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(54) Title: INDAZOLE BASED COMPOUNDS AND ASSOCIATED METHODS OF USE

(57) Abstract: Bifunctional compounds, which find utility as modulators of leucine-rich repeat kinase 2 (LRRK2), are described herein. In particular, the hetero-bifunctional compounds of the present disclosure contain on one end a moiety that binds to the cereblon E3 ubiquitin ligase and on the other end a moiety which binds LRRK2, such that the target protein is placed in proximity to the ubiquitin ligase to effect degradation (and inhibition) of target protein. The hetero-bifunctional compounds of the present disclosure exhibit a broad range of pharmacological activities associated with degradation/inhibition of target protein. Diseases or disorders that result from aberrant regulation of the target protein are treated or prevented with compounds and compositions of the present disclosure.



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## INDAZOLE BASED COMPOUNDS AND ASSOCIATED METHODS OF USE

### CROSS-REFERENCE TO RELATED APPLICATIONS

**[0001]** The present disclosure claims benefit of and priority to U.S. Provisional Application No. 62/992,952, filed 21 March 2020, titled INDAZOLE BASED COMPOUNDS AND ASSOCIATED METHODS OF USE, which is incorporated herein in by reference in its entirety for all purposes.

### INCORPORATION BY REFERENCE

**[0002]** All cited references are hereby incorporated herein by reference in their entirety, including 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. 15/953,108, filed on April 13, 2018, published as U.S. Patent Application Publication No. 2018/0228907; and U.S. Patent Application Publication No. 2016/0009689 A1, filed 2 September 2015; and U.S. Patent Application Publication No. 2016/0200722 A1, filed 18 February 2016.

### FIELD OF THE INVENTION

The invention provides hetero-bifunctional compounds comprising a target protein binding moiety and a E3 ubiquitin ligase binding moiety, and associated methods of use. The bifunctional compounds are useful as modulators of targeted ubiquitination of leucine-rich repeat kinase 2 (LRRK2), which is then degraded and/or inhibited.

### BACKGROUND

**[0003]** 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 that 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.

**[0004]** 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 ubiquitination 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.

**[0005]** Bifunctional compounds such as those described in U.S. Patent Application Publications 2015/0291562 and 2014/0356322 (incorporated herein by reference), function to recruit endogenous proteins to an E3 ubiquitin ligase for ubiquitination and subsequent degradation in the proteasome degradation pathway. In particular, the publications cited above describe bifunctional or proteolysis-targeting chimeric (PROTAC<sup>®</sup>) protein degrader compounds, which find utility as modulators of targeted ubiquitination of a variety of polypeptides and proteins, which are then degraded and/or inhibited by the bifunctional compounds.

**[0006]** Leucine-rich repeat kinase 2 (LRRK2) is a member of the leucine-rich repeat kinase family and is a large multi-domain protein with an N-terminal armadillo domain, ankryin repeat region, a leucine-rich repeat (LRR) domain, a tandem Roco type GTPase domain, a kinase domain containing a DFG-like motif, and a C-terminal WD40 domain. The LRRK2 protein is 2527 amino acids and a molecular weight of 280 kDa. Catalytic activities of LRRK2 are associated with the kinase and GTPase domain, and LRRK2 is a heterodimer in its active form (*Greggio E, et al.*: The Parkinson disease-associated leucine-rich repeat kinase 2 (LRRK2) is a dimer that undergoes intramolecular autophosphorylation. *J Biol Chem* 2008, 283:16906–16914). GTP binding is essential for kinase activity, and mutations that prevent GTP binding have been

shown to ablate LRRK2 kinase activity (*Ito G, et al.*: GTP binding is essential to the protein kinase activity of LRRK2, a causative gene product for familial Parkinson's disease. *Biochemistry* 2007, 46:1380–1388). The only validated physiological substrates (other than LRRK2 itself) are a subset of low-molecular weight G-proteins including Rab8a and Rab10, which are involved in regulation of vesicle trafficking and endosome function and trafficking on cytoskeletal networks (*Steger M, et al.*: Phosphoproteomics reveals that Parkinson's disease kinase LRRK2 regulates a subset of Rab GTPases. *Elife* 2016, 5. e12813). Expression levels of LRRK2 are highest in immune cells (neutrophils, monocytes and B cells), lung and kidney, with lower levels in the brain where it is expressed in dopaminergic neurons of the substantia nigra (*West AB, et al.*: Differential LRRK2 expression in the cortex, striatum, and substantia nigra in transgenic and nontransgenic rodents. *J Comp Neurol* 2014, 522:2465–2480).

**[0007]** There are several dominant gain-of-function pathogenic and characterized mutations to LRRK2, located either in the Roco domains (N1437H, R1441G/C/H, Y1699C), effecting GTP hydrolysis, or in the kinase domain (G2019S and I2020T). The G2019S is the most common LRRK2 mutation linked to Parkinson's disease (PD), which is a progressive neurodegenerative disorder characterized by resting tremors, rigidity, decreased movement (bradykinesia), and postural instability. The histological hallmarks of PD include neurodegeneration of the dopaminergic neurons in the substantia nigra pars compacta as well as intracellular inclusions called Lewy bodies and neurites consisting of the aggregated form of the alpha-synuclein protein. G2019S is associated with 1-2% of all PD patients and causes an increase in kinase activity of 2-fold *in vitro* (*West AB, et al.*: Parkinson's disease-associated mutations in leucine-rich repeat kinase 2 augment kinase activity. *Proc Natl Acad Sci U S A* 2005, 102: 16842–16847) and autophosphorylation at Ser1292 is increased 4-fold (*Sheng Z, et al.*: Ser1292 autophosphorylation is an indicator of LRRK2 kinase activity and contributes to the cellular effects of PD mutations. *Sci Transl Med* 2012, 4:164ra161). The G2019S and I2020T mutations lie within the DFG motif (DYGI in the case of LRRK2), common to all kinases, which controls catalytic activity. These mutations are thought to disrupt the inactive conformation and thus increase catalytic activity (*Schmidt SH, et al.*: The dynamic switch mechanism that leads to activation of LRRK2 is embedded in the DFGpsi motif in the kinase domain. *Proc Natl Acad Sci USA* 2019, 116:14979–14988). Several of the above Parkinson disease-associated mutations (R1441C/G, Y1699C and I2020T) suppress phosphorylation of LRRK2 at Ser910 and Ser935,



which in turn reduces LRRK2 association with 14-3-3 proteins, thought to represent an inactive form of LRRK2 ( *Nichols J, et al.*: 14-3-3 binding to LRRK2 is disrupted by multiple Parkinson's disease associated mutations and regulates cytoplasmic localisation. *Biochem J* 2010, 430:393–404).

**[0008]** Furthermore, LRRK2 is linked to autosomal dominant inherited PD through a mutation within a region of chromosome 12, termed PARK8, which is linked to the LRRK2 gene (*Funayama M, et al.*: A new locus for Parkinson's disease (PARK8) maps to chromosome 12p11.2-q13.1. *Ann Neurol* 2002, 51:296–301; *Zimprich A, et al.*: Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. *Neuron* 2004, 44:601–607; *Paisan-Ruiz C, et al.*: Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. *Neuron* 2004, 44:595–600). LRRK2 was first described as having a link to autosomal dominant inherited Parkinson's disease in 1978, where it was traced to a family in Japan (*Nukada H, et al.*: [A big family of paralysis agitans (author's transl)]. *Rinsho Shinkeigaku* 1978, 18:627–634). The most common pathogenic LRRK2 mutation (G2019S) occurs in 4-8% of familial and 1-3% of sporadic PD cases. In addition, the G2019S mutation is common among PD patients of select ancestry, with 30-40% of North African Berber and 14% of Jewish patients harboring the mutation.

**[0009]** LRRK2 kinase inhibitors have been proposed as having the potential to treat mutation-driven PD, where there is an increase in LRRK2 activity, such as G2019S, and idiopathic PD, where the activity of LRRK2 is increased (*Chen J, et al.*: Leucine-rich repeat kinase 2 in Parkinson's disease: updated from pathogenesis to potential therapeutic target. *Eur Neurol* 2018, 79:256–265; *Alessi DR, et al.*: LRRK2 kinase in Parkinson's disease. *Science* 2018, 360:36–37; *Di Maio R, et al.*: LRRK2 activation in idiopathic Parkinson's disease. *Sci Transl Med* 2018, 10). Several therapeutics are progressing into the clinic, including LRRK2 kinase inhibitors that will directly affect phosphorylation of downstream targets, and oligonucleotides (ASO's) directly infused into the CNS to block translation of LRRK2 protein, thereby reducing LRRK2 protein levels.

**[0010]** Lewy bodies are the main histological hallmark of PD. Lewy bodies are composed primarily of alpha-synuclein aggregates, and mutations in alpha-synuclein that increase this aggregation also increase the risk of developing PD (*Meade RM, et al.*: Alpha-synuclein structure and Parkinson's disease lessons and emerging principles. *Mol Neurodegener* 2019, 14.

29-29). Depletion of LRRK2 with ASOs (Zhao HT, et al.: LRRK2 antisense oligonucleotides ameliorate a-synuclein inclusion formation in a Parkinson's disease mouse model. *Molecular therapy. Nucleic acids* 2017, 8:508–519) and deletion of LRRK2 at a genomic level have been shown to reduce alpha-synuclein mediated pathology in mouse models of PD (Lin X, et al.: Leucine-rich repeat kinase 2 regulates the progression of neuropathology induced by Parkinson's-disease-related mutant alpha-synuclein. *Neuron* 2009, 64:807–827). Mutations increasing LRRK2 activity, such as G2019S, increase the aggregation of alpha-synuclein in neurons and mouse models of PD. This increase was reversed with LRRK2 kinase inhibitors (Volpicelli-Daley LA, et al. G2019S-LRRK2 Expression Augments  $\alpha$ -Synuclein Sequestration into Inclusions in Neurons. *J Neurosci.* 2016 Jul 13; 36(28):7415-27. doi: 10.1523/JNEUROSCI.3642-15.2016). There is some evidence to suggest that the G2019S mutant form of LRRK2 is resistant to inhibition by kinase inhibitors in the CNS, potentially reducing their disease modifying effect (Kelly K, et al. The G2019S mutation in LRRK2 imparts resiliency to kinase inhibition. *Exp Neurol.* 2018 Nov; 309:1-13). Even though most cases of PD also have Lewy bodies upon post-mortem examination, Lewy bodies are not present in a high number of LRRK2 G2019S mutation associated PD cases (Kalia LV, et al.: Clinical correlations with Lewy body pathology in LRRK2-related Parkinson disease. *JAMA neurol* 2015, 72:100–105). In addition to Lewy bodies being a common feature of PD, Tau pathology is also a major feature of LRRK2 mutation carriers at post-mortem (Henderson MX, et al.: Alzheimer's disease tau is a prominent pathology in LRRK2 Parkinson's disease. *Acta Neuropathol Commun* 2019, 7. 183-183). In one study, Tau pathology was observed in 100% of LRRK2 mutation carriers, thereby highlighting LRRK2 as an important target linking PD with Tau pathology in the context of PD, even though the genetic causal link was not as strong between LRRK2 and primary tauopathies, such as supranuclear palsy (PSP) or corticobasal degeneration (CBD) (Ross OA, et al. (2006) Lrrk2 R1441 substitution and progressive supranuclear palsy. *Neuropathol Appl Neurobiol* 32(1):23–25; Sanchez-Contreras M, et al. (2017) Study of LRRK2 variation in tauopathy: progressive supranuclear palsy and corticobasal degeneration. *Mov Disord* 32(1):115–123). A common variation at the LRRK2 locus as a genetic determinant of PSP survival was recently reported (Jabbari E, et al., Common variation at the LRRK2 locus is associated with survival in the primary tauopathy progressive supranuclear palsy. *bioRxiv* 2020.02.04.932335; doi: <https://doi.org/10.1101/2020.02.04.932335>). It has been reported that increased LRRK2

expression in PSP by expression quantitative trait loci (eQTL) analysis may result in a reactive microglia-induced proinflammatory state which drives ongoing accumulation of misfolded Tau protein and clinical disease progression. Functional variants of LRRK2 have also been linked to Crohn's Disease and leprosy type 1 inflammatory reactions (*Hui KY, et al.* Functional variants in the LRRK2 gene confer shared effects on risk for Crohn's disease and Parkinson's disease. *Sci Transl Med.* 2018 Jan 10;10(423). pii: eaai7795. doi: 10.1126/scitranslmed.aai7795; *Fava et al.* Pleiotropic effects for Parkin and LRRK2 in leprosy type-1 reactions and Parkinson's disease. *Proc Natl Acad Sci U S A.* 2019 Jul 30;116(31):15616-15624. doi: 10.1073/pnas.1901805116. Epub 2019 Jul 15).

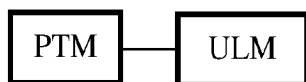
**[0011]** LRRK2 is highly expressed in the immune system in neutrophils, monocytes and macrophages, as well as in brain microglia, and is a modulator of the intrinsic regulation of microglial activation and of lysosomal degradation processes (*Ma et al.* Genetic comorbidities in Parkinson's disease. *Hum Mol Genet.* 2014 Feb 1;23(3):831-41. doi: 10.1093/hmg/ddt465. Epub 2013 Sep 20, which was reviewed in *Schapansky et al.* The complex relationships between microglia, alpha-synuclein, and LRRK2 in Parkinson's disease. *Neuroscience.* 2015 Aug 27;302:74-88. doi: 10.1016/j.neuroscience.2014.09.049. Epub 2014 Oct 2). Prolonged activation of these immune cells through PD disease processes or mutations in LRRK2 could increase neuroinflammation and lead to a greater risk of developing PD and/or Tau pathology. Treatment with anti-TNF agents reduces the risk of developing PD by 78% in patients with inflammatory bowel disorder (*Peter I, et al.*: Anti-tumor necrosis factor therapy and incidence of Parkinson disease among patients with inflammatory bowel disease. *JAMA Neurol* 2018), thereby demonstrating the strong linkage between inflammation and PD. In addition to PD, LRRK2 has been linked to other diseases such as cancer, leprosy, and Crohn's disease (*Lewis PA, Manzoni C.* LRRK2 and human disease: a complicated question or a question of complexes? (2012). *Sci Signal.* 5(207), pe2).

**[0012]** An ongoing need exists in the art for effective treatments for LRRK2 related disease and disorders, e.g., idiopathic PD, LRRK2 mutation associated PD (e.g., PD associated with one or more LRRK2 activating mutations), primary tauopathies (e.g., supranuclear palsy (PSP) or corticobasal degeneration (CBD)), lewy body dementia, Crohn's Disease, Leprosy (e.g., Leprosy with type 1 inflammatory reactions), and/or neuroinflammation.

## SUMMARY

**[0013]** The present disclosure describes hetero-bifunctional compounds that function to recruit leucine-rich repeat kinase 2 (LRRK2) to an E3 ubiquitin ligase for targeted ubiquitination and subsequent proteasomal degradation, and methods of making and using the same. In addition, the description provides methods of using an effective amount of a compound of the present disclosure for the treatment or amelioration of a disease condition, such as an LRRK2-related disease or disorder, e.g., accumulation or overactivity of an LRRK2 protein or a mutated LRRK2 protein or a mis-folded LRRK2 protein, or alpha-synuclein aggregation or accumulation, or Tau aggregation or accumulation, or idiopathic PD, or a LRRK2 mutation associated PD (e.g., PD associated with one or more LRRK2 activating mutations), or a primary tauopathy (e.g., supranuclear palsy (PSP) or corticobasal degeneration (CBD)), or lewy body dementia, or Crohn's Disease, or Leprosy (e.g., Leprosy with type 1 inflammatory reactions), or neuroinflammation.

**[0014]** As such, in one aspect the disclosure provides hetero-bifunctional compounds, which comprise an E3 ubiquitin ligase binding moiety (i.e., a ligand for an E3 ubiquitin ligase (a "ULM" group)), and a moiety that binds LRRK2 or a mutated version thereof (i.e., a protein targeting moiety or "PTM" group, that is, a LRRK2 targeting ligand or a "LTM" group) such that the LRRK2 protein is thereby placed in proximity to the ubiquitin ligase to effect ubiquitination and subsequent degradation (and/or inhibition) of the LRRK2 protein. In a preferred embodiment, the ULM (ubiquitination ligase binding moiety) is a cereblon E3 ubiquitin ligase binding moiety (CLM). For example, the structure of the bifunctional compound can be depicted as:



**[0015]** The respective positions of the PTM and ULM moieties (e.g., CLM), 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.

**[0016]** 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 LRRK2-targeting moiety (LTM), L is a linker, e.g., a bond or a chemical linking group coupling PTM to ULM, and ULM is a cereblon E3 ubiquitin ligase binding moiety (CLM).

**[0017]** For example, the structure of the bifunctional compound can be depicted as:



wherein: PTM is a LRRK2-targeting moiety (LTM); “L” is a linker (e.g. a bond or a chemical linking group) coupling the PTM and CLM; and CLM is cereblon E3 ubiquitin ligase binding moiety that binds to cereblon.

**[0018]** In certain embodiments, the compounds as described herein comprise multiple independently selected ULMs, multiple PTMs, multiple chemical linkers or a combination thereof.

**[0019]** In any of the aspects or embodiments described herein, the PTM is a small molecule that binds LRRK2 or a mutant thereof. In any of the aspects or embodiments described herein, the PTM is a small molecule that binds LRRK2. In any of the aspects or embodiments described herein, the PTM is a small molecule that binds both an LRRK2 wild type protein and an LRRK2 mutant, such as a LRRK2 mutant including one or more mutation selected from G2019S, I2020T, N1437H, R1441G/C/H, and Y1699C. In any of the aspects or embodiments described herein, the PTM is a small molecule that binds both an LRRK2 wild type protein and an LRRK2 mutant such as, but not limited to, G2019S, I2020T, N1437H, R1441G/C/H, Y1699C, or a combination thereof. In any aspect or embodiment described herein, the small molecule binds the LRRK2 is as described herein.

**[0020]** In an embodiment, the CLM comprises a chemical group derived from an imide, a thioimide, an amide, or a thioamide. In a particular embodiment, the chemical group is a phthalimido group, or an analog or derivative thereof. In a certain embodiment, the CLM is selected from thalidomide, lenalidomide, pomalidomide, analogs thereof, isosteres thereof, and

derivatives thereof. Other contemplated CLMs are described in U.S. Patent Application Publication No. 2015/0291562, which is incorporated herein by reference in its entirety.

**[0021]** In certain embodiments, “L” is a bond. In additional embodiments, the linker “L” is a connector with a linear non-hydrogen atom number in the range of 1 to 20. The connector “L” can contain, but is not limited to, one or more functional groups such as ether, amide, alkane, alkene, alkyne, ketone, hydroxyl, carboxylic acid, thioether, sulfoxide, and sulfone. The linker can contain aromatic, heteroaromatic, cyclic, bicyclic or tricyclic moieties. Substitution with halogen, such as Cl, F, Br and I can be included in the linker. In the case of fluorine substitution, single or multiple fluorines can be included.

**[0022]** In certain embodiments, CLM is a derivative of piperidine-2,6-dione, where piperidine-2,6-dione can be substituted at the 3-position, and the 3-substitution can be bicyclic hetero-aromatics with the linkage as C-N bond or C-C bond. Examples of CLM can be, but are not limited to, pomalidomide, lenalidomide and thalidomide and their analogs.

**[0023]** In an additional aspect, the description provides therapeutic compositions comprising an effective amount of a compound as described herein, or a salt form thereof, and a pharmaceutically acceptable carrier. The therapeutic compositions can be used to trigger targeted degradation of LRRK2 or a mutated version thereof and/or inhibition of LRRK2 or a mutated version thereof, in a patient or subject, for example, an animal such as a human, and can be used for treating or ameliorating one or more disease states, conditions, or symptoms causally related to LRRK2 or mutated version thereof, which treatment is accomplished through degradation or inhibition of the LRRK2 protein or mutated version thereof, or controlling or lowering LRRK2 protein levels or protein levels of a mutated version thereof, in a patient or subject. In certain embodiments, the therapeutic compositions as described herein may be used to effectuate the degradation of LRRK2, or a mutant form thereof, for the treatment or amelioration of a disease such as, e.g., LRRK2 accumulation or overactivity, alpha-synuclein aggregation or accumulation, Tau aggregation or accumulation, idiopathic PD, LRRK2 mutation associated PD (e.g., PD associated with one or more LRRK2 activating mutations), primary tauopathies (e.g., supranuclear palsy (PSP) or corticobasal degeneration (CBD)), lewy body dementia, Crohn’s Disease, Leprosy (e.g., Leprosy with type 1 inflammatory reactions), and/or neuroinflammation.

[0024] In yet another aspect, the present disclosure provides a method of ubiquitinating LRRK2 or a mutated form thereof in a cell. In certain embodiments, the method comprises administering a hetero-bifunctional compound as described herein comprising a PTM that binds LRRK2 or a mutant form thereof, and a CLM, preferably linked through a chemical linker moiety, as described herein, to effectuate degradation of the LRRK2 protein or mutant form thereof. Though not wanting to be limited by theory, the inventors believe that, pursuant to the invention, poly-ubiquitination of the LRRK2 wild-type or mutant protein will occur when it is placed in proximity to the E3 ubiquitin ligase via use of the hetero-bifunctional compound, thereby triggering subsequent degradation of the LRRK2 or mutant protein via the proteasomal pathway and control or reduction of LRRK2 protein levels in cells, such as cells of a subject in need of such treatment. The control or reduction in levels of the LRRK2 protein or mutated form thereof afforded by the present disclosure provides treatment of a LRRK2 causally related disease state, condition or related symptom, as modulated through a lowering of the amount of LRRK2 protein or mutated form thereof in cells of the subject.

[0025] In still another aspect, the description provides methods for treating or ameliorating a disease, condition, or symptom thereof causally related to LRRK2 or mutated form 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 hetero-bifunctional 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.

[0026] In another aspect, the description provides methods for identifying the effects of the degradation of LRRK2 protein in a biological system using compounds according to the present disclosure.

[0027] In another aspect, the description provides processes and intermediates for making a hetero-bifunctional compound of the present disclosure capable of targeted ubiquitination and degradation of the LRRK2 protein in a cell (e.g., *in vivo* or *in vitro*).

## BRIEF DESCRIPTION OF THE DRAWINGS

[0028] The accompanying drawings, which are incorporated into and form a part of the specification, illustrate several embodiments of the present disclosure and, together with the

description, serve to explain the principles of the disclosure. The drawings are only for the purpose of illustrating embodiments of the disclosure and are not to be construed as limiting the disclosure. Further objects, features and advantages of the disclosure will become apparent from the following detailed description taken in conjunction with the accompanying figures showing illustrative embodiments of the disclosure.

**[0029] Figures 1A and 1B.** Illustration of general principle for hetero-bifunctional protein-degrading compounds. Figure 1A. Exemplary hetero-biofunctional protein degrading compounds 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 the PTM to the ULM. Figure 1B Illustrates the functional use of the hetero-bifunctional protein degrading compounds (commercially known as PROTAC<sup>®</sup> protein degrader compounds) as described herein. Briefly, the ULM (triangle) recognizes and binds to a specific E3 ubiquitin ligase, and the PTM (large rectangle) 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 (E2), and either alone or via the E2 protein catalyzes attachment of multiple ubiquitin molecules (*black circles*) to a lysine on the target protein via an isopeptide bond. The poly-ubiquitinated protein (*far right*) has thereby been targeted for degradation by the proteosomal machinery of the cell.

## DETAILED DESCRIPTION

**[0030]** Presently described are compounds, compositions and methods that relate to the surprising discovery that an E3 ubiquitin ligase (e.g., a cereblon E3 ubiquitin ligase) ubiquitinates the LRRK2 protein or mutated form thereof once the E3 ubiquitin ligase and the LRRK2 protein are placed in proximity via a bifunctional compound that binds both the E3 ubiquitin ligase and the LRRK2 protein. Accordingly the present disclosure provides compounds and compositions comprising an E3 ubiquitin ligase binding moiety (“ULM”) coupled by a bond or chemical linking group (L) to a protein targeting moiety (“PTM”) that targets the LRRK2 protein, which results in the ubiquitination of the LRRK2 protein, and which leads to degradation of the LRRK2 protein by the proteasome (*see* FIG. 1).



**[0031]** In one aspect, the description provides compounds in which the PTM binds to the LRRK2 protein and/or a mutated form thereof. The present disclosure also provides a library of compositions and the use thereof to produce targeted degradation of the LRRK2 protein in a cell.

**[0032]** In certain aspects, the present disclosure provides hetero-bifunctional 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 an E3 ubiquitin ligase, such as cereblon. The compounds also comprise a small molecule moiety that is capable of binding to the LRRK2 protein or mutated form thereof in such a way that the LRRK2 protein or mutated form is placed in proximity to the ubiquitin ligase to effect ubiquitination and degradation (and/or inhibition) of the LRRK2 protein or mutated form. “Small molecule” means, in addition to the above, that the molecule is non-peptidyl, that is, it is not considered a peptide, e.g., comprises fewer than 4, 3, or 2 amino acid residues. In accordance with the present description, each of the PTM, ULM and hetero-bifunctional molecule is a small molecule.

**[0033]** The term “LRRK2” as used throughout the Specification, unless specifically indicated to the contrary, is intended to include both wild-type LRRK2 and mutant forms therefore, such as a LRRK2 mutant protein including one or more mutation selected from G2019S, I2020T, N1437H, R1441G/C/H, and Y1699C.

**[0034]** 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 disclosure belongs. The terminology used in the description is for describing particular embodiments only and is not intended to be limiting of the disclosure.

**[0035]** Where a range of values is provided, it is understood that each intervening value in the range, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise (such as in the case of a group containing a number of carbon atoms in which case each carbon atom number falling within the range is provided), between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the disclosure. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges and are also encompassed within the disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either/or both of those included limits are also included in the disclosure.

**[0036]** The following terms are used to describe the present disclosure. In instances where a term is not specifically defined herein, that term is given an art-recognized meaning by those of ordinary skill applying that term in context to its use in describing the present disclosure.

**[0037]** 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, unless otherwise indicated.

**[0038]** 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.

**[0039]** It should also be understood that, in certain methods or processes 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.

**[0040]** 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 two or more 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 hetero-bifunctional compounds described herein are coadministered with at least one additional bioactive agent, e.g., an anticancer agent. In particularly preferred aspects, the co-administration of such compounds results in synergistic activity and/or therapy such as, e.g., anticancer activity.

**[0041]** The term "compound", as used herein, unless otherwise indicated, refers to any specific hetero-bifunctional compound disclosed herein, pharmaceutically acceptable salts and solvates thereof, and deuterated forms of any of the aforementioned molecules, where applicable. Deuterated compounds contemplated are those in which one or more of the hydrogen atoms contained in the drug molecule have been replaced by deuterium. Such deuterated compounds

preferably have one or more improved pharmacokinetic or pharmacodynamic properties (e.g., longer half-life) compared to the equivalent “undeuterated” compound.

**[0042]** The term “ubiquitin ligase” refers to a family of proteins that facilitate the transfer of one or more ubiquitins to a specific substrate protein. Addition of a chain of several ubiquitins (poly-ubiquitination) targets the substrate protein for degradation. For example, cereblon is an E3 ubiquitin ligase that alone, or in combination with an E2 ubiquitin-conjugating enzyme, can ultimately cause the attachment of a chain of four ubiquitins to a lysine residue on the target protein, thereby targeting the protein for degradation by the proteasome. The ubiquitin ligase is involved in poly-ubiquitination such that a first ubiquitin is attached to a lysine on the target protein; a second ubiquitin is attached to the first; a third is attached to the second, and a fourth is attached to the third. Such poly-ubiquitination marks proteins for degradation by the proteasome.

**[0043]** 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 diseases, conditions or symptoms that 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 terms “patient” and “subject” refer to a human patient unless otherwise stated or implied from the context of the use of the term.

**[0044]** The terms “effective” and “therapeutically effective” are used to describe an amount of a compound or composition which, when used within the context of its intended use, and either in a single dose or, more preferably after multiple doses within the context of a treatment regimen, effects an intended result such as an improvement in a disease or condition, or amelioration or reduction in one or more symptoms associated with a disease or condition. The terms “effective” and “therapeutically effective” subsume all other “effective amount” or “effective concentration” terms, which are otherwise described or used in the present application.

**[0045]     Compounds and Compositions**

**[0046]** In one aspect, the description provides hetero-bifunctional compounds comprising an E3 ubiquitin ligase binding moiety (“ULM”) that is a cereblon E3 ubiquitin ligase binding moiety (a “CLM”), The CLM is covalently coupled to a protein targeting moiety (PTM) that

binds to the protein, which coupling is either directly by a bond or via a chemical linking group (L) according to the structure:



wherein L is the bond or chemical linking group, and PTM is a protein targeting moiety that binds to the protein LRRK2 or a mutant form thereof, e.g., G2019S, where the PTM is a LRRK2 targeting moiety (LTM). The term CLM is inclusive of all cereblon binding moieties.

**[0047]** In any of the aspects or embodiments, the CLM demonstrates a half maximal inhibitory concentration ( $IC_{50}$ ) for the E3 ubiquitin ligase (e.g., cereblon E3 ubiquitin ligase) of less than about 200  $\mu\text{M}$ . The  $IC_{50}$  can be determined according to any suitable method known in the art, e.g., a fluorescent polarization assay.

**[0048]** In certain embodiments, the hetero-bifunctional compounds described herein demonstrate an  $IC_{50}$  or a half maximal degradation concentration ( $DC_{50}$ ) of less than about 100, 50, 10, 1, 0.5, 0.1, 0.05, 0.01, 0.005, 0.001 mM, or less than about 100, 50, 10, 1, 0.5, 0.1, 0.05, 0.01, 0.005, 0.001  $\mu\text{M}$ , or less than about 100, 50, 10, 1, 0.5, 0.1, 0.05, 0.01, 0.005, 0.001 nM, or less than about 100, 50, 10, 1, 0.5, 0.1, 0.05, 0.01, 0.005, 0.001 pM.

**[0049]** The term “alkyl” shall mean within its context a linear, branch-chained or cyclic fully saturated hydrocarbon radical, preferably a  $C_1$ - $C_{10}$ , preferably a  $C_1$ - $C_6$ , or more preferably a  $C_1$ - $C_3$  alkyl group, which may be optionally substituted with any suitable functional group or groups. 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).

**[0050]** 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.

**[0051]** 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  $C\equiv C$  bond.

**[0052]** 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 suitable functional group) which may be further substituted with a polyethylene glycol chain (of from 1 to 10, preferably 1 to 6, or more preferably 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 (e.g., 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,  $\beta$ -alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, glutamine, glycine, phenylalanine, histidine, isoleucine, lysine, leucine, methionine, proline, serine, threonine, valine, tryptophan or tyrosine.

**[0053]** The term “unsubstituted” shall mean substituted only with hydrogen atoms. A range of carbon atoms which includes C<sub>0</sub> means that carbon is absent and is replaced with H. Thus, a range of carbon atoms which is C<sub>0</sub>-C<sub>6</sub> includes carbons atoms of 1, 2, 3, 4, 5 and 6 and for C<sub>0</sub>, H stands in place of carbon.

**[0054]** The term “substituted” or “optionally substituted” shall mean independently (i.e., where more than one substituent occurs, each substituent is selected independent of another substituent) one or more substituents (independently up to five substituents, preferably up to three substituents, more preferably 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 possible substituents hydroxyl, thiol, carboxyl, cyano (C $\equiv$ N), nitro (NO<sub>2</sub>), halogen (preferably, 1, 2 or 3 halogens, especially on an alkyl, especially a methyl group such as a trifluoromethyl), an alkyl group (preferably, C<sub>1</sub>-C<sub>10</sub>, more preferably, C<sub>1</sub>-C<sub>6</sub>), aryl (especially phenyl and substituted phenyl, for example benzyl or benzoyl), alkoxy group (preferably, C<sub>1</sub>-C<sub>6</sub> alkyl or aryl, including phenyl and substituted phenyl), thioether (preferably, C<sub>1</sub>-C<sub>6</sub> alkyl or aryl), acyl (preferably, C<sub>1</sub>-C<sub>6</sub> acyl), ester or thioester (preferably, C<sub>1</sub>-C<sub>6</sub> 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<sub>1</sub>-C<sub>6</sub> alkyl or aryl group), halogen (preferably, F or Cl), amine (including a five- or six-membered cyclic alkylene amine, further including a C<sub>1</sub>-C<sub>6</sub> alkyl amine or a C<sub>1</sub>-C<sub>6</sub> dialkyl amine which alkyl groups may be substituted with one or two hydroxyl groups) or an optionally substituted -N(C<sub>0</sub>-C<sub>6</sub> alkyl)C(O)(O-C<sub>1</sub>-C<sub>6</sub> 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 are preferably independently substituted with one or two C<sub>1</sub>-C<sub>6</sub> alkyl groups (including a carboxamide which is optionally substituted with one or two C<sub>1</sub>-C<sub>6</sub> alkyl groups), alkanol (preferably, C<sub>1</sub>-C<sub>6</sub> alkyl or aryl), or alkanoic acid (preferably, C<sub>1</sub>-C<sub>6</sub> alkyl or aryl). Substituents according to the present disclosure may include, for example -SiR<sub>1</sub>R<sub>2</sub>R<sub>3</sub> groups where each of R<sub>1</sub> and R<sub>2</sub> is as otherwise described herein and R<sub>3</sub> is H or a C<sub>1</sub>-C<sub>6</sub> alkyl group, preferably R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> together is a C<sub>1</sub>-C<sub>3</sub> alkyl group (including an isopropyl or t-butyl group). Each of the above-described groups may be linked directly to the substituted moiety or alternatively, the substituent may be linked to the substituted moiety (preferably in the case of an aryl or heteroaryl moiety) through an optionally substituted -(CH<sub>2</sub>)<sub>m</sub>- or alternatively an optionally substituted -(OCH<sub>2</sub>)<sub>m</sub>-, -(OCH<sub>2</sub>CH<sub>2</sub>)<sub>m</sub>- or -(CH<sub>2</sub>CH<sub>2</sub>O)<sub>m</sub>- group, which may be substituted with any one or more of the above-described substituents. Alkylene groups -(CH<sub>2</sub>)<sub>m</sub>- or -(CH<sub>2</sub>)<sub>n</sub>- groups or other chains such as ethylene glycol chains, as identified above, may be substituted anywhere on the chain. Preferred substituents on alkylene groups include halogen or C<sub>1</sub>-C<sub>6</sub> (preferably C<sub>1</sub>-C<sub>3</sub>) alkyl groups, which may be optionally substituted with one or two hydroxyl groups, one or two ether groups (O-C<sub>1</sub>-C<sub>6</sub> groups), up to three halo groups (preferably F), or a side chain 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<sub>0</sub>-C<sub>6</sub> alkyl substituents, 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<sub>1</sub>-C<sub>6</sub> alkyl groups, preferably C<sub>1</sub>-C<sub>4</sub> 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.

**[0055]** The term “substituted” (each substituent being independent of any other substituent) shall also mean within its context of use C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, amido, carboxamido, sulfone, including sulfonamide, keto, carboxy, C<sub>1</sub>-C<sub>6</sub> ester (oxyester or carbonylester), C<sub>1</sub>-C<sub>6</sub> keto, urethane -O-C(O)-NR<sub>1</sub>R<sub>2</sub> or -N(R<sub>1</sub>)-C(O)-O-R<sub>1</sub>, nitro, cyano and amine (especially including a C<sub>1</sub>-C<sub>6</sub> alkylene-NR<sub>1</sub>R<sub>2</sub>, a mono- or di- C<sub>1</sub>-C<sub>6</sub> 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<sub>2</sub>)<sub>m</sub>- (here, m and n are in context, 1, 2, 3, 4, 5 or 6), -S-, -S(O)-, SO<sub>2</sub>- or -NH-C(O)-NH-, -(CH<sub>2</sub>)<sub>n</sub>OH, -(CH<sub>2</sub>)<sub>n</sub>SH, -(CH<sub>2</sub>)<sub>n</sub>COOH, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>O-(C<sub>1</sub>-C<sub>6</sub> alkyl), -(CH<sub>2</sub>)<sub>n</sub>C(O)-(C<sub>1</sub>-C<sub>6</sub> alkyl), -(CH<sub>2</sub>)<sub>n</sub>OC(O)-(C<sub>1</sub>-C<sub>6</sub> alkyl), -(CH<sub>2</sub>)<sub>n</sub>C(O)O-(C<sub>1</sub>-C<sub>6</sub> alkyl), -(CH<sub>2</sub>)<sub>n</sub>NHC(O)-R<sub>1</sub>, -(CH<sub>2</sub>)<sub>n</sub>C(O)-NR<sub>1</sub>R<sub>2</sub>, -(OCH<sub>2</sub>)<sub>n</sub>OH, -(CH<sub>2</sub>O)<sub>n</sub>COOH, C<sub>1</sub>-C<sub>6</sub> alkyl, -(OCH<sub>2</sub>)<sub>n</sub>O-(C<sub>1</sub>-C<sub>6</sub> alkyl), -(CH<sub>2</sub>O)<sub>n</sub>C(O)-(C<sub>1</sub>-C<sub>6</sub> alkyl), -(OCH<sub>2</sub>)<sub>n</sub>NHC(O)-R<sub>1</sub>, -(CH<sub>2</sub>O)<sub>n</sub>C(O)-NR<sub>1</sub>R<sub>2</sub>, -S(O)<sub>2</sub>-R<sub>S</sub>, -S(O)-R<sub>S</sub> (R<sub>S</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl or a -(CH<sub>2</sub>)<sub>m</sub>-NR<sub>1</sub>R<sub>2</sub> group), NO<sub>2</sub>, CN or halogen (F, Cl, Br, I, preferably F or Cl), depending on the context of the use of the substituent. R<sub>1</sub> and R<sub>2</sub> are each, within context, H or a C<sub>1</sub>-C<sub>6</sub> 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<sub>1</sub>-C<sub>6</sub> 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<sub>1</sub>R<sub>2</sub> group where R<sub>1</sub> and R<sub>2</sub> 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.

**[0056]** The term “aryl” or “aromatic”, in context, refers to a substituted (as otherwise described herein) or unsubstituted monovalent aromatic radical (e.g., a 5-16 membered ring) having a single ring (e.g., benzene, phenyl, benzyl, or 5, 6, 7 or 8 membered ring) or condensed rings (e.g., naphthyl, anthracenyl, phenanthrenyl, 10-16 membered ring, 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 (monocyclic) 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, thiadiazole, isothiazole, benzoxazole, benzothiazole, benzothiadiazole, phenothiazine, isoxazole, furazan, phenoxazine, pyrazoloxazole, imidazothiazole, thienofuran, furopyrrrole, pyridoxazine, furopyridine, furopyrimidine, thienopyrimidine and oxazole, among others, all of which may be optionally substituted.

**[0057]** 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 connected to a PTM group, including a ULM group, via a linker group), and/or at least one of F, Cl, OH, COOH,  $CH_3$ ,

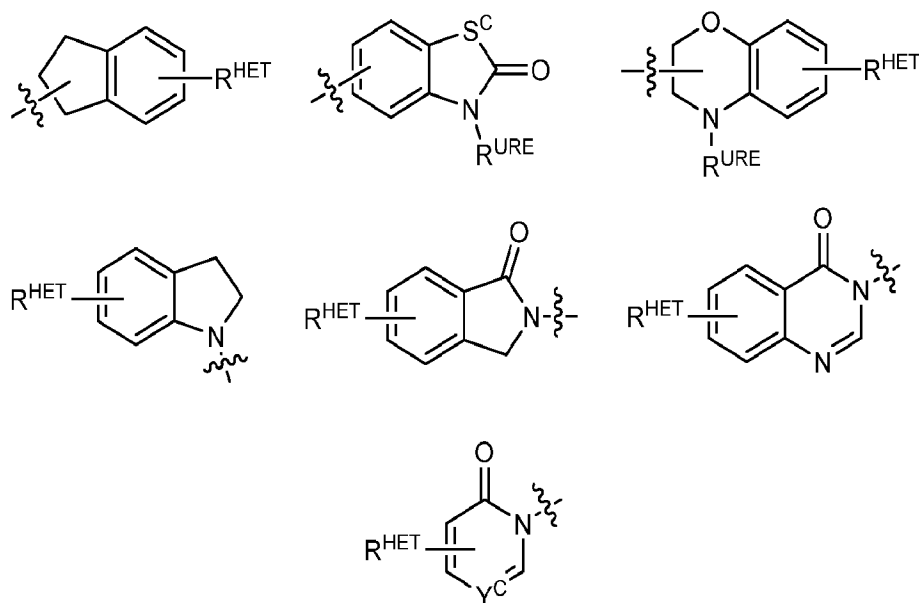


CF<sub>3</sub>, OMe, OCF<sub>3</sub>, NO<sub>2</sub>, or CN group (in ortho-, meta- and/or para- positions of the phenyl ring, preferably para-), a naphthyl group, which may be optionally substituted, an optionally substituted heteroaryl, preferably an optionally substituted isoxazole including a methyl substituted isoxazole, an optionally substituted oxazole including a methyl substituted 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 methyl substituted 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 methyl substituted pyridine 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.

**[0058]** "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.

**[0059]** The term "heteroaryl" or "hetaryl" can mean but is in no way limited to a 5-16 membered heteroaryl (e.g., 5, 6, 7 or 8 membered monocyclic ring or a 10-16 membered heteroaryl having multiple condensed rings), 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  $-C\equiv C-R_a$  where  $R_a$  is H or a  $C_1-C_6$  alkyl group (preferably  $C_1-C_3$  alkyl);

$R^{SS}$  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<sub>2</sub>, halo (preferably Cl or F), optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl (preferably substituted with one or two hydroxyl groups or up to three halo groups (e.g. CF<sub>3</sub>), optionally substituted O(C<sub>1</sub>-C<sub>6</sub> alkyl) (preferably substituted with one or two hydroxyl groups or up to three halo groups) or an optionally substituted acetylenic group  $-C\equiv C-R_a$  where  $R_a$  is H or a C<sub>1</sub>-C<sub>6</sub> alkyl group (preferably C<sub>1</sub>-C<sub>3</sub> alkyl).

**[0060]** The terms “aralkyl” and “heteroarylalkyl” refer to groups that comprise both aryl or, respectively, heteroaryl as well as alkyl and/or heteroalkyl and/or carbocyclic and/or heterocycloalkyl ring systems according to the above definitions.

**[0061]** The term “arylalkyl” as used herein refers to an aryl group as defined above appended to an alkyl group defined above. The arylalkyl group is attached to the parent moiety through an alkyl group wherein the alkyl group is one to six carbon atoms. The aryl group in the arylalkyl group may be substituted as defined above.

**[0062]** 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.

**[0063]** Exemplary heterocyclics include: azetidiny, 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, homopiperidiny, imidazolyl, imidazoliny, imidazolidiny, indoliny, indolyl, isoquinoliny, isothiazolidiny, isothiazolyl, isoxazolidiny, isoxazolyl, morpholiny, naphthyridiny, oxazolidiny, oxazolyl, pyridone, 2-pyrrolidone, pyridine, piperaziny, , N-methylpiperaziny, piperidiny, phthalimide, succinimide, pyraziny, pyrazoliny, pyridyl, pyrimidiny, pyrrolidiny, pyrroliny, pyrroly, quinoliny, tetrahydrofuranyl, tetrahydropyranyl, tetrahydroquinoline, thiazolidiny, thiazolyl, thienyl, tetrahydrothiophene, oxane, oxetanyl, oxathiolanyl, thiane among others.

**[0064]** 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, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, —SO-alkyl, —SO-substituted alkyl, —SOaryl, —SO-heteroaryl, —SO<sub>2</sub>-alkyl, —SO<sub>2</sub>-substituted alkyl, —SO<sub>2</sub>-aryl, oxo (=O), and -SO<sub>2</sub>-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).

**[0065]** The term "cycloalkyl" can mean but is in no way limited to univalent groups derived from monocyclic or polycyclic alkyl groups or cycloalkanes, as defined 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.

**[0066]** "Heterocycloalkyl" refers to a monocyclic or polycyclic alkyl group in which at least one ring carbon atom of its cyclic structure being replaced with a heteroatom selected from the group consisting of N, O, S or P. "Substituted heterocycloalkyl" refers to a monocyclic or

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

**[0067]** 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.

**[0068]** The term “independently” is used herein to indicate that the variable, which is independently applied, varies independently from application to application.

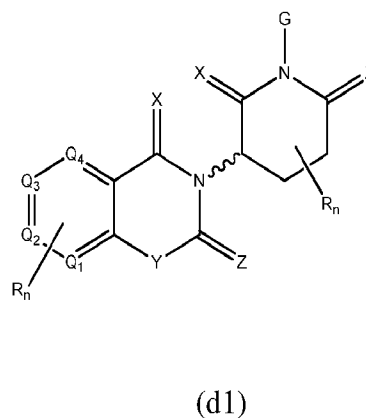
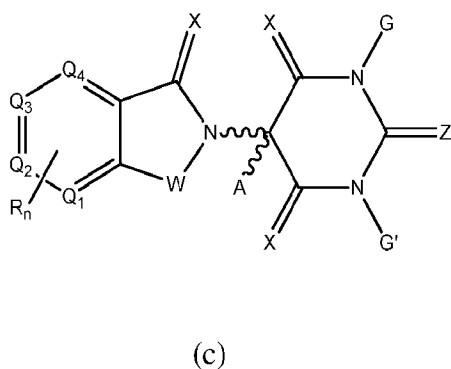
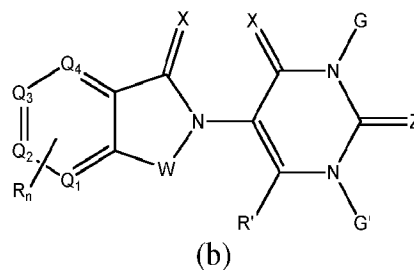
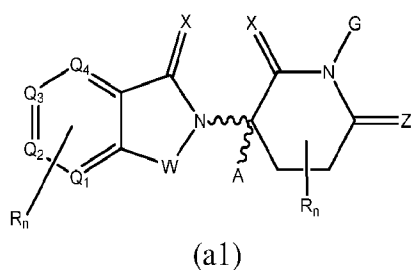
**[0069]** The term “lower alkyl” refers to methyl, ethyl or propyl

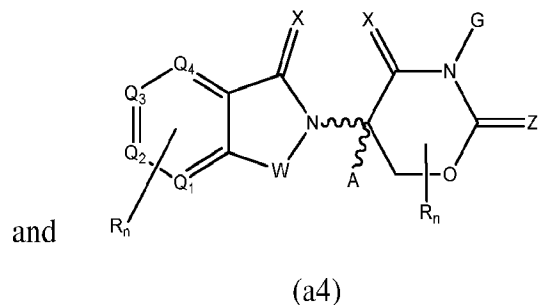
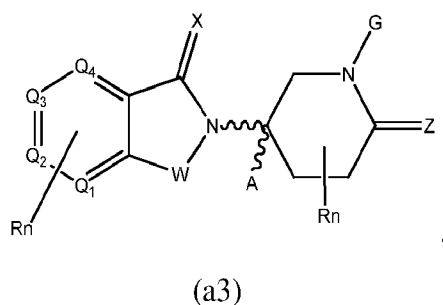
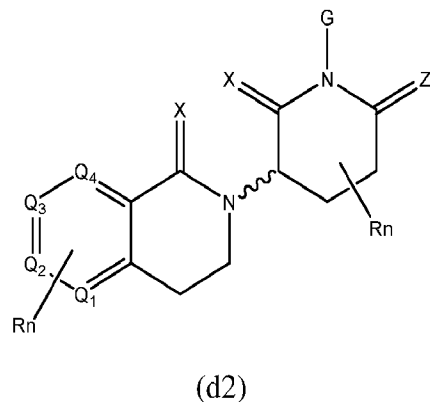
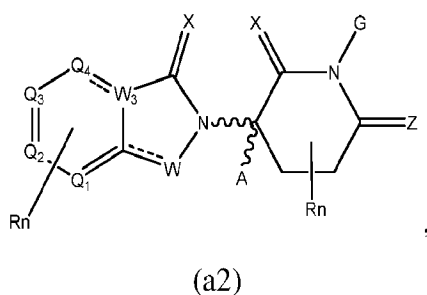
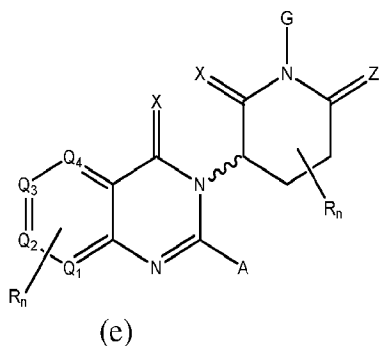
**[0070]** The term “lower alkoxy” refers to methoxy, ethoxy or propoxy.

**[0071]** **Exemplary CLMs**

**[0072]** **Neo-imide Compounds**

**[0073]** In one aspect the description provides CLMs useful for binding and recruiting cereblon. In certain embodiments, the CLM is selected from the group consisting of chemical structures:





wherein:

W of Formulas (a1) through (e) [e.g., (a1), (a2), (a3), (a4), (b), (c), (d1), (d2), and (e)] is independently selected from the group CH<sub>2</sub>, O, CHR, C=O, SO<sub>2</sub>, NH, N, optionally substituted cyclopropyl group, optionally substituted cyclobutyl group, and N-alkyl;

W<sub>3</sub> of Formulas (a1) through (e) is selected from C or N;

X of Formulas (a1) through (e) is independently selected from the group absent, O, S and CH<sub>2</sub>;

Y of Formulas (a1) through (e) is independently selected from the group CH<sub>2</sub>, -C=CR', NH, N-alkyl, N-aryl, N-heteroaryl, N-cycloalkyl, N-heterocyclyl, O, and S;

Z of Formulas (a1) through (e) is independently selected from the group absent, O, and S or CH<sub>2</sub> except that both X and Z cannot be CH<sub>2</sub> or absent;

G and G' of Formulas (a1) through (e) are independently selected from the group H, optionally substituted linear or branched alkyl, OH, R'OCOOR, R'OCONRR'', CH<sub>2</sub>-heterocyclyl optionally substituted with R', and benzyl optionally substituted with R';

Q1 – Q4 of Formulas (a1) through (e) represent a carbon C or N substituted with a group independently selected from H, R, N or N-oxide;

A of Formulas (a1) through (e) is independently selected from the group H, optionally substituted linear or branched alkyl, cycloalkyl, Cl and F;

n of Formulas (a1) through (e) represent an integer from 1 to 10 (e.g., 1-4, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10);

R of Formulas (a1) through (e) comprises, but is not limited to: H, -C(=O)R' (e.g., a carboxy group), -CONR'R'' (e.g., an amide group), -OR' (e.g., OH), -NR'R'' (e.g., an amine group), -SR', -SO<sub>2</sub>R', -SO<sub>2</sub>NR'R'', -CR'R''-, -CR'NR'R''-, (-CR'O)<sub>n</sub>R'', optionally substituted heterocyclyl, 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 heteroaryl, optionally substituted 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 alkoxy group (e.g., a methoxy, ethoxy, butoxy, propoxy, pentoxy, or hexoxy; wherein the alkoxy may be substituted with one or more halogen, alkyl, haloalkyl, fluoroalkyl, cycloalkyl (e.g., a C3-C6 cycloalkyl), or aryl (e.g., C5-C7 aryl)), optionally substituted cycloalkyl, optionally substituted heterocyclyl, -P(O)(OR')R'', -P(O)R'R'', -OP(O)(OR')R'', -OP(O)R'R'', -Cl, -F, -Br, -I, -CF<sub>3</sub>, -CN, -NR'SO<sub>2</sub>NR'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<sub>2</sub>)NR'R'', -SO<sub>2</sub>NR'COR'', -NO<sub>2</sub>, -CO<sub>2</sub>R', -C(C=N-OR')R'', -CR'=CR'R'', -CCR', -S(C=O)(C=N-R')R'', -SF<sub>5</sub> and -OCF<sub>3</sub>, wherein at least one W, X, Y, Z, G, G', R, R', R'', Q1-Q4, or A is modified to be covalently joined to a PTM, a chemical linking group (L), a ULM, CLM, or combination thereof;

each of x, y, and z of Formulas (a1) through (e) are independently 0, 1, 2, 3, 4, 5, or 6;

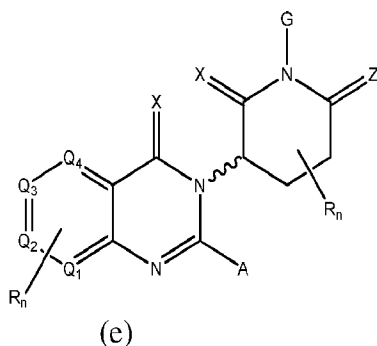
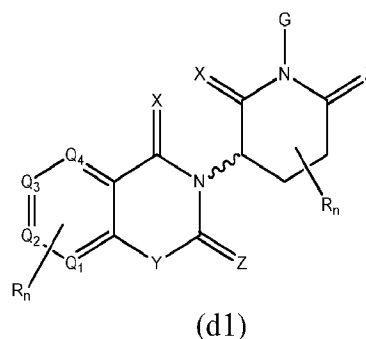
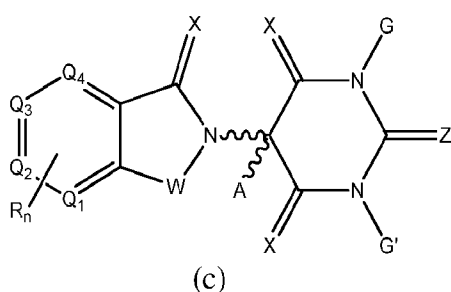
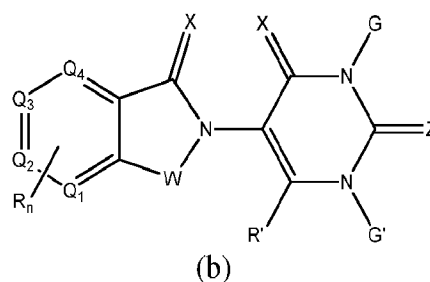
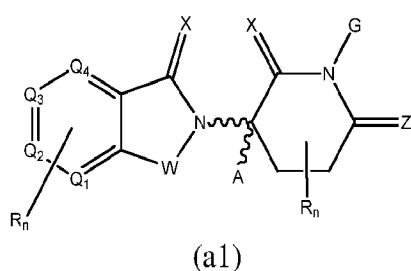
R' and R'' of Formulas (a1) through (e) are independently selected from H, optionally substituted linear or branched alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, -C(=O)R, optionally substituted heterocyclyl;

n' of Formulas (a1) through (e) is an integer from 1-10 (e.g. 1-4, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10);

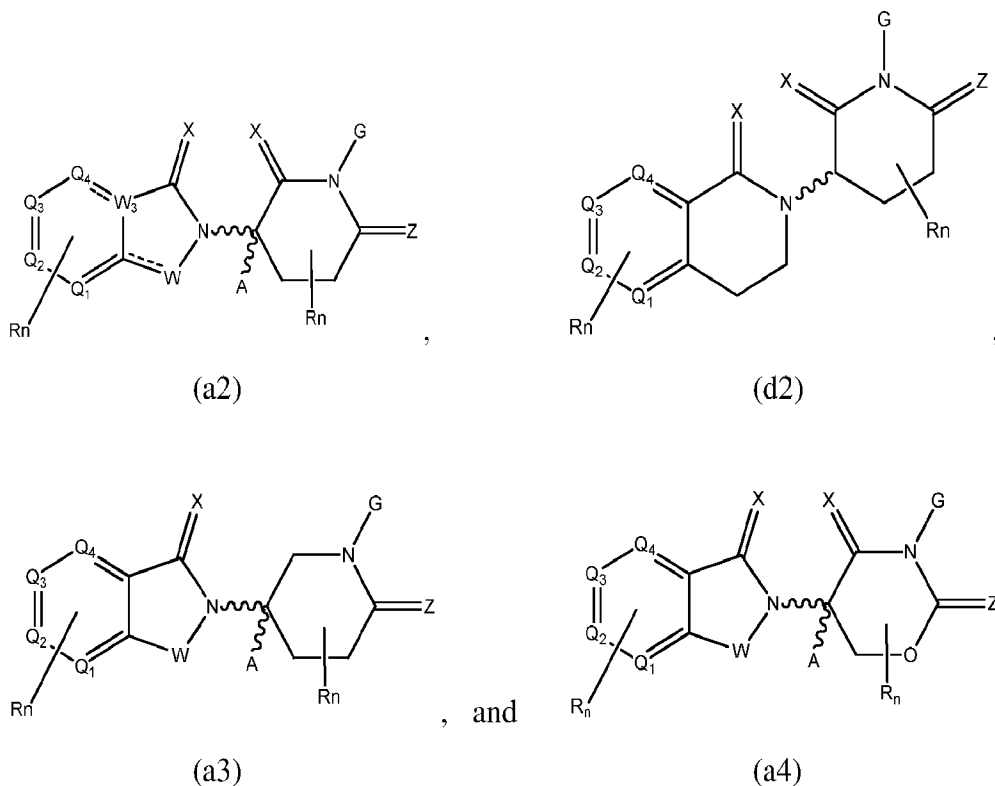
 represents a single bond or a double bond; and

 of Formulas (a1) through (e) represents a bond that may be stereospecific ((R) or (S)) or non-stereospecific.

**[0074]** In any aspect or embodiment described herein, the CLM comprises a chemical structure selected from the group consisting of:







wherein:

W of Formulas (a1) through (e) [e.g., (a1), (a2), (a3), (a4), (b), (c), (d1), (d2), and (e)] is independently selected from the group CH<sub>2</sub>, O, CHR, C=O, SO<sub>2</sub>, NH, N, optionally substituted cyclopropyl group, optionally substituted cyclobutyl group, and N-alkyl;

W<sub>3</sub> of Formulas (a1) through (e) is selected from C or N;

X of Formulas (a1) through (e) is independently selected from the group O, S and CH<sub>2</sub>;

Y of Formulas (a1) through (e) is independently selected from the group CH<sub>2</sub>, -C=CR', NH, N-alkyl, N-aryl, N-hetaryl, N-cycloalkyl, N-heterocyclyl, O, and S;

Z of Formulas (a1) through (e) is independently selected from the group O, and S or CH<sub>2</sub> except that both X and Z cannot be CH<sub>2</sub> or absent;

G and G' of Formulas (a1) through (e) are independently selected from the group H, optionally substituted linear or branched alkyl, OH, R'OCOOR, R'OCONRR'', CH<sub>2</sub>-heterocyclyl optionally substituted with R', and benzyl optionally substituted with R';

Q1 – Q4 of Formulas (a1) through (e) represent a carbon C or N substituted with a group independently selected from H, R, N or N-oxide;

A of Formulas (a1) through (e) is independently selected from the group H, optionally substituted linear or branched alkyl, cycloalkyl, Cl and F;

n of Formulas (a1) through (e) represent an integer from 1 to 10 (e.g., 1-4, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10);

R of Formulas (a1) through (e) comprises, but is not limited to: H,  $-C(=O)R'$  (e.g., a carboxy group),  $-CONR'R''$  (e.g., an amide group),  $-OR'$  (e.g., OH),  $-NR'R''$  (e.g. an amine group),  $-SR'$ ,  $-SO_2R'$ ,  $-SO_2NR'R''$ ,  $-CR'R''$ -,  $-CR'NR'R''$ -,  $(-CR'O)_nR''$ , 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 hetaryl, -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 alkoxy group (e.g., a methoxy, ethoxy, butoxy, propoxy, pentoxy, or hexoxy; wherein the alkoxy 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 cycloalkyl, optionally substituted 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  $-OCF_3$ , wherein at least one of W, X, Y, Z, G, G', R, R', R'', Q1-Q4, or A is covalently joined (directly or indirectly, e.g., via a functional group or an atom, such as O, S, N) to a PTM, a chemical linking group (L), a ULM, CLM, or combination thereof;

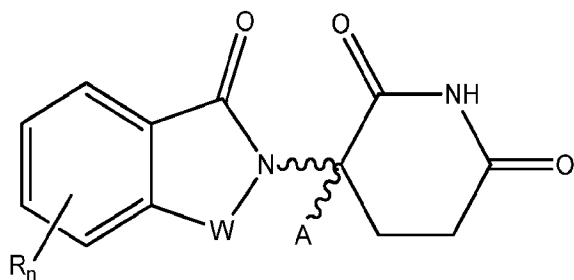
each of x, y, and z of Formulas (a1) through (e) are independently 0, 1, 2, 3, 4, 5, or 6;

R' and R'' of Formulas (a1) through (e) are independently selected from a bond, H, optionally substituted linear or branched alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic,  $-C(=O)R$ , optionally substituted heterocyclyl;

n' of Formulas (a1) through (e) is an integer from 1-10 (e.g., 1-4, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10); and

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

**[0075]** In any aspect or embodiment described herein, the CLM or ULM is selected from the structure of Formula (g):



Formula (g)

wherein:

W of Formula (g) is independently selected from the group CH<sub>2</sub>, O, C=O, NH, and N-alkyl;

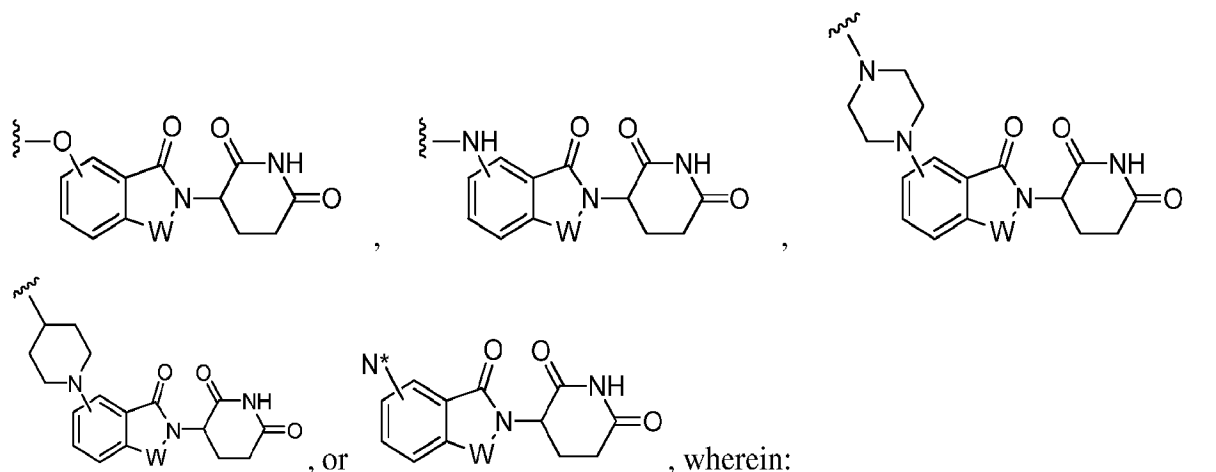
A of Formula (g) is selected from a H, methyl, or optionally substituted linear or branched alkyl;

n is an integer from 1 to 4;

R of Formula (g) is independently selected from a H, O, OH, N, NH, NH<sub>2</sub>, -Cl, -F, -Br, -I, methyl, optionally substituted linear or branched alkyl (e.g., optionally substituted linear or branched C1-C6 alkyl), optionally substituted linear or branched alkoxy (e.g., optionally substituted linear or branched C1-C6 alkoxy), -alkyl-aryl (e.g., an -alkyl-aryl comprising at least one of C1-C6 alkyl, C4-C7 aryl, or a combination thereof), aryl (e.g., C5-C7 aryl), amine, amide, or carboxy), wherein at least one R or W is modified to be covalently joined to a PTM, a chemical linking group (L), a ULM, CLM, or combination thereof; and

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

**[0076]** In any aspect or embodiment described herein, the CLM or ULM is selected from the group consisting of:



W is C=O or CH<sub>2</sub>;

N\* is a nitrogen atom that is covalently linked to the PTM or linker, or that is shared with the PTM or linker (L) (e.g., a heteroatom shared with an optionally substituted heterocyclyl of the linker (L) or PTM); and

— indicates the point of attachment of the CLM or ULM to the linker (L) or PTM.

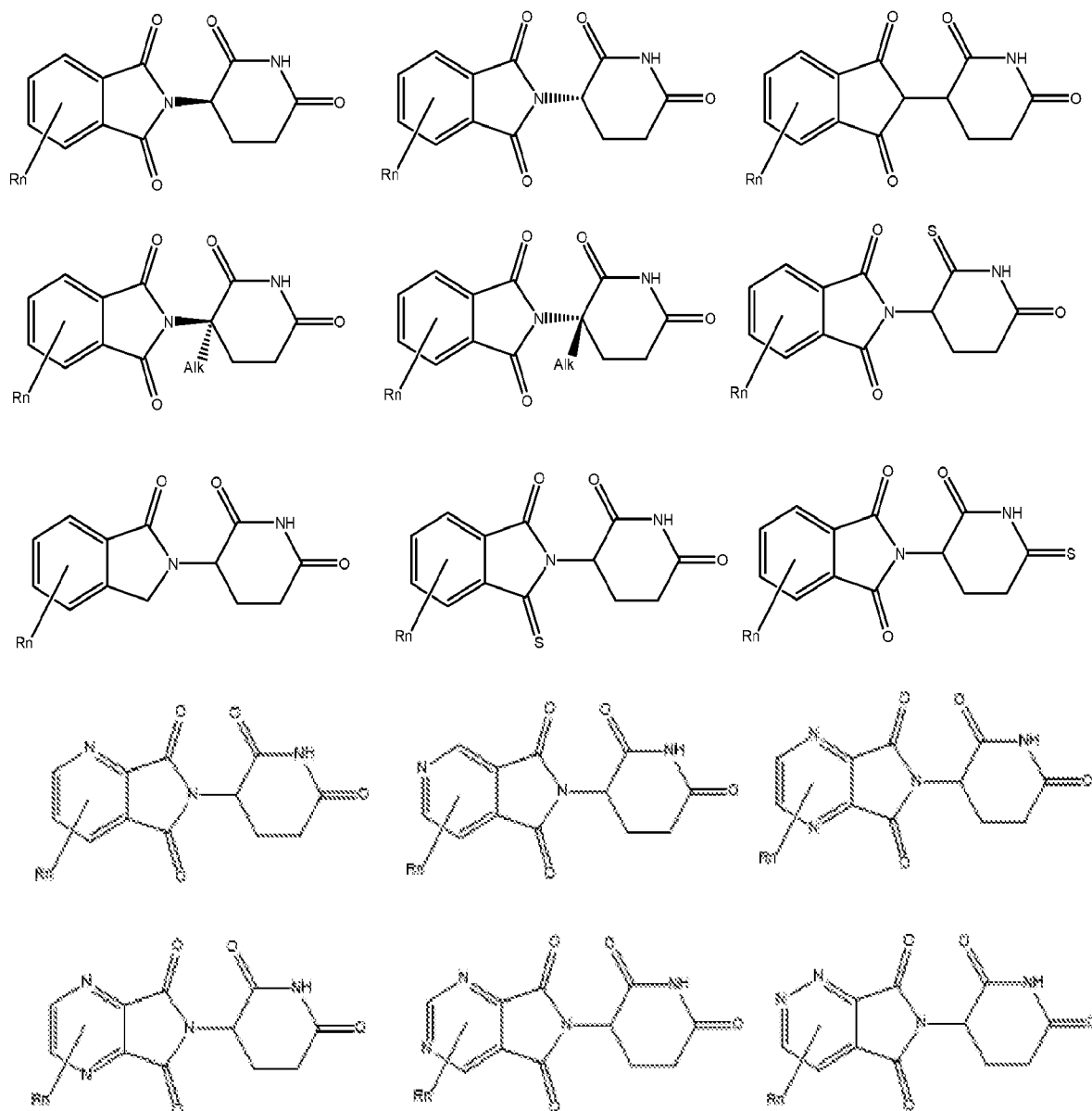
**[0077]** In any aspect or embodiment described herein, R is selected from: H, O, OH, N, NH, NH<sub>2</sub>, C1-C6 alkyl, C1-C6 alkoxy, -alkyl-aryl (e.g., an -alkyl-aryl comprising at least one of C1-C6 alkyl, C4-C7 aryl, or a combination thereof), aryl (e.g., C5-C7 aryl), amine, amide, or carboxy).

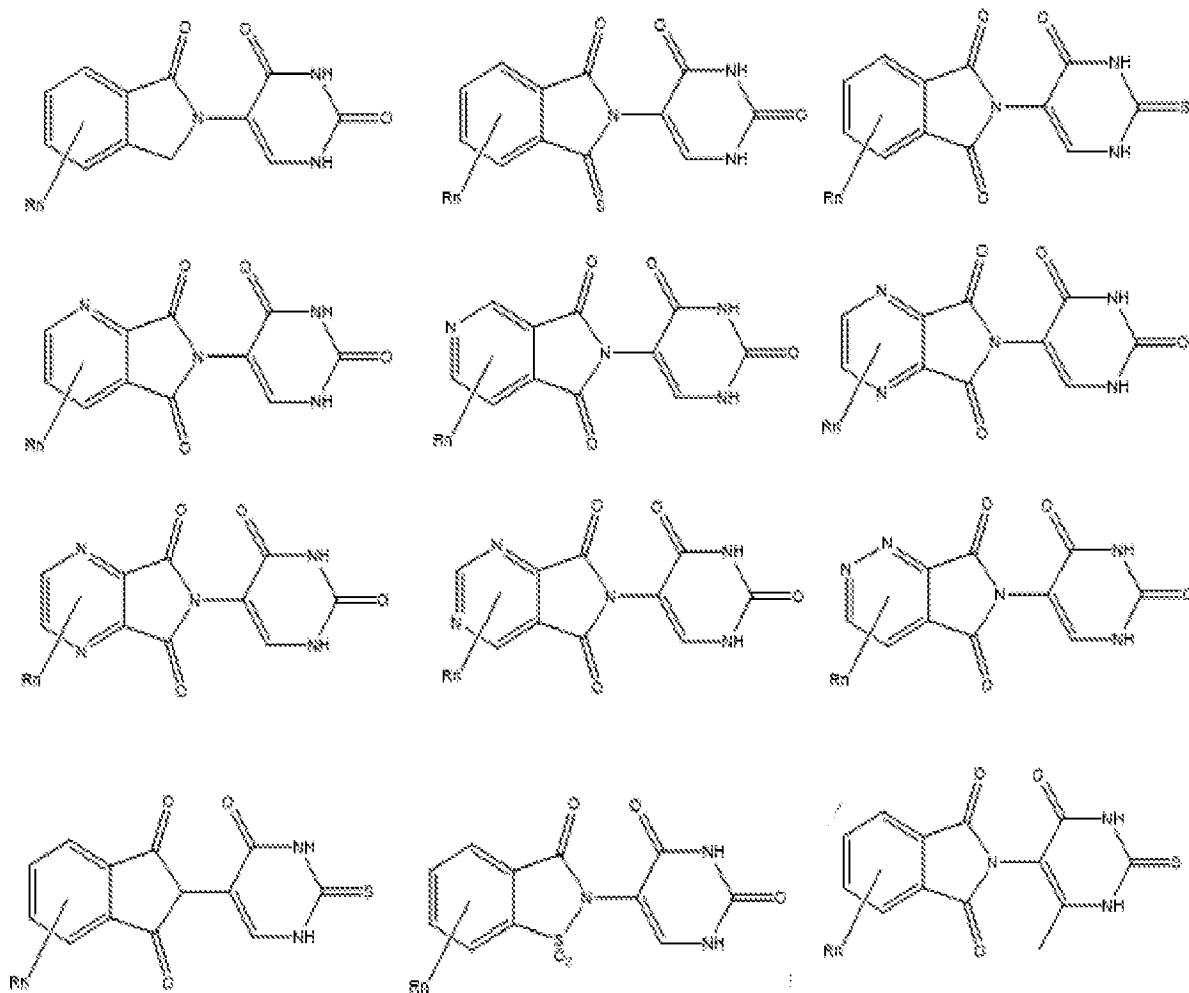
**[0078]** In any aspect or embodiment described herein, at least one R (e.g. an R group selected from the following H, O, OH, N, NH, NH<sub>2</sub>, C1-C6 alkyl, C1-C6 alkoxy, -alkyl-aryl (e.g., an -alkyl-aryl comprising at least one of C1-C6 alkyl, C4-C7 aryl, or a combination thereof), aryl (e.g., C5-C7 aryl), amine, amide, or carboxy) or W is modified to be covalently joined to a PTM, a chemical linker group (L), a ULM, a CLM, or a combination thereof

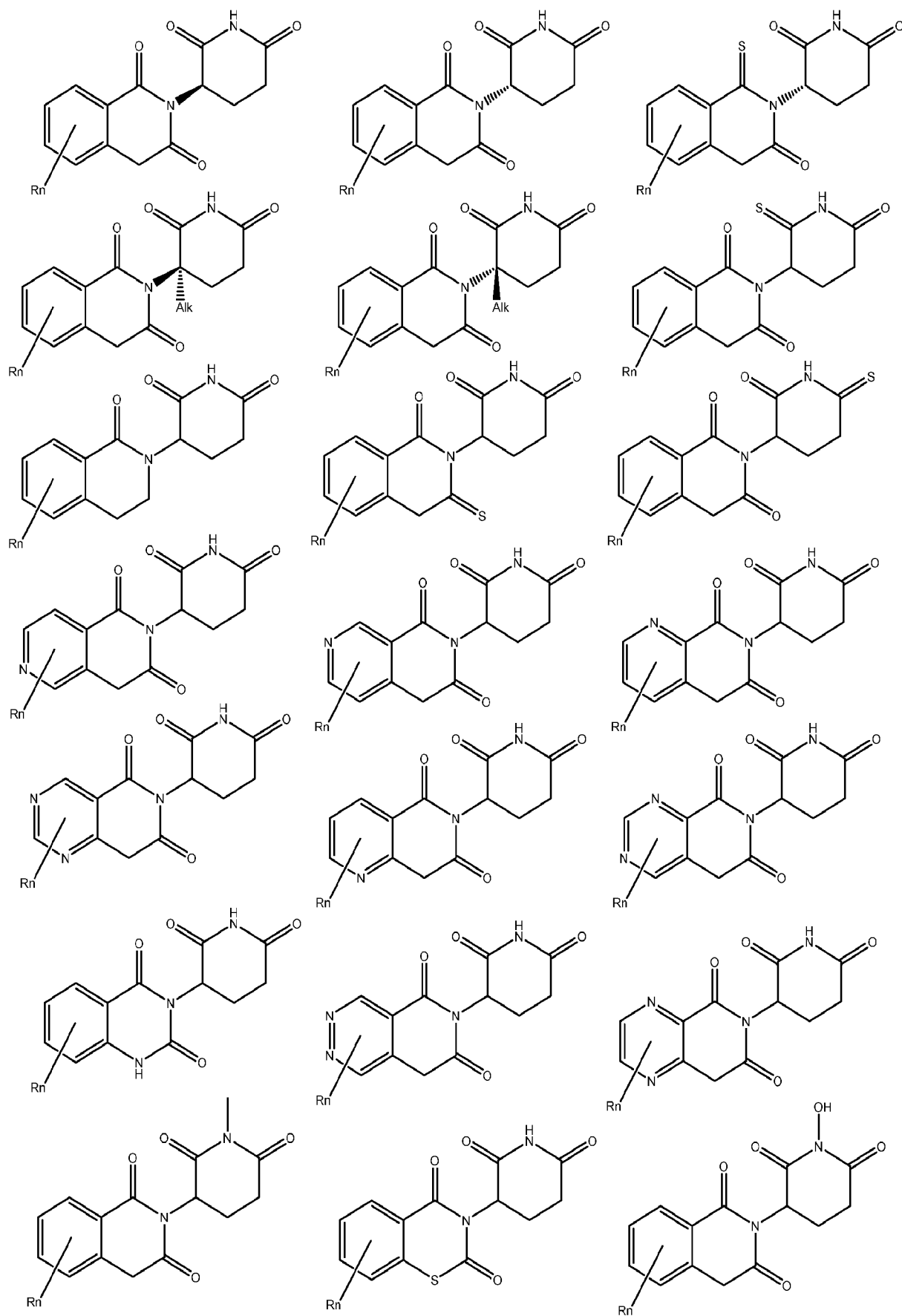
**[0079]** In any aspect or embodiment described herein, the W, X, Y, Z, G, G', R, R', R'', Q1-Q4, and A of Formulas (a) through (g) can independently be covalently coupled to a linker and/or a linker to which is attached one or more PTM, ULM, or CLM groups.

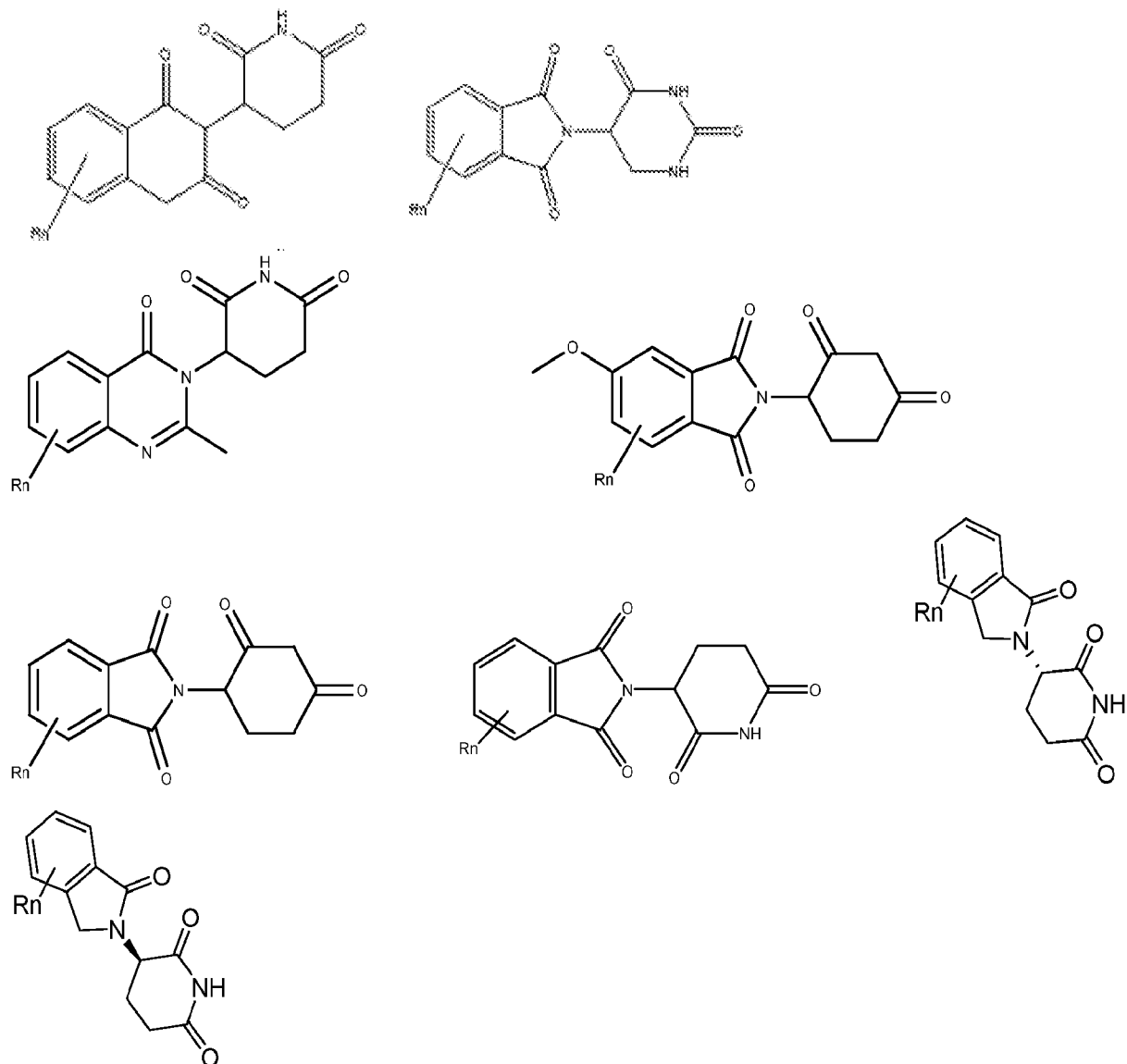
**[0080]** In any of the aspects or embodiments described herein, n is an integer from 1 to 4, and each R is independently selected functional groups or atoms, for example, O, OH, N, -Cl, -F, C1-C6 alkyl, C1-C6 alkoxy, -alkyl-aryl (e.g., an -alkyl-aryl comprising at least one of C1-C6 alkyl, C4-C7 aryl, or a combination thereof), aryl (e.g., C5-C7 aryl), amine, amide, or carboxy, on the aryl or heteroaryl of the CLM, and optionally, one of which is modified to be covalently joined to a PTM, a chemical linker group (L), a ULM, CLM or combination thereof.

**[0081]** More specifically, non-limiting examples of CLMs include those shown below as well as those “hybrid” molecules that arise from the combination of one or more of the different features shown in the molecules below wherein at least one R or W is modified to be covalently joined to a PTM, a chemical linking group (L), a ULM, CLM, or combination thereof.

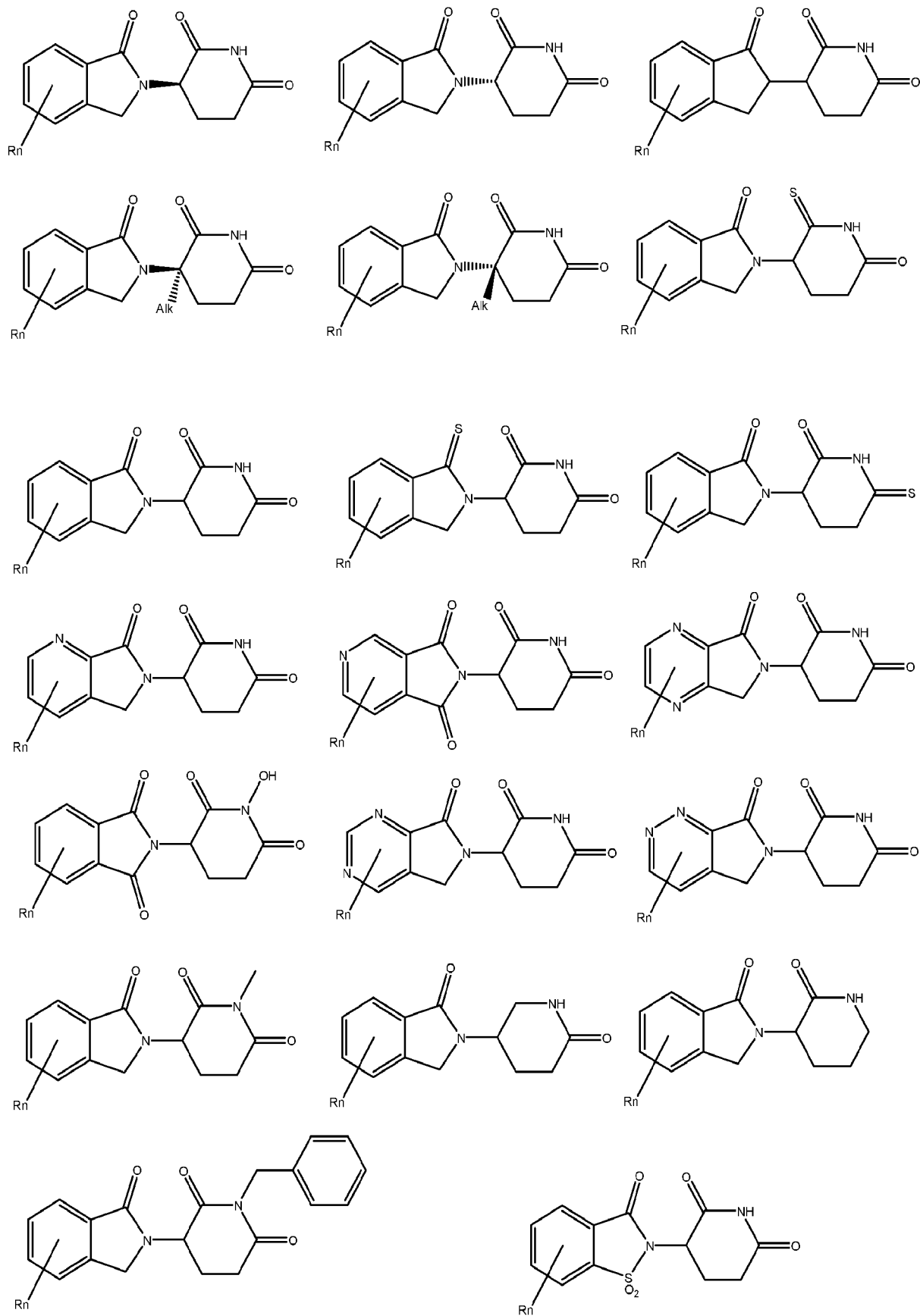


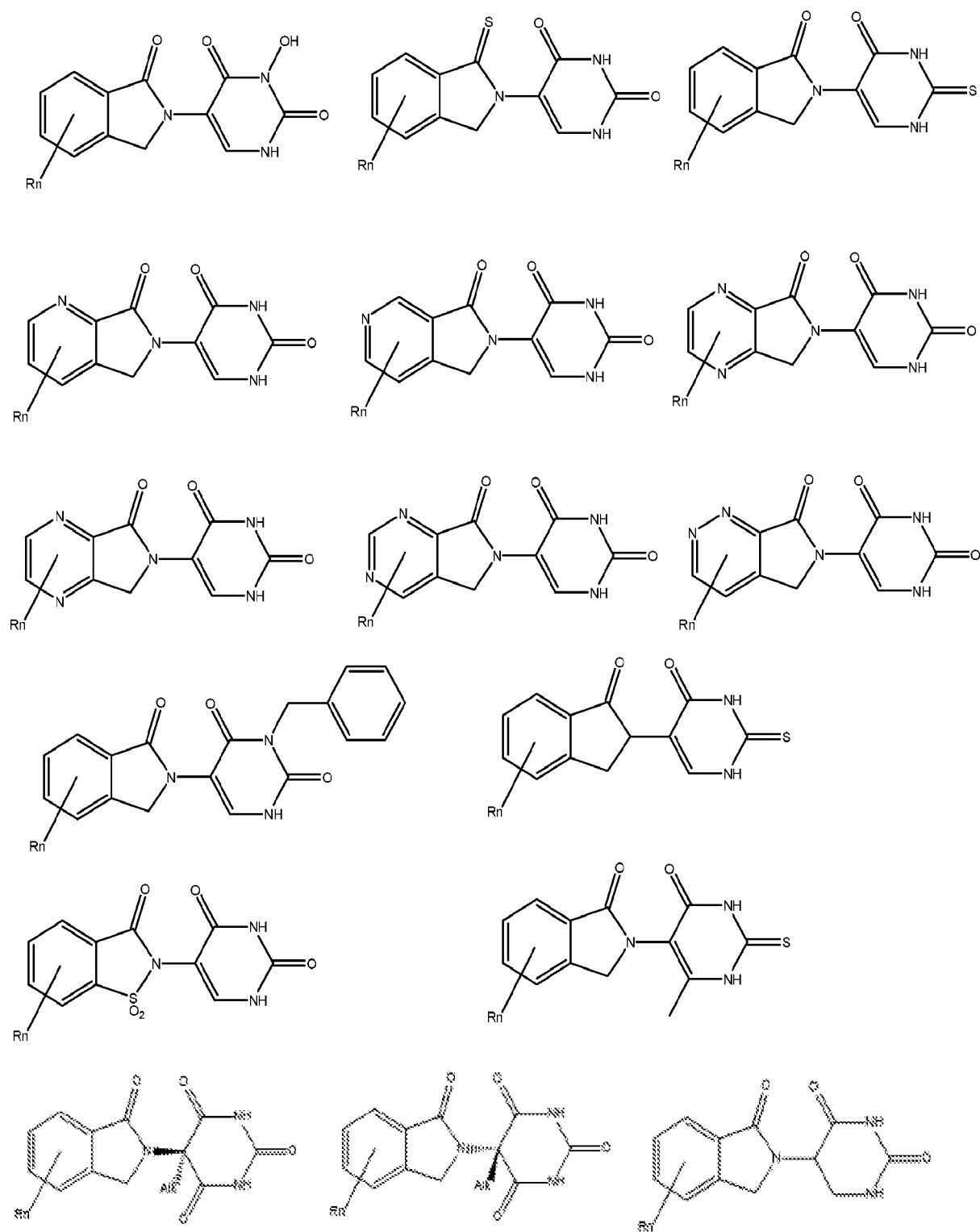


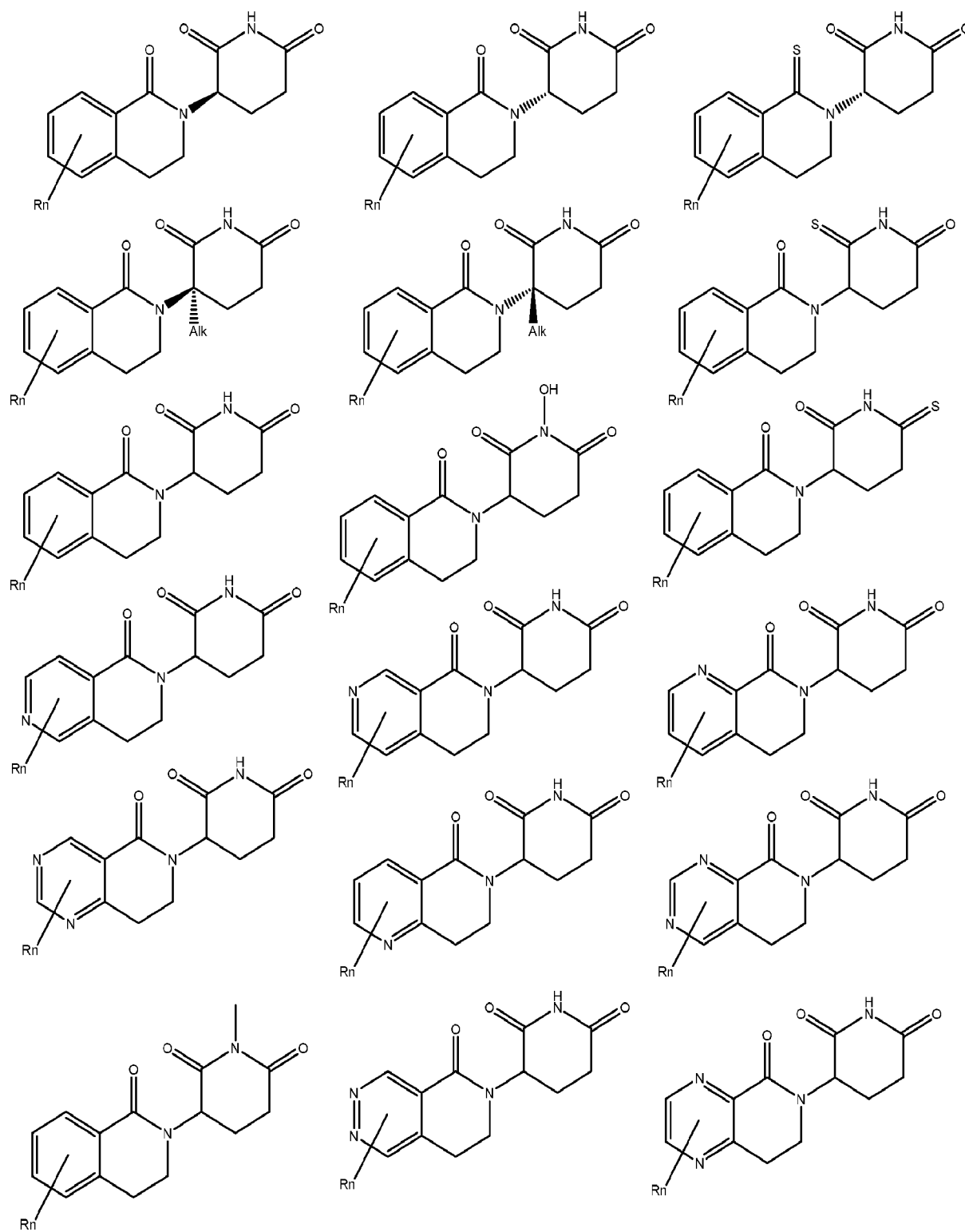


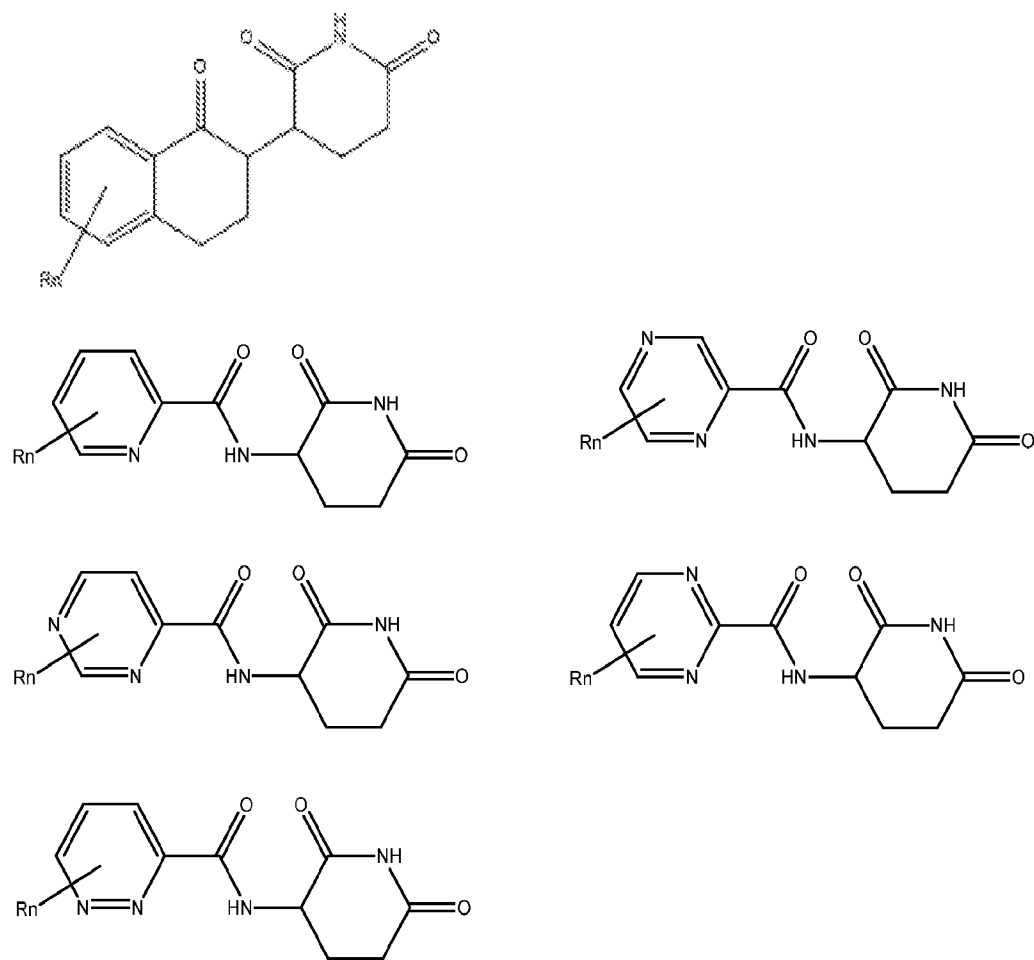




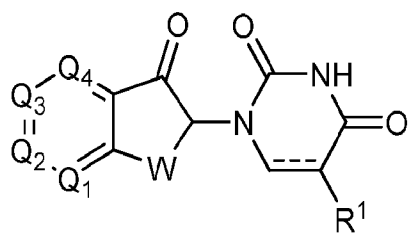




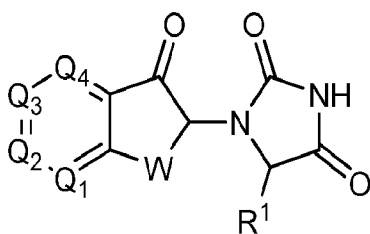




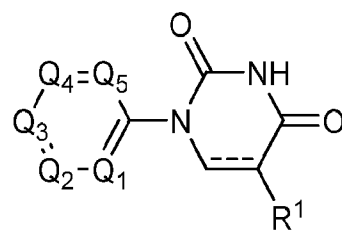
**[0082]** In any aspect or embodiment described herein, the CLM comprises a chemical structure selected from the group:



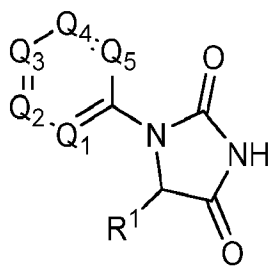
(h)



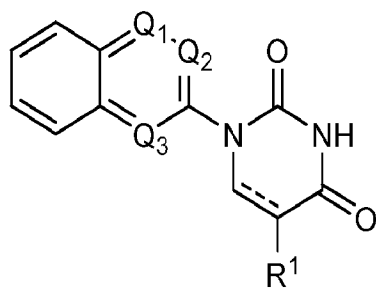
(i)



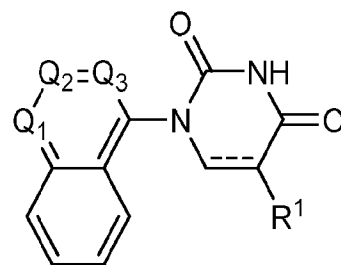
(j)



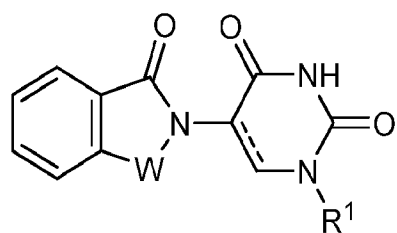
(k)



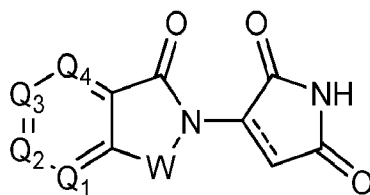
(l)



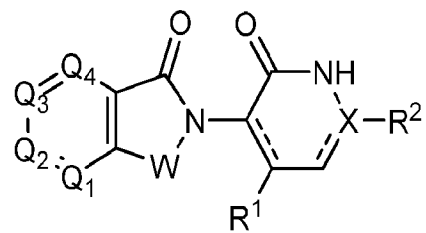
(m)



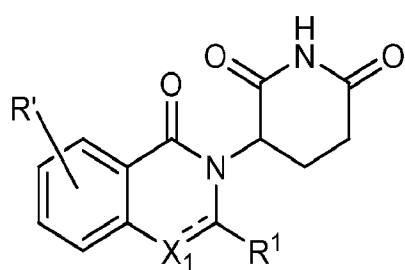
(n)



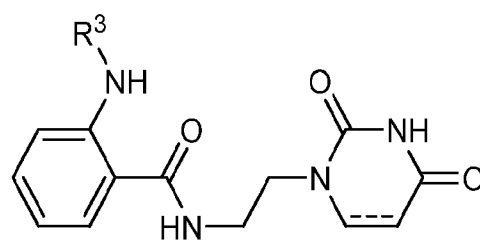
(o)



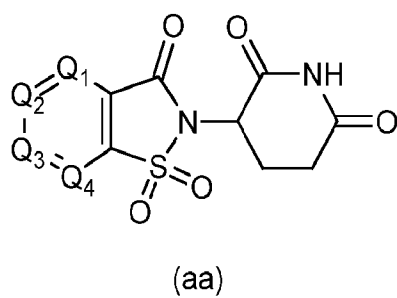
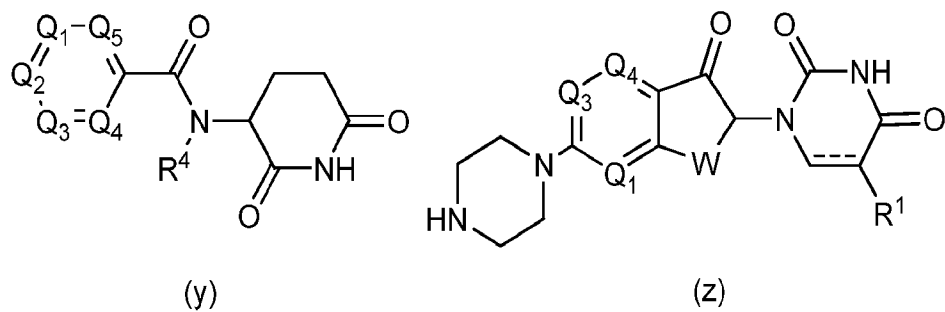
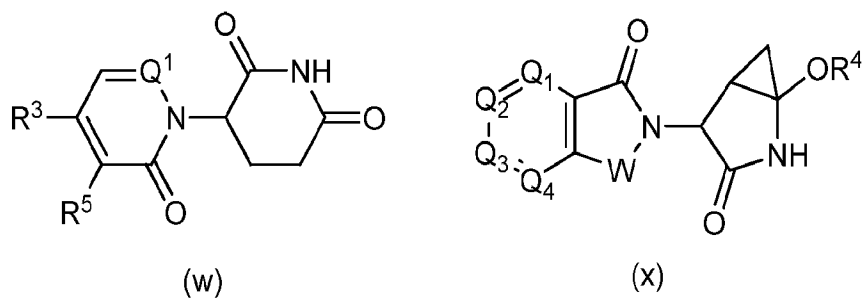
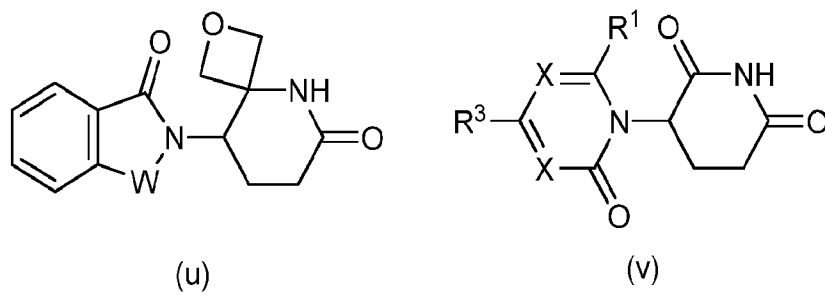
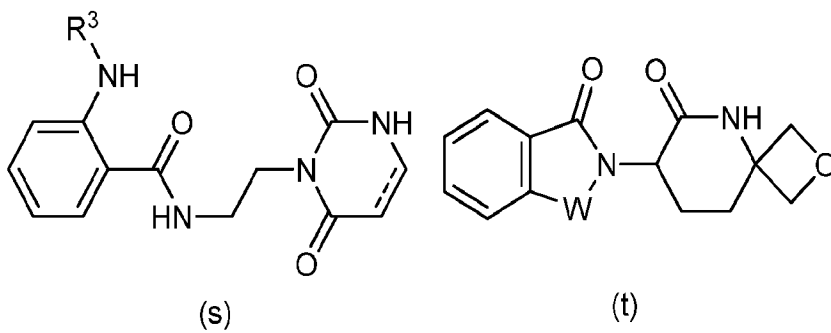
(p)

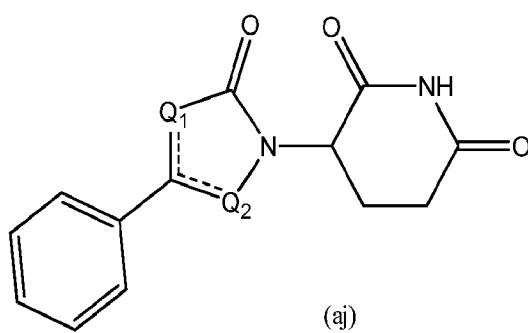
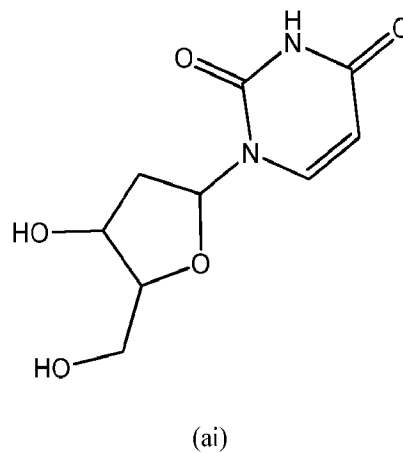
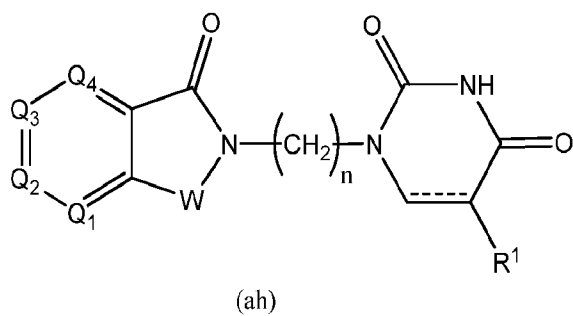
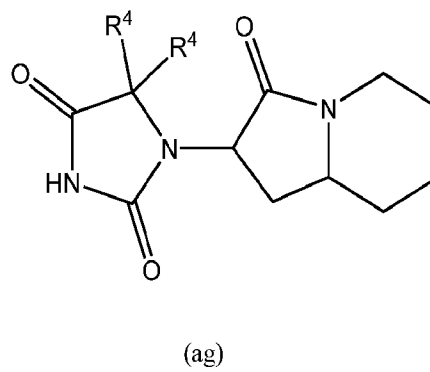
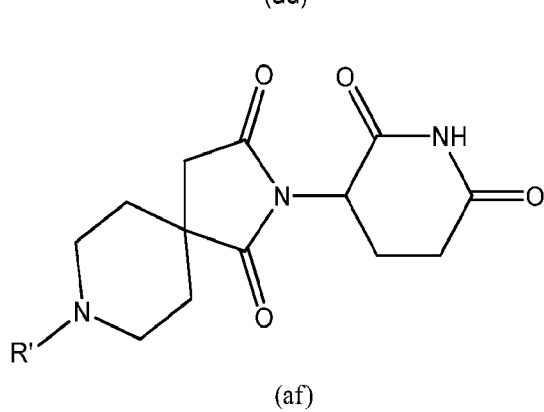
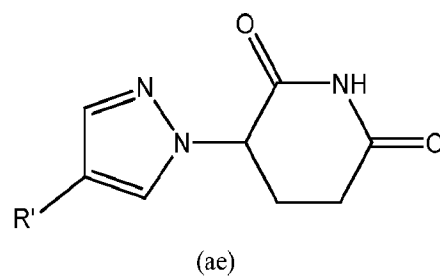
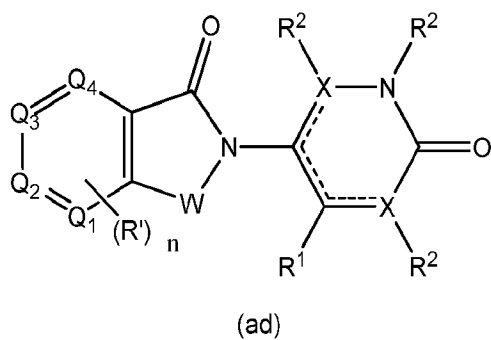
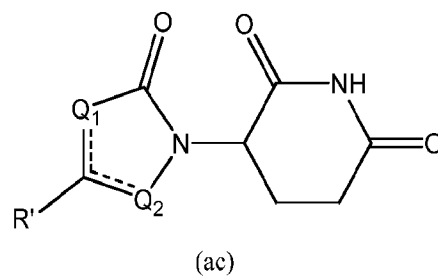
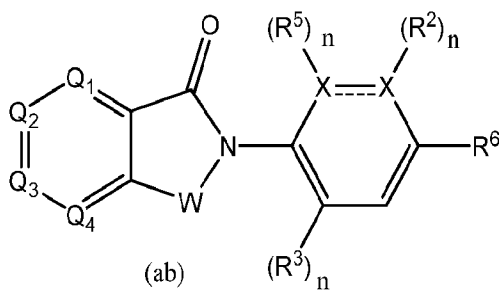


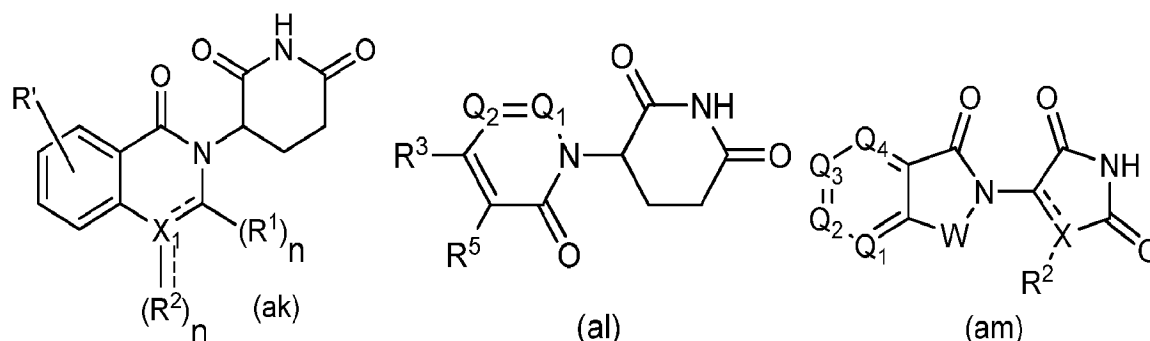
(q)



(r)







wherein:

W is independently selected from CH<sub>2</sub>, O, CHR, C=O, SO<sub>2</sub>, NH, N, optionally substituted cyclopropyl group, optionally substituted cyclobutyl group, and N-alkyl (e.g., CH<sub>2</sub>, CHR, C=O, SO<sub>2</sub>, NH, and N-alkyl);

Q<sub>1</sub>, Q<sub>2</sub>, Q<sub>3</sub>, Q<sub>4</sub>, Q<sub>5</sub> are each independently represent a carbon C or N substituted with a group independently selected from R', N or N-oxide;

R<sup>1</sup> is selected from absent, H, OH, CN, C1-C3 alkyl, C=O;

R<sup>2</sup> is selected from the group absent, H, OH, CN, C1-C3 alkyl, CHF<sub>2</sub>, CF<sub>3</sub>, CHO, C(=O)NH<sub>2</sub>;

R<sup>3</sup> is selected from H, alkyl (e.g., C1-C6 or C1-C3 alkyl), substituted alkyl (e.g., substituted C1-C6 or C1-C3 alkyl), alkoxy (e.g., C1-C6 or C1-C3 alkoxy), substituted alkoxy (e.g., substituted C1-C6 or C1-C3 alkoxy);

R<sup>4</sup> is selected from H, alkyl, substituted alkyl;

R<sup>5</sup> and R<sup>6</sup> are each independently H, halogen, C(=O)R', CN, OH, CF<sub>3</sub>;

X is C, CH, C=O, or N;

X<sub>1</sub> is C=O, N, CH, or CH<sub>2</sub>;

R' is selected from H, halogen, amine, alkyl (e.g., C1-C3 alkyl), substituted alkyl (e.g., substituted C1-C3 alkyl), alkoxy (e.g., C1-C3 alkoxy), substituted alkoxy (e.g., substituted C1-C3 alkoxy), NR<sup>2</sup>R<sup>3</sup>, C(=O)OR<sup>2</sup>, optionally substituted phenyl;

n is 0-4;

$\diagup$  is a single or double bond; and

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

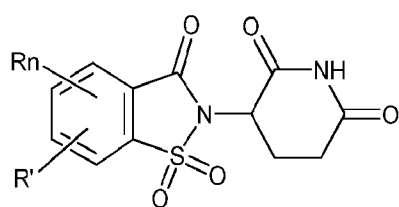


**[0083]** In any aspect or embodiment described herein, the CLM is covalently joined to a PTM, or a chemical linker group (L) via an R group (such as, R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> or R'), W, X, or a Q group (such as, Q<sub>1</sub>, Q<sub>2</sub>, Q<sub>3</sub>, Q<sub>4</sub>, or Q<sub>5</sub>).

