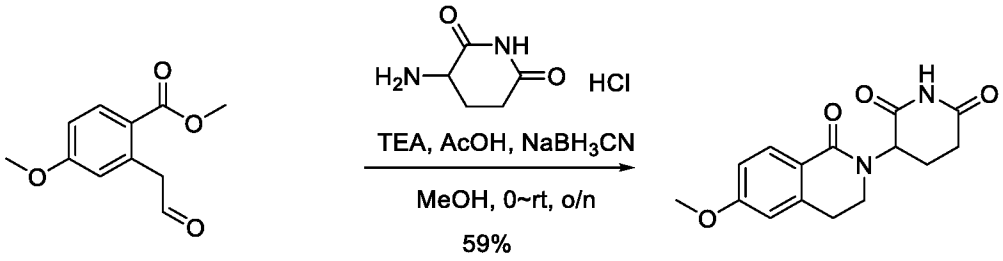


[0627] To a solution of methyl 2-allyl-4-methoxybenzoate (1.20 g, 5.83 mmol) and osmium tetraoxide (5 mg) in acetonitrile, acetone, and water (v: v: v=10 mL: 10 mL: 10 mL) was added sodium periodate (4.99 g, 23.3 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h. The mixture was filtered through a pad of celite and extracted with ethyl acetate (20 x 3 mL). The organic layer was separated, washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by prep-TLC (petroether/ethyl acetate = 4:1) to give compound methyl 4-methoxy-2-(2-oxoethyl)benzoate (420 mg, 35%) as yellow oil.

[0628] LC-MS (Agilent LCMS 1200-6110, Column: Waters X-Bridge C18 (50 mm x 4.6 mm x 3.5 μm); Column Temperature: 40 °C; Flow Rate: 1.5 mL/min; Mobile Phase: from 95% [water + 0.05% TFA] and 5% [CH_3CN + 0.05% TFA] to 0% [water + 0.05% TFA] and 100% [CH_3CN + 0.05 % TFA] in 1.5 min, then under this condition for 0.5 min, finally changed to

95% [water + 0.05% TFA] and 5% [CH_3CN + 0.05% TFA] in 0.1 min and under this condition for 0.5 min.). Purity is 96.26%, Rt = 1.007 min; MS Calcd.: 208.1; MS Found: 209.3 $[M+H]^+$.

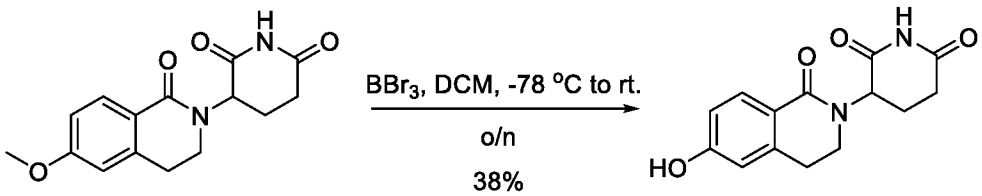
[0629] Step 4: Synthesis of 3-(6-methoxy-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)piperidine-2,6-dione



[0630] To a solution of methyl 4-methoxy-2-(2-oxoethyl)benzoate (420 mg, 2.02 mmol) in methanol (6 mL) was added a solution of 3-aminopiperidine-2,6-dione hydrochloride (397 mg, 2.42 mmol) and triethylamine (245 mg, 2.24 mmol) in methanol (2 mL). The reaction mixture was stirred at room temperature for 1 h, then sodium cyanoborohydride (254 mg, 4.04 mmol) was added at 0 °C. The reaction was stirred at room temperature overnight, water (10 mL) was added, and extracted with ethyl acetate (20 mL x 3), washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by prep-TLC (dichloromethane/methanol = 20:1) to give 3-(6-methoxy-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)piperidine-2,6-dione (340 mg, 59%) as a pale yellow solid.

[0631] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (30 mm x 3 mm x 2.5 μm); Column Temperature: 40 °C; Flow Rate: 1.5 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN + 10 mM NH_4HCO_3] to 5% [water + 10 mM NH_4HCO_3] and 95% [CH_3CN + 10 mM NH_4HCO_3] in 1.5 min, then under this condition for 0.5 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN + 10 mM NH_4HCO_3] in 0.1 min and under this condition for 0.5 min.). Purity is 80.84%, Rt = 0.924 min; MS Calcd.: 288.1; MS Found: 289.1 $[M+H]^+$.

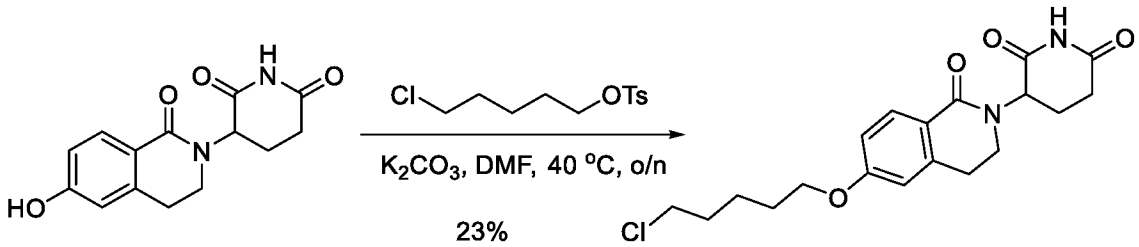
[0632] Step 5: Synthesis of 3-(6-hydroxy-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)piperidine-2,6-dione



[0633] To a solution of 3-(6-methoxy-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)piperidine-2,6-dione (220 mg, 0.76 mmol) in dichloromethane (10 mL) was added boron tribromide (0.5 mL) in dichloromethane (2 mL) dropwise at -78 °C and stirred overnight at room temperature. The reaction mixture was added to water (10 mL) and sodium bicarbonate (20 mL), then extracted with dichloromethane/ methanol (30 mL x 5). The organic layer was washed with brine (10 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by prep-TLC (dichloromethane/ methanol=10:1) to give compound 3-(6-hydroxy-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)piperidine-2,6-dione (80 mg, 38%) as a yellow solid.

[0634] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (30 mm x 3 mm x 2.5 μm); Column Temperature: 40 °C; Flow Rate: 1.5 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN + 10 mM NH_4HCO_3] to 5% [water + 10 mM NH_4HCO_3] and 95% [CH_3CN + 10 mM NH_4HCO_3] in 1.5 min, then under this condition for 0.5 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN + 10 mM NH_4HCO_3] in 0.1 min and under this condition for 0.5 min.). Purity is 96.22%, Rt = 0.736 min; MS Calcd.: 274.1; MS Found: 275.1 $[M+H]^+$.

[0635] Step 6: Synthesis of 3-(6-(5-chloropentyloxy)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)piperidine-2,6-dione

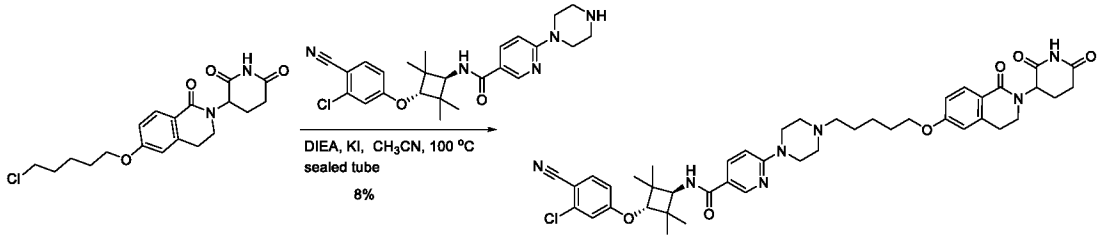


[0636] To a solution of 3-(6-hydroxy-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)piperidine-2,6-dione (80 mg, 0.292 mmol) in *N*,*N*-dimethylformamide (5.0 mL) was added 5-chloropentyl 4-methylbenzenesulfonate (64.5 mg, 0.234 mmol) and potassium carbonate (121 mg, 0.876 mmol). The mixture was heated to 40 °C overnight. After cooling to rt., the reaction mixture was added to water (10 mL), and extracted with ethyl acetate (20 mL x 3). The organic layer was washed with brine (10 mL x 3). The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by prep-TLC (dichloromethane/

methanol=10:1) to give 3-(6-(5-chloropentyloxy)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)piperidine-2,6-dione (25 mg, 23%) as a yellow solid.

[0637] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (30 mm x 3 mm x 2.5 μm); Column Temperature: 40 °C; Flow Rate: 1.5 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN + 10 mM NH_4HCO_3] to 5% [water + 10 mM NH_4HCO_3] and 95% [CH_3CN + 10 mM NH_4HCO_3] in 1.5 min, then under this condition for 0.5 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN + 10 mM NH_4HCO_3] in 0.1 min and under this condition for 0.5 min.). Purity is 93.68%, Rt = 1.263 min; MS Calcd.: 378.1; MS Found: 379.1 $[M+H]^+$.

[0638] Step 7: Synthesis of *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)pentyl)piperazin-1-yl)nicotinamide



[0639] A solution of 3-(6-(5-chloropentyloxy)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)piperidine-2,6-dione (25 mg, 0.066 mmol) was dissolved in acetonitrile (2 mL), N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(piperazin-1-yl)nicotinamide (31 mg, 0.066 mmol), ethyldiisopropylamine (17 mg, 0.132 mmol), potassium iodide (2 mg) was added to the solution. The mixture was heated to 100 °C for 16 h under sealed tube. After cooling to rt., the reaction mixture was added to water (10 mL), and extracted with ethyl acetate (10 mL x 3). The organic layer was washed with brine (10 mL x 3). The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*, then purified by prep-HPLC to give compound N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)pentyl)piperazin-1-yl)nicotinamide (4.1 mg, 8%) as a white solid.

[0640] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (50 mm x 4.6 mm x 3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100%

[CH_3CN] in 3.0 min, then under this condition for 1.0 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 0.7 min.). Purity is 87.84%, Rt = 2.923 min; MS Calcd.: 809.4; MS Found: 810.3 $[M+H]^+$.

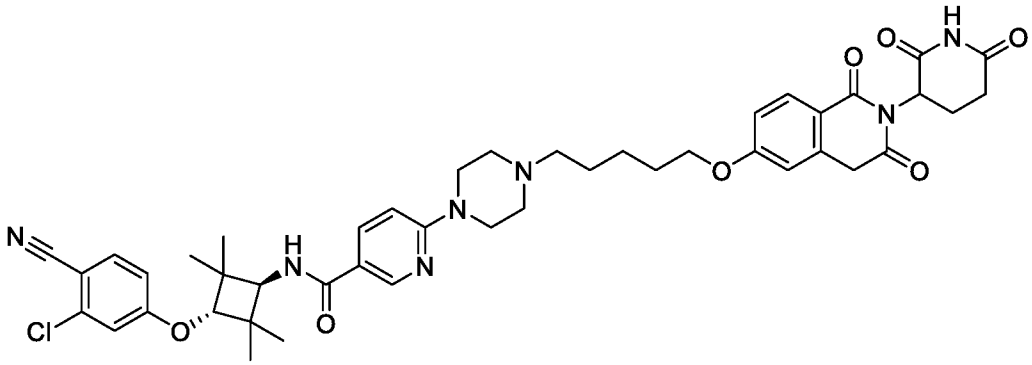
[0641] HPLC (Agilent HPLC 1200, Column: Waters X-Bridge C18 (150 mm x 4.6 mm x 3.5 µm); Column Temperature: 40 °C; Flow Rate: 1.0 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100% [CH_3CN] in 10 min, then under this condition for 5 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 5 min). Purity is 84.56%, Rt = 10.161 min.

[0642] ^1H NMR (400 MHz, DMSO-d_6) δ 1.12 (6H, s), 1.21 (6H, s), 1.43-1.54 (4H, m), 1.74-1.78 (2H, m), 1.88-1.91 (1H, m), 2.30-2.44 (8H, m), 2.90-2.97 (3H, m), 3.42-3.59 (7H, m), 4.03-4.07 (3H, m), 4.30 (1H, s), 6.86-6.91 (3H, m), 6.99-7.02 (1H, m), 7.22 (1H, d, *J* = 2.4 Hz), 7.64 (1H, d, *J* = 8.8 Hz), 7.79 (1H, d, *J* = 8.8 Hz), 7.90-7.97 (2H, m), 8.62 (1H, d, *J* = 2.0 Hz), 10.90 (1H, s).

[0643] Chemical Formula: $C_{44}H_{52}ClN_7O_6$, Molecular Weight: 810.38.

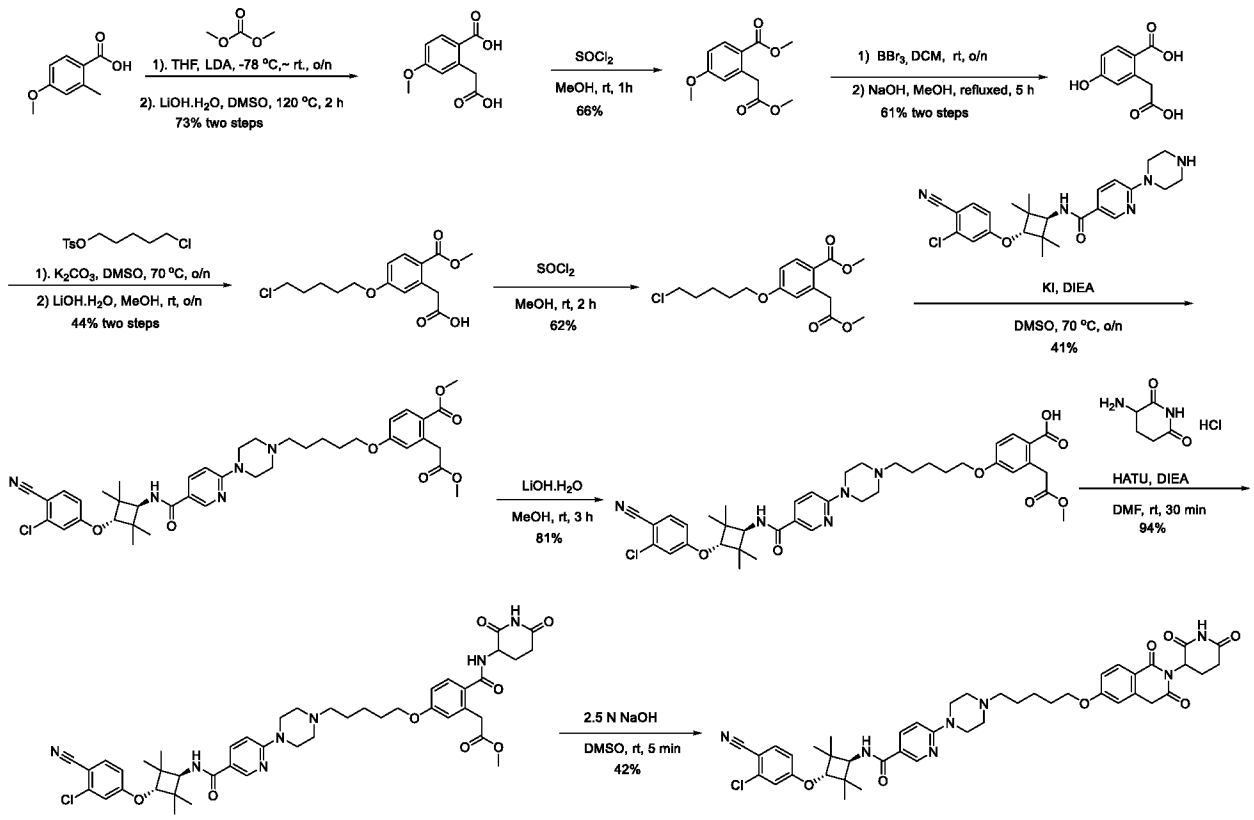
[0644] Total H count from HNMR data: 52.

[0645] **Exemplary Synthesis of Exemplary Compound 47**

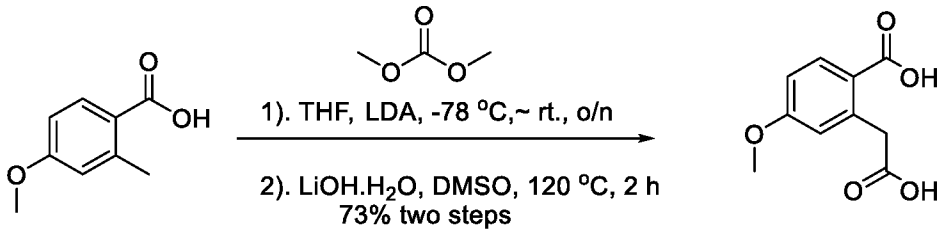


[0646] **N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy)pentyl)piperazin-1-yl)nicotinamide**

[0647] **Synthetic Scheme**



[0648] Step 1: Synthesis of 2-(carboxymethyl)-4-methoxybenzoic acid

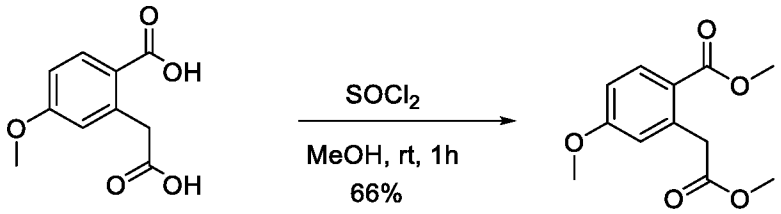


[0649] To a solution of of 4-methoxy-2-methylbenzoic acid (5.0 g, 30.1 mmol) in dry tetrahydrofuran (50 mL) was added lithium diisopropylamide in tetrahydrofuran (1.0 mol/L)(66.3 mL, 66.3 mmol) at -78 °C under nitrogen gas. The mixture was left to stir for 1 hour at that temperature and then dimethyl carbonate (2.98 g, 33.1 mmol) was added. The reaction mixture was left to stir overnight. Water (200 mL) and ethyl acetate (100 mL) was added. The aqueous layer was separated, extracted with ethyl acetate (50 mL x 2) and neutralized with hydrochloric acid (1 N) until pH < 4. The mixture was extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with saturated brine (50.0 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was dissolved in dimethyl sulfoxide (40 mL) and lithium hydroxide hydrate (5.06 g, 120.4 mmol) was added. The

mixture was stirred at 120 °C for 2 hour , cooled down to room temperature and poured into ice-water (200 mL). Hydrochloric acid (1 N) was added until pH < 4. The mixture was extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with saturated brine (50.0 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give 2-(carboxymethyl)-4-methoxybenzoic acid (4.6 g, 73% two steps) as a yellow solid.

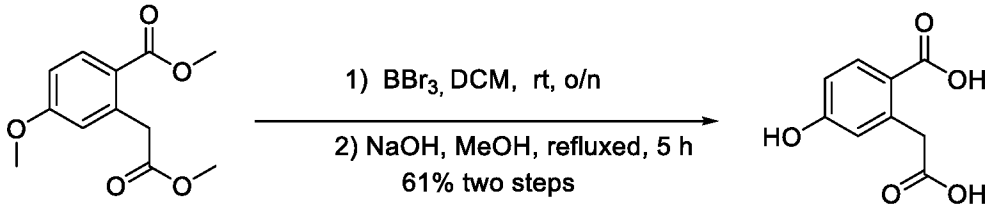
[0650] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (30 mm*4.6 mm*3.5 μm); Column Temperature: 40 °C; Flow Rate: 1.5 mL/min; Mobile Phase: from 95% [water + 0.1% TFA] and 5% [CH_3CN + 0.1% TFA] to 0% [water + 0.1% TFA] and 100% [CH_3CN + 0.1% TFA] in 0.5 min, then under this condition for 1.5 min, finally changed to 95% [water + 0.1% TFA] and 5% [CH_3CN + 0.1% TFA] in 0.1 min and under this condition for 0.5 min). Purity is 94.6%, Rt = 0.774 min; MS Calcd.: 210.1; MS Found: 233.1 $[M+23]^+$.

[0651] Step 2: Synthesis of methyl 4-methoxy-2-(2-methoxy-2-oxoethyl)benzoate



[0652] To a solution of (2-(carboxymethyl)-4-methoxybenzoic acid (1.2 g, 5.7 mmol) in methanol (10.0 mL) was added thionyl chloride (1.7 g, 14.3 mmol) dropwise. The mixture was refluxed for 2 hour. The mixture was cooled down to room temperature and then the solvent was removed *in vacuo* to give crude product which was purified by column chromatography on silica gel (ethyl acetate/ petroleum ether = 1: 1) to give 4-methoxy-2-(2-methoxy-2-oxoethyl)benzoate(900 mg, 66%) as a white solid.

[0653] Step 3: Synthesis of 2-(carboxymethyl)-4-hydroxybenzoic acid

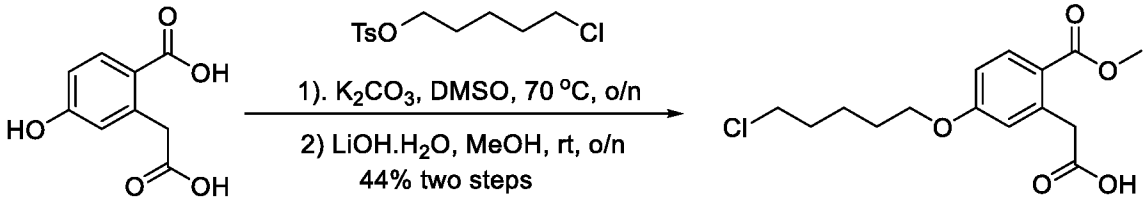


[0654] To a solution of 4-methoxy-2-(2-methoxy-2-oxoethyl)benzoate (0.9 g, 3.78 mmol) in dichloromethane (30 mL) was added boron tribromide (4.7 g, 18.9 mmol) dropwise under ice-waer bath. The resulting mixture was allowed to warm to room temperature and stirred overnight. Water (100 mL) was added. The organic layer was separated, washed with brine (50 mL x 2),

dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give a mixture. The mixture was dissolved in methanol (30 mL) and sodium hydroxide (0.76 g, 18.9 mmol) in water (4.0 mL) was added. The mixture was refluxed for 5 hour. The solvent was removed. The residue was dissolved in water (30 mL). Hydrochloric acid (1 N) was added until pH < 4. The mixture was extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with saturated brine (20.0 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give 2-(carboxymethyl)-4-hydroxybenzoic acid (0.45 g, 61% two steps) as a yellow solid.

[0655] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (30 mm*4.6 mm*3.5 μm); Column Temperature: 40 °C; Flow Rate: 1.5 mL/min; Mobile Phase: from 95% [water + 0.1% TFA] and 5% [CH_3CN + 0.1% TFA] to 0% [water + 0.1% TFA] and 100% [CH_3CN + 0.1% TFA] in 0.5 min, then under this condition for 1.5 min, finally changed to 95% [water + 0.1% TFA] and 5% [CH_3CN + 0.1% TFA] in 0.1 min and under this condition for 0.5 min). Purity is 95.2%, Rt = 0.570 min; MS Calcd.: 196.0; MS Found: 197.2 $[M+H]^+$.

[0656] Step 4: Synthesis of 2-(5-(5-chloropentyloxy)-2-(methoxycarbonyl)phenyl)acetic acid

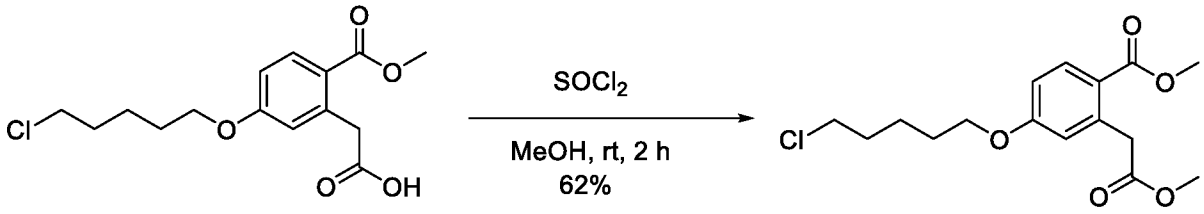


[0657] The mixture of 2-(carboxymethyl)-4-hydroxybenzoic acid (120 mg, 0.61 mmol), potassium carbonate (253 mg, 1.83 mmol) and 5-chloropentyl 4-methylbenzenesulfonate (506 mg, 1.83 mmol) in dimethyl sulfoxide (5 mL) was stirred at 70 °C overnight. The resulting mixture was allowed to cooled down to room temperature and stirred overnight. Water (20 mL) and ethyl acetate (20 mL) was added. The organic layer was separated, washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give a mixture. The mixture was dissolved in methanol (30 mL) and lithium hydroxide hydrate (128 mg, 3.05 mmol) was added. The mixture was stirred at room temperature overnight. The solvent was removed. The residue was dissolved in water (30 mL). Hydrochloric acid (1 N) was added until pH < 4. The mixture was extracted with ethyl acetate (20 mL x 2). The combined organic layers were washed with saturated brine (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and

concentrated *in vacuo* to give 2-(5-(5-chloropentyloxy)-2-(methoxycarbonyl)phenyl)acetic acid (85 mg, 44% two steps) as yellow oil.

[0658] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (30 mm*4.6 mm*3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 90% [water + 10 mM NH_4HCO_3] and 10% [CH_3CN] to 5% [water + 10 mM NH_4HCO_3] and 95% [CH_3CN] in 0.5 min, then under this condition for 1.5 min, finally changed to 90% [water + 10 mM NH_4HCO_3] and 10% [CH_3CN] in 0.1 min and under this condition for 0.5 min.). Purity is 69.9%, Rt =0.829 min; MS Calcd.: 314.1; MS Found: 315.1 $[M+H]^+$.

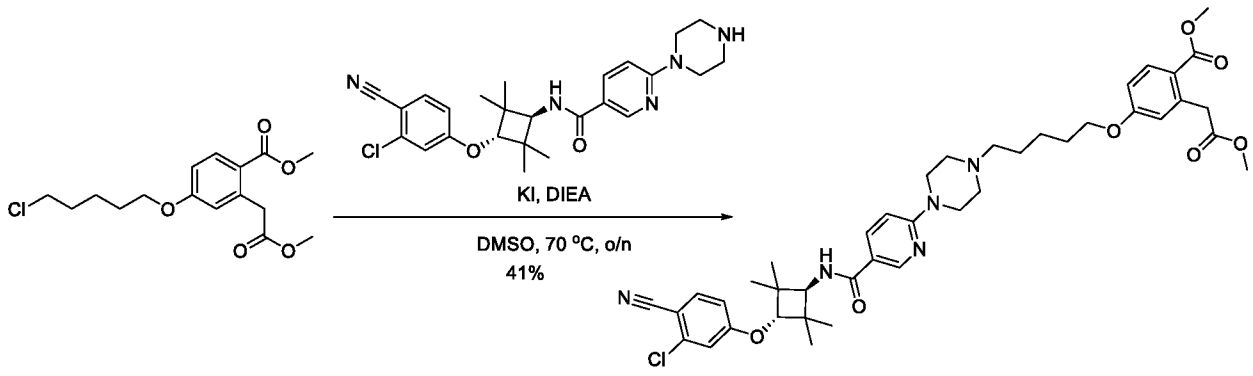
[0659] Step 5: Synthesis of methyl 4-(5-chloropentyloxy)-2-(2-methoxy-2-oxoethyl)benzoate



[0660] To a solution of 2-(5-(5-chloropentyloxy)-2-(methoxycarbonyl)phenyl)acetic acid (85 mg, 0.27 mmol) in methanol (2 mL) was added thionyl chloride (48.3 mg, 0.41 mmol) dropwise. The mixture was refluxed for 2 hour. The mixture was cooled down to room temperature and then the solvent was removed *in vacuo* to give crude product which was purified by prep-TLC (ethyl acetate/ petroleum ether = 1: 1) to give methyl 4-(5-chloropentyloxy)-2-(2-methoxy-2-oxoethyl)benzoate (55 mg, 62%) as yellow oil.

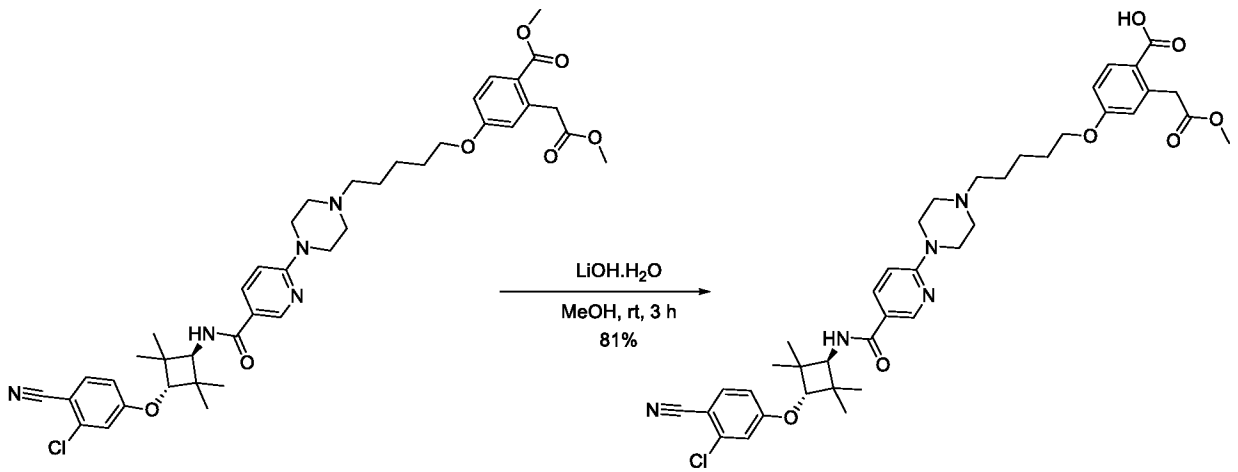
[0661] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (30 mm*4.6 mm*3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 90% [water + 10 mM NH_4HCO_3] and 10% [CH_3CN] to 5% [water + 10 mM NH_4HCO_3] and 95% [CH_3CN] in 0.5 min, then under this condition for 1.5 min, finally changed to 90% [water + 10 mM NH_4HCO_3] and 10% [CH_3CN] in 0.1 min and under this condition for 0.5 min.). Purity is 72.9%, Rt =1.208 min; MS Calcd.: 328.1; MS Found: 329.2 $[M+H]^+$.

[0662] Step 6: Synthesis of methyl 4-(5-(4-(5-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutylcarbamoyl)pyridin-2-yl)piperazin-1-yl)pentyloxy)-2-(2-methoxy-2-oxoethyl)benzoate



[0663] The mixture of methyl 4-(5-chloropentyloxy)-2-(2-methoxy-2-oxoethyl)benzoate (55 mg, 0.17 mmol), ethyldiisopropylamine (65.8 mg, 0.51 mmol), potassium iodide (28.2 mg, 0.17 mmol) and *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(piperazin-1-yl)nicotinamide (78.5 mg, 0.17 mmol) in dimethyl sulfoxide (2 mL) was stirred at 70 °C overnight. The resulting mixture was allowed to cooled down to room temperature and stirred overnight. Water (20 mL) and ethyl acetate (20 mL) was added. The organic layer was separated, washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give the crude product which was purified by column and flash chromatography (ethyl acetate/ petroleum ether = 1: 1) to give methyl 4-(5-(4-(5-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutylcarbamoyl)pyridin-2-yl)piperazin-1-yl)pentyloxy)-2-(2-methoxy-2-oxoethyl)benzoate (53 mg, 41%) as a white solid.

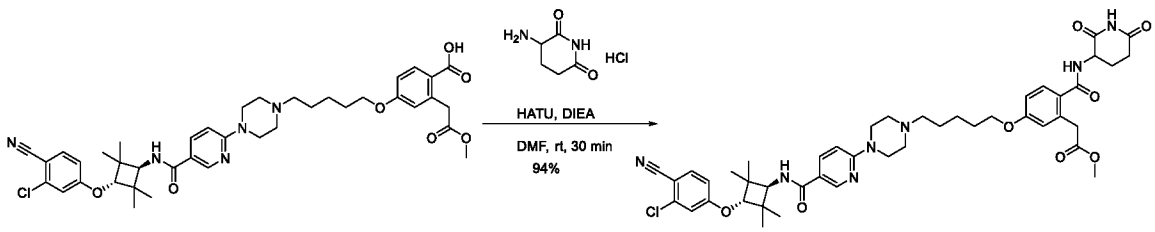
[0664] Step 7: Synthesis of 4-(5-(4-(5-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutylcarbamoyl)pyridin-2-yl)piperazin-1-yl)pentyloxy)-2-(2-methoxy-2-oxoethyl)benzoic acid



[0665] The mixture of methyl 4-(5-(4-(5-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutylcarbamoyl)pyridin-2-yl)piperazin-1-yl)pentyloxy)-2-(2-methoxy-2-oxoethyl)benzoate (53 mg, 0.07 mmol) was dissolved in methanol (2 mL) and lithium hydroxide hydrate (14.7 mg, 0.35 mmol) was added. The mixture was stirred at room temperature for 3 hour. The solvent was removed. The residue was dissolved in water (15 mL). Hydrochloric acid (1 N) was added until pH < 4. The mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with saturated brine (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give 4-(5-(4-(5-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutylcarbamoyl)pyridin-2-yl)piperazin-1-yl)pentyloxy)-2-(2-methoxy-2-oxoethyl)benzoic acid (42 mg, 81%) as a white solid.

[0666] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (30 mm*4.6 mm*3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 90% [water + 10 mM NH_4HCO_3] and 10% [CH_3CN] to 5% [water + 10 mM NH_4HCO_3] and 95% [CH_3CN] in 0.5 min, then under this condition for 1.5 min, finally changed to 90% [water + 10 mM NH_4HCO_3] and 10% [CH_3CN] in 0.1 min and under this condition for 0.5 min.). Purity is 75.4%, Rt =1.041 min; MS Calcd.: 745.3; MS Found: 746.2 $[M+H]^+$.

[0667] Step 8: Synthesis of methyl 2-(5-(5-(4-(5-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutylcarbamoyl)pyridin-2-yl)piperazin-1-yl)pentyloxy)-2-(2,6-dioxopiperidin-3-ylcarbamoyl)phenyl)acetate

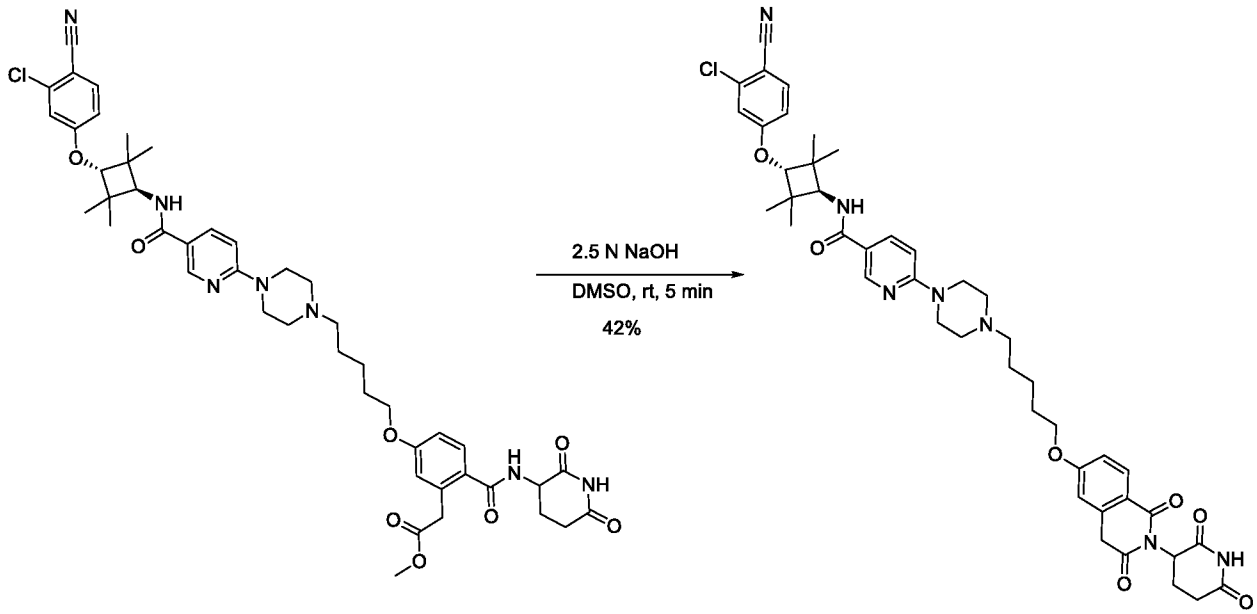


[0668] A solution of 4-(5-(4-(5-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutylcarbamoyl)pyridin-2-yl)piperazin-1-yl)pentyloxy)-2-(2-methoxy-2-oxoethyl)benzoic acid (42 mg, 0.056 mmol), HATU (25.5 mg, 0.067 mmol) and ethyldiisopropylamine (29.7 mg, 0.23 mmol) in *N, N*-dimethylformamide (2 mL) was stirred for 30 min, and then 3-aminopiperidine-2,6-dione hydrochloride (9.2 mg, 0.056 mmol) was added. The mixture was stirred at room temperature overnight and water (10 mL) was added. The mixture was extracted by ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*.

The residue was purified by prep-TLC (dichloromethane/ methanol=10:1) to give methyl 2-(5-(5-(4-(5-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutylcarbamoyl)pyridin-2-yl)piperazin-1-yl)pentyloxy)-2-(2,6-dioxopiperidin-3-ylcarbamoyl)phenyl)acetate (45 mg, 94%) as a white solid.

[0669] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (30 mm*4.6 mm*3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 90% [water + 10 mM NH_4HCO_3] and 10% [CH_3CN] to 5% [water + 10 mM NH_4HCO_3] and 95% [CH_3CN] in 0.5 min, then under this condition for 1.5 min, finally changed to 90% [water + 10 mM NH_4HCO_3] and 10% [CH_3CN] in 0.1 min and under this condition for 0.5 min.). Purity is 77.7%, Rt =1.213 min; MS Calcd.: 855.4; MS Found: 856.3 $[M+H]^+$.

[0670] Step 9: Synthesis of *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)pentyl)piperazin-1-yl)nicotinamide



[0671] A solution of methyl 2-(5-(5-(4-(5-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutylcarbamoyl)pyridin-2-yl)piperazin-1-yl)pentyloxy)-2-(2,6-dioxopiperidin-3-ylcarbamoyl)phenyl)acetate (45 mg, 0.053 mmol) in dimethyl sulfoxide (2 mL) was added sodium hydroxide in water (2.5 moL/L, 2 drops). The mixture was stirred at room temperature for 5 min. Water (20 mL) and ethyl acetate (20 mL) was added. The organic layer was separated, washed with brine (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated

in vacuo to give the crude product which was purified by prep-HPLC to give *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)pentyl)piperazin-1-yl)nicotinamide (18.5 mg, 42%) as a white solid.

[0672] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (50 mm*4.6 mm*3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 90% [(total 10mM $AcONH_4$) water/CH_3CN=900/100 (v/v)] and 10% [(total 10mM $AcONH_4$) water/CH_3CN=100/900 (v/v)] to 10% [(total 10mM $AcONH_4$) water /CH_3CN=900/100 (v/v)] and 90% [(total 10mM $AcONH_4$) water/CH_3CN=100/900 (v/v)] in 1.6 min, then under this condition for 2.4 min, finally changed to 90% [(total 10mM $AcONH_4$) water/CH_3CN=900/100 (v/v)] and 10% [(total 10mM $AcONH_4$) water/CH_3CN=100/900 (v/v)] in 0.1 min and under this condition for 0.7 min). Purity is 100.0%, Rt = 2.988 min; MS Calcd.:823.4; MS Found:824.3 $[M+H]^+$.

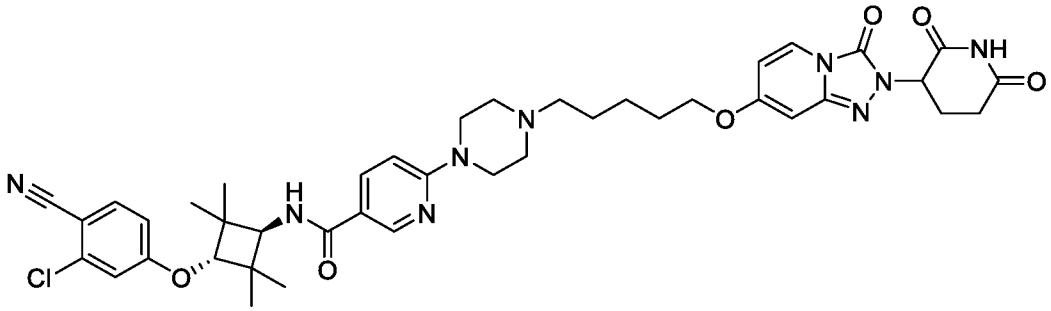
[0673] HPLC (Agilent HPLC 1200; Column: L-column2 ODS (150 mm*4.6 mm*5.0 μm); Column Temperature: 40 °C; Flow Rate: 1.0 mL/min; Mobile Phase: from 95% [water + 0.1% TFA] and 5% [CH_3CN + 0.1% TFA] to 0% [water + 0.1% TFA] and 100% [CH_3CN + 0.1% TFA] in 10 min, then under this condition for 5 min, finally changed to 95% [water + 0.1% TFA] and 5% [CH_3CN + 0.1% TFA] in 0.1 min and under this condition for 5 min). Purity is 95.2 %, Rt = 8.168 min.

[0674] ^1H NMR (400 MHz, DMSO-d^6) δ 1.12 (6H, s), 1.21 (6H, s), 1.37-1.58 (4H, m), 1.73-1.81 (2H, m), 1.86-1.91 (1H, m), 2.30-2.37 (2H, m), 2.40-2.46 (2H, m), 2.82-2.91(1H, m), 3.30-3.35 (4H, m), 3.55-3.65 (4H, m), 4.03-4.30 (6H, m), 5.54-5.63 (1H, m), 6.87 (1H, d, J = 9.6 Hz), 6.96-7.07 (3H, m), 7.21 (1H, d, J = 2.4 Hz), 7.63 (1H, d, J = 9.6 Hz), 7.90-8.04 (3H, m), 8.62 (1H, d, J = 2.4 Hz), 10.93 (1H, s).

[0675] Chemical Formula: $C_{44}H_{50}ClN_7O_7$, Molecular Weight: 824.36.

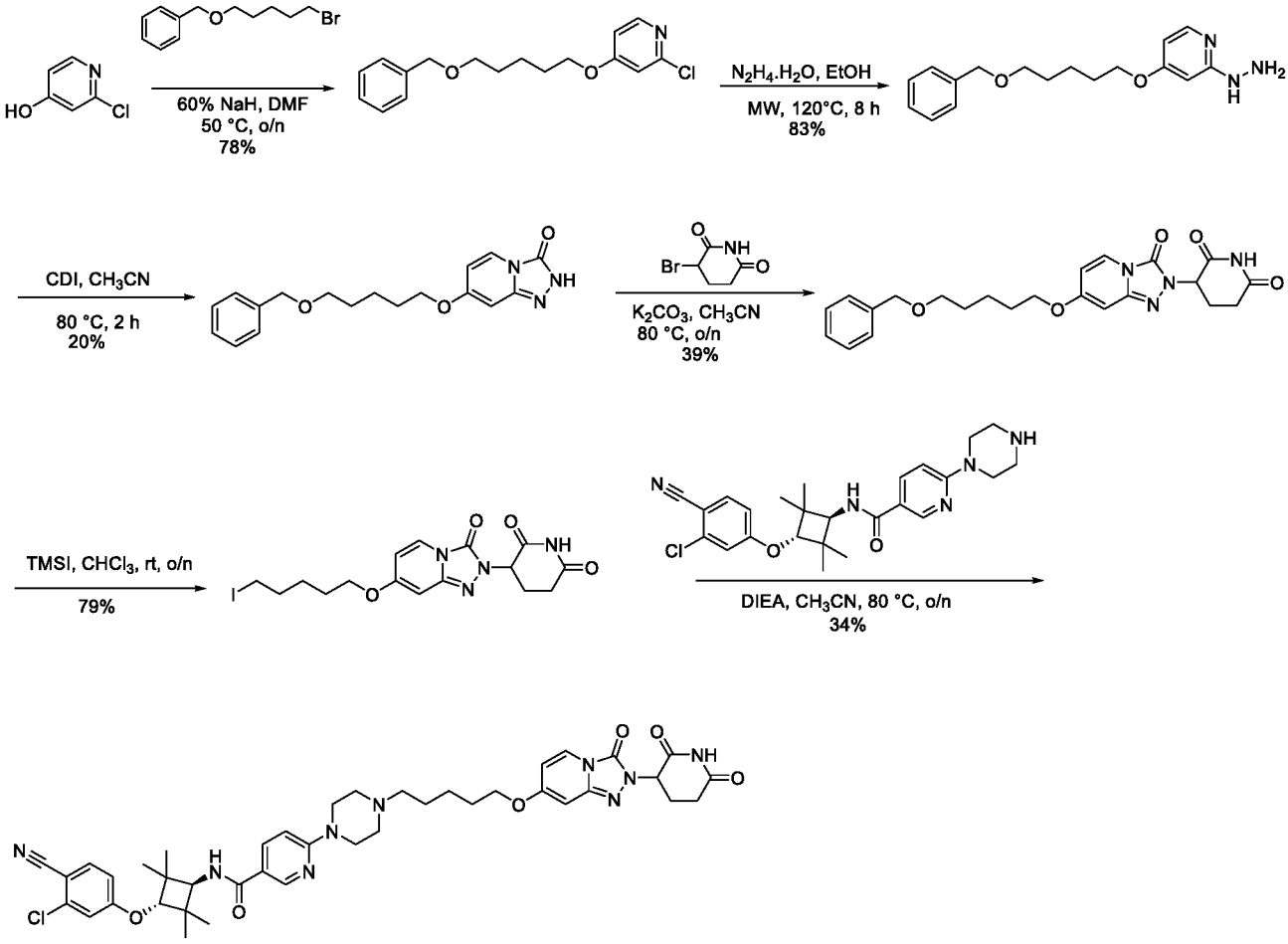
[0676] Total H count from HNMR data: 50.

[0677] **Exemplary Synthesis of Exemplary Compound 48**

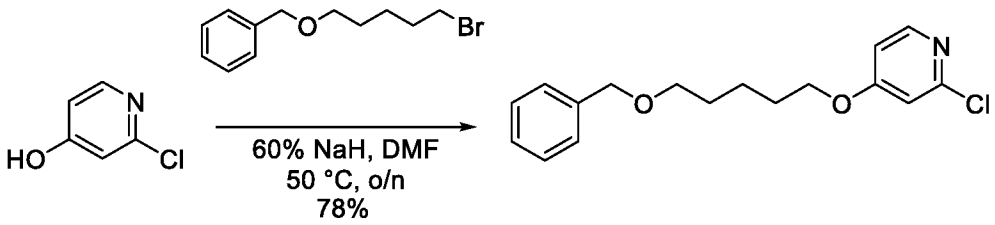


N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(5-((2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl)oxy)pentyl)piperazin-1-yl)nicotinamide

[0678] Synthetic Scheme



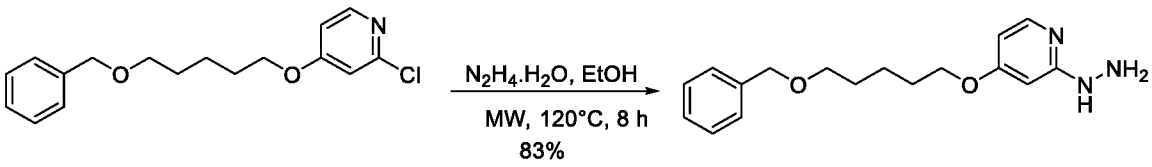
[0679] Step 1: Synthesis of 4-(5-(benzyloxy)pentyloxy)-2-chloropyridine



[0680] To a solution of 2-chloropyridin-4-ol (1.3 g, 10.0 mmol) in DMF (15 mL) was added sodium hydride (60% dispersed in mineral oil, 482 mg, 12.0 mmol) at 0 °C, and the mixture was stirred at room temperature for 30 min. Then ((5-bromopentyloxy)methyl)benzene (3.1 g, 12.0 mmol) was added to the reaction and the resulted mixture was stirred at 50 °C overnight. When the reaction was completed (monitored by TLC), water (30 mL) was added. The resultant mixture was extracted by ethyl acetate (10 mL x 3) and the combined organic layers were washed by brine (20 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica (petroleum/ethyl acetate = 1/4) to give 4-(5-(benzyloxy)pentyloxy)-2-chloropyridine (2.4 g, 78% yield) as a brown solid.

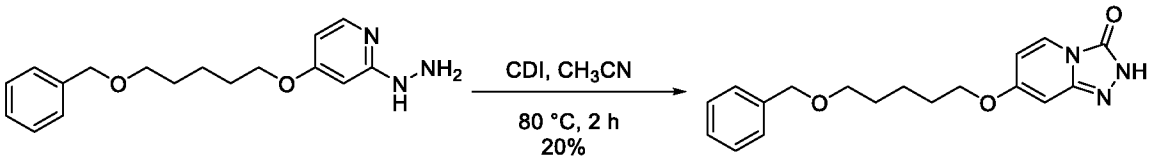
[0681] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47-1.53 (2 H, m), 1.59-1.64 (2 H, m), 1.71-1.76 (2 H, m), 3.42 (2 H, t, J = 6.4 Hz), 3.91 (2 H, t, J = 6.4 Hz), 4.44 (2 H, s), 7.07-7.15 (2 H, m), 7.23-7.28 (5 H, m), 7.96 (1 H, d, J = 3.2 Hz).

[0682] Step 2: Synthesis of 4-(5-(benzyloxy)pentyloxy)-2-hydrazinylpyridine



[0683] To a microwave glass vial was added 4-(5-(benzyloxy)pentyloxy)-2-chloropyridine (2.0 g, 6.5 mmol), hydrazine monohydrate (10 mL) and EtOH (10 mL), and the mixture was stirred under microwave conditions at 120 °C for 8 h. When it was cooled to room temperature, water (20 mL) was added to the reaction. The resultant mixture was extracted by ethyl acetate (10 mL x 3) and the combined organic layers were washed by brine (15 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated in *vacuo*. The residue (1.6 g, 83% yield) was directly used to the next step without further purification as brown oil.

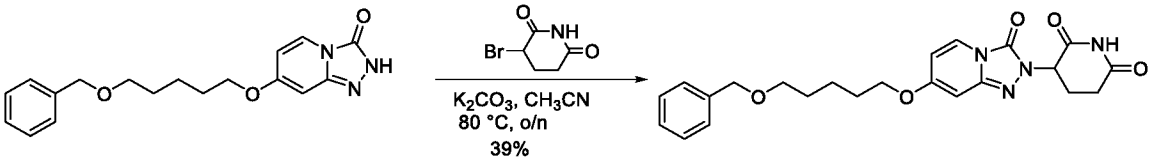
[0684] Step 3: Synthesis of 7-(5-(benzyloxy)pentyloxy)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



[0685] To a solution of 5-ethoxy-2-hydrazinylpyridine (1.6 g, 5.4 mmol) in acetonitrile (25 mL) was added CDI (1.3 g, 8.2 mmol), and the mixture was stirred at 80 °C for 2 h. When it was cooled to room temperature, water (20 mL) was added to the reaction. The resultant mixture was extracted by ethyl acetate (10 mL x 3) and the combined organic layers were washed by brine (15 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography on silica (DCM/MeOH = 20/1) to give 7-(5-(benzyloxy)pentyloxy)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one (360 mg, 20% yield) as a white solid.

[0686] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (50 mm x 4.6 mm x 3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100% [CH_3CN] in 1.6 min, then under this condition for 1.4 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 0.7 min.) Purity is 96.77%, Rt = 1.716 min. MS Calcd.: 327.16; MS Found: 328.2 $[M+H]^+$.

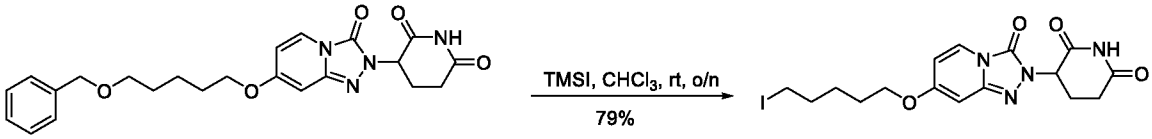
[0687] Step 4: Synthesis of 3-(7-(5-(benzyloxy)pentyloxy)-3-oxo-[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)piperidine-2,6-dione



[0688] The solution of 7-(5-(benzyloxy)pentyloxy)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one (300 mg, 0.9 mmol), 3-bromopiperidine-2,6-dione (438 mg, 2.3 mmol) and K_2CO_3 (253 mg, 1.8 mmol) in acetonitrale (10 mL) was stirred at 80 °C overnight. When it was cooled to room temperature, water (10 mL) was added. The resultant mixture was extracted by ethyl acetate (10 mL x 3) and the combined organic layers were washed by brine (10 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by Prep-TLC (DCM/MeOH = 20/1) to give 3-(7-(5-(benzyloxy)pentyloxy)-3-oxo-[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)piperidine-2,6-dione (157 mg, 39% yield) as a white solid.

[0689] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (50 mm x 4.6 mm x 3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100% [CH_3CN] in 1.6 min, then under this condition for 1.4 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 0.7 min.) Purity is 99.45%, Rt = 1.836 min. MS Calcd.: 438.19; MS Found: 439.3 $[M+H]^+$.

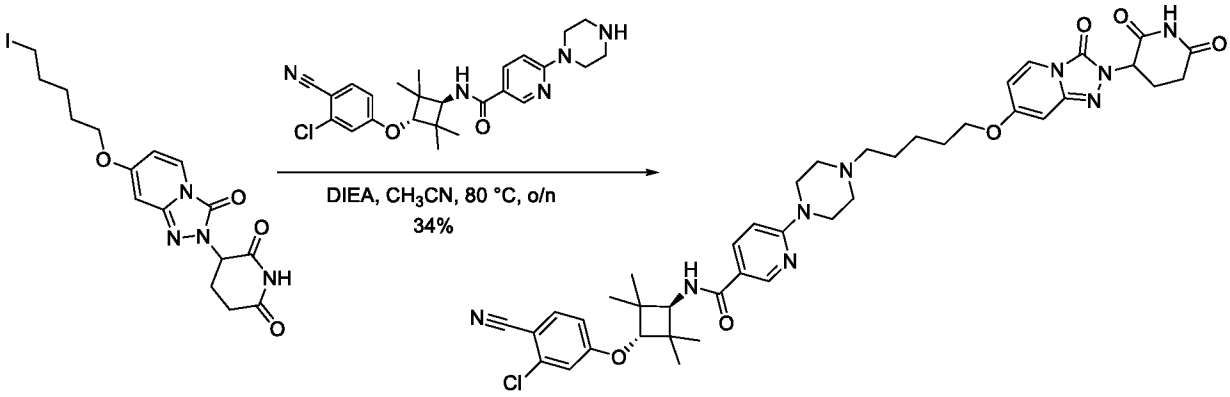
[0690] Step 5: Synthesis of 3-(7-(5-iodopentyloxy)-3-oxo-[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)piperidine-2,6-dione



[0691] To a solution of 3-(7-(5-(benzyloxy)pentyloxy)-3-oxo-[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)piperidine-2,6-dione (157 mg, 0.4 mmol) in $CHCl_3$ (5 mL) was added TMSI (143 mg, 0.7 mmol), and the mixture was stirred at room temperature overnight. Then the mixture was washed by sat. $NaHSO_3$ (5 mL x 2), washed by brine (5 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by Prep-TLC (DCM/MeOH = 15/1) to give 3-(7-(5-iodopentyloxy)-3-oxo-[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)piperidine-2,6-dione (130 mg, 79% yield) as a white solid.

[0692] LCMS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (50 mm x 4.6 mm x 3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100% [CH_3CN] in 1.6 min, then under this condition for 1.4 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 0.7 min.) Purity is 100%, Rt = 1.754 min. MS Calcd.: 458.05; MS Found: 459.1 $[M+H]^+$.

[0693] Step 6: Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yloxy)pentyl)piperazin-1-yl)nicotinamide



[0694] A solution of 3-(7-(5-iodopentyloxy)-3-oxo-[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)piperidine-2,6-dione (85 mg, 0.2 mmol), N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(piperazin-1-yl)nicotinamide (87 mg, 0.2 mmol), and ethyldiisopropylamine (72 mg, 0.6 mmol) in acetonitrile (5 mL) was stirred at 80 °C overnight. When it was cooled to room temprature, water (5 mL) was added and the mixture was extracted by ethyl acetate (5 mL x 3) and the combined organic layers were washed by brine (5 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by Prep-HPLC to give N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yloxy)pentyl)piperazin-1-yl)nicotinamide (50 mg, 34% yield) as a white solid.

[0695] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (50 mm x 4.6 mm x 3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100% [CH_3CN] in 3.0 min, then under this condition for 1.0 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 0.7 min.) Purity is 100%, Rt = 2.877 min; MS Calcd.: 797.34; MS Found: 798.3 $[M+H]^+$.

[0696] HPLC (Agilent HPLC 1200, Column: Waters X-Bridge C18 (150 mm x 4.6 mm x 3.5 μm); Column Temperature: 40 °C; Flow Rate: 1.0 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100% [CH_3CN] in 10 min, then under this condition for 5 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 5 min.) Purity is 93.85%, Rt = 9.967 min.

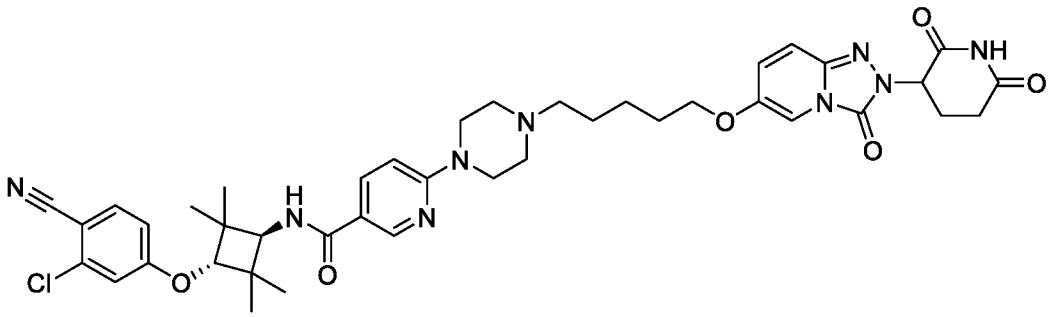
[0697] ^1H NMR (400 MHz, DMSO-d_6) δ 1.12 (6H, s), 1.21 (6H, s), 1.43-1.47 (2H, m), 1.49-1.53 (2H, m), 1.73-1.78 (2H, m), 2.13-2.17 (1H, m), 2.32 (2H, t, J = 7.2 Hz), 2.43-2.47 (5H, m),

2.61-2.62 (1H, m), 2.87-2.93 (1H, m), 3.59 (4H, s), 4.01-4.07 (3H, m), 4.30 (1H, s), 5.28 (1H, dd, J = 12.4, 5.2 Hz), 6.35 (1H, dd, J = 8.0, 2.4 Hz), 6.52 (1H, d, J =1.6 Hz), 6.86 (1H, d, J = 8.8 Hz), 7.00 (1H, dd, J = 8.8, 2.4 Hz), 7.21 (1H, d, J = 2.4 Hz), 7.63 (1H, d, J = 9.2 Hz), 7.80 (1H, d, J = 8.0 Hz), 7.90 (1H, d, J = 8.8 Hz), 7.95 (1H, dd, J = 9.2, 2.4 Hz), 8.62 (1H, d, J = 2.4 Hz), 11.09 (1H, s).

[0698] Chemical Formula: $C_{41}H_{48}ClN_9O_6$, Molecular Weight: 798.33.

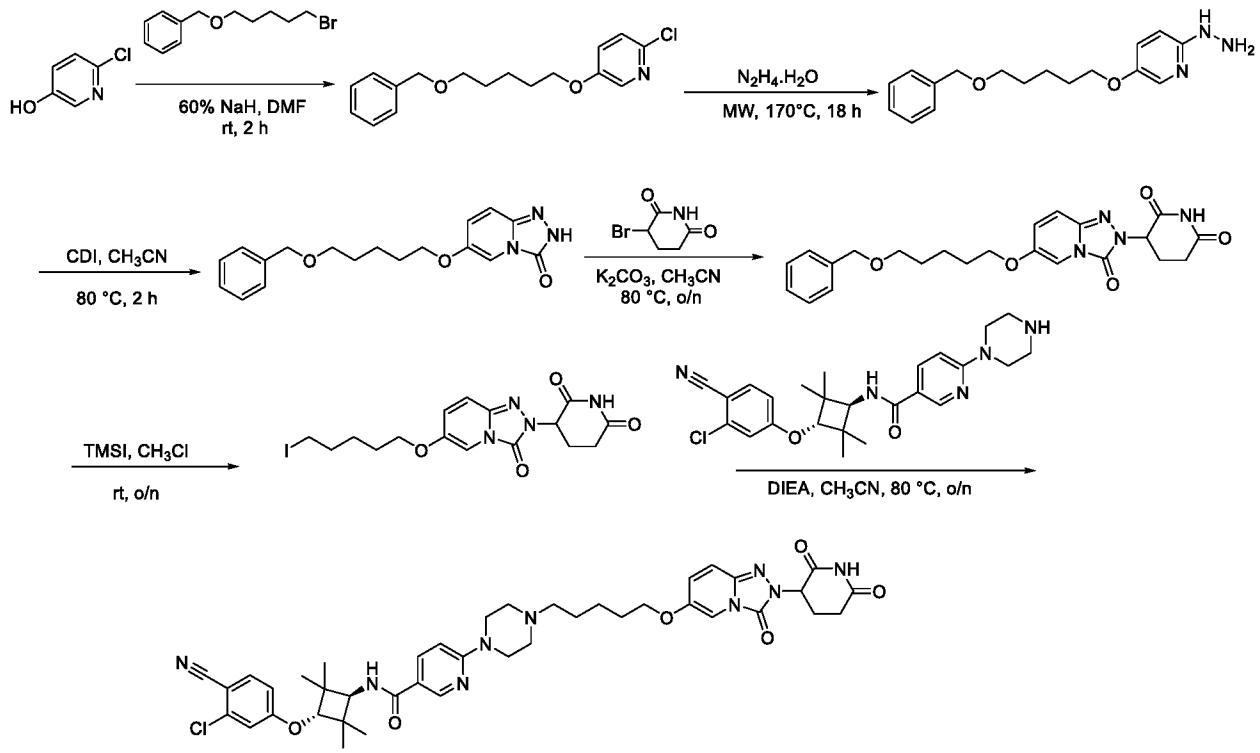
[0699] Total H count from HNMR data: 48.

[0700] **Exemplary Synthesis of Exemplary Compound 49**

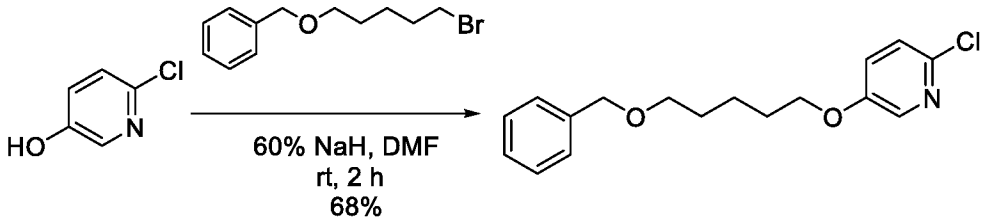


N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(5-((2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-6-yl)oxy)pentyl)piperazin-1-yl)nicotinamide

[0701] **Synthetic Scheme**

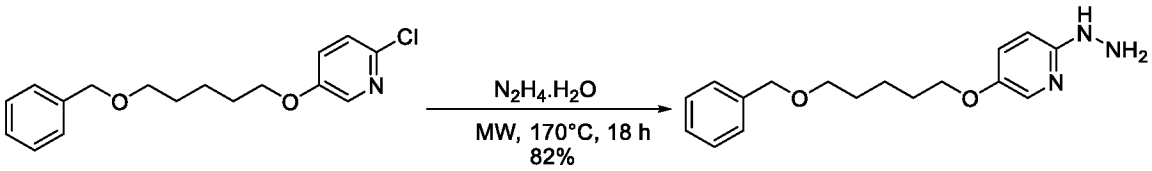


[0702] Step 1: Synthesis of 5-(5-(benzyloxy)pentyloxy)-2-chloropyridine



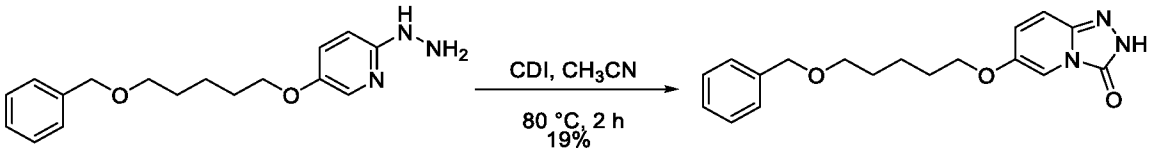
[0703] To a solution of 6-chloropyridin-3-ol (1.0 g, 7.7 mmol) in DMF (10 mL) was added sodium hydride (60% dispersed in mineral oil, 371 mg, 9.3 mmol) at 0 °C, and the mixture was stirred at room temperature for 30 min. Then ((5-bromopentyloxy)methyl)benzene (2.0 g, 7.7 mmol) was added to the reaction and the resulted mixture was stirred at room temperature for 2 h. When the reaction was completed (monitored by TLC), water (30 mL) was added. The resultant mixture was extracted by ethyl acetate (10 mL x 3) and the combined organic layers were washed by brine (10 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated. The residue (1.6 g, 68% yield) was directly used to the next step without further purification as a brown solid.

[0704] Step 2: Synthesis of 5-(5-(benzyloxy)pentyloxy)-2-hydrazinylpyridine



[0705] To a microwave glass vial was added 5-(5-(benzyloxy)pentyloxy)-2-chloropyridine (1.6 g, 5.2 mmol) and hydrazine monohydrate (20 mL), and the mixture was stirred under microwave conditions at 170 °C for 18 h. When it was cooled to room temperature, water (20 mL) was added to the reaction. The resultant mixture was extracted by ethyl acetate (10 mL x 3) and the combined organic layers were washed by brine (15 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo*. The residue (1.3 g, 82% yield) was directly used to the next step without further purification as brown oil.

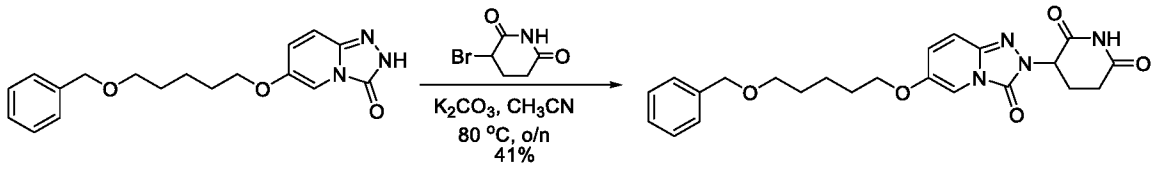
[0706] Step 3: Synthesis of 6-(5-(benzyloxy)pentyloxy)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



[0707] To a solution of 5-(5-(benzyloxy)pentyloxy)-2-hydrazinylpyridine (1.3 g, 4.4 mmol) in acetonitrile (30 mL) was added CDI (1.1 g, 6.7 mmol), and the mixture was stirred at 80 °C for 2 h. When it was cooled to room temperature, water (20 mL) was added to the reaction. The resultant mixture was extracted by ethyl acetate (10 mL x 3) and the combined organic layers were washed by brine (15 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo*. The residue was purified by column chromatography on silica (DCM/MeOH = 20/1) to give 6-(5-(benzyloxy)pentyloxy)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one (280 mg, 19% yield) as a white solid.

[0708] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (50 mm x 4.6 mm x 3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100% [CH_3CN] in 1.6 min, then under this condition for 1.4 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 0.7 min.) Purity is 98.98%, Rt = 1.728 min. MS Calcd.: 327.16; MS Found: 328.1 $[M+H]^+$.

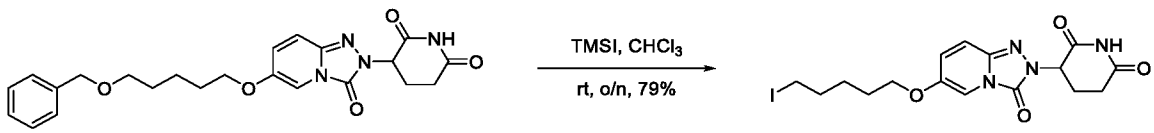
[0709] Step 4: Synthesis of 3-(6-(5-(benzyloxy)pentyloxy)-3-oxo-[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)piperidine-2,6-dione



[0710] The solution of 6-(5-(benzyloxy)pentyloxy)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one (280 mg, 0.9 mmol), 3-bromopiperidine-2,6-dione (438 mg, 2.3 mmol) and K_2CO_3 (253 mg, 1.8 mmol) in acetonitrile (10 mL) was stirred at 80 °C overnight. When it was cooled to room temperature, water (10 mL) was added. The resultant mixture was extracted by ethyl acetate (10 mL x 3) and the combined organic layers were washed by brine (10 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by Prep-TLC (DCM/MeOH = 20/1) to give 3-(6-(5-(benzyloxy)pentyloxy)-3-oxo-[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)piperidine-2,6-dione (155 mg, 41% yield) as a white solid.

[0711] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (50 mm x 4.6 mm x 3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100% [CH_3CN] in 1.6 min, then under this condition for 1.4 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 0.7 min.) Purity is 85.76%, Rt = 1.675 min. MS Calcd.: 438.19; MS Found: 439.2 $[M+H]^+$.

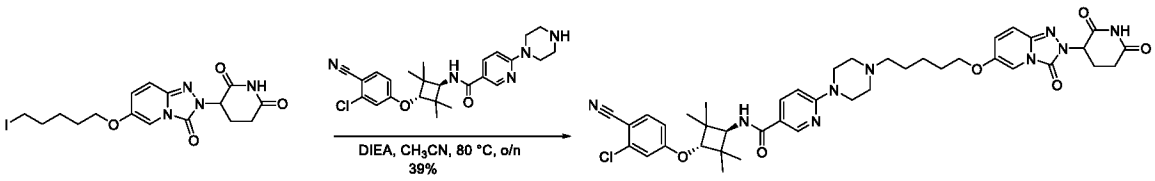
[0712] Step 5: Synthesis of 3-(6-(5-iodopentyloxy)-3-oxo-[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)piperidine-2,6-dione



[0713] To a solution of 3-(6-(5-(benzyloxy)pentyloxy)-3-oxo-[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)piperidine-2,6-dione (155 mg, 0.4 mmol) in $CHCl_3$ (5 mL) was added TMSI (143 mg, 0.7 mmol), and the mixture was stirred at room temperature overnight. Then the mixture was washed by sat. $NaHSO_3$ (5 mL x 2), washed by brine (5 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by Prep-TLC (DCM/MeOH = 15/1) to give 3-(7-(5-iodopentyloxy)-3-oxo-[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)piperidine-2,6-dione (130 mg, 79% yield) as a white solid.

[0714] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (50 mm x 4.6 mm x 3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100% [CH_3CN] in 1.6 min, then under this condition for 1.4 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 0.7 min.) Purity is 95.44%, Rt = 1.706 min. MS Calcd.: 458.05; MS Found: 459.1 $[M+H]^+$.

[0715] Step 6: Synthesis of N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-6-yloxy)pentyl)piperazin-1-yl)nicotinamide



[0716] A solution of 3-(6-(5-iodopentyloxy)-3-oxo-[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)piperidine-2,6-dione (85 mg, 0.2 mmol), N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(piperazin-1-yl)nicotinamide (87 mg, 0.2 mmol), and ethyldiisopropylamine (72 mg, 0.6 mmol) in acetonitrile (5 mL) was stirred at 80 °C overnight. When it was cooled to room temprature, water (5 mL) was added and the mixture was extracted by ethyl acetate (5 mL x 3) and the combined organic layers were washed by brine (5 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by Prep-HPLC to give N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-6-yloxy)pentyl)piperazin-1-yl)nicotinamide (58 mg, 39% yield) as a white solid.

[0717] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (50 mm x 4.6 mm x 3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100% [CH_3CN] in 3.0 min, then under this condition for 1.0 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 0.7 min.) Purity is 100%, Rt = 2.890 min; MS Calcd.: 797.34; MS Found: 798.3 $[M+H]^+$.

[0718] HPLC (Agilent HPLC 1200, Column: Waters X-Bridge C18 (150 mm x 4.6 mm x 3.5 μm); Column Temperature: 40 °C; Flow Rate: 1.0 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100% [CH_3CN] in 10

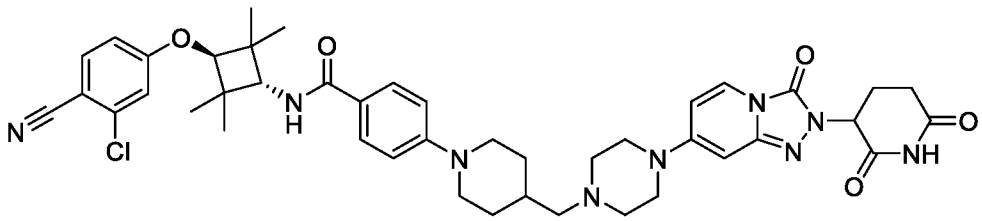
min, then under this condition for 5 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 5 min.) Purity is 93.46%, Rt = 10.027 min.

[0719] ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12 (6H, s), 1.21 (6H, s), 1.44-1.48 (2H, m), 1.52-1.58 (2H, m), 1.74-1.79 (2H, m), 2.15-2.19 (1H, m), 2.30 (2H, t, J = 7.2 Hz), 2.43-2.50 (4H, m), 2.51-2.67 (2H, m), 2.86-2.95 (1H, m), 3.60 (4H, s), 3.97 (2H, t, J = 6.4 Hz), 4.05 (1H, d, J = 9.2 Hz), 4.30 (1H, s), 5.38 (1H, dd, J = 5.2, 12.8 Hz), 6.86 (1H, d, J = 9.2 Hz), 7.00 (1H, dd, J = 8.4, 2.4 Hz), 7.10 (1H, dd, J = 10.0, 2.0 Hz), 7.21 (1H, d, J = 2.4 Hz), 7.25 (1H, d, J = 10.0 Hz), 7.36 (1H, s), 7.62 (1H, d, J = 9.2 Hz), 7.90 (1H, d, J = 8.8 Hz), 7.95 (1H, dd, J = 9.2, 2.4 Hz), 8.62 (1H, d, J = 2.4 Hz), 11.10 (1H, s).

[0720] Chemical Formula: $C_{41}H_{48}ClN_9O_6$, Molecular Weight: 798.33.

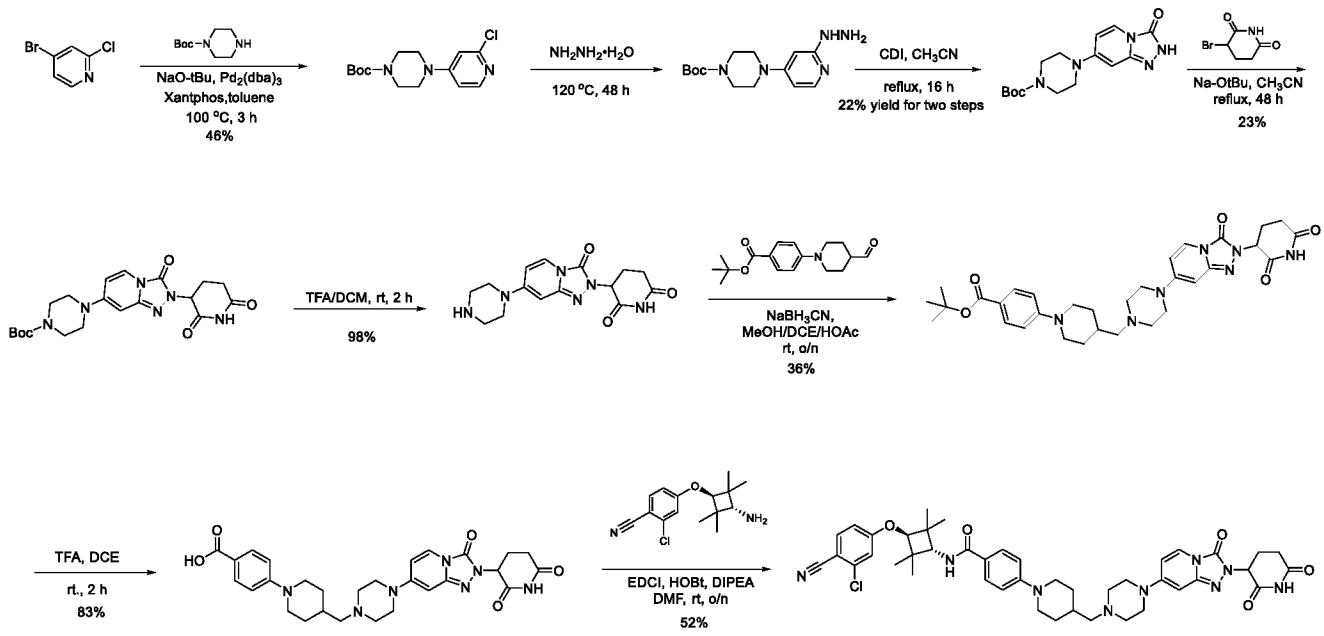
[0721] Total H count from HNMR data: 48.

[0722] **Exemplary Synthesis of Exemplary Compound 50**

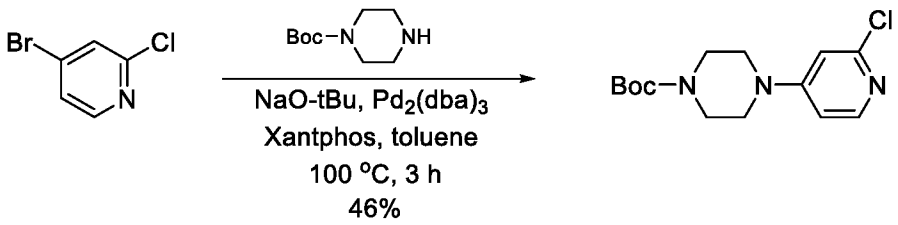


N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl)piperazin-1-yl)methyl)piperidin-1-yl)benzamide

[0723] **Synthetic Scheme**



[0724] Step 1: Synthesis of tert-butyl 4-(2-chloropyridin-4-yl)piperazine-1-carboxylate



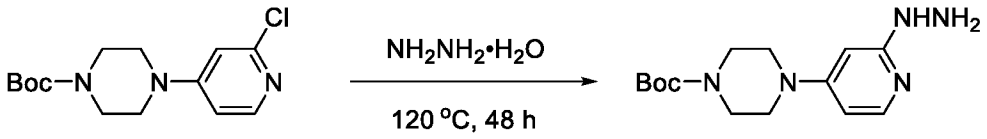
[0725] To a solution of 4-bromo-2-chloropyridine (5.8 g, 30.2 mmol) in dry toluene (150 mL) was added sodium tert-butoxide (4.3 g, 45.0 mmol), $Pd_2(dba)_3$ (0.55 g, 0.60 mmol), Xantphos (1.0 g, 1.80 mmol) and tert-butyl piperazine-1-carboxylate (5.6 g, 30.2 mmol). The reaction mixture was stirred at 100 °C for 3 h under nitrogen and then cooled to rt. The organic layer was washed with water and brine and then dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography column (PE/EA = 8:1) to give tert-butyl 4-(2-chloropyridin-4-yl)piperazine-1-carboxylate (3.6 g, 46%) as a yellow solid.

[0726] ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.42 (9H, s), 3.38-3.41 (8H, m), 6.83-6.86 (2H, m), 7.96 (1H, d, J = 6.0 Hz).

[0727] Chemical Formula: $C_{14}H_{20}ClN_3O_2$, Molecular Weight: 297.78.

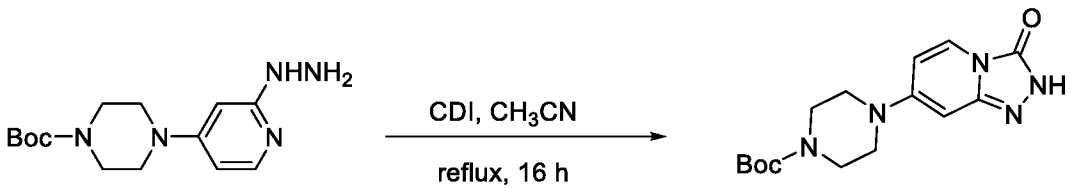
[0728] Total H count from HNMR data: 20.

[0729] Step 2: Synthesis of tert-butyl 4-(2-hydrazinylpyridin-4-yl)piperazine-1-carboxylate



[0730] To a solution of tert-butyl 4-(2-chloropyridin-4-yl)piperazine-1-carboxylate (5.0 g, 16.8 mmol) in hydrazine monohydrate (98%, 40 mL), was stirred at 120 °C for 48 h under nitrogen. Water (100 mL) was added to the mixture. The resultant mixture was extracted by ethyl acetate (50 mL x 3), washed by brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in *vacuo*. The residue (4.8 g, 30% purity) was directly used to the next step without further purification as a brown solid.

[0731] Step 3: Synthesis of tert-butyl 4-(3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl)piperazine-1-carboxylate



[0732] To a solution of tert-butyl 4-(2-hydrazinylpyridin-4-yl)piperazine-1-carboxylate (4.8 g, 30% purity, 4.9 mmol) in acetonitrile (100 mL) was added CDI (1.6 g, 9.8 mmol), and the mixture stirred at 100 °C for 16 h. When it was cooled to room temperature, water (100 mL) was added to the reaction. The resultant mixture was extracted by ethyl acetate (100 mL x 3), washed by brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in *vacuo*. The residue was purified by coloumn chromatography on silica (DCM/MeOH = 20/1) to give tert-butyl 4-(3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl)piperazine-1-carboxylate (1.2 g, 22% yield for two steps) as a yellow solid.

[0733] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (50 mm*4.6 mm*3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 90% [(total 10mM $AcONH_4$) water/CH_3CN=900/100 (v/v)] and 10% [(total 10mM $AcONH_4$) water/CH_3CN=100/900 (v/v)] to 10% [(total 10mM $AcONH_4$) water /CH_3CN=900/100 (v/v)] and 90% [(total 10mM $AcONH_4$) water/CH_3CN=100/900 (v/v)] in 1.6 min, then under this condition for 2.4 min, finally changed to 90% [(total 10mM $AcONH_4$) water/CH_3CN=900/100 (v/v)] and 10% [(total 10mM $AcONH_4$) water/CH_3CN=100/900 (v/v)] in 0.1 min and under this condition for 0.7 min). Purity is 99.11%, Rt = 1.418 min; MS Calcd.: 319.7; MS Found: 320.2

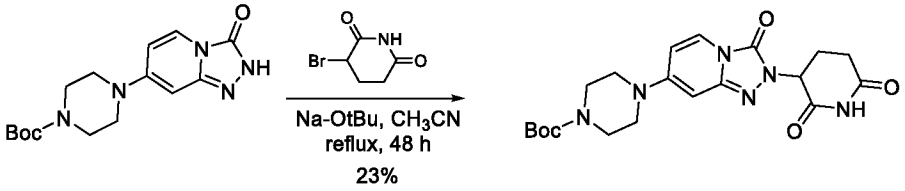
$[M+H]^+$.

[0734] ^1H NMR (400 MHz, DMSO-d^6) δ 1.42 (9H, s), 3.21-3.23 (4H, m), 3.42-3.43 (4H, m), 6.13 (1H, d, J = 1.6 Hz), 6.60 (1H, dd, J = 8.0, 2.0 Hz), 7.65 (1H, d, J = 8.0 Hz), 11.90 (1H, s).

[0735] Chemical Formula: $C_{15}H_{21}N_5O_3$, Molecular Weight: 319.36

[0736] Total H count from HNMR data: 21.

[0737] Step 4: Synthesis of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl)piperazine-1-carboxylate



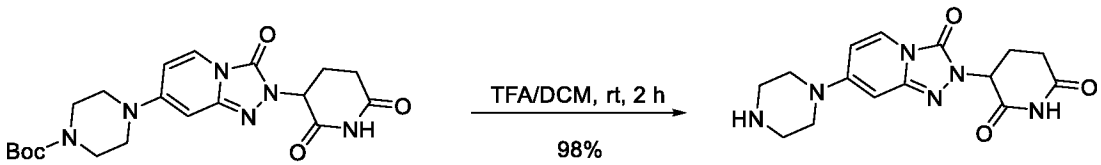
[0738] The solution of tert-butyl 4-(3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl)piperazine-1-carboxylate (320 mg, 1.0 mmol), 3-bromopiperidine-2,6-dione (390 mg, 2.0 mmol) and sodium tert-butoxide (120 mg, 1.2 mmol) in acetonitrale (20 mL) was stirred at 100 °C overnight. When it was cooled to room temperature, water (20 mL) was added. The resultant mixture was extracted by ethyl acetate (20 mL x 3), washed by brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by Prep-TLC (DCM/MeOH = 20/1) to give tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl)piperazine-1-carboxylate (100 mg, 23% yield) as a yellow solid.

[0739] ^1H NMR (400 MHz, DMSO-d_6) δ 1.47 (9H, s), 2.16-2.20 (1H, m), 2.47-2.50 (1H, m), 2.66-2.70 (1H, m), 2.90-2.99 (1H, m), 3.31-3.33 (4H, m), 3.47-3.49 (4H, m), 5.27-5.31 (1H, m), 6.20 (1H, d, J = 1.2 Hz), 6.73 (1H, dd, J = 7.6, 2.0 Hz), 7.80 (1H, d, J = 8.0 Hz), 11.11 (1H, s).

[0740] Chemical Formula: $C_{20}H_{26}N_6O_5$, Molecular Weight: 430.46.

[0741] Total H count from HNMR data: 26.

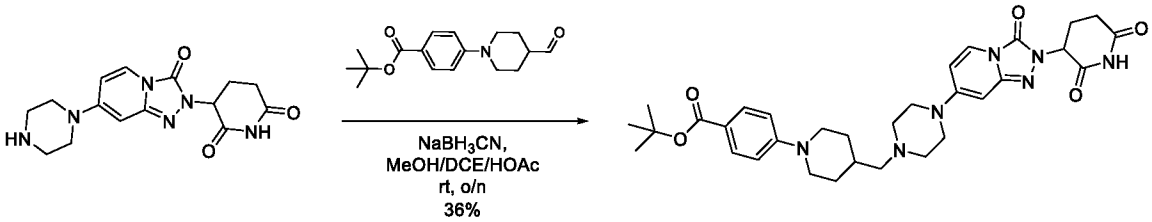
[0742] Step 5: Synthesis of 3-(3-oxo-7-(piperazin-1-yl)-[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)piperidine-2,6-dione



[0743] To a solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-

[1,2,4]triazolo[4,3-a]pyridin-7-yl)piperazine-1-carboxylate (0.40 g, 0.93 mmol) in dichloromethane (20 mL) was added TFA (8 mL), then stirred at room temperature for 2 h and concentrated *in vacuo* to give 3-(3-oxo-7-(piperazin-1-yl)-[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)piperidine-2,6-dione (0.30 g, 98%) as a yellow solid, which was used to the next step without further purification.

[0744] Step 6: Synthesis of tert-butyl 4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl)piperazin-1-yl)methyl)piperidin-1-yl)benzoate

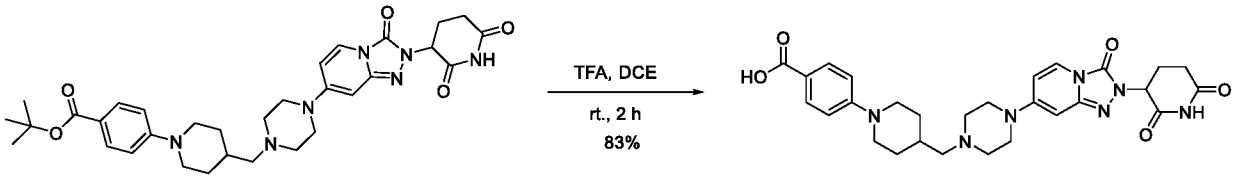


[0745] To a solution of 3-(3-oxo-7-(piperazin-1-yl)-[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)piperidine-2,6-dione (0.30 g, 0.91 mmol) in dry methanol/1,2-dichloroethane/HOAc (20 mL/4 mL/0.1 mL) was added tert-butyl 4-(4-formylpiperidin-1-yl)benzoate (0.26 g, 0.91 mmol). The mixture was left to stir for 30 min under N_2 gas. Then sodium cyanoborohydride (0.11 g, 1.82 mmol) was added and the reaction mixture was left to stir for 16 h at room temperature. The solvent was removed and the residue partitioned between dichloromethane and water, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give crude product. The residue was purified by prep-TLC to give compound tert-butyl 4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl)piperazin-1-yl)methyl)piperidin-1-yl)benzoate (0.20 g, 36%) as a yellow solid.

[0746] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (50 mm*4.6 mm*3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 90% [(total 10mM $AcONH_4$) water/CH_3CN=900/100 (v/v)] and 10% [(total 10mM $AcONH_4$) water/CH_3CN=100/900 (v/v)] to 10% [(total 10mM $AcONH_4$) water /CH_3CN=900/100 (v/v)] and 90% [(total 10mM $AcONH_4$) water/CH_3CN=100/900 (v/v)] in 1.6 min, then under this condition for 2.4 min, finally changed to 90% [(total 10mM $AcONH_4$) water/CH_3CN=900/100 (v/v)] and 10% [(total 10mM $AcONH_4$) water/CH_3CN=100/900 (v/v)] in 0.1 min and under this condition for 0.7 min). Purity is 87.07%, Rt = 2.195 min.; MS Calcd.: 603.3; MS Found: 604.4 $[M+H]^+$.

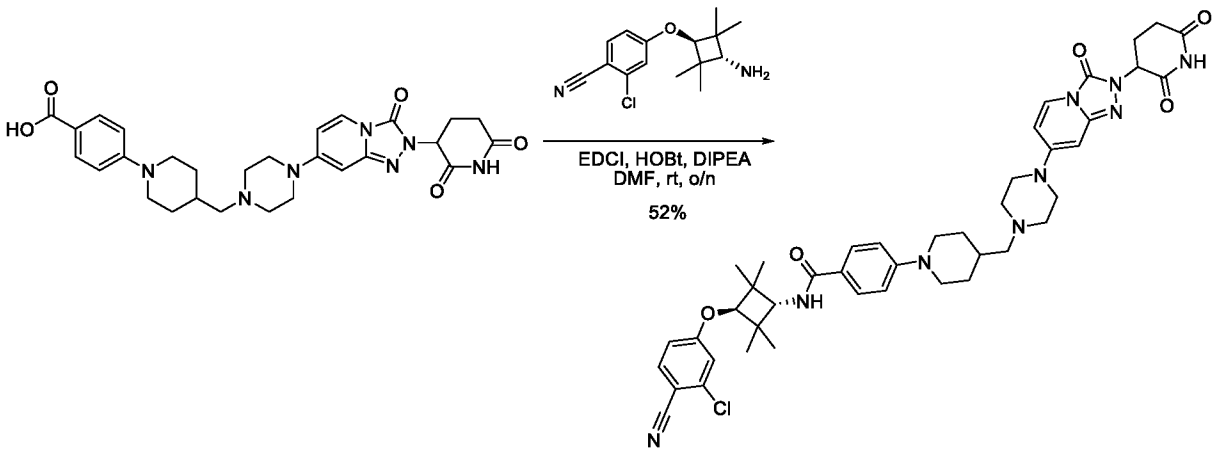
[0747] Step 7: Synthesis of 4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-

[1,2,4]triazolo[4,3-a]pyridin-7-yl)piperazin-1-yl)methyl)piperidin-1-yl)benzoic acid



[0748] To a solution of tert-butyl 4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl)piperazin-1-yl)methyl)piperidin-1-yl)benzoate (0.10 g, 0.16 mmol) in dichloromethane (10 mL) was added TFA (5 mL), then stirred at room temperature for 2 h, then concentrated *in vacuo* to give 4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl)piperazin-1-yl)methyl)piperidin-1-yl)benzoic acid (0.075 g, 83%) as a yellow solid, which was used to the next step without further purification.

[0749] Step 8: Synthesis of *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl)piperazin-1-yl)methyl)piperidin-1-yl)benzamide



[0750] A solution of 4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl)piperazin-1-yl)methyl)piperidin-1-yl)benzoic acid (75 mg, 0.14 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (39 mg, 0.21 mmol), 1-hydroxybenzotriazole hydrate (HOBt) (28 mg, 0.21 mmol) and ethyldiisopropylamine (88 mg, 0.69 mmol) in DMF (5 mL) was stirred for 30 min, and then 4-((1r,3r)-3-amino-2,2,4,4-tetramethylcyclobutoxy)-2-chlorobenzonitrile (38 mg, 0.14 mmol) was added. The mixture was stirred at room temperature overnight and water (10 mL) was added. The aqueous layer was extracted by dichloromethane (20 mL x 2). The combined organic layer was washed by brine (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue

was purified by prep-HPLC to give *N*-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl)piperazin-1-yl)methyl)piperidin-1-yl)benzamide (57 mg, 52%) as a white solid.

[0751] LC-MS (Agilent LCMS 1200-6120, Column: Waters X-Bridge C18 (50 mm*4.6 mm*3.5 μm); Column Temperature: 40 °C; Flow Rate: 2.0 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100% [CH_3CN] in 3.0 min, then under this condition for 1.0 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 0.7 min). Purity is 98.22%, Rt = 3.022 min; MS Calcd.: 807.4; MS Found: 808.3 $[M+H]^+$.

[0752] HPLC (Agilent HPLC 1200, Column: Waters X-Bridge C18 (150 mm*4.6 mm*3.5 μm); Column Temperature: 40 °C; Flow Rate: 1.0 mL/min; Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100% [CH_3CN] in 10 min, then under this condition for 5 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 5 min). Purity is 99.00%, Rt = 10.305 min.

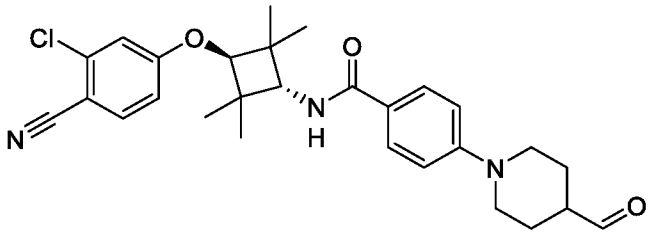
[0753] ^1H NMR (400 MHz, DMSO-d_6) δ 1.13 (6H, s), 1.22 (6H, s), 1.79-1.81 (3H, m), 2.09-2.15 (1H, m), 2.19-2.21 (2H, m), 2.49-2.50 (7H, m), 2.60-2.67 (1H, m), 2.76-2.92 (3H, m), 3.22-3.26 (4H, m), 3.86 (2H, d, *J* = 12.8 Hz), 4.05 (1H, d, *J* = 9.2 Hz), 4.32 (1H, s), 5.23 (1H, dd, *J* = 12.4, 5.2 Hz), 6.12 (1H, s), 6.70 (1H, dd, *J* = 8.0, 1.6 Hz), 6.95 (2H, d, *J* = 9.2 Hz), 7.00 (1H, dd, *J* = 8.8, 2.4 Hz), 7.21 (1H, d, *J* = 2.4 Hz), 7.48 (1H, d, *J* = 8.8 Hz), 7.72 (3H, t, *J* = 8.4 Hz), 7.91 (1H, d, *J* = 8.8 Hz), 11.04 (1H, s).

[0754] Chemical Formula: $C_{43}H_{50}ClN_9O_5$, Molecular Weight: 808.37.

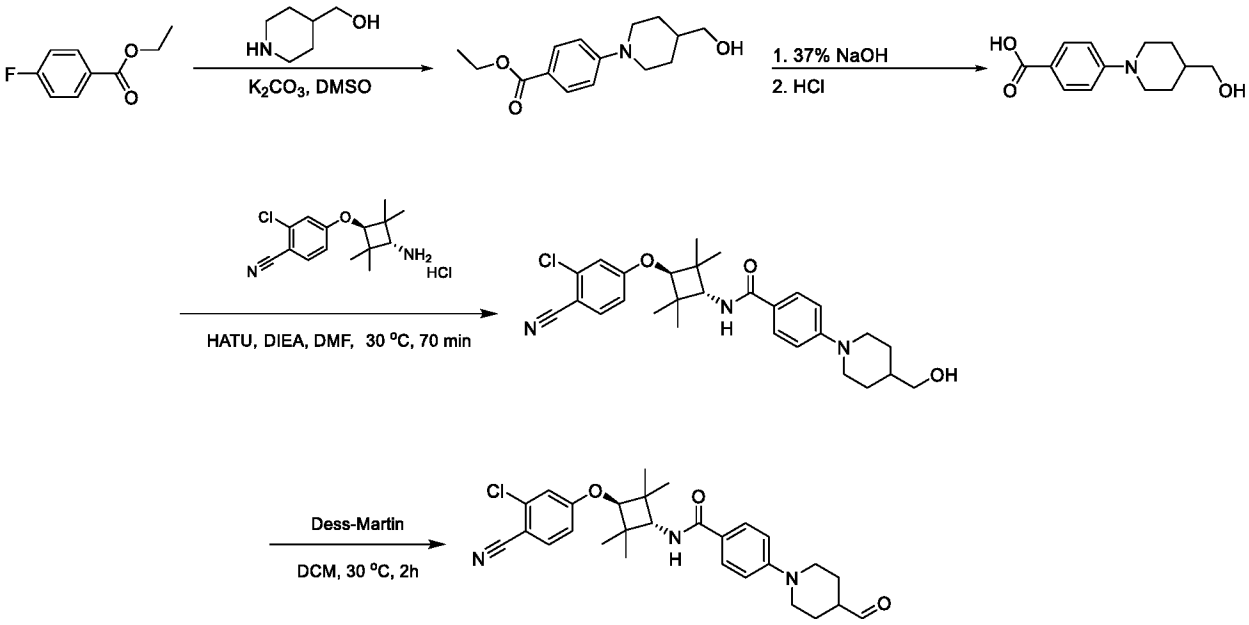
[0755] Total H count from HNMR data: 50.

[0756] **General Synthetic Scheme C-3**

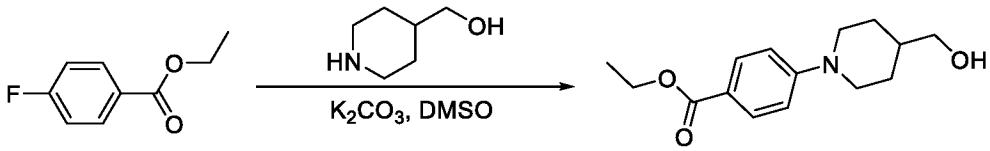
[0757] **Synthesis of building block N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-formylpiperidin-1-yl)benzamide**



[0758] Synthetic Scheme:



[0759] Step 1: Synthesis of Ethyl 4-(4-(hydroxymethyl)piperidin-1-yl)benzoate



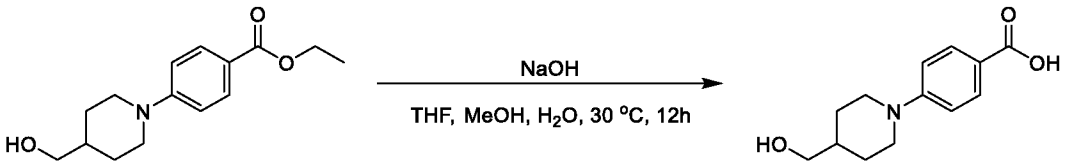
[0760] To a solution of ethyl 4-fluorobenzoate (27 g, 0.16 mol) in DMSO (500 mL) was added K_2CO_3 (44 g, 0.32 mol) and piperidin-4-ylmethanol (32 g, 0.19 mol) at 25°C. The resulting solution was stirred at 100 °C for 12 h. The reaction was diluted with H_2O (600 mL). The resulting mixture was extracted with EtOAc (200 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate and concentration. The crude product was slurry in PE/MTBE=1:1 to afford ethyl 4-(4-(hydroxymethyl)piperidin-1-yl)benzoate (30 g, 71% yield) as a white solid, which was used into next step without further purification.

[0761] Chemical Formula: $C_{15}H_{21}NO_3$; **Molecular Weight:** 263.34.

[0762] ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.30-4.35 (m, 2H), 3.90 (d, J = 12.8 Hz, 2H), 3.54 (d, J = 6.4 Hz, 2H), 2.82-2.89 (m, 2H), 1.85 (d, J = 12.8 Hz, 2H), 1.71-1.77 (m, 1H), 1.35-1.54 (m, 6H).

[0763] Total H count from ^{1}H NMR data: 21

[0764] Step 2: Synthesis of 4-(4-(Hydroxymethyl)piperidin-1-yl)benzoic acid



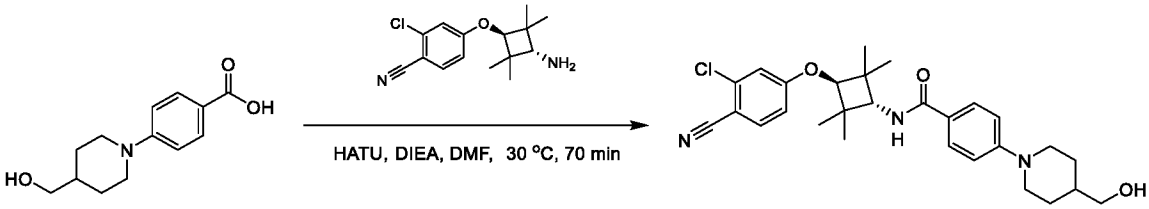
[0765] To a solution of ethyl 4-[4-(hydroxymethyl)-1-piperidyl]benzoate (52 g, 197.47 mmol, 1 *eq*) in tetrahydrofuran (250 mL), methanol (250 mL) and water (250 mL) was added sodium hydroxide (31.6 g, 0.79 mmol, 4 *eq*). The mixture was stirred at 30 °C for 12 hours. Thin layer chromatography (petroleum ether: ethyl acetate=1:1) showed the reaction was completed. The mixture was adjusted to pH 3~4 with hydrochloric acid (2 M) and filtered. The filter cake was dried in vacuum. The residue was triturated with ethyl acetate (500 mL) to give 4-[4-(hydroxymethyl)-1-piperidyl]benzoic acid (35 g, 148.76 mmol, 75% yield) as a white solid.

[0766] **^{1}H NMR:** (400MHz, DMSO-d_6) δ: 12.19 (s, 1H), 7.74 (d, J=8.8 Hz, 2H), 6.93 (d, J=8.8 Hz, 2H), 4.48 (br t, J=5.2 Hz, 1H), 3.90 (d, J=12.8 Hz, 2H), 3.27 (br t, J=5.2 Hz, 2H), 2.86 - 2.72 (m, 2H), 1.72 (d, J=12.8 Hz, 2H), 1.66 - 1.51 (m, 1H), 1.17 (dq, J=4.0, 12.0 Hz, 2H)

[0767] Chemical Formula: $C_{13}H_{17}NO_3$, Molecular Weight: 235.28.

[0768] Total H count from HNMR data: 17.

[0769] **Step 3: Synthesis of N-[3-(3-chloro-4-cyano-phenoxy)-2,2,4,4- tetramethyl-cyclobutyl]-4-[4-(hydroxymethyl)-1-piperidyl]benzamide**



[0770] To a solution of 4-[4-(hydroxymethyl)-1-piperidyl]benzoic acid (38 g, 161.51 mmol, 1 *eq*) and 4-(3-amino-2,2,4,4-tetramethyl-cyclobutoxy)-2-chloro-benzonitrile (50.9 g, 161.51 mmol, 1 *eq*, hydrochloride) in dimethylformamide (800 mL) was added diisopropylethylamine (83.5 g, 646.04 mmol, 112 mL, 4 *eq*). The mixture was stirred at 30°C for 10min, and then o-(7-azabenzotriazol-1-yl)-n,n,n',n'-tetramethyluronium hexafluorophosphate (64.48 g, 169.59 mmol, 1.05 *eq*) was added. The mixture was stirred at 30 °C for 1 hour. LCMS showed the reaction was completed and desired MS can be detected. The mixture was poured into water (4 L) and filtered. The filter cake was concentrated and triturated with methanol (500 mL x 2) to give N-[3-(3-chloro-4-cyano-phenoxy)-2,2,4,4-tetramethyl-cyclobutyl]-4- [4-(hydroxymethyl) -1-piperidyl]benzamide (72 g, 137.89 mmol, 85% yield, 95% purity) as a white solid.

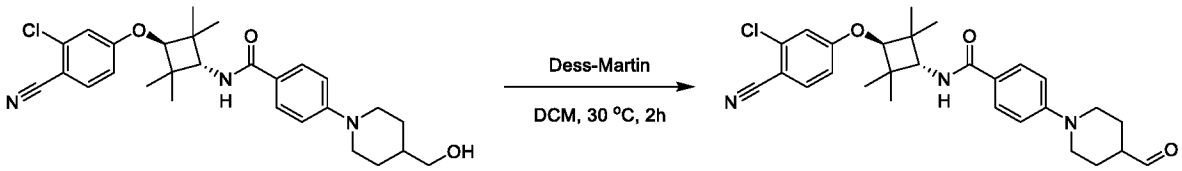
[0771] **LCMS:** MS (ESI) *m/z*: 496.1 $[M+1]^+$

[0772] **^{1}H NMR:** (400MHz, DMSO-d_6) *δ:* 7.90 (d, *J*=8.8 Hz, 1H), 7.73 (d, *J*=8.8 Hz, 2H), 7.48 (d, *J*=9.2 Hz, 1H), 7.20 (d, *J*=2.4 Hz, 1H), 7.00 (dd, *J*=2.4, 8.8 Hz, 1H), 6.95 (d, *J*=8.8 Hz, 2H), 4.48 (t, *J*=5.2 Hz, 1H), 4.31 (s, 1H), 4.05 (d, *J*=9.2 Hz, 1H), 3.86 (d, *J*=12.8 Hz, 2H), 3.27 (t, *J*=5.6 Hz, 2H), 2.80 - 2.70 (m, 2H), 1.73 (d, *J*=11.2 Hz, 2H), 1.63 - 1.52 (m, 1H), 1.27 - 1.15 (m, 8H), 1.12 (s, 6H).

[0773] Chemical Formula: $C_{28}H_{34}ClN_3O_3$, Molecular Weight: 496.04.

[0774] Total H count from HNMR data: 34.

[0775] **Step 4: Synthesis of N-[3-(3-chloro-4-cyano-phenoxy)-2,2,4,4- tetramethyl-cyclobutyl]-4-(4-formyl-1-piperidyl)benzamide**



[0776] To a solution of N-[3-(3-chloro-4-cyano-phenoxy)-2,2,4,4-tetramethyl-cyclobutyl]- 4-[4-(hydroxymethyl)-1-piperidyl]benzamide (65 g, 131.04 mmol, 1 *eq*) in dichloromethane (700 mL) was added Dess-Martin reagent (76.70 g, 180.83 mmol, 1.38 *eq*). The mixture was stirred at 30 °C for 2 hours. Thin layer chromatography (dichloromethane: methanol=1:1) showed the reaction was completed. The reaction was adjusted to pH 8~9 with saturated sodium bicarbonate. The mixture was diluted with water (3 L) and extracted with dichloromethane (1.5 L x 3). The combined organic phase was washed with saturated brine (1.5 L x 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (dichloromethane: methanol=100:0 to 50:1) to give N-[3-(3-chloro-4-cyano-phenoxy)-2,2,4,4-tetramethyl-cyclobutyl]-4-(4-formyl- 1-piperidyl)benzamide (34.6 g, 67.94 mmol, 51% yield, 97% purity) as a white solid.

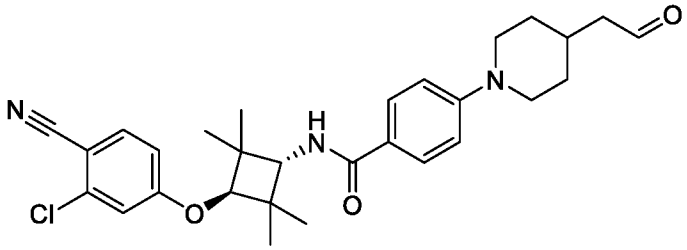
[0777] **^{1}H NMR:** (400MHz, DMSO-d_6) *δ:* 9.63 (s, 1H), 7.90 (d, *J*=8.8 Hz, 1H), 7.74 (d, *J*=8.8 Hz, 2H), 7.49 (d, *J*=9.2 Hz, 1H), 7.20 (d, *J*=2.4 Hz, 1H), 7.03 - 6.94 (m, 3H), 4.32 (s, 1H), 4.05 (d, *J*=9.2 Hz, 1H), 3.76 (td, *J*=3.6, 12.8 Hz, 2H), 3.01 - 2.92 (m, 2H), 2.62 - 2.55 (m, 1H), 2.62 - 2.55 (m, 1H), 1.92 (dd, *J*=3.6, 12.8 Hz, 2H), 1.62 - 1.48 (m, 2H), 1.21 (s, 6H), 1.12 (s, 6H).

[0778] Chemical Formula: $C_{28}H_{32}ClN_3O_3$, Molecular Weight: 494.02.

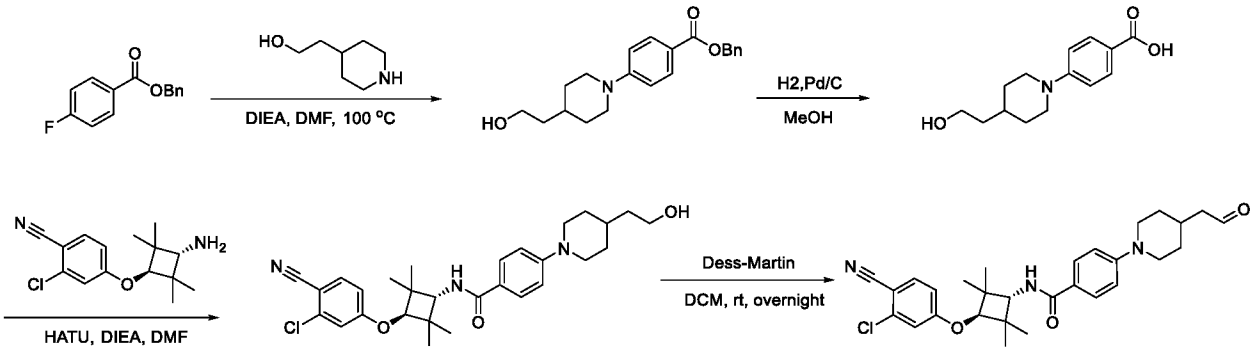
[0779] Total H count from HNMR data: 32.