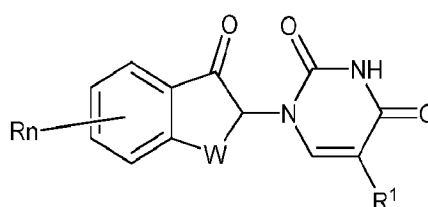
**[0084]** In any aspect or embodiment described herein, the CLM is covalently joined to a PTM, or a chemical linker group (L) via W, X, R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R', Q<sub>1</sub>, Q<sub>2</sub>, Q<sub>3</sub>, Q<sub>4</sub>, and Q<sub>5</sub>.

**[0085]** In any aspect or embodiment described herein, the W, X, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R', Q<sub>1</sub>, Q<sub>2</sub>, Q<sub>3</sub>, Q<sub>4</sub>, and Q<sub>5</sub> can independently be covalently coupled to a linker and/or a linker to which is attached to one or more PTM, ULM, CLM groups.

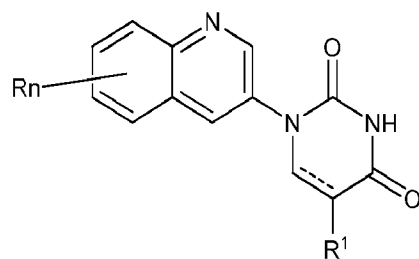
**[0086]** More specifically, non-limiting examples of CLMs include those shown below as well as "hybrid" molecules or compounds that arise from combining one or more features of the following compounds:



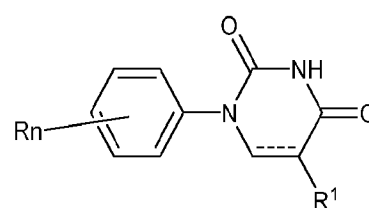
(an)



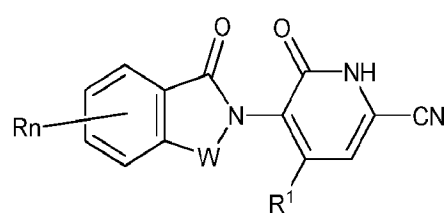
(ao)



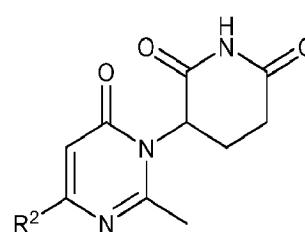
(ap)



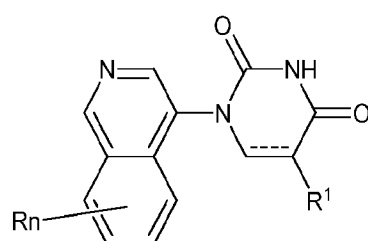
(aq)



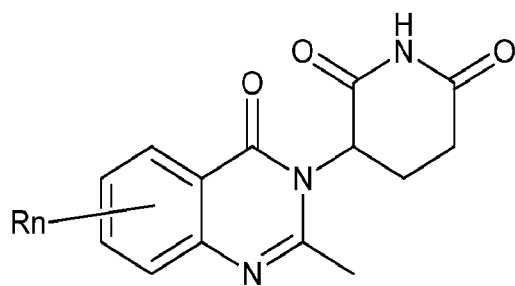
(ar)



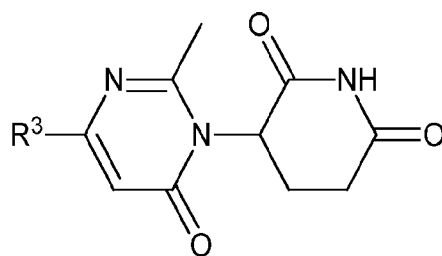
(as)



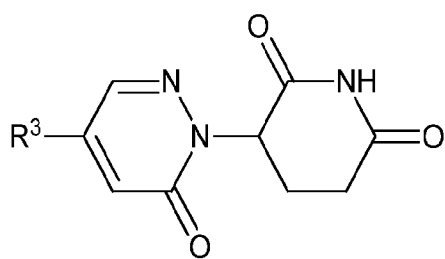
(at)



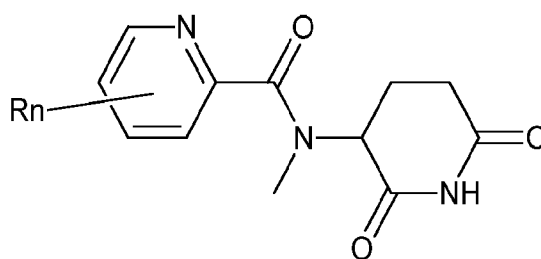
(au)



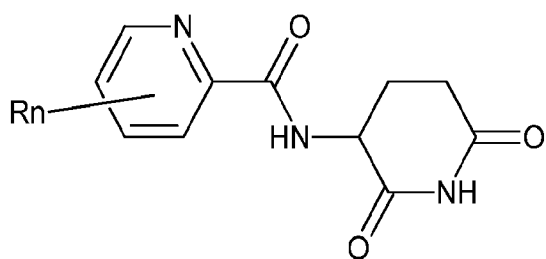
(av)



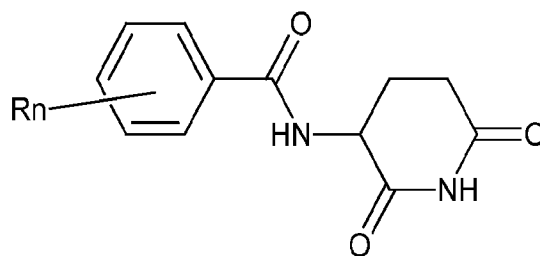
(aw)



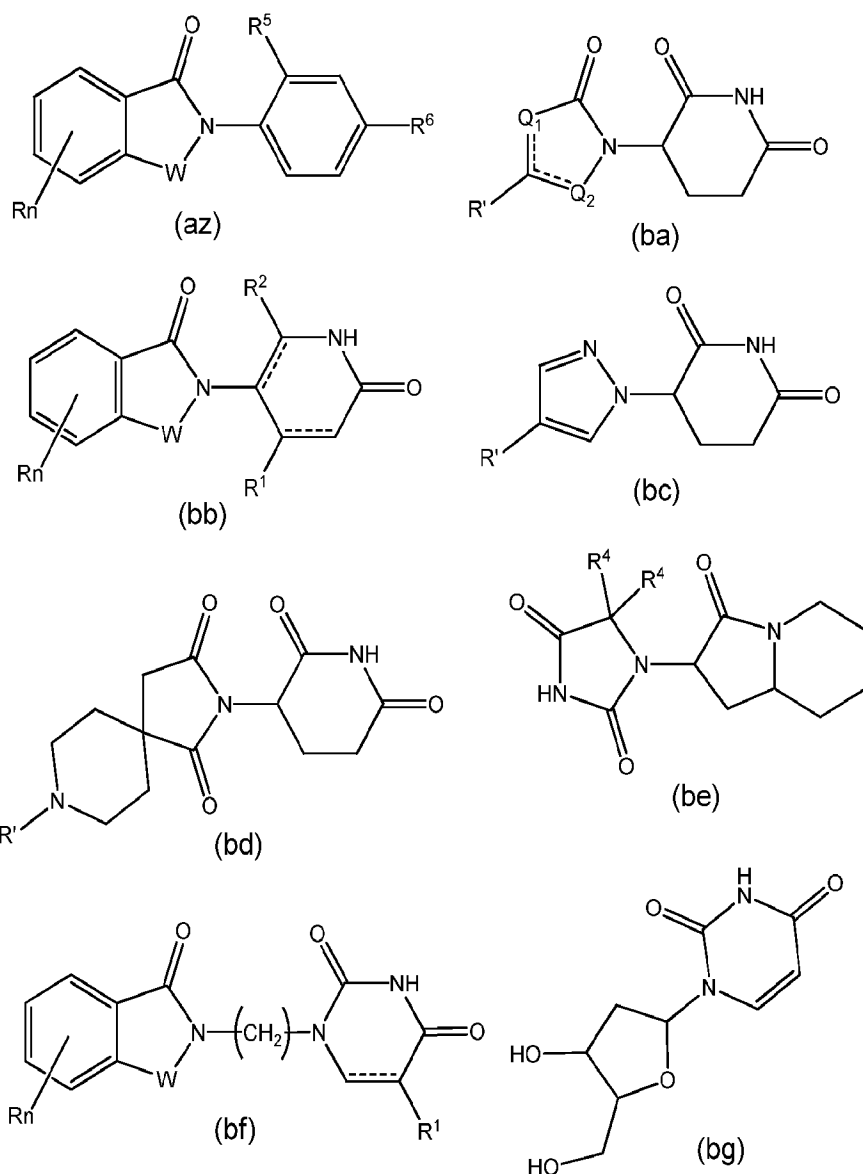
(ax)



(ay)



(ay')



wherein:

W is independently selected from the group CH<sub>2</sub>, CHR, C=O, SO<sub>2</sub>, NH, and N-alkyl;

R<sup>1</sup> is selected from the group absent, H, CH, CN, C1-C3 alkyl;

R<sup>2</sup> is H or a C1-C3 alkyl;

R<sup>3</sup> is selected from H, alkyl, substituted alkyl, alkoxy, substituted alkoxy;

R<sup>4</sup> is methyl or ethyl;

R<sup>5</sup> is H or halo;

R<sup>6</sup> is H or halo;

n is an integer from 0-4;

R and R' are independently H, a functional group or an atom (e.g., H, halogen (e.g., -Cl or -F), amine, C1-C3 alkyl, C1-C3 alkyl, C1-C3 alkoxy,  $\text{NR}^2\text{R}^3$ , or  $\text{C}(=\text{O})\text{OR}^2$ ); or an attachment point for a PTM, or a chemical linker group (L),

$\text{Q}_1$  and  $\text{Q}_2$  are each independently C or N substituted with a group independently selected from H or C1-C3 alkyl; and

$\text{--}$  is a single or double bond.

**[0087]** In any aspect or embodiment described herein, the W,  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{Q}_1$ ,  $\text{Q}_2$ ,  $\text{Q}_3$ ,  $\text{Q}_4$ , R, and R' can independently be covalently coupled to a linker and/or a linker to which is attached one or more PTM groups.

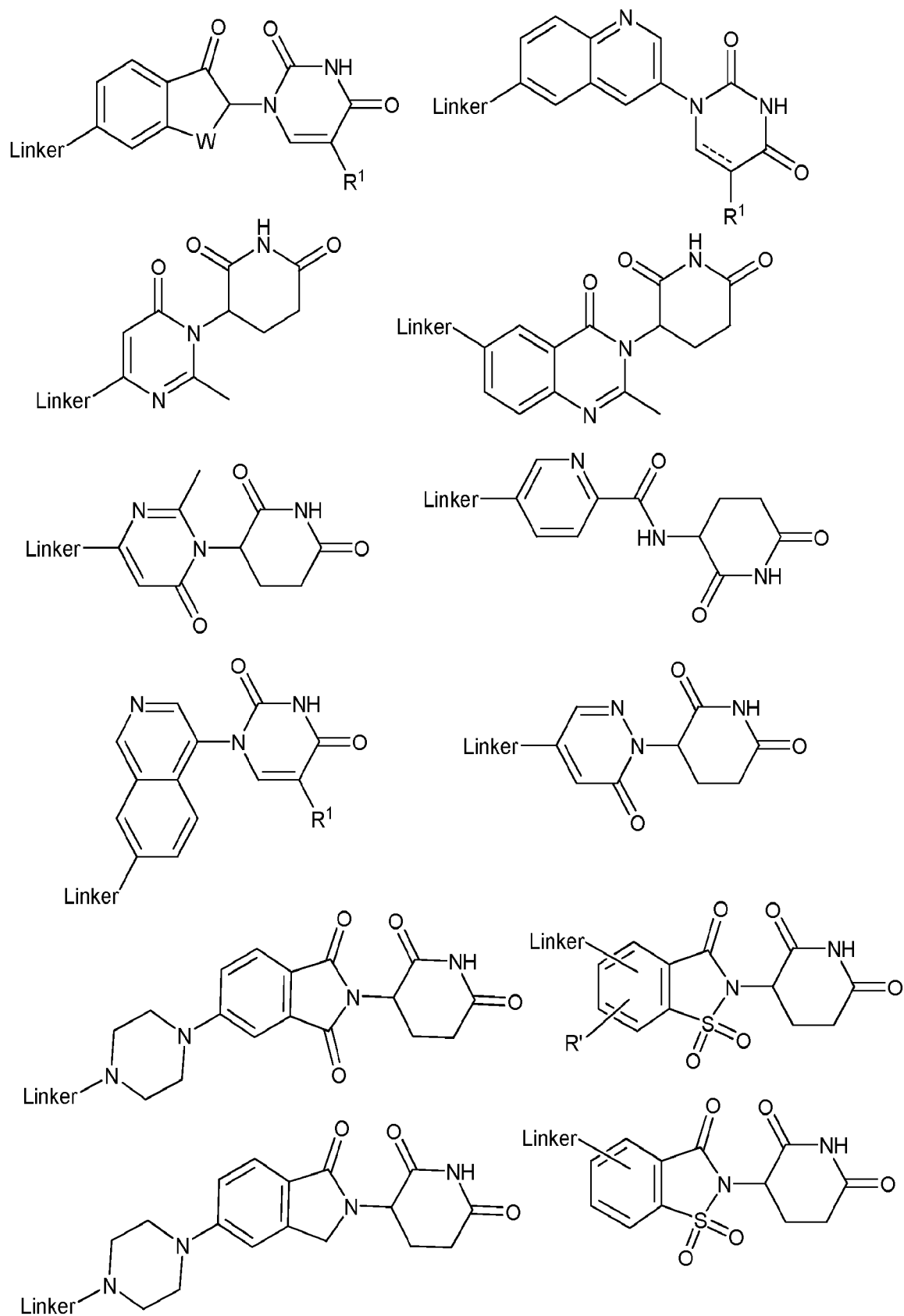
**[0088]** In any aspect or embodiment described herein, the  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{Q}_1$ ,  $\text{Q}_2$ ,  $\text{Q}_3$ ,  $\text{Q}_4$ , R, and R' can independently be covalently coupled to a linker and/or a linker to which is attached one or more PTM groups.

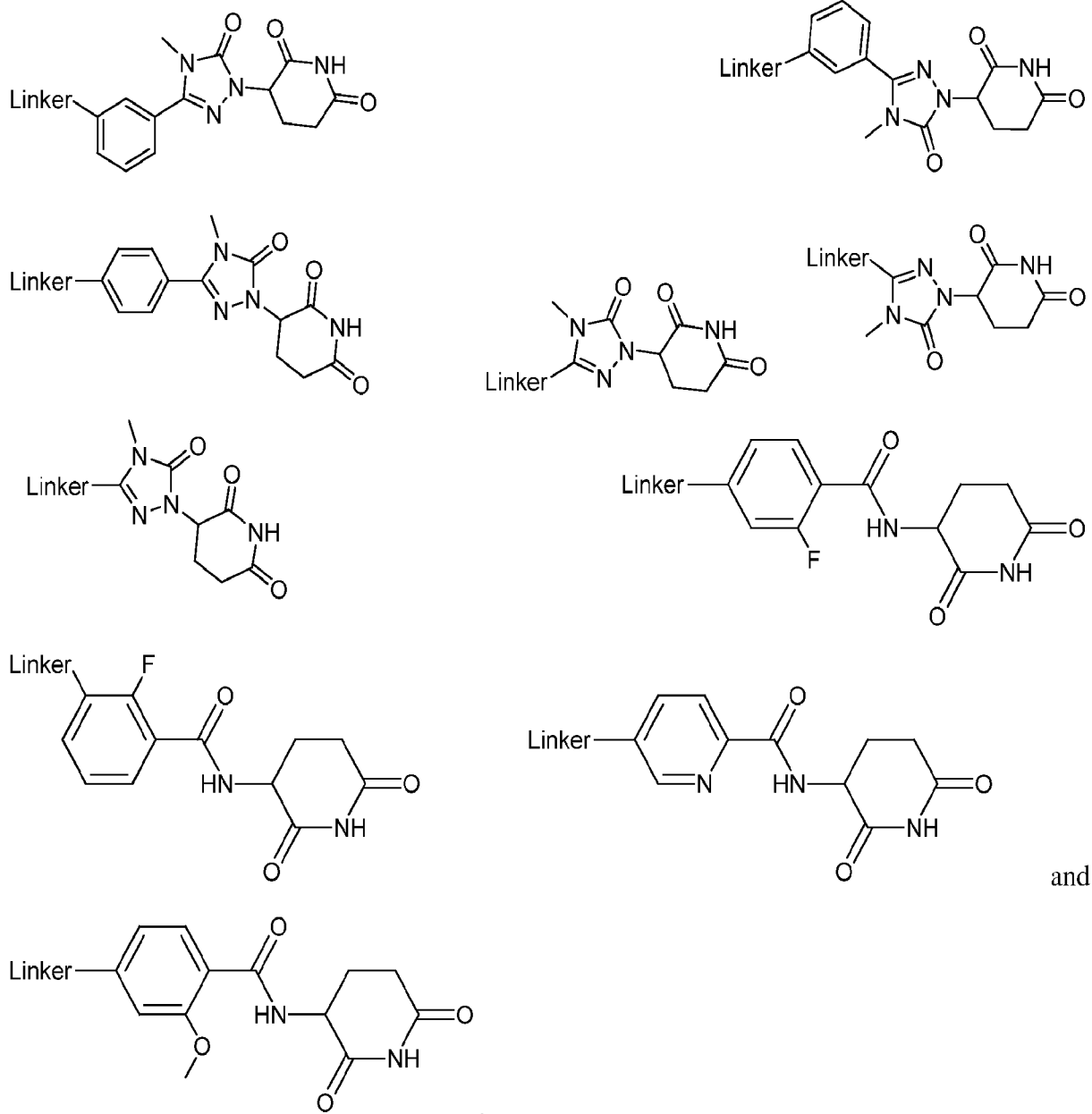
**[0089]** In any aspect or embodiment described herein, the  $\text{Q}_1$ ,  $\text{Q}_2$ ,  $\text{Q}_3$ ,  $\text{Q}_4$ , R, and R' can independently be covalently coupled to a linker and/or a linker to which is attached one or more PTM groups.

**[0090]** As would be readily apparent, in any aspect or embodiment described herein, R, R', R'',  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$ , and  $\text{R}^6$  of the CLM can be a bond.

**[0091]** In any aspect or embodiment described herein, R is a bond or modified to be covalently joined to the linker group (L) or, a PTM or combination thereof.

**[0092]** In any aspect or embodiment described herein, the CLM is selected from:

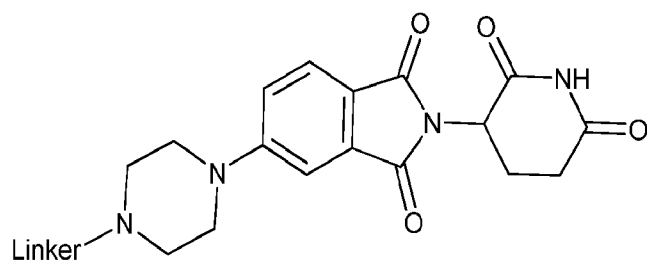
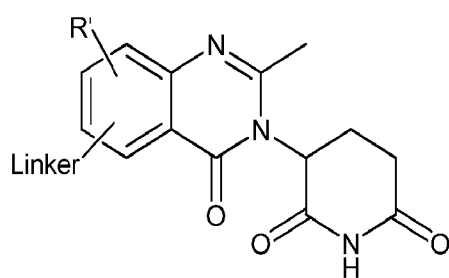
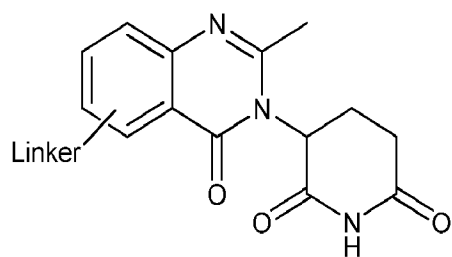
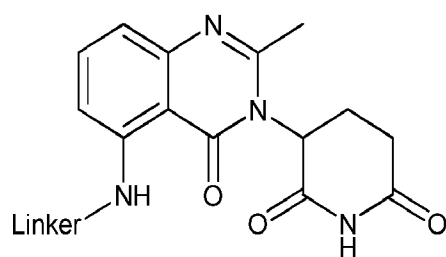
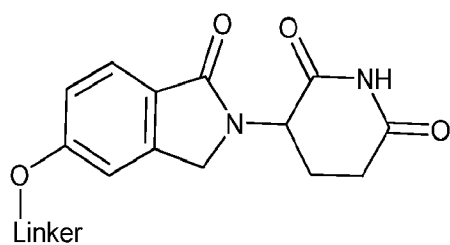
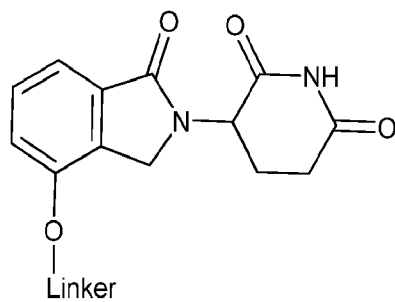
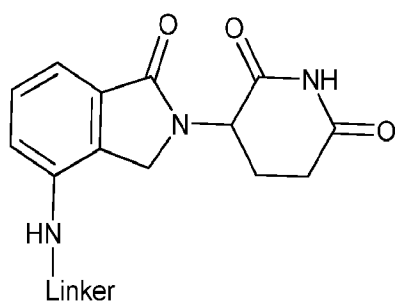
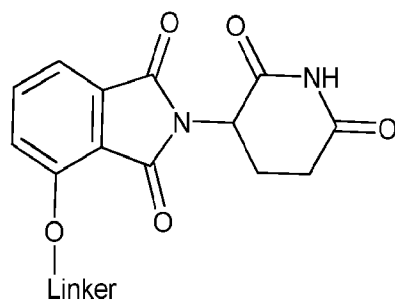
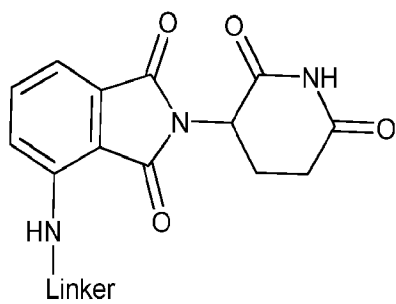




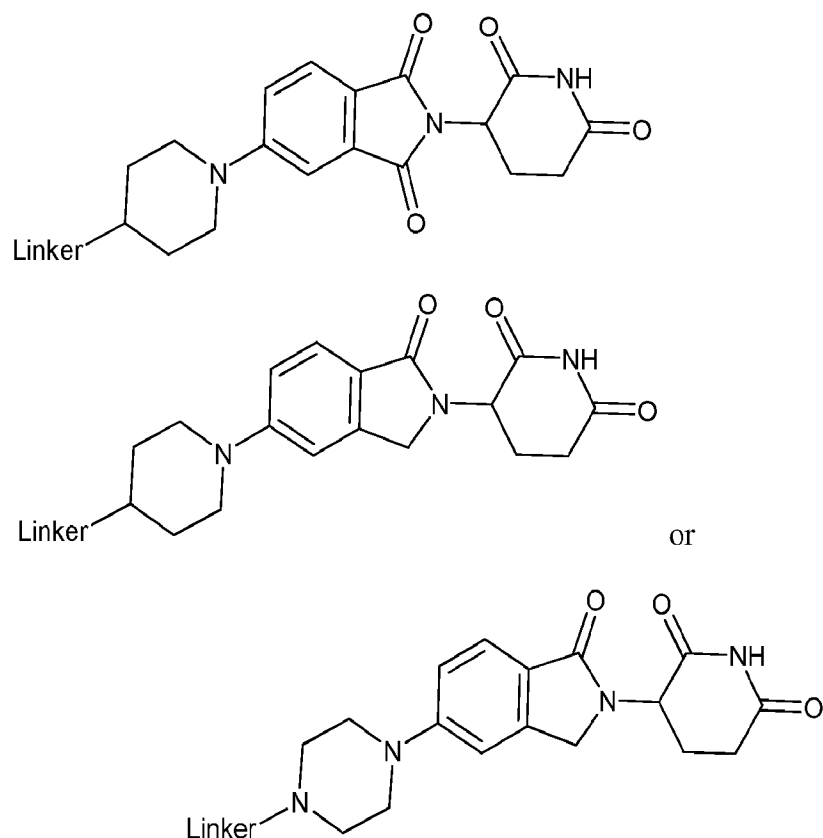
and

wherein R' is a halogen and R<sup>1</sup> is as described herein.

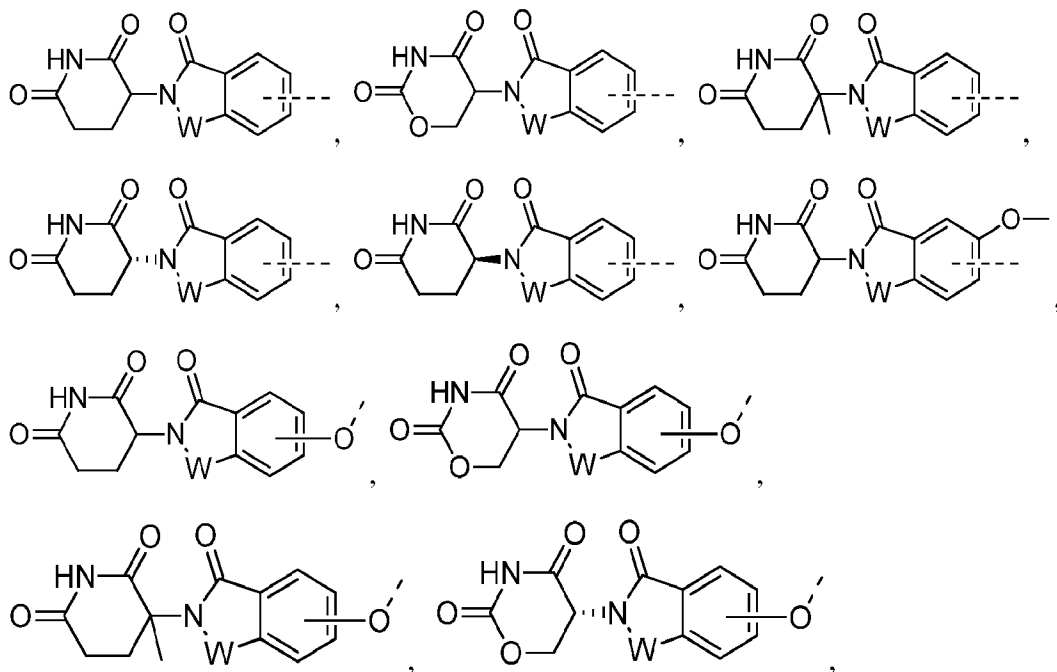
**[0093]** In certain cases, "CLM" can be an imide that binds to cereblon E3 ligase. These imides and linker attachment point can be, but not be limited to one of the following structures:

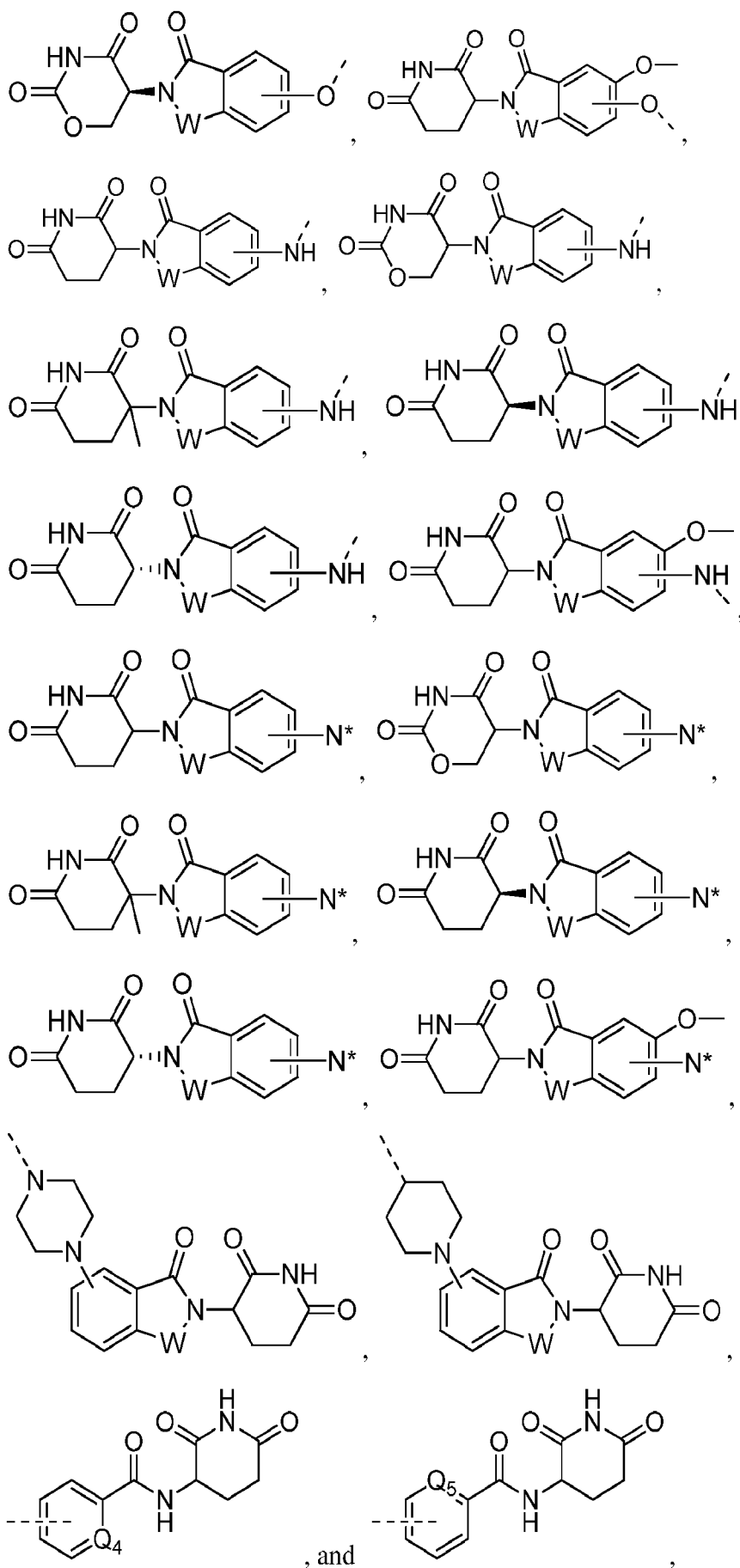






**[0094]** In any aspect or embodiment described herein, the ULM is selected from the group consisting of:





wherein:

-- of the ULM indicates the point of attachment with a linker group or a PTM;

N\* is a nitrogen atom that is shared with the chemical linker group or PTM; and

W, Q<sub>4</sub>, and Q<sub>5</sub> are each defined as described in any aspect or embodiment described herein.

### **Exemplary Linkers**

**[0095]** In certain embodiments, the compounds as described herein include a PTM chemically linked to a ULM (e.g., CLM) via a chemical linker (L). In certain embodiments, the linker group L comprises one or more covalently connected structural units (e.g.,  $-A^{L_1} \dots (A^L)_q-$  or  $-(A^L)_q-$ ), wherein  $A^{L_1}$  is a group coupled to PTM, and  $(A^L)_q$  is a group coupled to ULM.

**[0096]** In any aspect or embodiment described herein, the linker (L) to a ULM (e.g., CLM) connection is a stable L-ULM connection. For example, in any aspect or embodiment described herein, when a linker (L) and a ULM are connected via a heteroatom (e.g., N, O, S), any additional heteroatom, if present, is separated by at least a carbon atom (e.g.,  $-\text{CH}_2-$ ), such as with an acetal or aminal group. By way of further example, in any aspect or embodiment described herein, when a linker (L) and a ULM are connected via a heteroatom, the heteroatom is not part of an ester.

**[0097]** 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 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80), and wherein L is covalently bound to both the PTM and the ULM, and provides for binding of the PTM to the protein target and the ULM to an E3 ubiquitin ligase to effectuate target protein ubiquitination.

**[0098]** 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 6-30 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25), and wherein L is covalently bound to both the PTM and the ULM, and provides for binding of the PTM to the protein target and the ULM to an E3 ubiquitin ligase in sufficient proximity to result in target protein ubiquitination.

**[0099]** In any aspect or embodiment described herein, the linker group L is  $-(A^L)_q-$ , wherein:  $(A^L)_q$  is a group which connects a ULM (e.g., CLM), to PTM (TTM);

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,  $CR^{L1}=CR^{L2}$ ,  $C\equiv C$ ,  $SiR^{L1}R^{L2}$ ,  $P(O)R^{L1}$ ,  $P(O)OR^{L1}$ ,  $NR^{L3}C(=NCN)NR^{L4}$ ,  $NR^{L3}C(=NCN)$ ,  $NR^{L3}C(=CNO_2)NR^{L4}$ ,  $C_{3-11}$ cycloalkyl optionally substituted with 1-6  $R^{L1}$  and/or  $R^{L2}$  groups,  $C_{5-13}$  spirocycloalkyl optionally substituted with 1-9  $R^{L1}$  and/or  $R^{L2}$  groups,  $C_{3-11}$ heterocyclyl optionally substituted with 1-6  $R^{L1}$  and/or  $R^{L2}$  groups,  $C_{5-13}$  spiroheterocyclyl optionally substituted with 1-8  $R^{L1}$  and/or  $R^{L2}$  groups, aryl optionally substituted with 1-6  $R^{L1}$  and/or  $R^{L2}$  groups, and heteroaryl optionally substituted with 1-6  $R^{L1}$  and/or  $R^{L2}$  groups, where  $R^{L1}$  or  $R^{L2}$ , each independently are optionally linked to other groups to form cycloalkyl and/or heterocyclyl moiety, optionally substituted with 1-4  $R^{L5}$  groups; and

$R^{L1}$ ,  $R^{L2}$ ,  $R^{L3}$ ,  $R^{L4}$  and  $R^{L5}$  are, each independently, H, 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,  $OC_{3-8}$ cycloalkyl,  $SC_{3-8}$ cycloalkyl,  $NHC_{3-8}$ cycloalkyl,  $N(C_{3-8}cycloalkyl)_2$ ,  $N(C_{3-8}cycloalkyl)(C_{1-8}alkyl)$ , OH,  $NH_2$ , SH,  $SO_2C_{1-8}alkyl$ ,  $P(O)(OC_{1-8}alkyl)(C_{1-8}alkyl)$ ,  $P(O)(OC_{1-8}alkyl)_2$ ,  $CC-C_{1-8}alkyl$ , 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,  $CF_3$ ,  $CHF_2$ ,  $CH_2F$ ,  $NO_2$ ,  $SF_5$ ,  $SO_2NHC_{1-8}alkyl$ ,  $SO_2N(C_{1-8}alkyl)_2$ ,  $SONHC_{1-8}alkyl$ ,  $SON(C_{1-8}alkyl)_2$ ,  $CONHC_{1-8}alkyl$ ,  $CON(C_{1-8}alkyl)_2$ ,  $N(C_{1-8}alkyl)CONH(C_{1-8}alkyl)$ ,  $N(C_{1-8}alkyl)CON(C_{1-8}alkyl)_2$ ,  $NHCONH(C_{1-8}alkyl)$ ,  $NHCON(C_{1-8}alkyl)_2$ ,  $NHCONH_2$ ,  $N(C_{1-8}alkyl)SO_2NH(C_{1-8}alkyl)$ ,  $N(C_{1-8}alkyl)SO_2N(C_{1-8}alkyl)_2$ ,  $NH SO_2NH(C_{1-8}alkyl)$ ,  $NH SO_2N(C_{1-8}alkyl)_2$ , or  $NH SO_2NH_2$ .

**[00100]** In certain embodiments, q is an integer greater than or equal to 1.

**[00101]** In any aspect or embodiment described herein, e.g., where q of the linker is greater than 2,  $(A^L)_q$  is a group which is  $A^{L1}$  and  $(A^L)_q$  wherein the linker couples a PTM to a ULM.

**[00102]** In any aspect or embodiment described herein, e.g., where q of the linker is 2,  $A^{L2}$  is a group which is connected to  $A^{L1}$  and to a ULM.

**[00103]** In any aspect or embodiment described herein, 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 connects a ULM moiety to a PTM moiety.

**[00104]** In any aspect or embodiment described herein, the unit  $A^L$  of linker ( $L$ ) comprises a group represented by a general structure selected from the group consisting of:

$-NR(CH_2)_n-(\text{lower alkyl})-$ ,  $-NR(CH_2)_n-(\text{lower alkoxy})-$ ,  $-NR(CH_2)_n-(\text{lower alkoxy})-OCH_2-$ ,  
 $-NR(CH_2)_n-(\text{lower alkoxy})-(\text{lower alkyl})-OCH_2-$ ,  $-NR(CH_2)_n-(\text{cycloalkyl})-(\text{lower alkyl})-$   
 $OCH_2-$ ,  $-NR(CH_2)_n-(\text{heterocycloalkyl})-$ ,  $-NR(CH_2CH_2O)_n-(\text{lower alkyl})-O-CH_2-$ ,  
 $-NR(CH_2CH_2O)_n-(\text{heterocycloalkyl})-O-CH_2-$ ,  $-NR(CH_2CH_2O)_n-\text{Aryl}-O-CH_2-$ ,  
 $-NR(CH_2CH_2O)_n-(\text{heteroaryl})-O-CH_2-$ ,  $-NR(CH_2CH_2O)_n-(\text{cyclo alkyl})-O-(\text{heteroaryl})-O-$   
 $CH_2-$ ,  $-NR(CH_2CH_2O)_n-(\text{cyclo alkyl})-O-\text{Aryl}-O-CH_2-$ ,  $-NR(CH_2CH_2O)_n-(\text{lower alkyl})-$   
 $NH-\text{Aryl}-O-CH_2-$ ,  $-NR(CH_2CH_2O)_n-(\text{lower alkyl})-O-\text{Aryl}-CH_2-$ ,  $-NR(CH_2CH_2O)_n-$   
 $\text{cycloalkyl}-O-\text{Aryl}-$ ,  $-NR(CH_2CH_2O)_n-\text{cycloalkyl}-O-(\text{heteroaryl})-$ ,  $-NR(CH_2CH_2)_n-$   
 $(\text{cycloalkyl})-O-(\text{heterocyclyl})-CH_2-$ ,  $-NR(CH_2CH_2)_n-(\text{heterocyclyl})-(\text{heterocyclyl})-CH_2-$ ,  
 and  $-N(R_1R_2)-(\text{heterocyclyl})-CH_2$ ; where

$n$  of the linker can be 0 to 10;

$R$  of the linker can be H, or lower alkyl; and

$R_1$  and  $R_2$  of the linker can form a ring with the connecting N.

**[00105]** In any aspect or embodiment described herein, the linker ( $L$ ) includes an optionally substituted  $C_1$ - $C_{50}$  alkyl (e.g.,  $C_1$ ,  $C_2$ ,  $C_3$ ,  $C_4$ ,  $C_5$ ,  $C_6$ ,  $C_7$ ,  $C_8$ ,  $C_9$ ,  $C_{10}$ ,  $C_{11}$ ,  $C_{12}$ ,  $C_{13}$ ,  $C_{14}$ ,  $C_{15}$ ,  $C_{16}$ ,  $C_{17}$ ,  $C_{18}$ ,  $C_{19}$ ,  $C_{20}$ ,  $C_{21}$ ,  $C_{22}$ ,  $C_{23}$ ,  $C_{24}$ ,  $C_{25}$ ,  $C_{26}$ ,  $C_{27}$ ,  $C_{28}$ ,  $C_{29}$ ,  $C_{30}$ ,  $C_{31}$ ,  $C_{32}$ ,  $C_{33}$ ,  $C_{34}$ ,  $C_{35}$ ,  $C_{36}$ ,  $C_{37}$ ,  $C_{38}$ ,  $C_{39}$ ,  $C_{40}$ ,  $C_{41}$ ,  $C_{42}$ ,  $C_{43}$ ,  $C_{44}$ ,  $C_{45}$ ,  $C_{46}$ ,  $C_{47}$ ,  $C_{48}$ ,  $C_{49}$ , or  $C_{50}$  alkyl, and including all implied subranges, e.g.,  $C_1$ - $C_{10}$ ,  $C_1$ - $C_{20}$ ;  $C_2$ - $C_{10}$ ,  $C_2$ - $C_{20}$ ;  $C_{10}$ - $C_{20}$ ,  $C_{10}$ - $C_{50}$  etc.), wherein each carbon is optionally independently substituted or replaced with (1) a heteroatom selected from N, O, S, P, or Si atoms that has an appropriate number of hydrogens, substitutions, or both to complete valency, (2) an optionally substituted cycloalkyl or bicyclic cycloalkyl, (3) an optionally substituted heterocycloalkyl or bicyclic heterocycloalkyl, (4) an optionally substituted aryl or bicyclic aryl, or (5) optionally substituted heteroaryl or bicyclic heteroaryl. In any aspect or embodiment described herein, the linker ( $L$ ) does not have heteroatom-heteroatom bonding (e.g., no heteroatoms are covalently linked or adjacently located).

**[00106]** In any aspect or embodiment described herein, the linker (L) includes an optionally substituted C<sub>1</sub>-C<sub>50</sub> alkyl (e.g., C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, C<sub>6</sub>, C<sub>7</sub>, C<sub>8</sub>, C<sub>9</sub>, C<sub>10</sub>, C<sub>11</sub>, C<sub>12</sub>, C<sub>13</sub>, C<sub>14</sub>, C<sub>15</sub>, C<sub>16</sub>, C<sub>17</sub>, C<sub>18</sub>, C<sub>19</sub>, C<sub>20</sub>, C<sub>21</sub>, C<sub>22</sub>, C<sub>23</sub>, C<sub>24</sub>, C<sub>25</sub>, C<sub>26</sub>, C<sub>27</sub>, C<sub>28</sub>, C<sub>29</sub>, C<sub>30</sub>, C<sub>31</sub>, C<sub>32</sub>, C<sub>33</sub>, C<sub>34</sub>, C<sub>35</sub>, C<sub>36</sub>, C<sub>37</sub>, C<sub>38</sub>, C<sub>39</sub>, C<sub>40</sub>, C<sub>41</sub>, C<sub>42</sub>, C<sub>43</sub>, C<sub>44</sub>, C<sub>45</sub>, C<sub>46</sub>, C<sub>47</sub>, C<sub>48</sub>, C<sub>49</sub>, or C<sub>50</sub> alkyl), wherein:

each carbon is optionally independently substituted or replaced with CR<sup>L1</sup>R<sup>L2</sup>, O, S, SO, SO<sub>2</sub>, NR<sup>L3</sup>, SO<sub>2</sub>NR<sup>L3</sup>, SONR<sup>L3</sup>, CONR<sup>L3</sup>, NR<sup>L3</sup>CONR<sup>L4</sup>, NR<sup>L3</sup>SO<sub>2</sub>NR<sup>L4</sup>, CO, CR<sup>L1</sup>=CR<sup>L2</sup>, C≡C, SiR<sup>L1</sup>R<sup>L2</sup>, P(O)R<sup>L1</sup>, P(O)OR<sup>L1</sup>, NR<sup>L3</sup>C(=NCN)NR<sup>L4</sup>, NR<sup>L3</sup>C(=NCN), NR<sup>L3</sup>C(=CNO<sub>2</sub>)NR<sup>L4</sup>, C<sub>3-11</sub>cycloalkyl optionally substituted with 1-6 R<sup>L1</sup> and/or R<sup>L2</sup> groups, C<sub>5-13</sub>spirocycloalkyl optionally substituted with 1-9 R<sup>L1</sup> and/or R<sup>L2</sup> groups, C<sub>3-11</sub>heterocyclyl optionally substituted with 1-6 R<sup>L1</sup> and/or R<sup>L2</sup> groups, C<sub>5-13</sub>spiroheterocyclyl optionally substituted with 1-8 R<sup>L1</sup> and/or R<sup>L2</sup> groups, aryl optionally substituted with 1-6 R<sup>L1</sup> and/or R<sup>L2</sup> groups, or heteroaryl optionally substituted with 0-6 R<sup>L1</sup> and/or R<sup>L2</sup> groups, where R<sup>L1</sup> or R<sup>L2</sup>, each independently are optionally linked to other groups to form a cycloalkyl and/or a heterocyclyl moiety, optionally substituted with 1-4 R<sup>L5</sup> groups; and

R<sup>L1</sup>, R<sup>L2</sup>, R<sup>L3</sup>, R<sup>L4</sup> and R<sup>L5</sup> are, each independently, H, halo, C<sub>1-8</sub>alkyl, OC<sub>1-8</sub>alkyl, SC<sub>1-8</sub>alkyl, NHC<sub>1-8</sub>alkyl, N(C<sub>1-8</sub>alkyl)<sub>2</sub>, C<sub>3-11</sub>cycloalkyl, aryl, heteroaryl, C<sub>3-11</sub>heterocyclyl, OC<sub>3-8</sub>cycloalkyl, SC<sub>3-8</sub>cycloalkyl, NHC<sub>3-8</sub>cycloalkyl, N(C<sub>3-8</sub>cycloalkyl)<sub>2</sub>, N(C<sub>3-8</sub>cycloalkyl)(C<sub>1-8</sub>alkyl), OH, NH<sub>2</sub>, SH, SO<sub>2</sub>C<sub>1-8</sub>alkyl, P(O)(OC<sub>1-8</sub>alkyl)(C<sub>1-8</sub>alkyl), P(O)(OC<sub>1-8</sub>alkyl)<sub>2</sub>, CC-C<sub>1-8</sub>alkyl, CCH, CH=CH(C<sub>1-8</sub>alkyl), C(C<sub>1-8</sub>alkyl)=CH(C<sub>1-8</sub>alkyl), C(C<sub>1-8</sub>alkyl)=C(C<sub>1-8</sub>alkyl)<sub>2</sub>, Si(OH)<sub>3</sub>, Si(C<sub>1-8</sub>alkyl)<sub>3</sub>, Si(OH)(C<sub>1-8</sub>alkyl)<sub>2</sub>, COC<sub>1-8</sub>alkyl, CO<sub>2</sub>H, halogen, CN, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, NO<sub>2</sub>, SF<sub>5</sub>, SO<sub>2</sub>NHC<sub>1-8</sub>alkyl, SO<sub>2</sub>N(C<sub>1-8</sub>alkyl)<sub>2</sub>, SONHC<sub>1-8</sub>alkyl, SON(C<sub>1-8</sub>alkyl)<sub>2</sub>, CONHC<sub>1-8</sub>alkyl, CON(C<sub>1-8</sub>alkyl)<sub>2</sub>, N(C<sub>1-8</sub>alkyl)CONH(C<sub>1-8</sub>alkyl), N(C<sub>1-8</sub>alkyl)CON(C<sub>1-8</sub>alkyl)<sub>2</sub>, NHCONH(C<sub>1-8</sub>alkyl), NHCON(C<sub>1-8</sub>alkyl)<sub>2</sub>, NHCONH<sub>2</sub>, N(C<sub>1-8</sub>alkyl)SO<sub>2</sub>NH(C<sub>1-8</sub>alkyl), N(C<sub>1-8</sub>alkyl)SO<sub>2</sub>N(C<sub>1-8</sub>alkyl)<sub>2</sub>, NH SO<sub>2</sub>NH(C<sub>1-8</sub>alkyl), NH SO<sub>2</sub>N(C<sub>1-8</sub>alkyl)<sub>2</sub>, or NH SO<sub>2</sub>NH<sub>2</sub>.

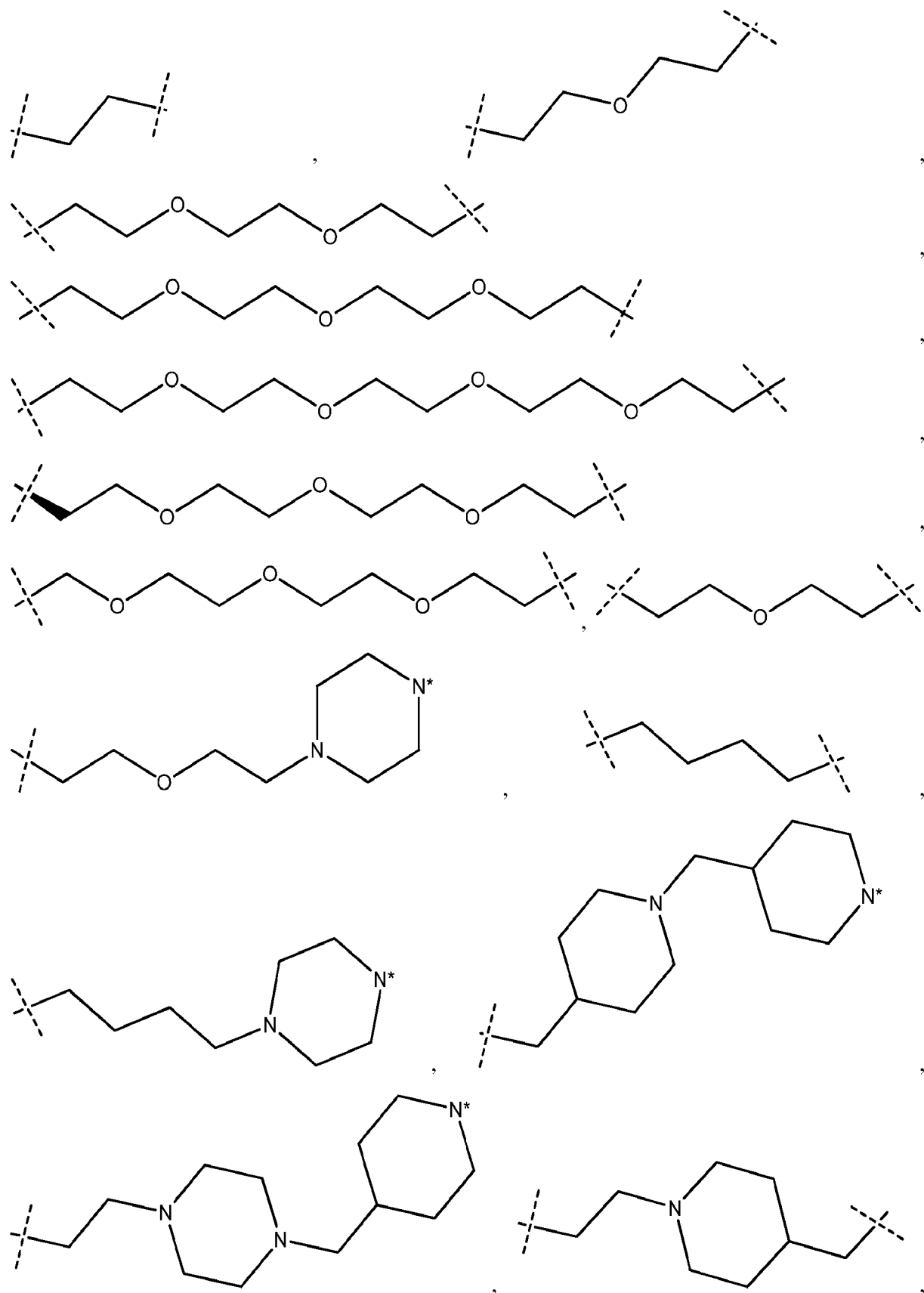
**[00107]** In any aspect or embodiment described herein, the linker group is optionally substituted an optionally substituted C<sub>1</sub>-C<sub>50</sub> alkyl (e.g., C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, C<sub>6</sub>, C<sub>7</sub>, C<sub>8</sub>, C<sub>9</sub>, C<sub>10</sub>, C<sub>11</sub>, C<sub>12</sub>, C<sub>13</sub>, C<sub>14</sub>, C<sub>15</sub>, C<sub>16</sub>, C<sub>17</sub>, C<sub>18</sub>, C<sub>19</sub>, C<sub>20</sub>, C<sub>21</sub>, C<sub>22</sub>, C<sub>23</sub>, C<sub>24</sub>, C<sub>25</sub>, C<sub>26</sub>, C<sub>27</sub>, C<sub>28</sub>, C<sub>29</sub>, C<sub>30</sub>, C<sub>31</sub>, C<sub>32</sub>, C<sub>33</sub>, C<sub>34</sub>, C<sub>35</sub>, C<sub>36</sub>, C<sub>37</sub>, C<sub>38</sub>, C<sub>39</sub>, C<sub>40</sub>, C<sub>41</sub>, C<sub>42</sub>, C<sub>43</sub>, C<sub>44</sub>, C<sub>45</sub>, C<sub>46</sub>, C<sub>47</sub>, C<sub>48</sub>, C<sub>49</sub>, or C<sub>50</sub> alkyl, and including all implied subranges, e.g., C<sub>1</sub>-C<sub>10</sub>, C<sub>1</sub>-C<sub>20</sub>; C<sub>2</sub>-C<sub>10</sub>, C<sub>2</sub>-C<sub>20</sub>; C<sub>10</sub>-C<sub>20</sub>, C<sub>10</sub>-C<sub>50</sub> etc.),

wherein each carbon atom optionally substituted or replaced with: a O, N, S, P or Si atom that has an appropriate number of hydrogens, substitutions (e.g., OH, halo, alkyl, methyl, ethyl, haloalkyl, hydroxyalkyl, alkoxy, methoxy, etc.), or both to complete valency; an optionally substituted aryl (e.g., an optionally substituted C5 or C6 aryl) or bicyclic aryl (e.g., an optionally substituted C5-C20 bicyclic heteraryl); an optionally substituted heteroaryl (e.g., an optionally substituted C5 or C6 heteroaryl) or bicyclic heteroaryl (e.g., an optionally substituted heteroaryl or bicyclic heteroaryl having one or more heteroatoms selected from N, O, S, P, and Si that has an appropriate number of hydrogens, substitutions (e.g., OH, halo, alkyl, methyl, ethyl, haloalkyl, hydroxyalkyl, alkoxy, methoxy, etc.), or both to complete valency); an optionally substituted C1-C6 alkyl; an optionally substituted C1-C6 alkenyl; an optionally substituted C1-C6 alkynyl; an optionally substituted cycloalkyl (e.g., an optionally substituted C3-C7 cycloalkyl) or bicyclic cycloalkyl (e.g., an optionally substituted C5-C20 bicyclic cycloalkyl); or an optionally substituted heterocycloalkyl (e.g., an optionally substituted 3-, 4-, 5-, 6-, or 7-membered heterocyclic group) or bicyclic heteroalkyl (e.g., an optionally substituted heterocycloalkyl bicyclic heteroalkyl having one or more heteroatoms selected from N, O, S, P, or Si atoms that has an appropriate number of hydrogens, substitutions (e.g., OH, halo, alkyl, methyl, ethyl, haloalkyl, hydroxyalkyl, alkoxy, methoxy, etc.), or both to complete valency). In any aspect or embodiment described herein, the optionally substituted alkyl linker is optionally substituted with one or more OH, halo, linear or branched C1-C6 alkyl (such as methyl or ethyl), linear or branched C1-C6 haloalkyl, linear or branched C1-C6 hydroxyalkyl, or linear or branched C1-C6 alkoxy (e.g., methoxy).

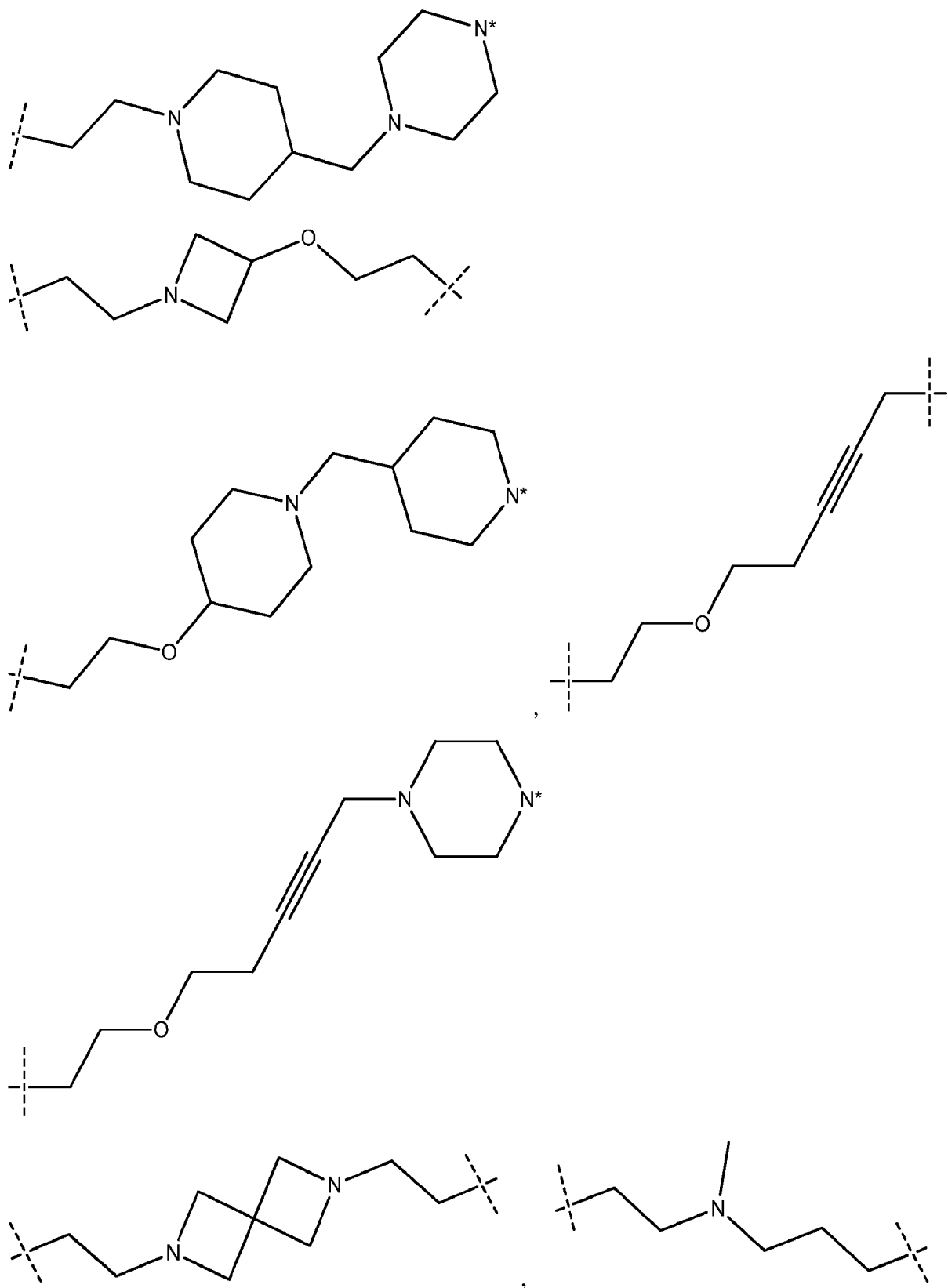
**[00108]** In any aspect or embodiment described herein, the linker (L) does not have heteroatom-heteroatom bonding (e.g., no heteroatoms are covalently linked or adjacently located).

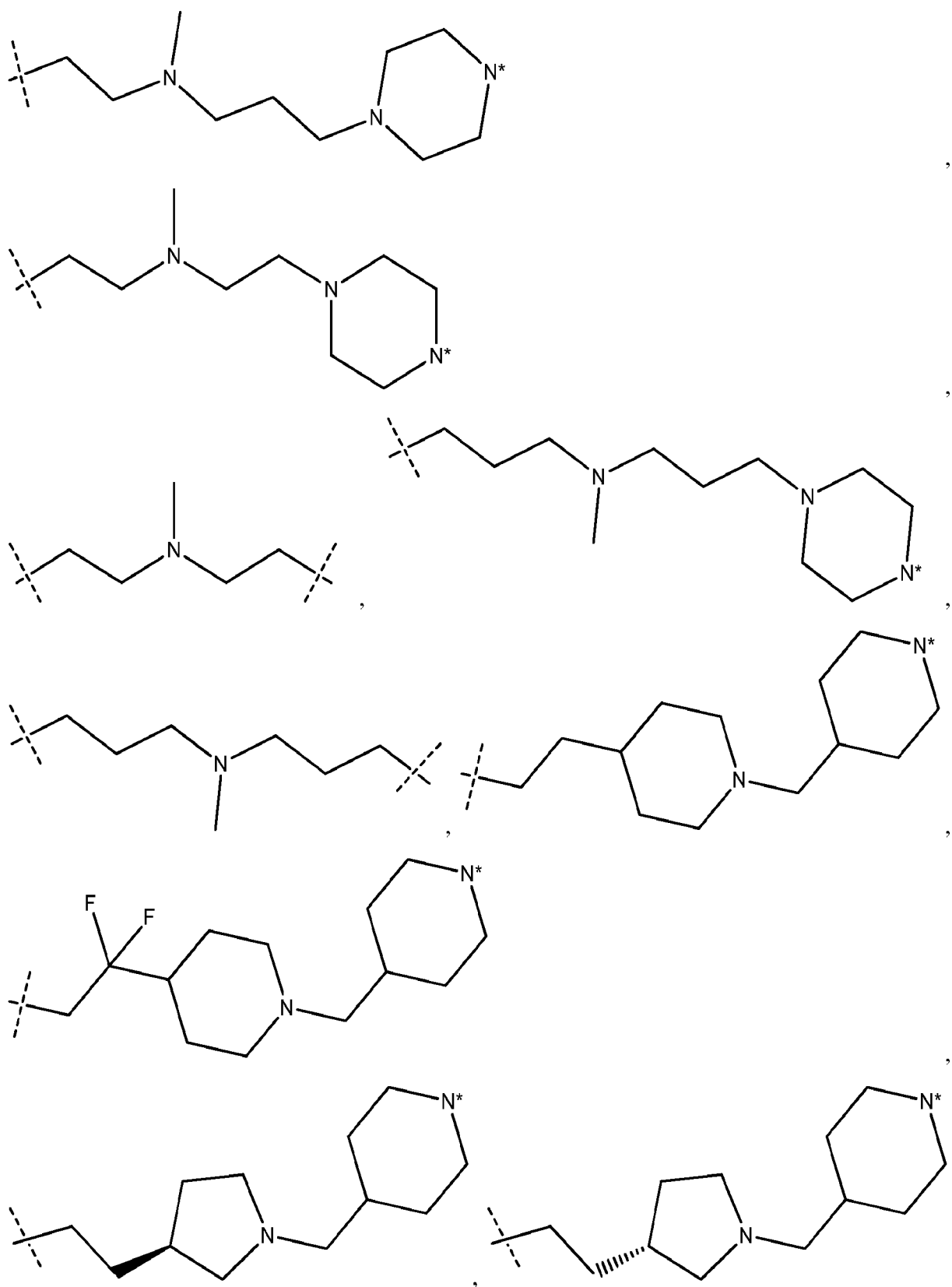
**[00109]** In any aspect or embodiment described herein, the linker (L) includes about 1 to about 50 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50) alkylene glycol units that are optionally substituted, wherein carbon or oxygen may be substituted with a heteroatom selected from N, S, P, or Si atoms with an appropriate number of hydrogens to complete valency.

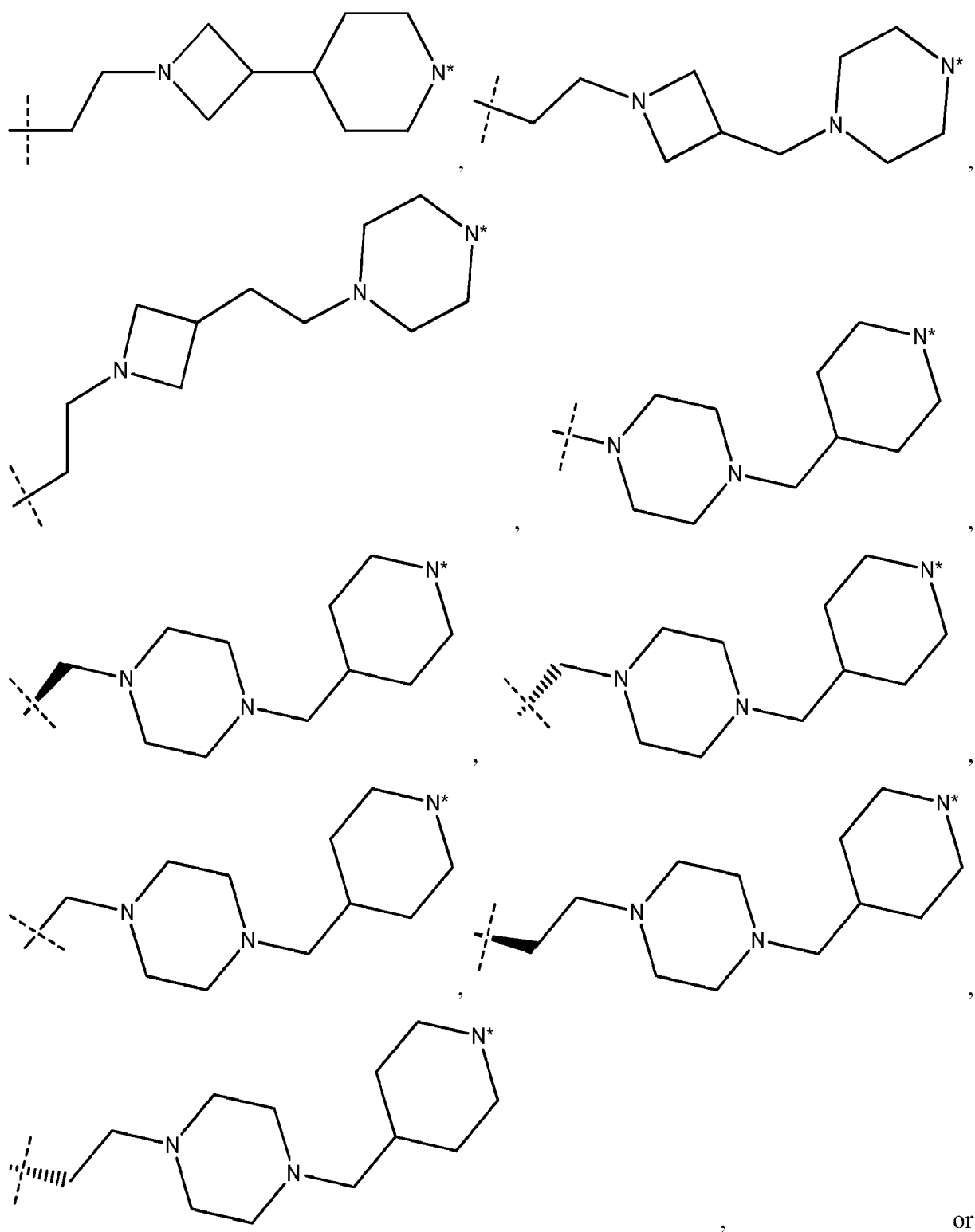
**[00110]** In any aspect or embodiment described herein, the unit  $A^L$  of the linker (L) comprises a structure selected from the group consisting of:

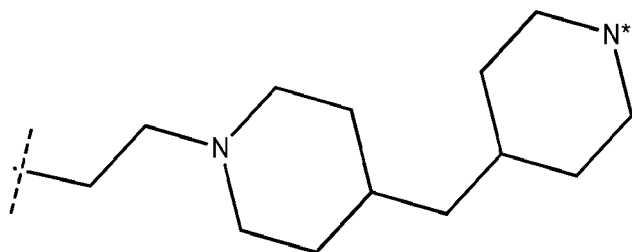






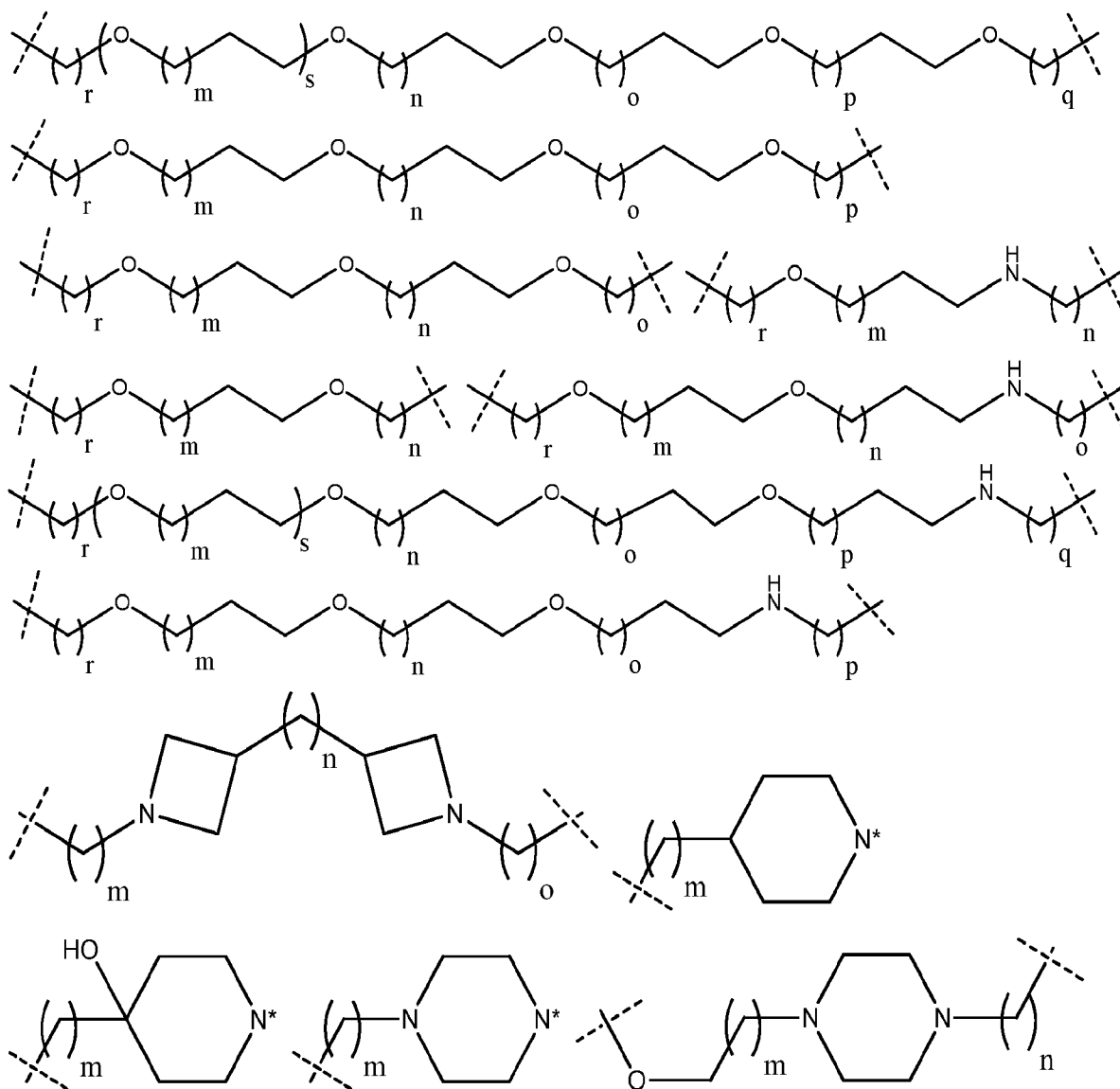


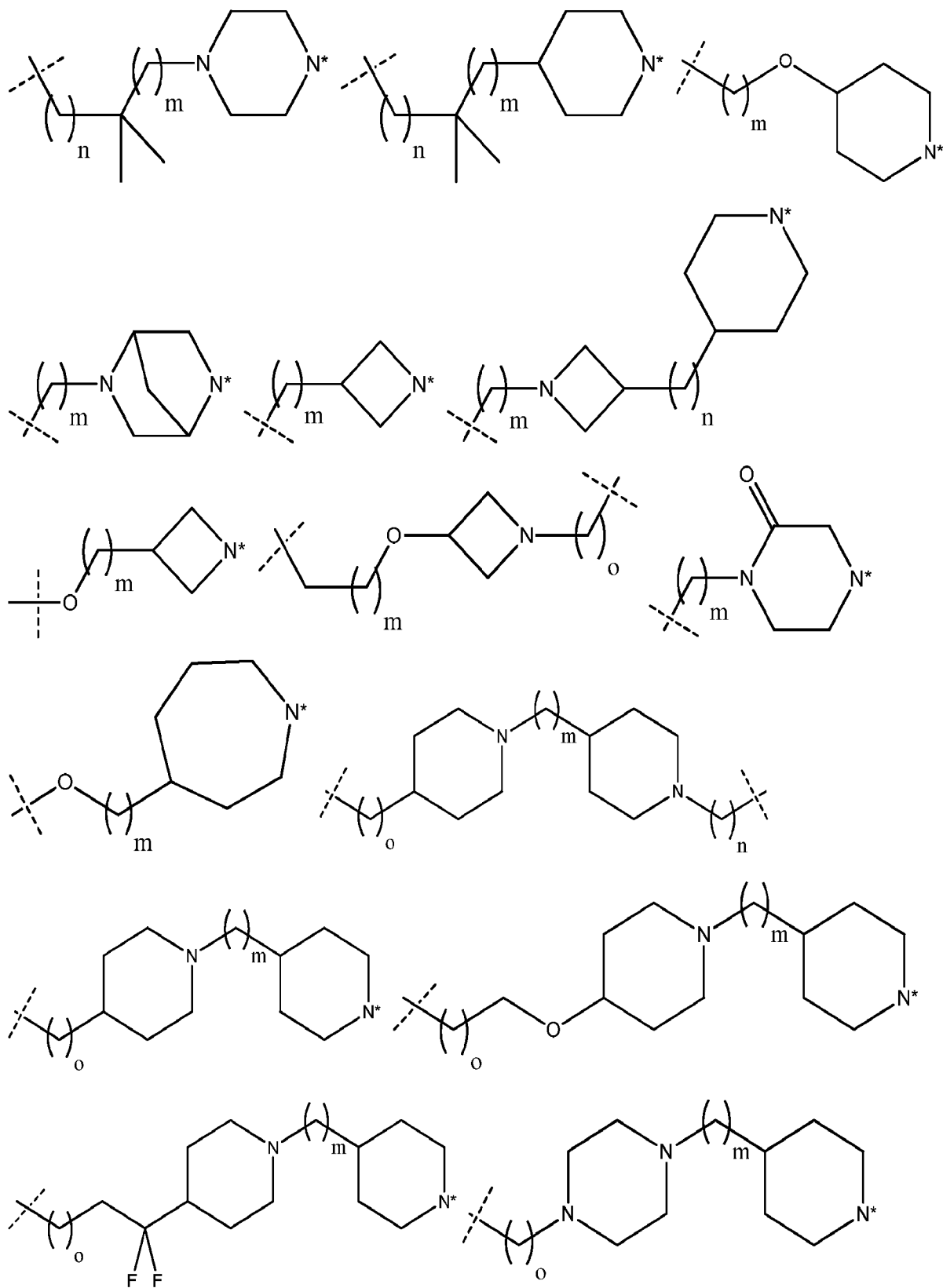


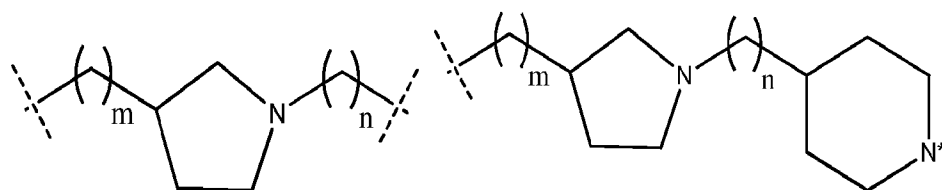
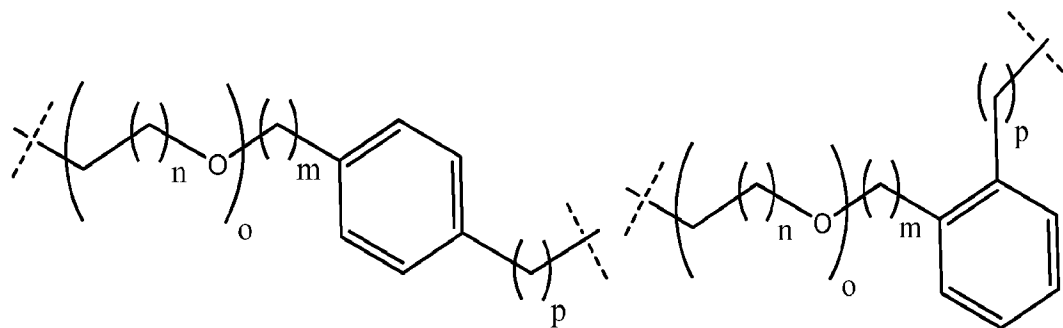
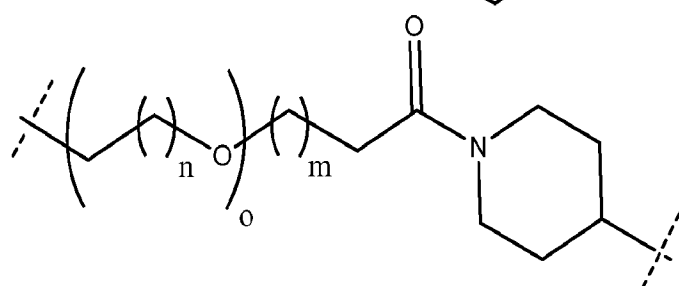
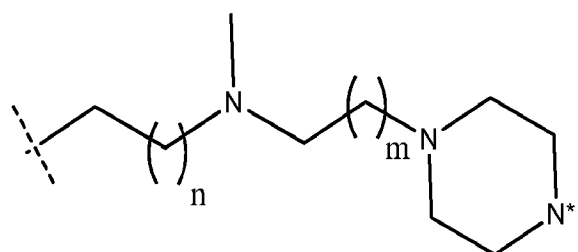
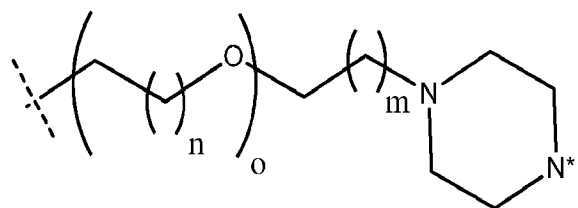
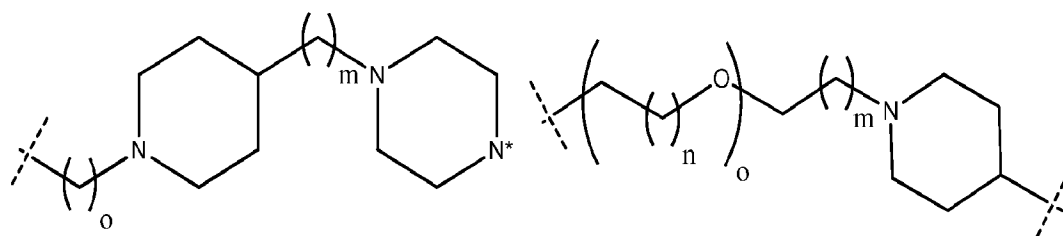


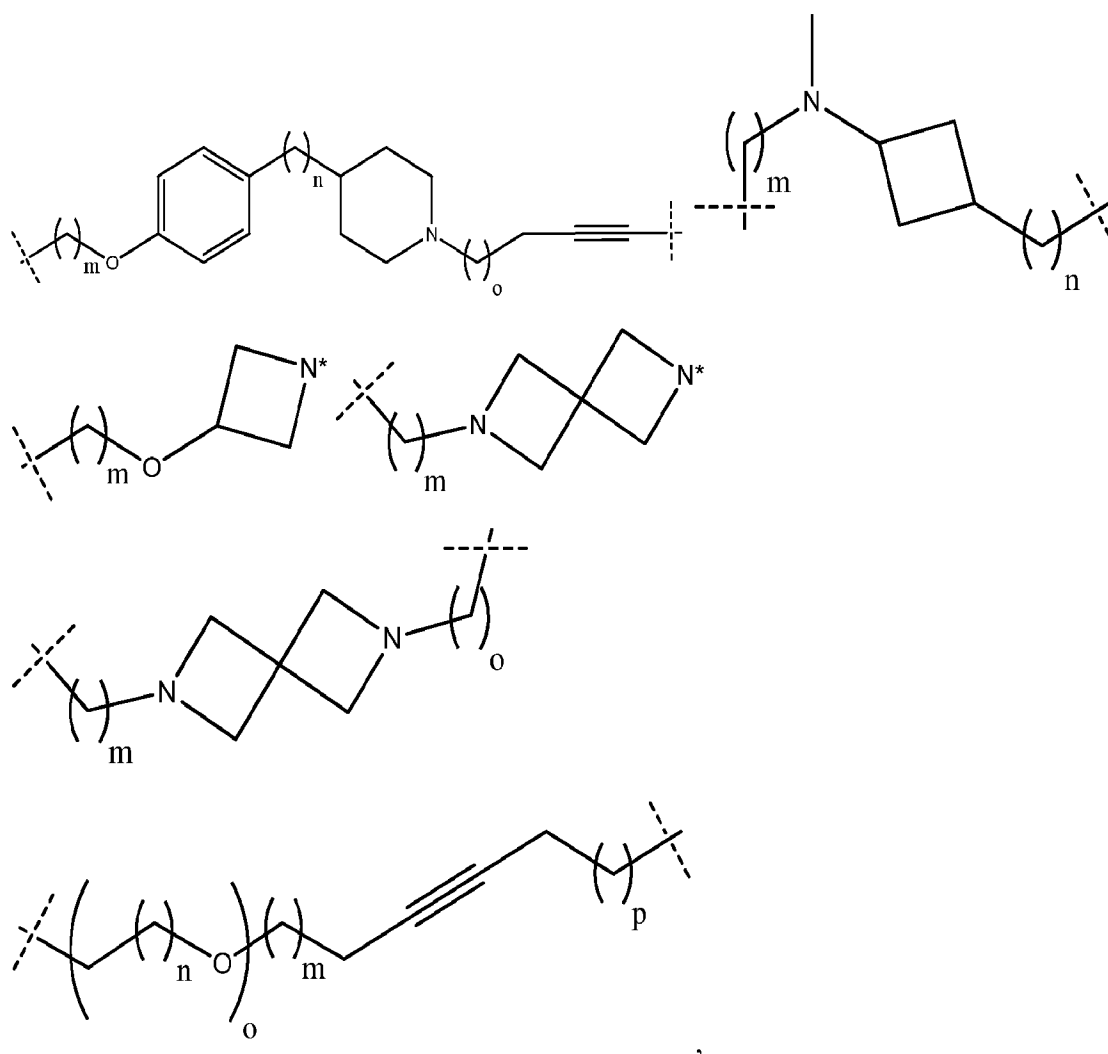
, wherein N\* is a nitrogen atom that is covalently linked to the ULM or the PTM, or that is shared with the ULM or the PTM.

**[00111]** In any aspect or embodiment described herein, the unit A<sup>L</sup> of the linker (L) comprises a structure selected from the group consisting of:







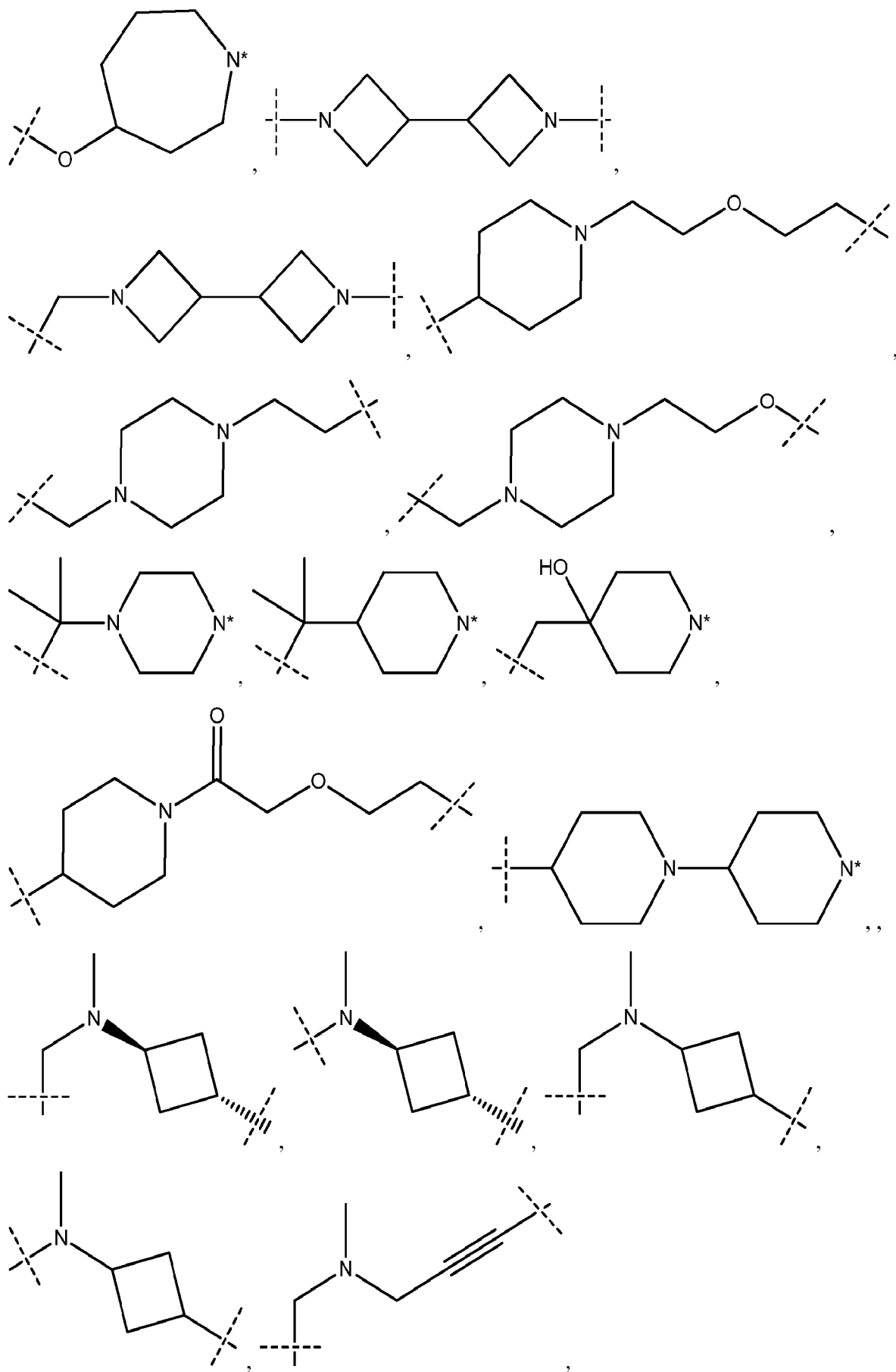


wherein:

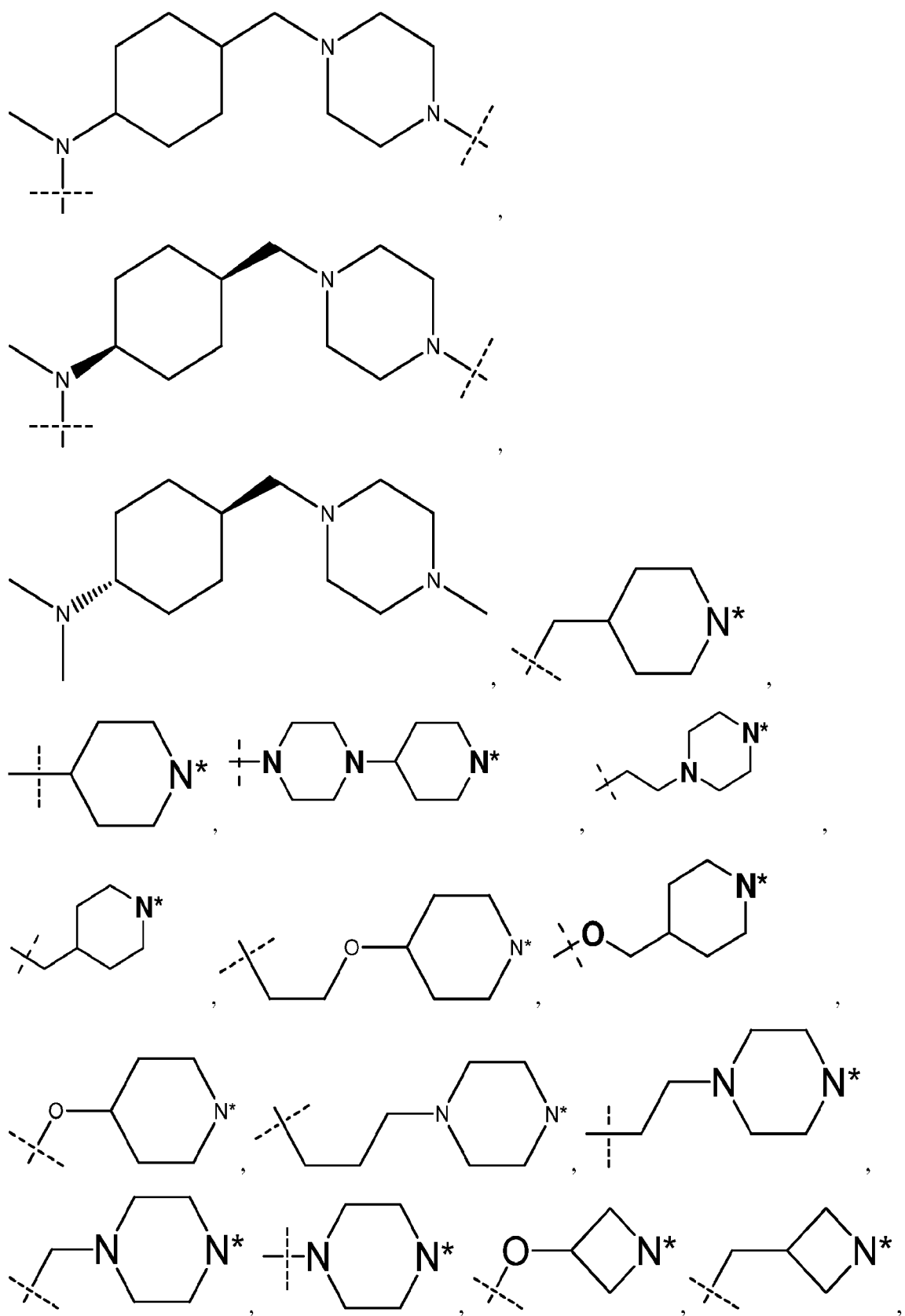
N\* is a nitrogen atom that is covalently linked to the ULM or the PTM, or that is shared with the ULM or the PTM; and

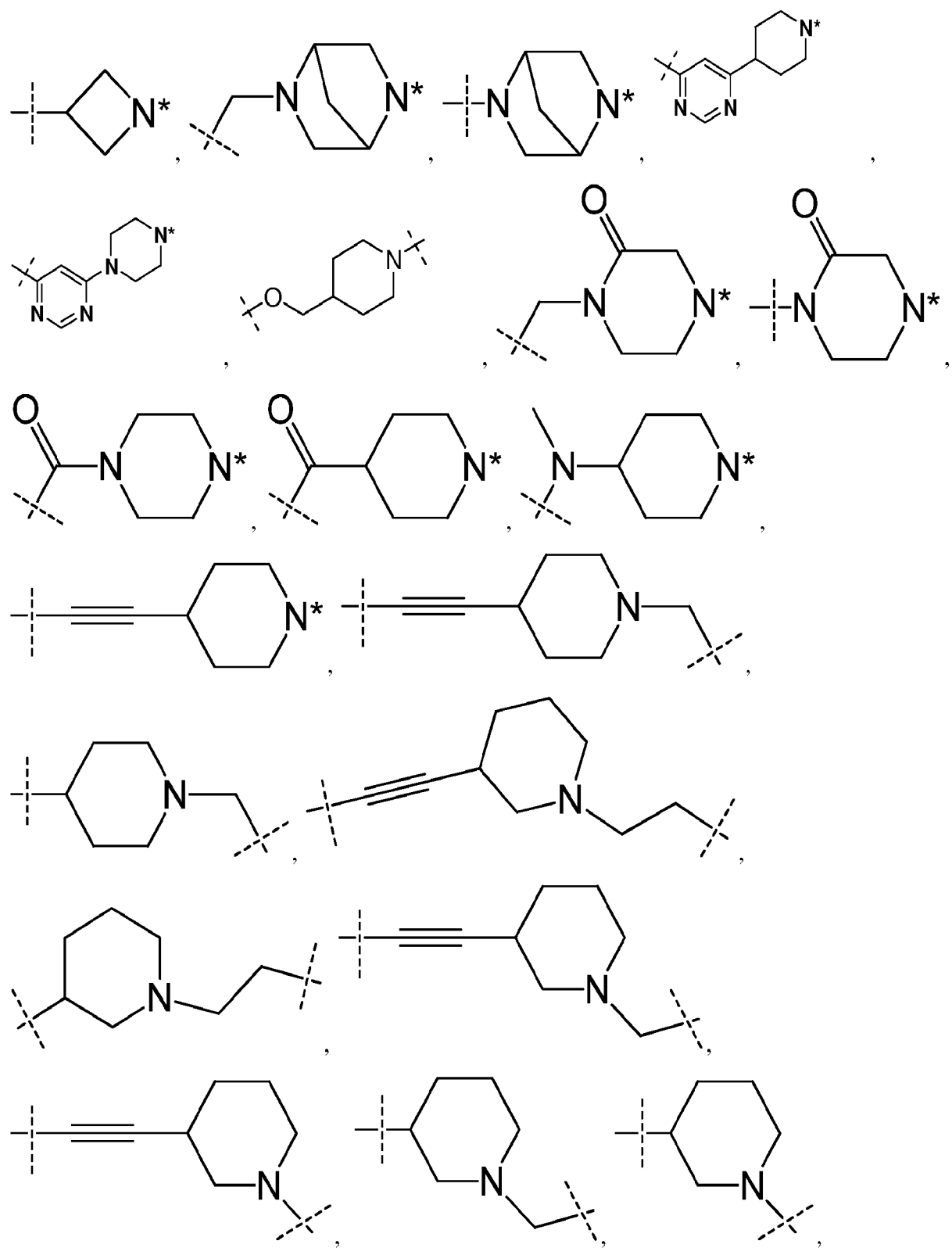
each m, n, o, p, q, and r is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

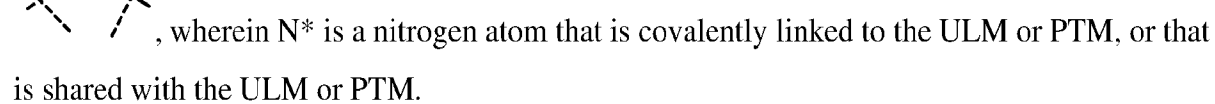
**[00112]** In any aspect or embodiment described herein, the unit A<sup>L</sup> of the linker (L) is selected from:



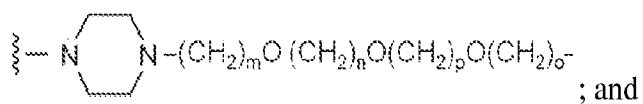










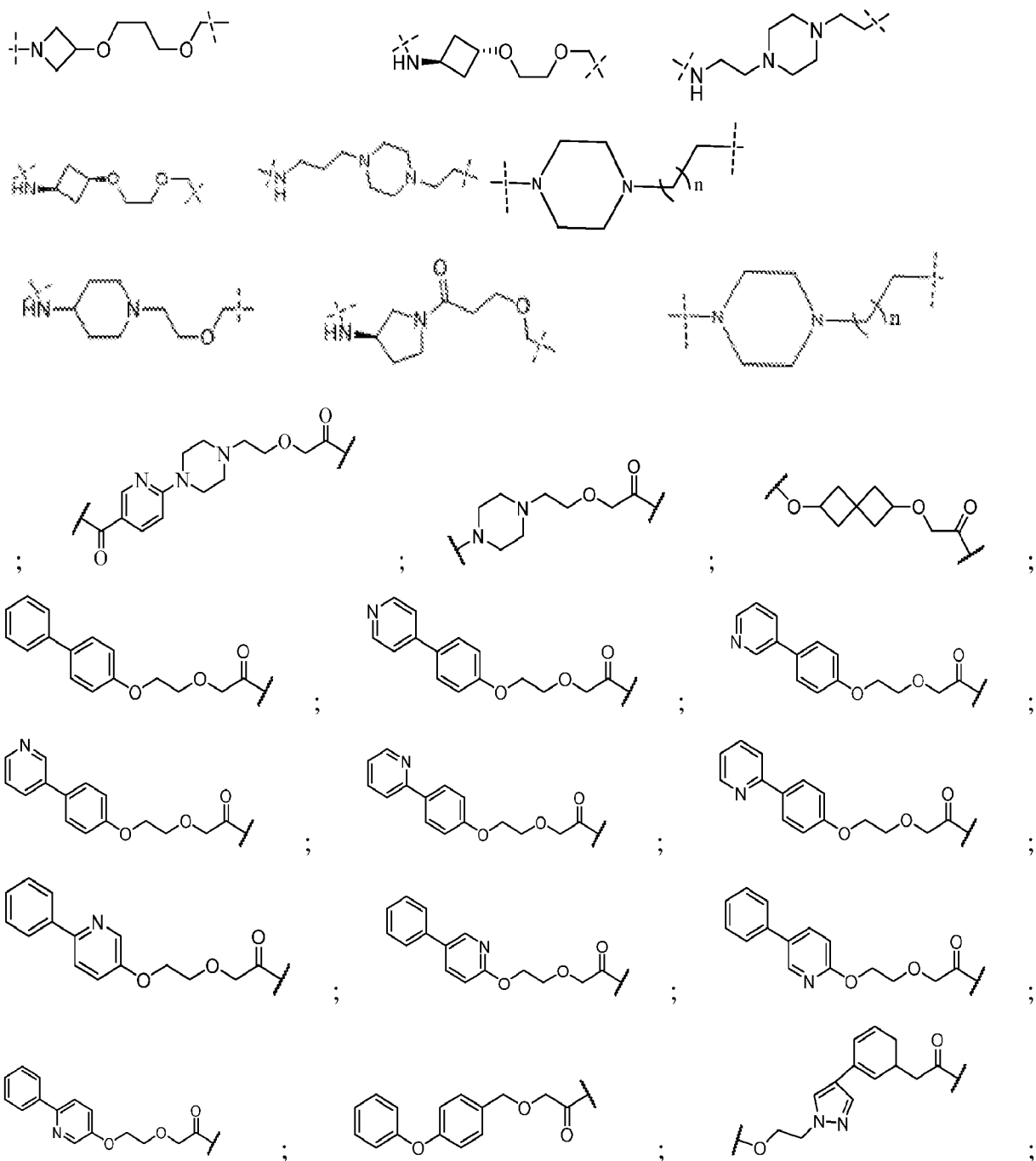


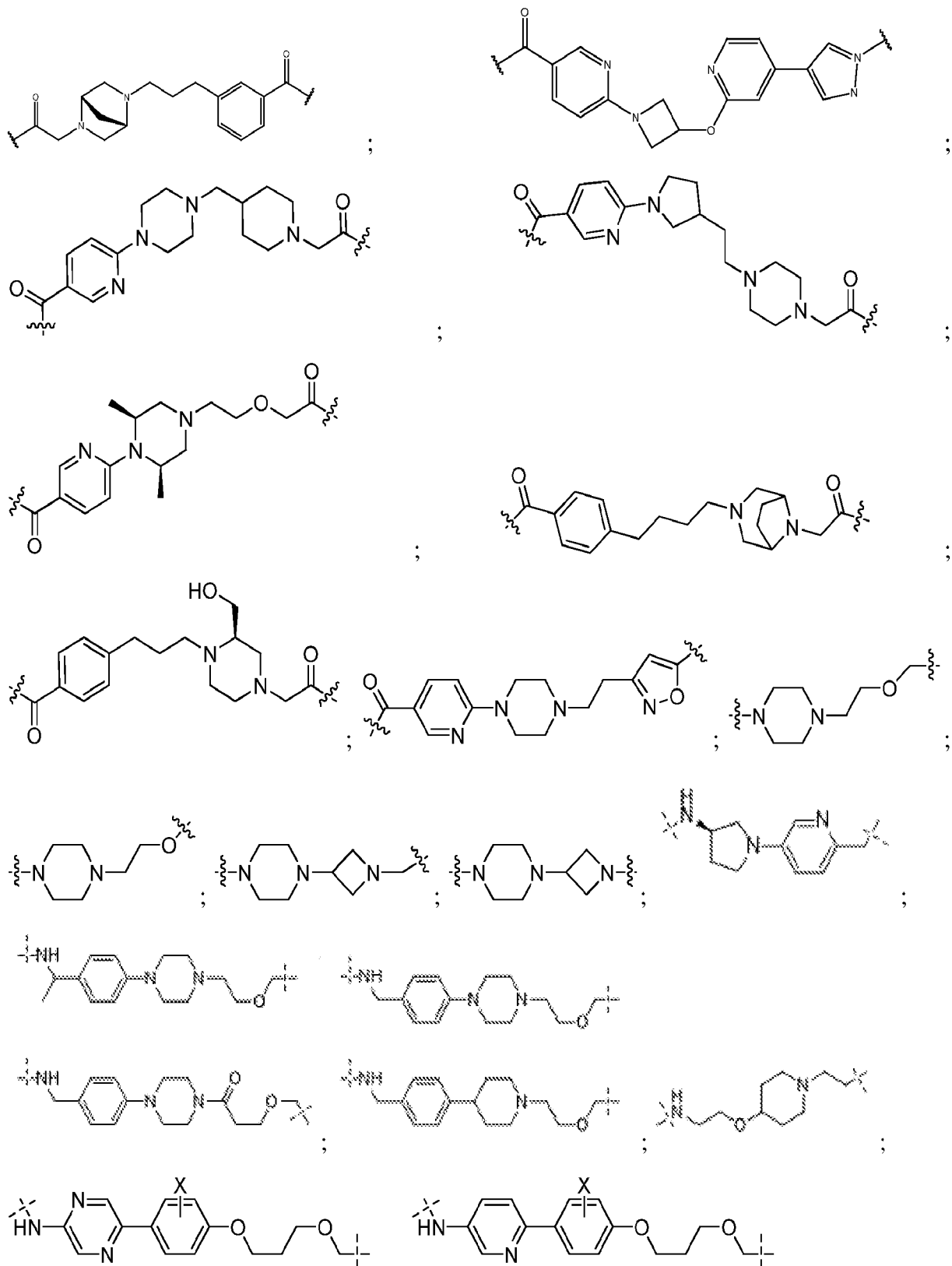
wherein

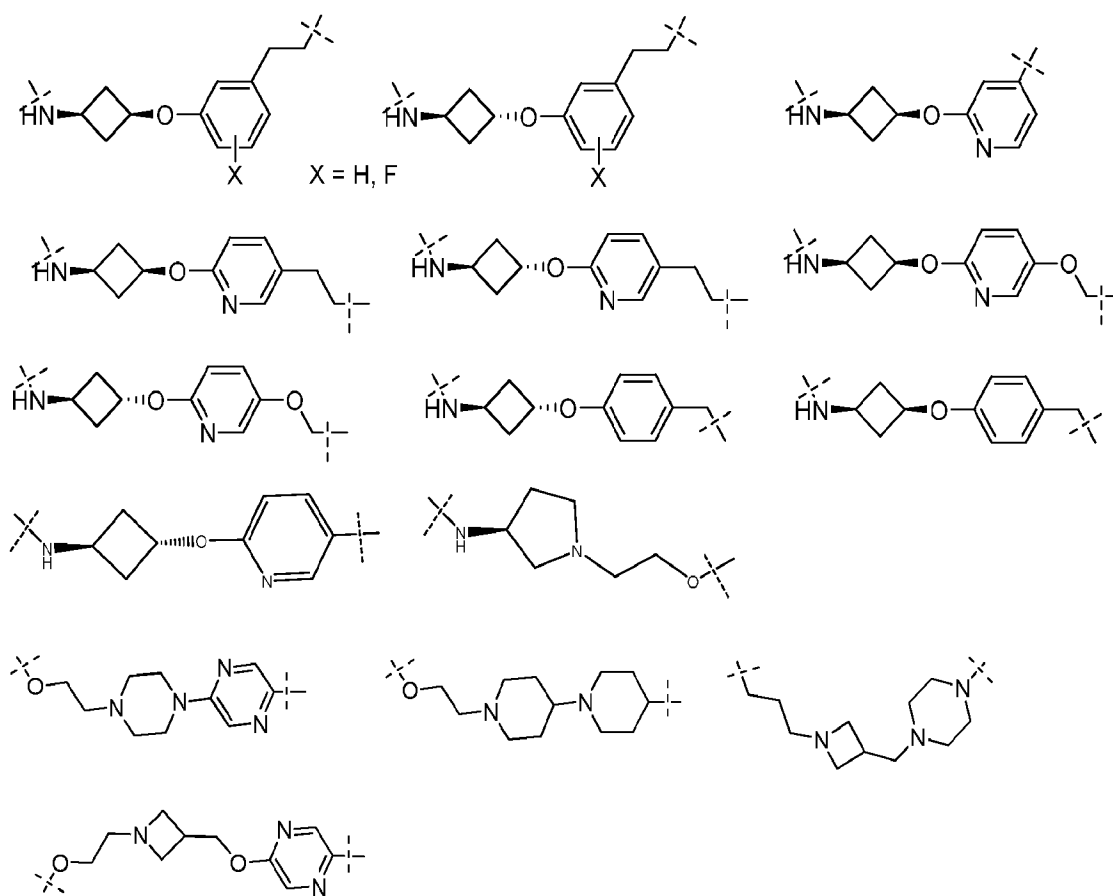
m, n, o, p, q, and r of the linker are independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20;

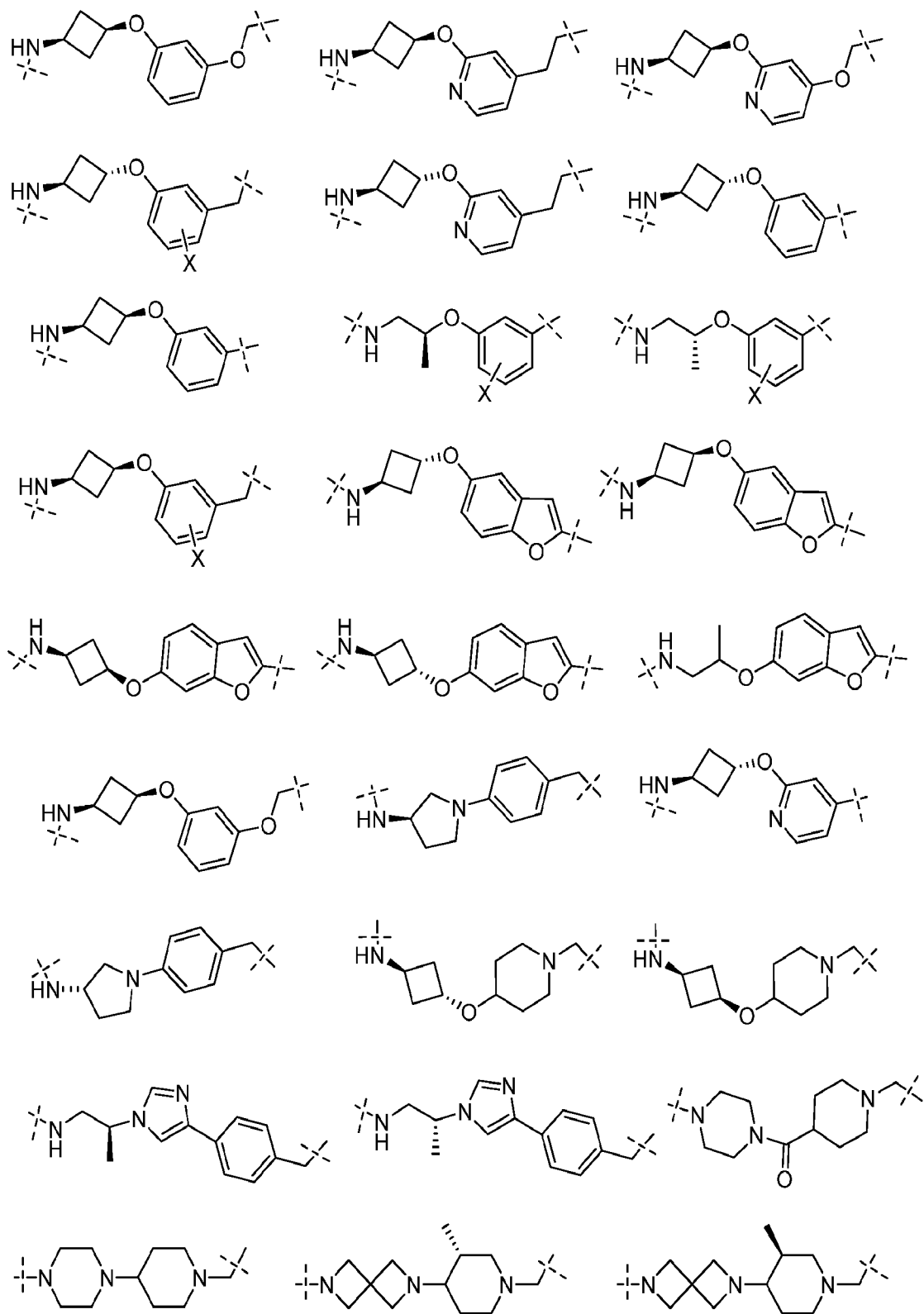
when m, n, o, p, q, and r are zero, N-O or O-O bond is absent,

X of the linker is H or F;

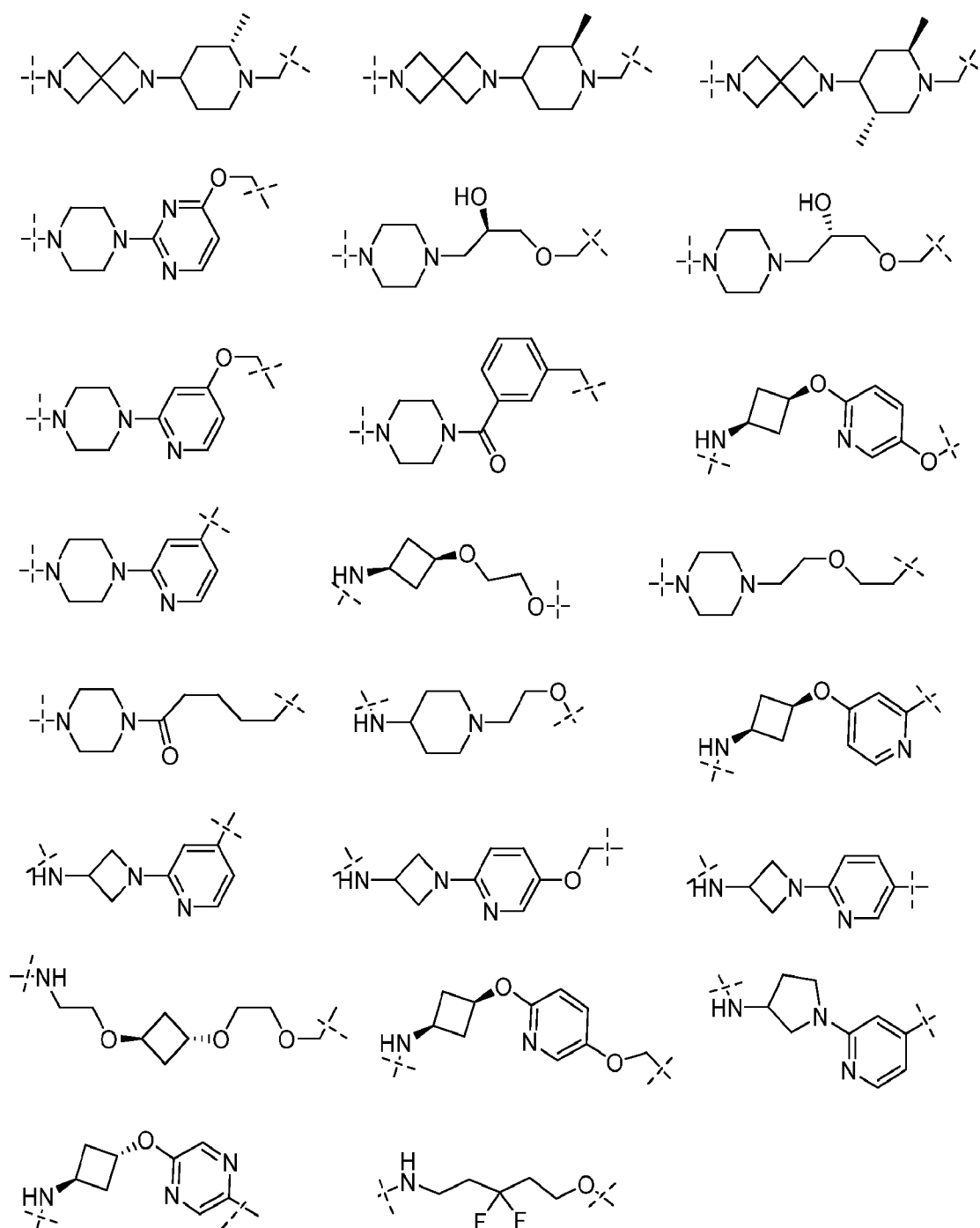






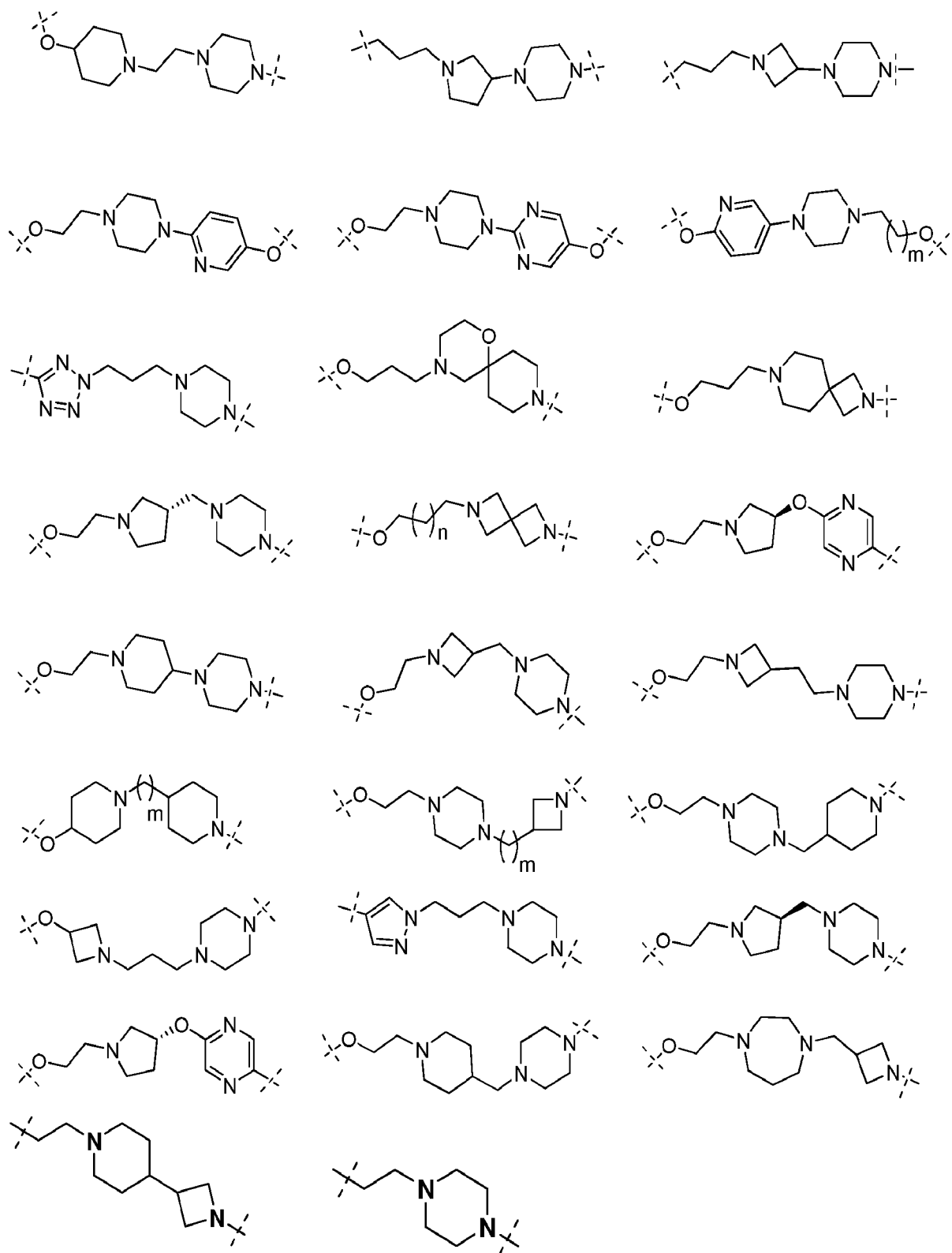


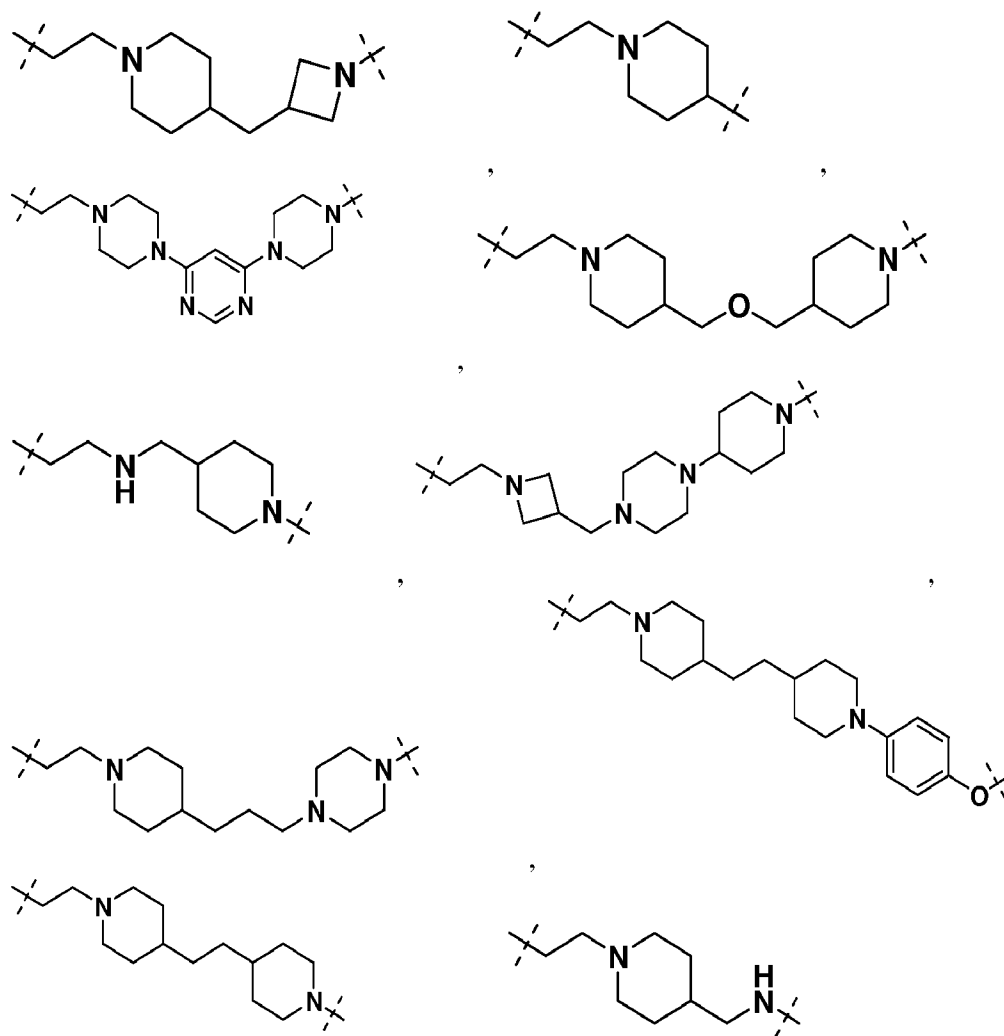




where each  $n$  and  $m$  of the linker can independently be 0, 1, 2, 3, 4, 5, or 6.

**[00114]** In any aspect or embodiment described herein, the unit A<sup>L</sup> of linker (L) is selected from the group consisting of:

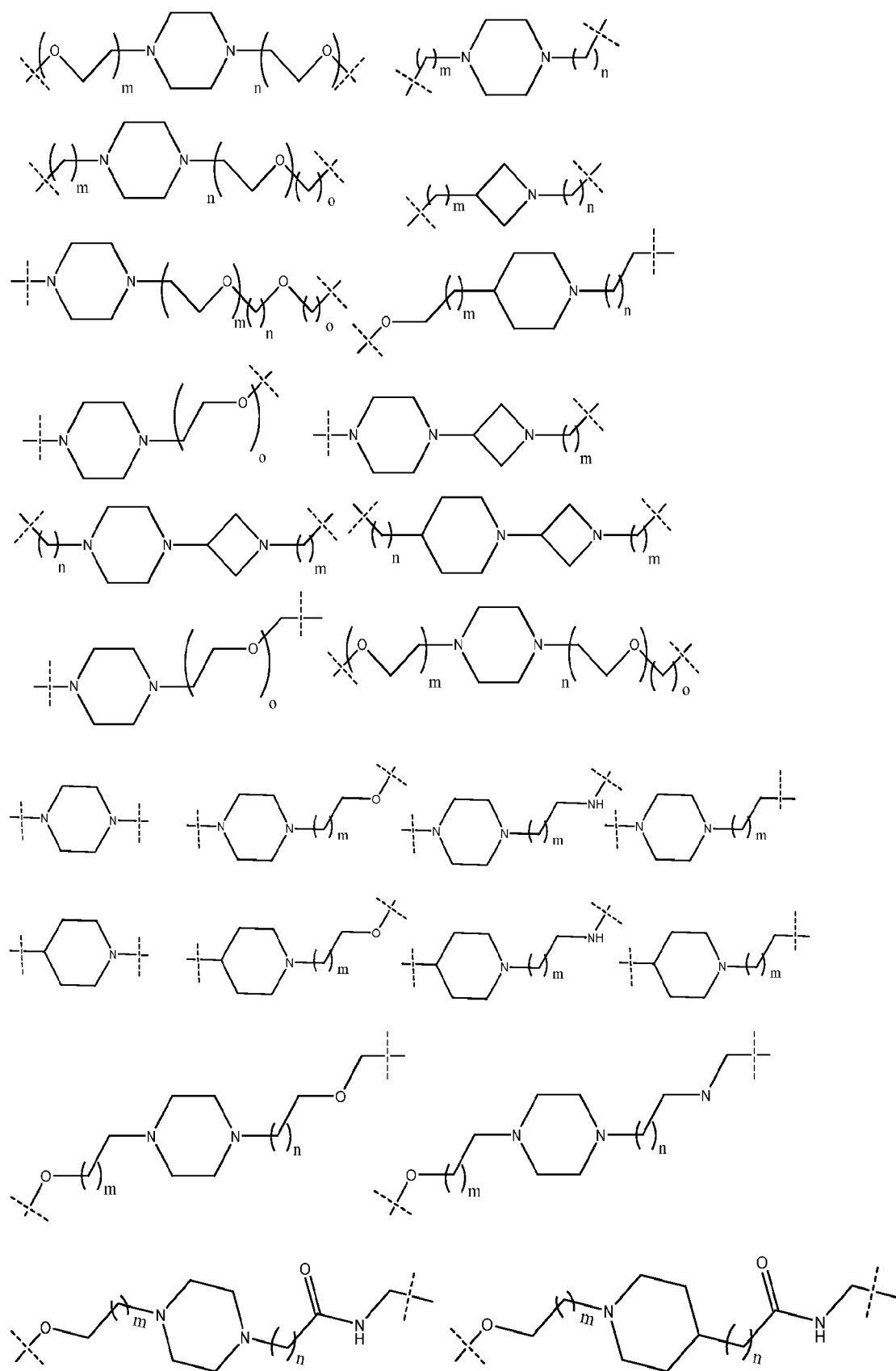


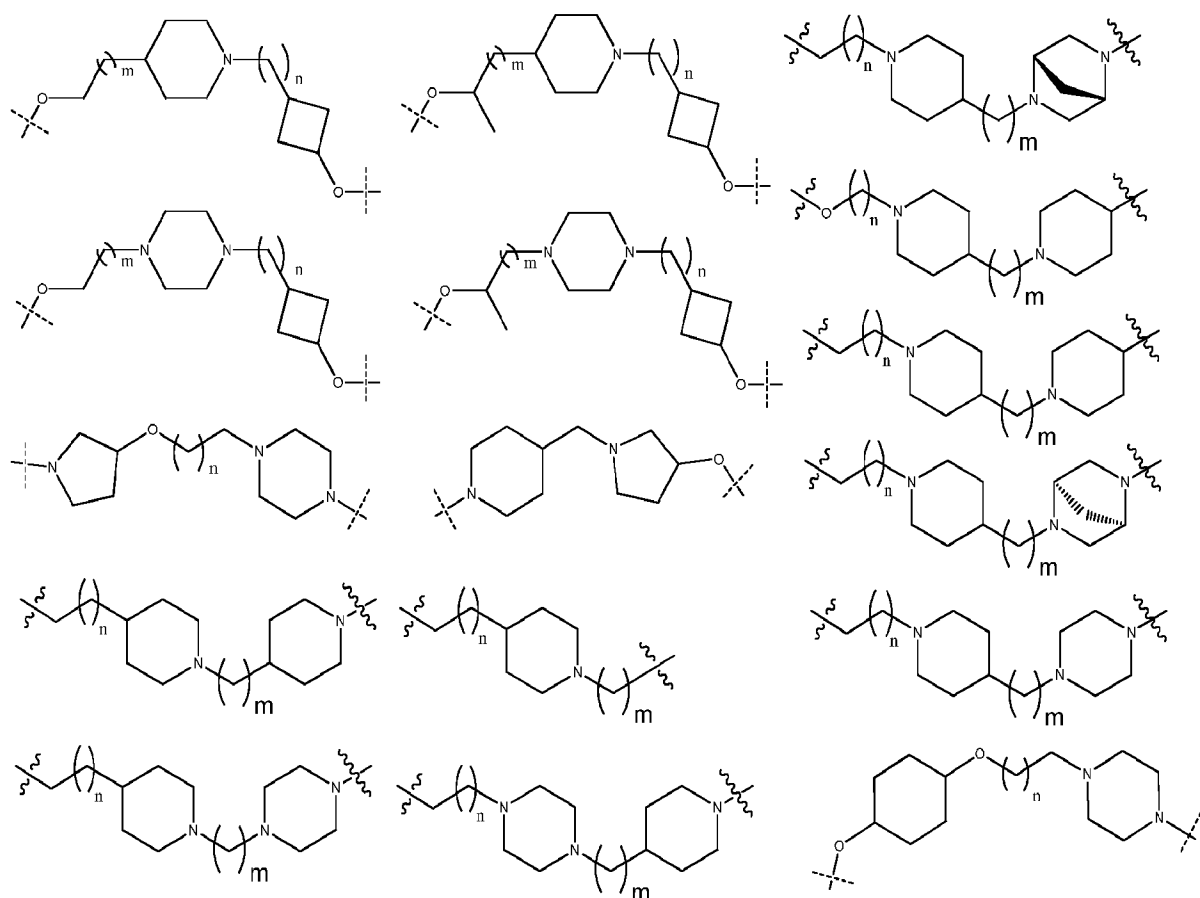


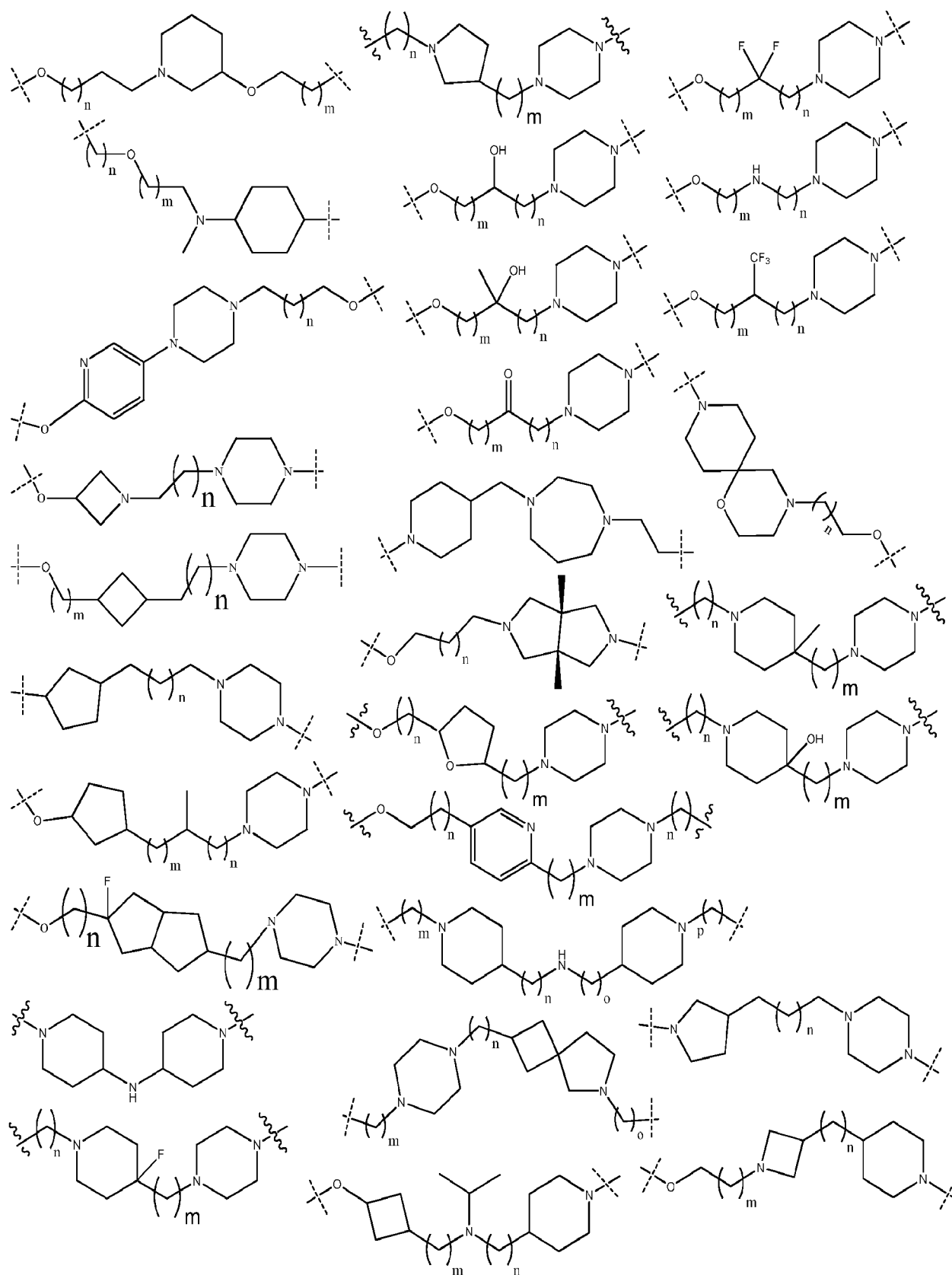
, and

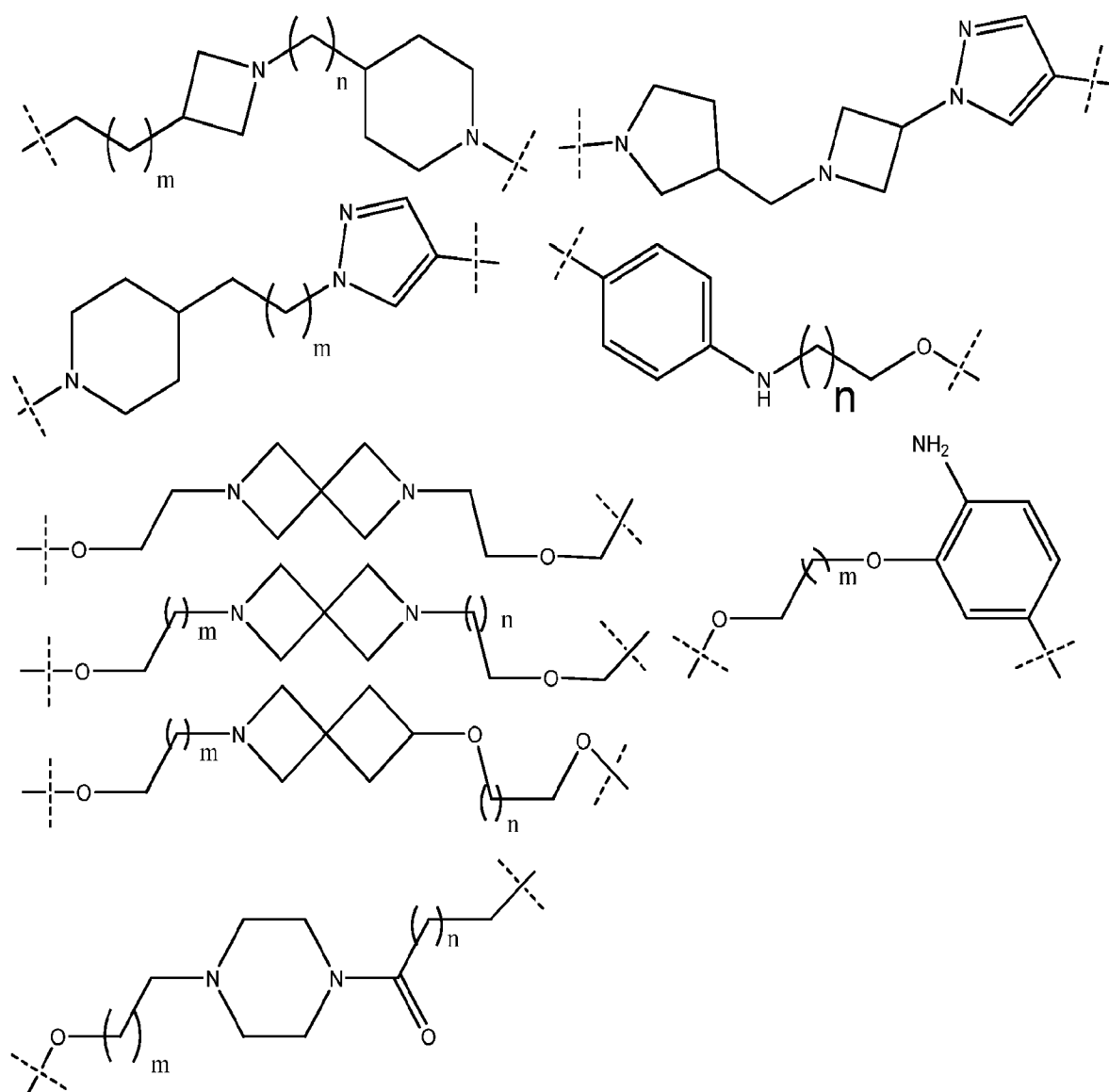
wherein each m and n is independently selected from 0, 1, 2, 3, 4, 5, or 6.

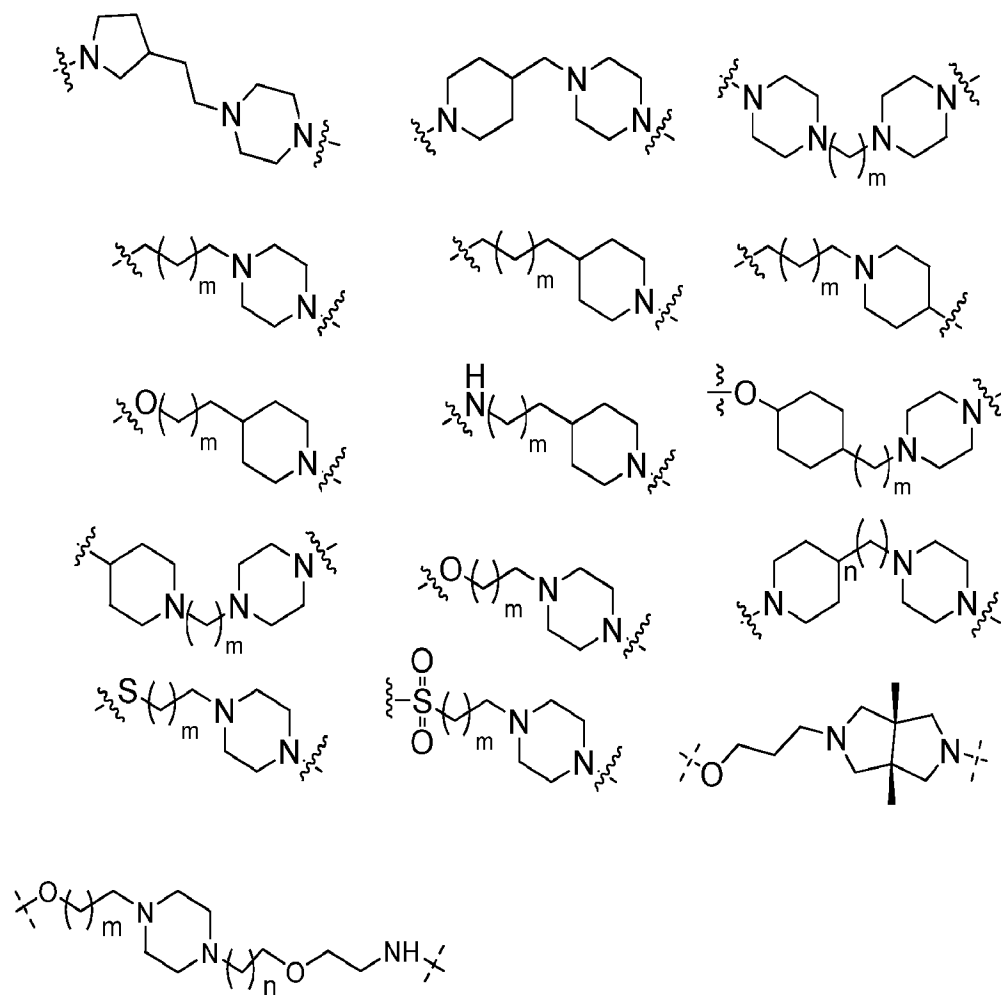
**[00115]** In any aspect or embodiment described herein, the unit  $A^L$  of linker (L) is selected from the group consisting of:



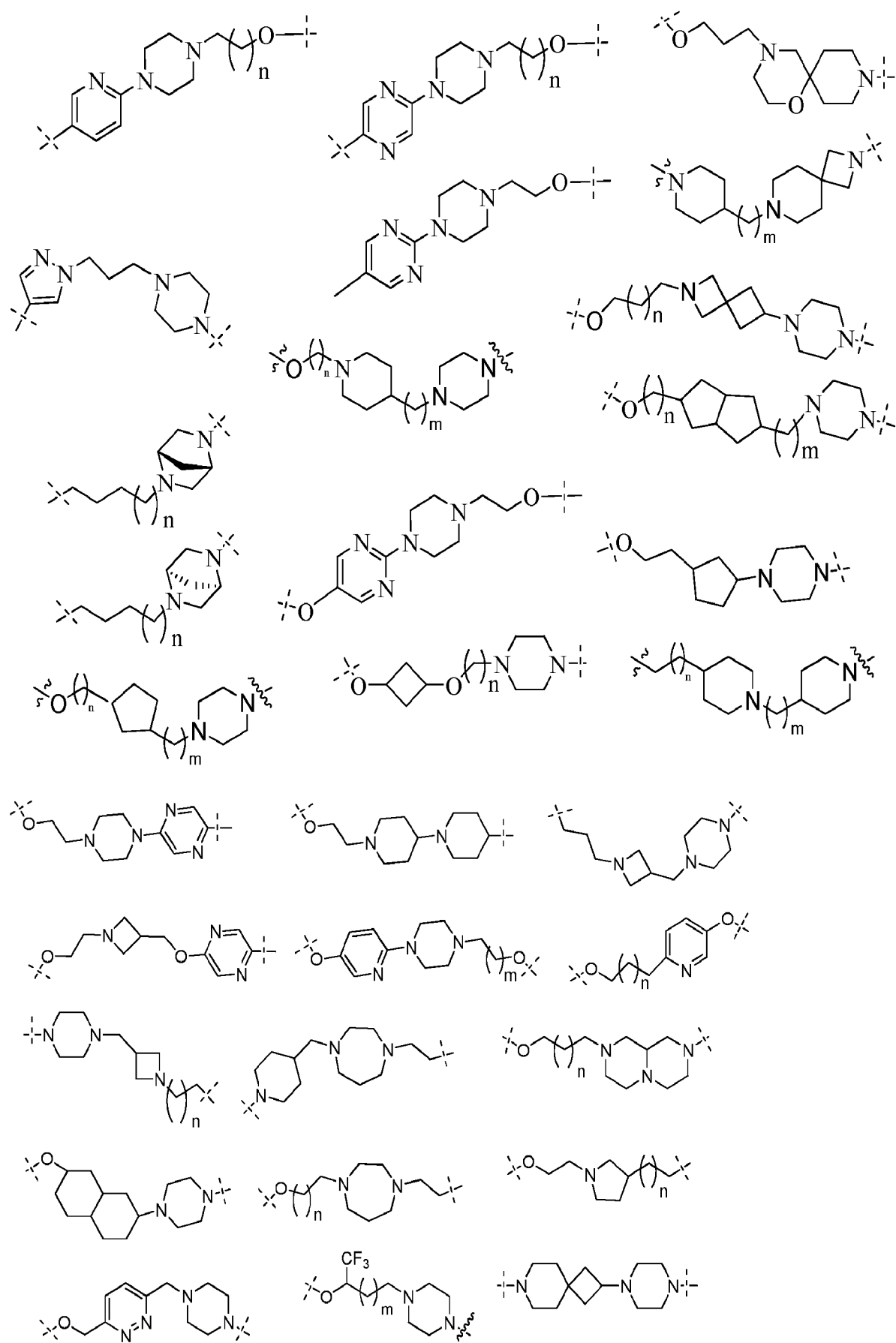


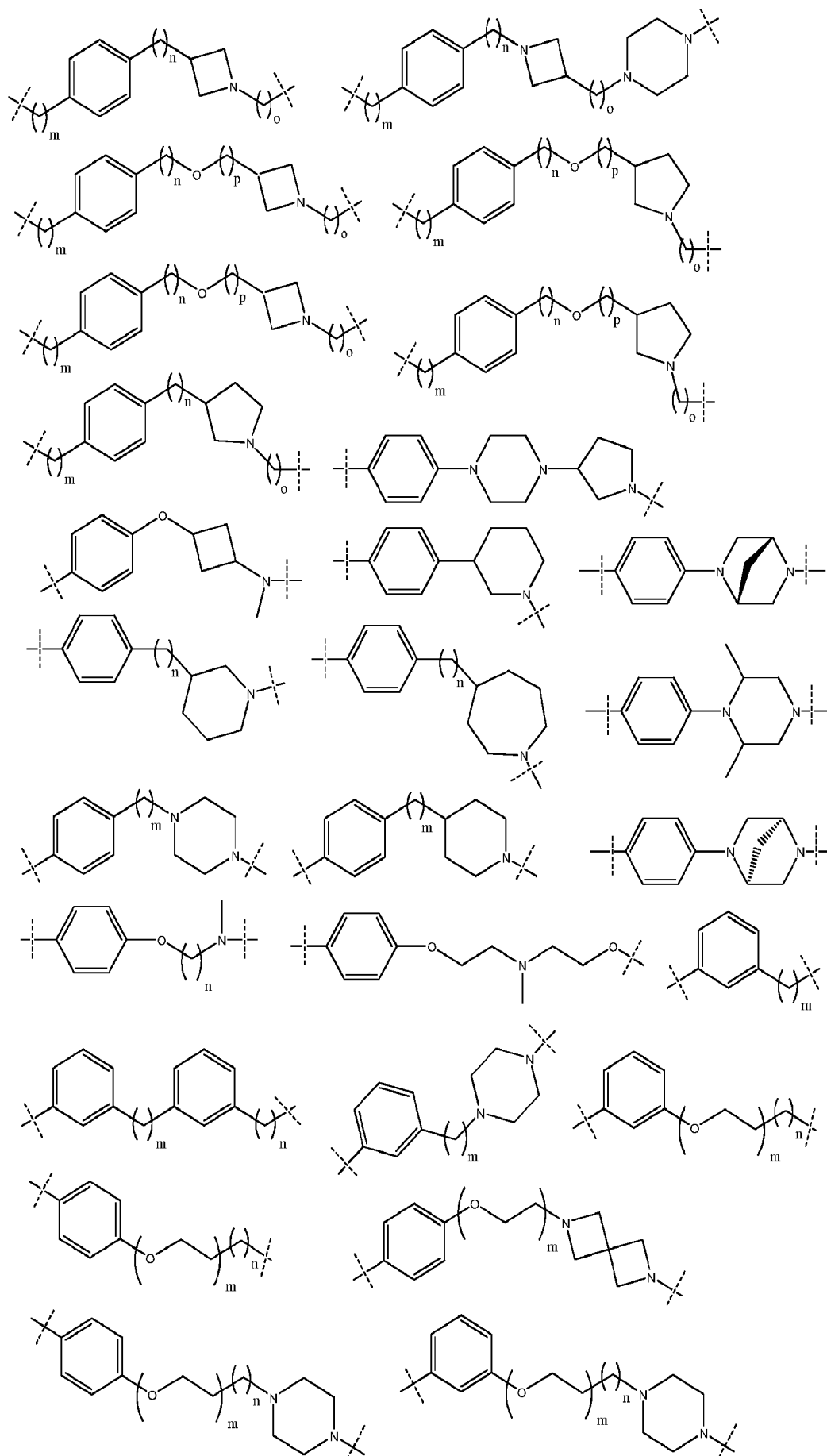


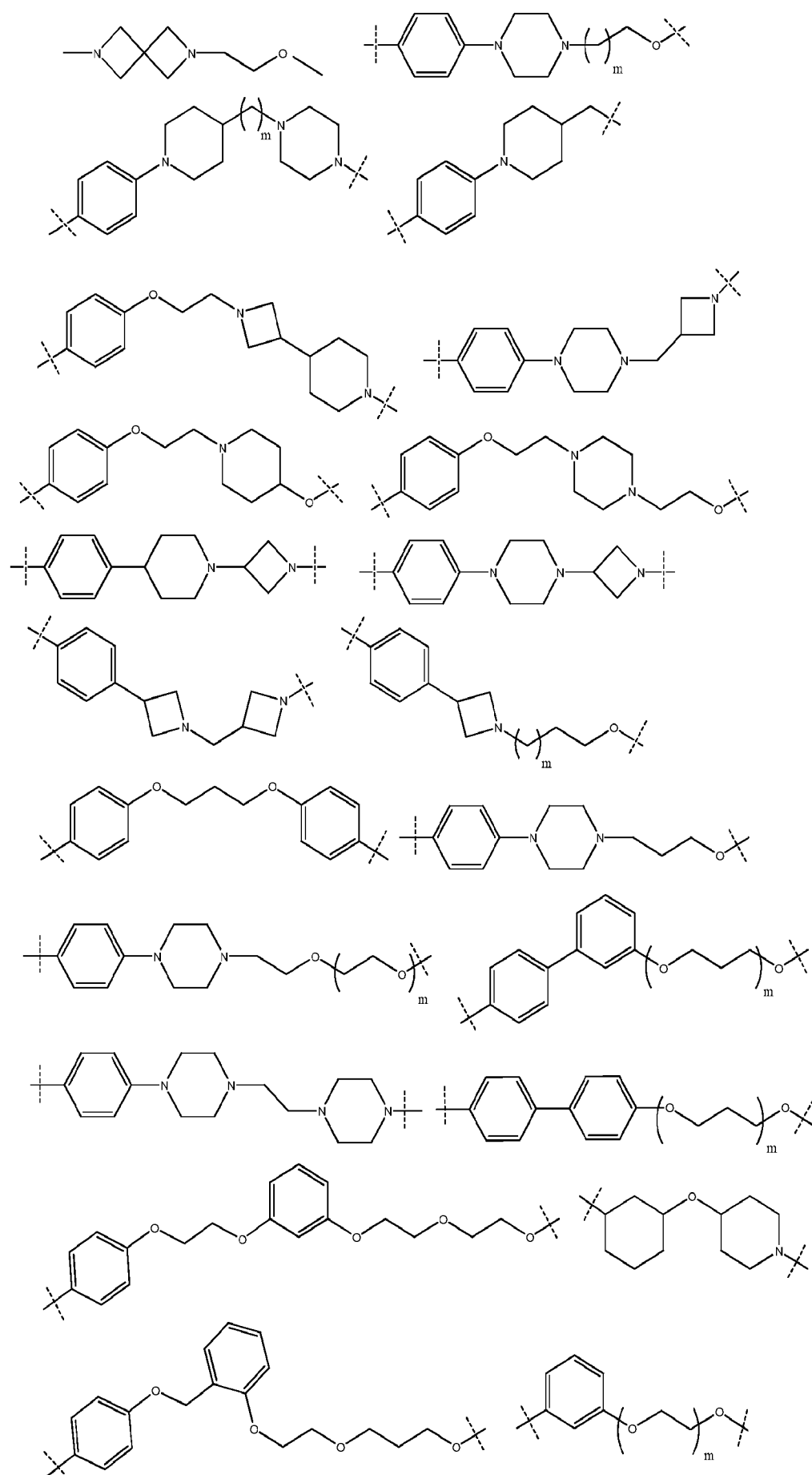


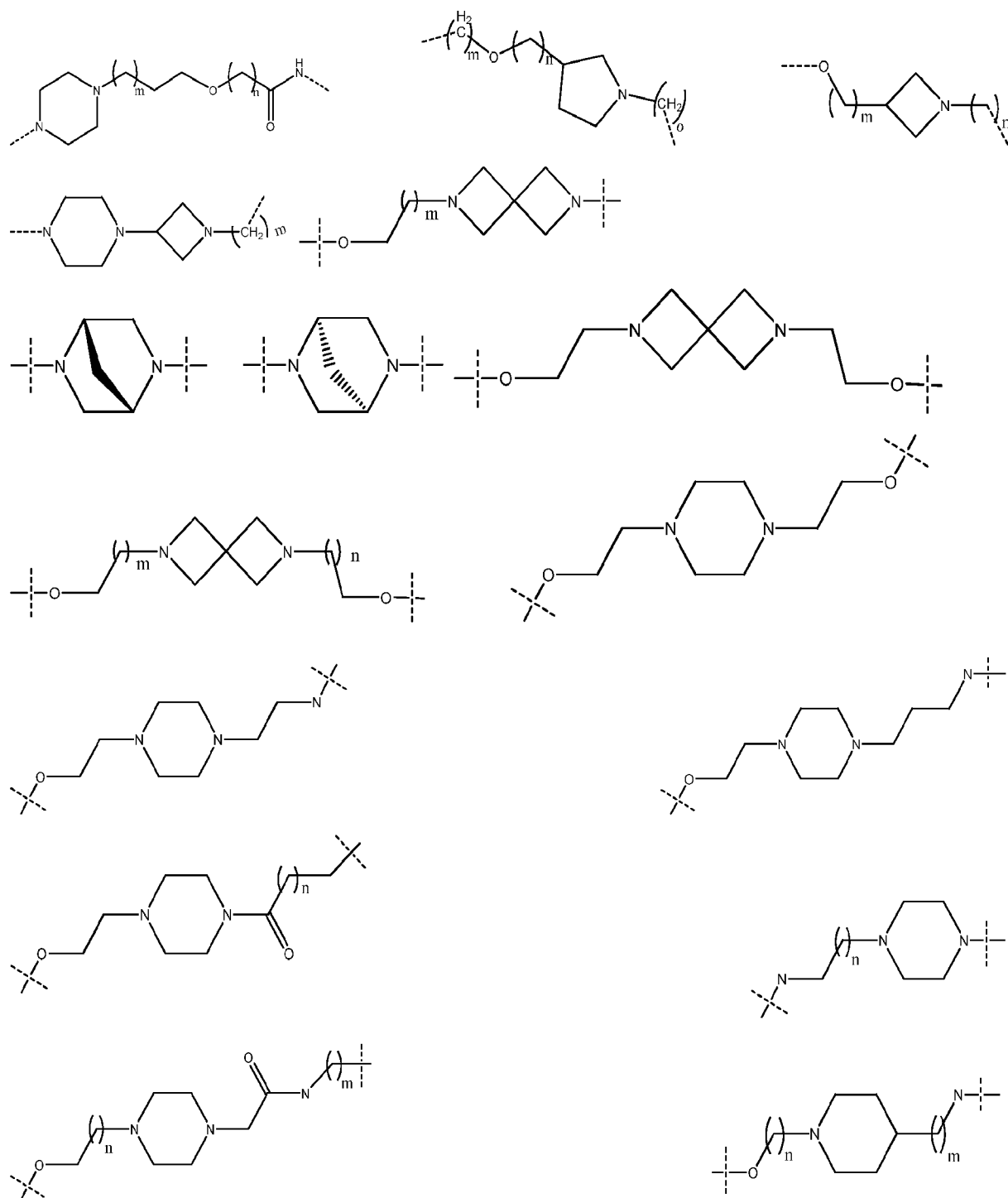


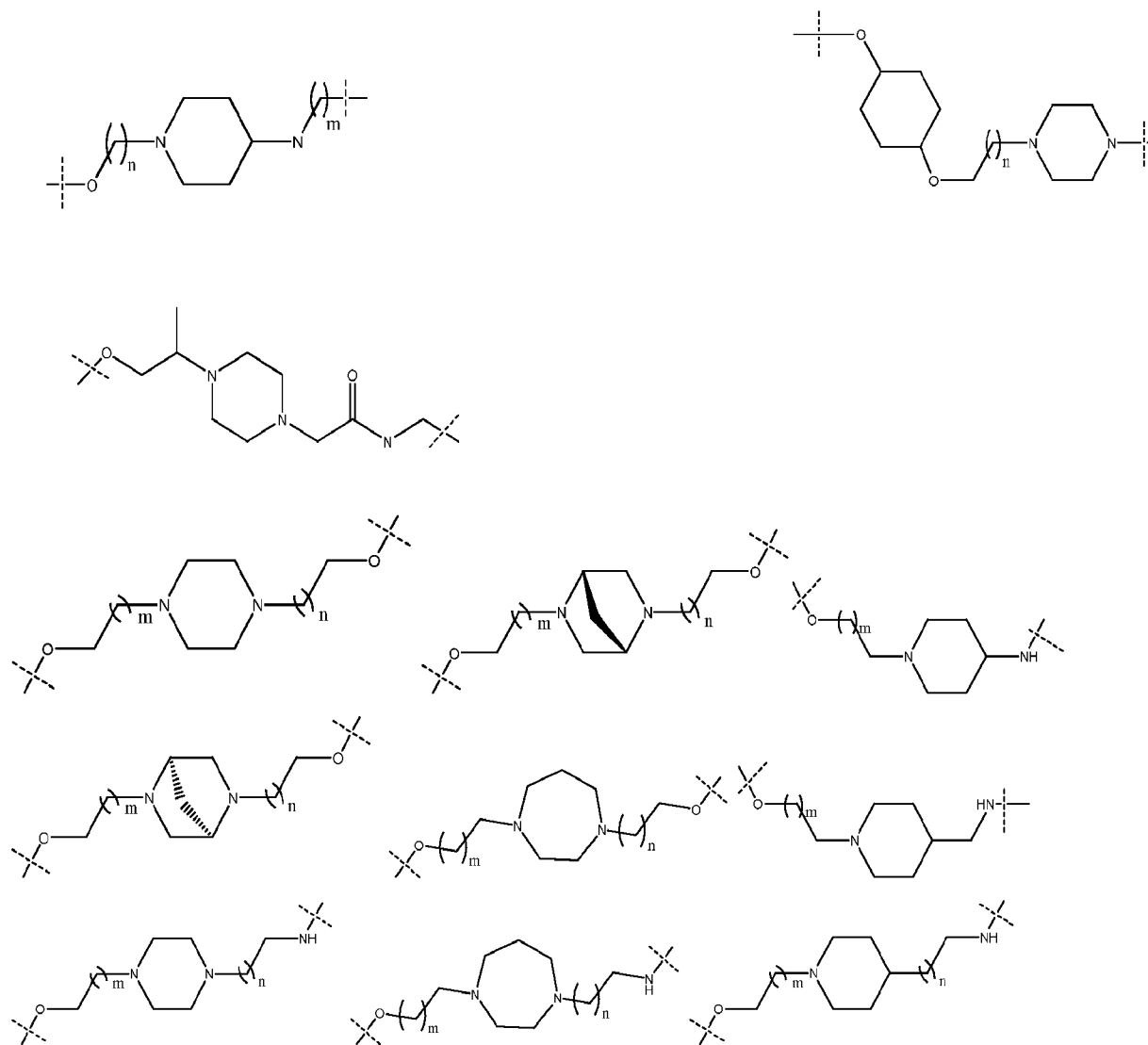


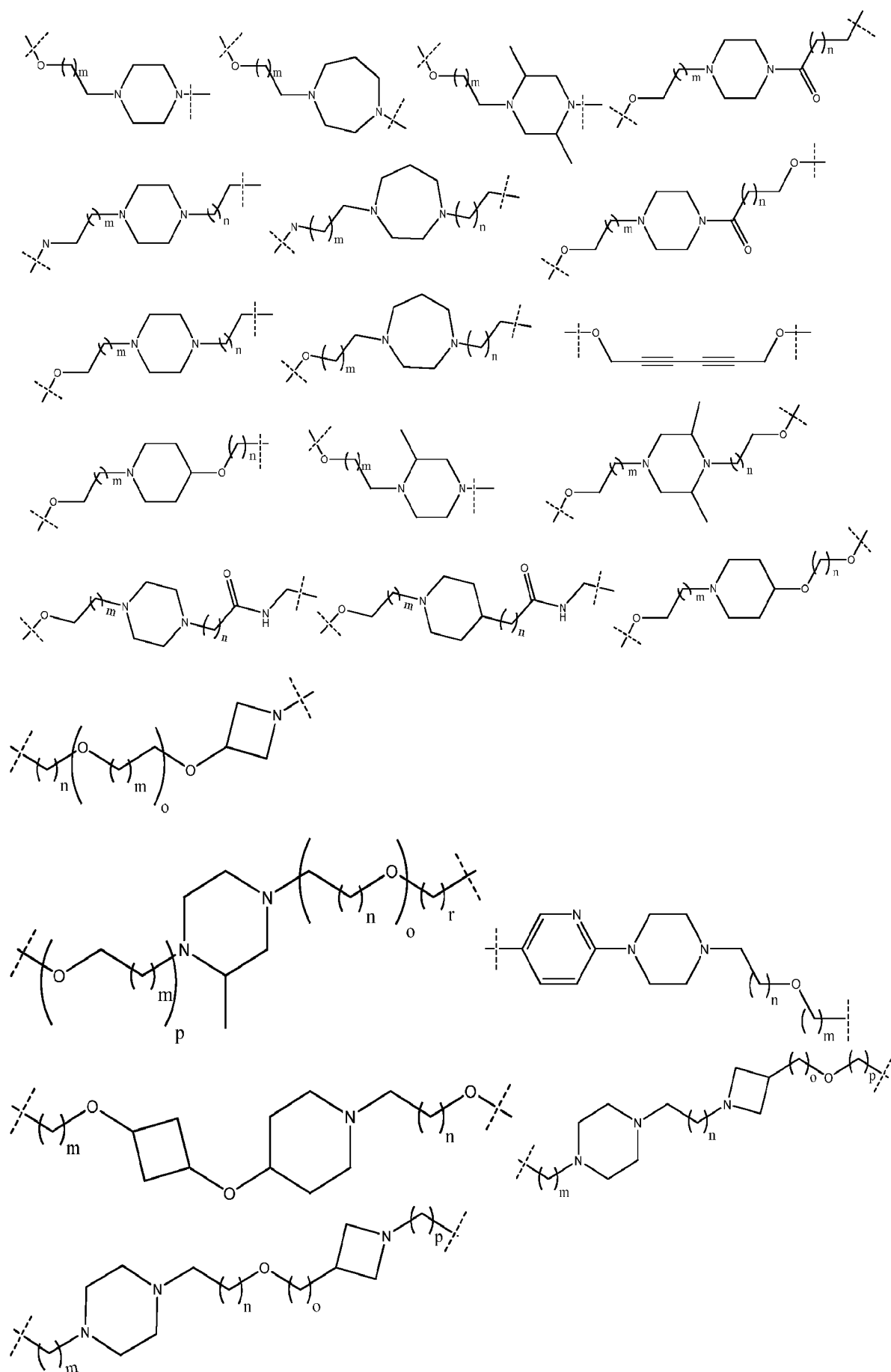


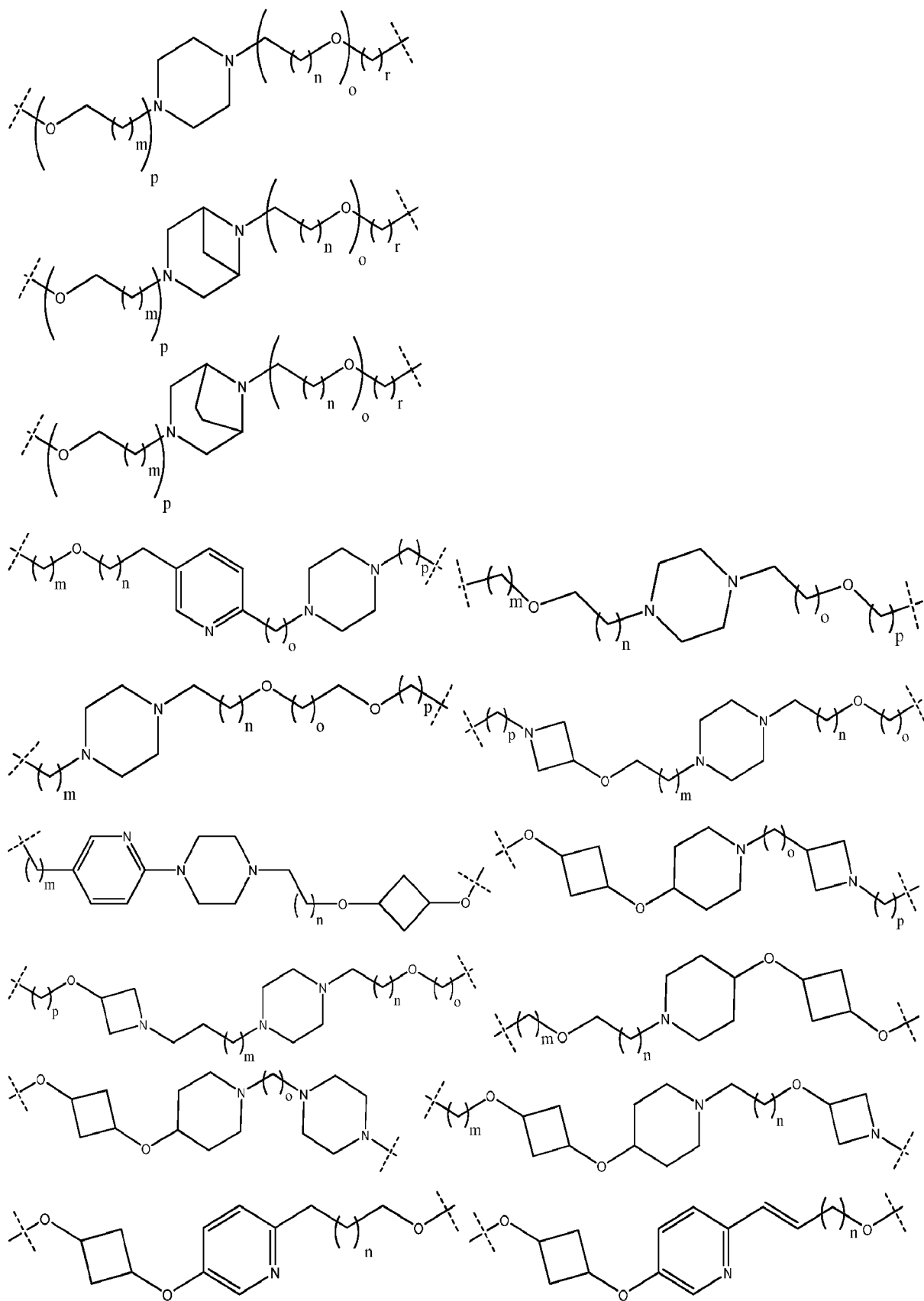


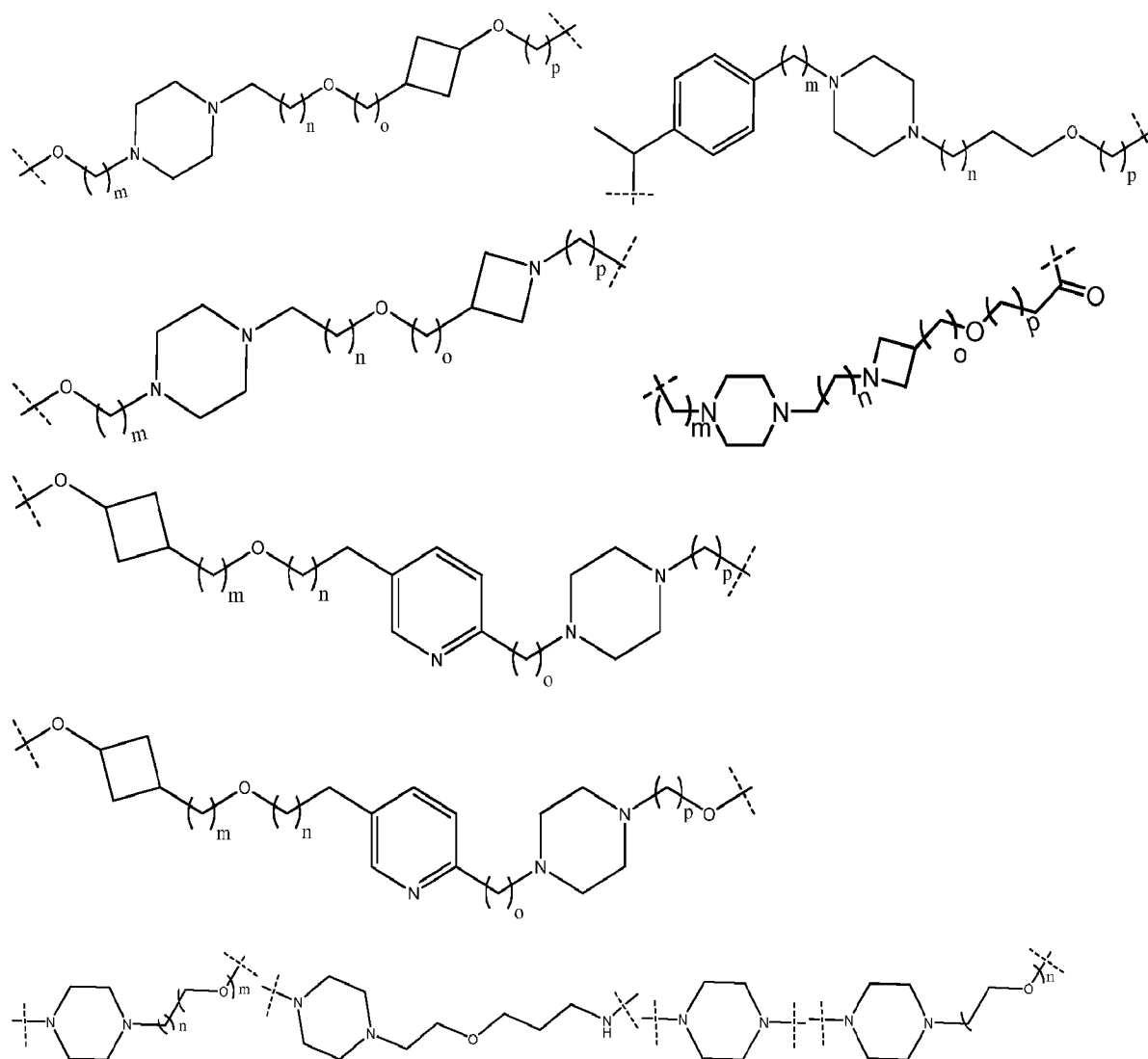




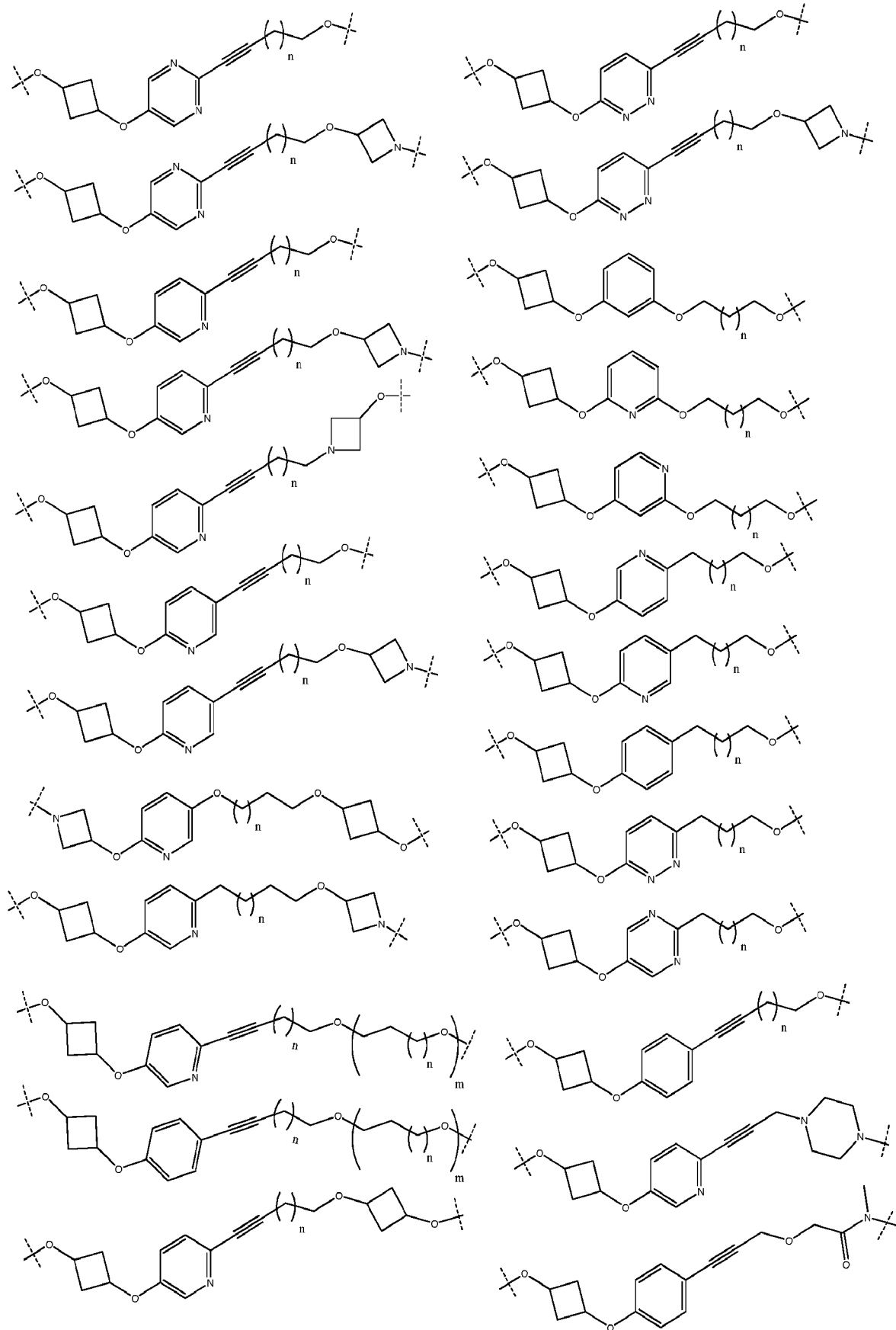


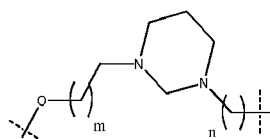
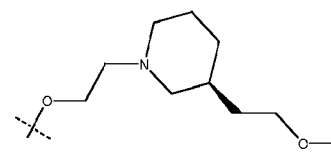
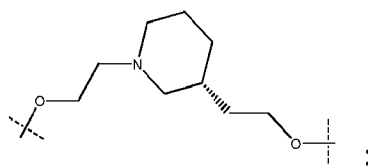
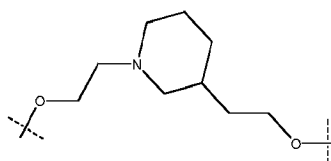
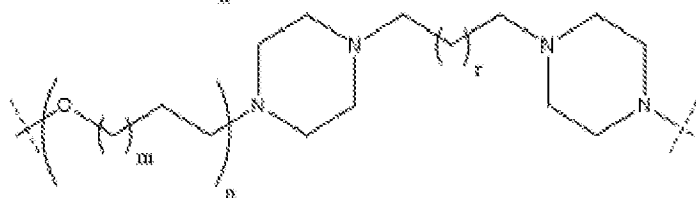
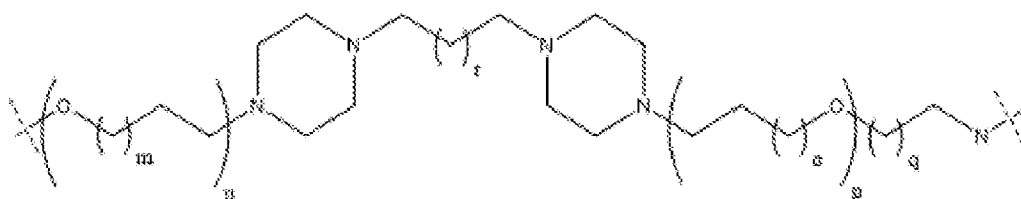
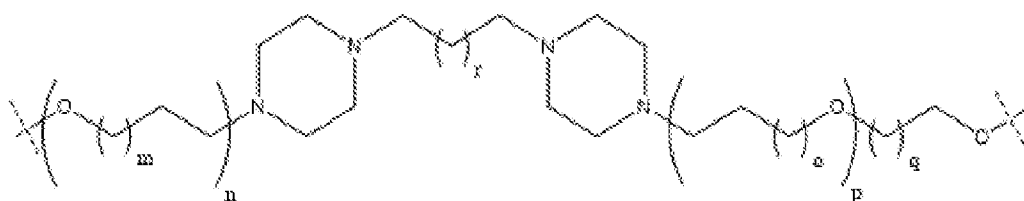
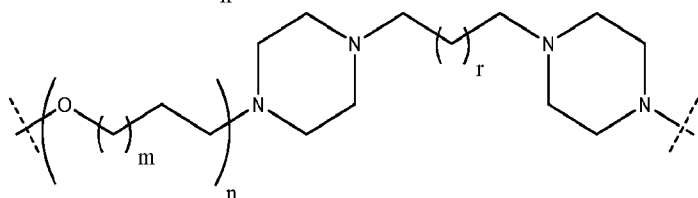
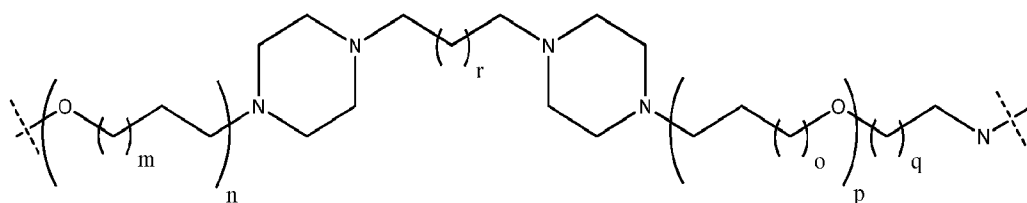
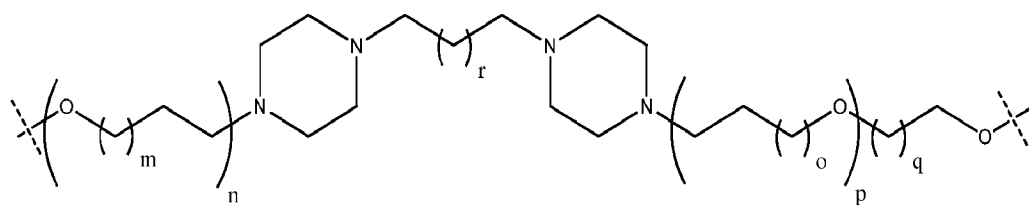


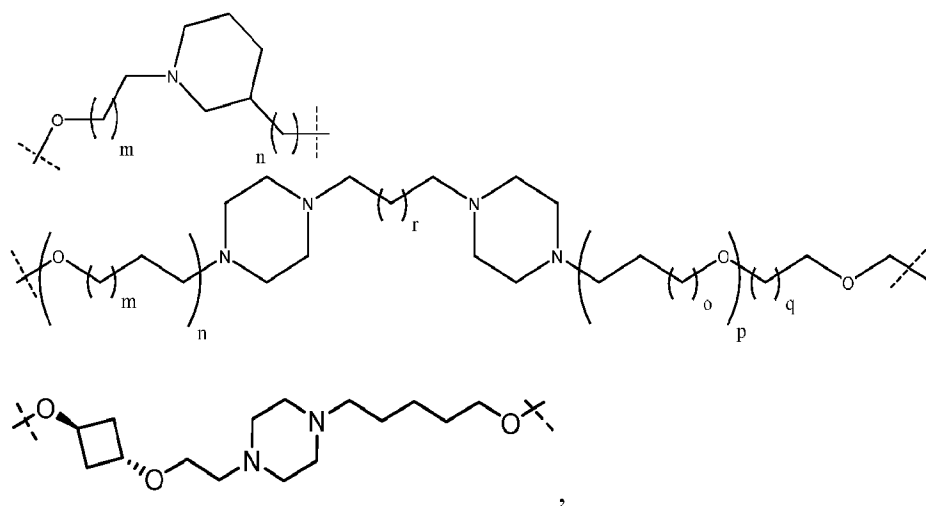






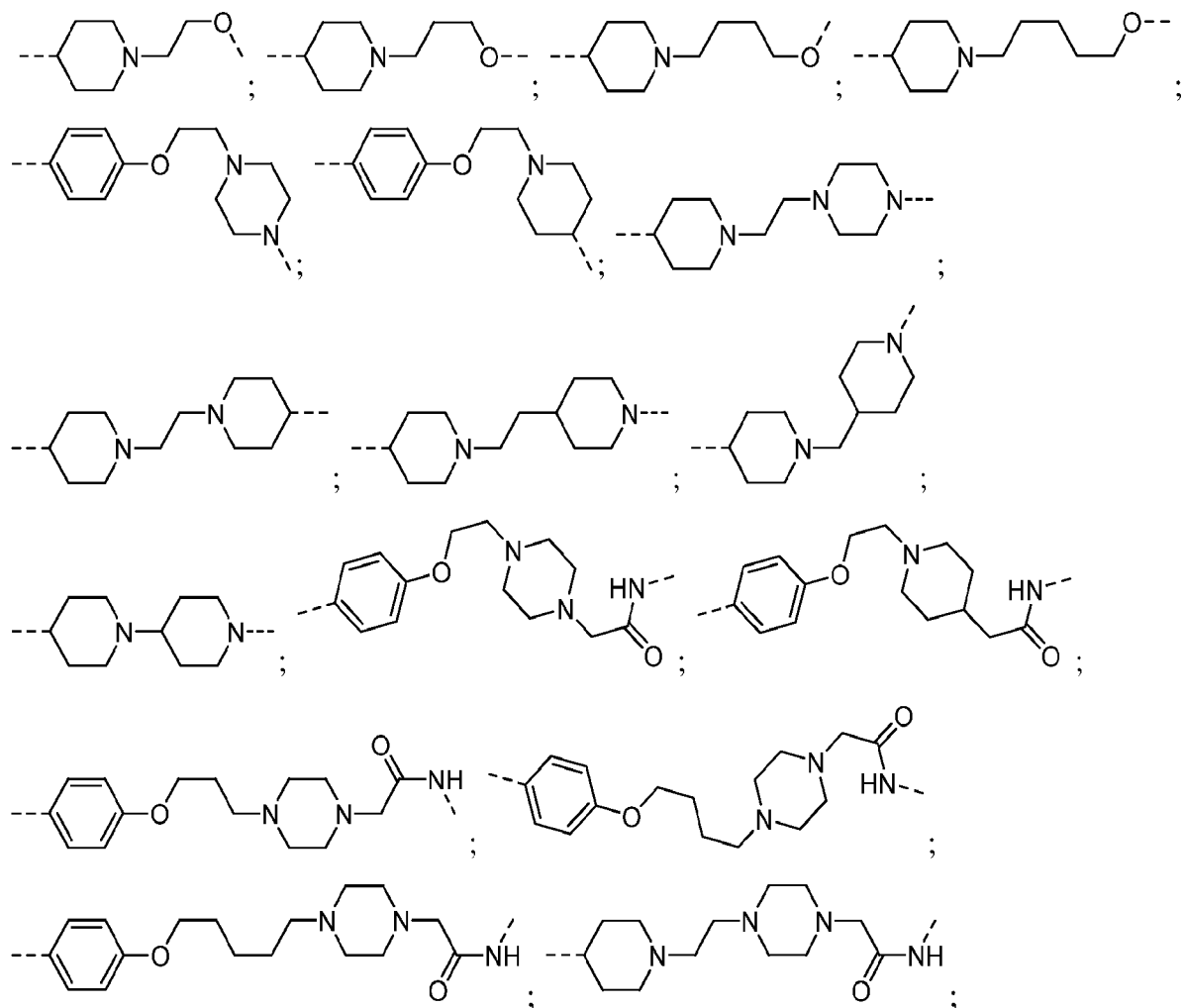


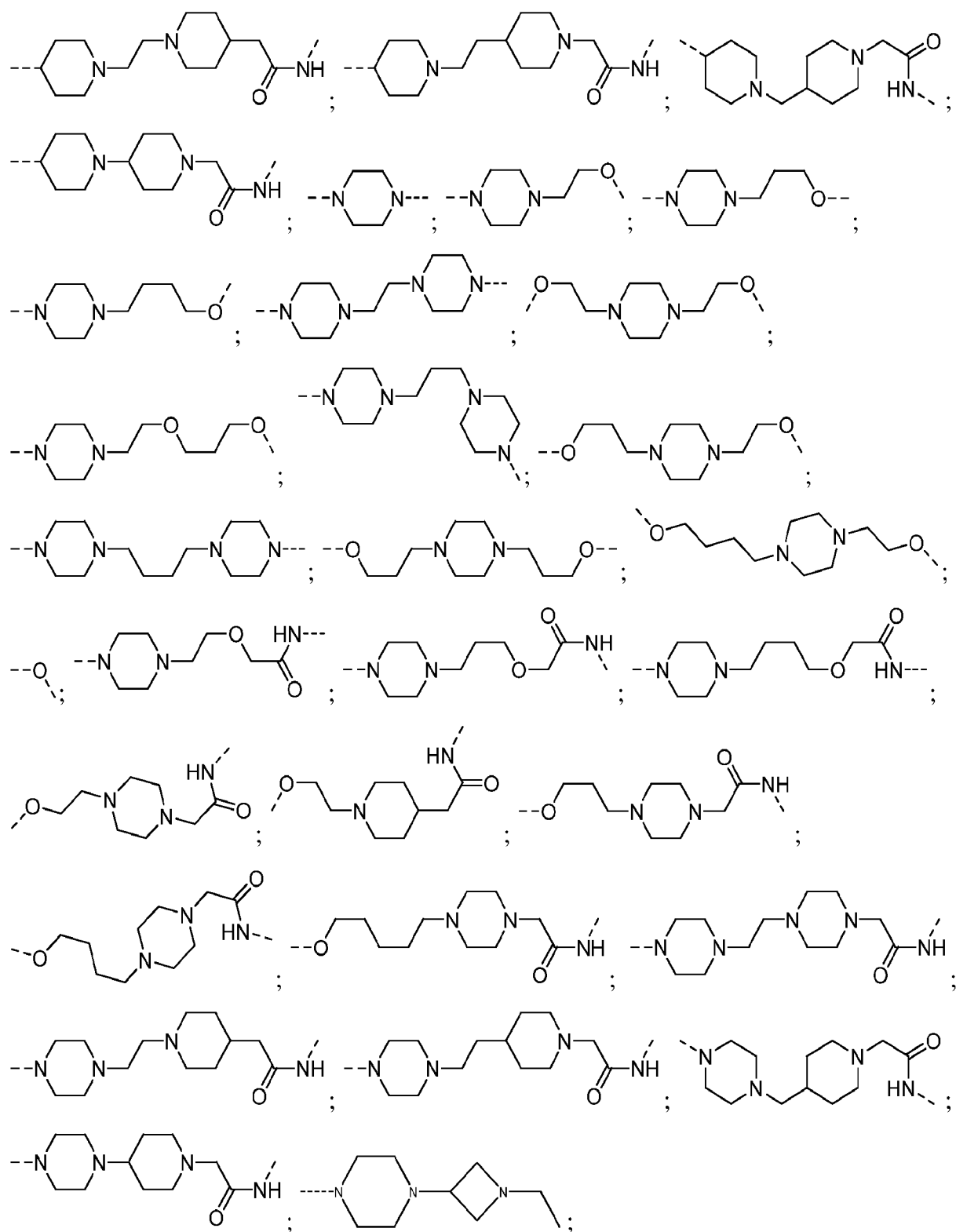




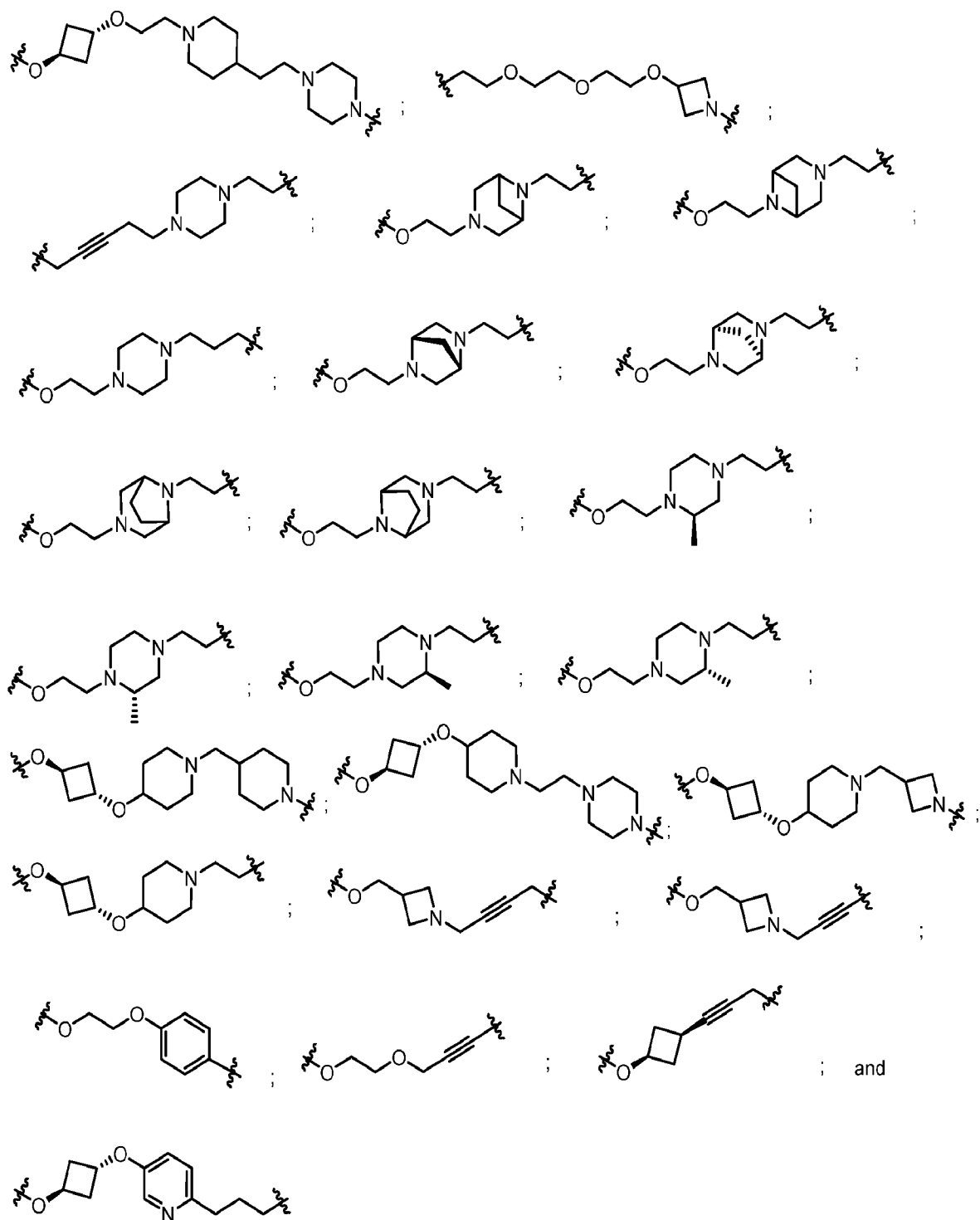
wherein each m, n, o, p, q, r, and s is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

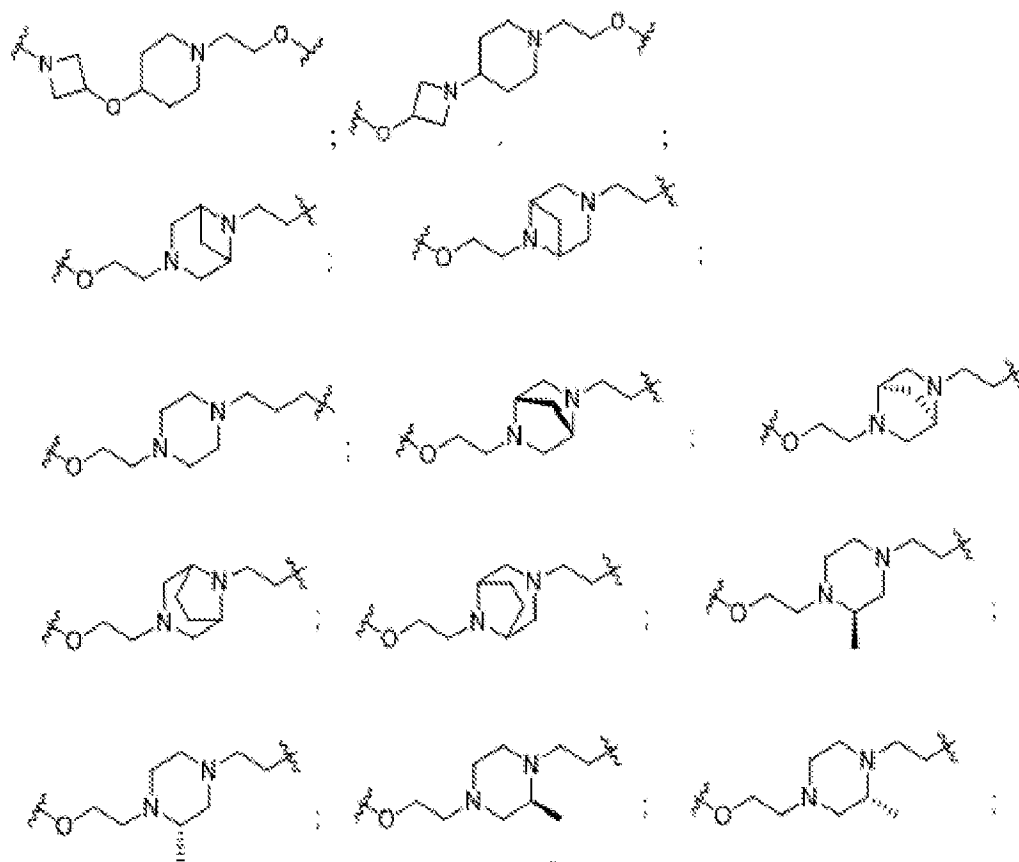
**[00116]** In any aspect or embodiment described herein, the unit A<sup>L</sup> of linker (L) is selected from the group consisting of:



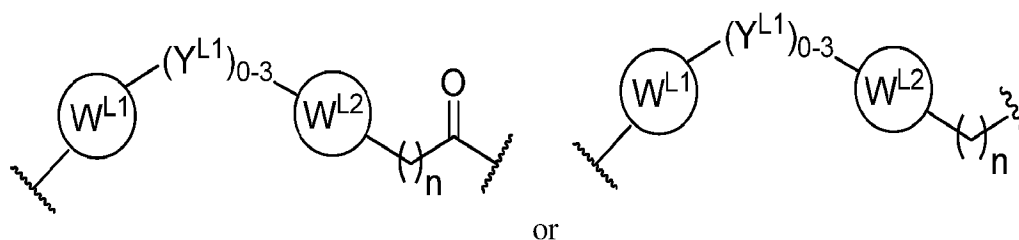








**[00117]** In any aspect or embodiment described herein, the linker (L) comprises a structure selected from the structure shown below:



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  $NR^{YL1}$ , optionally substituted  $C_1$ - $C_6$  alkene and optionally one or more C atoms are replaced with O, optionally substituted

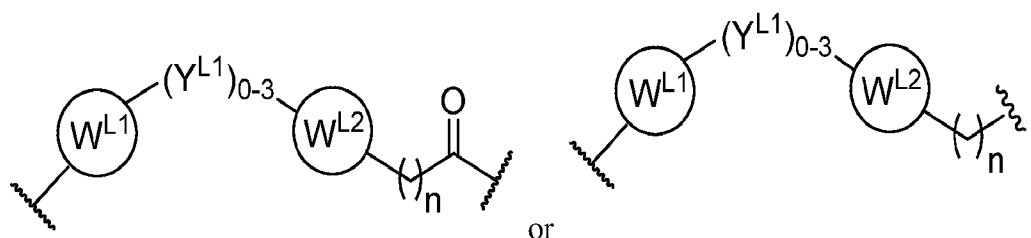
C<sub>1</sub>-C<sub>6</sub> alkyne, and optionally one or more C atoms are replaced with O, or optionally substituted linear or branched C<sub>1</sub>-C<sub>6</sub> alkoxy;

R<sup>YL1</sup> is H, or optionally substituted linear or branched C<sub>1-6</sub> alkyl;

n is 0-10; and

 and  indicates the attachment point to the PTM or the ULM.