[0780] **General Synthetic Scheme C-4**

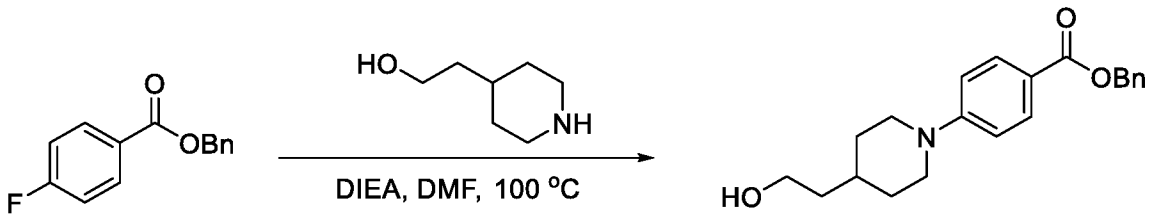
[0781] **Synthesis of building block N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-oxoethyl)piperidin-1-yl)benzamide**



[0782] **Synthetic Scheme:**



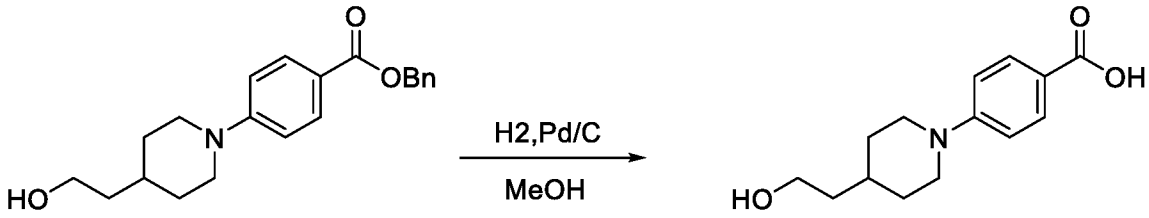
[0783] **Step 1: Synthesis of benzyl 4-[4-(2-hydroxyethyl)piperidin-1-yl]benzoate**



[0784] Into a 100-mL round-bottom flask, was placed benzyl 4-fluorobenzoate (2.3 g, 10.0 mmol, 1.0 equiv), N,N-dimethylformamide (30.0 mL), 2-(piperidin-4-yl)ethan-1-ol (1.3 g, 10.0 mmol, 1.0 equiv), N,N-Diisopropylethylamine (3.87 g, 29.9 mmol, 4.0 equiv). The resulting solution was stirred for 12 h at 90°C. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1/1). This resulted in 2.1 g (62%) of benzyl 4-[4-(2-hydroxyethyl)piperidin-1-yl]benzoate as a yellow solid.

[0785] LC-MS (ES^+): 340.25*m/z* [MH^+], t_R = 1.20min, (1.90 minute run).

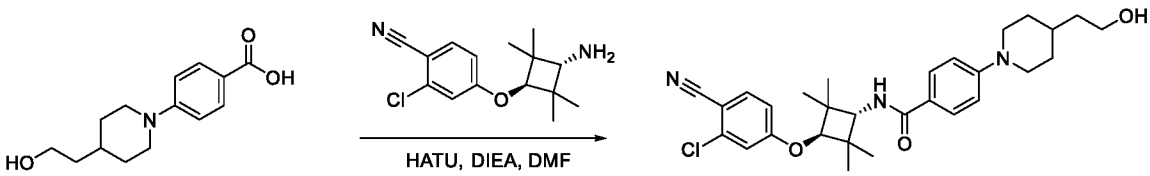
[0786] **Step 2: Synthesis of 4-[4-(2-hydroxyethyl)piperidin-1-yl]benzoic acid**



[0787] To a solution of benzyl 4-[4-(2-hydroxyethyl)piperidin-1-yl]benzoate (500 mg, 1.47 mmol, 1.00 equiv) in 20.0 mL methyl alcohol (30.0 mL)was added Pd/C (10%, 300 mg) under nitrogen atmosphere in a 100.0 mL round bottom flask. The flask was then vacuumed and flushed with hydrogen. The reaction mixture was hydrogenated at room temperature for 12 hours under hydrogen atmosphere using a hydrogen balloon, then filtered through a Celite pad and concentrated under reduced pressure. This resulted in 300.0m g (82.0%) of 4-[4-(2-hydroxyethyl)piperidin-1-yl]benzoic acid as a yellow solid.

[0788] LC-MS (ES^+): 250.00*m/z* [MH^+], t_R = 0.74min, (2.00 minute run).

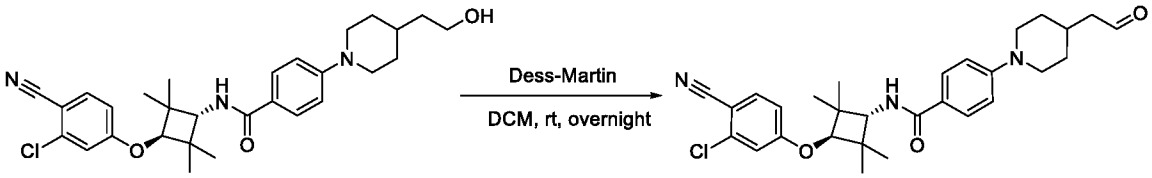
[0789] **Step 3: Synthesis of 4-[4-(2-hydroxyethyl)piperidin-1-yl]-N-[(1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide**



[0790] Into a 100-mL round-bottom flask, was placed 4-[4-(2-hydroxyethyl)piperidin-1-yl]benzoic acid (300.0 mg, 1.2 mmol, 2.0 equiv), N,N-dimethylformamide (10.0 g, 136.8 mmol, 227.0 equiv), N,N,N',N'-Tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophospate (686 mg, 1.8 mmol, 3.0 equiv), 2-chloro-4-[(1r,3r)-3-amino-2,2,4,4-tetramethylcyclobutoxy]benzonitrile hydrochloride (190.0 mg, 0.6 mmol, 1.0 equiv), N,N-Diisopropylethylamine (466.0 mg, 3.6 mmol, 6.0 equiv). The resulting solution was stirred for 1 h at room temperature. The reaction was then quenched by the addition of 60 mL of water. The resulting solution was extracted with 3x30 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 250.0 mg (81%) of 4-[4-(2-hydroxyethyl)piperidin-1-yl]-N-[(1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide as a yellow solid.

[0791] LC-MS (ES^+): 510.25*m/z* [MH^+], t_R = 1.35min, (1.90 minute run).

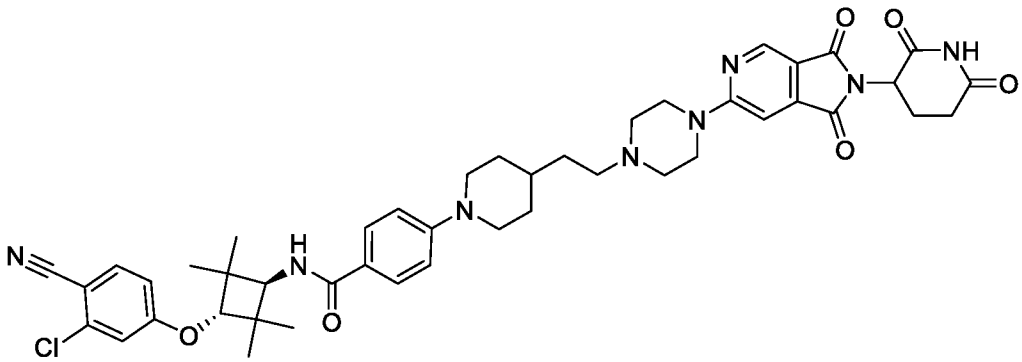
[0792] Step 4: Synthesis of 4-[4-(2-oxoethyl)piperidin-1-yl]-N-[(1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide



[0793] Into a 100-mL round-bottom flask, was placed 4-[4-(2-hydroxyethyl)piperidin-1-yl]-N-[(1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide (200.0 mg, 0.4 mmol, 1.0 equiv), dichloromethane (20.0 mL), Dess-Martin (249.0 mg, 0.60 mmol, 1.5 equiv). The resulting solution was stirred for 4 h at room temperature. The resulting solution was extracted with of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 80.0 mg (40%) of 4-[4-(2-oxoethyl)piperidin-1-yl]-N-[(1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide as a yellow solid.

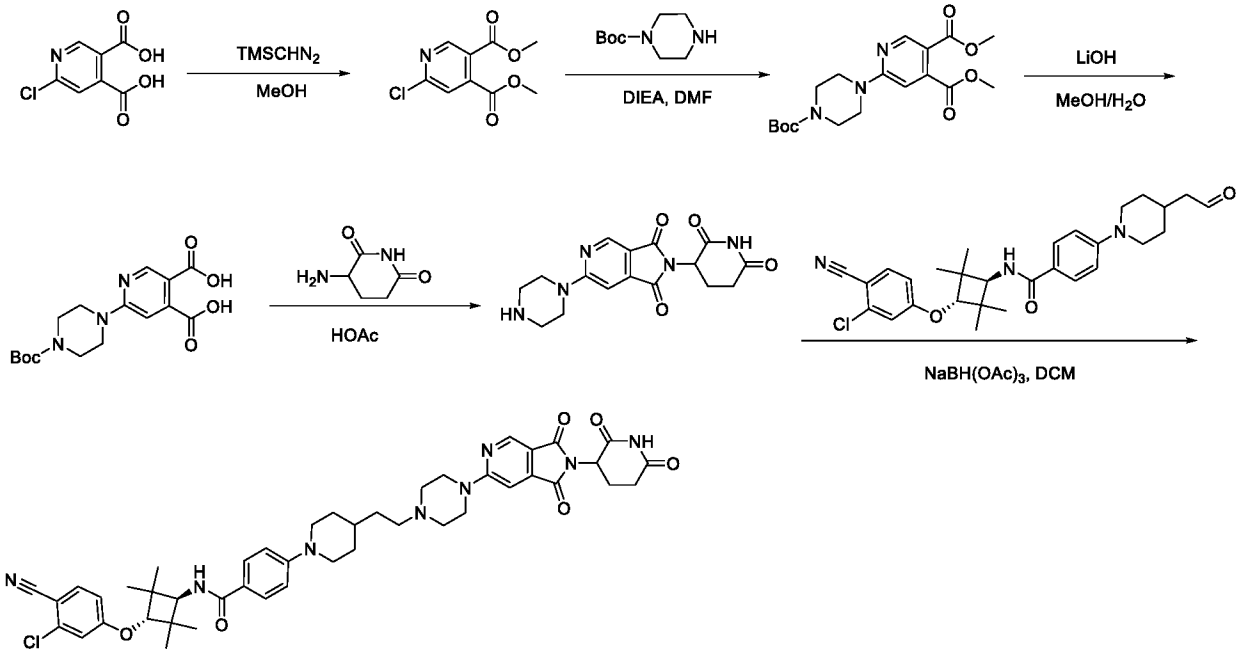
[0794] LC-MS (ES^+): 508.20*m/z* [MH^+], t_R = 1.19min, (2.00 minute run).

[0795] Exemplary Synthesis of Exemplary Compound 51

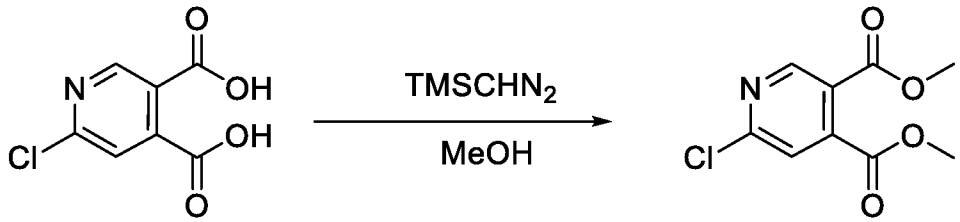


rac-N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)piperazin-1-yl)ethyl)piperidin-1-yl)benzamide

[0796] Synthetic scheme:



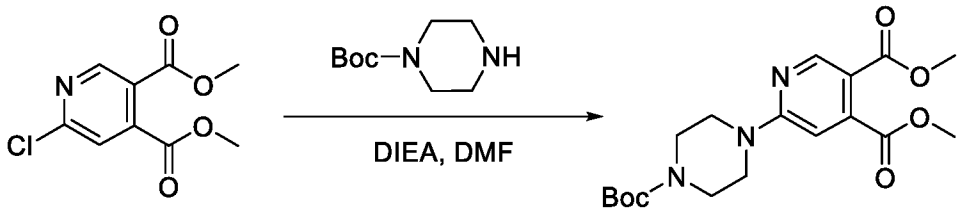
[0797] **Step 1: Synthesis of 3,4-dimethyl 6-chloropyridine-3,4-dicarboxylate**



[0798] Into a 100-mL round-bottom flask, was placed 6-chloropyridine-3,4-dicarboxylic acid (200.0 mg, 1.0 mmol, 1.0 equiv), methanol (5.0 mL), acetonitrile (5.0 mL), TMSCHN2 (2.0 mL), N,N-Diisopropylethylamine (516.0 mg, 4.0mmol, 4.0 equiv). The resulting solution was stirred for 2 h at room temperature. The reaction was then quenched by the addition of water (30mL). The resulting solution was extracted with ethyl acetate (20.0 mL x 3)and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1). The resulting mixture was concentrated under vacuum. This resulted in 220 mg (96%) of 3,4-dimethyl 6-chloropyridine-3,4-dicarboxylate as a yellow solid.

[0799] LC-MS (ES^+): 230.10*m/z* [MH^+], t_R = 1.01min, (1.90 minute run).

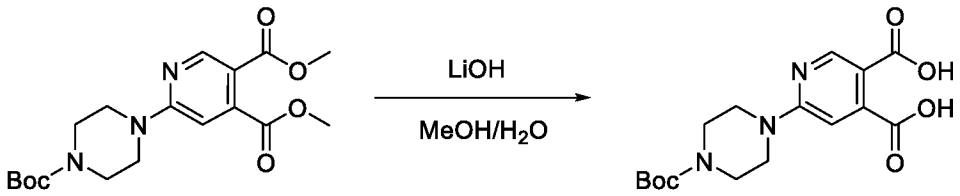
[0800] **Step 2: Synthesis of 3,4-dimethyl 6-[4-[(tert-butoxy)carbonyl]piperazin-1-yl]pyridine-3,4-dicarboxylate**



[0801] Into a 100-mL round-bottom flask, was placed 3,4-dimethyl 6-chloropyridine-3,4-dicarboxylate (200.0 mg, 0.9 mmol, 1.0 equiv), N,N-dimethylformamide (5.0 mL), tert-butyl piperazine-1-carboxylate (325.0 mg, 1.7 mmol, 2.0 equiv), N,N-Diisopropylethylamine (450.0 mg, 3.5 mmol, 4.0 equiv). The resulting solution was stirred for 2 h at 100°C. The reaction was then quenched by the addition of water(80mL). The resulting solution was extracted with ethyl acetate (30.0 mL x3) and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:3). This resulted in 320.0 mg (97%) of 3,4-dimethyl 6-[4-[(tert-butoxy)carbonyl]piperazin-1-yl]pyridine-3,4-dicarboxylate as a yellow solid.

[0802] LC-MS (ES^+): 380.10*m/z* [MH^+], t_R = 1.19min, (2.0 minute run).

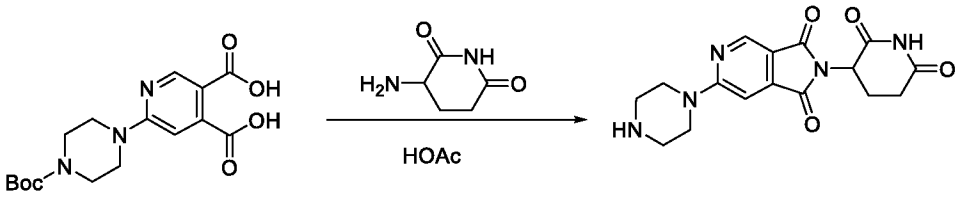
[0803] Step 3: Synthesis of 6-[4-[(tert-butoxy)carbonyl]piperazin-1-yl]pyridine-3,4-dicarboxylic acid



[0804] Into a 100-mL round-bottom flask, was placed 3,4-dimethyl 6-[4-[(tert-butoxy)carbonyl]piperazin-1-yl]pyridine-3,4-dicarboxylate (320.0 mg, 0.8 mmol, 1.0 equiv), methanol (10.0 mL), water(5 mL), lithium hydroxide (96 mg, 4 mmol, 5 equiv). The resulting solution was stirred for 5 h at room temperature. The resulting mixture was concentrated under vacuum. This resulted in 300.0 mg (101%) of 6-[4-[(tert-butoxy)carbonyl]piperazin-1-yl]pyridine-3,4-dicarboxylic acid as a white solid.

[0805] LC-MS (ES^+): 296.20*m/z* [MH^+], t_R = 0.52min, (1.90 minute run).

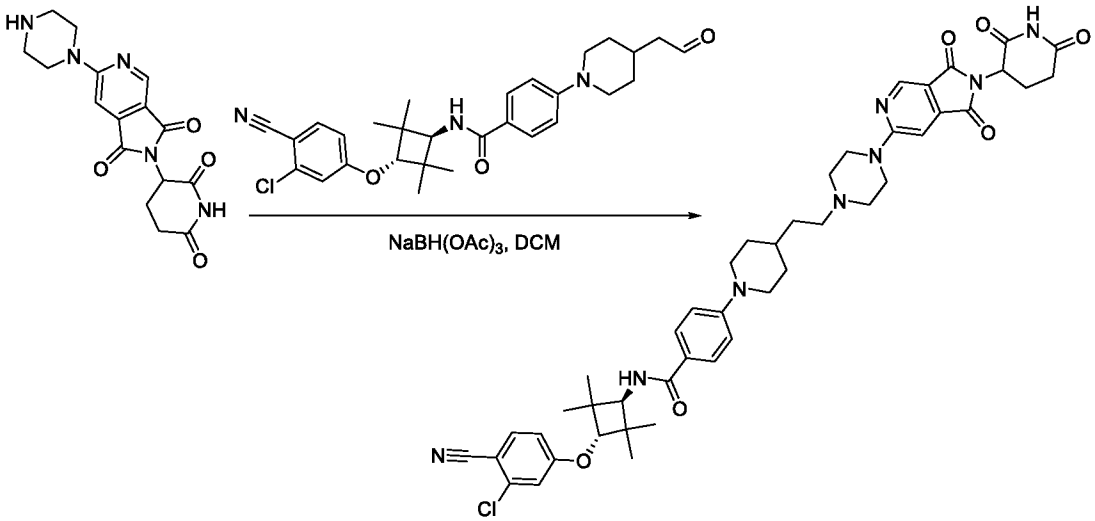
[0806] Step 4: Synthesis of 3-[1,3-dioxo-6-(piperazin-1-yl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-2-yl]piperidine-2,6-dione



[0807] Into a 100-mL round-bottom flask, was placed 6-[4-[(tert-butoxy)carbonyl]piperazin-1-yl]pyridine-3,4-dicarboxylic acid (300.0 mg, 0.8 mmol, 1.0 equiv), acetic acid (20.0 mL), 3-aminopiperidine-2,6-dione (218 mg, 1.7 mmol, 2.0 equiv). The resulting solution was stirred for 2 h at 130°C. The reaction was then quenched by the addition of water (30 mL). The resulting solution was extracted with ethyl acetate (30 mL x3)and the organic layers combined and dried in an oven under reduced pressure. and concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (3:1). This resulted in 60.0 mg (20%) of 3-[1,3-dioxo-6-(piperazin-1-yl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-2-yl]piperidine-2,6-dione as a yellow solid.

[0808] LC-MS (ES^+): 344.20*m/z* [MH^+], t_R = 0.66min, (1.90 minute run).

[0809] **Step 5: Synthesis of 4-[4-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]piperazin-1-yl]ethyl)piperidin-1-yl]-N-[(1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide**



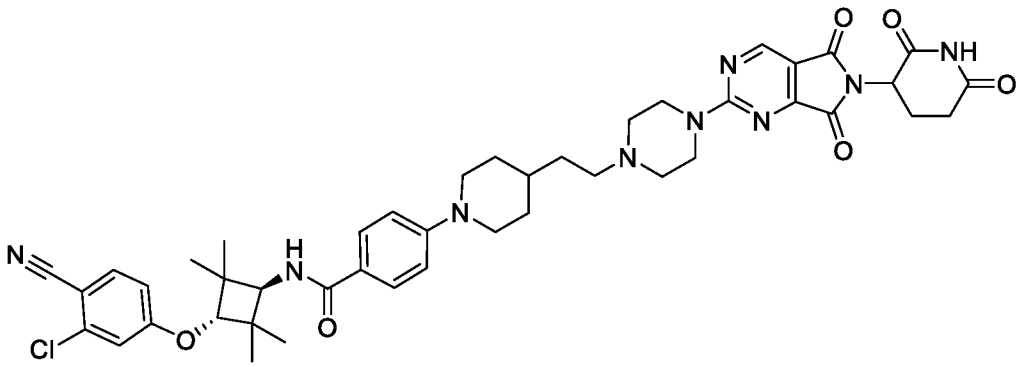
[0810] Into a 100-mL round-bottom flask, was placed 3-[1,3-dioxo-6-(piperazin-1-yl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-2-yl]piperidine-2,6-dione hydrochloride (60.0 mg, 0.2mmol, 1.0 equiv), dichloromethane (10 mL), 4-[4-(2-oxoethyl)piperidin-1-yl]-N-[(1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide (80.0 mg, 0.1 mmol, 1.0 equiv),

Sodium triacetoxyborohydride (110.0 mg, 3.0 equiv). The resulting solution was stirred for 4 h at room temperature. The reaction was then quenched by the addition of 40 mL of water. The resulting solution was extracted with dichloromethane (20 mL x 3)and the organic layers combined and concentrated under vacuum. The crude product (4.0 mL) was purified by Prep-HPLC with the following conditions: Column, Sunfire Prep C18 OBD Column,, 10um,19*250mm; mobile phase, Water(0.1% formic acid) and acetonitrile (30.0% acetonitrile up to 52.0% in 8 min); Detector, UV 254nm. 5.0 mL product was obtained. This resulted in 50.5 mg (38.2%) of 4-[4-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]piperazin-1-yl]ethyl)piperidin-1-yl]-N-[(1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide as a yellow solid.

[0811] 1H NMR (300 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.57 (s, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 9.1 Hz, 1H), 7.29 (s, 1H), 7.17 (d, J = 2.2 Hz, 1H), 7.02-6.87 (m, 3H), 5.07 (dd, J = 12.8, 5.3 Hz, 1H), 4.29 (s, 1H), 4.02 (d, J = 9.1 Hz, 1H), 3.28 (s, 5H), 2.59-2.41 (m, 9H), 2.00 (t, J = 11.3 Hz, 1H), 1.73 (d, J = 12.8 Hz, 2H), 1.45 (s, 3H), 1.14 (d, J = 27.2 Hz, 14H).

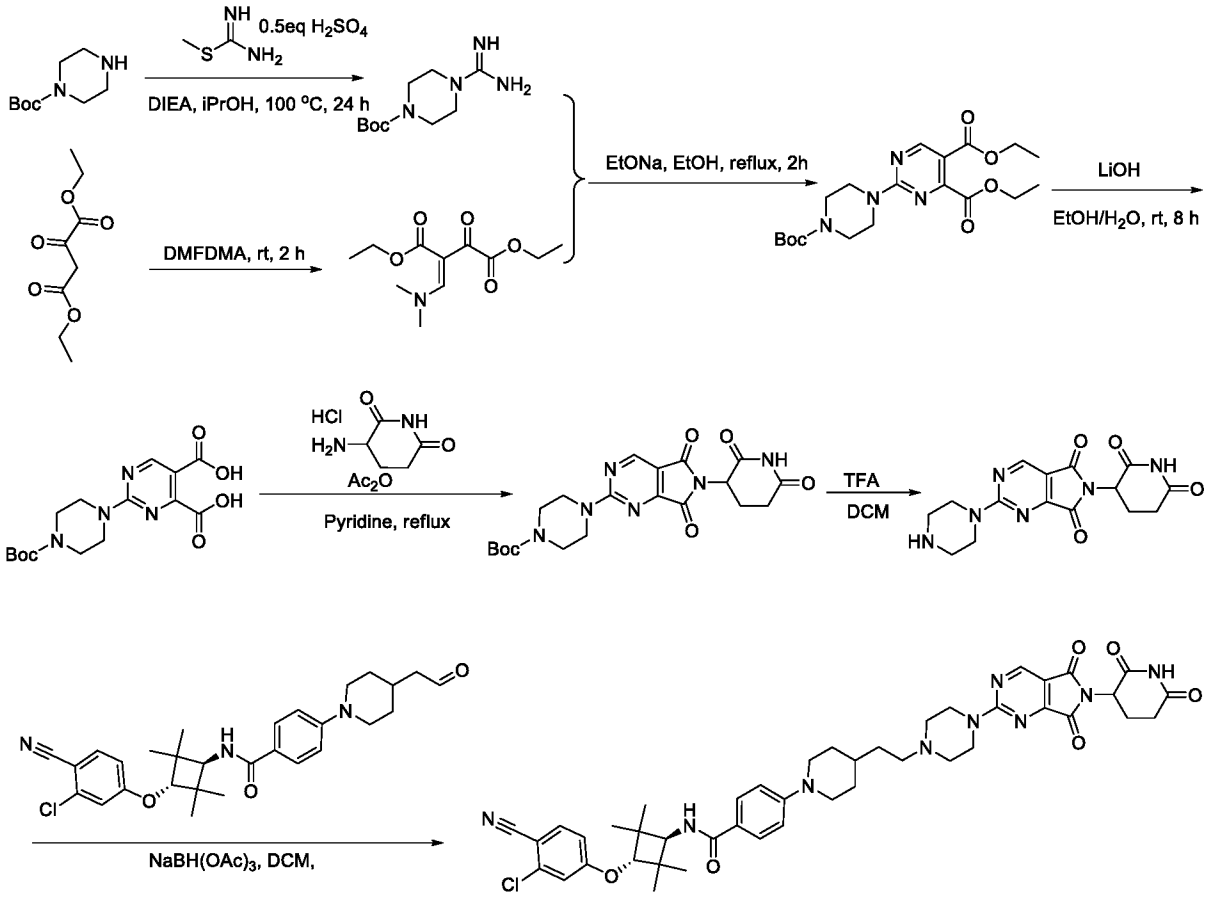
[0812] LC-MS (ES^+): 835.25*m/z* [MH^+], t_R = 2.56min, (4.80minute run).

[0813] **Exemplary Synthesis of Exemplary Compound 52**

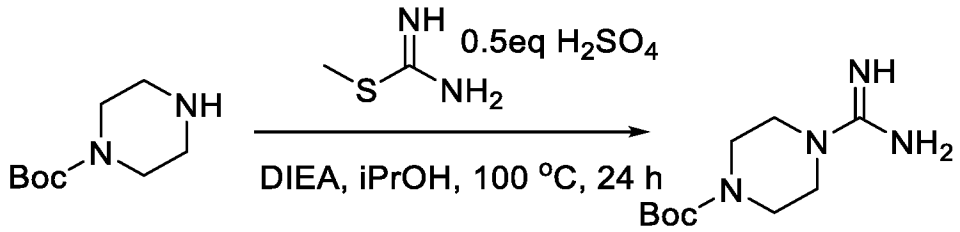


(rac)-N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(4-(6-(2,6-dioxopiperidin-3-yl)-5,7-dioxo-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)piperazin-1-yl)ethyl)piperidin-1-yl)benzamide

[0814] **Synthetic scheme:**

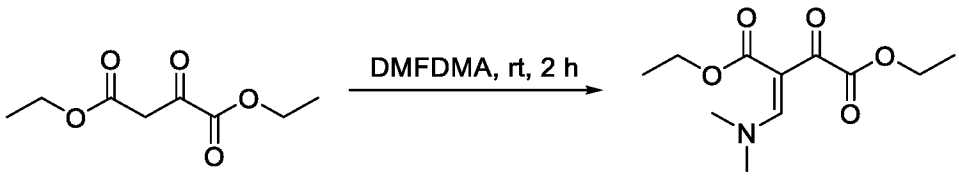


[0815] Step 1: Synthesis of tert-butyl 4-carbamimidoylpiperazine-1-carboxylate



[0816] Into a 250-mL round-bottom flask, was placed tert-butyl piperazine-1-carboxylate (10 g, 53.69 mmol, 1.00 equiv), i-propanol (150 mL), (methylsulfanyl)methanimidamide (7.4 g, 82.09 mmol, 1.00 equiv), DIEA (25 mL, 3.00 equiv). The resulting solution was stirred for 24 h at 100°C in an oil bath. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with acetonitrile (150 mL), then stirred for 30 min. The solids were collected by filtration. This resulted in 11.5 g (94%) of tert-butyl 4-carbamimidoylpiperazine-1-carboxylate as a white solid.

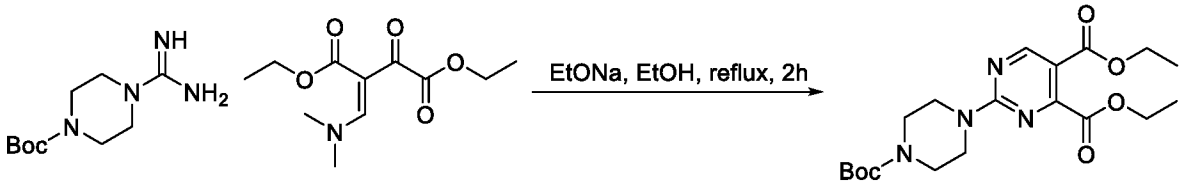
[0817] Step 2: Synthesis of 1,4-diethyl (2Z)-2-[(dimethylamino)methylidene]-3-oxobutanedioate



[0818] Into a 250-mL round-bottom flask, was placed 1,4-diethyl 2-oxobutanedioate (10 g, 53.14 mmol, 1.00 equiv), DMFDMA (12.65 g, 106.30 mmol, 2.00 equiv) at 0 °C. The resulting solution was stirred for 2 h at room temperature. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (7/3). This resulted in 2.79 g (22%) of 1,4-diethyl (2Z)-2-[(dimethylamino)methylidene]-3-oxobutanedioate as yellow oil.

[0819] LC-MS (ES^+): m/z 243.95 [MH^+], t_R =0.64min, (1.90minute run).

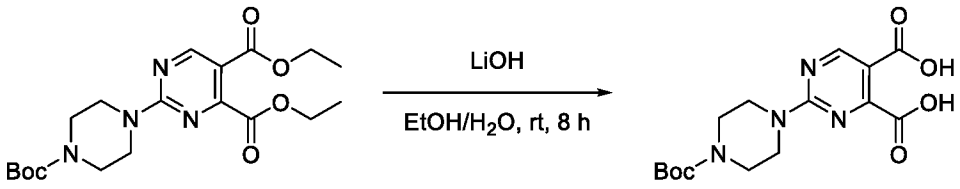
[0820] **Step 3: Synthesis of 4,5-diethyl 2-[4-[(tert-butoxy)carbonyl]piperazin-1-yl]pyrimidine-4,5-dicarboxylate**



[0821] Into a 250-mL round-bottom flask, was placed tert-butyl 4-carbamimidoylpiperazine-1-carboxylate (1.0 g, 4.38 mmol, 1.00 equiv), ethanol (20 mL), 1,4-diethyl (2Z)-2-[(dimethylamino)methylidene]-3-oxobutanedioate (1.065 g, 4.38 mmol, 1.00 equiv), EtONa (596 mg, 8.76 mmol, 1.00 equiv). The resulting solution was stirred for 2 h at 75°C in an oil bath. The resulting mixture was concentrated under vacuum. The resulting solution was extracted with ethyl acetate (100 mL) and the organic layers combined. The resulting mixture was washed with brine (100 mL). The mixture was dried over anhydrous sodium sulfate. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1/5). This resulted in 873.0 mg (49%) of 4,5-diethyl 2-[4-[(tert-butoxy)carbonyl]piperazin-1-yl]pyrimidine-4,5-dicarboxylate as light yellow oil.

[0822] LC-MS (ES^+): m/z 409.20 [MH^+], t_R = 1.19min, (1.90minute run).

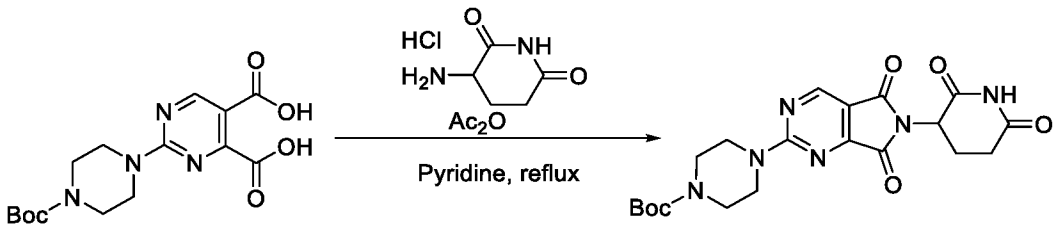
[0823] **Step 4: Synthesis of2-[4-[(tert-butoxy)carbonyl]piperazin-1-yl]pyrimidine-4,5-dicarboxylic acid**



[0824] Into a 100-mL round-bottom flask, was placed 4,5-diethyl 2-[4-[(tert-butoxy)carbonyl]piperazin-1-yl]pyrimidine-4,5-dicarboxylate (873.0 mg, 2.14 mmol, 1.00 equiv), ethanol/water(5/2) (14 mL), lithium hydroxide (256.7 mg, 10.72 mmol, 5.00 equiv). The resulting solution was stirred for 8 h at room temperature. The resulting mixture was concentrated under vacuum. This resulted in 1.02 g (crude) of 2-[4-[(tert-butoxy)carbonyl]piperazin-1-yl]pyrimidine-4,5-dicarboxylic acid as a white solid.

[0825] LC-MS (ES^+): m/z 352.45 [MH^+], t_R = 0.73min, (1.90minute run).

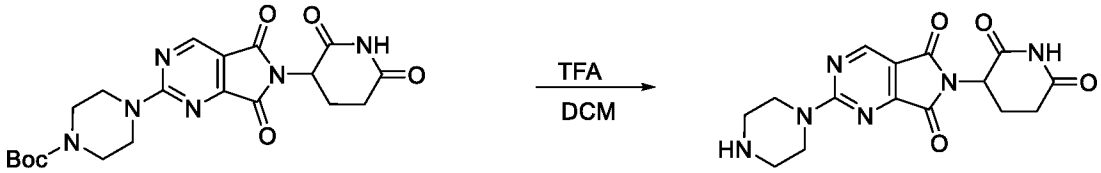
[0826] **Step 5: Synthesis of tert-butyl 4-[6-(2,6-dioxopiperidin-3-yl)-5,7-dioxo-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]piperazine-1-carboxylate**



[0827] Into a 100-mL round-bottom flask, was placed 2-[4-[(tert-butoxy)carbonyl]piperazin-1-yl]pyrimidine-4,5-dicarboxylic acid (735.0 mg, 2.09 mmol, 1.00 equiv). This was followed by the addition of acetic anhydride (10 mL), after stirred 2h at 130 °C, concentrated under vacuum. To this was added pyridine (10 mL), 3-aminopiperidine-2,6-dione hydrochloride (445.0 mg, 2.70 mmol, 1.30 equiv). The resulting solution was stirred overnight at 120°C in an oil bath. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with dichloromethane (100 mL). The solids were filtered out. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (7/3). This resulted in 243.0 mg (26%) of tert-butyl 4-[6-(2,6-dioxopiperidin-3-yl)-5,7-dioxo-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]piperazine-1-carboxylate as brown oil.

[0828] LC-MS (ES^+): m/z 467.10 [M Na^+], t_R = 1.10min, (2.00minute run).

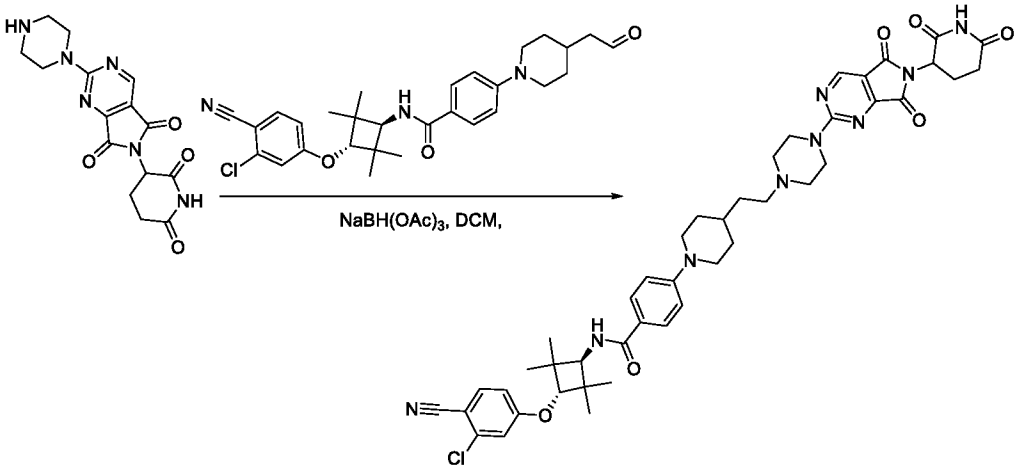
[0829] **Step 6: Synthesis of3-[5,7-dioxo-2-(piperazin-1-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]piperidine-2,6-dione**



[0830] Into a 50-mL round-bottom flask, was placed tert-butyl 4-[6-(2,6-dioxopiperidin-3-yl)-5,7-dioxo-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]piperazine-1-carboxylate (243.0 mg, 0.55 mmol, 1.00 equiv), dichloromethane (5.0 mL), trifluoroacetic acid (2.0 mL). The resulting solution was stirred for 2 h at room temperature. The resulting mixture was concentrated under vacuum. This resulted in 320.0 mg (crude) of 3-[5,7-dioxo-2-(piperazin-1-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]piperidine-2,6-dione as brown oil.

[0831] LC-MS (ES^+): m/z 345.25 [MH^+], t_R = 0.61min, (1.90minute run).

[0832] **Step 7: Synthesis of 4-[4-(2-[4-[6-(2,6-dioxopiperidin-3-yl)-5,7-dioxo-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]piperazin-1-yl]ethyl)piperidin-1-yl]-N-[(1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide**



[0833] Into a 100-mL round-bottom flask, was placed 4-[4-(2-oxoethyl)piperidin-1-yl]-N-[(1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide (90 mg, 0.18 mmol, 1.00 equiv), dichloromethane (10 mL), 3-[5,7-dioxo-2-(piperazin-1-yl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-6-yl]piperidine-2,6-dione (61.24 mg, 0.18 mmol, 1.00 equiv). This was followed by the addition of DIEA (0.5 mL), after stirred at 30 ℃ for 1h. To this was added $NaBH(OAc)_3$ (122.89 mg, 0.58 mmol, 3.00 equiv). The resulting solution was stirred for 5 h at 30 ℃in an oil bath. The resulting solution was extracted with dichloromethane (150 mL) and the organic layers combined. The resulting mixture was washed with brine (50 mL). The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product

was purified by Prep-HPLC with the following conditions: Column, XBridge Prep C18 OBD Column, 5um, 19*150 mm; mobile phase, water (10mmol/L bicarbonate amine) and acetonitrile (30.0% acetonitrile up to 51.0% in 8 min); Detector, UV 254nm. This resulted in 50 mg (34%) of 4-[4-(2-[4-[6-(2,6-dioxopiperidin-3-yl)-5,7-dioxo-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]piperazin-1-yl]ethyl)piperidin-1-yl]-N-[(1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl]benzamide as a yellow solid.

[0834] ^{1}H NMR (400 MHz, *d6*-DMSO): δ11.12 (s, 1H), 8.90 (s, 1H), 7.91-7.89 (d, *J*=8.4Hz, 1H), 7.74-7.72 (d, *J*=7.6Hz, 2H), 7.49-7.47 (d, *J*=8.8Hz, 1H), 7.20 (s, 1H), 6.99-6.94 (m, 3H), 5.16-5.13 (m, 1H), 4.32 (s, 1H), 4.06-3.83 (m, 7H), 2.88-2.57 (m, 5H), 2.39-2.33 (m, 2H), 2.07-2.01 (m, 1H), 1.78-1.75 (m, 2H), 1.54-1.35 (m, 3H), 1.21 (m, 8H), 1.12 (s, 6H); LC-MS (ES^+): m/z 836.45/838.45 [MH^+], t_R = 2.17min, (2.95minute run).

[0835] Chemical formula: $C_{44}H_{50}ClN_9O_6$ [835.36/837.36].

[0836] Total H count from HNMR data: 50.

[0837] **D. Exemplary Synthetic Schemes for Exemplary BRaf Targeting Moiety Based Compounds**

[0838] General Synthetic Approach

[0839] The synthetic realization and optimization of the bifunctional molecules as described herein may be approached in a step-wise or modular fashion. For example, identification of compounds that bind to the target molecules can involve high or medium throughput screening campaigns if no suitable ligands are immediately available. It is not unusual for initial ligands to require iterative design and optimization cycles to improve suboptimal aspects as identified by data from suitable in vitro and pharmacological and/or ADMET assays. Part of the optimization/SAR campaign would be to probe positions of the ligand that are tolerant of substitution and that might be suitable places on which to attach the linker chemistry previously referred to herein. Where crystallographic or NMR structural data are available, these can be used to focus such a synthetic effort.

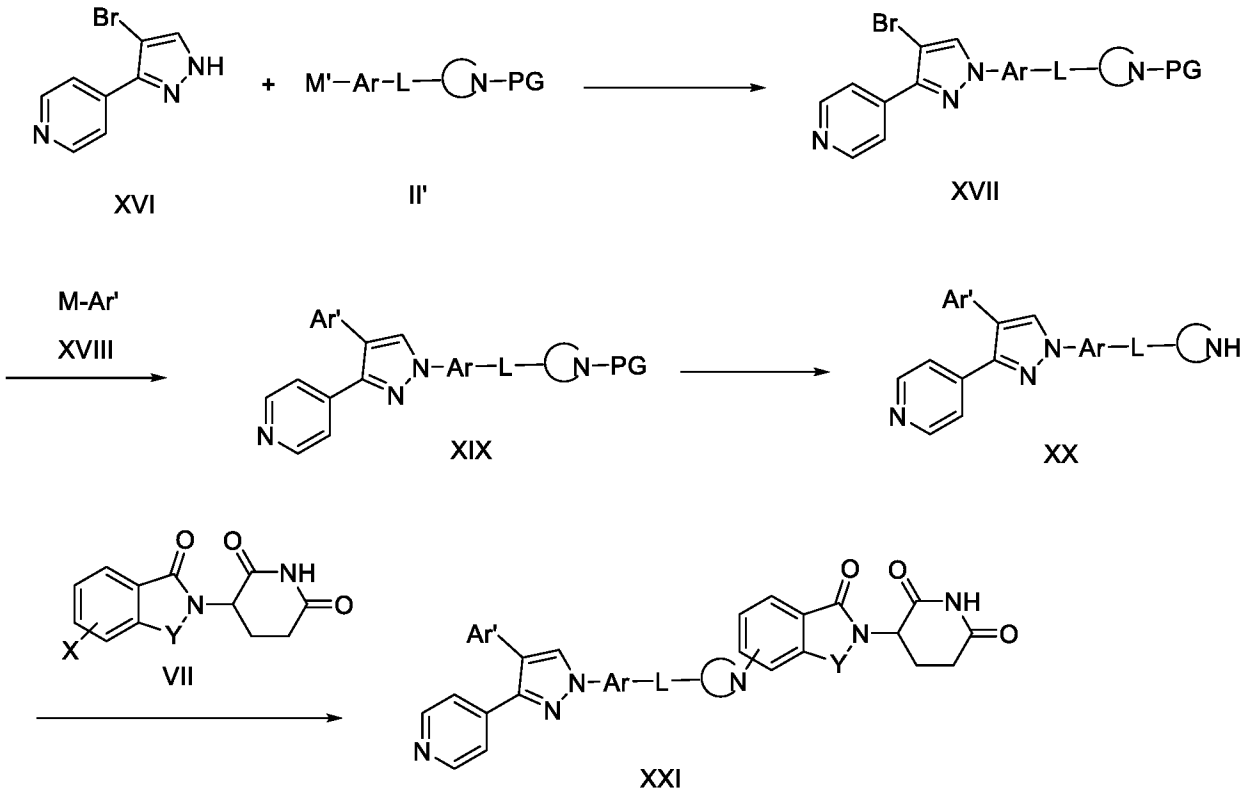
[0840] In a very analogous way one can identify and optimize ligands for an E3 Ligase, i.e. ULMs/ILMs/VLMs/CLMs/ILMs.

[0841] With PTMs and ULMs (e.g. ILMs, VLMs, CLMs, and/or ILMs) in hand, one skilled in the art can use known synthetic methods for their combination with or without a linker moiety. Linker moieties can be synthesized with a range of compositions, lengths and flexibility and

functionalized such that the PTM and ULM groups can be attached sequentially to distal ends of the linker. Thus a library of bifunctional molecules can be realized and profiled in in vitro and in vivo pharmacological and ADMET/PK studies. As with the PTM and ULM groups, the final bifunctional molecules can be subject to iterative design and optimization cycles in order to identify molecules with desirable properties.

[0842] In some instances, protecting group strategies and/or functional group interconversions (FGIs) may be required to facilitate the preparation of the desired materials. Such chemical processes are well known to the synthetic organic chemist and many of these may be found in texts such as "Greene's Protective Groups in Organic Synthesis" Peter G. M. Wuts and Theodora W. Greene (Wiley), and "Organic Synthesis: The Disconnection Approach" Stuart Warren and Paul Wyatt (Wiley).

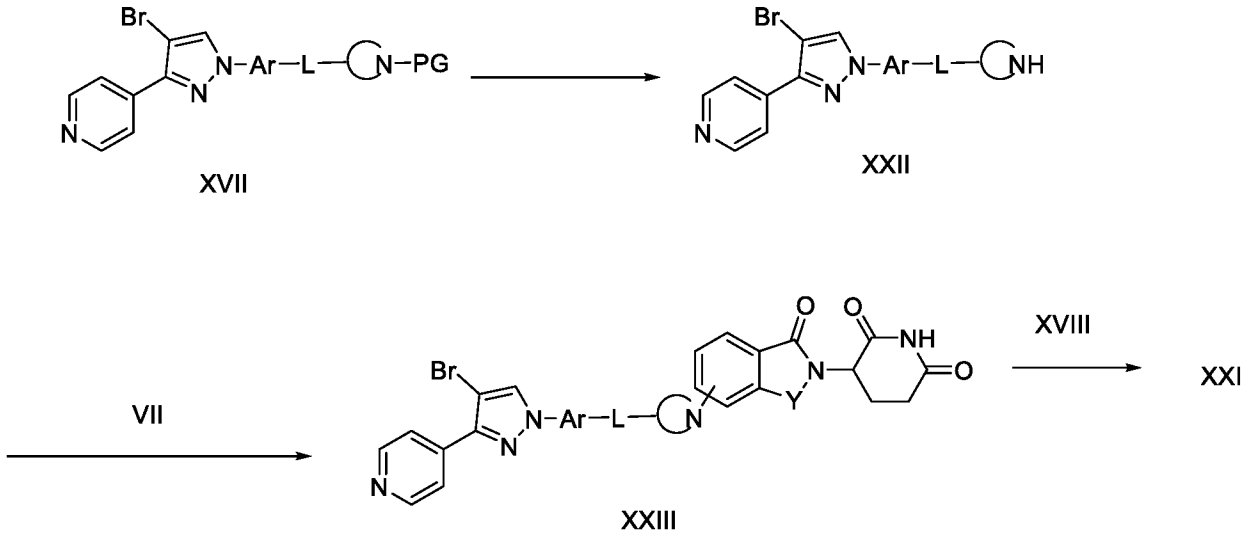
[0843] General Synthetic Scheme D-1



[0844] A compound of formula XVI may be reacted with a reagent II' (commercially available or readily prepared using standard reaction techniques known to one skilled in the art) under Chan-Lam cross-coupling conditions, e.g. copper (II) acetate, pyridine or diethylamine or triethylamine, 100 °C, to produce a compound of formula XVII. M' represents a boronic acid or

boronic ester; Ar represents an aromatic or heteroaromatic ring system; L represents an optional linker, represents a primary or secondary amine, optionally cyclized into a 4 to 8 membered heterocyclic ring, wherein PG represents a suitable protecting group, including but not limited to t-butoxycarbonyl or benzyl. Compounds of formula XVII may be may be reacted with a reagent XVIII under palladium-catalyzed cross-coupling conditions, e.g. [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium, tri-tert-butylphosphine tetrafluoroborate, cesium fluoride, 1,4-dioxane, 90 °C, to produce a compound of formula XIX. M represents a functional group capable of undergoing palladium-catalyzed transmetallation, e.g. a boronic acid, boronic ester, or trialkylstannane and Ar' represents an aromatic or heteroaromatic ring system with optional substituents. A compound of formula XIX may then be converted to a compound of formula XX by treatment with a reagent suitable for the removal of PG, e.g. hydrogen chloride in 1,4-dioxane or methanol when PG is t-butyl. A compound of formula XX may also be reacted with a compound of formula VII to provide compounds of formula XXI, wherein X is a suitable leaving group such as fluorine or chlorine, Y is C=O, the aromatic ring of VII may have further optional substituents, and reaction conditions are those for a nucleophilic aromatic substitution, e.g. triethylamine, DMSO, 80 °C. In cases where the group Ar' contains optional substituents, e.g. a ketone, these may undergo further functionalization, e.g. by treatment with hydroxylamine hydrochloride and pyridine at room temperature, to provide further compounds of formula XXI.

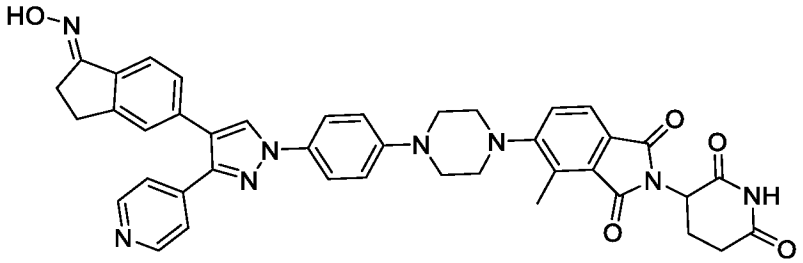
[0845] General Synthetic Scheme D-2



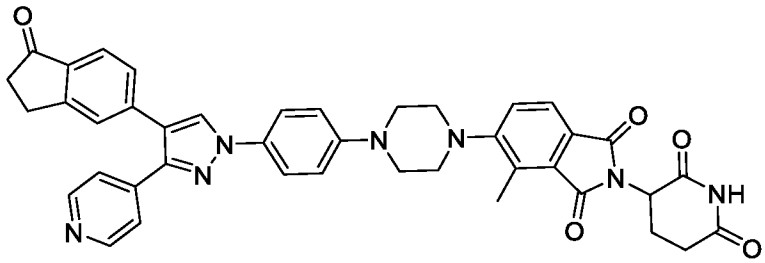
[0846] Alternatively, a compound of formula XVII may be converted to a compound of formula XXII by using conditions analogous to those for the conversion of XIX to XX in Scheme 5. A compound of formula XXII may then be treated with a compound of formula VII as defined in Scheme 5 to produce a compound of formula XXIII. The compound of formula XXIII may then be treated with a reagent XVIII as defined in Scheme 5 to produce a compound of formula XXI. In cases where the group Ar' contains optional substituents, e.g. a ketone, these may undergo further functionalization, e.g. by treatment with hydroxylamine hydrochloride and pyridine at room temperature, to provide further compounds of formula XXI.

[0847] **Exemplary Synthesis of Exemplary Compound 42:**

[0848] (E)-2-(2,6-dioxopiperidin-3-yl)-5-(4-(4-(4-(1-(hydroxyimino)-2,3-dihydro-1H-inden-5-yl)-3-(pyridin-4-yl)-1H-pyrazol-1-yl)phenyl)piperazin-1-yl)-4-methylisoindoline-1,3-dione



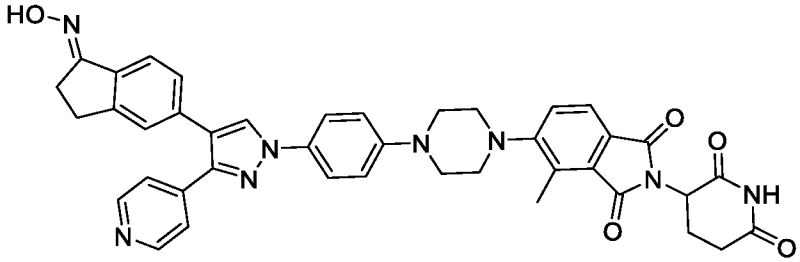
[0849] Step A: 2-(2,6-dioxopiperidin-3-yl)-4-methyl-5-(4-(4-(4-(1-oxo-2,3-dihydro-1H-inden-5-yl)-3-(pyridin-4-yl)-1H-pyrazol-1-yl)phenyl)piperazin-1-yl)isoindoline-1,3-dione



[0850] To a solution of 4-chloro-2-(2,6-dioxopiperidin-3-yl)-5-(4-(4-(4-(1-oxo-2,3-dihydro-1H-inden-5-yl)-3-(pyridin-4-yl)-1H-pyrazol-1-yl)phenyl)piperazin-1-yl)isoindoline-1,3-dione (100 mg, 0.14 mmol) in1,4-dioxane 10 mL and H2O 1 mL were added methylboronic acid (33.6 mg, 0.56 mmol), Pd(aMPhos)Cl_2 (9.9 mg, 0.014 mmol), and CsF (85.12 mg, 0.56 mmol). The resulting solution was irradiated at 90 °C with MW for 2 h. After cooling to rt, it was diluted with EA (50 mL), and the mixture was washed with brine (3 x 20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC to afford 2-(2,6-dioxopiperidin-3-yl)-4-methyl-5-(4-(4-(4-(1-oxo-2,3-dihydro-1H-

inden-5-yl)-3-(pyridin-4-yl)-1H-pyrazol-1-yl)phenyl)piperazin-1-yl)isoindoline-1,3-dione (70 mg, 72.1% yield). LCMS (ES^+): m/z 706.3 $[M+H]^+$.

[0851] Step B: (E)-2-(2,6-dioxopiperidin-3-yl)-5-(4-(4-(4-(1-(hydroxyimino)-2,3-dihydro-1H-inden-5-yl)-3-(pyridin-4-yl)-1H-pyrazol-1-yl)phenyl)piperazin-1-yl)-4-methylisoindoline-1,3-dione

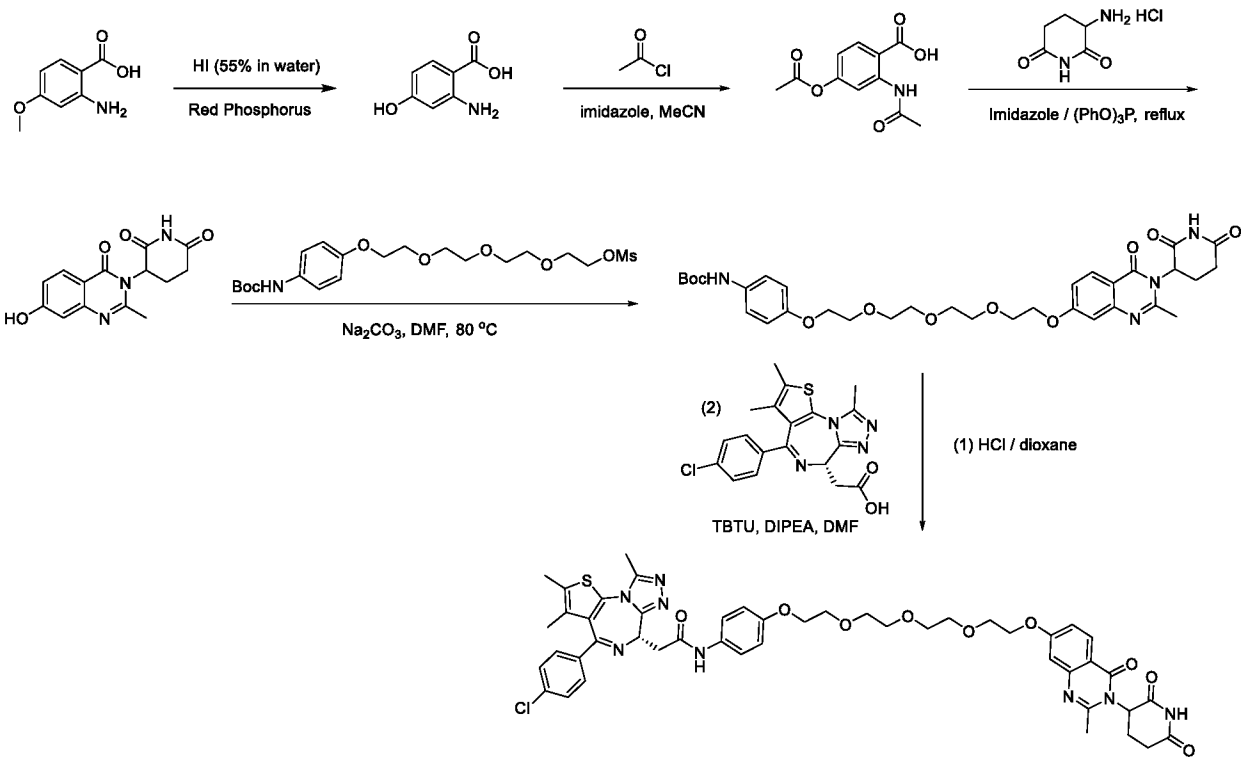


[0852] To a solution of 2-(2,6-dioxopiperidin-3-yl)-4-methyl-5-(4-(4-(4-(1-oxo-2,3-dihydro-1H-inden-5-yl)-3-(pyridin-4-yl)-1H-pyrazol-1-yl)phenyl)piperazin-1-yl)isoindoline-1,3-dione (70 mg, 0.10 mmol) in acetonitrile 3 mL and pyridine 3 mL was added hydroxylamine hydrochloride (69.5 mg, 1.0 mmol). The mixture was stirred at 40 °C for 20 min. Then it was diluted with DCM (20 mL), and the mixture was washed with brine (10 mL). The organic phase was concentrated and purified by prep-TLC to afford (E)-2-(2,6-dioxopiperidin-3-yl)-5-(4-(4-(4-(1-(hydroxyimino)-2,3-dihydro- 1H-inden-5-yl)-3-(pyridin-4-yl)-1H-pyrazol-1-yl)phenyl)piperazin-1-yl)-4-methylisoindoline-1,3-dione (19.6 mg, 27.8% yield) as yellow solid. ^1H NMR (400 MHz, DMSO-d_6): δ 11.09 (s, 1H), 10.89 (s, 1H), 8.72 (s, 1H), 8.58-8.57 (m, 2H), 7.83 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.50-7.41 (m, 4H), 7.23-7.17 (m, 3H), 5.13-5.09 (m, 1H), 3.61-3.42 (m, 8H), 3.04-2.97 (m, 2H), 2.93-2.82 (m, 3H), 2.62-2.56 (m, 5H), 2.08-2.00 (m, 1H); LCMS (ES^+): m/z 721.3 $[M+H]^+$.

[0853] Exemplary Compound 41 may be prepared by a procedure analogous to that described for Examplary Compound 42.

[0854] **E. Exemplary Synthetic Schemes for Exemplary BRD4 Binding Moiety Based Compounds**

[0855] **Exemplar Synthesis of Exemplary Compound 45: 2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-(2-(2-(2-(2-((3-(2,6-dioxopiperidin-3-yl)-2-methyl-4-oxo-3,4-dihydroquinazolin-7-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)phenyl)acetamide**



[0856] **Step 1:** Preparation of 2-amino-4-hydroxybenzoic acid

[0857] A mixture of 2-amino-4-methoxybenzoic acid (1.0 g, 5.98 mmol), red phosphorus (556 mg, 17.94 mmol) and 55% hydroiodic acid (10 mL) was heated at 100°C for 14 h in a sealed tube. The reaction mixture was poured into ice water. The pH of the solution was adjusted to 6-7 by sodium carbonate. The solution was extracted with ethyl acetate (20 mL x 3). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to afford crude 2-amino-4-hydroxybenzoic acid (400 mg, 44% yield) which was used in the next step without further purification. ^{1}HNMR (400MHz, DMSO- d_6): δ 7.53-7.55 (m, 1H), 6.12 (s, 1H), 5.99 - 6.02 (m, 1H).

[0858] **Step 2:** Preparation of 2-acetamido-4-acetoxybenzoic acid

[0859] To a mixture of 2-amino-4-hydroxybenzoic acid (400 mg, 2.61 mmol) and imidazole (888 mg, 10.06 mmol) in acetonitrile (20 mL) was added acetyl chloride (789 mg, 10.06 mmol) dropwise at 0 °C. The solution was stirred at rt for 10 h and then quenched by water (40 mL). The mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. Volatiles were evaporated in vacuum and the residue was purified by column chromatography (ethyl acetate/petroleum ether = 2:1) to afford 2-acetamido-4-acetoxybenzoic acid (350 mg, 57% yield). ^{1}HNMR

(400MHz, DMSO- d_6): δ 11.19 (s, 1H), 8.30 (s, 1H), 8.01-8.03 (m, 1H), 6.92-6.95 (m, 1H), 2.30 (s, 3H), 2.15 (s, 3H).

[0860] **Step 3:** Preparation of 3-(7-hydroxy-2-methyl-4-oxoquinazolin-3(4H)-yl)piperidine-2,6-dione

[0861] To a mixture of 2-acetamido-4-acetoxybenzoic acid (400 mg, 1.69 mmol), 3-aminopiperidine-2,6-dione hydrochloride (333 mg, 2.02 mmol), triphenyl phosphite (2.0 mL) in acetonitrile (10 mL) was added imidazole (383 mg, 5.63 mmol). The reaction solution was heated to reflux for 10 h. The solution was evaporated under reduced pressure and the residue was re-crystallized (20% ethyl acetate in hexane) to afford 3-(7-Hydroxy-2-methyl-4-oxoquinazolin-3(4H)-yl)piperidine-2,6-dione (110 mg, 19% yield).^{1}HNMR (400MHz, DMSO-d^6): δ 10.94 (s, 1H), 10.51 (s, 1H), 7.84-7.86(m, 1H), 6.92-6.94 (m, 1H), 6.85 (s, 1H), 5.16-5.20 (m, 1H), 2.73-2.85 (m, 1H), 2.58-2.63 (m, 5H), 2.13-2.15 (m, 1H).

[0862] **Step 4:** Preparation of *tert*-butyl (4-(2-(2-(2-(2-((3-(2,6-dioxopiperidin-3-yl)-2-methyl-4-oxo-3,4- dihydroquinazolin-7-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)phenyl)carbamate

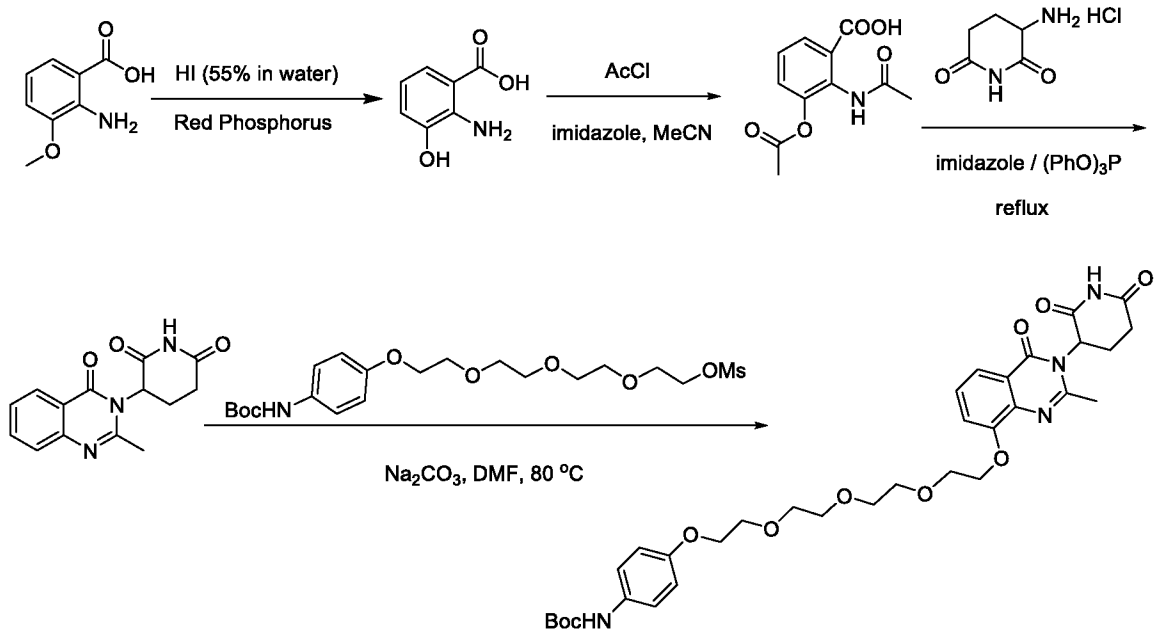
[0863] To a mixture of 3-(7-hydroxy-2-methyl-4-oxoquinazolin-3(4H)-yl)piperidine-2,6-dione (161 mg, 0.348 mmol) and 2-(2-(2-(2-(4-((tert-butoxycarbonyl)amino)phenoxy)ethoxy)ethoxy)ethoxy)ethyl methanesulfonate (100 mg, 0.348 mmol, prepared according to procedures of similar intermediate described in US 2015/0291562) in DMF (5.0 mL) was added sodium carbonate (74 mg, 0.696 mmol). The mixture was stirred at 80 °C for 6 h. The resulting mixture was cooled to rt. Ethyl acetate (30 mL) was added and the organic layer was washed with water and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purification by preparative TLC to afford *tert*-butyl (4-(2-(2-(2-(2-((3-(2,6-dioxopiperidin-3-yl)-2-methyl-4-oxo-3,4- dihydroquinazolin-7-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)phenyl)carbamate (55.4 mg, 24% yield).^{1}HNMR (400MHz, DMSO-d^6): δ 10.98 (s, 1H), 9.08 (s, 1H), 7.91-7.93 (m, 1H), 7.32-7.34 (m, 2H), 7.07-7.09 (m, 2H), 6.82-6.84 (m, 2H), 5.20-5.24 (m, 1H), 4.24 (s, 2H), 3.99 (m, 2H), 3.79 (m, 2H), 3.70-3.71 (m, 2H), 3.56-3.60 (m, 8H), 2.79-2.87 (m, 1H), 2.57-2.70 (m, 5H), 2.17-2.18 (m, 1H), 1.47 (s, 9H). LC-MS: (ES$^+$): m/z 655.3 $[M+H]^+$.

[0864] **Step 5:** Preparation of 2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-(2-(2-(2-(2-((3-(2,6-dioxopiperidin-3-yl)-2-

methyl-4-oxo-3,4-dihydroquinazolin-7-yl)oxy)ethoxy)ethoxy)ethoxy)phenyl)acetamide (Exemplary Compound 45)

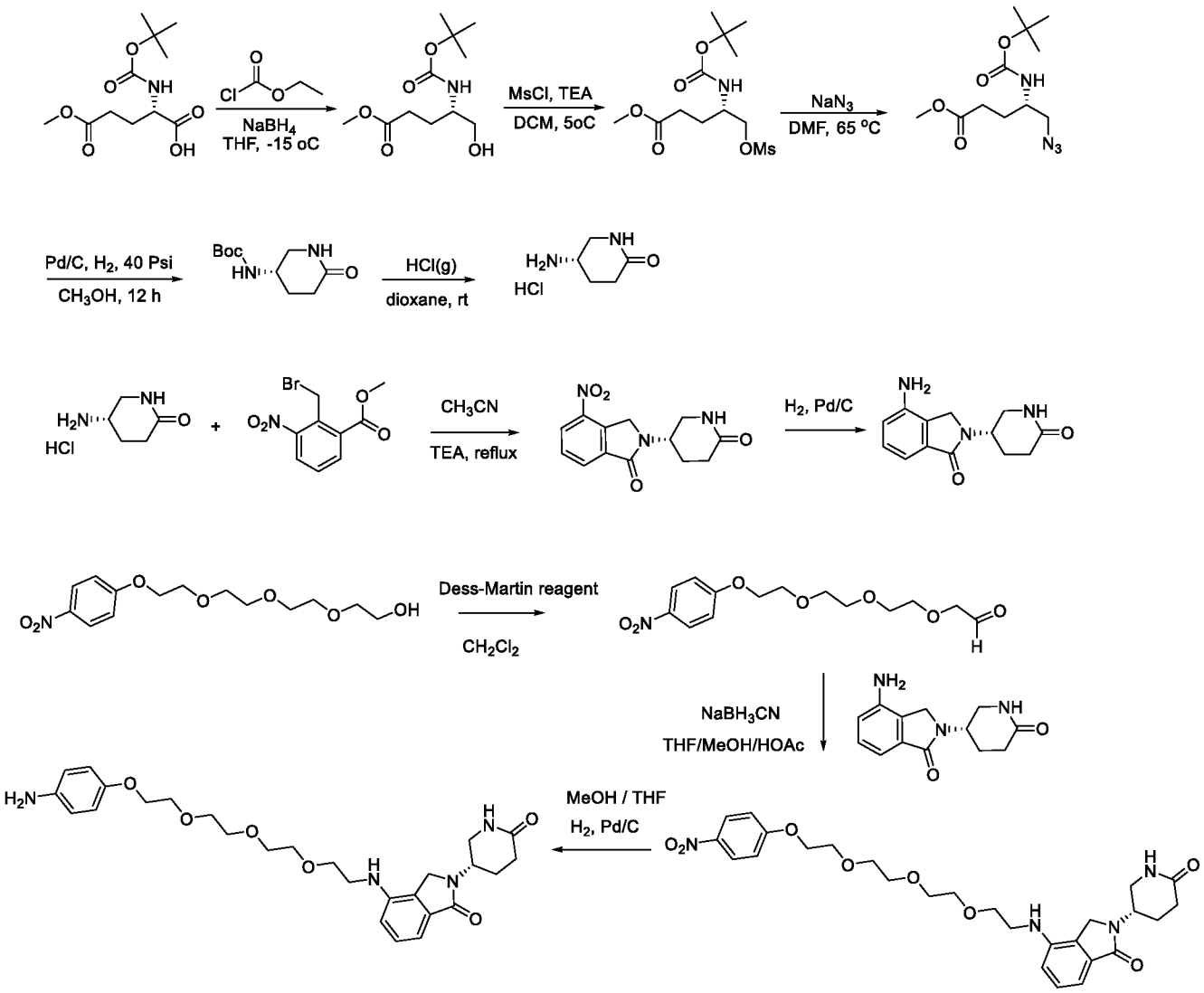
[0865] To a pre-mixed solution containing (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetic acid (6.11 mg, 0.01525 mmol) in DMF (2.00 ml), TBTU (7.34 mg, 0.02287 mmol) and DIPEA (7.96 µL, 0.04575 mmol) was added 3-(7-(2-(2-(2-(2-(4-aminophenoxy)ethoxy)ethoxy)ethoxy)ethoxy)-2-methyl-4-oxoquinazolin-3(4H)-yl)piperidine-2,6-dione (8.46 mg, 0.01525 mmol, prepared by treating the product from step 4 with HCl in dioxane) and the mixture was left to stir for 2 h. The mixture was diluted with ethyl acetate and water. The organic layer was washed with sodium bicarbonate, water (3 x) and brine. The resulting solution was filtered through a thin pad of silica gel and then concentrated in vacuo to give a crude solid. This material was purified by silica gel chromatography on a Teledyne Combiflash ISCO eluting with MeOH/DCM (0:100 to 7:93) to yield 2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-(2-(2-(2-(2-((3-(2,6-dioxopiperidin-3-yl)-2-methyl-4-oxo-3,4-dihydroquinazolin-7-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)phenyl)acetamide (10.1 mg, 0.01077 mmol, 71.1 % yield). ^{1}H NMR (400 MHz, methanol-d_4) □ 8.55 (s, 1H), 7.96 - 8.00 (m, 1H), 7.36 - 7.50 (m, 6H), 7.03 - 7.09 (m, 2H), 6.87 (dd, J = 3.03, 9.10 Hz, 2H), 5.22 (td, J = 5.40, 10.91 Hz, 1H), 4.70 - 4.74 (m, 1H), 4.22 (d, J = 3.33 Hz, 2H), 4.10 (d, J = 4.30 Hz, 2H), 3.85 - 3.91 (m, 2H), 3.79 - 3.84 (m, 2H), 3.64 - 3.71 (m, 7H), 3.55 - 3.64 (m, 2H), 3.42 - 3.50 (m, 2H), 2.71 (s, 3H), 2.66 (d, J = 3.33 Hz, 2H), 2.44 (d, J = 3.33 Hz, 3H), 1.89 (s, 3H), 1.68 (d, J = 3.33 Hz, 2H), 1.29 (br. s., 3H). LC/MS (ES$^+$): *m/z* 937.19/939.19 $[M+H]^+$.

[0866] Exemplar Synthesis of Exemplary Compound 44: 2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-(2-(2-(2-(2-((3-(2,6-dioxopiperidin-3-yl)-2-methyl-4-oxo-3,4-dihydroquinazolin-8-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)phenyl)acetamide



[0867] This molecule was synthesized using the same method as described in Example 1. The key intermediate was prepared according the scheme listed above. ^{1}H NMR (400 MHz, methanol-d_4) □ 8.55 (s, 1H), 7.96 - 8.00 (m, 1H), 7.36 - 7.50 (m, 6H), 7.03 - 7.09 (m, 2H), 6.87 (dd, J = 3.03, 9.10 Hz, 2H), 5.22 (td, J = 5.40, 10.91 Hz, 1H), 4.70 - 4.74 (m, 1H), 4.22 (d, J = 3.33 Hz, 2H), 4.10 (d, J = 4.30 Hz, 2H), 3.85 - 3.91 (m, 2H), 3.79 - 3.84 (m, 2H), 3.64 - 3.71 (m, 7H), 3.55 - 3.64 (m, 2H), 3.42 - 3.50 (m, 2H), 2.71 (s, 3H), 2.66 (d, J = 3.33 Hz, 2H), 2.44 (d, J = 3.33 Hz, 3H), 1.89 (s, 3H), 1.68 (d, J = 3.33 Hz, 2H), 1.29 (br. s., 3H). LCMS (ES$^+$): *m/z* 937.19/939.19 $[M+H]^+$.

[0868] **Exemplary Synthesis of Exemplar Compound 43: 2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-(2-(2-(2-(2-((1-oxo-2-((S)-6-oxopiperidin-3-yl)isoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)ethoxy)phenyl)acetamide**



[0869] The key intermediate for the preparation of this compound was synthesized according the scheme listed above. The final step of amide coupling was carried out under the same condition as described in Example 1. ^{1}H NMR (400 MHz, $CDCl_3$) d 9.03 (s, 1H), 7.45 (dd, J = 8.71, 13.21 Hz, 4H), 7.31 - 7.37 (m, 3H), 7.24 (d, J = 7.24 Hz, 1H), 6.84 (d, J = 9.00 Hz, 2H), 6.78 (d, J = 8.02 Hz, 1H), 6.75 (br. s., 1H), 4.66 - 4.73 (m, 2H), 4.20 (d, J = 2.74 Hz, 1H), 4.07 - 4.12 (m, 2H), 3.80 - 3.90 (m, 3H), 3.64 - 3.77 (m, 10H), 3.52 - 3.58 (m, 1H), 3.35 - 3.42 (m, 3H), 2.68 (br. s., 3H), 2.52 - 2.59 (m, 2H), 2.41 (s, 3H), 2.02 - 2.08 (m, 2H), 1.69 (s, 3H), 1.26 (s, 3H). LC-MS (ES^+): m/z 895.22/897.22 $[M+H]^+$.

[0870] **Protein Level Control**

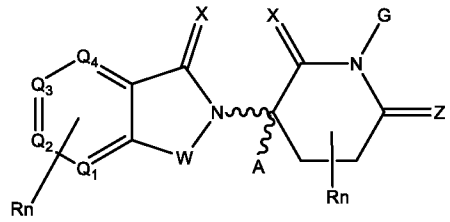
[0871] This description also provides methods for the control of protein levels with a cell. This is based on the use of compounds as described herein, which are known to interact with a specific target protein such that degradation of a target protein *in vivo* will result in the control of the amount of protein in a biological system, prerferably to a particular therapeutic benefit.

[0872] The following examples are used to assist in describing the present invention, but should not be seen as limiting the present invention in any way.

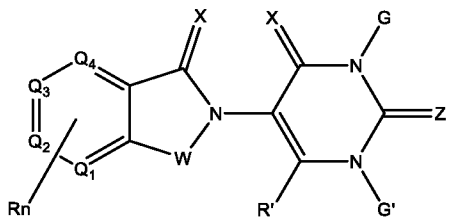
[0873] **Exemplary Embodiments of the Present Disclosure**

[0874] The present disclosure encompasses the following specific embodiments. These following embodiments may include all of the features recited in a proceeding embodiment, as specified. Where applicable, the following embodiments may also include the features recited in any proceeding embodiment inclusively or in the alternative.

[0875] An aspect of the present disclosure provides a cereblon E3 ubiquitin ligase binding compound having a chemical structure selected from:



(a1)



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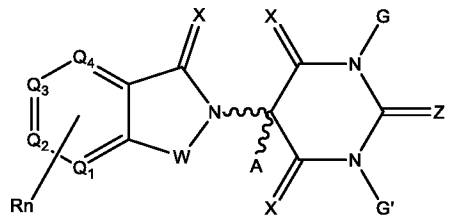

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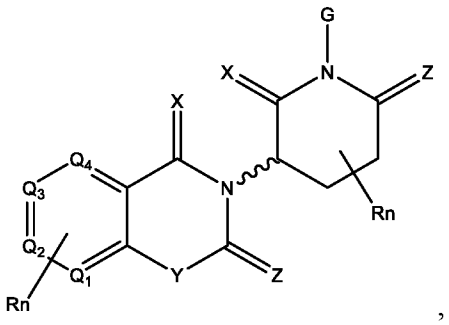

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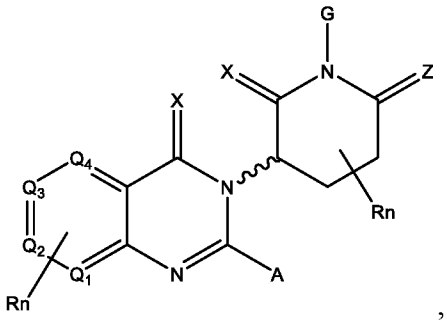

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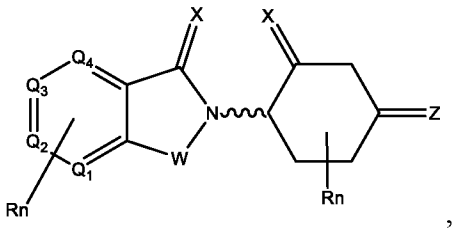

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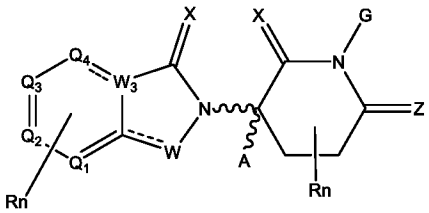
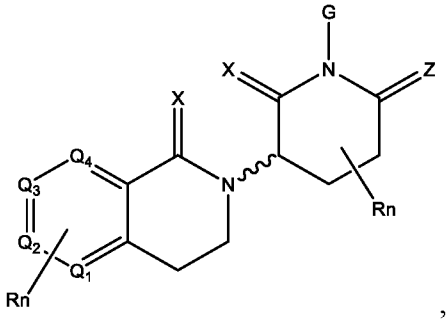


(a2)



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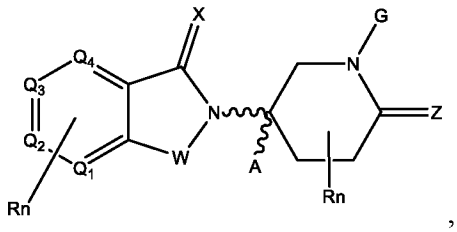


(a3)

wherein:

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

W_3 is selected from C or N;

each X is absent or independently selected from the group consisting of O and S;

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;

each Z is absent or independently selected from the group consisting of O and S;

G and G' are independently selected from the group consisting of H, alkyl (linear, branched, optionally substituted), 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 (linear, branched, optionally substituted), cycloalkyl, Cl and F;

R comprises -CONR'R", -OR', -NR'R", -SR', -SO_2R', -SO_2NR'R", -CR'R"-, -CR'NR'R"-, (-CR'O)$_{n'}$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 and -OCF_3;

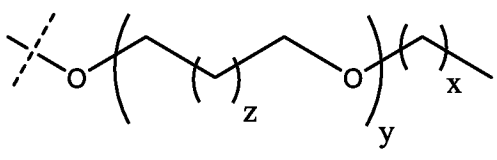
R' and R" are independently selected from the group consisting of a bond, H, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclic, -C(=O)R, heterocyclyl, each of which is optionally substituted;

n' integer from 1-10;

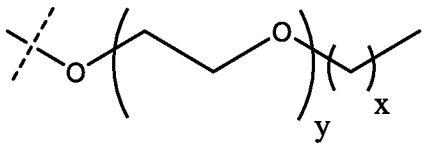
represents a single bond or a double bond;

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

Rn comprises 1-4 independent functional groups, optionally substituted linear or branched alkyl (e.g., a C1-C6 linear or branched alkyl optionally substituted with one or more halogen, cycloalkyl (e.g., a C3-C6 cycloalkyl), or aryl (e.g., C5-C7 aryl)), optionally substituted aryl (e.g., an optionally substituted C5-C7 aryl), optionally substituted alkyl-aryl (e.g., an alkyl-aryl comprising at least one of an optionally substituted C1-C6 alkyl, an optionally substituted C5-C7 aryl, or combinations thereof), optionally substituted alkoxyl group (e.g., a methoxy, ethoxy, butoxy, propoxy, pentoxy, or hexoxy; wherein the alkoxyl may be substituted with one or more halogen, alkyl, haloalky, fluoroalkyl, cycloalkyl (e.g., a C3-C6 cycloalkyl), or aryl (e.g., C5-C7 aryl)), optionally substituted



(e.g., optionally substituted with one or more

halogen, alkyl, haloalky, fluoroalkyl, cycloalkyl (e.g., a C3-C6 cycloalkyl), or aryl (e.g., C5-C7 aryl)), optionally substituted  (e.g., optionally substituted with one or more halogen, alkyl, haloalky, fluoroalkyl, cycloalkyl (e.g., a C3-C6 cycloalkyl), or aryl (e.g., C5-C7 aryl)), or atoms; and

each of x, y, and z are independently 0, 1, 2, 3, 4, 5, or 6,

n is an integer from 1-10 (e.g., 1-4).

[0876] Another aspect of the present disclosure provides a bifunctional compound having the chemical structure:

CLM—L—PTM,

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

wherein:

the PTM is a small molecule comprising a protein targeting moiety;

the L is a bond or a chemical linking moiety covalently coupling the CLM and the PTM; and

the CLM is a small molecule cereblon E3 ubiquitin ligase binding moiety of claim 1, wherein when n is 2, 3, or 4, then at least one of R_n or W is modified to be covalently joined to the linker group (L) or a PTM.

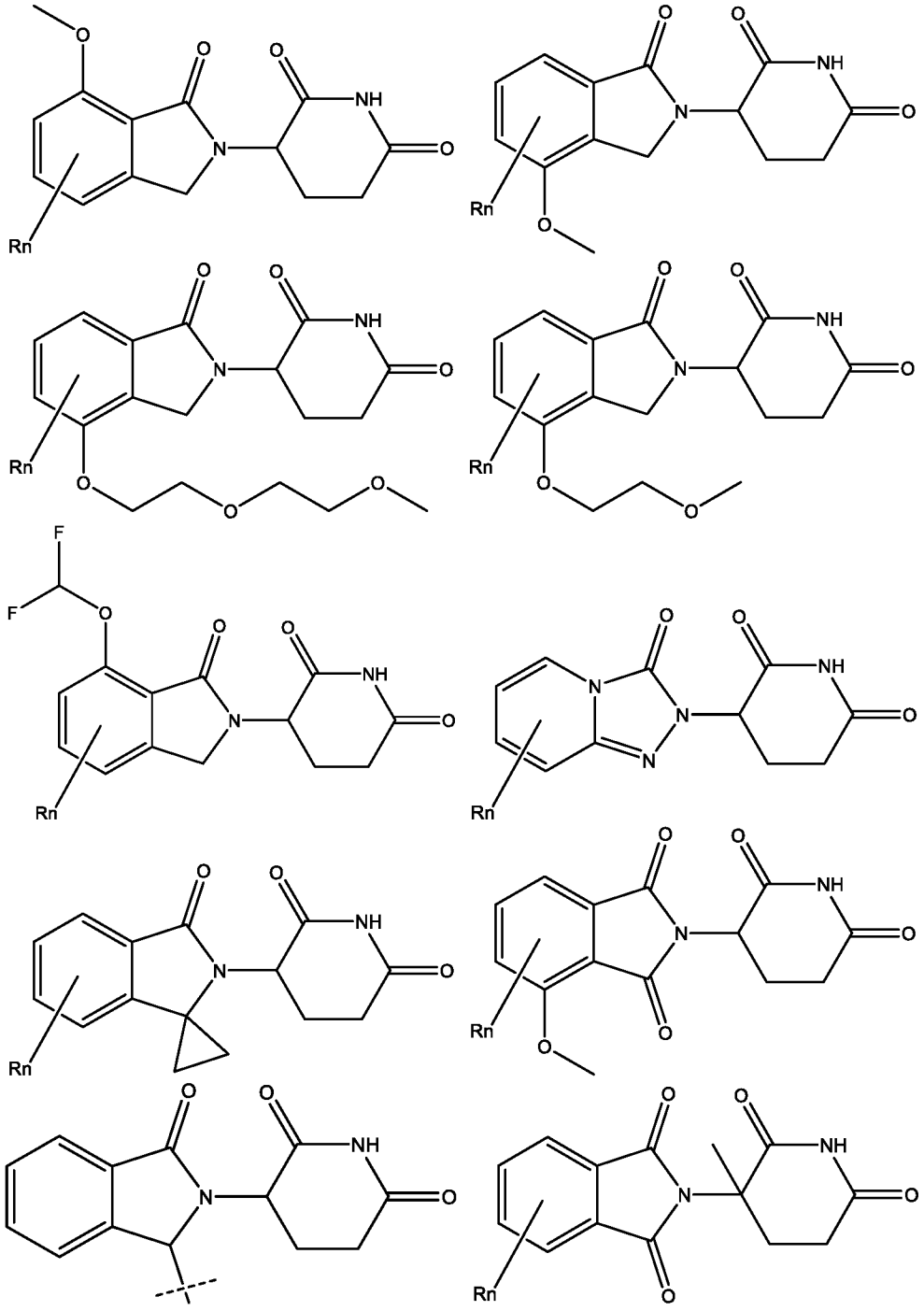
[0877] In any aspect or embodiment described herein, the CLM is linked to the PTM, the chemical linker group (L), or a combination thereof via W, X, R^1, R^2, R^3, R^4, R', Q_1, Q_2, Q_3, Q_4, and Q_5.

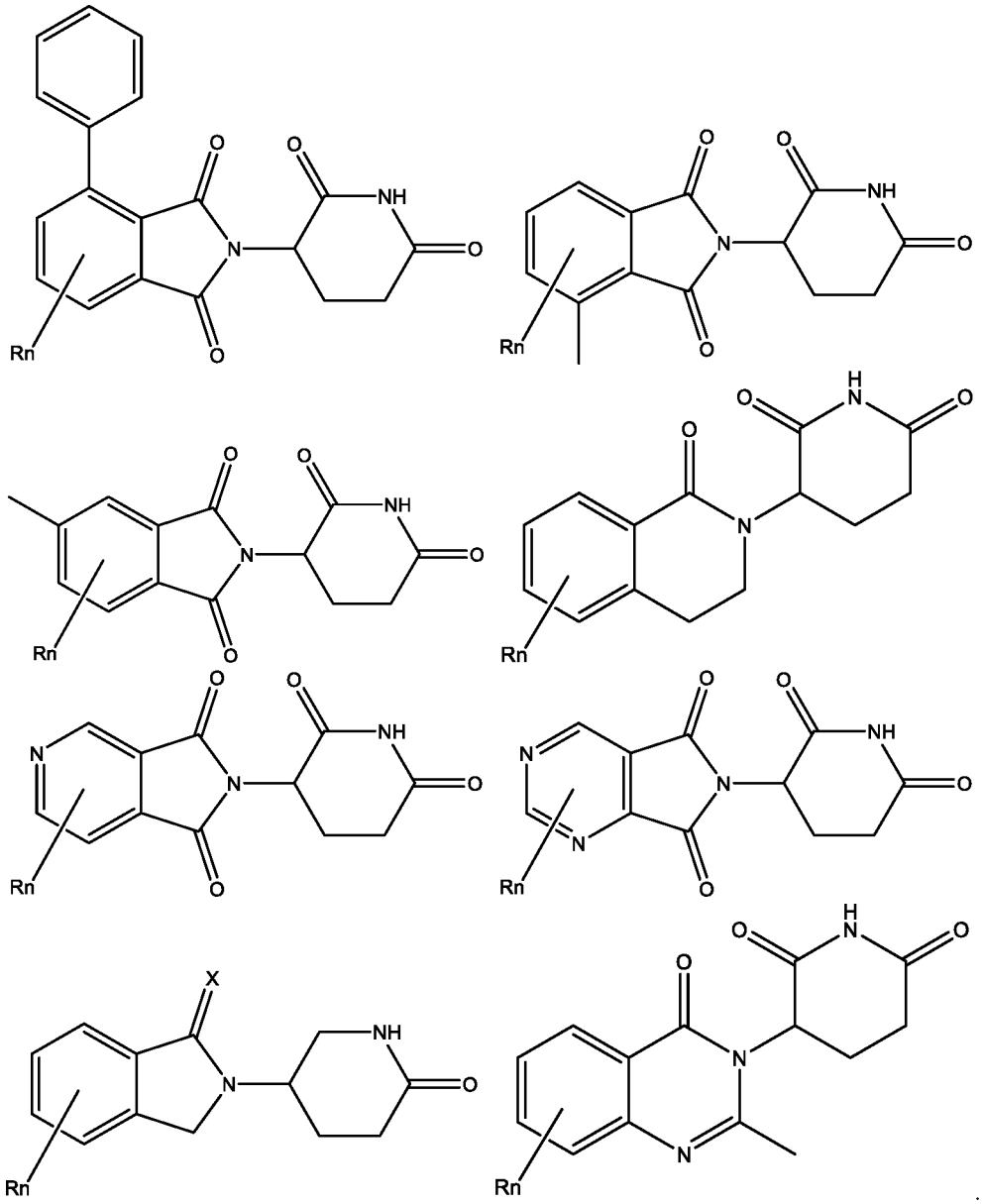
[0878] In any aspect or embodiment described herein, the PTM is a moiety that binds BRD4, BRaf, Estrogen Receptor (ER), or Androgen Receptor (AR).

[0879] In any aspect or embodiment described herein, the compound may further comprise a second E3 ubiquitin ligase binding moiety coupled through a linker group.

[0880] In any aspect or embodiment described herein, the second E3 ubiquitin ligase binding moiety binds or targets an E3 ubiquitin ligase selected from the group consisting of Von Hippel-Lindau (VLM), cereblon (CLM), mouse double-minute homolog2 (MLM), and inhibitors of apoptosis proteins (ILM).

[0881] In any aspect or embodiment described herein, the CLM is represented by a chemical structure selected from the group consisting of:





[0882] In any aspect or embodiment described herein, the linker (L) comprises a chemical structural unit represented by the formula:

$$-(A^L)q-$$

wherein:

$(A^L)_q$ is a group which is connected to at least one of the CLM, the PTM, or a combination thereof;

q is an integer greater than or equal to 1;

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

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.

[0883] In any aspect or embodiment described herein, the A^L is 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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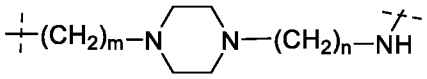
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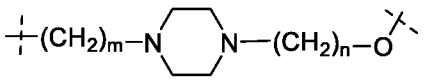
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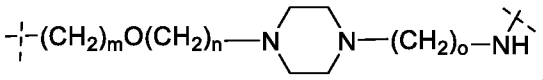
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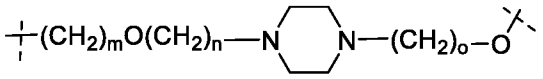
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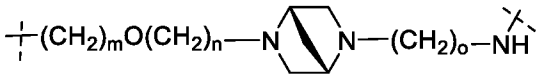
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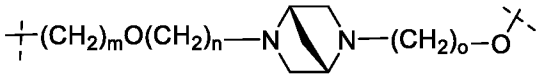

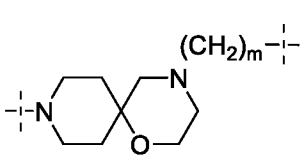
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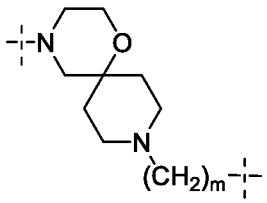
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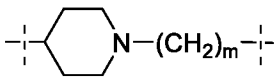
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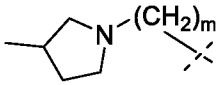
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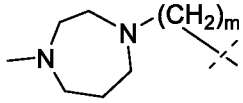

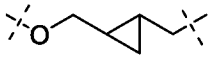
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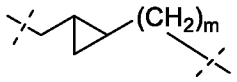
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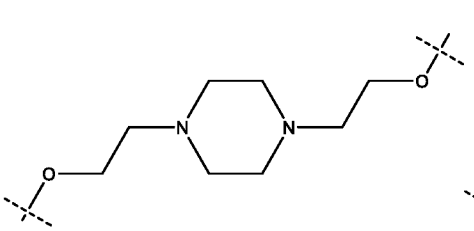

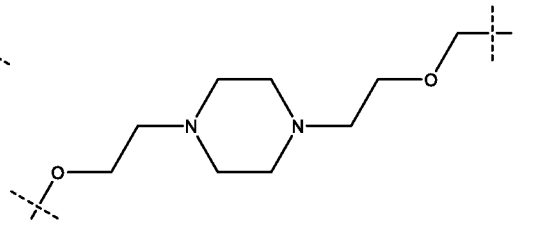

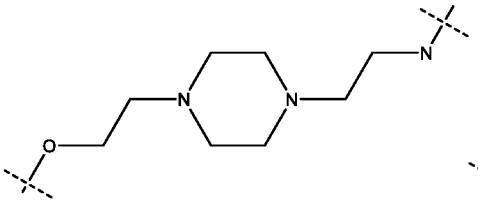

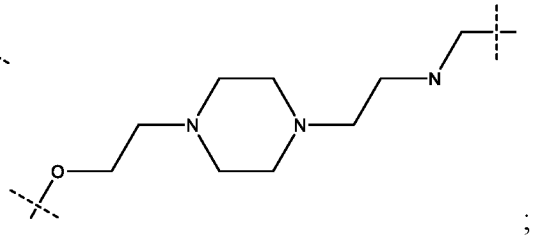
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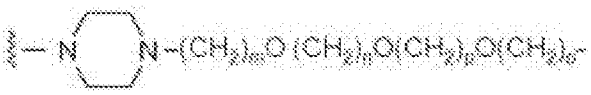
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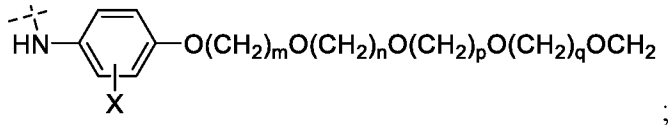
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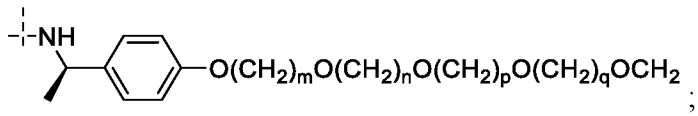
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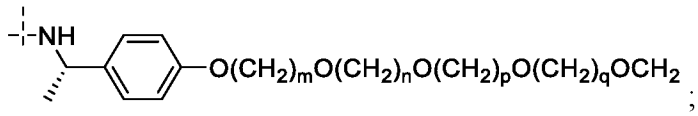
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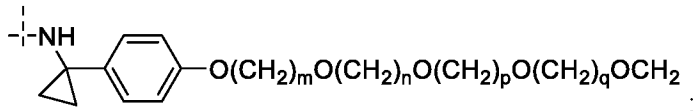
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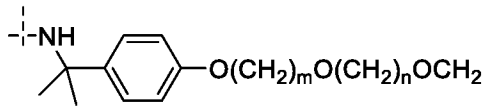
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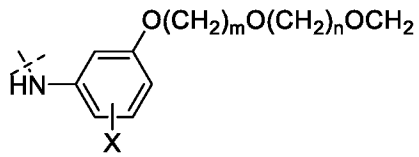
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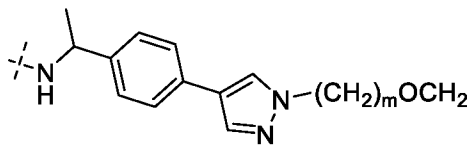
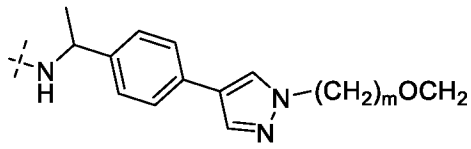

; wherein

m, n, o, p, q, and r of the linker are independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20;

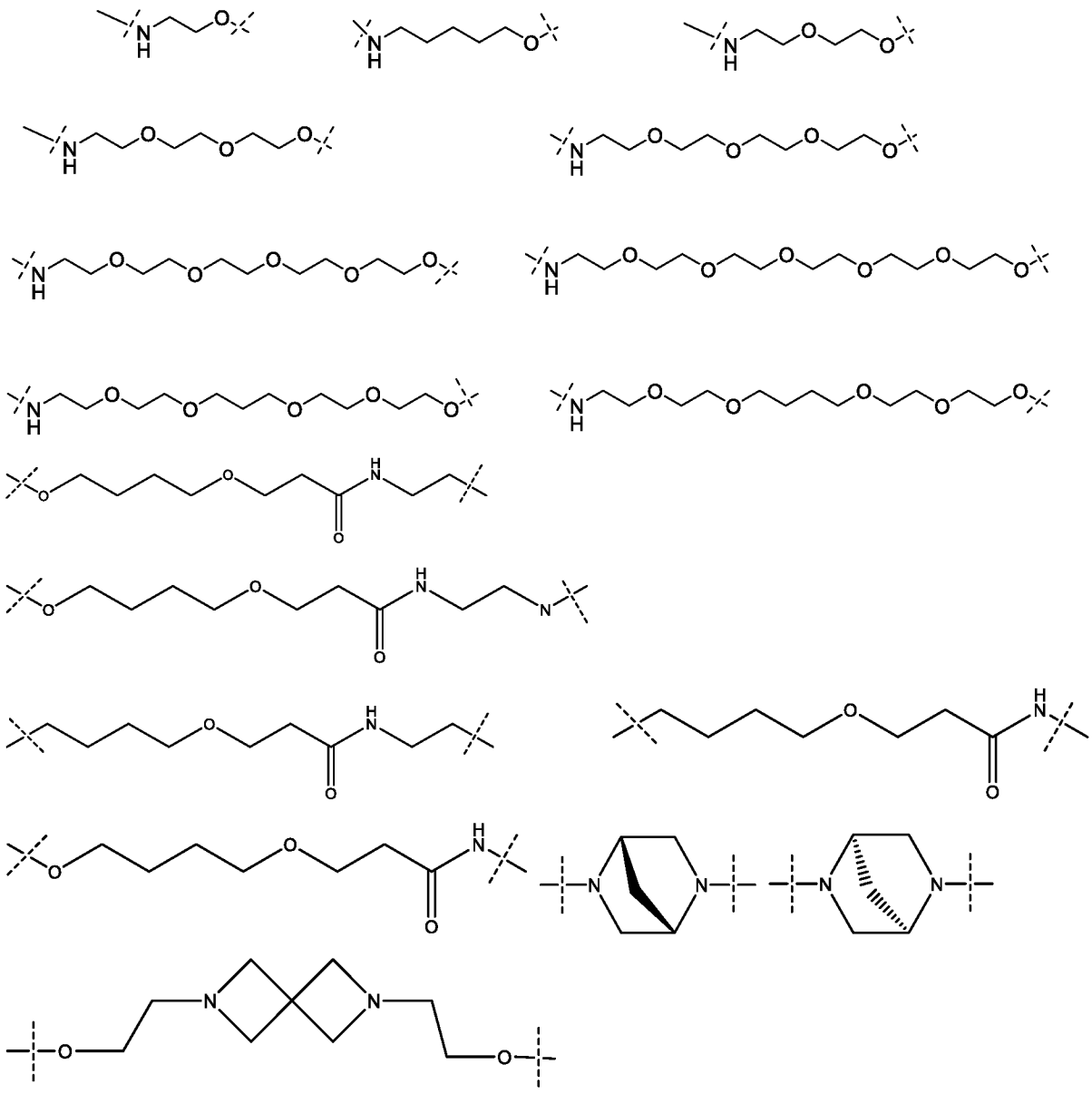
when the number is zero, there is no N-O or O-O bond

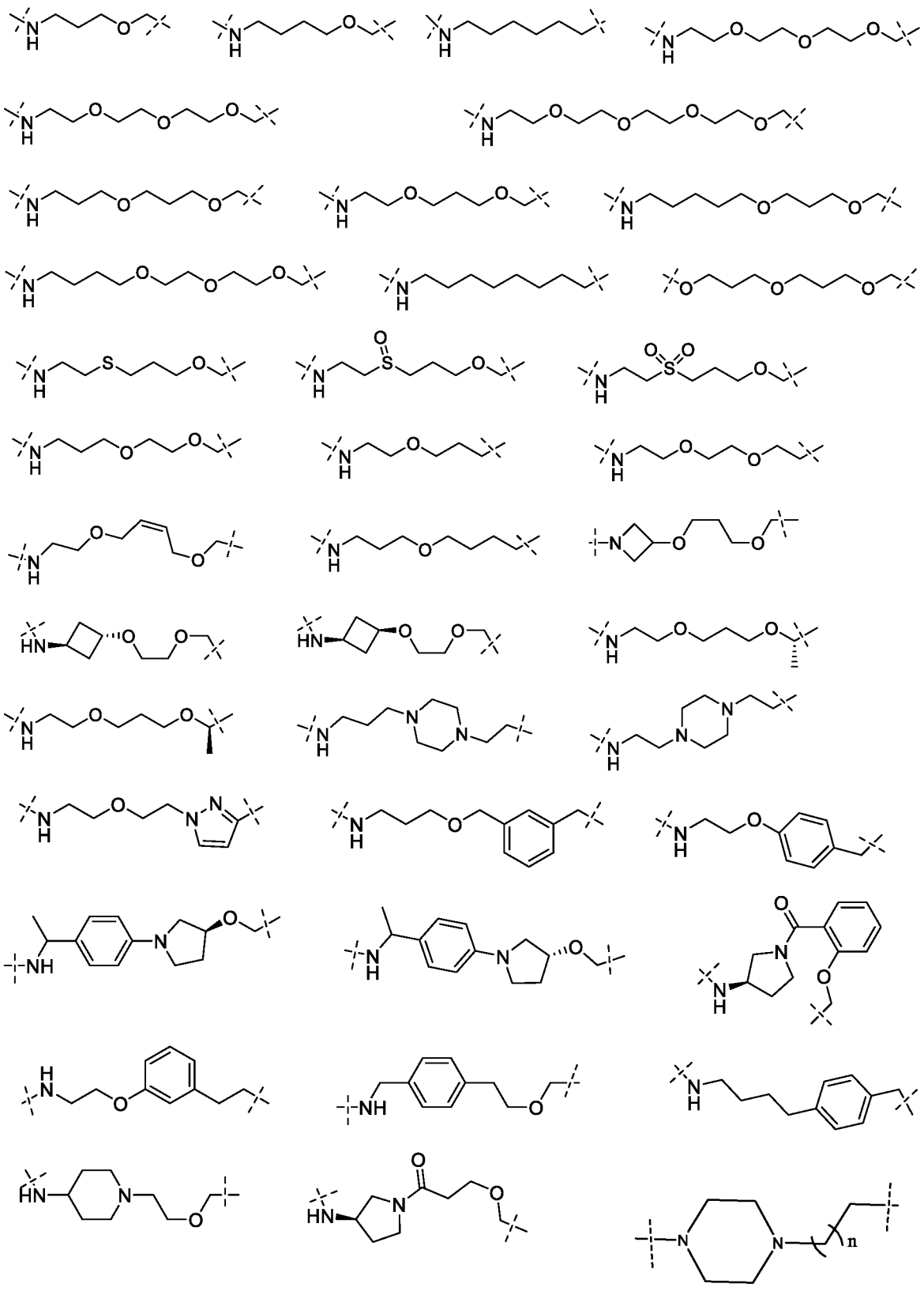
R of the linker is H, methyl and ethyl;

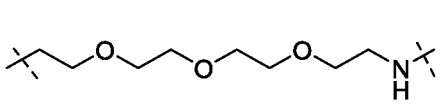
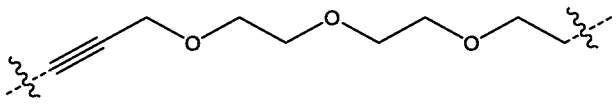
X of the linker is H and F



where m of the linker can be 2, 3, 4, 5;



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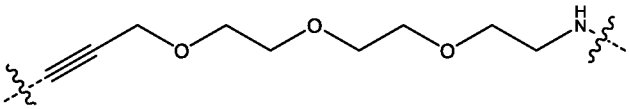
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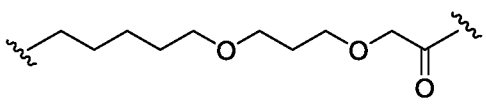
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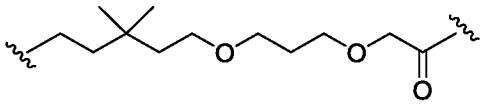
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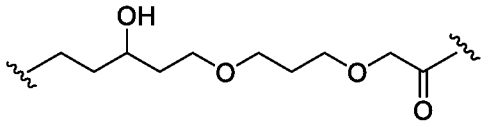
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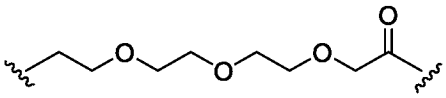
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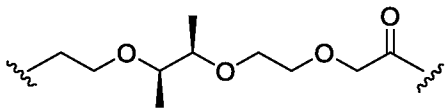
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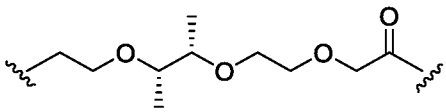
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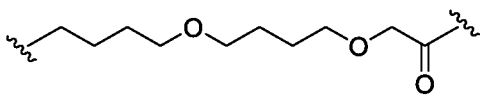
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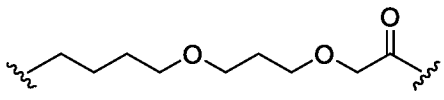
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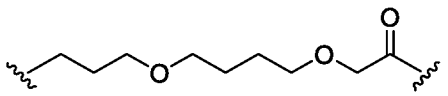
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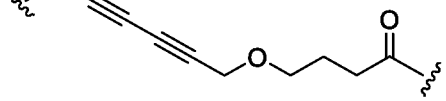
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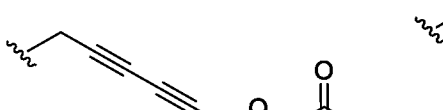
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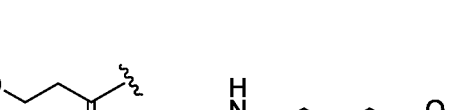
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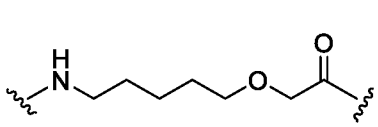
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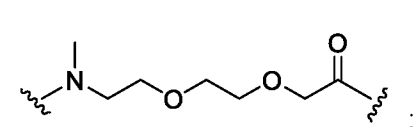
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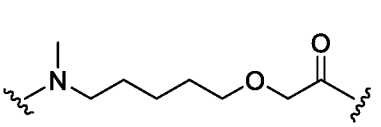
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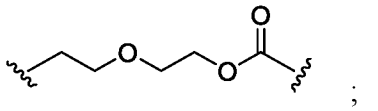
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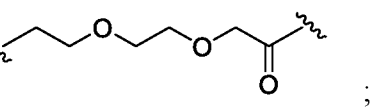
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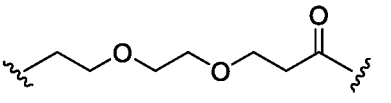
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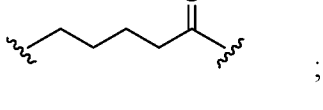
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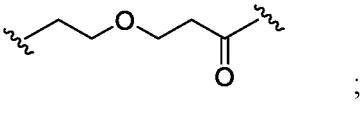
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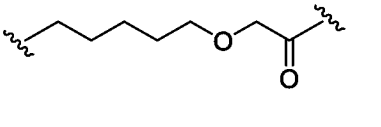
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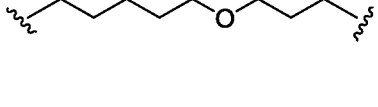
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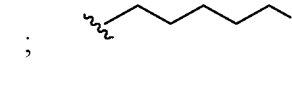
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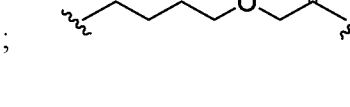
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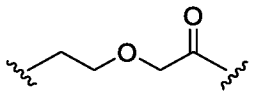
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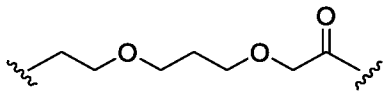
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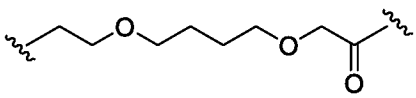
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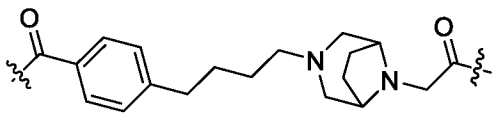
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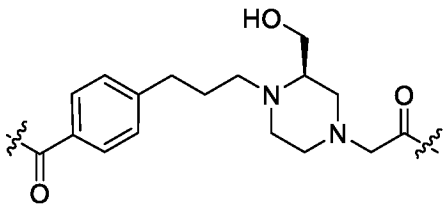
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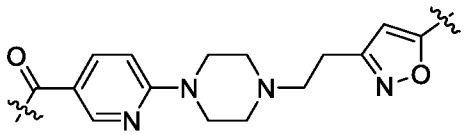
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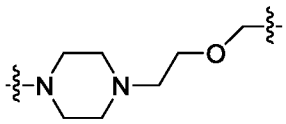
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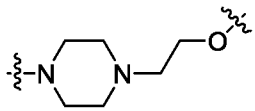
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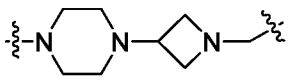
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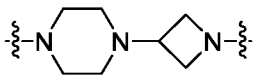
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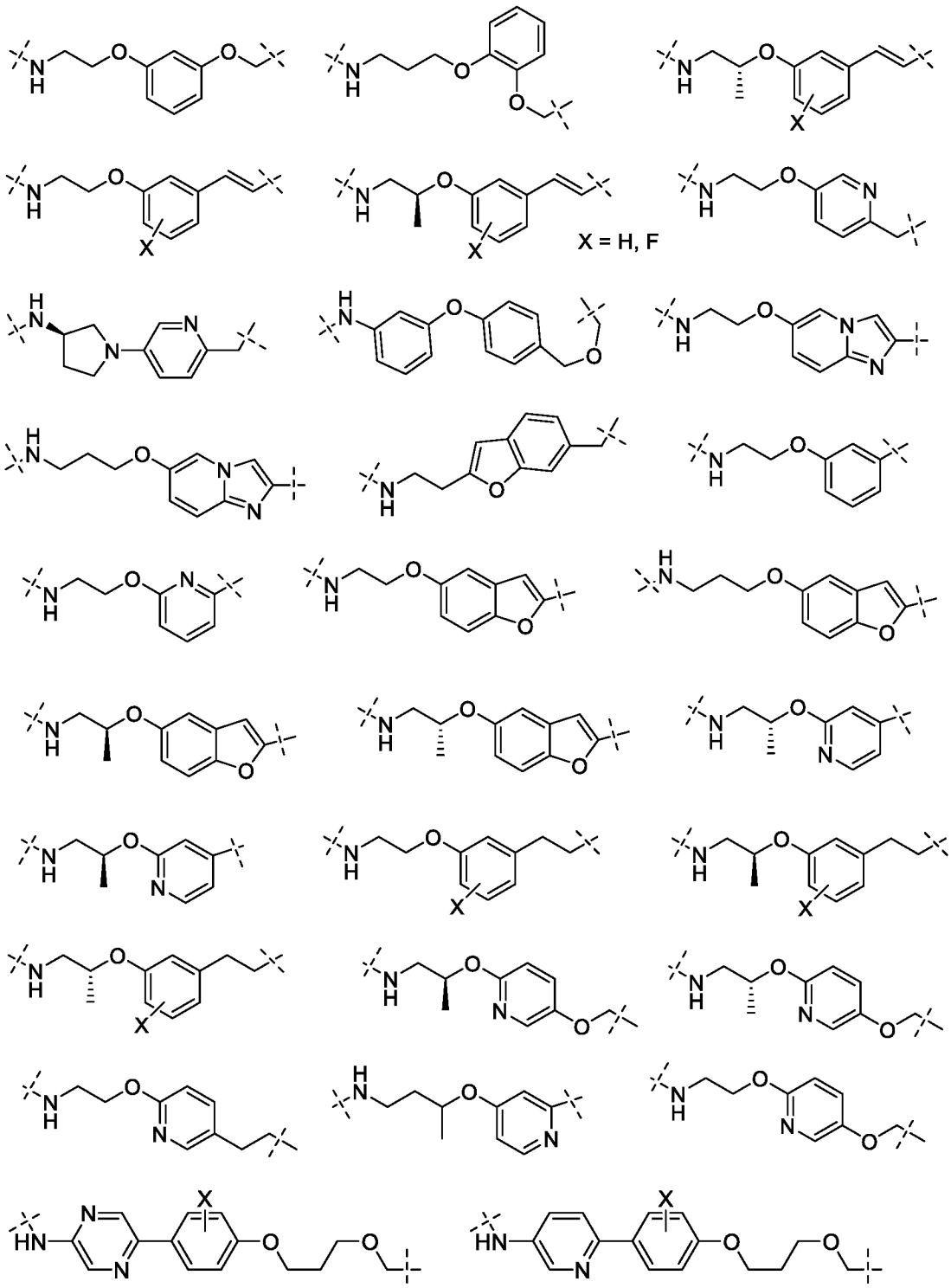
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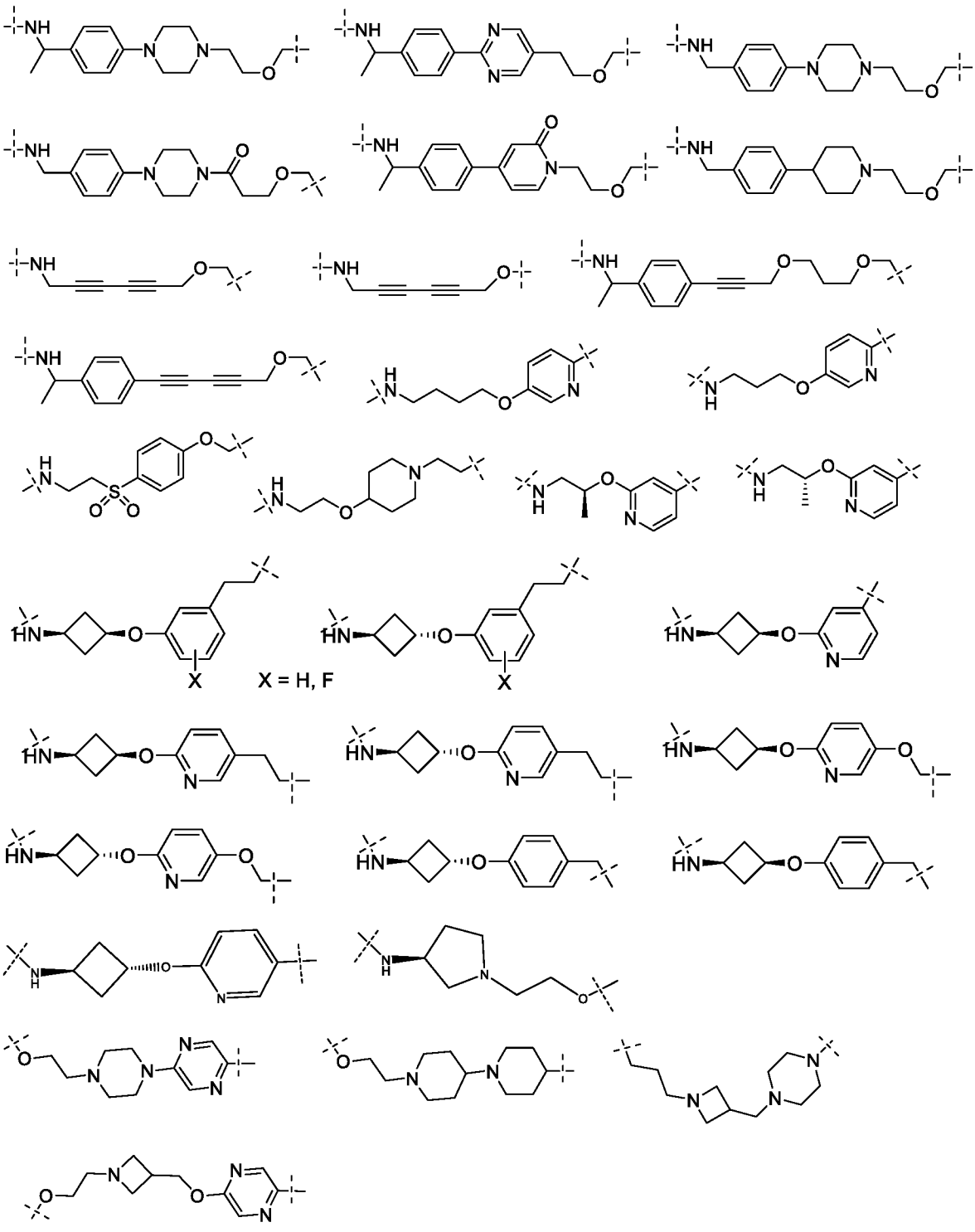
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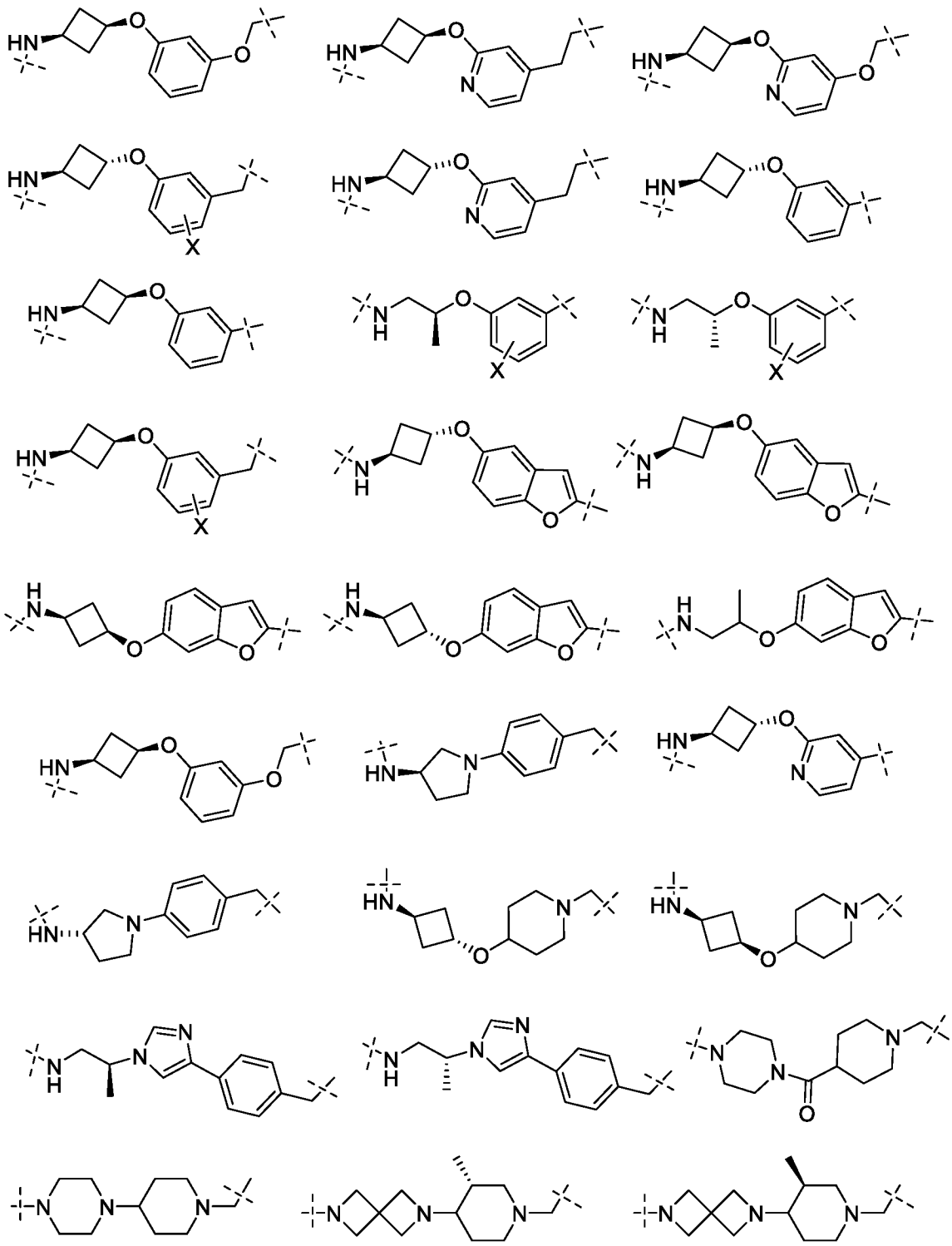
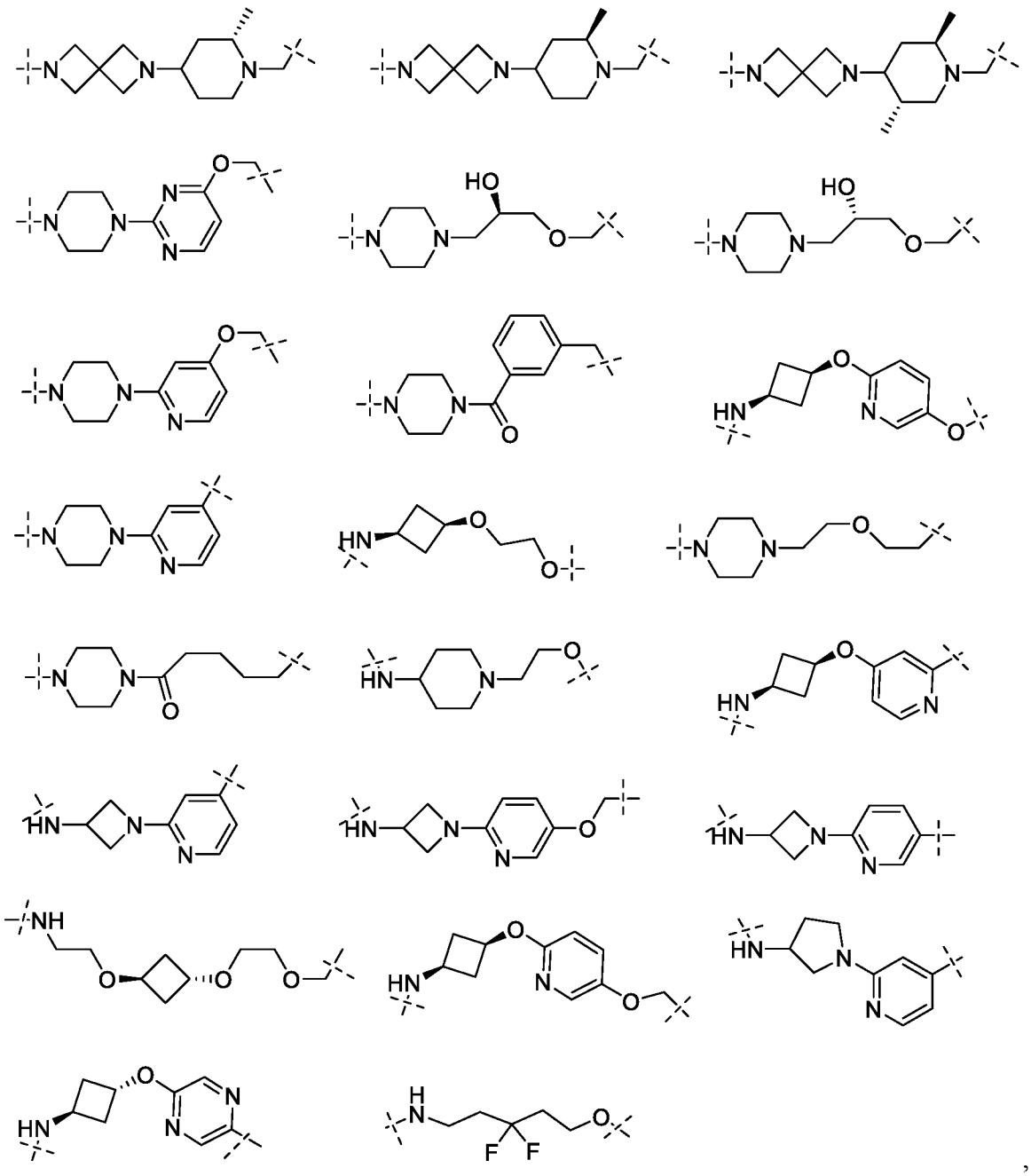
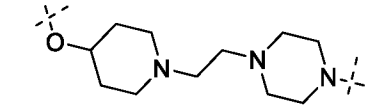
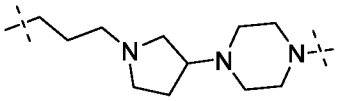
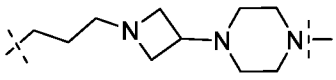
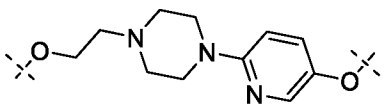
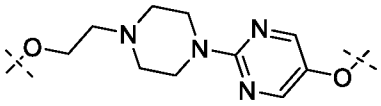
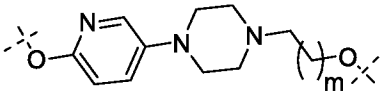
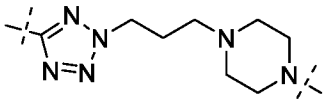
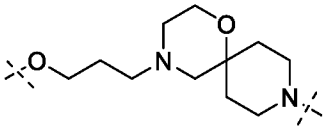
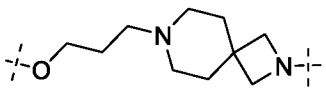
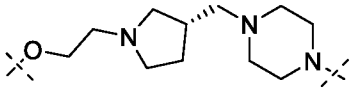
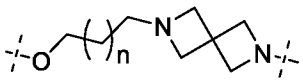
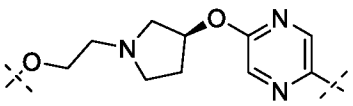
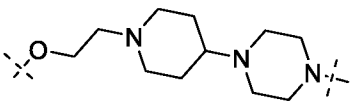
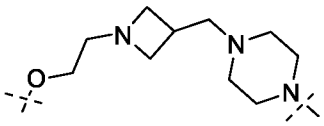
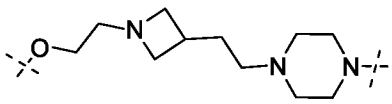
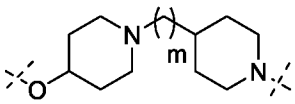
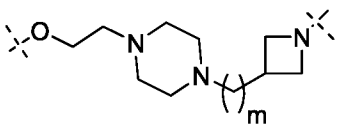
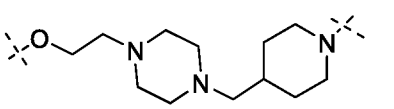
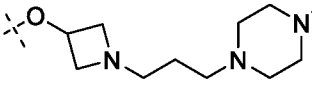
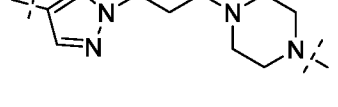
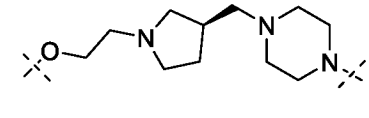
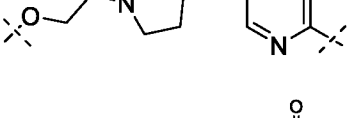
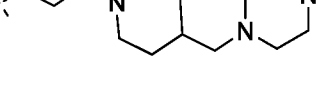
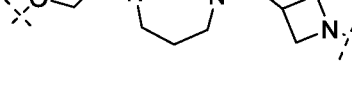
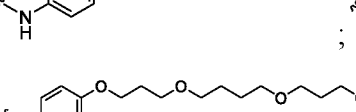
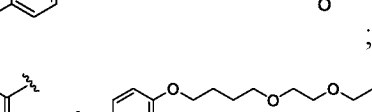
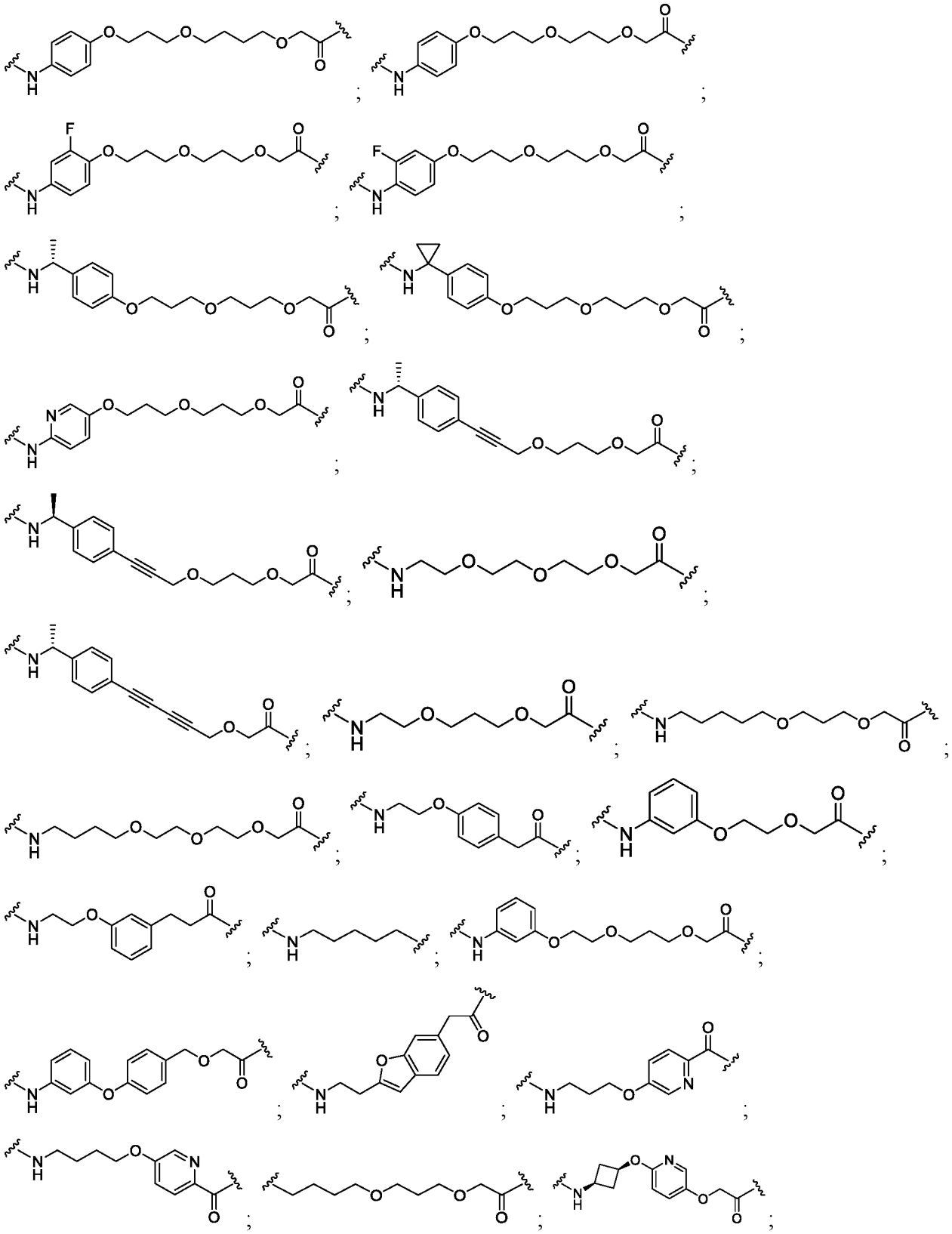


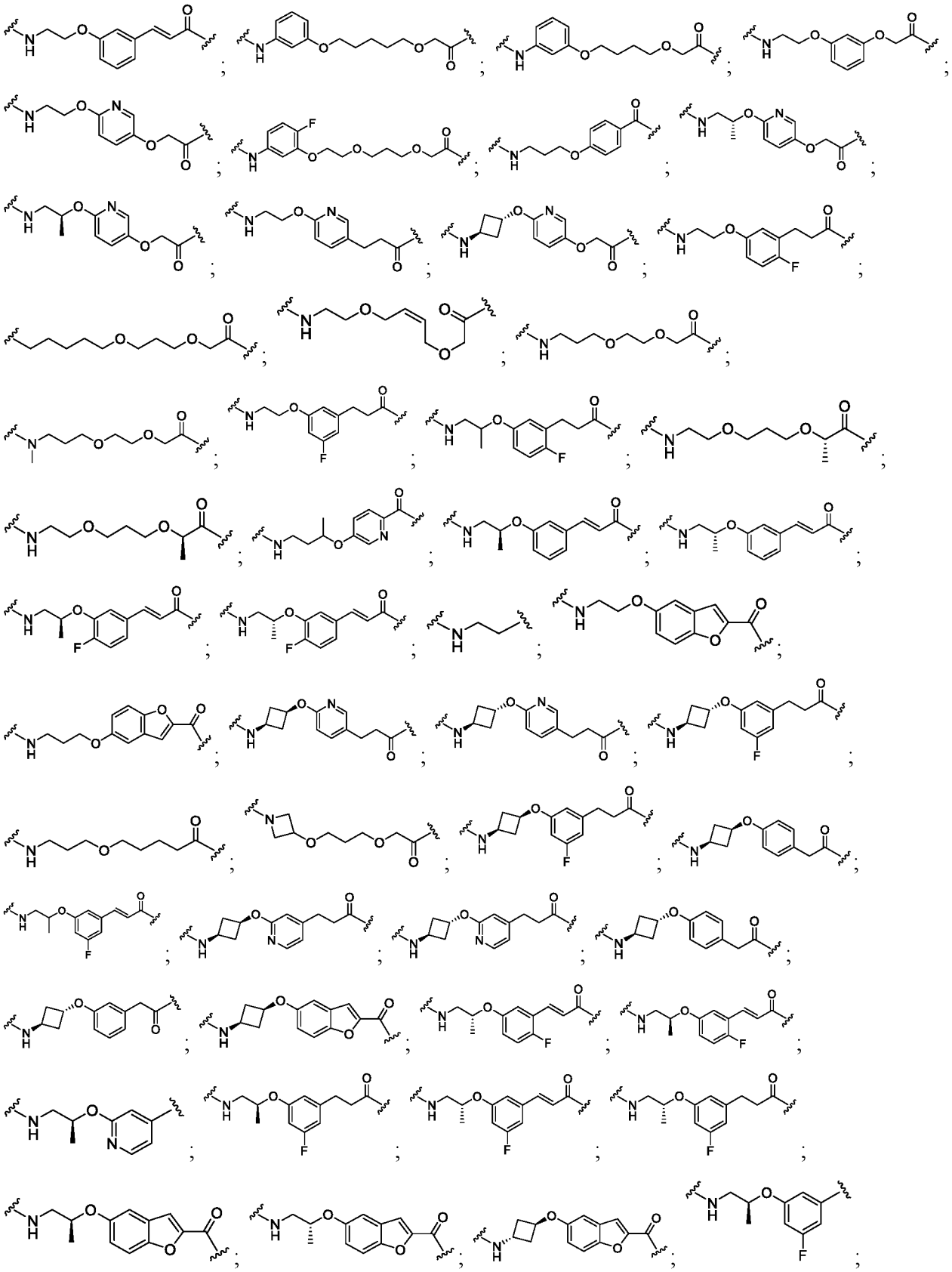


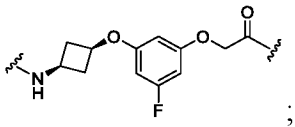
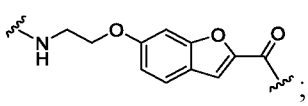
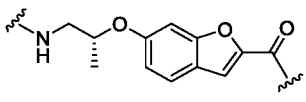
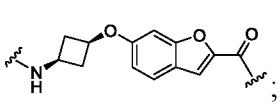
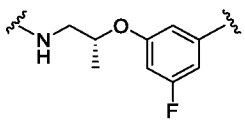
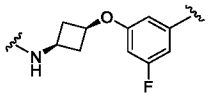
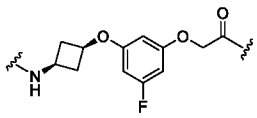
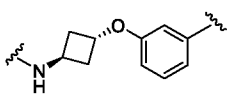
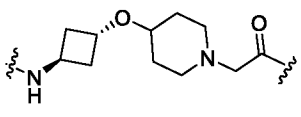
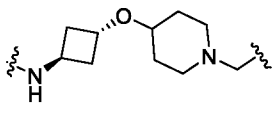
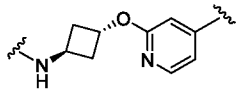
where each n and m of the linker can independently be 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20.

[0884] In any aspect or embodiment described herein, the A^L is selected from the group consisting of:

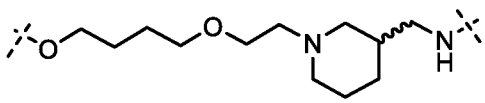
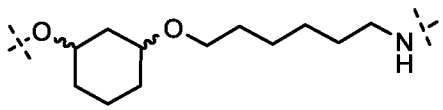
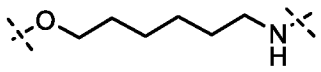
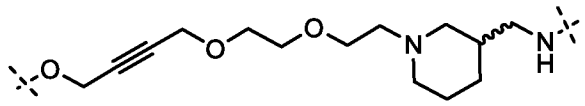
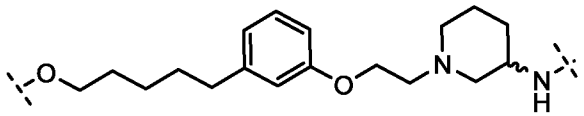
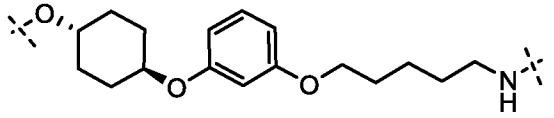
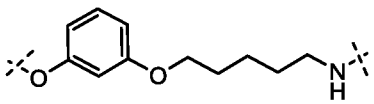
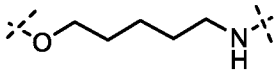
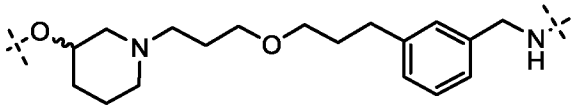
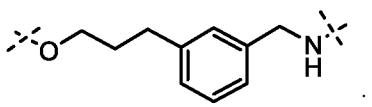
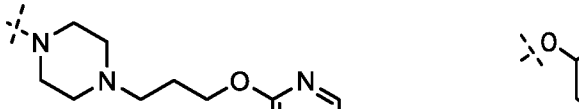



























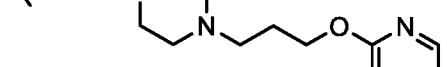
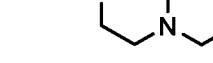


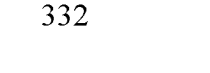


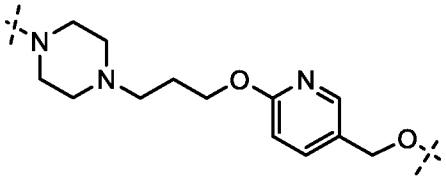










and  , wherein each m and n is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20.

[0885] In any aspect or embodiment described herein, the A^L is selected from the group consisting of:

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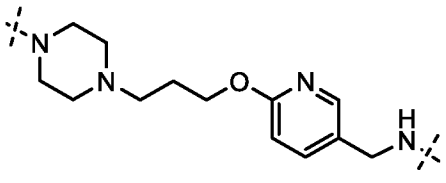
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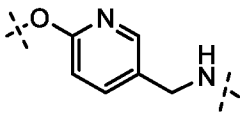
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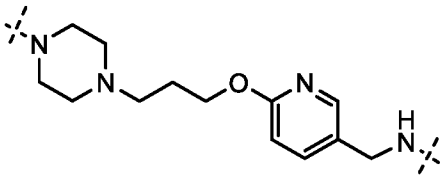
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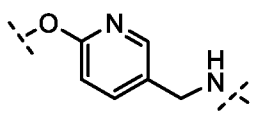
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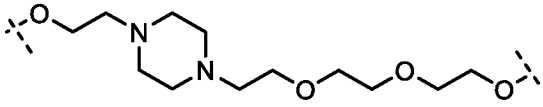
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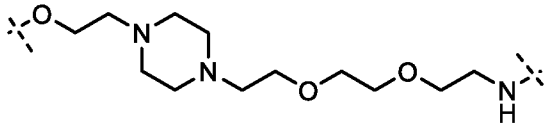
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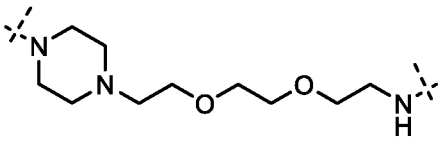
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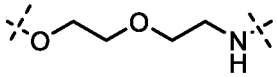
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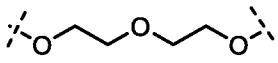
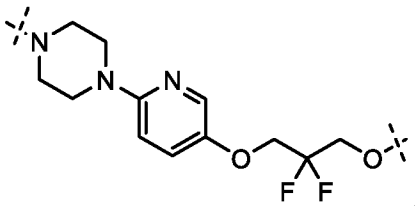
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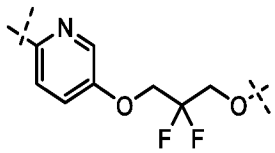
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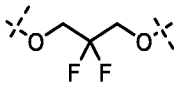
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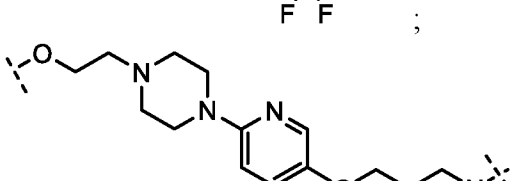
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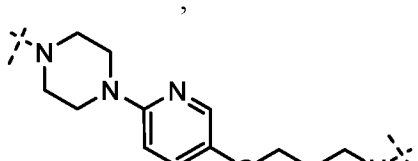
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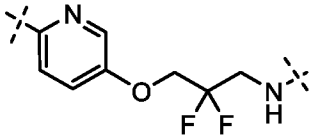
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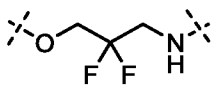
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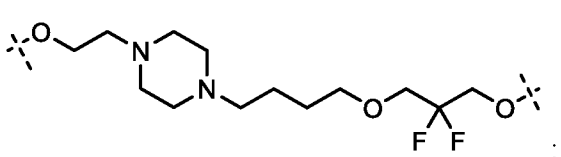
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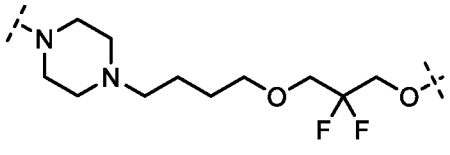
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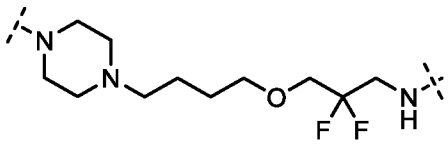
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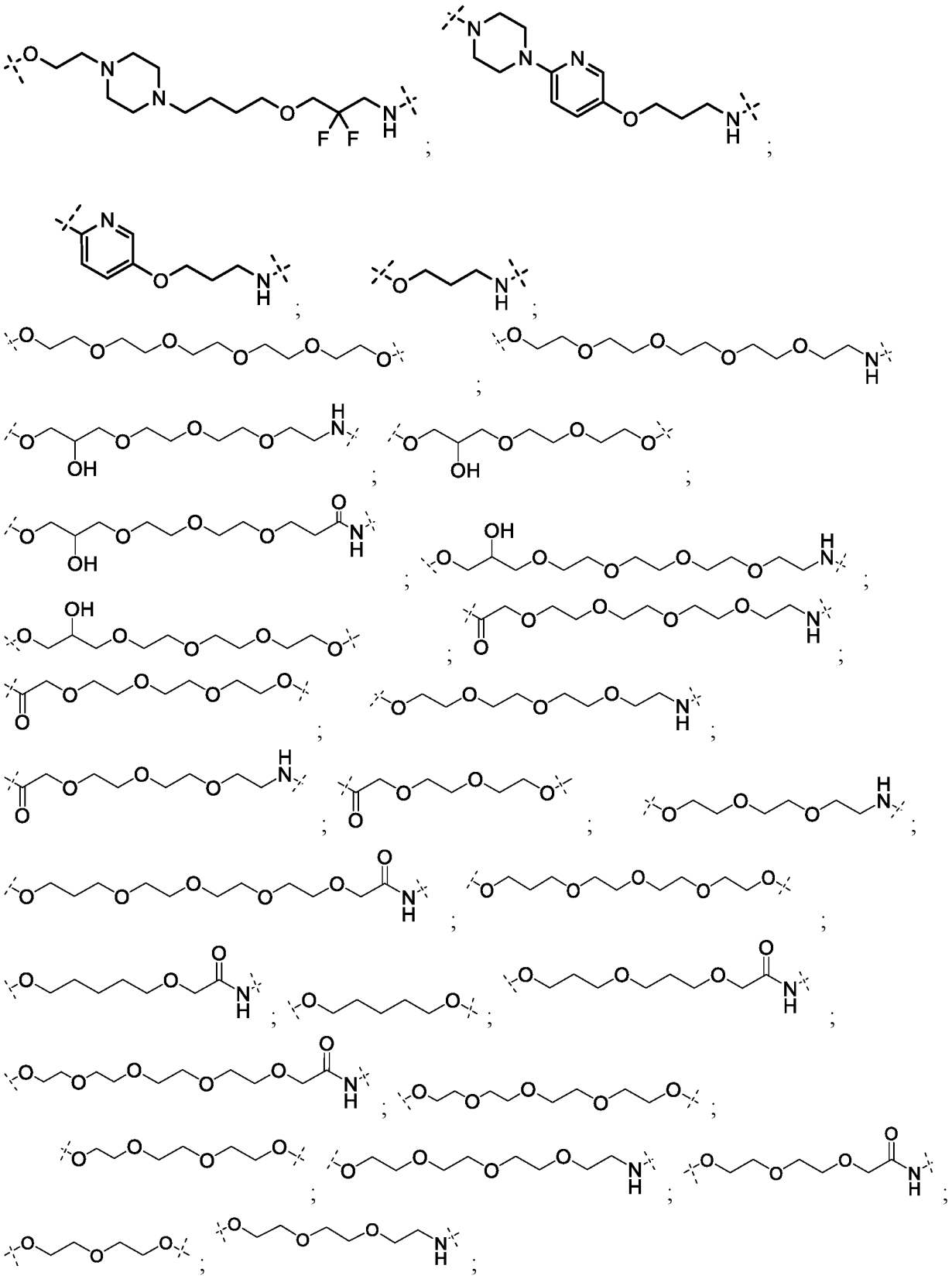
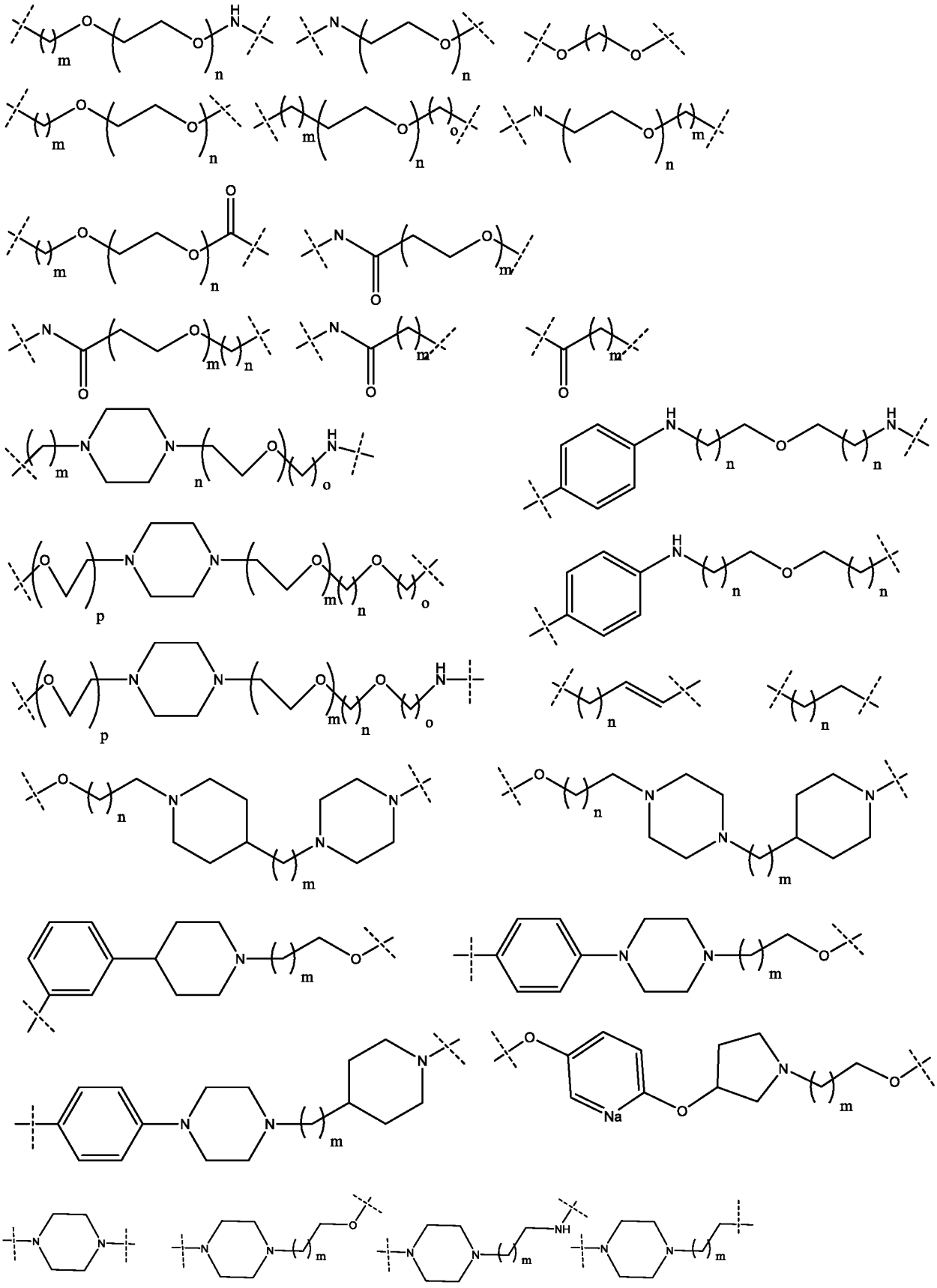
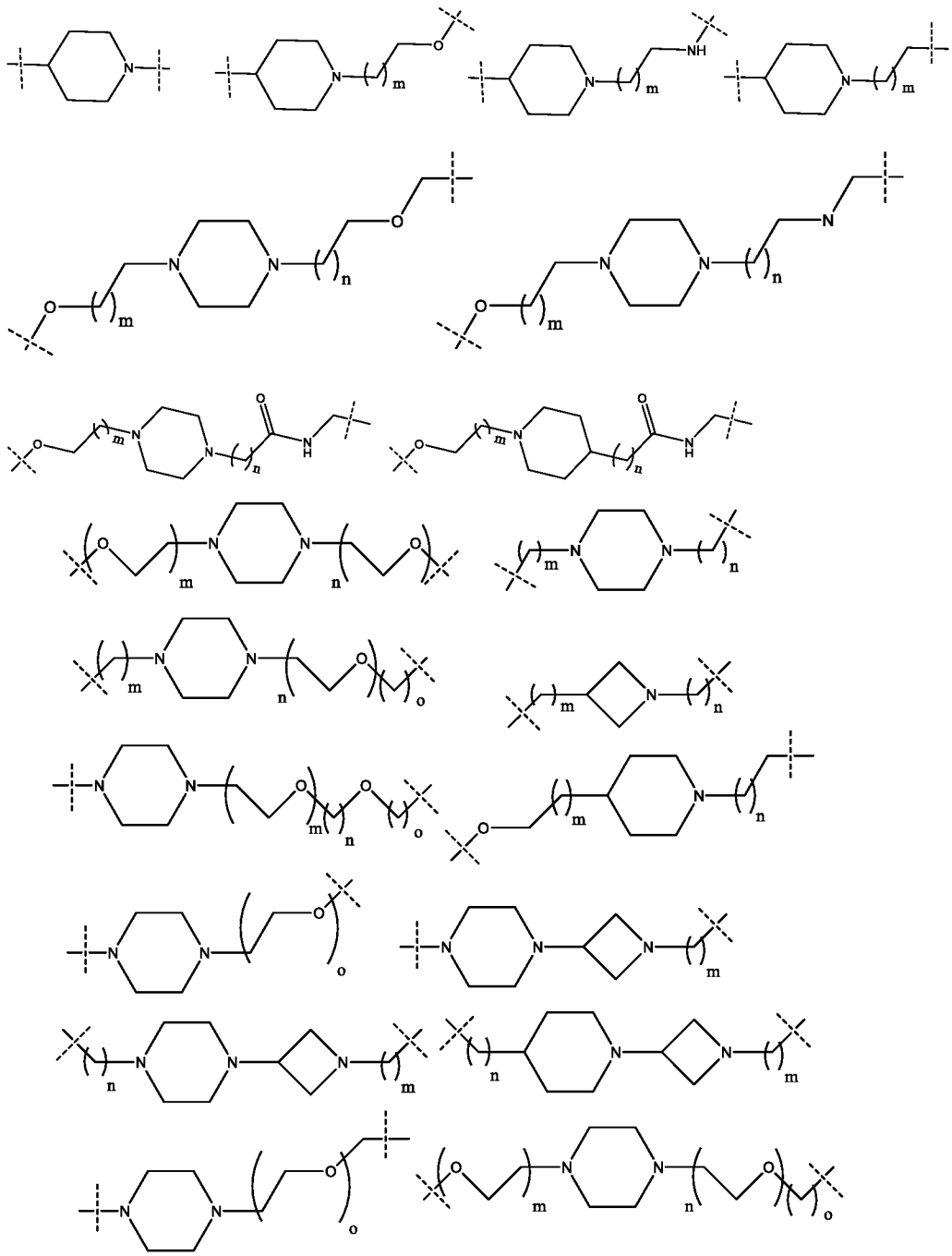
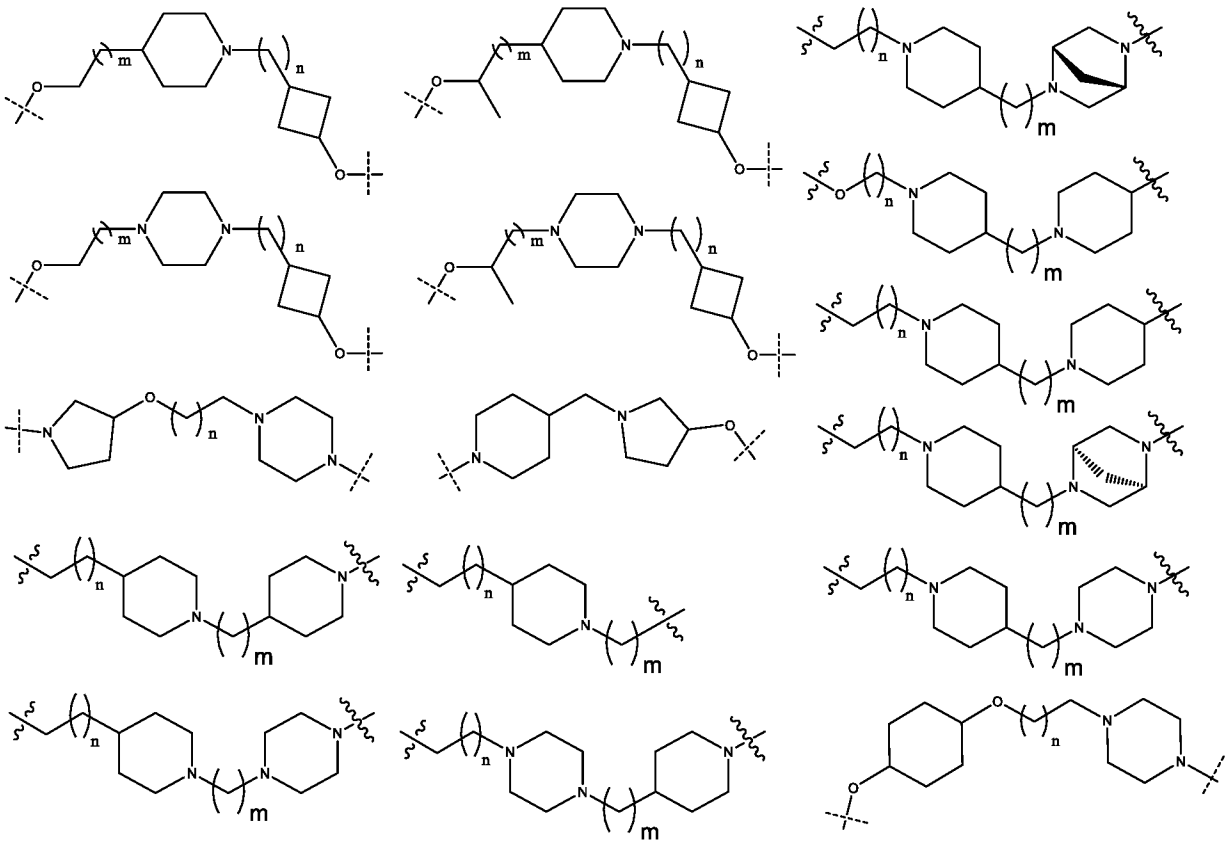
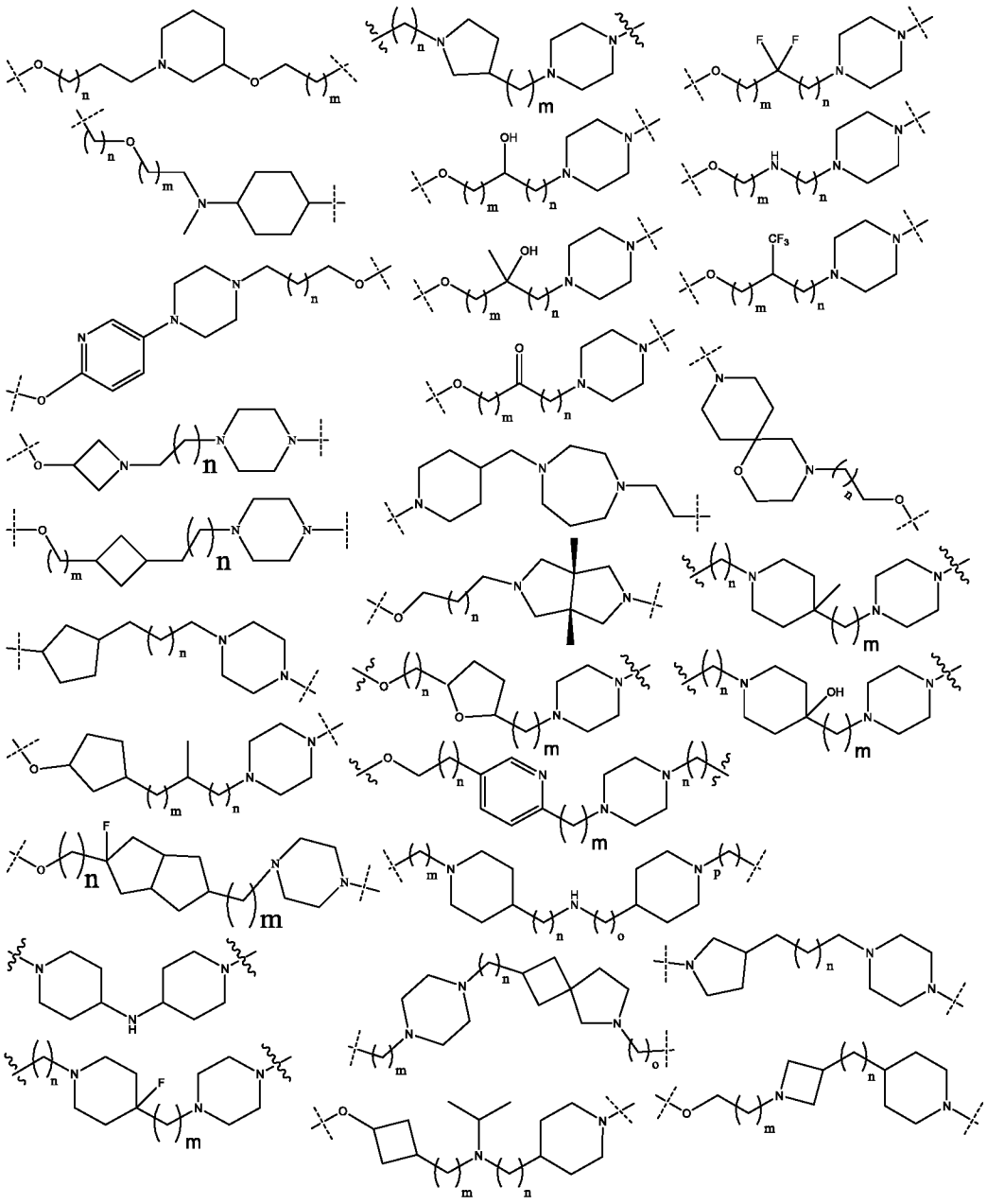
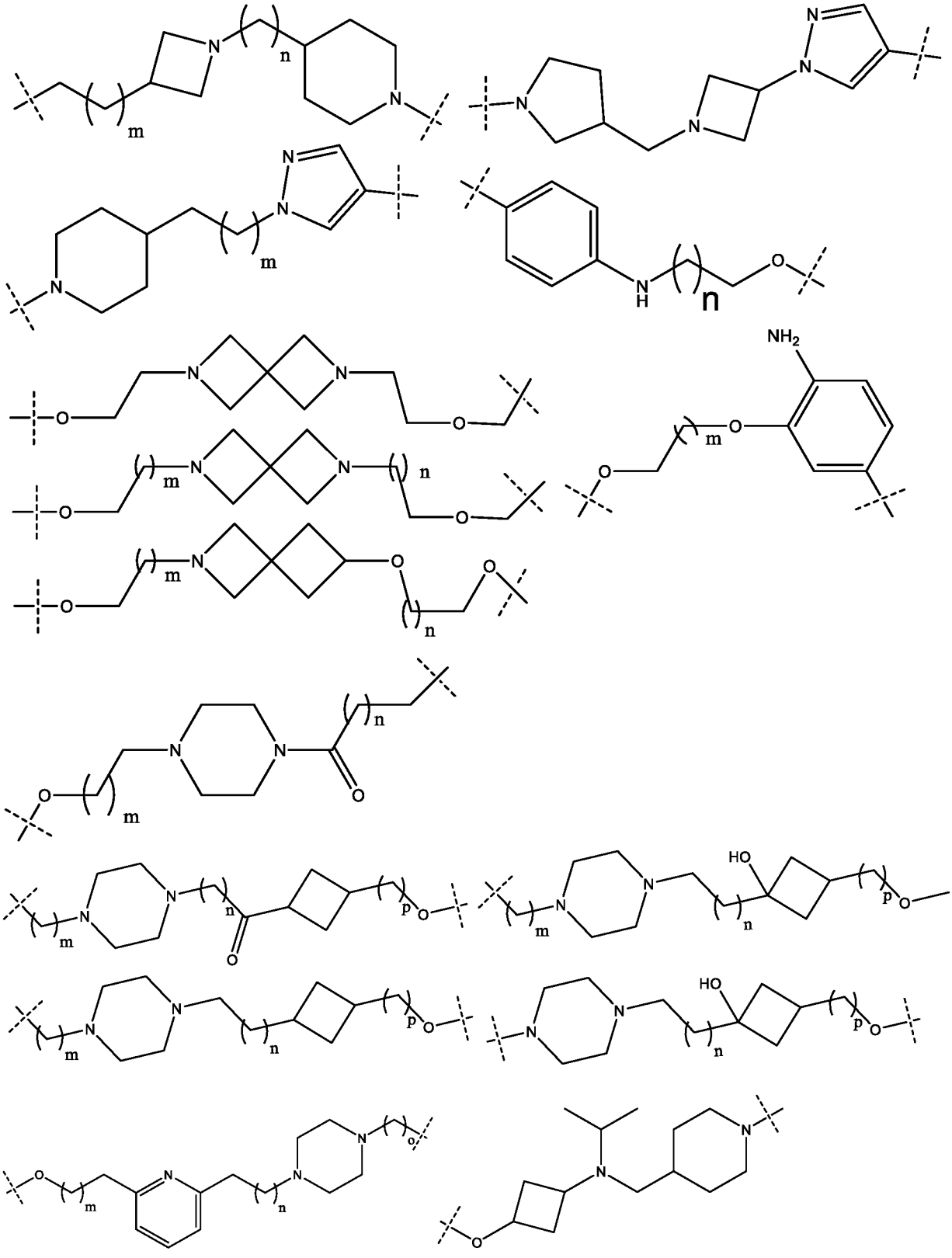