**[00118]** In any aspect or embodiment described herein, the linker (L) comprises a structure selected from the structure shown below:



wherein:

W<sup>L1</sup> and W<sup>L2</sup> are each independently absent, piperazine, piperidine, morpholine, optionally substituted with R<sup>Q</sup>, each R<sup>Q</sup> is independently a H, -Cl-, -F-, OH, CN, CF<sub>3</sub>, optionally substituted linear or branched C<sub>1</sub>-C<sub>6</sub> alkyl (e.g. methyl, ethyl), optionally substituted linear or branched C<sub>1</sub>-C<sub>6</sub> alkoxy (e.g. methoxy, ethoxy);

Y<sup>L1</sup> is each independently a bond, optionally substituted linear or branched C<sub>1</sub>-C<sub>6</sub> alkyl and optionally one or more C atoms are replaced with O or NR<sup>YL1</sup>; optionally substituted C<sub>1</sub>-C<sub>6</sub> alkene and optionally one or more C atoms are replaced with O, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyne and optionally one or more C atoms are replaced with O, or optionally substituted linear or branched C<sub>1</sub>-C<sub>6</sub> alkoxy;

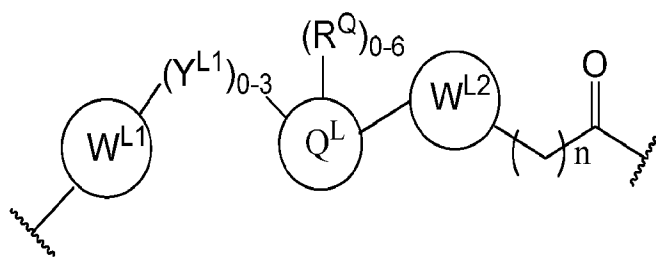
R<sup>YL1</sup> is H, or optionally substituted linear or branched C<sub>1-6</sub> alkyl (e.g. methyl, ethyl);

n is 0-10; and

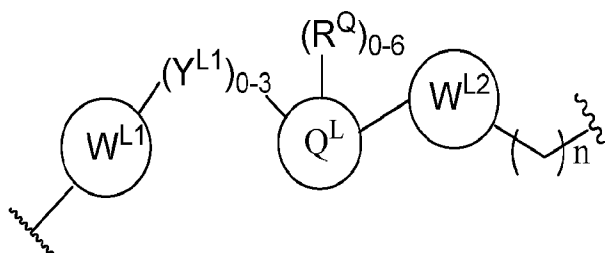
 and  indicates the attachment point to the PTM or the ULM.

**[00119]** In any aspect or embodiment described herein, the linker (L) comprises a structure selected from the structure shown below:





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 or  $NR^{YL1}$ ,  $C_{1-6}$  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, optionally substituted linear or branched  $C_1$ - $C_6$  alkyl, optionally substituted linear or branched  $C_1$ - $C_6$  alkoxy, optionally substituted  $OC_{1-3}$ alkyl (e.g., 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;

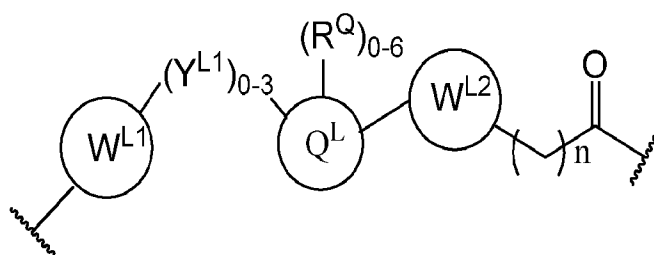
$Y^{L1}$  is each independently a bond,  $NR^{YL1}$ , O, S,  $NR^{YL2}$ ,  $CR^{YL1}R^{YL2}$ ,  $C=O$ ,  $C=S$ , SO,  $SO_2$ , optionally substituted linear or branched  $C_1$ - $C_6$  alkyl and optionally one or more C atoms are replaced with O; optionally substituted linear or branched  $C_1$ - $C_6$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

$Q^L$  is a 3-6 membered alicyclic, bicyclic or aromatic ring with 0-4 heteroatoms, optionally bridged, optionally substituted with 0-6  $R^Q$ , each  $R^Q$  is independently H, optionally substitute linear or branched  $C_{1-6}$  alkyl (e.g., optionally substituted by 1 or more halo,  $C_{1-6}$  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;

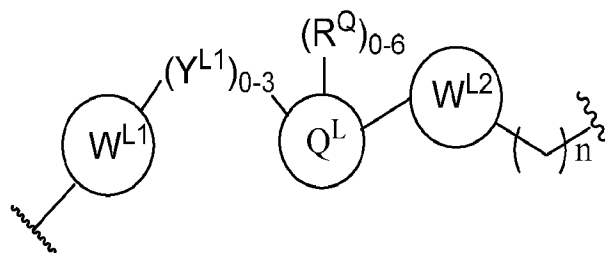
$R^{YL1}$ ,  $R^{YL2}$  are each independently H, OH, optionally substituted linear or branched  $C_{1-6}$  alkyl (e.g., optionally substituted by 1 or more halo,  $C_{1-6}$  alkoxy), or  $R^1$ ,  $R^2$  together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms; n is 0-10; and

 and  indicates the attachment point to the PTM or the ULM.

**[00120]** In any aspect or embodiment described herein, the linker (L) comprises a structure selected from the structure shown below:



or



wherein:

$W^{L1}$  and  $W^{L2}$  are each independently absent, cyclohexane, cyclopentane, , piperazine, piperidine, morpholine,  $C_{1-6}$  alkyl and optionally one or more C atoms are replaced with O or  $NR^{YL1}$ ,  $C_{1-6}$  alkene 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, or  $C_{1-6}$  alkyne and optionally one or more C atoms are replaced with O, each optionally substituted with  $R^Q$ , each  $R^Q$  is independently a H, -Cl, -F, OH, CN,  $CF_3$ , hydroxyl, optionally substituted linear or branched  $C_1$ - $C_6$  alkyl (e.g., methyl, ethyl), or optionally substituted linear or branched  $C_1$ - $C_6$  alkoxy;

$Y^{L1}$  is each independently a bond,  $NR^{YL1}$ , O,  $CR^{YL1}R^{YL2}$ ,  $C=O$ , optionally substituted linear or branched  $C_1$ - $C_6$  alkyl and optionally one or more C atoms are replaced with O or  $NR^{YL1}$ , ,  $C_{1-6}$  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,, or optionally substituted linear or branched C<sub>1</sub>-C<sub>6</sub> alkoxy;

Q<sup>L</sup> is a 3-6 membered heterocyclic, heterobicyclic, or heteroaryl ring, optionally substituted with 0-6 R<sup>Q</sup>, each R<sup>Q</sup> is independently H, or optionally substituted linear or branched C<sub>1-6</sub> alkyl (e.g., optionally substituted by 1 or more halo, C<sub>1-6</sub> alkoxy);

R<sup>YL1</sup>, R<sup>YL2</sup> are each independently H, optionally substituted linear or branched C<sub>1-6</sub> alkyl (e.g., methyl, ethyl, optionally substituted by 1 or more halo, C<sub>1-6</sub> alkoxy);

n is 0-10; and

 and  indicates the attachment point to the PTM or the ULM.

### **Exemplary PTMs**

**[00121]** In one aspect of the disclosure, the PTM group (also referred as the LTM group) binds to the target protein, LRRK2 or mutated form thereof.

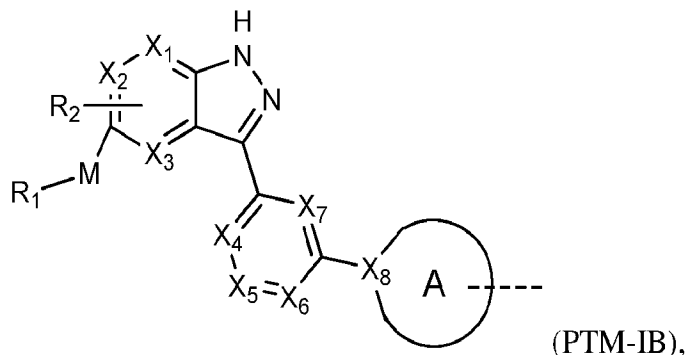
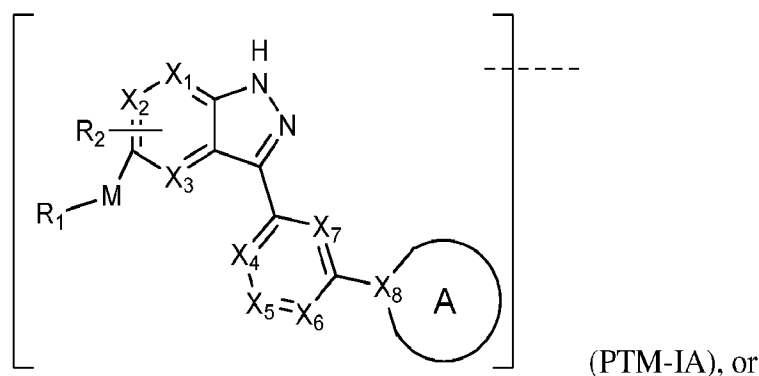
**[00122]** The compositions described below exemplify members of LRRK2 binding moieties that can be used according to the present invention. These binding moieties are linked to the ubiquitin ligase binding moiety (CLM) preferably through a chemical linking group in order to present the LRRK2 protein (to which LTM is bound) in proximity to the ubiquitin ligase for ubiquitination and subsequent degradation.

**[00123]** In certain contexts, the term “target protein” is used to refer to the LRRK2 protein, a member of the leucine-rich repeat kinase family, which is a target protein to be ubiquitinated and degraded. In other contexts, the term “target protein” is used to refer to a mutated form of the LRRK2 protein, such as a LRRK protein having one or mutation selected from the group consisting of G2019S, I2020T, N1437H, R1441G/C/H, and Y1699C.

**[00124]** The term “protein target moiety” or PTM is used to describe a small molecule which binds to LRRK2 or mutated form thereof, and can be used to target the protein for ubiquitination and degradation.

**[00125]** The compositions described herein exemplify the use of some of these PTMs.

**[00126]** In any aspect or embodiment described herein, the PTM is a small molecule that binds LRRK2. For example, in any aspect or embodiment described herein, the PTM is represented by the chemical structure PTM-IA or PTM-IB:



wherein:

R<sub>1</sub> is selected from a linear or branched C1-C6 alkyl (e.g., isopropyl or tert-butyl), an optionally substituted C3-C6 cycloalkyl (e.g., an optionally substituted C3-C5 cycloalkyl,

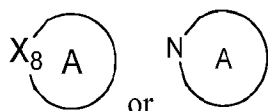
a methylated C3-C5 cycloalkyl, or , wherein the dashed line is the point of attachment to the M of the PTM), linear or branched C1-C6 haloalkyl (e.g., linear or branched C1-C4 haloalkyl), an optionally substituted C3-C6 halocycloalkyl (e.g., C3-C5 halocycloalkyl), an optionally substituted alkylnitrile (e.g., a C1-C4 alkyl nitrile), an optionally substituted C3-C6 cyclonitrile (e.g., a C3-C5 cyclonitrile);

R<sub>2</sub> is selected from hydrogen, halogen (e.g., F, Cl, or Br), C1-C3 alkyl, or C1-C3 fluoroalkyl;

X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub>, X<sub>6</sub>, and X<sub>7</sub> are each independently C, CH or N, wherein X<sub>1</sub>, X<sub>2</sub>, and X<sub>3</sub> are each optionally substituted with R<sub>2</sub> when CH;

X<sub>8</sub> is CH, S, or N;

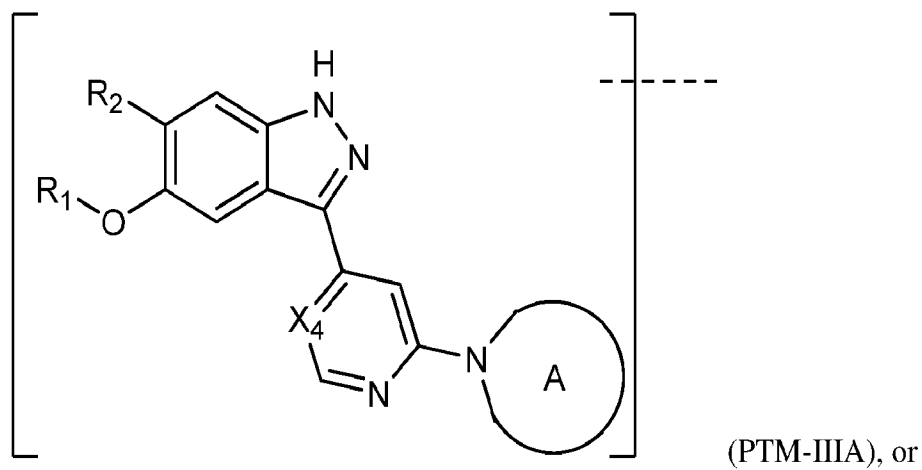
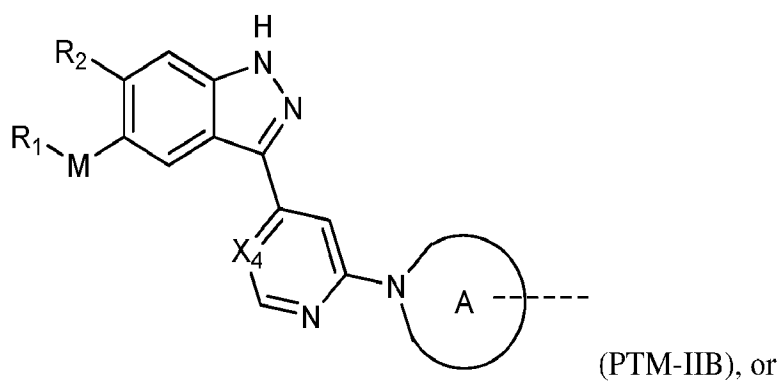
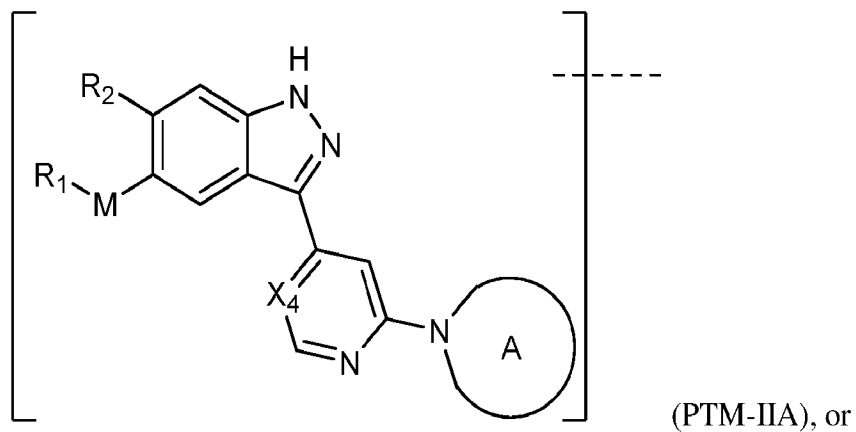
M is a CH<sub>2</sub>, NH, or O;

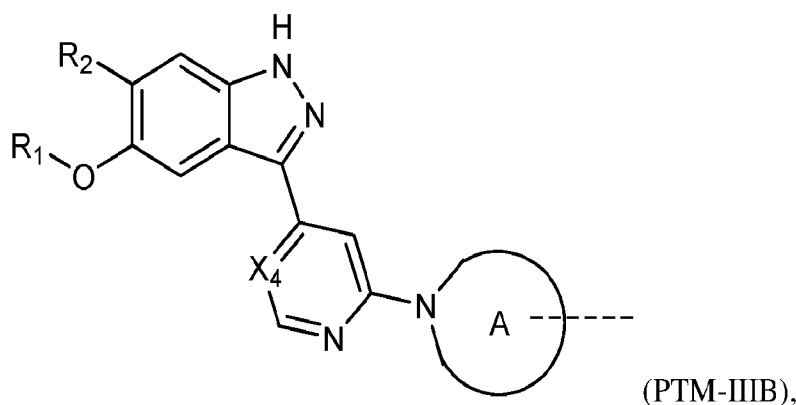


is an optionally substituted 3-10 membered cycloalkyl or heterocycloalkyl containing 1-4 (e.g., 1, 2, 3, or 4) heteroatoms selected from N, O, and S (e.g., optionally substituted with one or more (e.g., 1, 2, 3, or 4) substitutions, and

of the PTM indicates the point of attachment with a linker (L) or a ULM.

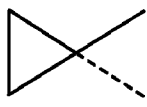
[00127] In any aspect or embodiment described herein, the PTM is represented by the chemical structure PTM-IIA, PTM-IIB, PTM-IIIA, and PTM-IIIB.





wherein:

R<sub>1</sub> is a linear or branched C1-C6 alkyl (e.g., isopropyl or tert-butyl), an optionally substituted C3-C6 cycloalkyl (e.g., an optionally substituted C3-C5 cycloalkyl, a methylated C3-C5

cycloalkyl, or , wherein the dashed line is the point of attachment to the M or the oxygen atom of the PTM), linear or branched C1-C6 haloalkyl (e.g., linear or branched C1-C4 haloalkyl), an optionally substituted C3-C6 halocycloalkyl (e.g., C3-C5 halocycloalkyl), an optionally substituted alkylnitrile (e.g., a C1-C4 alkyl nitrile), an optionally substituted C3-C6 cyclonitrile (e.g., a C3-C5 cyclonitrile);

R<sub>2</sub> is hydrogen, halogen (e.g., F, Cl, or Br), C1-C3 alkyl, or C1-C3 fluoroalkyl;

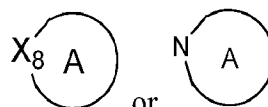
X<sub>4</sub> CH or N;

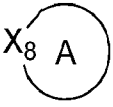
M is a CH<sub>2</sub>, NH, or O;



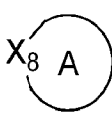
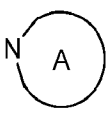
is an optionally substituted 3-10 membered heterocycloalkyl containing 1-4 (e.g., 1, 2, 3, or 4) heteroatoms selected from N, O, and S (e.g., optionally substituted with one or more (e.g., 1, 2, 3, or 4) substitutions, and

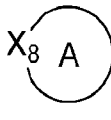
of the PTM indicates the point of attachment with a chemical linker group or a ULM.

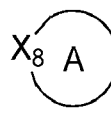
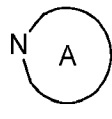


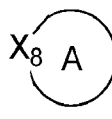
**[00128]** In any aspect or embodiment described herein,  or  includes 1-4 substitution, each independently selected from a halogen, OH, NH<sub>2</sub>, N(C1-C3 alkyl)<sub>2</sub>, linear or branched C1-C4 alkyl (e.g., methyl or ethyl), linear or branched C1-C4 hydroxyalkyl, linear or branched C1-C4 alkoxy, and linear or branched C1-C4 haloalkyl).

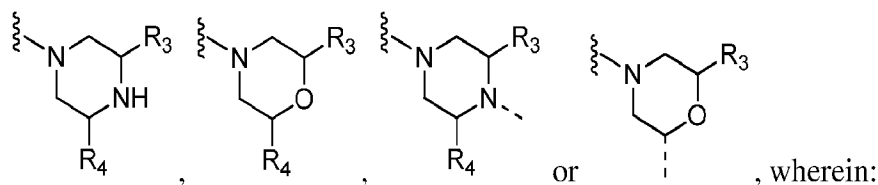
**[00129]** In any aspect or embodiment described herein, the PTM is covalently linked to L or

ULM via an atom of the heterocycloalkyl of  or , or a substituent thereof.

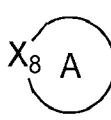
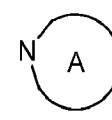
**[00130]** In any aspect or embodiment described herein,  or  is a 4-7 (e.g., 4, 5, 6, or 7) membered cycloalkyl or heterocycloalkyl containing 1-4 (e.g., 1, 2, 3, or 4) heteroatoms selected from N, O, and S, optionally substituted with one or more (e.g., 1, 2, 3, or 4) substitutions, each independently selected from a halogen, OH, NH<sub>2</sub>, N(C1-C3 alkyl)<sub>2</sub>, linear or branched C1-C4 alkyl, linear or branched C1-C4 hydroxyalkyl, linear or branched C1-C4 alkoxy, and linear or branched C1-C4 haloalkyl.

**[00131]** In any aspect or embodiment described herein,  or  is a 4-7 (e.g., 5 or 6) membered cycloalkyl or heterocycloalkyl containing 1-4 (e.g., 1, 2, 3, or 4) heteroatoms selected from N, O, and S, the ring optionally substituted with one or more (e.g., 1, 2, 3, or 4) substitutions, each independently selected from linear or branched C1-C3 alkyl (e.g., methyl), linear or branched C1-C3 alkoxy (e.g., methoxy), and linear or branched C1-C3 haloalkyl.

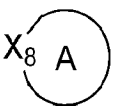
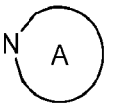
**[00132]** In any aspect or embodiment described herein described herein,  or  is:



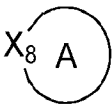
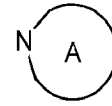
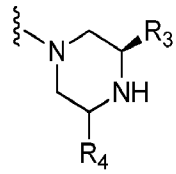
R<sub>3</sub> and R<sub>4</sub> are each independently selected from a H, halogen, OH, NH<sub>2</sub>, N(C1-C3 alkyl)<sub>2</sub>, linear or branched C1-C4 alkyl, linear or branched C1-C4 hydroxyalkyl, linear or branched C1-C4 alkoxy, and linear or branched C1-C4 haloalkyl;

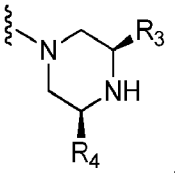
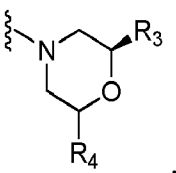
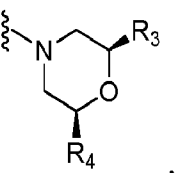
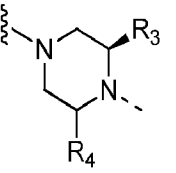
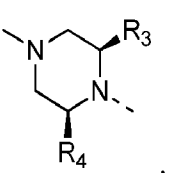
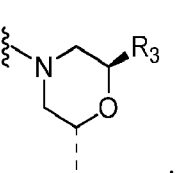
 indicates the point of attachment of the  or  (i.e., the point of attachment with the 6-membered heteroaryl of the PTM); and

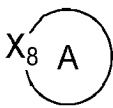
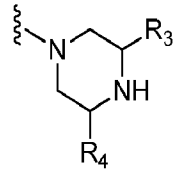
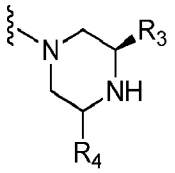
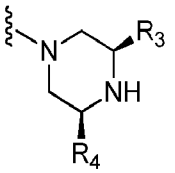
--- indicates the point of attachment of the PTM with the L or ULM, and where not present,

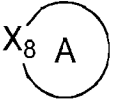
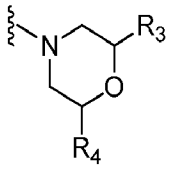
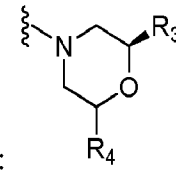
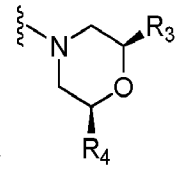
the  or  may be attached to the L or ULM via an atom of the 6-membered heterocycloalkyl (e.g., a carbon or nitrogen), R<sub>3</sub>, or R<sub>4</sub>.

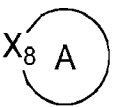
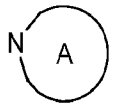
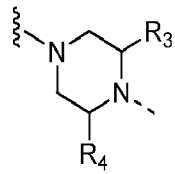
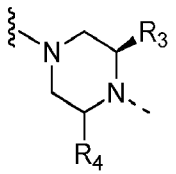
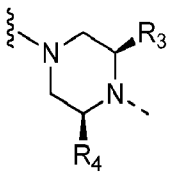
**[00133]** In any aspect or embodiment described herein, such as but not limited to that in the

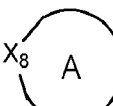
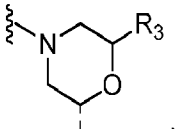
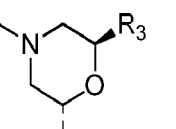
preceding paragraph or the following paragraph,  or  is:  ,

 ,  ,  ,  ,  , or  . In any aspect or embodiment described herein, such as but not limited to that in the preceding

paragraph,  or  or  is:  or  . In any aspect or embodiment described herein, such as but not limited to that in the preceding paragraph,

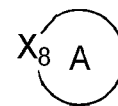
 or  or  , is:  or  . In any aspect or embodiment described herein, such as but not limited to that in the preceding paragraph,

 or  or  is:  or  . In any aspect or embodiment described herein, such as but not limited to that in the preceding paragraph,

 or  or  is:  .



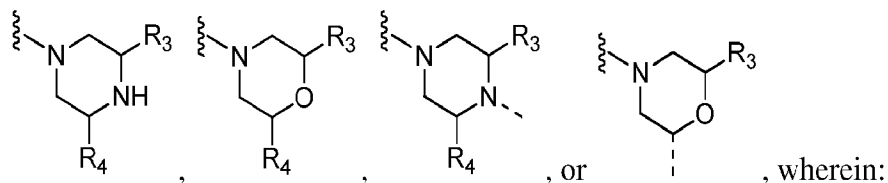
[00134] In any aspect or embodiment described herein described herein,



or



is:



R<sub>3</sub> is H or linear or branched C1-C3 alkyl (e.g., methyl or ethyl);

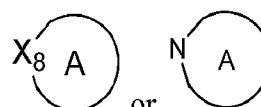
R<sub>4</sub> is H or linear or branched C1-C3 alkyl (e.g., methyl or ethyl);

— indicates the point of attachment of the or (i.e., the point of attachment with the 6-membered heteroaryl of the PTM); and

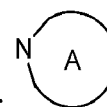
- - indicates the point of attachment of the PTM with the L or ULM, and where not present,

the or may be attached to the L or ULM via an atom of the 6-membered heterocycloalkyl (e.g., a carbon or nitrogen of the 6-membered heterocycloalkyl), R<sub>3</sub>, or R<sub>4</sub>.

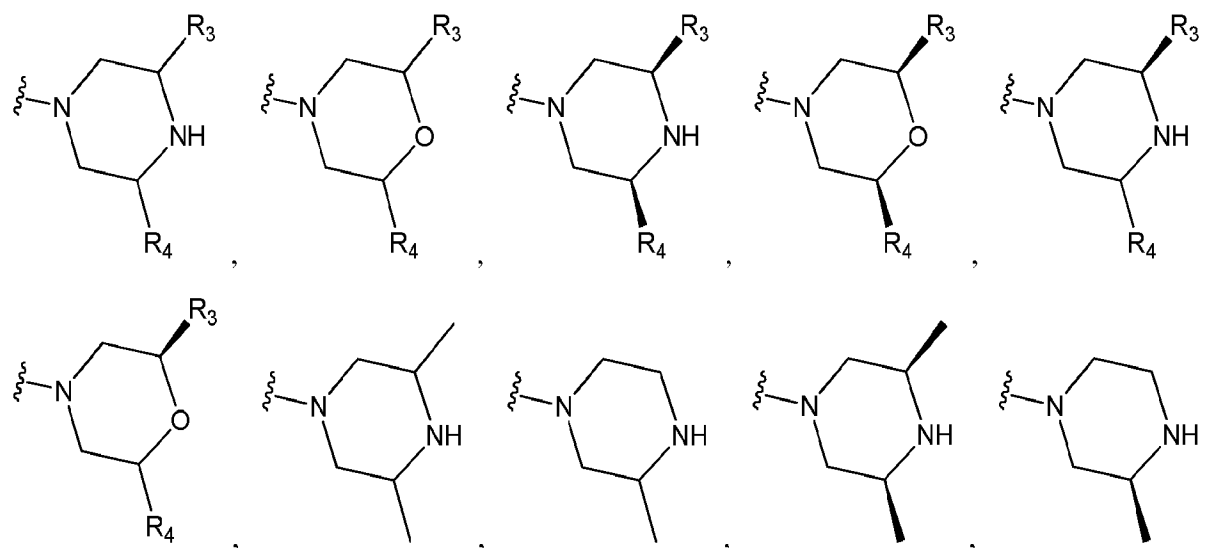
[00135] In any aspect or embodiment described herein,

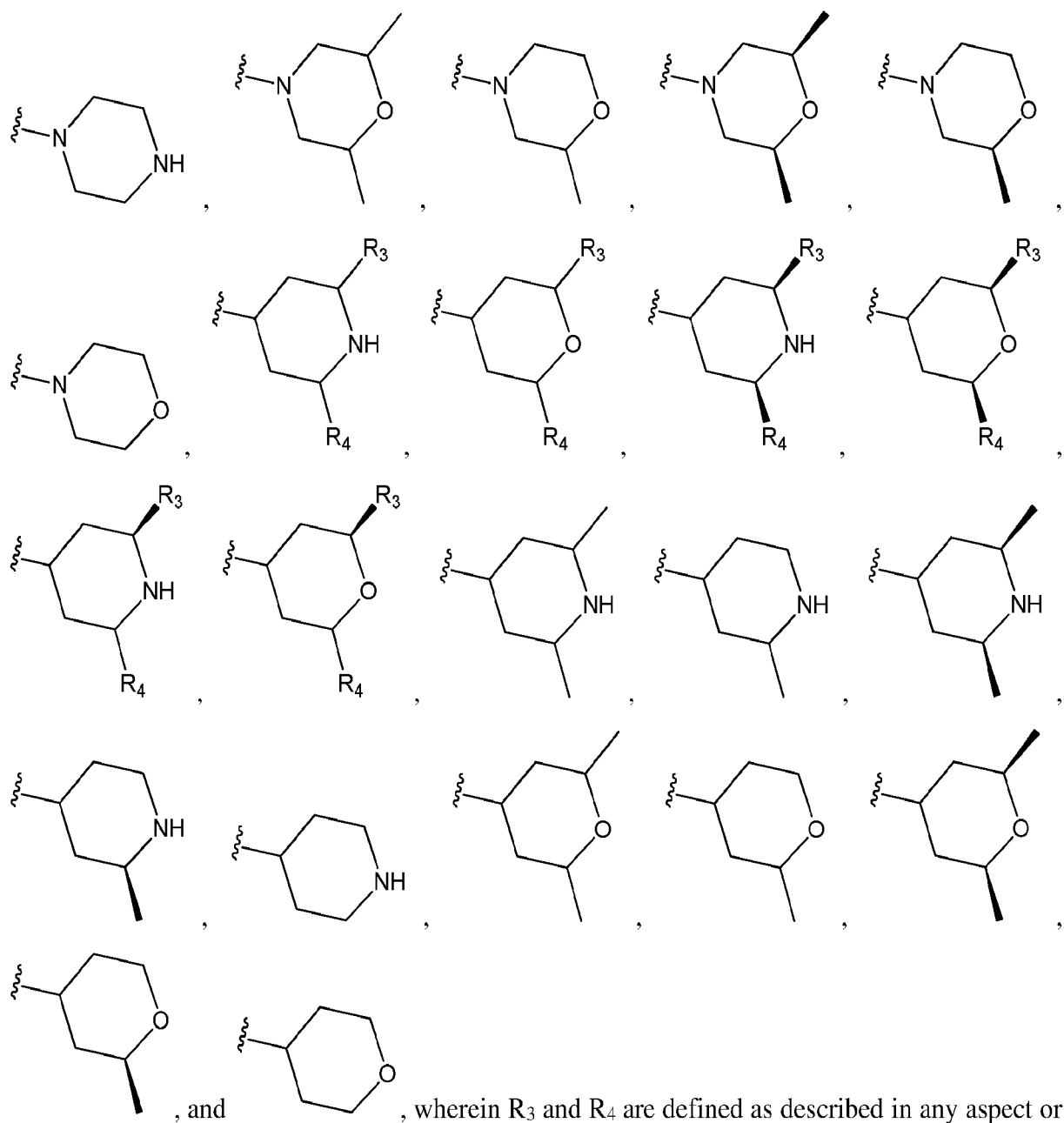


or



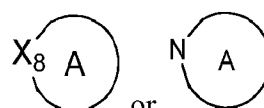
is selected from:





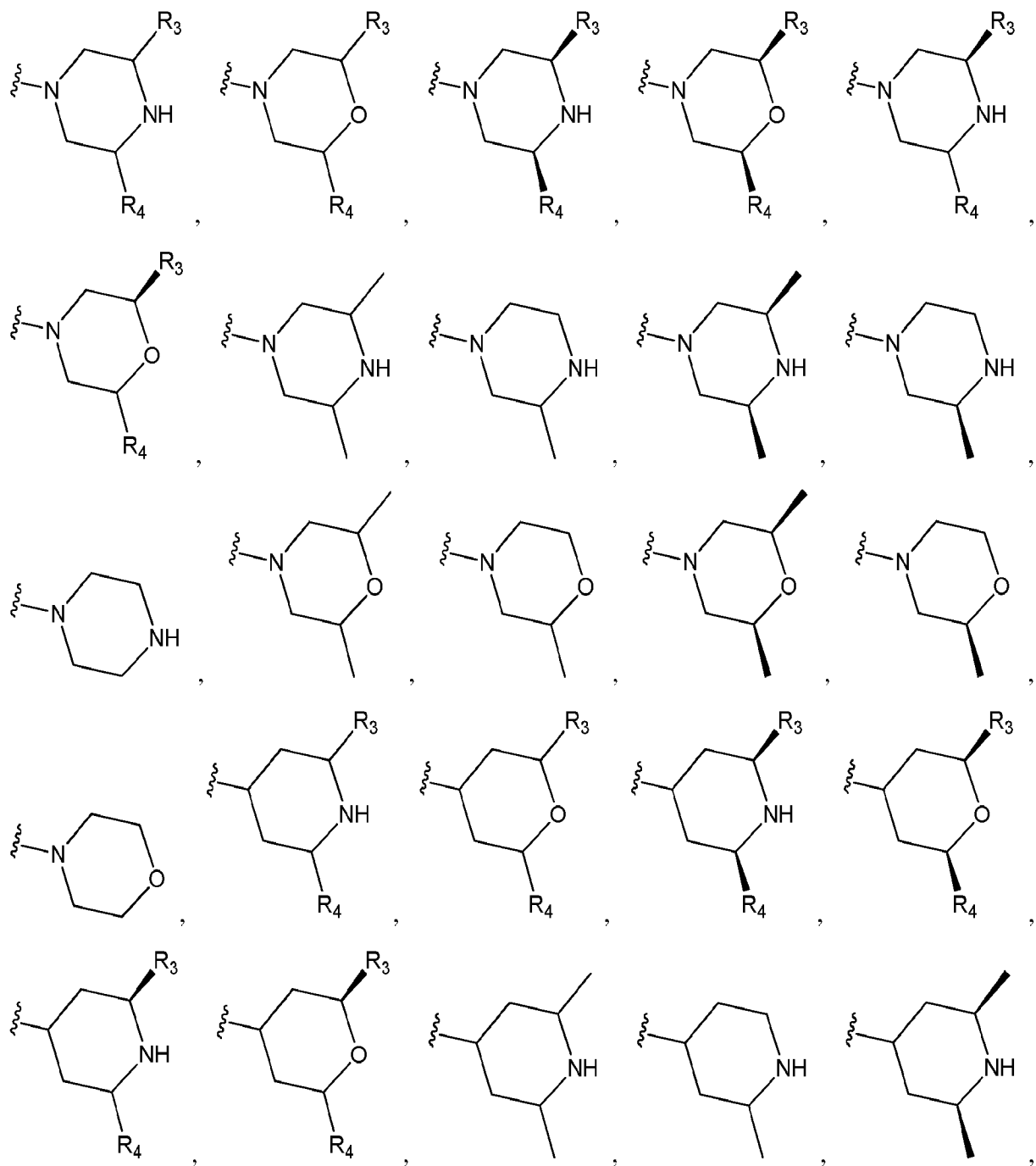
, wherein R<sub>3</sub> and R<sub>4</sub> are defined as described in any aspect or embodiment described herein.

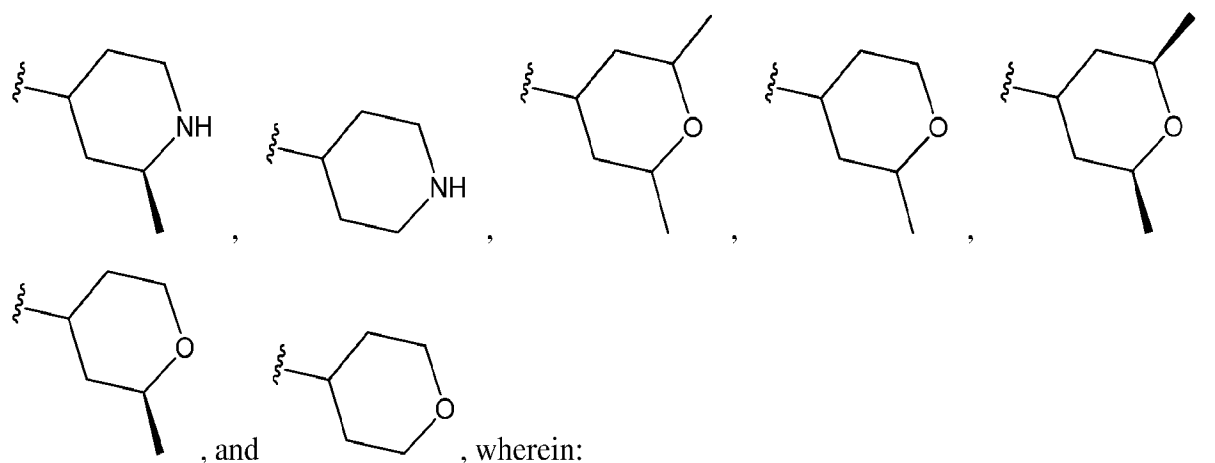
[00136] In any aspect or embodiment described herein,



or

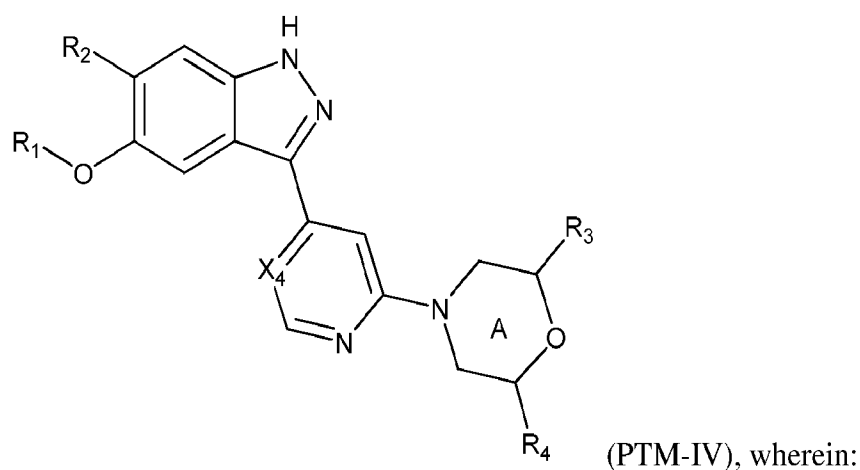
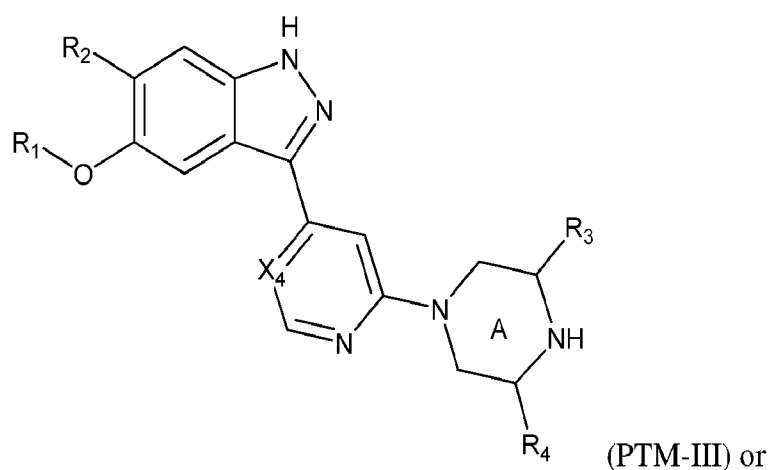
is selected from:





$R_3$  and  $R_4$  are defined as described in any aspect or embodiment described herein; and the heterocycloalkyl is attached to L or PTM via an atom of the heterocycloalkyl or a substituent thereof (e.g.,  $R_3$ ,  $R_4$ , or a methyl group).

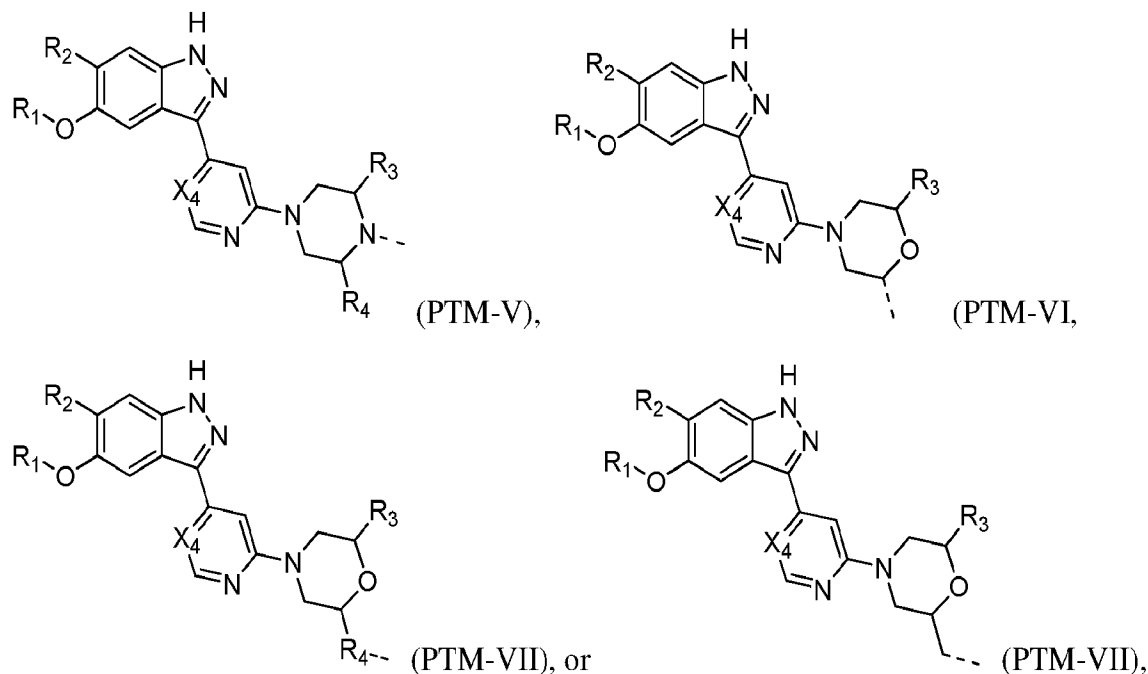
**[00137]** In any aspect or embodiment described herein, the PTM has the chemical structure:



$X_4$ ,  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  are defined as described in any aspect or embodiment described herein; and

the PTM is attached to the L or ULM via an atom of heterocycloalkyl A (e.g., a carbon or nitrogen of the heterocycloalkyl), R<sub>3</sub>, or R<sub>4</sub>.

**[00138]** In any aspect or embodiment described herein, the PTM has the chemical structure:



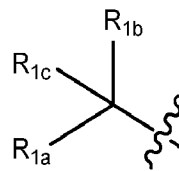
wherein:

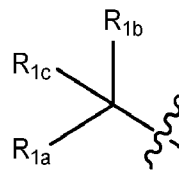
X<sub>4</sub>, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are defined as described in any aspect or embodiment described herein;

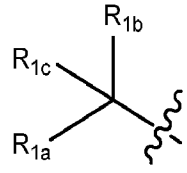
and

--- of the PTM indicates the point of attachment with the L or ULM.

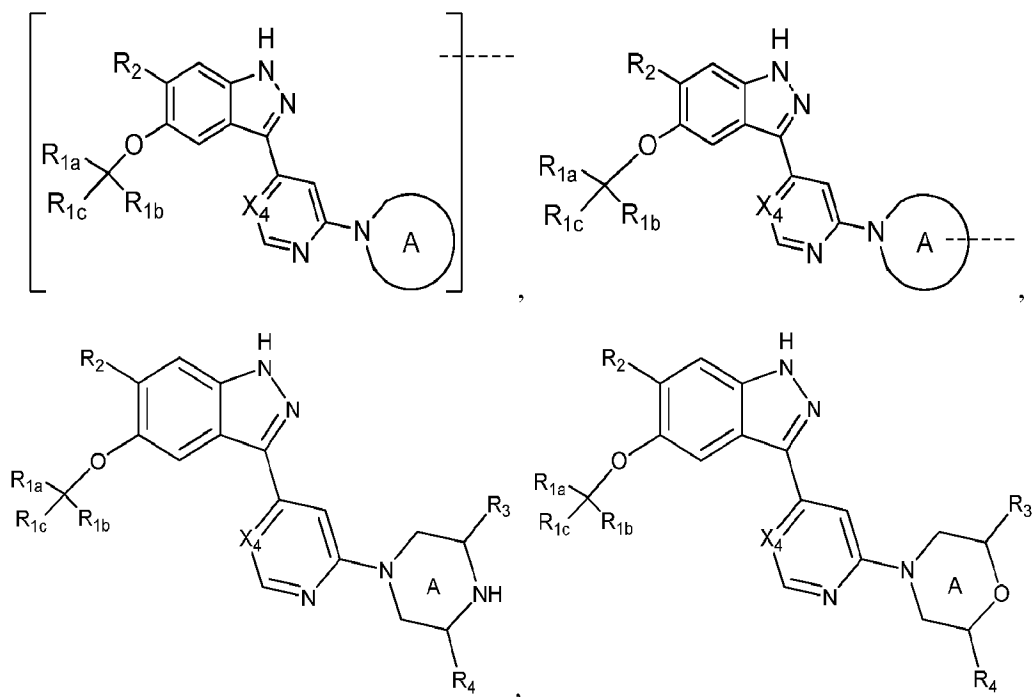
**[00139]** In any aspect or embodiment described herein, the R<sub>1</sub> is selected from an optionally substituted C3-C5 cycloalkyl and a linear or branched C1-C4 alkyl.



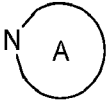
**[00140]** In any aspect or embodiment described herein, R<sub>1</sub> is , wherein: R<sub>1a</sub>, R<sub>1b</sub>, and R<sub>1c</sub> are each independently a H or a linear or branched C1-C2 alkyl, each optionally substituted with one or more halogen or nitrile group; or R<sub>1a</sub> or R<sub>1b</sub> together with the carbon to which they are attached form a C3-C6 cycloalkyl that is optionally substituted with one or more C1-C3 alkyl, nitrile group, or halogen.

**[00141]** In any aspect or embodiment described herein,  $R_1$  is , wherein:  $R_{1a}$ ,  $R_{1b}$ , and  $R_{1c}$  are each independently a H, or a linear or branched C1-C2 alkyl; or  $R_{1a}$  or  $R_{1b}$  together with the carbon to which they are attached form a C3-C6 cycloalkyl.

**[00142]** In any aspect or embodiment described herein, the PTM is selected from:

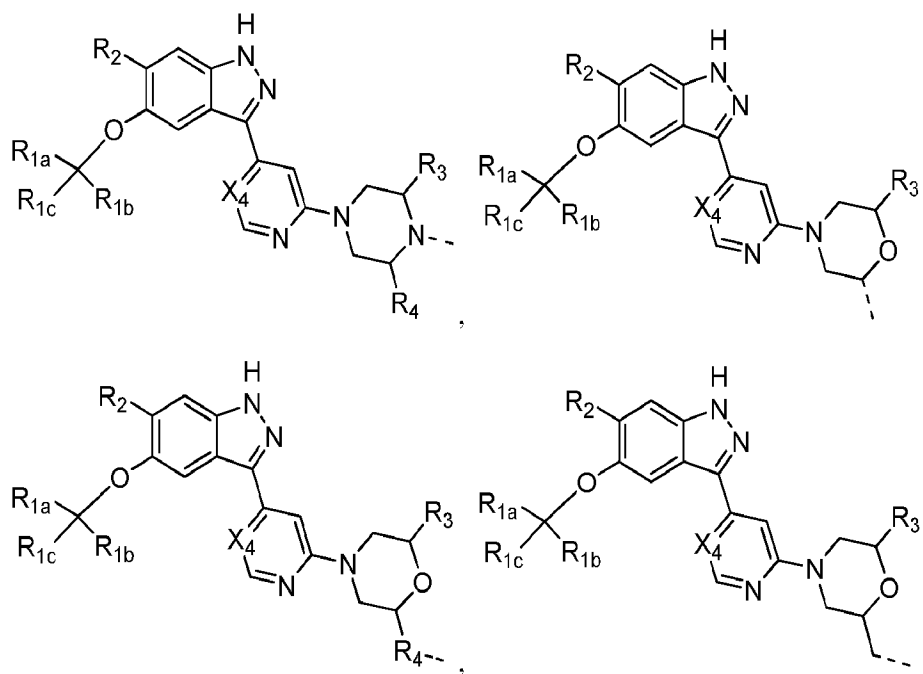


wherein:

each of X,  $R_{1a}$ ,  $R_{1b}$ ,  $R_{1c}$ ,  $R_3$ ,  $R_4$ , and  are defined as described in any aspect or embodiment described herein; and

the L or ULM is attached via an atom of the heterocycloalkyl A (e.g., a carbon or nitrogen of the heterocycloalkyl),  $R_3$ , or  $R_4$ .

**[00143]** In any aspect or embodiment described herein, the PTM is selected from:



wherein:

each of X<sub>4</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub>, R<sub>3</sub>, and R<sub>4</sub> are defined as described in any aspect or embodiment described herein; and

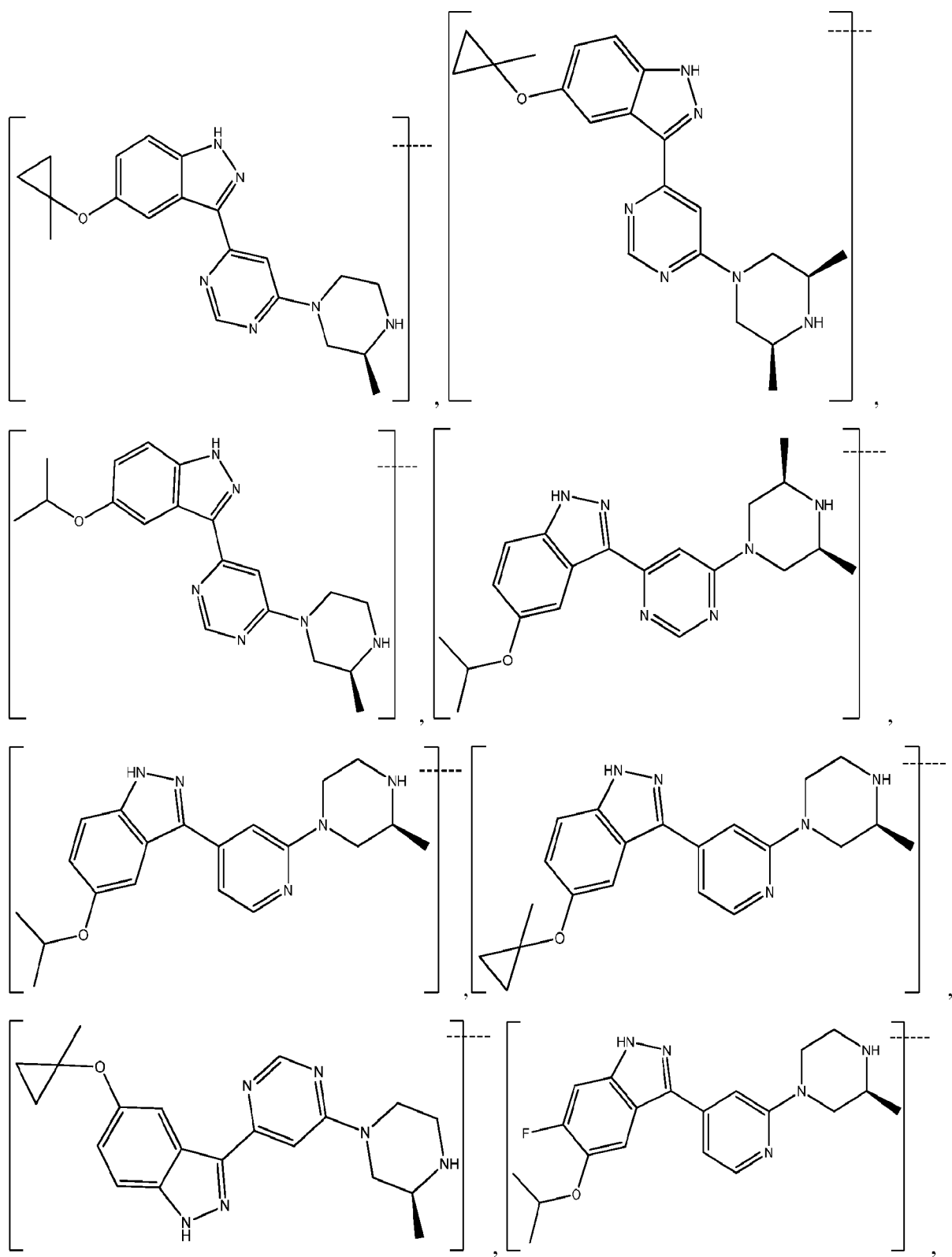
--- of the PTM indicates the point of attachment with the L or ULM, and where not present.

[00144] In any aspect or embodiment described herein, the R<sub>1</sub> is selected from .

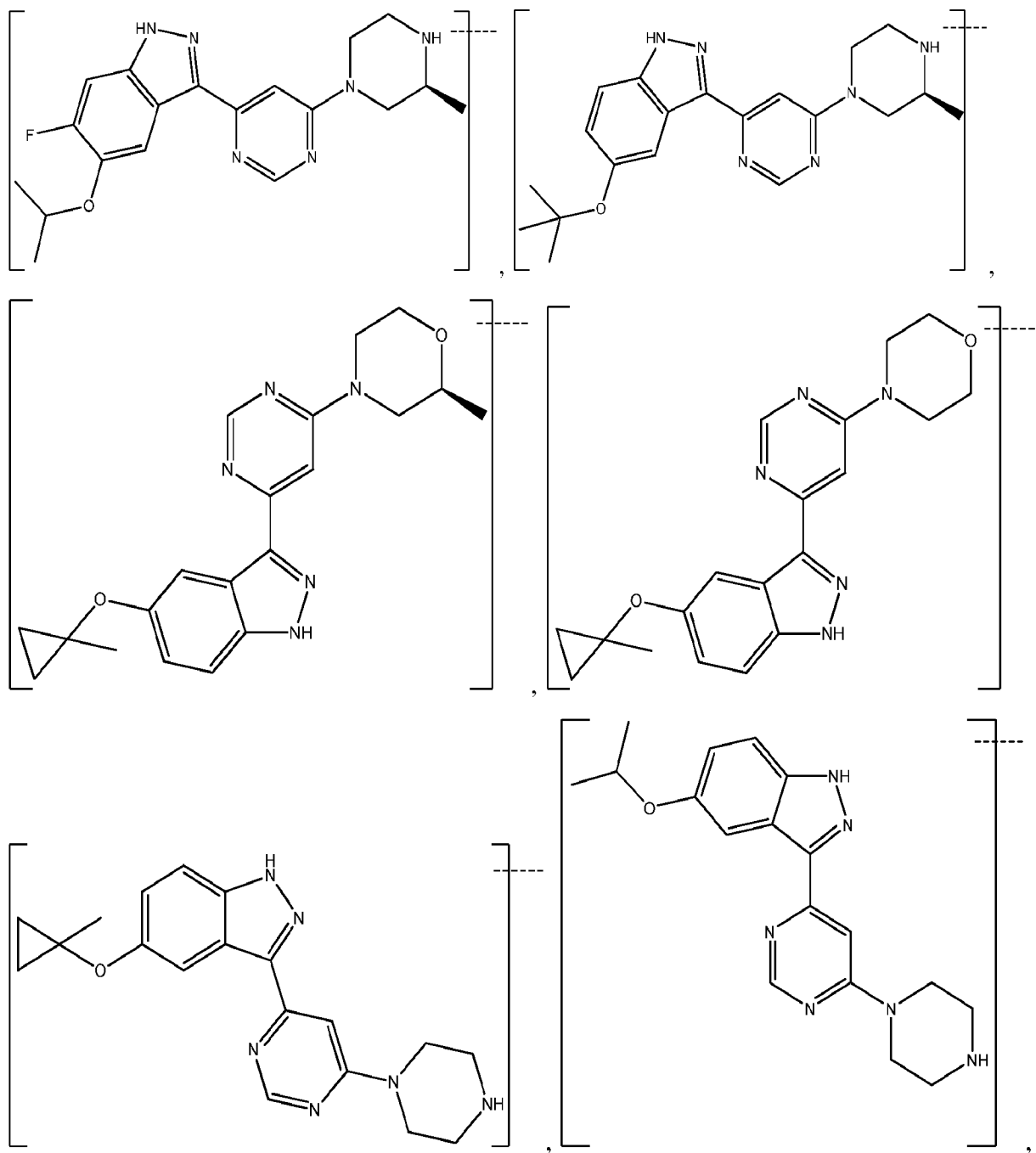
, and , wherein the dashed line is the point of attachment to the M or oxygen atom of the PTM.

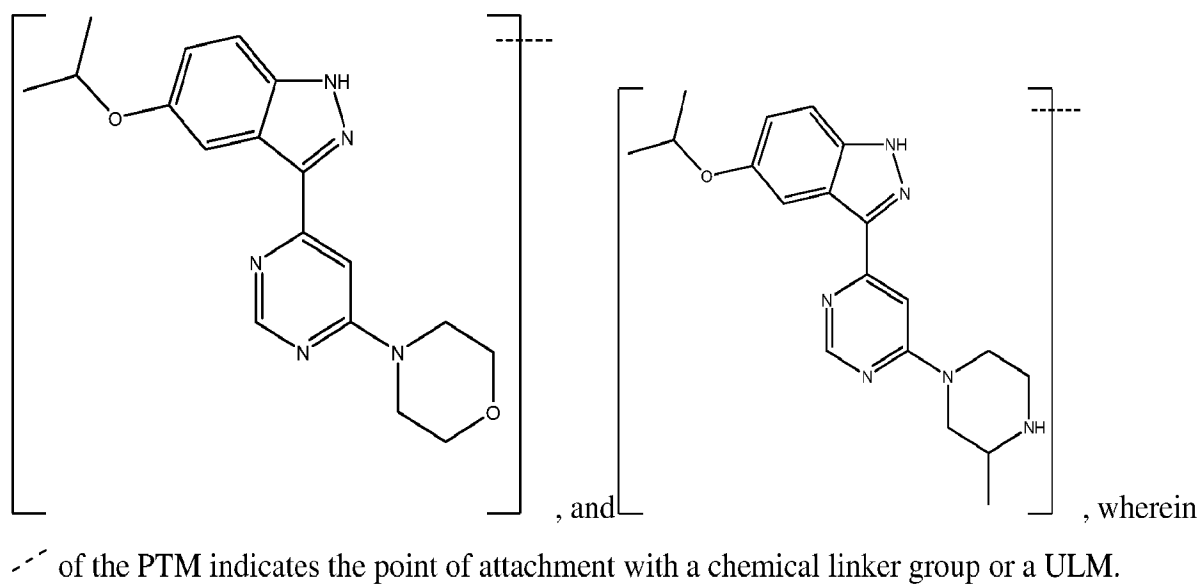
**[00145]** In any aspect or embodiment described herein, the R<sub>2</sub> is H or F.

**[00146]** In any aspect or embodiment described herein, the PTM has the chemical structure:

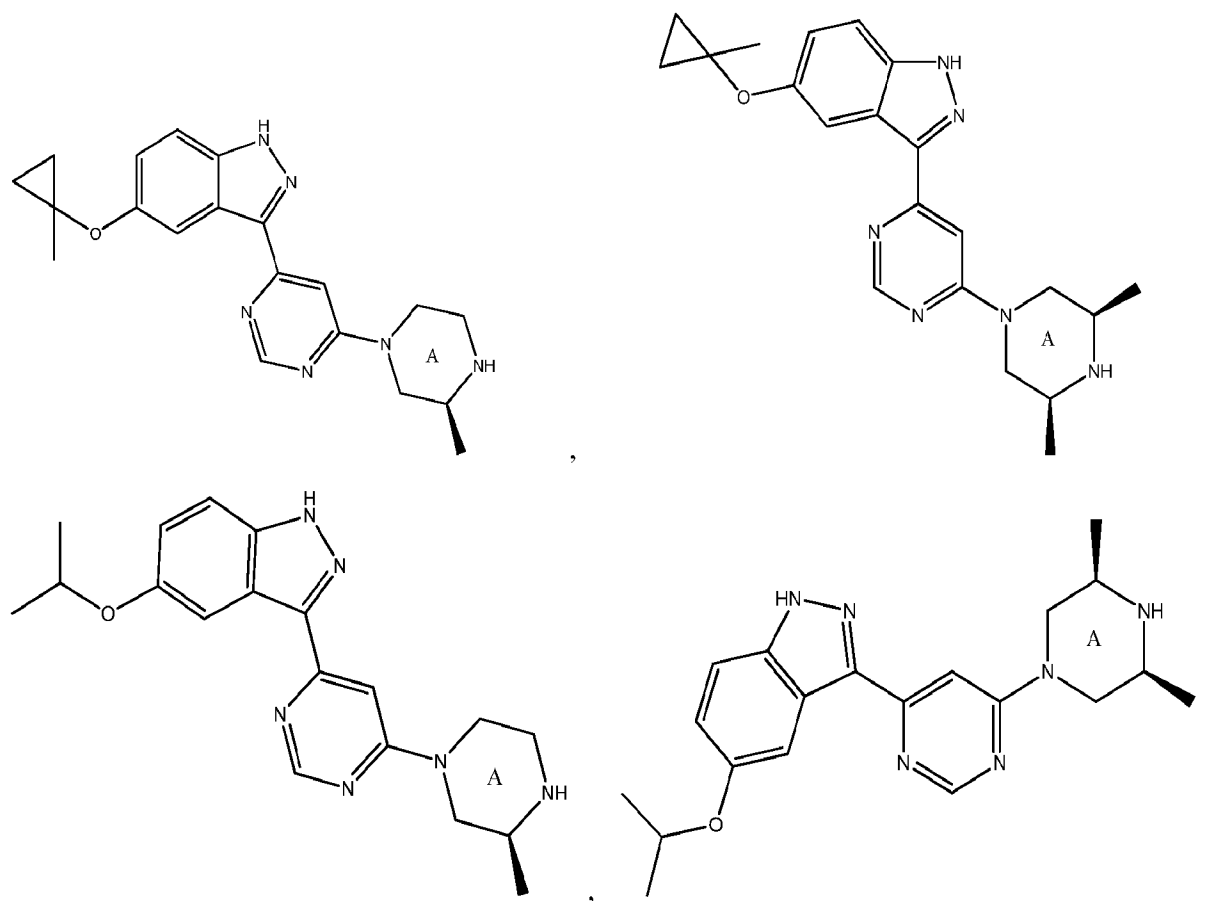


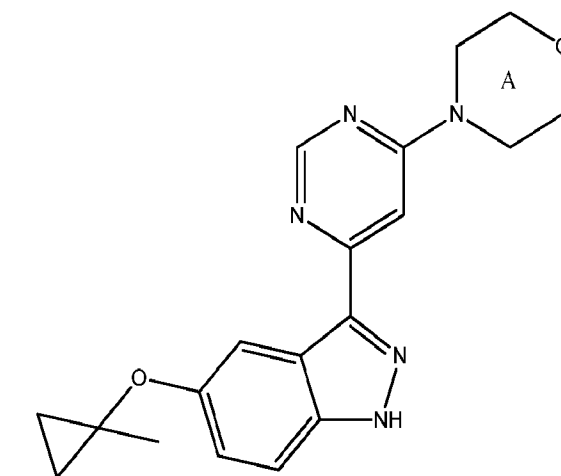
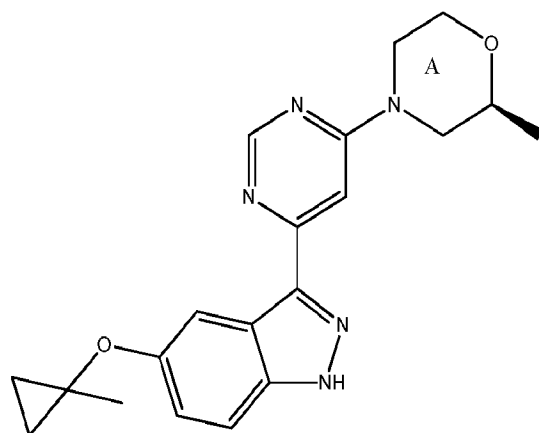
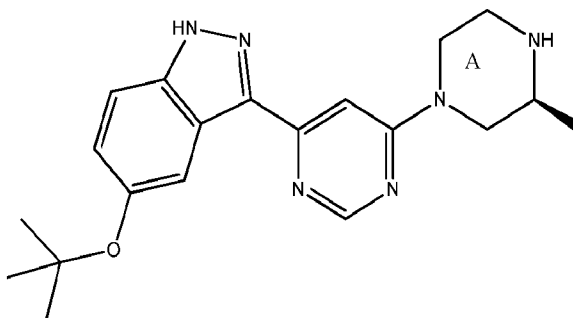
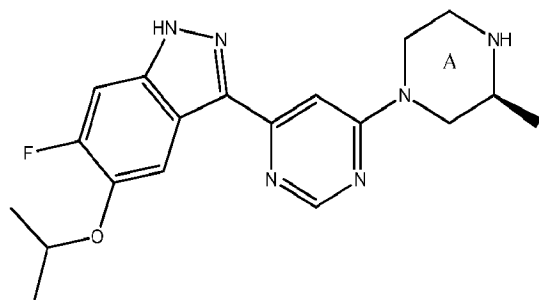
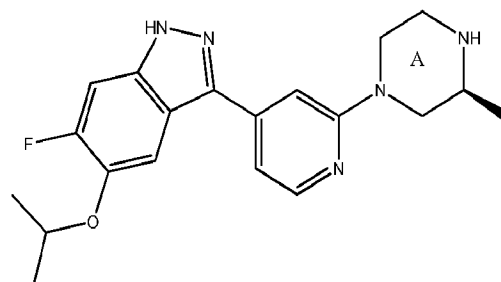
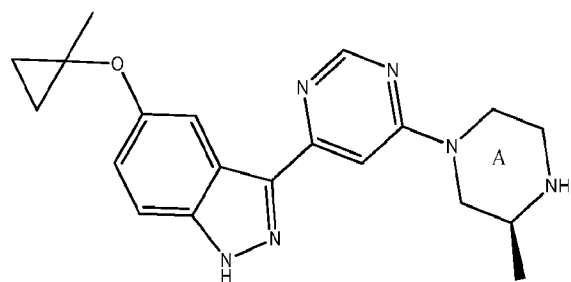
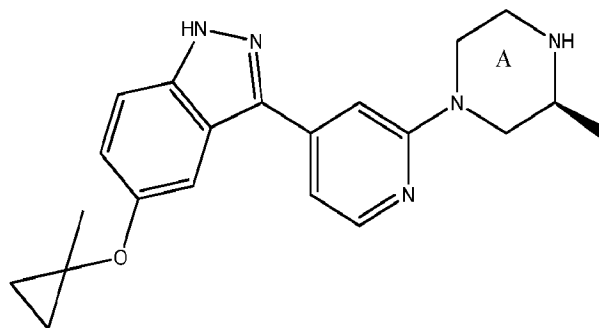
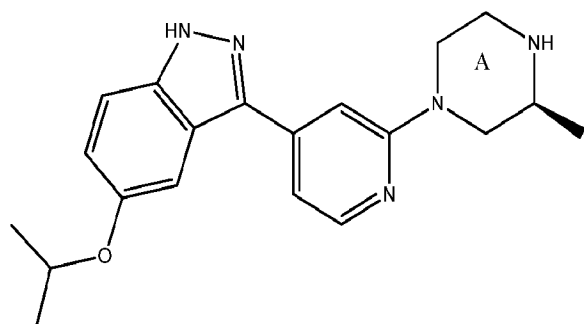


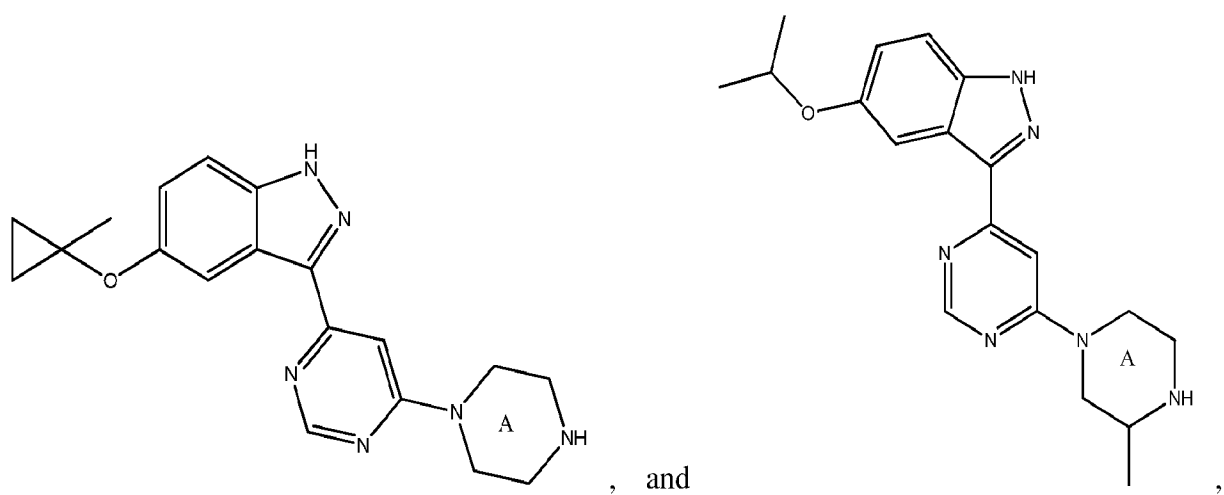




**[00147]** In any aspect embodiment described herein, the PTM has the chemical structure:

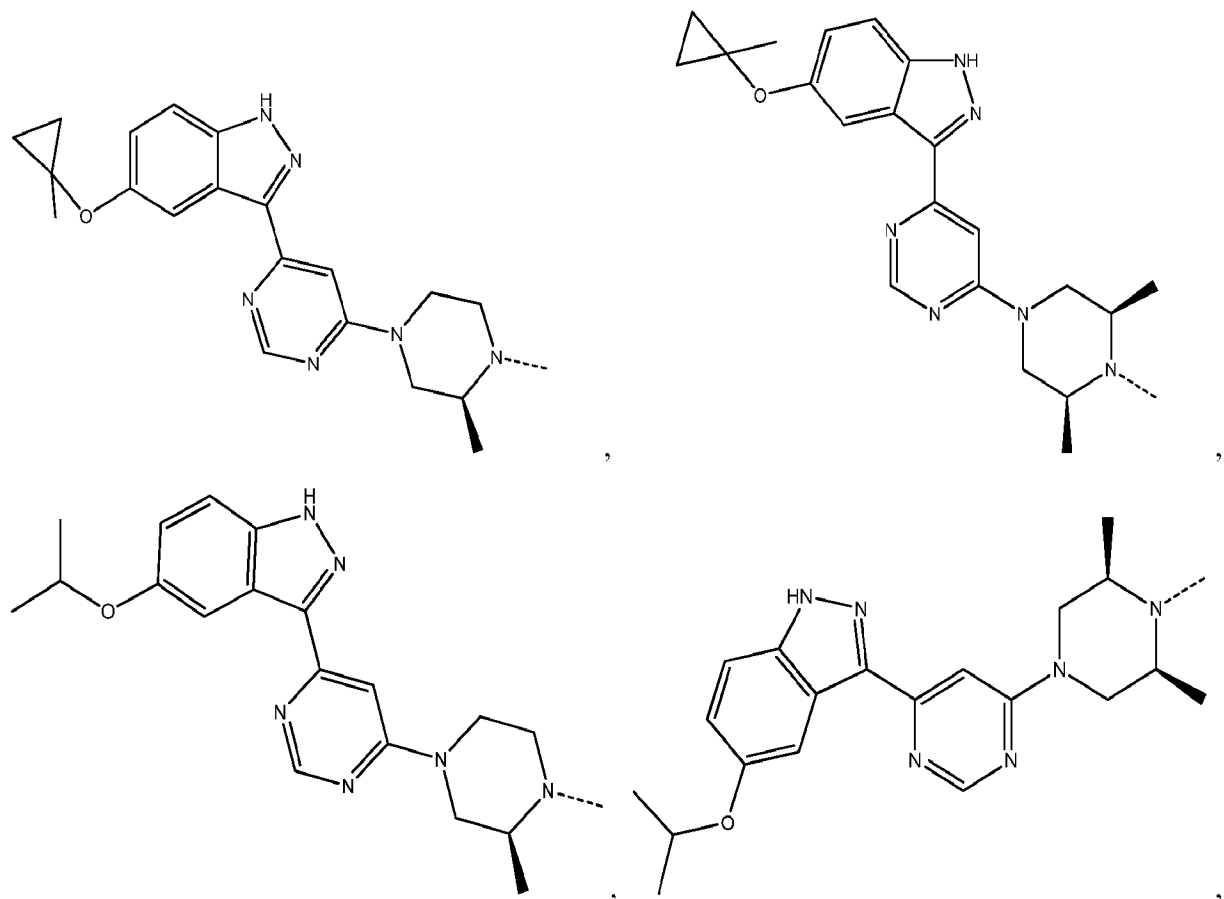


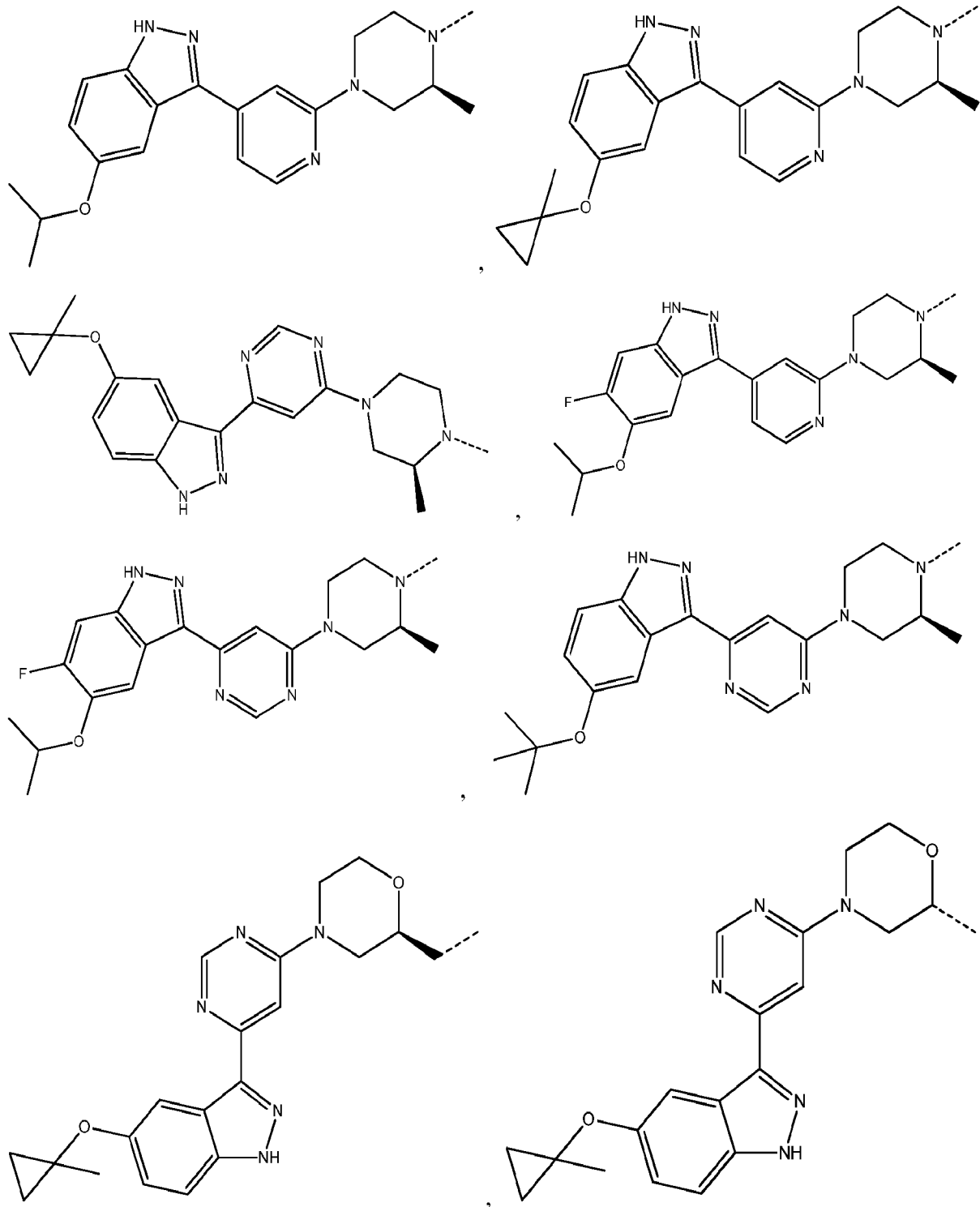


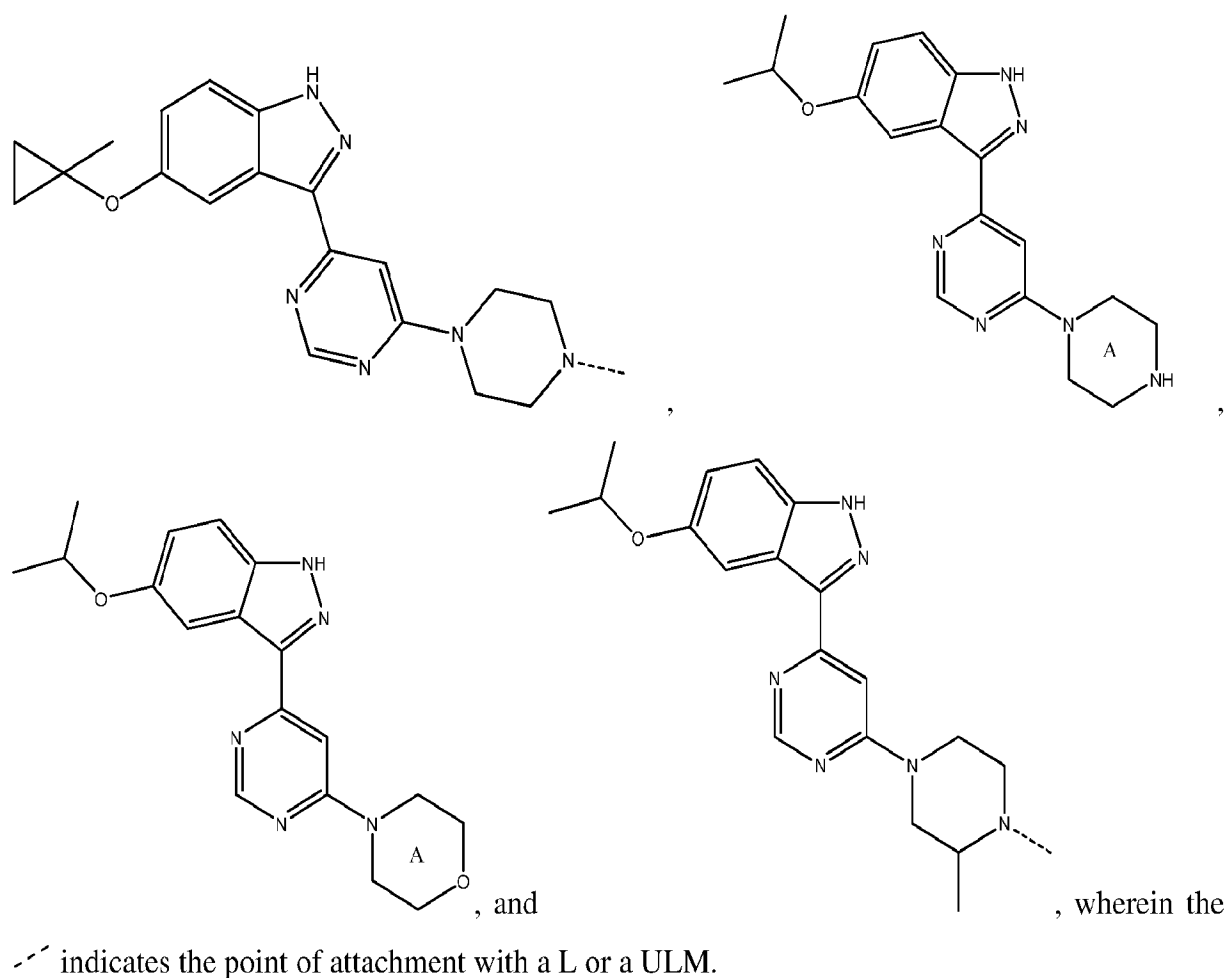


wherein the PTM is covalently linked to the L or ULM via an atom of the heterocycloalkyl A or a substituent thereof.

**[00148]** In any aspect or embodiment described herein, the PTM has the chemical structure:







### **Therapeutic Compositions**

**[00149]** The present invention further provides pharmaceutical compositions comprising therapeutically effective amounts of at least one bifunctional compound as described herein, in combination with a pharmaceutically acceptable carrier, additive or excipient.

**[00150]** 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 effect targeted 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 by degrading the target protein. In certain embodiments, the therapeutic compositions as described herein may be used to effectuate the degradation of protein for the treatment or amelioration of LRRK2-mediated inflammatory

diseases, autoimmune diseases or cancer. In certain additional embodiments, the disease is idiopathic PD, LRRK2 mutation-associated PD (e.g., PD associated with one or more LRRK2 activating mutations), primary tauopathies (e.g., supranuclear palsy (PSP) or corticobasal degeneration (CBD)), lewy body dementia, Crohn's Disease, Leprosy (e.g., Leprosy with type 1 inflammatory reactions), and/or neuroinflammation.