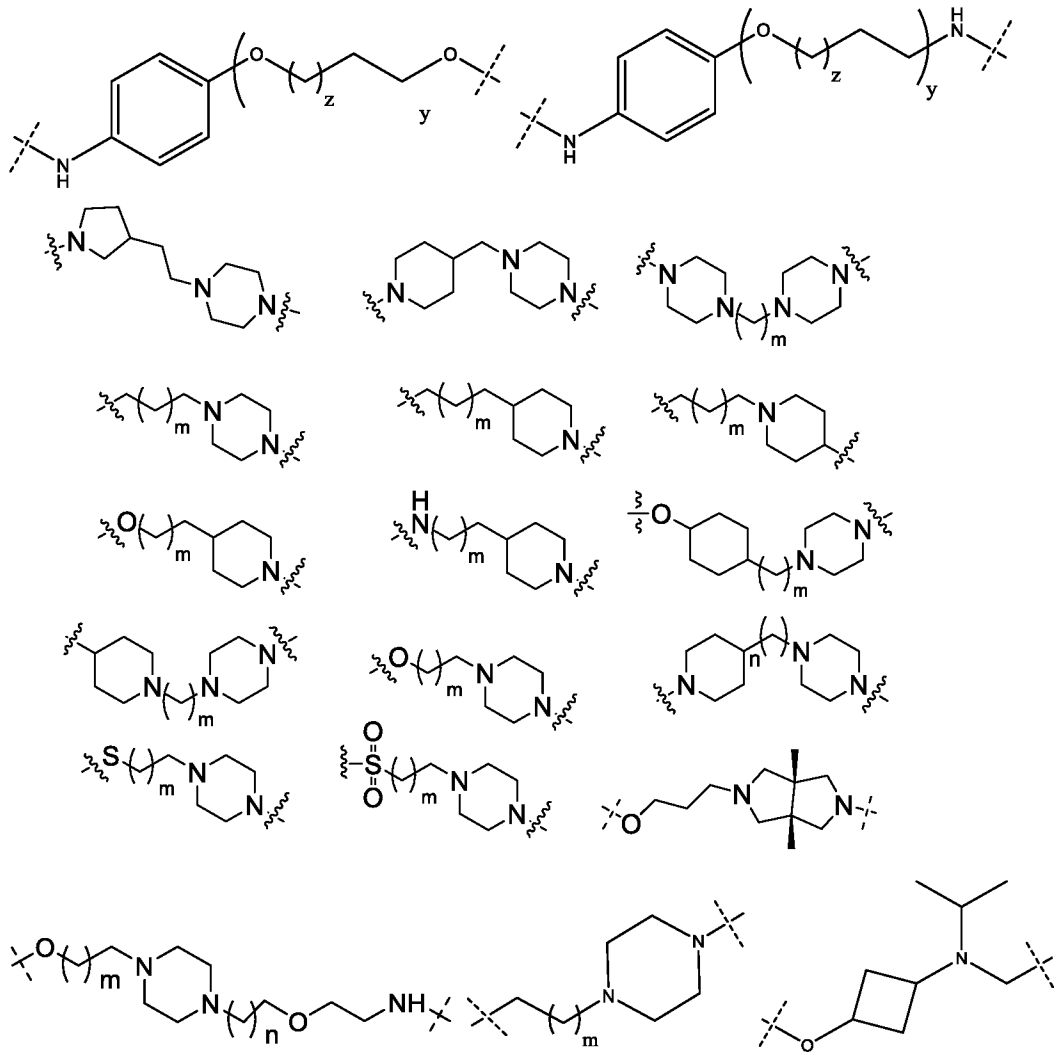


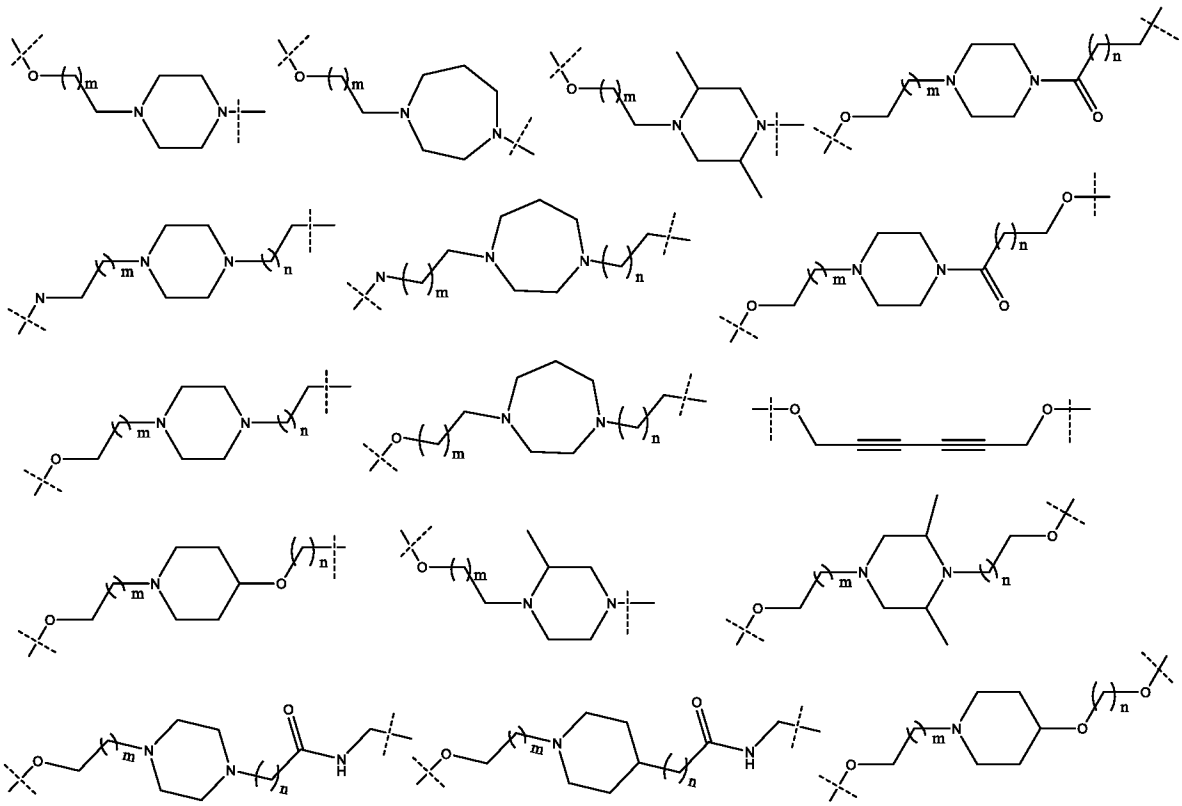


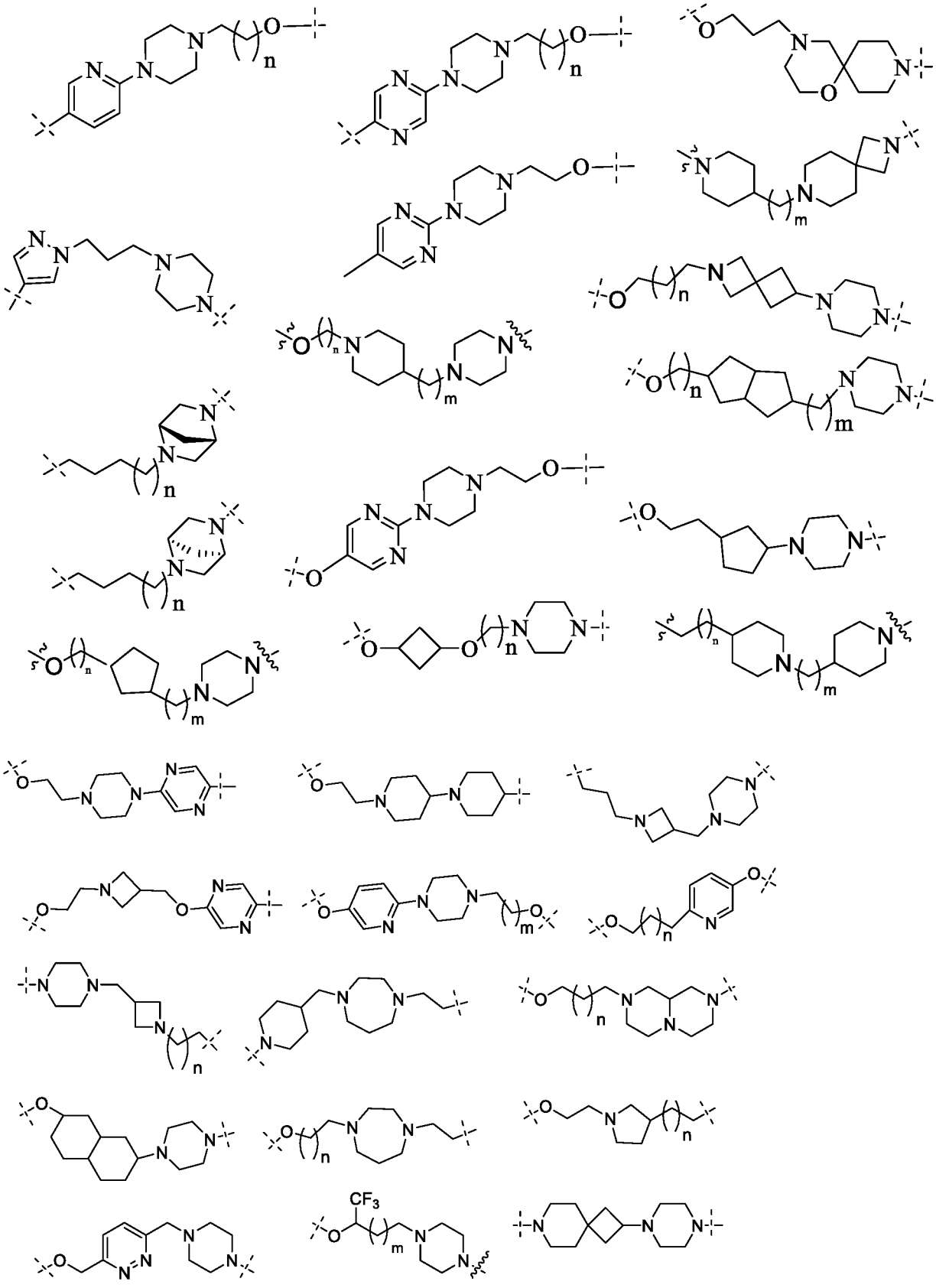


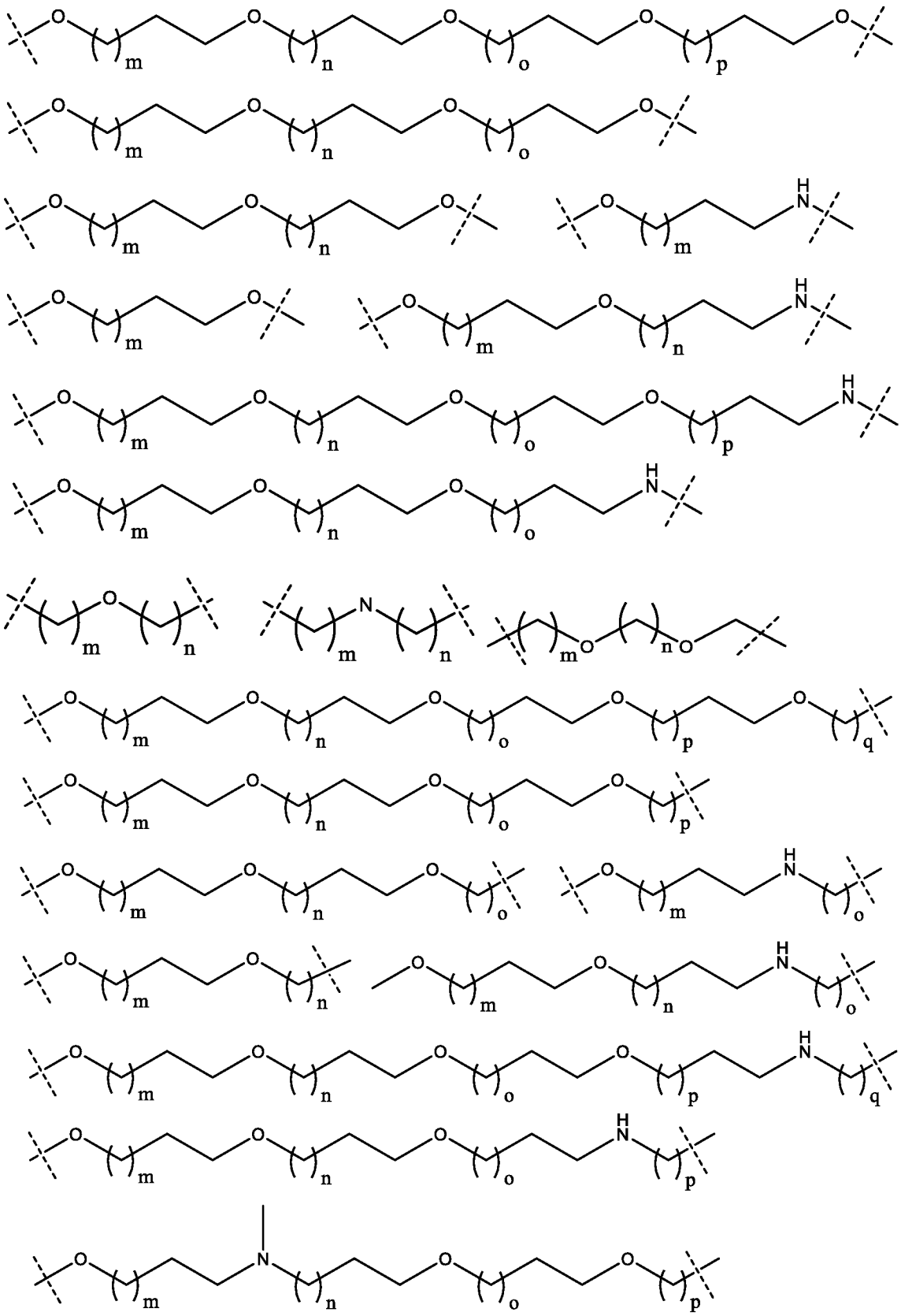


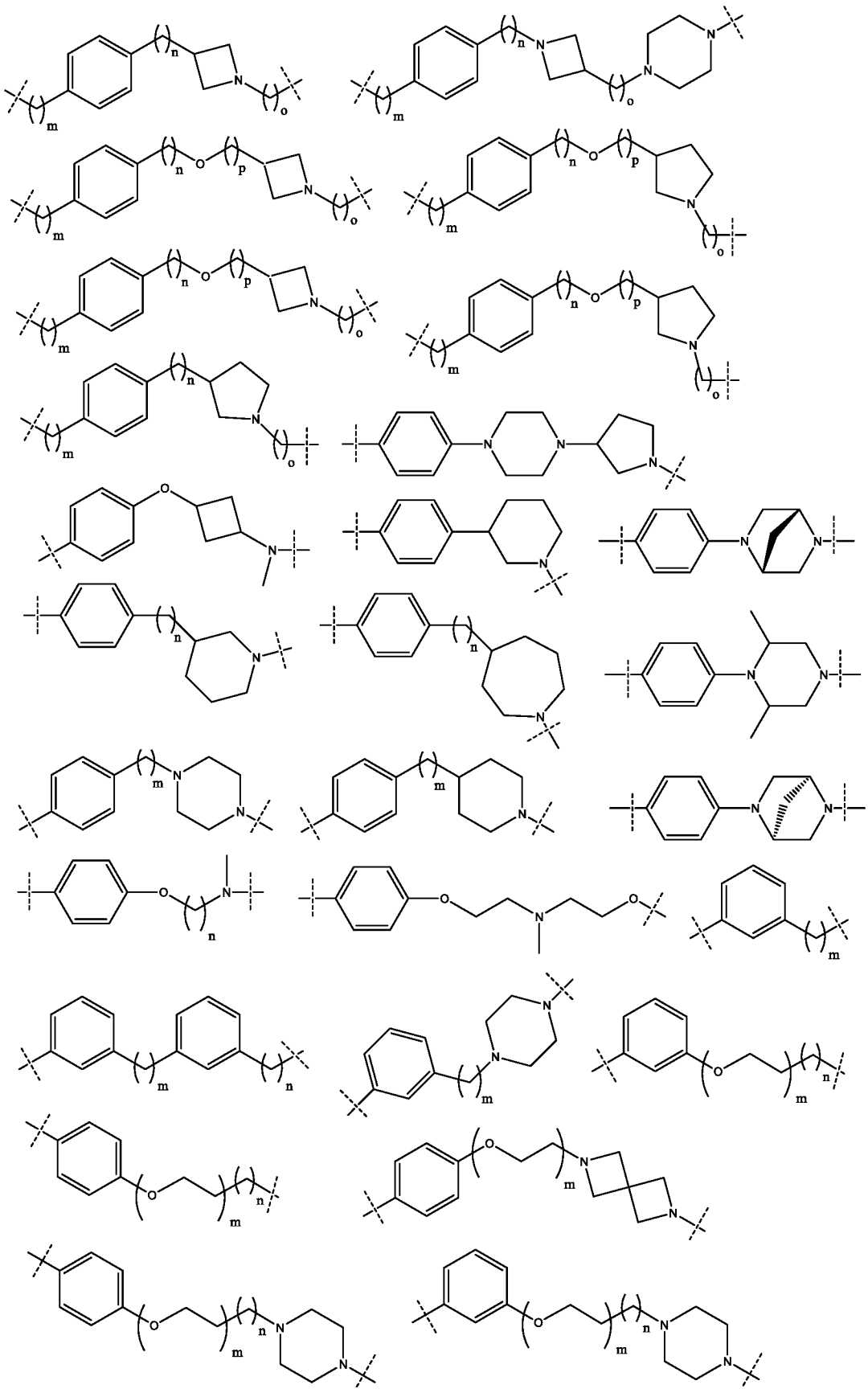


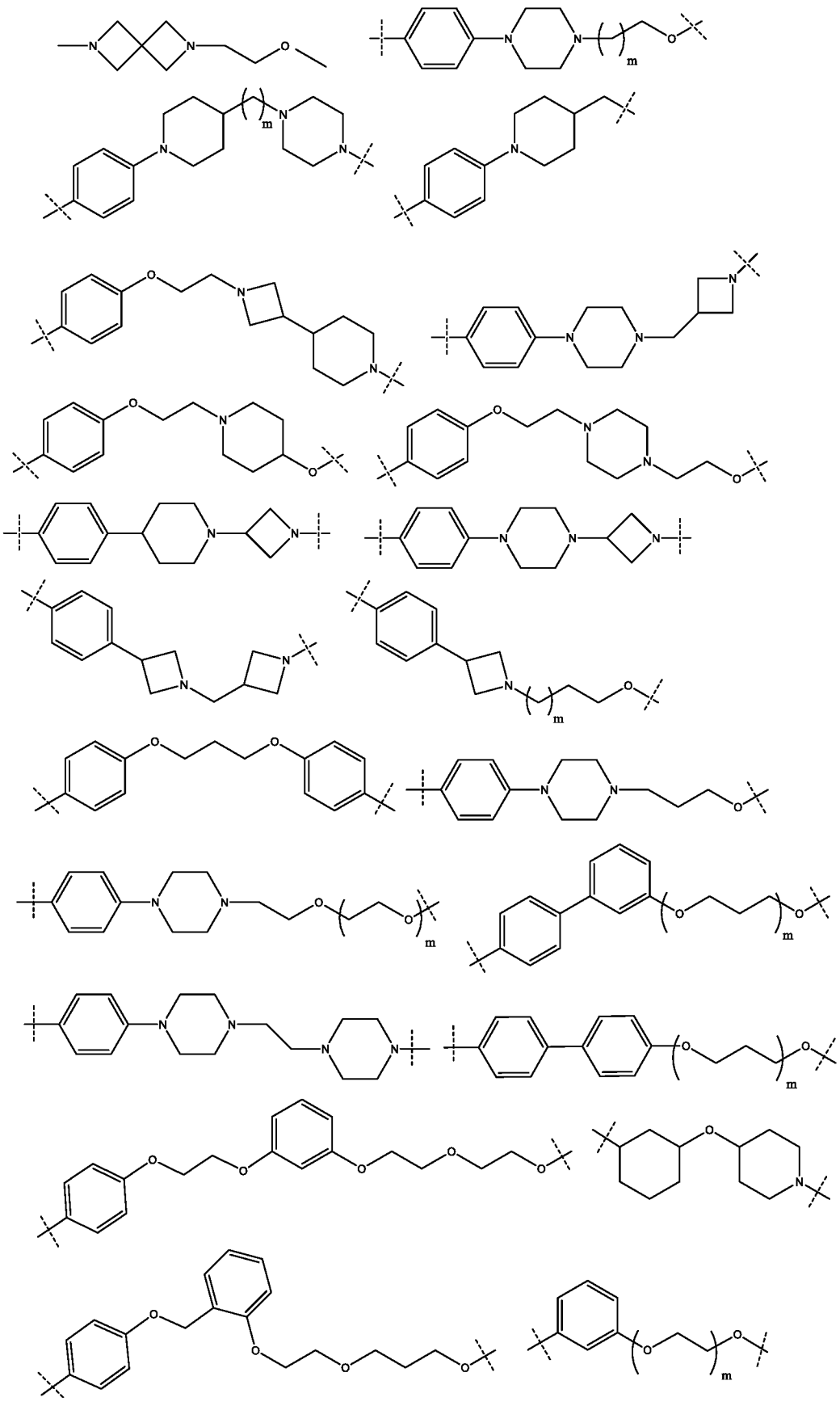


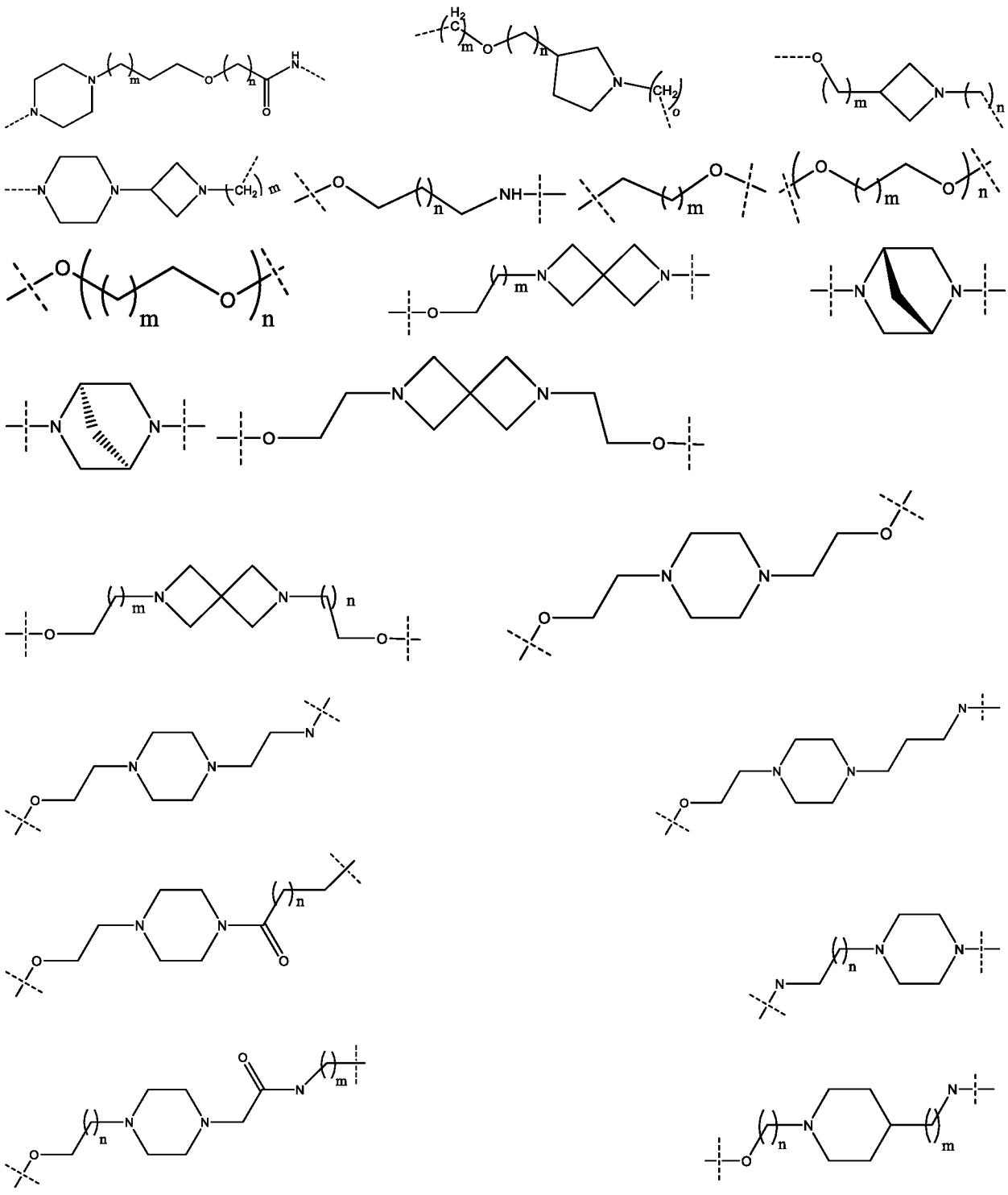


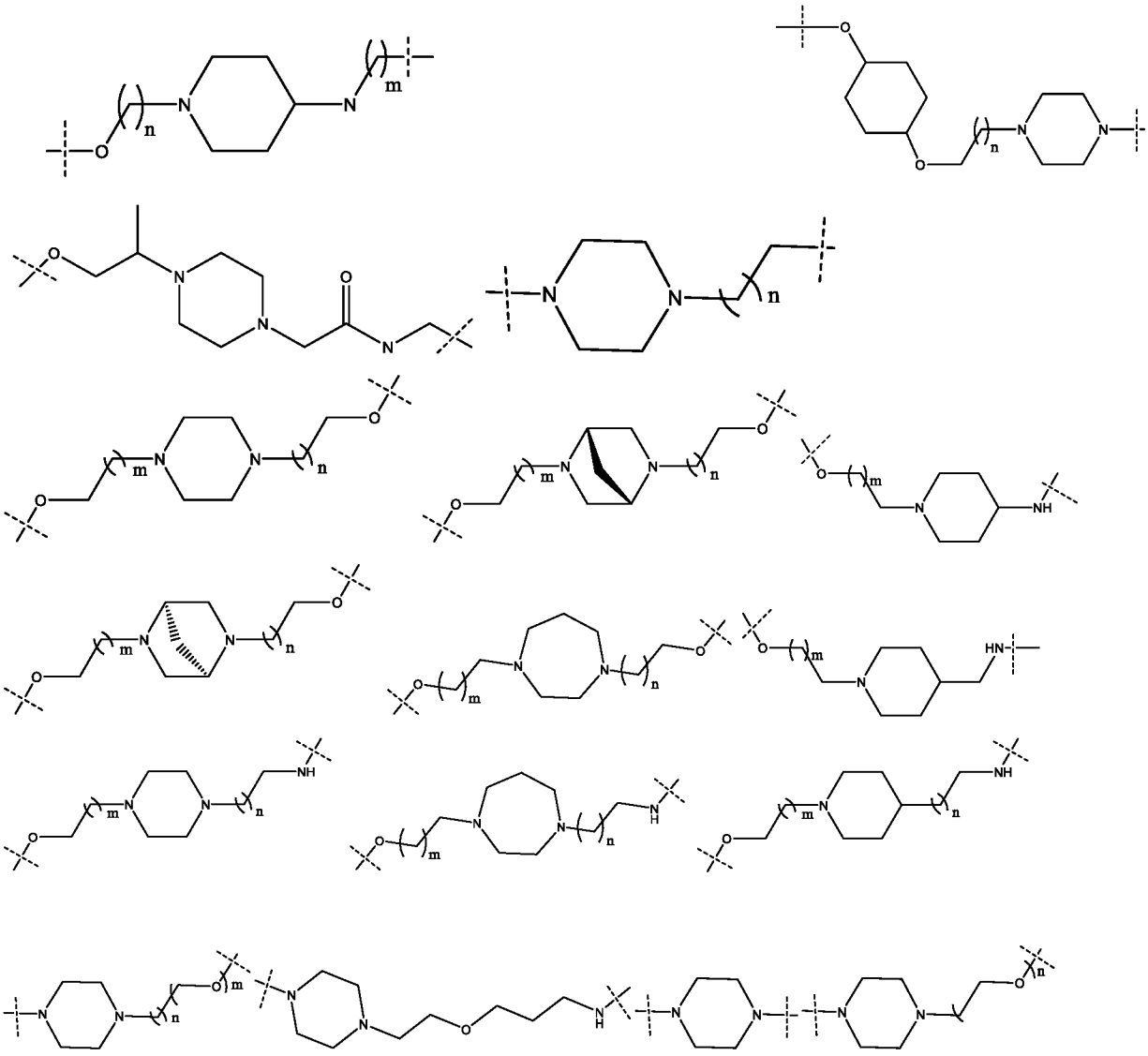


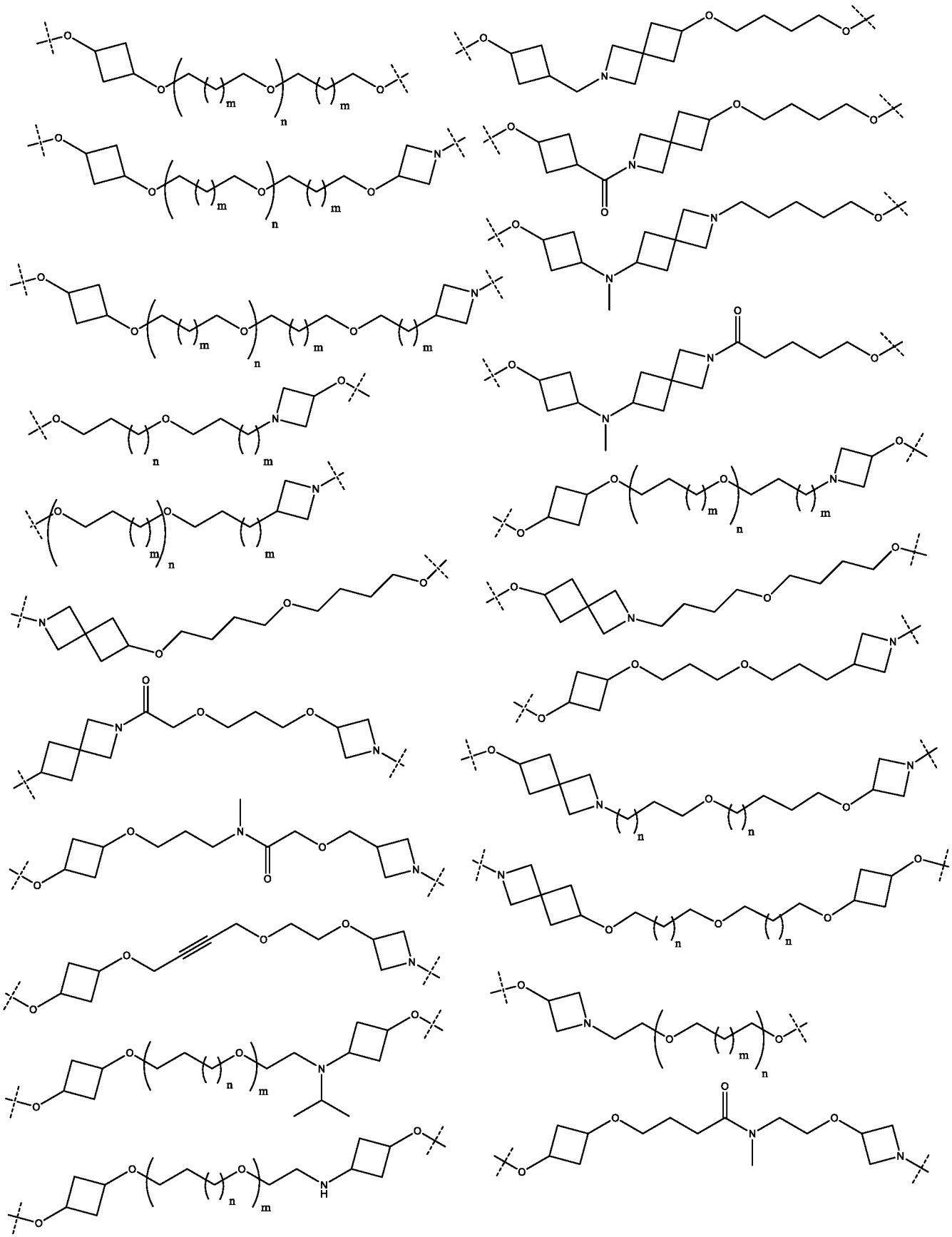


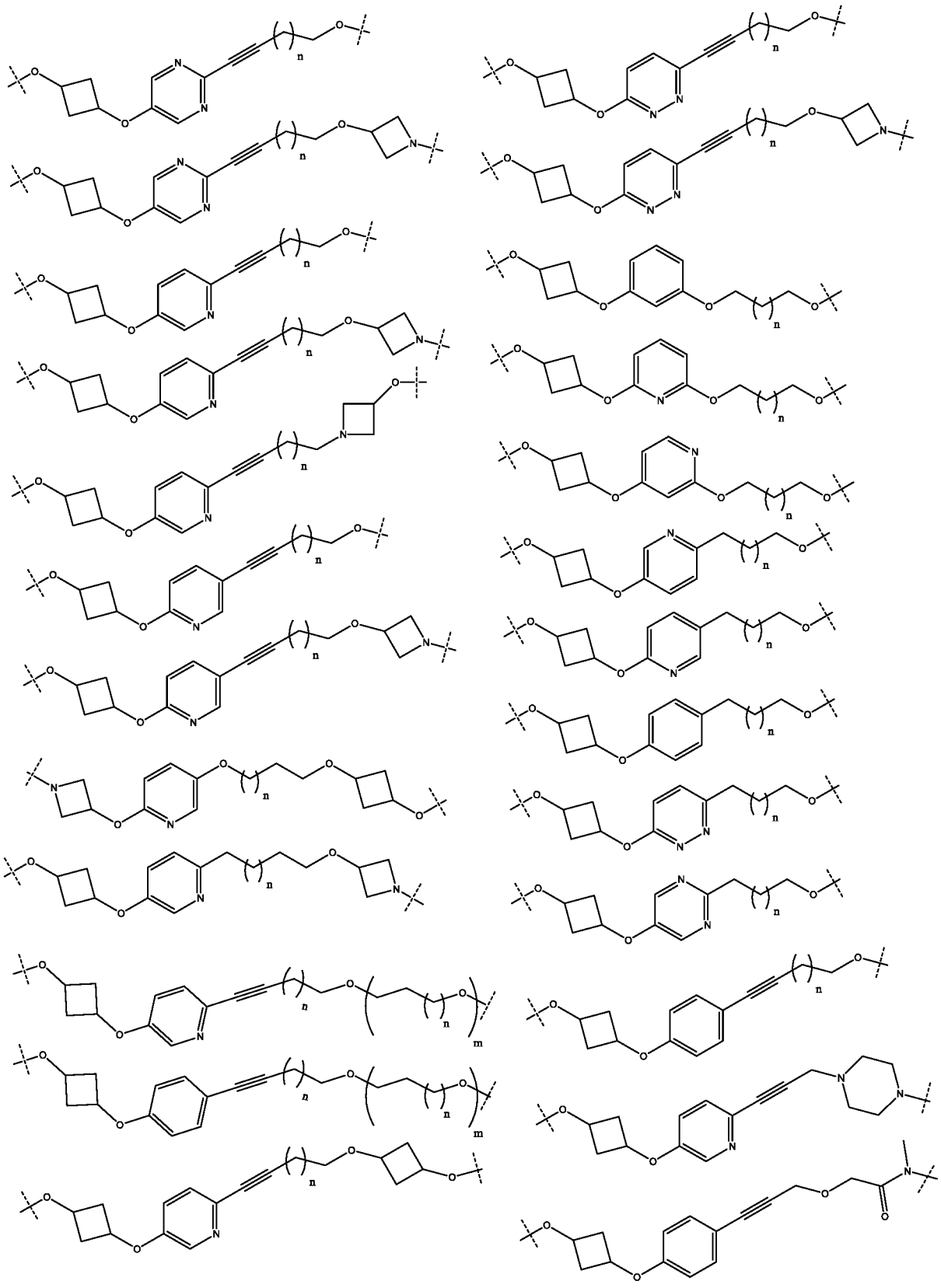


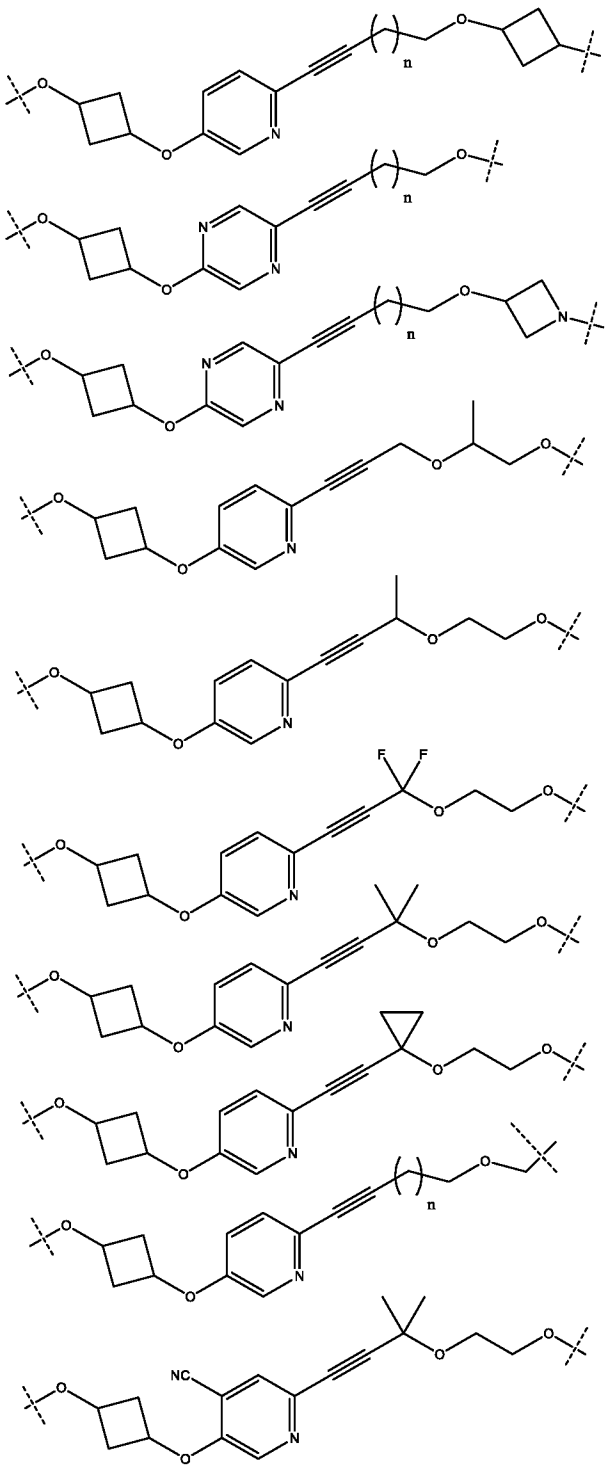


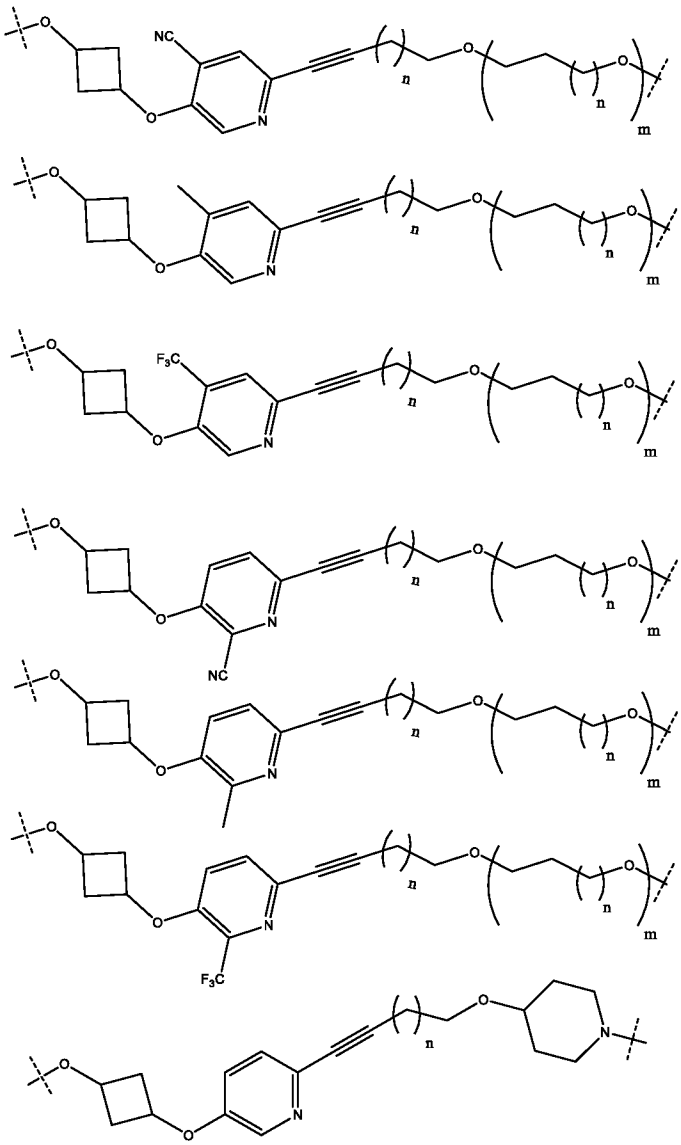


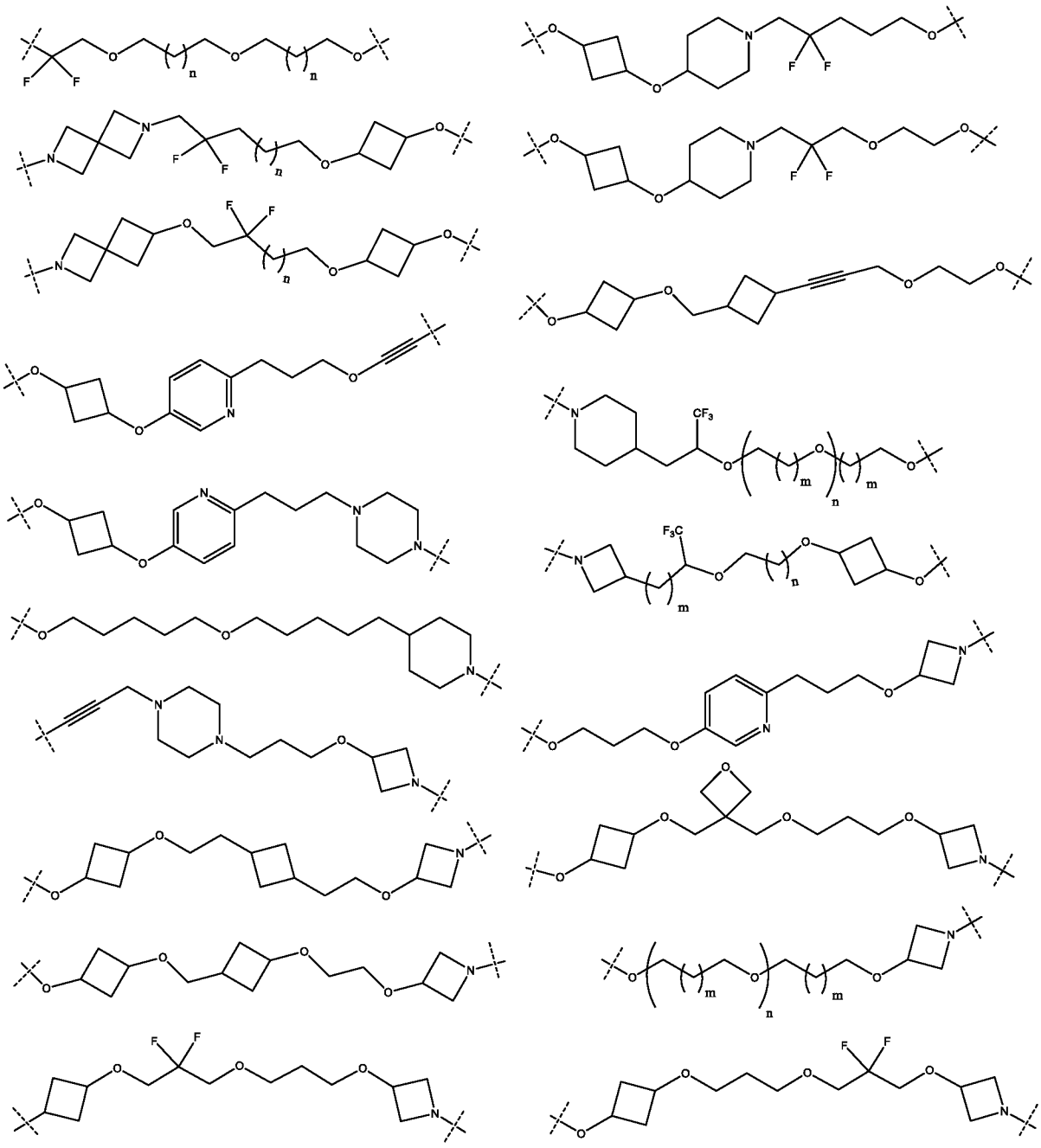


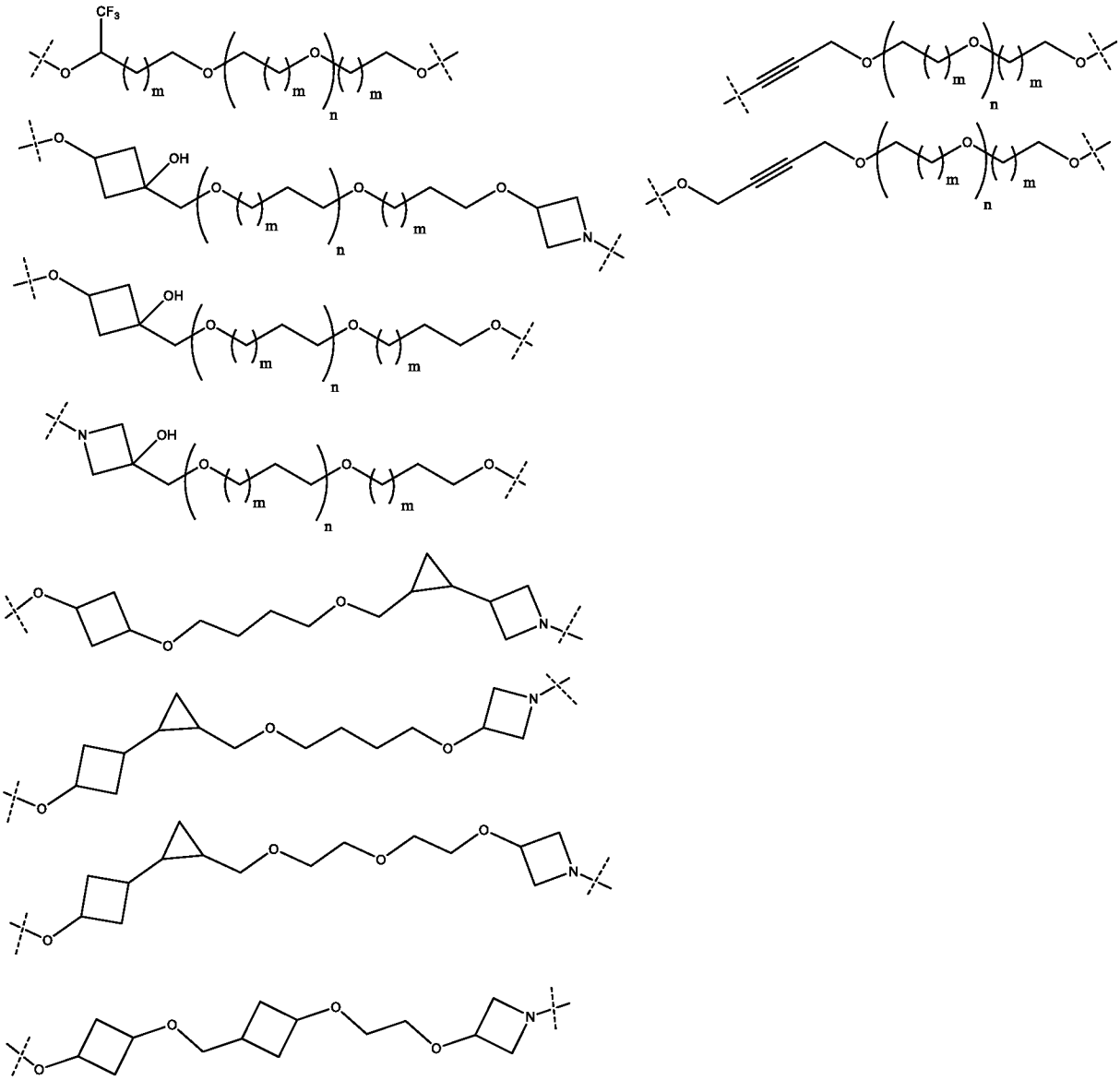


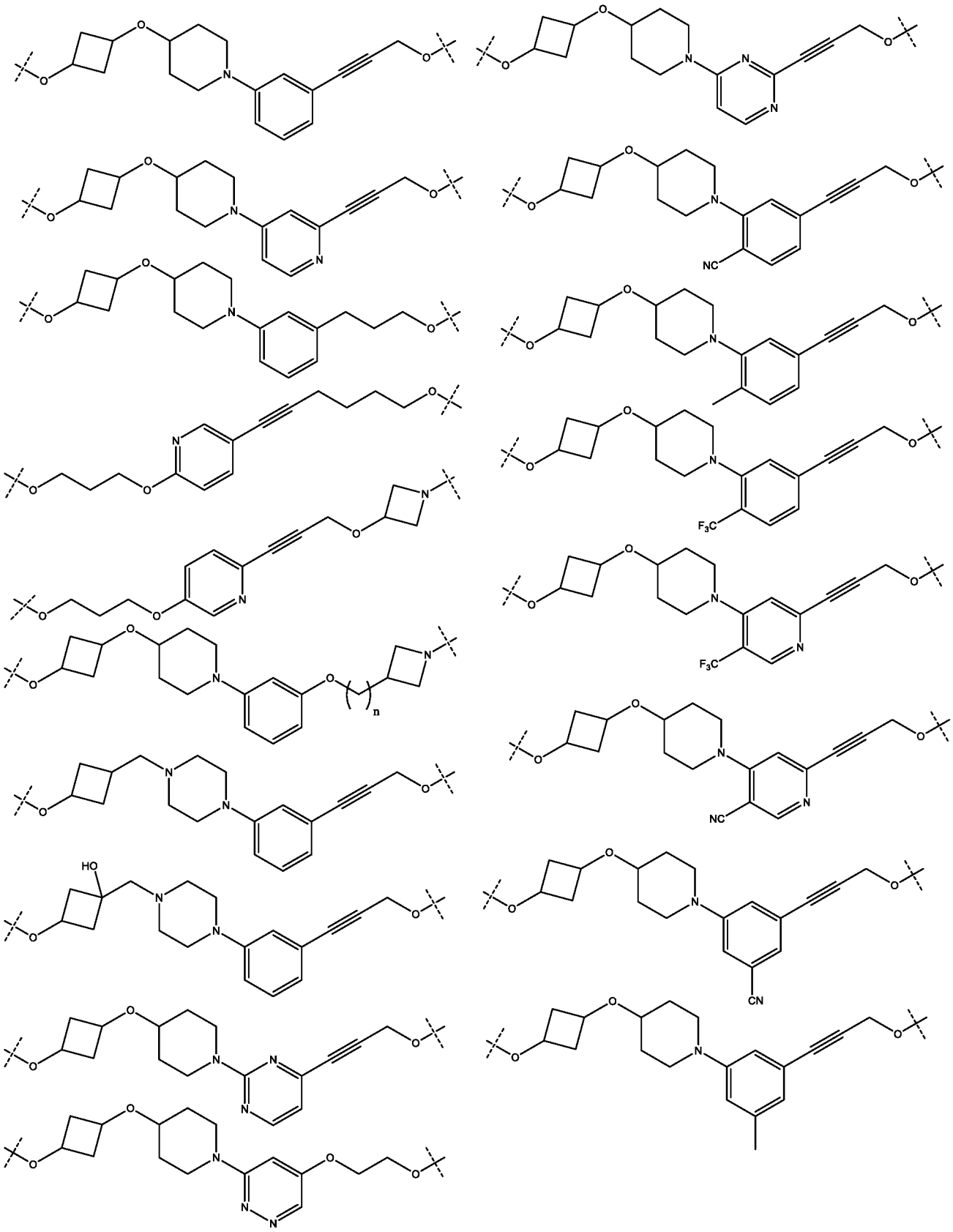


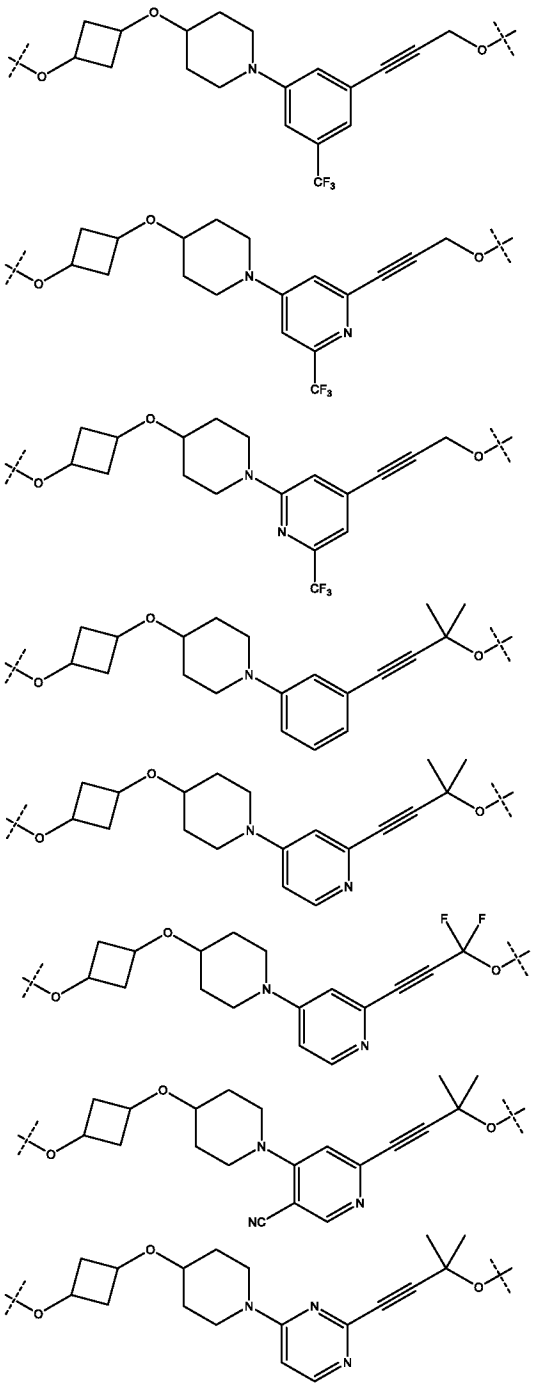


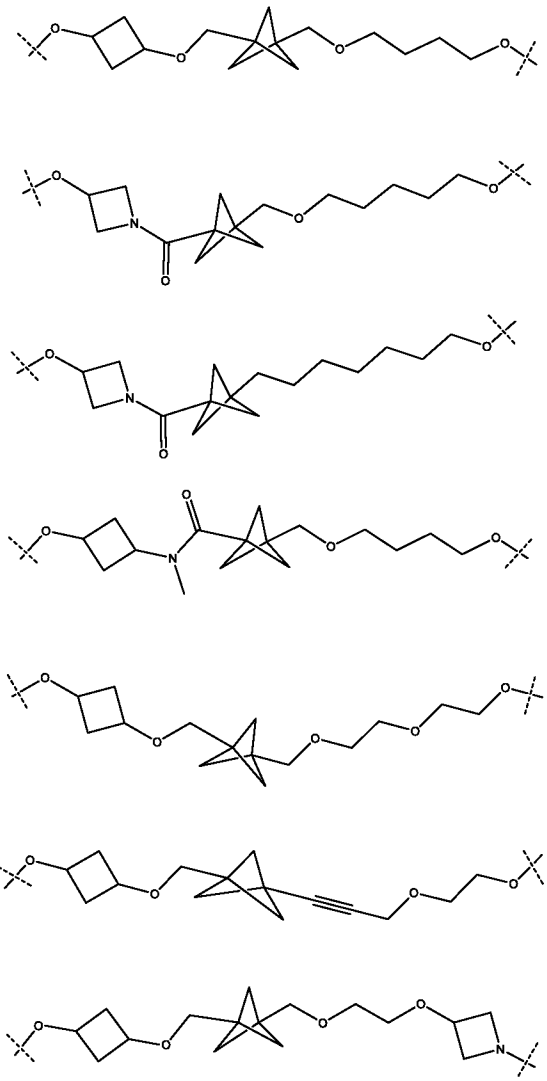


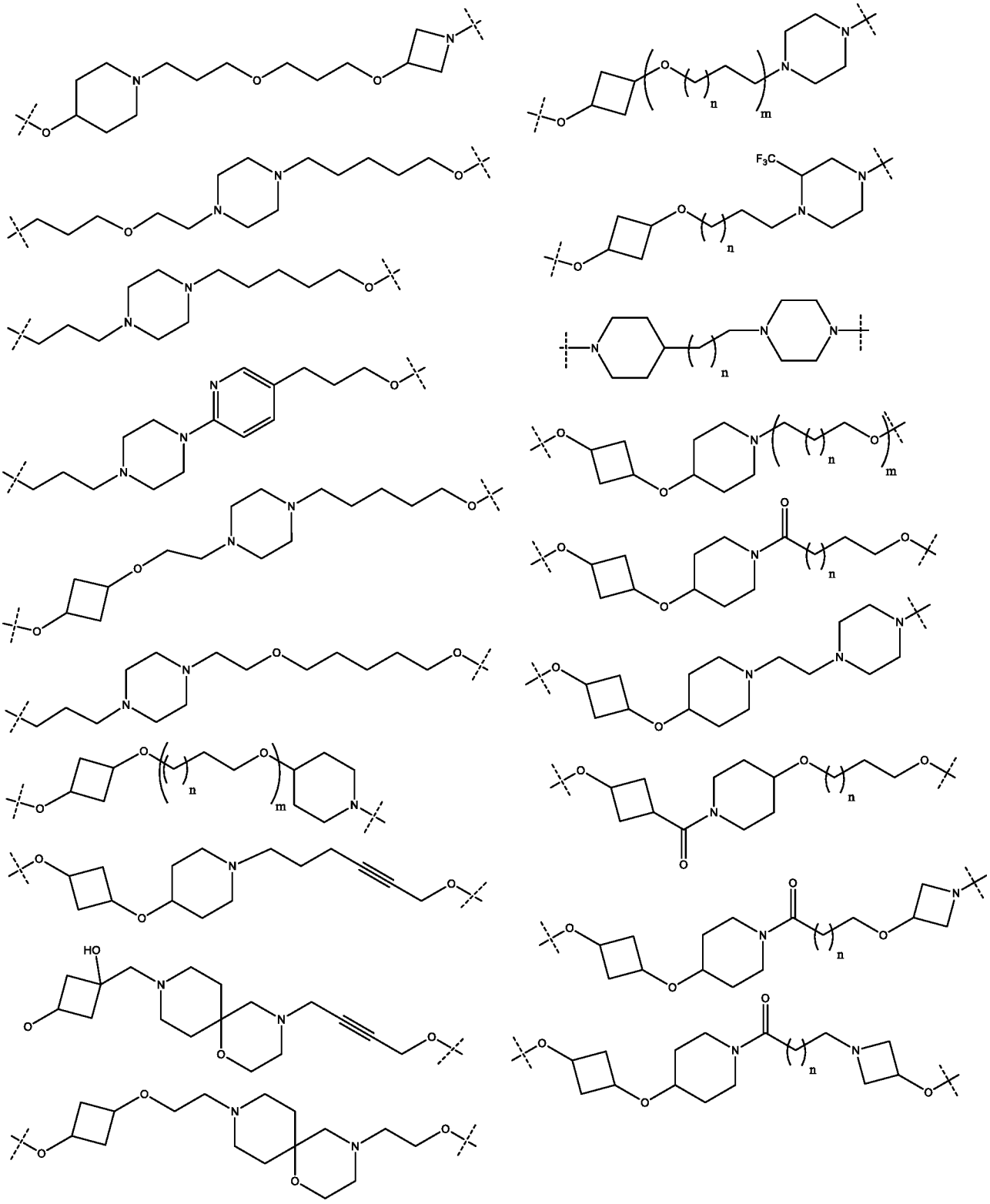


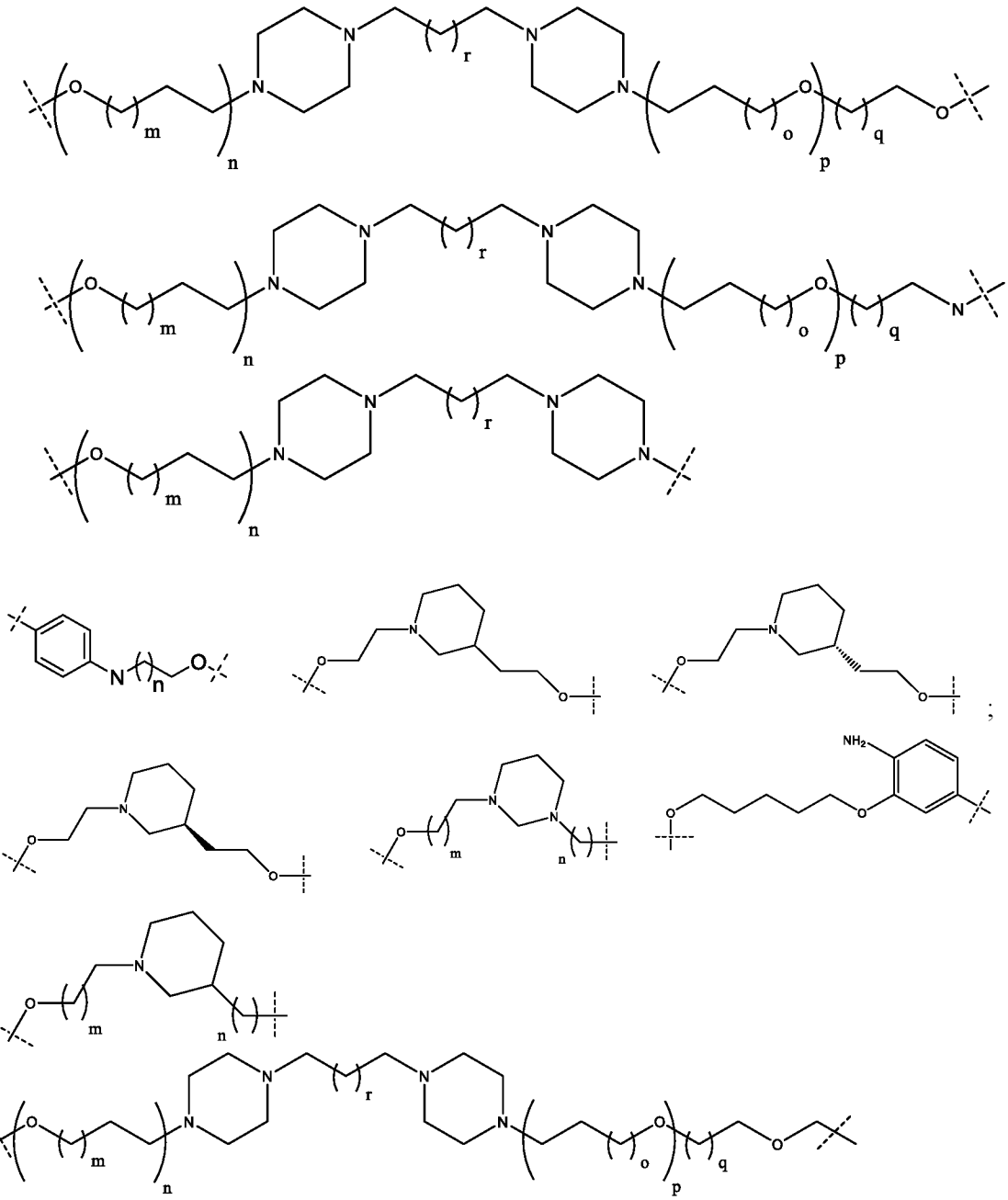


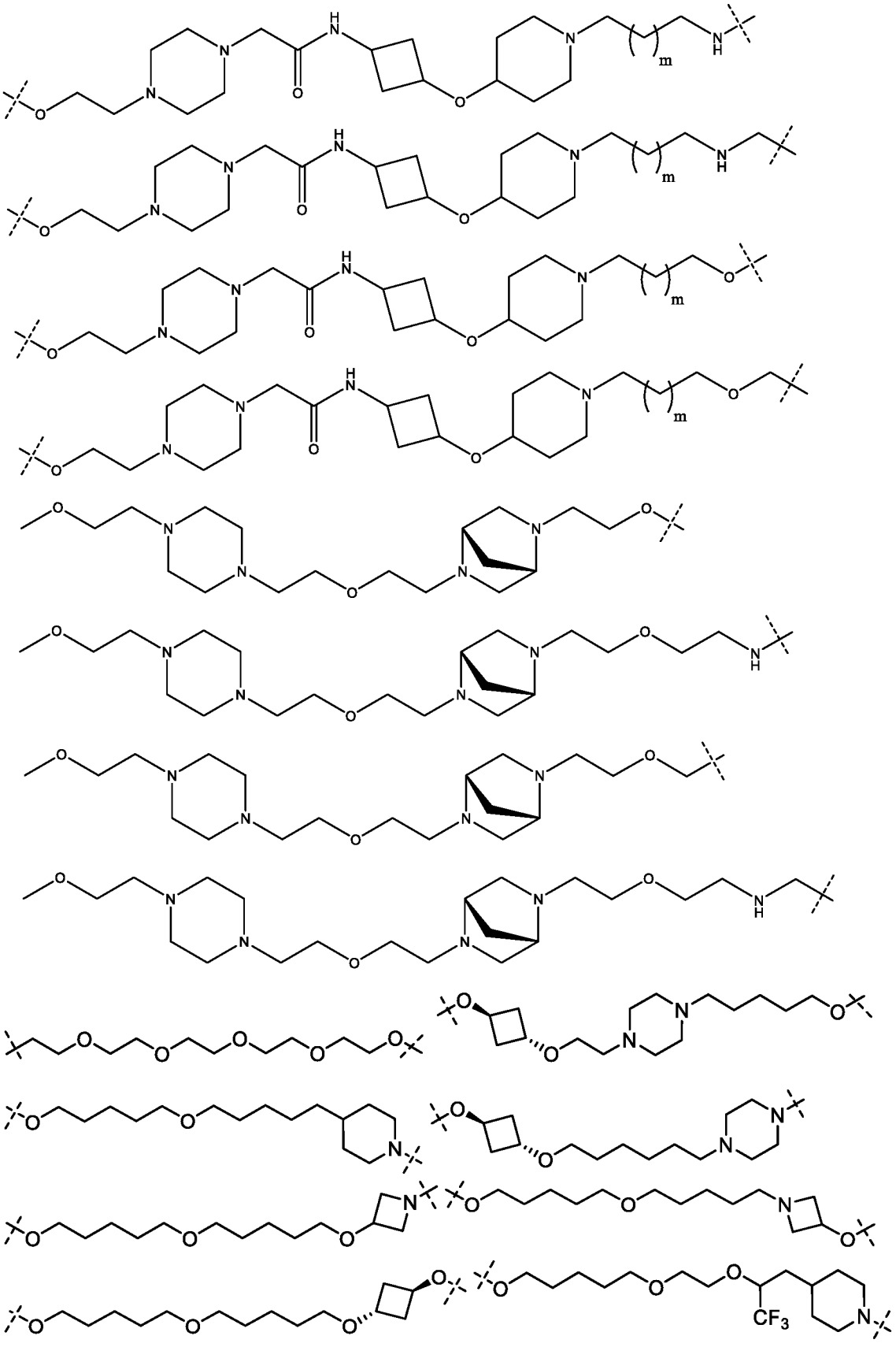


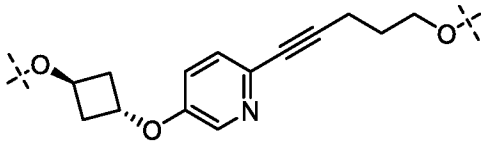






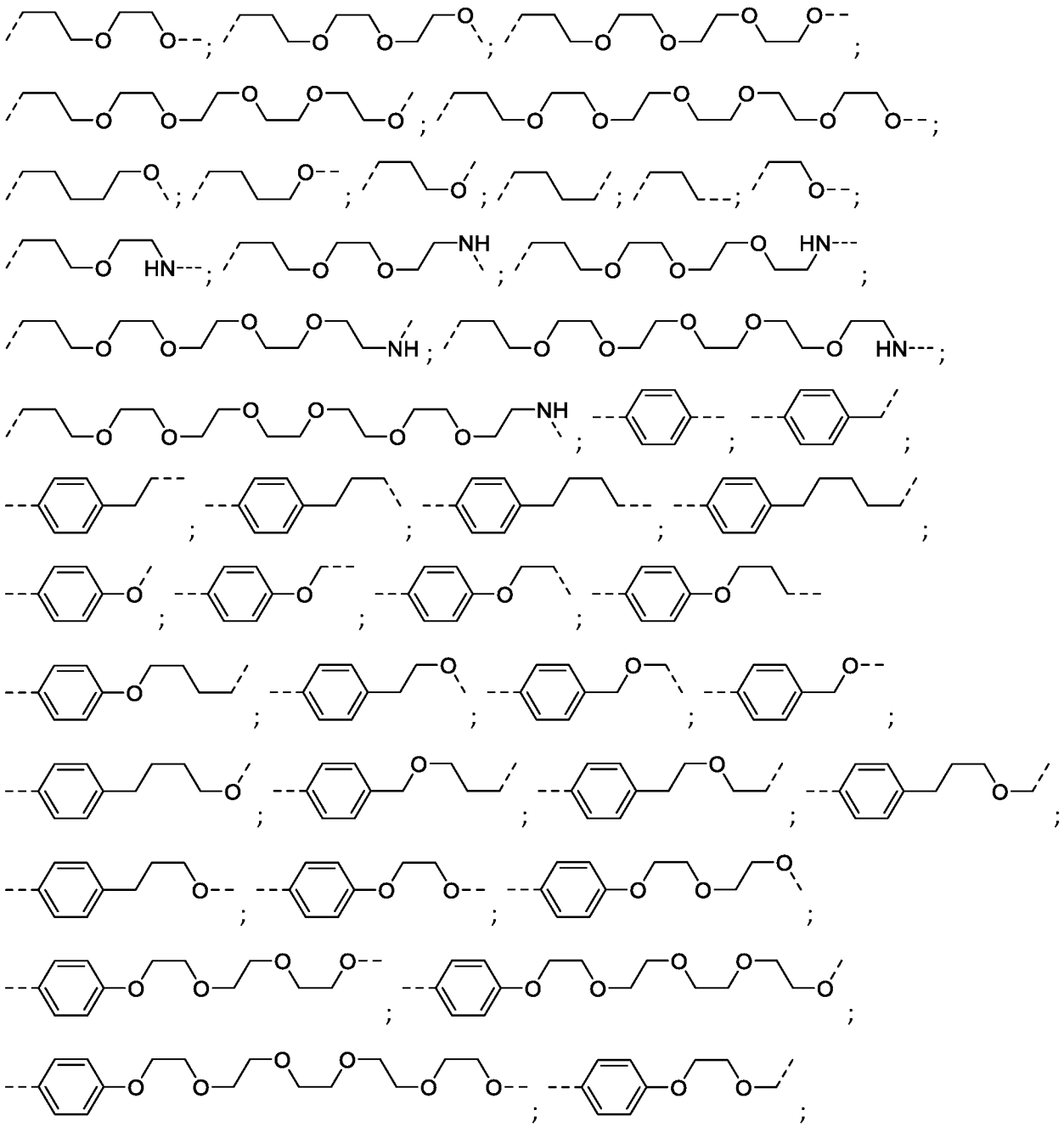


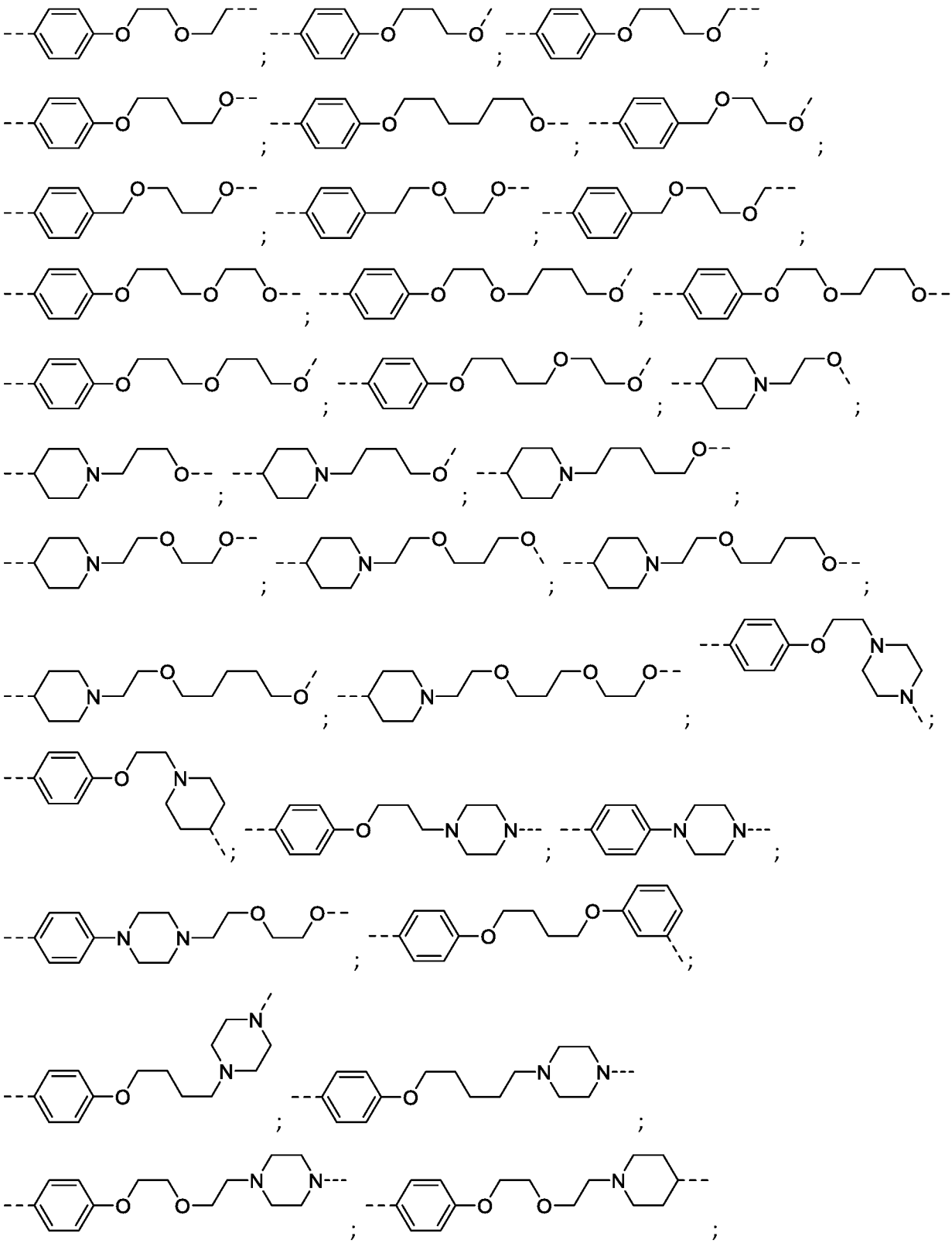


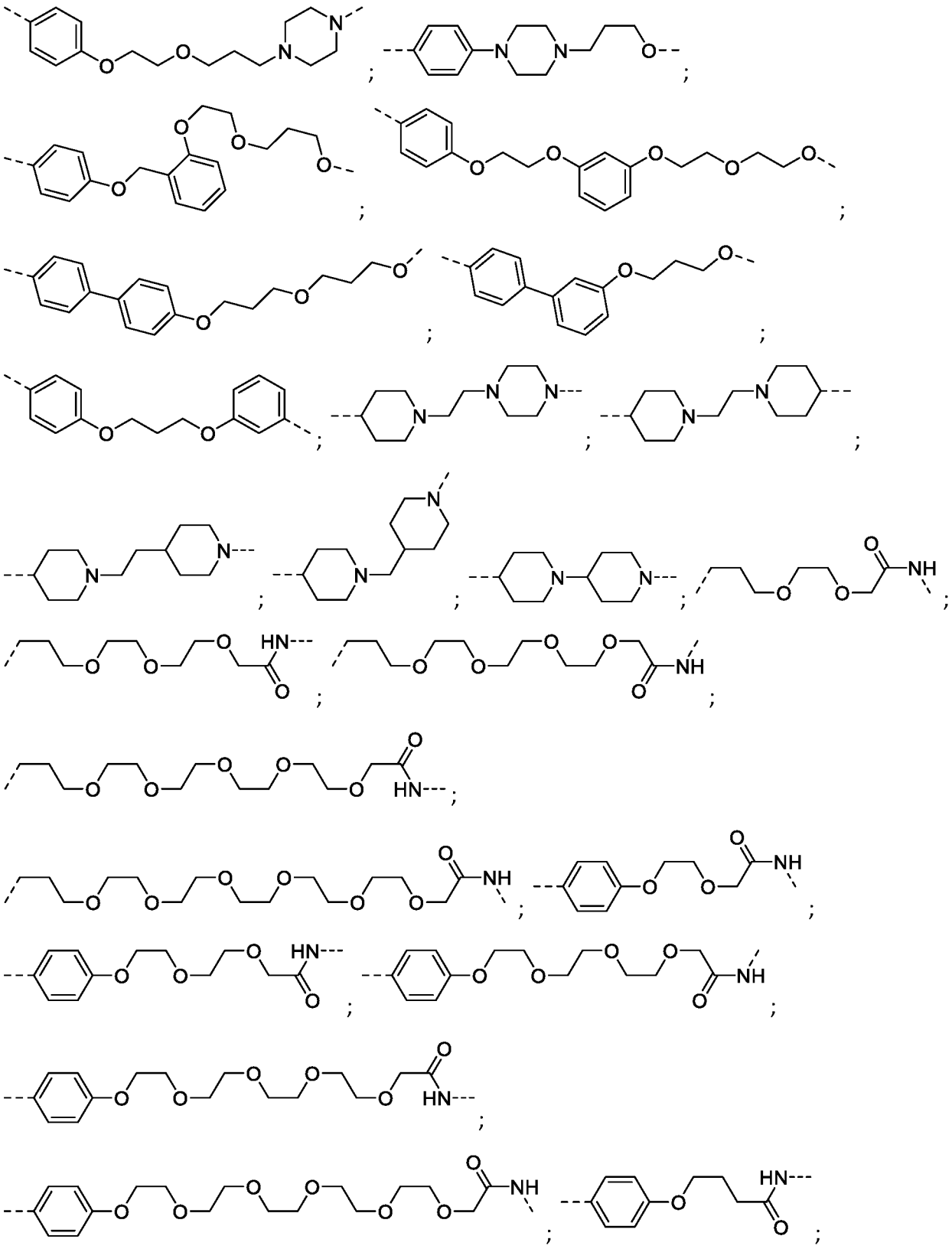


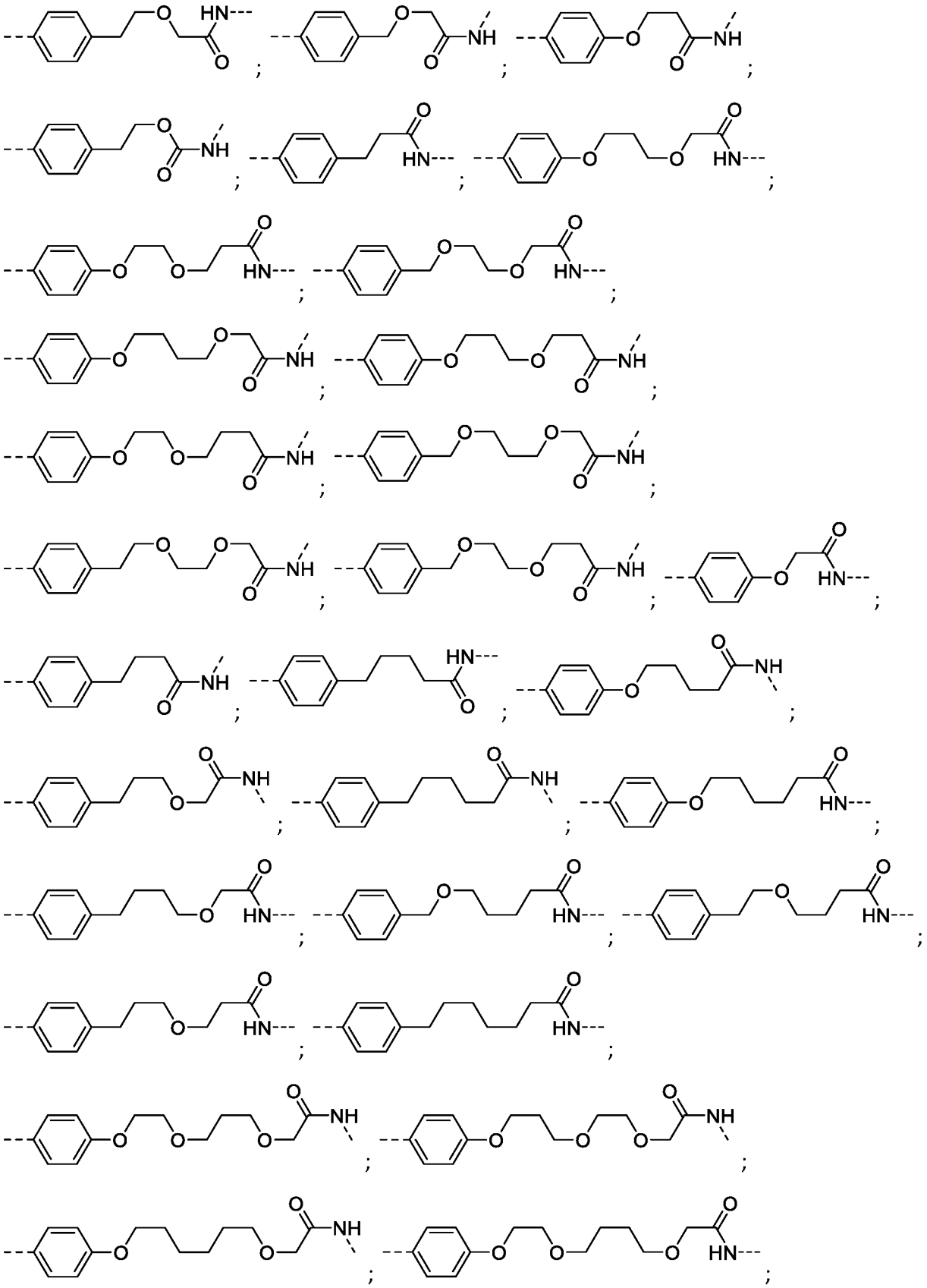
, wherein each m, n, o, p, q, and r is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

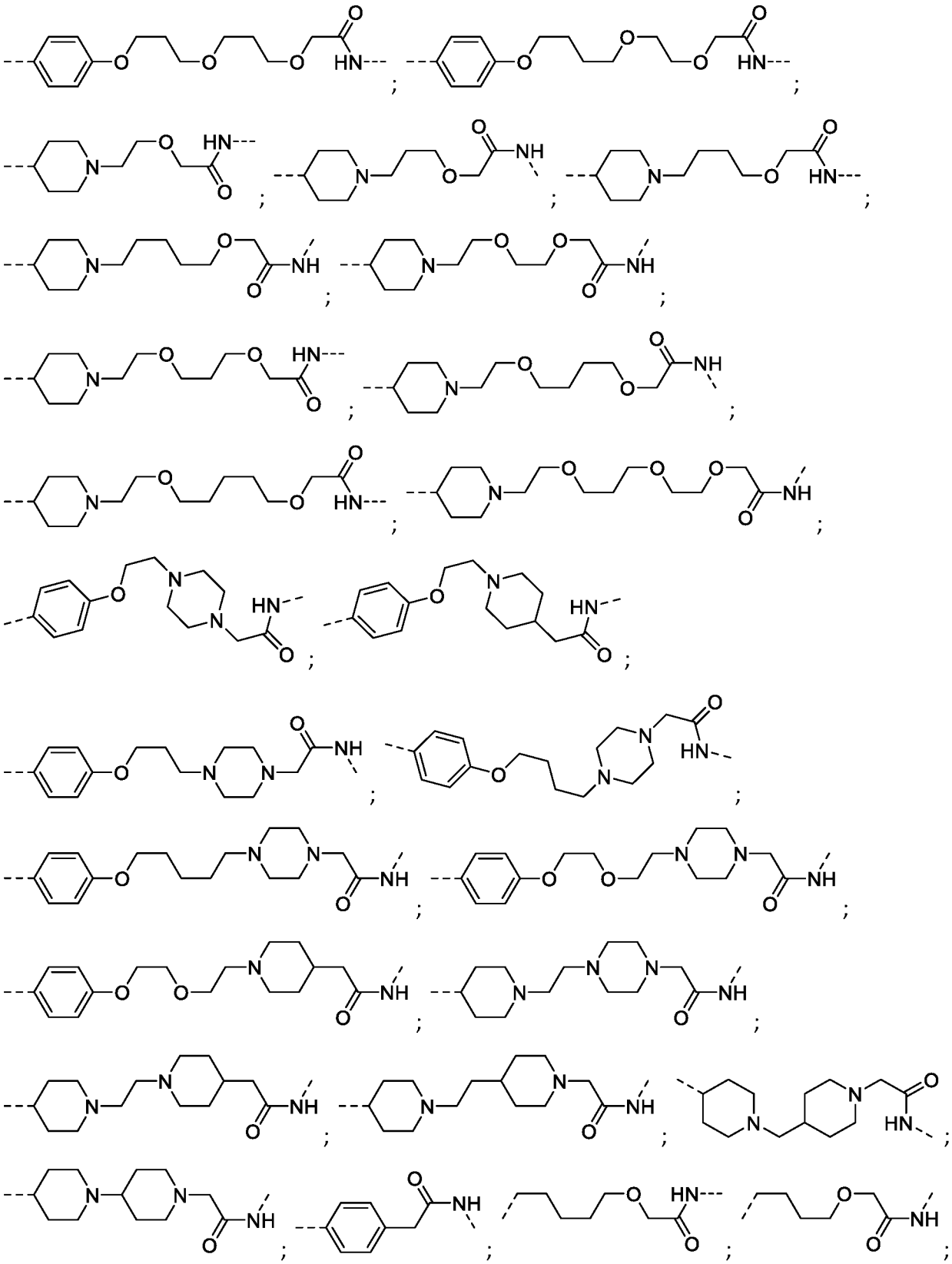
[0886] In any aspect or embodiment described herein, the A^L is selected from the group consisting of:

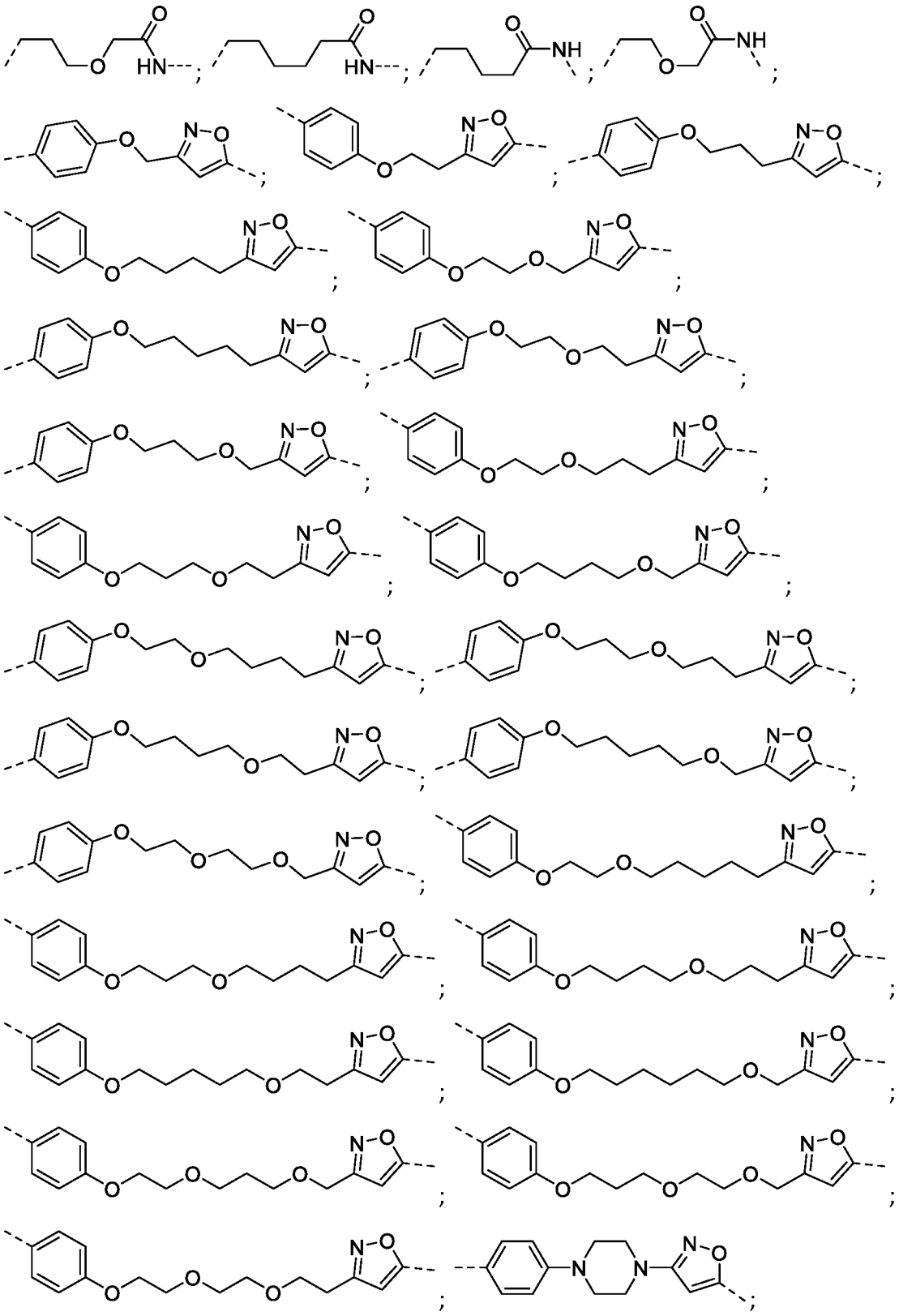


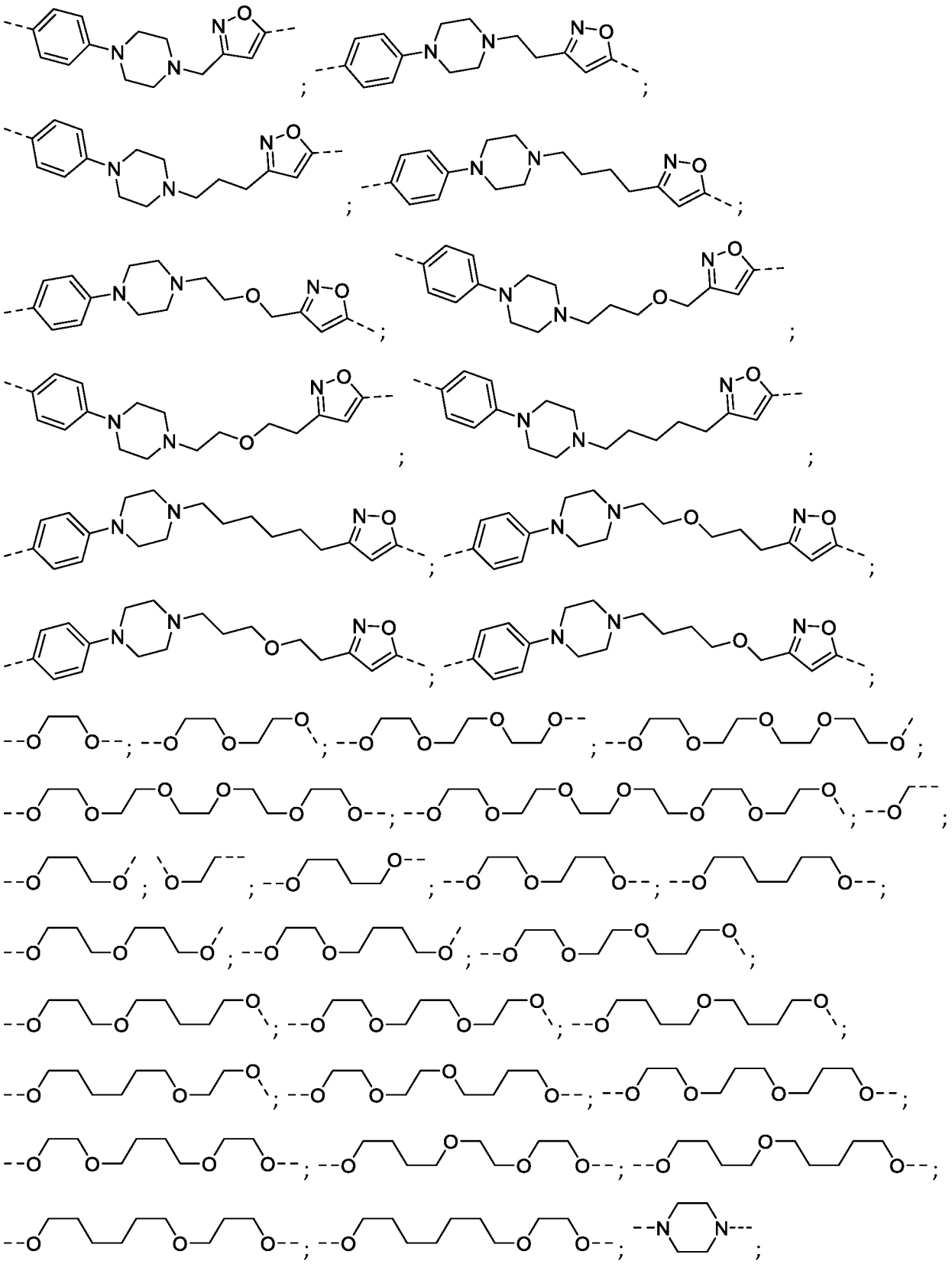


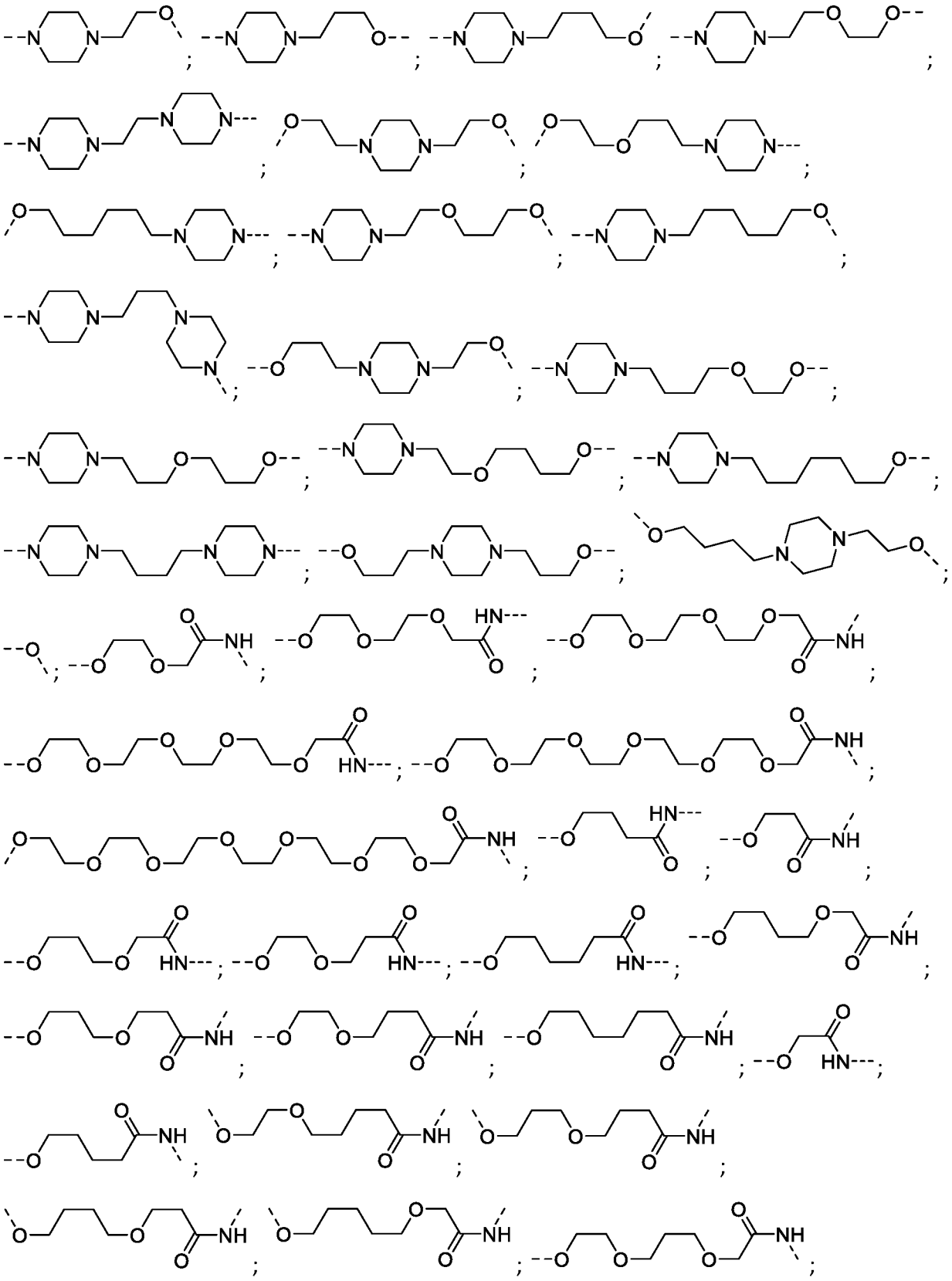


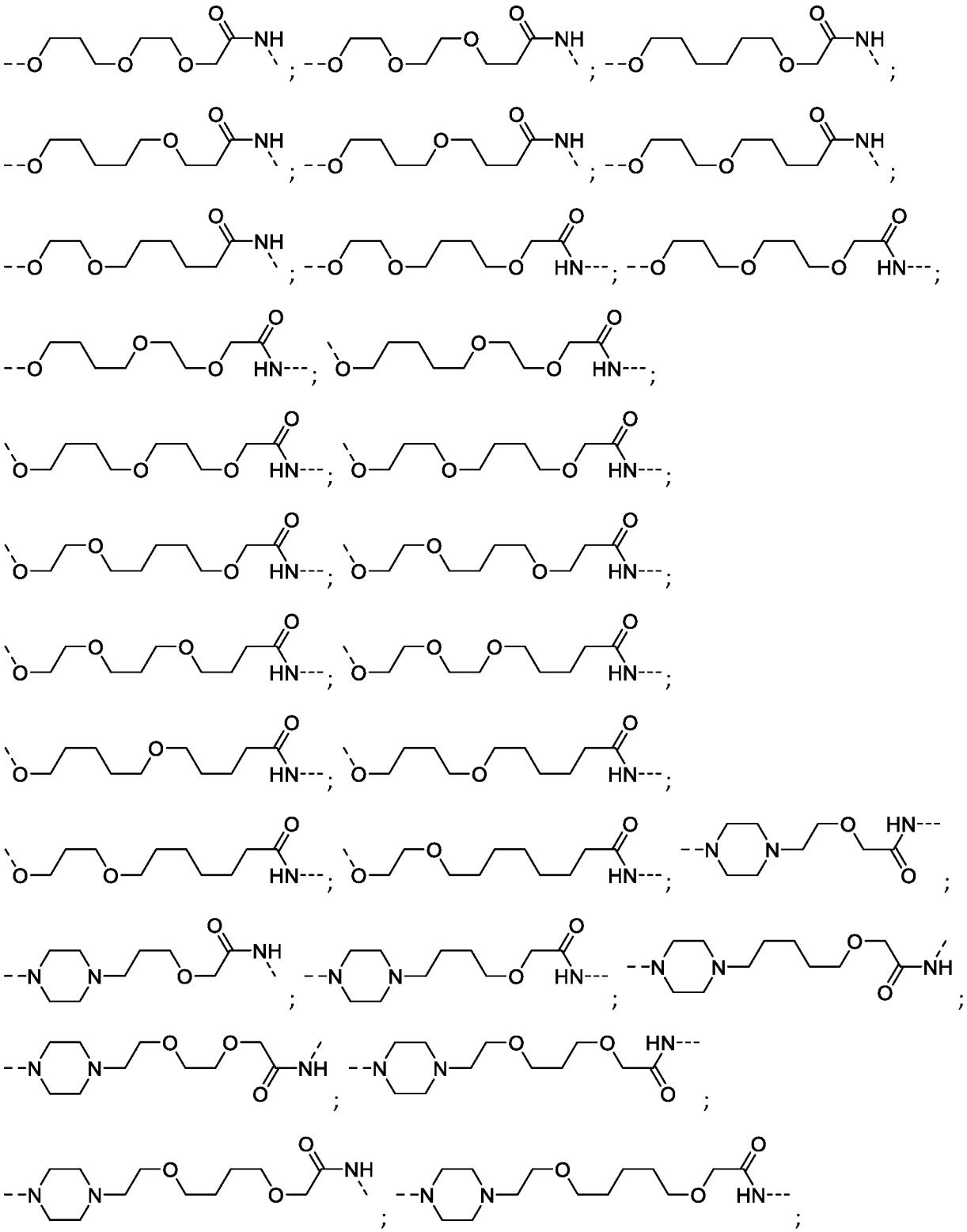


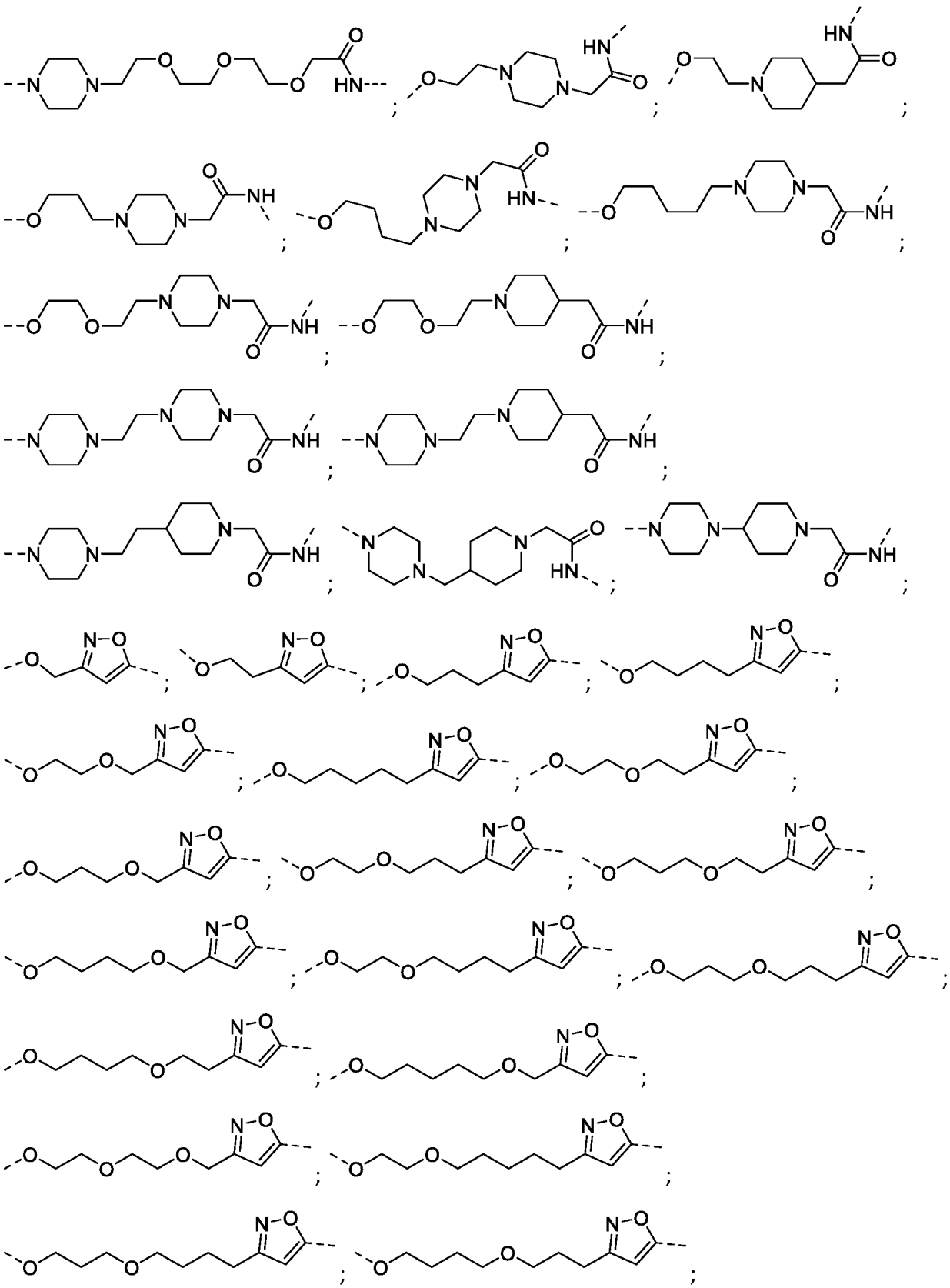


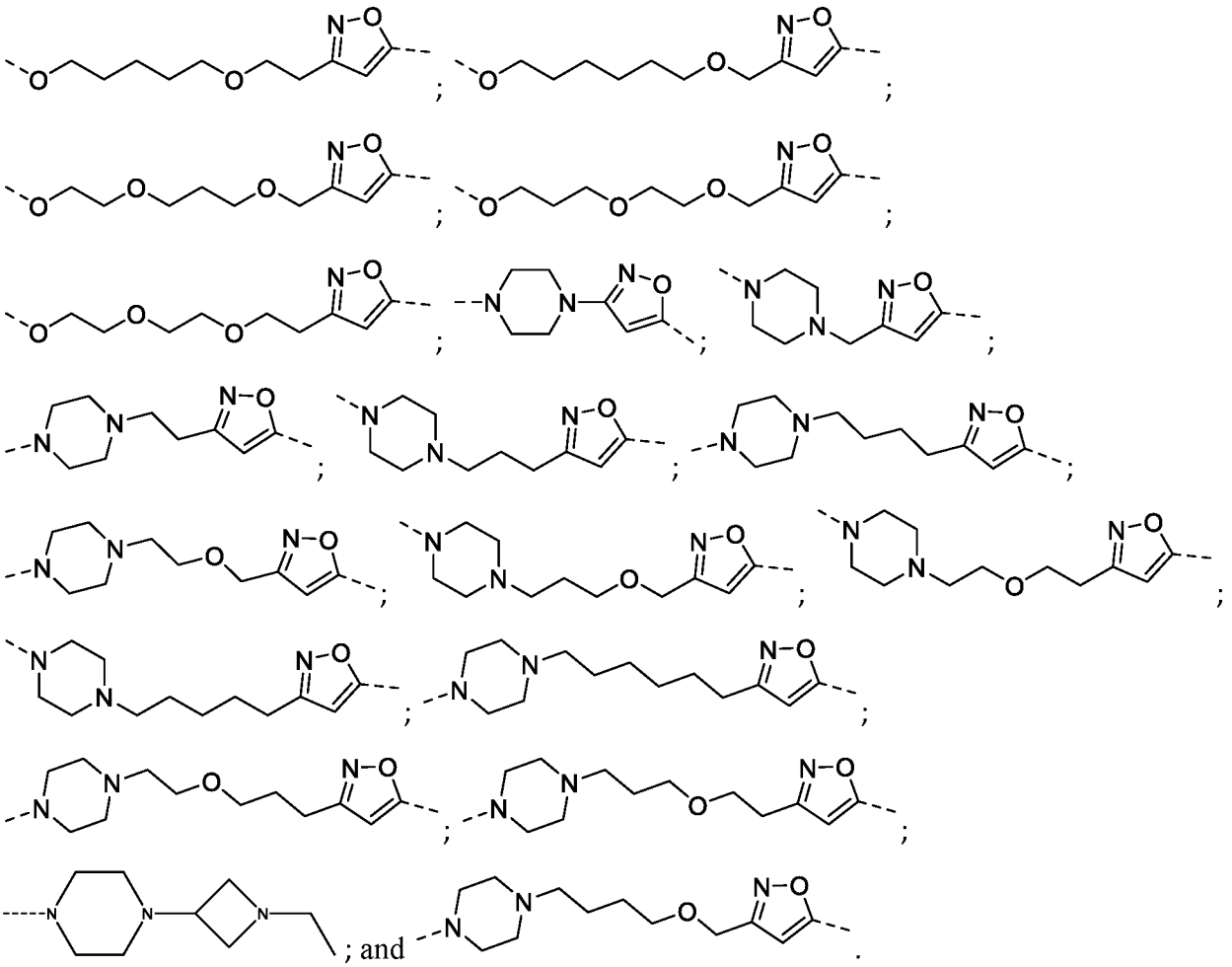




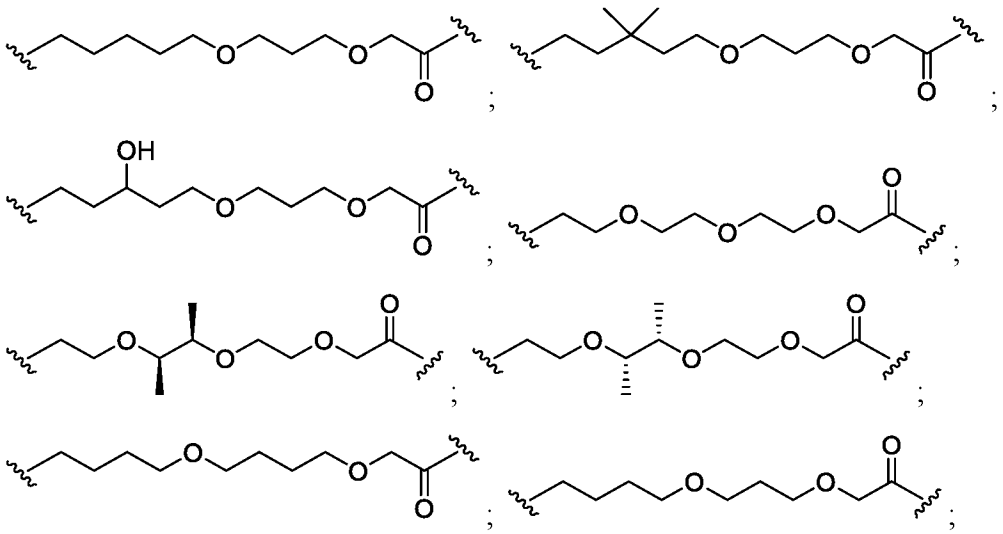


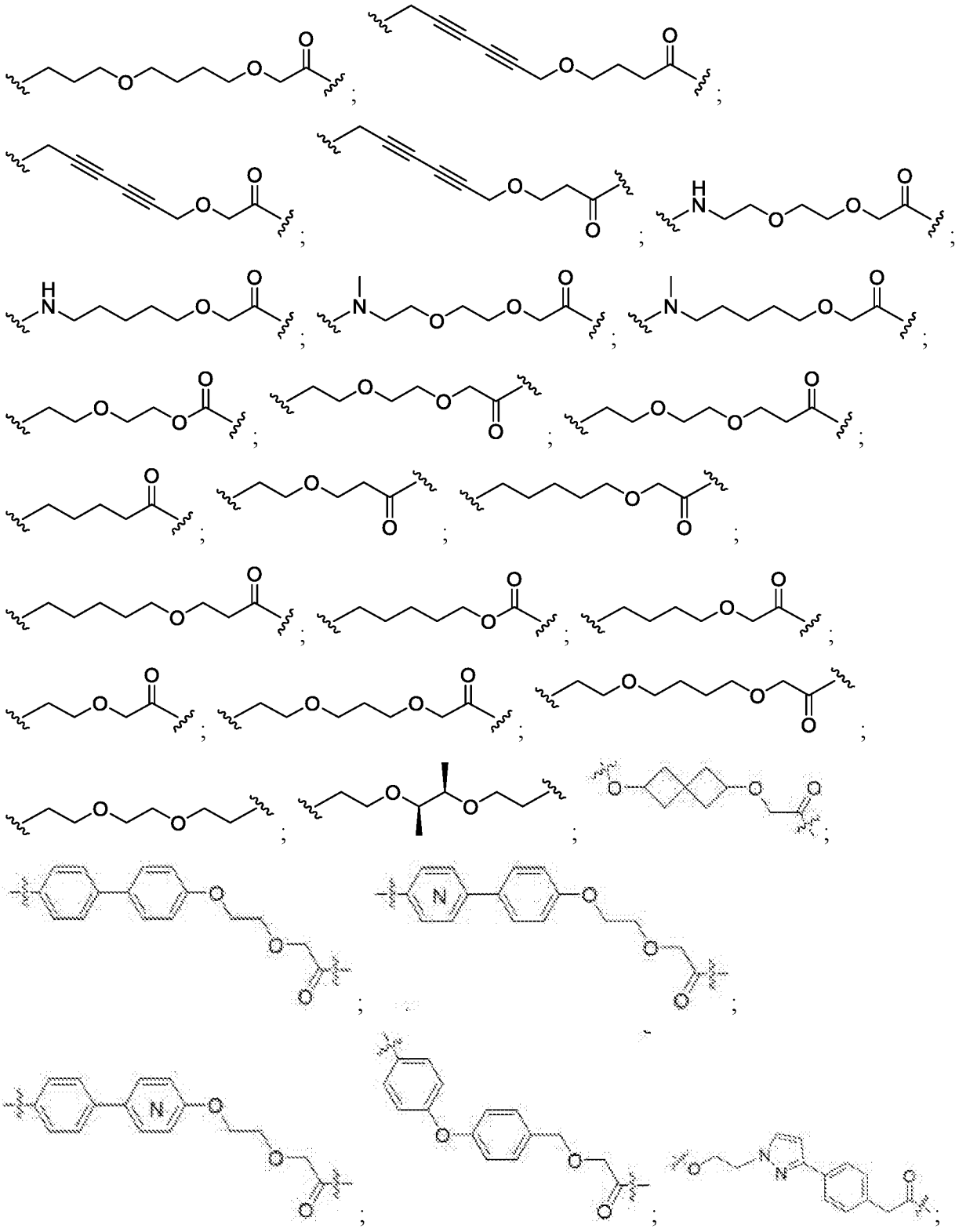


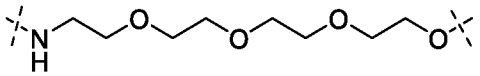
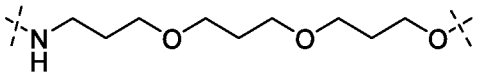
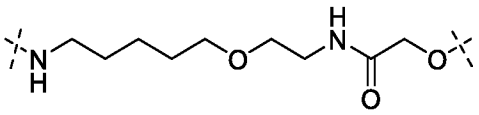
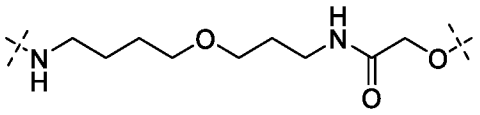




[0887] In any aspect or embodiment described herein, the A^L is selected from:



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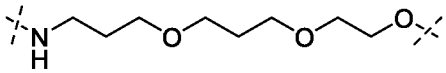
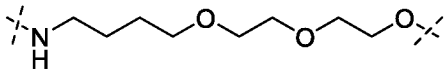
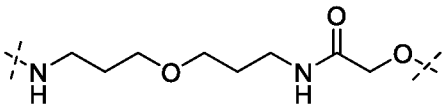
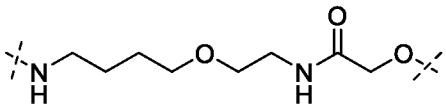
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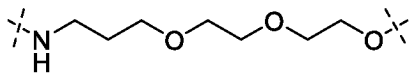
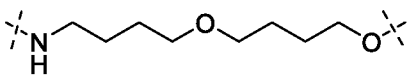
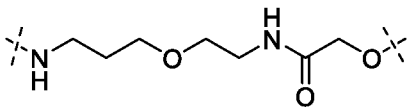
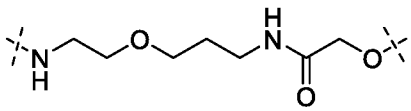
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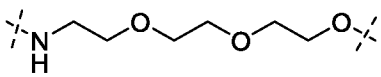
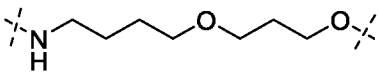
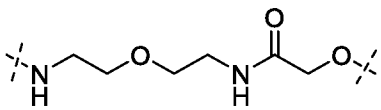
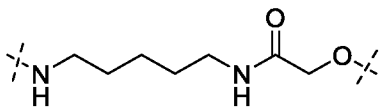
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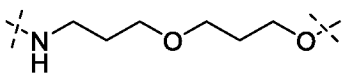
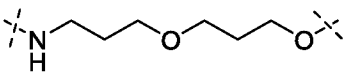
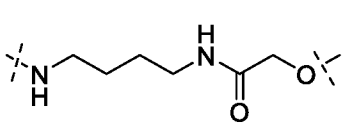
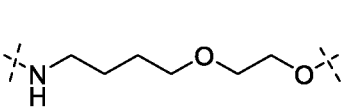
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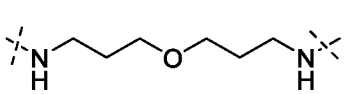
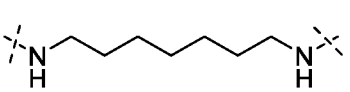
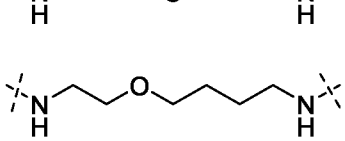
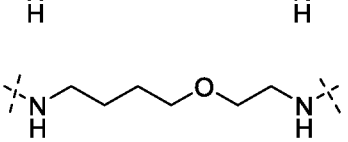
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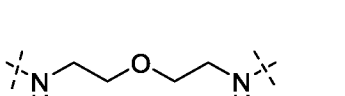
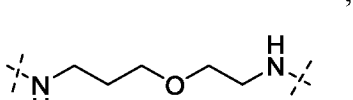

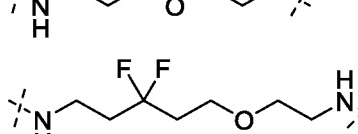
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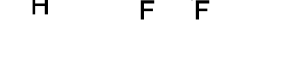

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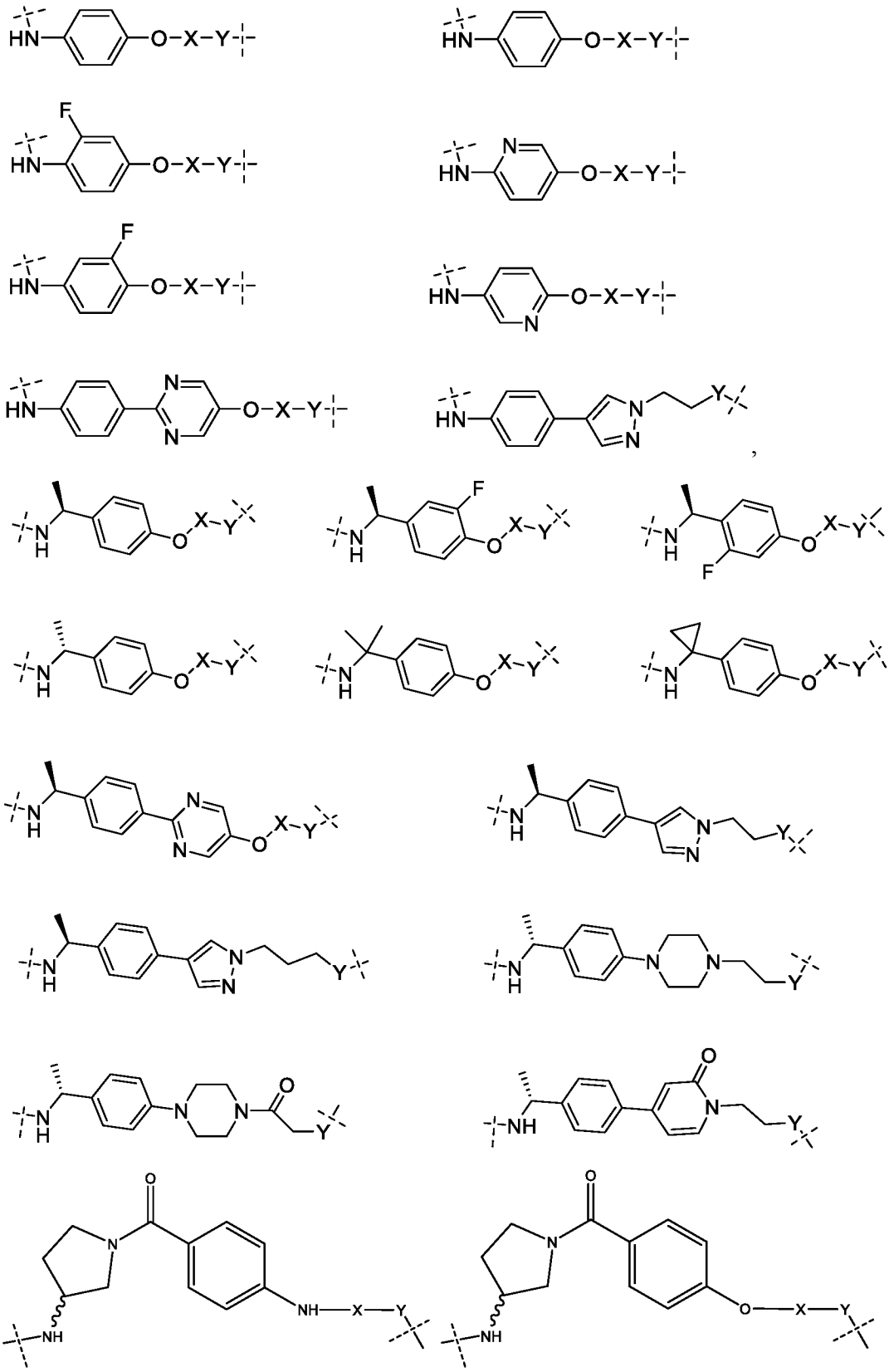
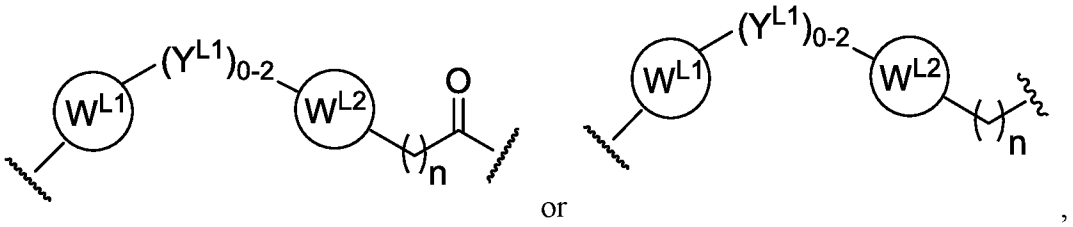


wherein:

'X" in above structures can be linear chain with atoms ranging from 2 to 14, and the mentioned chain can contain heteroatoms such as oxygen; and

"Y" in above structures can be O, N, $S(O)_n$ (n=0, 1, 2).

[0888] In any aspect or embodiment described herein, the linker (L) comprises a structure selected from:



,

wherein:

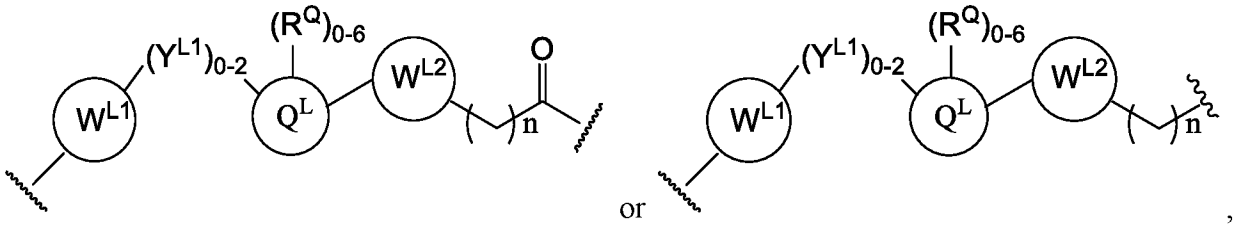
W^{L1} and W^{L2} are each independently absent, a 4-8 membered ring with 0-4 heteroatoms, optionally substituted with R^Q, each R^Q is independently a H, halo, OH, CN, CF_3, C_1-C_6 alkyl (linear, branched, optionally substituted), C_1-C_6 alkoxy (linear, branched, optionally substituted), or 2 R^Q 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, C_1-C_6 alkyl (linear, branched, optionally substituted) and optionally one or more C atoms are replaced with O; or C_1-C_6 alkoxy (linear, branched, optionally substituted);

n is 0-10; and

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

[0889] In any aspect or embodiment described herein, the linker comprises a structure selected from:



,

wherein:

W^{L1} and W^{L2} are each independently absent, aryl, heteroaryl, cyclic, heterocyclic, C_{1-6} alkyl and optionally one or more C atoms are replaced with O, C_{1-6} alkene and optionally one or more C atoms are replaced with O, C_{1-6} alkyne and optionally one or more C atoms are

replaced with O, 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 $\equiv$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);

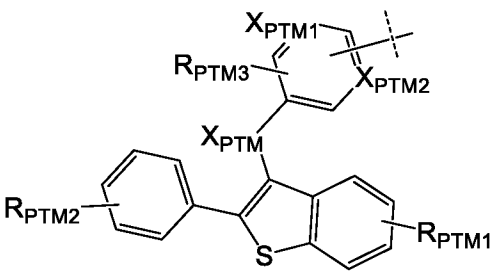
R^{YL1}, R^{YL2} are each independently H, OH, C_{1-6} alkyl (linear, branched, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), or R^1, R^2 together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms);

n is 0-10; and

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

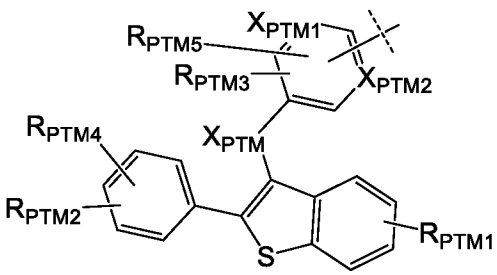
[0890] In any aspect or embodiment described herein, the linker (L) is a polyethylenoxy group optionally substituted with aryl or phenyl comprising from 1 to 10 ethylene glycol units.

[0891] In any aspect or embodiment described herein, the PTM is an estrogen receptor (ER) binding moiety represented by the chemical structure:



PTM-I

or



PTM-II ,

wherein:

X_{PTM} is O or C=O;

each of X_{PTM1} and X_{PTM2} is independently selected from N or CH;

R_{PTM1} is independently selected from OH, $O(CO)R_{PTM}$, O-lower alkyl, wherein R_{PTM} is an alkyl or aryl group in the ester;

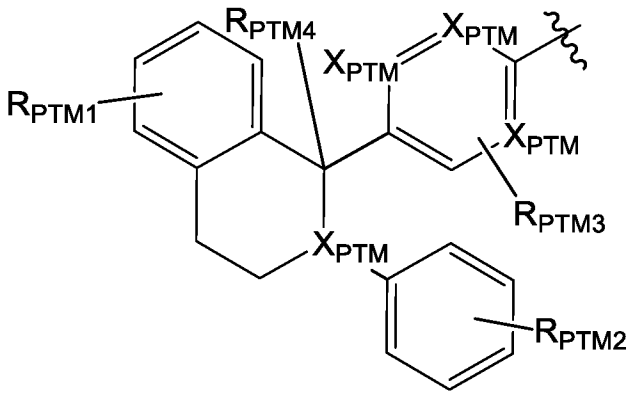
R_{PTM2} and R_{PTM4} are independently selected from H, OH, halogen, CN, CF_3, SO_2-alkyl, O-lower alkyl;

R_{PTM3} and R_{PTM5} are independently selected from H, halogen;

PTM-I has at least one R_{PTM2} and at least one R_{PTM3} on each respective rings; and

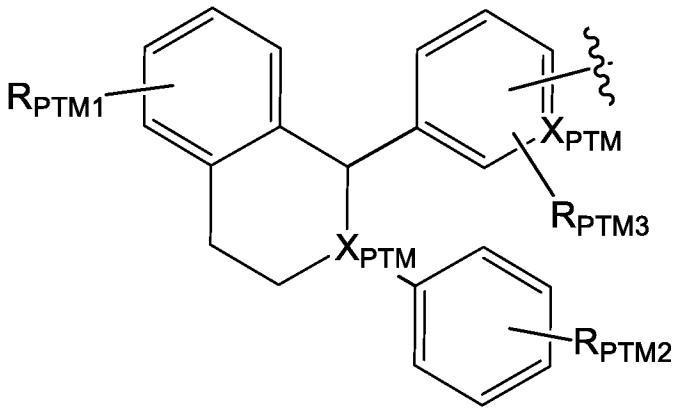
the indicates the site of attachment of at least one of the linker, the CLM, a CLM', or a combination thereof.

[0892] In any aspect or embodiment described herein, the PTM is an estrogen receptor (ER) binding moiety represented by the chemical structure:



or

Formula (I_{PTM})



,

Formula (II_{PTM})

wherein:

each X_{PTM} is independently CH, N;

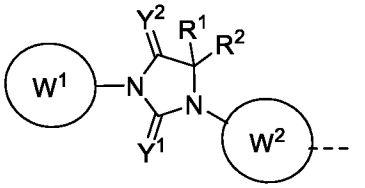
~~ indicates the site of attachment of at least one of the linker (L), the CLM, a CLM', ULM, an ILM, a VLM, MLM, a ULM', a ILM', a VLM', a MLM', or a combination thereof;

each R_{PTM1} is independently OH, halogen, alkoxy, methoxy, ethoxy, $O(CO)R_{PTM}$, wherein the substitution can be a mono-, di- or tri-substitution and the R_{PTM} is alkyl or cycloalkyl group with 1 to 6 carbons or aryl groups;

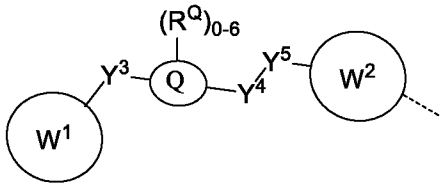
each R_{PTM2} is independently H, halogen, CN, CF_3, liner or branched alkyl, alkoxy, methoxy, ethoxy, wherein the substitution can be mono- or di-substitution;

each R_{PTM3} is independently H, halogen, wherein the substitution can be mono- or di-substitution; and R_{PTM4} is a H, alkyl, methyl, ethyl.

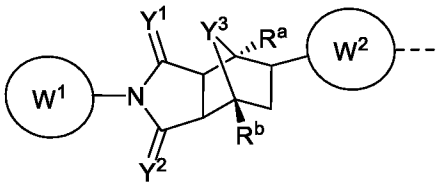
[0893] In any aspect or embodiment described herein, the PTM is an androgen receptor (AR) binding moiety (ABM) represented by a structure selected from the group consisting of:



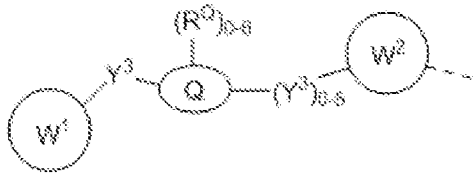
ABM-a ;



ABM-b ;



ABM-c ; and



ABM-d ,

wherein:

W^1 is aryl, heteroaryl, bicyclic, or biheterocyclic, each independently substituted by 1 or more H, halo, hydroxyl, nitro, CN, C≡CH, C_{1-6} alkyl (linear, branched, optionally substituted; for example, optionally substituted by 1 or more halo, C_{1-6} alkoxyl), C_{1-6} alkoxyl (linear, branched, optionally substituted; for example, optionally substituted by 1 or more halo), C_{2-6} alkenyl, C_{2-6} alkynyl, or CF_3;

Y^1, Y^2 are each independently NR^{Y1}, O, S, SO2, heteroaryl, or aryl;

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

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

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

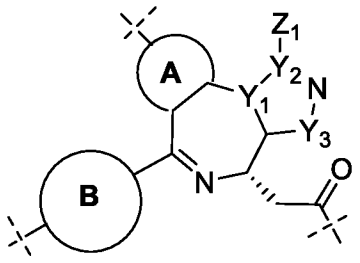
W^2 is a bond, C_{1-6} alkyl, C_{1-6} heteroalkyl, O, aryl, heteroaryl, alicyclic, heterocyclic, biheterocyclic, biaryl, or biheteroaryl,each optionally substituted by 1-10 R^{W2};

each R^{W2} is independently H, halo, C_{1-6} alkyl (linear or branched optionally substituted; for example, optionally substituted by 1 or more F), $-OR^{W2A}$, C_{3-6} cycloalkyl, C_{4-6} cycloheteroalkyl, C_{1-6} alkyl (optionally substituted), , heterocyclic (optionally substituted), aryl (optionally substituted), or heteroaryl (optionally substituted), bicyclic hereoaryl or aryl, OC_{1-3}alkyl (optionally substituted; for example, optionally substituted by 1 or more –F) , OH, NH_2, $NR^{Y1}R^{Y2}$, CN;

R^{W2A} is H, C_{1-6} alkyl (linear, branched), or C_{1-6} heteroalkyl (linear, branched), each optionally substituted by a cycloalkyl, cycloheteroalkyl, aryl, heterocyclic, heteroaryl, halo, or OC_{1-3}alkyl; and

the dashed line indicates the site of attachment of at least one of the linker, the CLM, a CLM', or a combination thereof.

[0894] In any aspect or embodiment described herein, the PTM is a BET/BRD4 targeting moiety comprising a group according to the chemical structure PTM-a:



PTM-a ,

wherein:

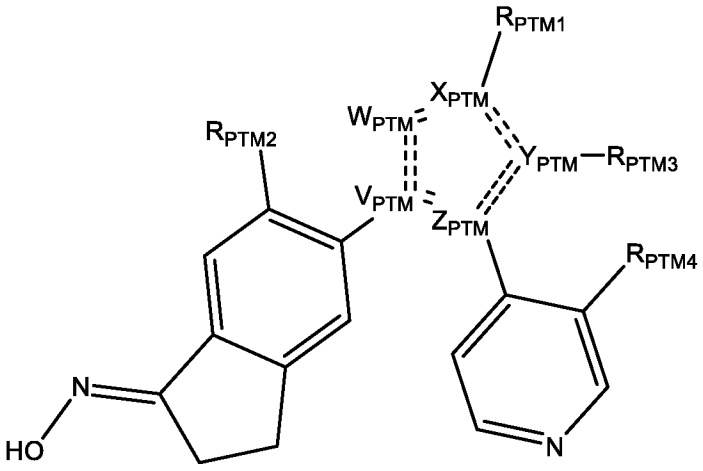
Y_1, Y_2 and Y_3 are independently selected from the group of carbon, nitrogen or oxygen and together with the atoms to form an aromatic fused ring.

A and B are independently selected from the group of a 5-membered aromatic ring, a 6-membered aromatic ring, a heteroaromatic ring, a carbocyclic, a thiophene a pyrrole ring, a pyridine, a pyrimidine, a pyrazine, a pyrazole ring each optionally substituted with alkyl, alkoxy, halogen, an aromatic and a heteroaromatic ring; wherein ring A is fused to the central azepine (Y1=C) or diazepine (Y1 = N) moiety; and

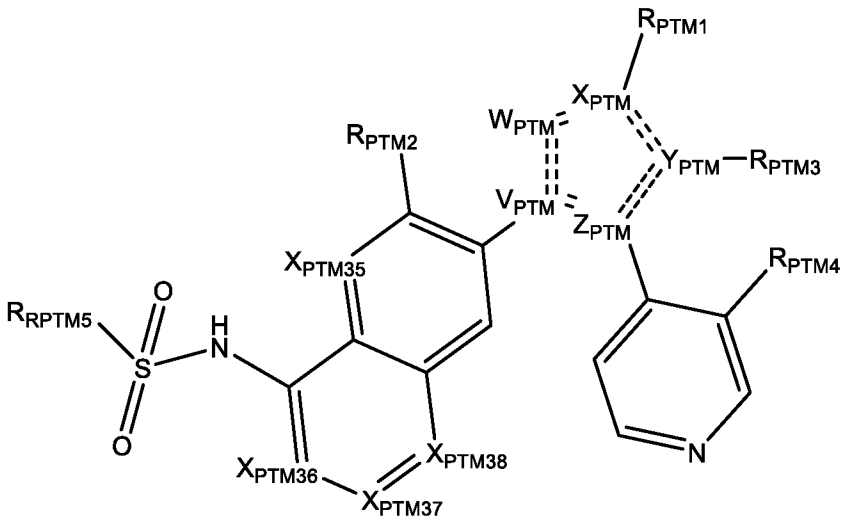
Z1 is selected from the group of methyl or analkyl group, and

wherein the dashed line indicates the site of attachment of at least one of the linker, the CLM, a CLM', or a combination thereof.

[0895] In any aspect or embodiment described herein, the PTM is a BRaf targeting moiety that is represented by at least one of chemical structures PTM-Ia, PTM-Ib, PTM-IIa, PTM-IIb, PTM-IIIa, PTM-IIIb, PTM-IVa, PTM-IVb:



PTM-Ia ,



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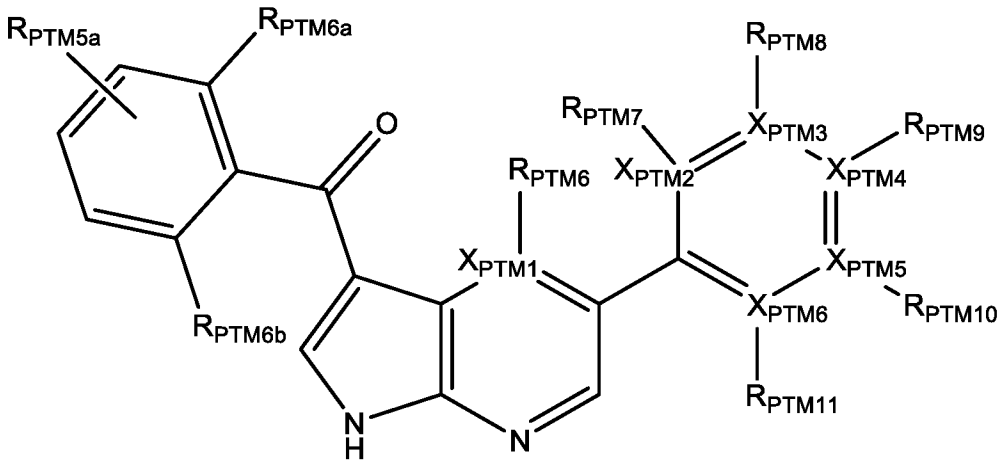
PTM-Ib



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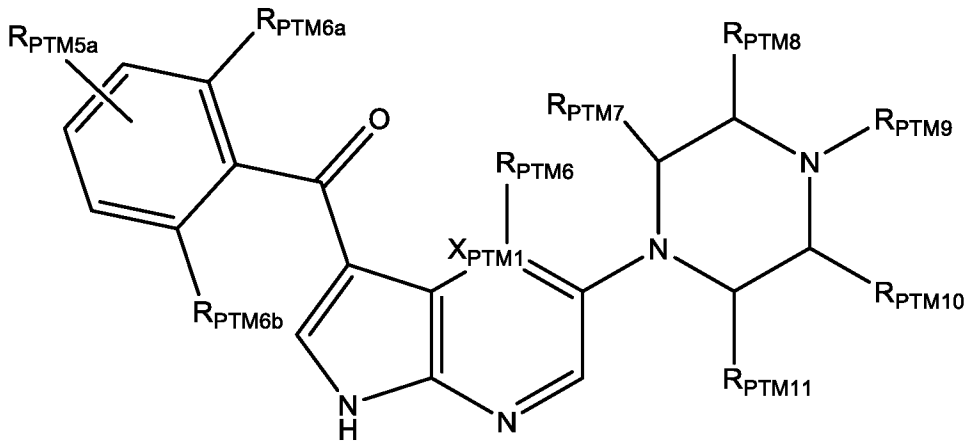
PTM-IIa



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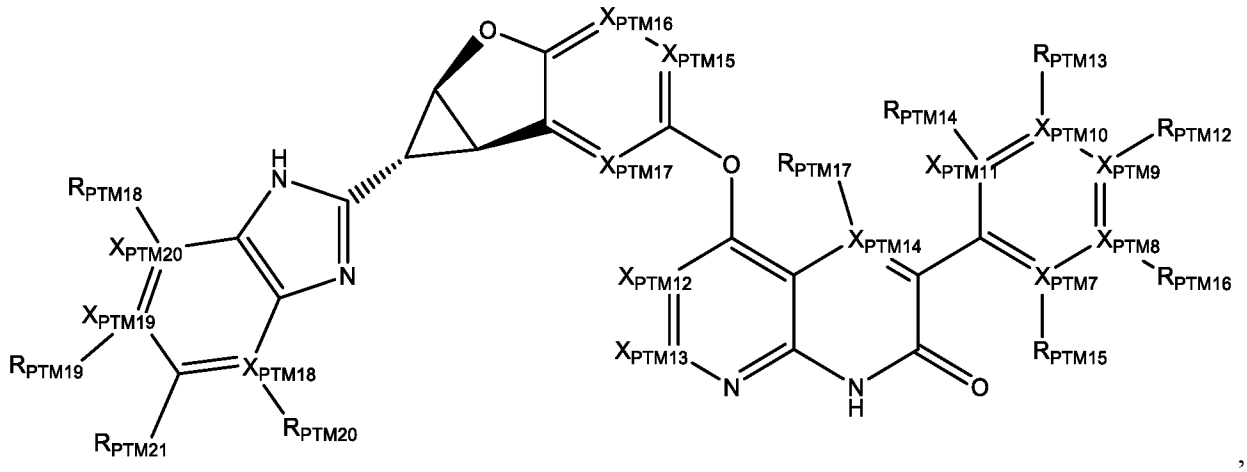
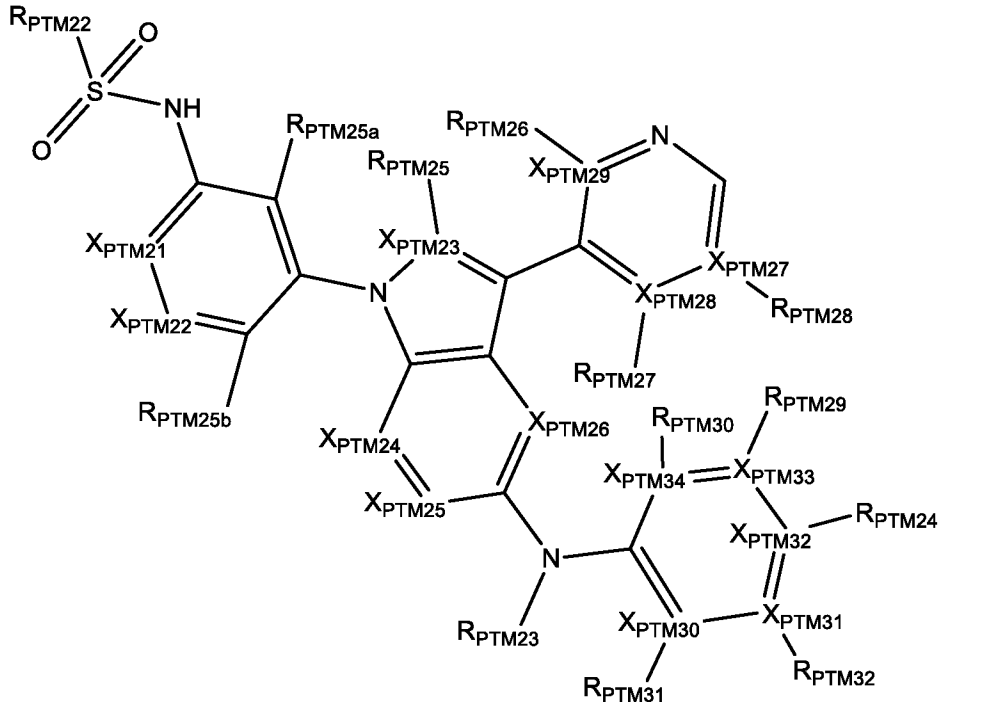
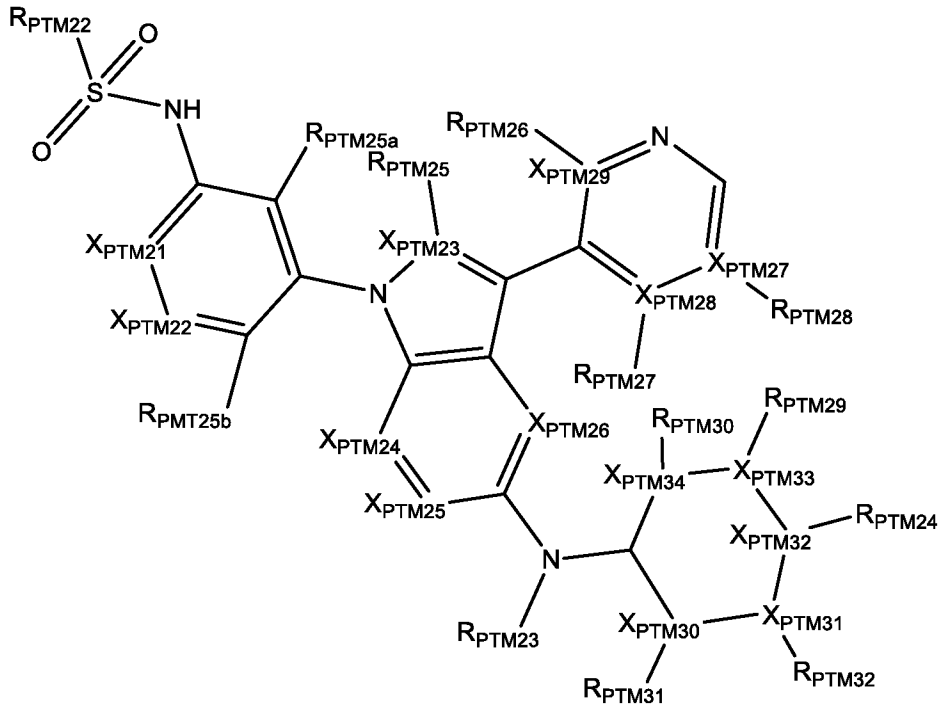
PTM-IIb



PTM-III



PTM-IVa



,

PTM-IVb

wherein:

double dotted bonds are aromaric bonds;

V_{PTM}, W_{PTM}, X_{PTM}, Y_{PTM}, Z_{PTM} is one of the following combinations: C, CH, N, N, C; C, N, N, CH, C; C, O, C, CH, C; C, S, C, CH, C; C, CH, C, O, C; C, CH, C, S, C; C, CH, N, CH, C; N, CH, C, CH, C; C, CH, C, CH, N; N, N, C, CH, C; N, CH, C, N, C; C, CH, C, N, N; C, N, C, CH, N; C, N, C, N, C; and C, N, N, N, C;

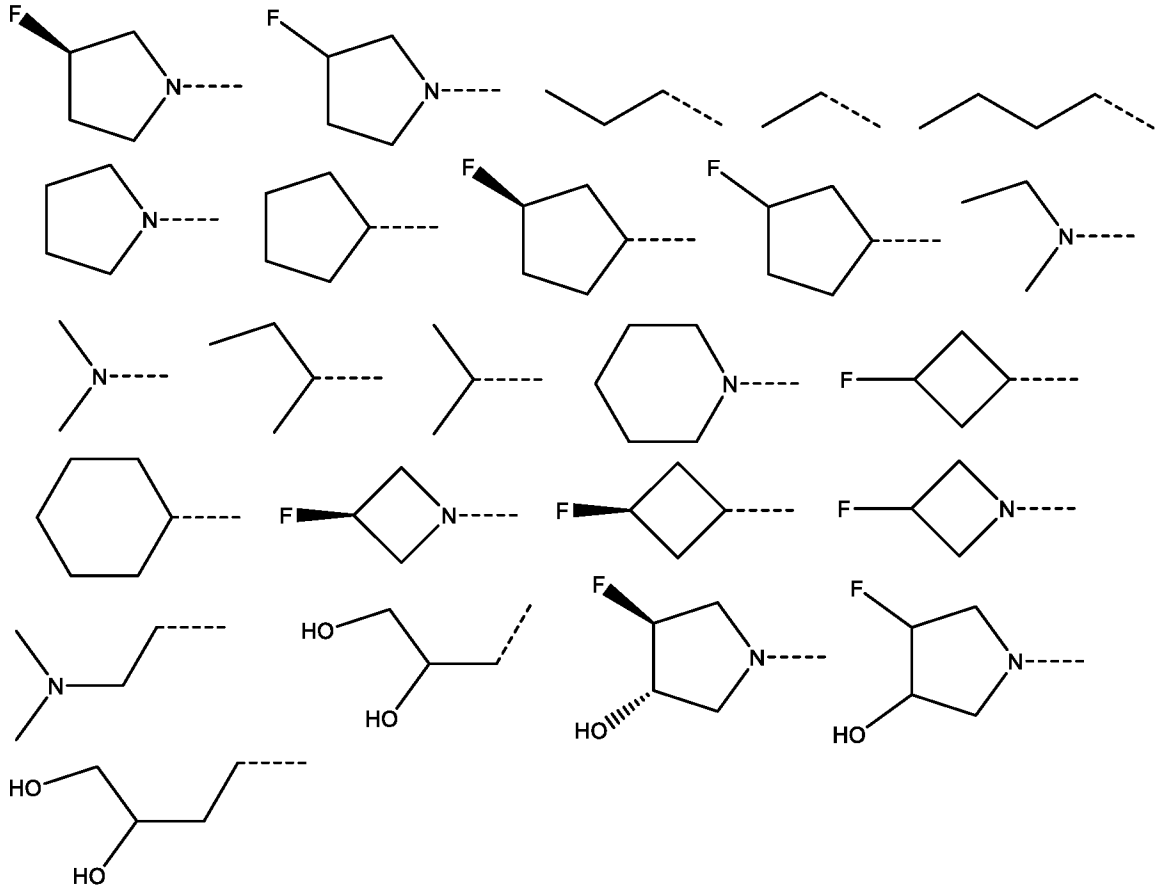
R_{PTM1} is covalently joined to a ULM, a chemical linker group (L), a CLM, an ILM, a VLM, MLM, a ULM', a CLM', a ILM', a VLM', a MLM', or combination thereof;

R_{PTM2} is hydrogen, halogen, aryl, methyl, ethyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

R_{PTM3} is absent, hydrogen, aryl, methyl, ethyl, other alkyl, cyclic alkyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

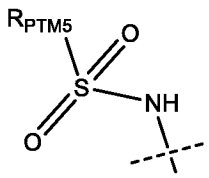
R_{PTM4} is hydrogen, halogen, aryl, methyl, ethyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

each of R_{PTM5} and R_{PTM22} is independently selected from the group consisting of



;

X_{PTM1}, X_{PTM2}, X_{PTM3}, X_{PTM4}, X_{PTM5}, X_{PTM6}, X_{PTM7}, X_{PTM8}, X_{PTM9}, X_{PTM10}, X_{PTM11}, X_{PTM12}, X_{PTM13}, X_{PTM14}, X_{PTM15}, X_{PTM16}, X_{PTM17}, X_{PTM18}, X_{PTM19}, X_{PTM20}, X_{PTM21}, X_{PTM22}, X_{PTM23}, X_{PTM24}, X_{PTM25}, X_{PTM26}, X_{PTM27}, X_{PTM28}, X_{PTM29}, X_{PTM30}, X_{PTM31}, X_{PTM32}, X_{PTM33}, X_{PTM34}, X_{PTM35}, X_{PTM36}, X_{PTM37}, X_{PTM38} are independently selected from CH or N;

R_{PTM5a} is selected from the group consisting of: H, optionally substituted amide (e.g., optionally substituted with an alkyl, methyl, ethyl, propyl, or butyl group), optionally substituted amine,  , -NHC(O)R_{PTM5};

R_{PTM6a} and R_{PTM6b} are each independently selected from hydrogen, halogen, or C_1-C_6 alkyl (linear, branched, optionally substituted);

R_{PTM6} is either of the following groups: absent, hydrogen, halogen, aryl, methyl, ethyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle.

R_{PTM7} is absent, hydrogen, halogen, aryl, methyl, ethyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle.

R_{PTM8}, R_{PTM9} or R_{PTM10} are independently selected from the group consisting of absent, hydrogen, halogen, aryl, heteroaryl, alkyl, cycloalkyl, heterocycle, methyl, ethyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

R_{PTM11} is absent, hydrogen, halogen, methyl, ethyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2 in which M1, wherein CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

R_{PTM12}, R_{PTM13}, R_{PTM14}, R_{PTM15}, R_{PTM16}, R_{PTM17}, R_{PTM18}, R_{PTM19} are independently selected from the group consisting of absent, hydrogen, halogen, aryl, heteroaryl, cycloalkyl, heterocycle, methyl, ethyl, other alkyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

R_{PTM20} is a small group containing less than four non-hydrogen atoms;

R_{PTM21} is selected from the group consisting of trifluoromethyl, chloro, bromo, fluoro, methyl, ethyl, propyl, isopropyl, *tert*-butyl, butyl, iso-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, OCH_3, $NHCH_3$, dimethylamino or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O or NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

R_{PTM25a} and R_{PTM25b} are each independently selected from hydrogen, halogen, or C_1-C_6 alkyl (linear, branched, optionally substituted);

R_{PTM23}, R_{PTM24}, R_{PTM28}, R_{PTM29}, R_{PTM30}, R_{PTM31}, R_{PTM32} are independently selected from the group consisting of absent, bond, hydrogen, halogen, aryl (optionally substituted), heteroaryl (optionally substituted), cycloalkyl (optionally substituted), heterocycle (optionally substituted), methyl, ethyl (optionally substituted), other alkyl (linear, branched, optionally substituted), OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is

CH_2, O and NH, and M2 is hydrogen, alkyl (linear, branched, optionally substituted), cyclic alkyl (optionally substituted), aryl (optionally substituted)or heterocycle (optionally substituted);

R_{PTM25} is selected from absent, hydrogen, halogen, C_1-C_6 alkyl (linear, branched, optionally substituted), OCH_3, $NHCH_3$ or SCH_3;

R_{PTM26} is selected from absent, hydrogen, halogen, C_1-C_6 alkyl (linear, branched, optionally substituted), OCH3, $NHCH_3$ or SCH_3;

R_{PTM27} is selected from the group consisting of absent, hydrogen, halogen, C_1-C_6 alkyl (linear, branched, optionally substituted), OCH_3, $NHCH_3$ or SCH_3; and

at least one of R_{PTM8}, R_{PTM9} or R_{PTM10}, R_{PTM12}, R_{PTM13}, R_{PTM16}, R_{PTM24}, R_{PTM29}, and R_{PTM32} is modified to be covalently joined to a ULM, a chemical linker group (L), a CLM, an ILM, a VLM, MLM, a ULM', a CLM', a ILM', a VLM', a MLM', or combination thereof.

[0896] In any aspect or embodiment described herein, when R_{PTM9} is the covalently joined position, R_{PTM7} and R_{PTM8} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM7} and R_{PTM8} are attached.

[0897] In any aspect or embodiment described herein, when R_{PTM8} is the covalently joined position, R_{PTM9} and R_{PTM10} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM9} and R_{PTM10} are attached.

[0898] In any aspect or embodiment described herein, when RPTM10 is the covalently joined position, RPTM8 and RPTM9 are connected together via a covalent bond in a way to form a bicyclic group with the ring to which RPTM8 and RPTM9 are attached.

[0899] In any aspect or embodiment described herein, when R_{PTM12} is the covalently joined position, R_{PTM13} and R_{PTM14} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM13} and R_{PTM14} are attached, and/or R_{PTM15} and R_{PTM16} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM15} and R_{PTM16} are attached.

[0900] In any aspect or embodiment described herein, when R_{PTM13} is the covalently joined position, R_{PTM12} and R_{PTM16} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM12} and R_{PTM16} are attached, and/or R_{PTM15} and R_{PTM16} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM15} and R_{PTM16} are attached.

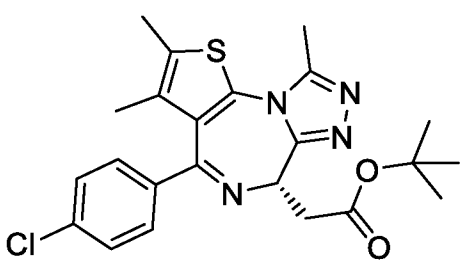
[0901] In any aspect or embodiment described herein, when R_{PTM16} is the covalently joined position, R_{PTM12} and R_{PTM13} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM12} and R_{PTM13} are attached, and/or R_{PTM13} and R_{PTM14} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM13} and R_{PTM14} are attached.

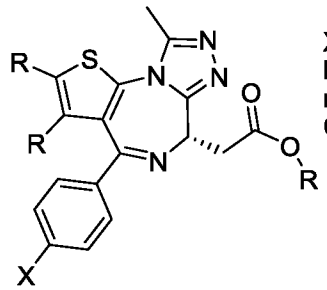
[0902] In any aspect or embodiment described herein, when R_{PTM24} is the covalently joined position, R_{PTM31} and R_{PTM32} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM31} and R_{PTM32} are attached, or R_{PTM29} and R_{PTM30} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM29} and R_{PTM30} are attached.

[0903] In any aspect or embodiment described herein, when R_{PTM29} is the covalently joined position, R_{PTM24} and R_{PTM32} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM24} and R_{PTM32} are attached, and/or R_{PTM31} and R_{PTM32} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM31} and R_{PTM32} are attached.

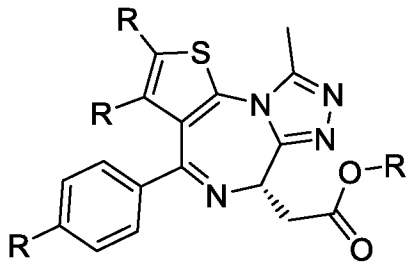
[0904] In any aspect or embodiment described herein, when R_{PTM32} is the covalently joined position, R_{PTM24} and R_{PTM29} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM24} and R_{PTM29} are attached, and/or R_{PTM29} and R_{PTM30} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM29} and R_{PTM30} are attached.