**[00151]** In alternative aspects, the present disclosure relates to a method for treating a disease state or ameliorating one or more symptoms of a disease or condition in a subject in need thereof by degrading the LRRK2 protein (e.g., a wildtype LRRK2 protein or an LRRK2 mutant protein (e.g., a LRRK2 mutant protein including one or more mutation selected from G2019S, I2020T, N1437H, R1441G/C/H, and Y1699C) comprising administering to said patient or subject an effective amount, e.g., a therapeutically effective amount, of at least one compound as described herein, optionally in combination with a pharmaceutically acceptable carrier, additive or excipient, and optionally coadministered with an additional bioactive agent, wherein the composition is effective for treating or ameliorating the disease or disorder or one or more symptoms thereof in the subject. The method according to the present disclosure may be used to treat certain disease states, conditions or symptoms including inflammatory disease, autoimmune disease, or cancer, by virtue of the administration of effective amounts of at least one compound described herein. For example, the method according to the present disclosure may be used to treat one or more of Parkinson's Disease (PD), idiopathic PD, LRRK2 mutation associated PD (e.g., PD associated with one or more LRRK2 activating mutations), primary tauopathies (e.g., supranuclear palsy (PSP) or corticobasal degeneration (CBD)), lewy body dementia, Crohn's Disease, Leprosy (e.g., Leprosy with type 1 inflammatory reactions), and neuroinflammation (such as is observed in Alzheimer's disease, PD, multiple sclerosis, traumatic brain injury, spinal cord injury, etc.).

**[00152]** The present disclosure further includes pharmaceutical compositions comprising a pharmaceutically acceptable salt, in particular, acid or base addition salts of the compounds as described herein. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned 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.

**[00153]** Pharmaceutically acceptable base addition salts may also be used to produce pharmaceutically acceptable salt forms of the compounds according to the present disclosure. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of the present compounds 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 (e.g., potassium and sodium) and alkaline earth metal cations (e.g., 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.

**[00154]** 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, intranasal, intraocular, intrathecal, vaginal, and suppository administration, among other routes of administration. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. 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 type, location and severity of disease, condition or symptom, and the health of 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 disclosure 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 or in depot formulation may also be used to control or sustain the release of compound at an injection site.

**[00155]** 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, and combinations thereof.

**[00156]** 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.

**[00157]** 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, among others known in the art. For oral administration in a

capsule form, useful diluents include lactose and corn starch. When aqueous suspensions are required for oral use, the active ingredient may be combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added. Lubricating agents, such as magnesium stearate, are also typically added.

**[00158]** 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.

**[00159]** The pharmaceutical compositions as described herein may also be administered topically. For topical applications, the pharmaceutical composition can be formulated in a transdermal patch, which can either be a reservoir patch or a matrix patch comprising the active compound combined with one or more carriers, buffers, absorption enhancers, and providing from 1 day to two weeks of continuous administration.

**[00160]** Alternatively, the pharmaceutical compositions of the present disclosure may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this disclosure include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water.

**[00161]** Alternatively, the pharmaceutical compositions of the present disclosure 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.

**[00162]** Alternatively, the pharmaceutical compositions of the present disclosure can be formulated for ophthalmic use. For example, 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 or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

**[00163]** 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.

**[00164]** The amount of active pharmaceutical ingredient 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 condition of the subject and disease, condition or symptom treated, the particular mode of administration, and the condition of the subject. Preferably, the compositions should be formulated to contain between about 0.05 milligram and 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 another compound according to the present disclosure.

**[00165]** 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 and bioavailability 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.

**[00166]** 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 depending upon the pharmaceutically acceptable salt or solvate thereof, optionally in a pharmaceutically acceptable carrier or diluent, either alone, or in combination with another known therapeutic agent.

**[00167]** In certain aspects, the active compound is combined with 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 an undue degree of 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 nanograms per kilograms (ng/kg) to 300 milligrams per kilograms (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.

**[00168]** In certain aspects, the compound is conveniently administered in any suitable unit dosage form, including but not limited to a dosage form containing less than 1 milligrams (mg), 1 mg to 3000 mg, or 5 mg to 500 mg of active ingredient per unit dosage form. An oral dosage of about 25 mg-250 mg is often convenient.

**[00169]** In certain aspects, the active ingredient is preferably administered to achieve peak plasma concentrations of the active compound of about 0.00001-30 millimole (mM), preferably about 0.1-30 micromole ( $\mu$ M). 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 may also be appropriate to generate effective plasma concentrations of active agent.

**[00170]** 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.

**[00171]** 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.

**[00172]** 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.

**[00173]** 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.

**[00174]** 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 anti-cancer agents, as described herein among others. In certain preferred aspects of the disclosure, one or more compounds according to the present disclosure are coadministered with another bioactive agent, such as an anti-cancer agent or a wound healing agent, including an antibiotic, as otherwise described herein.

**[00175]** 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.

**[00176]** If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

**[00177]** In any aspect or 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.

**[00178]** 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 stearyl phosphatidyl ethanolamine, stearyl 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.

**[00179]    Therapeutic Methods**

**[00180]**    In an additional aspect, the description provides therapeutic methods comprising administration of an effective amount of a compound as described herein or salt form thereof, and a pharmaceutically acceptable carrier. The therapeutic methods are useful to effect protein degradation in a patient or subject in need thereof, for example, an animal such as a human, for treating or ameliorating a disease state, condition or related symptom that may be treated through targeted protein degradation.

**[00181]**    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, condition, or symptom which is related to 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.

**[00182]**    The description provides therapeutic methods for effectuating the degradation of proteins of interest for the treatment or amelioration of a disease, e.g., Parkinson’s Disease (PD), primary tauopathies, lewy body dementia, Crohn’s Disease, Leprosy, and/or neuroinflammation (such as is observed in . In any aspect or embodiment, the disease is idiopathic PD, LRRK2 mutation associated PD (e.g., PD associated with one or more LRRK2 activating mutations), PSP, CBD, Leprosy with type 1 inflammatory reactions, Alzheimer’s disease, PD, multiple sclerosis, traumatic brain injury, and/or spinal cord injury. 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 of the invention. The control or reduction of specific protein levels in cells of a subject as afforded by the present disclosure provides treatment of a disease state, condition, or symptom. In any aspect or

embodiment, the method comprises administering an effective amount of a compound as described herein, optionally including a pharmaceutically acceptable excipient, carrier, adjuvant, another bioactive agent or combination thereof.

**[00183]** In additional embodiments, the description provides methods for treating or ameliorating 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.

**[00184]** 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.

**[00185]** In another aspect, the description provides a process for making a molecule that can cause degradation of LRRK2 in a cell, comprising the steps of: (i) providing a small molecule that binds to the LRRK2 or a mutated form thereof; (ii) providing an E3 ubiquitin ligase binding moiety (ULM), preferably a CLM such as thalidomide, pomalidomide, lenalidomide or an analog thereof; and (iii) covalently coupling the small molecule of step (i) to the ULM of step (ii) via a chemical linking group (L) to form a compound which binds to both a cereblon E3 ubiquitin ligase and LRRK2 protein and/or mutated form in the cell, such that the cereblon E3 ubiquitin ligase is in proximity to, and ubiquitinates the LRRK2 protein bound thereto, such that the ubiquitinated LRRK2 is then degraded.

**[00186]** In another aspect, the description provides a method for detecting whether a molecule can trigger degradation of a LRRK2 protein in a cell, the method comprising the steps of: (i) providing a molecule for which the ability to trigger degradation of LRRK2 protein in a cell is to be detected, said molecule comprising the structure: CLM–L–PTM, wherein CLM is a cereblon E3 ubiquitin ligase binding moiety capable of binding a cereblon E3 ubiquitin ligase in a cell, which CLM is thalidomide, pomalidomide, lenalidomide, or an analog thereof; PTM is a protein targeting moiety, which is a small molecule that binds to LRRK2 and/or mutated LRRK form thereof, said LRRK2 having at least one lysine residue available to be ubiquitinated by a cereblon E3 ubiquitin ligase bound to the CLM of the molecule; and L is a chemical linking

group that covalently links the CLM to the PTM to form the molecule; (ii) incubating a LRRK2 protein-expressing cell in the presence of the molecule of step (i); and (iii) detecting whether the LRRK2 protein in the cell has been degraded.

**[00187]** In any of the aspects or embodiments described herein, the small molecule capable of binding LRRK2, is a small molecule that binds of LRRK2. In certain embodiments, the small molecule that binds the LRRK2 is as described herein.

**[00188]** In another aspect of said treatment, the present disclosure provides a method of treating a human patient in need of said treatment of a disease state, condition, or symptom causally related to LRRK2, and/or LRRK2 mutated form, expression, over-expression, mutation, aggregation, accumulation, misfolding or dysregulation where the degradation of the LRRK2 protein will produce a therapeutic effect in the patient, the method comprising administering to the patient an effective amount of a compound according to the present disclosure, optionally in combination with another bioactive agent.

**[00189]** In another aspect of said treatment, the present disclosure provides a method of treating a human patient in need of said treatment of a disease state, condition, or symptom causally related to alpha-synuclein expression, over-expression, mutation, aggregation, accumulation, misfolding or dysregulation where the degradation of the LRRK2 protein and/or mutated form thereof will produce a therapeutic effect in the patient, the method comprising administering to the patient an effective amount of a compound according to the present disclosure, optionally in combination with another bioactive agent.

**[00190]** In another aspect of said treatment, the present disclosure provides a method of treating a human patient in need of said treatment of a disease state, condition, or symptom causally related to alpha-synuclein expression, over-expression, mutation, aggregation, misfolding or dysregulation where the degradation of the LRRK2 protein and/or mutated form thereof will produce a therapeutic effect in the patient, the method comprising administering to the patient an effective amount of a compound according to the present disclosure, optionally in combination with another bioactive agent.

**[00191]** In another aspect of said treatment, the present disclosure provides a method of treating a human patient in need of said treatment of a disease state, condition, or symptom causally related to Tau expression, over-expression, mutation, aggregation, misfolding or dysregulation where the degradation of the LRRK2 protein and/or mutated form thereof will



produce a therapeutic effect in the patient, the method comprising administering to the patient an effective amount of a compound according to the present disclosure, optionally in combination with another bioactive agent.

**[00192]** The disease state, condition, or symptom may be 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 expression, overexpression, mutation, misfolding, or dysregulation of the protein, which leads to a disease state, condition, or symptom.

**[00193]** In another aspect, the present disclosure provides a method of treating or ameliorating at least one symptom of a disease or condition in a subject, comprising the steps of: providing a subject identified as having a symptom of a disease or condition causally related to expression, overexpression, mutation, misfolding, or dysregulation of LRRK2 protein and/or mutated form thereof in the subject, and the symptom of the disease or condition is treated or ameliorated by degrading LRRK2 protein and/or mutated form thereof in cells of the subject; and administering to the subject therapeutically effective amount of a compound comprising a small molecule of the present invention such that the LRRK2 protein and/or mutated form thereof is degraded, thereby treating or ameliorating at least one symptom of a disease or condition in the subject.

**[00194]** The term “disease state or condition” is used to describe any disease state or condition wherein protein expression overexpression, mutation, misfolding, or dysregulation (e.g., the amount of protein expressed in a patient is elevated) occurs and where degradation of the LRRK2 protein and/or mutated form thereof to reduce or stabilize the level of LRRK2 protein (whether mutated or not) in a patient provides beneficial therapy or relief of symptoms to a patient in need thereof. In certain instances, the disease state, condition, or symptom may be cured.

**[00195]** Disease state, condition, or symptom which may be treated using compounds according to the present disclosure include, for example, Parkinson’s Disease (PD), idiopathic PD, LRRK2 mutation associated PD (e.g., PD associated with one or more LRRK2 activating mutations), primary tauopathies (e.g., supranuclear palsy (PSP) or corticobasal degeneration (CBD)), lewy body dementia, Crohn’s Disease, Leprosy (e.g., Leprosy with type 1 inflammatory reactions), and/or neuroinflammation (such as is observed in Alzheimer’s disease, PD, multiple sclerosis, traumatic brain injury, spinal cord injury, etc.).

[00196] 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 a present compound 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.

[00197] The term “additional anti-autoimmune disease agent” is used to describe an anti-autoimmune disease therapeutic agent, which may be combined with a compound according to the present disclosure to treat autoimmune disease. These agents include, for example, infliximab, tofacitinib, baricitinib, secukinumab, adalimumab, etanercept, golimumab, certolizumab pegol, anti-proliferative drugs (for example, mycophenolate mofetil) and corticosteroids.

[00198] The term “pharmaceutically acceptable derivative” is used throughout the specification to describe any pharmaceutically acceptable prodrug form (such as an ester, amide or other prodrug group), which, upon administration to a patient, provides directly or indirectly the present compound or an active metabolite of the present compound.

[00199] **EXAMPLES**

[00200] ABBREVIATIONS

|          |                                    |
|----------|------------------------------------|
| ACN      | Acetonitrile                       |
| AcOH     | Acetic acid                        |
| Boc      | <i>tert</i> -butoxycarbonyl        |
| dba      | Dibenzylideneacetone               |
| DBU      | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DCM      | Dichloromethane                    |
| DMA      | Dimethylacetamide                  |
| DME      | Dimethoxyethane                    |
| DMF      | Dimethylformamide                  |
| DMSO     | Dimethyl Sulfoxide                 |
| DMAC/DMA | Dimethylacetamide                  |

|            |                                           |
|------------|-------------------------------------------|
| DIEA       | N, N-Diisopropylethylamine                |
| EDTA       | Ethylenediaminetetraacetic acid           |
| EtOAc/EA   | Ethyl Acetate                             |
| EtOH       | Ethanol                                   |
| FA         | Formic Acid                               |
| HPLC       | High pressure liquid chromatography       |
| Hz         | Hertz                                     |
| IBX        | 2-Iodoxybenzoic acid                      |
| LAH        | Lithium aluminium hydride                 |
| LCMS       | Liquid Chromatography / Mass Spectrometry |
| LiHMDS     | Lithium bis(trimethylsilyl)amide          |
| MHz        | Megahertz                                 |
| NBS        | N-Bromosuccinimide                        |
| NCS        | N-Chlorosuccinimide                       |
| NMR        | Nuclear Magnetic Resonance                |
| NMP        | N-Methyl-2-pyrrolidone                    |
| MeOH       | Methanol                                  |
| MPLC       | Medium pressure liquid chromatography     |
| MTBE       | Methyl tert-butyl ether                   |
| PE         | Petroleum ether                           |
| Psi        | Pound-force per square inch               |
| RT or r.t. | Room temperature                          |
| SFC        | Supercritical fluid chromatography        |
| TEA        | Triethylamine                             |
| THF        | Tetrahydrofuran                           |
| TFA        | Trifluoroacetic acid                      |
| TLC        | Thin layer chromatography                 |
| TMS        | Trimethylsilyl                            |

**[00201] General Synthetic Approach**

**[00202]** The synthetic realization and optimization of the bifunctional molecules as described herein may be approached in a stepwise or modular fashion. For example, identification of

compounds that bind to the target protein, i.e., LRRK2 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 chemical linking group previously referred to herein. Where crystallographic or NMR structural data are available, these can be used to focus such a synthetic effort.

**[00203]** In a very analogous way one can identify and optimize ligands for an E3 Ligase.

**[00204]** 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 chemical linking group(s). Chemical linking group(s) 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.

**[00205]** 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).

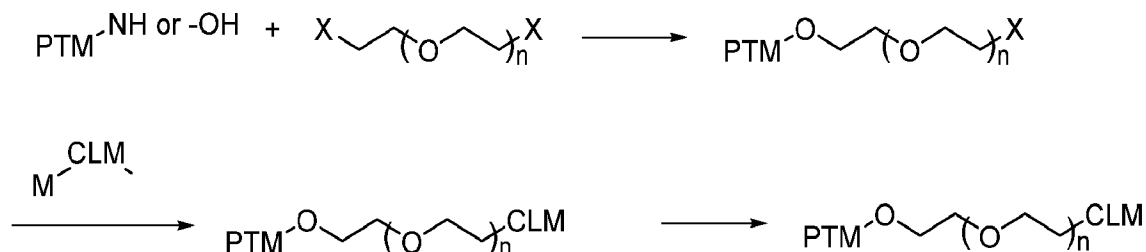
**[00206]** **Synthetic Procedures**

**[00207]** **General Synthetic Scheme**

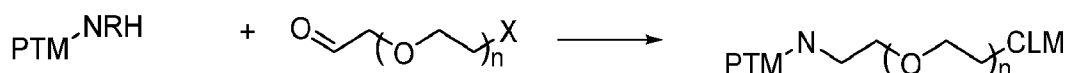
Scheme 1:



Scheme 2:



Scheme 3:



X represents a suitable leaving group (e.g. OTs, OMs, Cl, Br, etc.)

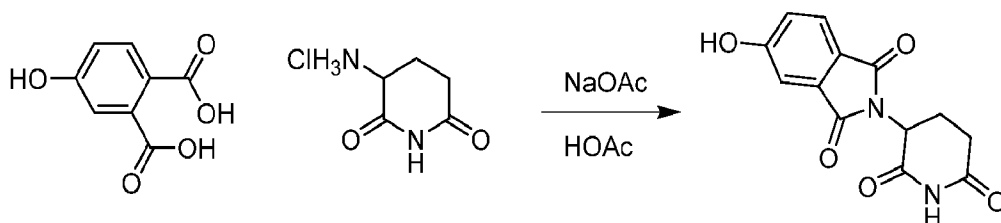
Y represents either a primary or secondary amine or alcohol

M represents a metalated version of the TLM ( $\text{Na}^+$ ,  $\text{Cs}^+$ ,  $\text{Li}^+$ , etc)

PG represents a suitable protecting group

#### [00208] Exemplary Synthesis of Intermediate 1, 2-(2,6-dioxo-3-piperidyl)-5-hydroxy-isoindoline-1,3-dione

##### Step 1

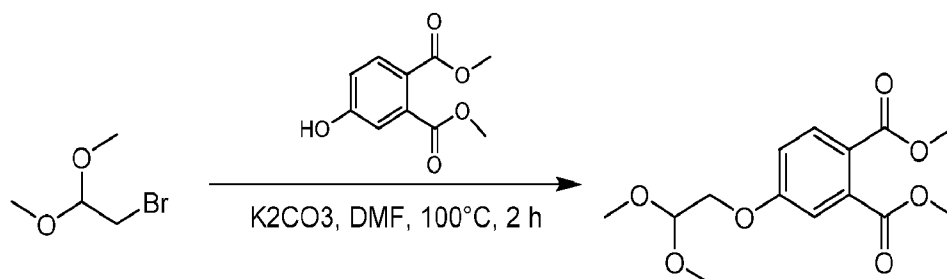


To a solution of 3-aminopiperidine-2,6-dione (4.1 g, 24.7 mmol, 1.50 *eq*, HCl salt) in acetic acid (45 mL) was added sodium acetate (4.1 g, 49.4 mmol, 3.00 *eq*), then the mixture was stirred at 25°C for 1h. Then 4-hydroxyphthalic acid (3.0g, 16.5 mmol, 1.00 *eq*) was added into the mixture and heated to 120°C, stirred for additional 11h. LCMS showed the desired MS was detected and

the reaction was complete. The mixture was concentrated and then poured into water (20 mL), and then filtered. The crude product was purified by column chromatography (dichloromethane: methanol=50: 1 to 10: 1) to afford 2-(2,6-dioxo-3-piperidyl)-5-hydroxy- isoindoline-1,3-dione (3.9 g, 14.3 mmol, 86% yield) as a colorless solid.

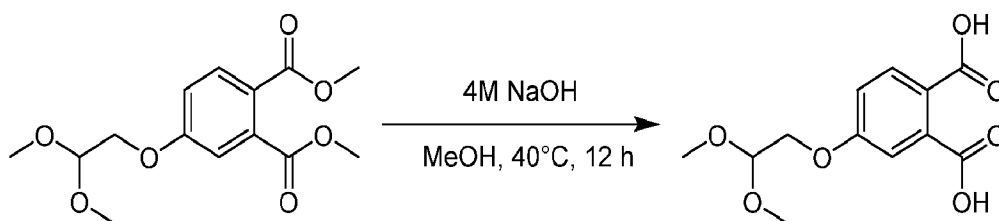
**[00209] Exemplary Synthesis of Intermediate 2, 2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl] oxyacetaldehyde**

**Step 1**



To a solution of 2-bromo-1,1-dimethoxy-ethane (3.22 g, 19.04 mmol, 2 eq) in dimethyl formamide (20 mL) was added potassium carbonate (3.95 g, 28.56 mmol, 3 eq) and dimethyl 4-hydroxybenzene-1, 2-dicarboxylate (2 g, 9.52 mmol, 1 eq). The mixture was stirred at  $100^\circ C$  for 3 hours. LCMS indicated 4-hydroxybenzene-1, 2-dicarboxylate was consumed completely and one new spot formed. The reaction mixture was quenched by water 200 mL at  $25^\circ C$ , and then extracted with ethyl acetate (50 mL X 3). The combined organic layers were washed with brines (50 mL X 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (Petroleum ether: Ethyl acetate=15:1 to 8:1). Compound dimethyl 4-(2,2-dimethoxyethoxy)benzene-1,2-dicarboxylate (2.64 g, 8.85 mmol, 92% yield) was obtained as a yellow oil.

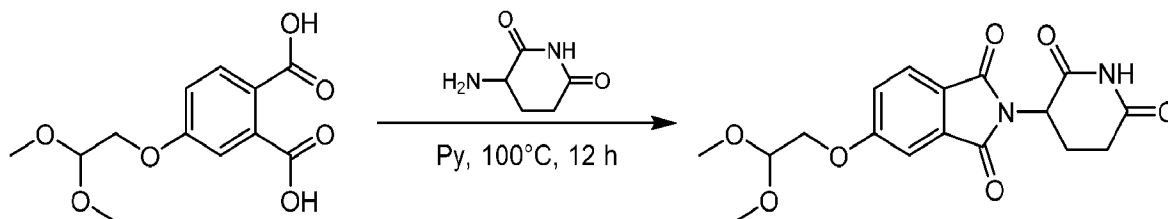
**Step 2**



To a solution of dimethyl 4-(2,2-dimethoxyethoxy)benzene-1,2-dicarboxylate (2.64 g, 8.86 mmol, 1 eq) in methyl alcohol (20 mL) was added sodium hydroxide (4 M, 4.43 mL, 2 eq). The mixture was stirred at  $40^\circ C$  for 12 hours. The reaction mixture was quenched by hydrochloric acid 20 mL at  $20^\circ C$ , and then diluted with water 100 mL and extracted with ethyl acetate (50

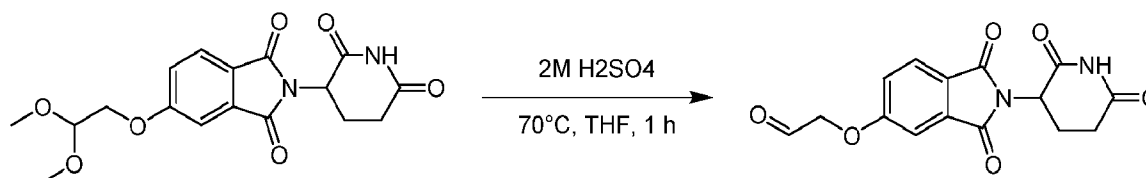
mL X 3). The combined organic layers were washed with brines (50 mL X 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used into the next step without further purification. Compound 4-(2,2-dimethoxyethoxy)phthalic acid (2.2 g, 8.14 mmol, 91% yield) was obtained as a yellow oil.

### Step 3



To a solution of 4-(2,2-dimethoxyethoxy)phthalic acid (2.2 g, 8.14 mmol, 1 eq) in pyridine (10 mL) was added 3-aminopiperidine-2,6-dione (2.01 g, 12.21 mmol, 1.5 eq, hydrochloride). The mixture was stirred at 100 °C for 12 hours. The reaction mixture was concentrated under reduced pressure to remove pyridine (10 mL). The residue was diluted with water 200 mL and extracted with ethyl acetate (50 mL X 3). The combined organic layers were washed with brines (50 mL X 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Petroleum ether/Ethyl acetate=10:1 to 3:1). Compound 5-(2,2-dimethoxyethoxy)-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (1.6 g, 4.20 mmol, 51% yield, 95% purity) was obtained as a yellow oil.

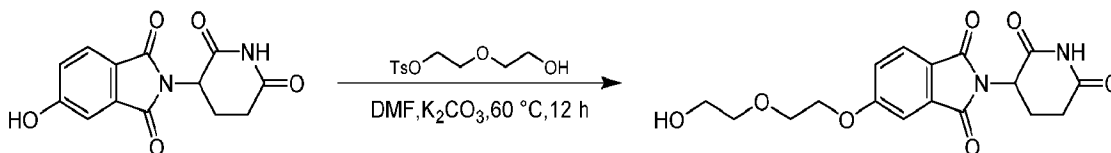
### Step 4



To a solution of 5-(2,2-dimethoxyethoxy)-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (192 mg, 0.53 mmol, 1 eq) in tetrahydrofuran (10 mL) was added sulfuric acid (2 M, 10.6 mL, 40 eq) and The mixture was stirred at 70 °C for 1 hour. The reaction mixture was quenched by addition sodium bicarbonate 5 mL at 20 °C, and then diluted with water 50 mL and extracted with ethyl acetate (20 mL X 3). The combined organic layers were washed with brines (20 mL X 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used into the next step without further purification. Compound 2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl] oxyacetaldehyde (160 mg, 0.50 mmol, 95% yield) was obtained as a white solid.

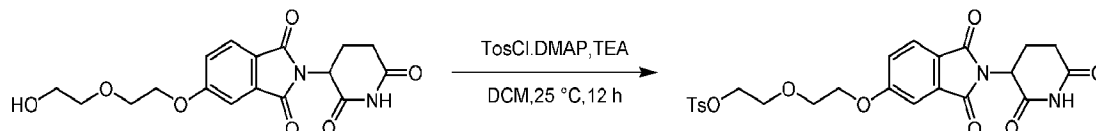
**[00210] Exemplary Synthesis of Intermediate 3, 2-[2-[2-(2,6-dioxo-3-piperidyl)- 1,3-dioxo-isoindolin-5-yl]oxyethoxy]ethyl 4-methylbenzenesulfonate**

**Step 1**



To a solution of 2-(2,6-dioxo-3-piperidyl)-5-hydroxy-isoindoline-1,3-dione (300 mg, 1.09 mmol, 1 *eq*) and 2-(2-hydroxyethoxy)ethyl 4-methylbenzenesulfonate (341 mg, 1.31 mmol, 1.2 *eq*) in N,N-dimethylformamide (4 mL) was added potassium carbonate (302 mg, 2.19 mmol, 2 *eq*). The mixture was stirred at 60 °C for 12 hours. LCMS showed the reaction was completed. The mixture was diluted with water (10 mL) and extracted with dichloromethane (10 mL x 3). The combined organic layer was washed with brine (20 mL x 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by column chromatography (dichloromethane: methanol=1:0 to 50:1) to give 2-(2,6-dioxo-3-piperidyl)-5-[2-(2-hydroxyethoxy)ethoxy]isoindoline-1,3-dione (400 mg) as a yellow oil.

**Step 2**



To a solution of 2-(2,6-dioxo-3-piperidyl)-5-[2-(2-hydroxyethoxy)ethoxy]isoindoline-1,3-dione (400 mg, 1.10 mmol, 1 *eq*) in dichloromethane (5 mL) was added paratoluensulfonyl chloride (315 mg, 1.66 mmol, 1.5 *eq*), 4-dimethylaminopyridine (13 mg, 0.11 mmol, 0.1 *eq*) and triethylamine (335 mg, 3.31 mmol, 3 *eq*). The mixture was stirred at 25 °C for 12 hours. LCMS showed the reaction was completed. The mixture was diluted with water (10 mL) and extracted with dichloromethane (10 mL x 3). The combined organic layer was washed with brine (20 mL x 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by preparative reverse phase thin layer chromatography (dichloromethane: methanol=20:1) to give 2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]oxyethoxy]ethyl 4-methylbenzenesulfonate (150 mg, 0.29 mmol, 26% yield) as a colorless oil.

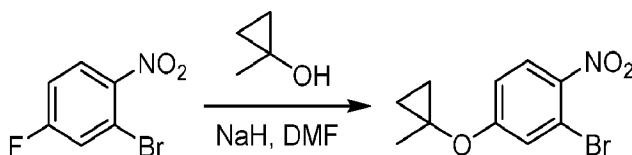
**[00211]** Related intermediates 2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]oxyethoxy]ethoxy]ethyl 4-methylbenzenesulfonate, 2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-



dioxo- isoindolin-5-yl]oxyethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate, and 2-[2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate were prepared in a manner analogous with 2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]oxyethoxy]ethyl 4-methylbenzenesulfonate.

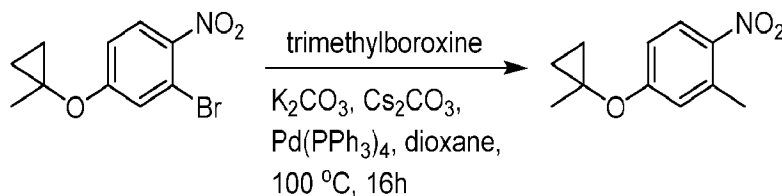
## [00212] Exemplary Synthesis of Exemplary Compound 1

### Step 1



To a solution of 2-bromo-4-fluoro-1-nitro-benzene (16.78 g, 76.28 mmol, 1.1 *eq*) and 1-methylcyclopropanol (5 g, 69.34 mmol, 1 *eq*) in DMF (160 mL) was added NaH (4.16 g, 104.01 mmol, 60% in mineral oil, 1.5 *eq*) in one portion at 0°C under N<sub>2</sub>. Then the mixture was heated to 20°C and stirred for 4 hours. TLC showed there were new spots. The residue was poured into water (200 mL) and stirred for 10 min. The aqueous phase was extracted with ethyl acetate (3 x 300 mL). The combined organic phase was washed with brine (2 x 200 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (100-200 mesh silica gel, 0-2% of Ethyl acetate in Petroleum ether) to afford 2-bromo-4-(1-methylcyclopropoxy)-1-nitro-benzene (14.3 g, 52.56 mmol, 75.79% yield) as a yellow oil.

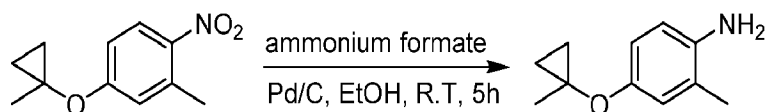
### Step 2



To a mixture of 2-bromo-4-(1-methylcyclopropoxy)-1-nitro-benzene (14.3 g, 52.56 mmol, 1 *eq*), K<sub>2</sub>CO<sub>3</sub> (14.53 g, 105.11 mmol, 2 *eq*) and Cs<sub>2</sub>CO<sub>3</sub> (17.12 g, 52.56 mmol, 1 *eq*) in 1,4-dioxane (100 mL) was added 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (32.99 g, 131.39 mmol, 36.73 mL, 50% purity in EtOAc, 2.5 *eq*) and Pd(PPh<sub>3</sub>)<sub>4</sub> (6.07 g, 5.26 mmol, 0.1 *eq*)) at 20°C, then heated to 100°C and stirred for 16 hours to give yellow solution. TLC showed the reaction was completed. The reaction was cooled to 20°C and concentrated under vacuum. To this residue was

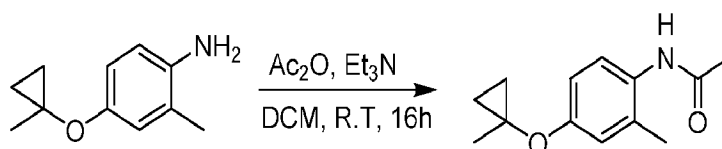
added PE: EtOAc (10:1, 100 mL), and the mixture was filtered through a pad of silica. The filter pad was washed with petroleum ether : EtOAc (10:1, 1000 mL) solvent. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 0-1% of Ethyl acetate in Petroleum ether) to afford 2-methyl-4-(1-methylcyclopropoxy)-1-nitro-benzene (11 g, crude) as a yellow oil.

### **Step 3**



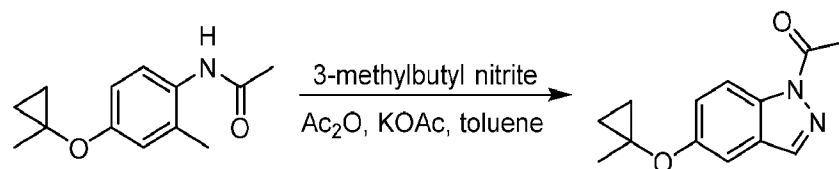
To a mixture of 2-methyl-4-(1-methylcyclopropoxy)-1-nitro-benzene (11 g, 53.08 mmol, 1 *eq*) in EtOH (100 mL) was added 10% of Pd/C (4 g, 5.31 mmol, 0.1 *eq*) and ammonium formate (40.17 g, 636.99 mmol, 12 *eq*) in one portion at 20°C under N<sub>2</sub>. The mixture was stirred at 20°C for 2 h to give a black mixture. TLC showed the reaction was completed. The mixture was filtered through a pad of silica gel, washed with EtOAc (3 x 200 mL) and concentrated in vacuum. The residue was purified by silica gel chromatography (0-10% of Ethyl acetate in Petroleum ether) to afford 2-methyl-4-(1-methylcyclopropoxy) aniline (9.8 g, crude) as a red oil.

### **Step 4**



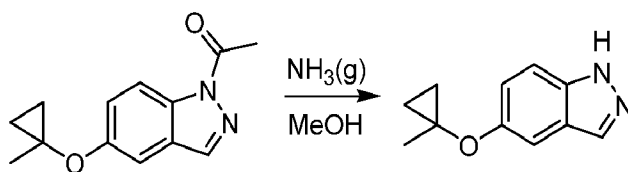
To a mixture of 2-methyl-4-(1-methylcyclopropoxy) aniline (9.8 g, 55.29 mmol, 1 *eq*) and Et<sub>3</sub>N (13.99 g, 138.23 mmol, 19.24 mL, 2.5 *eq*) in DCM (100 mL) was added Ac<sub>2</sub>O (11.29 g, 110.58 mmol, 10.36 mL, 2 *eq*) in one portion at 0°C under N<sub>2</sub>. The mixture was stirred at 0°C for 30 min, then heated to 20°C and stirred for 16 hours. TLC showed the reaction was completed. The reaction was quenched with a saturated solution of aqueous NaHCO<sub>3</sub> (30 mL) to adjusted pH=7-8 and extracted with DCM (3x50 mL). The combined organic phase was washed with brine (3x50 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (20-40% Ethyl acetate in Petroleum ether) to afford N-[2-methyl-4-(1-methylcyclopropoxy) phenyl] acetamide (9.3 g, 42.41 mmol, 76.71% yield) as a yellow oil.

### **Step 5**



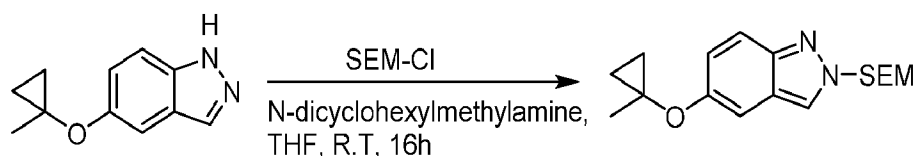
To a solution of N-[2-methyl-4-(1-methylcyclopropoxy)phenyl]acetamide (9.3 g, 42.41 mmol, 1 *eq*) in toluene (100 mL) was added KOAc (6.24 g, 63.62 mmol, 1.5 *eq*) and Ac<sub>2</sub>O (19.92 g, 195.09 mmol, 18.27 mL, 4.6 *eq*) at 20°C, the solution was heated to 80°C, then 3-methylbutyl nitrite (19.87 g, 169.65 mmol, 22.84 mL, 4 *eq*) was added dropwise. After addition, the mixture was stirred at 80°C for 2h. TLC showed the reaction was completed. The reaction was then filtered, the wet cake was washed with EtOAc (70mL), and the filtrate was concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 0-10% Ethyl acetate in Petroleum ether) to afford 1-[5-(1-methylcyclopropoxy) indazol-1-yl] ethanone (8 g, crude) as a yellow solid.

#### Step 6



To a mixture of 1-[5-(1-methylcyclopropoxy)indazol-1-yl]ethanone (8 g, 34.74 mmol, 1 *eq*) in MeOH (80 mL) was added NH<sub>3</sub>(g)/MeOH (7 M, 24.82 mL, 5 *eq*) in one portion at 20°C. The mixture was stirred at 20°C for 2 hours to give a yellow solution. TLC showed the reaction was completed. The solution was concentrated in vacuum to afford 5-(1-methylcyclopropoxy)-1H-indazole (7.8 g, crude) as a yellow solid.

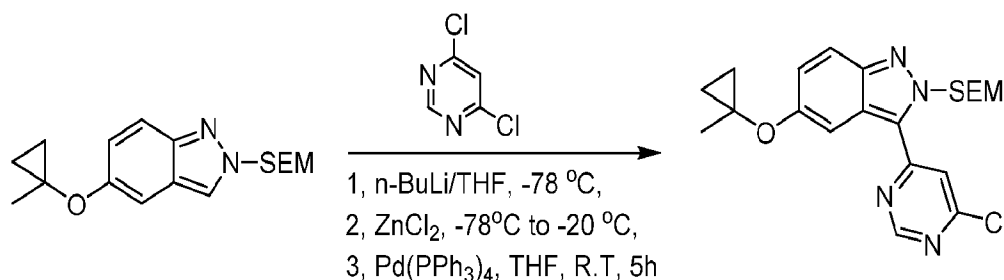
#### Step 7



To a mixture of 5-(1-methylcyclopropoxy)-1H-indazole (7.8 g, 41.44 mmol, 1 *eq*) in THF (80 mL) was added N-dicyclohexylmethylamine (10.52 g, 53.87 mmol, 1.3 *eq*) and SEM-Cl (8.29 g, 49.73 mmol, 8.80 mL, 1.2 *eq*) in one portion at 20°C. The mixture was stirred at 20°C for 16 hours to give an orange solution. TLC showed the reaction was completed. The residue was poured into water (60 mL). The aqueous phase was extracted with ethyl acetate (3x50 mL). The

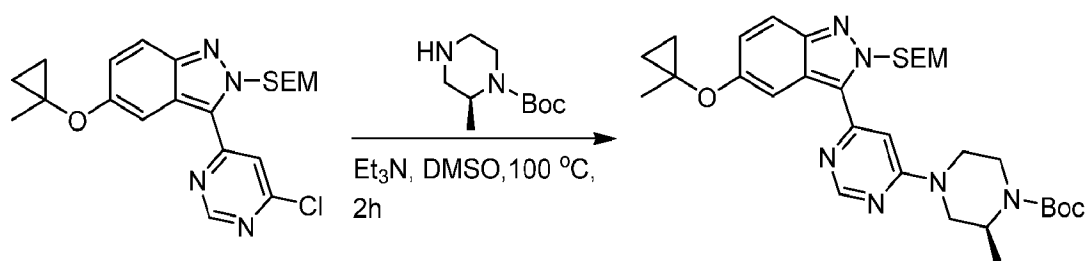
combined organic phase was washed with brine (2x50 mL), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 0-10% of ethyl acetate in Petroleum ether) to afford trimethyl-[2-[[5-(1-methylcyclopropoxy) indazol-2-yl] methoxy] ethyl] silane (5.4 g, 16.96 mmol, 40.92% yield) as a yellow oil.

### Step 8



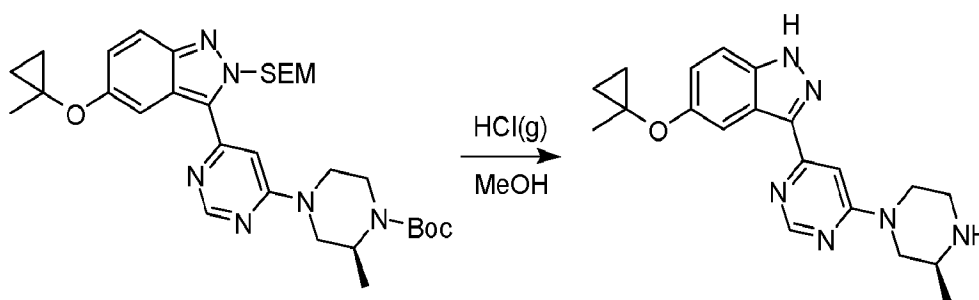
To a mixture of trimethyl-[2-[[5-(1-methylcyclopropoxy)indazol-2-yl]methoxy]ethyl]silane (4.36 g, 13.70 mmol, 5.32e-1 *eq*) in THF (6mL) was dropwise added n-BuLi (2.5 M, 13.40 mL, 1.3 *eq*) dropwise at -70°C under  $\text{N}_2$ . The mixture was then stirred at -20°C for 1h, and a solution of  $\text{ZnCl}_2$  (0.7 M, 55.20 mL, 1.5 *eq*) was dropwise added at -70°C. The mixture was stirred for 1 h at -40°C. A mixture of 4, 6-dichloropyrimidine (4.22 g, 28.34 mmol, 1.1 *eq*) and  $\text{Pd}(\text{PPh}_3)_4$  (1.49 g, 1.29 mmol, 0.05 *eq*) in THF (4mL) was stirred at 20°C for 1h and was added to that solution. The cold bath was removed, and the mixture was stirred at 20°C for 16 h to give a yellow solution. TLC showed there was starting material remained and at the same time some new spots were formed. The residue was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with brine (2 x 20mL), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 0-10% of Ethyl acetate in Petroleum ether) to afford 2-[[3-(6-chloropyrimidin-4-yl)-5-(1-methylcyclopropoxy) indazol-2-yl] methoxy] ethyl-trimethyl-silane (2.9 g, crude) as a yellow oil.

### Step 9



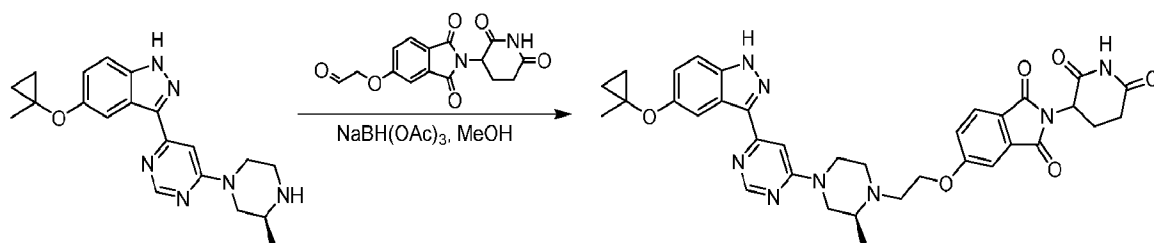
To a mixture of 2-[[3-(6-chloropyrimidin-4-yl)-5-(1-methylcyclopropoxy) indazol-2-yl]methoxy]ethyl-trimethyl-silane (500 mg, 1.16 mmol, 1 *eq*) and tert-butyl (2S)-2-methylpiperazine-1-carboxylate (697.02 mg, 3.48 mmol, 3 *eq*) in DMSO (5 mL) was added Et<sub>3</sub>N (704.34 mg, 6.96 mmol, 968.82  $\mu$ L, 6 *eq*) in one portion and then the mixture was stirred at 100°C for 1h. TLC showed the reaction was completed. The mixture was cooled to 20°C. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (3 x 5 mL). The combined organic phase was washed with brine (2 x 5 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give tert-butyl (2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-2-(2-trimethylsilylethoxymethyl) indazol-3-yl] pyrimidin-4-yl] piperazine-1-carboxylate (802 mg, crude) as a yellow oil.

### Step 10



To a mixture of tert-butyl (2S)-2-methyl-4-[6-[5-[(1-methylcyclopropyl)methyl]-2-(2-trimethylsilylethoxymethyl)indazol-3-yl]pyrimidin-4-yl]piperazine-1-carboxylate (802 mg, 1.35 mmol, 1 *eq*) in DCM (5 mL) was added TFA (771.25 mg, 6.76 mmol, 500.81  $\mu$ L, 5 *eq*) in one portion at 25°C. The mixture was stirred at 25°C for 16 hours. The HCl (4 M, 338.20  $\mu$ L, 1 *eq*) in MeOH (5 mL) was added at 25°C, then heated to 60°C and stirred for 0.5 hours. LCMS showed the reaction was completed. The mixture was cooled to 20°C. The residue was poured into NaHCO<sub>3</sub> (5 mL) to adjust pH=7-8. The aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic phase was washed with brine (2 x 10 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (0-40 % of Ethyl acetate in MeOH) to give 5-(1-methylcyclopropoxy)-3-[6-[(3S)-3-methylpiperazin-1-yl]pyrimidin-4-yl]-1H-indazole (450 mg, 1.18 mmol, 87.41% yield, 95.77% purity) as a yellow solid.

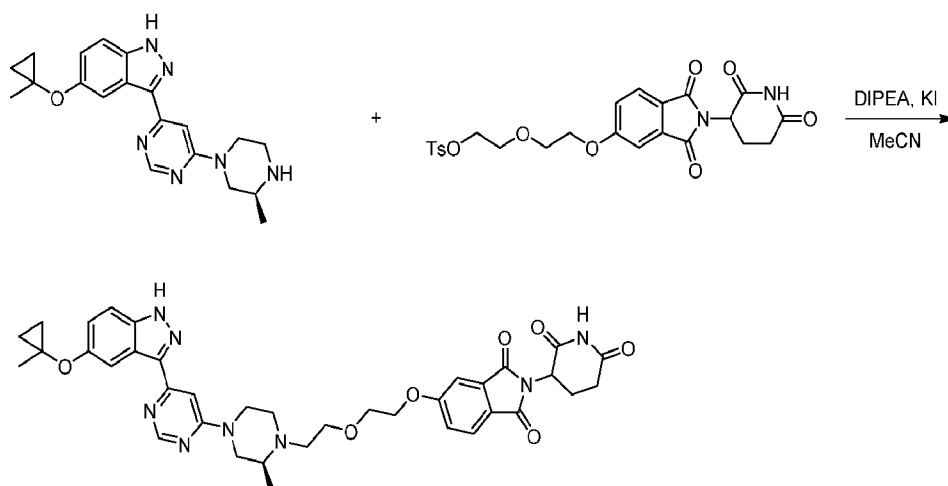
### Step 11



A mixture of 5-(1-methylcyclopropoxy)-3-[6-[(3S)-3-methylpiperazin-1-yl]pyrimidin-4-yl]-1H-indazole (104.76 mg, 287.45  $\mu\text{mol}$ , 1 *eq*), 2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]oxyacetaldehyde (100 mg, 316.19  $\mu\text{mol}$ , 1.1 *eq*), NaOAc (70.74 mg, 862.34  $\mu\text{mol}$ , 3 *eq*),  $\text{CH}_3\text{COOH}$  (17.26 mg, 287.45  $\mu\text{mol}$ , 16.44  $\mu\text{L}$ , 1 *eq*) and  $\text{NaBH}_3\text{CN}$  (36.13 mg, 574.89  $\mu\text{mol}$ , 2 *eq*) in DMF (2 mL) was stirred at 25°C for 1 h. LCMS showed the reaction was completed. The mixture was cooled to 20 °C. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (3 x 5 mL). The combined organic phase was washed with brine (2 x 5 mL), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 0-10% Ethyl acetate in MeOH). The mixture was further purification by prep-HPLC (column: YMC-Actus Triart C18 150\*30mm\*5 $\mu\text{m}$ ; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 48%-68%, 10 min) to give 2-(2,6-dioxo-3-piperidyl)-5-[2-[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-2H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethoxy]isoindoline-1,3-dione (12.08 mg, 18.17  $\mu\text{mol}$ , 6.32% yield, 100% purity) as a white solid.

## [00213] Exemplary Synthesis of Exemplary Compound 2

### Step 1

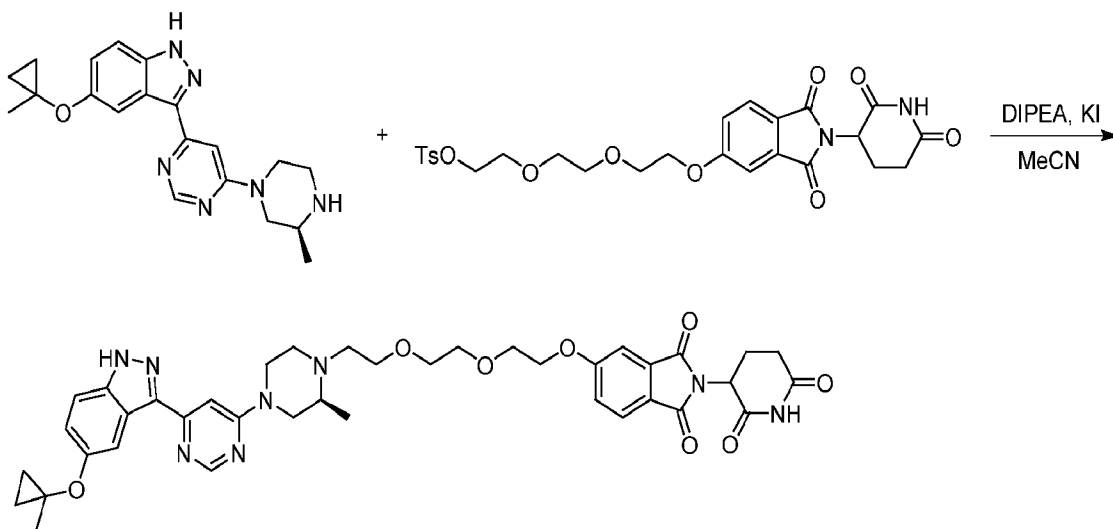


To a mixture of 5-(1-methylcyclopropoxy)-3-[6-[(3S)-3-methylpiperazin-1-yl] pyrimidin-4-yl]-1H-indazole (70 mg, 192.07  $\mu\text{mol}$ , 1 *eq*), KI (63.77 mg, 384.15  $\mu\text{mol}$ , 2 *eq*) and 2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]oxyethoxy]ethyl 4-methylbenzenesulfonate (99.21 mg, 192.07  $\mu\text{mol}$ , 1 *eq*) in ACN (2 mL) was added DIPEA (124.12 mg, 960.37  $\mu\text{mol}$ , 167.28  $\mu\text{L}$ , 5 *eq*) in one portion. The mixture was stirred at 100 °C for 16 h. The residue was poured into water (2 mL). The aqueous phase was extracted with ethyl acetate (3 x 2 mL). The combined organic phase was washed with brine (2 x 2 mL), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 0-10% Ethyl acetate in MeOH). The crude product was purified by prep-HPLC (column: YMC-Actus Triart C18 150\*30mm\*5 $\mu\text{m}$ ; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 45%-65%, 10 min) to give 2-(2,6-dioxo-3-piperidyl)-5-[2-[2-[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethoxy]ethoxy]isoindoline-1,3-dione (11.63 mg, 16.41  $\mu\text{mol}$ , 8.54% yield, 100% purity) as a white solid.

Exemplary Compounds 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, and 19 were prepared in a manner analogous to Exemplary Compound 2.

### [00214] Exemplary Synthesis of Exemplary Compound 3

#### Step 1

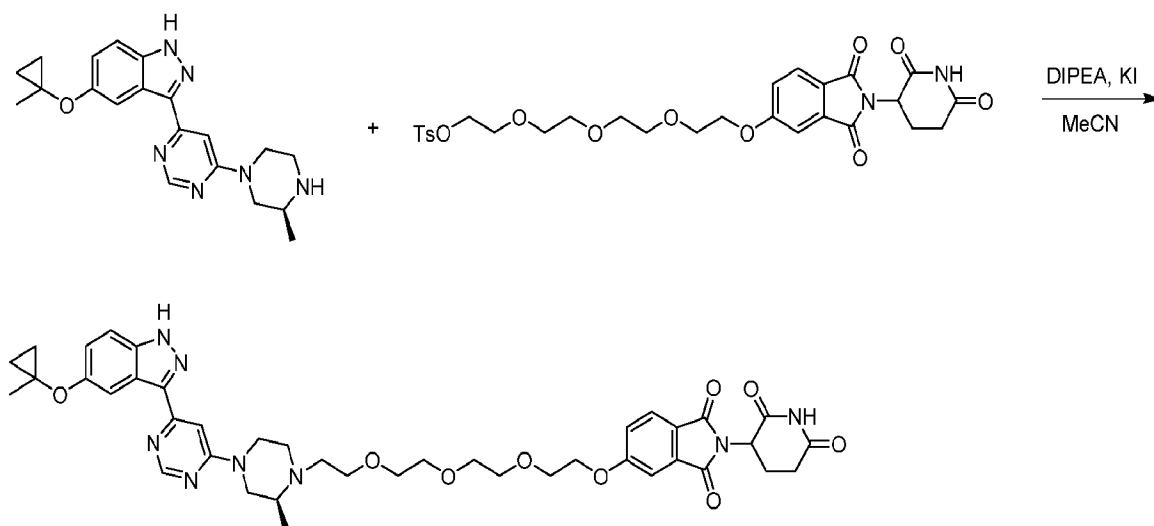


To a mixture of 5-(1-methylcyclopropoxy)-3-[6-[(3S)-3-methylpiperazin-1-yl] pyrimidin-4-yl]-1H-indazole (72.24 mg, 198.21  $\mu\text{mol}$ , 1 *eq*), KI (65.81 mg, 396.42  $\mu\text{mol}$ , 2 *eq*) and 2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]oxyethoxy]ethoxy]ethyl 4-methylbenzenesulfonate (100 mg, 178.39  $\mu\text{mol}$ , 0.9 *eq*) in ACN (2 mL) was added DIPEA

(128.08 mg, 991.05  $\mu\text{mol}$ , 172.62  $\mu\text{L}$ , 5 *eq*) in one portion. The mixture was stirred at 100°C for 16 h. The residue was poured into water (2 mL) and the aqueous phase was extracted with ethyl acetate (3 x 2 mL). The combined organic phase was washed with brine (2x2mL), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 0-10% Ethyl acetate in MeOH). The crude product was purified by prep-HPLC (column: YMC-Actus Triart C18 150\*30mm\*5 $\mu\text{m}$ ; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 45%-65%, 10 min) to give 2-(2,6-dioxo-3-piperidyl)-5-[2-[2-[2-[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy) -1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethoxy]ethoxy]ethoxy]isoindoline-1,3-dione (14.84 mg, 19.71  $\mu\text{mol}$ , 9.95% yield, 100% purity) as a white solid.

#### [00215] Exemplary Synthesis of Exemplary Compound 4

##### Step 1



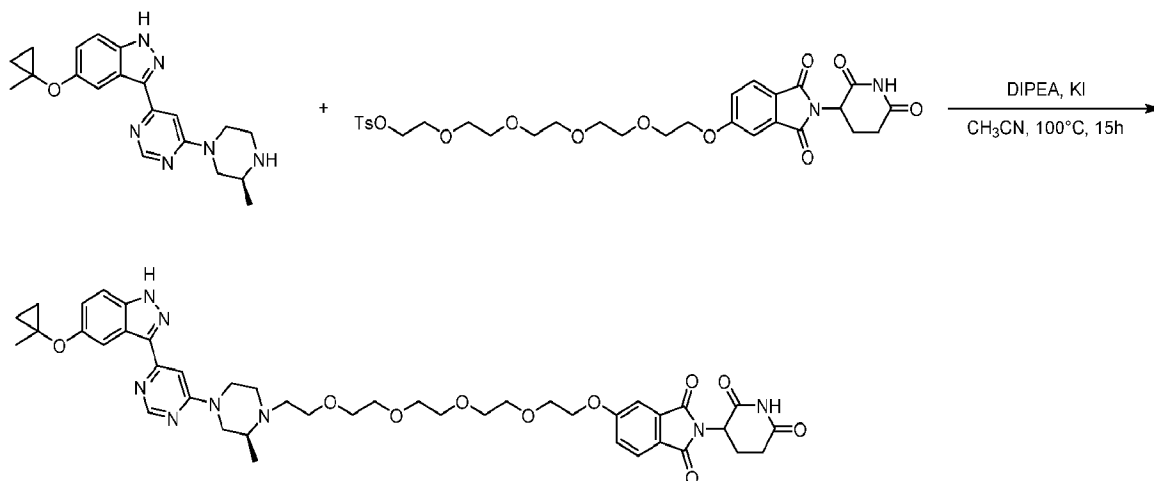
To a mixture of 5-(1-methylcyclopropoxy)-3-[6-[(3S)-3-methylpiperazin-1-yl]pyrimidin-4-yl]-1H-indazole (66.97 mg, 183.77  $\mu\text{mol}$ , 1 *eq*), KI (61.01 mg, 367.54  $\mu\text{mol}$ , 2 *eq*) and 2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]oxyethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate (100 mg, 165.39  $\mu\text{mol}$ , 0.9 *eq*) in MeCN (2 mL) was added DIPEA (118.75 mg, 918.84  $\mu\text{mol}$ , 160.04  $\mu\text{L}$ , 5 *eq*) in one portion. The mixture was stirred at 100°C for 16 h. The residue was poured into water (2 mL). The aqueous phase was extracted with ethyl acetate (3 x 2 mL). The combined organic phase was washed with brine (2 x 2mL), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 0-10 % Ethyl acetate in MeOH). The crude product was purified by prep-HPLC (column: YMC-Actus Triart C18 150\*30mm\*5 $\mu\text{m}$ ; mobile phase:



[water (0.05% ammonia hydroxide v/v)-ACN]; B%: 45%-65%, 10 min) to give 2-(2, 6-dioxo-3-piperidyl)-5-[2-[2-[2-[2-[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethoxy]ethoxy]ethoxy]ethoxy]isoindoline-1,3-dione (5.1 mg, 6.23 umol, 3.39% yield, 97.275% purity) as a white solid.

## [00216] Exemplary Synthesis of Exemplary Compound 5

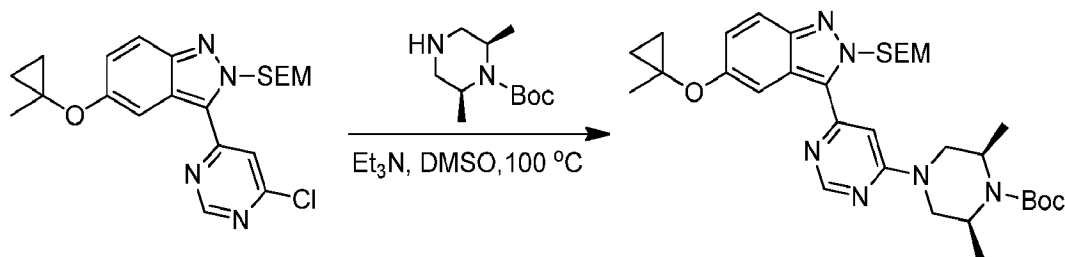
### Step 1



The mixture of 5-(1-methylcyclopropoxy)-3-[6-[(3S)-3-methylpiperazin-1-yl]pyrimidin-4-yl]-1H-indazole (55.00 mg, 150.92 umol, 0.979 *eq*), 2-[2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate (100 mg, 154.16 umol, 1 *eq*), KI (51.18 mg, 308.32 umol, 2 *eq*) and DIPEA (99.62 mg, 770.80 umol, 134.26 uL, 5.00 *eq*) in CH<sub>3</sub>CN (2 mL) was stirred at 100°C for 15 hours. The mixture was diluted with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was further purified by prep.HPLC (column: YMC-Actus Triart C18 150\*30mm\*5um; mobile phase: [water (0.225% FA)-ACN]; B%: 23%-63%, 11min). Then the collected fraction was concentrated to remove most of acetonitrile and lyophilized to give 2-(2,6-dioxo-3-piperidyl)-5-[2-[2-[2-[2-[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethoxy]ethoxy]ethoxy]ethoxy]isoindoline-1,3-dione (10.1 mg, 11.41 umol, 7.40% yield, 95% purity) as a red solid.

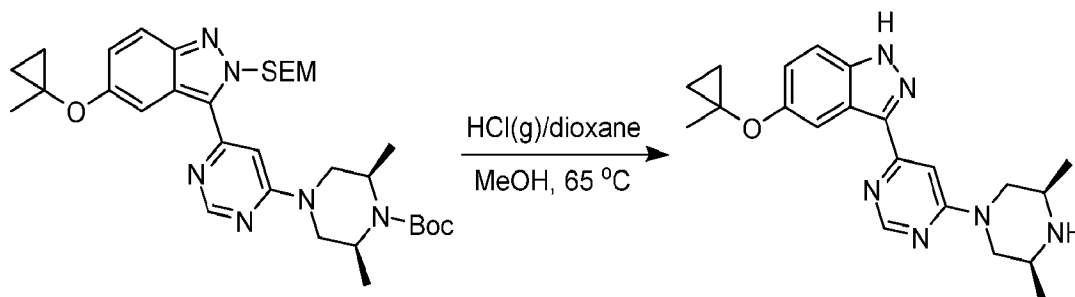
## [00217] Exemplary Synthesis of Exemplary Compound 6

### Step 1



To a mixture of 2-[[3-(6-chloropyrimidin-4-yl)-5-(1-methylcyclopropoxy)indazol-2-yl]methoxy]ethyl-trimethyl-silane (500 mg, 1.16 mmol, 1 *eq*), tert-butyl (2S,6R)-2,6-dimethylpiperazine-1-carboxylate (248.61 mg, 1.16 mmol, 1 *eq*) in DMSO (5 mL) was added Et<sub>3</sub>N (352.17 mg, 3.48 mmol, 484.41  $\mu$ L, 3 *eq*) in one portion and then the solution was stirred at 100°C for 1h. LCMS (EB16-35-P1A1) showed the starting material was consumed completely. The mixture was cooled to 20°C. The residue was poured into water (5 mL). The mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic phase was washed with brine (2 x 5 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=10/1 to 5/1) to give tert-butyl (2S, 6R)-2,6-dimethyl-4-[6-[5-(1-methylcyclopropoxy)-2-(2-trimethylsilylethoxymethyl)indazol-3-yl]pyrimidin-4-yl]piperazine-1-carboxylate (811 mg, crude) as a yellow oil.

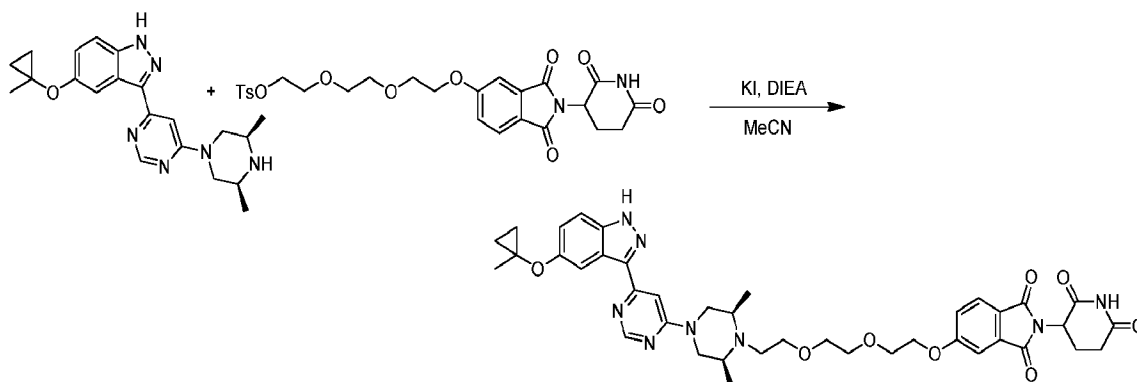
## Step 2



To a mixture of tert-butyl (2S,6R)-2,6-dimethyl-4-[6-[5-(1-methylcyclopropoxy)-2-(2-trimethylsilylethoxymethyl)indazol-3-yl]pyrimidin-4-yl]piperazine-1-carboxylate (811 mg, 1.33 mmol, 1 *eq*) in MeOH (5 mL) was added HCl(g)/dioxane (4 M, 1.67 mL, 5 *eq*) in one portion at 20°C. The mixture was stirred at 65°C for 0.5 h. LCMS showed the reaction was completed. The mixture was cooled to 20°C. The residue was poured into NaHCO<sub>3</sub> (10 mL) to adjust pH=7-8. The mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic phase was washed with brine (2 x 10 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 0-25 %

of Ethyl acetate in MeOH) to give 3-[6-[(3S,5R)-3,5-dimethylpiperazin-1-yl]pyrimidin-4-yl]-5-(1-methylcyclopropoxy)-1H-indazole (400 mg, 978.01  $\mu\text{mol}$ , 73.42% yield, 92.537% purity) as a yellow solid.

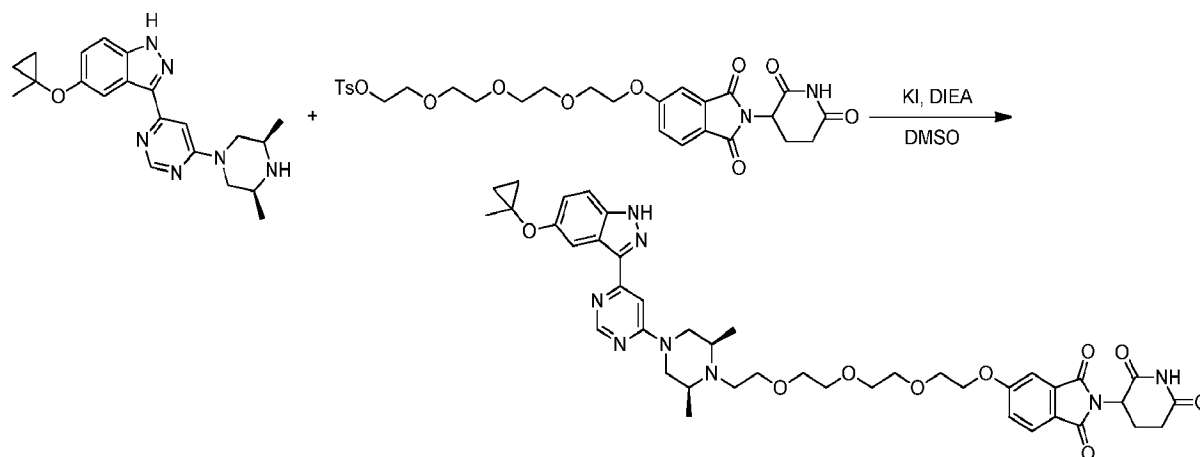
### Step 3



To a solution of 3-[6-[(3S,5R)-3,5-dimethylpiperazin-1-yl]pyrimidin-4-yl]-5-(1-methylcyclopropoxy)-1H-indazole (70 mg, 184.96  $\mu\text{mol}$ , 1.1 *eq*) and 2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]oxyethoxy]ethoxy]ethyl 4-methylbenzenesulfonate (94.26 mg, 168.15  $\mu\text{mol}$ , 1 *eq*) in MeCN (5 mL) was added DIPEA (108.66 mg, 840.73  $\mu\text{mol}$ , 146.44  $\mu\text{L}$ , 5 *eq*) and KI (55.82 mg, 336.29  $\mu\text{mol}$ , 2 *eq*). The reaction mixture was stirred at 100°C for 24 h. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (3x 5 mL). The combined organic phase was washed with brine (2 x 5 mL), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 10-25% of Ethyl acetate in Petroleum ether). The crude product was purified by reversed-phase HPLC (column: Agela DuraShell C18 250\*25mm\*10 $\mu\text{m}$ ; mobile phase: water(0.04%  $\text{NH}_3\text{H}_2\text{O}$ +10mM  $\text{NH}_4\text{HCO}_3$ )-ACN; B%: 45%-75%, Gradient Time(min):8min; FlowRate(ml/min):25)) to give 5-[2-[2-[2-[(2S,6R)-2,6-dimethyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethoxy]ethoxy]ethoxy]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (10.09 mg, 12.98  $\mu\text{mol}$ , 7.72% yield, 98.681% purity) as a yellow solid.

### [00218] Exemplary Synthesis of Exemplary Compound 7

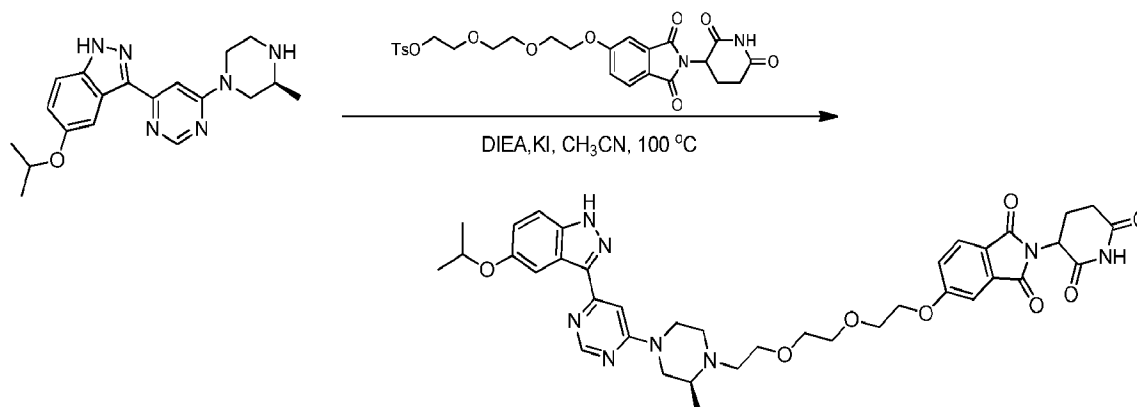
#### Step 1



To a solution of 3-[6-[(3S,5R)-3,5-dimethylpiperazin-1-yl]pyrimidin-4-yl]-5-(1-methylcyclopropoxy)-1H-indazole (80 mg, 211.38  $\mu\text{mol}$ , 1.1 *eq*) and 2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isindolin-5-yl]oxyethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate (116.19 mg, 192.16  $\mu\text{mol}$ , 1 *eq*) in MeCN (5 mL) was added DIPEA (124.18 mg, 960.82  $\mu\text{mol}$ , 167.36  $\mu\text{L}$ , 5 *eq*) and KI (63.80 mg, 384.33  $\mu\text{mol}$ , 2 *eq*). The reaction mixture was stirred at 100°C for 24 h. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (3 x 5 mL). The combined organic phase was washed with brine (2 x 5 mL), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 10-25% of Ethyl acetate in Petroleum ether). The crude product was purified by reversed-phase HPLC (column: Agela DuraShell C18 250\*25mm\*10 $\mu\text{m}$ ; mobile phase: water(0.04%  $\text{NH}_3$  in  $\text{H}_2\text{O}$ +10mM  $\text{NH}_4\text{HCO}_3$ )-ACN; B%: 45%-75%, Gradient Time(min):8min; FlowRate(ml/min):25)) to give 5-[2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isindolin-5-yl]oxyethoxy]ethoxy]ethoxy]-6-[(3S,5R)-3,5-dimethylpiperazin-1-yl]pyrimidin-4-yl]-1H-indazole (5.9 mg, 6.98  $\mu\text{mol}$ , 3.63% yield, 95.895% purity) as a yellow solid.

## [00219] Exemplary Synthesis of Exemplary Compound 8

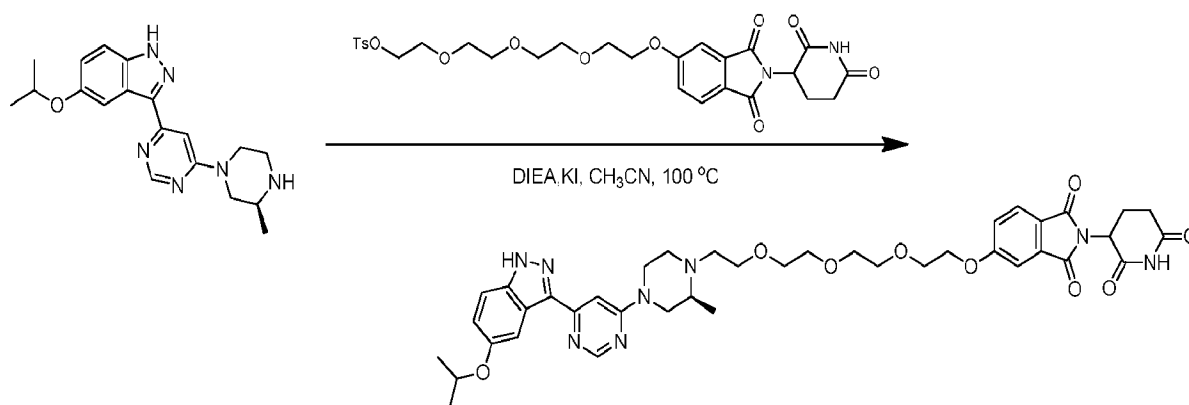
### Step 1



To a mixture of 5-isopropoxy-3-[6-[(3S)-3-methylpiperazin-1-yl]pyrimidin-4-yl]-1H-indazole (160 mg, 453.99  $\mu\text{mol}$ , 1 *eq*) in MeCN (5 mL) was added 2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isindolin-5-yl]oxyethoxy]ethoxymethyl 4-methylbenzenesulfonate (347.37 mg, 635.58  $\mu\text{mol}$ , 1.4 *eq*), DIEA (293.37 mg, 2.27 mmol, 395.38  $\mu\text{L}$ , 5 *eq*) and KI (602.90 mg, 3.63 mmol, 8 *eq*). The mixture was stirred at 95°C for 12 hours to give a brown mixture. The mixture was cooled to room temperature and 20 mL water was added into reaction mixture. The resulting mixture was extracted with EtOAc (10 mL x 3). The combined extracts were washed with brine (10 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and the filtrate was concentrated under reduced pressure to give a residue (300 mg). The residue was purified by prep-HPLC (FA) to give 2-(2,6-dioxo-3-piperidyl)-5-[2-[2-[2-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethoxy]ethoxy]ethoxy]isoindoline-1,3-dione (104.3 mg, 137.94  $\mu\text{mol}$ , 30.38% yield, 97.97% purity) as a pink solid.

## [00220] Exemplary Synthesis of Exemplary Compound 9

### Step 1

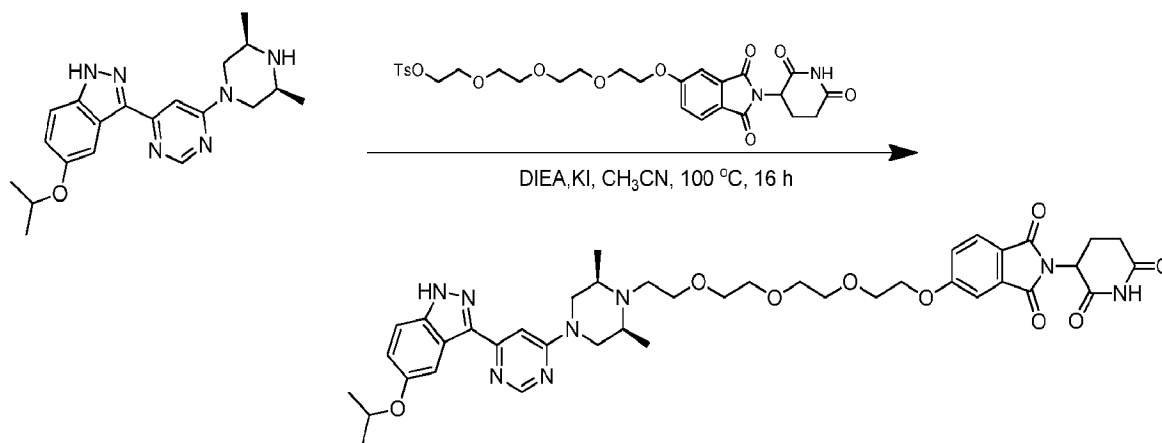


To a mixture of 5-isopropoxy-3-[6-[(3S)-3-methylpiperazin-1-yl]pyrimidin-4-yl]-1H-indazole (160 mg, 453.99  $\mu\text{mol}$ , 1 *eq*) in MeCN (8 mL) was added 2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isindolin-5-yl]oxyethoxy]ethoxy]ethoxymethyl 4-methylbenzenesulfonate (384.29 mg,

635.58  $\mu\text{mol}$ , 1.4 *eq*), DIEA (293.37 mg, 2.27 mmol, 395.38  $\mu\text{L}$ , 5 *eq*) and KI (602.90 mg, 3.63 mmol, 8 *eq*). The mixture was stirred at 95 °C for 12 hours to give a brown mixture. The mixture was cooled to room temperature and water (20 mL) was added into reaction mixture. The resulting mixture was extracted with EtOAc (10 mL x 3). The combined extracts were washed with brine (10 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and the filtrate was concentrated under reduced pressure to give a residue (320 mg). The residue was purified by prep-HPLC (FA) to give 2-(2,6-dioxo-3-piperidyl)-5-[2-[2-[2-[2-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethoxy]ethoxy]ethoxy]ethoxy]isoindoline-1,3-dione (44.9 mg, 56.05  $\mu\text{mol}$ , 12.35% yield, 97.98% purity) as pink solid.

### [00221] Exemplary Synthesis of Exemplary Compound 10

#### Step 1

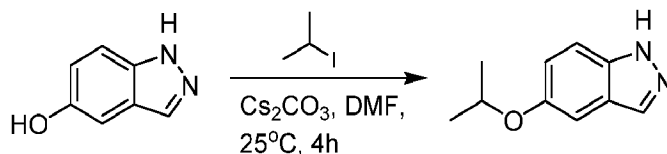


To a mixture of 3-[6-[(3R,5S)-3,5-dimethylpiperazin-1-yl]pyrimidin-4-yl]-5-isopropoxy-1H-indazole (0.15 g, 409.32  $\mu\text{mol}$ , 1 *eq.*) and 2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxoisoindolin-5-yl]oxyethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate (296.98 mg, 491.19  $\mu\text{mol}$ , 1.2 *eq.*), DIEA (793.53 mg, 6.14 mmol, 1.07 mL, 15 *eq.*) in MeCN (8 mL) and DMSO (2 mL) was added KI (1.02 g, 6.14 mmol, 15 *eq*) in one portion at 25°C under  $\text{N}_2$ . The mixture was stirred at 100°C and stirred for 16 hours. The reaction mixture was concentrated, cooled with an ice bath, and sat  $\text{NH}_4\text{Cl}$  was added to adjust the pH to 6. Saturated brine was added thereto, followed by extraction with ethyl acetate (50 mL x 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by prep-TLC (silica gel, EA: MeOH = 10:1) to give 2-(2,6-dioxo-3-piperidyl)-5-[2-[2-[2-[2-[(2R,6S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2,6-dimethyl-piperazin-1-

yl]ethoxy]ethoxy]ethoxy]ethoxy]isoindoline-1,3-dione (8.5 mg, 10.19  $\mu$ mol, 2.49% yield, 95.81% purity) as a light yellow solid.

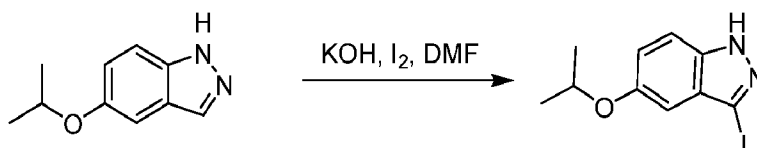
## [00222] Exemplary Synthesis of Exemplary Compound 11

### Step 1



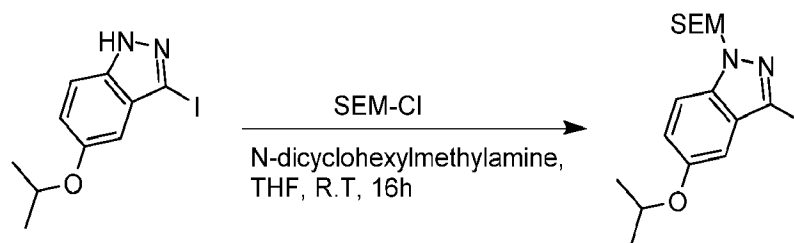
To a mixture of 1H-indazol-5-ol (5 g, 37.28 mmol, 1 eq) and  $\text{Cs}_2\text{CO}_3$  (18.22 g, 55.91 mmol, 1.5 eq) in DMF (50 mL) was added 2-iodopropane (8.24 g, 48.46 mmol, 4.85 mL, 1.3 eq) in one portion at 25°C. The mixture was stirred at 25 °C for 4 hours. TLC (petroleum ether: ethyl acetate= 3:1,  $R_f$ =0.58) showed the reaction completed. The mixture was poured into water (50 mL) and the aqueous phase was extracted with ethyl acetate (60 mL\*3). The combined organic phase was washed with brine (20 mL\*2), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=3/1) to afford 5-isopropoxy-1H-indazole (4.1 g, 23.27 mmol, 62.42% yield) as a light yellow solid.

### Step 2



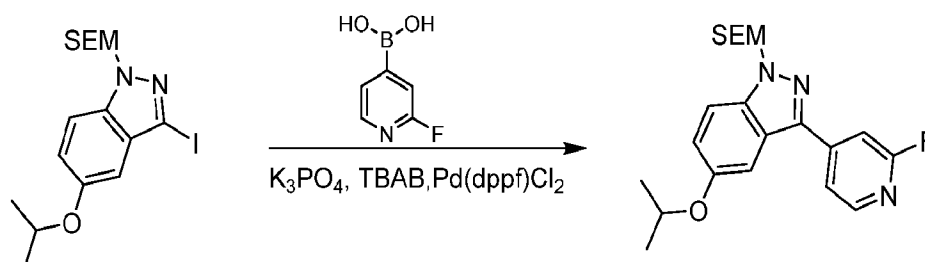
To a mixture of 5-isopropoxy-1H-indazole (4 g, 22.70 mmol, 1 eq) in MeCN (80 mL) was added  $\text{K}_2\text{CO}_3$  (3.14 g, 22.70 mmol, 1 eq) and  $\text{I}_2$  (5.76 g, 22.70 mmol, 4.57 mL, 1 eq) in one portion at 25°C under  $\text{N}_2$ . The mixture was stirred at 25 °C for 16 hours. TLC (Petroleum ether: Ethyl acetate=3:1) showed the reaction was completed. The mixture was diluted with brine (100 mL) and the aqueous phase was extracted with dichloromethane (100 mL\*3). The combined organic phase was dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=10/3) to afford 3-iodo-5-isopropoxy-1H-indazole (5.5 g, 18.21 mmol, 80.20% yield) as a light-yellow oil.

### Step 3



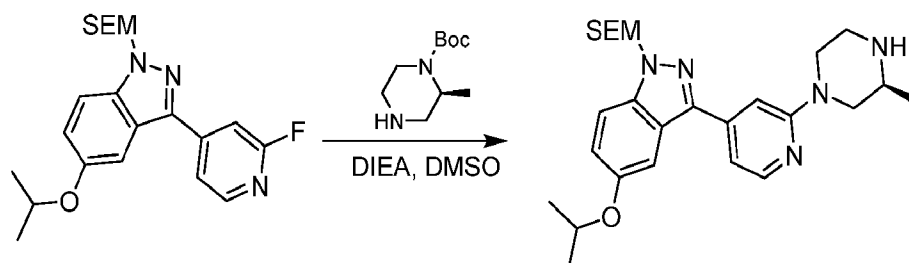
To a mixture of 3-iodo-5-isopropoxy-1H-indazole (5.5 g, 18.21 mmol, 1 eq) in THF (100 mL) was added N-cyclohexyl-N-methyl-cyclohexanamine (4.62 g, 23.67 mmol, 5.02 mL, 1.3 eq) and SEM-Cl (3.04 g, 18.21 mmol, 3.22 mL, 1 eq) in one portion at 25°C. The mixture was stirred at 25 °C for 16 hours to give orange solution. TLC (Petroleum ether: Ethyl acetate=20/1) showed the reaction was completed. The residue was poured into water (100 mL). The aqueous phase was extracted with ethyl acetate (3 x 80 mL). The combined organic phase was washed with brine (2 x 20 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=100/3) to afford 2-[(3-iodo-5-isopropoxy-indazol-1-yl)methoxy]ethyl-trimethyl-silane (7.4 g, 15.75 mmol, 86.47% yield, 92% purity) as a light yellow oil.

#### Step 4

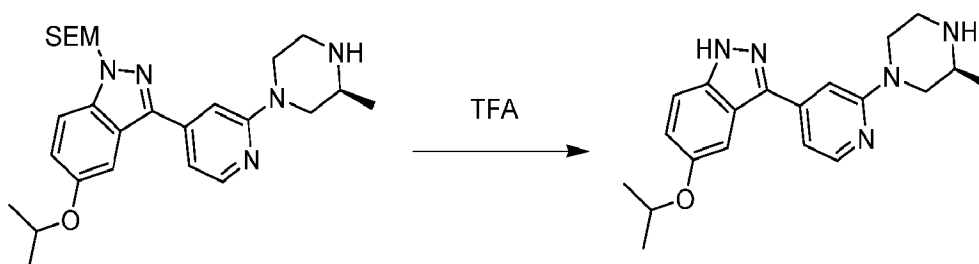


To a mixture of 2-[(3-iodo-5-isopropoxy-indazol-1-yl)methoxy]ethyl-trimethyl-silane (7.4 g, 17.11 mmol, 1 eq) and (2-fluoro-4-pyridyl)boronic acid (3.62 g, 25.67 mmol, 1.5 eq) in dioxane (100 mL) was added K<sub>3</sub>PO<sub>4</sub> (14.53 g, 68.46 mmol, 4 eq) and Pd(dppf)Cl<sub>2</sub> (2.50 g, 3.42 mmol, 0.2 eq) in one portion at 25°C under N<sub>2</sub>. The mixture was heated to 90 °C with stirring for 5 hours under N<sub>2</sub>. TLC (Petroleum ether: Ethyl acetate=20/1) showed the reaction was completed. The mixture was cooled to 25 °C and the residue was poured into water (80 mL). The aqueous phase was extracted with ethyl acetate (90mL\*2). The combined organic phase was washed with brine (30 mL\*2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=10/1) to give 2-[[3-(2-fluoro-4-pyridyl)-5-isopropoxy-indazol-1-yl]methoxy]ethyl-trimethyl-silane (5.96 g, 12.32 mmol, 71.98% yield, 83% purity) as a light yellow solid.



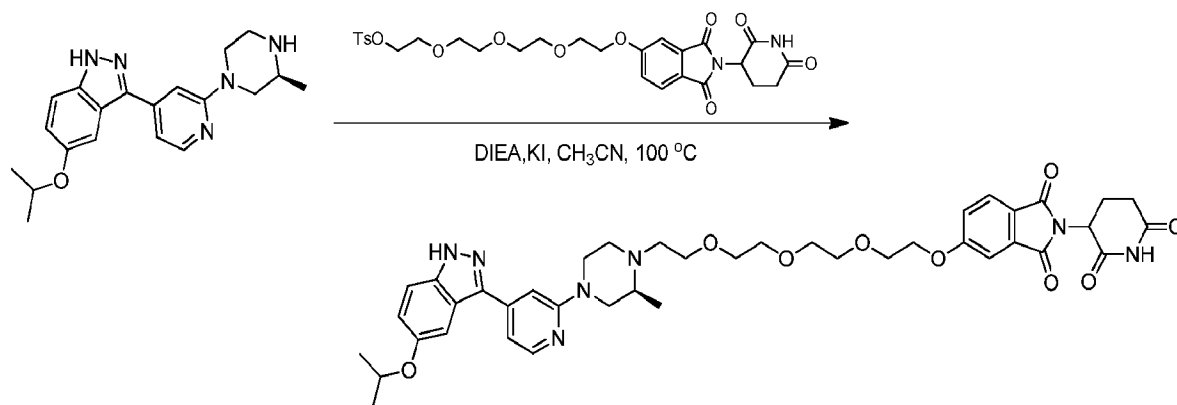
**Step 5**

2-[[3-(2-Fluoro-4-pyridyl)-5-isopropoxy-indazol-1-yl]methoxy]ethyl-trimethyl-silane (300 mg, 747.11  $\mu\text{mol}$ , 1 eq), tert-butyl (2S)-2-methylpiperazine-1-carboxylate (224.44 mg, 1.12 mmol, 1.5 eq) and DIEA (965.56 mg, 7.47 mmol, 1.30 mL, 10 eq) were taken up into a microwave tube in DMSO (10 mL). The sealed tube was heated at 180 °C for 5 hr under microwave. The mixture was cooled to 25 °C. The mixture was diluted with ethyl acetate (30 mL) and washed with brine (10 mL\*3), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (Dichloromethane: Methanol=3/1) to afford 2-[[5-isopropoxy-3-[2-[(3S)-3-methylpiperazin-1-yl]-4-pyridyl]indazol-1-yl]methoxy]ethyl-trimethyl-silane (200 mg, 357.07  $\mu\text{mol}$ , 47.79% yield, 86% purity) as a dark liquid.

**Step 6**

A mixture of 2-[[5-isopropoxy-3-[2-[(3S)-3-methylpiperazin-1-yl]-4-pyridyl]indazol-1-yl]methoxy]ethyl-trimethyl-silane (200 mg, 415.19  $\mu\text{mol}$ , 1 eq) and TFA (5 mL) were stirred at 25 °C for 1 hour. The mixture was concentrated under reduced pressure at 60 °C to give a residue. The residue was purified by silica gel chromatography (Dichloromethane/Methanol=100/5) to afford 5-isopropoxy-3-[2-[(3S)-3-methylpiperazin-1-yl]-4-pyridyl]-1H-indazole (200 mg, 352.83  $\mu\text{mol}$ , 84.98% yield, 62% purity) as a dark oil.

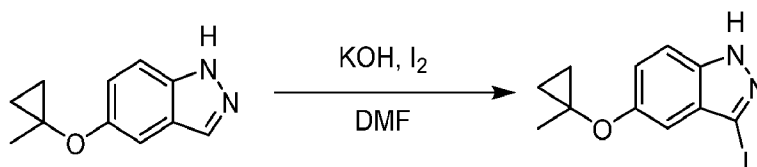
**Step 7**



To a mixture of 5-isopropoxy-3-[2-[(3S)-3-methylpiperazin-1-yl]-4-pyridyl]-1H-indazole (100 mg, 284.54  $\mu\text{mol}$ , 1 eq) and 2-[2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isindolin-5-yl]oxyethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate (206.45 mg, 341.45  $\mu\text{mol}$ , 1.2 eq) in  $\text{CH}_3\text{CN}$  (3 mL) was added DIEA (367.74 mg, 2.85 mmol, 495.61  $\mu\text{L}$ , 10 eq) and KI (236.17 mg, 1.42 mmol, 5 eq) in one portion at 25 °C. The mixture was stirred at 100°C for 16 hours. The mixture was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (15 mL\*3) and the combined organic phase was washed with brine (5 mL\*2), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100\*30mm\*5 $\mu\text{m}$ ; mobile phase: [water(0.05% $\text{HCl}$ )-ACN];B%: 15%-45%,9min) to give 2-(2,6-dioxo-3-piperidyl)-5-[2-[2-[2-[2-[(2S)-4-[4-(5-isopropoxy-1H-indazol-3-yl)-2-pyridyl]-2-methyl-piperazin-1-yl]ethoxy]ethoxy]ethoxy]ethoxy]isindoline-1,3-dione (11.6 mg, 13.85  $\mu\text{mol}$ , 4.87% yield, 93.6% purity) as a light yellow solid.

## [00223] Exemplary Synthesis of Exemplary Compound 12

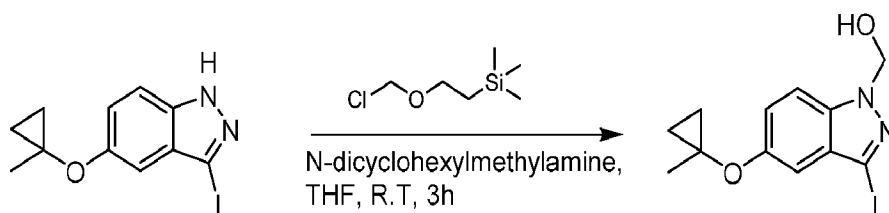
### Step 1



To a solution of 5-(1-methylcyclopropoxy)-1H-indazole (500 mg, 2.66 mmol, 1 eq) in DMF (5 mL) was added KOH (558.89 mg, 9.96 mmol, 3.75 eq) and  $\text{I}_2$  (1.35 g, 5.31 mmol, 1.07 mL, 2 eq). The mixture was stirred at 25°C for 2 hr. The reaction mixture was diluted with sat  $\text{Na}_2\text{SO}_3$  (10 mL) and extracted with EtOAc (20 mL \* 3). The combined organic layers were washed with brine (20 mL \* 2), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give a

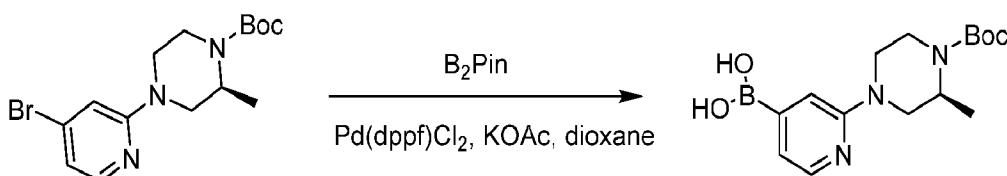
residue. The crude product was purified by column chromatography on silica gel (PE in EA = 0 to 10%) to give 3-iodo-5-(1-methylcyclopropoxy)-1H-indazole (458 mg, 1.26 mmol, 47.53% yield, 86.592% purity) as a yellow solid.

### Step 2

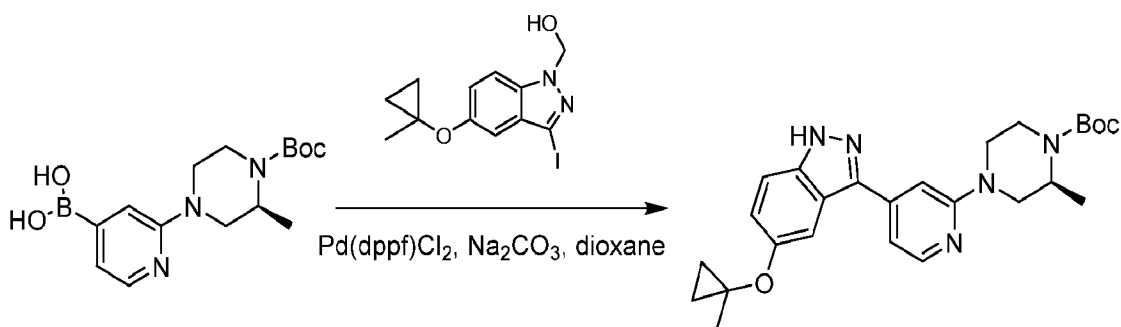


To a mixture of 3-iodo-5-(1-methylcyclopropoxy)-1H-indazole (458 mg, 1.30 mmol, 1 *eq*) in THF (20 mL) was added N-cyclohexyl-N-methyl-cyclohexanamine (760.45 mg, 3.89 mmol, 825.68  $\mu$ L, 3 *eq*) and SEM-Cl (432.69 mg, 2.60 mmol, 459.33  $\mu$ L, 2 *eq*) in one portion at 20°C. The mixture was stirred at 20°C for 3 hours to give orange suspension. TLC showed the reaction was completed. The residue was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL \* 2). The combined organic phase was washed with brine (10 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 0-10% of ethyl acetate in Petroleum ether) to give [3-iodo-5-(1-methylcyclopropoxy)indazol-1-yl]methanol (300 mg, 706.09  $\mu$ mol, 54.41% yield, 81% purity) as a yellow solid.

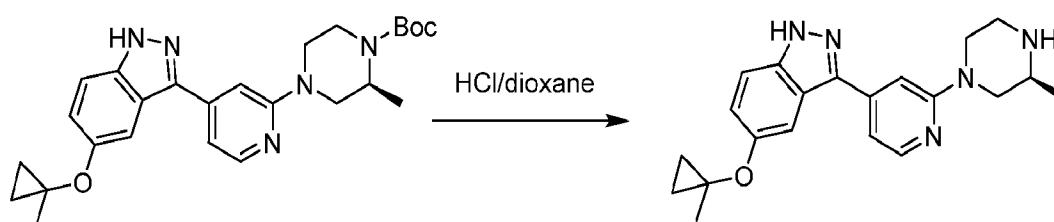
### Step 3



To a solution of tert-butyl (2S)-4-(4-bromo-2-pyridyl)-2-methyl-piperazine-1-carboxylate (600 mg, 1.68 mmol, 1 *eq*) and 4,4,5,5-tetramethyl-2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (641.51 mg, 2.53 mmol, 1.5 *eq*) in 1,4-dioxane (8 mL) was added Pd(dppf)Cl<sub>2</sub> (184.85 mg, 252.63  $\mu$ mol, 0.15 *eq*) and KOAc (495.87 mg, 5.05 mmol, 3 *eq*). The mixture was stirred at 90°C under N<sub>2</sub> for 1 hr to give brown solution. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL \* 2), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give [2-[(3S)-4-tert-butoxycarbonyl-3-methyl-piperazin-1-yl]-4-pyridyl]boronic acid (1.2 g, crude) as a brown gum.