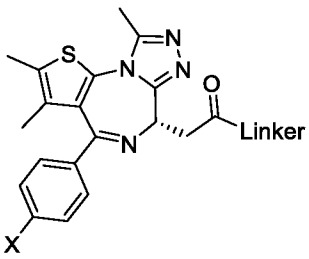
[0905] In any aspect or embodiment described herein, the PTM has a structure selected from the group consisting of:



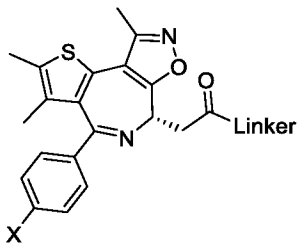


X = Cl, Br, F, H, bond, or a chemical moiety coupling the CLM to the PTM





X = Cl, Br, F, H



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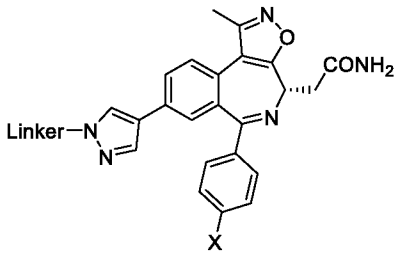

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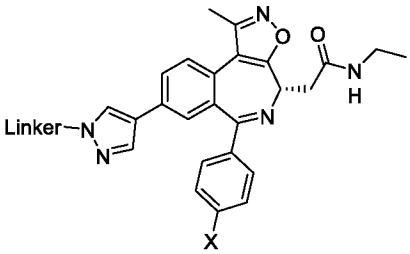
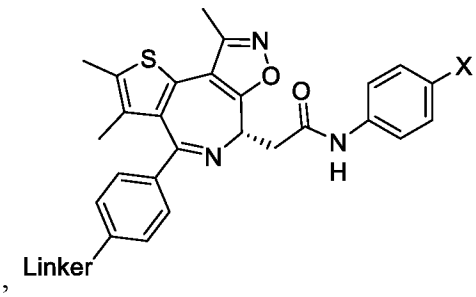
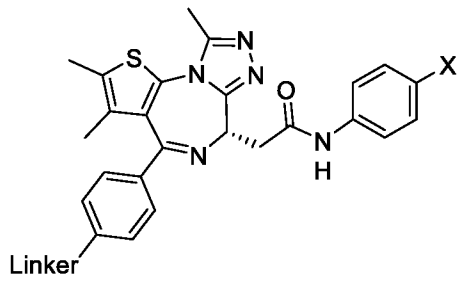


X = Cl, Br, F, H





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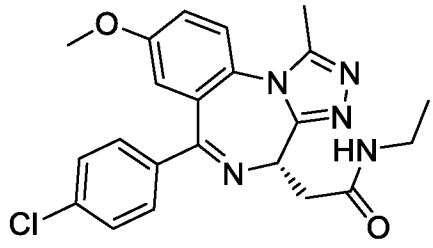

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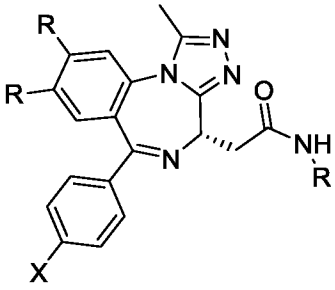

X = Cl, Br, F, H, bond, or a chemical moiety coupling the CLM to the PTM

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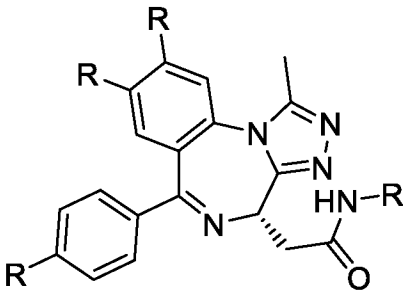

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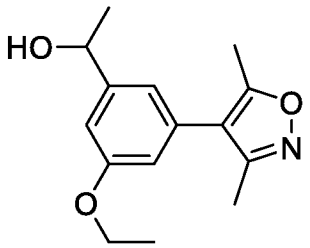

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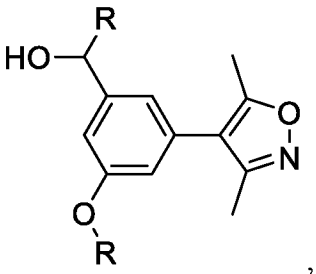

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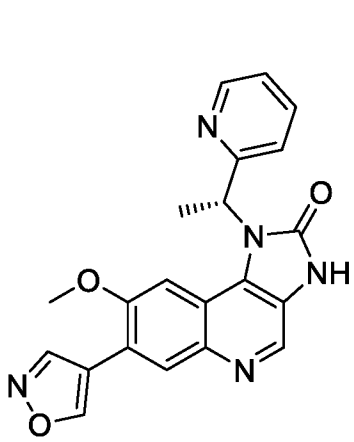
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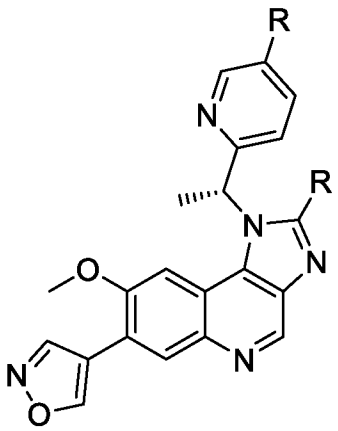
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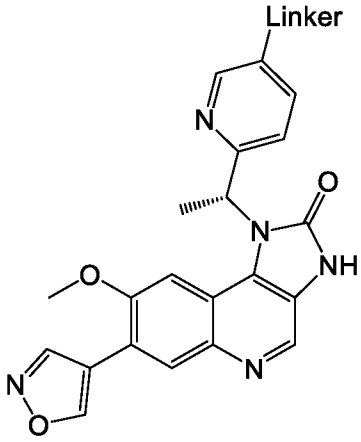
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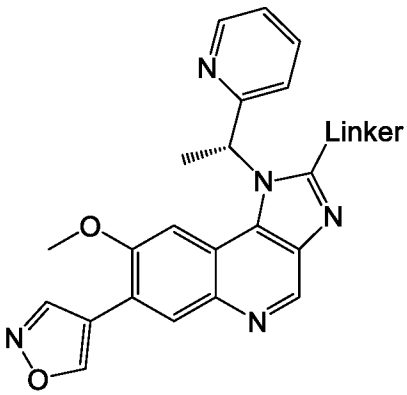
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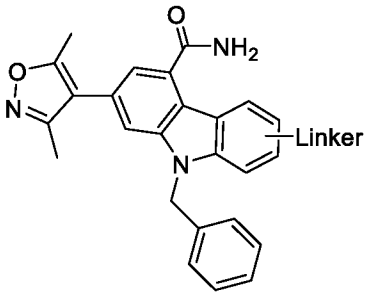
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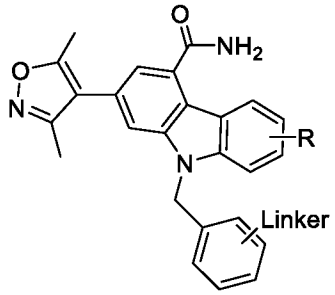
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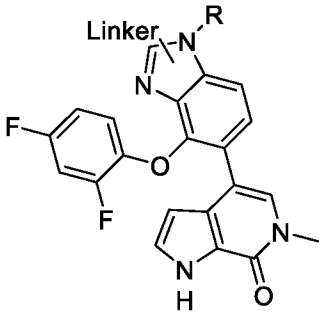
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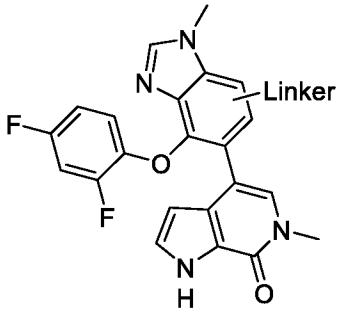
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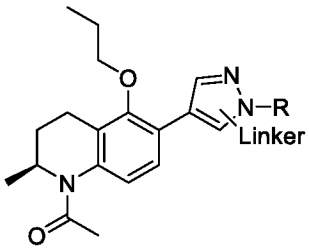
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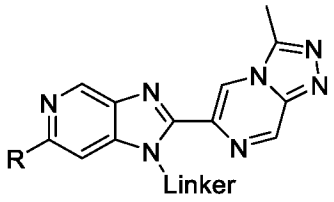
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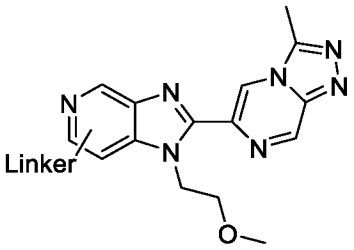
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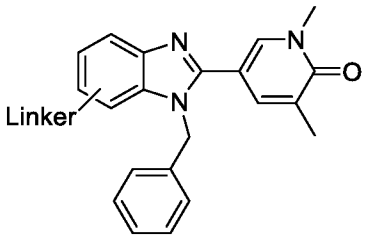
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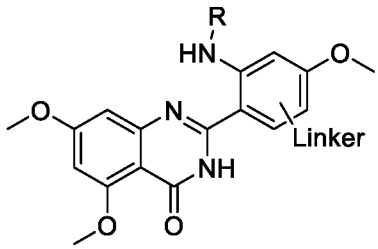
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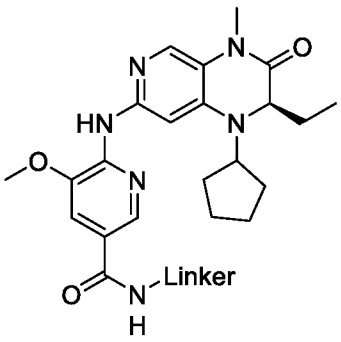

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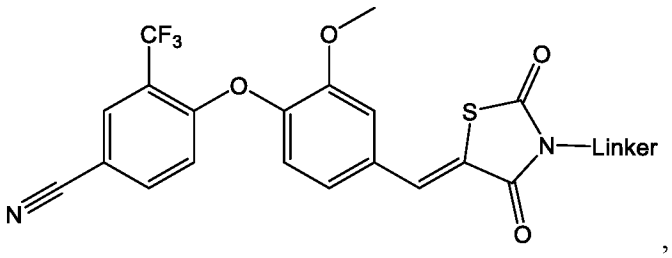

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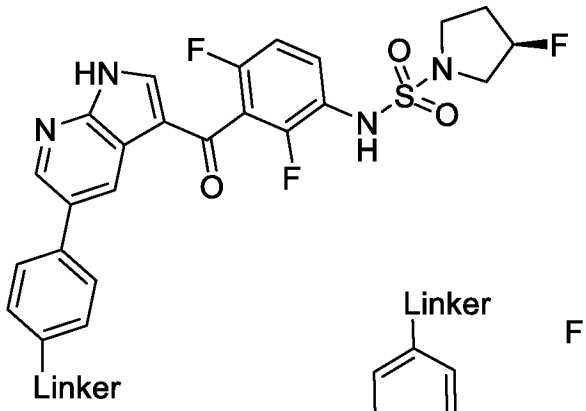

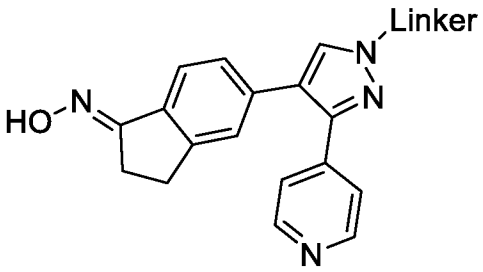

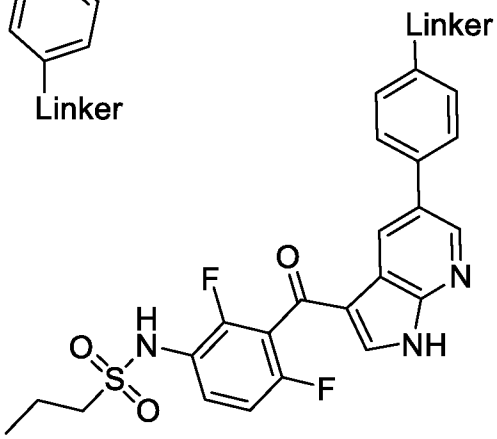

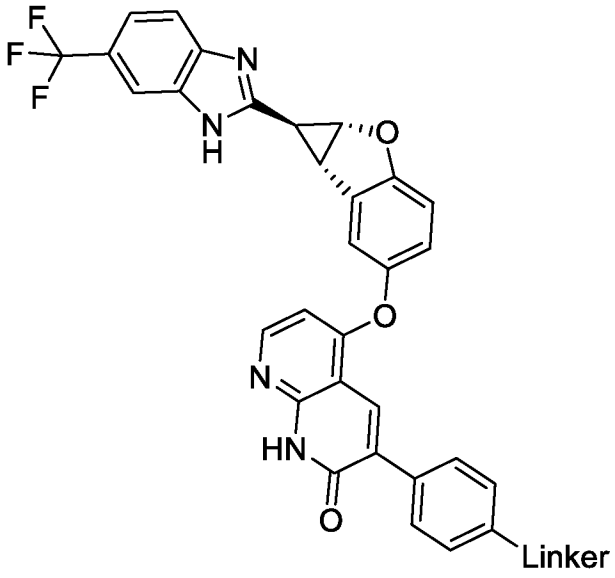

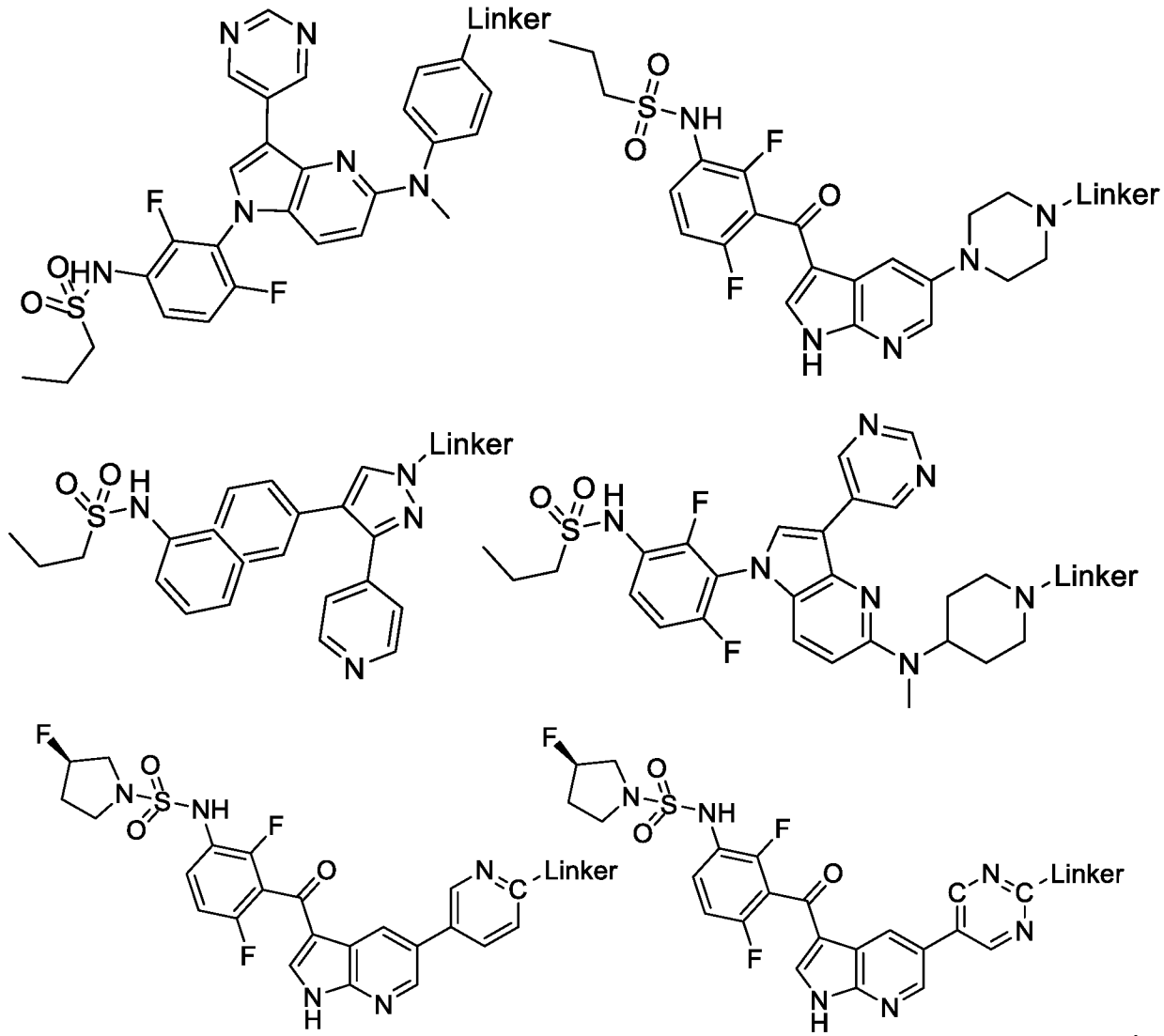

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wherein:

R is H, a lower alkyl, a bond, or a chemical moiety coupling the CLM to the PTM; and

Linker is a bond or a chemical linker moiety coupling the CLM to the PTM, including pharmaceutically acceptable salt forms thereof.

[0906] In any aspect or embodiment described herein, the compound is selected from the group consisting of compounds 1-52.

[0907] A further aspect of the present disclosure provides a composition comprising an effective amount of a bifunctional compound of the present disclosure, and a pharmaceutically acceptable carrier.

[0908] In any aspect or embodiment described herein, the composition further comprises at least one of additional bioactive agent or another bifunctional compound of the present disclosure.

[0909] In any aspect or embodiment described herein, the additional bioactive agent is anti-cancer agent, an anti-neurodegenerative agent, an antimicrobial agent, an antiviral agent, an anti-HIV agent, or an antifungal agent.

[0910] An additiona aspect of the present disclosure provides a composition comprising an effective amount of at least one compound of the present disclosure and a pharmaceutically acceptable carrier, additive, and/or excipient for treating a disease or disorder in a subject, the method comprising administering the composition to a subject in need thereof, wherein the compound is effective in treating or ameliorating at least one symptom of the disease or disorder.

[0911] In any aspect or embodiment described herein, the disease or disorder is associated with the accumulation and/or aggregation of the target protein.

[0912] In any aspect or embodiment described herein, the disease or disorder is selected from the group consisting of asthma, autoimmune diseases such as multiple sclerosis, various cancers, ciliopathies, cleft palate, diabetes, heart disease, hypertension, inflammatory bowel disease, mental retardation, mood disorder, obesity, refractive error, infertility, Angelman syndrome, Canavan disease, Coeliac disease, Charcot–Marie–Tooth disease, Cystic fibrosis, Duchenne muscular dystrophy, Haemochromatosis, Haemophilia, Klinefelter's syndrome, Neurofibromatosis, Phenylketonuria, Polycystic kidney disease, (PKD1) or 4 (PKD2) Prader–Willi syndrome, Sickle-cell disease, Tay–Sachs disease, Turner syndrome.

[0913] In any aspect or embodiment described herein, the disease or disorder is selected from the group consisting of Alzheimer's disease, Amyotrophic lateral sclerosis (Lou Gehrig's disease), Anorexia nervosa, Anxiety disorder, Atherosclerosis, Attention deficit hyperactivity disorder, Autism, Bipolar disorder, Chronic fatigue syndrome, Chronic obstructive pulmonary disease, Crohn's disease, Coronary heart disease, Dementia, Depression, Diabetes mellitus type 1, Diabetes mellitus type 2, Epilepsy, Guillain–Barré syndrome, Irritable bowel syndrome, Lupus, Metabolic syndrome, Multiple sclerosis, Myocardial infarction, Obesity, Obsessive–compulsive disorder, Panic disorder, Parkinson's disease, Psoriasis, Rheumatoid arthritis, Sarcoidosis, Schizophrenia, Stroke, Thromboangiitis obliterans, Tourette syndrome, Vasculitis.

[0914] In any aspect or embodiment described herein, the disease or disorder is selected from the group consisting of aceruloplasminemia, Achondrogenesis type II, achondroplasia, Acrocephaly, Gaucher disease type 2, acute intermittent porphyria, Canavan disease, Adenomatous Polyposis Coli, ALA dehydratase deficiency, adenylosuccinate lyase deficiency, Adrenogenital syndrome, Adrenoleukodystrophy, ALA-D porphyria, ALA dehydratase deficiency, Alkaptonuria, Alexander disease, Alkaptonuric ochronosis, alpha 1-antitrypsin deficiency, alpha-1 proteinase inhibitor, emphysema, amyotrophic lateral sclerosis Alström syndrome, Alexander disease, Amelogenesis imperfecta, ALA dehydratase deficiency, Anderson-Fabry disease, androgen insensitivity syndrome, Anemia Angiokeratoma Corporis Diffusum, Angiomatosis retinae (von Hippel–Lindau disease) Apert syndrome, Arachnodactyly (Marfan syndrome), Stickler syndrome, Arthrochalasis multiplex congenital (Ehlers–Danlos syndrome#arthrochalasia type) ataxia telangiectasia, Rett syndrome, primary pulmonary hypertension, Sandhoff disease, neurofibromatosis type II, Beare-Stevenson cutis gyrata syndrome, Mediterranean fever, familial, Benjamin syndrome, beta-thalassemia, Bilateral Acoustic Neurofibromatosis (neurofibromatosis type II), factor V Leiden thrombophilia, Bloch-Sulzberger syndrome (incontinentia pigmenti), Bloom syndrome, X-linked sideroblastic anemia, Bonnevie-Ullrich syndrome (Turner syndrome), Bourneville disease (tuberous sclerosis), prion disease, Birt–Hogg–Dubé syndrome, Brittle bone disease (osteogenesis imperfecta), Broad Thumb-Hallux syndrome (Rubinstein-Taybi syndrome), Bronze Diabetes/Bronzed Cirrhosis (hemochromatosis), Bulbospinal muscular atrophy (Kennedy's disease), Burger-Grutz syndrome (lipoprotein lipase deficiency), CGD Chronic granulomatous disorder, Campomelic dysplasia, biotinidase deficiency, Cardiomyopathy (Noonan syndrome), Cri du chat, CAVD (congenital absence of the vas deferens), Caylor cardiofacial syndrome (CBAVD), CEP (congenital erythropoietic porphyria), cystic fibrosis, congenital hypothyroidism, Chondrodystrophy syndrome (achondroplasia), otospondylomegaepiphyseal dysplasia, Lesch-Nyhan syndrome, galactosemia, Ehlers–Danlos syndrome, Thanatophoric dysplasia, Coffin-Lowry syndrome, Cockayne syndrome, (familial adenomatous polyposis), Congenital erythropoietic porphyria, Congenital heart disease, Methemoglobinemia/Congenital methaemoglobinaemia, achondroplasia, X-linked sideroblastic anemia, Connective tissue disease, Conotruncal anomaly face syndrome, Cooley's Anemia (beta-thalassemia), Copper storage disease (Wilson's disease), Copper transport disease (Menkes disease), hereditary coproporphyria, Cowden syndrome,

Craniofacial dysarthrosis (Crouzon syndrome), Creutzfeldt-Jakob disease (prion disease), Cockayne syndrome, Cowden syndrome, Curschmann-Batten-Steinert syndrome (myotonic dystrophy), Beare-Stevenson cutis gyrata syndrome, primary hyperoxaluria, spondyloepimetaphyseal dysplasia (Strudwick type), muscular dystrophy, Duchenne and Becker types (DBMD), Usher syndrome, Degenerative nerve diseases including de Grouchy syndrome and Dejerine-Sottas syndrome, developmental disabilities, distal spinal muscular atrophy, type V, androgen insensitivity syndrome, Diffuse Globoid Body Sclerosis (Krabbe disease), Di George's syndrome, Dihydrotestosterone receptor deficiency, androgen insensitivity syndrome, Down syndrome, Dwarfism, erythropoietic protoporphyria Erythroid 5-aminolevulinate synthetase deficiency, Erythropoietic porphyria, erythropoietic protoporphyria, erythropoietic uroporphyria, Friedreich's ataxia,, familial paroxysmal polyserositis, porphyria cutanea tarda, familial pressure sensitive neuropathy, primary pulmonary hypertension (PPH), Fibrocystic disease of the pancreas, fragile X syndrome, galactosemia, genetic brain disorders, Giant cell hepatitis (Neonatal hemochromatosis), Gronblad-Strandberg syndrome (pseudoxanthoma elasticum), Gunther disease (congenital erythropoietic porphyria), haemochromatosis, Hallgren syndrome, sickle cell anemia, hemophilia, hepatoerythropoietic porphyria (HEP), Hippel-Lindau disease (von Hippel-Lindau disease), Huntington's disease, Hutchinson-Gilford progeria syndrome (progeria), Hyperandrogenism, Hypochondroplasia, Hypochromic anemia, Immune system disorders, including X-linked severe combined immunodeficiency, Insley-Astley syndrome, Kennedy’s syndrome, Jackson-Weiss syndrome, Joubert syndrome, Lesch-Nyhan syndrome, Jackson-Weiss syndrome, Kidney diseases, including hyperoxaluria, Klinefelter's syndrome, Kniest dysplasia, Lacunar dementia,Langer-Saldino achondrogenesis, ataxia telangiectasia, Lynch syndrome, Lysyl-hydroxylase deficiency, Machado-Joseph disease, Metabolic disorders, including Kniest dysplasia, Marfan syndrome, Movement disorders, Mowat-Wilson syndrome, cystic fibrosis, Muenke syndrome, Multiple neurofibromatosis, Nance-Insley syndrome, Nance-Sweeney chondrodysplasia, Niemann–Pick disease, Noack syndrome (Pfeiffer syndrome), Osler-Weber-Rendu disease, Peutz-Jeghers syndrome, Polycystic kidney disease, polyostotic fibrous dysplasia (McCune–Albright syndrome), Peutz-Jeghers syndrome, Prader-Labhart-Willi syndrome, hemochromatosis, primary hyperuricemia syndrome (Lesch-Nyhan syndrome), primary pulmonary hypertension, primary senile degenerative dementia, prion disease, progeria (Hutchinson Gilford Progeria Syndrome), progressive chorea, chronic hereditary (Huntington)

(Huntington's disease), progressive muscular atrophy, spinal muscular atrophy, propionic acidemia, protoporphyria, proximal myotonic dystrophy, pulmonary arterial hypertension, PXE (pseudoxanthoma elasticum), Rb (retinoblastoma), Recklinghausen disease (neurofibromatosis type I), Recurrent polyserositis, Retinal disorders, Retinoblastoma, Rett syndrome, RFALS type 3, Ricker syndrome, Riley-Day syndrome, Roussy-Levy syndrome, severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), Li-Fraumeni syndrome, sarcoma, breast, leukemia, and adrenal gland (SBLA) syndrome, sclerosis tuberose (tuberous sclerosis), SDAT, SED congenital (spondyloepiphyseal dysplasia congenita), SED Strudwick (spondyloepimetaphyseal dysplasia, Strudwick type), SEDc (spondyloepiphyseal dysplasia congenita) SEMD, Strudwick type (spondyloepimetaphyseal dysplasia, Strudwick type), Shprintzen syndrome, Skin pigmentation disorders, Smith-Lemli-Opitz syndrome, South-African genetic porphyria (variegate porphyria), infantile-onset ascending hereditary spastic paralysis, Speech and communication disorders, sphingolipidosis, Tay-Sachs disease, spinocerebellar ataxia, Stickler syndrome, stroke, androgen insensitivity syndrome, tetrahydrobiopterin deficiency, beta-thalassemia, Thyroid disease, Tomaculous neuropathy (hereditary neuropathy with liability to pressure palsies), Treacher Collins syndrome, Triplo X syndrome (triple X syndrome), Trisomy 21 (Down syndrome), Trisomy X, VHL syndrome (von Hippel-Lindau disease), Vision impairment and blindness (Alström syndrome), Vrolik disease, Waardenburg syndrome, Warburg Sjo Fledelius Syndrome, Weissenbacher-Zweymüller syndrome, Wolf–Hirschhorn syndrome, Wolff Periodic disease, Weissenbacher-Zweymüller syndrome and Xeroderma pigmentosum.

[0915] In any aspect or embodiment described herein, the composition further comprises an additional bioactive agent.

[0916] In any aspect or embodiment described herein, the additional bioactive agent is at least one of an anti-cancer agent, an anti-neurodegenerative agent, an antimicrobial agent, an antiviral agent, an anti-HIV agent, an antifungal agent, or a combination thereof.

[0917] In any aspect or embodiment described herein, the anticancer agent is selected from the group consisting of everolimus, trabectedin, abraxane, TLK 286, AV-299, DN-101, pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, a FLT-3 inhibitor, a VEGFR inhibitor, an EGFR TK inhibitor, an

aurora kinase inhibitor, a PIK-1 modulator, a Bcl-2 inhibitor, an HDAC inhbitor, a c-MET inhibitor, a PARP inhibitor, a Cdk inhibitor, an EGFR TK inhibitor, an IGFR-TK inhibitor, an anti-HGF antibody, a PI3 kinase inhibitors, an AKT inhibitor, an mTORC1/2 inhibitor, a JAK/STAT inhibitor, a checkpoint-1 or 2 inhibitor, a focal adhesion kinase inhibitor, a Map kinase kinase (mek) inhibitor, a VEGF trap antibody, pemetrexed, erlotinib, dasatanib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab, zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111, 131-I-TM-601 , ALT-110, BIO 140, CC 8490, cilengitide, gimatecan, IL13-PE38QQR, INO 1001 , $IPdR_1$ KRX-0402, lucanthone, LY 317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311 , romidepsin, ADS-100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, liposomal doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709, seliciclib; PD0325901 , AZD-6244, capecitabine, L-Glutamic acid, N -[4-[2-(2-amino-4,7-dihydro-4-oxo-1 H - pyrrolo[2,3- d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate, camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrazole, exemestane, letrozole, DES(diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11 , CHIR-258,); 3-[5-(methylsulfonylpiperadinemethyl)- indolylj-quinolone, vatalanib, AG-013736, AVE-0005, the acetate salt of [D- Ser(Bu t) 6 ,Azgly 10] (pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu t)-Leu-Arg-Pro- Azgly-NH_2 acetate [$C_{59}H_{84}N_{18}Oi_4$ -$(C_2H_4O_2)_X$ where x = 1 to 2.4], goserelin acetate, leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714; TAK-165, HKI-272, erlotinib, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-166, GW-572016, Ionafarnib, BMS-214662, tipifarnib; amifostine, NVP-LAQ824, suberoyl analide hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib, KRN951 , aminoglutethimide, arnsacrine, anagrelide, L-asparaginase, Bacillus Calmette-Guerin (BCG) vaccine, adriamycin, bleomycin, buserelin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, diethylstilbestrol, epirubicin, fludarabine, fludrocortisone, fluoxymesterone, flutamide, gleevac, gemcitabine, hydroxyurea, idarubicin, ifosfamide, imatinib, leuprolide, levamisole, lomustine, mechlorethamine, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide,

octreotide, oxaliplatin, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, teniposide, testosterone, thalidomide, thioguanine, thiotepa, tretinoin, vindesine, 13-cis-retinoic acid, phenylalanine mustard, uracil mustard, estramustine, altretamine, floxuridine, 5-deooxyuridine, cytosine arabinoside, 6-mecaptopurine, deoxycoformycin, calcitriol, valrubicin, mithramycin, vinblastine, vinorelbine, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291 , squalamine, endostatin, SU5416, SU6668, EMD121974, interleukin-12, IM862, angiostatin, vitaxin, droloxifene, idoxyfene, spironolactone, finasteride, cimitidine, trastuzumab, denileukin diftitox,gefitinib, bortezimib, paclitaxel, cremophor-free paclitaxel, docetaxel, epithilone B, BMS- 247550, BMS-310705, droloxifene, 4-hydroxytamoxifen, pipendoxifene, ERA- 923, arzoxifene, fulvestrant, acolbifene, lasofoxifene, idoxifene, TSE-424, HMR- 3339, ZK186619, topotecan, PTK787/ZK 222584, VX-745, PD 184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-23573, RAD001 , ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684, LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, erythropoietin, granulocyte colony-stimulating factor, zolendronate, prednisone, cetuximab, granulocyte macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-2a, pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L-asparaginase, lenalidomide, gemtuzumab, hydrocortisone, interleukin-11 , dexrazoxane, alemtuzumab, all-transretinoic acid, ketoconazole, interleukin-2, megestrol, immune globulin, nitrogen mustard, methylprednisolone, ibritgumomab tiuxetan, androgens, decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, cortisone, editronate, mitotane, cyclosporine, liposomal daunorubicin, Edwina-asparaginase, strontium 89, casopitant, netupitant, an NK-1 receptor antagonists, palonosetron, aprepitant, diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone, methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, erythropoietin, epoetin alfa, darbepoetin alfa and mixtures thereof.

[0918] An additional aspect of the present disclosure provides a method for inducing degradation of a target protein in a cell comprising administering an effective amount of a compound of the present disclosure to the cell, wherein the compound effectuates degradation of the target protein.

[0919] Another aspect of the present disclosure provides a composition comprising an effective amount of a compound of the present disclosure for use in a method for treating cancer, said method comprising administering the composition to a patient in need thereof, wherein the composition is effectuates for the treatment or alleviation of at least one symptom of cancer in the patient.

[0920] In any aspect or embodiment described herein, the cancer is squamous-cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinomas, and renal cell carcinomas, cancer of the bladder, bowel, breast, cervix, colon, esophagus, head, kidney, liver, lung, neck, ovary, pancreas, prostate, and stomach; leukemias; benign and malignant lymphomas, particularly Burkitt's lymphoma and Non-Hodgkin's lymphoma; benign and malignant melanomas; myeloproliferative diseases; multiple myeloma, sarcomas, including Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma, synovial sarcoma, gliomas, astrocytomas, oligodendrogliomas, ependymomas, gliobastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors, meningiomas, meningeal sarcomas, neurofibromas, and Schwannomas; bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, esophageal cancer, pancreatic cancer, stomach cancer, liver cancer, colon cancer, melanoma; carcinosarcoma, Hodgkin's disease, Wilms' tumor or teratocarcinomas, T-lineage Acute lymphoblastic Leukemia (T-ALL), T-lineage lymphoblastic Lymphoma (T-LL), Peripheral T-cell lymphoma, Adult T-cell Leukemia, Pre-B ALL, Pre-B Lymphomas, Large B-cell Lymphoma, Burkitts Lymphoma, B-cell ALL, Philadelphia chromosome positive ALL and Philadelphia chromosome positive CML.

[0921] While preferred embodiments of the invention have been shown and described herein, it will be understood that such embodiments are provided by way of example only. Numerous variations, changes and substitutions will occur to those skilled in the art without departing from the spirit of the invention. Accordingly, it is intended that the appended claims cover all such variations as fall within the spirit and scope of the invention.

[0922] **EXAMPLES**

[0923] **A. Protein Degradation Bioassays:**

[0924] The following bioassays evaluate the level of protein degradation observed in various cell types using representative compounds disclosed herein.

[0925] In each bioassay, cells were treated with varying amounts of compounds encompassed by the present disclosure. The degradation of the following proteins may be evaluated: estrogen receptor α (ERα), bromodomain-containing protein 4 (BRD4), androgen receptor (AR), and BRaf protein .

[0926] **1. ERE Luciferase Assay for compounds in Table 5.**

[0927] T47D-KBluc cells (ATCC® #CRL_2865, T47D human breast cancer cells stably transfected with estrogen responsive element/promoter/luciferase reporter gene) were seeded into 96-well white opaque plates in RPMI growth medium supplemented with 10% fetal bovine serum (FBS) and allowed to adhere overnight in a 37°C humidified incubator. The following day, cells were treated with PROTACs in a 12-point concentration curve (top final concentration of 300 nM with subsequent concentrations being 3-fold less with 2 pM being the lowest concentration in the assay). Each PROTAC was tested independently in two experiments on 96-well plates. After 24 hours, media was removed and lysis buffer was added to the wells. Following lysis, Bright-Glo™ Luciferase Assay Substrate (Promega, Madison WI) was added and the luciferase activity was measured using a Cytation 3 plate reader (BioTek™, Winooski, VT). Each compound was assayed in duplicate and the activity was calculated as IC50 using GraphPad Prism software (San Diego, CA).

[0928] **2. Estrogen Receptor-alpha (ERα) degradation assay in MCF-7 cells using western blot method for Table 5.**

[0929] The exemplary novel ERα degraders were assessed for their activity in degrading ERα in MCF-7 cells via western blot. The assay was carried out in the presence of 10% FBS or high percentage of human or mouse serum. Protocols of the western blot assay are described below.

[0930] MCF7 cells were grown in DMEM/F12 with 10% FBS and seeded at 24,000 cells per well in 100 µl into 96-well clear tissue culture plates. The following day, the cells were treated with PROTACs in a 7-point concentration curve with 100 nM being the top concentration and serial dilutions to make the other concentrations (30 nM, 10 nM, 3 nM, 1 nM, and 0.3 nM). At all concentrations, 0.01% DMSO is the final concentration in the well. The following day, the plates are aspirated, washed with 50 µl of cold PBS. The cells are lysed with 50 µl/well 4°C Cell

Lysis Buffer (Catalog# 9803; Cell Signaling Technology, Danvers, MA) (20mM Tris-HCL (pH 7.5), 150 mM NaCl, 1mM Na_2EDTA, 1 mM EGTA, 1% Triton, 2.5 mM sodium pyrophosphate, 1 mM B-glycerophosphate, 1 mM sodium vanadate, 1 ug/ml leupeptin). Lysates were clarified at 16,000 x g for 10 minutes, and 2 µg of protein was subjected to SDS-PAGE analysis and followed by immunoblotting according to standard protocols. The antibodies used were ERα (Cell Signaling Technologies Catalog #8644), and Tubulin (Sigma Catalog #T9026; St. Louis, MO). Detection reagents were Clarity Western ECL substrate (Bio-Rad Catalog #170-5060; Hercules, CA).

[0931] Alternatively, MCF7 cells were grown in DMEM/F12 with 10% FBS and seeded at 24,000 cells per well in 500 µl in 24-well clear tissue culture plates. The following day, the cells were treated with PROTACs in a 5-point concentration curve (100 nM, 33 nM, 11 nM, 3.7 nM, and 1.2 nM) in the presence of 0.01% DMSO. After 72 hours, the wells are aspirated and washed with 500 µl of PBS. The cells are lysed with 100 µl/well 4°C Cell Lysis Buffer (Catalog# 9803; Cell Signaling Technology, Danvers, MA) (20mM Tris-HCL (pH 7.5), 150 mM NaCl, 1mM Na_2EDTA, 1 mM EGTA, 1% Triton, 2.5 mM sodium pyrophosphate, 1 mM B-glycerophosphate, 1 mM sodium vanadate, 1 ug/ml leupeptin). Lysates were clarified at 16,000 x g for 10 minutes, and 2 µg of protein was subjected to SDS-PAGE analysis and followed by immunoblotting according to standard protocols. The antibodies used were ERα (Cell Signaling Technologies Catalog #8644), and Tubulin (Sigma Catalog #T9026; St. Louis, MO). Detection reagents were Clarity Western ECL substrate (Bio-Rad Catalog #170-5060, Hercules, CA).

[0932] 3. Estrogen receptor-alpha (ERα) degradation assay using In-Cell Western™ Assay for Table 5.

[0933] Degradation of ERα by claimed compounds were determined in MCF7 cells using an In-Cell Western™ assay. Briefly, MCF7 cells were plated in 96-well plates (2000 cells per well in 100 µl media) and incubated at 37°C under an atmosphere of 5% CO_2 in a humidified incubator overnight. One-hundred (100) µl of media containing test compound (at 2x concentration) was added to the appropriate wells to provide 11 serially decreasing concentrations (top final concentration, 1 µM then 3-fold less for the next 10 concentrations); a vehicle control (DMSO) was also added for each compound. For each experiment, all compounds were assayed in duplicate plates. Cells were then incubated for 3 or 5 days in the above-mentioned environment. The assay was terminated by removal of media, a single wash

with ice-cold PBS and the addition of 50 µl paraformaldehyde (PFA: 4% in PBS). After 15 minutes in PFA at room temperature, the cells were permeabilized in Tris-phosphate-buffered saline with Tween (0.1%) (TBST) supplemented with Triton X-100 (0.5%) for 15 minutes. Cells were then blocked in BSA (TBST with BSA, 3%) for one hour. Primary antibodies for the detection of ERα (rabbit monoclonal, 1:1000, Cell Signaling Technology Catalog #8644) and tubulin (mouse monoclonal, 1:5000, Sigma Catalog #T6074) in TBST with BSA (3%) were added. The cells were incubated overnight at 4°C. The cells were then washed thrice with TBST at room temperature and then incubated with anti-rabbit and anti-mouse fluorescently-labelled secondary antibodies (IRDye®; LI-COR; Lincoln, NE) in LI-COR blocking buffer (Catalog #927-50000) for one hour at room temperature. Following 3 washes with TBST, the buffer was removed and the plates were read on an Odyssey® infrared imaging system (LI-COR®; Lincoln, NE) at 700 nm and 800 nm. Using commercial software (ImageStudio™; LI-COR, Lincoln, NE), the staining intensity for ERα and tubulin in each well was quantified and exported for analysis. For each data point, ERα intensity was normalized to tubulin intensity and for each compound all normalized intensity values were normalized to the vehicle control. DC_{50} and D_{max} values were determined following a 4-parameter IC_{50} curve fit using ACAS dose response module (McNeil & Co Inc.).

[0934] 4. AR ELISA Assay Protocol for Table 6

[0935] Compounds were evaluated in this assay in LNCaP and/or VCaP cells utilizing similar protocols. The protocols used with VCaP cells are described below. The androgen receptor ELISA assay was performed using PathScan AR Sandwich ELISA (Cell Signaling Catalog#12850) according to the following assay steps:

[0936] VCaP cells were seeded at 40,000 cells/well at a volume of 100 µL/well in VCaP assay medium [Phenol red free RPMI (Gibco Cat#11835-030); 5% Charcoal Stripped (Dextran treated) FBS (Omega Scientific, Cat#FB-04); 1% penstrep (Life Technologies,Gibco Cat#: 10378-016)] in Corning 3904 plates. The cells were incubated for a minimum of 3 days. Cells were dosed with PROTACs diluted in 0.01% DMSO and the drug treatment was allowed for 5 hours.

[0937] AR ELISA (Cell Signaling) was performed as follows. 1x Cell Signaling Cell lysis buffer was made (Catalogue #9803; comes with the kit). Media from the treated wells is aspirated, and 100 µL lx cell lysis buffer/well is added. The cells were placed on a shaker for 10

minutes at 4°C. Twenty microliters of lysate was transferred to 100µl of Diluent in ELISA plate (0.15µg/ml – 0.075 µg/ml). The lysate-diluent mixture was shaken for 30 minutes at 37°C. Allow mouse AR antibody, anti-mouse antibody, TMB, and STOP solution to come to room temperature. The 1x ELISA buffer included in kit was made and loaded in the reservoir.. Media from the plates was discarded, the ELISA plate tapped hard on paper towel, and washed 4x 200 µl ELISA wash buffer using a plate washer.

[0938] One-hundred (100) µL/well of mouse AR detection Ab was added; the plates were covered and shaken at 37°C for 1 hour; media was discarded from the plates, the plates were tapped on a paper towel, washed 4x with 200 µL ELISA wash buffer with a plate washer.

[0939] One-hundred (100) µL/well of anti-mouse – HRP conjugated Ab (comes with the kit) was added; the plates were covered and shaken at 37°C for 30 minutes; the TMB reagent was allowed to come to room temperature; the media was discard from the plate, the plates were tapped on paper towl, washed 4x with 200 µL of ELISA wash buffer; the plates were tapped the plates on paper towl. One-hundred (100) µL of TMB was added and the plates shaken for 2 minutes – while watching for color development. One-hundred (100) µL Stop solution was added when light blue color developed. Plates were shaken and read at 450 nM.

[0940] Progression of prostate cancer in patients treated with anti-androgen therapy usually involves one of several mechanisms of enhanced Androgen Receptor (AR) signaling, including increased intratumoral androgen synthesis, increased AR expression and AR mutations. PROTACs (PROteolysis TArgeting Chimera), which use bi-functional molecules that simultaneously bind a target of choice and an E3 ligase, cause ubiquitination via induced proximity and degradation of the targeted, pathological protein. As opposed to traditional target inhibition, which is a competitive process, degradation is a progressive process. As such, it is less susceptible to increases in endogenous ligand, target expression, or mutations in the target. Thus, this technology appears to be ideal for addressing the mechanisms of AR resistance in patients with prostate cancer. Data was analyzed and plotted using GraphPad Prism software.

[0941] **5. BRaf Protein In Vitro Degradation Assay (A375 cells) of Table 7**

[0942] A375 cells were cultured in ATCC DMEM+10%FBS in 12 well plates, and treated with indicated compound from Tables 1-41 or 0.1% DMSO vehicle control for 16 hours. Cells were harvested in Cell Signaling lysis buffer (Cat# 9803) with the addition of Roche protease inhibitor tablets (Cat# 11873580001), and lysates clarified by microcentrifugation. Proteins were

separated by SDS-PAGE, and transferred onto nitrocellulose membranes using an Invitrogen iBlot system. Immunoblotting was performed for BRaf (Santa Cruz Cat# 9002), CRAF (BD Cat#610151), and pErk (Cell Signaling Cat#9106). GAPDH (Cell Signaling Cat#2118) was used as a loading control. Quantification was carried out using the BioRad Image Lab 5 software.

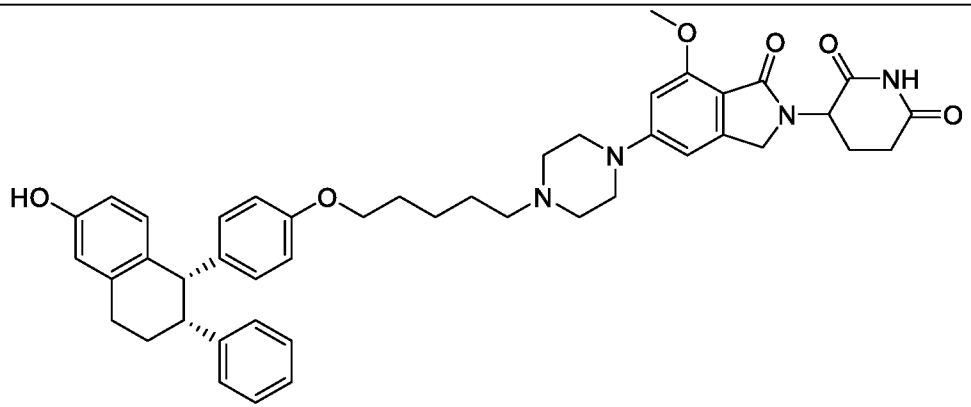
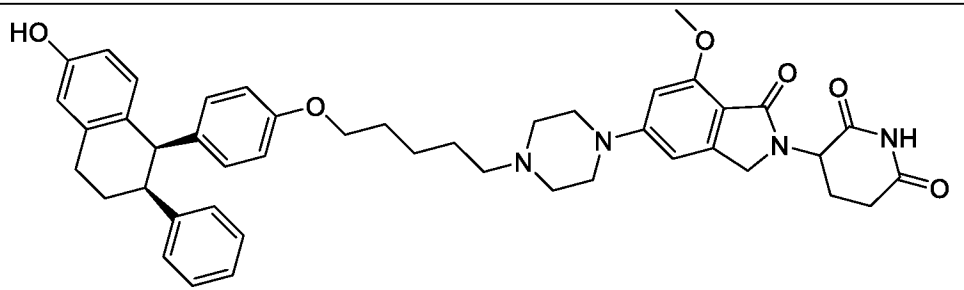
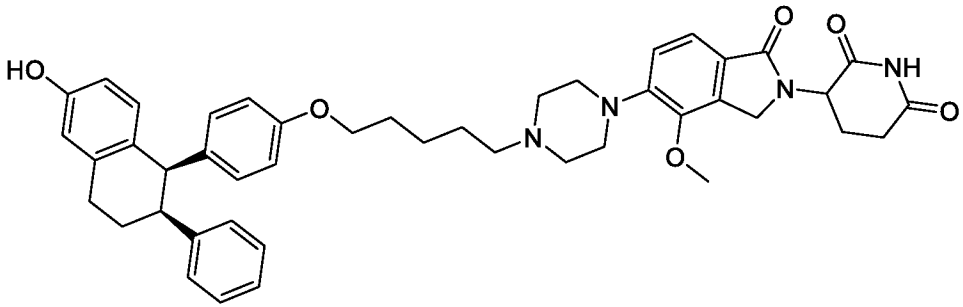
[0943] 6. BRaf In-Cell Western Cellular Degradation Assay (A375 cells) of Table 7

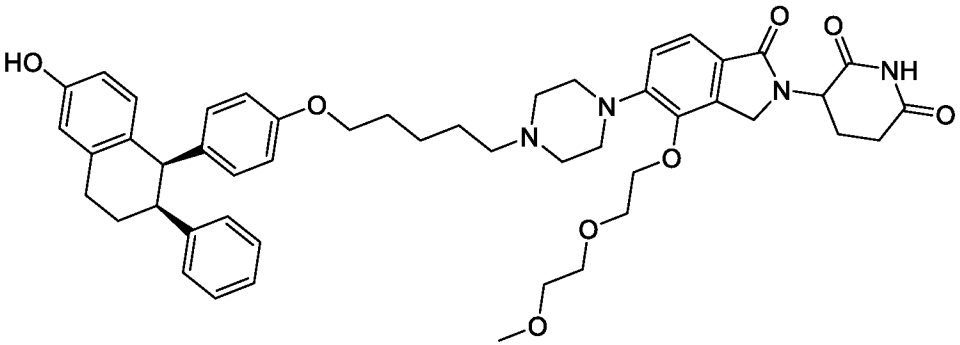
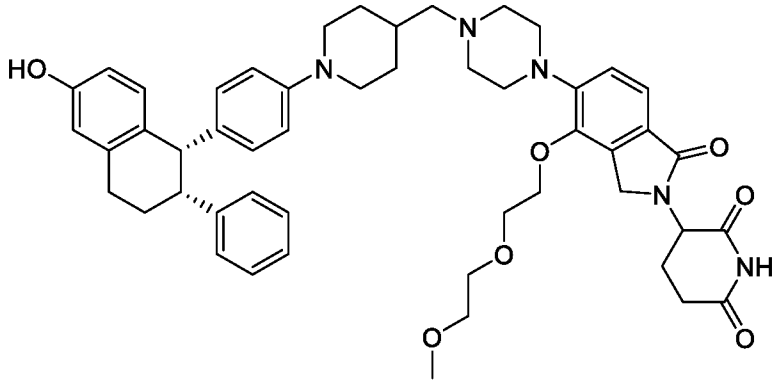
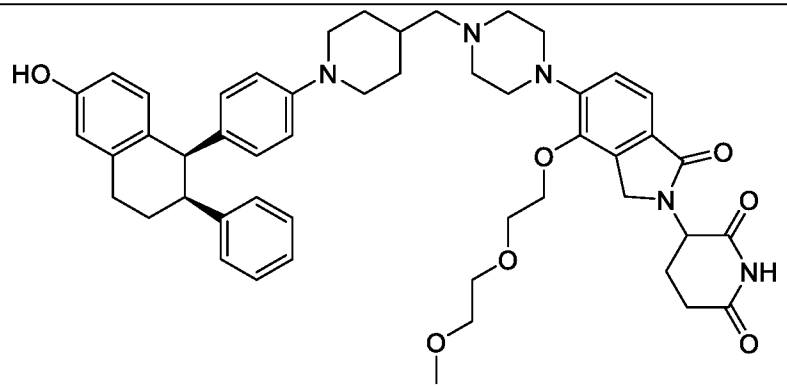
[0944] A375 cells were cultured in ATCC DMEM+10% FBS in 96-well plates, and treated with indicated compounds from Tables-43 or 0.1% DMSO vehicle control for 72 hours. Cells were washed with PBS 1x, and affixed to plate using 4% PFA in phosphate buffered saline for 15 minutes; washed 1X and permeabilized using 0.1% Triton-X-100 in PBS for 5 minutes; washed 1X and blocked with LICOR blocker (Cat.# 927-50000) for 1 hour. Cells were then incubated with B-Raf antibody (Santa Cruz Cat# 9002, Santa Cruz Cat#528) and tubulin antibody (Sigma #T6074) in LICOR blocker for 18 hours. Cells were washed 3x prior to adding secondary antibodies (LICOR cat #926-32210 and 926-68071) and incubated for 1 hour. Cells were washed 3x and imaged using LICOR Odyssey Software.

[0945] 7. BRD4 Western Protocol for Table 8

[0946] 22Rv-1 or VCaP cells were purchased from ATCC and cultured in Dulbecco's Modified Eagle's Medium (ATCC), supplemented with 10% FBS (ATCC) and Penicillin/Streptomycin (Life Technologies). DMSO control and compound treatments (0.003μM, 0.01μM, 0.03 μM and 0.1μM) were performed in 12-well plates for 16 hours. Cells were harvested, and lysed in RIPA buffer (50mM Tris pH8, 150mM NaCl, 1% Tx-100, 0.1% SDS, 0.5% sodium deoxycholate) supplemented with protease and phosphatase inhibitors. Lysates were clarified at 16,000g for 10 minutes, and protein concentration was determined. Equal amount of protein (20μg) was subjected to SDS-PAGE analysis and followed by immunoblotting according to standard protocols. The antibodies used were BRD4 (Cell Signaling #13440), and Actin (Sigma #5441). Detection reagents were Clarity Western ECL substrate (Bio-rad #170-5060).

[0947] Table 1. Exemplary Estrogen Receptor PROTACs

Ex. #	Chemical Structure	Name	General Synthetic Method
1		3-{5-[4-(5-{4-[(1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl]phenoxy}pentyl)piperazin-1-yl]-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-2-yl}piperidine-2,6-dione	A-2, A-8
2		3-(5-(4-(5-(4-((1R, 2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)pentyl)piperazin-1-yl)-7-methoxy-1-oxoisoindolin-2-yl)piperidine-2,6-dione	A-2, A-8 Exp. Procedure included
3		3-[5-[4-[5-[4-[(1R,2S)-6-hydroxy-2-phenyl- tetralin-1-yl] phenoxy]pentyl]piperazin-1-yl]-4-methoxy-1-oxo-isoindolin-2-yl]piperidine -2,6-dione	A-4, A-8 Exp. Procedure included

4		3-[5-[4-[5-[4-[(1R,2S)-6-hydroxy-2-phenyl- tetralin-1-yl]phenoxy]pentyl]piperazin-1-yl]-4-[2-(2-methoxyethoxy)ethoxy]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione	A-4, A-5, A-8
5		3-(5-{4-[(1-{4-[(1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl]phenyl}piperidin-4-yl)methyl]piperazin-1-yl}-4-[2-(2-methoxyethoxy)ethoxy]-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione	A-4, A-5, A-12
6		3-(5-{4-[(1-{4-[(1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl]phenyl}piperidin-4-yl)methyl]piperazin-1-yl}-4-[2-(2-methoxyethoxy)ethoxy]-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione	A-4, A-5, A-12

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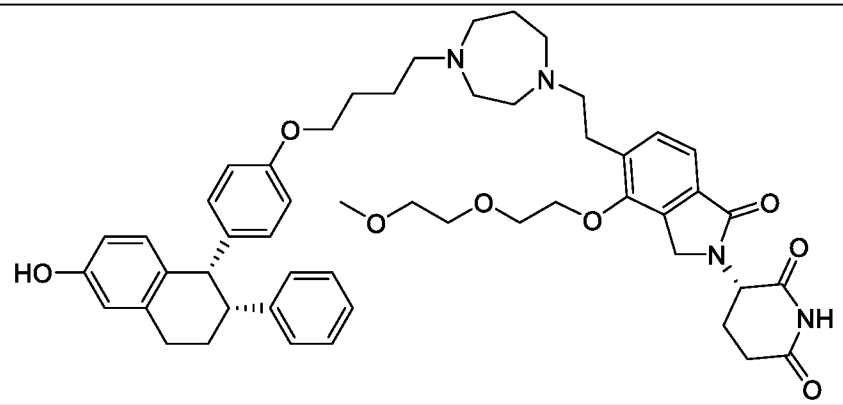
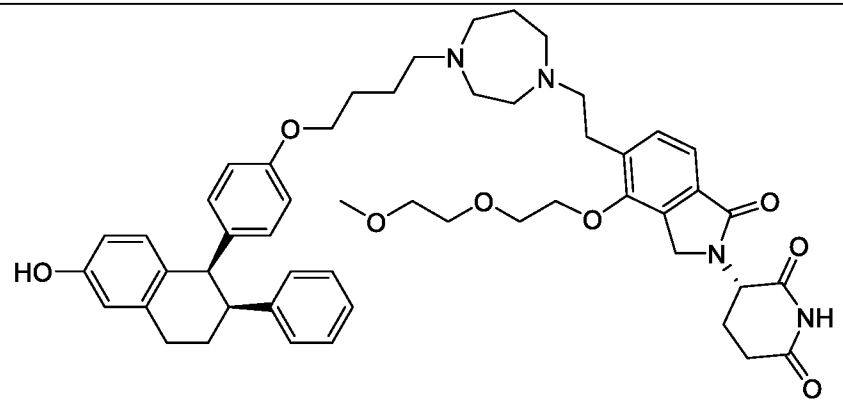
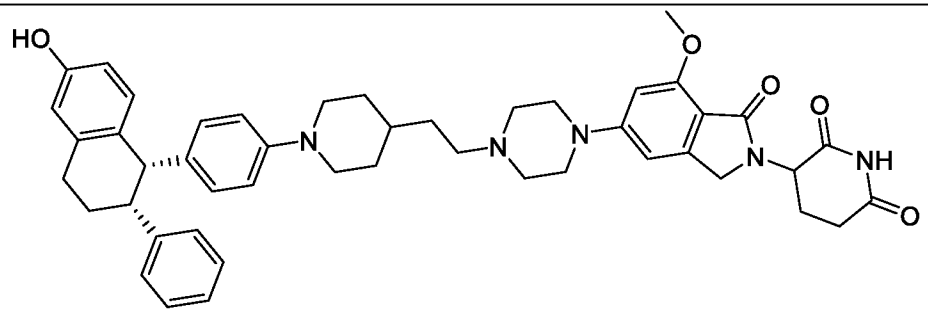
7		(3S)-3-(5-{2-[4-(4-{4-[(1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl]phenoxy}butyl)-1,4-diazepan-1-yl]ethyl}-4-[2-(2-methoxyethoxy)ethoxy]-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione	A-5, A-9
8		(3S)-3-[5-[2-[4-[4-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenoxy]butyl]-1,4-diazepan-1-yl]ethyl]-4-[2-(2-methoxyethoxy)ethoxy]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione	A-5, A-9
9		3-(5-{4-[2-(1-{4-[(1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl]phenyl}piperidin-4-yl)ethyl]piperazin-1-yl}-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione	A-2, A-13

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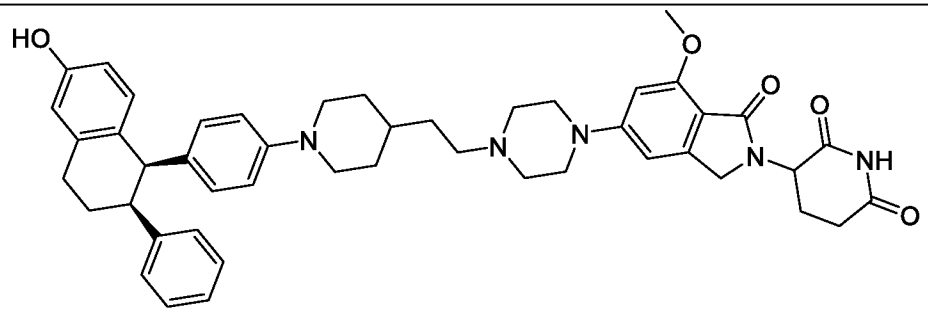
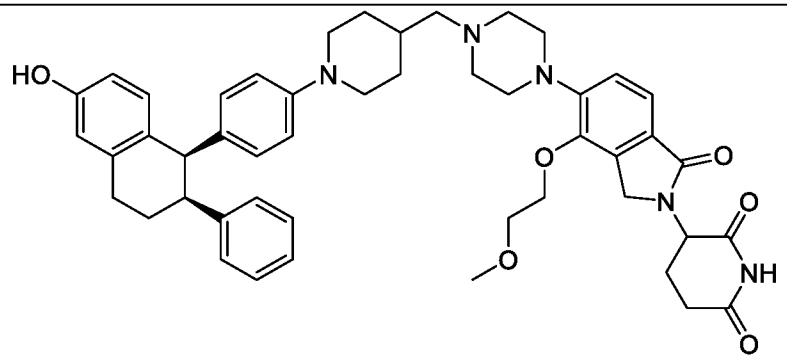
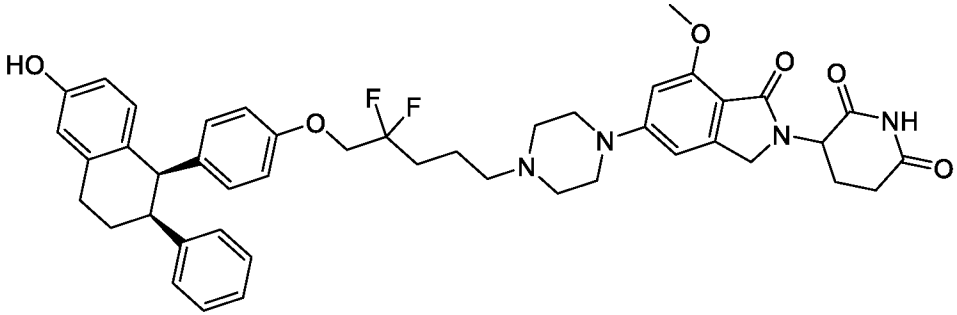
10		3-[5-[4-[2-[1-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenyl]-4-piperidyl]ethyl]piperazin-1-yl]-7-methoxy-1-oxo-isoindolin-2-yl]piperidine-2,6-dione	A-2, A-13
11		3-[5-[4-[[1-[4 -[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenyl]-4-piperidyl]methyl]piperazin-1-yl]-4-(2-methoxyethoxy)-1-oxo-isoindolin-2-yl]piperidine-2,6-dione	A-4, A-12
12		3-[5-[4-[4,4-difluoro-5-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenoxy]pentyl]piperazin-1-yl]-7-methoxy-1-oxo-isoindolin-2-yl]piperidine-2,6-dione	A-2, A-10

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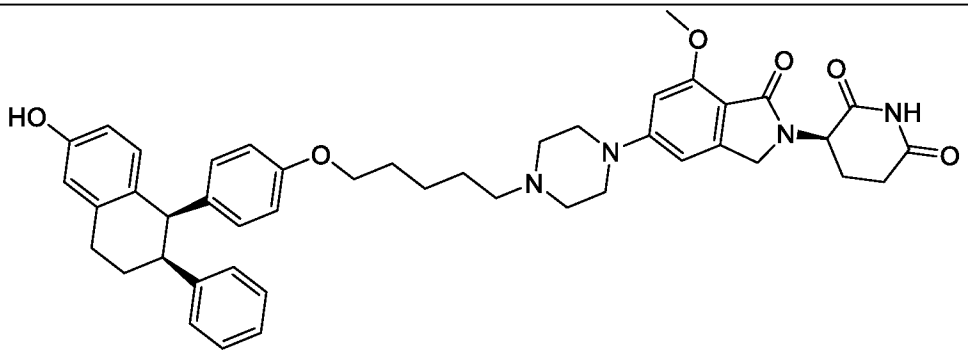
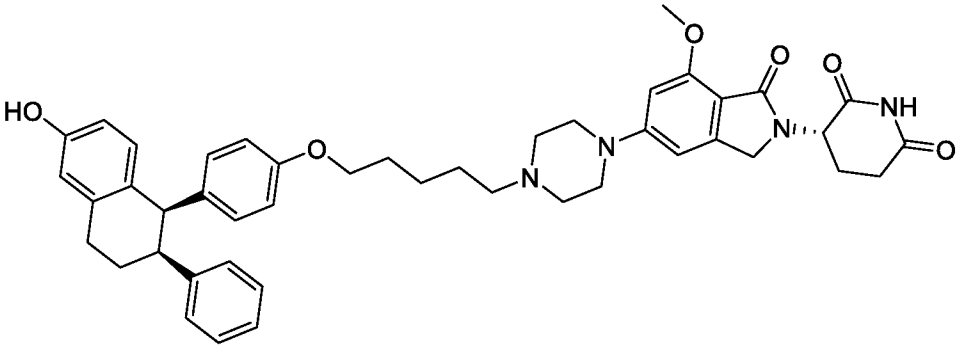
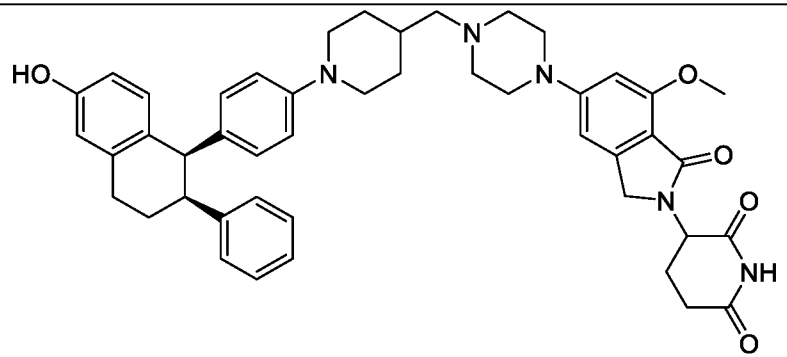
13		(3R)-3-[5-[4-[5-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenoxy]pentyl]piperazin-1-yl]-7-methoxy-1-oxo-isoindolin-2-yl]piperidine-2,6-dione	A-2, A-8
14		(3S)-3-[5-[4-[5-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenoxy]pentyl]piperazin-1-yl]-7-methoxy-1-oxo-isoindolin-2-yl]piperidine-2,6-dione	A-2, A-8
15		3-[5-[4-[[1-[4-[(1R,2S)-6-hydroxy-2-phenyl -tetralin-1-yl]phenyl]-4-piperidyl]methyl]piperazin-1-yl]-7-methoxy-1-oxo-isoindolin-2-yl]piperidine-2,6-dione	A-2, A-12

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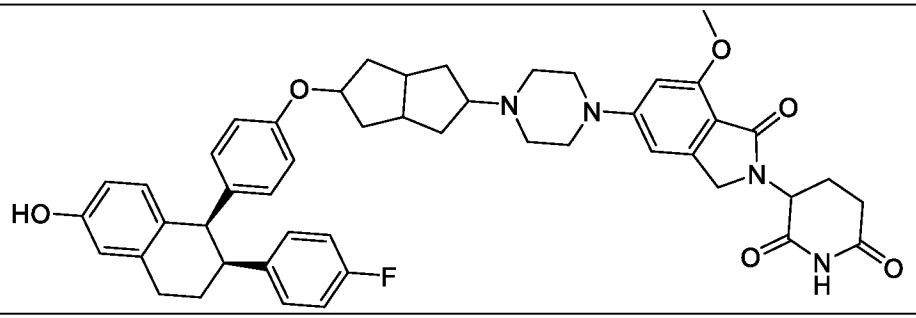
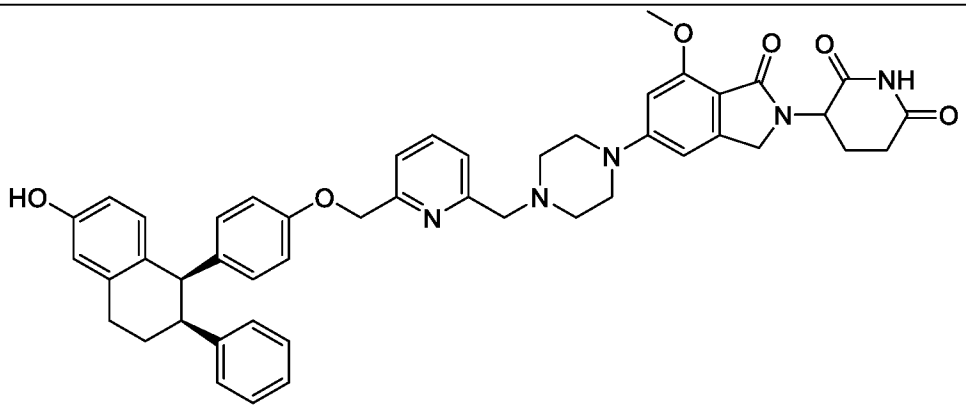
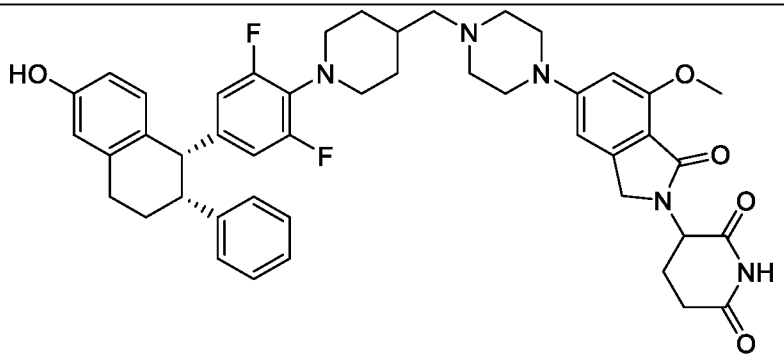
16		3-[5-[4-[5-[4-[(1R,2S)-2-(4-fluorophenyl)-6- hydroxy-tetralin-1-yl]phenoxy]-1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl]piperazin-1-yl]-7-methoxy-1-oxo-isoindolin-2-yl]piperidine-2,6-dione	A-2, A-11
17		3-[5-[4-[[6-[[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenoxy]methyl]-2-pyridyl]methyl]piperazin-1-yl]-7-methoxy-1-oxo-isoindolin-2-yl]piperidine-2,6-dione	A-16
18		3-(5-{4-[(1-{2,6-difluoro-4-[(1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl]phenyl}piperidin-4-yl)methyl]piperazin-1-yl}-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione	A-1, A-2

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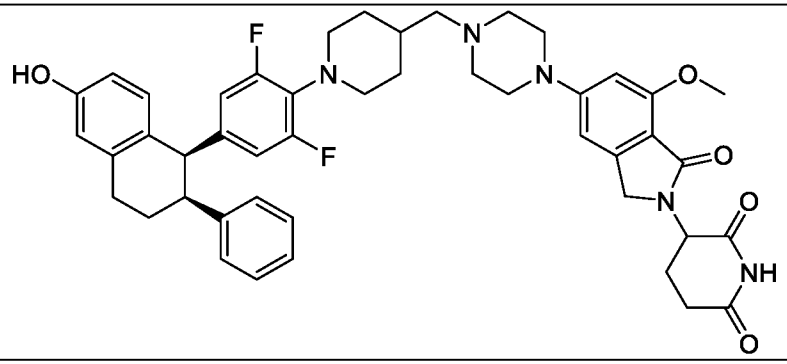
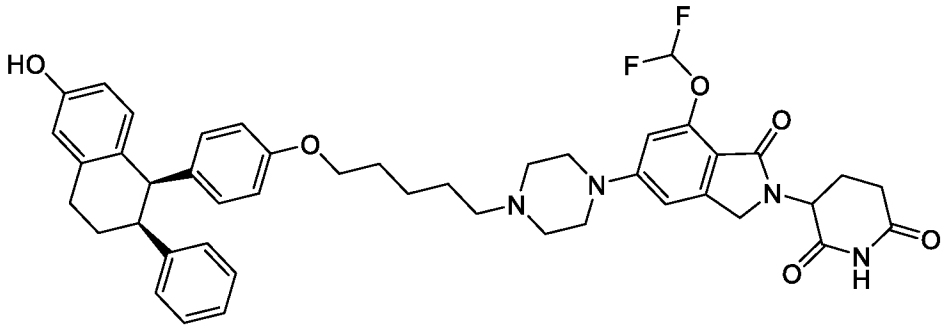
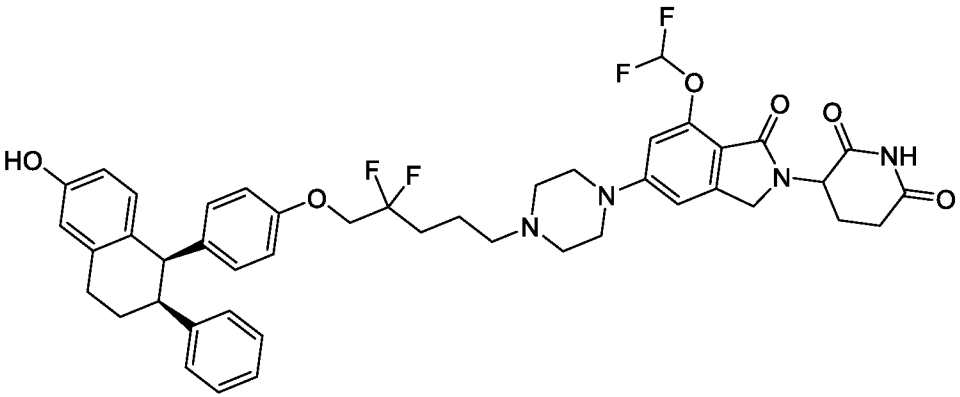
19		3-(5-(4-((1-(2,6-difluoro-4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-7-methoxy-1-oxoisoindolin-2-yl)piperidine-2,6-dione	A-1, A-2, A-8
20		3-[7-(difluoromethoxy)-5-[4-[5-[4-[(1R,2S)-6- hydroxy-2-phenyl-tetralin-1-yl]phenoxy]pentyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione	A-3, A-8
21		3-[5-[4-[4,4-difluoro-5-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenoxy]pentyl]piperazin-1-yl]-7-(difluoromethoxy)-1-oxo-isoindolin-2-yl]piperidine-2,6-dione	A-6, A-10

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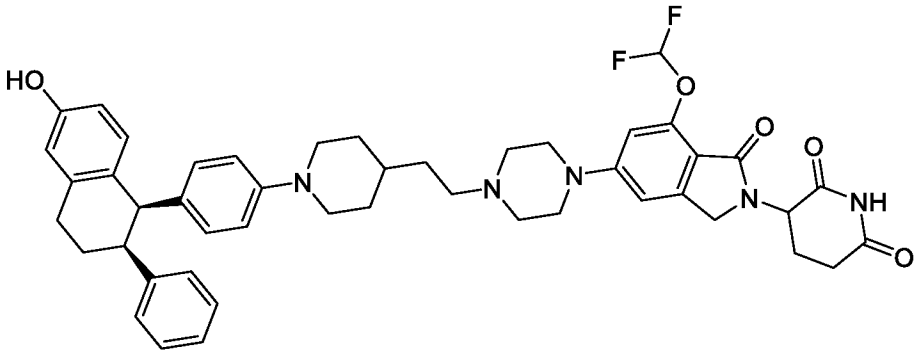
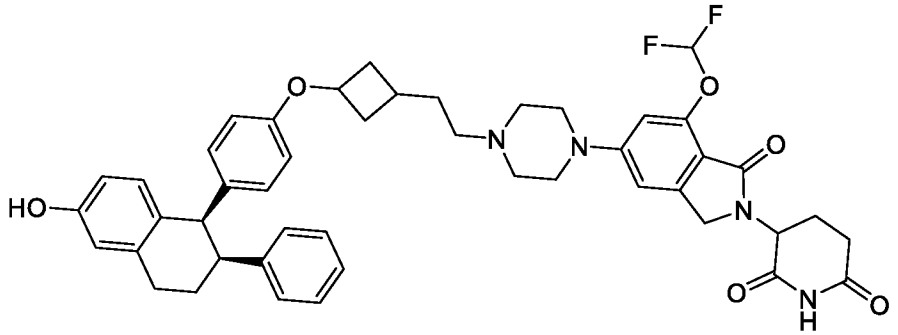
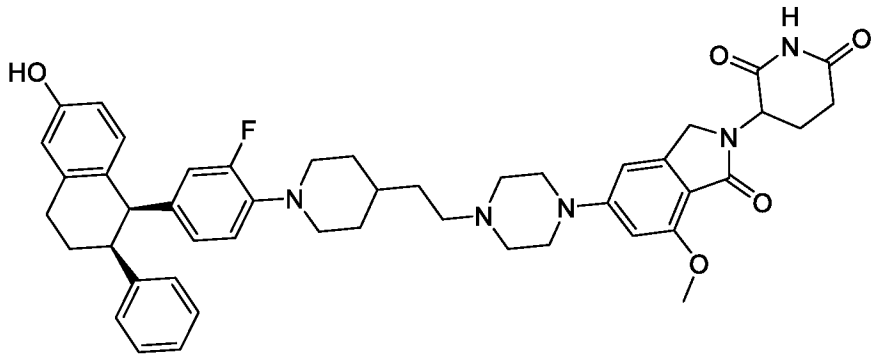
22		3-[7-(difluoromethoxy)-5-[4-[2-[1-[4-[(1R,2S) -6-hydroxy-2-phenyl-tetralin-1-yl]phenyl]-4-piperidyl]ethyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione	A-2, A-13
23		3-[7-(difluoromethoxy)-5-[4-[2-[3-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenoxy]cyclobutyl]ethyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione	A-3, A-14
24		3-[5-[4-[2-[1-[2-fluoro-4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenyl]-4-piperidyl]ethyl]piperazin-1-yl]-7-methoxy-1-oxo-isoindolin-2-yl]piperidine-2,6-dione	A-2, A-12

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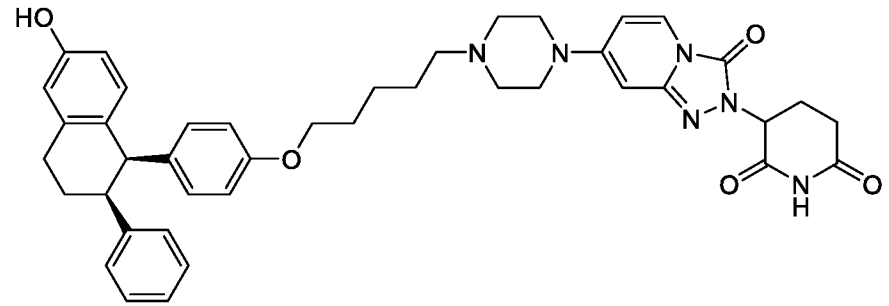
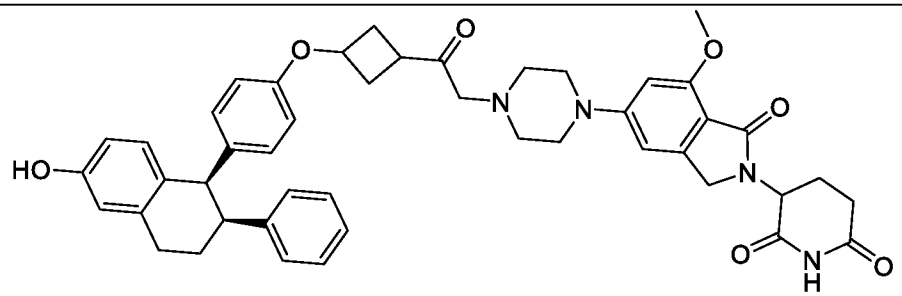
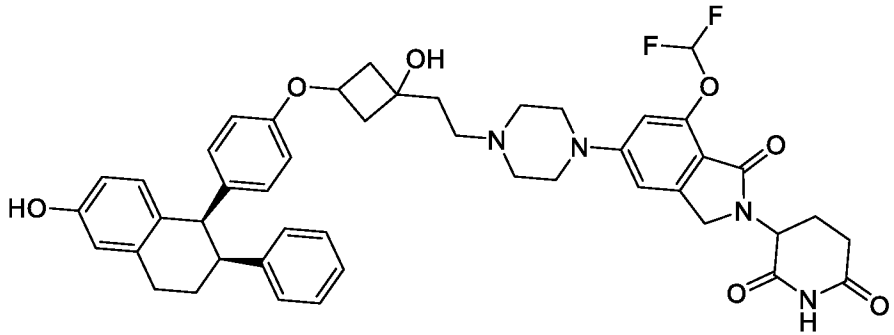
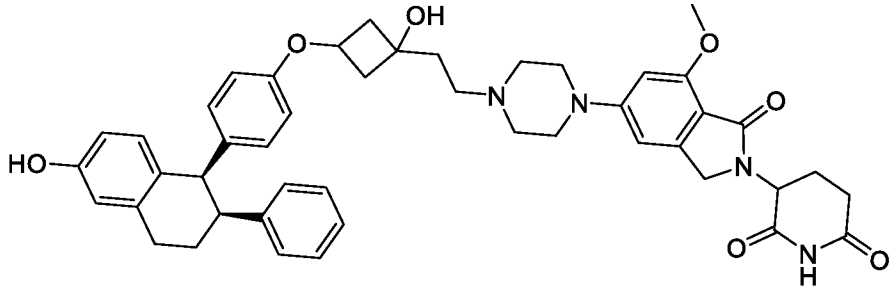
25		3-{7-[4-(5-{4-[(1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl]phenoxy}pentyl)piperazin-1-yl]-3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-2-yl}piperidine-2,6-dione	A-7, A-8
26		3-[5-[4-[2-[3-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenoxy]cyclobutyl]-2-oxo-ethyl]piperazin-1-yl]-7-methoxy-1-oxo-isoindolin-2-yl]piperidine-2,6-dione	A-17
27		3-[7-(difluoromethoxy)-5-[4-[2-[1-hydroxy-3-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenoxy]cyclobutyl]ethyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione	A-3, A-15
28		3-[5-[4-[2-[1-hydroxy-3-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenoxy]cyclobutyl]ethyl]piperazin-1-yl]-7-methoxy-1-oxo-isoindolin-2-yl]piperidine-2,6-dione	A-2, A-15

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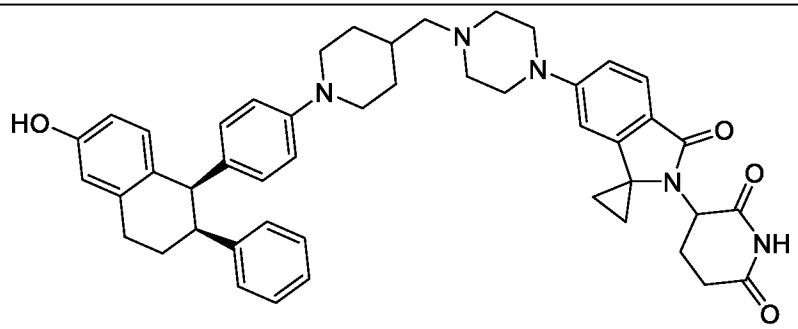
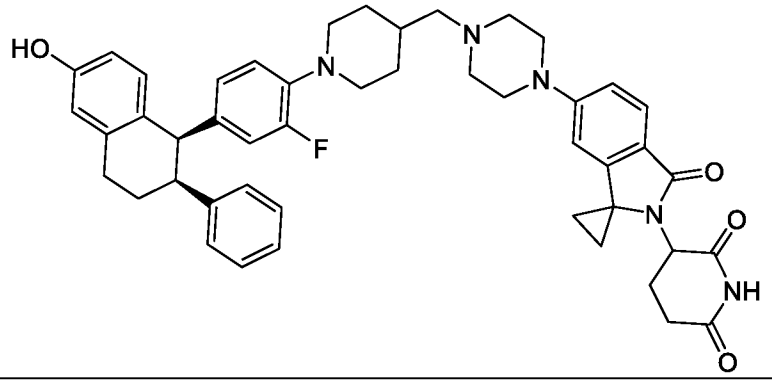
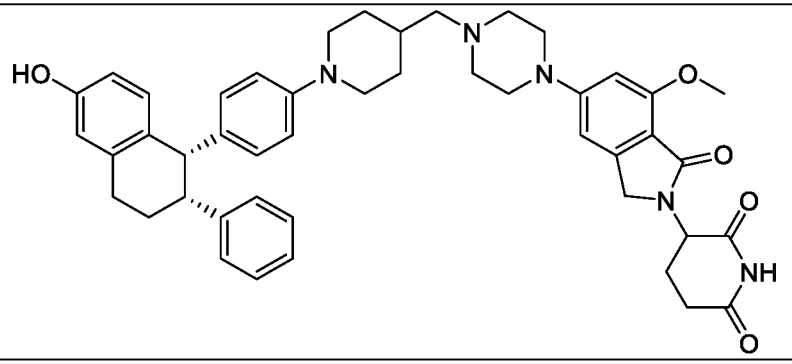
29		3-(6'-{4-[(1-{4-[(1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl]phenyl}piperidin-4-yl)methyl]piperazin-1-yl}-3'-oxo-2',3'-dihydrospiro[cyclopropane-1,1'-isoindole]-2'-yl)piperidine-2,6-dione	A-6, A-12
30		3-[6'-[4-[[1-[2-fluoro-4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenyl]-4-piperidyl]methyl]piperazin-1-yl]-3'-oxo-spiro[cyclopropane-1,1'-isoindoline]-2'-yl]piperidine-2,6-dione	A-6, A-12
31			A-1, A-2

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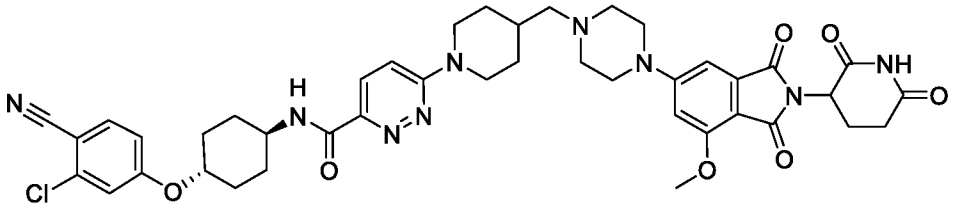
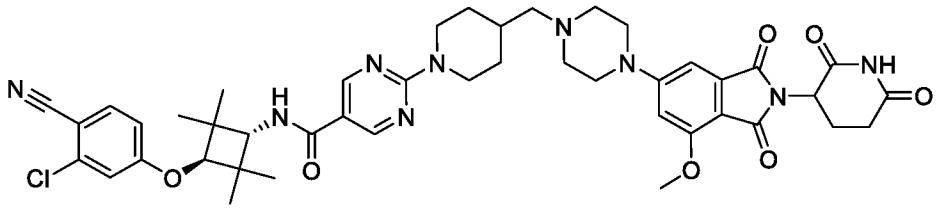
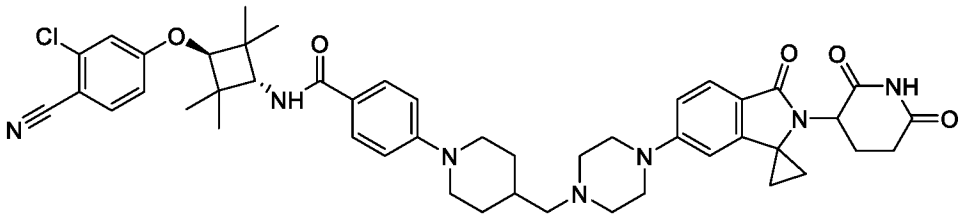
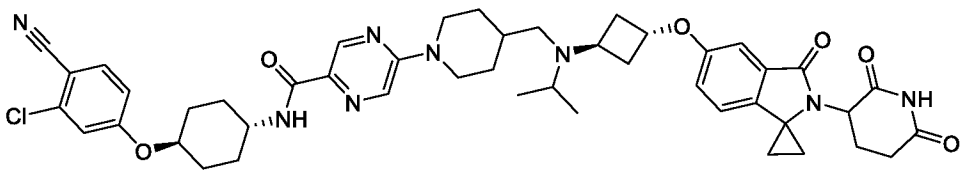
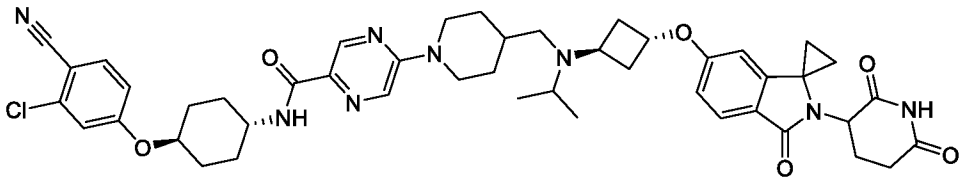
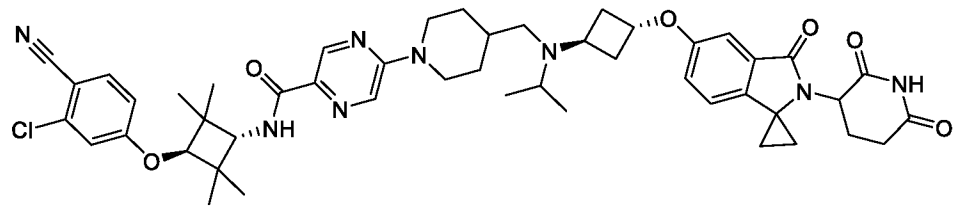
[0948] Table 2. Exemplary Androgen Receptor PROTACs

Ex. #	Chemical Structure	Name	General scheme
32		rac-N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1,3-dioxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)pyridazine-3-carboxamide	Exp. procedure provided
33		rac-N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-2-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1,3-dioxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)pyrimidine-5-carboxamide	B-1, B-2
34		rac-N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((4-(2'-(2,6-dioxopiperidin-3-yl)-3'-oxospiro[cyclopropane-1,1'-isoindolin]-6'-yl)piperazin-1-yl)methyl)piperidin-1-yl)benzamide	Synthesis described in detail

35		rac-N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-5-(4-((((1r,3r)-3-((2'-(2,6-dioxopiperidin-3-yl)-3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl)oxy)cyclobutyl)(isopropyl)amino)methyl)piperidin-1-yl)pyrazine-2-carboxamide	Synthesized following the route described for Ex. Comp. 34
36		rac-N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-5-(4-((((1r,3r)-3-((2'-(2,6-dioxopiperidin-3-yl)-3'-oxospiro[cyclopropane-1,1'-isoindolin]-6'-yl)oxy)cyclobutyl)(isopropyl)amino)methyl)piperidin-1-yl)pyrazine-2-carboxamide	Synthesized following the route described for Ex. Comp. 34
37		rac-N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-5-(4-((((1r,3r)-3-((2'-(2,6-dioxopiperidin-3-yl)-3'-oxospiro[cyclopropane-1,1'-isoindolin]-5'-yl)oxy)cyclobutyl)(isopropyl)amino)methyl)piperidin-1-yl)pyrazine-2-carboxamide	Synthesized following the route described for Ex. Comp. 34

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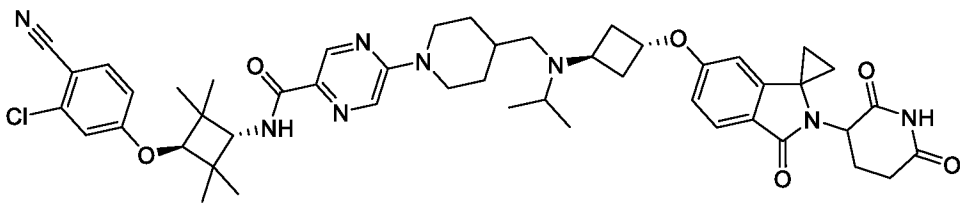
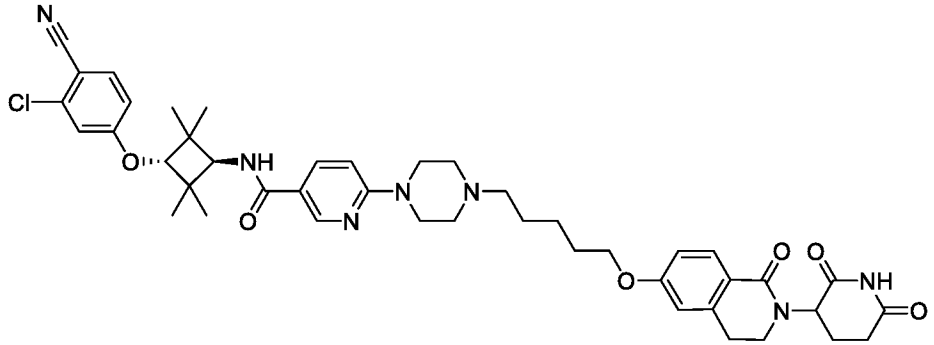
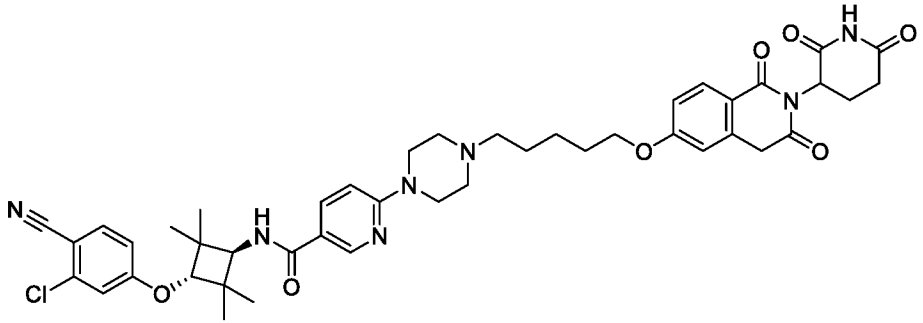
38		rac-N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-5-(4-((((1r,3r)-3-((2'-(2,6-dioxopiperidin-3-yl)-3'-oxospiro[cyclopropane-1,1'-isoindolin]-6'-yl)oxy)cyclobutyl)(isopropyl)amino)methyl)piperidin-1-yl)pyrazine-2-carboxamide	Synthesized following the route described for Ex. Comp. 34
46		rac-N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(5-((2-(2,6-dioxopiperidin-3-yl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy)pentyl)piperazin-1-yl)nicotinamide	C-1 and Exp. procedure provided as well
47		rac-N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy)pentyl)piperazin-1-yl)nicotinamide	C-1 and Exp. procedure provided as well

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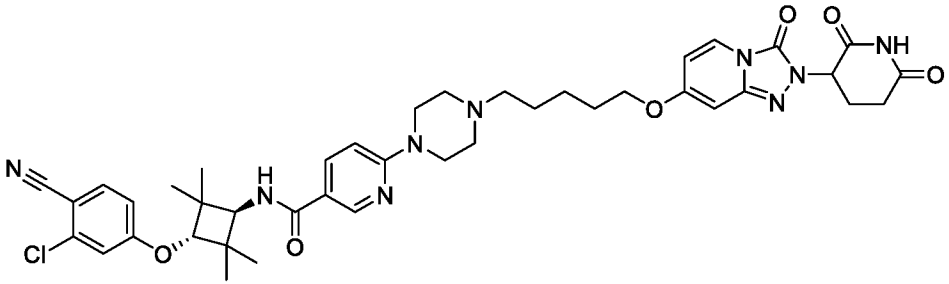
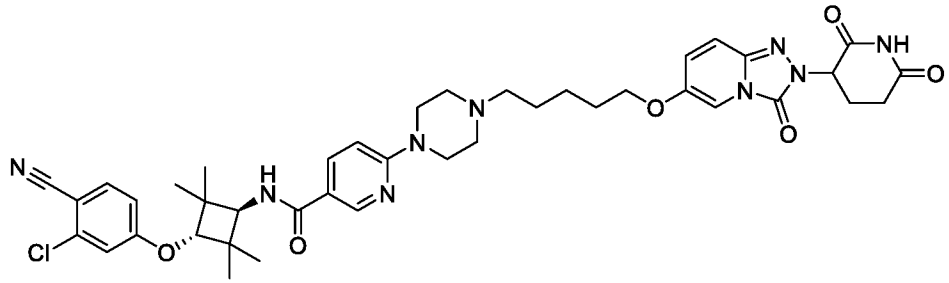
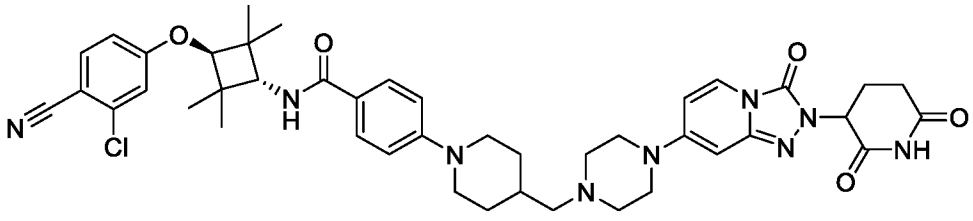
48		rac-N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(5-((2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl)oxy)pentyl)piperazin-1-yl)nicotinamide	Exp procedure provided
49		rac-N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-6-(4-(5-((2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-6-yl)oxy)pentyl)piperazin-1-yl)nicotinamide	Exp procedure provided
50		rac-N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl)piperazin-1-yl)methyl)piperidin-1-yl)benzamide	Exp procedure provided

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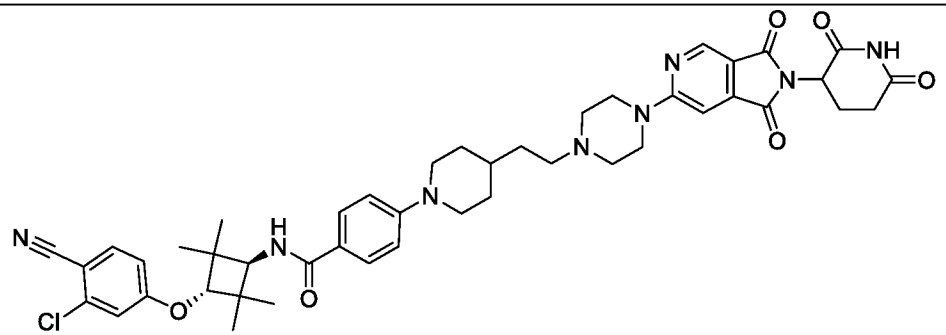
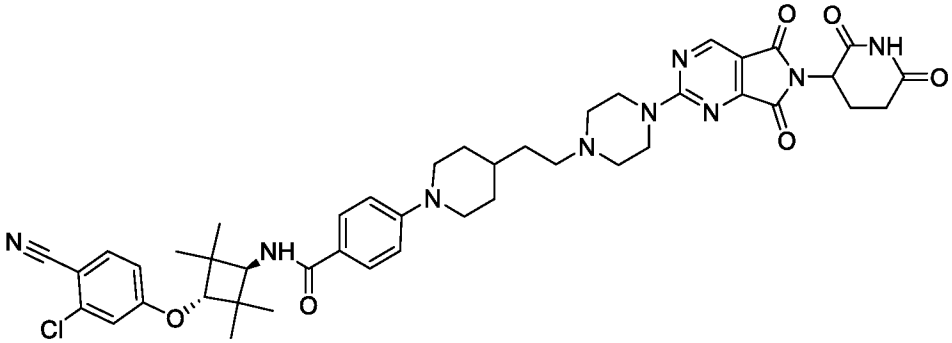
51		N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)piperazin-1-yl)ethyl)piperidin-1-yl)benzamide	C-3, C-4 and Exp procedure provided
52		N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(4-(6-(2,6-dioxopiperidin-3-yl)-5,7-dioxo-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)piperazin-1-yl)ethyl)piperidin-1-yl)benzamide	C-3, c-4 and exp procedure provided

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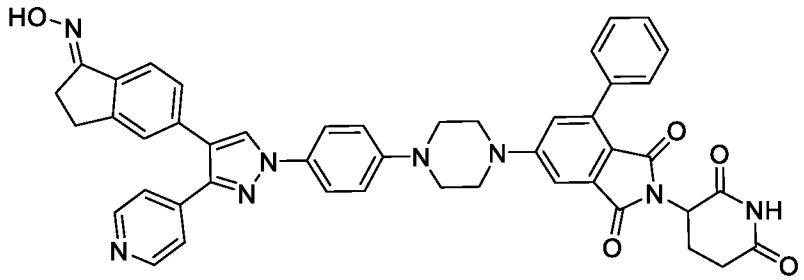
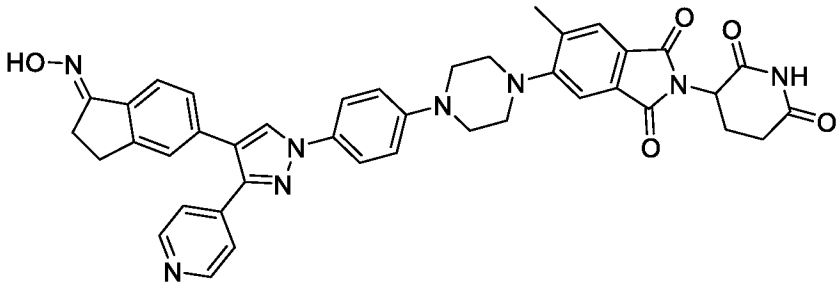
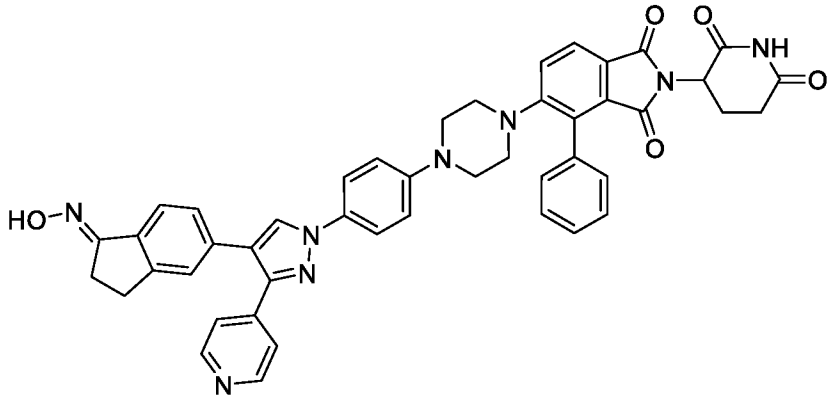
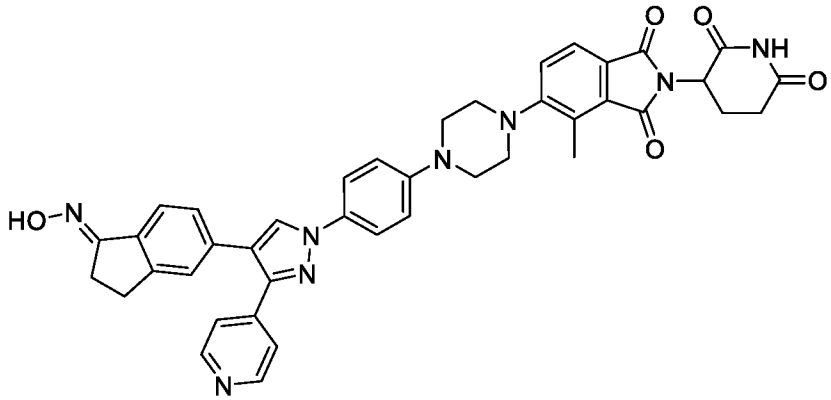
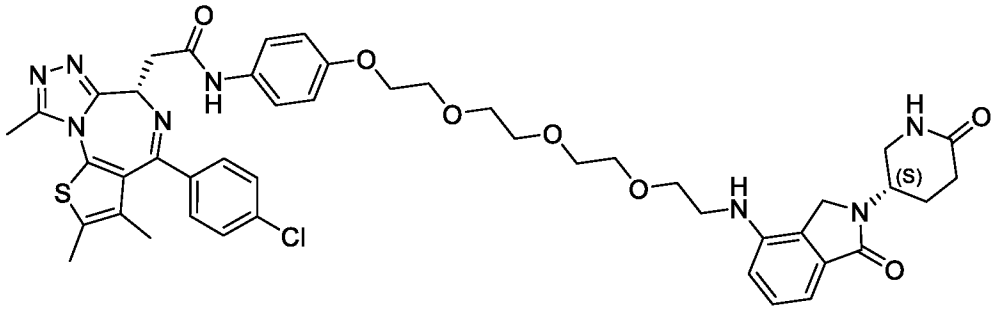
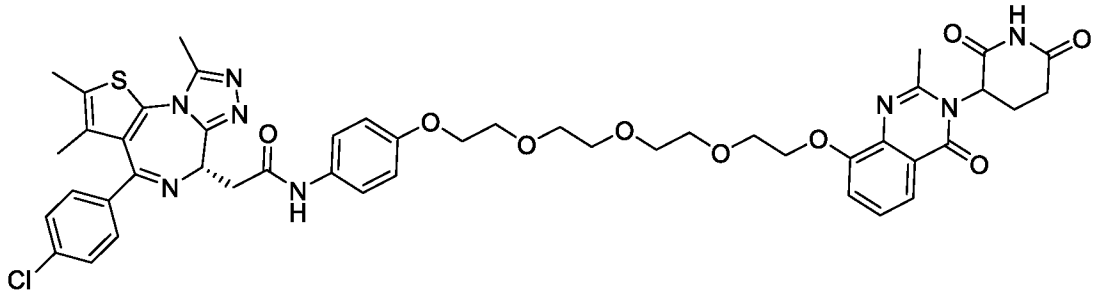
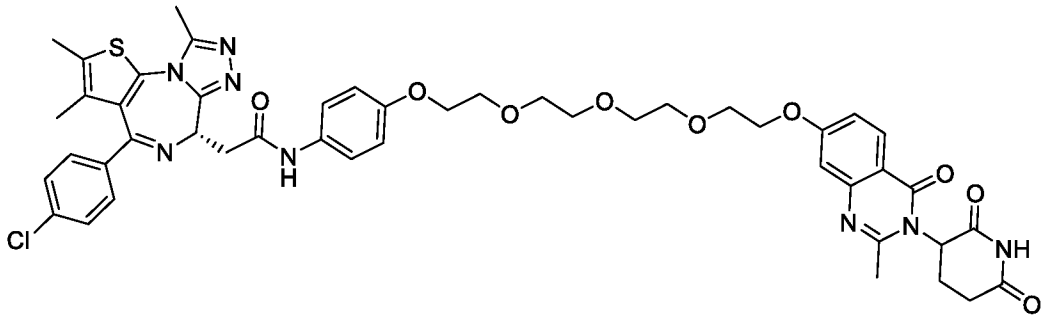
[0949] Table 3. Exemplary BRaf PROTACs

Ex. #	Chemical Structure	Name	Synthetic Scheme
39		(E)-2-(2,6-dioxopiperidin-3-yl)-6-(4-(4-(4-(1-(hydroxyimino)-2,3-dihydro-1H-inden-5-yl)-3-(pyridin-4-yl)-1H-pyrazol-1-yl)phenyl)piperazin-1-yl)-4-phenylisoindoline-1,3-dione	D-1
40		(E)-2-(2,6-dioxopiperidin-3-yl)-5-(4-(4-(4-(1-(hydroxyimino)-2,3-dihydro-1H-inden-5-yl)-3-(pyridin-4-yl)-1H-pyrazol-1-yl)phenyl)piperazin-1-yl)-6-methylisoindoline-1,3-dione	D-1
41		(E)-2-(2,6-dioxopiperidin-3-yl)-5-(4-(4-(4-(1-(hydroxyimino)-2,3-dihydro-1H-inden-5-yl)-3-(pyridin-4-yl)-1H-pyrazol-1-yl)phenyl)piperazin-1-yl)-4-phenylisoindoline-1,3-dione	Custom synthesis provided

42		(E)-2-(2,6-dioxopiperidin-3-yl)-5-(4-(4-(4-(1-(hydroxyimino)-2,3-dihydro-1H-inden-5-yl)-3-(pyridin-4-yl)-1H-pyrazol-1-yl)phenyl)piperazin-1-yl)-4-methylisoindoline-1,3-dione	Custom synthesis provided

[0950] Table 4. Exemplary BRD4 PROTACs

Ex. #	Chemical Structure	Name
43		2-((R)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-(2-(2-(2-(2-((1-oxo-2-((R)-6-oxopiperidin-3-yl)isoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)ethoxy)phenyl)acetamide
44		2-((R)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-(2-(2-(2-(2-((3-(2,6-dioxopiperidin-3-yl)-2-methyl-4-oxo-3,4-dihydroquinazolin-8-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)phenyl)acetamide
45		2-((R)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-(2-(2-(2-(2-((3-(2,6-dioxopiperidin-3-yl)-2-methyl-4-oxo-3,4-dihydroquinazolin-7-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)phenyl)acetamide

[0951] Table 5. Characterization of Exemplary Estrogen Receptor PROTACs

Ex. #	Observed [M+H]/Z	Target Engagement IC_{50} (nM)	ER DC_{50}*	ER D_{max}*	NMR
1	743.58	58.2	C	B	
2	743.58	0.79	B	A	δ 10.93 (s, 1H), 10.56-10.43 (m, 1H), 9.18-9.13 (m, 1H), 7.16-7.13 (m, 3H), 6.84-6.83 (d, J = 6.4Hz, 2H), 6.69 (s, 1H), 6.62-6.61 (m, 2H), 6.55-6.52 (m, 3H), 6.28-6.26 (d, J = 8.4Hz, 2H), 4.99-4.97 (m, 1H), 4.29-4.25 (m, 1H), 4.23-4.18 (m, 1H), 4.17-4.15 (m, 1H), 4.06-4.00 (m, 2H), 3.85-3.83 (m, 5H), 3.56-3.53 (m, 1H), 3.34-3.33 (m, 4H), 3.10-3.02 (m, 4H), 3.00-2.85 (m, 2H), 2.60-2.58 (m, 3H), 2.16-2.08 (m, 1H), 1.91-1.88 (m, 1H), 1.76-1.69 (m, 5H), 1.43-1.41 (m, 2H). (DMSO-d6, 400 MHz)
3	743.57	1.35	A	A	δ: 10.96 (s, 1H), 9.12 (s, 1H), 7.39 (d, J=8.0 Hz, 1H), 7.25 - 6.98 (m, 4H), 6.83 (d, J=6.8 Hz, 2H), 6.72 - 6.43 (m, 5H), 6.26 (d, J=8.6 Hz, 2H), 5.06 (dd, J=5.0, 13.2 Hz, 1H), 4.56 - 4.11 (m, 3H), 3.94 - 3.70 (m, 5H), 3.30 - 3.25 (m, 1H), 3.21 - 2.77 (m, 8H), 2.64-2.55 (m, 5H), 2.46 - 2.26 (m, 2H), 2.16 - 1.94 (m, 2H), 1.80 - 1.22 (m, 7H). (DMSO-d6, 400 MHz)
4	831.65	1.42	A	A	δ 10.98 (s, 1H), 9.13 (s, 1H), 8.14 (s, 1H), 7.40 (d, J= 8.8 Hz, 1H), 7.17 - 7.07 (m, 4H), 6.83 - 6.82 (m, 2H), 6.65 - 6.60 (m, 2H), 6.54 - 6.47 (m, 3H), 6.27 - 6.29 (m, 2H), 5.07 (dd, J= 5.2, 13.2 Hz, 1H), 4.44 - 4.40 (m, 1H), 4.29 - 4.17 (m, 4H), 3.81 (t, J= 6.4 Hz, 2H), 3.62 - 3.60 (m, 3H), 3.53 - 3.51 (m, 3H), 3.43 - 3.41 (m, 4H), 3.24 - 3.17 (m, 6H), 2.97 - 2.88 (m, 4H), 2.78 - 2.74 (m, 3H), 2.61 - 2.56 (m, 2H), 2.44 - 2.37 (m, 2H), 2.10 - 1.97 (m, 2H), 1.71 - 1.53 (m, 5H), 1.41 - 1.38 (m, 2H). (DMSO-d6, 400 MHz)
5	842.66	>300		C	
6	842.67	2.18		C	
7	859.68	102	D	B	
8	859.68	0.34	B	B	δ 10.99 (s, 1H), 9.12 (s, 1H), 8.16 (s, 1H), 7.36 (s, 2H), 7.17 - 7.10 (m, 3H), 6.83 (d, J=6.8 Hz, 2H), 6.66 - 6.59 (m, 2H), 6.52 (d, J=8.8 Hz, 2H), 6.50 - 6.46 (m, 1H), 6.26 (d, J=8.4 Hz, 2H), 5.10 (dd, J=5.2, 13.2 Hz, 1H), 4.59 (d, J=17.2 Hz, 1H), 4.41 (d, J=17.2 Hz, 1H), 4.22 - 4.16 (m, 3H), 3.82 (t, J=6.0 Hz, 2H), 3.73 - 3.67 (m, 2H), 3.60 - 3.55 (m, 2H), 3.48 - 3.42 (m,

					2H), 3.37 - 3.35 (m, 2H), 3.22 (s, 3H), 3.03 - 2.82 (m, 6H), 2.82 - 2.69 (m, 10H), 2.63 - 2.61 (m, 1H), 2.42 - 2.36 (m, 1H), 2.15 - 2.04 (m, 1H), 2.03 - 1.95 (m, 1H), 1.81 - 1.69 (m, 3H), 1.66 - 1.60 (m, 2H), 1.58 - 1.50 (m, 2H). (DMSO-d6, 400 MHz)
9	768.61	>300	D	B	
10	768.61	0.86	B	A	δ 10.90 (s, 1H), 8.28 (s, 1H), 7.19 - 7.07 (m, 3H), 6.83 (d, J=6.4 Hz, 2H), 6.64 (d, J=8.4 Hz, 1H), 6.59 (s, 2H), 6.52 (d, J=8.8 Hz, 2H), 6.49 - 6.44 (m, 2H), 6.19 (d, J=8.8 Hz, 2H), 5.02 - 4.91 (m, 1H), 4.96 (dd, J=5.2, 13.2 Hz, 1H), 4.26 - 4.19 (m, 1H), 4.14 - 4.06 (m, 2H), 3.82 (s, 3H), 3.55 - 3.45 (m, 2H), 3.30 - 3.10 (m, 12H), 2.98 - 2.85 (m, 3H), 2.59 - 2.53 (m, 1H), 2.44 - 2.41 (m, 1H), 2.38 - 2.35 (m, 2H), 2.13 - 2.03 (m, 1H), 1.95 - 1.87 (m, 1H), 1.75 - 1.65 (m, 3H), 1.48 - 1.33 (m, 3H), 1.26 - 1.12 (m, 2H). (DMSO-d6, 400 MHz)
11	798.63	2	B	B	δ 10.95 (s, 1H), 9.09 (s, 1H), 7.38 (d, J= 8.03 Hz, 1H), 7.14 (m, 4H), 6.83 (d, J= 6.53 Hz, 2H), 6.64 - 6.59 (m, 2H), 6.56 - 6.45 (m, 3H), 6.19 (d, J= 8.66 Hz, 2H), 5.06 (dd, J= 12.99,5.08 Hz, 1H), 4.36 – 4.27 (m, 1H), 4.19 - 4.18 (m, 4H), 3.55 – 3.53 (m, 4H), 3.26 (s, 3H), 3.11 (s, 4H), 2.96 (d, J= 5.9 Hz, 2H), 2.69 – 2.57 (m, 1H), 2.32 – 2.31 (m, 1H), 2.19 (d, J= 6.65 Hz, 4H), 2.14 - 2.04 (m, 3H), 1.98 – 1.89 (m, 2H), 11.56 (m, 6H), 1.29- 1.01 (m, 3H). (DMSO-d6, 400 MHz)
12	779.56	1	A	A	10.91 (br s, 1H), 8.20 (s, 1H), 7.19 - 7.09 (m, 3H), 6.84 (br d, J=6.9 Hz, 2H), 6.67 - 6.58 (m, 5H), 6.54 - 6.43 (m, 2H), 6.30 (d, J=8.5 Hz, 2H), 4.97 (dd, J=5.1, 13.2 Hz, 1H), 4.27 - 4.07 (m, 5H), 3.83 (s, 3H), 3.39 - 3.28 (m, 5H), 3.04 - 2.85 (m, 4H), 2.59 (br s, 3H), 2.43 - 2.22 (m, 4H), 2.15 - 1.88 (m, 4H), 1.82 - 1.56 (m, 4H). (DMSO-d6, 400 MHz)
13	743.58	0.37	A	A	δ 10.91 (s, 1H), 9.13 (s, 1H), 8.14 (s, 1H), 7.18 - 7.07 (m, 3H), 6.82 (d, J=6.8 Hz, 2H), 6.69 - 6.58 (m, 3H), 6.55 - 6.47 (m, 4H), 6.26 (d, J=8.8 Hz, 2H), 4.96 (dd, J=5.2, 13.2 Hz, 1H), 4.29 - 4.06 (m, 3H), 3.85 - 3.78 (m, 5H), 3.30 - 3.28 (m, 4H), 3.04 - 2.80 (m, 3H), 2.60 - 2.52 (m, 6H), 2.45 - 2.34(m, 3H), 2.17 - 1.99 (m, 1H), 1.97 - 1.82 (m, 1H), 1.76 - 1.58 (m, 3H), 1.56 - 1.45 (m, 2H), 1.43 - 1.29 (m, 2H). (DMSO-d6, 400 MHz)
14	743.58	0.49	A	A	δ 10.91 (s, 1H), 9.13 (s, 1H), 8.14 (s, 1H), 7.18 - 7.08 (m, 3H), 6.82 (d, J=6.8 Hz, 2H), 6.66 - 6.58 (m, 3H), 6.55 - 6.47 (m, 4H), 6.26 (d, J=8.8 Hz,

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					2H), 4.96 (dd, J=5.2, 13.2 Hz, 1H), 4.28 - 4.10 (m, 3H), 3.85 - 3.78 (m, 5H), 3.30 - 3.28 (m, 4H), 3.05 - 2.80 (m, 3H), 2.58 - 2.51 (m, 6H), 2.38 - 2.33 (m, 2H), 2.32 - 2.24 (m, 1H), 2.18 - 2.00 (m, 1H), 1.97 - 1.86 (m, 1H), 1.74 - 1.58 (m, 3H), 1.55 - 1.44 (m, 2H), 1.43 - 1.34 (m, 2H). (DMSO-d6, 400 MHz)
15	754.60	1.7	A	A	δ 10.91 (s, 1H), 8.23 (s, 2H), 7.17 - 7.09 (m, 3H), 6.83 (d, J=6.8 Hz, 2H), 6.64 (d, J=8.4 Hz, 1H), 6.59 (s, 2H), 6.53 (d, J=8.8 Hz, 2H), 6.49 - 6.45 (m, 2H), 6.20 (d, J=8.8 Hz, 2H), 4.96 (dd, J=5.0, 13.2 Hz, 1H), 4.25 - 4.19 (m, 1H), 4.14 - 4.06 (m, 1H), 4.15 - 4.06 (m, 1H), 3.84 - 3.80 (m, 3H), 3.51 (d, J=9.2 Hz, 7H), 3.28 (s, 4H), 2.98 - 2.83 (m, 1H), 3.03 - 2.82 (m, 2H), 2.58 (s, 1H), 2.32 - 2.26 (m, 1H), 2.22 - 2.04 (m, 4H), 1.94 - 1.87 (m, 1H), 1.80 - 1.55 (m, 5H), 1.21 - 1.11 (m, 2H). (DMSO-d6, 400 MHz)
16	799.6	0.82	A	B	δ 10.90 (s, 1H), 9.13 (s, 1H), 8.14 (s, 1H), 7.01 - 6.92 (m, 2H), 6.87 - 6.79 (m, 2H), 6.65 (d, J=8.4 Hz, 1H), 6.60 (s, 2H), 6.55 (d, J=8.8 Hz, 2H), 6.51 - 6.44 (m, 2H), 6.26 (d, J=8.4 Hz, 2H), 4.96 (dd, J=5.4, 13.4 Hz, 1H), 4.75 (t, J=4.8 Hz, 1H), 4.27 - 4.06 (m, 3H), 3.85 - 3.80 (m, 3H), 3.29 - 3.25 (m, 6H), 2.99 - 2.84 (m, 3H), 2.54 (d, J=4.4 Hz, 8H), 2.19 - 1.86 (m, 4H), 1.85 - 1.58 (m, 5H), 1.24 - 1.07 (m, 2H). (DMSO-d6, 400 MHz)
17	778.57	1.5	B	B	δ 10.91 (s, 1H), 9.14 (s, 1H), 7.85 (br s, 1H), 7.48 - 7.34 (m, 2H), 7.18 - 7.10 (m, 3H), 6.83 (br d, J=6.7 Hz, 2H), 6.69 - 6.60 (m, 5H), 6.54 - 6.47 (m, 2H), 6.30 (d, J=8.5 Hz, 2H), 5.08 - 4.94 (m, 3H), 4.28 - 4.17 (m, 2H), 4.16 - 4.08 (m, 1H), 3.84 (s, 4H), 3.66 (br s, 1H), 3.04 - 2.83 (m, 4H), 2.82 - 2.71 (m, 1H), 2.68 (br s, 1H), 2.63 - 2.54 (m, 2H), 2.48 - 2.26 (m, 2H), 2.15 - 2.03 (m, 1H), 1.97 - 1.88 (m, 1H), 1.71 (br d, J=7.5 Hz, 1H). (DMSO-d6, 400 MHz)
18	790.59	17.5	B	B	
19	790.58	4.5	B	A	δ 10.89 (s, 1H), 8.19 (s, 1H), 7.22 - 7.16 (m, 3H), 6.90 (br d, J = 6.8 Hz, 2H), 6.68 (d, J = 8.4 Hz, 1H), 6.61 (br d, J = 9.2 Hz, 2H), 6.54 - 6.50 (m, 1H), 6.47 (s, 1H), 5.87 (d, J = 11.2 Hz, 2H), 4.95 (dd, J = 5.2, 13.2 Hz, 1H), 4.25 - 4.20 (m, 2H), 4.13 - 4.07 (m, 1H), 3.82 (s, 3H), 3.27 - 3.25 (m, 6H), 3.03 - 2.83 (m, 9H), 2.19 (br d, J = 7.2 Hz, 3H), 2.07 - 1.89 (m, 3H), 1.76 - 1.58 (m, 5H), 1.16 (br d, J = 9.2 Hz, 2H). (DMSO-d6, 400 MHz)

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20	779.6	1.2	B	B	δ 10.96 (s, 1H), 8.20 (s, 1H), 7.62 - 7.20 (m, 1H), 7.18 - 7.05 (m, 3H), 6.94 (s, 1H), 6.82 (d, J=6.4 Hz, 2H), 6.71 (s, 1H), 6.67 - 6.58 (m, 2H), 6.56 - 6.43 (m, 3H), 6.26 (d, J=8.8 Hz, 2H), 5.00 (dd, J=5.2, 13.2 Hz, 1H), 4.37 - 4.29 (m, 1H), 4.26 - 4.14 (m, 2H), 3.81 (t, J=6.4 Hz, 2H), 3.31 - 3.27 (m, 5H), 3.04 - 2.82 (m, 3H), 2.64 - 2.52 (m, 2H), 2.48 -2.42 (m, 3H), 2.41 - 2.25 (m, 3H), 2.17 - 2.02 (m, 1H), 2.00 - 1.90 (m, 1H), 1.75 - 1.59 (m, 3H), 1.53 - 1.43 (m, 2H), 1.42 - 1.32 (m, 2H). (DMSO-d6, 400 MHz)
21	815.6	2.5	B	B	δ 10.98 (s, 1H), 8.15 (s, 1H), 7.68 - 7.34 (m, 1H), 7.21 - 7.05 (m, 3H), 6.95 (s, 1H), 6.84 (d, J=7.2 Hz, 2H), 6.73 (s, 1H), 6.68 - 6.58 (m, 4H), 6.50 (d, J=8.2 Hz, 1H), 6.31 (d, J=8.4 Hz, 2H), 5.02 (dd, J=4.8, 13.2 Hz, 1H), 4.42 - 4.27 (m, 1H), 4.27 - 4.04 (m, 4H), 3.31 (s, 4H), 3.03 - 2.78 (m, 3H), 2.68 - 2.55 (m, 1H), 2.48 (s, 6H), 2.41 - 2.32 (m, 3H), 2.16 - 1.90 (m, 4H), 1.72 (m,1H), 1.63 (m, 2H). (DMSO-d6, 400 MHz)
22	804.6	4.4	B	A	δ 10.97 (s, 1H), 8.19 (s, 1H), 7.68 - 7.20 (m, 1H), 7.18 - 7.07 (m, 3H), 6.94 (s, 1H), 6.83 (d, J=6.4 Hz, 2H), 6.71 (s, 1H), 6.66 - 6.57 (m, 2H), 6.55 - 6.43 (m, 3H), 6.19 (d, J=8.4 Hz, 2H), 5.00 (dd, J=5.0, 13.2 Hz, 1H), 4.38 - 4.28 (m, 1H), 4.26 - 4.17 (m, 1H), 4.12 (d, J=4.6 Hz, 1H), 3.30 (s, 9H), 3.01 - 2.78 (m, 4H), 2.71 - 2.55 (m, 2H), 2.44 - 2.26 (m, 5H), 2.16 - 2.03 (m, 1H), 2.02 - 1.89 (m, 1H), 1.79 - 1.62 (m, 3H), 1.40 (m, 3H), 1.27 - 1.06 (m, 2H). (DMSO-d6, 400 MHz)
23	791.6	1.8	B	B	δ 10.96 (s, 1H), 9.12 (s, 1H), 8.16 (s, 1H), 7.63 - 7.20 (m, 1H), 7.18 - 7.06 (m, 3H), 6.94 (s, 1H), 6.81 (d, J=6.4 Hz, 2H), 6.71 (s, 1H), 6.67 - 6.58 (m, 2H), 6.51 - 6.37 (m, 3H), 6.24 (d, J=8.4 Hz, 2H), 5.00 (dd, J=5.2, 13.2 Hz, 1H), 4.71 - 4.60 (m, 1H), 4.40 - 4.29 (m, 1H), 4.26 - 4.13 (m, 2H), 3.32 - 3.27 (m, 9H), 3.04 - 2.80 (m, 3H), 2.63 - 2.54 (m, 2H), 2.42 - 2.31 (m, 1H), 2.30 - 2.19 (m, 3H), 2.13 - 2.03 (m, 4H), 2.02 - 1.91 (m, 1H), 1.74 - 1.51 (m, 3H). (DMSO-d6, 400 MHz)
24	786.6	0.7	B	A	δ 10.89 (s, 1H), 9.17 (s, 1H), 8.32 (s, 1H), 7.21 - 7.10 (m, 3H), 6.86 (d, J=6.4 Hz, 2H), 6.68 - 6.58 (m, 4H), 6.52 - 6.44 (m, 2H), 6.08 (d, J=8.0 Hz, 1H), 5.97 (d, J=14.2 Hz, 1H), 4.95 (dd, J=5.2, 13.2 Hz, 1H), 4.28 - 4.16 (m, 2H), 4.14 - 4.05 (m, 1H), 3.83 (s, 3H), 3.18 (s, 2H), 2.99 - 2.85 (m, 3H), 2.54 - 2.52 (m, 13H), 2.12 - 1.86 (m, 3H), 1.71 (d, J=10.8 Hz, 3H), 1.48 - 1.19 (m, 6H). (DMSO-d6, 400 MHz)

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25	715.6	0.5		C	
26	769.6	0.7	A	A	δ 10.90 (s, 1H), 9.16 (s, 1H), 7.19 - 7.09 (m, 3H), 6.82 (br d, J = 6.6 Hz, 2H), 6.68 - 6.57 (m, 3H), 6.53 - 6.40 (m, 4H), 6.29 - 6.23 (m, 2H), 4.96 (dd, J = 5.1, 13.3 Hz, 1H), 4.53 (quin, J = 7.3 Hz, 1H), 4.31 - 4.01 (m, 3H), 3.83 (s, 3H), 3.63 (br s, 1H), 3.33 - 3.23 (m, 11H), 3.10 (td, J=8.8, 17.4 Hz, 1H), 3.03 - 2.79 (m, 3H), 2.55 (br s, 2H), 2.46 - 2.25 (m, 2H), 2.16 - 2.00 (m, 3H), 1.99 - 1.87 (m, 1H), 1.70 (br d, J=6.0 Hz, 1H). (DMSO-d6, 400 MHz)
27	807.6	0.5	A	B	δ 10.96 (s, 1H), 9.13 (br s, 1H), 8.20 - 7.39 (m, 1H), 7.22 - 7.08 (m, 3H), 6.97 - 6.93 (m, 1H), 6.81 (br d, J=7.7 Hz, 2H), 6.73 - 6.69 (m, 1H), 6.67 - 6.62 (m, 1H), 6.60 (d, J=2.3 Hz, 1H), 6.50 - 6.38 (m, 3H), 6.27 - 6.21 (m, 2H), 5.00 (br dd, J=5.1, 13.2 Hz, 1H), 4.65 (br t, J=5.8 Hz, 1H), 4.37 - 4.30 (m, 1H), 4.25 - 4.18 (m, 1H), 4.16 (br d, J=4.9 Hz, 1H), 3.28 - 3.25 (m, 6H), 3.02 - 2.81 (m, 3H), 2.61 - 2.53 (m, 4H), 2.45 - 2.37 (m, 4H), 2.12 - 1.90 (m, 5H), 1.76 - 1.64 (m, 3H). (DMSO-d6, 400 MHz)
28	771.6	0.3	A	A	δ 10.91 (s, 1H), 9.13 (s, 1H), 8.14 (s, 1H), 7.18 - 7.08 (m, 3H), 6.81 (br d, J=7.7 Hz, 2H), 6.66 - 6.59 (m, 3H), 6.51 - 6.39 (m, 4H), 6.27 - 6.22 (m, 2H), 4.96 (br dd, J=5.1, 12.9 Hz, 1H), 4.65 (br t, J=6.3 Hz, 1H), 4.26 - 4.19 (m, 1H), 4.16 (br d, J=4.6 Hz, 1H), 4.13 - 4.07 (m, 1H), 3.84 - 3.80 (m, 3H), 3.29 - 3.23 (m, 5H), 3.00 - 2.84 (m, 3H), 2.62 - 2.52 (m, 8H), 2.35 (br s, 2H), 2.09 - 1.88 (m, 4H), 1.78 - 1.66 (m, 3H). (DMSO-d6, 400 MHz)
29	750.6	2.4		C	
30	768.6	2.1	B	B	δ 10.87 (s, 1H), 9.20 (s, 1H), 8.26 (s, 1H), 7.46 (d, J=8.8 Hz, 1H), 7.24 - 7.07 (m, 3H), 6.99 (d, J=8.8 Hz, 1H), 6.86 (d, J=6.8 Hz, 2H), 6.75 - 6.56 (m, 4H), 6.50 (d, J=8.0 Hz, 1H), 6.09 (d, J=8.0 Hz, 1H), 5.97 (d, J=14.4 Hz, 1H), 4.18 (d, J=4.4 Hz, 1H), 3.89 (s, 1H), 3.35 - 3.23 (m, 8H), 3.19 (d, J=6.8 Hz, 3H), 3.05 - 2.84 (m, 2H), 2.76 - 2.60 (m, 2H), 2.54 (s, 3H), 2.20 (d, J=6.8 Hz, 2H), 2.06 (dd, J=6.0, 12.0 Hz, 1H), 1.83 (s, 1H), 1.75 (d, J=12.0 Hz, 3H), 1.62 (s, 1H), 1.54 - 1.44 (m, 2H), 1.44 - 1.29 (m, 2H), 1.21 (d, J=10.0 Hz, 2H). (DMSO-d6, 400 MHz)
31				C	

[0952] *ER DC_{50} (nM) A<1; 1<=B<10; 10<=C<100; D>=100

[0953] **ER D_{max}(%) A>=75; 50<=B<75; C<50

[0954] Table 6. Characterization of Exemplary Androgen Receptor PROTACs

Ex. #	m/z observed	AR DC_{50}*	AR D_{max}**	NMR
32	824.54	A		
33	852.58	A		
34	832.61		C	*1H NMR (400 MHz, d6-DMSO):* δ 10.88 (s, 1H), 8.22 (s, 1H), 7.91 (d, *J*=8.8 Hz, 1H), 7.74 (d, *J*=8.8 Hz, 2H), 7.53 - 7.45 (m, 2H), 7.21 (d, *J*=2.4 Hz, 1H), 6.99 (dd, *J*=9.2, 17.6 Hz, 4H), 6.73 (s, 1H), 4.33 (s, 1H), 4.06 (d, *J*=9.2 Hz, 1H), 3.86 (d, *J*=12.4 Hz, 3H), 3.32 - 3.29 (m, 9H), 2.80 (t, *J*=12.0 Hz, 3H), 2.59 - 2.54 (m, 4H), 2.22 (d, *J*=6.8 Hz, 2H), 1.81 (d, *J*=10.3 Hz, 4H), 1.55 - 1.47 (m, 2H), 1.45 - 1.31 (m, 2H), 1.25 - 1.17 (s, 8H), 1.13 (s, 6H)
35	849.6		C	
36	849.61		C	
37	877.64		C	
38	877.64		C	
46	810.3	A	A	^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12 (6H, s), 1.21 (6H, s), 1.43-1.54 (4H, m), 1.74-1.78 (2H, m), 1.88-1.91 (1H, m), 2.30-2.44 (8H, m), 2.90-2.97 (3H, m), 3.42-3.59 (7H, m), 4.03-4.07 (3H, m), 4.30 (1H, s), 6.86-6.91 (3H, m), 6.99-7.02 (1H, m), 7.22 (1H, d, *J* = 2.4 Hz), 7.64 (1H, d, *J* = 8.8 Hz), 7.79 (1H, d, *J* = 8.8 Hz), 7.90-7.97 (2H, m), 8.62 (1H, d, *J* = 2.0 Hz), 10.90 (1H, s).
47	824.3	B	B	^{1}H NMR (400 MHz, DMSO-d^6) δ 1.12 (6H, s), 1.21 (6H, s), 1.37-1.58 (4H, m), 1.73-1.81 (2H, m), 1.86-1.91 (1H, m), 2.30-2.37 (2H, m), 2.40-2.46 (2H, m), 2.82-2.91(1H, m), 3.30-3.35 (4H, m), 3.55-3.65 (4H, m), 4.03-4.30 (6H, m), 5.54-5.63 (1H, m), 6.87 (1H, d, *J* = 9.6 Hz), 6.96-7.07 (3H, m), 7.21 (1H, d, *J* = 2.4 Hz), 7.63 (1H, d, *J* = 9.6 Hz), 7.90-8.04 (3H, m), 8.62 (1H, d, *J* = 2.4 Hz), 10.93 (1H, s).
48	798.6	A	B	^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12 (6H, s), 1.21 (6H, s), 1.43-1.47 (2H, m),

				1.49-1.53 (2H, m), 1.73-1.78 (2H, m), 2.13-2.17 (1H, m), 2.32 (2H, t, *J* = 7.2 Hz), 2.43-2.47 (5H, m), 2.61-2.62 (1H, m), 2.87-2.93 (1H, m), 3.59 (4H, s), 4.01-4.07 (3H, m), 4.30 (1H, s), 5.28 (1H, dd, *J* = 12.4, 5.2 Hz), 6.35 (1H, dd, *J* = 8.0, 2.4 Hz), 6.52 (1H, d, *J* =1.6 Hz), 6.86 (1H, d, *J* = 8.8 Hz), 7.00 (1H, dd, *J* = 8.8, 2.4 Hz), 7.21 (1H, d, *J* = 2.4 Hz), 7.63 (1H, d, *J* = 9.2 Hz), 7.80 (1H, d, *J* = 8.0 Hz), 7.90 (1H, d, *J* = 8.8 Hz), 7.95 (1H, dd, *J* = 9.2, 2.4 Hz), 8.62 (1H, d, *J* = 2.4 Hz), 11.09 (1H, s).
49	798.6	A	A	^{1}H NMR (400 MHz, DMSO-*d*$_6$) *δ* 1.12 (6H, s), 1.21 (6H, s), 1.44-1.48 (2H, m), 1.52-1.58 (2H, m), 1.74-1.79 (2H, m), 2.15-2.19 (1H, m), 2.30 (2H, t, *J* = 7.2 Hz), 2.43-2.50 (4H, m), 2.51-2.67 (2H, m), 2.86-2.95 (1H, m), 3.60 (4H, s), 3.97 (2H, t, *J* = 6.4 Hz), 4.05 (1H, d, *J* = 9.2 Hz), 4.30 (1H, s), 5.38 (1H, dd, *J* = 5.2, 12.8 Hz), 6.86 (1H, d, *J* = 9.2 Hz), 7.00 (1H, dd, *J* = 8.4, 2.4 Hz), 7.10 (1H, dd, *J* = 10.0, 2.0 Hz), 7.21 (1H, d, *J* = 2.4 Hz), 7.25 (1H, d, *J* = 10.0 Hz), 7.36 (1H, s), 7.62 (1H, d, *J* = 9.2 Hz), 7.90 (1H, d, *J* = 8.8 Hz), 7.95 (1H, dd, *J* = 9.2, 2.4 Hz), 8.62 (1H, d, *J* = 2.4 Hz), 11.10 (1H, s).
50	808.6	A	A	^{1}H NMR (400 MHz, DMSO-d^6) δ 1.13 (6H, s), 1.22 (6H, s), 1.79-1.81 (3H, m), 2.09-2.15 (1H, m), 2.19-2.21 (2H, m), 2.49-2.50 (7H, m), 2.60-2.67 (1H, m), 2.76-2.92 (3H, m), 3.22-3.26 (4H, m), 3.86 (2H, d, *J* = 12.8 Hz), 4.05 (1H, d, *J* = 9.2 Hz), 4.32 (1H, s), 5.23 (1H, dd, *J* = 12.4, 5.2 Hz), 6.12 (1H, s), 6.70 (1H, dd, *J* = 8.0, 1.6 Hz), 6.95 (2H, d, *J* = 9.2 Hz), 7.00 (1H, dd, *J* = 8.8, 2.4 Hz), 7.21 (1H, d, *J* = 2.4 Hz), 7.48 (1H, d, *J* = 8.8 Hz), 7.72 (3H, t, *J* = 8.4 Hz), 7.91 (1H, d, *J* = 8.8 Hz), 11.04 (1H, s).
51	835.59	A	A	1H NMR (300 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.57 (s, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 9.1 Hz, 1H), 7.29 (s, 1H), 7.17 (d, J = 2.2 Hz, 1H), 7.02-6.87 (m, 3H), 5.07 (dd, J = 12.8, 5.3 Hz, 1H), 4.29 (s, 1H), 4.02 (d, J = 9.1 Hz, 1H), 3.88-3.70 (m, 5H), 3.29 (br s, 5H), 2.95-2.65 (m, 3H), 2.59-2.41 (m, 6H), 2.00 (m, 1H), 1.73 (d, J = 12.8 Hz, 2H), 1.45 (br, 3H), 1.17 (s, 6H), 1.09 (s, 6H)
52	836.59	A	B	^{1}H NMR (400 MHz, *d6*-DMSO): δ 11.12 (s, 1H), 8.90 (s, 1H), 7.91-7.89 (d, *J*=8.4Hz, 1H), 7.74-7.72 (d, *J*=7.6Hz, 2H), 7.49-7.47 (d, *J*=8.8Hz, 1H), 7.20 (s, 1H), 6.99-6.94 (m, 3H), 5.16-5.13 (m, 1H), 4.32 (s, 1H), 4.06-3.83 (m, 7H), 2.88-2.57 (m, 5H), 2.39-2.33 (m, 2H), 2.07-2.01 (m, 1H), 1.78-1.75 (m, 2H), 1.54-1.35 (m, 3H), 1.21 (m, 8H), 1.12 (s, 6H)

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*AR DC_{50} (nM) A<1; 1<=B<10; 10<=C<100; D>=100

**AR D_{max}(%) A>=75; 50<=B<75; C<50

[0955] Table 7. Characterization of Exemplary BRaf PROTACs

Ex. #	BRaf DC_{50}*	BRaf D_{max}**	MH+	NMR Transcript
39	C	B	783.51	1H NMR (400 MHz, DMSO-d6): δ 11.03 (s, 1H), 10.87 (s, 1H), 8.72 (s, 1H), 8.57 (m, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.62-7.60 (m, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.50-7.41 (m, 6H), 7.22 (d, J = 8.0 Hz, 2H), 7.17-7.15(m, 3H), 5.07-5.03 (m, 1H), 3.73 (m, 8H), 3.01 (s, 2H), 2.83-2.81 (m, 3H), 2.67 (s, 2H), 2.03-2.00 (m, 1H)
40	C	A	721.48	1H NMR (400 MHz, DMSO-d6): δ 11.15 (bs, 1H), 8.72 (s, 1H), 8.72 (s, 1H), 8.57 (d, J = 5.6Hz, 2H), 7.83 (d, J = 8.8 Hz, 2H), 7.77 (s, 1H), 7.49-7.57 (m, 4H), 7.41 (s, 1H), 7.17-7.30 (m, 3H), 5.09-5.13 (m, 1H), 3.20-3.35 (m, 8H), 2.80-3.12 (m, 6H), 2.52-2.75 (m, 3H), 1.90-2.12 (m, 2H)
41	C	A	783.51	1H NMR (400 MHz, DMSO-d6): δ 11.04 (s, 1H), 10.88 (s, 1H), 8.69 (s, 1H), 8.57 (d, J = 4.8 Hz, 2H), 7.87 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.8 Hz, 2H), 7.40-7.56 (m, 10H), 7.22 (d, J = 4.8 Hz, 1H), 7.03 (d, J = 9.2 Hz, 2H), 5.00-5.05 (m, 1H), 3.02 (m, 9H), 2.83 (t, J = 6.8 Hz, 2H), 1.99-2.01 (m, 3H)
42	C	B	721.48	1H NMR (400 MHz, DMSO-d6): δ 11.09 (s, 1H), 10.89 (s, 1H), 8.72 (s, 1H), 8.58-8.57 (m, 2H), 7.83 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.50-7.41 (m, 4H), 7.23-7.17 (m, 3H), 5.13-5.09 (m, 1H), 3.61-3.42 (m, 8H), 3.04-2.97 (m, 2H), 2.93-2.82 (m, 3H), 2.62-2.56 (m, 5H), 2.08-2.00 (m, 1H)

*BRaf DC_{50} (nM) A<1; 1<=B<10; 10<=C<100; D>=100

**BRaf D_{max}(%) A>=75; 50<=B<75; C<50

[0956] Table 8. Characterization of Exemplary BRD4 PROTACs

Ex. #	BRD4 DC_{50}*	BRD4 D_{max}**	Observed [M+H]+	NMR

43	D	B	895.22	^{1}H NMR (400 MHz, CHLOROFORM-d) d 9.03 (s, 1H), 7.45 (dd, J = 8.71, 13.21 Hz, 4H), 7.31 - 7.37 (m, 3H), 7.24 (d, J = 7.24 Hz, 1H), 6.84 (d, J = 9.00 Hz, 2H), 6.78 (d, J = 8.02 Hz, 1H), 6.75 (br. s., 1H), 4.66 - 4.73 (m, 2H), 4.20 (d, J = 2.74 Hz, 1H), 4.07 - 4.12 (m, 2H), 3.80 - 3.90 (m, 3H), 3.64 - 3.77 (m, 10H), 3.52 - 3.58 (m, 1H), 3.35 - 3.42 (m, 3H), 2.68 (br. s., 3H), 2.52 - 2.59 (m, 2H), 2.41 (s, 3H), 2.02 - 2.08 (m, 2H), 1.69 (s, 3H), 1.26 (s, 3H).
44	D	C	937.19	1H NMR (400 MHz, METHANOL-d4) d 7.60 - 7.65 (m, 1H), 7.30 - 7.47 (m, 8H), 6.82 - 6.87 (m, 2H), 5.24 (dd, J = 5.67, 10.76 Hz, 1H), 4.69 (ddd, J = 2.84, 5.62, 8.56 Hz, 1H), 4.26 - 4.31 (m, 2H), 4.02 - 4.07 (m, 2H), 3.91 - 3.96 (m, 2H), 3.77 - 3.81 (m, 2H), 3.70 - 3.74 (m, 2H), 3.63 - 3.69 (m, 6H), 3.53 - 3.61 (m, 1H), 3.43 - 3.49 (m, 2H), 2.81 (dt, J = 4.60, 14.33 Hz, 2H), 2.70 (s, 6H), 2.43 (s, 3H), 2.13 - 2.20 (m, 1H), 1.68 (s, 2H), 1.26 - 1.29 (m, 2H).
45	C	A	937.19	^{1}H NMR (400 MHz, METHANOL-d4) d 8.55 (s, 1H), 7.96 - 8.00 (m, 1H), 7.36 - 7.50 (m, 6H), 7.03 - 7.09 (m, 2H), 6.87 (dd, J = 3.03, 9.10 Hz, 2H), 5.22 (td, J = 5.40, 10.91 Hz, 1H), 4.70 - 4.74 (m, 1H), 4.22 (d, J = 3.33 Hz, 2H), 4.10 (d, J = 4.30 Hz, 2H), 3.85 - 3.91 (m, 2H), 3.79 - 3.84 (m, 2H), 3.64 - 3.71 (m, 7H), 3.55 - 3.64 (m, 2H), 3.42 - 3.50 (m, 2H), 2.71 (s, 3H), 2.66 (d, J = 3.33 Hz, 2H), 2.44 (d, J = 3.33 Hz, 3H), 1.89 (s, 3H), 1.68 (d, J = 3.33 Hz, 2H), 1.29 (br. s., 3H).

*BRD4 DC_{50} (nM) A<1; 1<=B<10; 10<=C<100; D>=100

**BRD4 D_{max}(%) A>=75; 50<=B<75; C<50

WO 2019/199816 PCT/US2019/026570

[0957] 5. Industrial applicability

[0958] A novel bifunctional molecule, which contains a BRD4 or an androgen receptor recruiting moiety and an E3 Ligase Cereblon recruiting moiety, through PROTAC technology is described. The bifunctional molecules of the present disclosure actively degrades BRD4, leading to significant and persistent downstream MYC suppression and robust cellular proliferation suppression and apoptosis induction. PROTAC mediated protein degradation provides a promising strategy in targeting the "undruggable" pathological proteins by traditional approaches.

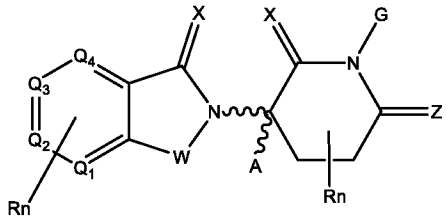
[0959] The contents of all references, patents, pending patent applications and published patents, cited throughout this application are hereby expressly incorporated by reference.

[0960] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims. It is understood that the detailed examples and embodiments described herein are given by way of example for illustrative purposes only, and are in no way considered to be limiting to the invention. Various modifications or changes in light thereof will be suggested to persons skilled in the art and are included within the spirit and purview of this application and are considered within the scope of the appended claims. For example, the relative quantities of the ingredients may be varied to optimize the desired effects, additional ingredients may be added, and/or similar ingredients may be substituted for one or more of the ingredients described. Additional advantageous features and functionalities associated with the systems, methods, and processes of the present disclosure will be apparent from the appended claims. Moreover, those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS

What Is Claimed Is:

1. A cereblon E3 ubiquitin ligase binding compound having a chemical structure selected from:



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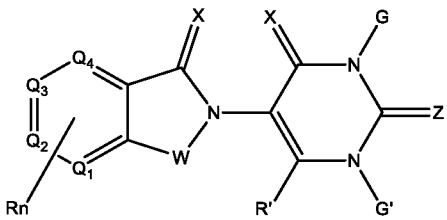
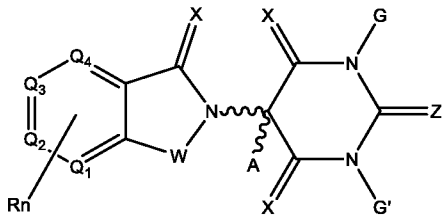
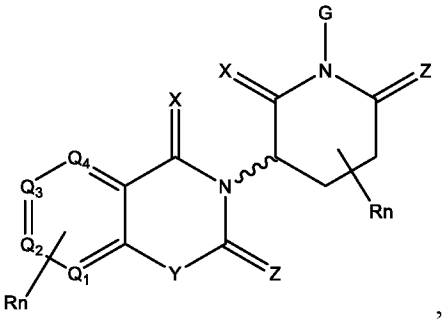


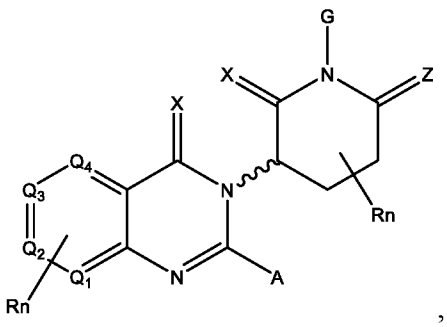
(b),



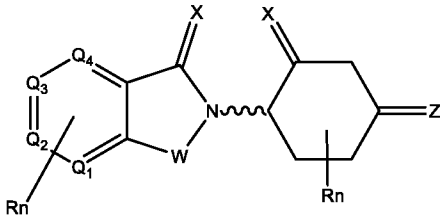
(c),



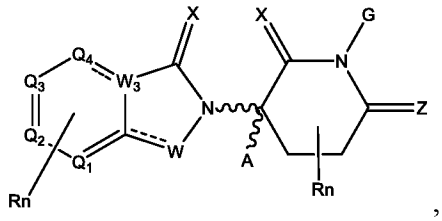
(d1),



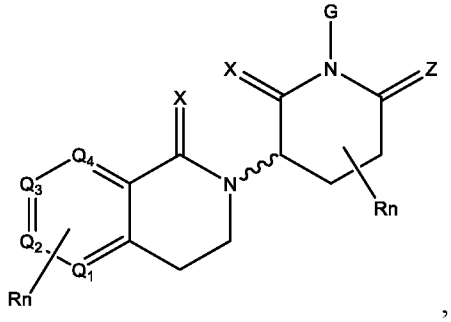
(e),



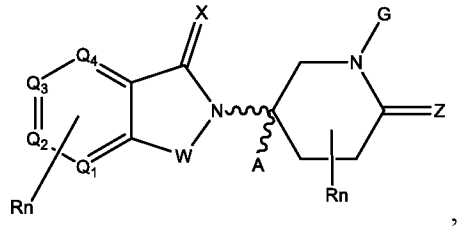
(f),



(a2)



(d2)



(a3)

wherein:

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

W_3 is selected from C or N;

each X is absent or independently selected from the group consisting of O and S;

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;

each Z is absent or independently selected from the group consisting of O or S;

G and G' are independently selected from the group consisting of H, optionally substituted linear or branched alkyl, 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, optionally substituted linear or branched alkyl, cycloalkyl, Cl and F;

R comprises -CONR'R", -OR', -NR'R", -SR', -SO_2R', -SO_2NR'R", -CR'R"-, -CR'NR'R"-, (-CR'O)$_n$R", -aryl, -hetaryl, -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,

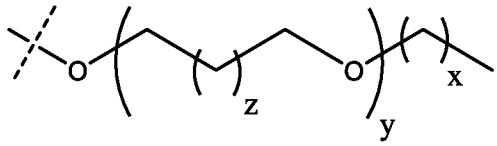
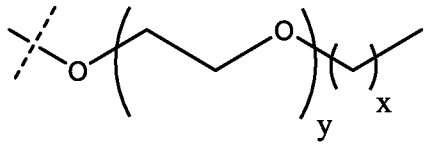
$-CF_3$, -CN, $-NR'SO_2NR'R''$, $-NR'CONR'R''$, $-CONR'COR''$, $-NR'C(=N-CN)NR'R''$, $-C(=N-CN)NR'R''$, $-NR'C(=N-CN)R''$, $-NR'C(=C-NO_2)NR'R''$, $-SO_2NR'COR''$, $-NO_2$, $-CO_2R'$, $-C(C=N-OR')R''$, $-CR'=CR'R''$, -CCR', $-S(C=O)(C=N-R')R''$, $-SF_5$ and $-OCF_3$;

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

n' integer from 1-10;

represents a single bond or a double bond;

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

Rn comprises 1-4 independent functional groups, optionally substituted linear or branched alkyl, optionally substituted aryl, optionally substituted alkyl-aryl, optionally substituted alkoxyl group, optionally substituted  , optionally substituted  , or aryl, or atoms; and

each of x, y, and z are independently 0, 1, 2, 3, 4, 5, or 6,

n is an integer from 1-10.

2. A bifunctional compound having the chemical structure:

CLM—L—PTM,

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

wherein:

the PTM is a small molecule comprising a protein targeting moiety;

the L is a bond or a chemical linking moiety covalently coupling the CLM and the PTM; and

the CLM is a small molecule cereblon E3 ubiquitin ligase binding moiety of claim 1, wherein when n is 2, 3, or 4, then at least one of R_n or W is modified to be covalently joined to the linker group (L) or a PTM.

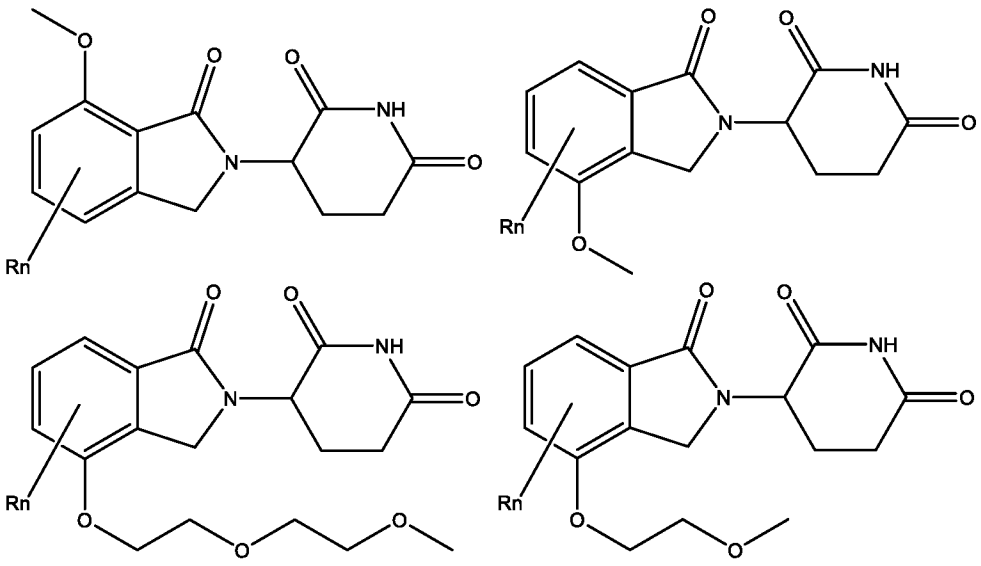
3. The bifunctional compound according to claim 2, wherein the CLM is linked to the PTM, the chemical linker group (L), or a combination thereof via W, X, R^1, R^2, R^3, R^4, R', Q_1, Q_2, Q_3, Q_4, and Q_5.

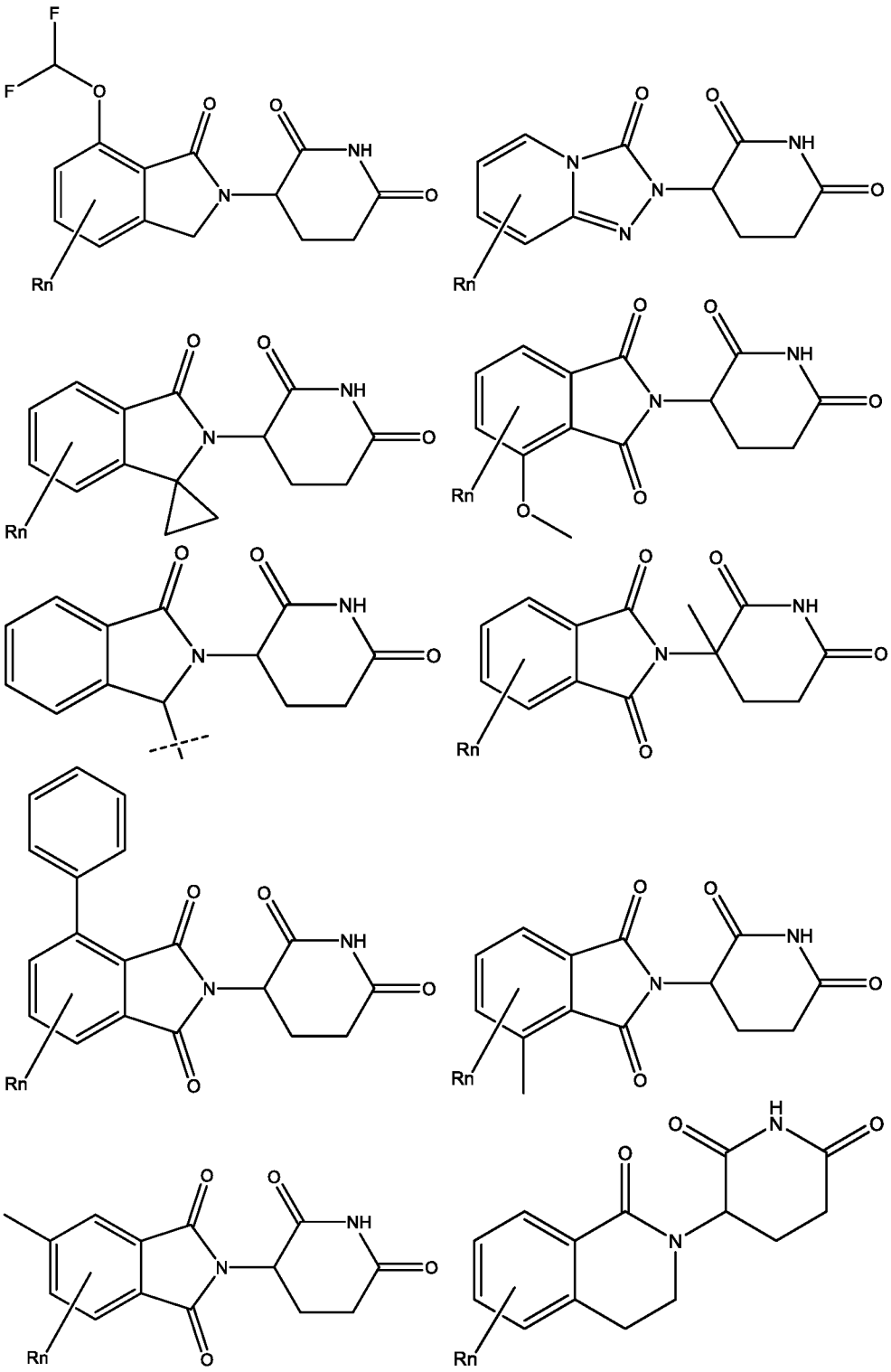
4. The bifunctional compound according to claim 2 or 3, wherein the PTM is a moiety that binds BRD4, BRaf, Estrogen Receptor (ER), or Androgen Receptor (AR).

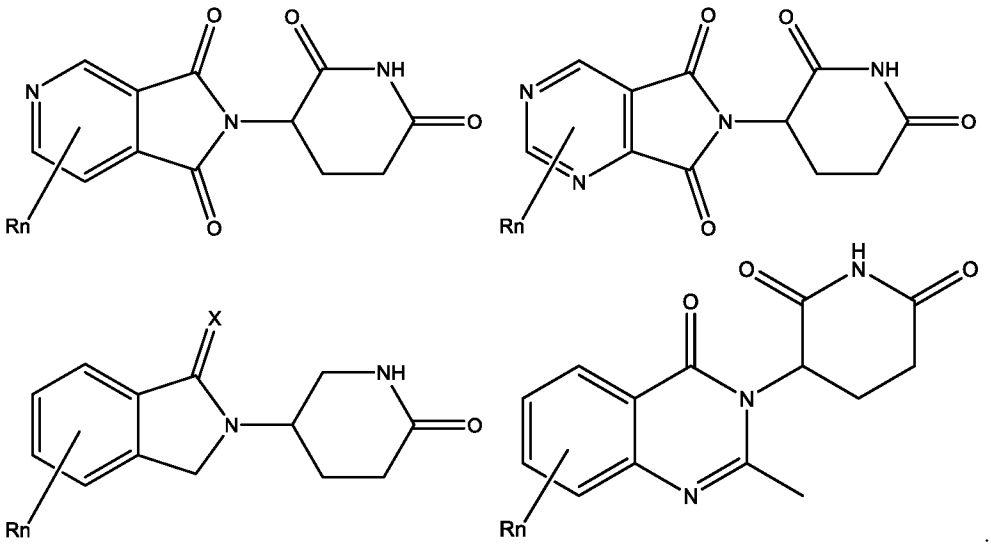
5. The bifunctional compound according to any of claims 2-4, wherein the compound further comprises a second E3 ubiquitin ligase binding moiety coupled through a linker group.

6. The bifunctional compound according to claim 5, wherein the second E3 ubiquitin ligase binding moiety binds or targets an E3 ubiquitin ligase selected from the group consisting of Von Hippel-Lindau (VLM), cereblon (CLM), mouse double-minute homolog2 (MLM), and inhibitors of apoptosis proteins (ILM).

7. The bifunctional compound according to any of claims 2-6, wherein the CLM is represented by a chemical structure selected from the group consisting of:







8. The bifunctional compound according to any of claims 2-7, wherein the linker (L) comprises a chemical structural unit represented by the formula:

$$-(A^L)q-$$

wherein:

$(A^L)_q$ is a group which is connected to at least one of the CLM, the PTM, or a combination thereof;

q is an integer greater than or equal to 1;

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

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, $P(O)(OC_{1-8}alkyl)(C_{1-8}alkyl)$,

$P(O)(OC_{1\text{-}8}alkyl)_2$, CC-$C_{1\text{-}8}$alkyl, CCH, CH=CH($C_{1\text{-}8}$alkyl), C($C_{1\text{-}8}$alkyl)=CH($C_{1\text{-}8}$alkyl), C($C_{1\text{-}8}$alkyl)=C($C_{1\text{-}8}$alkyl)$_2$, $Si(OH)_3$, Si($C_{1\text{-}8}$alkyl)$_3$, Si(OH)($C_{1\text{-}8}$alkyl)$_2$, $COC_{1\text{-}8}$alkyl, CO_2H, halogen, CN, CF_3, CHF_2, CH_2F, NO_2, SF_5, $SO_2NHC_{1\text{-}8}$alkyl, $SO_2N(C_{1\text{-}8}alkyl)_2$, $SONHC_{1\text{-}8}$alkyl, $SON(C_{1\text{-}8}alkyl)_2$, $CONHC_{1\text{-}8}$alkyl, $CON(C_{1\text{-}8}alkyl)_2$, N($C_{1\text{-}8}$alkyl)CONH($C_{1\text{-}8}$alkyl), N($C_{1\text{-}8}$alkyl)CON($C_{1\text{-}8}alkyl)_2$, NHCONH($C_{1\text{-}8}$alkyl), NHCON($C_{1\text{-}8}alkyl)_2$, $NHCONH_2$, N($C_{1\text{-}8}$alkyl)SO_2NH($C_{1\text{-}8}$alkyl), N($C_{1\text{-}8}$alkyl) $SO_2N(C_{1\text{-}8}alkyl)_2$, NH SO_2NH($C_{1\text{-}8}$alkyl), NH $SO_2N(C_{1\text{-}8}alkyl)_2$, NH SO_2NH_2.

9. The bifunctional compound according to any of claims 2-8, wherein A^L is 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-,

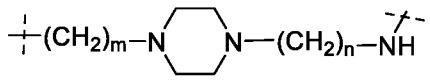
-O-$(CH2)_m$-O$(CH2)_n$-O$(CH2)_o$-O$(CH2)_p$-O$(CH2)_q$-O$(CH2)_r$-O-;

-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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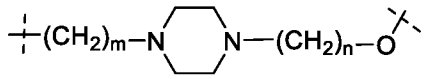
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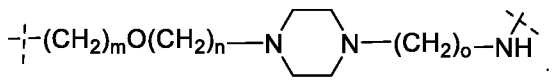
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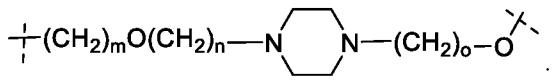
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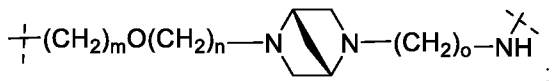
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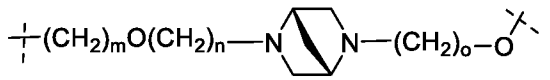

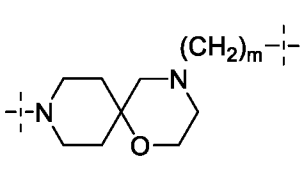
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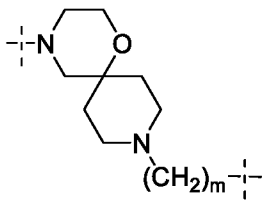
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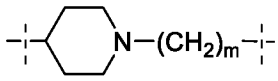
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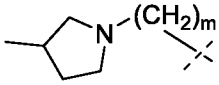
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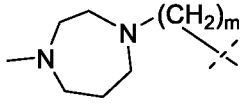

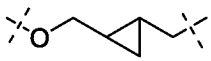
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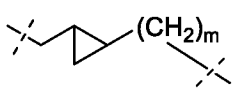
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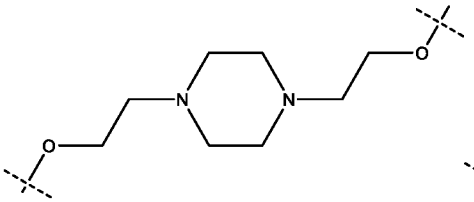
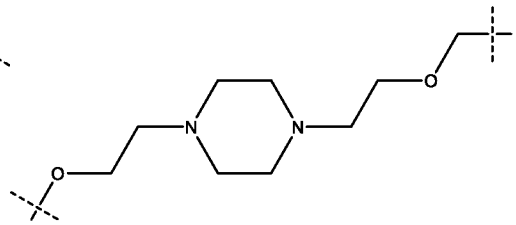
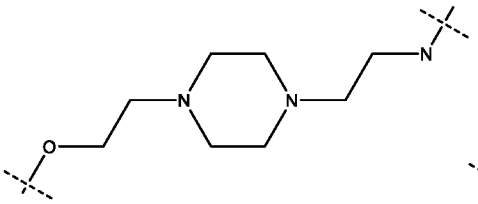
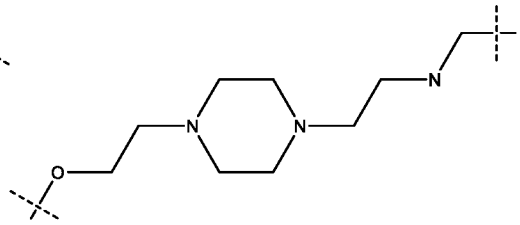
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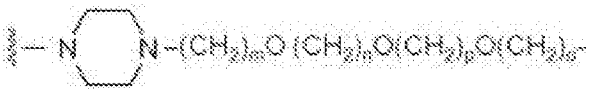
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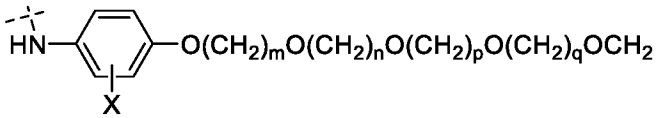
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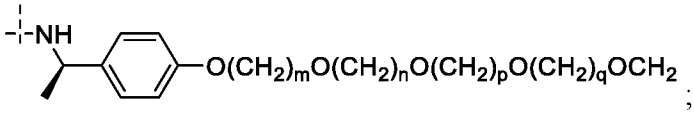
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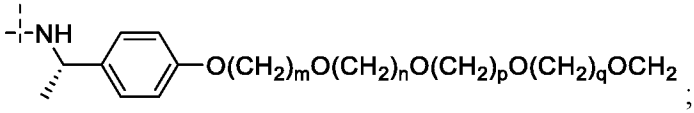
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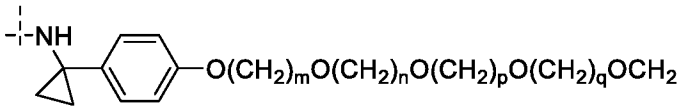
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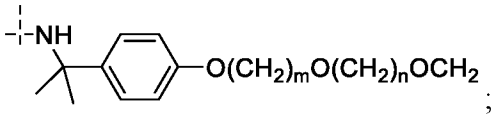

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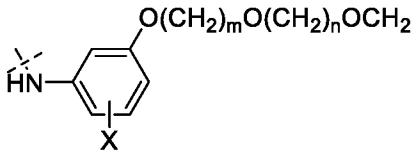

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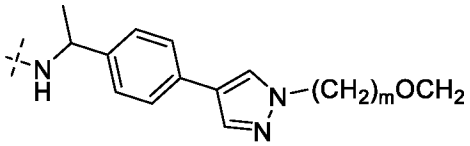


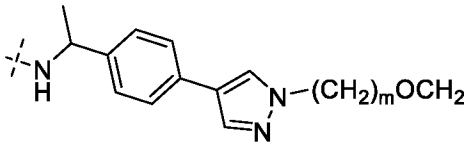
; wherein

m, n, o, p, q, and r of the linker are independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20;

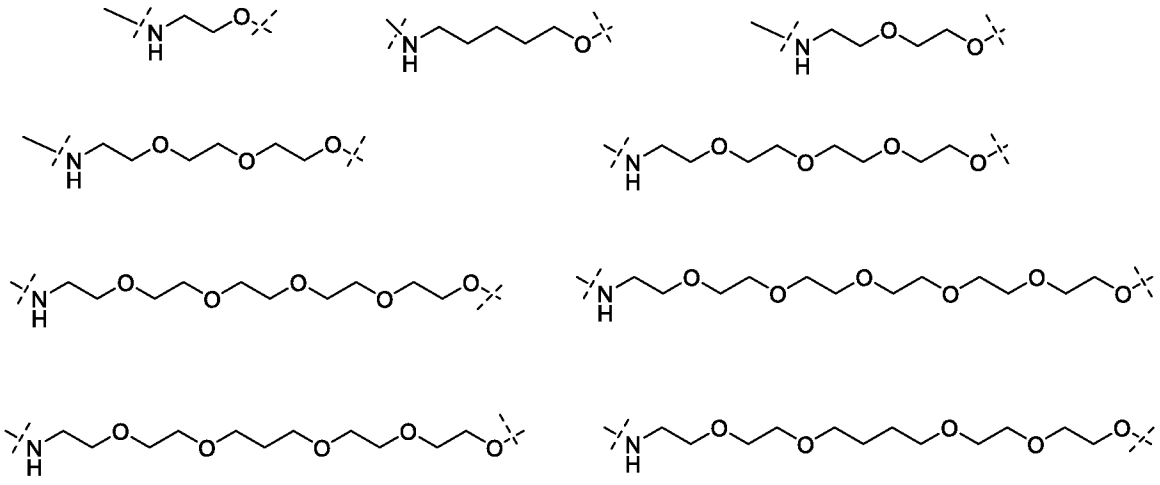
when the number is zero, there is no N-O or O-O bond

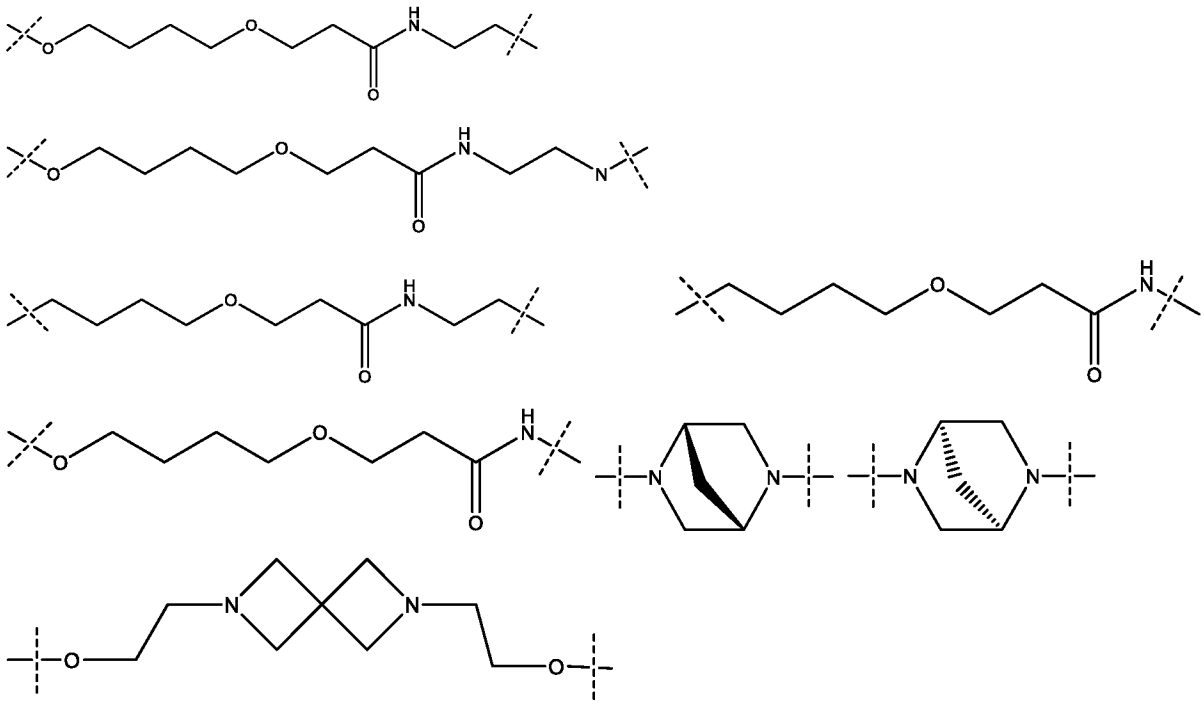
R of the linker is H, methyl and ethyl;

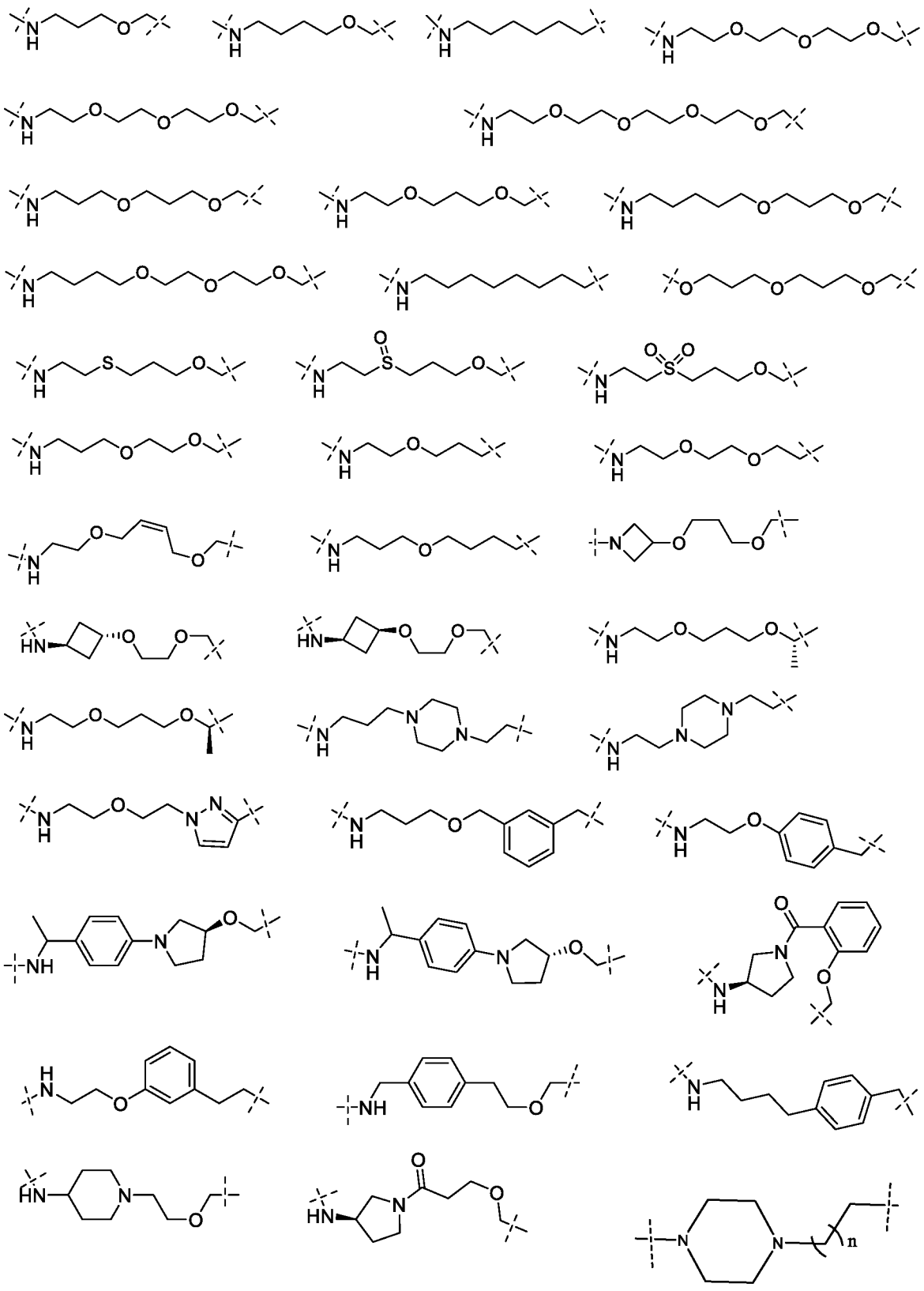
X of the linker is H and F

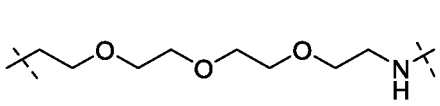
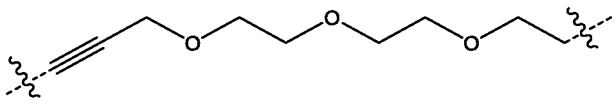


where m of the linker can be 2, 3, 4, 5;





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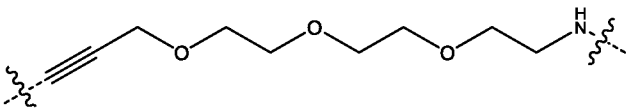
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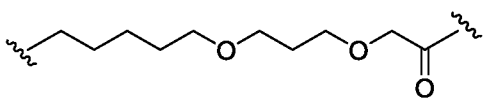
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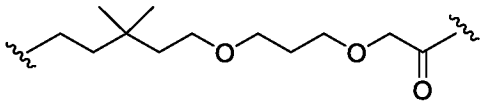
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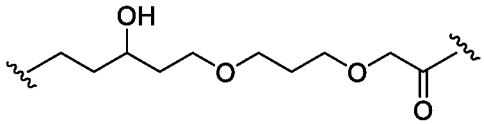
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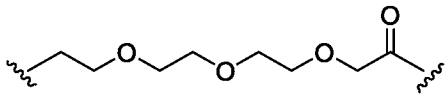
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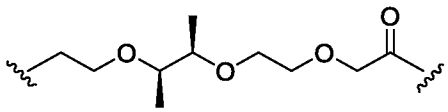
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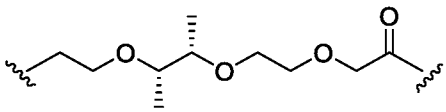
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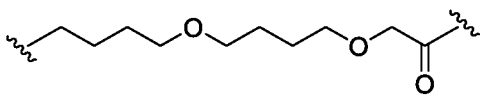
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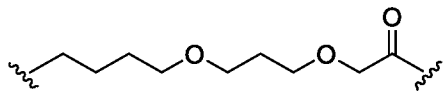
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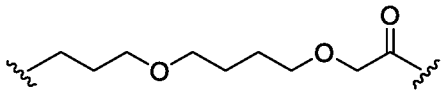
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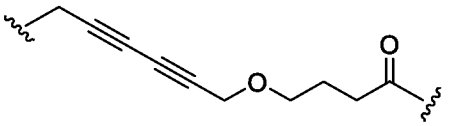
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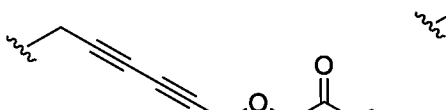
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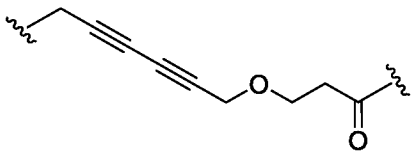
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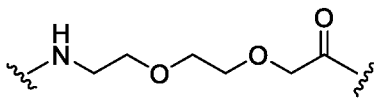
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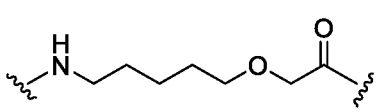
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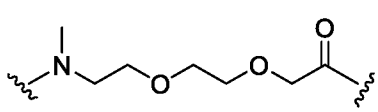
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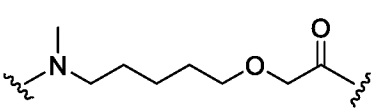
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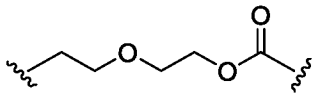
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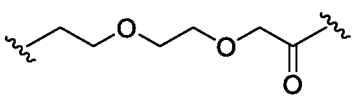
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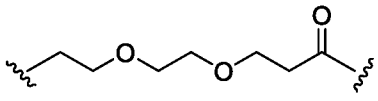
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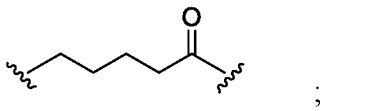
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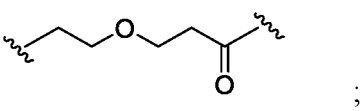
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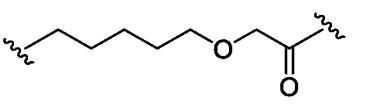
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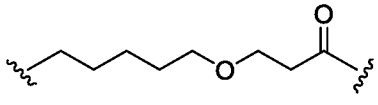
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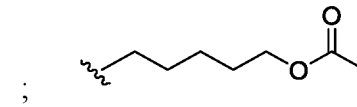
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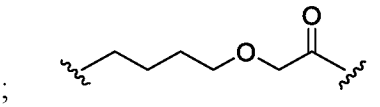
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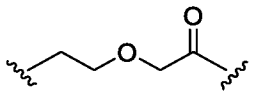
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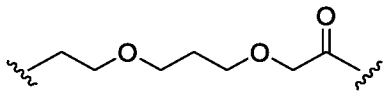
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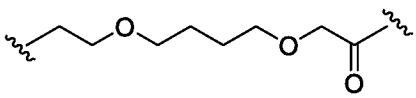
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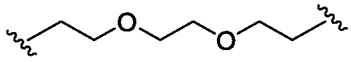
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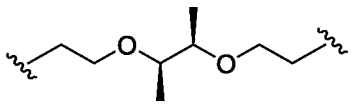
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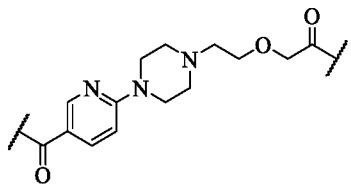
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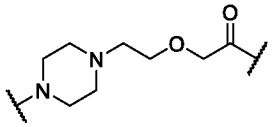
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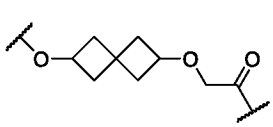
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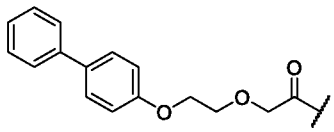
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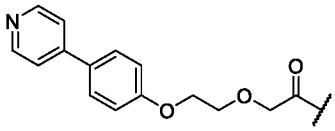
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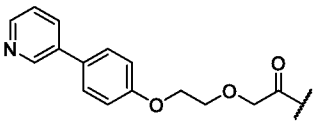
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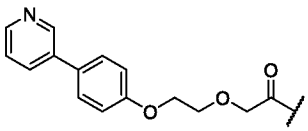
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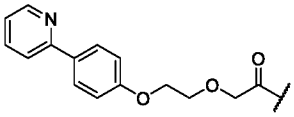
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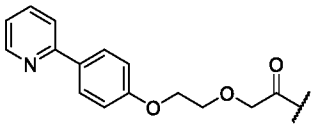
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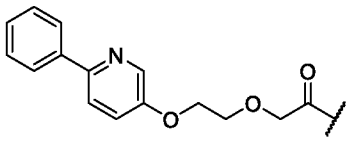
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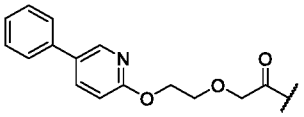
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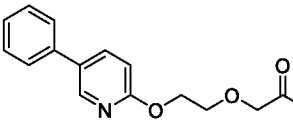
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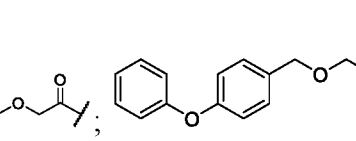
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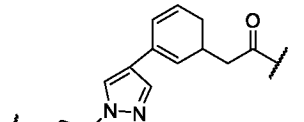
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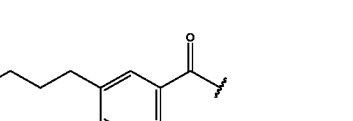
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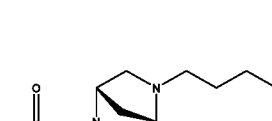
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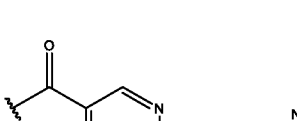
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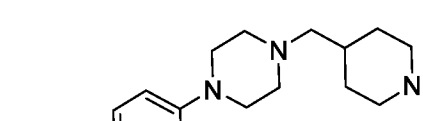
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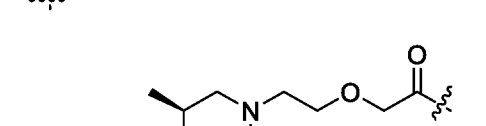
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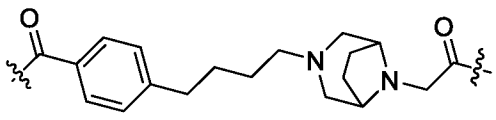
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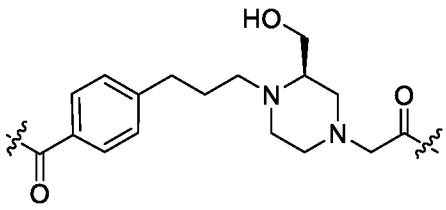
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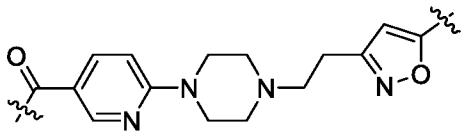
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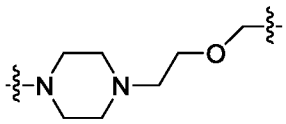
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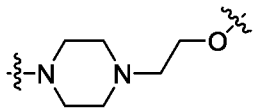
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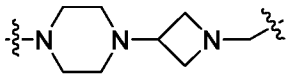
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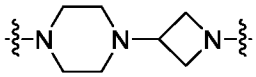
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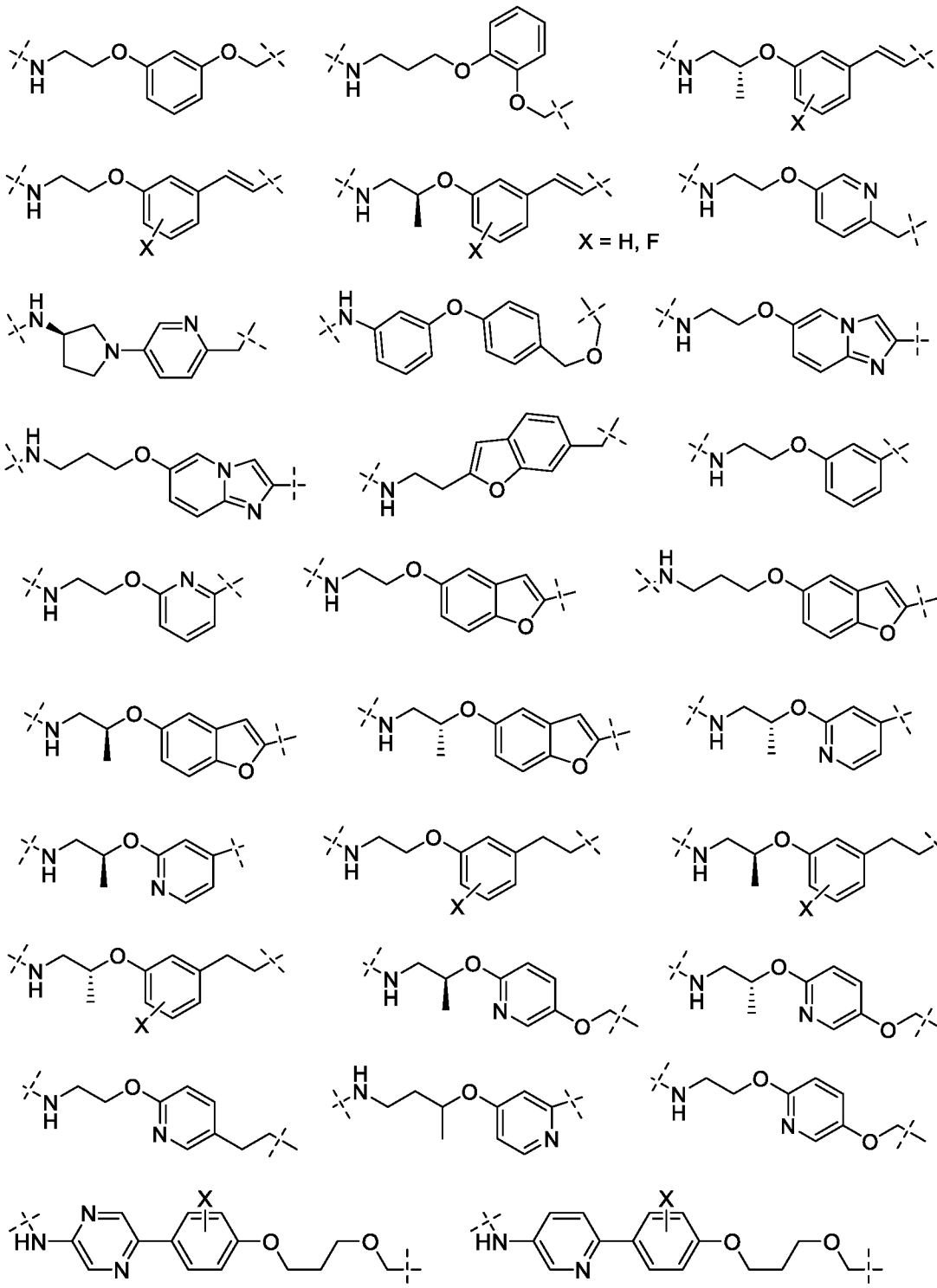
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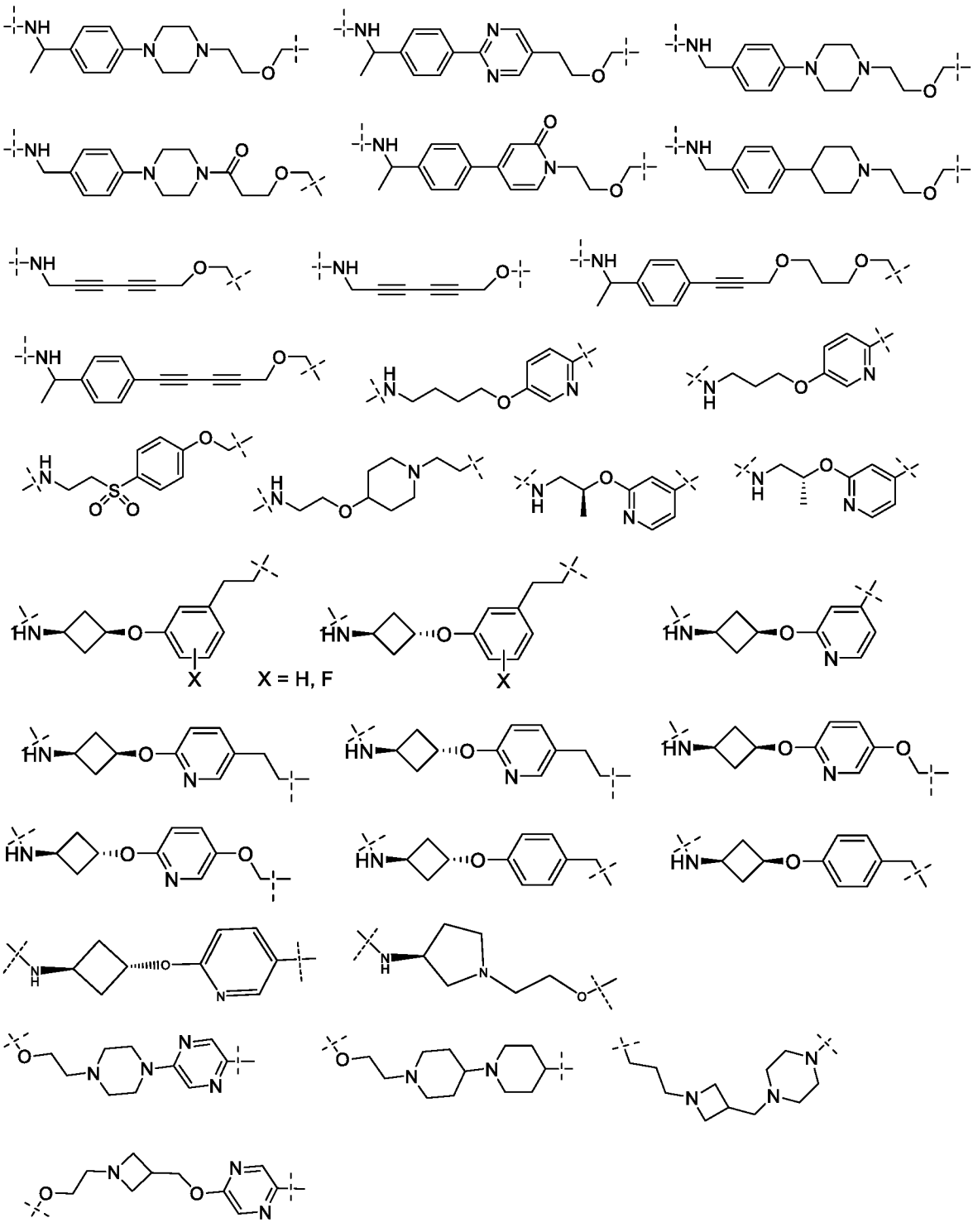
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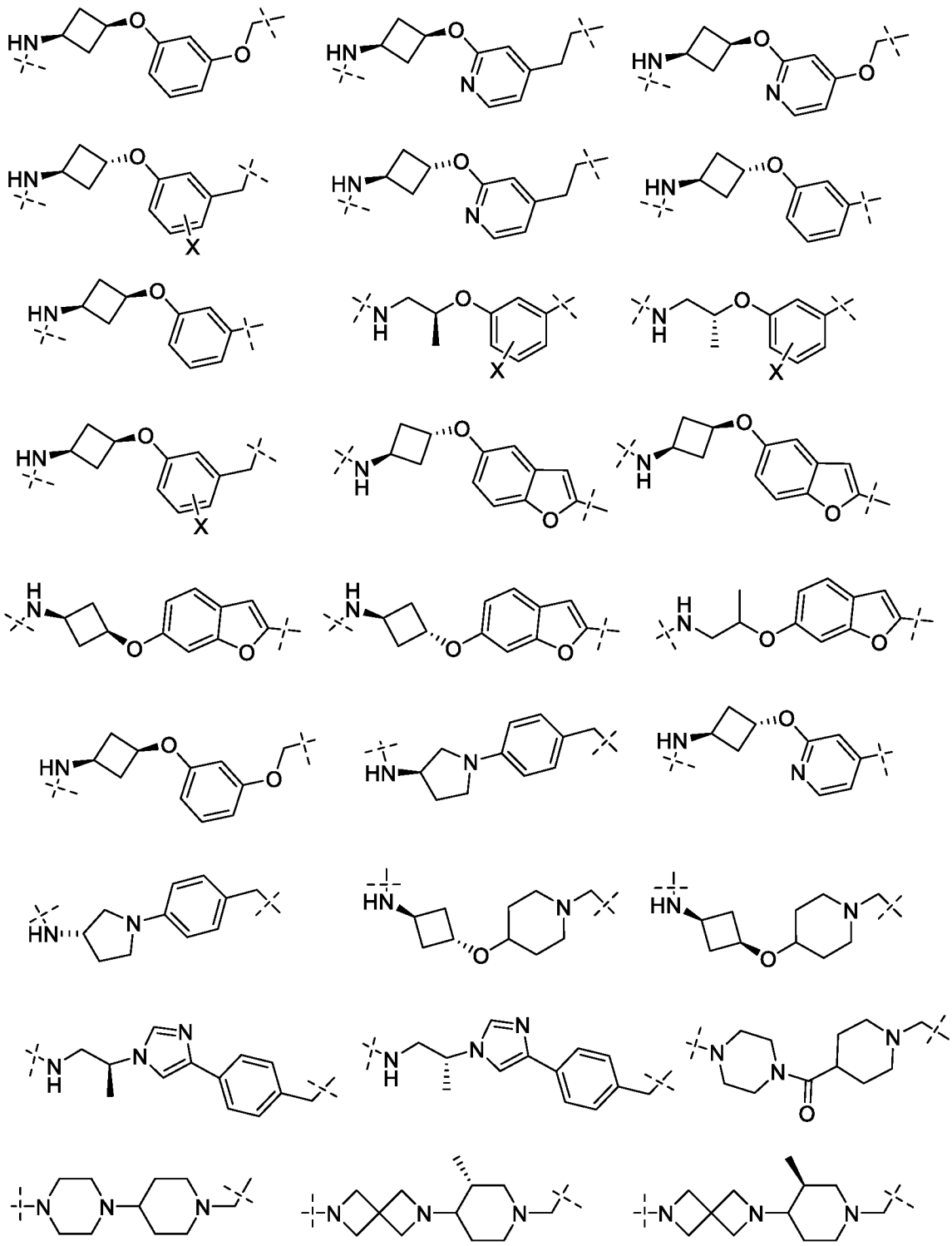

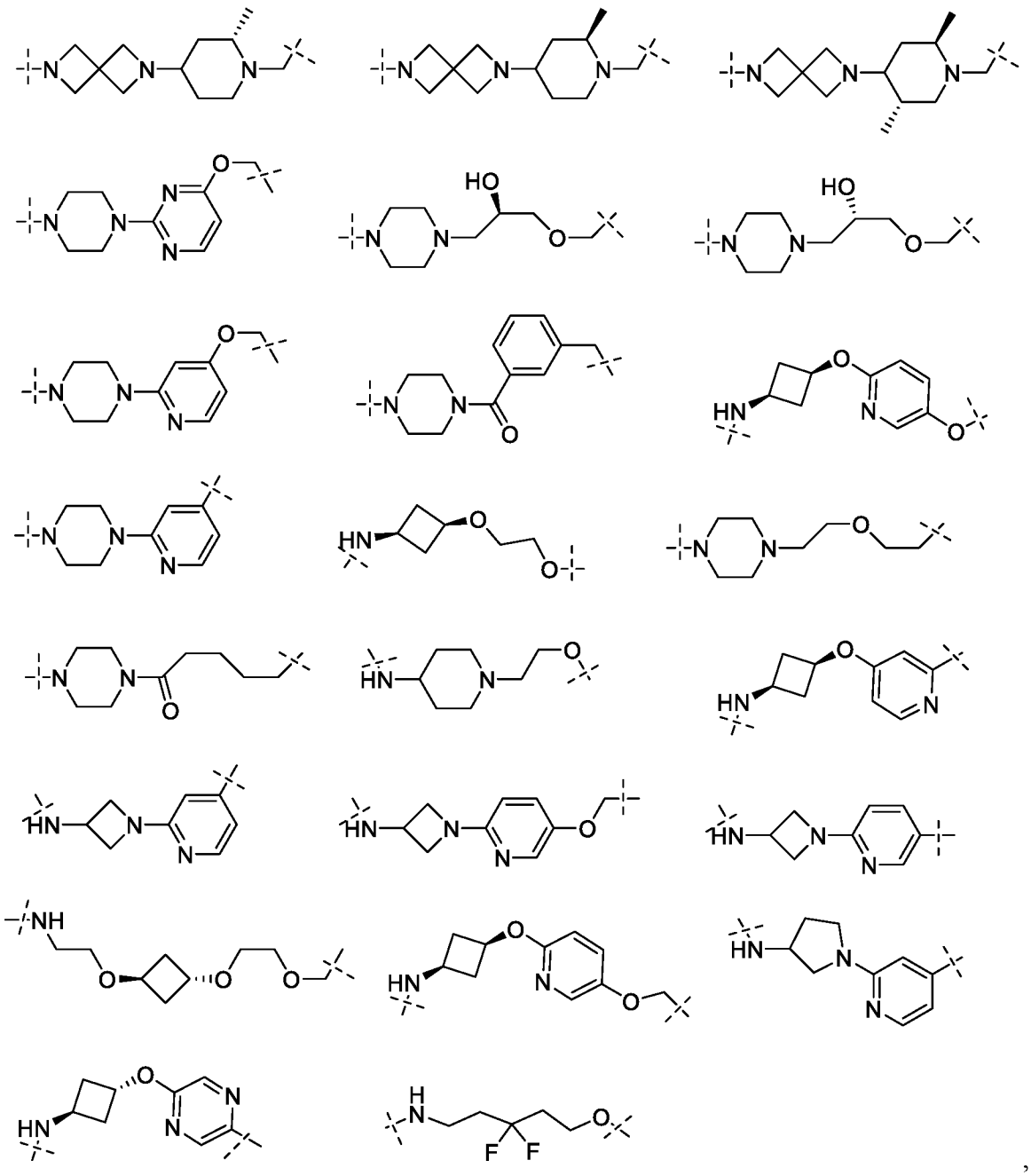

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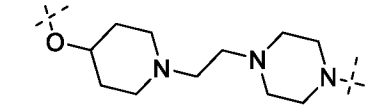
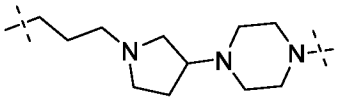
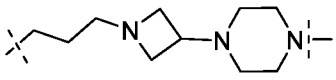
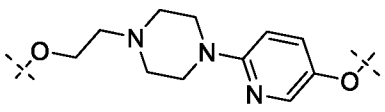
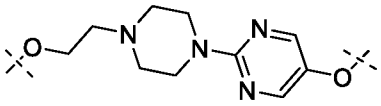
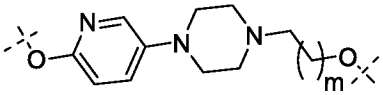
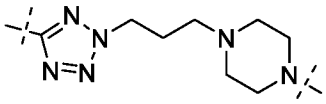
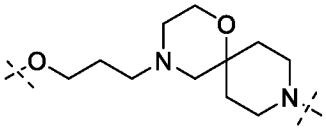
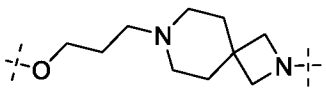
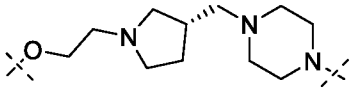
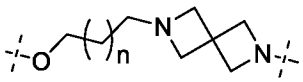
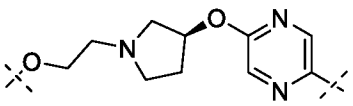
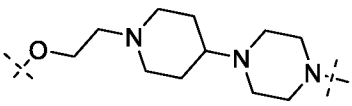
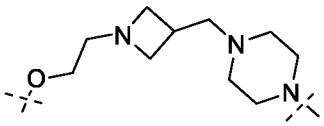
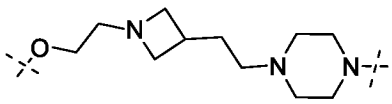
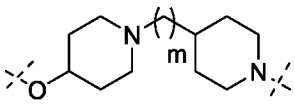
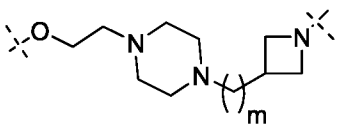
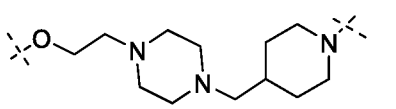
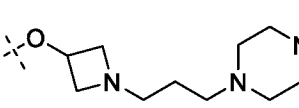
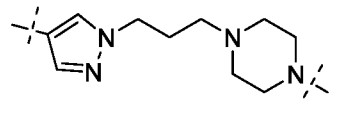
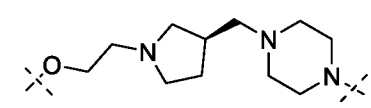
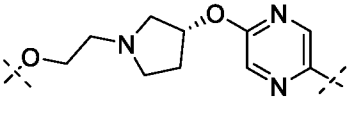
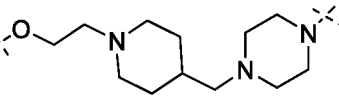
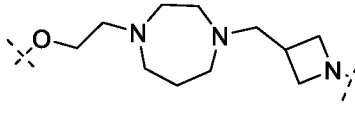
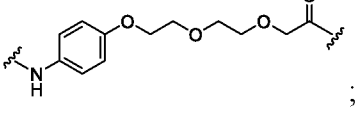
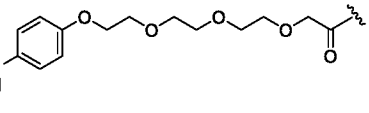
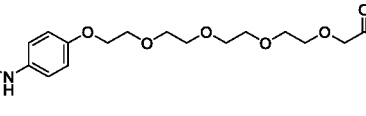
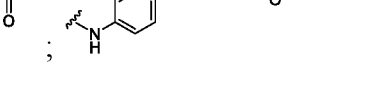
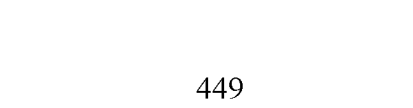
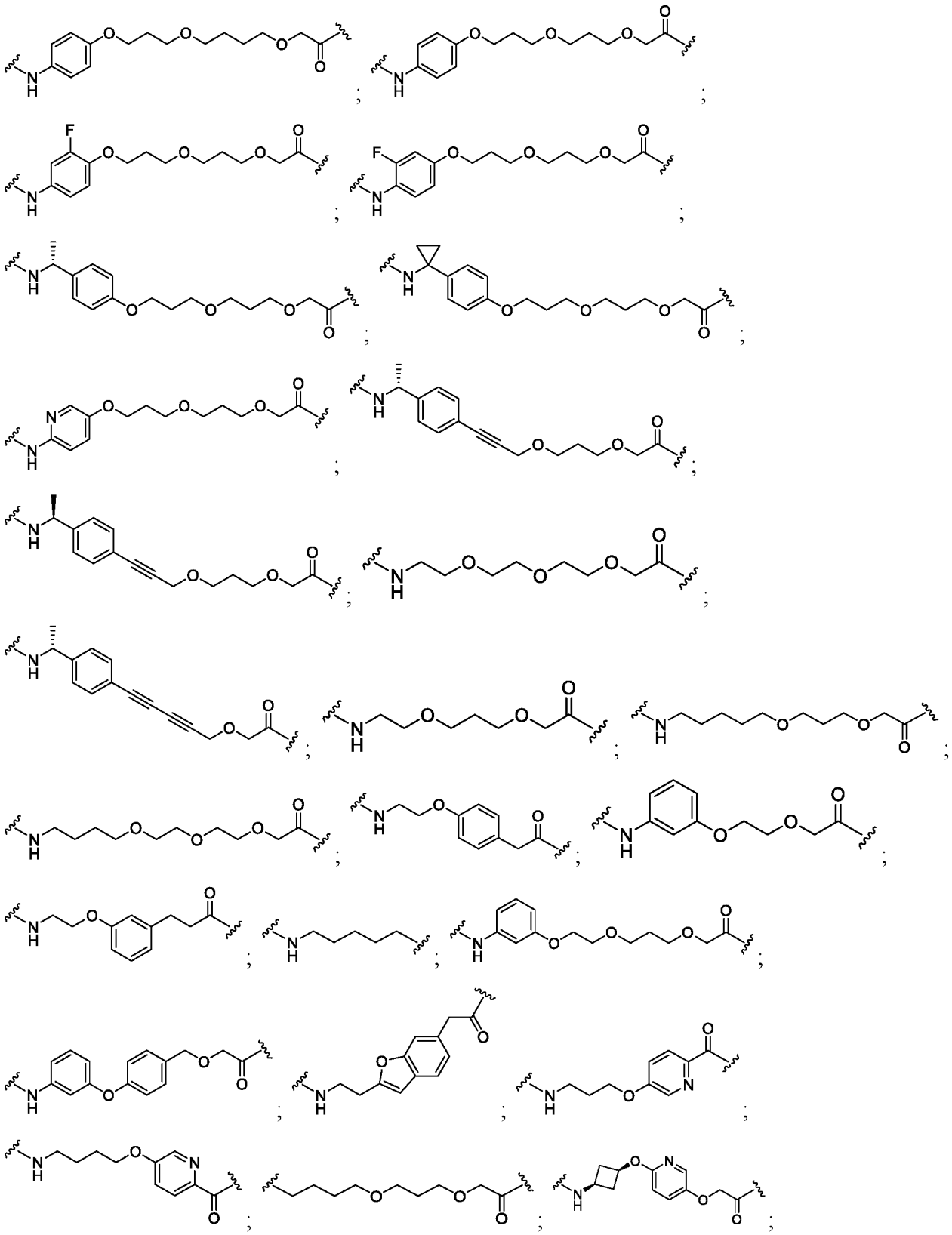
where each n and m of the linker can independently be 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20.

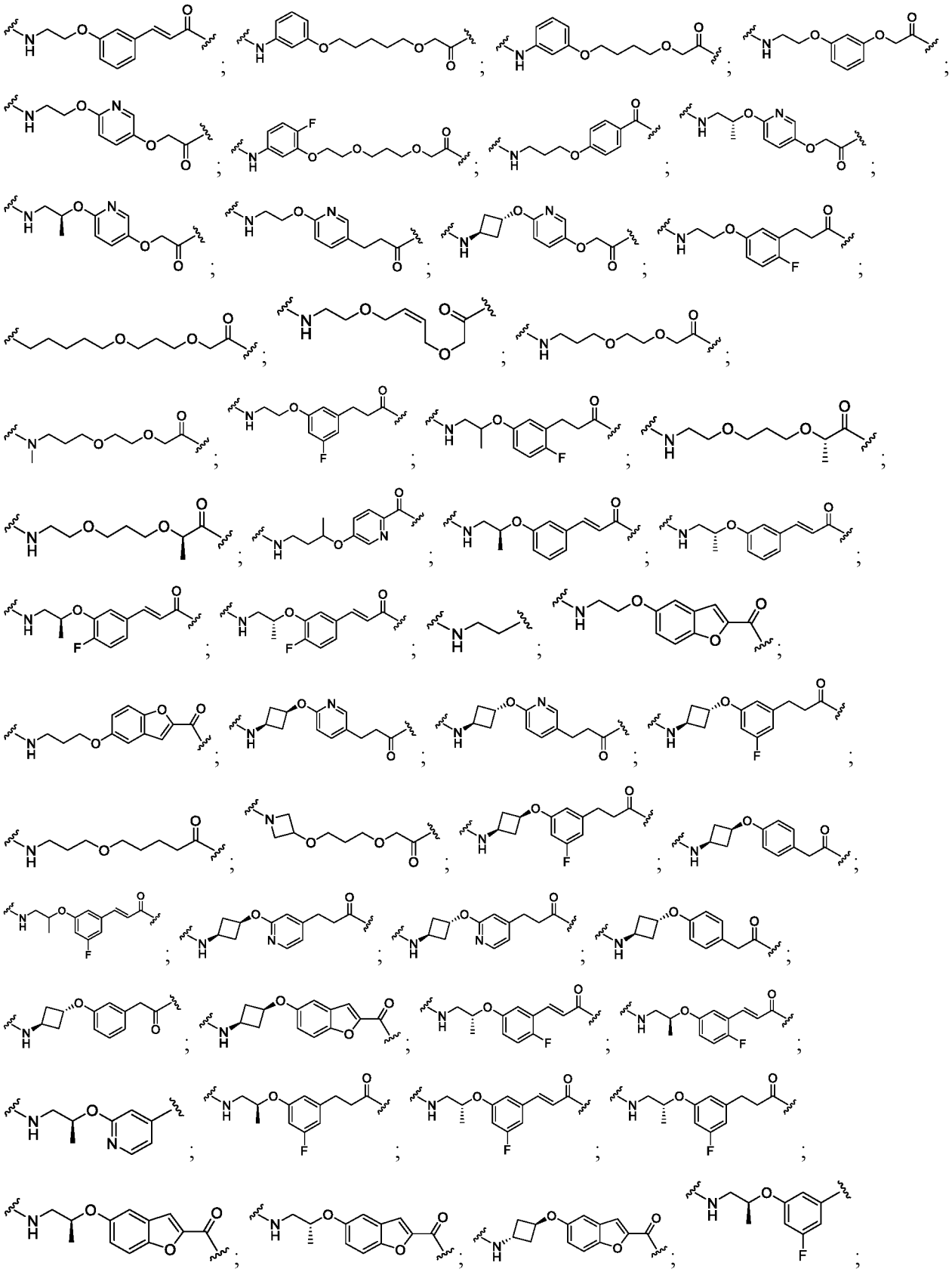
10. The bifunctional compound according to any of claims 2-8, wherein A^L is selected from the group consisting of:

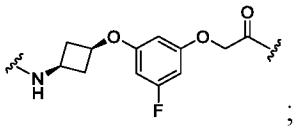


































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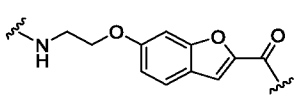
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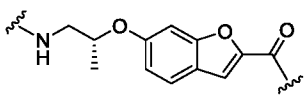
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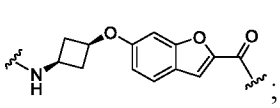
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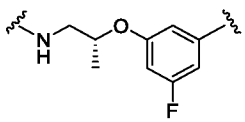
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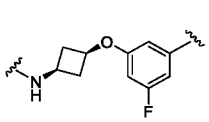
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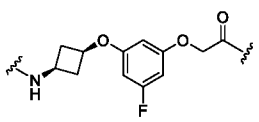
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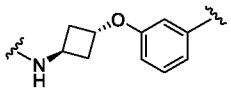
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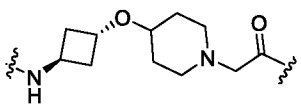
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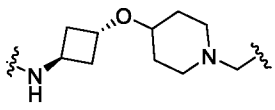
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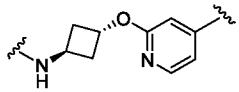
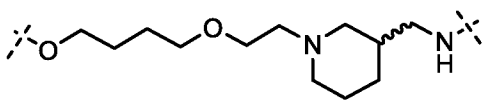

, wherein each m and n is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20.