**Step 4**

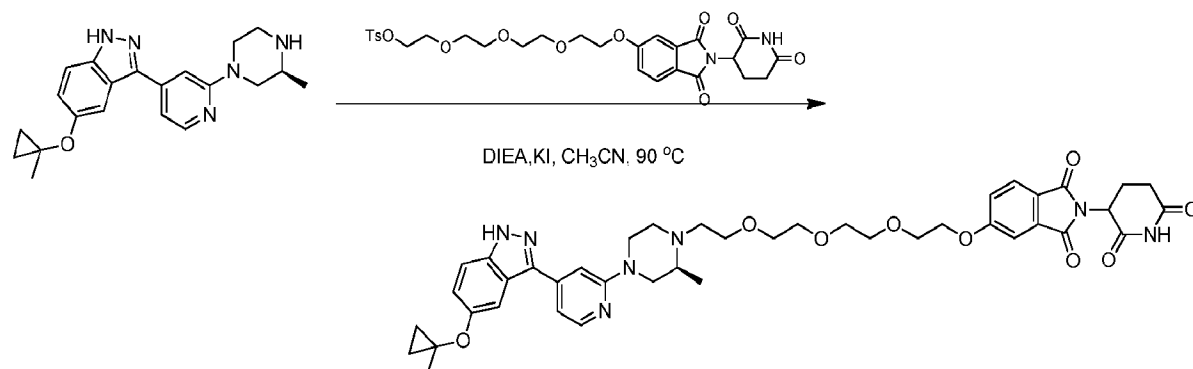
To a solution of [2-[(3S)-4-tert-butoxycarbonyl-3-methyl-piperazin-1-yl]-4-pyridyl]boronic acid (857.08 mg, 1.31 mmol, 1.5 *eq*) and [3-iodo-5-(1-methylcyclopropoxy)indazol-1-yl]methanol (300.00 mg, 871.72  $\mu$ mol, 1 *eq*) in 1,4-dioxane (10 mL) and H<sub>2</sub>O (2 mL) was added Pd(dppf)Cl<sub>2</sub> (95.68 mg, 130.76  $\mu$ mol, 0.15 *eq*) and Na<sub>2</sub>CO<sub>3</sub> (277.18 mg, 2.62 mmol, 3 *eq*). The mixture was stirred at 90°C under N<sub>2</sub> for 1.5 hr. The mixture was cooled to 20°C and concentrated under reduced pressure. The residue was poured into water (10 mL) and the aqueous phase was extracted with ethyl acetate (10 mL \* 3). The combined organic phase was washed with brine (10 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (column height: 20 g, 100-200 mesh silica gel, 0-20% of Ethyl acetate in Petroleum ether) to give tert-butyl (2S)-2-methyl-4-[4-[5-(1-methylcyclopropoxy)-2H-indazol-3-yl]-2-pyridyl]piperazine-1-carboxylate (400 mg, crude) as a yellow oil.

**Step 5**

To a mixture of tert-butyl (2S)-2-methyl-4-[4-[5-(1-methylcyclopropoxy)-2H-indazol-3-yl]-2-pyridyl]piperazine-1-carboxylate (400 mg, 422.80  $\mu$ mol, 1 *eq*) in MeOH (10 mL) was added HCl/dioxane (4 M, 528.51  $\mu$ L, 5 *eq*) in one portion at 20°C. The mixture was stirred at 65°C for 0.5 h. TLC (EtOAc, R<sub>f</sub> = 0.07) and LCMS showed the reaction was completed. The mixture was cooled to 20°C and the residue was poured into saturated aq. NaHCO<sub>3</sub> (pH = 7-8). The aqueous phase was extracted with ethyl acetate (20 mL \* 3). The combined organic phase was washed with brine (20 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum.

The residue was purified by silica gel chromatography (100-200 mesh silica gel, 0-25% of MeOH in DCM) to give 5-(1-methylcyclopropoxy)-3-[2-[(3S)-3-methylpiperazin-1-yl]-4-pyridyl]-1H-indazole (170 mg, 241.82  $\mu\text{mol}$ , 57.19% yield, 51.7% purity) as a yellow solid.

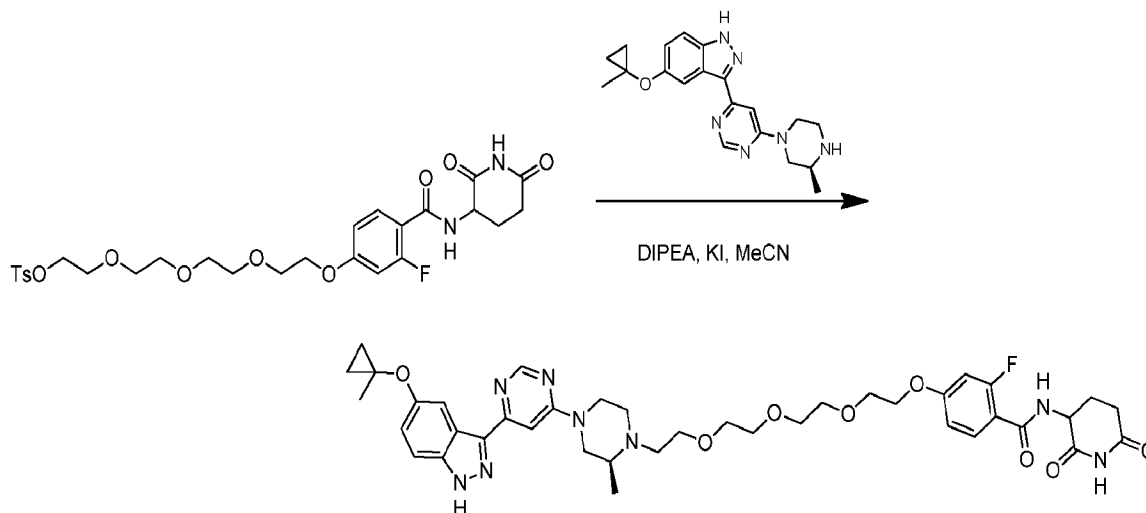
### Step 6



To a solution of 5-(1-methylcyclopropoxy)-3-[2-[(3S)-3-methylpiperazin-1-yl]-4-pyridyl]-1H-indazole (100 mg, 275.14  $\mu\text{mol}$ , 1 *eq*) and 2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxoisoindolin-5-yl]oxyethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate (166.35 mg, 275.14  $\mu\text{mol}$ , 1 *eq*) in MeCN (4 mL) was added KI (548.08 mg, 3.30 mmol, 12 *eq*) and DIPEA (426.71 mg, 3.30 mmol, 575.09  $\mu\text{L}$ , 12 *eq*). The mixture was stirred at 90°C for 12 hr. The residue was poured into water (3 mL). The aqueous phase was extracted with ethyl acetate (3 mL \* 2). The combined organic phase was washed with brine (3 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The crude product was purified by reversed-phase HPLC (column: Phenomenex Luna C18 100\*30mm\*5 $\mu\text{m}$ ; mobile phase: [water(0.225%FA)-ACN]; B%: 23%-53%, 9min) to give 2-(2,6-dioxo-3-piperidyl)-5-[2-[2-[2-[2-[(2S)-2-methyl-4-[4-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]-2-pyridyl]piperazin-1-yl]ethoxy]ethoxy]ethoxy]ethoxy]isoindoline-1,3-dione (12.5 mg, 15.14  $\mu\text{mol}$ , 5.50% yield, 96.4% purity) as a yellow solid.

### [00224] Exemplary Synthesis of Exemplary Compound 13

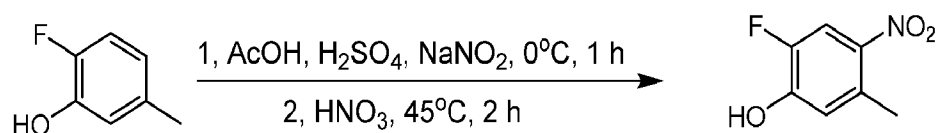
#### Step 1



To a mixture of 2-[2-[2-[2-[4-[(2,6-dioxo-3-piperidyl)carbamoyl]-3-fluorophenoxy]ethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate (162.07 mg, 271.65  $\mu\text{mol}$ , 1.1 *eq*) and 5-(1-methylcyclopropoxy)-3-[6-[(3S)-3-methylpiperazin-1-yl]pyrimidin-4-yl]-1H-indazole (90 mg, 246.95  $\mu\text{mol}$ , 1.00 *eq*) in MeCN (5 mL) was added KI (122.98 mg, 740.86  $\mu\text{mol}$ , 3 *eq*) and DIPEA (159.58 mg, 1.23 mmol, 215.07  $\mu\text{L}$ , 5 *eq*) in one portion at 20°C under  $\text{N}_2$ . The mixture was stirred at 80°C for 16 hours. The mixture was cooled to 20°C and concentrated in reduced pressure at 20°C. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (3 x 5 mL). The combined organic phase was washed with brine (3 x 5 mL), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under vacuum. The crude product was purified by reversed-phase HPLC (column: Welch Xtimate C18 150\*30mm\*5 $\mu\text{m}$ ; mobile phase: water(0.225%FA)-ACN; B%: 12%-42%, Gradient Time(min):8min; FlowRate(ml/min):25) to give N-(2,6-dioxo-3-piperidyl)-2-fluoro-4-[2-[2-[2-[2-[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethoxy]ethoxy]ethoxy]ethoxy]benzamide (23.23 mg, 28.98  $\mu\text{mol}$ , 11.73% yield, 98.399% purity) as a red solid.

#### [00225] Exemplary Synthesis of Exemplary Compound 14

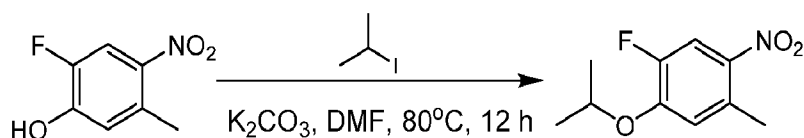
##### Step 1



To a mixture of 2-fluoro-5-methylphenol (7 g, 55.50 mmol, 1 *eq*) in AcOH (15.2 mL) and  $\text{H}_2\text{SO}_4$  (2 mL) was added  $\text{NaNO}_2$  (3.83 g, 55.50 mmol, 1 *eq*) in  $\text{H}_2\text{O}$  (35 mL) at 0 °C. Then the

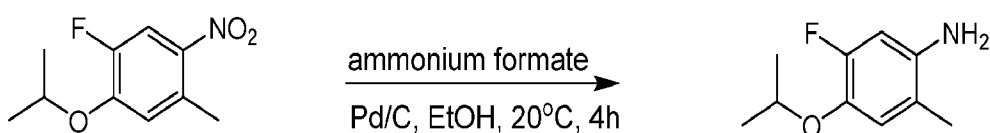
mixture was stirred at 0 °C for 1 hour. The reaction mixture was poured into ice-water (100 mL). The precipitate was collected by filtration followed by washing with water (3 x 100 mL). The resulting solid was added portion-wise to a mixture of HNO<sub>3</sub> (12 mL) and H<sub>2</sub>O (35 mL) with stirring. The resulting suspension was stirred at 45 °C for 2 hours. After cooling to room temperature, the mixture was diluted with cold water (100 mL) and filtered. The solid was washed with water (2 x 100 mL) and then dissolved in ethyl acetate (100 mL). The organic layer was washed with brine (2 x 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give 2-fluoro-5-methyl-4-nitro-phenol (5.3 g, 30.35 mmol, 54.69% yield, 98% purity) as a yellow solid.

### **Step 2**



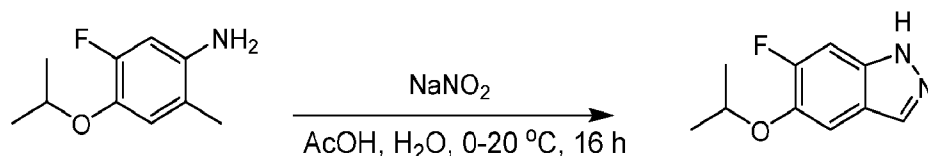
To a mixture of 2-fluoro-5-methyl-4-nitro-phenol (5.3 g, 30.97 mmol, 1 eq) and 2-iodopropane (10.53 g, 61.94 mmol, 6.19 mL, 2 eq) in CH<sub>3</sub>CN (60 mL) was added K<sub>2</sub>CO<sub>3</sub> (8.56 g, 61.94 mmol, 2 eq) at 20°C under N<sub>2</sub>. The reaction mixture was stirred 80° C for 12 hours. TLC (PE: EA = 10: 1) indicated one major new spot with lower polarity. The reaction mixture was filtered and concentrated to give 1-fluoro-2-isopropoxy-4-methyl-5-nitro-benzene (5 g, 23.45 mmol, 75.72% yield) as a yellow solid.

### **Step 3**



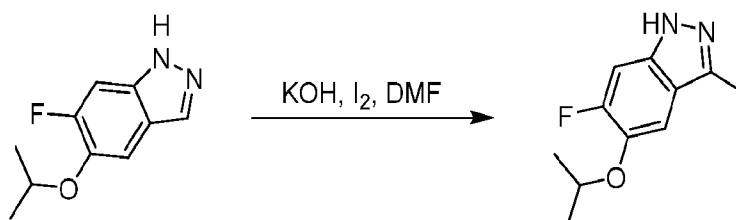
To a stirred solution of 1-fluoro-2-isopropoxy-4-methyl-5-nitro-benzene (5 g, 23.45 mmol, 1 eq) in EtOH (120 mL) was added ammonium formate (16.27 g, 257.97 mmol, 11 eq) followed by Pd/C (2.5 g, 23.45 mmol, 10% purity, 1.00 eq). The reaction mixture was stirred at 20°C for 4 hours. The reaction mixture was filtered and concentrated under vacuum to obtain the residue. Dichloromethane (50 mL) was added to the residue and filtered. The filtrate was concentrated under vacuum to give 5-fluoro-4-isopropoxy-2-methyl-aniline (4.2 g, 20.63 mmol, 87.97% yield, 90% purity) as a brown oil

### **Step 4**



To a stirred solution of 5-fluoro-4-isopropoxy-2-methyl-aniline (4.2 g, 20.63 mmol, 1 eq) in AcOH (40 mL) was added NaNO<sub>2</sub> (1.57 g, 22.69 mmol, 1.1 eq) in H<sub>2</sub>O (5 mL) at 0°C. The reaction mixture was stirred at 20°C for 16 hours. The reaction mixture color was changed from yellow to brown. The reaction mixture was concentrated under vacuum to obtain the residue. Saturated NaHCO<sub>3</sub> solution (40 mL) was added and the mixture was extracted with EA (40 mL). The combined organic layers were washed with brine 40 mL, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give the residue. The residue was purified by column chromatography on silica gel (PE /EA=100:20, 100:30) to give 6-fluoro-5-isopropoxy-1H-indazole (3.5 g, 18.02 mmol, 87.36% yield) as a brown oil.

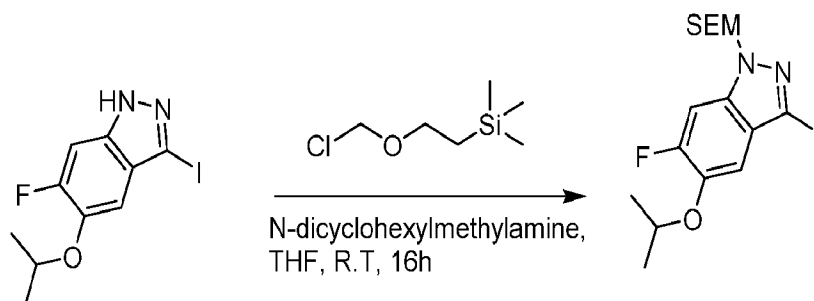
#### **Step 5**



To a solution of 6-fluoro-5-isopropoxy-1H-indazole (1.4 g, 7.21 mmol, 1 eq) in DMF (30 mL) was added KOH (1.52 g, 27.03 mmol, 3.75 eq) and I<sub>2</sub> (3.66 g, 14.42 mmol, 2.90 mL, 2 eq). The mixture was stirred at 25°C for 3 hr. The reaction mixture was diluted with sat Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (30 mL) and extracted with EtOAc (50 mL). The combined organic layers were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography on silica gel (0 to 10% ethyl acetate in petroleum ether) to afford 6-fluoro-3-iodo-5-isopropoxy-1H-indazole (1.62 g, 3.95 mmol, 54.76% yield, 78% purity) as a yellow solid.

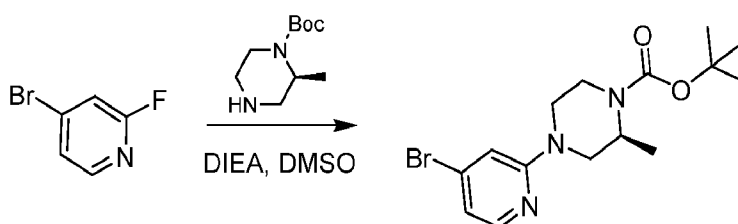
#### **Step 6**





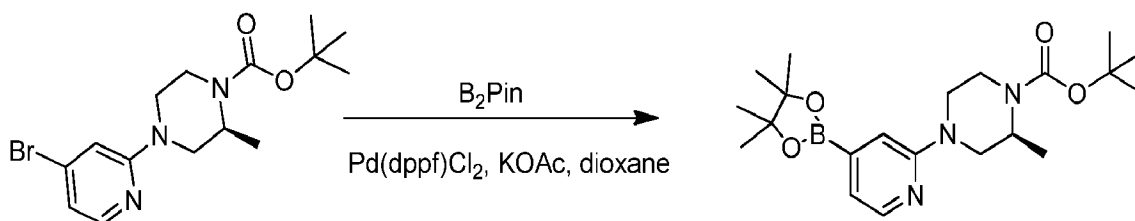
To a solution of 6-fluoro-3-iodo-5-isopropoxy-1H-indazole (1.61 g, 5.03 mmol, 1 *eq*) and 2-(chloromethoxy)ethyl-trimethyl-silane (838.61 mg, 5.03 mmol, 890.24  $\mu$ L, 1 *eq*) in THF (20 mL) was added N-cyclohexyl-N-methylcyclohexanamine (1.28 g, 6.54 mmol, 1.39 mL, 1.3 *eq*). The mixture was stirred at 25°C for 16 hr. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (50 mL). The combined organic layers were washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography on silica gel (0 to 5% ethyl acetate in petroleum ether) to afford 2-[(6-fluoro-3-iodo-5-isopropoxy-indazol-1-yl)methoxy]ethyl-trimethyl-silane (2.05 g, 4.23 mmol, 84.16% yield, 93% purity) as a yellow oil.

### Step 7



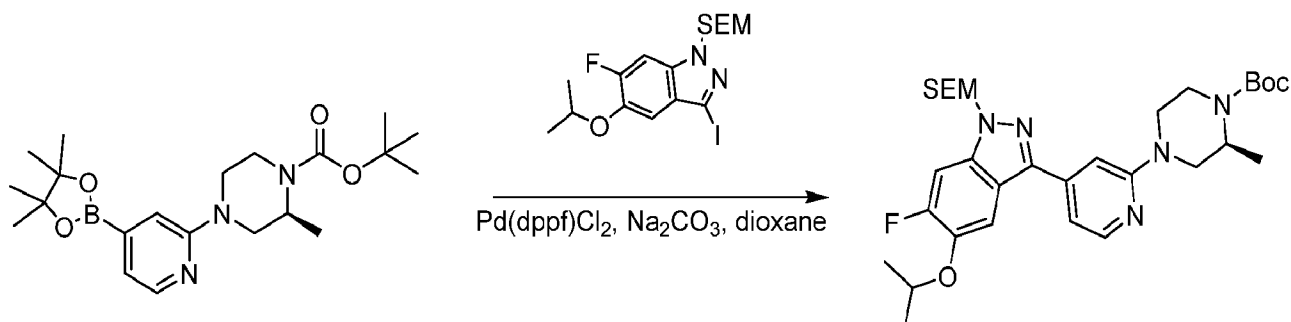
To a solution of 4-bromo-2-fluoropyridine (1 g, 5.68 mmol, 1 *eq*) and tert-butyl (2S)-2-methylpiperazine-1-carboxylate (1.71 g, 8.52 mmol, 1.5 *eq*) in DMSO (8 mL) was added K<sub>2</sub>CO<sub>3</sub> (2.36 g, 17.05 mmol, 3 *eq*). The mixture was stirred at 100°C for 4 hr. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL). The combined organic layers were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography on silica gel (0 to 10% ethyl acetate in petroleum ether) to afford tert-butyl (2S)-4-(4-bromo-2-pyridyl)-2-methyl-piperazine-1-carboxylate (1.7 g, 4.68 mmol, 82.30% yield, 98% purity) as a colorless oil.

### Step 8



To a solution of tert-butyl (2S)-4-(4-bromo-2-pyridyl)-2-methyl-piperazine-1-carboxylate (600 mg, 1.68 mmol, 1 *eq*) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (641.51 mg, 2.53 mmol, 1.5 *eq*) in 1,4-dioxane (8 mL) was added Pd(dppf)Cl<sub>2</sub> (184.85 mg, 252.63  $\mu$ mol, 0.15 *eq*) and KOAc (495.87 mg, 5.05 mmol, 3 *eq*). The mixture was stirred at 90°C under N<sub>2</sub> for 1 hr. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (30 mL). The combined organic layers were washed with brine 20 mL, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give tert-butyl (S)-2-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine-1-carboxylate (540 mg, 571.64  $\mu$ mol, 33.94% yield) as a brown oil.

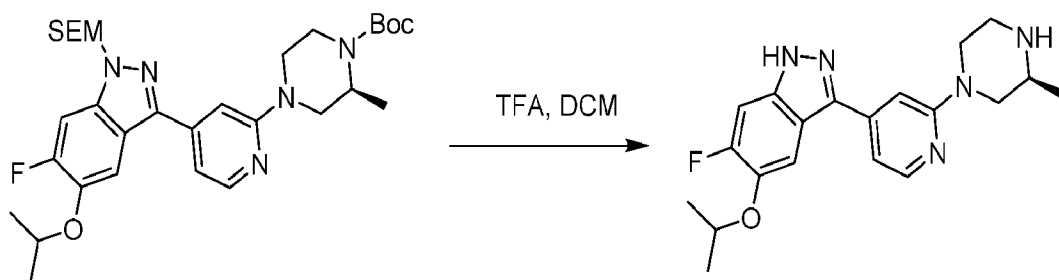
### Step 9



To a solution of tert-butyl (S)-2-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine-1-carboxylate (540 mg, 1.68 mmol, 1 *eq*) and 2-[(6-fluoro-3-iodo-5-isopropoxy-indazol-1-yl)methoxy] ethyl-trimethyl-silane (1.14 g, 2.52 mmol, 1.5 *eq*) in 1,4-dioxane (10 mL) and H<sub>2</sub>O (2 mL) was added Pd(dppf)Cl<sub>2</sub> (184.53 mg, 252.20  $\mu$ mol, 0.15 *eq*) and Na<sub>2</sub>CO<sub>3</sub> (534.61 mg, 5.04 mmol, 3 *eq*). The mixture was stirred at 90°C under N<sub>2</sub> for 2 hr. The reaction mixture was diluted with water (20 mL) and extracted with EA (30 mL). The combined organic layers were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography on silica gel (0 to 20% ethyl acetate in petroleum ether) to afford tert-butyl

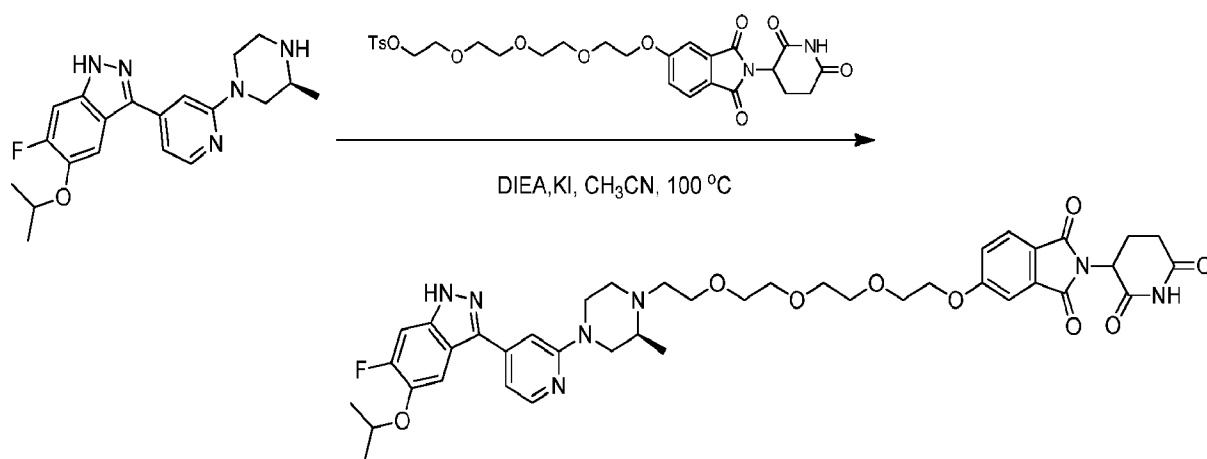
(2S)-4-[4-[6-fluoro-5-isopropoxy-1-(2-trimethylsilylethoxymethyl)indazol-3-yl]-2-pyridyl]-2-methyl-piperazine-1-carboxylate (1 g, 1.60 mmol, 95.19% yield, 96% purity) as a yellow oil.

### Step 10



To a solution of tert-butyl (2S)-4-[4-[6-fluoro-5-isopropoxy-1-(2-trimethylsilylethoxymethyl)indazol-3-yl]-2-pyridyl]-2-methyl-piperazine-1-carboxylate (1 g, 1.67 mmol, 1 *eq*) in DCM (5 mL) was added TFA (1.54 g, 13.51 mmol, 1 mL, 8.10 *eq*). The mixture was stirred at 25°C for 6 h. And then NH<sub>3</sub>·H<sub>2</sub>O (701.14 mg, 5.00 mmol, 770.48 uL, 25% purity, 3 *eq*) was added to solution and the mixture was stirred for 2 h. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (30 mL). The combined organic layers were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give 6-fluoro-5-isopropoxy-3-[2-[(3S)-3-methylpiperazin-1-yl]-4-pyridyl]-1H-indazole (590 mg, 1.39 mmol, 83.34% yield, 87% purity) as a yellow gum.

### Step 11

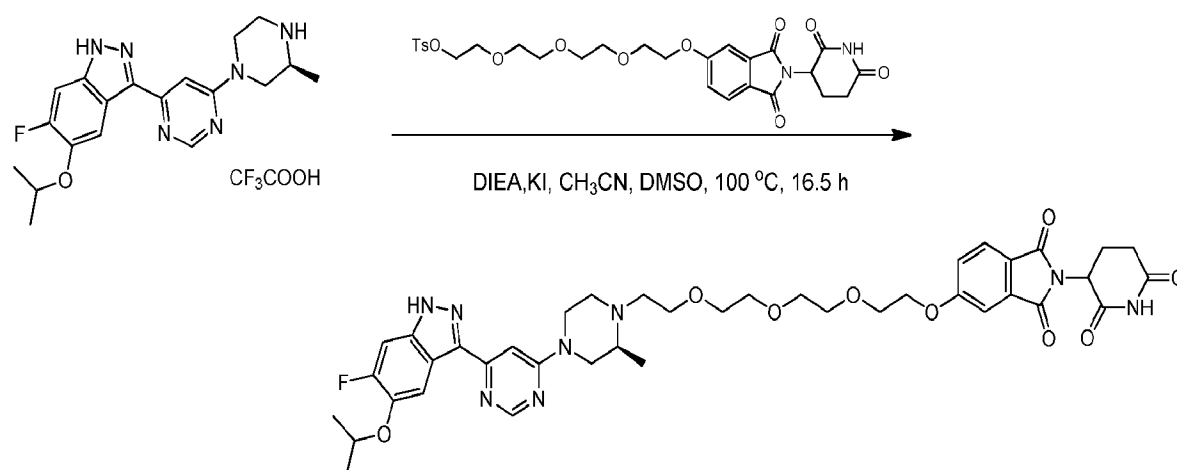


To a solution of 6-fluoro-5-isopropoxy-3-[2-[(3S)-3-methylpiperazin-1-yl]-4-pyridyl]-1H-indazole (100 mg, 270.68 umol, 1 *eq*) and 2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxoisoindolin-5-yl]oxyethoxy]ethoxy]ethyl 4-methylbenzenesulfonate (163.66 mg, 270.68 umol, 1 *eq*) in CH<sub>3</sub>CN (2 mL) was added KI (539.21 mg, 3.25 mmol, 12 *eq*) and DIEA (419.81 mg, 3.25 mmol, 565.78 uL, 12 *eq*). The mixture was stirred at 90°C for 12 hr. The reaction

mixture was diluted with water (20 mL) and extracted with EtOAc (30 mL). The combined organic layers were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Column: Phenomenex Luna C18 100\*30mm\*5um; mobile phase:[water(0.225%FA)-ACN];B%:0-26%;12min) to afford 2-(2,6-dioxo-3-piperidyl)-5-[2-[2-[2-[2-[(2S)-4-[4-(6-fluoro-5-isopropoxy-1H-indazol-3-yl)-2-pyridyl]-2-methyl-piperazin-1-yl]ethoxy]ethoxy]ethoxy]ethoxy]isoindoline-1,3-dione (24.3 mg, 29.74 umol, 10.99% yield, 98.14% purity) as a white solid.

## [00226] Exemplary Synthesis of Exemplary Compound 15

### Step 1

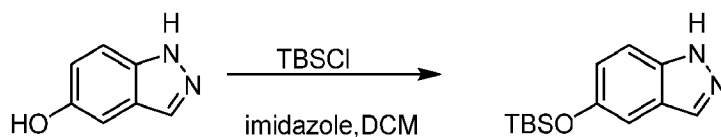


A mixture of 2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]oxyethoxy]ethoxy]ethyl 4-methylbenzenesulfonate (280.82 mg, 464.45 umol, 1.5 eq) and KI (770.99 mg, 4.64 mmol, 15 eq) in DMSO (3 mL) was stirred at 50°C for 0.5 hour under N<sub>2</sub>. Then a solution of 6-fluoro-5-isopropoxy-3-[6-[(3S)-3-methylpiperazin-1-yl]pyrimidin-4-yl]-1H-indazole (150 mg, 309.63 umol, 1 eq, TFA) and DIEA (600.27 mg, 4.64 mmol, 808.98 uL, 15 eq) in CH<sub>3</sub>CN (3 mL) was added to the mixture. Then the mixture was stirred at 90°C under N<sub>2</sub> for 16 hours. The reaction mixture was diluted with water (20 mL) and extracted with EA (30 mL). The combined organic layers were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a residue. The residue was purified by Pre-TLC (PE:EA=0:1) to obtain the crude product. The crude product was purified by prep-TLC (Column: Phenomenex Luna C18 100\*30mm\*5um; Condition: water(0.225%FA)-ACN; Begin: B 16%, End: B 46%; Gradient Time: 9 min; 100%B Hold Time: 1 min; Flow-Rate: 25 ml/min) to give 2-(2,6-dioxo-3-piperidyl)-5-[2-[2-[2-[2-[(2S)-4-[4-(6-fluoro-5-isopropoxy-1H-indazol-3-

yl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethoxy]ethoxy]ethoxy]ethoxy]isoindoline-1,3-dione (15 mg, 18.68  $\mu$ mol, 6.03% yield, FA) as a white solid.

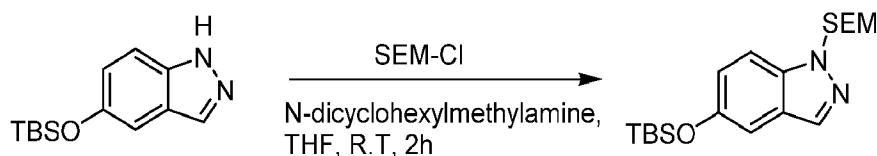
## [00227] Exemplary Synthesis of Exemplary Compound 16

### Step 1

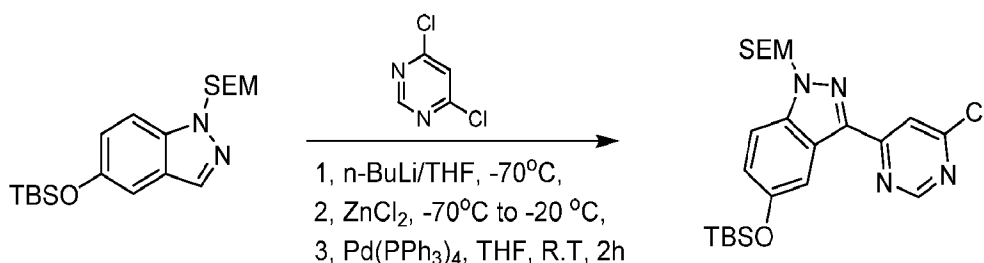


To a mixture of 1H-indazol-5-ol (1 g, 7.46 mmol, 1 *eq*) in DCM (10 mL) was added imidazole (1.52 g, 22.37 mmol, 3 *eq*) and TBSCl (1.69 g, 11.18 mmol, 1.37 mL, 1.5 *eq*) in one portion at 20°C under N<sub>2</sub>. The mixture was stirred at 20°C for 2 hours to give brown solution. TLC (DCM: MeOH =10:1, R<sub>f</sub>=0.23) showed the reaction was completed. The residue was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL \* 3). The combined organic phase was washed with brine (10 mL \* 3), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (12 g, 30mL/min, 100-200 mesh silica gel, 0-5% (10 min) of MeOH in DCM) to give tert-butyl-(1H-indazol-5-yloxy)-dimethyl-silane (1.5 g, 5.87 mmol, 78.73% yield, 97.2% purity) as a yellow oil.

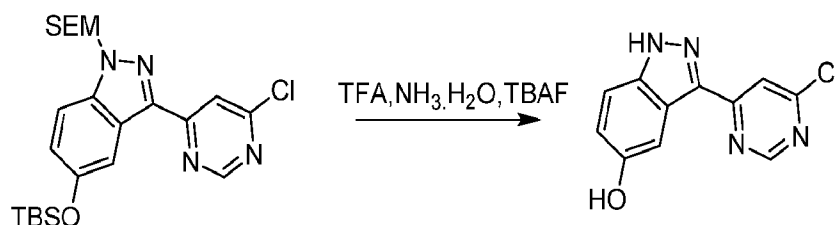
### Step 2



To a mixture of tert-butyl-(1H-indazol-5-yloxy)-dimethyl-silane (1.5 g, 6.04 mmol, 1 *eq*) in THF (20 mL) was added N,N-dicyclohexylmethylamine (2.36 g, 12.08 mmol, 2.56 mL, 2 *eq*) and SEM-Cl (2.01 g, 12.08 mmol, 2.14 mL, 2 *eq*) in one portion at 20°C under N<sub>2</sub>. The mixture was stirred at 20°C for 2 hours to give yellow suspension. TLC (PE: EtOAc =3:1, R<sub>f</sub>= 0.37) showed the reaction was completed. The residue was poured into water (20 mL). The aqueous phase was extracted with ethyl acetate (20 mL \* 3). The combined organic phase was washed with brine (20 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 40 g, 30 mL/min, 100-200 mesh silica gel, 0% (5 min) of Ethyl acetate in Petroleum ether, 1% (20 min) of Ethyl acetate in Petroleum ether) to give tert-butyl-dimethyl-[1-(2-trimethylsilylethoxymethyl)indazol-5-yl]oxy-silane (1.82 g, 4.81 mmol, 79.59% yield) as a yellow oil.

**Step 3**

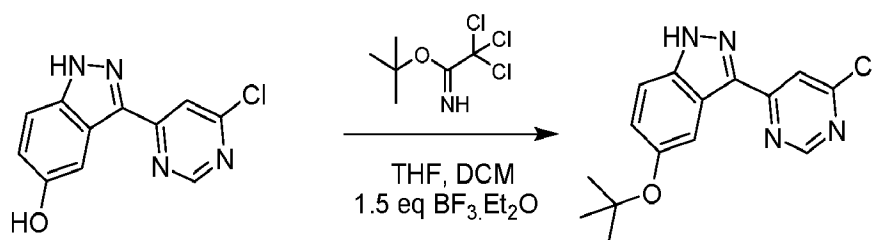
To a mixture of tert-butyl-dimethyl-[1-(2-trimethylsilylethoxymethyl)indazol-5-yl]oxy-silane (1.82 g, 4.81 mmol, 1 *eq*) in THF (5 mL) was dropwise added n-BuLi (2.5 M, 2.50 mL, 1.3 *eq*) at -70°C under N<sub>2</sub>. The mixture was then stirred at -20 °C for 5 min, and a solution of ZnCl<sub>2</sub> (1 M, 7.21 mL, 1.5 *eq*) was dropwise added at -70°C. The mixture was stirred for 10min at -40°C. A mixture of 4,6-dichloropyrimidine (787.67 mg, 5.29 mmol, 1.1 *eq*) and Pd(PPh<sub>3</sub>)<sub>4</sub> (277.71 mg, 240.32  $\mu$ mol, 0.05 *eq*) in THF (1 mL) was stirred at 20°C for 30 min and added to the reaction. The cold bath was removed and the mixture was stirred at 20°C for 2 h to give yellow solution. TLC (PE: EtOAc =10:1, R<sub>f</sub> =0.83) showed there was a new spot. The residue was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (20 mL \* 3). The combined organic phase was washed with brine (20 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (40 g, 35mL/min, 100-200 mesh silica gel, 0-5% (30 min) of Ethyl acetate in Petroleum ether) to give tert-butyl-[3-(6-chloropyrimidin-4-yl)-1-(2-trimethylsilylethoxymethyl)indazol-5-yl] oxy-dimethyl-silane (1.18 g, 2.40 mmol, 49.98% yield) as a yellow oil.

**Step 4**

To a mixture of tert-butyl-[3-(6-chloropyrimidin-4-yl)-1-(2-trimethylsilylethoxymethyl)indazol-5-yl]oxy-dimethyl-silane (1.18 g, 2.40 mmol, 1 *eq*) in DCM (10 mL) was added TFA (3 g, 26.31 mmol, 1.95 mL, 10.95 *eq*) in one portion at 20°C under N<sub>2</sub>. The mixture was stirred at 20°C for 1 h. Then the NH<sub>3</sub>.H<sub>2</sub>O (2.55 g, 24.02 mmol, 2.80 mL, 33% purity, 10 *eq*) was added and the solution was stirred at 20°C for 1 h. The solution was concentrated under vacuum. The crude was dissolved in THF (5 mL) and TBAF (1 M, 2.40 mL, 1 *eq*) was added and the solution was

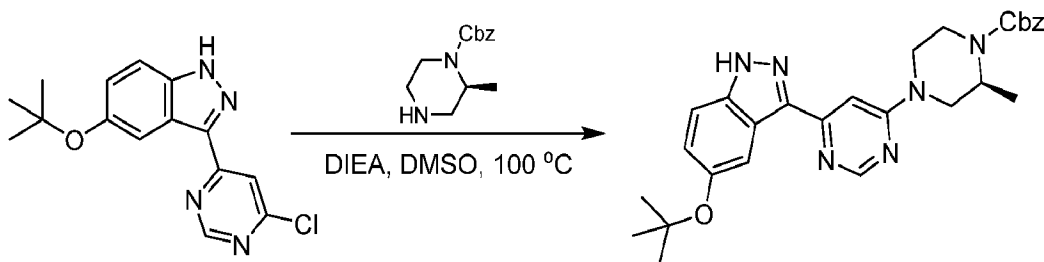
stirred for 1h to give yellow solution. The aqueous phase was extracted with ethyl acetate (5 mL \* 3). The combined organic phase was washed with brine (5 mL \* 3), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 12 g, 30 mL/min, 0-32% (18 min) of Ethyl acetate in Petroleum ether, 32% (12 min) of Ethyl acetate in Petroleum ether) to give 3-(6-chloropyrimidin-4-yl)-1H-indazol-5-ol (140 mg, 567.60  $\mu\text{mol}$ , 23.63% yield) as a yellow oil.

### Step 5



To a mixture of 3-(6-chloropyrimidin-4-yl)-1H-indazol-5-ol (140 mg, 567.60  $\mu\text{mol}$ , 1 *eq*) in THF (5 mL) and DCM (5 mL) was added tert-butyl 2,2,2-trichloroethanimidate (744.15 mg, 3.41 mmol, 609.96  $\mu\text{L}$ , 6 *eq*) and  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (241.68 mg, 851.40  $\mu\text{mol}$ , 210.15  $\mu\text{L}$ , 50% purity, 1.5 *eq*) in one portion at 25°C under  $\text{N}_2$ . The mixture was stirred at 25°C for 10 min to give yellow solution. The residue was poured into water (5 mL) and stirred for 5 min. The aqueous phase was extracted with DCM (5 mL \* 3). The combined organic phase was washed with brine (3 mL \* 2), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (DCM: MeOH= 10:1,  $R_f$ =0.38, 12 g, 30 mL/min, 100-200 mesh silica gel, 0-20%(10 min) of Ethyl acetate in Petroleum ether, 20% (10 min) of Ethyl acetate in Petroleum ether) to give 5-tert-butoxy-3-(6-chloropyrimidin-4-yl)-1H-indazole (80 mg, 264.24  $\mu\text{mol}$ , 46.55% yield) as a yellow solid.

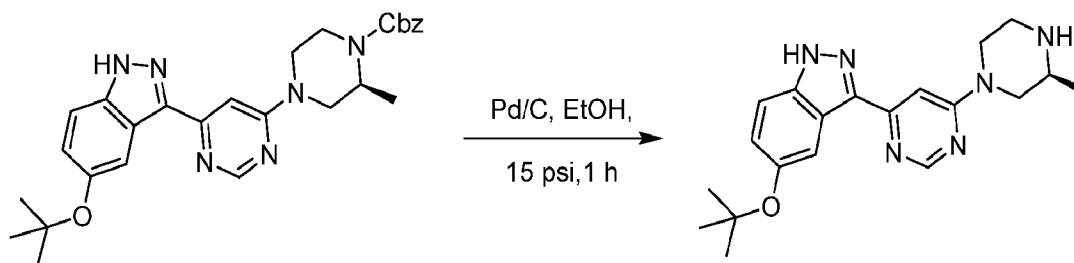
### Step 6



To a mixture of 5-tert-butoxy-3-(6-chloropyrimidin-4-yl)-1H-indazole (200 mg, 660.59  $\mu\text{mol}$ , 1 *eq*), benzyl (2S)-2-methylpiperazine-1-carboxylate (154.77 mg, 660.59  $\mu\text{mol}$ , 1 *eq*) in DMSO (10 mL) was added  $\text{Et}_3\text{N}$  (200.54 mg, 1.98 mmol, 275.84  $\mu\text{L}$ , 3 *eq*) in one portion and then was

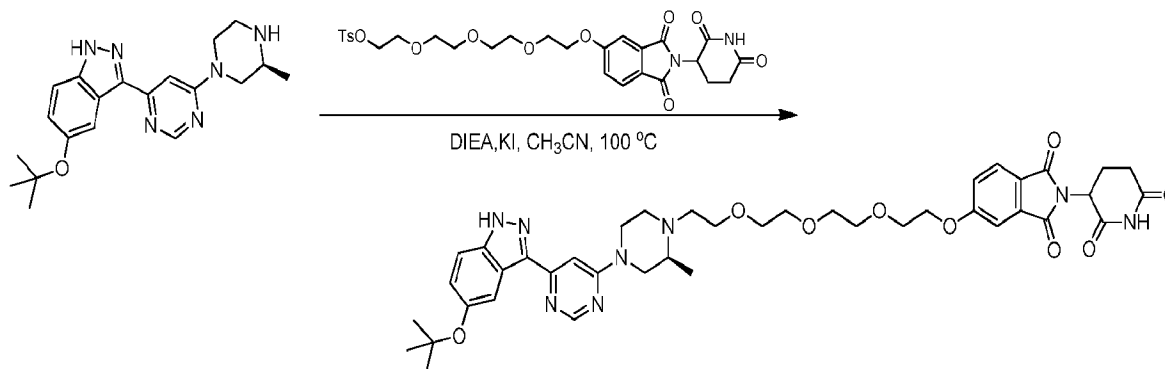
stirred at 100°C for 1h. TLC (PE: EtOAc=5:1, R<sub>f</sub>= 0.50) showed the starting material was consumed completely. The mixture was cooled to 20°C, then the residue was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic phase was washed with brine (2 x 10 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (20 g, 40 mL/min, 100-200 mesh silica gel, 0-17% (3 min) of Ethyl acetate in Petroleum ether, 17% (5 min) of Ethyl acetate in Petroleum ether) to give benzyl (2S)-4-[6-(5-tert-butoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methyl-piperazine-1-carboxylate (230 mg, 450.27 umol, 68.16% yield, 98% purity) as a yellow gum.

### Step 7



To a mixture of benzyl (2S)-4-[6-(5-tert-butoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methylpiperazine-1-carboxylate (230 mg, 459.46  $\mu\text{mol}$ , 1 *eq*) in EtOH (5 mL) was added Pd/C (100 mg, 459.46  $\mu\text{mol}$ , 10% purity, 1 *eq*) in one portion at 20°C under N<sub>2</sub>. The suspension was degassed under vacuum and purged with H<sub>2</sub> several times. The mixture was stirred under H<sub>2</sub> (15 psi) at 20°C for 1 h. The suspension was filtered through a pad of Celite and the pad was washed with EtOAc (3 x 50 mL) to give 5-tert-butoxy-3-[6-[(3S)-3-methylpiperazin-1-yl]pyrimidin-4-yl]-1H-indazole (140 mg, 382.03  $\mu\text{mol}$ , 83.15% yield) as a yellow gum. The crude product was used for next step.

### Step 8

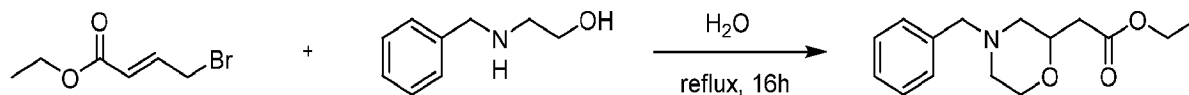




To a mixture of 5-tert-butoxy-3-[6-[(3S)-3-methylpiperazin-1-yl]pyrimidin-4-yl]-1H-indazole (140 mg, 382.03  $\mu\text{mol}$ , 1 *eq*), KI (317.09 mg, 1.91 mmol, 5 *eq*) and 2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isindolin-5-yl]oxyethoxy]ethoxy]ethyl 4-methylbenzenesulfonate (254.09 mg, 420.24  $\mu\text{mol}$ , 1.1 *eq*) in MeCN (5 mL) was added DIPEA (246.87 mg, 1.91 mmol, 332.71  $\mu\text{L}$ , 5 *eq*) in one portion. The mixture was stirred at 100°C for 16 h. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (3 x 5 mL). The combined organic phase was washed with brine (2 x 5 mL), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The crude product was purified by reversed-phase HPLC (Column: Phenomenex luna C18 100\*40mm\*3  $\mu\text{m}$ ; Condition: water (0.225%FA)-ACN; Begin B: 20-50; FlowRate: 25 mL/min; Gradient Time: 8.5 min; 100%B Hold Time: 2 min). And the crude was purified by prep-TLC (DCM: MeOH=10:1,  $R_f$ = 0.27) to give 5-[2-[2-[2-[(2S)-4-[6-(5-tert-butoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethoxy]ethoxy]ethoxy]ethoxy]-2-(2,6-dioxo-3-piperidyl)isindoline-1,3-dione (34.9 mg, 41.94  $\mu\text{mol}$ , 10.98% yield, 96% purity) as a white solid.

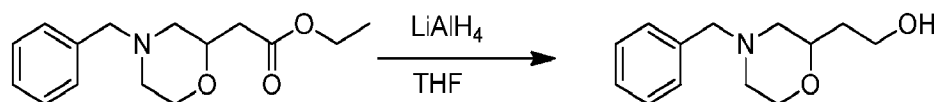
## [00228] Exemplary Synthesis of Exemplary Compound 17

### Step 1



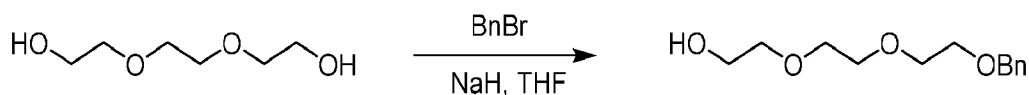
A solution of 2-(benzylamino)ethanol (17 g, 112.43 mmol, 15.89 mL, 1 *eq*) and  $\text{Et}_3\text{N}$  (11.38 g, 112.43 mmol, 15.65 mL, 1 *eq*) in  $\text{H}_2\text{O}$  (200 mL) was heated to 105°C. Ethyl (E)-4-bromobut-3-enoate (23.87 g, 123.67 mmol, 1.1 *eq*) was added dropwise and the reaction was heated at 105°C for 16 h to give red solution. The mixture was cooled to 20°C and concentrated in reduced pressure at 20°C. The residue was poured into NaOH (50 mL, 10%) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (100 mL \* 3). The combined organic phase was washed with brine (100 mL \* 2), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 80 g, 100-200 mesh silica gel, 0-20% (30 min) of Ethyl acetate in Petroleum ether) to give ethyl 2-(4-benzylmorpholin-2-yl)acetate (16 g, 60.76 mmol, 54.04% yield) as a yellow oil.

### Step 2



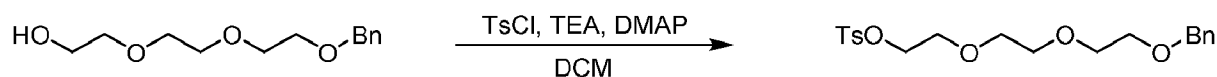
To a solution of ethyl 2-(4-benzylmorpholin-2-yl)acetate (5 g, 18.99 mmol, 1 *eq*) in THF (50 mL) was added LiAlH<sub>4</sub> (1.08 g, 28.48 mmol, 1.5 *eq*). After addition, the reaction mixture was stirred at 20°C for 1 h. TLC (PE: EtOAc = 5: 1, R<sub>f</sub> = 0.18) showed the reaction was completed. The reaction mixture was quenched with water (5 mL), then 15% sodium hydroxide aqueous solution (5 mL) and water (15 mL) was added. The solid was removed by filtration. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (column height: 40 g, 100-200 mesh silica gel, 0-50% (20 min) of Ethyl acetate in Petroleum ether) to give 2-(4-benzylmorpholin-2-yl)ethanol (2.73 g, 12.34 mmol, 64.97% yield) as a yellow oil.

### Step 3



To a mixture of 2-[2-(2-hydroxyethoxy)ethoxy]ethanol (5 g, 33.29 mmol, 4.46 mL, 1 *eq*) in THF (50 mL) was added NaH (1.33 g, 33.29 mmol, 60% purity, 1 *eq*) in one portion at 0°C under N<sub>2</sub>. The mixture was stirred at 0°C for 30 min, then (chloromethyl)benzene (3.79 g, 29.97 mmol, 3.45 mL, 0.9 *eq*) was added to solution. Then the solution was heated to 25°C and stirred for 16 hours. The residue was poured into water (30 mL). The aqueous phase was extracted with ethyl acetate (30 mL \* 3). The combined organic phase was washed with brine (30 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 40 g, 100-200 mesh silica gel, 0-2% (10min) of MeOH in DCM, 2% (5 min) of MeOH in DCM, 5% (15 min) of MeOH in DCM ) to give 2-[2-(2-benzyloxyethoxy)ethoxy]ethanol (3 g, 12.48 mmol, 37.50% yield) as a yellow oil.

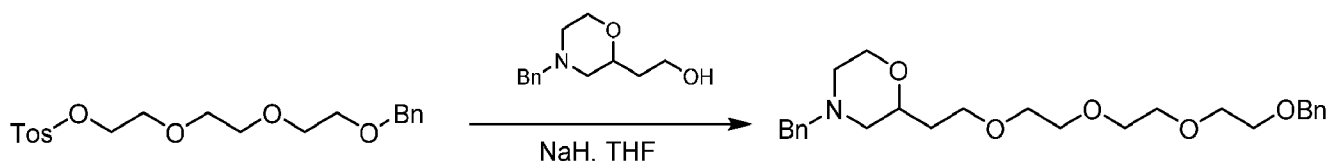
### Step 4



To a mixture of 2-[2-(2-benzyloxyethoxy)ethoxy]ethanol (3 g, 12.48 mmol, 9.01 mL, 1 *eq*), Et<sub>3</sub>N (1.26 g, 12.48 mmol, 1.74 mL, 1 *eq*) and DMAP (1.53 g, 12.48 mmol, 1 *eq*) in DCM (20 mL) was added 4-methylbenzene-1-sulfonyl chloride (3.57 g, 18.73 mmol, 1.5 *eq*) in one portion at 0°C under N<sub>2</sub>. Then the reaction solution was warmed to 20°C and stirred for 2 hours to give white suspension. TLC (MeOH: DCM=10:1, R<sub>f</sub>= 0.83) and LCMS showed the reaction was completed. The mixture was poured into HCl (2 M) to adjust the pH to 7-8. The aqueous phase

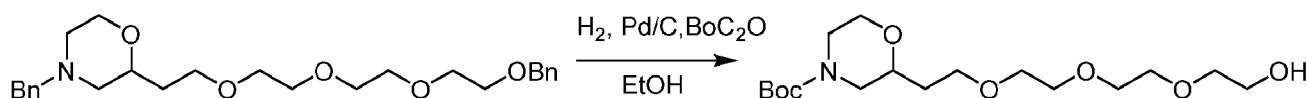
was extracted with ethyl acetate (50 mL \* 3). The combined organic phase was washed with brine (50 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 10-20% of Ethyl acetate in Petroleum ether) to give 2-[2-(2-benzyloxyethoxy)ethoxy]ethyl 4-methylbenzenesulfonate (3.14 g, 7.96 mmol, 63.76% yield) as a yellow oil.

### Step 5



To a mixture of 2-(4-benzylmorpholin-2-yl)ethanol (1 g, 4.52 mmol, 1 *eq*) in DMF (10 mL) was added NaH (542.26 mg, 13.56 mmol, 60% purity, 3 *eq*) in one portion at 0°C under N<sub>2</sub>. The mixture was stirred at 20°C for 30 min, Then 2-[2-(2-benzyloxyethoxy)ethoxy]ethyl 4-methylbenzenesulfonate (1.78 g, 4.52 mmol, 1 *eq*) was added to solution. The mixture was stirred at 20°C for 16 hours. The residue was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL \* 3). The combined organic phase was washed with brine (10 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 20 g, diameter: 100 mm, 100-200 mesh silica gel, 0-100% (60 min) of Ethyl acetate in Petroleum ether) to give 4-benzyl-2-[2-[2-[2-(2-benzyloxyethoxy)ethoxy]ethoxy]ethyl]morpholine (920 mg, 2.07 mmol, 45.90% yield) as a yellow oil.

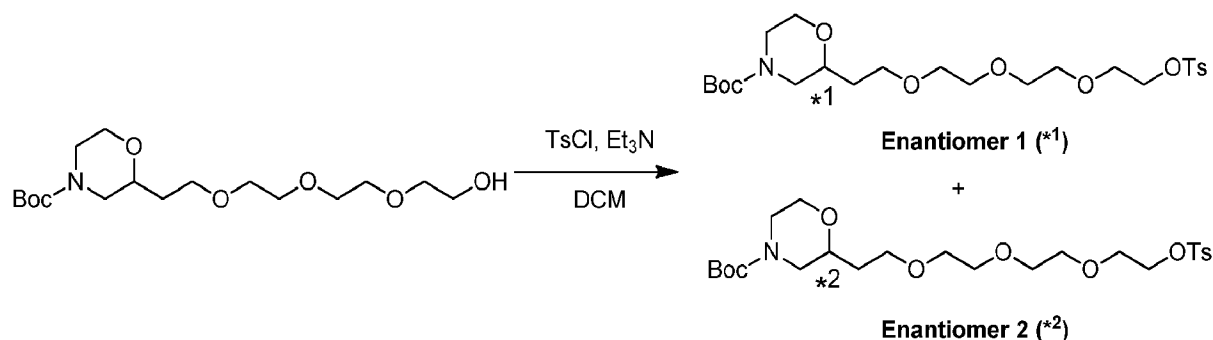
### Step 6



To a solution of 4-benzyl-2-[2-[2-[2-(2-benzyloxyethoxy)ethoxy]ethoxy]ethyl]morpholine (920 mg, 2.07 mmol, 1 *eq*) and Boc<sub>2</sub>O (905.31 mg, 4.15 mmol, 952.96 uL, 2 *eq*) in MeOH (10 mL) was added Pd/C (100 mg, 2.07 mmol, 10% purity, 1 *eq*) under N<sub>2</sub>. The suspension was degassed under vacuum and purged with H<sub>2</sub> several times. The mixture was stirred under H<sub>2</sub> (45 psi) at 50°C for 4 hours. TLC showed there was no starting material. The suspension was filtered through a pad of Celite or silica gel and the pad or filter cake was washed with EtOAc (50 mL \* 3). The residue was purified by silica gel chromatography (column height: 20 g, 100-200 mesh

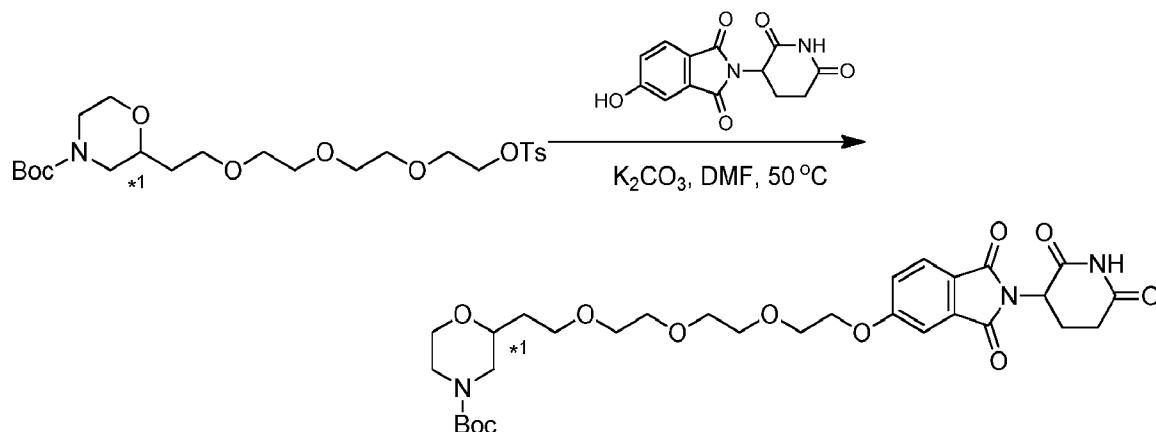
silica gel, 0-10% of MeOH in DCM) to give tert-butyl 2-[2-[2-[2-(2-hydroxyethoxy)ethoxy]ethoxy]ethyl]morpholine-4-carboxylate (684 mg, 1.88 mmol, 90.74% yield) as a colourless oil.

### Step 7



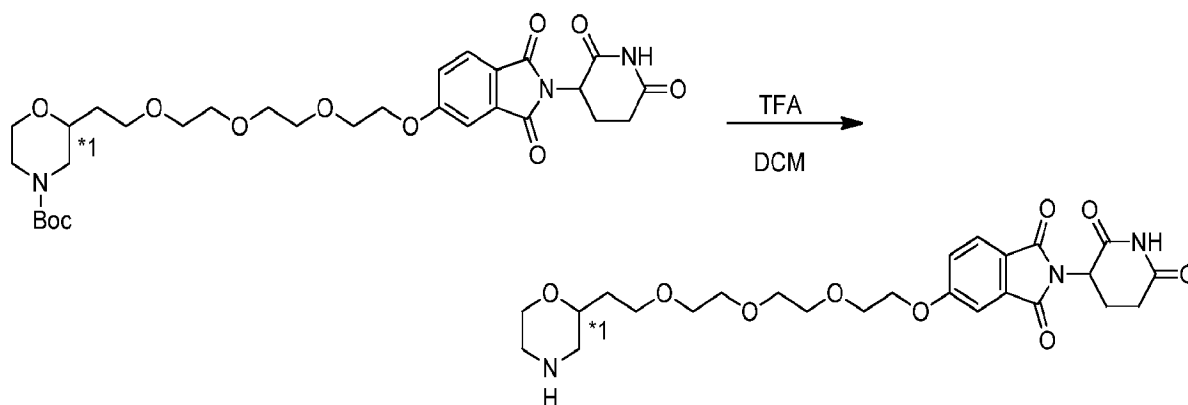
To a mixture of tert-butyl 2-[2-[2-[2-(2-hydroxyethoxy)ethoxy]ethoxy]ethyl]morpholine-4-carboxylate (400 mg, 1.10 mmol, 1 *eq*), Et<sub>3</sub>N (334.10 mg, 3.30 mmol, 459.56  $\mu$ L, 3 *eq*) and DMAP (134.46 mg, 1.10 mmol, 1 *eq*) in DCM (10 mL) was added 4-methylbenzenesulfonyl chloride (419.64 mg, 2.20 mmol, 2 *eq*) in one portion at 0°C under N<sub>2</sub>. The mixture was stirred at 0°C for 2 hours to give white suspension. TLC (DCM: MeOH=10:1, R<sub>f</sub>= 0.54) and LCMS showed the reaction was completed. The residue was poured into water (5 mL) and stirred for 5 min. The aqueous phase was extracted with DCM (5 mL \* 3). The combined organic phase was washed with brine (5 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, 0-10% of MeOH in DCM) and SFC {Column: REGIS (s, s) WHELK-O1 (250mm\*50mm,10 $\mu$ m) ;Condition: 0.1%NH<sub>3</sub>H<sub>2</sub>O IPA; Begin B: 20% ;End B 20%; FlowRate (ml/min): 70)} to give enantiomer 1 tert-butyl (2<sup>\*1</sup>)-2-[2-[2-[2-(p-tolylsulfonyloxy)ethoxy]ethoxy]ethoxy]ethyl]morpholine-4-carboxylate (148 mg, 234.51  $\mu$ mol, 21.31% yield, 82.019% purity) (R<sub>t</sub> = 2.832 min, 148 mg) as a colourless oil and enantiomer 2 tert-butyl (2<sup>\*2</sup>)-2-[2-[2-[2-(p-tolylsulfonyloxy)ethoxy]ethoxy]ethoxy]ethyl]morpholine-4-carboxylate (146 mg, 259.63  $\mu$ mol, 23.59% yield, 92.051% purity) (R<sub>t</sub> = 3.004 min, 146 mg) as a colourless oil.

### Step 8



To a mixture of enantiomer 1 tert-butyl (2<sup>\*1</sup>)-2-[2-[2-[2-[2-(p-tolylsulfonyloxy)ethoxy]ethoxy]ethoxy]ethyl]morpholine-4-carboxylate (70 mg, 135.23 umol, 1 *eq*) and 2-(2,6-dioxo-3-piperidyl)-5-hydroxy-isindoline-1,3-dione (40.79 mg, 148.75 umol, 1.1 *eq*) in DMF (5 mL) was added K<sub>2</sub>CO<sub>3</sub> (37.38 mg, 270.46 umol, 2 *eq*) in one portion at 20°C under N<sub>2</sub>. The mixture was stirred at 65°C for 1 h to give green suspension. The mixture was cooled to 25°C and concentrated in reduced pressure at 25°C. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (5 mL \* 3). The combined organic phase was washed with brine (5 mL \* 3), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 12 g, 100-200 mesh silica gel, 0-100% (30 min) of Ethyl acetate in Petroleum ether, 100% (10 min) of Ethyl acetate in Petroleum ether) to give tert-butyl (2<sup>\*1</sup>)-2-[2-[2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isindolin-5-yl]oxyethoxy]ethoxy]ethoxy]ethyl]morpholine-4-carboxylate (50 mg, 72.22 umol, 53.40% yield, 89.5% purity) as a colourless gum.

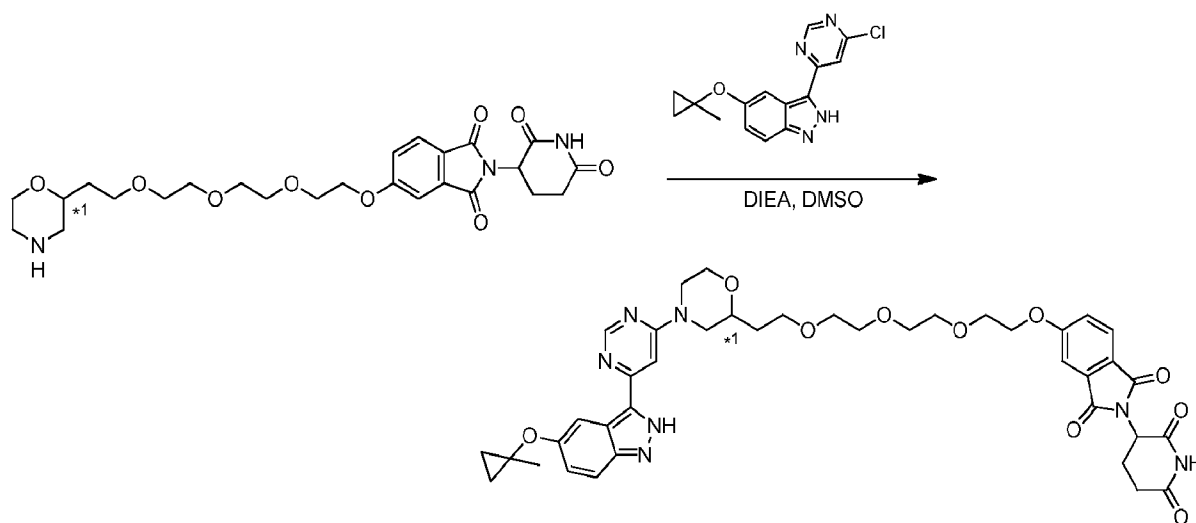
### Step 9



To a mixture of tert-butyl (2<sup>\*1</sup>)-2-[2-[2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isindolin-5-yl]oxyethoxy]ethoxy]ethoxy]ethyl]morpholine-4-carboxylate (50 mg, 80.69 umol, 1 *eq*) in DCM

(5 mL) was added TFA (27.60 mg, 242.07  $\mu\text{mol}$ , 17.92  $\mu\text{L}$ , 3 *eq*) in one portion at 25°C under  $\text{N}_2$ . The mixture was stirred at 25°C for 30 min. TLC showed the reaction was completed. The reaction mixture was concentrated under reduced pressure to remove solvent to give 2-(2,6-dioxo-3-piperidyl)-5-[2-[2-[2-[2-[(2<sup>\*1</sup>)-morpholin-2-yl]ethoxy]ethoxy]ethoxy]ethoxy]isoindoline-1,3-dione (50 mg, 71.72  $\mu\text{mol}$ , 88.88% yield, 90.873% purity, TFA) as a yellow gum.

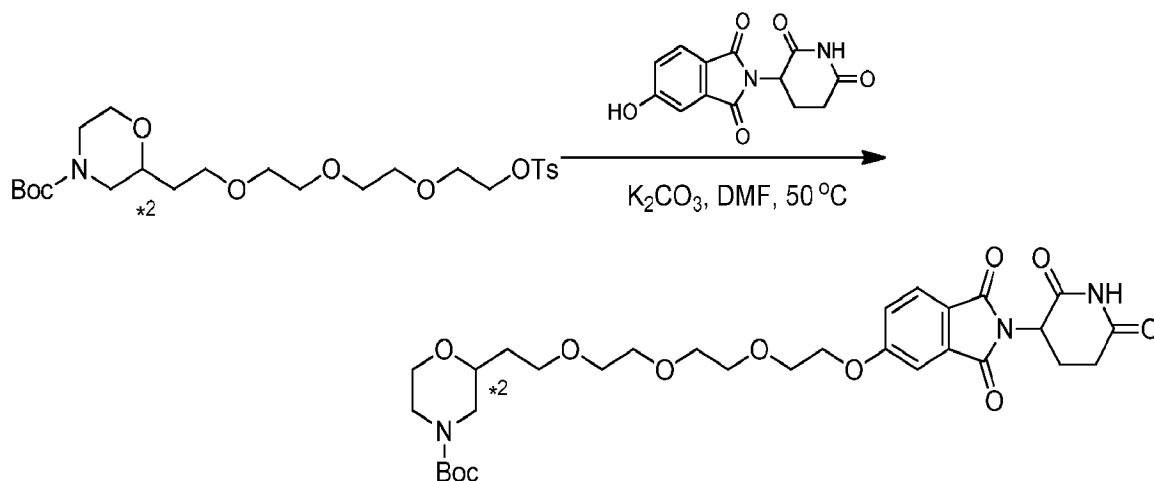
### Step 10



To a mixture of 3-(6-chloropyrimidin-4-yl)-5-(1-methylcyclopropoxy)-2H-indazole (26.11 mg, 86.81  $\mu\text{mol}$ , 1.1 *eq*) and 2-(2,6-dioxo-3-piperidyl)-5-[2-[2-[2-[2-[(2R)-morpholin-2-yl]ethoxy]ethoxy]ethoxy]ethoxy]isoindoline-1,3-dione (50 mg, 78.92  $\mu\text{mol}$ , 1 *eq*, TFA) in DMSO (2 mL) was added DIPEA (20.40 mg, 157.84  $\mu\text{mol}$ , 27.49  $\mu\text{L}$ , 2 *eq*) in one portion at 20°C under  $\text{N}_2$ . The mixture was stirred at 100°C for 1 h. The aqueous phase was extracted with ethyl acetate (3 mL \* 2). The combined organic phase was washed with brine (3 mL), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The crude product was purified by reversed-phase HPLC (Column: Phenomenex Luna C18 100\*30mm\*5 $\mu\text{m}$ ; Condition: water (0.225%FA)-ACN; B: 23%-53%; 9 min) to give 2-(2,6-dioxo-3-piperidyl)-5-[2-[2-[2-[2-[(2R)-4-[6-[5-(1-methylcyclopropoxy)-2H-indazol-3-yl]pyrimidin-4-yl]morpholin-2-yl]ethoxy]ethoxy]ethoxy]ethoxy]isoindoline-1,3-dione (7.6 mg, 9.21  $\mu\text{mol}$ , 11.67% yield, 95% purity) as a yellow solid.

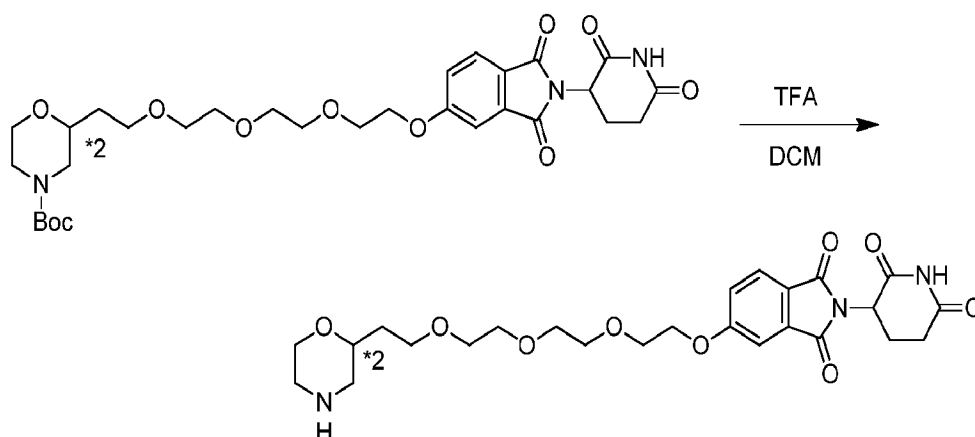
### [00229] Exemplary Synthesis of Exemplary Compound 18

#### Step 1



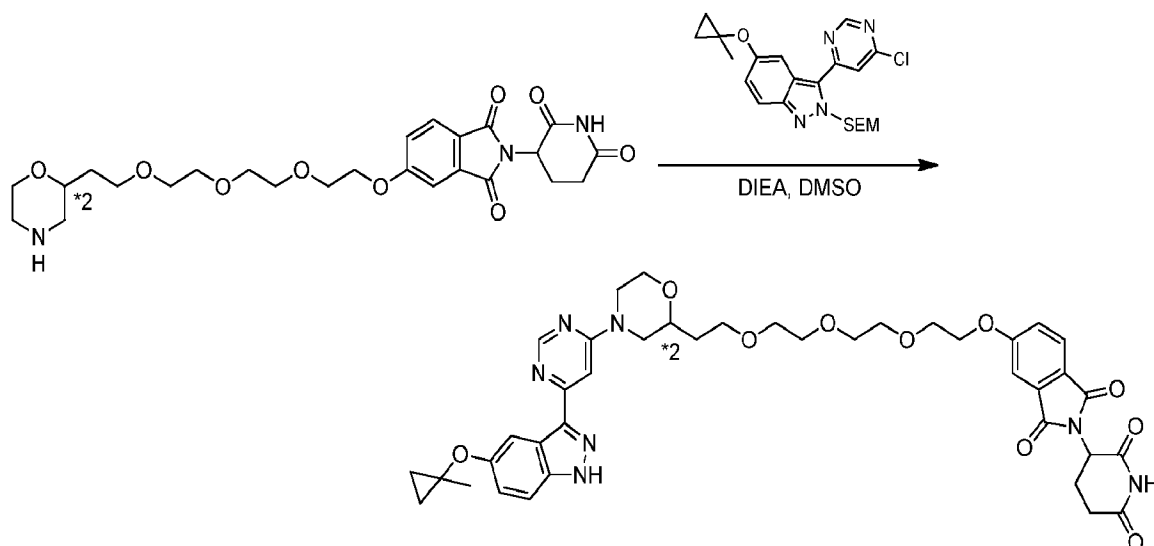
To a mixture of tert-butyl (2<sup>\*2</sup>)-2-[2-[2-[2-(p-tolylsulfonyloxy)ethoxy]ethoxy]ethoxy]ethyl]morpholine-4-carboxylate (146 mg, 282.05  $\mu\text{mol}$ , 1 *eq*) and 2-(2,6-dioxo-3-piperidyl)-5-hydroxy-isindoline-1,3-dione (85.08 mg, 310.26  $\mu\text{mol}$ , 1.1 *eq*) in DMF (2 mL) was added  $\text{K}_2\text{CO}_3$  (77.97 mg, 564.11  $\mu\text{mol}$ , 2 *eq*) in one portion at 20°C under  $\text{N}_2$ . The mixture was stirred at 70°C for 2 hours. The mixture was cooled to 25°C and concentrated in reduced pressure at 25°C. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (5 mL \* 3). The combined organic phase was washed with brine (5 mL \* 3), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 12 g, 100-200 mesh silica gel, 0-80% (20 min) of Ethyl acetate in Petroleum ether, 80% (10 min) of Ethyl acetate in Petroleum ether) to give tert-butyl (2<sup>\*2</sup>)-2-[2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isindolin-5-yl]oxyethoxy]ethoxy]ethoxy]ethyl]morpholine-4-carboxylate (118 mg, 190.43  $\mu\text{mol}$ , 67.51% yield) as a colourless gum.

## Step 2



To a mixture of tert-butyl (2<sup>\*2</sup>)-2-[2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]oxyethoxy]ethoxy]ethoxy]ethyl]morpholine-4-carboxylate (118 mg, 190.43  $\mu$ mol, 1 *eq*) in DCM (5 mL) was added TFA (21.71 mg, 190.43  $\mu$ mol, 14.10  $\mu$ L, 1 *eq*) in one portion at 25°C under N<sub>2</sub>. The mixture was stirred at 25°C for 30 min. TLC showed starting material consumed. The reaction mixture was concentrated under reduced pressure to remove solvent to give 2-(2,6-dioxo-3-piperidyl)-5-[2-[2-[2-[2-[(2<sup>\*2</sup>)-morpholin-2-yl]ethoxy]ethoxy]ethoxy]ethoxy]isoindoline-1,3-dione (118 mg, 143.60  $\mu$ mol, 75.41% yield, 77.102% purity, TFA) as a yellow gum.

### Step 3



To a mixture of 2-[[3-(6-chloropyrimidin-4-yl)-5-(1-methylcyclopropoxy)indazol-2-yl]methoxy]ethyl-trimethyl-silane (107.68 mg, 249.83  $\mu$ mol, 1.1 *eq*) and 2-(2,6-dioxo-3-piperidyl)-5-[2-[2-[2-[2-[(2<sup>\*2</sup>)-morpholin-2-yl]ethoxy]ethoxy]ethoxy]ethoxy]isoindoline-1,3-dione (118 mg, 227.12  $\mu$ mol, 1 *eq*, TFA) in DMSO (2 mL) was added DIPEA (58.71 mg, 454.25  $\mu$ mol, 79.12  $\mu$ L, 2 *eq*) in one portion at 20°C under N<sub>2</sub>. The mixture was stirred at 100°C for 1 h, then HCl (4 M, 283.90  $\mu$ L, 5 *eq*) was added, the solution was stirred at 65°C for 30 min. The aqueous phase was extracted with ethyl acetate (3 mL \* 2). The combined organic phase was washed with brine (3 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The crude product was purified by reversed-phase HPLC (Column: Phenomenex Luna C18 100\*30mm\*5 $\mu$ m; Condition: water (0.225%FA)-ACN; B%: 23%-53%; 9 min) to give 2-(2,6-dioxo-3-piperidyl)-5-[2-[2-[2-[2-[(2<sup>\*2</sup>)-4-[6-[5-(1-methylcyclopropoxy)-2H-indazol-3-

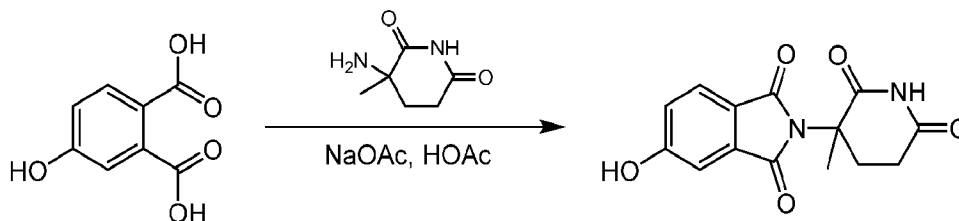


yl]pyrimidin-4-yl]morpholin-2-yl]ethoxy]ethoxy]ethoxy]ethoxy]isoindoline-1,3-dione (43.1 mg, 53.17  $\mu\text{mol}$ , 23.41% yield, 96.7% purity) as a pink solid.

Total H count from HNMR data: 43

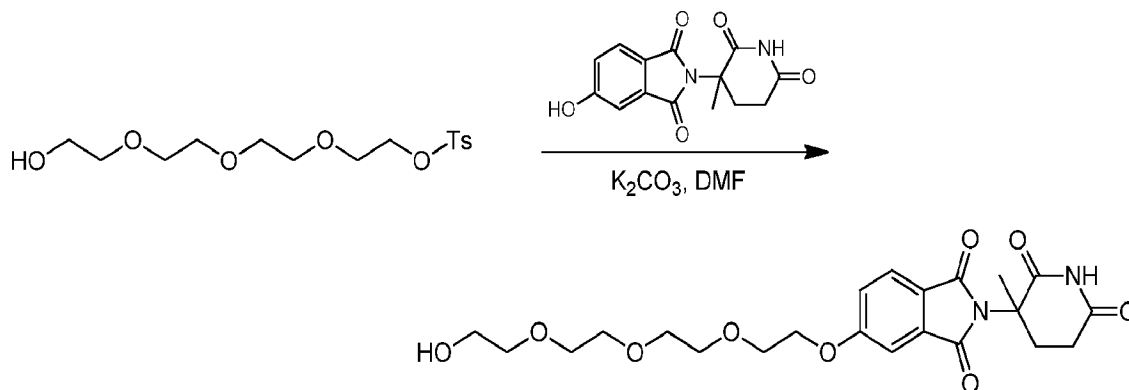
### [00230] Exemplary Synthesis of Exemplary Compound 19

#### Step 1

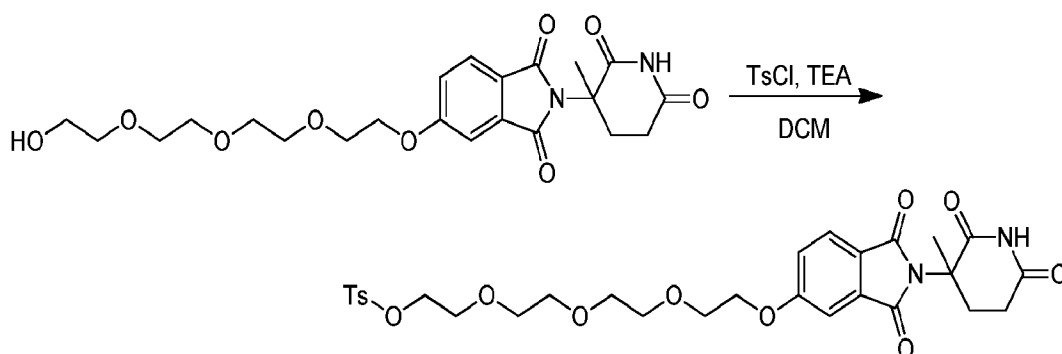


To a solution of 4-hydroxyphthalic acid (256.24 mg, 1.41 mmol, 1 eq) and 3-amino-3-methylpiperidine-2,6-dione (200 mg, 1.41 mmol, 1 eq) in HOAc (4 mL) was added NaOAc (346.24 mg, 4.22 mmol, 3 eq). The reaction mixture was stirred at 120 °C for 16 hr under N<sub>2</sub>. The reaction mixture was poured into H<sub>2</sub>O (10 mL\*2) and removed residual water by centrifuge to afford 5-hydroxy-2-(3-methyl-2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (114 mg, 355.93  $\mu\text{mol}$ , 25.30% yield, 90% purity) as a white solid. The crude product was used for next step directly.

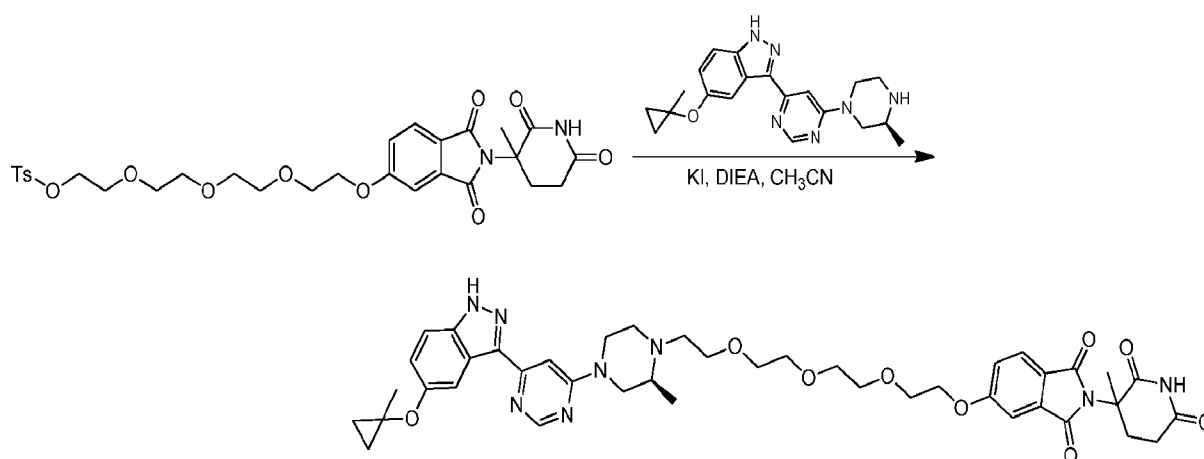
#### Step 2



To a solution of 2-[2-[2-(2-hydroxyethoxy)ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate (165.35 mg, 474.58  $\mu\text{mol}$ , 1.2 eq) and 5-hydroxy-2-(3-methyl-2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (114 mg, 395.48  $\mu\text{mol}$ , 1 eq) in DMF (5 mL) was added K<sub>2</sub>CO<sub>3</sub> (163.97 mg, 1.19 mmol, 3 eq). After addition, the reaction mixture was stirred at 70 °C for 2 hr. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (0 to 100% ethyl acetate in petroleum ether) to afford 5-[2-[2-[2-(2-hydroxyethoxy)ethoxy]ethoxy]ethoxy]-2-(3-methyl-2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (180 mg, 313.91  $\mu\text{mol}$ , 79.37% yield, 81% purity) as a colorless oil.

**Step 3**

To a solution of 5-[2-[2-[2-(2-hydroxyethoxy)ethoxy]ethoxy]ethoxy]-2-(3-methyl-2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (180 mg, 387.54  $\mu\text{mol}$ , 1 eq) and 4-methylbenzenesulfonyl chloride (147.77 mg, 775.09  $\mu\text{mol}$ , 2 eq) in DCM (3 mL) was added DMAP (4.73 mg, 38.75  $\mu\text{mol}$ , 0.1 eq) and TEA (117.65 mg, 1.16 mmol, 161.82  $\mu\text{L}$ , 3 eq). After addition, the mixture was stirred at 20°C for 16 hours. The filtrate was quenched by water (10 mL) and extracted with ethyl acetate (3 \* 10 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by prep.TLC (silica gel, Petroleum ether : Ethyl acetate=0:1,  $R_f$ =0.43) to afford 2-[2-[2-[2-(3-methyl-2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]oxyethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate (140 mg, 193.94  $\mu\text{mol}$ , 50.04% yield, 85.70% purity) as a colorless solid.

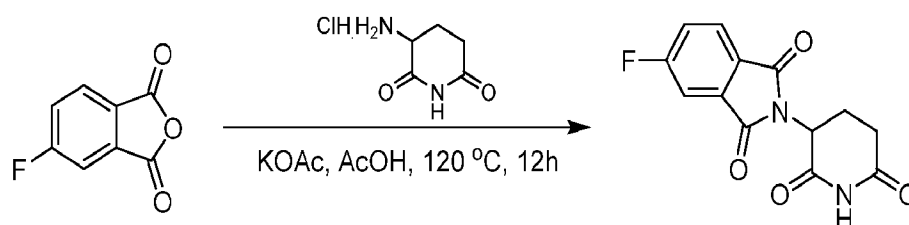
**Step 4**

To a solution of 2-[2-[2-[2-(3-methyl-2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]oxyethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate (140 mg, 226.30  $\mu\text{mol}$ , 1 eq) and 5-(1-methylcyclopropoxy)-3-[6-[(3S)-3-methylpiperazin-1-yl]pyrimidin-4-yl]-1H-indazole (82.47 mg, 226.30  $\mu\text{mol}$ , 1 eq) in ACN (4 mL) was added KI (187.83 mg, 1.13 mmol, 5 eq) and DIEA (146.24 mg, 1.13 mmol, 197.09  $\mu\text{L}$ , 5 eq). The mixture was stirred at 100 °C for 6 hr. The

reaction allowed to cool, water (10 mL) was added, and the mixture was extracted with ethyl acetate (3 x 10 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100\*30mm\*5um; mobile phase: [water(0.225%FA)-ACN]; B%: 15%-45%, 9min) to afford 2-(3-methyl-2,6-dioxo-3-piperidyl)-5-[2-[2-[2-[2-[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethoxy]ethoxy]ethoxy]ethoxy]isoindoline-1,3-dione (11.1 mg, 13.58 umol, 6.00% yield, 99.21% purity) as a red solid.

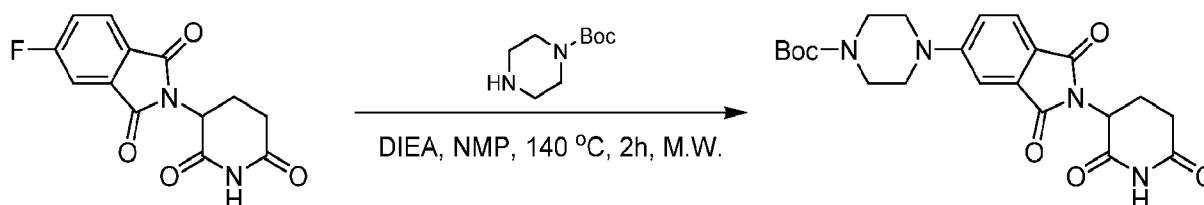
### [00231] Exemplary Synthesis of Exemplary Compound 20

#### Step 1



To a solution of 5-fluoroisobenzofuran-1,3-dione (1 g, 6.02 mmol, 1 *eq*) and 3-aminopiperidine-2,6-dione HCl salt (1.49 g, 9.03 mmol, 1.5 *eq*) in CH<sub>3</sub>COOH (10 mL) was added KOAc (1.18 g, 12.04 mmol, 2 *eq*). After addition, the reaction mixture was stirred at 120°C for 12 hours. The mixture was diluted with water (40 mL). The mixture was filtered, and the filtrate cake was washed with water (100 mL) to afford 2-(2,6-dioxo-3-piperidyl)-5-fluoro-isoindoline-1,3-dione (1.4 g, 5.07 mmol, 84.19% yield) as a black solid.

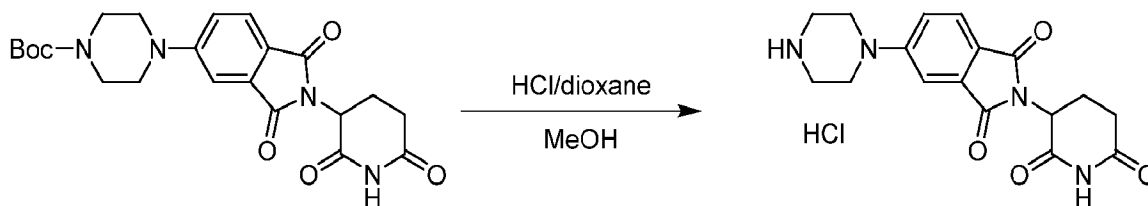
#### Step 2



To a solution of 2-(2,6-dioxo-3-piperidyl)-5-fluoro-isoindoline-1,3-dione (1.15 g, 4.16 mmol, 1 *eq*) and tert-butyl piperazine-1-carboxylate (852.97 mg, 4.58 mmol, 1.1 *eq*) in NMP (10 mL) was added DIEA (1.61 g, 12.49 mmol, 2.18 mL, 3 *eq*). The sealed tube was heated at 140°C for 2 hours under microwave. The mixture was combined with batch EB12-30-P1 and diluted with water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic phase was washed with saturated brine (2 x 30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to

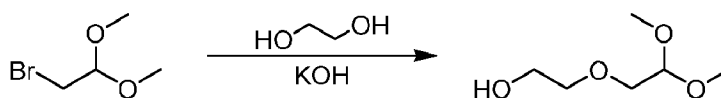
50% ethyl acetate in petroleum ether) to afford tert-butyl 4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazine-1-carboxylate (1.4 g, 3.16 mmol, 76.00% yield) as a yellow solid. Based on EB12-30 (905.08  $\mu$ mol starting material) and EB12-32 (4.16 mmol starting material), the average yield is 62.49%.

### Step 3



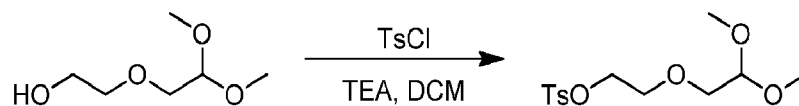
To a solution of tert-butyl 4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazine-1-carboxylate (1.2 g, 2.71 mmol, 1 *eq*) in MeOH (10 mL) was added HCl/dioxane (4 M, 2.00 mL, 2.95 *eq*). After addition, the reaction solution was stirred at 65°C for 1h. The reaction solution was combined with batch EB12-34-P1. The mixture was concentrated under reduced pressure to afford 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindoline-1,3-dione hydrochloride (1.1 g, crude) as a yellow solid. Based on EB12-34 (452.01  $\mu$ mol starting material) and EB12-35 (2.71 mmol starting material), the average yield is 91.04%.

### Step 4



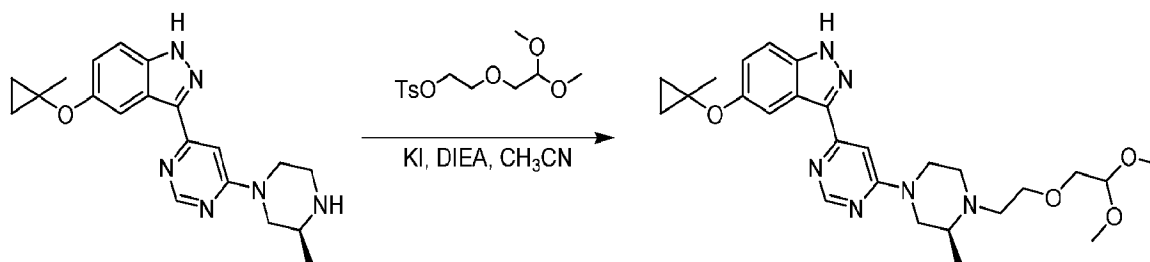
A solution of KOH (2.21 g, 39.46 mmol, 2 *eq*) in ethylene glycol (3.67 g, 59.17 mmol, 3.31 mL, 5 *eq*) was stirred at 115°C. After the potassium hydroxide dissolved, 2-bromo-1,1-dimethoxyethane (2 g, 11.83 mmol, 1.39 mL, 1 *eq*) was added dropwise over 5 minutes, and the reaction mixture was stirred for 20 hours. TLC (ethyl acetate: petroleum ether=1:1) showed a new spot. The mixture was then allowed to cool to room temperature (20°C), and the whole was diluted with water (40 mL), then extracted with dichloromethane (3 x 20 mL). The organic layer was washed with brine (3 x 20 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 50% ethyl acetate in petroleum ether) to afford 2-(2,2-dimethoxyethoxy)ethanol (200 mg, 1.33 mmol, 11.25% yield) as a light yellow oil.

### Step 5



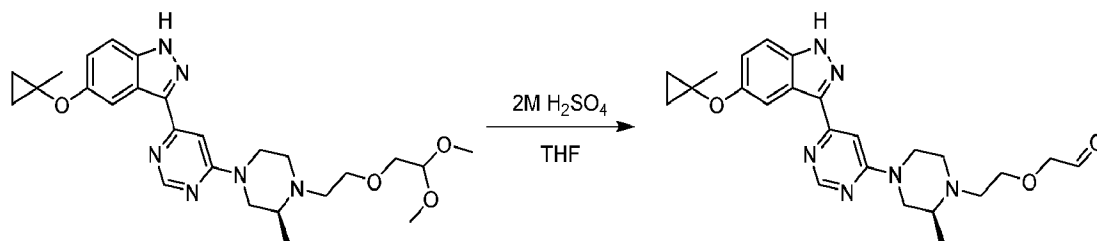
To a solution of 2-(2,2-dimethoxyethoxy)ethanol (200 mg, 1.33 mmol, 1 *eq*) and 4-methylbenzenesulfonyl chloride (507.81 mg, 2.66 mmol, 2 *eq*) in DCM (3 mL) was added TEA (269.53 mg, 2.66 mmol, 370.74  $\mu$ L, 2 *eq*). After addition, the reaction solution was stirred at 20°C for 16h. TLC (Petroleum ether: Ethyl acetate=1:1) showed starting material was consumed and TLC (Petroleum ether: Ethyl acetate=5:1) showed a new spot. The reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 30% ethyl acetate in petroleum ether) to afford 2-(2-(2,2-dimethoxyethoxy)ethyl 4-methylbenzenesulfonate (350 mg, 1.15 mmol, 86.35% yield) as a light yellow oil.

#### Step 6



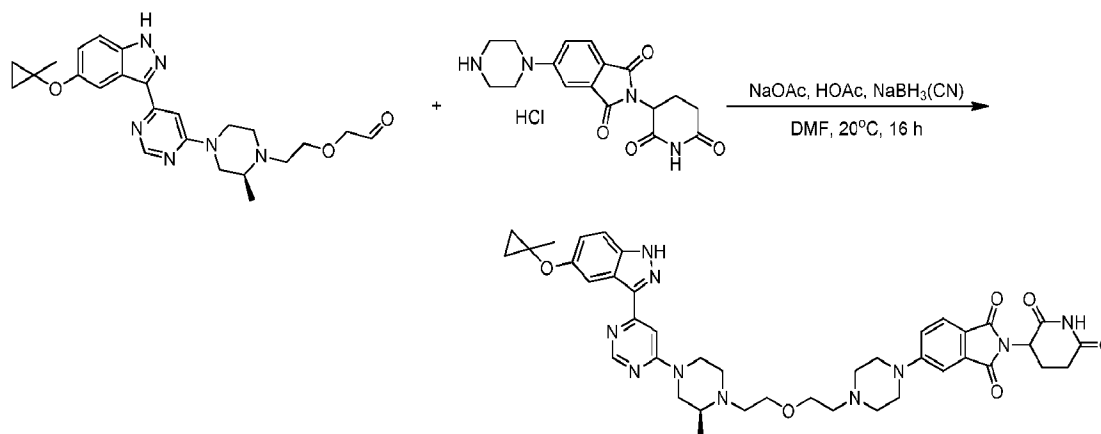
To a solution of 5-(1-methylcyclopropoxy)-3-[6-[(3S)-3-methylpiperazin-1-yl]pyrimidin-4-yl]-1H-indazole (100 mg, 274.39  $\mu$ mol, 1 *eq*) and 2-(2-(2,2-dimethoxyethoxy)ethyl 4-methylbenzenesulfonate (83.51 mg, 274.39  $\mu$ mol, 1 *eq*) in CH<sub>3</sub>CN (3 mL) was added KI (227.75 mg, 1.37 mmol, 5 *eq*) and DIEA (70.93 mg, 548.78  $\mu$ mol, 95.59  $\mu$ L, 2 *eq*). After addition, the reaction mixture was stirred at 90°C for 12h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 10% methanol in dichloromethane) to afford 3-[6-[(3S)-4-[2-(2,2-dimethoxyethoxy)ethyl]-3-methyl-piperazin-1-yl]pyrimidin-4-yl]-5-(1-methylcyclopropoxy)-1H-indazole (80 mg, 146.60  $\mu$ mol, 53.43% yield, 91% purity) as a yellow oil.

#### Step 7



To a solution of 3-[6-[(3S)-4-[2-(2,2-dimethoxyethoxy)ethyl]-3-methyl-piperazin-1-yl]pyrimidin-4-yl]-5-(1-methylcyclopropoxy)-1H-indazole (80 mg, 161.10  $\mu\text{mol}$ , 1 *eq*) in THF (3 mL) was added  $\text{H}_2\text{SO}_4$  (2 M, 3.22 mL, 40 *eq*). After addition, the reaction solution was stirred at 70°C for 1h. The reaction solution was quenched with saturated  $\text{NaHCO}_3$  (pH=7). The resulting mixture was extracted with ethyl acetate (3 x 10mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 2-[2-[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethoxy]acetaldehyde (60 mg, 118.53  $\mu\text{mol}$ , 73.58% yield, 89% purity) as a yellow solid. The crude product was used directly.

### Step 8

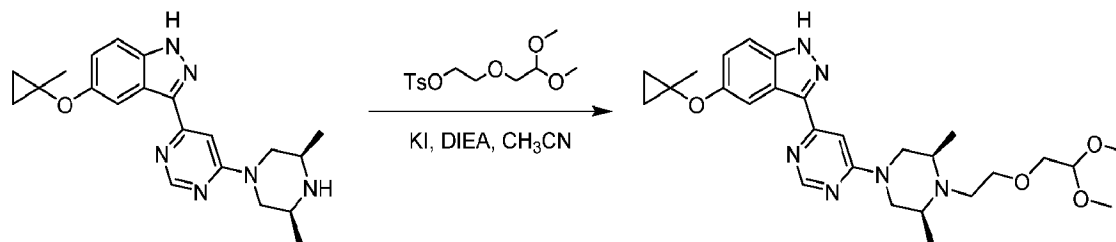


To a solution of 2-[2-[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethoxy]acetaldehyde (60 mg, 133.18  $\mu\text{mol}$ , 1 *eq*) and 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindoline-1,3-dione hydrochloride (50.45 mg, 133.18  $\mu\text{mol}$ , 1 *eq*) in DMF (3 mL) was added NaOAc (32.77 mg, 399.53  $\mu\text{mol}$ , 3 *eq*), HOAc (8.00 mg, 133.18  $\mu\text{mol}$ , 7.62  $\mu\text{L}$ , 1 *eq*) and  $\text{NaBH}_3\text{CN}$  (16.74 mg, 266.35  $\mu\text{mol}$ , 2 *eq*). After addition, the reaction mixture was stirred at 20°C for 16h. The filtrate was purified by prep.HPLC(column: Agela DuraShell C18 150\*25mm\*5 $\mu\text{m}$ ;mobile phase: [water(0.04% $\text{NH}_3\text{H}_2\text{O}$ +10mM  $\text{NH}_4\text{HCO}_3$ )-ACN];B%: 40%-70%,8min) to afford 2-(2,6-dioxo-3-piperidyl)-5-[4-[2-[2-[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-

yl]ethoxy]ethyl]piperazin-1-yl]isoindoline-1,3-dione (15.8 mg, 20.13  $\mu\text{mol}$ , 15.12% yield, 99% purity) as a yellow solid.

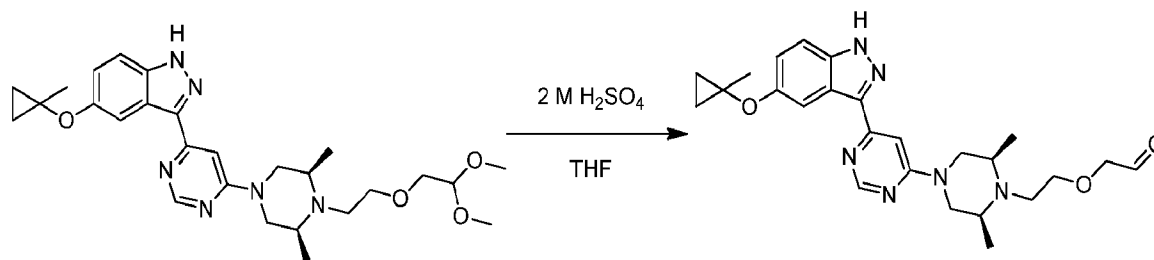
## [00232] Exemplary Synthesis of Exemplary Compound 21

### Step 1



To a mixture of 3-[6-[(3R,5S)-3,5-dimethylpiperazin-1-yl]pyrimidin-4-yl]-5-(1-methylcyclopropoxy)-1H-indazole (100 mg, 264.22  $\mu\text{mol}$ , 1 *eq*) and 2-(2,2-dimethoxyethoxy)ethyl 4-methylbenzenesulfonate (80.42 mg, 264.22  $\mu\text{mol}$ , 1 *eq*) in  $\text{CH}_3\text{CN}$  (3 mL) was added KI (43.86 mg, 264.22  $\mu\text{mol}$ , 1 *eq*) and DIPEA (34.15 mg, 264.22  $\mu\text{mol}$ , 46.02  $\mu\text{L}$ , 1 *eq*) one portion at 20°C under  $\text{N}_2$ , then the reaction mixture was heated to 100°C and stirred for 24 h to give brown suspension. The suspension was filtered and filtrate was concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 0-10% of MeOH in DCM) to give 3-[6-[(3R,5S)-4-[2-(2,2-dimethoxyethoxy)ethyl]-3,5-dimethylpiperazin-1-yl]pyrimidin-4-yl]-5-(1-methylcyclopropoxy)-1H-indazole (110 mg, crude) as a yellow solid.

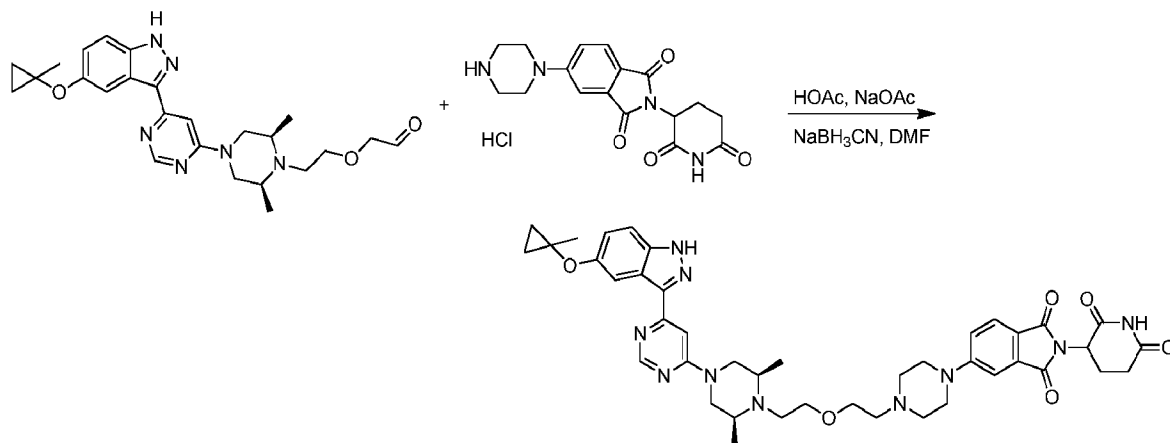
### Step 2



To a solution of 3-[6-[(3R,5S)-4-[2-(2,2-dimethoxyethoxy)ethyl]-3,5-dimethylpiperazin-1-yl]pyrimidin-4-yl]-5-(1-methylcyclopropoxy)-1H-indazole (110 mg, 215.42  $\mu\text{mol}$ , 1 *eq*) in THF (5 mL) was added  $\text{H}_2\text{SO}_4$  (2 M, 4.31 mL, 40 *eq*) in one portion at 20°C under  $\text{N}_2$ . Then the solution was heated to 70°C and stirred for 1 h to give yellow solution. TLC (DCM: MeOH=10:1,  $R_f = 0.06$ ) showed the reaction was completed. The solution was cooled to 20°C. The solution as poured into water (5 mL) and  $\text{NaHCO}_3$  to adjusted the pH to 7-8. The aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic phase was washed with brine (2

x 10 mL), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum to give 2-[2-[(2R,6S)-2,6-dimethyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethoxy]acetaldehyde (50 mg, 75.72  $\mu\text{mol}$ , 35.15% yield, 70.353% purity) as a yellow solid.

### Step 3

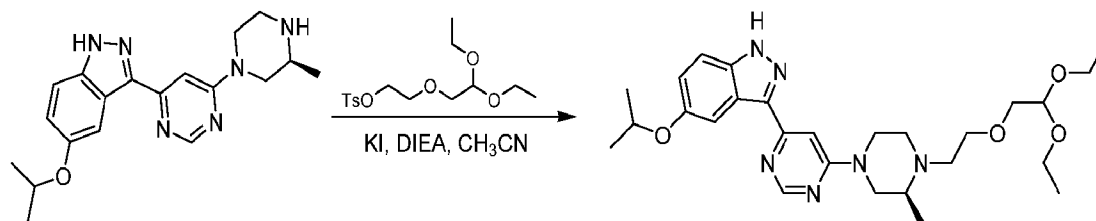


To a mixture of 2-[2-[(2R,6S)-2,6-dimethyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethoxy]acetaldehyde (50 mg, 107.63  $\mu\text{mol}$ , 1 *eq*) and 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindoline-1,3-dione hydrochloride (81.54 mg, 215.26  $\mu\text{mol}$ , 2 *eq*) in DMF (2 mL) was added NaOAc (26.49 mg, 322.89  $\mu\text{mol}$ , 3 *eq*) and acetic acid (3.23 mg, 53.81  $\mu\text{mol}$ , 3.08  $\mu\text{L}$ , 0.5 *eq*). The mixture was stirred at 25°C for 0.5 h. Then  $\text{NaBH}_3\text{CN}$  (13.53 mg, 215.26  $\mu\text{mol}$ , 2 *eq*) was added to the mixture. The mixture was stirred at 20°C for 16 h. The starting material was consumed completely, and desired compound was detected by LCMS. The residue was filtered and filtrate was purified directly by prep-HPLC (column: Agela DuraShell C18 150\*25mm\*5 $\mu\text{m}$ ; mobile phase: water (0.04%  $\text{NH}_3\text{H}_2\text{O}$ +10mM  $\text{NH}_4\text{HCO}_3$ )-ACN; B%: 50%-80%, Gradient Time (min):8min; FlowRate (ml/min):25) to give 5-[4-[2-[2-[(2R,6S)-2,6-dimethyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethoxy]ethyl]piperazin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (16.4 mg, 20.74  $\mu\text{mol}$ , 19.27% yield, 100% purity) as a yellow solid.

## [00233] Exemplary Synthesis of Exemplary Compound 22

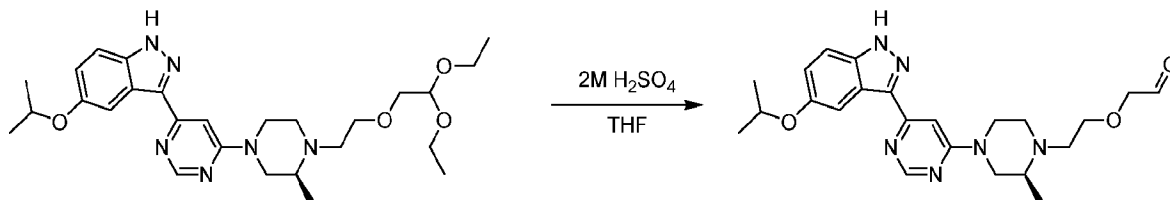
### Step 1





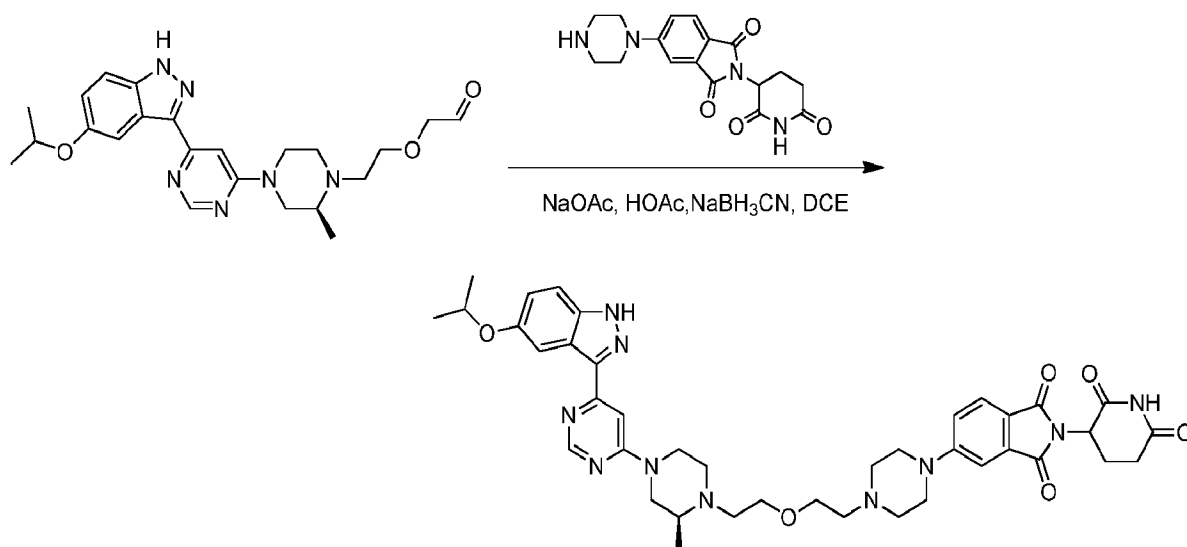
To a solution of 5-isopropoxy-3-[6-[(3S)-3-methylpiperazin-1-yl]pyrimidin-4-yl]-1H-indazole (320 mg, 822.85  $\mu\text{mol}$ , 1 *eq.*, HCl salt) and 2-(2,2-diethoxyethoxy)ethyl 4-methylbenzenesulfonate (328.23 mg, 987.42  $\mu\text{mol}$ , 1.2 *eq.*) in  $\text{CH}_3\text{CN}$  (6 mL) was added KI (1.37 g, 8.23 mmol, 10 *eq.*) and DIEA (1.06 g, 8.23 mmol, 1.43 mL, 10 *eq.*). The mixture was stirred at  $90^\circ\text{C}$  for 18 hr. Several new peaks were shown on LC-MS and ~41% of desired compound was detected. The reaction mixture was diluted with water (20 mL) and extracted with EA (30 mL). The combined organic layers were washed with brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography on silica gel (DCM in MeOH = 0 to 10%) to afford 3-[6-[(3S)-4-[2-(2,2-diethoxyethoxy)ethyl]-3-methyl-piperazin-1-yl]pyrimidin-4-yl]-5-isopropoxy-1H-indazole (250 mg, 419.40  $\mu\text{mol}$ , 50.97% yield, 86% purity) as a yellow oil.

### Step 2



To a solution of 3-[6-[(3S)-4-[2-(2,2-diethoxyethoxy)ethyl]-3-methyl-piperazin-1-yl]pyrimidin-4-yl]-5-isopropoxy-1H-indazole (125 mg, 243.83  $\mu\text{mol}$ , 1 *eq.*) in THF (1 mL) was added  $\text{H}_2\text{SO}_4$  (2 M, 1.25 mL, 10.25 *eq.*). The mixture was stirred at  $70^\circ\text{C}$  for 1 hr. TLC indicated reactant was consumed and one major new spot with larger polarity was detected. The reaction mixture was diluted with saturated  $\text{NaHCO}_3$  (20 mL) and extracted with EA (30 mL). The combined organic layers were washed with brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give 2-[2-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethoxy]acetaldehyde (100 mg, 207.52  $\mu\text{mol}$ , 85.11% yield, 91% purity) as a light yellow solid.

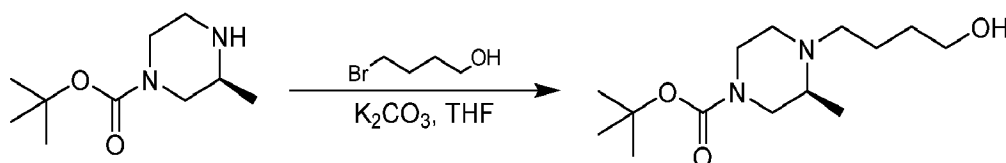
### Step 3



To a solution of 2-[2-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethoxy]acetaldehyde (100 mg, 228.04  $\mu\text{mol}$ , 1 *eq.*) and 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindoline-1,3-dione 2,2,2-trifluoroacetate (104.07 mg, 228.04  $\mu\text{mol}$ , 1 *eq.*) in DCE (3 mL) was added NaOAc (56.12 mg, 684.12  $\mu\text{mol}$ , 3 *eq.*), HOAc (13.69 mg, 228.04  $\mu\text{mol}$ , 13.04  $\mu\text{L}$ , 1 *eq.*) and  $\text{NaBH}_3\text{CN}$  (42.99 mg, 684.12  $\mu\text{mol}$ , 3 *eq.*). The mixture was stirred at 25°C for 18 hr. LC-MS (EB134-92-P1C) showed reactant 1 was consumed. Several new peaks were shown on LC-MS and ~86% of desired compound was detected. The reaction solution was filtered to remove insoluble substance. The reaction solution was purified by prep-HPLC (FA condition: column: Phenomenex Luna C18 100\*30mm\*5 $\mu\text{m}$ ; mobile phase: [water (0.225%FA)-ACN]; B%: 5%-35%, 18min) to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[2-[2-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethoxy]ethyl]piperazin-1-yl]isoindoline-1,3-dione (27.70 mg, 34.88  $\mu\text{mol}$ , 15.29% yield, 96.3% purity) as a yellow solid.

### [00234] Exemplary Synthesis of Exemplary Compound 23

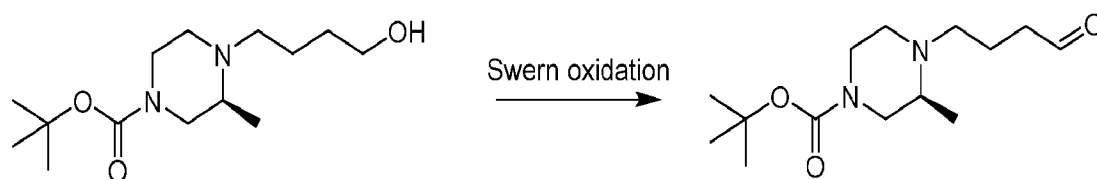
#### Step 1



To a solution of tert-butyl (3S)-3-methylpiperazine-1-carboxylate (3.5 g, 17.48 mmol, 1 *eq.*) and 4-bromobutan-1-ol (3.34 g, 17.48 mmol, 1 *eq.*) in THF (10 mL) was added  $\text{K}_2\text{CO}_3$  (7.25 g, 52.43 mmol, 3 *eq.*). Then the mixture was stirred at 60°C for 16 hours under  $\text{N}_2$ . TLC

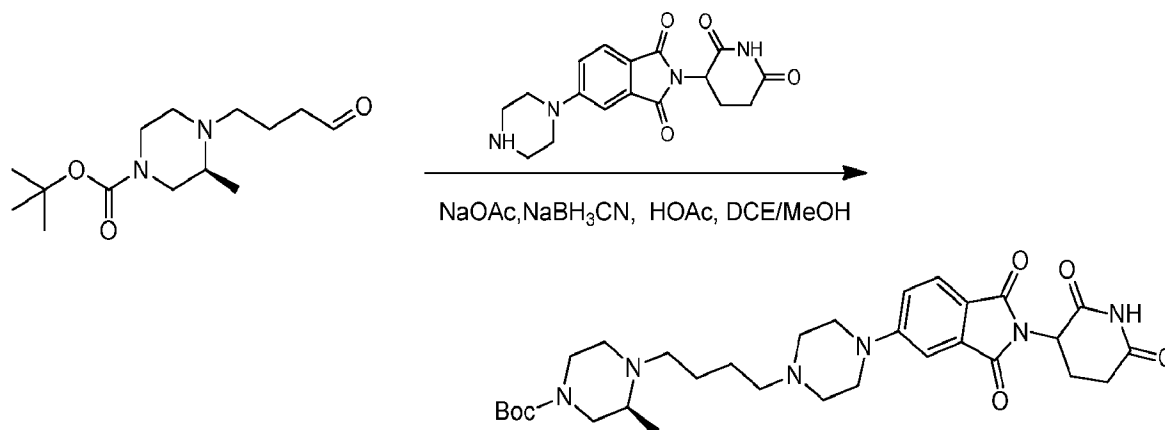
(Dichloromethane: Methanol=10:1,  $R_f$ =0.2) showed the reaction new spot. The reaction mixture was filtered and the filtrate was concentrated. The crude was purified by a flash chromatography on silica(0-10% Methanol in Dichloromethane) to afford tert-butyl (3S)-4-(4-hydroxybutyl)-3-methyl-piperazine-1-carboxylate (4 g, 14.69 mmol, 84.03% yield) as a colorless liquid.

### Step 2



A solution of OXALYL CHLORIDE (512.58 mg, 4.04 mmol, 353.51  $\mu$ L, 1.1 *eq*) in DCM (10 mL) was cooled to  $-60\text{ }^{\circ}\text{C}$  under an atmosphere of dry nitrogen. A solution of DMSO (717.13 mg, 9.18 mmol, 717.13  $\mu$ L, 2.5 *eq*) in DCM (10 mL) was added dropwise, and the mixture was subsequently stirred for 15 min at  $-60\text{ }^{\circ}\text{C}$ . Next, a solution of tert-butyl (3R)-4-(4-hydroxybutyl)-3-methyl-piperazine-1-carboxylate (1 g, 3.67 mmol, 1 *eq*) in DCM (10 mL) was added dropwise and the mixture was stirred for 45 min at  $-60\text{ }^{\circ}\text{C}$ . Subsequently, TEA (1.11 g, 11.01 mmol, 1.53 mL, 3 *eq*) was added, and the mixture was warmed to  $-60\text{ }^{\circ}\text{C}$  for 1 h. TLC (Dichloromethane: Methanol=10:1,  $R_f$ =0.4) showed a new spot. The reaction mixture was filtered and the filtrate was used directly in the next step. tert-butyl (3S)-3-methyl-4-(4-oxobutyl)piperazine-1-carboxylate (990 mg, crude) in DCM solution as Colorless Liquid, which was used directly in the next step.

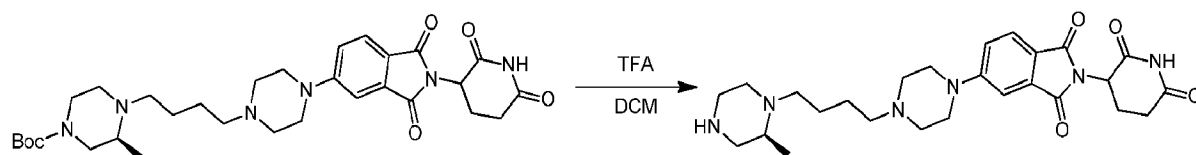
### Step 3



To a solution of 2-(2,6-dioxo-3-piperidyl)-5-piperazin-1-yl-isoindoline-1,3-dione (500 mg, 1.10 mmol, 1 *eq*, TFA) and tert-butyl (3S)-3-methyl-4-(4-oxobutyl)piperazine-1-carboxylate (446.11 mg, 1.65 mmol, 1.5 *eq*) in DCM (15 mL) and MeOH (15 mL) was added NaOAc (270.70 mg,

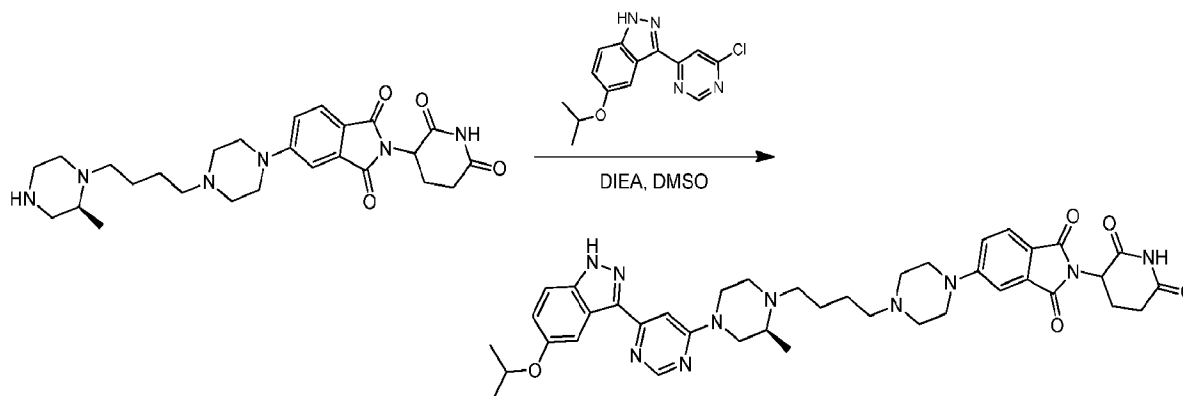
3.30 mmol, 3 *eq*) and the mixture was stirred at 20 °C for 20 min. Then the HOAc (6.61 mg, 110.00  $\mu$ mol, 6.29  $\mu$ L, 0.1 *eq*) and NaBH<sub>3</sub>CN (691.24 mg, 11.00 mmol, 10 *eq*) was added of the solution and stirred at 20 °C for 2hr. TLC (Dichloromethane: Methanol= 10:1, R<sub>f</sub>=0.01) was showed the reaction completed. The reaction mixture was poured into H<sub>2</sub>O (20 mL). The mixture was extracted with ethyl acetate (30 mL\*3). The organic phase was washed with brine (20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuum to give a residue. The residue was purified by silica gel column chromatography (0-20% Methanol in Dichloromethane) to give tert-butyl (3S)-4-[4-[4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazin-1-yl]butyl]-3-methyl-piperazine-1-carboxylate (600 mg, 703.85  $\mu$ mol, 63.99% yield, 70% purity) as a yellow gum.

#### Step 4



To a solution of tert-butyl (3S)-4-[4-[4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazin-1-yl]butyl]-3-methyl-piperazine-1-carboxylate (200 mg, 335.17  $\mu$ mol, 1 *eq*) in DCM (4 mL) was added TFA (3.08 g, 27.01 mmol, 2 mL, 80.59 *eq*) and the mixture was stirred at 15 °C for 1 hr. TLC (Dichloromethane: Methanol= 5:1, R<sub>f</sub>=0.01) was showed the reaction completed. The reaction mixture was concentrated in vacuum to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[4-[(2S)-2-methylpiperazin-1-yl]butyl]piperazin-1-yl]isoindoline-1,3-dione (200 mg, crude, TFA) as a yellow gum.

#### Step 5

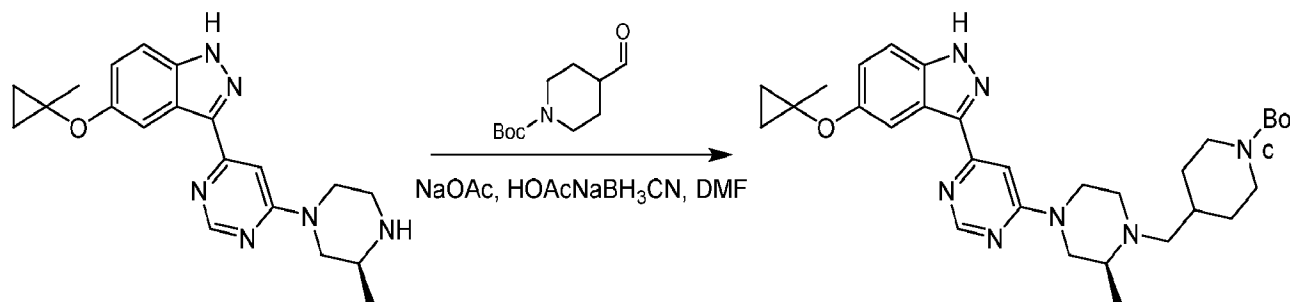


To a solution of 2-(2,6-dioxo-3-piperidyl)-5-[4-[4-[(2S)-2-methylpiperazin-1-yl]butyl]piperazin-1-yl]isoindoline-1,3-dione (200 mg, 327.53  $\mu$ mol, 1 *eq*, TFA) and 3-(6-chloropyrimidin-4-yl)-5-

isopropoxy-1H-indazole (66.20 mg, 229.27  $\mu\text{mol}$ , 0.7 *eq*) in DMSO (5 mL) was added DIEA (211.66 mg, 1.64 mmol, 285.25  $\mu\text{L}$ , 5 *eq*). Then the mixture was stirred at 100 °C for 2 hr under  $\text{N}_2$ . The reaction mixture was poured into  $\text{H}_2\text{O}$  (10 mL). The mixture was extracted with ethyl acetate (10 mL\*3). The aqueous phase was concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 100\*40mm\*3  $\mu\text{m}$ ; mobile phase: [water(0.225%FA)-ACN]; B%: 12%-42%, 10 min).to afford 2-(2,6-dioxo-3-piperidyl)-5-[4-[4-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]butyl]piperazin-1-yl]isoindoline-1,3-dione (7.9 mg, 10.35  $\mu\text{mol}$ , 3.16% yield, 98.07% purity) as a yellow solid.

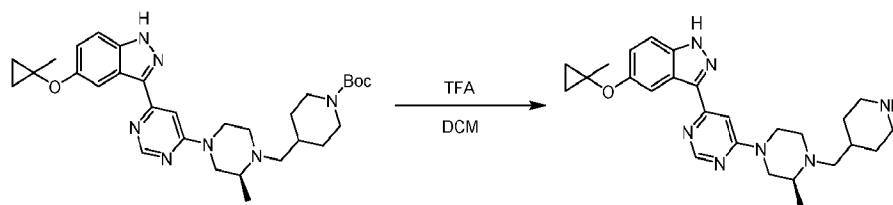
### [00235] Exemplary Synthesis of Exemplary Compound 24

#### Step 1



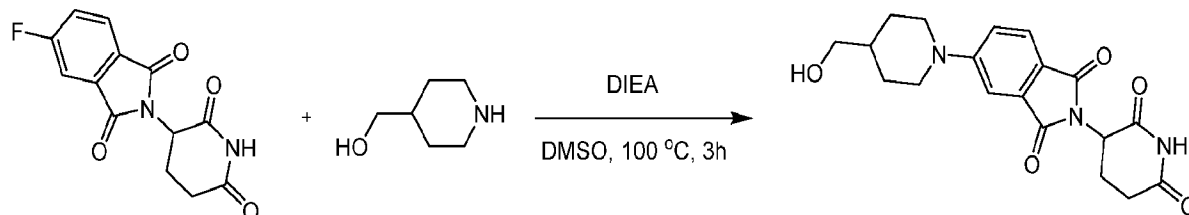
To a solution of 5-(1-methylcyclopropoxy)-3-[6-[(3S)-3-methylpiperazin-1-yl]pyrimidin-4-yl]-1H-indazole (100 mg, 274.39  $\mu\text{mol}$ , 1 *eq*) and tert-butyl 4-formylpiperidine-1-carboxylate (117.04 mg, 548.78  $\mu\text{mol}$ , 2 *eq*) in DMF (2 mL) was added  $\text{CH}_3\text{COOH}$  (823.89  $\mu\text{g}$ , 13.72  $\mu\text{mol}$ ,  $7.85 \times 10^{-1}$   $\mu\text{L}$ , 0.05 *eq*) and NaOAc (45.02 mg, 548.78  $\mu\text{mol}$ , 2 *eq*) in one portion at 20°C under  $\text{N}_2$ . The solution was stirred at 20°C for 5 h. then  $\text{NaBH}_3\text{CN}$  (34.49 mg, 548.78  $\mu\text{mol}$ , 2 *eq*) was added and the solution was stirred for 1h to give pale yellow solution. The residue was poured into water (5 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic phase was washed with brine (2 x 5 mL), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 50 -80% of Ethyl acetate in Petroleum ether) to give tert-butyl 4-[[[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]methyl]piperidine-1-carboxylate (110 mg, 172.72  $\mu\text{mol}$ , 62.95% yield, 88.199% purity) as a yellow oil.

#### Step 2



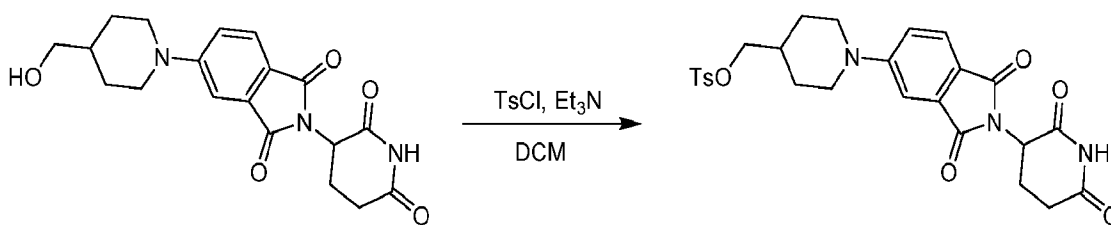
To a mixture of tert-butyl 4-[[[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]methyl]piperidine-1-carboxylate (110 mg, 195.83  $\mu\text{mol}$ , 1 *eq*) in DCM (5 mL) was added TFA (66.99 mg, 587.48  $\mu\text{mol}$ , 43.50  $\mu\text{L}$ , 3 *eq*) in one portion at 20°C under  $\text{N}_2$ . The mixture was stirred at 20°C for 1 h. The residue was poured into  $\text{NaHCO}_3$  (5 mL) to adjust the pH=7-8. The aqueous phase was extracted with ethyl acetate (3 x 5 mL). The combined organic phase was washed with brine (3 x 5 mL), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum to give crude product (150 mg). The crude product was purified by silica gel chromatography (100-200 mesh silica gel, 0-100 % of MeOH in EtOAc) to give 5-(1-methylcyclopropoxy)-3-[6-[(3S)-3-methyl-4-(4-piperidylmethyl)piperazin-1-yl]pyrimidin-4-yl]-1H-indazole (100 mg, crude) as a yellow gum.

### Step 3



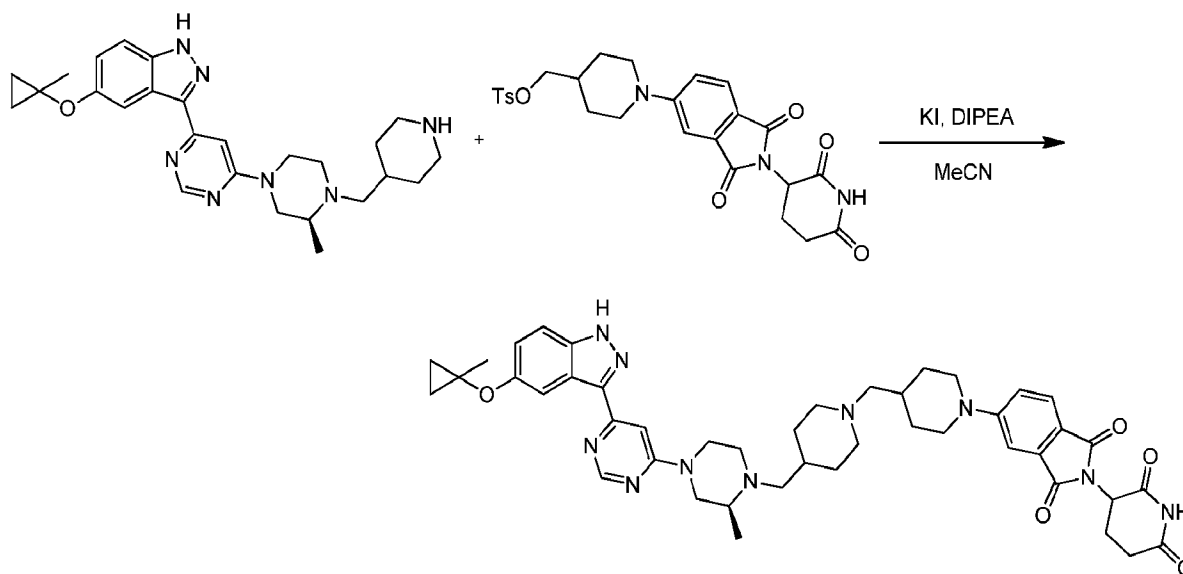
To a mixture of 2-(2,6-dioxo-3-piperidyl)-5-fluoro-isoindoline-1,3-dione (100 mg, 362.03  $\mu\text{mol}$ , 1 *eq*) and 4-piperidylmethanol (83.39 mg, 724.06  $\mu\text{mol}$ , 2 *eq*) in DMSO (2 mL) was added DIEA (140.37 mg, 1.09 mmol, 189.18  $\mu\text{L}$ , 3 *eq*) in one portion at 20°C. The mixture was stirred at 100°C for 3 h. TLC (DCM: MeOH = 10: 1,  $R_f$  = 0.36) showed the reaction was completed. The mixture was cooled to 20°C. The residue was poured into  $\text{NaHCO}_3$  (10 mL) to adjust pH=7-8. The aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic phase was washed with brine (2 x 10 mL), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 0-10% of MeOH in DCM) to give 2-(2,6-dioxo-3-piperidyl)-5-[4-(hydroxymethyl)-1-piperidyl]isoindoline-1,3-dione (120 mg, 283.18  $\mu\text{mol}$ , 78.22% yield, 87.640% purity) as a yellow gum.

### Step 4



To a solution of 2-(2,6-dioxo-3-piperidyl)-5-[4-(hydroxymethyl)-1-piperidyl]isoindoline-1,3-dione (120 mg, 323.11  $\mu\text{mol}$ , 1 *eq*) and TEA (98.09 mg, 969.34  $\mu\text{mol}$ , 134.92  $\mu\text{L}$ , 3 *eq*) in DCM (5 mL) was added TsCl (27.35 mg, 387.74  $\mu\text{mol}$ , 1.2 *eq*) in one portion at 0°C under  $\text{N}_2$ . The mixture was stirred at 20°C for 20 hours to give yellow solution. TLC (DCM: MeOH= 10: 1,  $R_f$  = 0.45) showed the reaction was completed. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (3 x 5 mL). The combined organic phase was washed with brine (2 x 5 mL), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 0-50 % of Ethyl acetate in Petroleum ether for 5 min, 50-100 of Ethyl acetate in Petroleum ether for 10 min) to give [1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]methyl 4-methylbenzenesulfonate (160 mg, 228.91  $\mu\text{mol}$ , 70.85% yield, 75.194% purity) as a yellow solid.

### Step 5

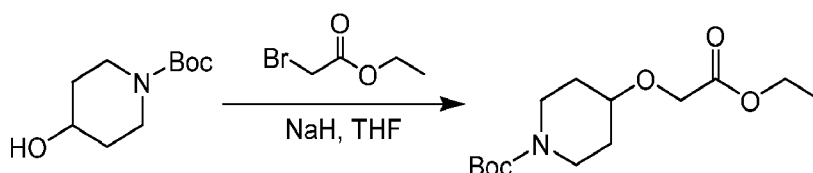


To a solution of 5-(1-methylcyclopropoxy)-3-[6-[(3S)-3-methyl-4-(4-piperidylmethyl)piperazin-1-yl]pyrimidin-4-yl]-1H-indazole (100 mg, 216.64  $\mu\text{mol}$ , 1 *eq*) and [1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]methyl 4-methylbenzenesulfonate (159.40 mg, 303.29  $\mu\text{mol}$ , 1.4 *eq*) in MeCN (5 mL) was added KI (179.81 mg, 1.08 mmol, 5 *eq*) and DIPEA (84.00 mg, 649.91  $\mu\text{mol}$ , 113.20  $\mu\text{L}$ , 3 *eq*) in one portion at 20°C under  $\text{N}_2$ . The solution was

stirred at 80°C for 16 h. The residue was poured into water (5 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic phase was washed with brine (2 x 5 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give 200 mg crude product. The crude product was purified by prep-HPLC (column: Welch Xtimate C18 150\*30mm\*5um; mobile phase: water(0.225%FA)-ACN; B%: 10%-40%, Gradient Time(min):8min; FlowRate(ml/min):25) to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[[4-[[[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]methyl]-1-piperidyl]methyl]-1-piperidyl]isoindoline-1,3-dione (53.77 mg, 65.33 umol, 30.15% yield, 99.013% purity) as a yellow solid.

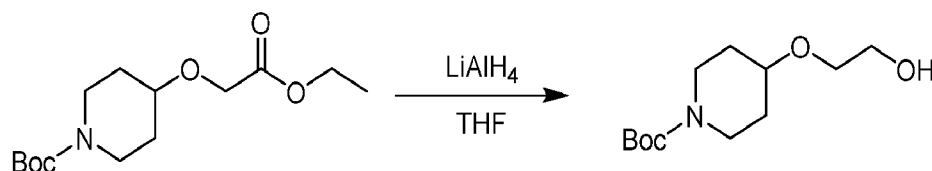
### [00236] Exemplary Synthesis of Exemplary Compound 25

#### Step 1



To a solution of tert-butyl 4-hydroxypiperidine-1-carboxylate (2 g, 9.94 mmol, 1 *eq*) in THF (20 mL) was added NaH (516.69 mg, 12.92 mmol, 60% purity in oil, 1.3 *eq*) in portions under nitrogen at 0 °C. After hydrogen gas evolution ceased, ethyl 2-bromoacetate (3.32 g, 19.87 mmol, 2.20 mL, 2 *eq*) was added dropwise. The resulting mixture was stirred at 0°C for 2h. TLC (petroleum ether: ethyl acetate=5:1) showed two new spots. The reaction mixture was quenched by aq. NH<sub>4</sub>Cl (20mL) and extracted with ethyl acetate (3 x 20mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 20% ethyl acetate in petroleum ether) to afford tert-butyl 4-(2-ethoxy-2-oxo-ethoxy)piperidine-1-carboxylate (800 mg, 2.78 mmol, 28.02% yield) as a colorless oil.

#### Step 2

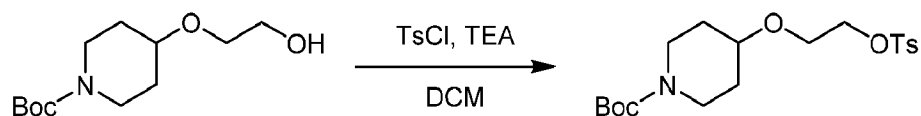


To a solution of tert-butyl 4-(2-ethoxy-2-oxo-ethoxy)piperidine-1-carboxylate (800 mg, 2.78 mmol, 1 *eq*) in THF (10 mL) was added LiAlH<sub>4</sub> (158.50 mg, 4.18 mmol, 1.5 *eq*) at 0°C. After



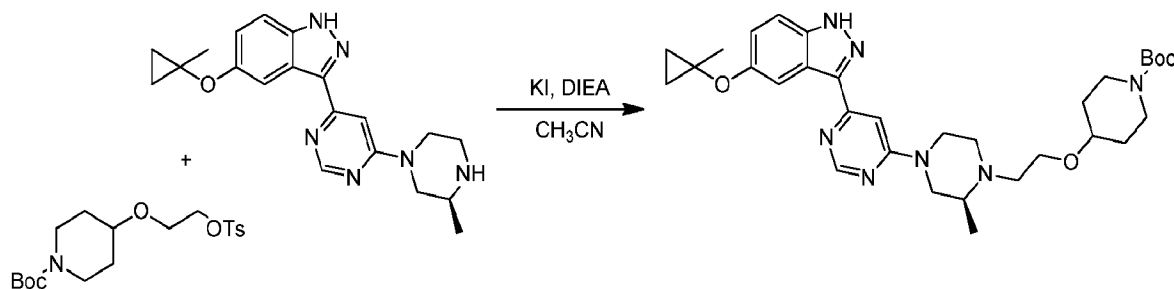
addition, the reaction mixture was stirred at 20°C for 2h. TLC (petroleum ether: ethyl acetate= 1:1) showed starting material consumed and a new spot formed. The reaction mixture was quenched by addition of water (0.5 mL), followed by 15% aqueous NaOH (0.5 mL) and water (1.5 mL). The solid was removed by filtration. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 50% ethyl acetate in petroleum ether) to afford tert-butyl 4-(2-hydroxyethoxy)piperidine-1-carboxylate (400 mg, 1.63 mmol, 58.57% yield) as a colorless oil.

### Step 3



To a solution of tert-butyl 4-(2-hydroxyethoxy)piperidine-1-carboxylate (400 mg, 1.63 mmol, 1 *eq*) in DCM (2 mL) was added 4-methylbenzenesulfonyl chloride (621.72 mg, 3.26 mmol, 2 *eq*) and TEA (329.99 mg, 3.26 mmol, 453.91 uL, 2 *eq*) at 20°C. After addition, the reaction solution was stirred at 20°C for 16h. TLC (petroleum ether: ethyl acetate= 3: 1) showed major two spots. The reaction solution was diluted with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 30% ethyl acetate in petroleum ether) to afford tert-butyl 4-[2-(p-tolylsulfonyloxy)ethoxy]piperidine-1-carboxylate (490 mg, 1.23 mmol, 75.22% yield, 100% purity) as a colorless oil.

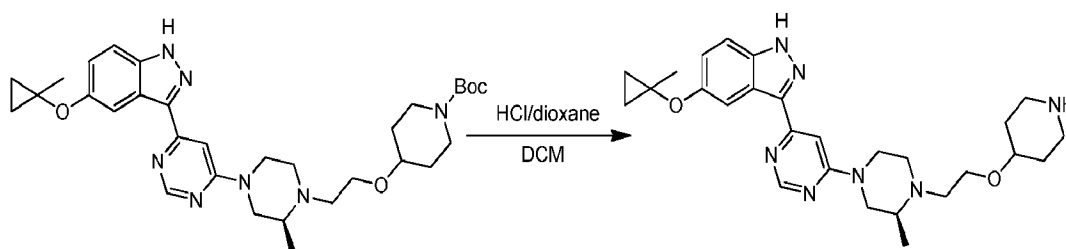
### Step 4



To a solution of tert-butyl 4-[2-(p-tolylsulfonyloxy)ethoxy]piperidine-1-carboxylate (131.54 mg, 329.27 umol, 1 *eq*) and 5-(1-methylcyclopropoxy)-3-[6-[(3S)-3-methylpiperazin-1-yl]pyrimidin-4-yl]-1H-indazole (120 mg, 329.27 umol, 1 *eq*) in CH<sub>3</sub>CN (3 mL) was added KI (273.30 mg, 1.65 mmol, 5 *eq*) and DIEA (127.67 mg, 987.81 umol, 172.06 uL, 3 *eq*). After addition, the reaction mixture was stirred at 90°C for 16h. The reaction mixture was diluted with water

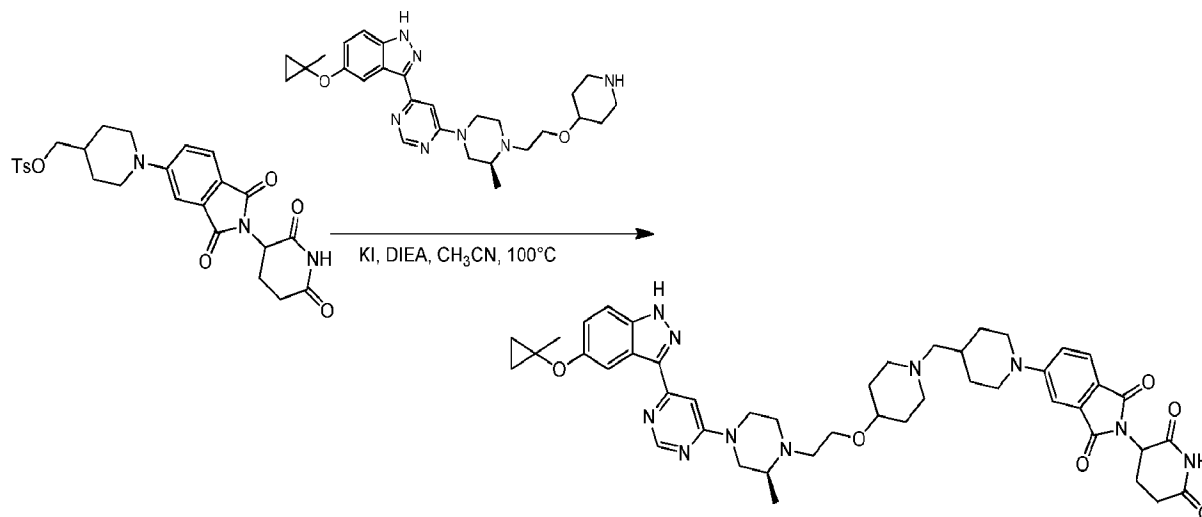
(10mL) and extracted with ethyl acetate (3 x 10mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 5% methanol in dichloromethane) to afford tert-butyl 4-[2-[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethoxy]piperidine-1-carboxylate (130 mg, 204.31  $\mu$ mol, 62.05% yield, 93% purity) as a yellow gum.

### Step 5



To a solution of tert-butyl 4-[2-[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethoxy]piperidine-1-carboxylate (130 mg, 219.69  $\mu$ mol, 1 eq) in DCM (2 mL) was added HCl/dioxane (4 M, 549.23  $\mu$ L, 10 eq) at 20°C. After addition, the reaction mixture was stirred at 20°C for 30min. TLC (dichloromethane: methanol= 10: 1) showed starting material consumed. The reaction mixture was concentrated under reduced pressure to afford 5-(1-methylcyclopropoxy)-3-[6-[(3S)-3-methyl-4-[2-(4-piperidyloxy)ethyl]piperazin-1-yl]pyrimidin-4-yl]-1H-indazole (108 mg, 206.50  $\mu$ mol, 94.00%)

### Step 6

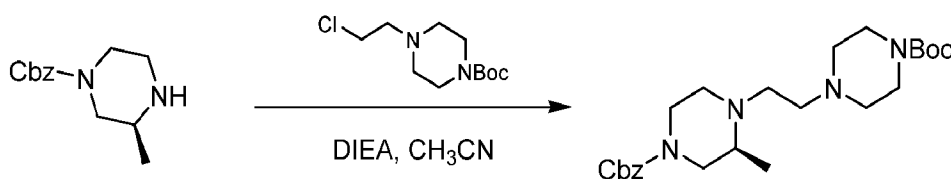


To a solution of 5-(1-methylcyclopropoxy)-3-[6-[(3S)-3-methyl-4-[2-(4-piperidyloxy)ethyl]piperazin-1-yl]pyrimidin-4-yl]-1H-indazole (105.23 mg, 214.05  $\mu$ mol, 1.25

*eq*) and [1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]methyl 4-methylbenzenesulfonate (90 mg, 171.24  $\mu$ mol, 1 *eq*) in CH<sub>3</sub>CN (5 mL) was added KI (142.13 mg, 856.21  $\mu$ mol, 5 *eq*) and DIEA (177.05 mg, 1.37 mmol, 238.62  $\mu$ L, 8 *eq*). After addition, the reaction mixture was stirred at 100°C for 16h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep.HPLC (column: Welch Xtimate C18 150\*25mm\*5 $\mu$ m; mobile phase: [water(0.225%FA)-ACN];B%: 5%-35%,8min) to afford 2-(2,6-dioxo-3-piperidyl)-5-[4-[[4-[2-[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethoxy]-1-piperidyl]methyl]-1-piperidyl]isoindoline-1,3-dione (12.5 mg, 14.50  $\mu$ mol, 8.47% yield, 98% purity) as a yellow solid.

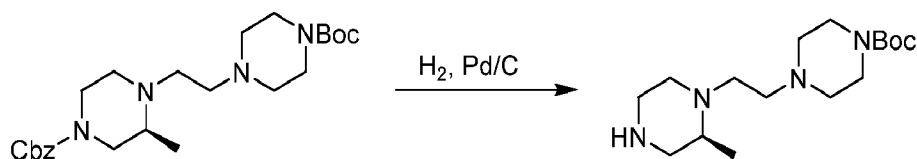
### [00237] Exemplary Synthesis of Exemplary Compound 26

#### Step 1



To a solution of benzyl (3S)-3-methylpiperazine-1-carboxylate (500 mg, 2.13 mmol, 1 *eq*) and tert-butyl 4-(2-chloroethyl)piperazine-1-carboxylate (637.02 mg, 2.56 mmol, 1.2 *eq*) in CH<sub>3</sub>CN (1 mL) was added DIEA (827.44 mg, 6.40 mmol, 1.12 mL, 3 *eq*). The mixture was stirred at 80°C for 32 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The crude product was purified by column chromatography on silica gel (DCM in MeOH = 0 to 3%) to give benzyl (3S)-4-[2-(4-tert-butoxycarbonylpiperazin-1-yl)ethyl]-3-methylpiperazine-1-carboxylate (460 mg, 1.03 mmol, 48.27% yield) as a brown gum.

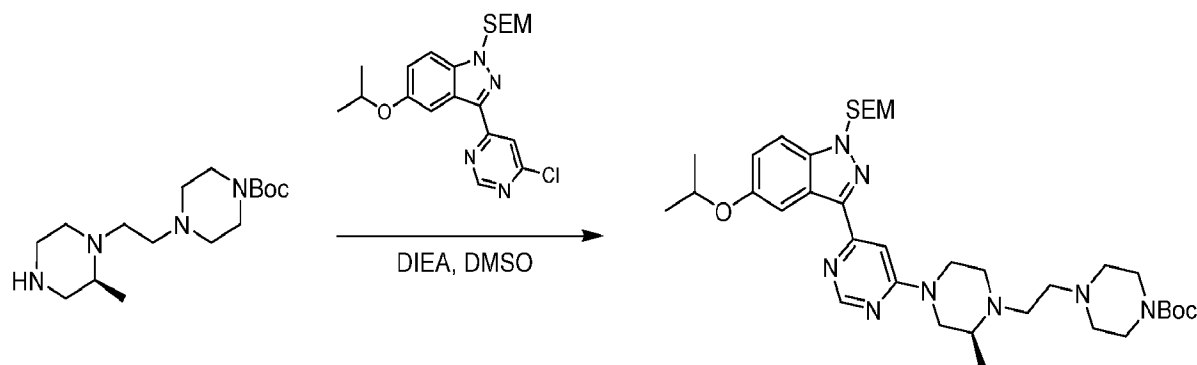
#### Step 2



To a solution of benzyl (3S)-4-[2-(4-tert-butoxycarbonylpiperazin-1-yl)ethyl]-3-methylpiperazine-1-carboxylate (460 mg, 1.03 mmol, 1 *eq*) in MeOH (5 mL) was added Pd/C (200 mg, 2.06 mmol, 10% purity, 2 *eq*) under N<sub>2</sub>. The suspension was degassed under vacuum and purged with H<sub>2</sub> several times. The mixture was stirred under H<sub>2</sub> (15 psi) at 25°C for 2 hours. TLC

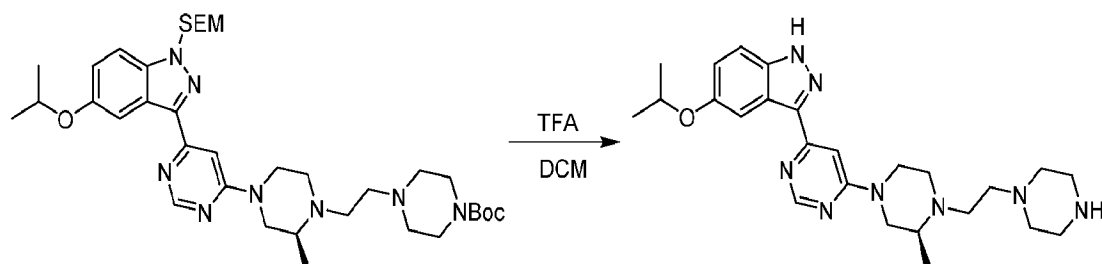
indicated no reactant was remained, and one major new spot with larger polarity was detected. The reaction mixture was filtered and the filter was concentrated to give tert-butyl 4-[2-[(2S)-2-methylpiperazin-1-yl]ethyl]piperazine-1-carboxylate (290 mg, 928.15  $\mu\text{mol}$ , 90.11% yield) as a light yellow oil.

### Step 3



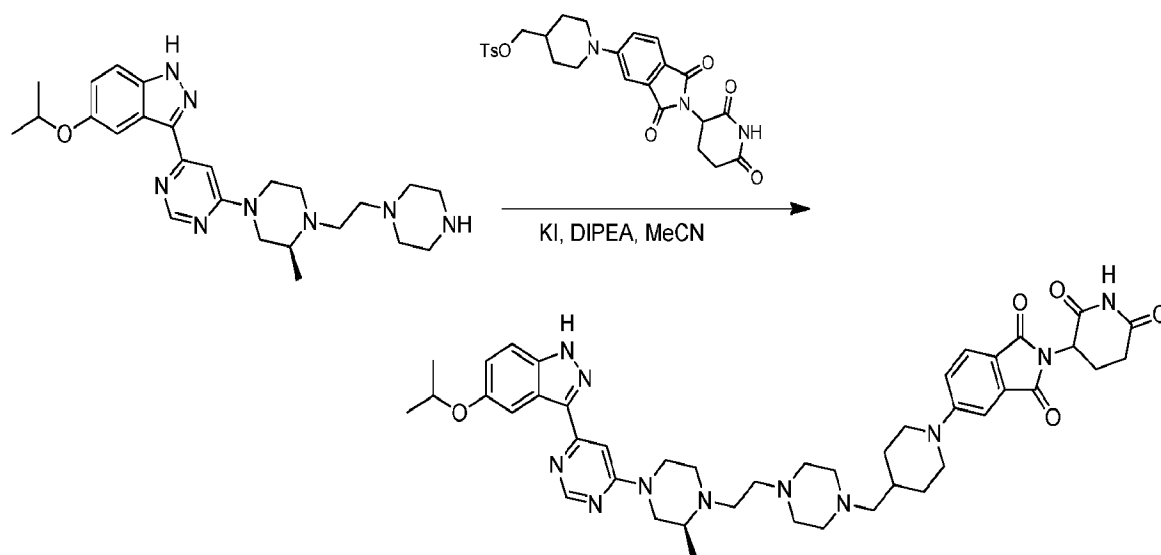
To a solution of tert-butyl 4-[2-[(2S)-2-methylpiperazin-1-yl]ethyl]piperazine-1-carboxylate (290 mg, 928.15  $\mu\text{mol}$ , 1 *eq*) and 2-[[3-(6-chloropyrimidin-4-yl)-5-isopropoxy-indazol-1-yl]methoxy]ethyl-trimethyl-silane (388.89 mg, 928.15  $\mu\text{mol}$ , 1 *eq*) in DMSO (3 mL) was added DIEA (359.87 mg, 2.78 mmol, 485.00  $\mu\text{L}$ , 3 *eq*). The mixture was stirred at 100°C for 2 hr. LC-MS (EB134-185-P1A) showed no reactant 1 was remained. Several new peaks were shown on LC-MS and ~64% of desired compound was detected. The reaction mixture was diluted with water (20 mL) and extracted with EA (30 mL). The combined organic layers were washed with brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography on silica gel (DCM in MeOH = 0 to 3%) to give tert-butyl 4-[2-[(2S)-4-[6-[5-isopropoxy-1-(2-trimethylsilylethoxymethyl) indazol-3-yl]pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethyl]piperazine-1-carboxylate (590 mg, 812.44  $\mu\text{mol}$ , 87.53% yield, 95.7% purity) as a brown gum.

### Step 4



To a solution of tert-butyl 4-[2-[(2S)-4-[6-[5-isopropoxy-1-(2-trimethylsilylethoxymethyl)indazol-3-yl]pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethyl]piperazine-1-carboxylate (350 mg, 503.61  $\mu\text{mol}$ , 1 *eq*) in DCM (3 mL) was added TFA (7.19 g, 63.03 mmol, 4.67 mL, 125.15 *eq*). The mixture was stirred at 25°C for 16 h. And then  $\text{NH}_3\cdot\text{H}_2\text{O}$  (211.79 mg, 1.51 mmol, 232.74  $\mu\text{L}$ , 25% purity, 3 *eq*) was added to solution and the mixture was stirred for 2 h. LC-MS (EB134-187-P1B) showed no reactant was remained. Several new peaks were shown on LC-MS and ~97% of desired compound was detected. The reaction mixture was diluted with water (20 mL) and extracted with EA (30 mL). The combined organic layers were washed with brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give 5-isopropoxy-3-[6-[(3S)-3-methyl-4-(2-piperazin-1-ylethyl)piperazin-1-yl]pyrimidin-4-yl]-1H-indazole (150 mg, 313.17  $\mu\text{mol}$ , 62.18% yield, 97% purity) as a yellow gum.

### Step 5

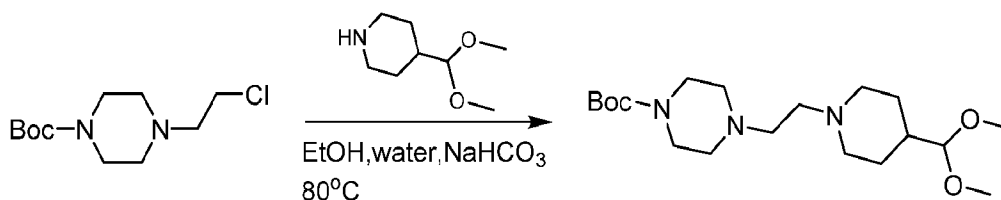


To a solution of 5-isopropoxy-3-[6-[(3S)-3-methyl-4-(2-piperazin-1-ylethyl)piperazin-1-yl]pyrimidin-4-yl]-1H-indazole (150 mg, 322.85  $\mu\text{mol}$ , 1 *eq*) and [1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]methyl 4-methylbenzenesulfonate (169.68 mg, 322.85  $\mu\text{mol}$ , 1 *eq*) in  $\text{CH}_3\text{CN}$  (5 mL) was added KI (428.76 mg, 2.58 mmol, 8 *eq*) and DIEA (333.81 mg, 2.58 mmol, 449.88  $\mu\text{L}$ , 8 *eq*). The mixture was stirred at 80°C for 16 hr. LC-MS (EB134-190-P1D2) showed no reactant 1 was remained. Several new peaks were shown on LC-MS and ~56% of desired compound was detected. The reaction mixture was diluted with water (20 mL) and extracted with EA (30 mL). The combined organic layers were washed with brine (20 mL),

dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Column: Phenomenex Luna C18 100\*30mm\*5um; mobile phase: [water (0.225%FA)-ACN]; B%:10%-40%; 11min) to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[[4-[2-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethyl]piperazin-1-yl]methyl]-1-piperidyl]isoindoline-1,3-dione (47 mg, 55.39 umol, 17.16% yield, 96.4% purity) as a yellow solid.

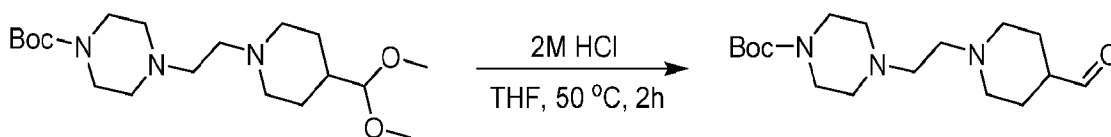
### [00238] Exemplary Synthesis of Exemplary Compound 27

#### Step 1



To a solution of tert-butyl 4-(2-chloroethyl)piperazine-1-carboxylate (1 g, 4.02 mmol, 1 *eq*) and 4-(dimethoxymethyl)piperidine (960.16 mg, 6.03 mmol, 1.5 *eq*) in EtOH (30 mL) and water (4 mL) was added  $\text{NaHCO}_3$  (1.01 g, 12.06 mmol, 469.07 uL, 3 *eq*) at  $25^\circ\text{C}$  under  $\text{N}_2$ . Then the reaction mixture was heated to  $80^\circ\text{C}$  and stirred for 5 hr to give a white suspension. TLC (Dichloromethane: methanol =10:1) showed the reaction was completed. The mixture was concentrated under vacuum, the residue was putted into water (30 mL). The aqueous phase was extracted with ethyl acetate (30 mL\*3). The combined organic phase was washed with brine (30 mL), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue was purified with silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Dichloromethane: Methanol=100/1, 5/1) to afford tert-butyl 4-[2-[4-(dimethoxymethyl)-1-piperidyl]ethyl]piperazine-1-carboxylate (900 mg, 2.42 mmol, 60.26% yield) as a yellow oil.

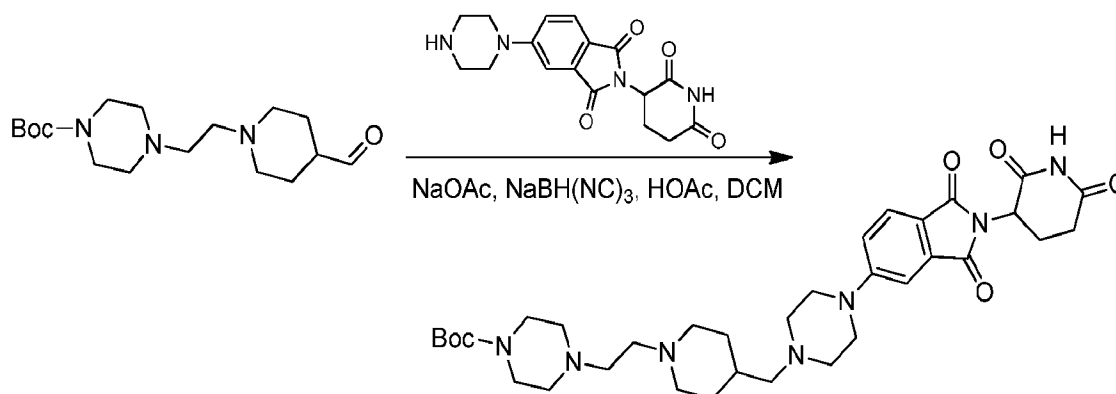
#### Step 2



To a solution of tert-butyl 4-[2-[4-(dimethoxymethyl)-1-piperidyl]ethyl]piperazine-1-carboxylate (800 mg, 2.15 mmol, 1 *eq*) in THF (5 mL) was added HCl (2 M, 5 mL, 4.64 *eq*) at  $25^\circ\text{C}$ , then the reaction mixture was stirred at  $50^\circ\text{C}$  for 2 h to give an off-yellow solution. TLC (Dichloromethane: methanol =10: 1) showed the reaction was completed. The residue was

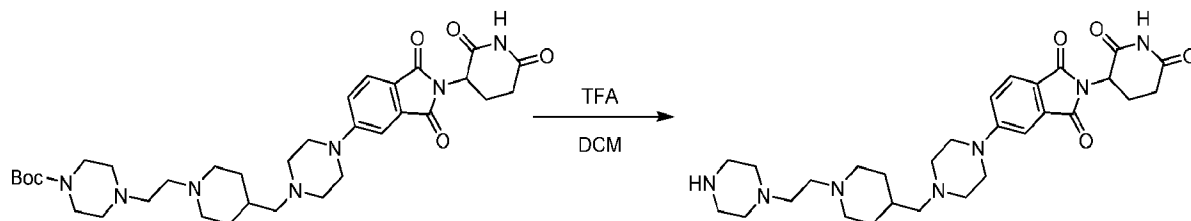
adjusted to pH = 8 with NaHCO<sub>3</sub>(s), then the mixture was poured into water (25 mL). The aqueous phase was extracted with ethyl acetate (25 mL\*2). The combined organic phase was washed with brine (30 mL\*2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to afford tert-butyl 4-[2-(4-formyl-1-piperidyl)ethyl]piperazine-1-carboxylate (420 mg, crude) as an off-yellow oil.

### Step 3



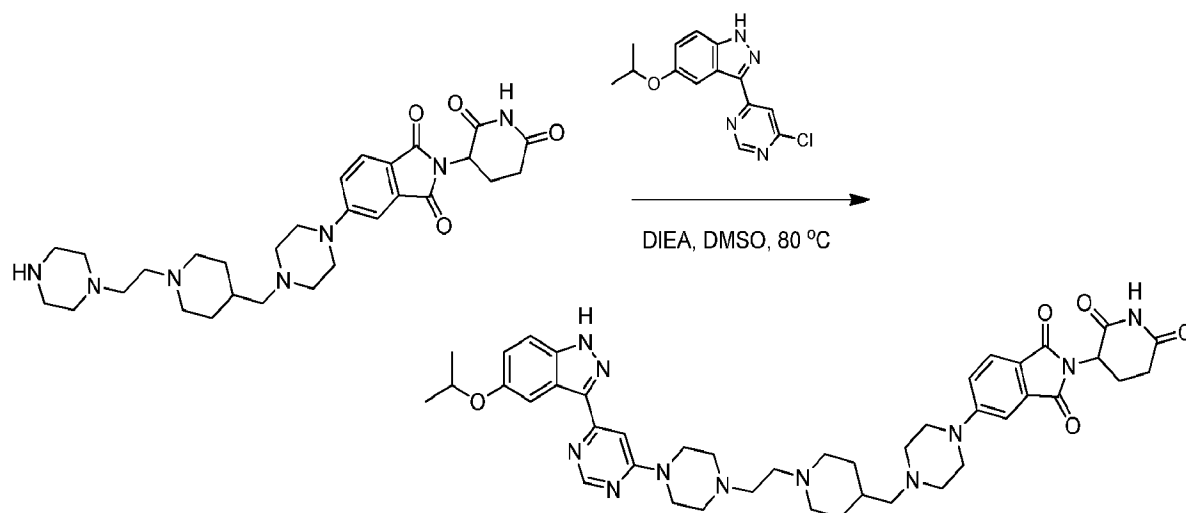
To a solution of 2-(2,6-dioxo-3-piperidyl)-5-piperazin-1-yl-isoindoline-1,3-dione (601.45 mg, 1.55 mmol, 1.2 *eq*, FA) and NaOAc (423.47 mg, 5.16 mmol, 4 *eq*) in DCM (5 mL) and MeOH (5 mL) at 25°C, then the reaction was stirred at 25°C for 1 h, then tert-butyl 4-[2-(4-formyl-1-piperidyl)ethyl]piperazine-1-carboxylate (420 mg, 1.29 mmol, 1 *eq*) was added and stirred for 1 h, then acetic acid (193.75 mg, 3.23 mmol, 184.52 uL, 2.5 *eq*) and sodium cyanoborohydride (162.20 mg, 2.58 mmol, 2 *eq*) were stirred at 25°C for 1 h, then the reaction mixture was stirred at 25°C for 14 h to give a yellow solution. TLC (Dichloromethane: methanol =10:1) showed there was new spot detected. The residue was poured into ice-water (w/w = 1/1) (35 mL). The aqueous phase was extracted with ethyl acetate (35 mL\*2). Then the aqueous phase was lyophilized to give a yellow solid. The solid was washed with MeOH/DCM (1/1, 40mL) to give a yellow suspension. The suspension was filtered and concentrated in vacuum to give yellow oil. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Dichloromethane : Methanol=100/1, 5/1) to afford tert-butyl 4-[2-[4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl] piperazin-1-yl]methyl]-1-piperidyl]ethyl]piperazine-1-carboxylate (320 mg, 490.95 umol, 38.04% yield) as a yellow oil.

### Step 4



To a solution of tert-butyl 4-[2-[4-[[4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]ethyl]piperazine-1-carboxylate (320 mg, 490.95  $\mu\text{mol}$ , 1 *eq*) in DCM (10 mL) was added TFA (3.08 g, 27.01 mmol, 2 mL, 55.02 *eq*) at 25°C, then the reaction mixture was stirred at 25°C for 0.5 h to give a yellow solution. TLC (Dichloromethane: methanol =10:1) showed starting material consumed and a new spot formed. The reaction mixture was concentrate in vacuum to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[[1-(2-piperazin-1-ylethyl)-4-piperidyl]methyl]piperazin-1-yl]isoindoline-1,3-dione (480 mg, 395.33  $\mu\text{mol}$ , 80.52% yield, 83% purity, 4TFA) as a yellow solid.

### Step 5



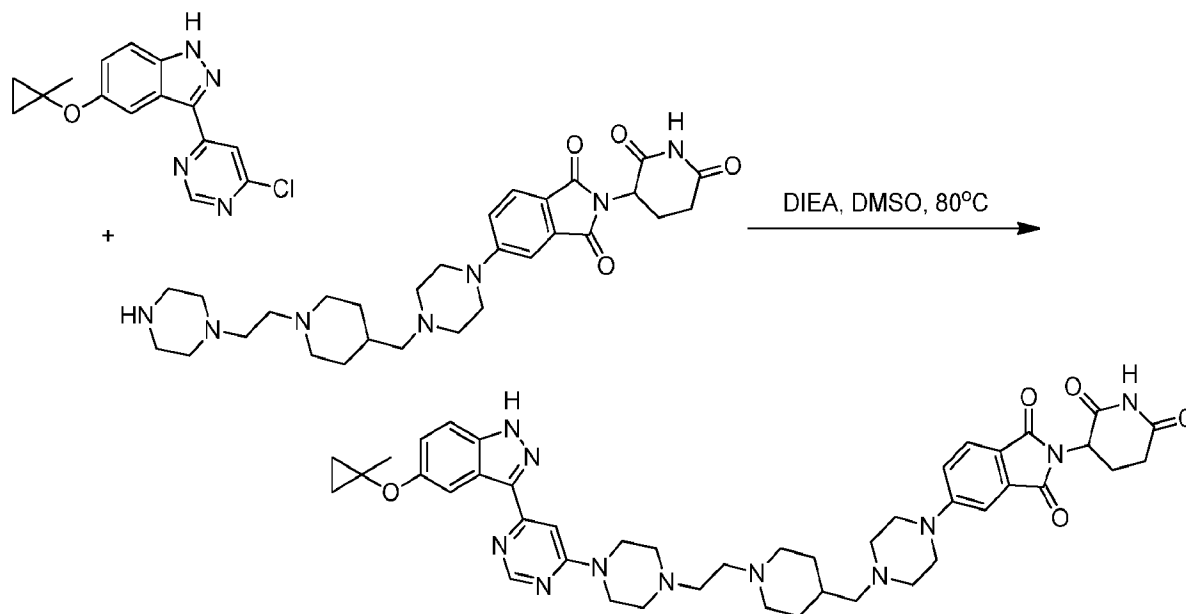
To a solution of 2-(2,6-dioxo-3-piperidyl)-5-[4-[[1-(2-piperazin-1-ylethyl)-4-piperidyl]methyl]piperazin-1-yl]isoindoline-1,3-dione (160 mg, 158.77  $\mu\text{mol}$ , 1 *eq*, 4TFA) and 3-(6-chloropyrimidin-4-yl)-5-isopropoxy-1H-indazole (45.84 mg, 158.77  $\mu\text{mol}$ , 1 *eq*) in DMSO (10 mL) was added DIEA (102.60 mg, 793.83  $\mu\text{mol}$ , 138.27  $\mu\text{L}$ , 5 *eq*) at 25°C, then the reaction mixture was stirred at 25°C for 30 min, and then the reaction mixture was stirred at 80°C for 1.5 h to give a yellow solution. The residue was poured into ice-water (30 mL). The aqueous phase was extracted with ethyl acetate (25 mL\*2). The combined organic phase was washed with brine (30 mL\*2), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The residue was purification by prep-HPLC (column: Phenomenex Luna C18 100\*30mm\*5 $\mu\text{m}$ , mobile phase:



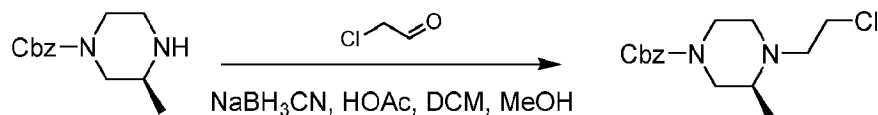
water (0.225%FA)-ACN);B%: 5%-35%; 9 min) to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[[1-[2-[4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]piperazin-1-yl]ethyl]-4-piperidyl]methyl]piperazin-1-yl]isoindoline-1,3-dione (6.8 mg, 8.42 umol, 5.31% yield, 99.6% purity) as a yellow solid.

### [00239] Exemplary Synthesis of Exemplary Compound 28

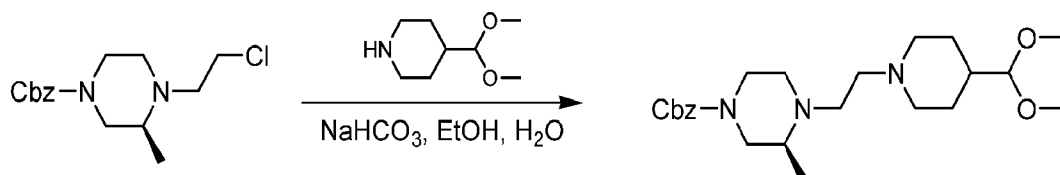
#### Step 1



To a solution of 2-(2,6-dioxo-3-piperidyl)-5-[4-[[1-(2-piperazin-1-ylethyl)-4-piperidyl]methyl]piperazin-1-yl]isoindoline-1,3-dione (160 mg, 158.77 umol, 1 eq, 4TFA) and 3-(6-chloropyrimidin-4-yl)-5-(1-methylcyclopropoxy)-1H-indazole (47.75 mg, 158.77 umol, 1 eq) in DMSO (5 mL) were added DIEA (102.60 mg, 793.83 umol, 138.27 uL, 5 eq) at 25°C and stirred for 30 min, then the reaction mixture was stirred at 80°C for 1.5 h to give a yellow solution. The residue was poured into water (35mL). The aqueous phase was extracted with ethyl acetate (30mL\*2). The combined organic phase was washed with brine (35mL\*2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purification by prep-HPLC (column Phenomenex Luna C18 100\*30mm\*5um, mobile phase: water (0.225%FA)-ACN); B%: 5%-35%; 9 min) to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[[1-[2-[4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethyl]-4-piperidyl]methyl]piperazin-1-yl]isoindoline-1,3-dione (7.0 mg, 8.56 umol, 5.39% yield, 99.8% purity) as a yellow solid.

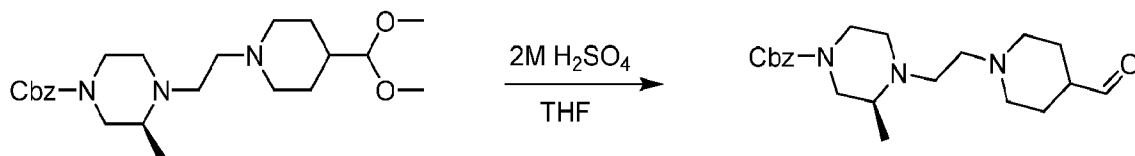
**[00240] Exemplary Synthesis of Exemplary Compound 29****Step 1**

To a solution of benzyl (3S)-3-methylpiperazine-1-carboxylate (300 mg, 1.28 mmol, 1 *eq*) and 2-chloroacetaldehyde (753.84 mg, 3.84 mmol, 617.90  $\mu\text{L}$ , 3 *eq*) in  $\text{DCM}$  (5 mL) and  $\text{MeOH}$  (5 mL) was added  $\text{HOAc}$  (7.69 mg, 128.04  $\mu\text{mol}$ , 7.32  $\mu\text{L}$ , 0.1 *eq*). Then the mixture was stirred at 25 °C for 20 min. Then the  $\text{NaBH}_3\text{CN}$  (241.39 mg, 3.84 mmol, 3 *eq*) was added to the solution and the reaction was stirred at 25 °C for 1h. TLC (Petroleum ether: Ethyl acetate= 1:1,  $R_f$ =0.5) was showed the reaction completed. The reaction mixture was poured into  $\text{H}_2\text{O}$  (10 mL). The mixture was extracted with ethyl acetate (20 mL\*3). The organic phase was washed with brine (20 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , concentrated in vacuum to give a residue. The residue was purified by silica gel column chromatography (0-100% Ethyl acetate in Petroleum ether) to give benzyl (3S)-4-(2-chloroethyl)-3-methyl-piperazine-1-carboxylate (180 mg, 606.49  $\mu\text{mol}$ , 47.37% yield) as a colorless oil.

**Step 2**

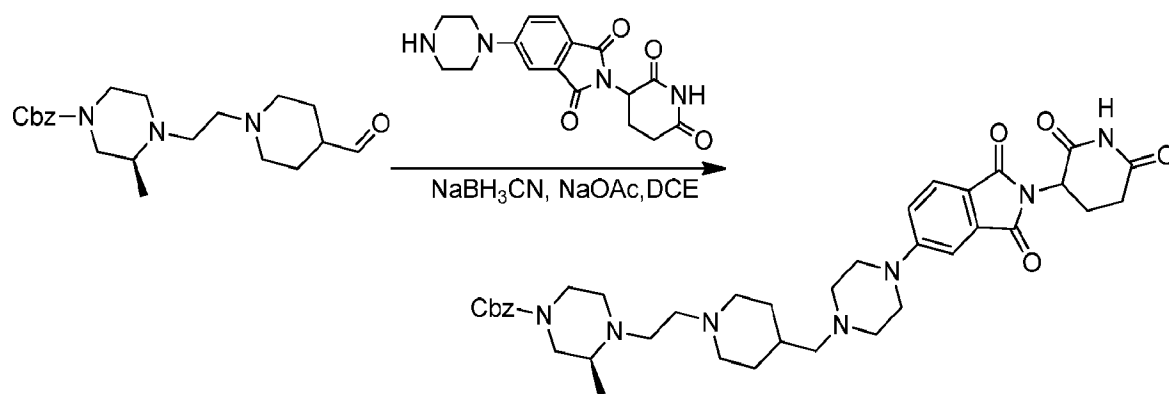
Benzyl (3S)-4-(2-chloroethyl)-3-methyl-piperazine-1-carboxylate (180 mg, 606.49  $\mu\text{mol}$ , 1 *eq*) and 4-(dimethoxymethyl)piperidine (144.85 mg, 909.73  $\mu\text{mol}$ , 1.5 *eq*) were dissolved in  $\text{EtOH}$  (5 mL) and Water (0.5 mL), then  $\text{NaHCO}_3$  (101.90 mg, 1.21 mmol, 47.17  $\mu\text{L}$ , 2 *eq*) was added the reaction and stirred at 80°C for 5hr. TLC (Dichloromethane: Methanol=10:1,  $R_f$ =0.4) indicated that the reaction was completed. The reaction mixture was poured into  $\text{H}_2\text{O}$  (20 mL). The mixture was extracted with ethyl acetate (20 mL\*2). The organic phase was washed with brine (15 mL\*3), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , concentrated in vacuum to give a residue. The residue was purified by prep-TLC (10% Methanol in Dichloromethane,  $R_f$ =0.4) to give benzyl (3S)-4-[2-[4-(dimethoxymethyl)-1-piperidyl]ethyl]-3-methyl-piperazine-1-carboxylate (165 mg, 393.27  $\mu\text{mol}$ , 64.84% yield) as a colorless oil.

**Step 3**



A solution of benzyl (3S)-4-[2-[4-(dimethoxymethyl)-1-piperidyl]ethyl]-3-methyl-piperazine-1-carboxylate (65 mg, 154.93  $\mu$ mol, 1 *eq*) in THF (2 mL) and H<sub>2</sub>SO<sub>4</sub> (2 M, 2 mL, 25.82 *eq*) was stirred at 70 °C for 1 hr. TLC(Dichloromethane: Methanol= 10:1, R<sub>f</sub>=0.2) showed starting material consumed. The reaction mixture was poured into H<sub>2</sub>O (20mL) and basified with aqueous NaHCO<sub>3</sub> till PH = 8. The mixture was extracted with ethyl acetate (20mL\*5) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuum to give benzyl (3S)-4-[2-(4-formyl-1-piperidyl)ethyl]-3-methyl-piperazine-1-carboxylate (57 mg, crude) as a colorless oil.

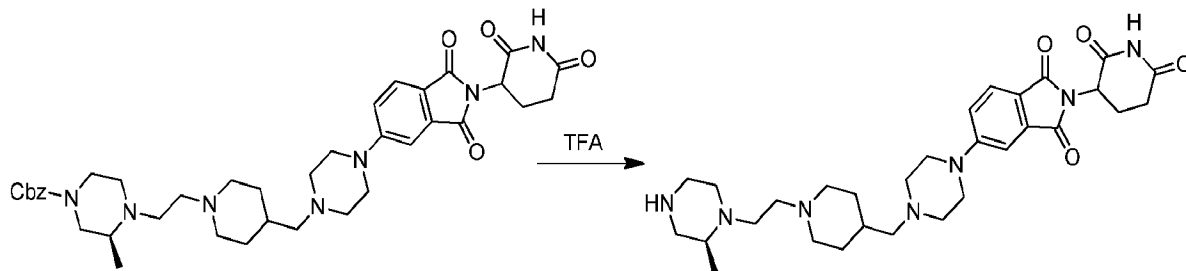
#### Step 4



To a solution of benzyl (3S)-4-[2-(4-formyl-1-piperidyl)ethyl]-3-methyl-piperazine-1-carboxylate (57 mg, 152.62  $\mu$ mol, 1 *eq*) and 2-(2,6-dioxo-3-piperidyl)-5-piperazin-1-ylisoindoline-1,3-dione (69.65 mg, 152.62  $\mu$ mol, 1 *eq*, TFA) in DCE (3 mL) and MeOH (0.5 mL) was added NaOAc (54.81 mg, 668.11  $\mu$ mol, 4.38 *eq*) and the mixture was stirred at 25°C for 20 min. Then the mixture was added HOAc (916.49  $\mu$ g, 15.26  $\mu$ mol, 8.73e-1  $\mu$ L, 0.1 *eq*) and stirred at 25 °C for 20 min. Then the NaBH<sub>3</sub>CN (54.81 mg, 872.15  $\mu$ mol, 5.71 *eq*) was added to the solution and stirred at 25 °C for 16h. TLC (Dichloromethane: Methanol=10:1, R<sub>f</sub>=0.2) indicated that the reaction was complete. The reaction mixture was poured into H<sub>2</sub>O (20 mL). The mixture was extracted with ethyl acetate (20 mL\*2). The organic phase was washed with brine (15 mL\*3), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuum to give a residue. The residue was purified by prep-TLC (10% Methanol in Dichloromethane, R<sub>f</sub>=0.2) to give benzyl (3S)-4-[2-[4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-

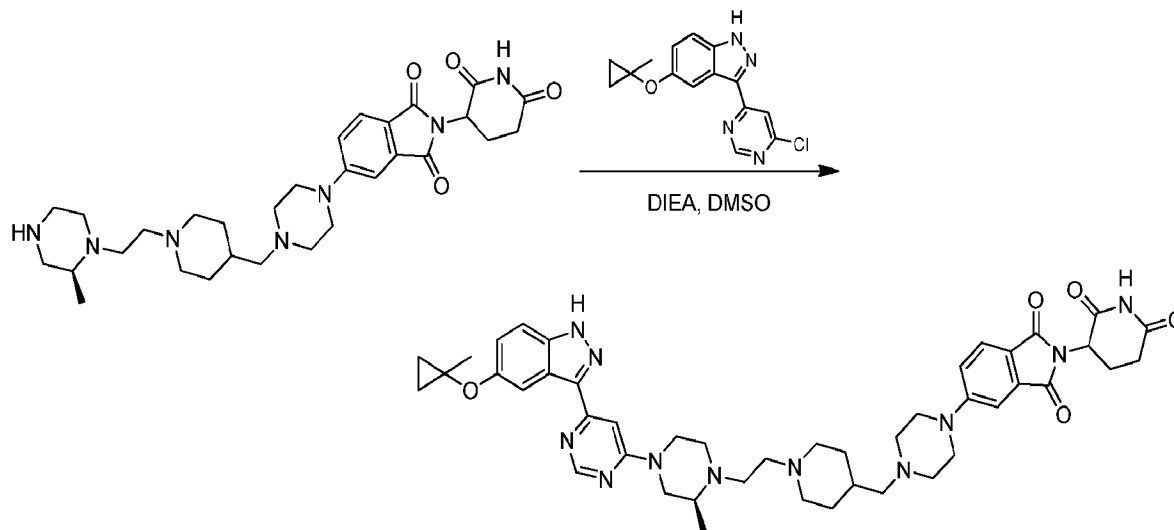
piperidyl]ethyl]-3-methyl-piperazine-1-carboxylate (60 mg, 68.59  $\mu\text{mol}$ , 44.94% yield, 80% purity) as a white solid.

### Step 5



A mixture of benzyl (3S)-4-[2-[4-[[4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]ethyl]-3-methyl-piperazine-1-carboxylate (60 mg, 85.73  $\mu\text{mol}$ , 1 *eq*) in TFA (4.62 g, 40.52 mmol, 3 mL, 472.60 *eq*) was stirred at 70 °C for 8 hr. TLC (Dichloromethane: Methanol=10:1,  $R_f$ =0.01) indicated that the reaction was complete. The reaction mixture was concentrated in vacuum to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[[1-[2-[(2S)-2-methylpiperazin-1-yl]ethyl]-4-piperidyl]methyl]piperazin-1-yl]isoindoline-1,3-dione (48 mg, crude, TFA) as a yellow solid.

### Step 6

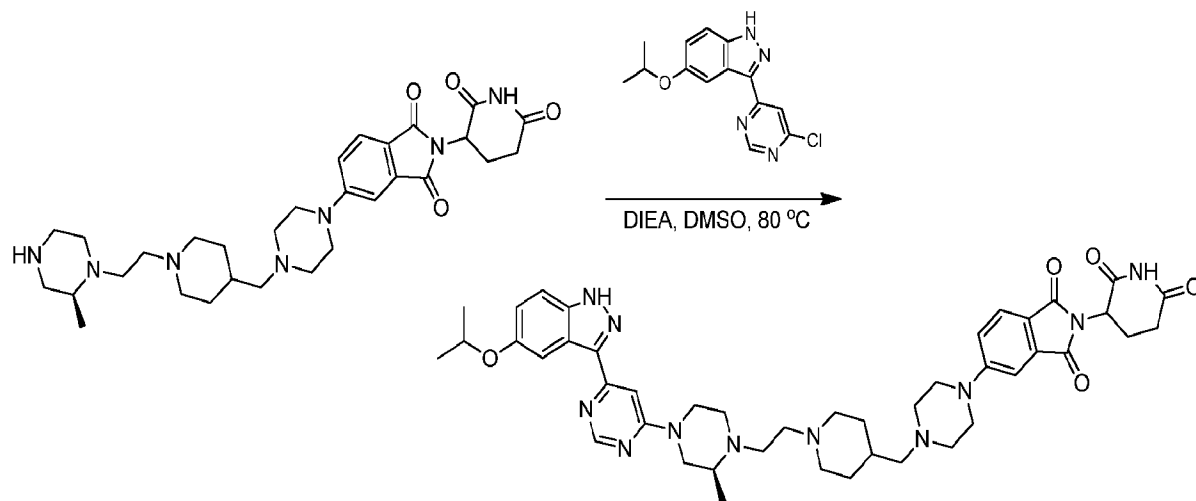


2-(2,6-dioxo-3-piperidyl)-5-[4-[[1-[2-[(2S)-2-methylpiperazin-1-yl]ethyl]-4-piperidyl]methyl]piperazin-1-yl]isoindoline-1,3-dione (48 mg, 70.62  $\mu\text{mol}$ , 1 *eq*, TFA) and 3-(6-chloropyrimidin-4-yl)-5-(1-methylcyclopropoxy)-1H-indazole (21.24 mg, 70.62  $\mu\text{mol}$ , 1 *eq*) were dissolved in DMSO (5 mL) then DIEA (91.27 mg, 706.16  $\mu\text{mol}$ , 123.00  $\mu\text{L}$ , 10 *eq*) was added to the reaction. The reaction was stirred at 80°C for 8hr. The reaction mixture was poured into H<sub>2</sub>O (20 mL). The mixture was extracted with ethyl acetate (20 mL\*2). The organic phase

was washed with brine (15 mL\*3), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (Phenomenex Luna C18 100\*30mm\*5um; mobile phase: [water(0.225%FA)-ACN];B%: 23%-53%, 9min) to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[[1-[2-[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethyl]-4-piperidyl]methyl]piperazin-1-yl]isoindoline-1,3-dione (8.4 mg, 9.78 umol, 13.85% yield, 96.64% purity) as a yellow solid.

#### [00241] Exemplary Synthesis of Exemplary Compound 30

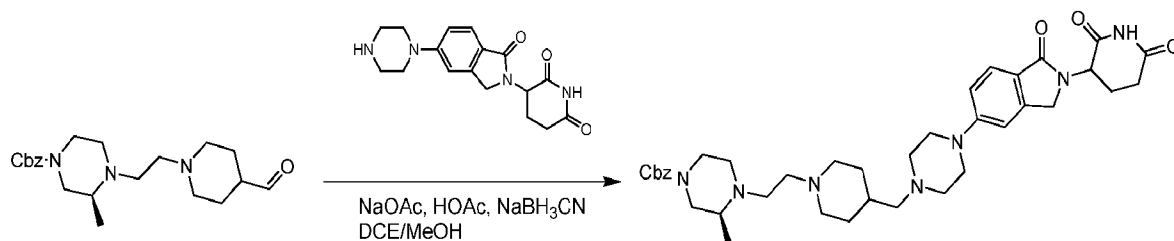
##### Step 1



To a solution of 2-(2,6-dioxo-3-piperidyl)-5-[4-[[1-[2-[(2S)-2-methylpiperazin-1-yl]ethyl]-4-piperidyl]methyl]piperazin-1-yl]isoindoline-1,3-dione (100 mg, 176.77 umol, 1 eq) and 3-(6-chloropyrimidin-4-yl)-5-isopropoxy-1H-indazole (51.04 mg, 176.77 umol, 1 eq) in DMSO (3 mL) was added DIEA (228.46 mg, 1.77 mmol, 307.90 uL, 10 eq). The reaction mixture was stirred at 80 °C for 6 hr under N<sub>2</sub>. The reaction mixture was quenched by water (10 mL) and extracted with ethyl acetate (3 \* 10 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100\*30mm\*5um; mobile phase: [water(0.225%FA)-ACN]; B%: 12%-42%, 9min) to afford 2-(2,6-dioxo-3-piperidyl)-5-[4-[[1-[2-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethyl]-4-piperidyl]methyl]piperazin-1-yl]isoindoline-1,3-dione (32.1 mg, 39.00 umol, 22.06% yield, 99.38% purity) as a yellow solid.

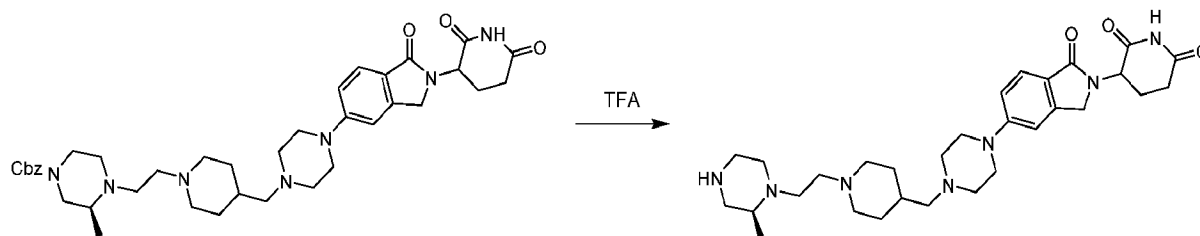
#### [00242] Exemplary Synthesis of Exemplary Compound 31

##### Step 1



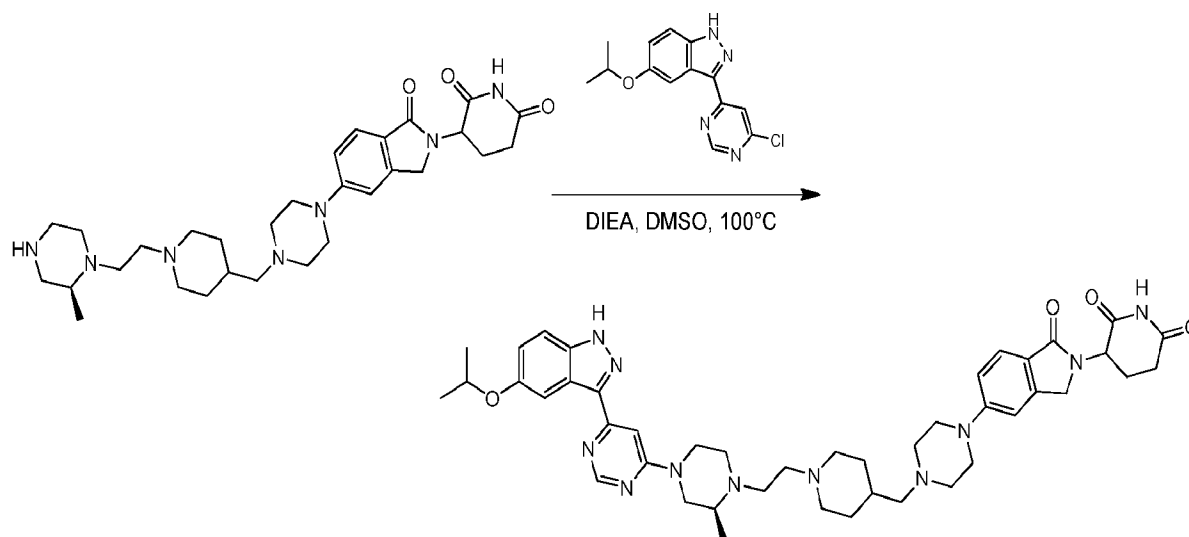
To a solution of 3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (118.69 mg, 361.46  $\mu\text{mol}$ , 1.5 *eq*) and NaOAc (59.30 mg, 722.91  $\mu\text{mol}$ , 3 *eq*) in DCE (8 mL) and MeOH (2 mL) was added HOAc (14.47 mg, 240.97  $\mu\text{mol}$ , 13.78  $\mu\text{L}$ , 1 *eq*) and benzyl (3S)-4-[2-(4-formyl-1-piperidyl)ethyl]-3-methyl-piperazine-1-carboxylate (90 mg, 240.97  $\mu\text{mol}$ , 1 *eq*). The reaction mixture was stirred at 25°C for 1h. Then NaBH<sub>3</sub>CN (30.29 mg, 481.94  $\mu\text{mol}$ , 2 *eq*) was added. After addition, the reaction mixture was stirred at 25°C for 16h. The reaction solution was diluted with water (15 mL) and extracted with ethyl acetate (3 x 10mL). The organic layer was washed with brine (20 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by prep.TLC (chloromethane: methanol=7:1, R<sub>f</sub>=0.1) to afford benzyl (3S)-4-[2-[4-[[4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]ethyl]-3-methyl-piperazine-1-carboxylate (70 mg, 85.32  $\mu\text{mol}$ , 35.41% yield, 83.6% purity) as a colorless gum.