11. The bifunctional compound of any of claims 2-8, wherein A^L is selected from the group consisting of: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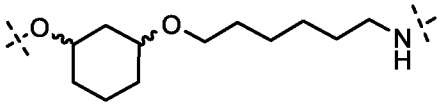
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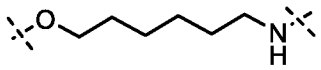
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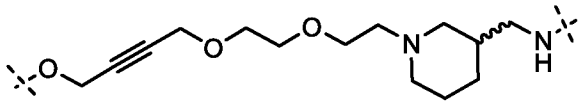
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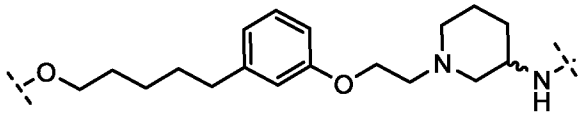
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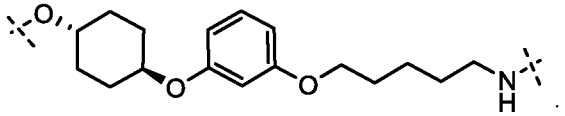
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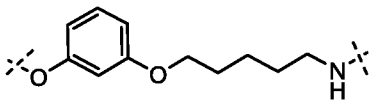
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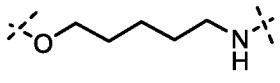
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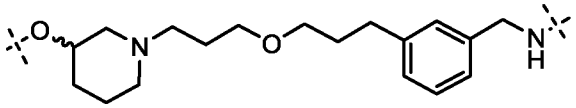
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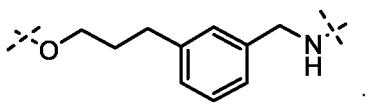
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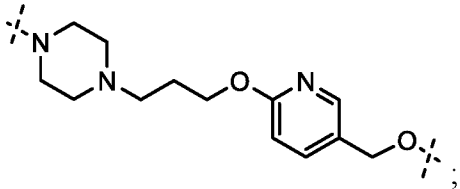
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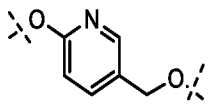
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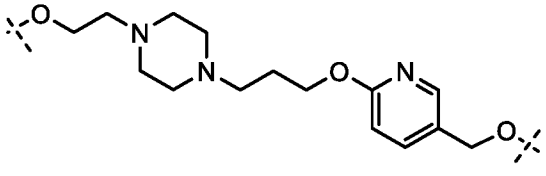
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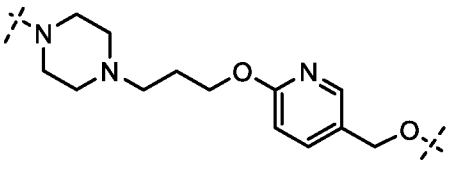
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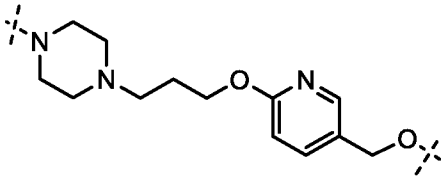
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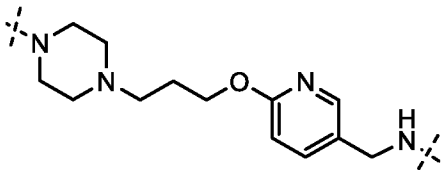
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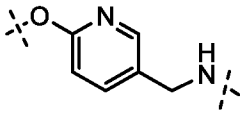
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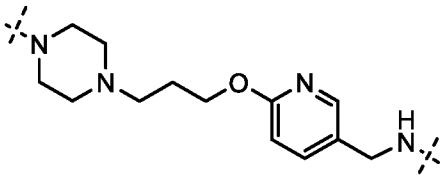
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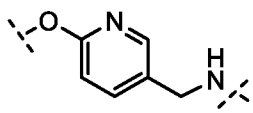
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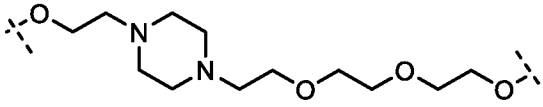
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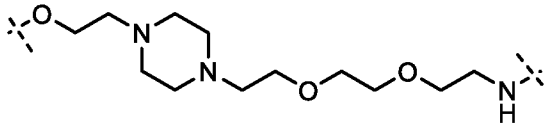
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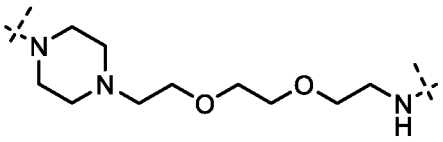
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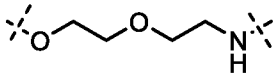
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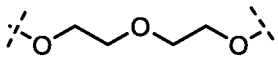
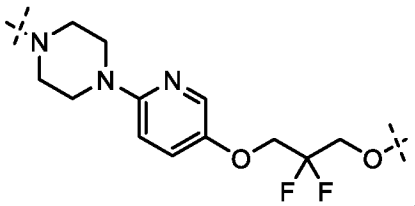
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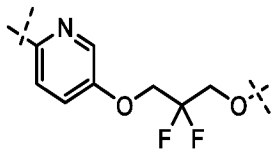
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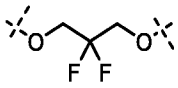
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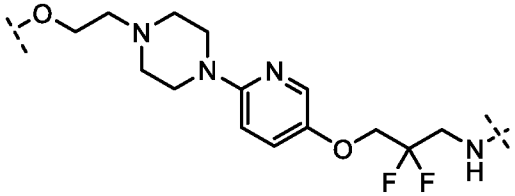
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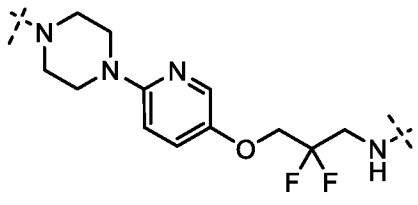
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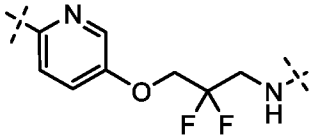
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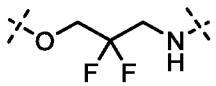
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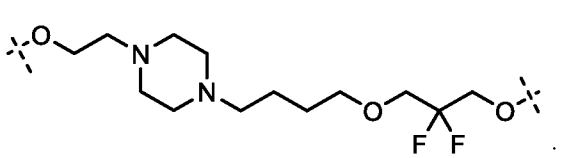
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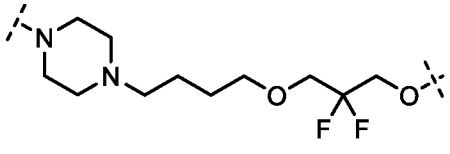
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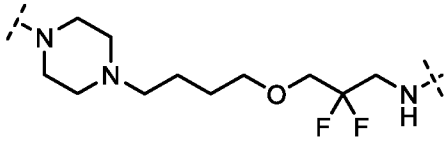
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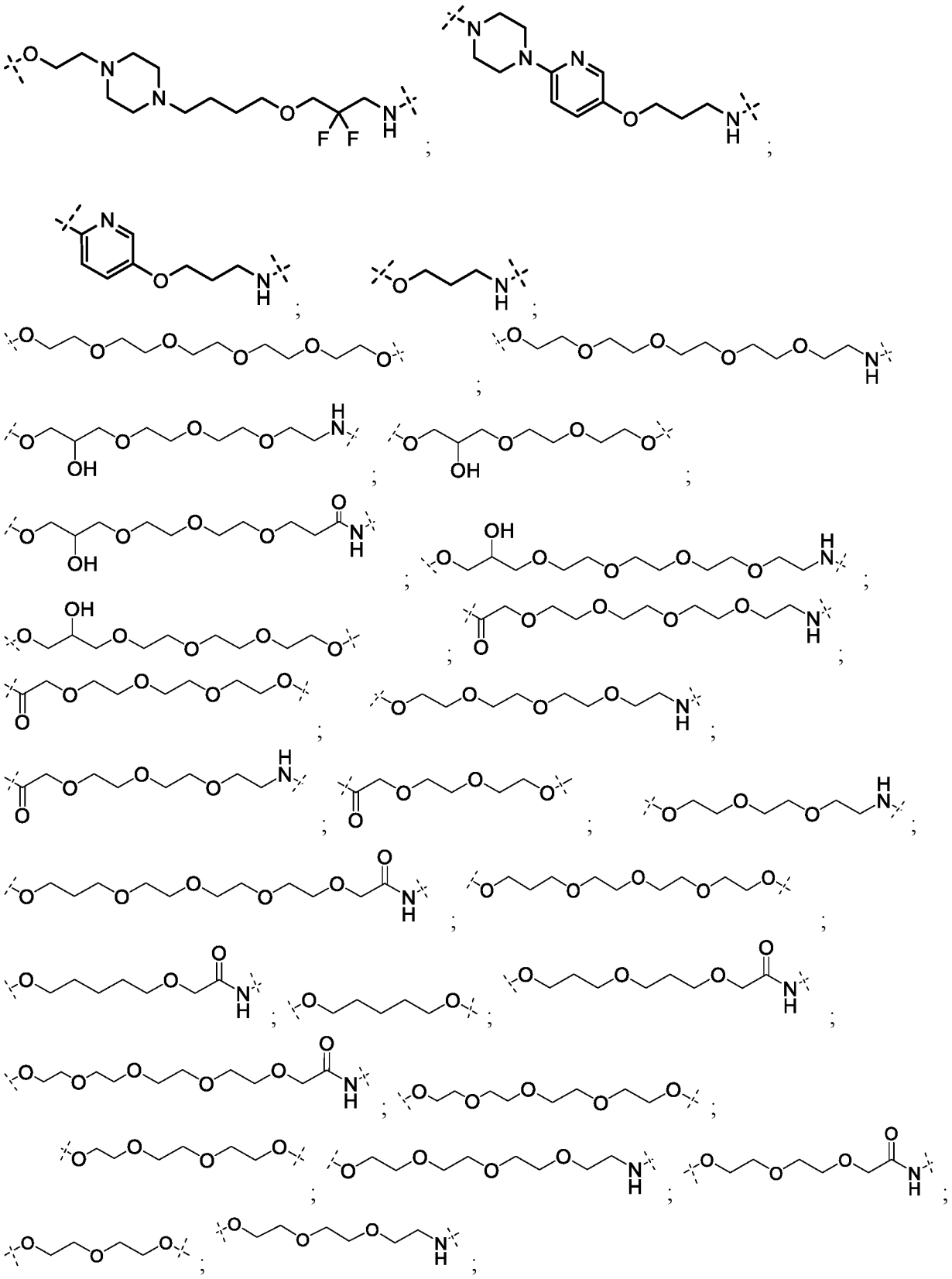
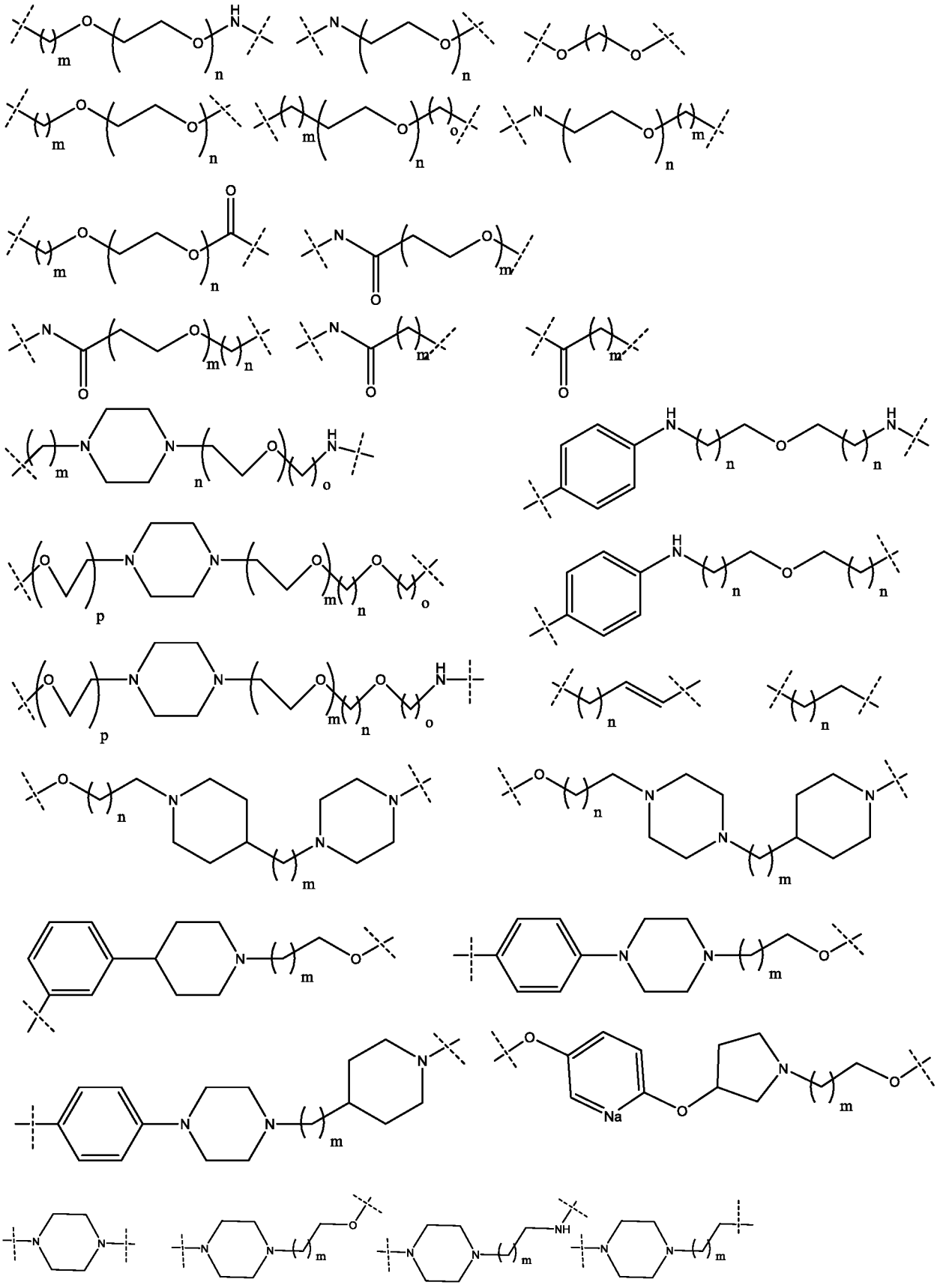
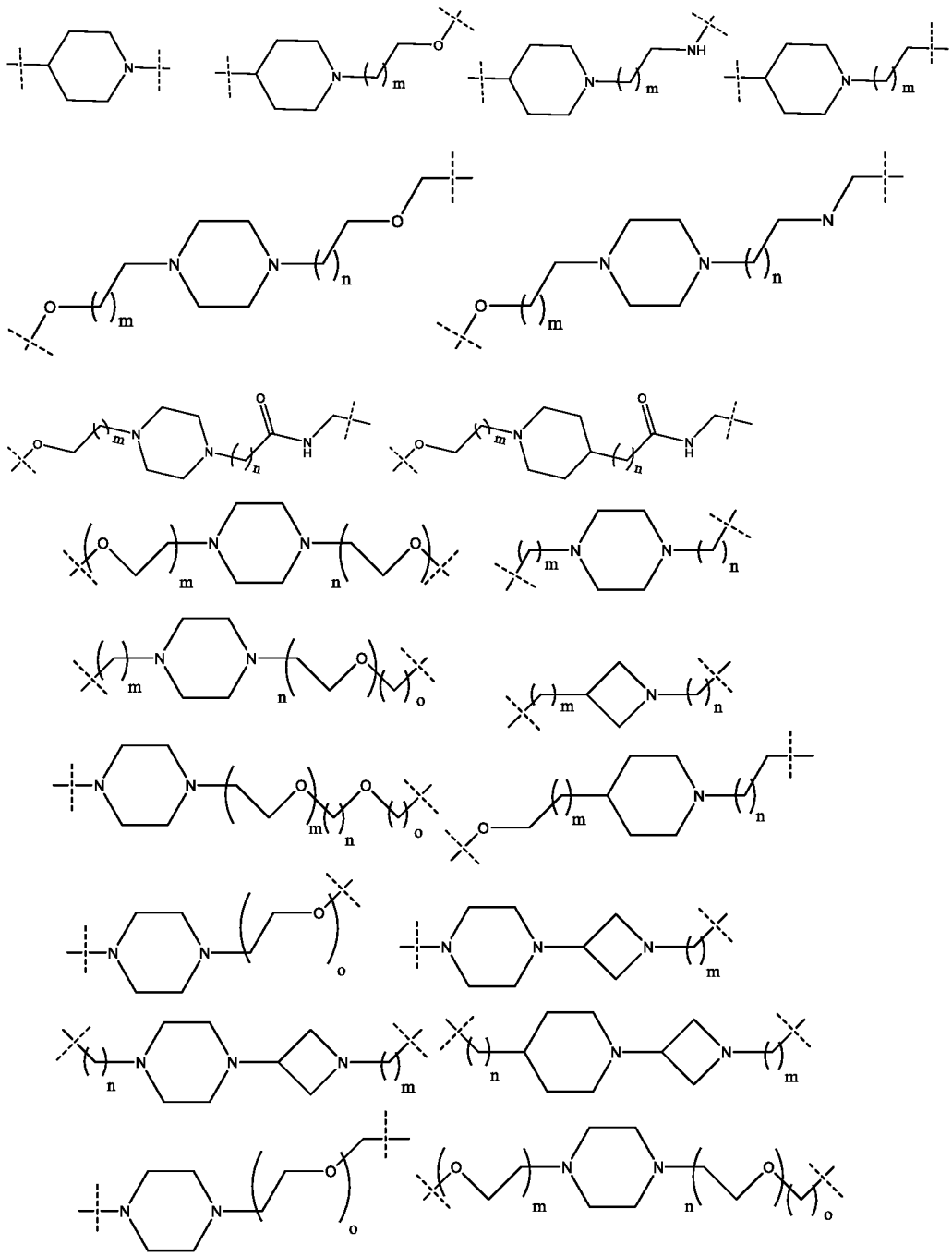
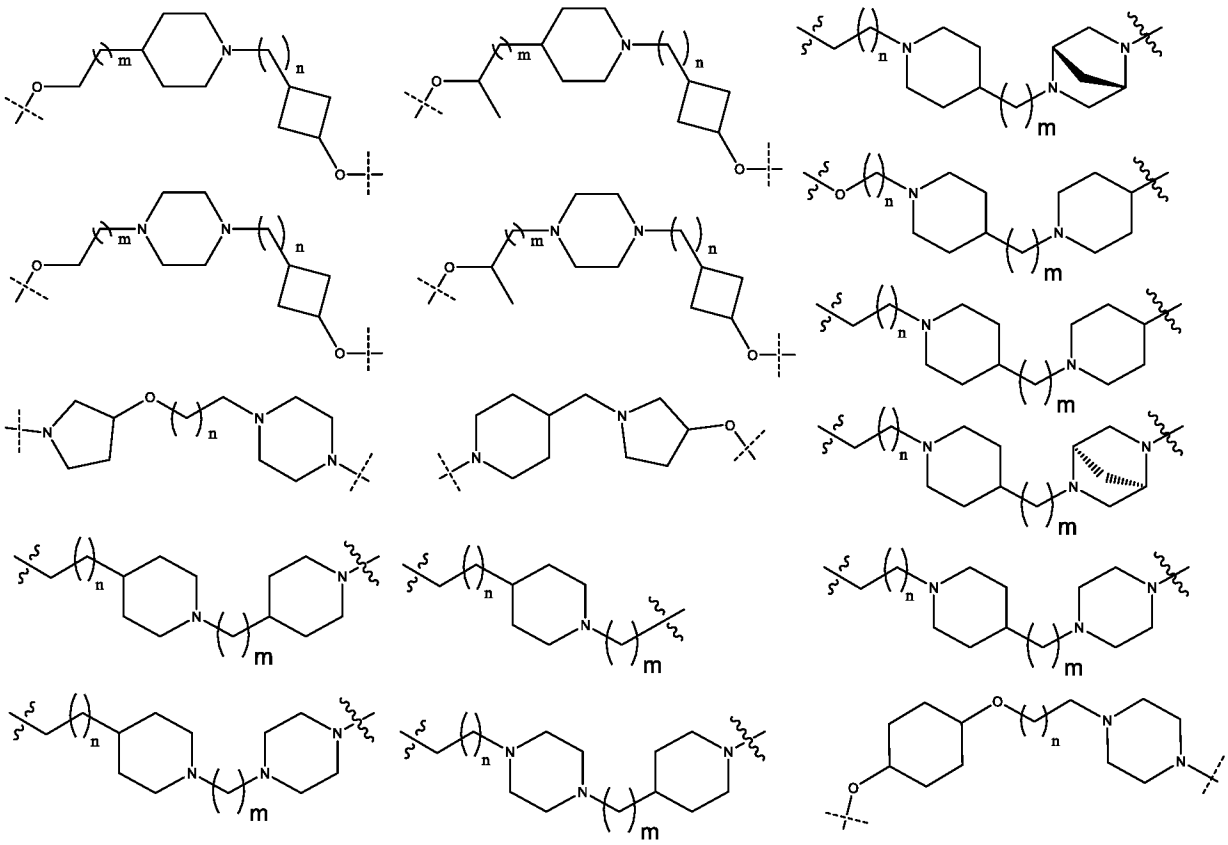
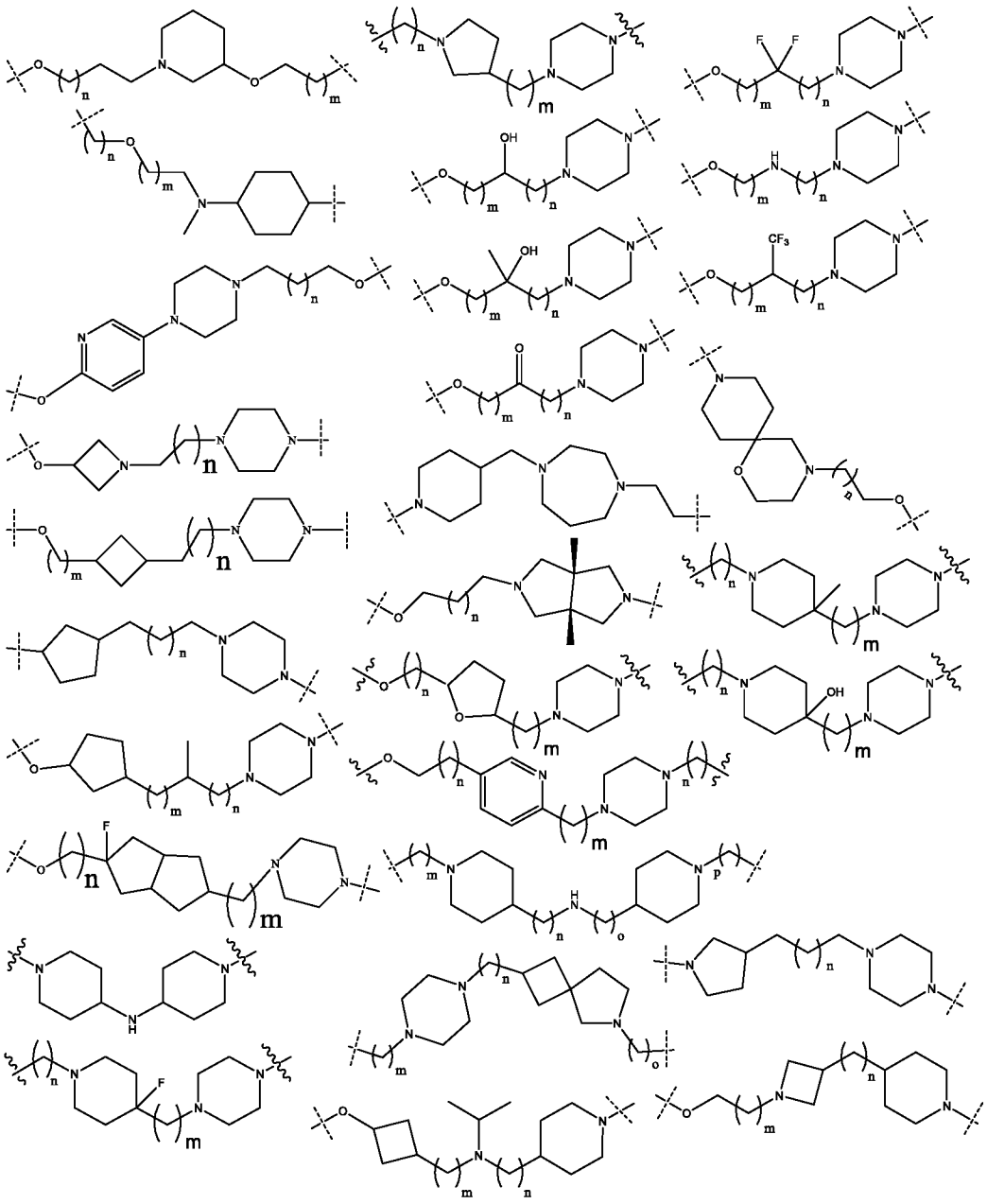
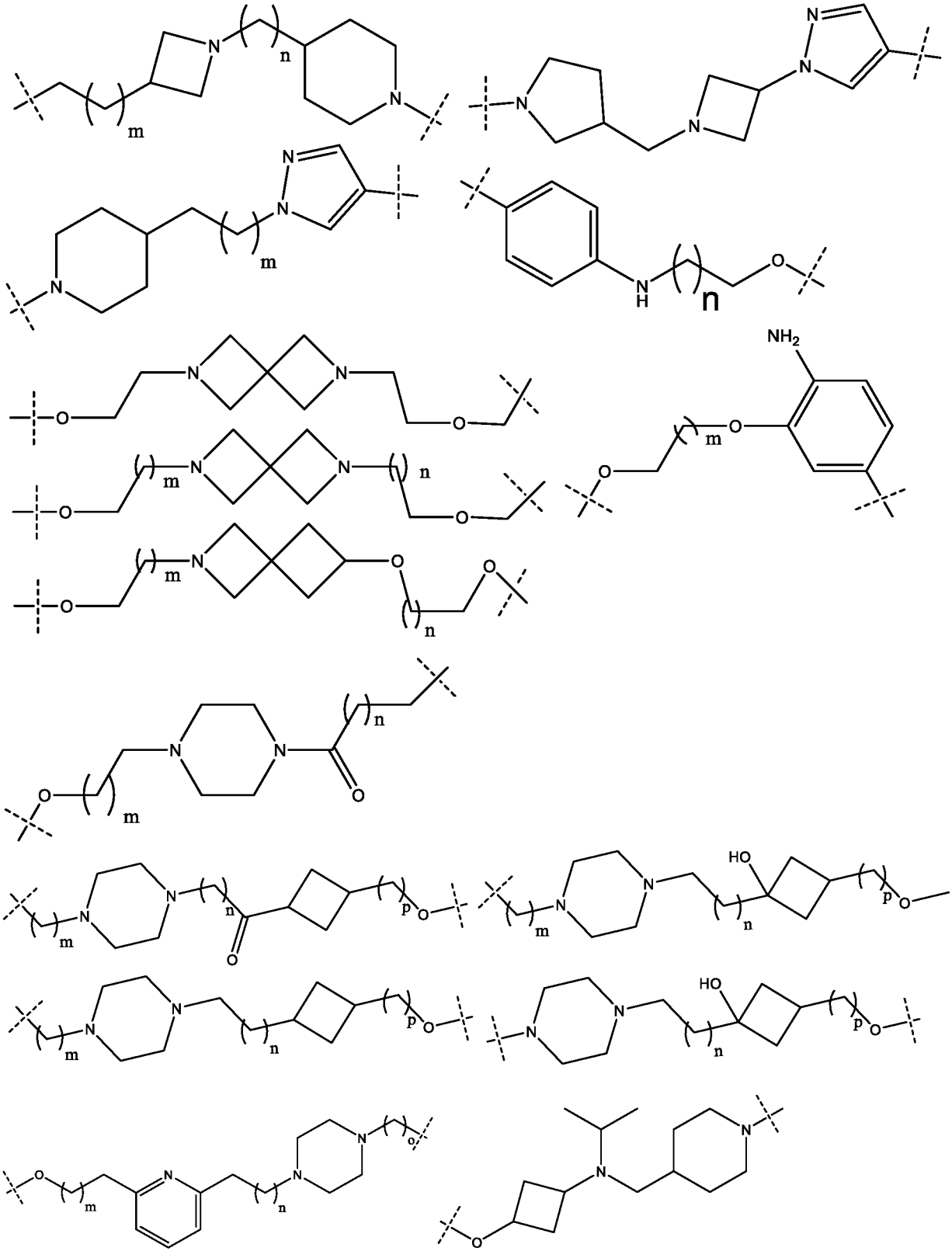


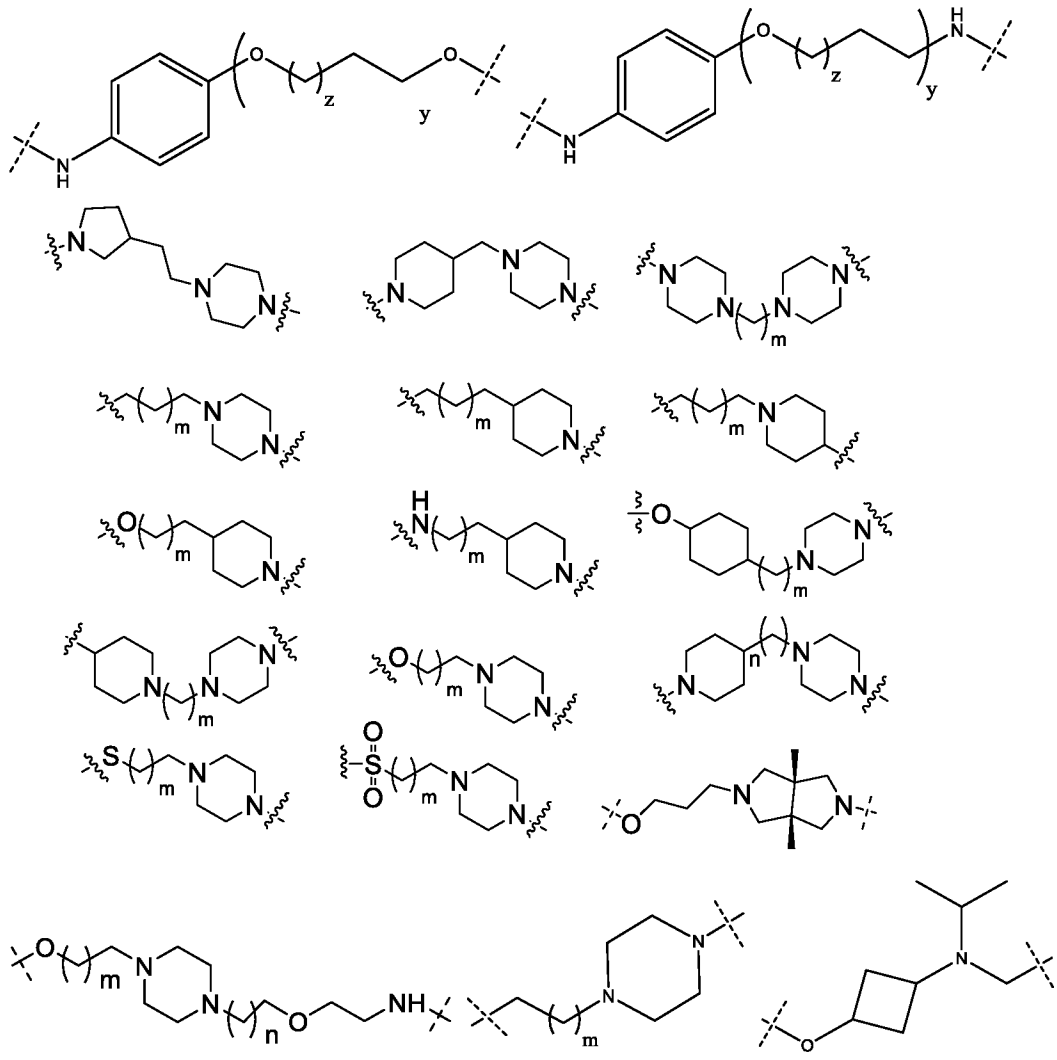


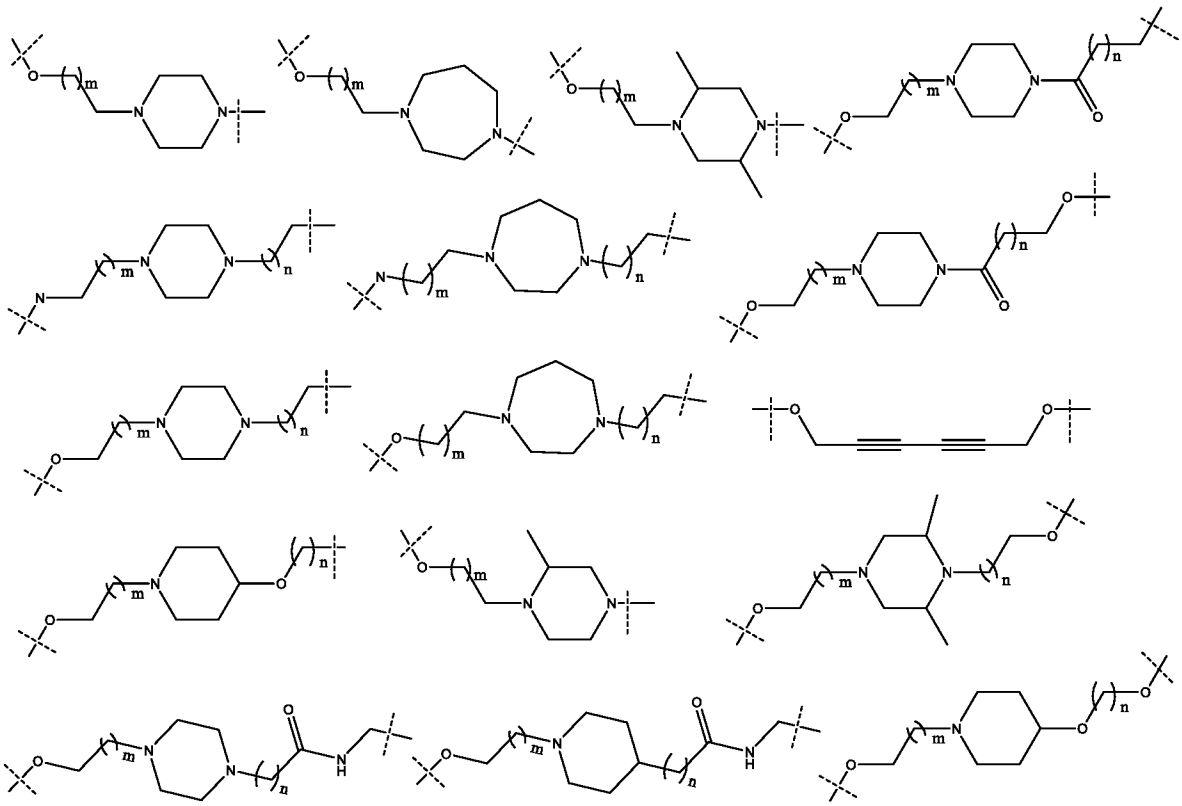


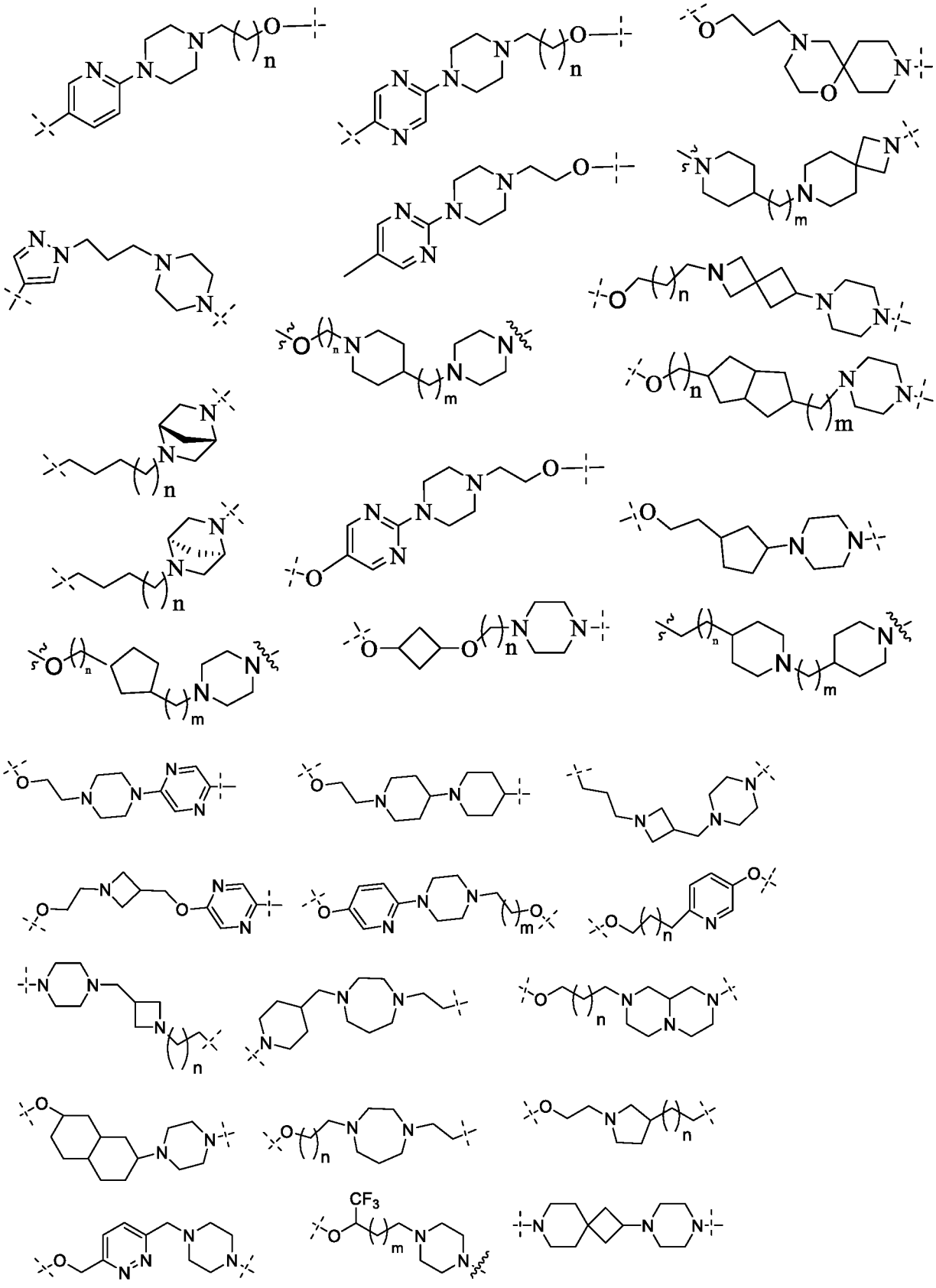


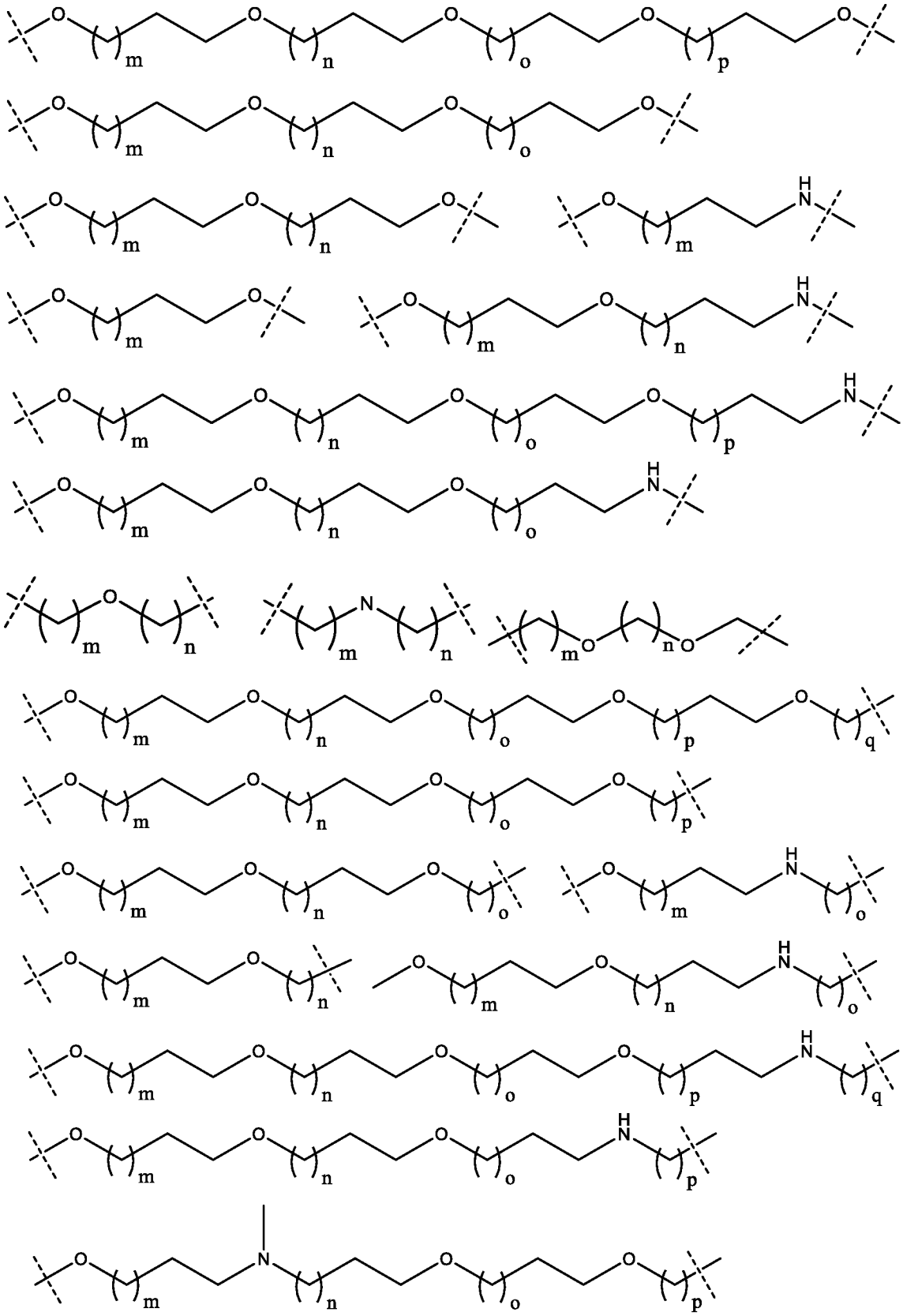


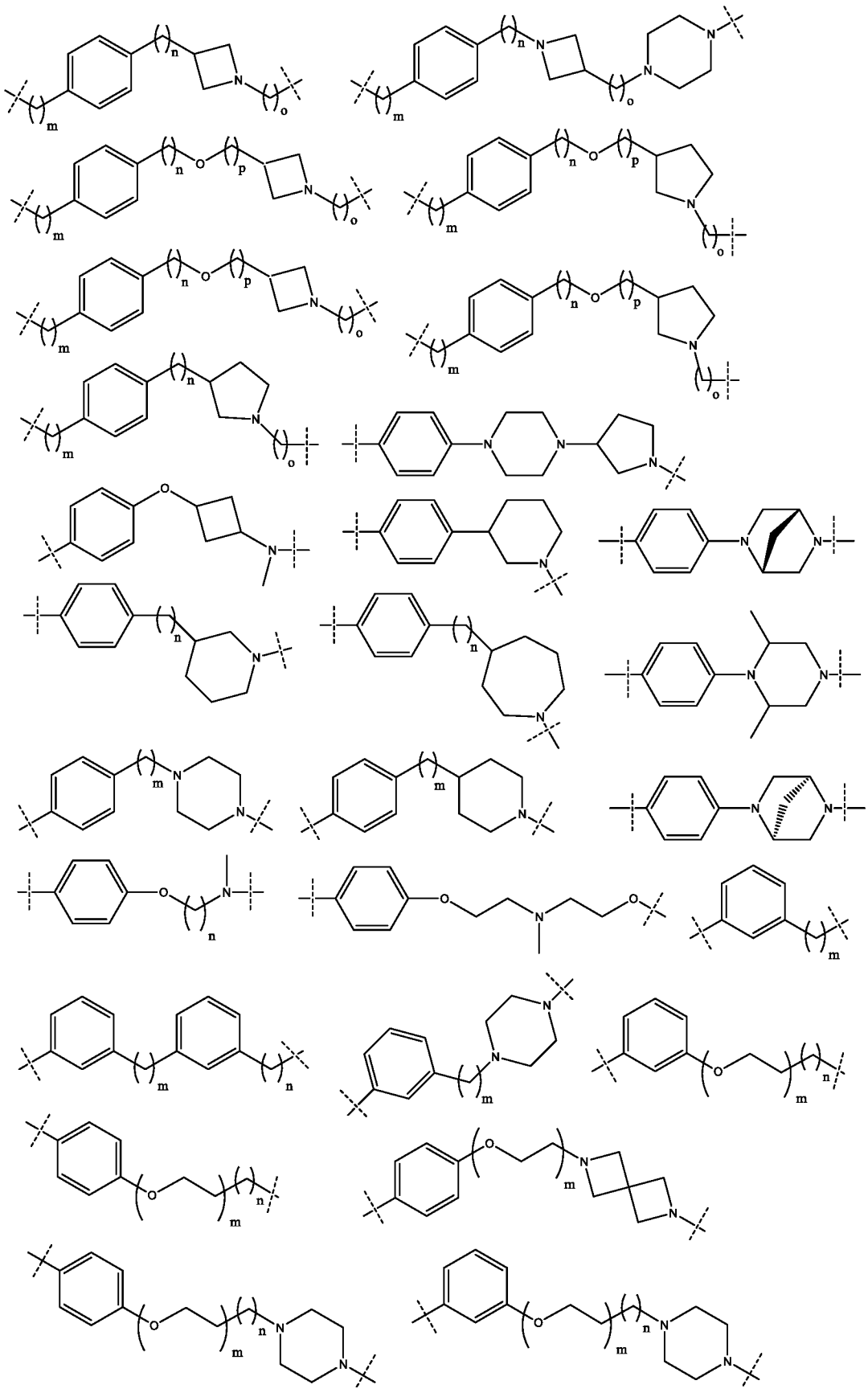


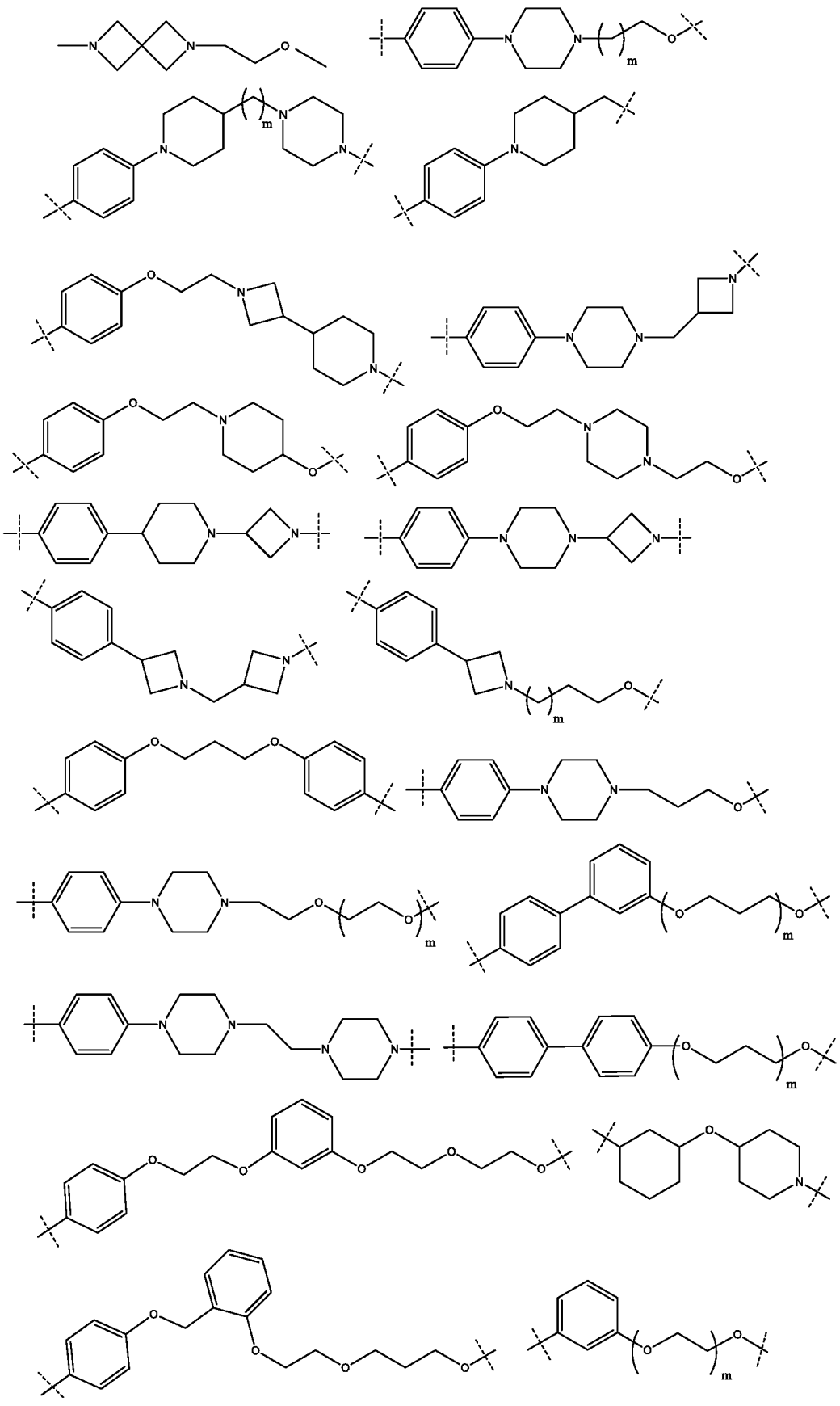


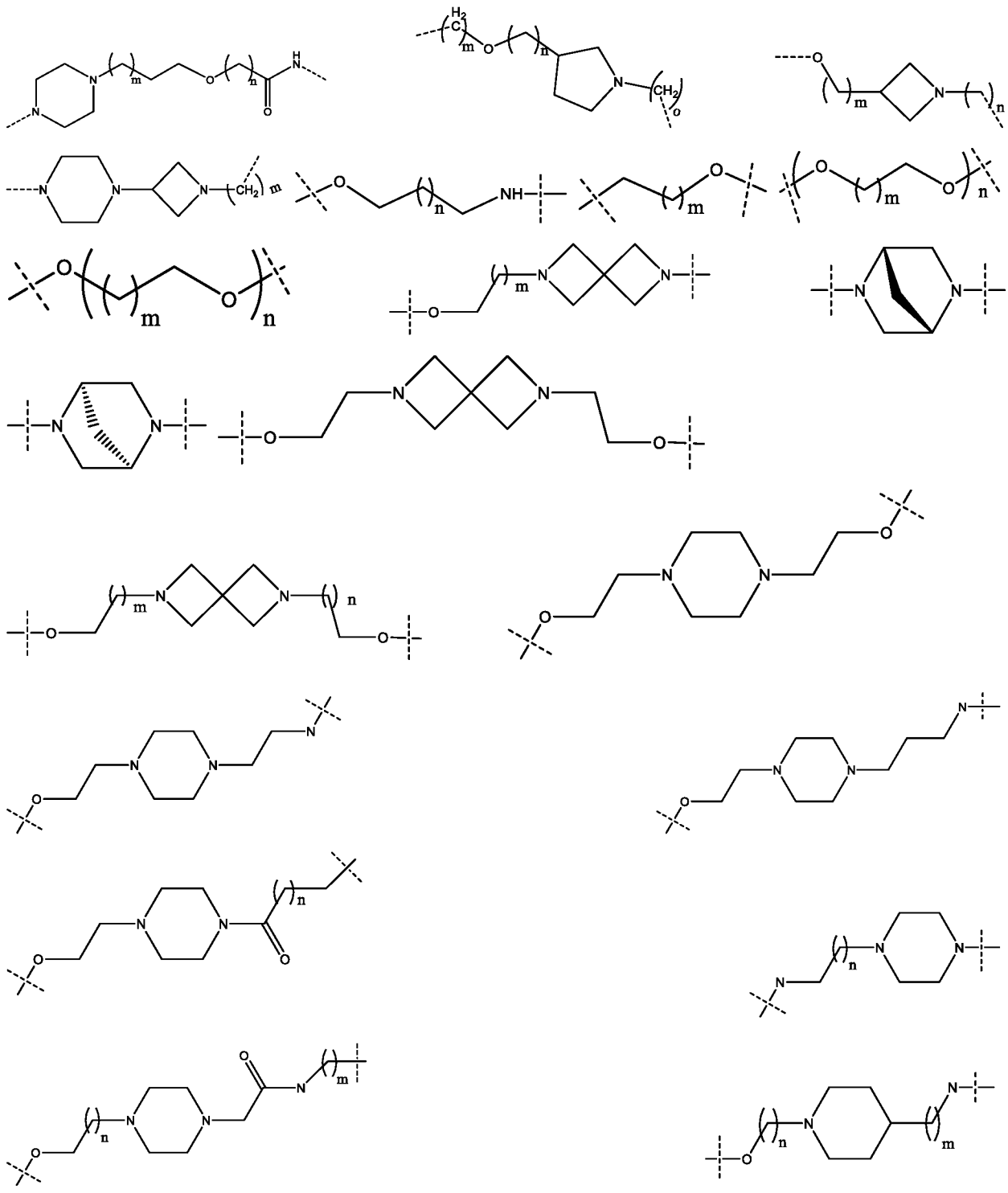


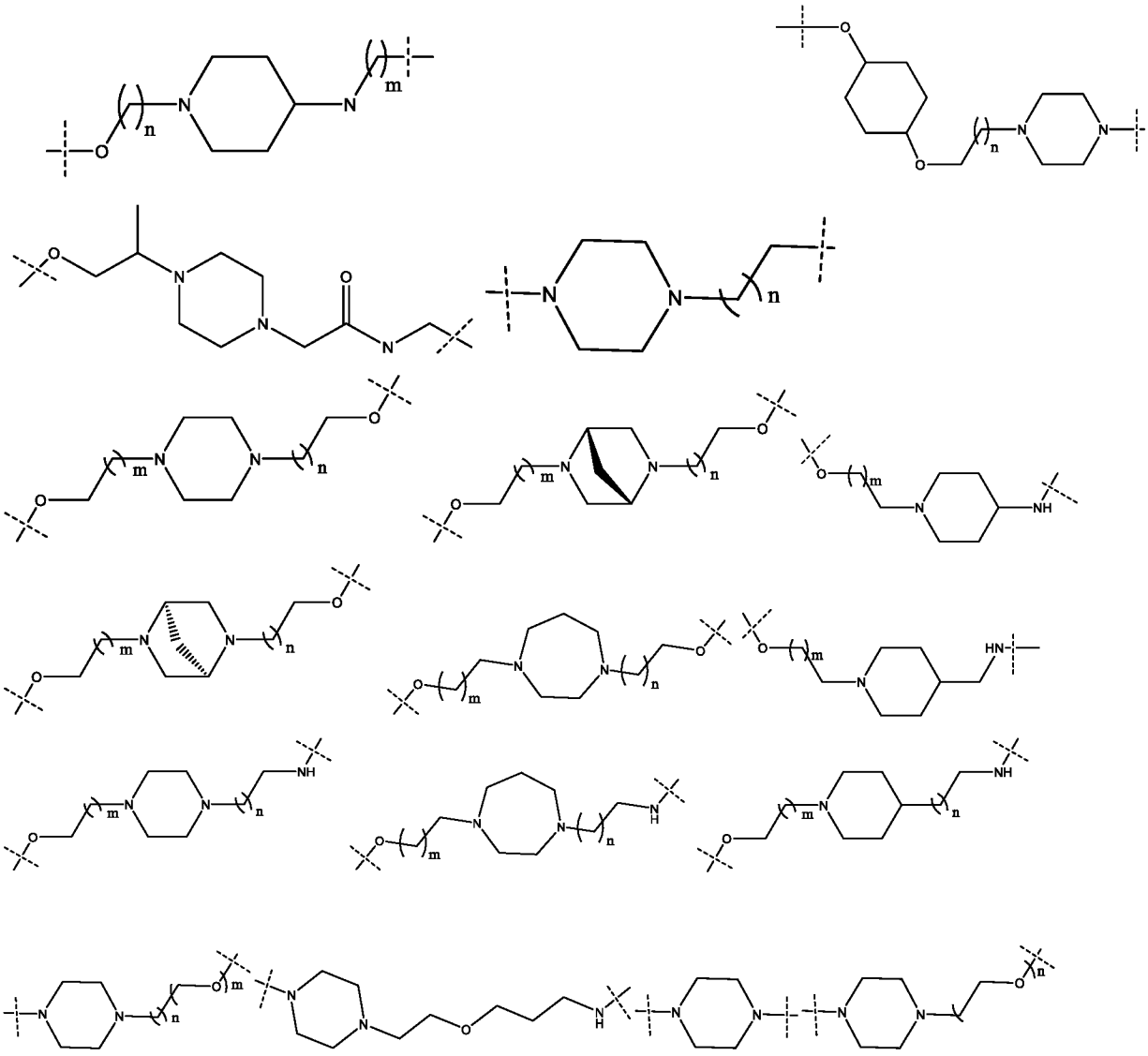


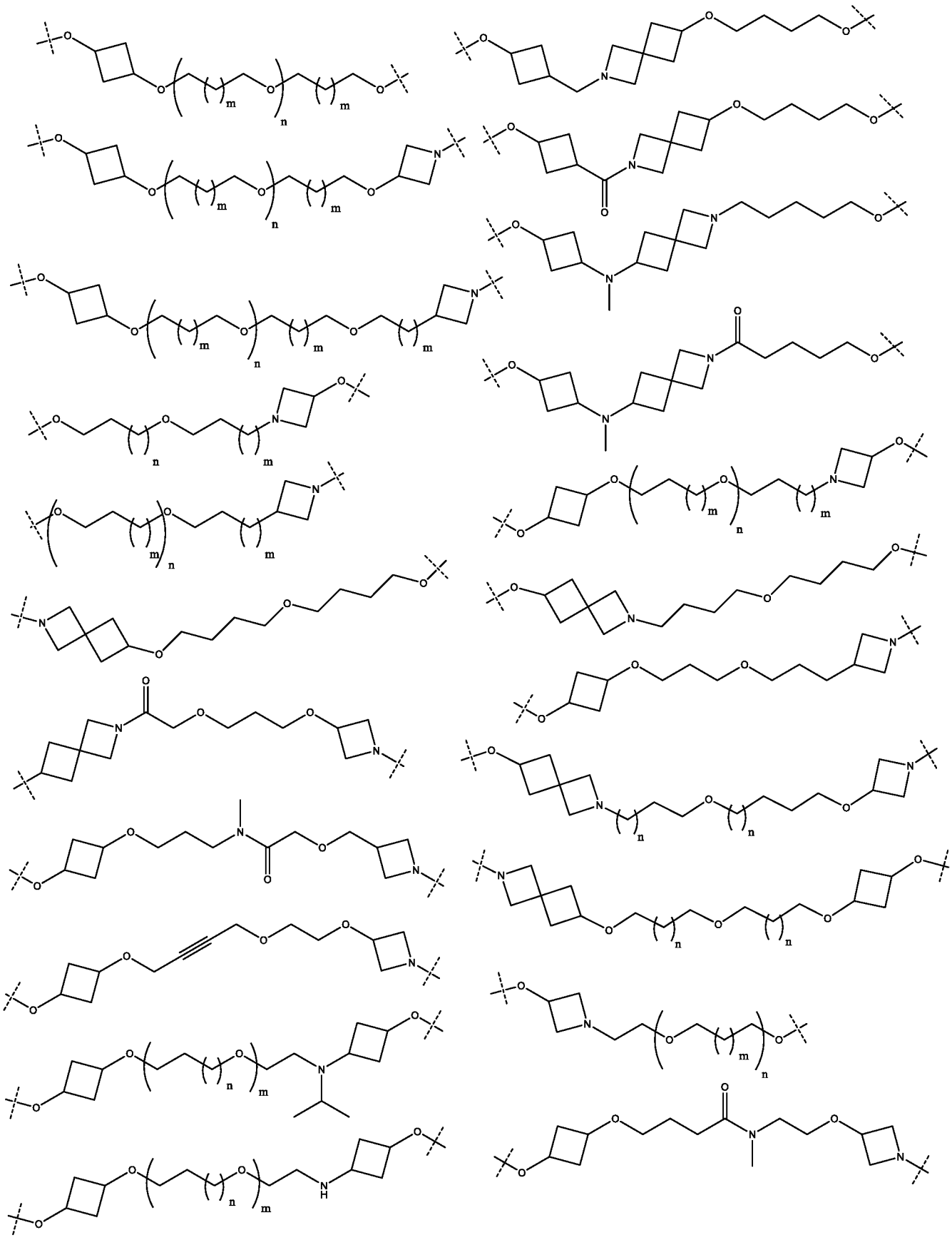


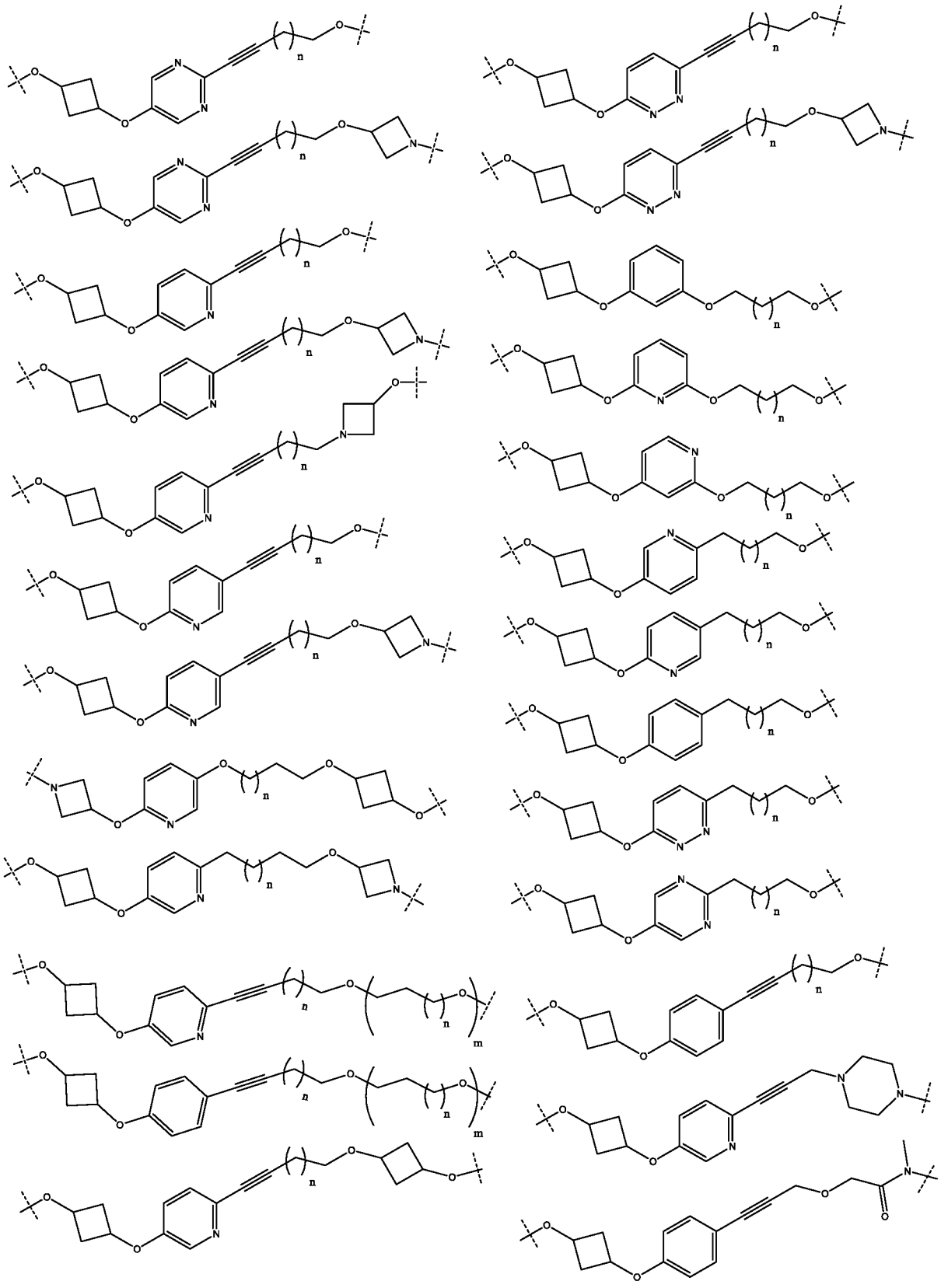


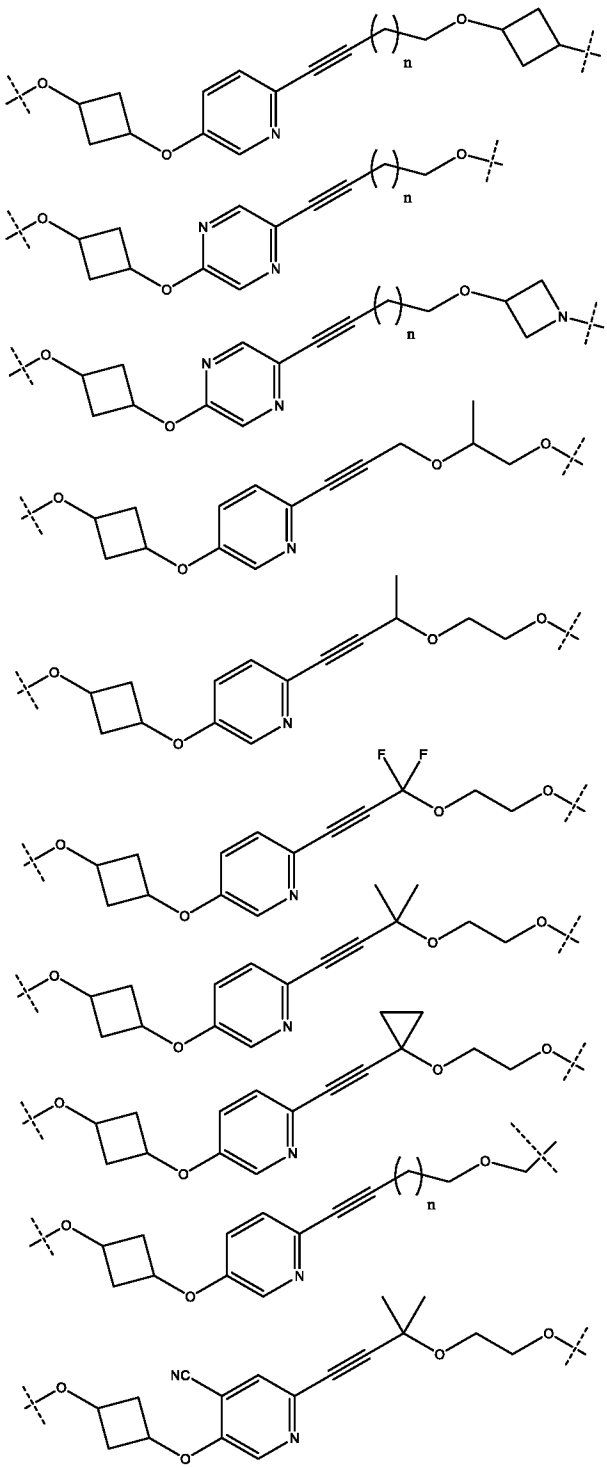


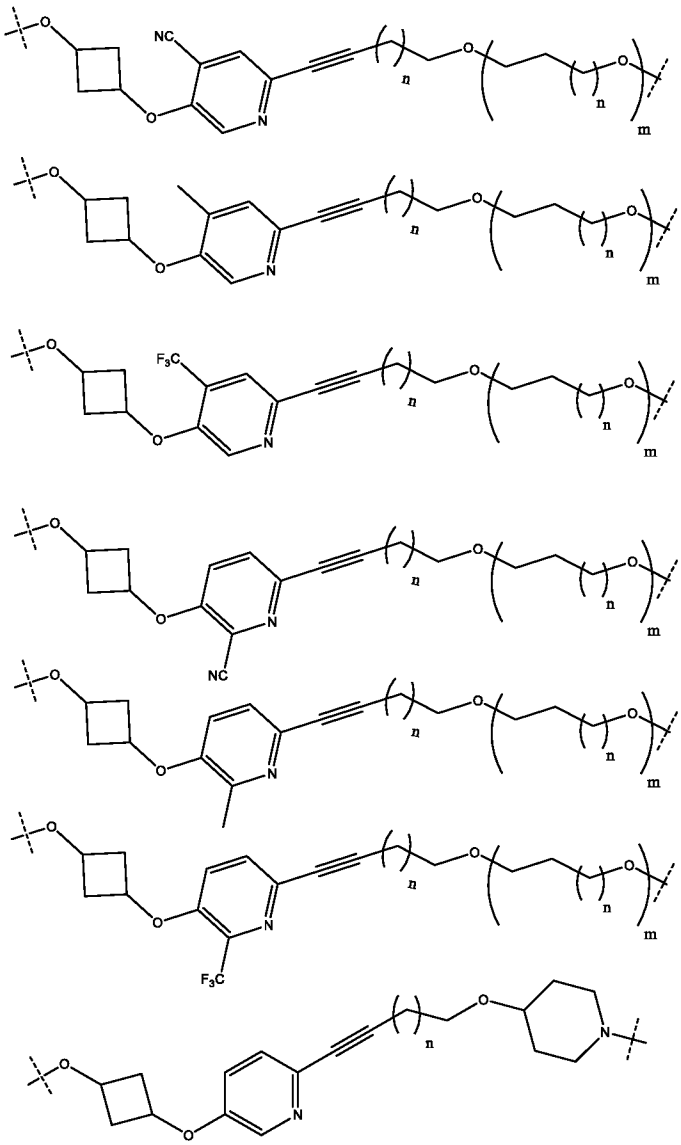


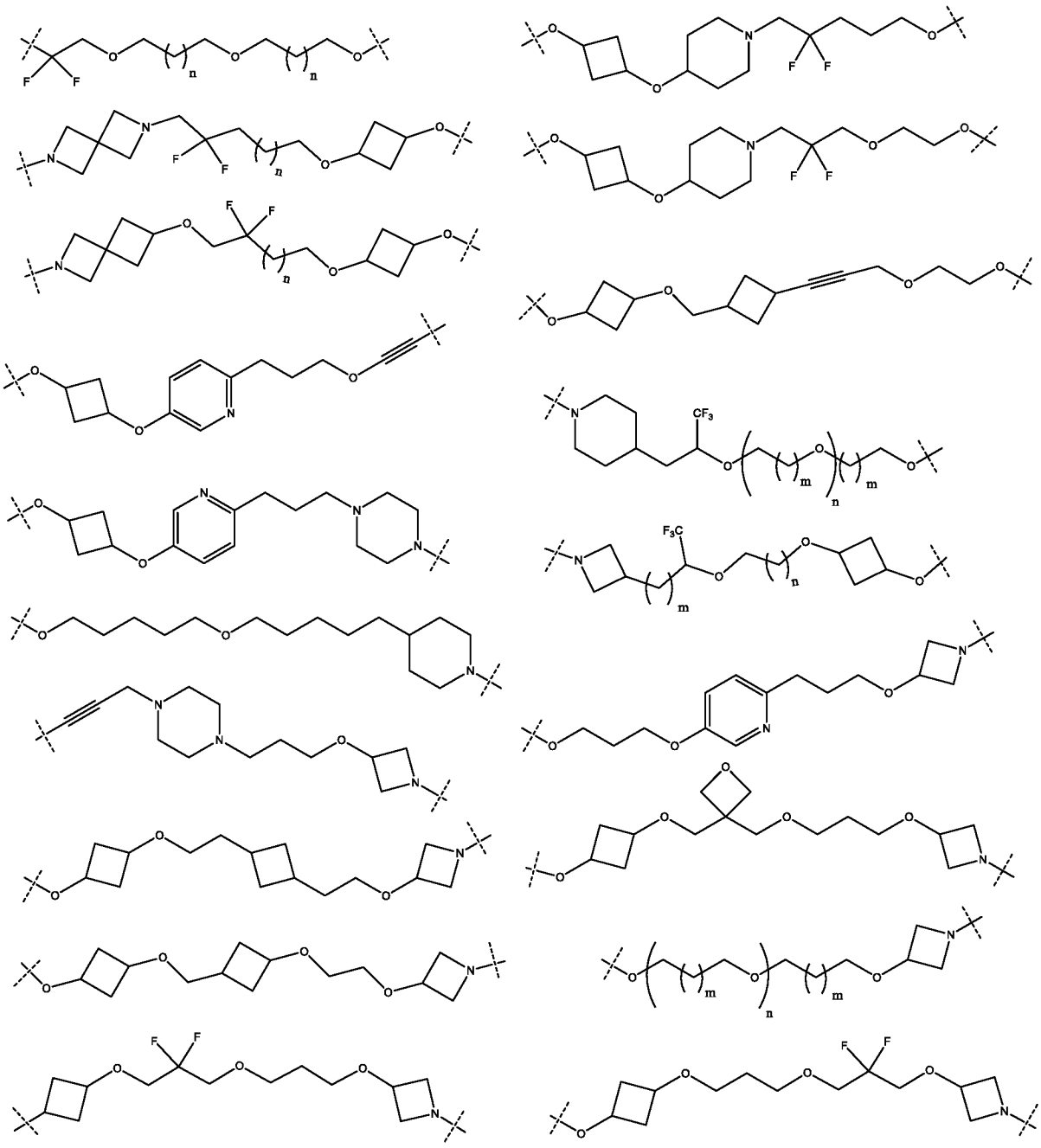


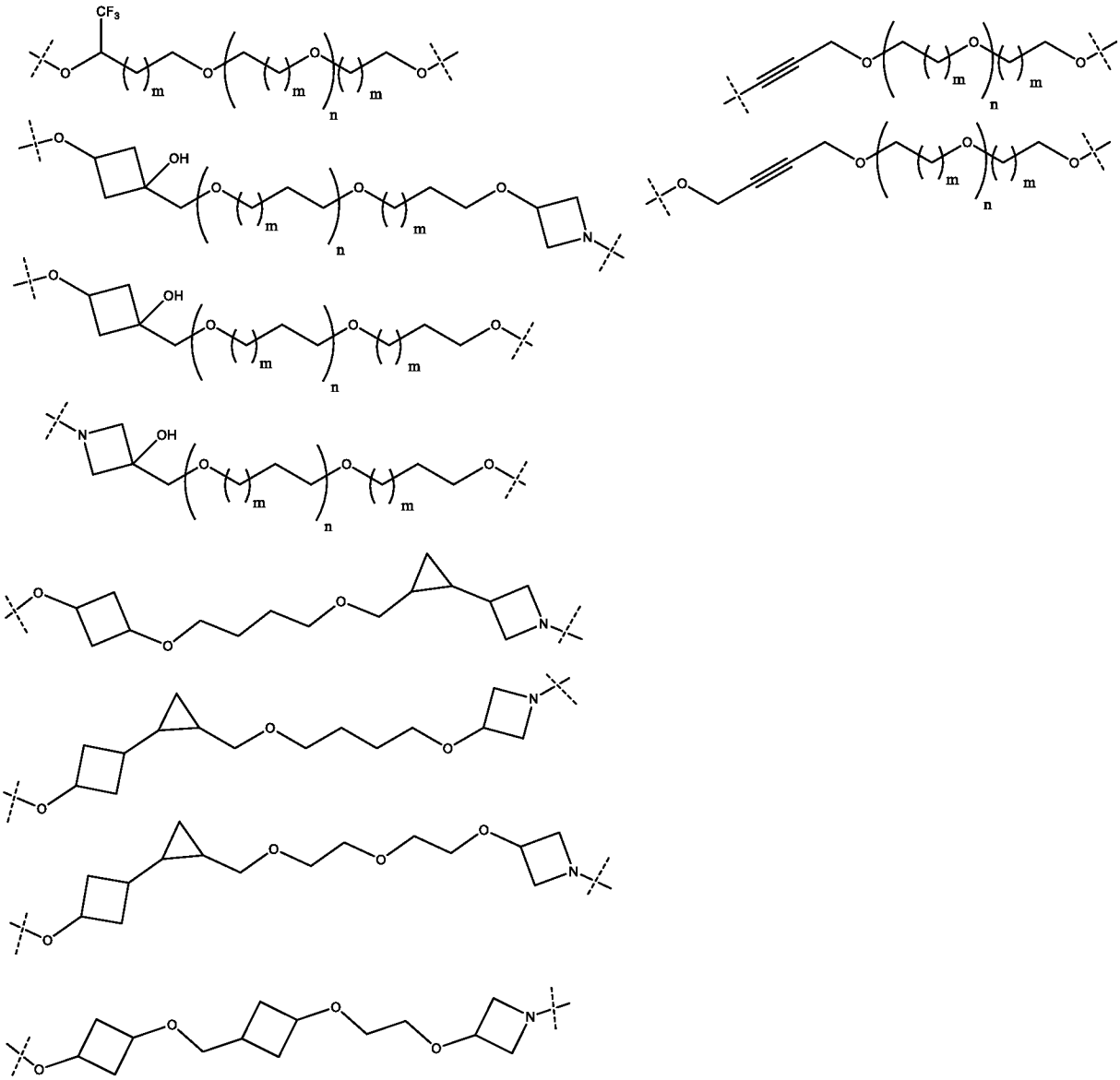


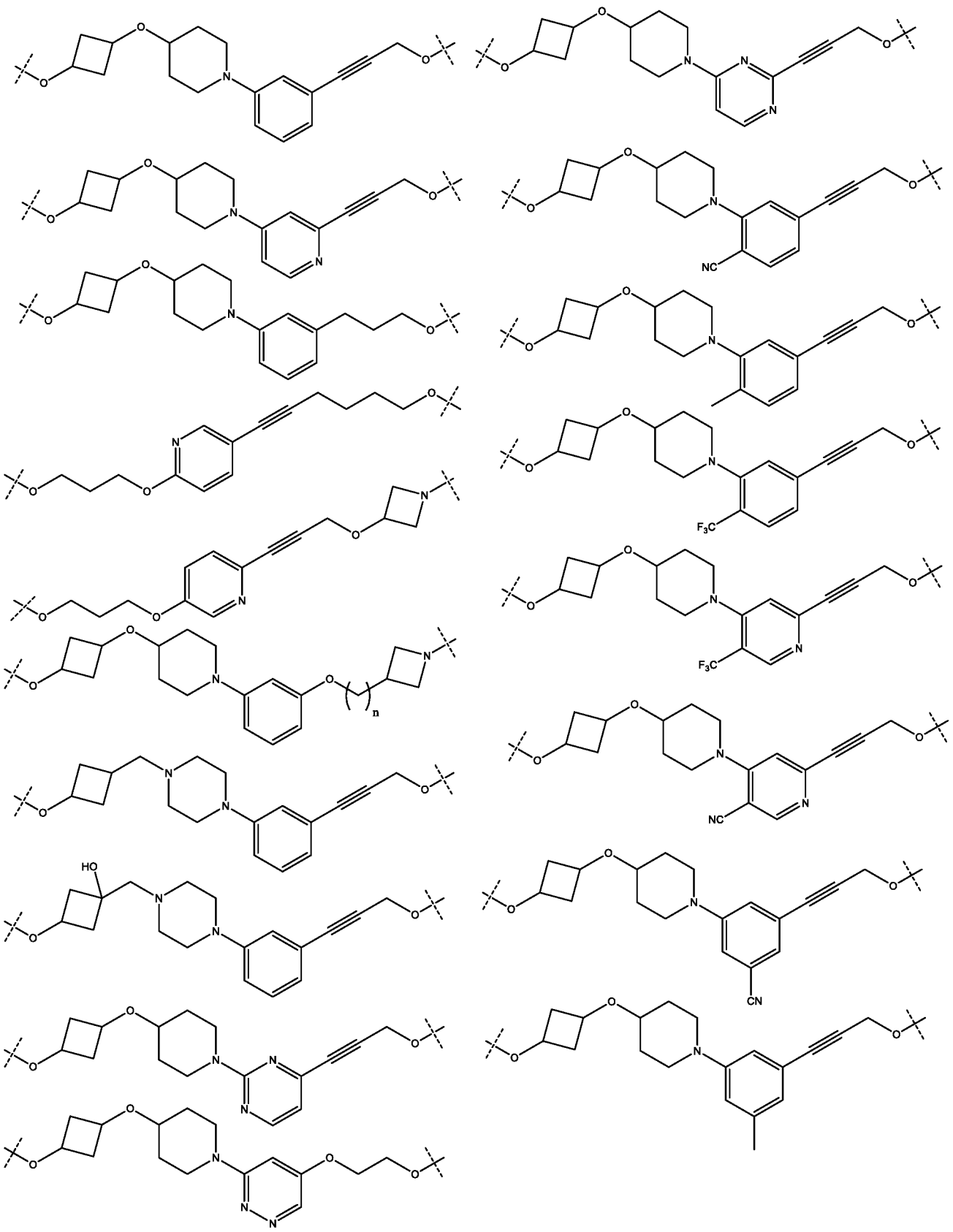


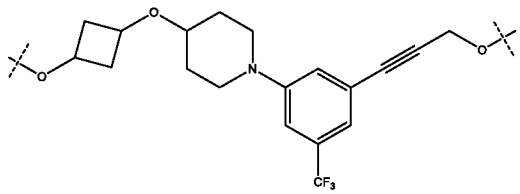


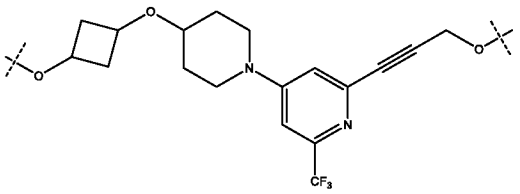


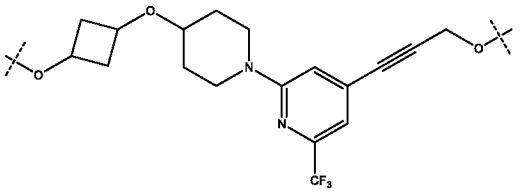


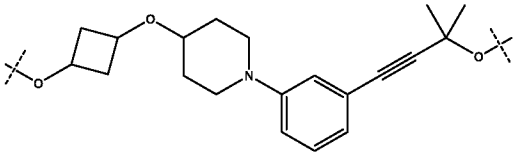


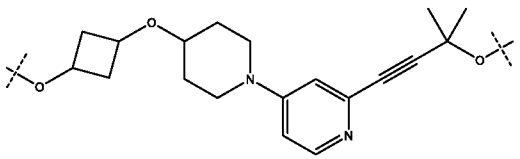


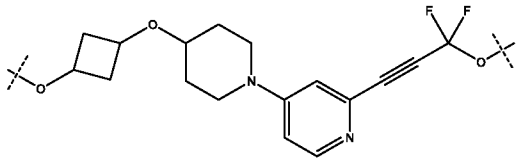


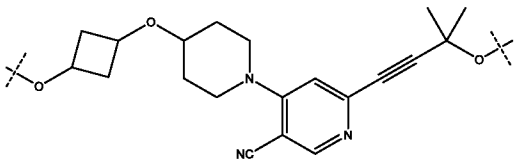


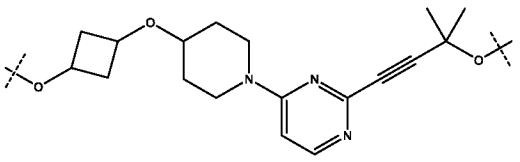


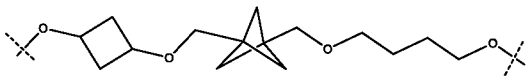


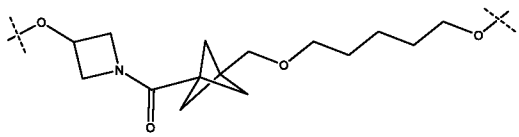


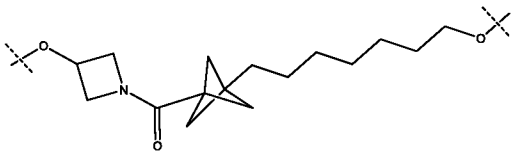


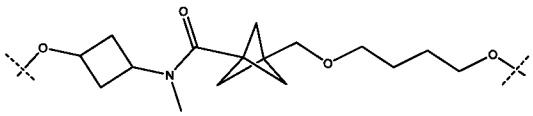


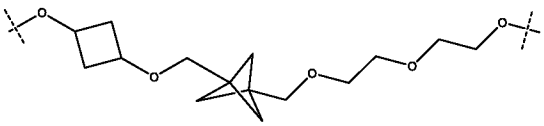


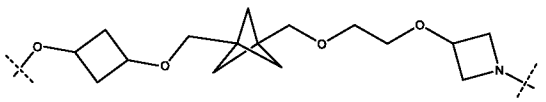


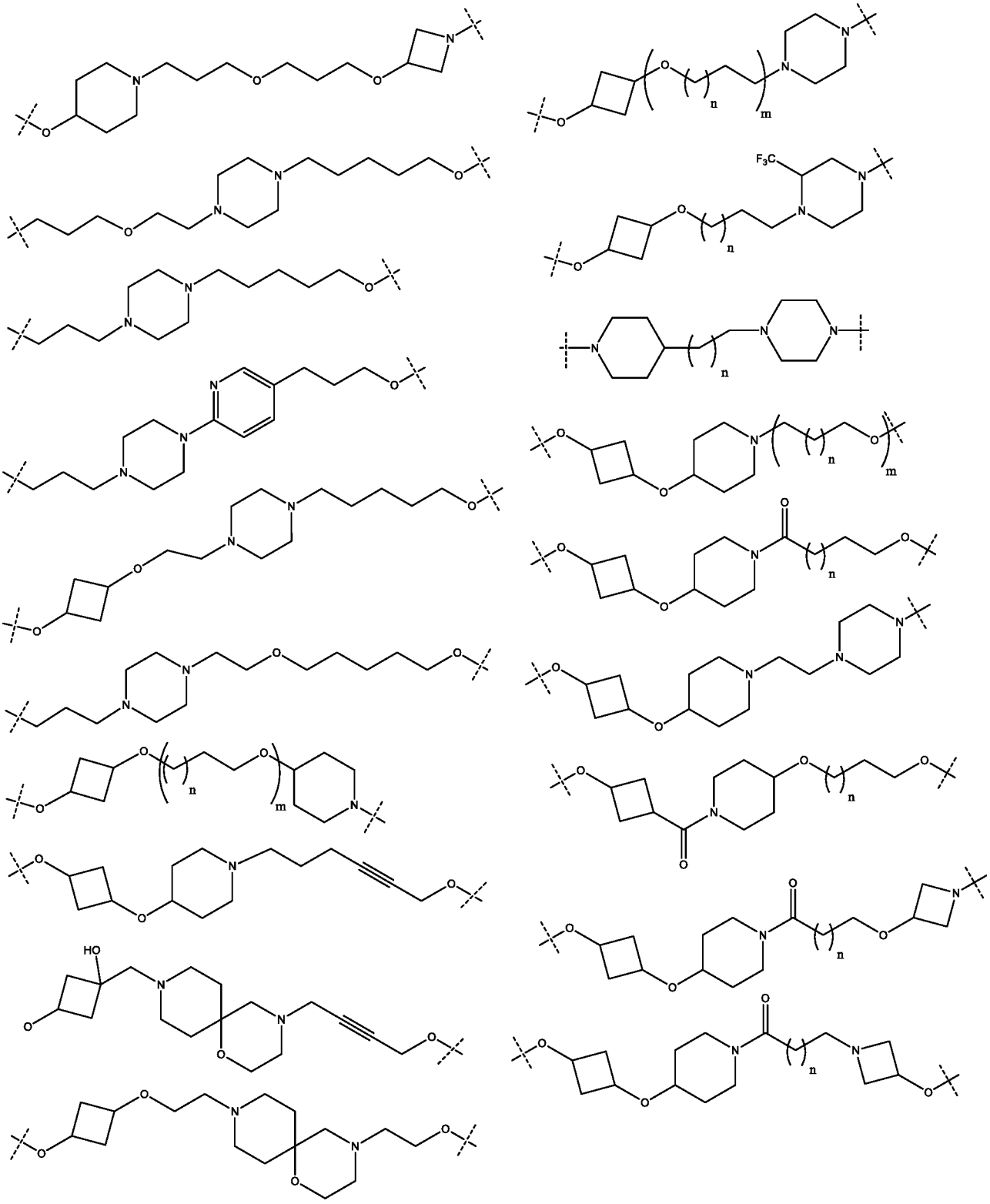


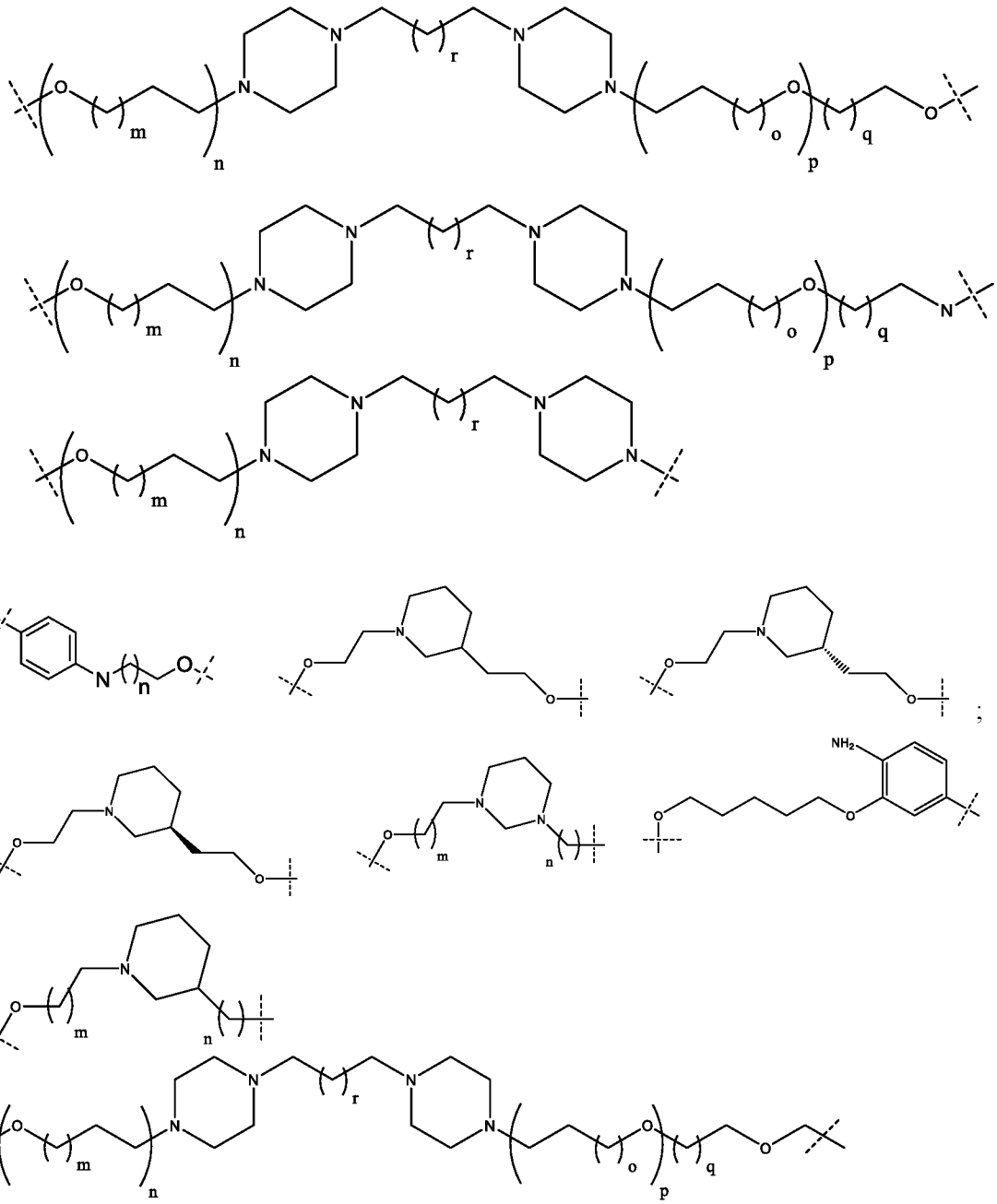


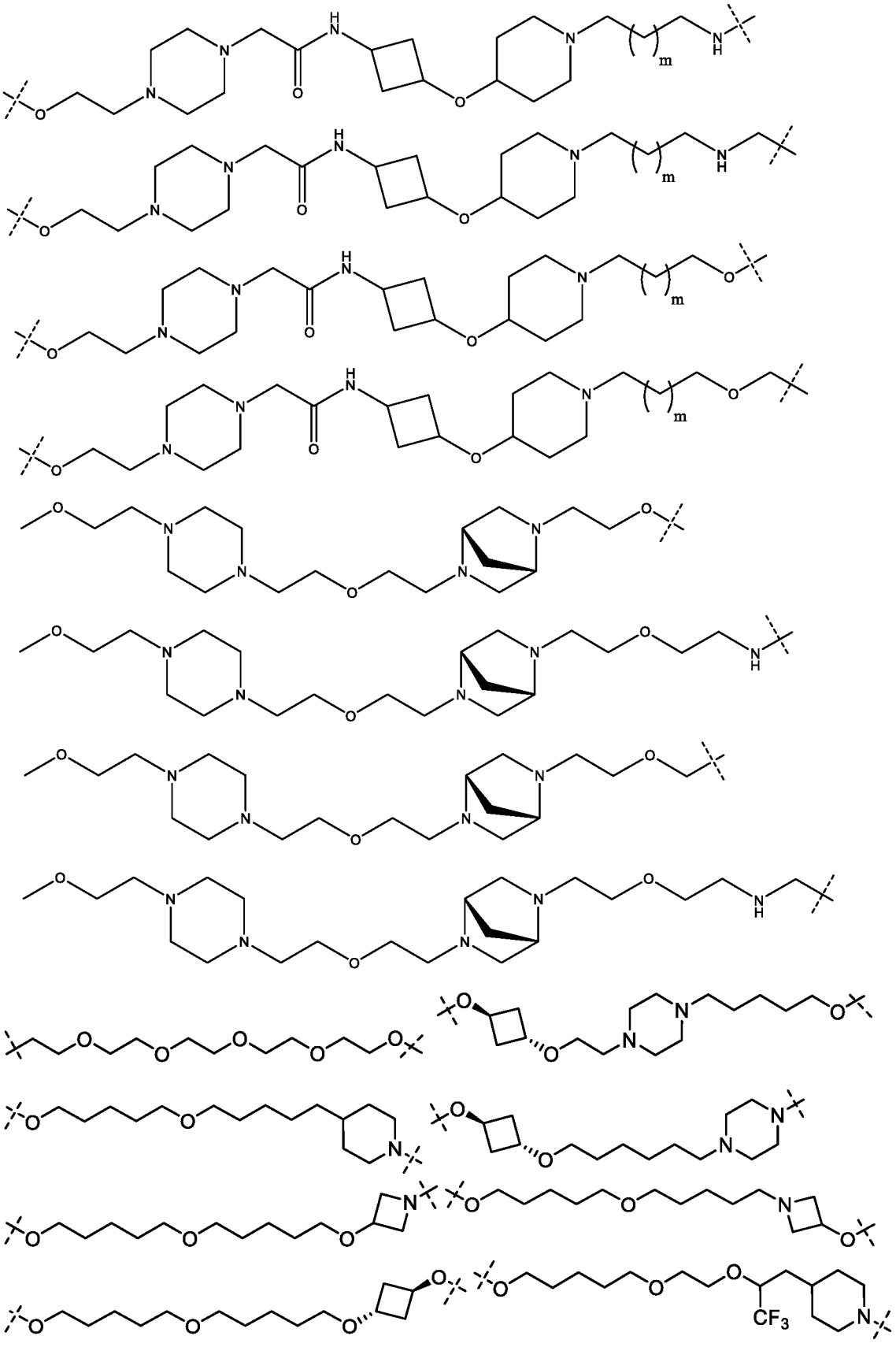


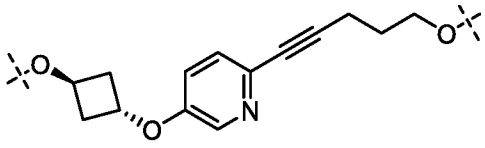






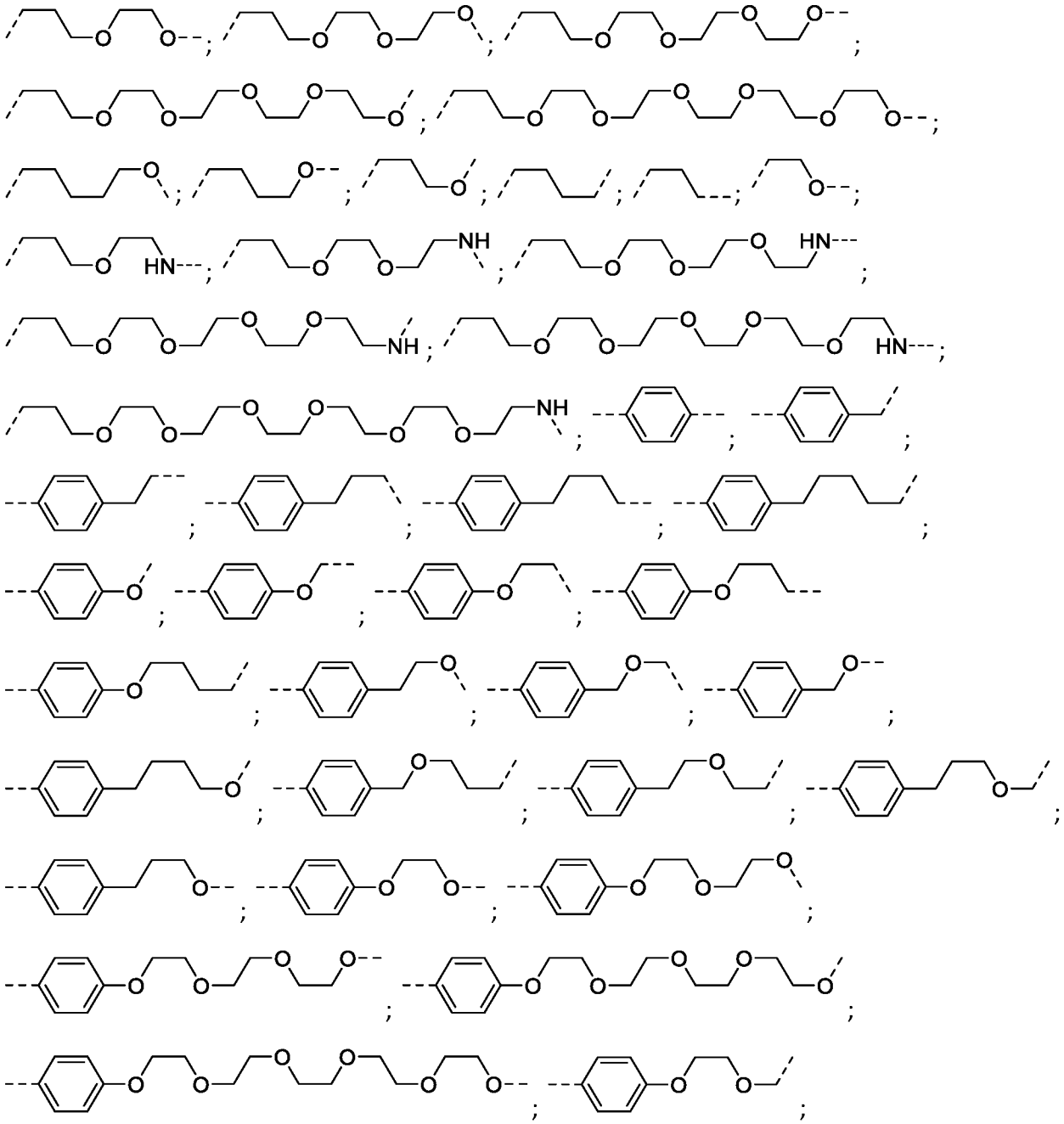


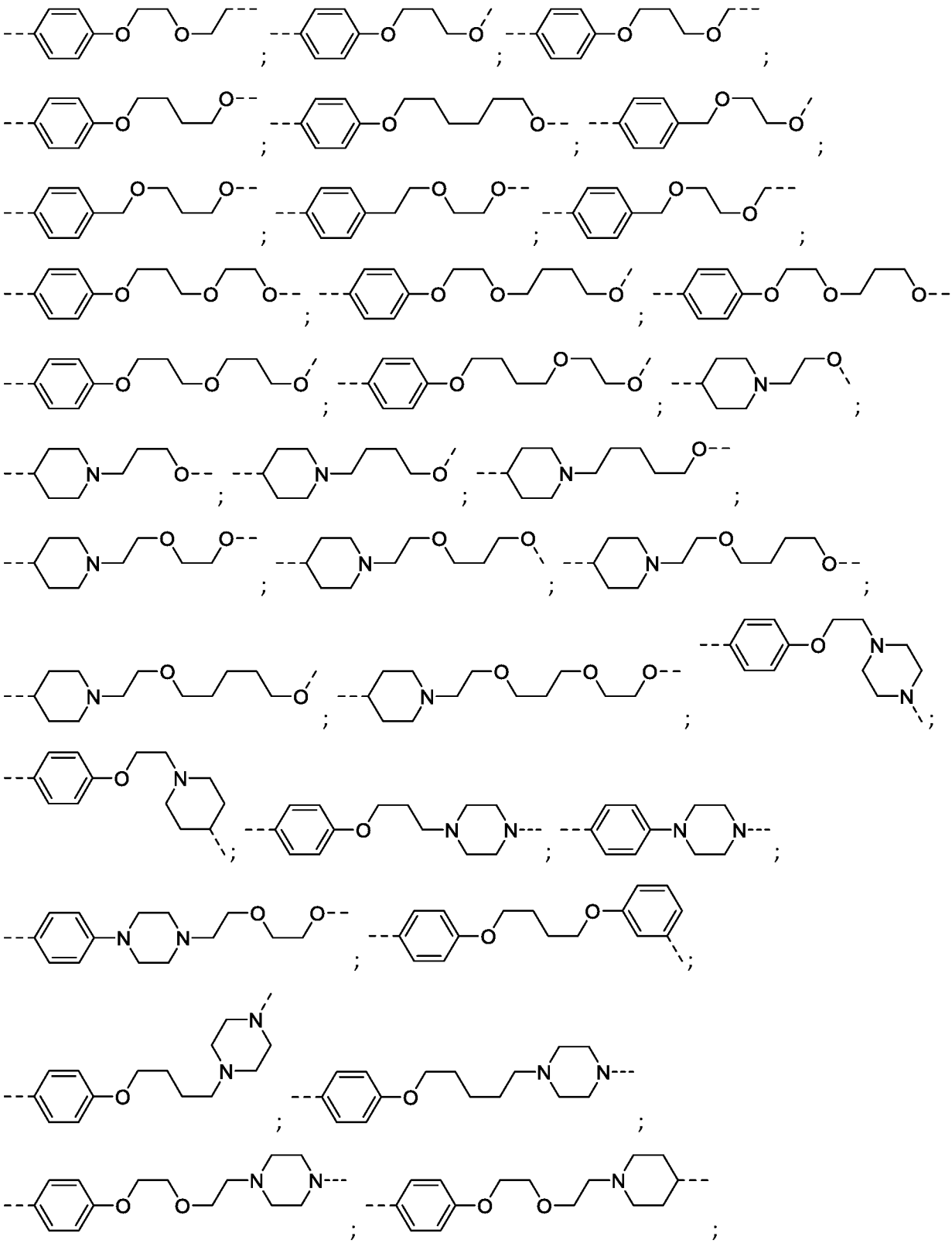


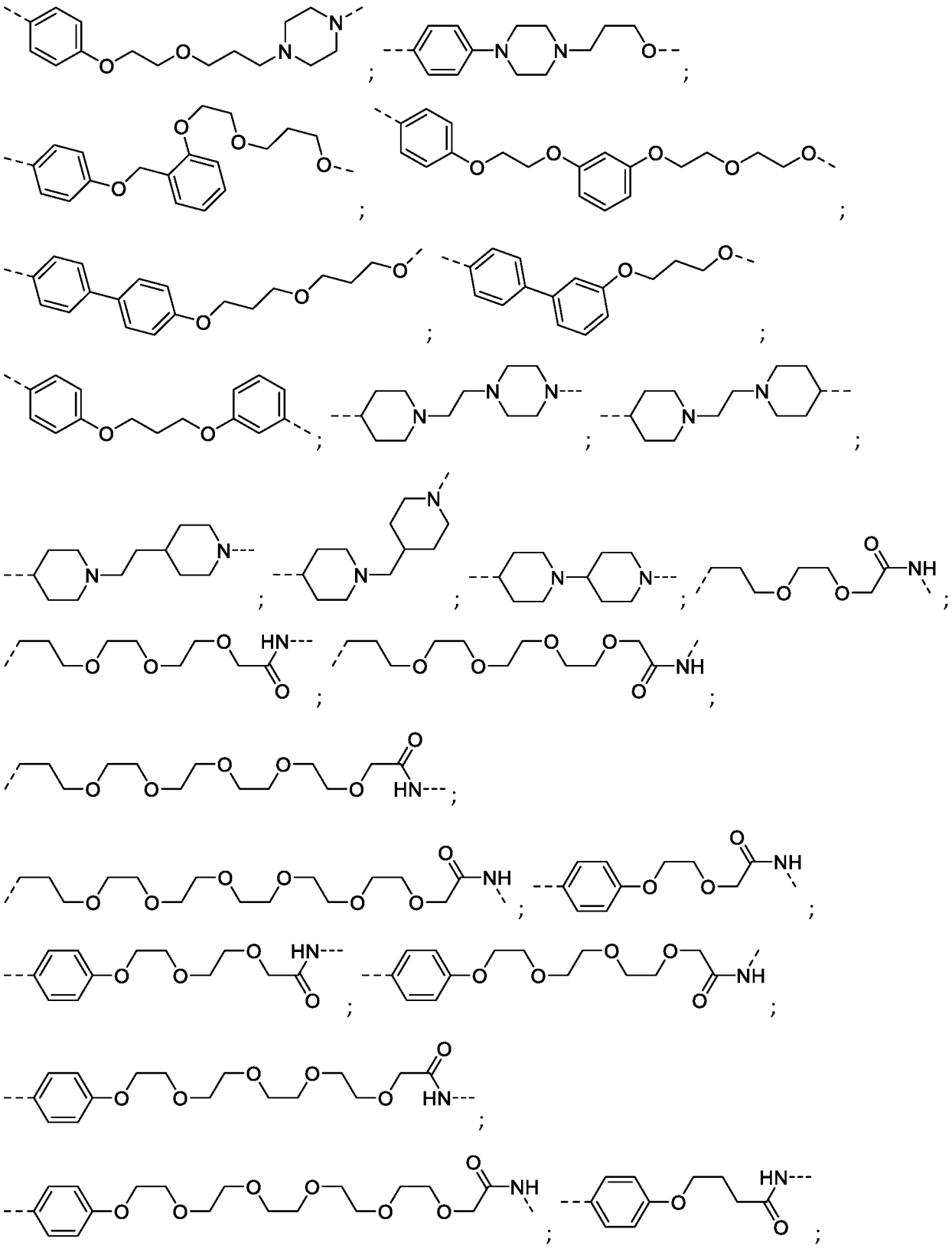


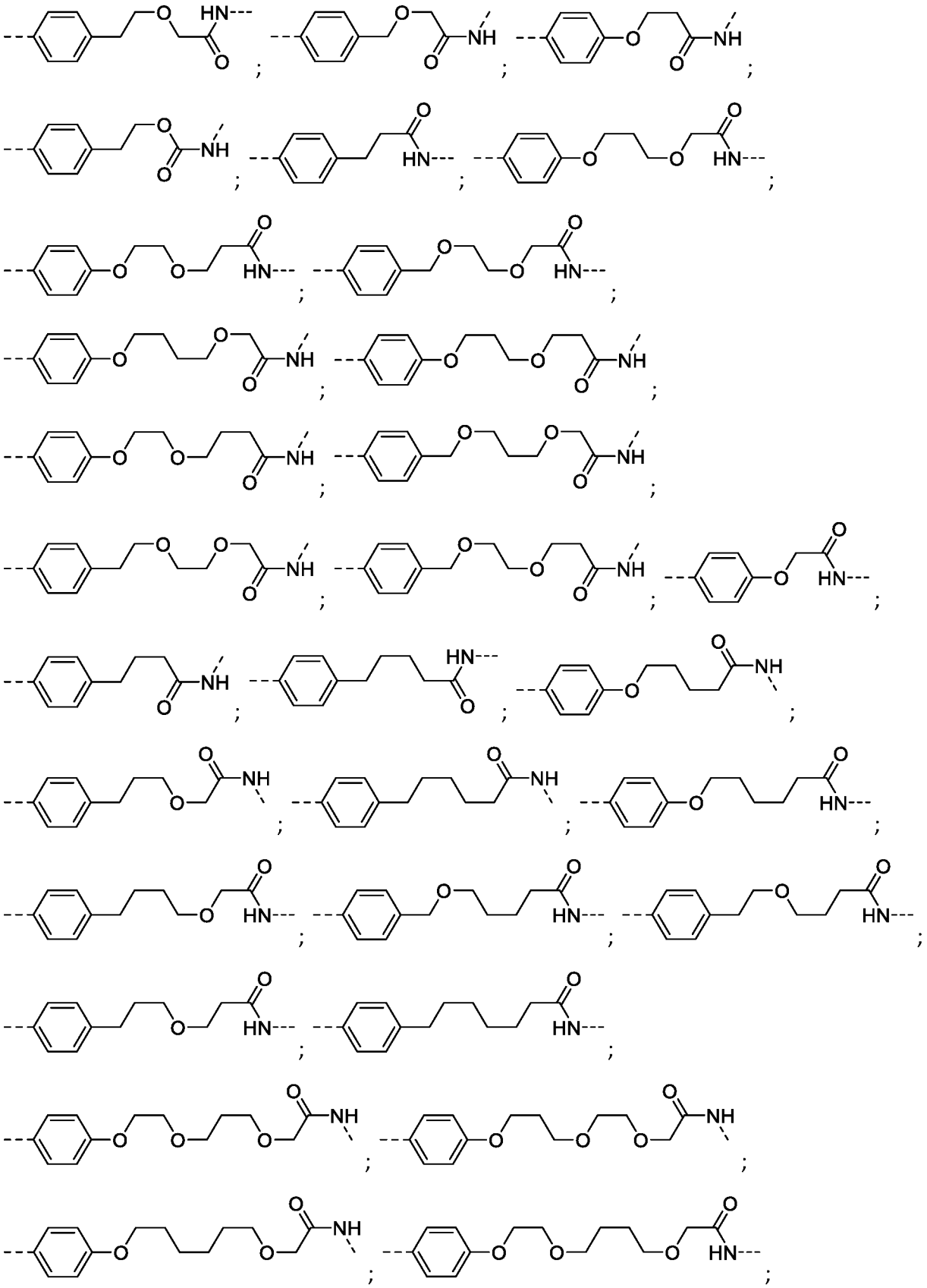
, wherein each m, n, o, p, q, and r is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

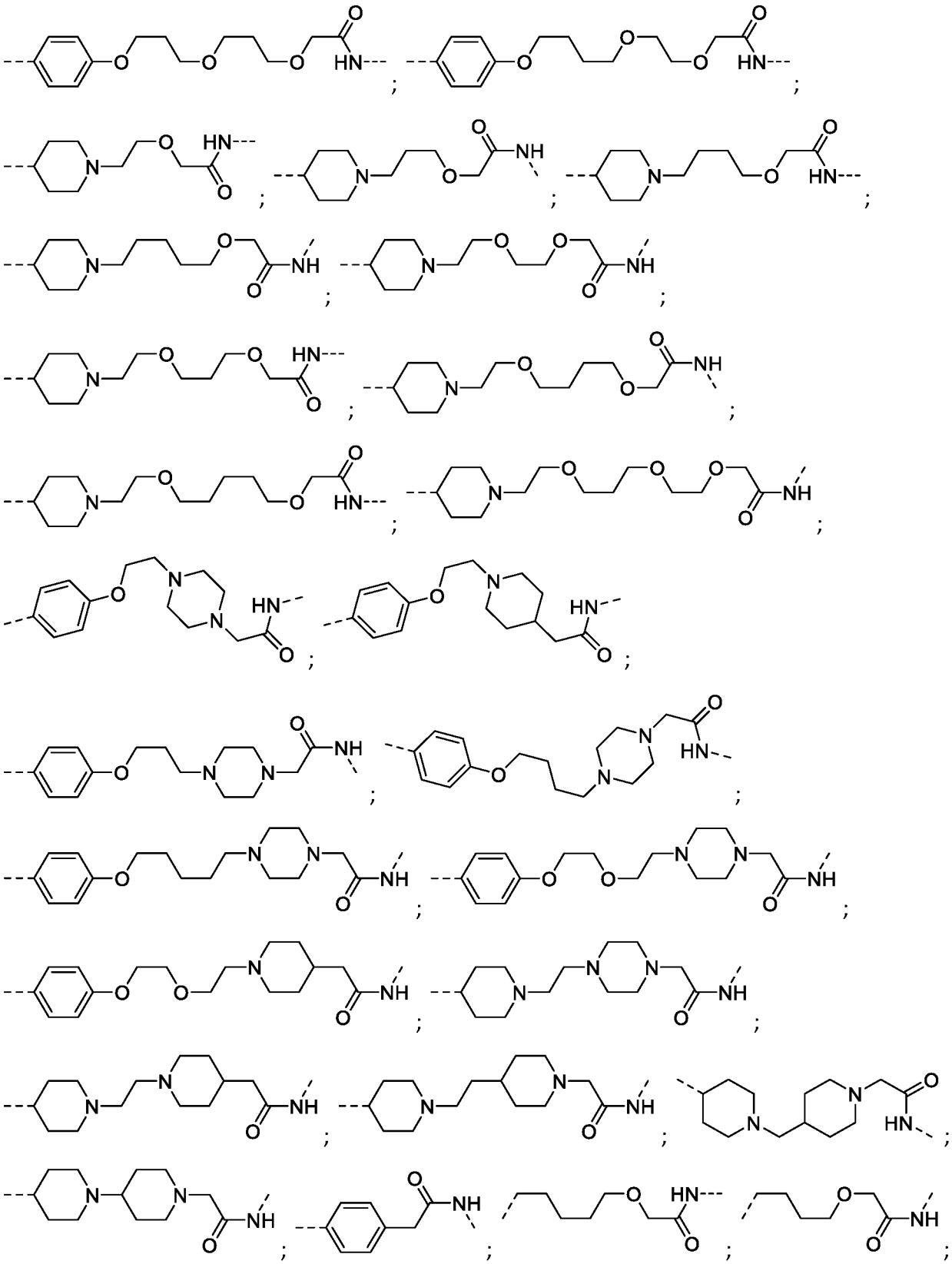
12. The bifunctional compound according to any of claims 2-8, wherein A^L is selected from the group consisting of:

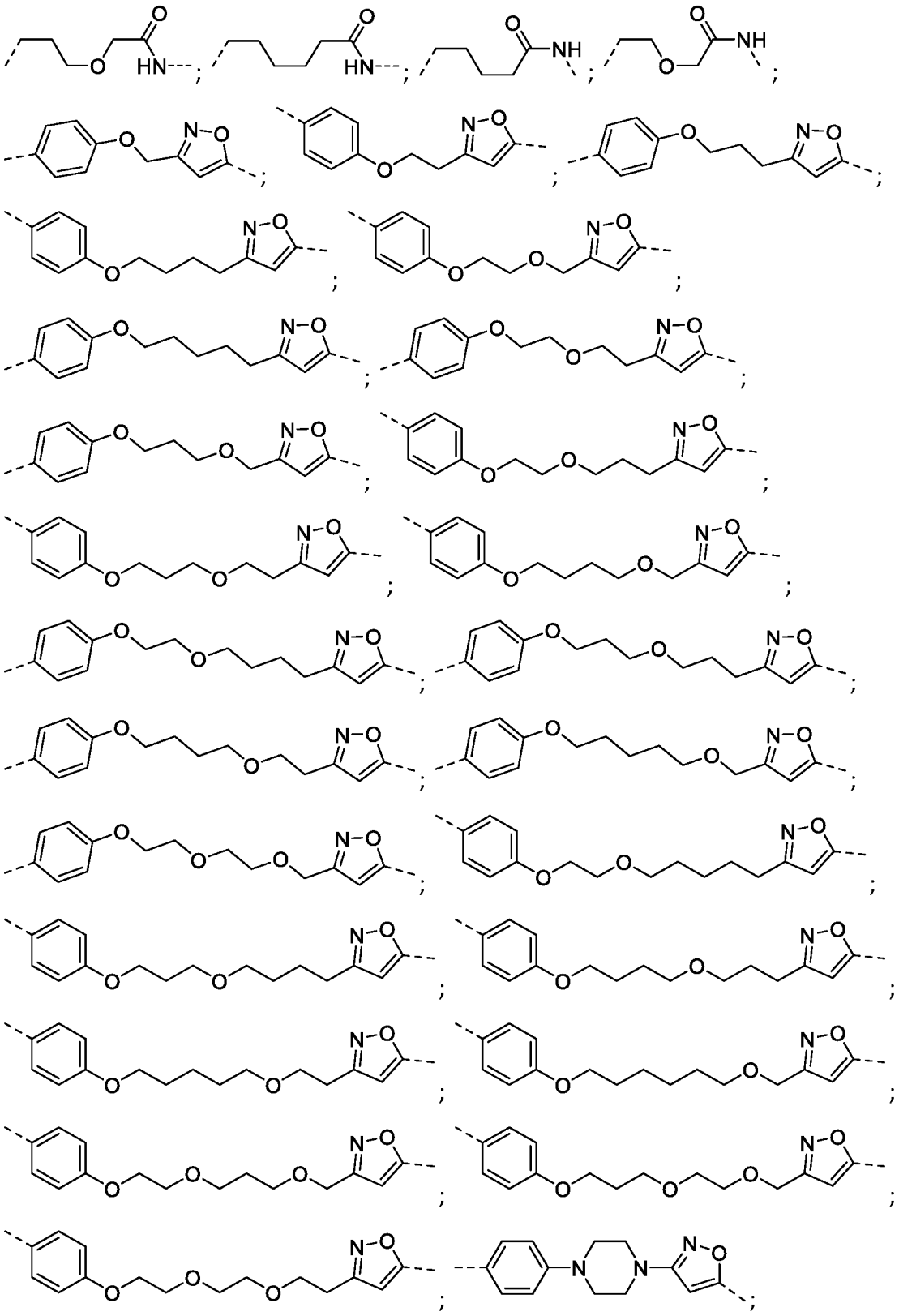


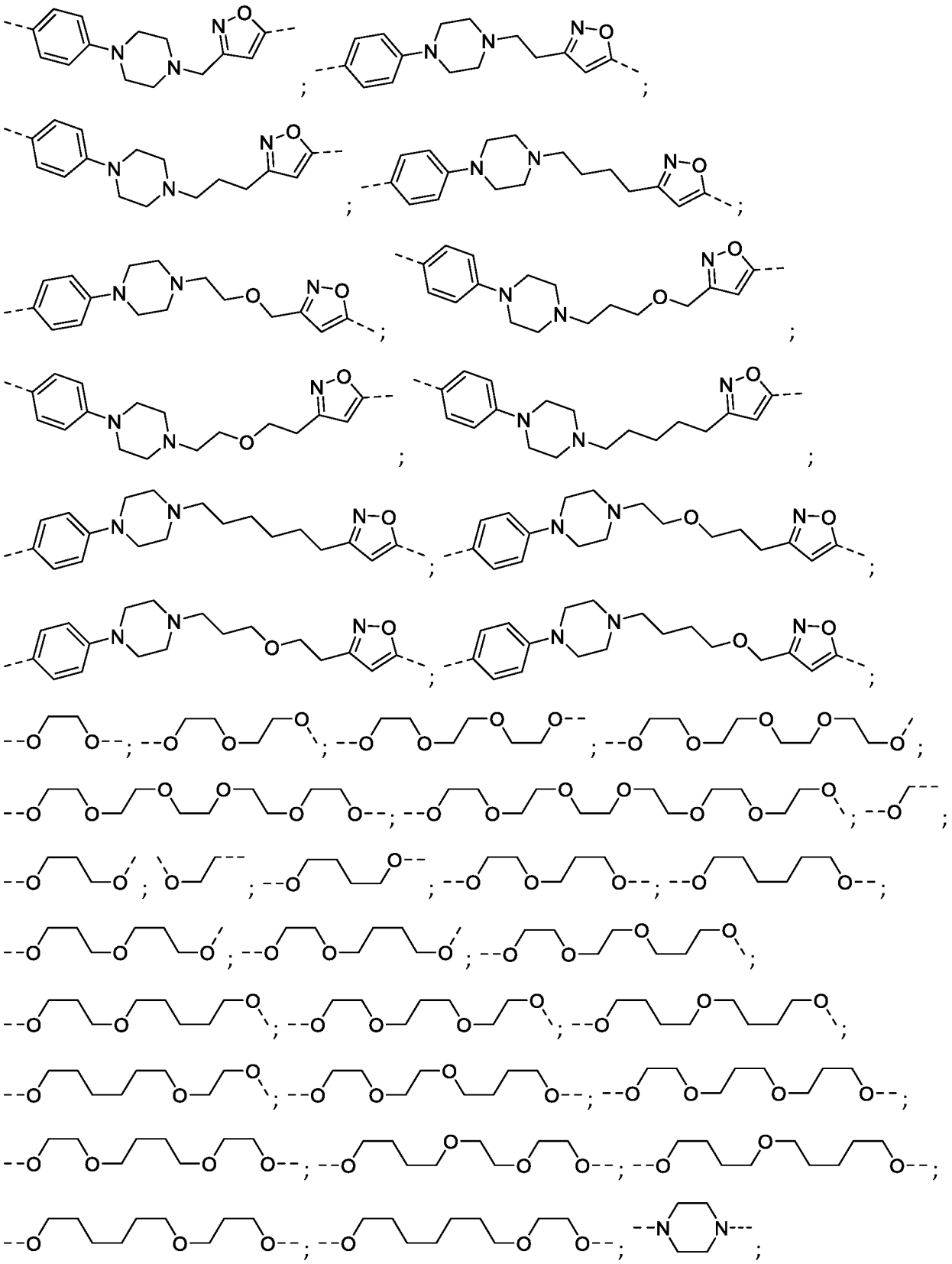


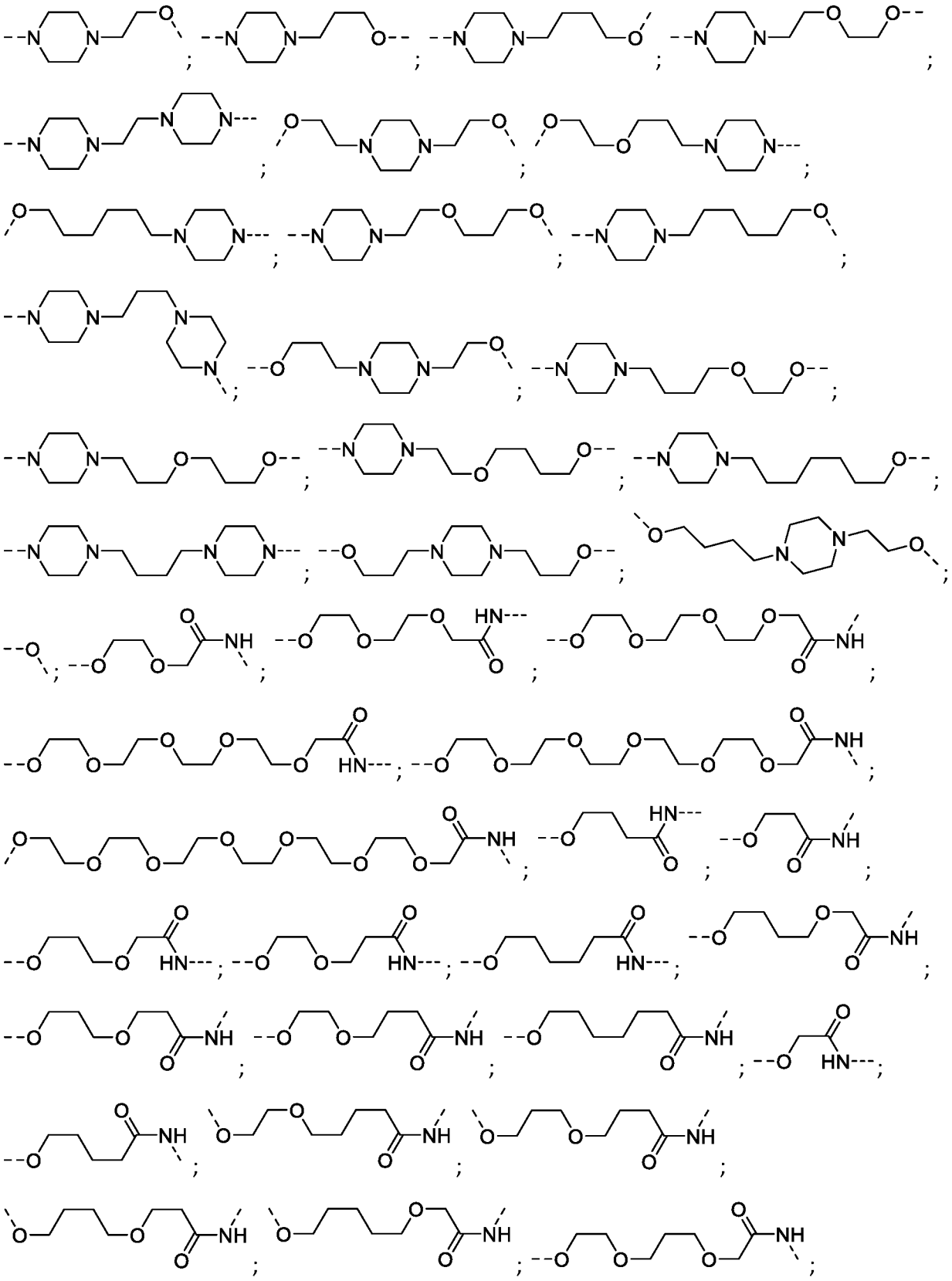


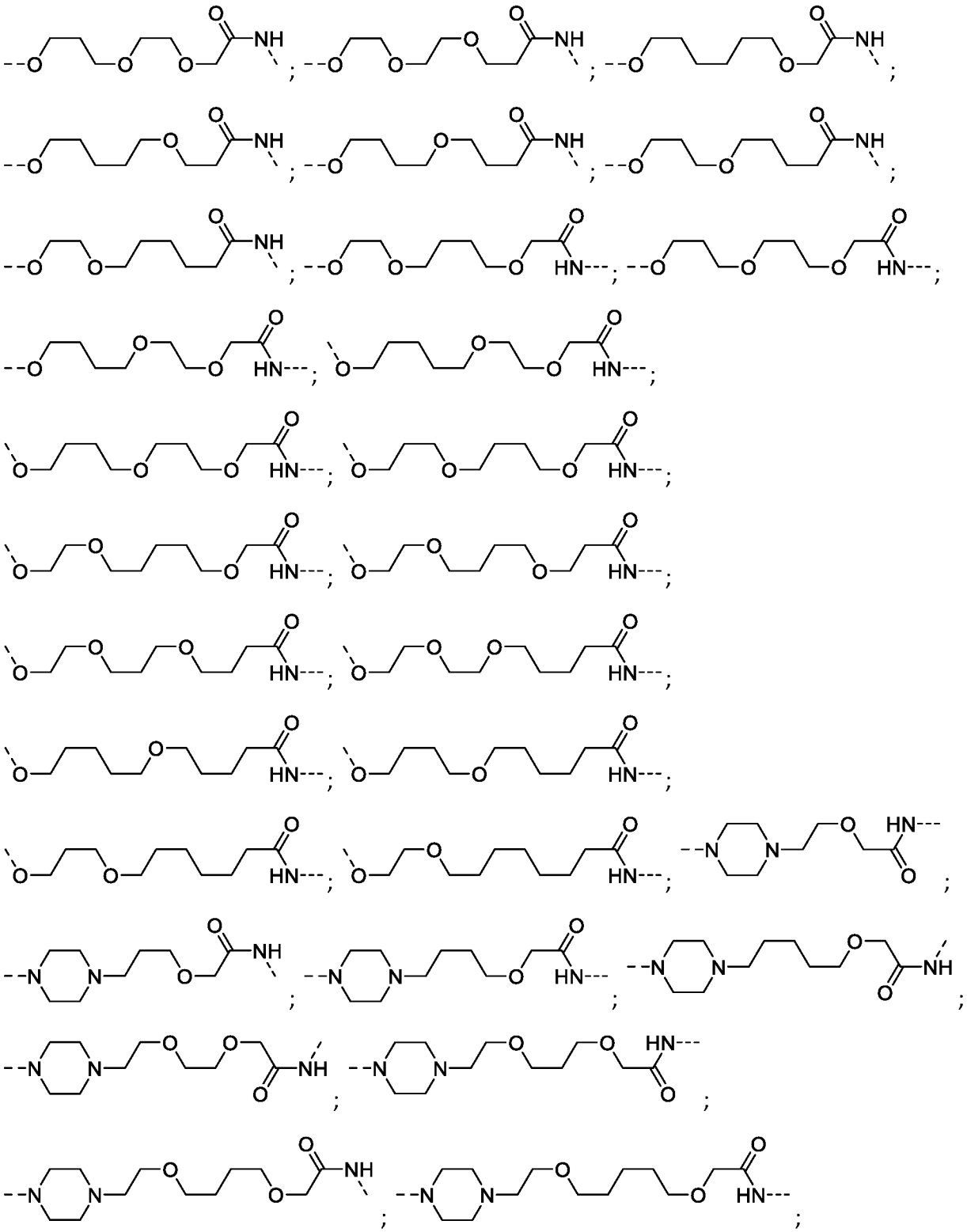


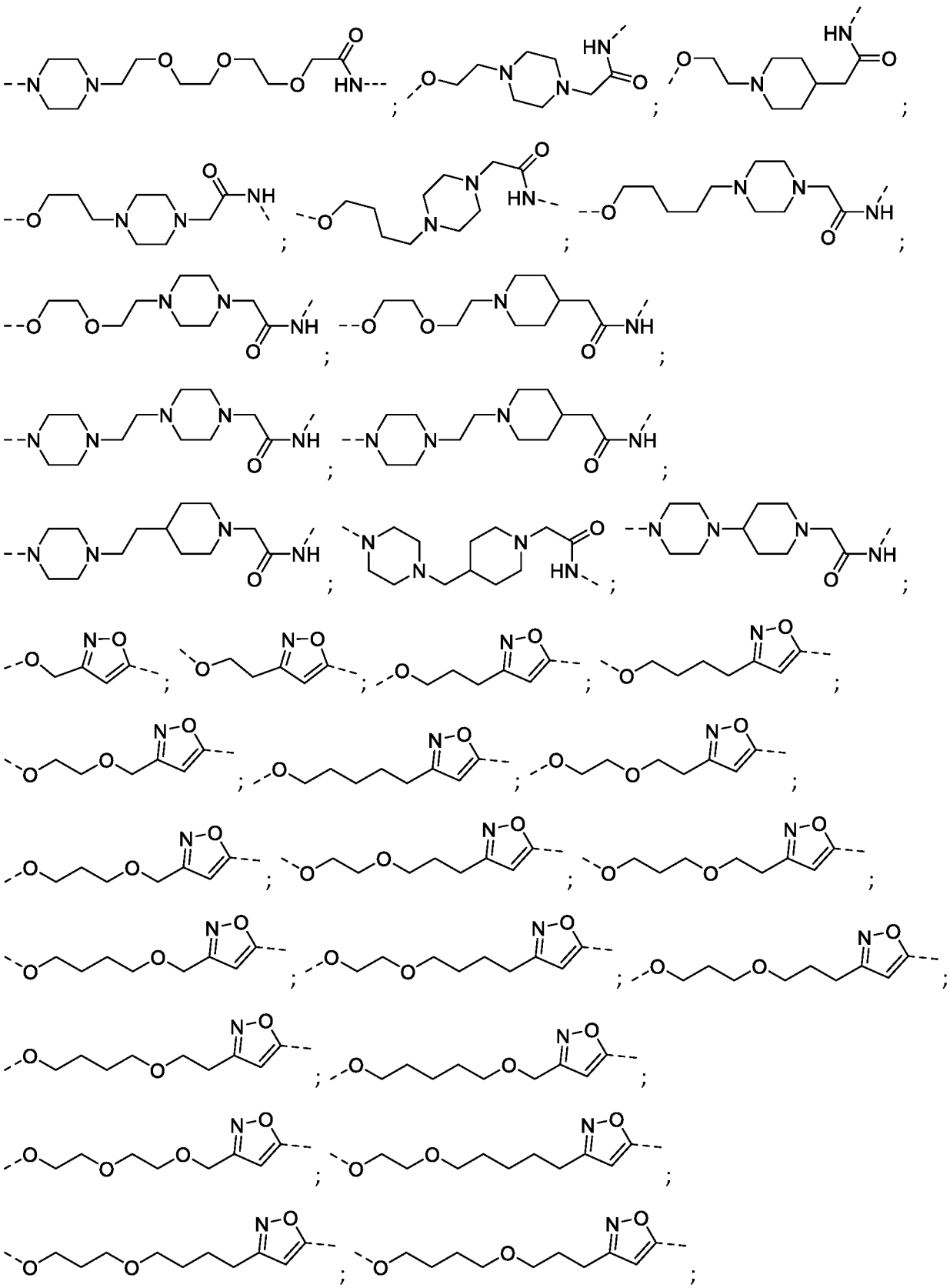


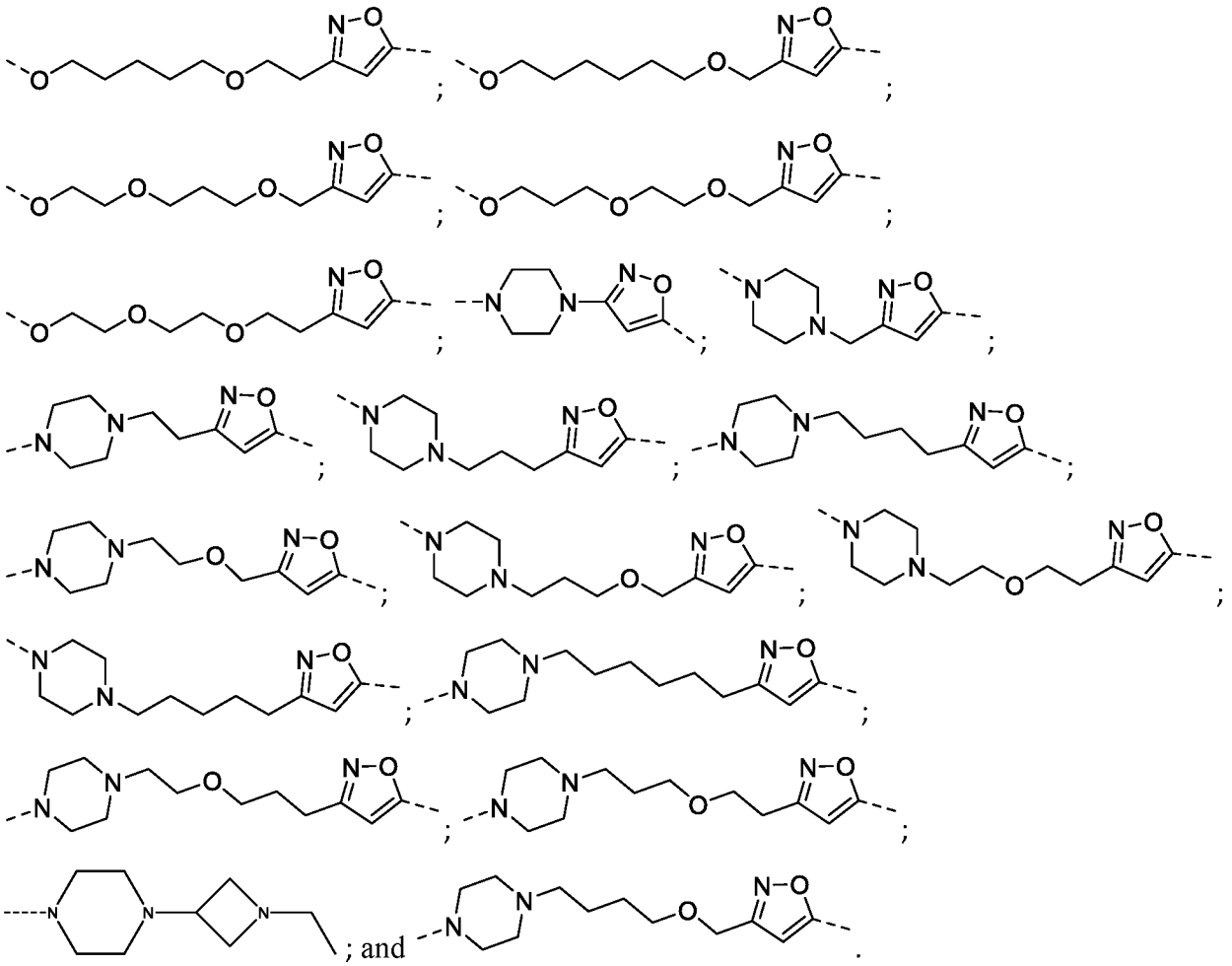




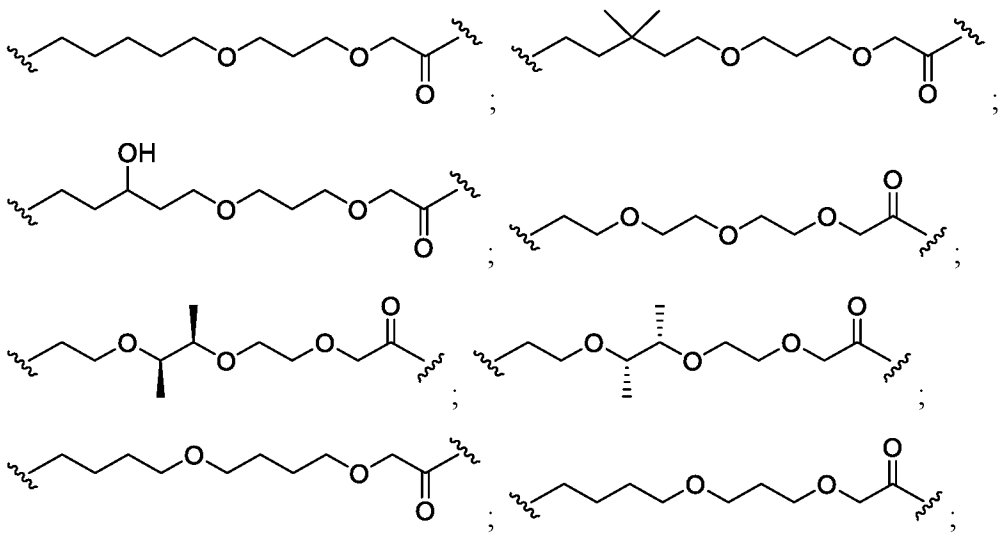


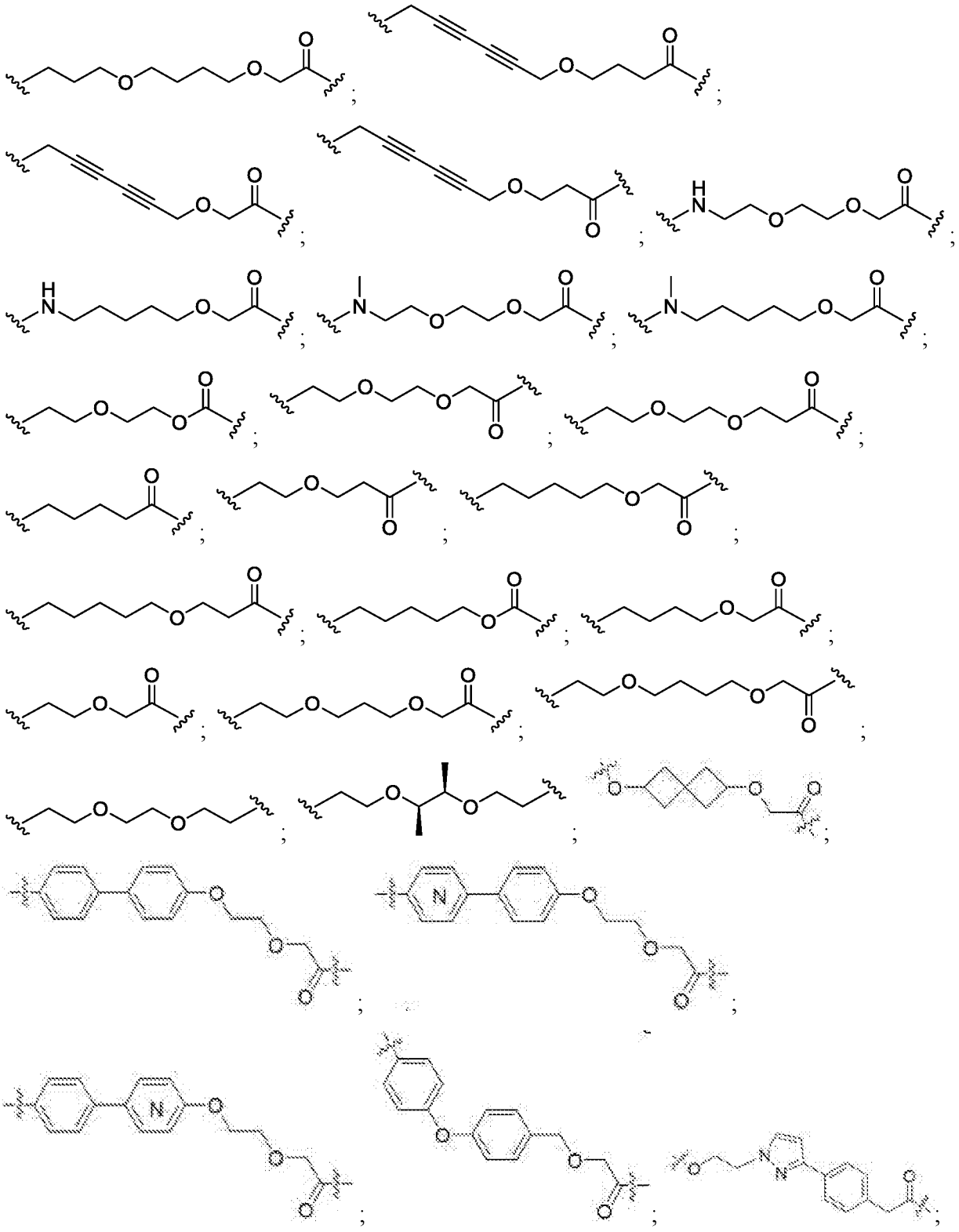


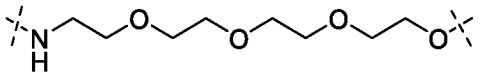
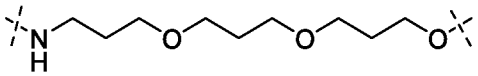
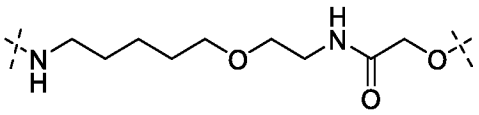
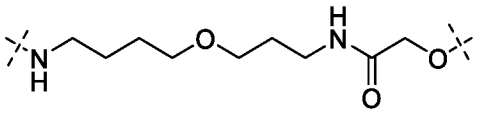




13. The bifunctional compound according to any of claims 2-8, wherein A^L is selected from:



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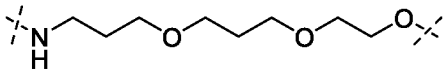
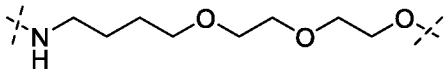
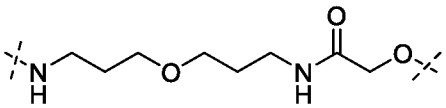
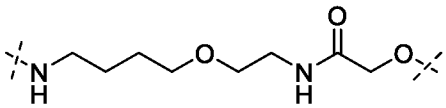
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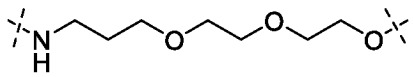
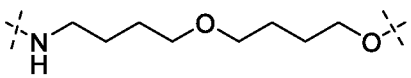
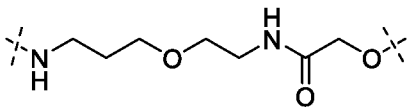
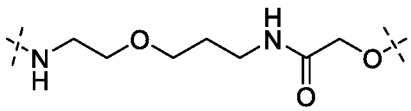
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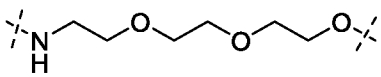
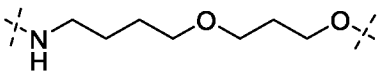
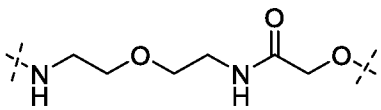
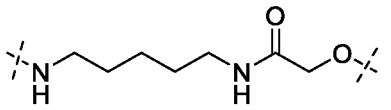
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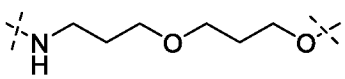
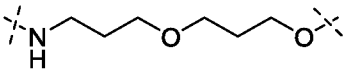
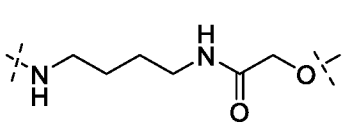
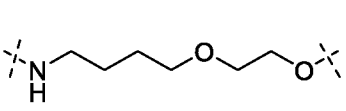
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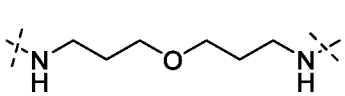
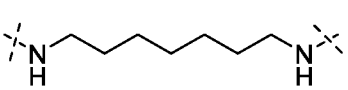
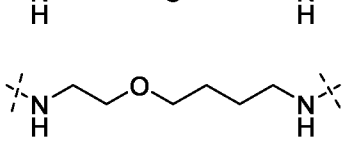
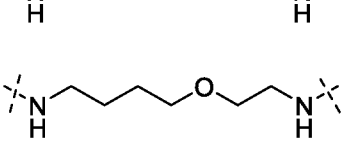
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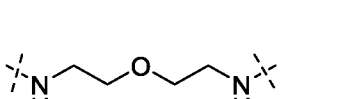
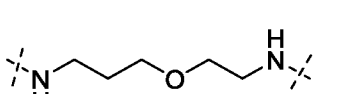

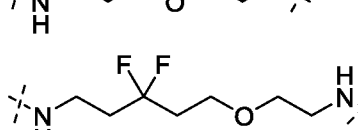
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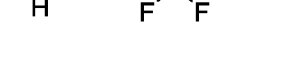

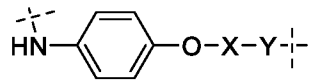
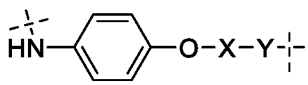
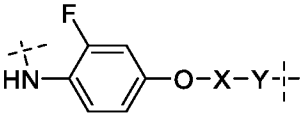
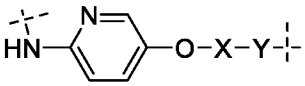
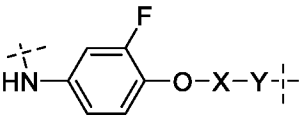
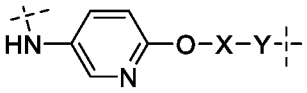
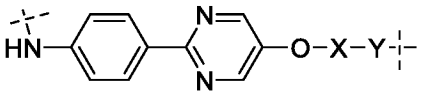
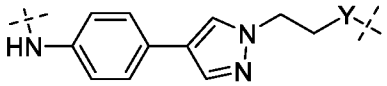
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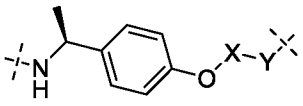
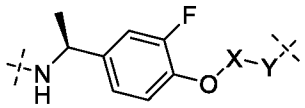
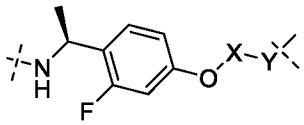
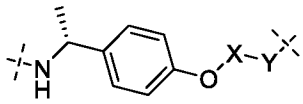
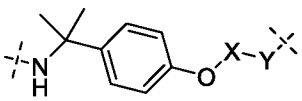
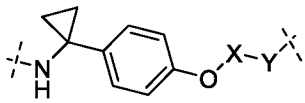
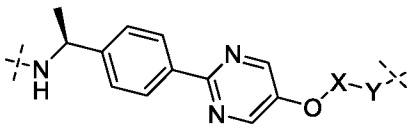
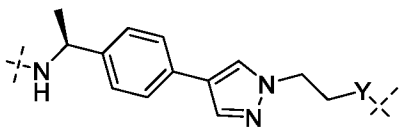
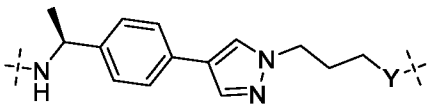
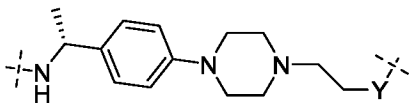
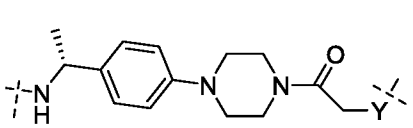
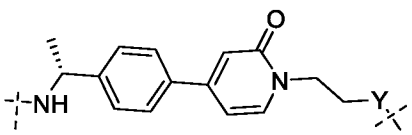
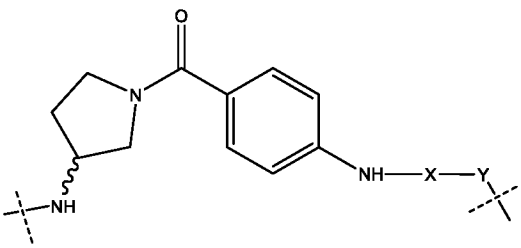
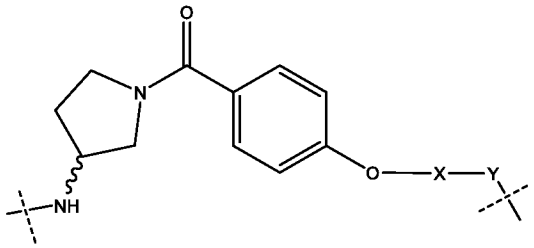
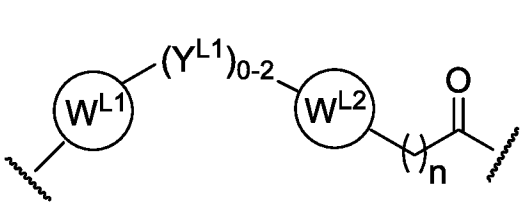















wherein:

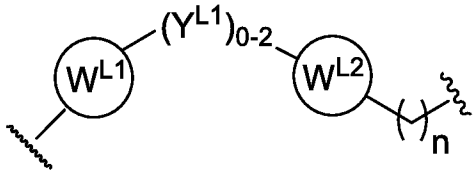
'X" in above structures can be linear chain with atoms ranging from 2 to 14, and the mentioned chain can contain heteroatoms such as oxygen; and

"Y" in above structures can be O, N, $S(O)_n$ (n=0, 1, 2).

14. The bifunctional compound according to any of claims 2-7, wherein the linker (L) comprises a structure selected from:



or



,

wherein:

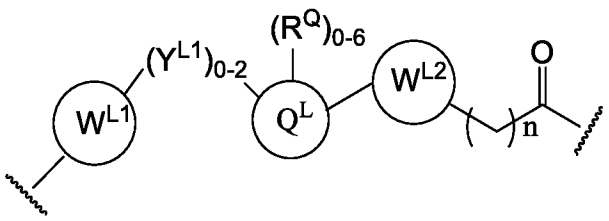
W^{L1} and W^{L2} are each independently absent, a 4-8 membered ring with 0-4 heteroatoms, optionally substituted with R^Q, each R^Q is independently a H, halo, OH, CN, CF_3, optionally substituted linear or branched C_1-C_6 alkyl, optionally substituted linear or branched C_1-C_6 alkoxy, or 2 R^Q groups 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; optionally substituted linear or branched C_1-C_6 alkyl and optionally one or more C atoms are replaced with O; or optionally substituted linear or branched C_1-C_6 alkoxy;

n is 0-10; and

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

15. The bifunctional compound according to any of claims 2-7, wherein the linker comprises a structure selected from:



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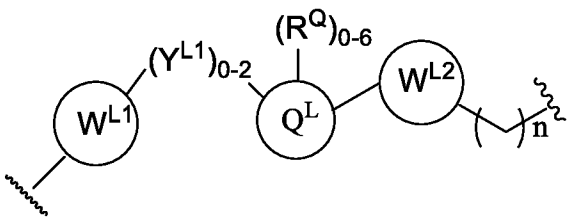


,

wherein:

W^{L1} and W^{L2} are each independently absent, aryl, heteroaryl, cyclic, heterocyclic, C_{1-6} alkyl and optionally one or more C atoms are replaced with O, C_{1-6} alkene and optionally one or more C atoms are replaced with O, C_{1-6} alkyne and optionally one or more C atoms are replaced with O, bicyclic, biaryl, biheteroaryl,or biheterocyclic, each optionally substituted with R^Q, each R^Q is independently a H, halo, OH, CN, NH_2, $NR^{Y1}R^{Y2}$, CF_3, hydroxyl, nitro, C≡CH, C_{2-6} alkenyl, C_{2-6} alkynyl, optionally substitute linear or branched C_1-C_6 alkyl, optionally substituted linear or branched C_1-C_6 alkoxy, OC_{1-3}alkyl optionally substituted by 1 or more –F, 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; optionally substituted linear or branched C_1-C_6 alkyl and optionally one or more C atoms are replaced with O; optionally substituted linear or branched C_1-C_6 alkoxy;

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, linear or branched C_{1-6} alkyl optionally substituted by 1 or more halo or 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;

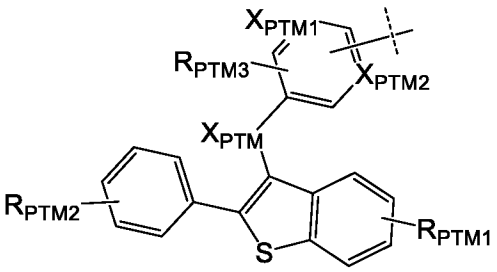
R^{YL1}, R^{YL2} are each independently H; OH; linear or branched C_{1-6} alkyl optionally substituted by 1 or more halo or C_{1-6} alkoxyl; or R^1, R^2 together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms;

n is 0-10; and

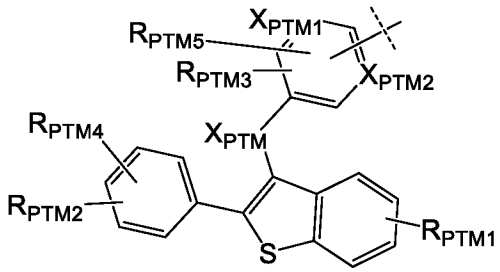
a dashed line indicates the attachment point to the PTM or CLM moieties.

16. The bifunctional compound according to any of claims 2-8, wherein the linker (L) is a polyethylenoxy group optionally substituted with aryl or phenyl comprising from 1 to 10 ethylene glycol units.

17. The bifuncitonal compound according to any of claims 2-16, wherein the PTM is an estrogen receptor (ER) binding moiety represented by the chemical structure:



PTM-I or



PTM-II ,

wherein:

X_{PTM} is O or C=O;

each of X_{PTM1} and X_{PTM2} is independently selected from N or CH;

R_{PTM1} is independently selected from OH, O(CO)R_{PTM}, O-lower alkyl, wherein R_{PTM} is an alkyl or aryl group in the ester;

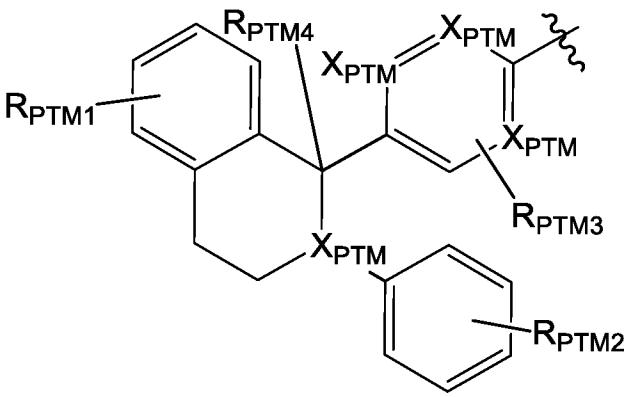
R_{PTM2} and R_{PTM4} are independently selected from H, OH, halogen, CN, CF_3, SO_2-alkyl, O-lower alkyl;

R_{PTM3} and R_{PTM5} are independently selected from H, halogen;

PTM-I has at least one R_{PTM2} and at least one R_{PTM3} on each respective rings; and

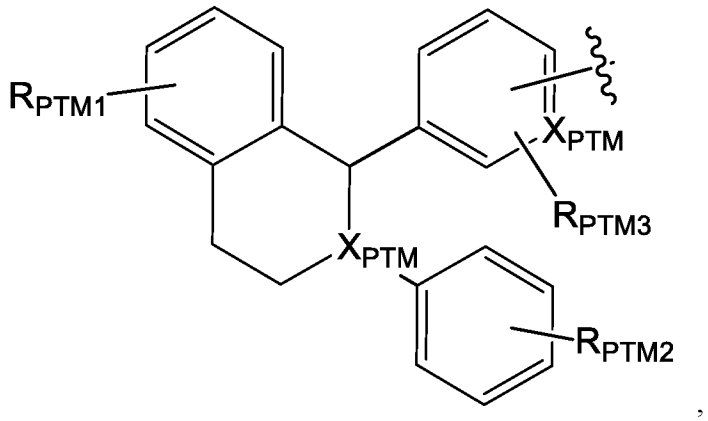
the indicates the site of attachment of at least one of the linker, the CLM, a CLM', or a combination thereof.

18. The bifuncitonal compound according to any of claims 2-16, wherein the PTM is an estrogen receptor (ER) binding moiety represented by the chemical structure:



or

Formula (I_{PTM})



,

Formula (II_{PTM})

wherein:

each X_{PTM} is independently CH, N;

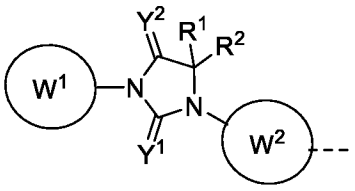
indicates the site of attachment of at least one of the linker (L), the CLM, a CLM', ULM, an ILM, a VLM, MLM, a ULM', a ILM', a VLM', a MLM', or a combination thereof;

each R_{PTM1} is independently OH, halogen, alkoxy, methoxy, ethoxy, $O(CO)R_{PTM}$, wherein the substitution can be a mono-, di- or tri-substitution and the R_{PTM} is alkyl or cycloalkyl group with 1 to 6 carbons or aryl groups;

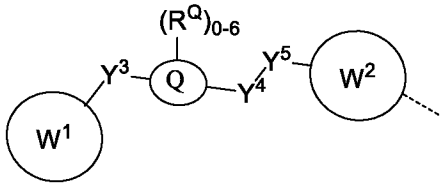
each R_{PTM2} is independently H, halogen, CN, CF_3, liner or branched alkyl, alkoxy, methoxy, ethoxy, wherein the substitution can be mono- or di-substitution;

each R_{PTM3} is independently H, halogen, wherein the substitution can be mono- or di-substitution; and R_{PTM4} is a H, alkyl, methyl, ethyl.

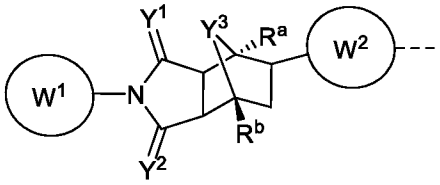
19. The bifuncitonal compound according to any of claims 2-16, wherein the PTM is an androgen receptor (AR) binding moiety (ABM) represented by a structure selected from the group consisting of:



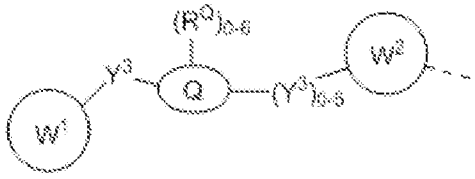
ABM-a ;



ABM-b ;



ABM-c ; and



ABM-d ,

wherein:

W^1 is aryl, heteroaryl, bicyclic, or biheterocyclic, each independently substituted by 1 or more H, halo, hydroxyl, nitro, CN, C≡CH, optionally substituted linear or branched C_{1-6} alkyl, optionally substituted linear or branched C_{1-6} alkoxyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or CF_3;

Y^1, Y^2 are each independently NR^{Y1}, O, S, SO2, heteroaryl, or aryl;

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

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

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

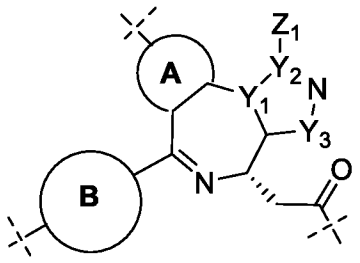
W^2 is a bond, C_{1-6} alkyl, C_{1-6} heteroalkyl, O, aryl, heteroaryl, alicyclic, heterocyclic, biheterocyclic, biaryl, or biheteroaryl,each optionally substituted by 1-10 R^{W2};

each R^{W2} is independently H, halo, optionally substituted linear or branched C_{1-6} alkyl, -OR^{W2A} , C_{3-6} cycloalkyl, C_{4-6} cycloheteroalkyl, optionally substituted C_{1-6} alkyl, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl, bicyclic hereoaryl or aryl, optionally substituted OC_{1-3}alkyl, OH, NH_2, $NR^{Y1}R^{Y2}$, CN;

R^{W2A} is H, linear or branched C_{1-6} alkyl, or linear or branched C_{1-6} heteroalkyl, each optionally substituted by a cycloalkyl, cycloheteroalkyl, aryl, heterocyclic, heteroaryl, halo, or OC_{1-3}alkyl; and

the dashed line indicates the site of attachment of at least one of the linker, the CLM, a CLM', or a combination thereof.

20. The bifuncitonal compound according to any of claims 2-16, wherein the PTM is a BET/BRD4 targeting moiety comprising a group according to the chemical structure PTM-a:



PTM-a

,

wherein:

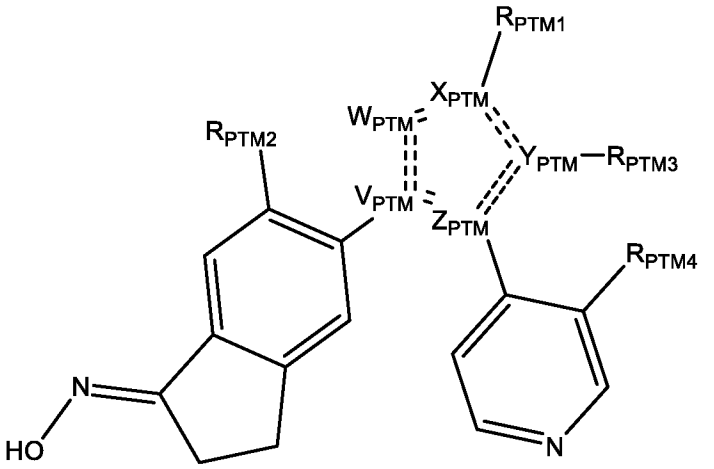
Y_1, Y_2 and Y_3 are independently selected from the group of carbon, nitrogen or oxygen and together with the atoms to form an aromatic fused ring.

A and B are independently selected from the group of a 5-membered aromatic ring, a 6-membered aromatic ring, a heteroaromatic ring, a carbocyclic, a thiophene a pyrrole ring, a pyridine, a pyrimidine, a pyrazine, a pyrazole ring each optionally substituted with alkyl, alkoxy, halogen, an aromatic and a heteroaromatic ring; wherein ring A is fused to the central azepine (Y1=C) or diazepine (Y1 = N) moiety; and

Z1 is selected from the group of methyl or analkyl group, and

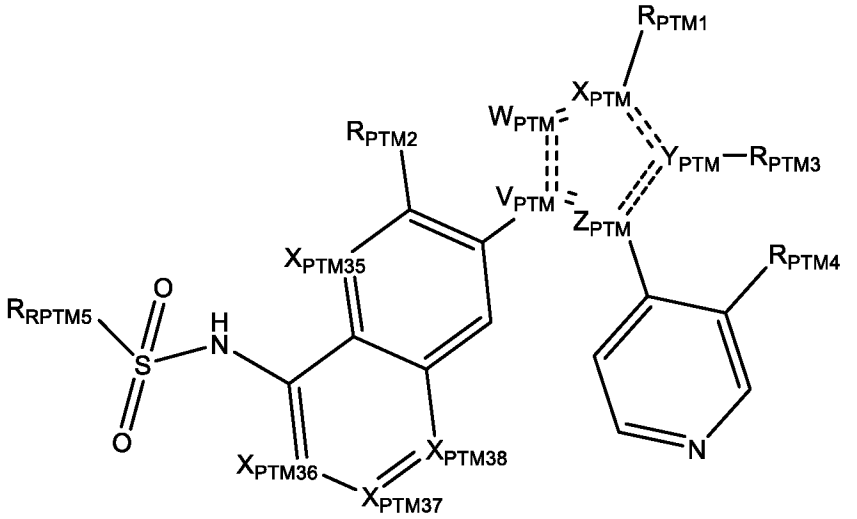
wherein the dashed line indicates the site of attachment of at least one of the linker, the CLM, a CLM', or a combination thereof.

21. The bifuncitonal compound according to any of claims 2-16, wherein the PTM is a BRaf targeting moiety that is represented by at least one of chemical structures PTM-Ia, PTM-Ib, PTM-IIa, PTM-IIb, PTM-IIIa, PTM-IIIb, PTM-IVa, PTM-IVb:


R_PTM1
X_PTM
W_PTM
R_PTM2
Y_PTM
R_PTM3
V_PTM
Z_PTM
R_PTM4
N
HO
N

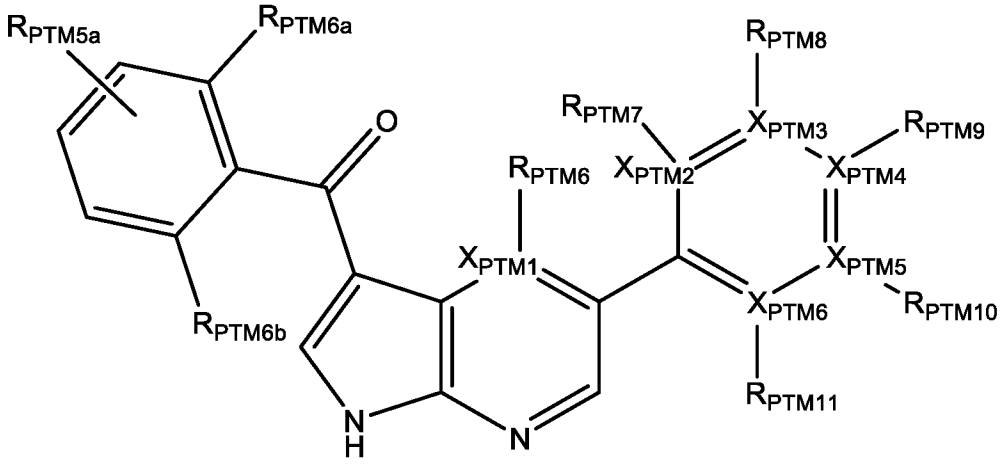
,

PTM-Ia


R_PTM1
X_PTM
W_PTM
R_PTM2
Y_PTM
R_PTM3
V_PTM
Z_PTM
X_PTM35
R_PTM4
R_RPTM5
O
S
O
H
N
X_PTM36
X_PTM38
X_PTM37
N

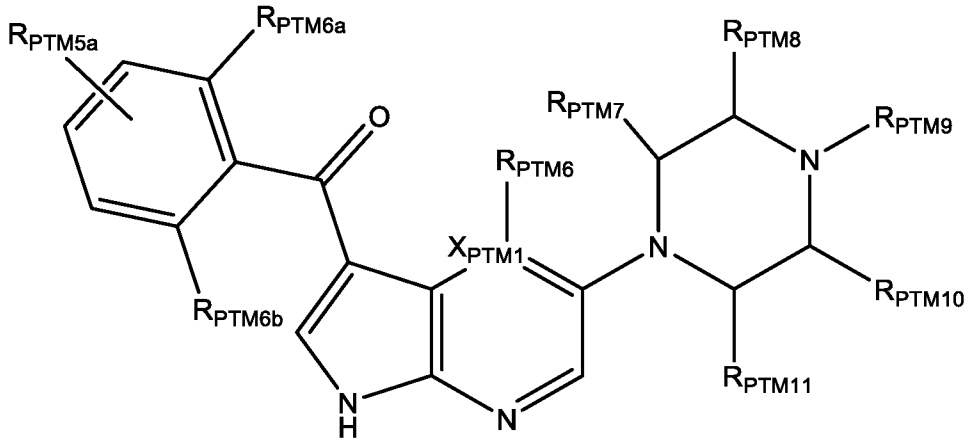
,

PTM-Ib


R_PTM5a
R_PTM6a
R_PTM8
R_PTM7
X_PTM3
R_PTM9
O
R_PTM6
X_PTM2
X_PTM4
X_PTM1
X_PTM5
X_PTM6
R_PTM10
R_PTM6b
R_PTM11
N
H
N

,

PTM-IIa



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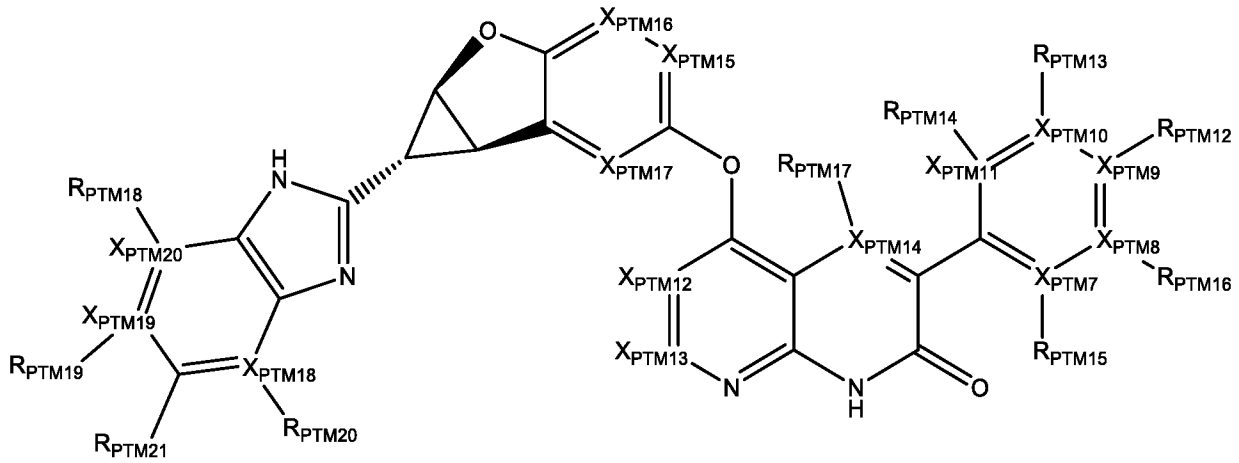
PTM-IIb



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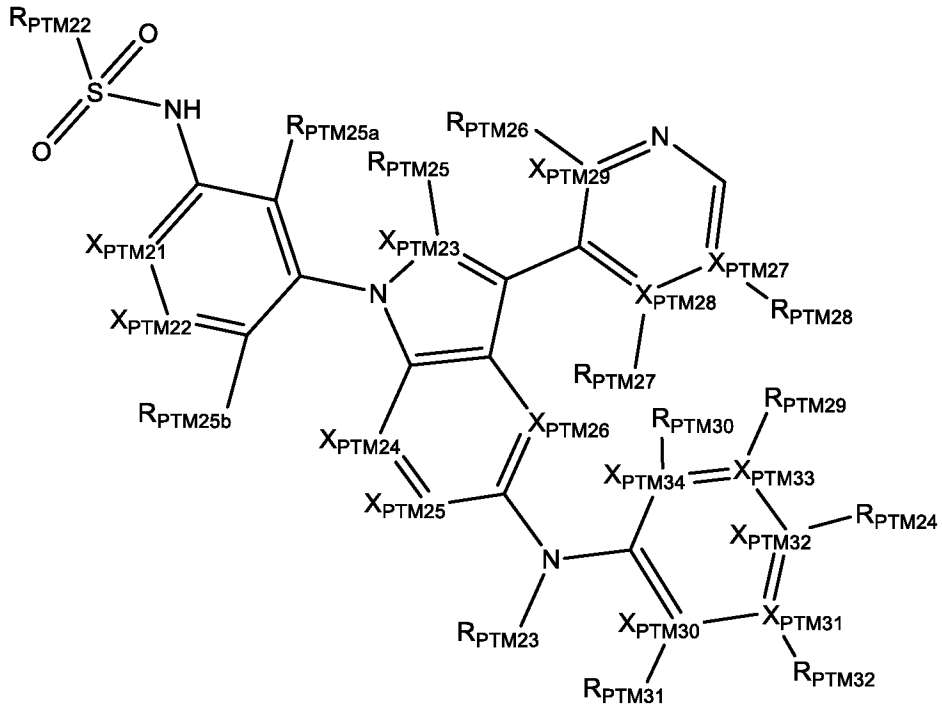
PTM-III



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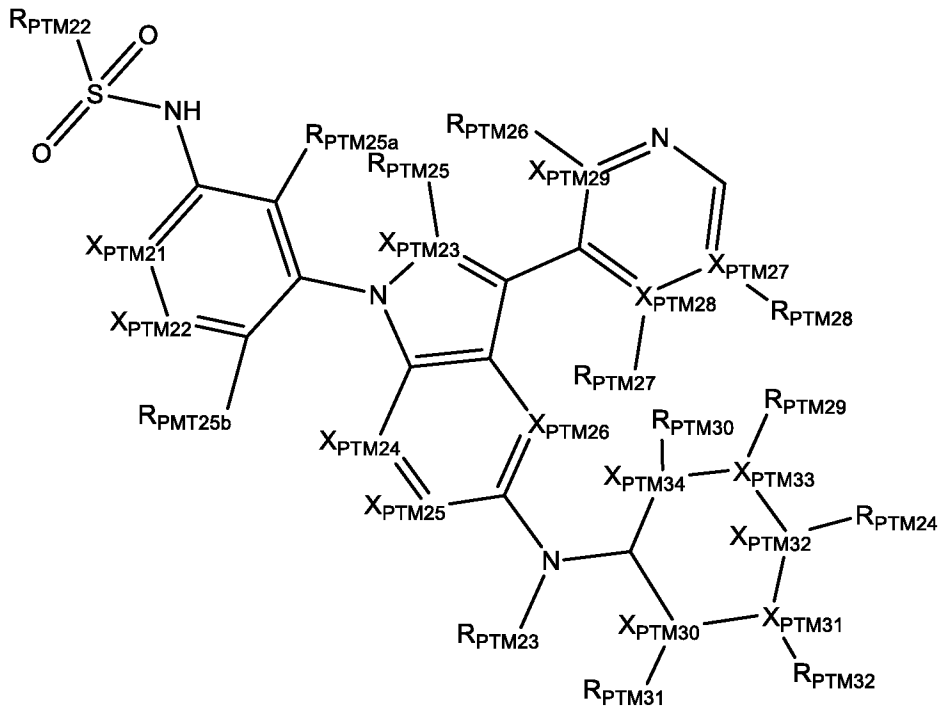
PTM-IVa



,

PTM-IVb

wherein:

double dotted bonds are aromaric bonds;

V_{PTM}, W_{PTM}, X_{PTM}, Y_{PTM}, Z_{PTM} is one of the following combinations: C, CH, N, N, C; C, N, N, CH, C; C, O, C, CH, C; C, S, C, CH, C; C, CH, C, O, C; C, CH, C, S, C; C, CH, N, CH, C; N, CH, C, CH, C; C, CH, C, CH, N; N, N, C, CH, C; N, CH, C, N, C; C, CH, C, N, N; C, N, C, CH, N; C, N, C, N, C; and C, N, N, N, C;

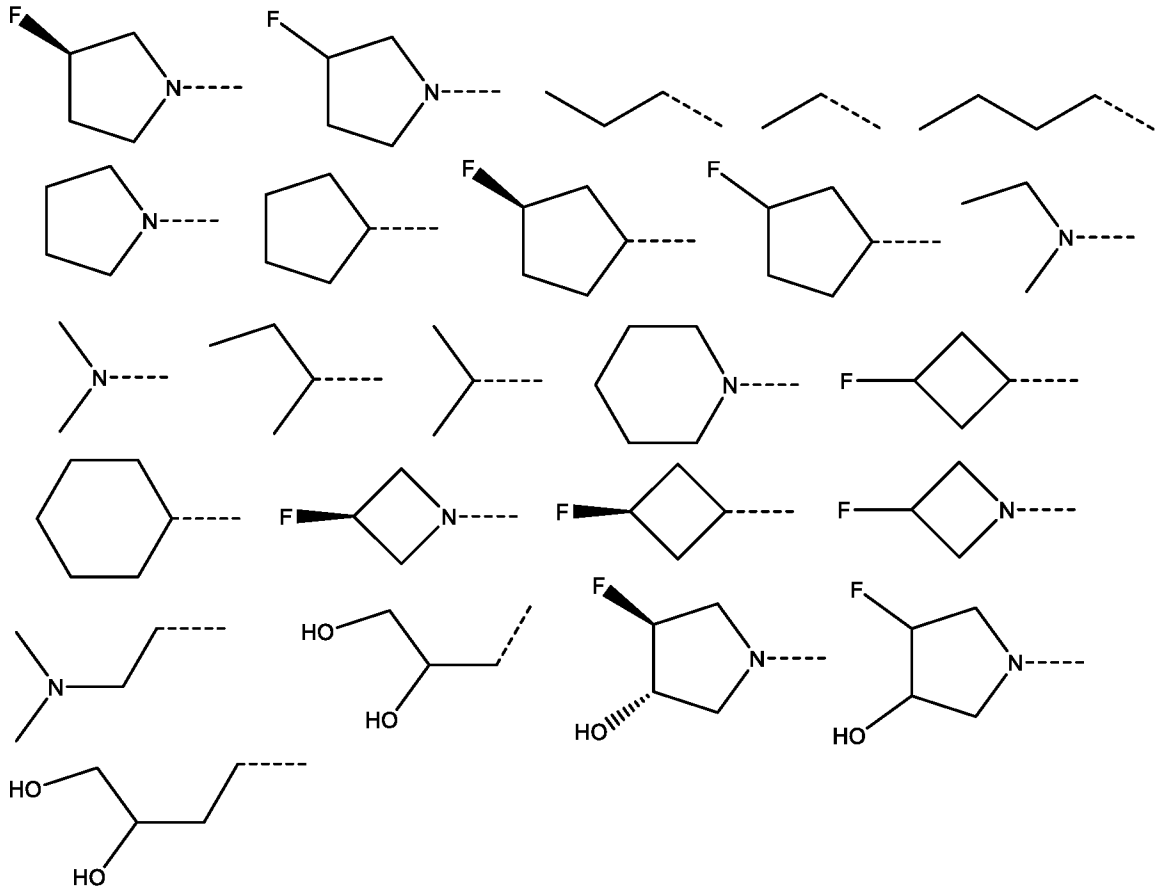
R_{PTM1} is covalently joined to a ULM, a chemical linker group (L), a CLM, an ILM, a VLM, MLM, a ULM', a CLM', a ILM', a VLM', a MLM', or combination thereof;

R_{PTM2} is hydrogen, halogen, aryl, methyl, ethyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

R_{PTM3} is absent, hydrogen, aryl, methyl, ethyl, other alkyl, cyclic alkyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

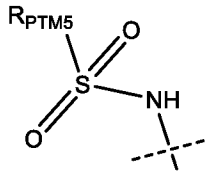
R_{PTM4} is hydrogen, halogen, aryl, methyl, ethyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

each of R_{PTM5} and R_{PTM22} is independently selected from the group consisting of



;

X_{PTM1}, X_{PTM2}, X_{PTM3}, X_{PTM4}, X_{PTM5}, X_{PTM6}, X_{PTM7}, X_{PTM8}, X_{PTM9}, X_{PTM10}, X_{PTM11}, X_{PTM12}, X_{PTM13}, X_{PTM14}, X_{PTM15}, X_{PTM16}, X_{PTM17}, X_{PTM18}, X_{PTM19}, X_{PTM20}, X_{PTM21}, X_{PTM22}, X_{PTM23}, X_{PTM24}, X_{PTM25}, X_{PTM26}, X_{PTM27}, X_{PTM28}, X_{PTM29}, X_{PTM30}, X_{PTM31}, X_{PTM32}, X_{PTM33}, X_{PTM34}, X_{PTM35}, X_{PTM36}, X_{PTM37}, X_{PTM38} are independently selected from CH or N;

R_{PTM5a} is selected from the group consisting of: H, optionally substituted amide, optionally substituted amine,  , -NHC(O)R_{PTM5};

R_{PTM6a} and R_{PTM6b} are each independently selected from hydrogen, halogen, or optionally substituted linear or branched C_1-C_6 alkyl;

R_{PTM6} is either of the following groups: absent, hydrogen, halogen, aryl, methyl, ethyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle.

R_{PTM7} is absent, hydrogen, halogen, aryl, methyl, ethyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle.

R_{PTM8}, R_{PTM9} or R_{PTM10} are independently selected from the group consisting of absent, hydrogen, halogen, aryl, heteroaryl, alkyl, cycloalkyl, heterocycle, methyl, ethyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

R_{PTM11} is absent, hydrogen, halogen, methyl, ethyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2 in which M1, wherein CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

R_{PTM12}, R_{PTM13}, R_{PTM14}, R_{PTM15}, R_{PTM16}, R_{PTM17}, R_{PTM18}, R_{PTM19} are independently selected from the group consisting of absent, hydrogen, halogen, aryl, heteroaryl, cycloalkyl, heterocycle, methyl, ethyl, other alkyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

R_{PTM20} is a small group containing less than four non-hydrogen atoms;

R_{PTM21} is selected from the group consisting of trifluoromethyl, chloro, bromo, fluoro, methyl, ethyl, propyl, isopropyl, *tert*-butyl, butyl, iso-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, OCH_3, $NHCH_3$, dimethylamino or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O or NH, and M2 is hydrogen, alkyl, cyclic alkyl, aryl or heterocycle;

R_{PTM25a} and R_{PTM25b} are each independently selected from hydrogen, halogen, or C_1-C_6 alkyl (linear, branched, optionally substituted);

R_{PTM23}, R_{PTM24}, R_{PTM28}, R_{PTM29}, R_{PTM30}, R_{PTM31}, R_{PTM32} are independently selected from the group consisting of absent, bond, hydrogen, halogen, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted, optionally substituted heterocycle, methyl, optionally substituted ethyl, optionally substituted linear or branched alkyl, OCH_3, $NHCH_3$ or M1-CH_2-CH_2-M2, wherein M1 is CH_2, O and NH, and M2 is hydrogen, optionally substituted linear or branched alkyl, optionally substituted cyclic alkyl, optionally substituted aryl or optionally substituted heterocycle;

R_{PTM25} is selected from absent, hydrogen, halogen, optionally substituted linear or branched C_1-C_6 alkyl, OCH_3, $NHCH_3$ or SCH_3;

R_{PTM26} is selected from absent, hydrogen, halogen, optionally substituted linear or branched C_1-C_6 alkyl, OCH3, $NHCH_3$ or SCH_3;

R_{PTM27} is selected from the group consisting of absent, hydrogen, halogen, optionally substituted linear or branched C_1-C_6 alkyl, OCH_3, $NHCH_3$ or SCH_3; and

at least one of R_{PTM8}, R_{PTM9} or R_{PTM10}, R_{PTM12}, R_{PTM13}, R_{PTM16}, R_{PTM24}, R_{PTM29}, and R_{PTM32} is modified to be covalently joined to a ULM, a chemical linker group (L), a CLM, an ILM, a VLM, MLM, a ULM', a CLM', a ILM', a VLM', a MLM', or combination thereof.

22. The bifunctional compound according to claim 21, wherein:

when R_{PTM9} is the covalently joined position, R_{PTM7} and R_{PTM8} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM7} and R_{PTM8} are attached; or

when R_{PTM8} is the covalently joined position, R_{PTM9} and R_{PTM10} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM9} and R_{PTM10} are attached; or

when RPTM10 is the covalently joined position, RPTM8 and RPTM9 are connected together via a covalent bond in a way to form a bicyclic group with the ring to which RPTM8 and RPTM9 are attached.; or

when R_{PTM12} is the covalently joined position, R_{PTM13} and R_{PTM14} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM13} and R_{PTM14} are attached, and/or R_{PTM15} and R_{PTM16} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM15} and R_{PTM16} are attached; or

when R_{PTM13} is the covalently joined position, R_{PTM12} and R_{PTM16} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM12} and R_{PTM16} are attached, and/or R_{PTM15} and R_{PTM16} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM15} and R_{PTM16} are attached; or

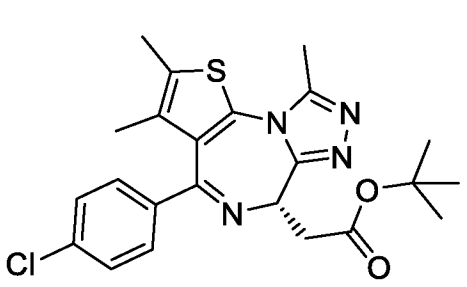
when R_{PTM16} is the covalently joined position, R_{PTM12} and R_{PTM13} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM12} and R_{PTM13} are attached, and/or R_{PTM13} and R_{PTM14} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM13} and R_{PTM14} are attached; or

when R_{PTM24} is the covalently joined position, R_{PTM31} and R_{PTM32} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM31} and R_{PTM32} are attached, or R_{PTM29} and R_{PTM30} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM29} and R_{PTM30} are attached; or

when R_{PTM29} is the covalently joined position, R_{PTM24} and R_{PTM32} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM24} and R_{PTM32} are attached, and/or R_{PTM31} and R_{PTM32} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM31} and R_{PTM32} are attached; or

when R_{PTM32} is the covalently joined position, R_{PTM24} and R_{PTM29} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM24} and R_{PTM29} are attached, and/or R_{PTM29} and R_{PTM30} are connected together via a covalent bond in a way to form a bicyclic group with the ring to which R_{PTM29} and R_{PTM30} are attached.

23. The bifunctional compound according to any of claims 2-23, wherein the PTM has a structure selected from the group consisting of:



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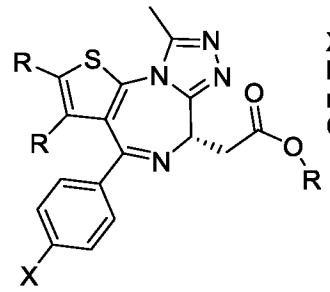

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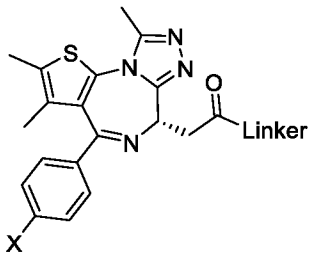

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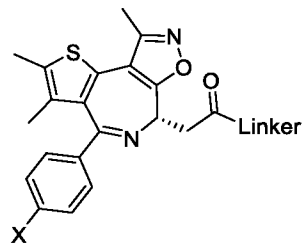

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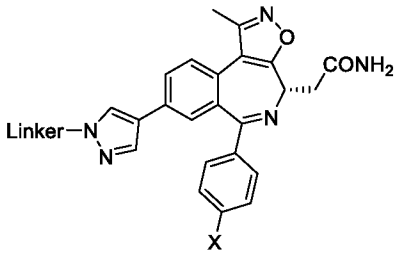

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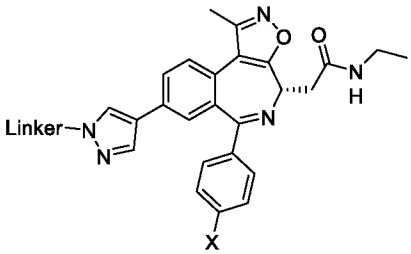

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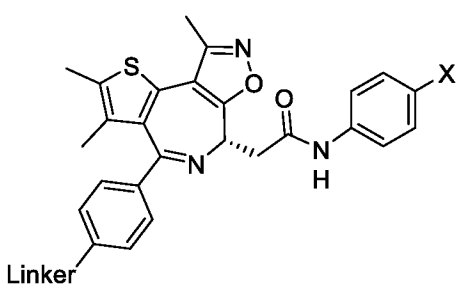

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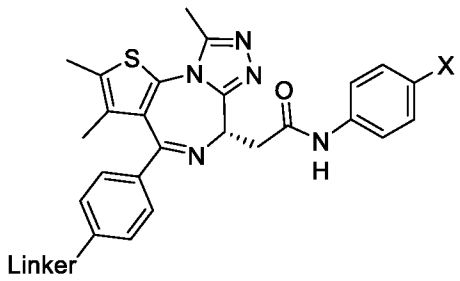
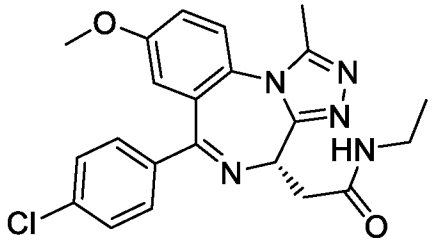


X = H, F ,



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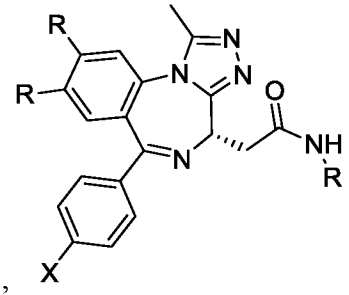

X = Cl, Br, F, H, bond, or a chemical moiety coupling the CLM to the PTM

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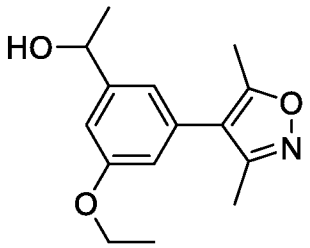

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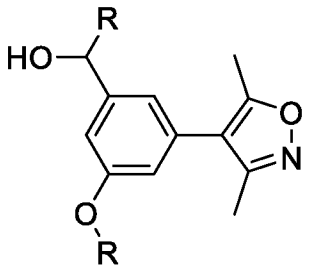

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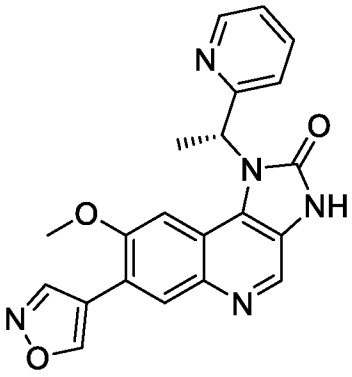

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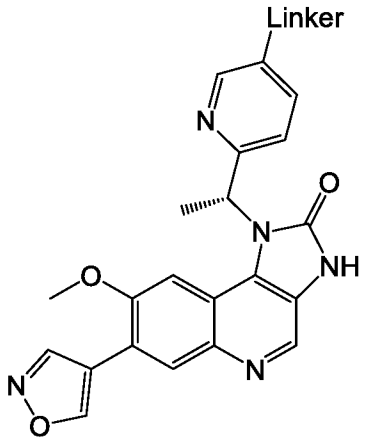

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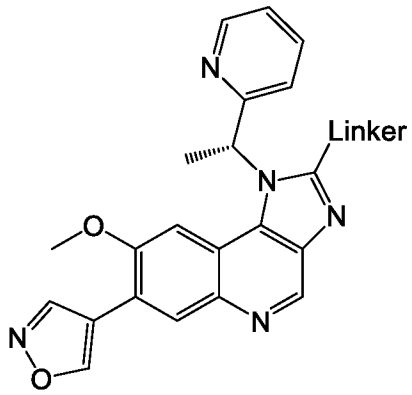

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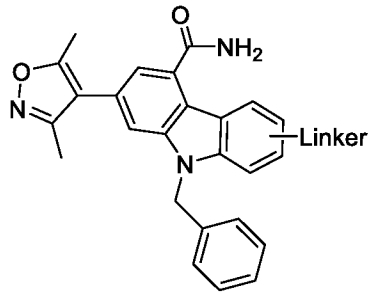
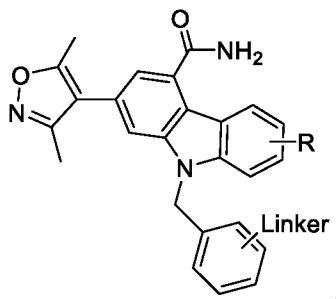
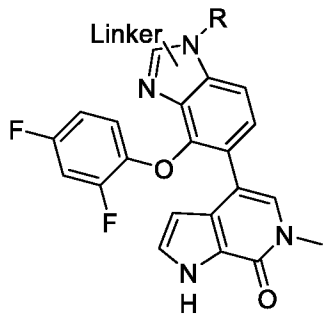
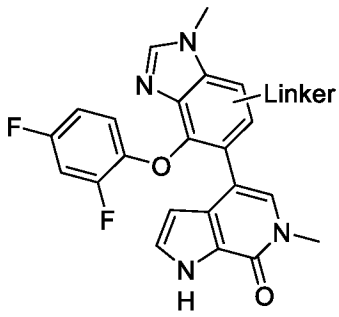
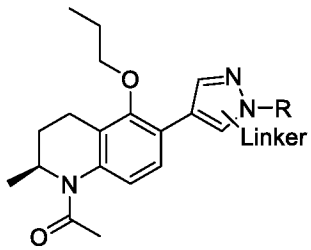
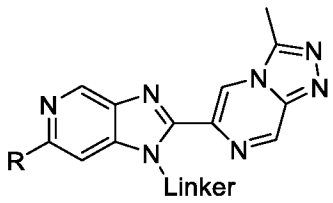
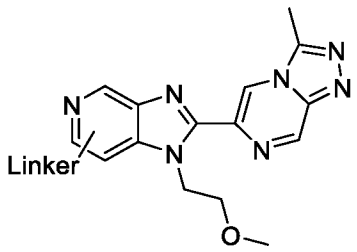
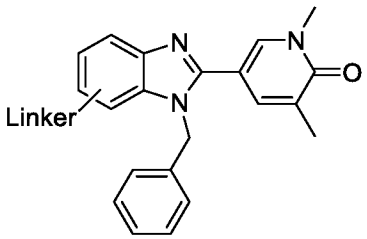
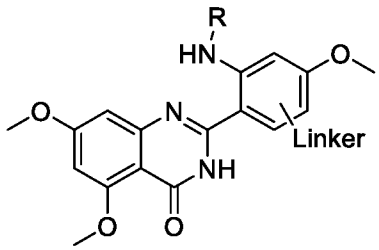

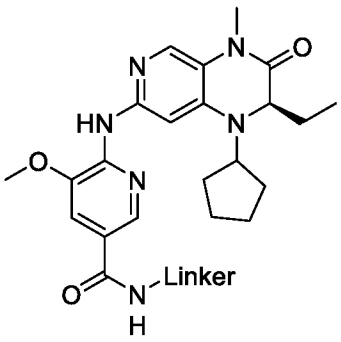

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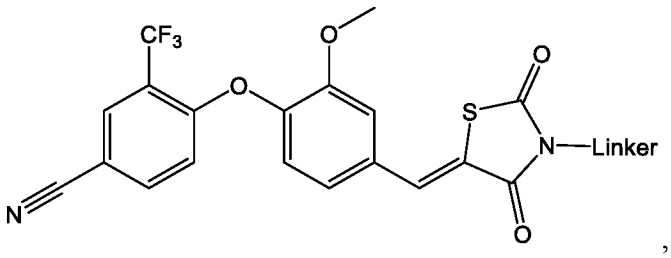

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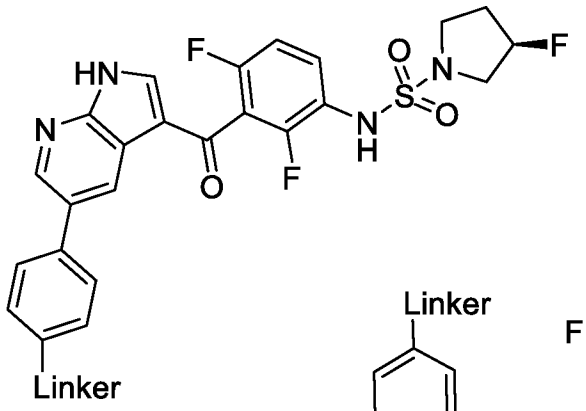
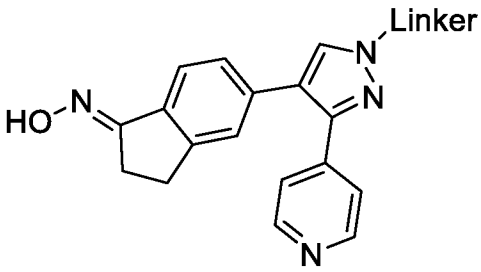
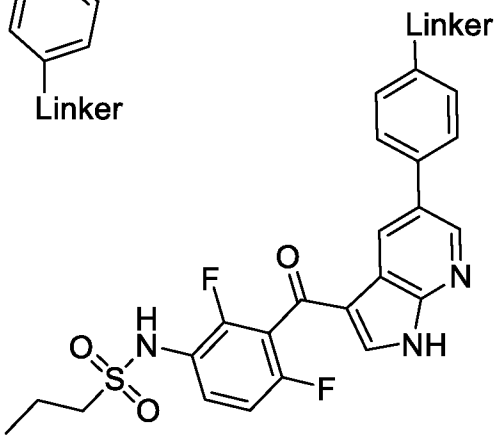
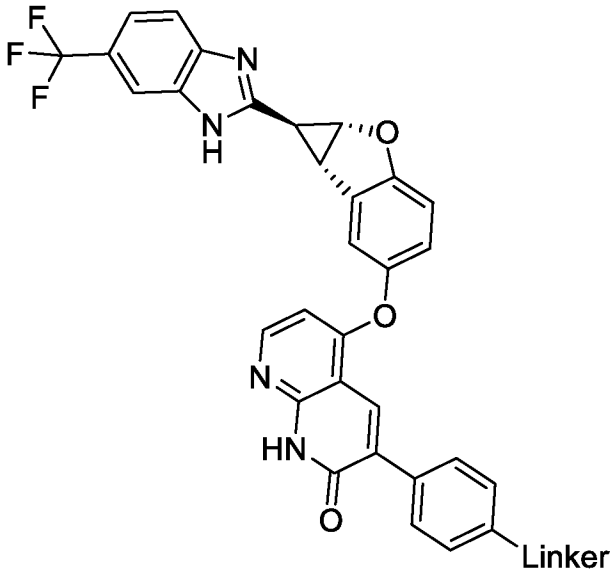
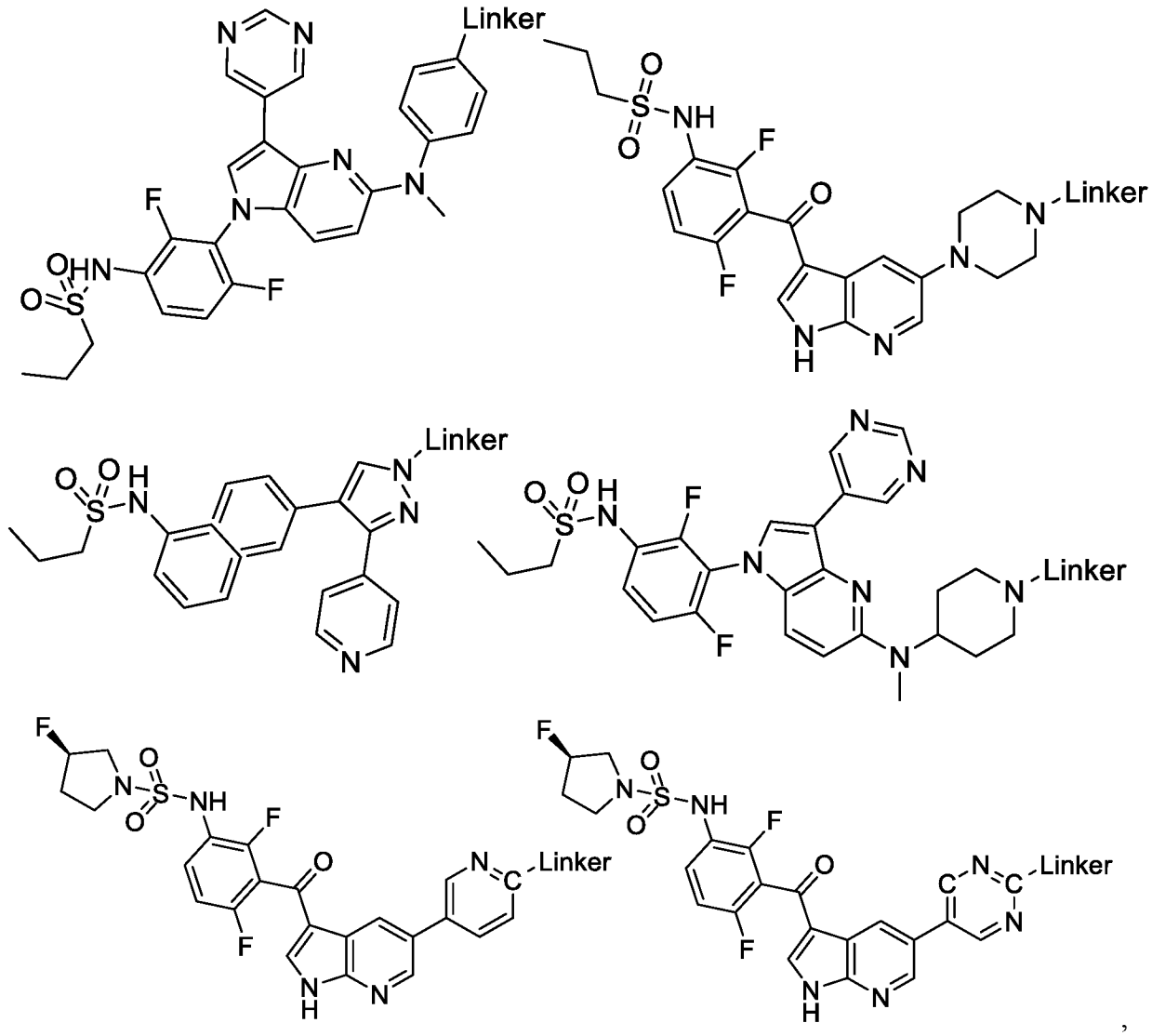










,

wherein:

R is H, a lower alkyl, a bond, or a chemical moiety coupling the CLM to the PTM; and

Linker is a bond or a chemical linker moiety coupling the CLM to the PTM, including pharmaceutically acceptable salt forms thereof.

24. The bifunctional compound according to claim 2, wherein the compound is selected from the group consisting of compounds 1-52.

25. A composition comprising an effective amount of a bifunctional compound of any of claims 2- 24, and a pharmaceutically acceptable carrier.

26. The composition of claim 25, wherein the composition further comprises at least one of additional bioactive agent or another bifunctional compound of any of claims 2-24.

27. The composition of claim 26, wherein the additional bioactive agent is anti-cancer agent, an anti-neurodegenerative agent, an antimicrobial agent, an antiviral agent, an anti-HIV agent, or an antifungal agent.

28. A composition comprising an effective amount of at least one compound of any of claims 2-24 and a pharmaceutically acceptable carrier, additive, and/or excipient for treating a disease or disorder in a subject, the method comprising administering the composition to a subject in need thereof, wherein the compound is effective in treating or ameliorating at least one symptom of the disease or disorder.

29. The composition of claim 28, wherein the disease or disorder is associated with the accumulation and/or aggregation of the target protein.

30. The composition of claim 28 or 29, wherein the disease or disorder is selected from the group consisting of asthma, autoimmune diseases such as multiple sclerosis, various cancers, ciliopathies, cleft palate, diabetes, heart disease, hypertension, inflammatory bowel disease, mental retardation, mood disorder, obesity, refractive error, infertility, Angelman syndrome, Canavan disease, Coeliac disease, Charcot–Marie–Tooth disease, Cystic fibrosis, Duchenne muscular dystrophy, Haemochromatosis, Haemophilia, Klinefelter's syndrome, Neurofibromatosis, Phenylketonuria, Polycystic kidney disease, (PKD1) or 4 (PKD2) Prader–Willi syndrome, Sickle-cell disease, Tay–Sachs disease, Turner syndrome.

31. The composition of claim 28 or 29, wherein the disease or disorder is selected from the group consisting of Alzheimer's disease, Amyotrophic lateral sclerosis (Lou Gehrig's disease), Anorexia nervosa, Anxiety disorder, Atherosclerosis, Attention deficit hyperactivity disorder, Autism, Bipolar disorder, Chronic fatigue syndrome, Chronic obstructive pulmonary disease, Crohn's disease, Coronary heart disease, Dementia, Depression, Diabetes mellitus type 1, Diabetes mellitus type 2, Epilepsy, Guillain–Barré syndrome, Irritable bowel syndrome, Lupus,

Metabolic syndrome, Multiple sclerosis, Myocardial infarction, Obesity, Obsessive–compulsive disorder, Panic disorder, Parkinson's disease, Psoriasis, Rheumatoid arthritis, Sarcoidosis, Schizophrenia, Stroke, Thromboangiitis obliterans, Tourette syndrome, Vasculitis.

32. The composition of claim 28 or 29, wherein the disease or disorder is selected from the group consisting of aceruloplasminemia, Achondrogenesis type II, achondroplasia, Acrocephaly, Gaucher disease type 2, acute intermittent porphyria, Canavan disease, Adenomatous Polyposis Coli, ALA dehydratase deficiency, adenylosuccinate lyase deficiency, Adrenogenital syndrome, Adrenoleukodystrophy, ALA-D porphyria, ALA dehydratase deficiency, Alkaptonuria, Alexander disease, Alkaptonuric ochronosis, alpha 1-antitrypsin deficiency, alpha-1 proteinase inhibitor, emphysema, amyotrophic lateral sclerosis Alström syndrome, Alexander disease, Amelogenesis imperfecta, ALA dehydratase deficiency, Anderson-Fabry disease, androgen insensitivity syndrome, Anemia Angiokeratoma Corporis Diffusum, Angiomatosis retinae (von Hippel–Lindau disease) Apert syndrome, Arachnodactyly (Marfan syndrome), Stickler syndrome, Arthrochalasis multiplex congenital (Ehlers–Danlos syndrome#arthrochalasia type) ataxia telangiectasia, Rett syndrome, primary pulmonary hypertension, Sandhoff disease, neurofibromatosis type II, Beare-Stevenson cutis gyrata syndrome, Mediterranean fever, familial, Benjamin syndrome, beta-thalassemia, Bilateral Acoustic Neurofibromatosis (neurofibromatosis type II), factor V Leiden thrombophilia, Bloch-Sulzberger syndrome (incontinentia pigmenti), Bloom syndrome, X-linked sideroblastic anemia, Bonnevie-Ullrich syndrome (Turner syndrome), Bourneville disease (tuberous sclerosis), prion disease, Birt–Hogg–Dubé syndrome, Brittle bone disease (osteogenesis imperfecta), Broad Thumb-Hallux syndrome (Rubinstein-Taybi syndrome), Bronze Diabetes/Bronzed Cirrhosis (hemochromatosis), Bulbospinal muscular atrophy (Kennedy's disease), Burger-Grutz syndrome (lipoprotein lipase deficiency), CGD Chronic granulomatous disorder, Campomelic dysplasia, biotinidase deficiency, Cardiomyopathy (Noonan syndrome), Cri du chat, CAVD (congenital absence of the vas deferens), Caylor cardiofacial syndrome (CBAVD), CEP (congenital erythropoietic porphyria), cystic fibrosis, congenital hypothyroidism, Chondrodystrophy syndrome (achondroplasia), otospondylomegaepiphyseal dysplasia, Lesch-Nyhan syndrome, galactosemia, Ehlers–Danlos syndrome, Thanatophoric dysplasia, Coffin-Lowry syndrome, Cockayne syndrome, (familial adenomatous polyposis), Congenital erythropoietic porphyria,

Congenital heart disease, Methemoglobinemia/Congenital methaemoglobinaemia, achondroplasia, X-linked sideroblastic anemia, Connective tissue disease, Conotruncal anomaly face syndrome, Cooley's Anemia (beta-thalassemia), Copper storage disease (Wilson's disease), Copper transport disease (Menkes disease), hereditary coproporphyria, Cowden syndrome, Craniofacial dysarthrosis (Crouzon syndrome), Creutzfeldt-Jakob disease (prion disease), Cockayne syndrome, Cowden syndrome, Curschmann-Batten-Steinert syndrome (myotonic dystrophy), Beare-Stevenson cutis gyrata syndrome, primary hyperoxaluria, spondyloepimetaphyseal dysplasia (Strudwick type), muscular dystrophy, Duchenne and Becker types (DBMD), Usher syndrome, Degenerative nerve diseases including de Grouchy syndrome and Dejerine-Sottas syndrome, developmental disabilities, distal spinal muscular atrophy, type V, androgen insensitivity syndrome, Diffuse Globoid Body Sclerosis (Krabbe disease), Di George's syndrome, Dihydrotestosterone receptor deficiency, androgen insensitivity syndrome, Down syndrome, Dwarfism, erythropoietic protoporphyria Erythroid 5-aminolevulinate synthetase deficiency, Erythropoietic porphyria, erythropoietic protoporphyria, erythropoietic uroporphyria, Friedreich's ataxia,, familial paroxysmal polyserositis, porphyria cutanea tarda, familial pressure sensitive neuropathy, primary pulmonary hypertension (PPH), Fibrocystic disease of the pancreas, fragile X syndrome, galactosemia, genetic brain disorders, Giant cell hepatitis (Neonatal hemochromatosis), Gronblad-Strandberg syndrome (pseudoxanthoma elasticum), Gunther disease (congenital erythropoietic porphyria), haemochromatosis, Hallgren syndrome, sickle cell anemia, hemophilia, hepatoerythropoietic porphyria (HEP), Hippel-Lindau disease (von Hippel-Lindau disease), Huntington's disease, Hutchinson-Gilford progeria syndrome (progeria), Hyperandrogenism, Hypochondroplasia, Hypochromic anemia, Immune system disorders, including X-linked severe combined immunodeficiency, Insley-Astley syndrome, Kennedy’s syndrome, Jackson-Weiss syndrome, Joubert syndrome, Lesch-Nyhan syndrome, Jackson-Weiss syndrome, Kidney diseases, including hyperoxaluria, Klinefelter's syndrome, Kniest dysplasia, Lacunar dementia,Langer-Saldino achondrogenesis, ataxia telangiectasia, Lynch syndrome, Lysyl-hydroxylase deficiency, Machado-Joseph disease, Metabolic disorders, including Kniest dysplasia, Marfan syndrome, Movement disorders, Mowat-Wilson syndrome, cystic fibrosis, Muenke syndrome, Multiple neurofibromatosis, Nance-Insley syndrome, Nance-Sweeney chondrodysplasia, Niemann–Pick disease, Noack syndrome (Pfeiffer syndrome), Osler-Weber-Rendu disease, Peutz-Jeghers syndrome, Polycystic kidney disease, polyostotic fibrous

dysplasia (McCune–Albright syndrome), Peutz-Jeghers syndrome, Prader-Labhart-Willi syndrome, hemochromatosis, primary hyperuricemia syndrome (Lesch-Nyhan syndrome), primary pulmonary hypertension, primary senile degenerative dementia, prion disease, progeria (Hutchinson Gilford Progeria Syndrome), progressive chorea, chronic hereditary (Huntington) (Huntington's disease), progressive muscular atrophy, spinal muscular atrophy, propionic acidemia, protoporphyria, proximal myotonic dystrophy, pulmonary arterial hypertension, PXE (pseudoxanthoma elasticum), Rb (retinoblastoma), Recklinghausen disease (neurofibromatosis type I), Recurrent polyserositis, Retinal disorders, Retinoblastoma, Rett syndrome, RFALS type 3, Ricker syndrome, Riley-Day syndrome, Roussy-Levy syndrome, severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), Li-Fraumeni syndrome, sarcoma, breast, leukemia, and adrenal gland (SBLA) syndrome, sclerosis tuberose (tuberous sclerosis), SDAT, SED congenital (spondyloepiphyseal dysplasia congenita), SED Strudwick (spondyloepimetaphyseal dysplasia, Strudwick type), SEDc (spondyloepiphyseal dysplasia congenita) SEMD, Strudwick type (spondyloepimetaphyseal dysplasia, Strudwick type), Shprintzen syndrome, Skin pigmentation disorders, Smith-Lemli-Opitz syndrome, South-African genetic porphyria (variegate porphyria), infantile-onset ascending hereditary spastic paralysis, Speech and communication disorders, sphingolipidosis, Tay-Sachs disease, spinocerebellar ataxia, Stickler syndrome, stroke, androgen insensitivity syndrome, tetrahydrobiopterin deficiency, beta-thalassemia, Thyroid disease, Tomaculous neuropathy (hereditary neuropathy with liability to pressure palsies), Treacher Collins syndrome, Triplo X syndrome (triple X syndrome), Trisomy 21 (Down syndrome), Trisomy X, VHL syndrome (von Hippel-Lindau disease), Vision impairment and blindness (Alström syndrome), Vrolik disease, Waardenburg syndrome, Warburg Sjo Fledelius Syndrome, Weissenbacher-Zweymüller syndrome, Wolf–Hirschhorn syndrome, Wolff Periodic disease, Weissenbacher-Zweymüller syndrome and Xeroderma pigmentosum.

33. The composition of any of claims 28-32, further comprising an additional bioactive agent.

34. The composition of claim 33, wherein the additional bioactive agent is at least one of an anti-cancer agent, an anti-neurodegenerative agent, an antimicrobial agent, an antiviral agent, an anti-HIV agent, an antifungal agent, or a combination thereof.

35. The composition of claim 34, wherein said anticancer agent is selected from the group consisting of everolimus, trabectedin, abraxane, TLK 286, AV-299, DN-101, pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, a FLT-3 inhibitor, a VEGFR inhibitor, an EGFR TK inhibitor, an aurora kinase inhibitor, a PIK-1 modulator, a Bcl-2 inhibitor, an HDAC inhbitor, a c-MET inhibitor, a PARP inhibitor, a Cdk inhibitor, an EGFR TK inhibitor, an IGFR-TK inhibitor, an anti-HGF antibody, a PI3 kinase inhibitors, an AKT inhibitor, an mTORC1/2 inhibitor, a JAK/STAT inhibitor, a checkpoint-1 or 2 inhibitor, a focal adhesion kinase inhibitor, a Map kinase kinase (mek) inhibitor, a VEGF trap antibody, pemetrexed, erlotinib, dasatanib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab, zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111, 131-I-TM-601 , ALT-110, BIO 140, CC 8490, cilengitide, gimatecan, IL13-PE38QQR, INO 1001 , $IPdR_1$ KRX-0402, lucanthone, LY 317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311 , romidepsin, ADS-100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, liposomal doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709, seliciclib; PD0325901 , AZD-6244, capecitabine, L-Glutamic acid, N -[4-[2-(2-amino-4,7-dihydro-4-oxo-1 H - pyrrolo[2,3- d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate, camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrazole, exemestane, letrozole, DES(diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11 , CHIR-258,); 3-[5-(methylsulfonylpiperadinemethyl)- indolylj-quinolone, vatalanib, AG-013736, AVE-0005, the acetate salt of [D- Ser(Bu t) 6 ,Azgly 10] (pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu t)-Leu-Arg-Pro- Azgly-NH_2 acetate [$C_{59}H_{84}N_{18}Oi_4$ -$(C_2H_4O_2)_X$ where x = 1 to 2.4], goserelin acetate, leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714; TAK-165, HKI-272, erlotinib, lapatanib, canertinib, ABX-EGF

antibody, erbitux, EKB-569, PKI-166, GW-572016, Ionafarnib, BMS-214662, tipifarnib; amifostine, NVP-LAQ824, suberoyl analide hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib, KRN951 , aminoglutethimide, arnsacrine, anagrelide, L-asparaginase, Bacillus Calmette-Guerin (BCG) vaccine, adriamycin, bleomycin, buserelin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, diethylstilbestrol, epirubicin, fludarabine, fludrocortisone, fluoxymesterone, flutamide, gleevac, gemcitabine, hydroxyurea, idarubicin, ifosfamide, imatinib, leuprolide, levamisole, lomustine, mechlorethamine, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, octreotide, oxaliplatin, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, teniposide, testosterone, thalidomide, thioguanine, thiotepa, tretinoin, vindesine, 13-cis-retinoic acid, phenylalanine mustard, uracil mustard, estramustine, altretamine, floxuridine, 5-deooxyuridine, cytosine arabinoside, 6-mecaptopurine, deoxycoformycin, calcitriol, valrubicin, mithramycin, vinblastine, vinorelbine, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291 , squalamine, endostatin, SU5416, SU6668, EMD121974, interleukin-12, IM862, angiostatin, vitaxin, droloxifene, idoxyfene, spironolactone, finasteride, cimitidine, trastuzumab, denileukin diftitox,gefitinib, bortezimib, paclitaxel, cremophor-free paclitaxel, docetaxel, epithilone B, BMS- 247550, BMS-310705, droloxifene, 4-hydroxytamoxifen, pipendoxifene, ERA- 923, arzoxifene, fulvestrant, acolbifene, lasofoxifene, idoxifene, TSE-424, HMR- 3339, ZK186619, topotecan, PTK787/ZK 222584, VX-745, PD 184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-23573, RAD001 , ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684, LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, erythropoietin, granulocyte colony-stimulating factor, zolendronate, prednisone, cetuximab, granulocyte macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-2a, pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L-asparaginase, lenalidomide, gemtuzumab, hydrocortisone, interleukin-11 , dexrazoxane, alemtuzumab, all-transretinoic acid, ketoconazole, interleukin-2, megestrol, immune globulin, nitrogen mustard, methylprednisolone, ibritgumomab tiuxetan, androgens, decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, cortisone, editronate, mitotane, cyclosporine, liposomal daunorubicin, Edwina-asparaginase, strontium 89, casopitant, netupitant, an NK-1 receptor antagonists, palonosetron, aprepitant,

diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone, methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, erythropoietin, epoetin alfa, darbepoetin alfa and mixtures thereof.

36. A method for inducing degradation of a target protein in a cell comprising administering an effective amount of a compound of any of claims 2-24 to the cell, wherein the compound effectuates degradation of the target protein.

37. A composition comprising an effective amount of a compound of any of claims 2-24 for use in a method for treating cancer, said method comprising administering the composition to a patient in need thereof, wherein the composition is effectuates for the treatment or alleviation of at least one symptom of cancer in the patient.

38. The composition of claim 37, wherein the cancer is squamous-cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinomas, and renal cell carcinomas, cancer of the bladder, bowel, breast, cervix, colon, esophagus, head, kidney, liver, lung, neck, ovary, pancreas, prostate, and stomach; leukemias; benign and malignant lymphomas, particularly Burkitt's lymphoma and Non-Hodgkin's lymphoma; benign and malignant melanomas; myeloproliferative diseases; multiple myeloma, sarcomas, including Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma, synovial sarcoma, gliomas, astrocytomas, oligodendrogliomas, ependymomas, gliobastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors, meningiomas, meningeal sarcomas, neurofibromas, and Schwannomas; bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, esophageal cancer, pancreatic cancer, stomach cancer, liver cancer, colon cancer, melanoma; carcinosarcoma, Hodgkin's disease, Wilms' tumor or teratocarcinomas, T-lineage Acute lymphoblastic Leukemia (T-ALL), T-lineage lymphoblastic Lymphoma (T-LL), Peripheral T-cell lymphoma, Adult T-cell Leukemia, Pre-B ALL, Pre-B Lymphomas, Large B-cell Lymphoma, Burkitts Lymphoma, B-cell ALL, Philadelphia chromosome positive ALL and Philadelphia chromosome positive CML.

FIG. 1A

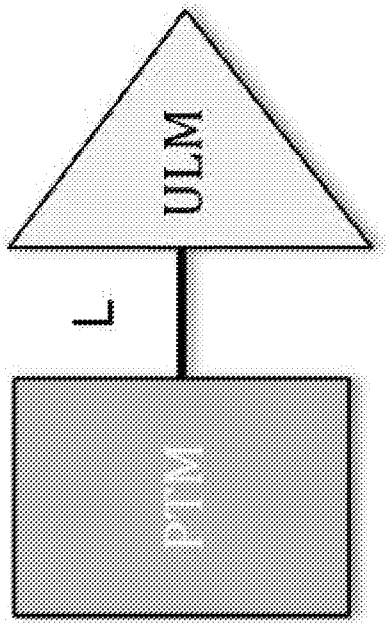
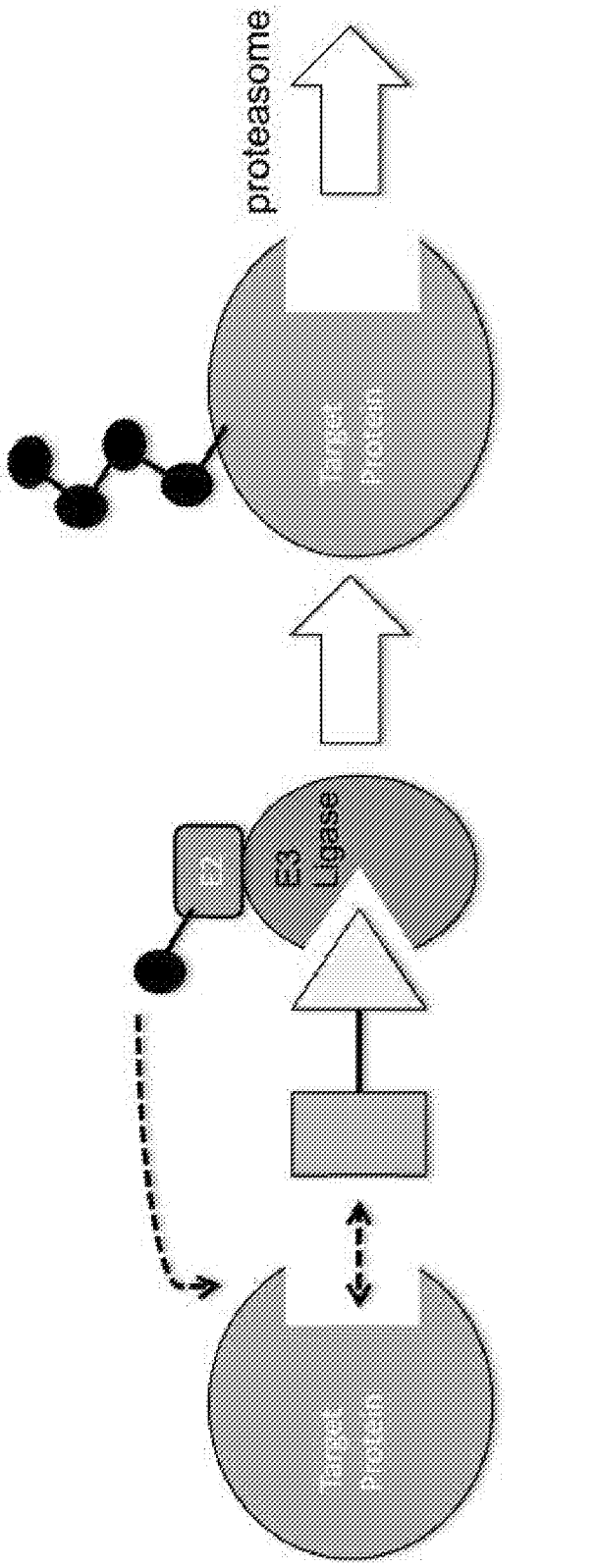

ULM
L
PTM

FIG. 1B


Degraded Target Protein
proteasome
Target Protein
E3 Ligase
E2
Target Protein

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/026570

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D471/04 C07D487/04 C07D495/14 A61P35/00
A61K31/438 A61K31/496 A61K31/53 A61K31/519
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/197051 A1 (C4 THERAPEUTICS INC [US]) 16 November 2017 (2017-11-16) page 19; claims compounds 179, 182, 197-202, 212, 213, 222, 224-225, 232, 235-236, 240, 249, 251, 291-296, 298, 301-305, 307-328.	1
X	US 2008/051432 A1 (ZHANG HESHENG [CN]) 28 February 2008 (2008-02-28) claims; figures	1
X	WO 2015/160845 A2 (ARVINAS INC [US]) 22 October 2015 (2015-10-22) claim 7 pages 25-29 page 108	1

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 May 2019	25/07/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Österle, Carmen

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/026570

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ASHTON C. LAI ET AL: "Modular PROTAC Design for the Degradation of Oncogenic BCR-ABL", ANGEWANDTE CHEMIE, INTERNATIONAL EDITION, vol. 55, no. 2, 11 January 2016 (2016-01-11), pages 807-810, XP055388339, DE ISSN: 1433-7851, DOI: 10.1002/anie.201507634 page 10; figure 5	1
X	RUCHELMAN ALEXANDER L ET AL: "Isosteric analogs of lenalidomide and pomalidomide: Synthesis and biological activity", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 23, no. 1, 27 October 2012 (2012-10-27), pages 360-365, XP028961553, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2012.10.071 scheme 1; page 361 page 363; table 1	1
X,P	WO 2019/038717 A1 (NOVARTIS AG [CH]; BECKWITH ROHAN ERIC JOHN [US] ET AL.) 28 February 2019 (2019-02-28) claims; examples	1
X,P	WO 2019/042444 A1 (SHANGHAI MEIZER PHARMACEUTICALS CO LTD [CN]) 7 March 2019 (2019-03-07) scheme a) and b); page 4 pages 10,12-14	1
X,P	WO 2018/226542 A1 (ARVINAS INC [US]; UNIV YALE [US]) 13 December 2018 (2018-12-13) page 129 - page 152 page 310 claims 9-12	1
X,P	WO 2018/102725 A1 (ARVINAS INC [US]) 7 June 2018 (2018-06-07) page 382 - page 398 claim 8; examples	1
X,P	WO 2019/014429 A1 (DANA FARBER CANCER INST INC [US] ET AL.) 17 January 2019 (2019-01-17) pages 155,161 pages 165,167	1

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claim: 1

   Cereblon E3 ubiquitin ligase binding compound

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2. claims: 17, 18(completely); 2-16, 24-38(partially)

   Bifunctional compound having the chemical structure as claimed in claim 2, wherein the group PTM is an estrogen binding moiety as defined in claims 17 and 18. Compositions comprising said compound and medical use of said compounds or compositions.

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3. claims: 19(completely); 2-16, 24-38(partially)

   Bifunctional compound having the chemical structure as claimed in claim 2, wherein the group PTM is an androgen receptor binding moiety as defined in claim 19. Compositions comprising said compound and medical use of said compounds or compositions.

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4. claims: 20(completely); 2-16, 23-38(partially)

   Bifunctional compound having the chemical structure as claimed in claim 2, wherein the group PTM is a BET targeting moiety as defined in claim 20. Compositions comprising said compound and medical use of said compounds or compositions.

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5. claims: 21, 22(completely); 2-16, 23-38(partially)

   Bifunctional compound having the chemical structure as claimed in claim 2, wherein the group PTM is BRaf targeting moiety as defined in claim 21. Compositions comprising said compound and medical use of said compounds or compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2019/026570

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		WO 2017197051 A1	16-11-2017
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