## Step 2



A mixture of benzyl (3S)-4-[2-[4-[[4-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]ethyl]-3-methyl-piperazine-1-carboxylate (70 mg, 102.06  $\mu\text{mol}$ , 1 *eq*) and TFA (3 mL) was stirred at 80°C for 2h. The reaction solution was concentrated under reduced pressure to give 3-[5-[4-[[1-[2-[(2S)-2-methylpiperazin-1-yl]ethyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (110 mg, crude, TFA) as a brown gum. The crude product was used directly.

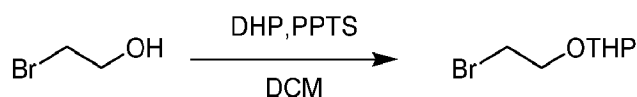
## Step 3



To a solution of 3-[5-[4-[[1-[2-[(2S)-2-methylpiperazin-1-yl]ethyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (103.76 mg, 155.85  $\mu\text{mol}$ , 1.5 *eq*, TFA) and 3-(6-chloropyrimidin-4-yl)-5-isopropoxy-1H-indazole (30 mg, 103.90  $\mu\text{mol}$ , 1 *eq*) in DMSO (3 mL) was added DIEA (94.00 mg, 727.32  $\mu\text{mol}$ , 126.69  $\mu\text{L}$ , 7 *eq*). After addition, the reaction was stirred at 100°C for 4h to give brown solution. The reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100\*30mm\*5 $\mu\text{m}$ ; mobile phase: [water (0.225%FA)-ACN]; B%: 5%-35%; 9min) to afford 3-[5-[4-[[1-[2-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (9.1 mg, 11.32  $\mu\text{mol}$ , 10.89% yield, 100% purity) as a yellow solid.

## [00243] Exemplary Synthesis of Exemplary Compound 32

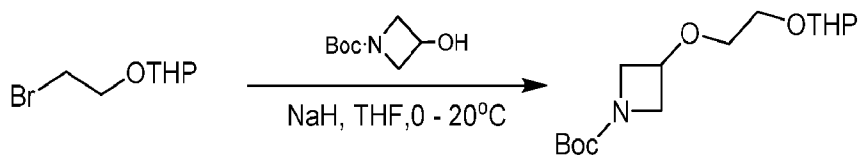
### Step 1



To a mixture of 2-bromoethanol (9 g, 72.02 mmol, 5.11 mL, 1 *eq*) and DHP (9.09 g, 108.03 mmol, 9.88 mL, 1.5 *eq*) in DCM (100 mL) was added PPTS (1.81 g, 7.20 mmol, 0.1 *eq*) in one portion at 0°C under N<sub>2</sub>. The mixture was stirred at 20°C for 16 hours. TLC (DCM: MeOH= 10:1, R<sub>f</sub> = 0.77) showed the reaction was completed. The residue was poured into water (50 mL) and stirred for 10 min. The aqueous phase was extracted with ethyl acetate (50 mL \* 3). The combined organic phase was washed with brine (50 mL \* 3), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>,

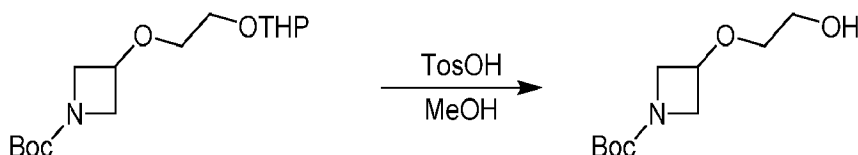
filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (40 g, 0-10% (10 mL) of Ethyl acetate in Petroleum ether) to give tert-butyl 3-(2-tetrahydropyran-2-yloxyethoxy)azetidine-1-carboxylate (12 g, 57.39 mmol, 79.69% yield) as a yellow oil.

## Step 2



A mixture of NaH (2.31 g, 57.73 mmol, 60% purity, 2 *eq*) in DMF (20 mL) was added tert-butyl 3-hydroxyazetidine-1-carboxylate (5 g, 28.87 mmol, 1 *eq*) in DMF (20 mL) at 0°C. The mixture was stirred at 25°C for 0.5 hours and then 2-(2-bromoethoxy)tetrahydropyran (6.64 g, 31.75 mmol, 4.81 mL, 1.1 *eq*) in DMF (20 mL) was added into reaction mixture at 0°C. The mixture was stirred at 20°C for 16 hours to give a brown mixture. TLC (DCM: MeOH= 10:1, R<sub>f</sub>= 0.56) showed there was a new spot. The residue was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (50 mL \* 3). The combined organic phase was washed with brine (50 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (45 g, 30 mL/min, 0-50% (15 min) of Ethyl acetate in Petroleum ether) to give tert-butyl 3-(2-tetrahydropyran-2-yloxyethoxy)azetidine-1-carboxylate (6.6 g, 21.90 mmol, 75.86% yield) as a yellow oil.

## Step 3

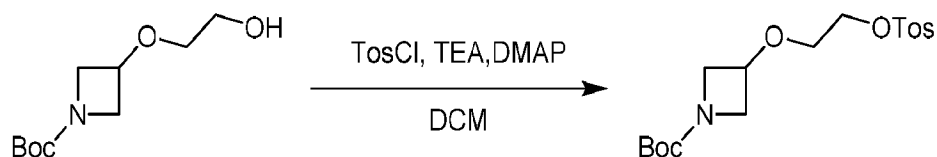


To a mixture of tert-butyl 3-(2-tetrahydropyran-2-yloxyethoxy)azetidine-1-carboxylate (6 g, 19.91 mmol, 1 *eq*) in MeOH (60 mL) was added TsOH (3.43 g, 19.91 mmol, 1 *eq*) in one portion at 20°C under N<sub>2</sub>. The mixture was stirred at 20°C for 1 h. TLC (Petroleum ether: Ethyl acetate =2:3, R<sub>f</sub>=0.30) showed the reaction was completed. H<sub>2</sub>O (30 mL) was added into reaction mixture and the mixture was extracted with EtOAc (30 mL \* 3). The combined extracts were washed with sat. NaHCO<sub>3</sub> (30 mL \* 2, aq.), brine (30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (40 g, 30 mL/min, 0-100% (30 min) of Ethyl acetate in Petroleum



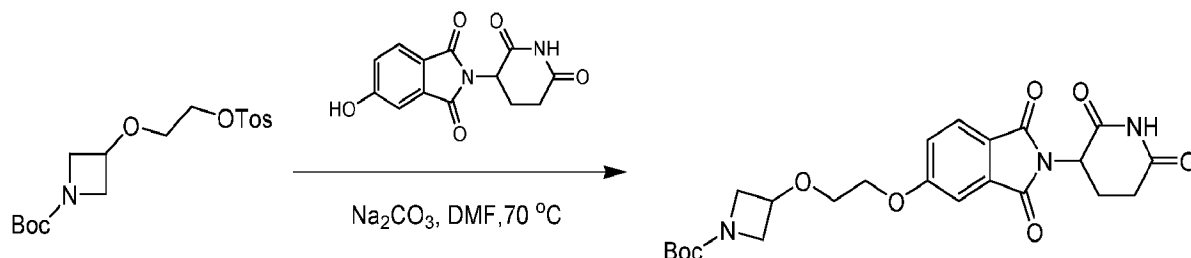
ether) to give tert-butyl 3-(2-hydroxyethoxy)azetidine-1-carboxylate (1.5 g, 6.90 mmol, 34.68% yield) as a yellow oil.

#### Step 4



To a mixture of tert-butyl 3-(2-hydroxyethoxy)azetidine-1-carboxylate (1.5 g, 6.90 mmol, 1 *eq*) TEA (1.75 g, 17.26 mmol, 2.40 mL, 2.5 *eq*) and DMAP (253.04 mg, 2.07 mmol, 0.3 *eq*) in DCM (15 mL) was added TosCl (1.97 g, 10.36 mmol, 1.5 *eq*) at 0°C. The mixture was stirred at 20°C for 2 hours to give a brown mixture. TLC (Petroleum ether: Ethyl acetate =1:1, R<sub>f</sub>= 0.56) showed the reaction was completed. Most of DCM was removed under reduced pressure to give a residue. The residue was dissolved in EtOAc (30 mL), and the resulting mixture was washed with water (10 mL \* 2), sat.NaHCO<sub>3</sub> (10 mL \* 2, aq.), brine (10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and the filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography (20 g, 0-15% (10 min) of Ethyl acetate in Petroleum ether, 15% (5 min) of Ethyl acetate in Petroleum ether) to give tert-butyl 3-[2-(p-tolylsulfonyloxy)ethoxy]azetidine-1-carboxylate (2.3 g, 6.19 mmol, 89.69% yield) as a yellow oil.

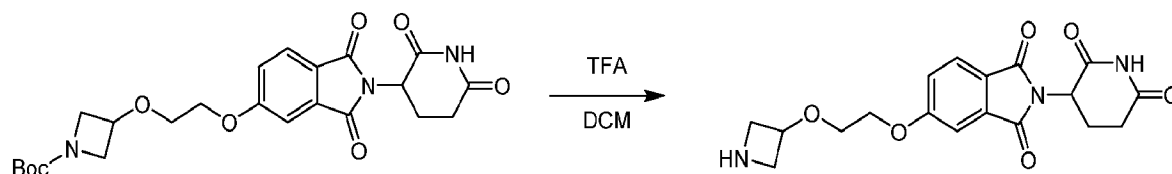
#### Step 5



To a mixture of 2-(2,6-dioxo-3-piperidyl)-5-hydroxy-isoindoline-1,3-dione (1.55 g, 5.65 mmol, 1 *eq*) in DMF (20 mL) was added Na<sub>2</sub>CO<sub>3</sub> (1.20 g, 11.31 mmol, 2 *eq*) and tert-butyl 3-[2-(p-tolylsulfonyloxy)ethoxy]azetidine-1-carboxylate (2.1 g, 5.65 mmol, 1 *eq*). The mixture was stirred at 70°C for 16 hours to give a yellow mixture. The reaction mixture was cooled to room temperature and added into aq. HCl (100 mL, 2%, v/v) at 0°C, and the resulting mixture was extracted with EtOAc (30 mL \* 3). The combined extracts were washed with water (30 mL), brine (30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and the filtrate was concentrated under

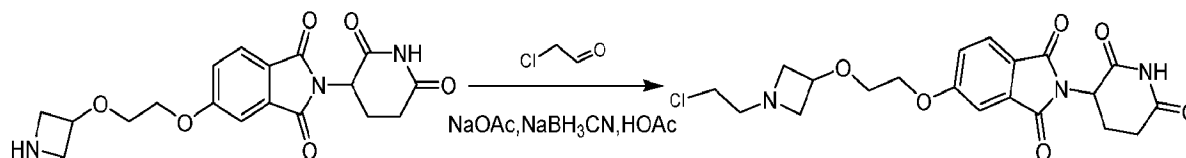
reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (DCM: MeOH= 10:1, Rf= 0.31, 80 g, 0-50% (30 min) of Ethyl acetate in Petroleum ether, 50% (60 min) of Ethyl acetate in Petroleum ether) to give tert-butyl 3-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]oxyethoxy]azetidine-1-carboxylate (1.8 g, 3.80 mmol, 67.24% yield) as a white gum.

### Step 6

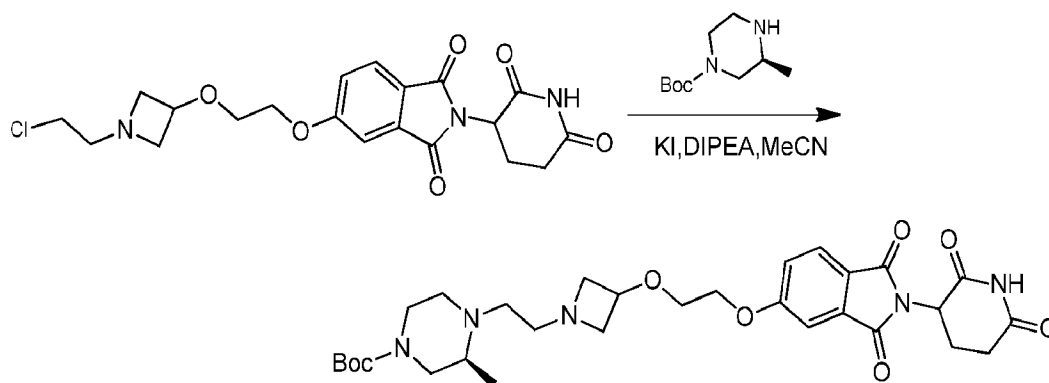


To a mixture of tert-butyl 3-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]oxyethoxy]azetidine-1-carboxylate (1.2 g, 2.53 mmol, 1 *eq*) in DCM (10 mL) was added TFA (866.94 mg, 7.60 mmol, 562.95 uL, 3 *eq*) in one portion at 20°C under N<sub>2</sub>. The mixture was stirred at 20°C for 30 min. TLC showed the reaction was completed. The mixture was concentrated under reduced pressure to give 5-[2-(azetidin-3-yloxy)ethoxy]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (2 g, crude) as a colourless gum.

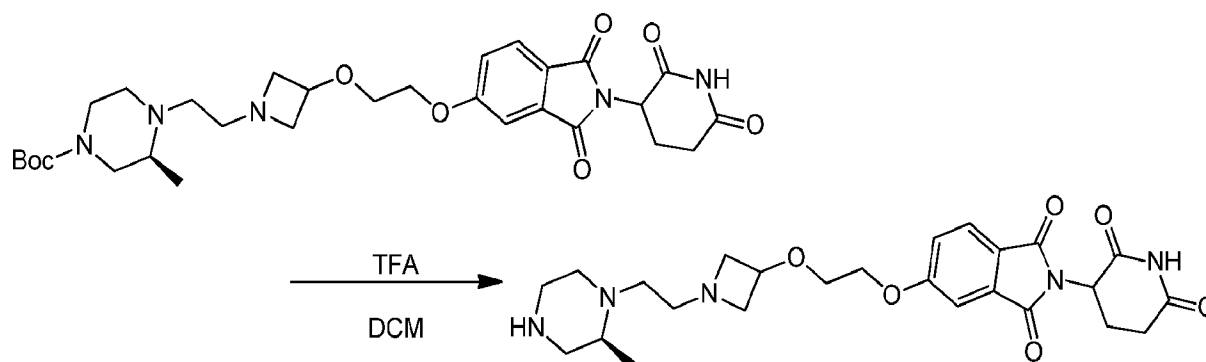
### Step 7



To a solution of 5-[2-(azetidin-3-yloxy)ethoxy]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (2 g, 5.36 mmol, 1 *eq*) and 2-chloroacetaldehyde (3.15 g, 16.07 mmol, 2.58 mL, 3 *eq*) in DCE (10 mL) and MeOH (2 mL) was added NaOAc (2.20 g, 26.78 mmol, 5 *eq*) and NaBH<sub>3</sub>CN (1.01 g, 16.07 mmol, 3 *eq*). Then the mixture was stirred at 20°C for 30 min. Then the HOAc (321.67 mg, 5.36 mmol, 306.36 uL, 1 *eq*) was added to the solution and was stirred at 20°C for 1 h. TLC (DCM: MeOH= 10:1, Rf= 0.29) showed there was a new spot. The residue was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL \* 3). The combined organic phase was washed with brine (10 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (20 g, 30 mL/min, 0-5% (10 min) of MeOH in DCM, 5% (10 min) of MeOH in DCM) to give 5-[2-[1-(2-chloroethyl)azetidin-3-yl]oxyethoxy]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (700 mg, 1.61 mmol, 29.98% yield) as a yellow gum.

**Step 8**

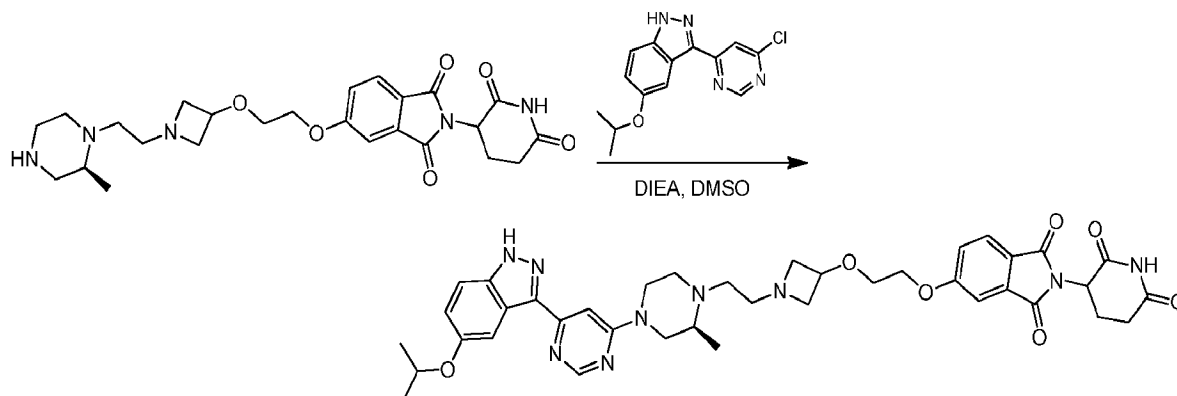
To a mixture of tert-butyl (3S)-3-methylpiperazine-1-carboxylate (229.75 mg, 1.15 mmol, 2 *eq*) and 5-[2-[1-(2-chloroethyl)azetidin-3-yl]oxyethoxy]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (250 mg, 573.58  $\mu\text{mol}$ , 1 *eq*) in MeCN (5 mL) was added KI (476.07 mg, 2.87 mmol, 5 *eq*) and DIPEA (370.65 mg, 2.87 mmol, 499.53  $\mu\text{L}$ , 5 *eq*) in one portion at 20°C under N<sub>2</sub>. The mixture was stirred at 80°C for 16 hours. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (5 mL \* 3). The combined organic phase was washed with brine (5 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (0-100% (30 min) of Ethyl acetate in Petroleum ether) to give tert-butyl (3S)-4-[2-[3-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]oxyethoxy]azetidin-1-yl]ethyl]-3-methyl-piperazine-1-carboxylate (200 mg, 333.51  $\mu\text{mol}$ , 58.15% yield) as a yellow solid.

**Step 9**

To a mixture of tert-butyl (3S)-4-[2-[3-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]oxyethoxy]azetidin-1-yl]ethyl]-3-methyl-piperazine-1-carboxylate (200 mg, 333.51  $\mu\text{mol}$ , 1 *eq*) in DCM (5 mL) was added TFA (114.09 mg, 1.00 mmol, 74.08  $\mu\text{L}$ , 3 *eq*) in one portion at 20°C under N<sub>2</sub>. The mixture was stirred at 20°C for 30 min. The solution was concentrated in vacuum to give 2-(2,6-dioxo-3-piperidyl)-5-[2-[1-[2-[(2S)-2-methylpiperazin-1-

yl]ethyl]azetidin-3-yl]oxyethoxy]isoindoline-1,3-dione (130 mg, 166.55  $\mu\text{mol}$ , 49.94% yield, 64% purity) as colourless gum.

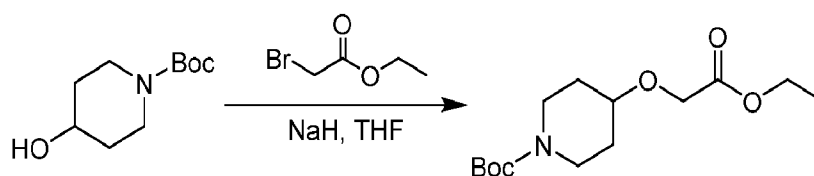
### Step 10



3-(6-chloropyrimidin-4-yl)-5-isopropoxy-2H-indazole (60.11 mg, 208.18  $\mu\text{mol}$ , 0.8 *eq*) and 2-(2,6-dioxo-3-piperidyl)-5-[2-[1-[2-[(2S)-2-methylpiperazin-1-yl]ethyl]azetidin-3-yl]oxyethoxy]isoindoline-1,3-dione (130 mg, 260.23  $\mu\text{mol}$ , 1 *eq*) were dissolved in DMSO (5 mL) then DIPEA (100.90 mg, 780.69  $\mu\text{mol}$ , 135.98  $\mu\text{L}$ , 3 *eq*) was added at 20°C under  $\text{N}_2$ . The solution was stirred at 100°C for 2 h to give yellow solution. The mixture was cooled to 20°C and concentrated in reduced pressure at 20°C. The residue was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL \* 3). The combined organic phase was washed with brine (10 mL \* 3), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The crude product was purified by reversed-phase HPLC (Column: Phenomenex luna C18 150\*25mm\* 10 $\mu\text{m}$ ; Condition: water (0.2%FA)-ACN; Begin B: 20; End B: 40; FlowRate: 25 mL/min; Gradient Time: 20 min; 100%B Hold Time: 4 min) to give 2-(2,6-dioxo-3-piperidyl)-5-[2-[1-[2-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methylpiperazin-1-yl]ethyl]azetidin-3-yl]oxyethoxy]isoindoline-1,3-dione (26.3 mg, 34.98  $\mu\text{mol}$ , 13.44% yield, 100% purity) as a white solid.

### [00244] Exemplary Synthesis of Exemplary Compound 33

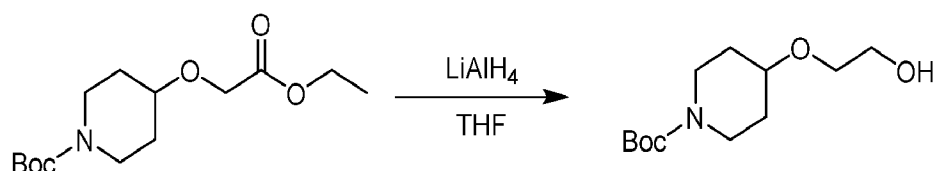
#### Step 1



To a solution of tert-butyl 4-hydroxypiperidine-1-carboxylate (2 g, 9.94 mmol, 1 *eq*) in THF (20 mL) was added NaH (516.69 mg, 12.92 mmol, 60% purity in oil, 1.3 *eq*) in portions under

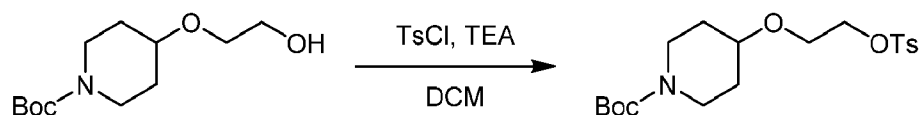
nitrogen at 0 °C. After hydrogen gas evolution ceased, ethyl 2-bromoacetate (3.32 g, 19.87 mmol, 2.20 mL, 2 *eq*) was added dropwise. The resulting mixture was stirred at 0°C for 2h. TLC (petroleum ether: ethyl acetate=5:1) showed two new spots. The reaction mixture was quenched by aq. NH<sub>4</sub>Cl (20mL) and extracted with ethyl acetate (3 x 20mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 20% ethyl acetate in petroleum ether) to afford tert-butyl 4-(2-ethoxy-2-oxo-ethoxy)piperidine-1-carboxylate (800 mg, 2.78 mmol, 28.02% yield) as a colorless oil.

### Step 2



To a solution of tert-butyl 4-(2-ethoxy-2-oxo-ethoxy)piperidine-1-carboxylate (800 mg, 2.78 mmol, 1 *eq*) in THF (10 mL) was added LiAlH<sub>4</sub> (158.50 mg, 4.18 mmol, 1.5 *eq*) at 0°C. After addition, the reaction mixture was stirred at 20°C for 2h. TLC (petroleum ether: ethyl acetate= 1:1) showed starting material consumed and a new spot formed. The reaction mixture was quenched by addition of water (0.5 mL), followed by 15% aqueous NaOH (0.5 mL) and water (1.5 mL). The solid was removed by filtration. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 50% ethyl acetate in petroleum ether) to afford tert-butyl 4-(2-hydroxyethoxy)piperidine-1-carboxylate (400 mg, 1.63 mmol, 58.57% yield) as a colorless oil.

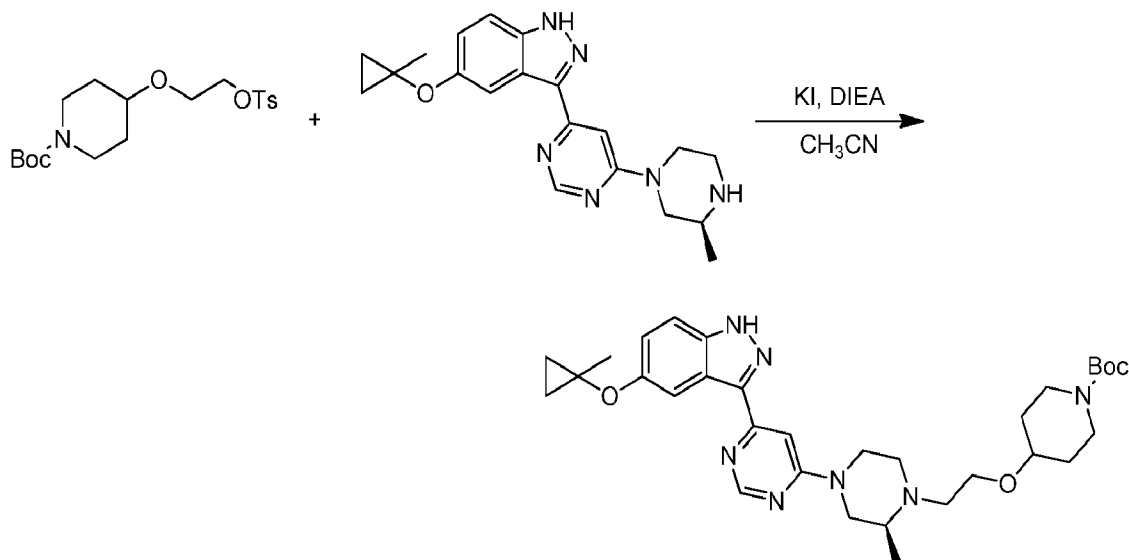
### Step 3



To a solution of tert-butyl 4-(2-hydroxyethoxy)piperidine-1-carboxylate (400 mg, 1.63 mmol, 1 *eq*) in DCM (2 mL) was added 4-methylbenzenesulfonyl chloride (621.72 mg, 3.26 mmol, 2 *eq*) and TEA (329.99 mg, 3.26 mmol, 453.91 uL, 2 *eq*) at 20°C. After addition, the reaction solution was stirred at 20°C for 16h. TLC (petroleum ether: ethyl acetate= 3: 1) showed major two spots. The reaction solution was diluted with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under

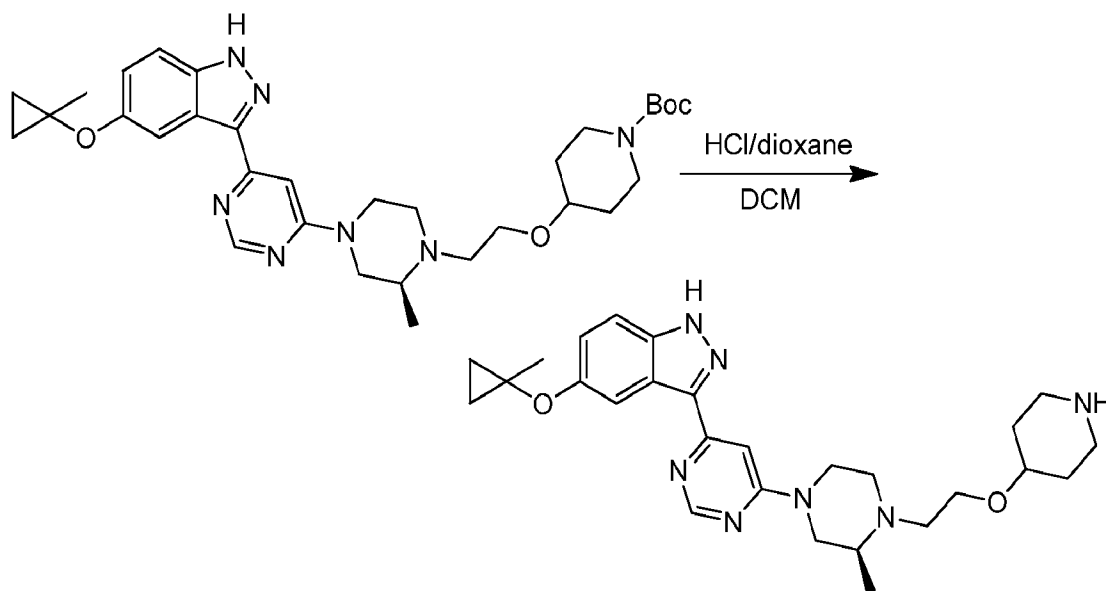
reduced pressure. The residue was purified by silica gel column chromatography (0 to 30% ethyl acetate in petroleum ether) to afford tert-butyl 4-[2-(p-tolylsulfonyloxy)ethoxy]piperidine-1-carboxylate (490 mg, 1.23 mmol, 75.22% yield, 100% purity) as a colorless oil.

#### Step 4



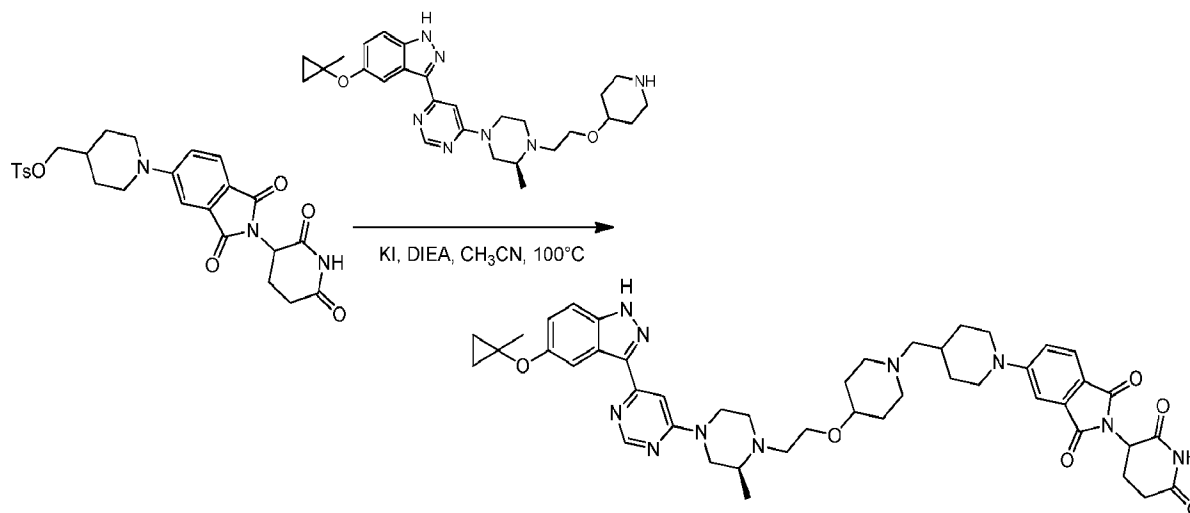
To a solution of tert-butyl 4-[2-(p-tolylsulfonyloxy)ethoxy]piperidine-1-carboxylate (131.54 mg, 329.27  $\mu$ mol, 1 eq) and 5-(1-methylcyclopropoxy)-3-[6-[(3S)-3-methylpiperazin-1-yl]pyrimidin-4-yl]-1H-indazole (120 mg, 329.27  $\mu$ mol, 1 eq) in CH<sub>3</sub>CN (3 mL) was added KI (273.30 mg, 1.65 mmol, 5 eq) and DIEA (127.67 mg, 987.81  $\mu$ mol, 172.06  $\mu$ L, 3 eq). After addition, the reaction mixture was stirred at 90°C for 16h. The reaction mixture was diluted with water (10mL) and extracted with ethyl acetate (3 x 10mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 5% methanol in dichloromethane) to afford tert-butyl 4-[2-[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethoxy]piperidine-1-carboxylate (130 mg, 204.31  $\mu$ mol, 62.05% yield, 93% purity) as a yellow gum.

#### Step 5



To a solution of tert-butyl 4-[2-[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethoxy]piperidine-1-carboxylate (130 mg, 219.69  $\mu\text{mol}$ , 1 eq) in DCM (2 mL) was added HCl/dioxane (4 M, 549.23  $\mu\text{L}$ , 10 eq) at 20°C. After addition, the reaction mixture was stirred at 20°C for 30min. TLC (dichloromethane: methanol= 10: 1) showed starting material consumed. The reaction mixture was concentrated under reduced pressure to afford 5-(1-methylcyclopropoxy)-3-[6-[(3S)-3-methyl-4-[2-(4-piperidyloxy)ethyl]piperazin-1-yl]pyrimidin-4-yl]-1H-indazole (108 mg, 206.50  $\mu\text{mol}$ , 94.00% yield, 94% purity) as a yellow solid. The crude product was used directly.

### Step 6

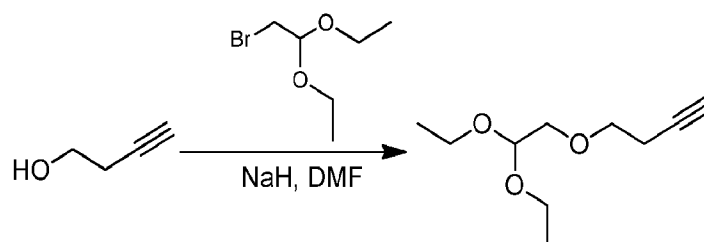


To a solution of 5-(1-methylcyclopropoxy)-3-[6-[(3S)-3-methyl-4-[2-(4-piperidyloxy)ethyl]piperazin-1-yl]pyrimidin-4-yl]-1H-indazole (105.23 mg, 214.05  $\mu\text{mol}$ , 1.25

*eq*) and [1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]methyl 4-methylbenzenesulfonate (90 mg, 171.24  $\mu\text{mol}$ , 1 *eq*) in  $\text{CH}_3\text{CN}$  (5 mL) was added KI (142.13 mg, 856.21  $\mu\text{mol}$ , 5 *eq*) and DIEA (177.05 mg, 1.37 mmol, 238.62  $\mu\text{L}$ , 8 *eq*). After addition, the reaction mixture was stirred at  $100^\circ\text{C}$  for 16h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep.HPLC (column: Welch Xtimate C18 150\*25mm\*5 $\mu\text{m}$ ; mobile phase: [water(0.225%FA)-ACN]; B%: 5%-35%, 8min) to afford 2-(2,6-dioxo-3-piperidyl)-5-[4-[[4-[2-[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethoxy]-1-piperidyl]methyl]-1-piperidyl]isoindoline-1,3-dione (12.5 mg, 14.50  $\mu\text{mol}$ , 8.47% yield, 98% purity) as a yellow solid.

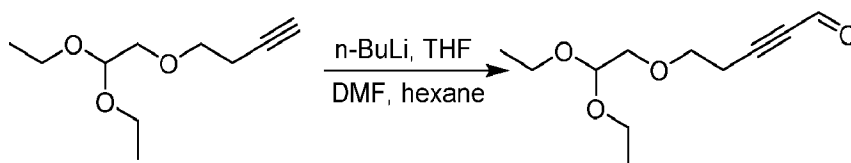
#### [00245] Exemplary Synthesis of Exemplary Compound 34

##### Step 1



but-3-yn-1-ol (1 g, 14.27 mmol, 1.08 mL, 1 *eq*) and 2-bromo-1,1-diethoxyethane (2.81 g, 14.27 mmol, 2.15 mL, 1 *eq*) were dissolved in dry DMF (10 mL) and then NaH (684.77 mg, 17.12 mmol, 60% purity, 1.2 *eq*) was added in small portions at  $0^\circ\text{C}$ . Then the mixture was stirred at  $0^\circ\text{C}$  for 3 h. TLC (Petroleum ether: Ethyl acetate=5:1,  $R_f$ =0.2) showed the reaction new spot. The reaction was quenched by aq. $\text{NH}_4\text{Cl}$  (10 mL) solution and extracted with ethyl acetate (3\*20 mL). The combined organic phases were washed with water, dried with  $\text{Na}_2\text{SO}_4$ , concentrated in vacuum to give a residue. The residue was purified by silica gel column chromatography (0-20% ethyl acetate in Petroleum ether) to give 4-(2,2-diethoxyethoxy)but-1-yne (600 mg, 3.22 mmol, 22.58% yield) as a colorless oil.

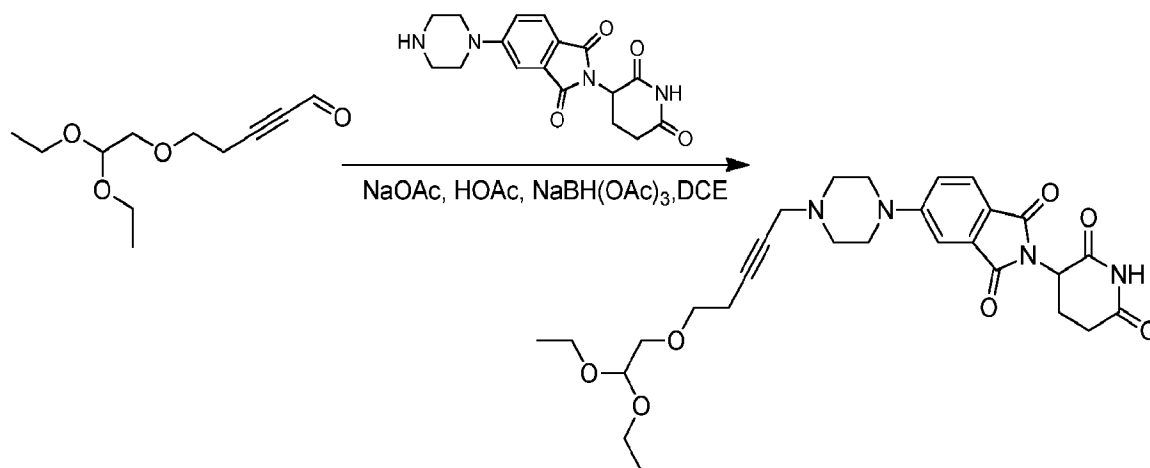
##### Step 2





To a flame-dried three-neck 100 mL round-bottomed flask equipped with an argon inlet adapter, a septum, and a stir bar was added 4-(2,2-diethoxyethoxy)but-1-yne (600 mg, 3.22 mmol, 1 *eq*) and THF (10 mL) via syringe. The solution was cooled at -78°C (bath temperature) in a dry ice/acetone bath, and *n*-BuLi (2.5 M, 1.55 mL, 1.2 *eq*) was added dropwise via syringe turning the reaction brown. The reaction was stirred at -78° C for 30 min, and DMF (470.95 mg, 6.44 mmol, 495.73 uL, 2 *eq*) was added dropwise via syringe turning the reaction colorless. The reaction was stirred at -78° C for 30 min, and was then warmed to 25°C and stirred for 2 h. TLC(Petroleum ether : Ethyl acetate=2:1, R<sub>f</sub>=0.1) showed a new spot. The reaction was added to a cold solution of ethyl acetate (10 mL) and 10percent KH<sub>2</sub>PO<sub>4</sub> (10 mL) and stirred for 30 min. The aqueous layer was separated and the organic layer was washed with brine(20 mL), dried over magnesium sulfate, gravity filtered, and concentrated under reduced pressure to afford 5-(2,2-diethoxyethoxy)pent-2-ynal (350 mg, crude) as a yellow oil.

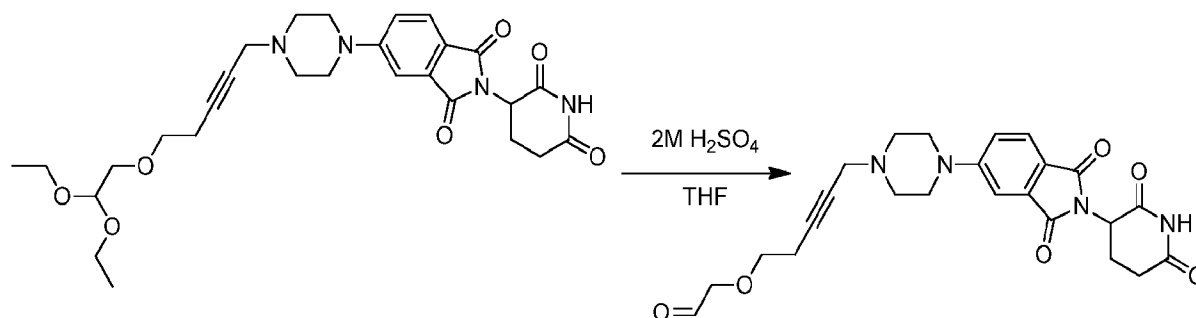
### Step 3



To a solution of 2-(2,6-dioxo-3-piperidyl)-5-piperazin-1-yl-isoindoline-1,3-dione (100 mg, 219.12 umol, 1 *eq*, TFA) and 5-(2,2-diethoxyethoxy)pent-2-ynal (93.90 mg, 438.24 umol, 2 *eq*) in DCE (5 mL) and MeOH (1 mL) was added NaOAc (53.92 mg, 657.36 umol, 3 *eq*) and HOAc (2.63 mg, 43.82 umol, 2.51 uL, 0.2 *eq*). Then the mixture was stirred at 20 °C for 30 min. Then the NaBH<sub>3</sub>CN (41.31 mg, 657.36 umol, 3 *eq*) was added and the solution was stirred at 20 °C for 2h. TLC (Dichloromethane: Methanol= 10:1, R<sub>f</sub>=0.37) showed starting material consumed. The reaction mixture was poured into H<sub>2</sub>O (10 mL). The mixture was extracted with ethyl acetate (20 mL\*5). The organic phase was washed with brine (20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuum to give a residue. The residue was purified by prep-TLC (10% Methanol in Dichloromethane) to give 5-[4-[5-(2,2-diethoxyethoxy)pent-2-ynyl]piperazin-1-yl]-2-(2,6-

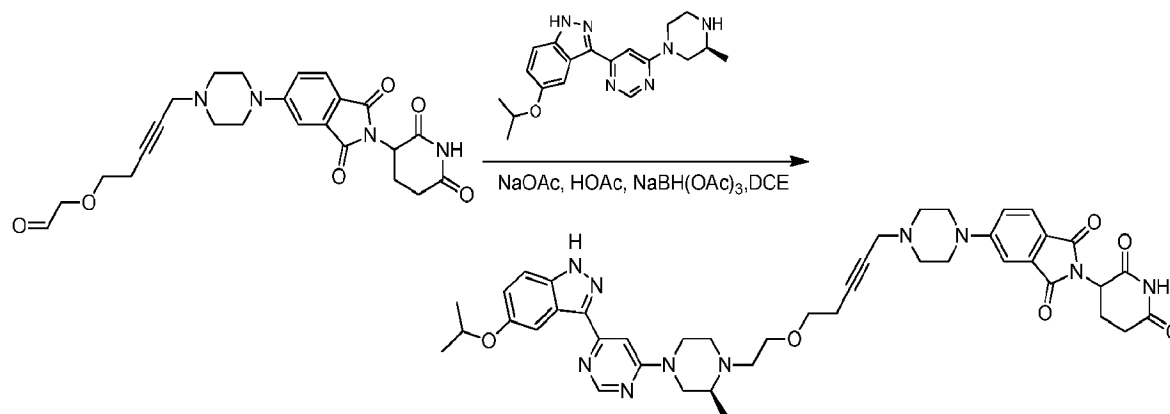
dioxo-3-piperidyl)isoindoline-1,3-dione (120 mg, 188.68  $\mu\text{mol}$ , 86.11% yield, 85% purity) as a yellow solid.

#### Step 4



To a solution of 5-[4-[5-(2,2-diethoxyethoxy)pent-2-ynyl]piperazin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (95 mg, 175.73  $\mu\text{mol}$ , 1 *eq*) in THF (2 mL) was added  $\text{H}_2\text{SO}_4$  (2 M, 2 mL, 86.50 *eq*). Then the mixture was stirred at 65 °C for 1 hr. TLC (Dichloromethane: Methanol= 10:1,  $R_f=0.37$ ) showed starting material consumed. The reaction mixture was poured into  $\text{H}_2\text{O}$  (2 mL) and basified with aqueous  $\text{NaHCO}_3$  till PH =8. The mixture was extracted with ethyl acetate (15 mL\*5), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , concentrated in vacuum to give 2-[5-[4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazin-1-yl]pent-3-ynoxy]acetaldehyde (80 mg, crude) as a yellow solid.

#### Step 5

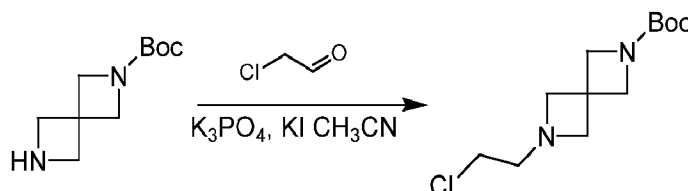


To a solution of 5-isopropoxy-3-[6-[(3S)-3-methylpiperazin-1-yl]pyrimidin-4-yl]-1H-indazole (100 mg, 283.74  $\mu\text{mol}$ , 1 *eq*) and 2-[5-[4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazin-1-yl]pent-3-ynoxy]acetaldehyde (80.00 mg, 171.50  $\mu\text{mol}$ , 6.04e-1 *eq*) in DCE (5 mL) and MeOH (2 mL) was added NaOAc (69.83 mg, 851.23  $\mu\text{mol}$ , 3 *eq*) and HOAc (3.41 mg, 56.75  $\mu\text{mol}$ , 3.25  $\mu\text{L}$ , 0.2 *eq*). Then the mixture was stirred at 25 °C for 60 min. Then the  $\text{NaBH}_3\text{CN}$  (53.49 mg, 851.23  $\mu\text{mol}$ , 3 *eq*) was added and the solution was stirred at 25 °C for

16hr. TLC (Dichloromethane: Methanol= 10:1,  $R_f=0.37$ ) showed the reaction no start material. The reaction mixture was poured into H<sub>2</sub>O (10 mL). The mixture was extracted with ethyl acetate (20 mL\*5). The organic phase was washed with brine (20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (Phenomenex Luna C18 100\*30mm\*5um; mobile phase: [water(0.225%FA)-ACN];B%: 8%-38%, 9min) to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[5-[2-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethoxy]pent-2-ynyl]piperazin-1-yl]isoindoline-1,3-dione (19.4 mg, 23.60 umol, 8.32% yield, 97.68% purity) as a yellow solid.

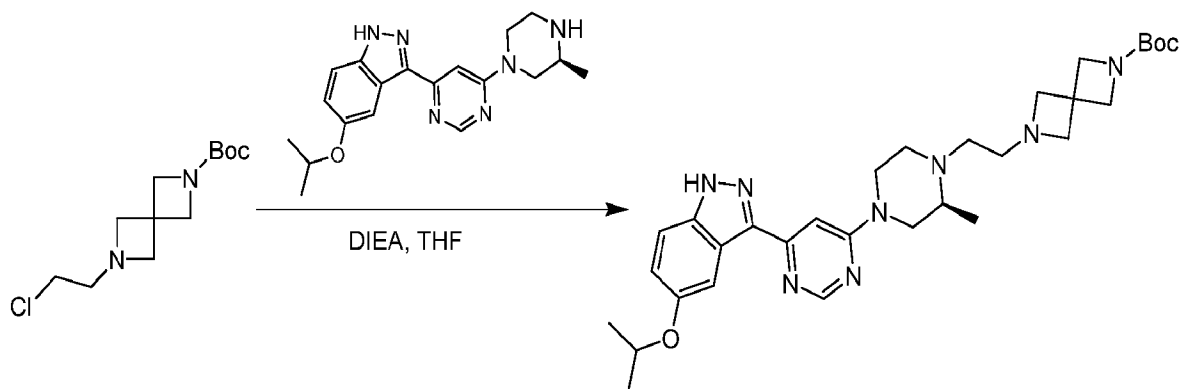
### [00246] Exemplary Synthesis of Exemplary Compound 35

#### Step 1



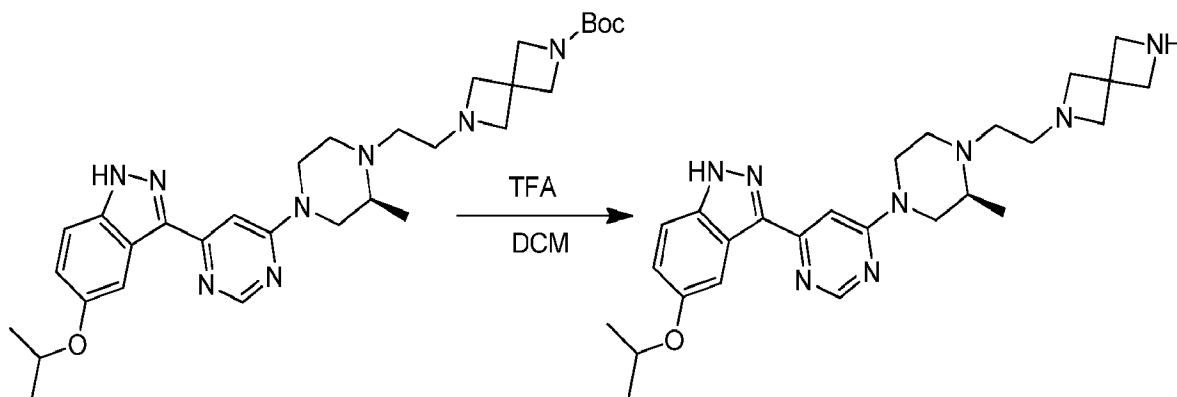
To a solution of tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate (200 mg, 1.01 mmol, 1 *eq*) and 2-chloroacetaldehyde (593.89 mg, 3.03 mmol, 486.80 uL, 3 *eq*) in DCM (5 mL) and MeOH (5 mL) was added NaOAc (165.51 mg, 2.02 mmol, 2 *eq*) and HOAc (6.06 mg, 100.88 umol, 5.77 uL, 0.1 *eq*). Then the mixture was stirred at 20 °C for 20 min. Then the NaBH<sub>3</sub>CN (190.18 mg, 3.03 mmol, 3 *eq*) was added to the solution and the mixture was stirred at 20 °C for 16 hr. TLC (Petroleum ether: Ethyl acetate= 1:1,  $R_f=0.5$ ) was showed the reaction completed. The reaction mixture was poured into H<sub>2</sub>O (20 mL). The mixture was extracted with ethyl acetate (30 mL\*3). The organic phase was washed with brine (20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuum to give a residue. The residue was purified by silica gel column chromatography (0-100% ethyl acetate in Petroleum ether) to give tert-butyl 6-(2-chloroethyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (165 mg, 632.77 umol, 62.73% yield) as a colorless oil.

#### Step 2



Tert-butyl 6-(2-chloroethyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (81.39 mg, 312.12  $\mu\text{mol}$ , 1 *eq*) and 5-isopropoxy-3-[6-[(3S)-3-methylpiperazin-1-yl]pyrimidin-4-yl]-1H-indazole (110 mg, 312.12  $\mu\text{mol}$ , 1 *eq*) were dissolved in dry  $\text{CH}_3\text{CN}$  (10 mL), then KI (777.17 mg, 4.68 mmol, 15 *eq*) and DIEA (605.07 mg, 4.68 mmol, 815.46  $\mu\text{L}$ , 15 *eq*) were added to the reaction. The reaction was stirred at  $100^\circ\text{C}$  for 16hr. The reaction mixture was poured into  $\text{H}_2\text{O}$  (20 mL). The mixture was extracted with ethyl acetate (20 mL\*2). The organic phase was washed with brine (15 mL\*3), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , concentrated in vacuum to give a residue. The residue was purified by prep-TLC (10% Methanol in Dichloromethane,  $R_f=0.2$ ) to give tert-butyl 6-[2-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethyl]-2,6-diazaspiro[3.3]heptane-2-carboxylate (124 mg, 154.80  $\mu\text{mol}$ , 49.60% yield) as a white solid.

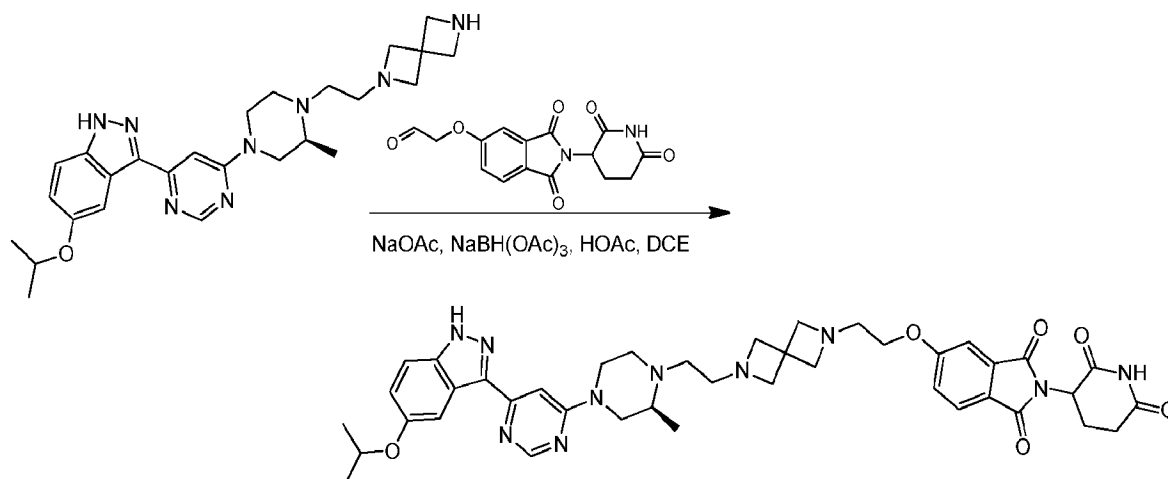
### Step 3



Tert-butyl 6-[2-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethyl]-2,6-diazaspiro[3.3]heptane-2-carboxylate (124 mg, 215.00  $\mu\text{mol}$ , 1 *eq*) was dissolved in DCM (3 mL) and TFA (3.08 g, 27.01 mmol, 2 mL, 125.63 *eq*). The reaction was stirred at  $25^\circ\text{C}$  for 1hr. TLC (Dichloromethane: Methanol=10:1,  $R_f=0.01$ ) indicated that the reaction was complete. The reaction mixture was concentrated in vacuum to give 3-[6-[(3S)-4-[2-(2,6-diazaspiro[3.3]heptan-2-yl)ethyl]-3-methyl-piperazin-1-yl]pyrimidin-4-yl]-5-isopropoxy-1H-

indazole (126 mg, crude, TFA) as a yellow gum. The crude product was used for next step directly.

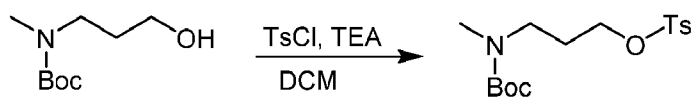
#### Step 4



To a solution of 2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]oxyacetaldehyde (67.47 mg, 213.33  $\mu\text{mol}$ , 1 *eq*) and 3-[6-[(3S)-4-[2-(2,6-diazaspiro[3.3]heptan-2-yl)ethyl]-3-methyl-piperazin-1-yl]pyrimidin-4-yl]-5-isopropoxy-1H-indazole (126 mg, 213.33  $\mu\text{mol}$ , 1 *eq*, TFA) in DCE (5 mL) and MeOH (1 mL) was added NaOAc (52.50 mg, 639.99  $\mu\text{mol}$ , 3. *eq*) and the mixture was stirred at 25°C for 20 min. Then the mixture was added HOAc (1.28 mg, 21.33  $\mu\text{mol}$ , 1.22  $\mu\text{L}$ , 0.1 *eq*) and stirred at 25 °C for 20 min. Then the NaBH<sub>3</sub>CN (53.62 mg, 853.31  $\mu\text{mol}$ , 4 *eq*) was added to the solution and the mixture was stirred at 25 °C for 16h. The reaction mixture was poured into H<sub>2</sub>O (20 mL). The mixture was extracted with ethyl acetate (20 mL\*2). The organic phase was washed with brine (15 mL\*3), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (Phenomenex Luna C18 100\*30mm\*5um: [water(0.225%FA)-ACN];B%: 5%-35%, 9min) to give 2-(2,6-dioxo-3-piperidyl)-5-[2-[6-[2-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethyl]-2,6-diazaspiro[3.3]heptan-2-yl]ethoxy]isoindoline-1,3-dione (14.7 mg, 17.35  $\mu\text{mol}$ , 8.13% yield, 97.1% purity, FA) as a yellow solid.

#### [00247] Exemplary Synthesis of Exemplary Compound 36

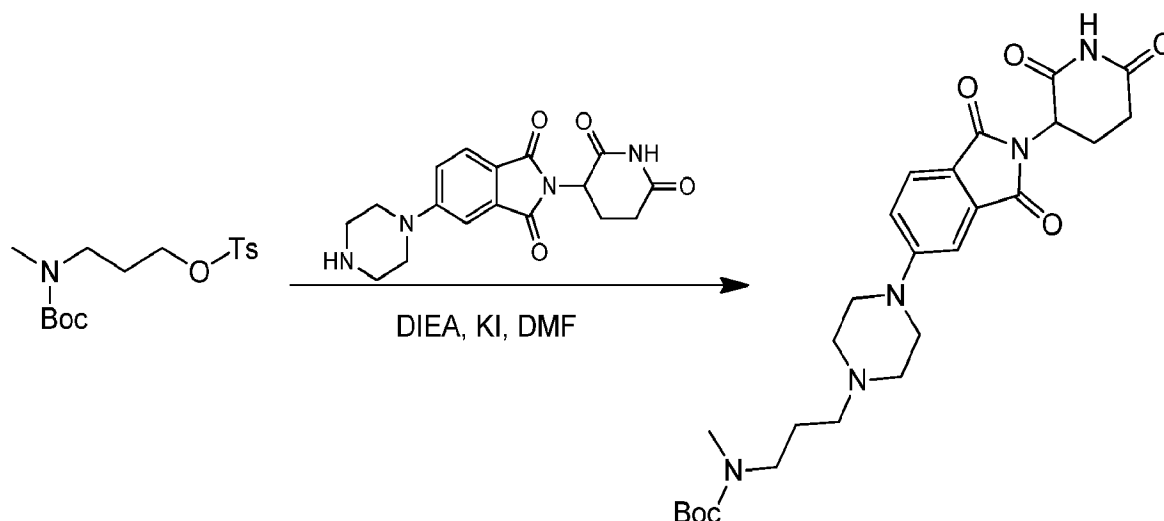
##### Step 1



To a mixture of tert-butyl N-(3-hydroxypropyl)-N-methyl-carbamate (500 mg, 2.64 mmol, 1 *eq*), DMAP (322.77 mg, 2.64 mmol, 1 *eq*) and Et<sub>3</sub>N (267.34 mg, 2.64 mmol, 367.73  $\mu\text{L}$ , 1 *eq*) in

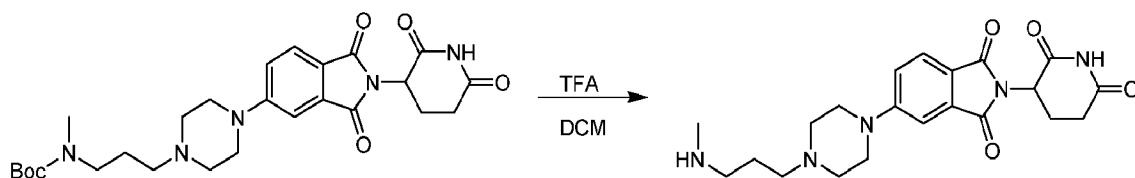
DCM (5 mL) was added 4-methylbenzene-1-sulfonyl chloride (503.69 mg, 2.64 mmol, 1 *eq*) in one portion at 0°C under N<sub>2</sub>. The mixture was stirred at 20°C for 1 h to give white suspension. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (5 mL \* 3). The combined organic phase was washed with brine (5 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 12 g, 100-200 mesh silica gel, 0-20% (10 min) of Ethyl acetate in Petroleum ether, 20% (5 min) of Ethyl acetate in Petroleum ether) to give 3-[tert-butoxycarbonyl(methyl)amino]propyl 4-methylbenzenesulfonate (670 mg, 1.95 mmol, 73.84% yield) as a colorless oil.

### Step 2



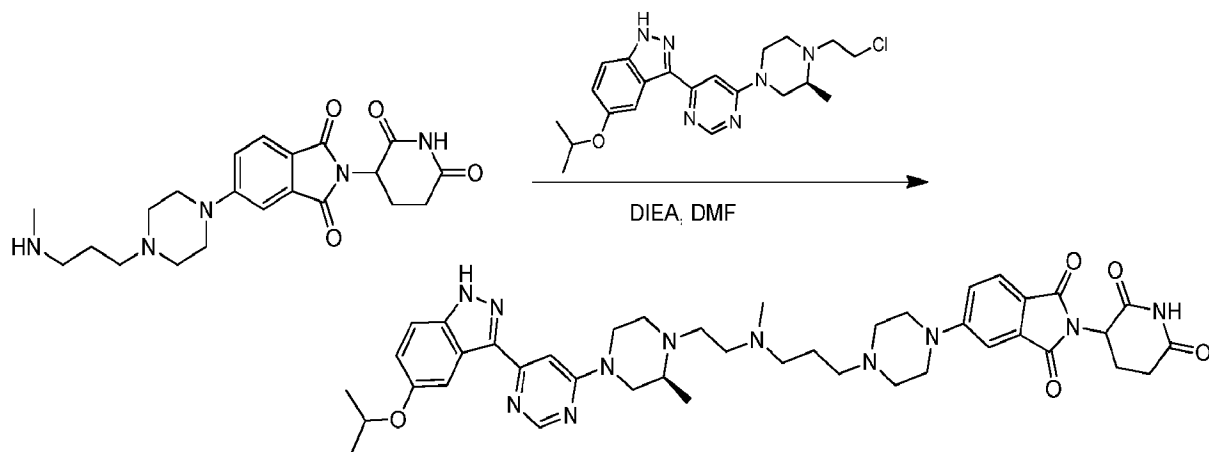
To a mixture of 3-[tert-butoxycarbonyl(methyl)amino]propyl 4-methylbenzenesulfonate (670 mg, 1.95 mmol, 1 *eq*) and 2-(2,6-dioxo-3-piperidyl)-5-piperazin-1-yl-isoindoline-1,3-dione (890.32 mg, 2.60 mmol, 1.33 *eq*) in MeCN (5 mL) was added KI (1.62 g, 9.75 mmol, 5 *eq*) and DIPEA (1.26 g, 9.75 mmol, 1.70 mL, 5 *eq*) in one portion at 20°C under N<sub>2</sub>. The mixture was stirred at 80°C for 16 hours. The mixture was cooled to 20°C and concentrated under reduced pressure at 20°C. The residue was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL \* 3). The combined organic phase was washed with brine (10 mL \* 3), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 40 g, 100-200 mesh silica gel, 0-100% of Ethyl acetate in Petroleum ether) to give tert-butyl N-[3-[4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazin-1-yl]propyl]-N-methyl-carbamate (1 g, crude) as a yellow solid.

### Step 3



To a mixture of tert-butyl N-[3-[4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazin-1-yl]propyl]-N-methyl-carbamate (1 g, 1.95 mmol, 1 *eq*) in DCM (5 mL) was added TFA (222.01 mg, 1.95 mmol, 144.16  $\mu$ L, 1 *eq*) in one portion at 20°C under N<sub>2</sub>. The mixture was stirred at 20°C for 30 min. The residue was poured into NaHCO<sub>3</sub> (pH=7-8). The aqueous phase was extracted with DCM (5 mL \* 3). The combined organic phase was washed with brine (5 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The crude product was purified by reversed-phase HPLC (Column: Phenomenex Luna C18 75\*30mm\*3 $\mu$ m; Condition: water (0.225%FA)-ACN; B%: 5%-35%; 9 min) to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[3-(methylamino)propyl]piperazin-1-yl]isoindoline-1,3-dione (250 mg, 604.64  $\mu$ mol, 31.05% yield) as a yellow gum.

#### Step 4

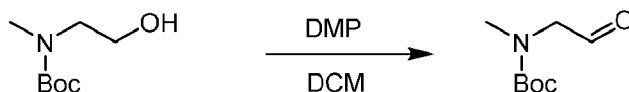


To a solution of 2-(2,6-dioxo-3-piperidyl)-5-[1-[3-(methylamino)propyl]-4-piperidyl]isoindoline-1,3-dione (100 mg, 242.44  $\mu$ mol, 1.13 *eq*) and 3-[6-[(3S)-4-(2-chloroethyl)-3-methyl-piperazin-1-yl]pyrimidin-4-yl]-5-isopropoxy-1H-indazole (89 mg, 214.49  $\mu$ mol, 1 *eq*) in MeCN (5 mL) was added DIPEA (83.17 mg, 643.48  $\mu$ mol, 112.08  $\mu$ L, 3 *eq*). The mixture was stirred at 80°C for 16 hr to give yellow suspension. The mixture was cooled to 20°C and concentrated under reduced pressure at 20°C. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (5 mL \* 3). The combined organic phase was washed with brine (5 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC (Column: Phenomenex Luna C18

75\*30mm\*3um; Condition: water(0.225%FA)-ACN; B%: 17%-47%; 9 min) to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[3-[2-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethyl-methyl-amino]propyl]piperazin-1-yl]isoindoline-1,3-dione (13.6 mg, 17.17 umol, 8.01% yield, 100% purity) as a yellow solid.

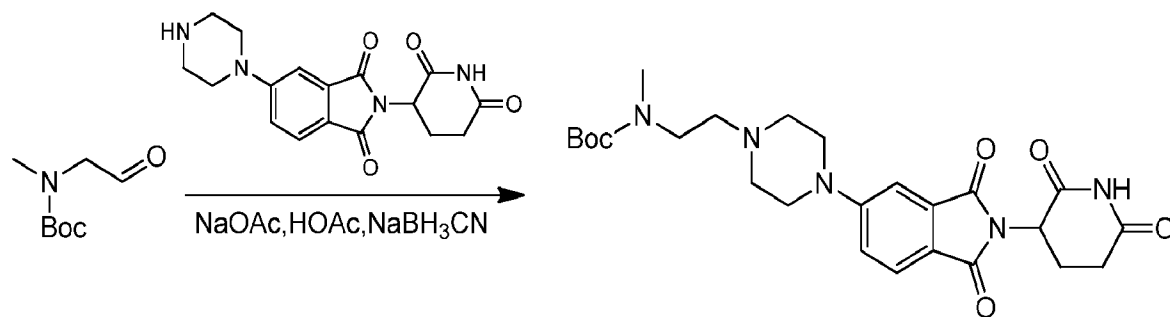
## [00248] Exemplary Synthesis of Exemplary Compound 37

### Step 1



To a mixture of tert-butyl N-(2-hydroxyethyl)-N-methyl-carbamate (200 mg, 1.14 mmol, 1 *eq*) in DCM (5 mL) was added DMP (968.22 mg, 2.28 mmol, 706.73 uL, 2 *eq*) in one portion at 20°C under N<sub>2</sub>. The mixture was stirred at 20°C for 16 h to give white suspension. TLC (Ethyl acetate: Petroleum ether=10:1) showed the starting material was consumed completely. The residue was poured into NaHCO<sub>3</sub> to adjust the pH=7-8, and Na<sub>2</sub>SO<sub>3</sub> (10 mL) was added. The aqueous phase was extracted with DCM (5 mL \* 3). The combined organic phase was washed with brine (5 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 12 g, 100-200 mesh silica gel, 0-20% (10 min) of Ethyl acetate in Petroleum ether, 20% (5 min) of Ethyl acetate in Petroleum ether) to give tert-butyl N-methyl-N-(2-oxoethyl)carbamate (150 mg, 866.01 umol, 75.87% yield) as a colourless oil.

### Step 2

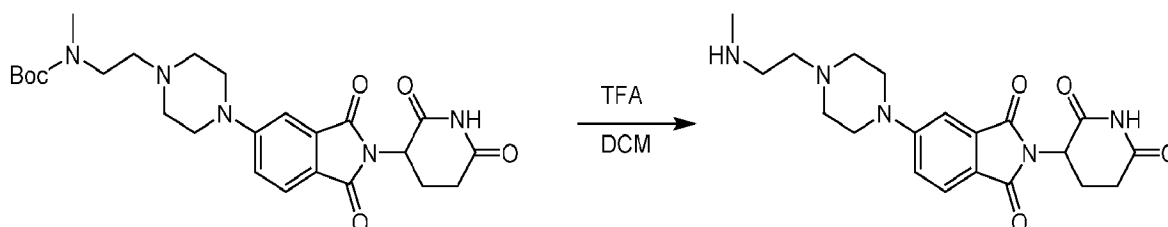


To a mixture of 2-(2,6-dioxo-3-piperidyl)-5-piperazin-1-yl-isoindoline-1,3-dione (180 mg, 394.42 umol, 1 *eq*, TFA) in MeOH (5 mL) was added NaOAc (97.07 mg, 1.18 mmol, 3 *eq*) under N<sub>2</sub> and the mixture was stirred at 25°C for 30 min. Then tert-butyl N-methyl-N-(2-oxoethyl)carbamate (68.32 mg, 394.42 umol, 1 *eq*) and HOAc (18.95 mg, 394.42 umol, 1.19 mL, 1 *eq*) was added, the solution was stirred at 25°C for 30 min, then NaBH<sub>3</sub>CN (74.36 mg, 1.18



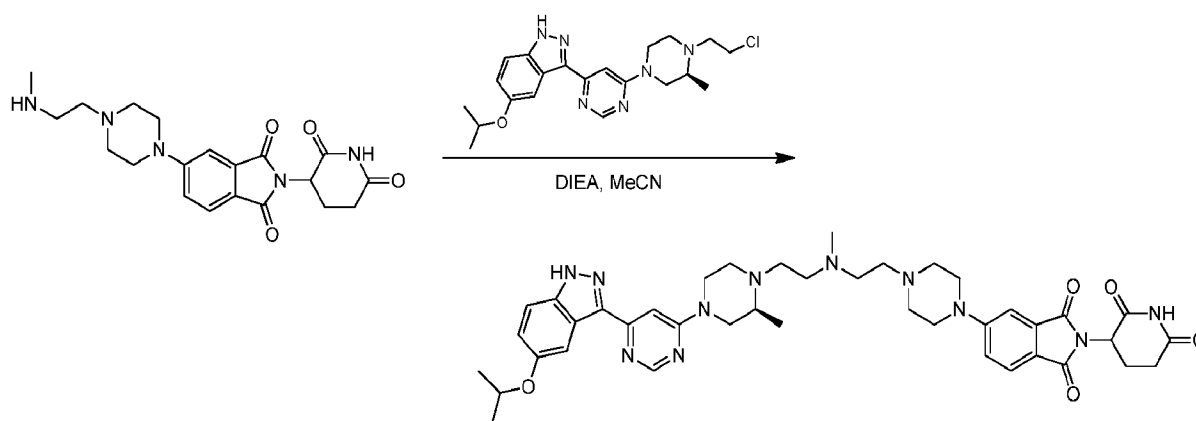
mmol, 3 *eq*) was added in one portion at 25°C under N<sub>2</sub>. The mixture was stirred at 25°C for 1 h to give yellow solution. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (5 mL \* 3). The combined organic phase was washed with brine (5 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 12 g, 40 mL/min, 0-6% (5 min) of Ethyl acetate in MeOH) to give tert-butyl N-[2-[4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazin-1-yl]ethyl]-N-methyl-carbamate (180 mg, 360.32  $\mu$ mol, 91.36% yield) as a yellow gum.

### Step 3



To a mixture of tert-butyl N-[2-[4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazin-1-yl]ethyl]-N-methyl-carbamate (180 mg, 360.32  $\mu$ mol, 1 *eq*) in DCM (5 mL) was added TFA (123.25 mg, 1.08 mmol, 80.03  $\mu$ L, 3 *eq*) in one portion at 25°C under N<sub>2</sub>. The mixture was stirred at 25°C for 30 min to give yellow solution. The solution was concentrated in vacuum to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[2-(methylamino)ethyl]piperazin-1-yl]isoindoline-1,3-dione (200mg, crude, TFA) as a yellow gum.

### Step 4

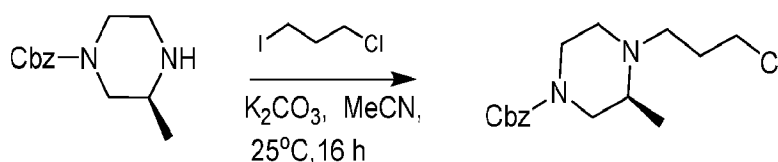


To a solution of 2-(2,6-dioxo-3-piperidyl)-5-[1-[2-(methylamino)ethyl]-4-piperidyl]isoindoline-1,3-dione (144.04 mg, 361.51  $\mu$ mol, 1 *eq*) and 3-[6-[(3S)-4-(2-chloroethyl)-3-methyl-piperazin-1-yl]pyrimidin-4-yl]-5-isopropoxy-1H-indazole (165.00 mg, 397.66  $\mu$ mol, 1.1 *eq*) in CH<sub>3</sub>CN (5 mL) was added DIPEA (140.16 mg, 1.08 mmol, 188.90  $\mu$ L, 3 *eq*). The mixture was stirred at

80°C for 16 hr to give yellow suspension. The mixture was cooled to 20°C and concentrated in reduced pressure at 20°C. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (5 mL \* 3). The combined organic phase was washed with brine (5 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The crude product was purified by reversed-phase HPLC (column: Phenomenex Luna C18 100\*30mm\*5um; mobile phase: [water (0.225%FA)-ACN]; B%: 10%-40%, 9 min) to give crude product (16 mg). The crude was purified by prep-TLC (DCM: MeOH=10:1, R<sub>f</sub>=0.51) to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[2-[2-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methylpiperazin-1-yl]ethyl-methyl-amino]ethyl]piperazin-1-yl]isoindoline-1,3-dione (10.4 mg, 13.18 umol, 3.65% yield, 98.6% purity) as a yellow solid.

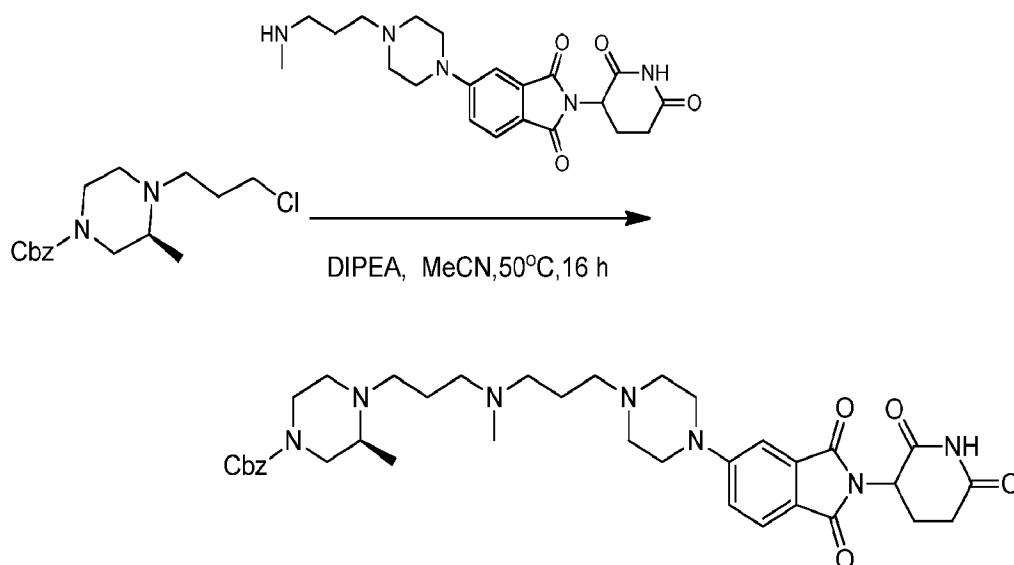
#### [00249] Exemplary Synthesis of Exemplary Compound 38

##### Step 1



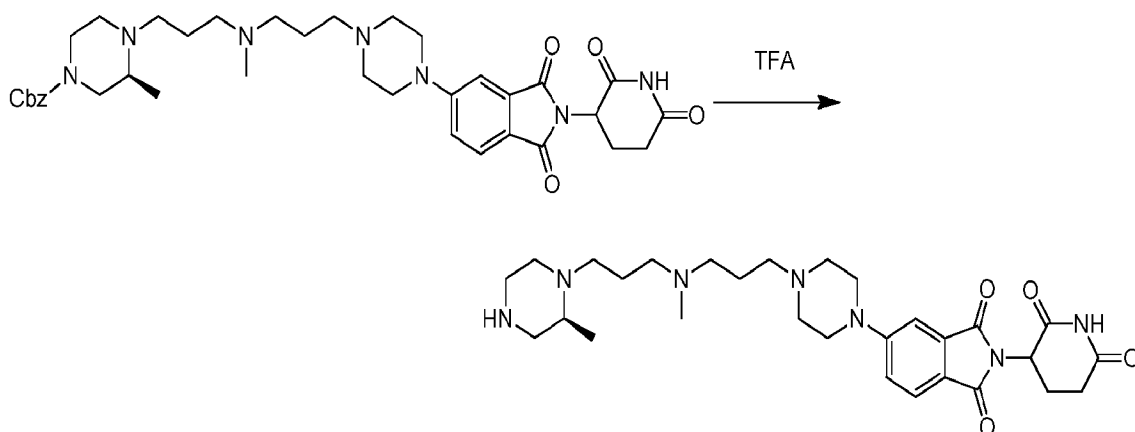
To a mixture of benzyl (3S)-3-methylpiperazine-1-carboxylate (500 mg, 2.13 mmol, 1 *eq*) and 1-chloro-3-iodo-propane (1.31 g, 6.40 mmol, 688.87 uL, 3 *eq*) in MeCN (3 mL) was added K<sub>2</sub>CO<sub>3</sub> (589.90 mg, 4.27 mmol, 2 *eq*) in one portion at 25°C under N<sub>2</sub>. The mixture was stirred at 25°C for 16 h. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (5 mL \* 3). The combined organic phase was washed with brine (5 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (12 g, 30 mL/min, 100-200 mesh silica gel, 0-14% (10 min) of Ethyl acetate in Petroleum ether, 14% (20 min) of Ethyl acetate in Petroleum ether) to give benzyl (3S)-4-(3-chloropropyl)-3-methyl-piperazine-1-carboxylate (300 mg, 965.19 umol, 45.23% yield) as a yellow gum.

##### Step 2



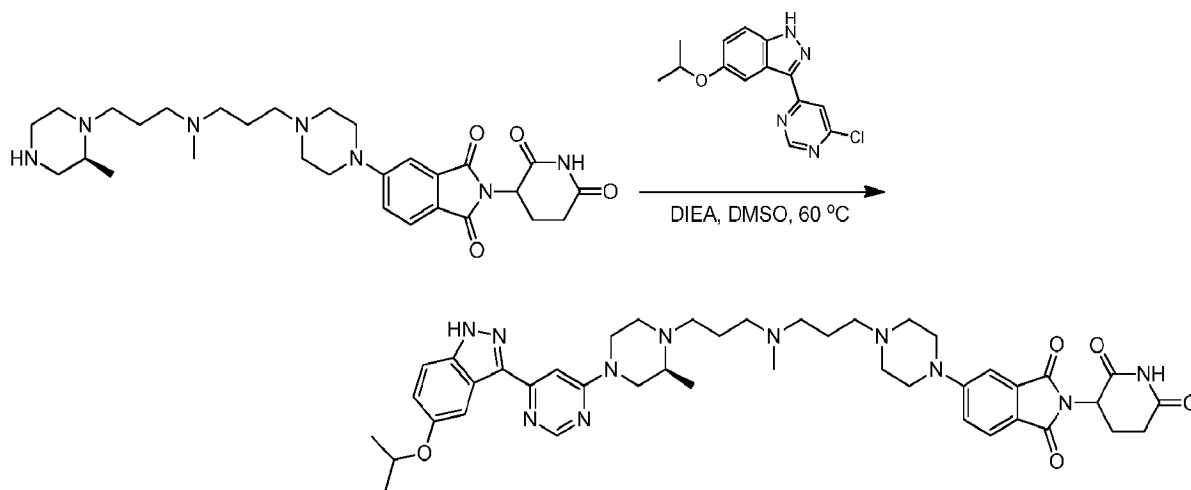
To a solution of 2-(2,6-dioxo-3-piperidyl)-5-[4-[3-(methylamino)propyl]piperazin-1-yl]isoindolin-1,3-dione (140.34 mg, 339.41  $\mu\text{mol}$ , 1 *eq*) and benzyl (3S)-4-(3-chloropropyl)-3-methyl-piperazine-1-carboxylate (105.49 mg, 339.41  $\mu\text{mol}$ , 1 *eq*) in MeCN (5 mL) was added DIPEA (131.60 mg, 1.02 mmol, 177.35  $\mu\text{L}$ , 3 *eq*). The mixture was stirred at 80°C for 16 hr to give yellow suspension. The mixture was cooled to 20°C and concentrated in reduced pressure at 20°C. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (5 mL \* 3). The combined organic phase was washed with brine (5 mL \* 2), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The crude product was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, 0-100% of DCM in MeOH) to give benzyl (3S)-4-[3-[3-[4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazin-1-yl]propyl-methyl-amino]propyl]-3-methyl-piperazine-1-carboxylate (200 mg, crude) as a yellow solid.

### Step 3



To a solution of benzyl (3S)-4-[3-[3-[4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazin-1-yl]propyl-methyl-amino]propyl]-3-methyl-piperazine-1-carboxylate (200 mg, 290.77  $\mu\text{mol}$ , 1 *eq*) in TFA (33.15 mg, 290.77  $\mu\text{mol}$ , 21.53  $\mu\text{L}$ , 1 *eq*). Then the reaction mixture was stirred at 70°C for 1 hr to give yellow solution. The reaction mixture was poured into DCM (20 mL), concentrated in rotary evaporator to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[3-[methyl-[3-[(2S)-2-methylpiperazin-1-yl]propyl]amino]propyl]piperazin-1-yl]isoindoline-1,3-dione (200 mg, crude, TFA) as a yellow gum.

#### Step 4



3-(6-chloropyrimidin-4-yl)-5-isopropoxy-2H-indazole (80.00 mg, 277.07  $\mu\text{mol}$ , 1 *eq*) and 2-(2,6-dioxo-3-piperidyl)-5-[4-[3-[methyl-[3-[(2S)-2-methylpiperazin-1-yl]propyl]amino]propyl]piperazin-1-yl]isoindoline-1,3-dione (185.01 mg, 277.07  $\mu\text{mol}$ , 1 *eq*, TFA) were dissolved in DMSO (5 mL) then DIPEA (107.43 mg, 831.22  $\mu\text{mol}$ , 144.78  $\mu\text{L}$ , 3 *eq*) was added, the reaction and stirred at 50°C for 16 h. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (5 mL \* 3). The combined organic phase was washed with brine (5 mL \* 3), dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuum. The crude product was purified by reversed-phase HPLC (Column: Phenomenex Luna C18 100\*30mm\*5 $\mu\text{m}$ ; Condition: water (0.225%FA)-ACN; B%: 0-30%; 7 min;) to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[3-[3-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]propyl-methyl-amino]propyl]piperazin-1-yl]isoindoline-1,3-dione (41.8 mg, 51.03  $\mu\text{mol}$ , 18.42% yield, 98.4% purity) to give yellow solid.

#### [00250] Exemplary Synthesis of Exemplary Compound 39

##### Step 1

To a solution of tert-butyl 4-(2-chloroethyl)piperazine-1-carboxylate (200 mg, 804.02  $\mu\text{mol}$ , 1 eq) in DCM (2 mL) was added TFA (3.08 g, 27.01 mmol, 2 mL, 33.60 eq) and the mixture was stirred at 20 °C for 1 hr. TLC (Dichloromethane: Methanol=10:1,  $R_f$ =0.02) showed no starting material and a new spot. The residue was concentrated under reduced pressure to give 1-(2-chloroethyl)piperazine (119 mg, crude, TFA) as a colorless oil.

### **Step 2**

A solution of 1-(2-chloroethyl)piperazine (119 mg, 800.63  $\mu\text{mol}$ , 1 eq) and 1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isindolin-5-yl]piperidine-4-carbaldehyde (295.73 mg, 800.63  $\mu\text{mol}$ , 1 eq) in HOAC (1 mL) and MeOH (10 mL) was stirred at 20°C for 20min, then borane:2-methylpyridine (171.27 mg, 1.60 mmol, 2 eq) was added. Then the mixture was stirred at 30 °C for 16h under N<sub>2</sub>. TLC (Dichloromethane : Methanol=10:1,  $R_f$ =0.3) showed no start material and a new spot. The residue was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (0 to 25% Dichloromethane in Methanol) to give 5-[4-[[4-(2-chloroethyl)piperazin-1-yl]methyl]-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isindoline-1,3-dione (390 mg, 769.12  $\mu\text{mol}$ , 96.06% yield, 99% purity) as a yellow solid.

### **Step 3**

To a mixture of 1H-indazol-5-ol (10 g, 74.55 mmol, 1 eq) in DMF (100 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (36.44 g, 111.83 mmol, 1.5 eq) and 2-iodopropane (19.01 g, 111.83 mmol, 11.18 mL, 1.5 eq). The mixture was stirred at 20°C for 16 hours to give a brown mixture. LCMS showed the reaction was completed, and the desired MS value was in main peak. TLC (Petroleum ether: Ethyl acetate =2:1, UV =254 nm, Plate1) showed new spots. The mixture was filtered and the filter cake was washed with EtOAc (50 mL) and then 150 mL saturated NH<sub>4</sub>Cl (aq.) was added into the filtrate. The resulting mixture was extracted with EtOAc (50 mL \* 3), and the combined extracts were washed with saturated NH<sub>4</sub>Cl (50 mL \* 3), brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-20% (10 min) of Ethyl acetate in Petroleum ether, 20% (10 min) of Ethyl acetate in Petroleum ether) to give 5-isopropoxy-1H-indazole (7.6 g, 43.13 mmol, 57.85% yield) as a yellow solid.

### **Step 4**

To a mixture of 5-isopropoxy-1H-indazole (7.6 g, 43.13 mmol, 1 eq) in THF (100 mL) was added N-cyclohexyl-N-methyl-cyclohexanamine (25.27 g, 129.39 mmol, 27.44 mL, 3 eq) and SEM-Cl (14.38 g, 86.26 mmol, 15.27 mL, 2 eq) in one portion at 20°C. The mixture was stirred at 20°C for 2 hours to give orange suspension. TLC showed the reaction was completed. The residue was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (50 mL \*3). The combined organic phase was washed with brine (50 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 0-3% (20 min) of ethyl acetate in Petroleum ether, 3-10% (10 min) of ethyl acetate in Petroleum ether) to give 2-[(5-isopropoxyindazol-2-yl)methoxy]ethyl-trimethyl-silane (11.5 g, 36.77 mmol, 85.26% yield, 98% purity) as a yellow oil.

#### **Step 5**

To a mixture of 2-[(5-isopropoxyindazol-2-yl)methoxy]ethyl-trimethyl-silane (11 g, 35.89 mmol, 1 eq) in THF (60 mL) was dropwise added n-BuLi (2.5 M, 15.79 mL, 1.1 eq) at -70°C under N<sub>2</sub>. The mixture was then stirred at -20°C for 5 minutes, and a solution of ZnCl<sub>2</sub> (2 M, 26.92 mL, 1.5 eq) was dropwise added at -70°C. The mixture was stirred for 10 min at -40°C. A mixture of 4,6-dichloropyrimidine (5.35 g, 35.89 mmol, 1 eq) and Pd(PPh<sub>3</sub>)<sub>4</sub> (2.07 g, 1.79 mmol, 0.05 eq) in THF (10 mL) was stirred at 20°C for 30 minutes and was added to that solution. The cold bath was removed, and the mixture was stirred at 20°C for 10 h to give yellow solution. TLC (Petroleum ether: Ethyl acetate= 3:1, R<sub>f</sub>= 0.83) and LCMS showed the reaction was completed. The residue was poured into water (60 mL). The aqueous phase was extracted with ethyl acetate (60 mL \* 3). The combined organic phase was washed with brine (20 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 0-5% (30 minutes) of Ethyl acetate in Petroleum ether, 5% (60 min) of Ethyl acetate in Petroleum ether) to give 2-[[3-(6-chloropyrimidin-4-yl)-5-isopropoxy-indazol-2-yl]methoxy]ethyl-trimethyl-silane (8.5 g, 20.29 mmol, 56.52% yield) as a yellow oil

#### **Step 6**

To a mixture of 2-[[3-(6-chloropyrimidin-4-yl)-5-isopropoxy-indazol-2-yl]methoxy]ethyl-trimethyl-silane (2 g, 4.77 mmol, 1 eq), tert-butyl piperazine-1-carboxylate (1.07 g, 5.73 mmol, 1.2 eq) in DMSO (10 mL) was added Et<sub>3</sub>N (1.45 g, 14.32 mmol, 1.99 mL, 3 eq) in one portion

and then was stirred at 100°C for 1 h. TLC showed the starting material was consumed completely. The mixture was cooled to 20°C, the residue was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL \* 3). The combined organic phase was washed with brine (10 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give tert-butyl 4-[6-[5-isopropoxy-2-(2-trimethylsilylethoxymethyl)indazol-3-yl]pyrimidin-4-yl]piperazine-1-carboxylate (2.4 g, 4.01 mmol, 83.98% yield, 95% purity) as a yellow oil.

### **Step 7**

To a mixture of tert-butyl 4-[6-[5-isopropoxy-2-(2-trimethylsilylethoxymethyl)indazol-3-yl]pyrimidin-4-yl]piperazine-1-carboxylate (2.4 g, 4.22 mmol, 1 eq) in MeOH (10 mL) was added HCl(g)/dioxane (4 M, 5.27 mL, 5 eq) in one portion at 20°C. The mixture was stirred at 65°C for 0.5 h to give yellow mixture. TLC (EtOAc, R<sub>f</sub>= 0.07) showed the reaction was completed. The mixture was cooled to 20°C. The residue was poured into NaHCO<sub>3</sub> (20 mL) to adjust pH=7-8. The aqueous phase was extracted with ethyl acetate (20 mL \*3). The combined organic phase was washed with brine (20 mL \*2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, 0-25% of MeOH in DCM) to give 5-isopropoxy-3-(6-piperazin-1-ylpyrimidin-4-yl)-1H-indazole (1.6 g, crude) as a yellow gum.

### **Step 8**

To a solution of 5-isopropoxy-3-(6-piperazin-1-ylpyrimidin-4-yl)-1H-indazole (100 mg, 295.50 umol, 1 eq) and 5-[4-[[4-(2-chloroethyl)piperazin-1-yl]methyl]-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (100 mg, 199.20 umol, 6.74e-1 eq) and DIEA (190.95 mg, 1.48 mmol, 257.35 uL, 5 eq) and KI (245.27 mg, 1.48 mmol, 5 eq) in MeCN (10 mL). Then the mixture was stirred at 100 °C for 16hr under N<sub>2</sub>. LCMS showed desired product. The residue was diluted with H<sub>2</sub>O (20 mL) extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: 3\_Phenomenex Luna C18 75\*30mm\*3um;mobile phase: [water(0.225%FA)-ACN];B%: 0%-30%,35min) to afford 2-(2,6-dioxo-3-piperidyl)-5-[4-[[4-[2-[4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]piperazin-1-yl]ethyl]piperazin-1-yl]methyl]-1-

piperidyl]isoindoline-1,3-dione (27.6 mg, 34.21  $\mu$ mol, 11.58% yield, 99.66% purity) as a yellow solid.

## **[00251] Exemplary Synthesis of Exemplary Compound 40**

### **Step 1**

To a solution of tert-butyl 4-(2-bromoacetyl)piperidine-1-carboxylate (695.05 mg, 2.27 mmol, 1 eq) in MeCN (10 mL) was stirred at 20°C for 20min. Then the mixture was added benzyl piperazine-1-carboxylate (500 mg, 2.27 mmol, 438.60  $\mu$ L, 1 eq) and stirred at 20 °C for 16hr under N<sub>2</sub>. TLC (Dichloromethane: Methanol=10:1, R<sub>f</sub>=0.6) showed no start material and a new spot. The residue was diluted with H<sub>2</sub>O (30 mL) extracted with ethyl acetate (50 mL  $\times$  3). The combined organic layers were washed with brine (45 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (0 to 10% Dichloromethane in Methanol) to give benzyl 4-[2-(1-tert-butoxycarbonyl-4-piperidyl)-2-oxo-ethyl]piperazine-1-carboxylate (950 mg, 1.58 mmol, 69.51% yield, 74% purity) as a yellow gum.

### **Step 2**

To a solution of benzyl 4-[2-(1-tert-butoxycarbonyl-4-piperidyl)-2-oxo-ethyl]piperazine-1-carboxylate (920 mg, 2.06 mmol, 1 eq) in DCM (30 mL) was stirred at 0°C for 20min. Then the mixture was added DAST (11.65 g, 72.27 mmol, 9.55 mL, 35 eq) and stirred at 20 °C for 2hr under N<sub>2</sub>. TLC (Dichloromethane: Methanol=10:1, R<sub>f</sub>=0.5) showed no start material and a new spot. The reaction was cooled to 0 °C and quenched with aqueous NaHCO<sub>3</sub> (90mL) extracted with ethyl acetate (50 mL  $\times$  2). The combined organic layers were washed with brine (45 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (0 to 10% Dichloromethane in Methanol) to give benzyl 4-[2-(1-tert-butoxycarbonyl-4-piperidyl)-2,2-difluoro-ethyl]piperazine-1-carboxylate (330 mg, 515.24  $\mu$ mol, 24.95% yield, 73% purity) as a yellow gum.

### **Step 3**

To a solution of benzyl 4-[2-(1-tert-butoxycarbonyl-4-piperidyl)-2,2-difluoro-ethyl]piperazine-1-carboxylate (100 mg, 213.88  $\mu$ mol, 1 eq) in DCM (2 mL) was added TFA (2.31 g, 20.26 mmol, 1.5 mL, 94.72 eq) and stirred at 20 °C for 1hr. TLC (Dichloromethane: Methanol=10:1,



R<sub>f</sub>=0.01) showed no start material and a new spot. The residue was concentrated under reduced pressure to give benzyl 4-[2,2-difluoro-2-(4-piperidyl)ethyl]piperazine-1-carboxylate (78 mg, crude) as a yellow gum.

#### **Step 4**

To a solution of benzyl 4-[2,2-difluoro-2-(4-piperidyl)ethyl]piperazine-1-carboxylate (78 mg, 212.28  $\mu$ mol, 1 eq) and 1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperidine-4-carbaldehyde (78.41 mg, 212.28  $\mu$ mol, 1 eq) in HOAC (1 mL) and MeOH (10 mL) was stirred at 20°C for 20min, then was added borane;2-methylpyridine (45.41 mg, 424.57  $\mu$ mol, 2 eq). Then the mixture was stirred at 25 °C for 16h under N<sub>2</sub>. TLC (Dichloromethane: Methanol=10:1, R<sub>f</sub>=0.5) showed no start material and a new spot. The residue was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (0 to 10% Dichloromethane in Methanol) to give benzyl 4-[2-[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]-2,2-difluoro-ethyl]piperazine-1-carboxylate (150 mg, 167.52  $\mu$ mol, 78.91% yield, 80.5% purity) as a yellow solid.

#### **Step 5**

To a solution of benzyl 4-[2-[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]-2,2-difluoro-ethyl]piperazine-1-carboxylate (150 mg, 208.10  $\mu$ mol, 1 eq) was added TFA (3.08 g, 27.01 mmol, 2 mL, 129.81 eq) stirred at 70 °C for 4hr. TLC(Dichloromethane : Methanol=10:1, R<sub>f</sub>=0.01) showed no start material and a new spot. The residue was concentrated under reduced pressure to give 5-[4-[[4-(1,1-difluoro-2-piperazin-1-yl)-ethyl]-1-piperidyl]methyl]-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (140 mg, crude, TFA) as a yellow gum.

#### **Step 6**

To a solution of 5-[4-[[4-(1,1-difluoro-2-piperazin-1-yl)-ethyl]-1-piperidyl]methyl]-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (140 mg, 199.80  $\mu$ mol, 1 eq, TFA) and 3-(6-chloropyrimidin-4-yl)-5-isopropoxy-1H-indazole (57.69 mg, 199.80  $\mu$ mol, 1 eq) in DMSO (5 mL) and added DIEA (258.22 mg, 2.00 mmol, 348.01  $\mu$ L, 10 eq). Then the mixture was stirred at 80°C for 16hr under N<sub>2</sub>. LCMS showed desired product. The residue was diluted with H<sub>2</sub>O (20 mL) extracted with ethyl acetate (20 mL  $\times$  3). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column:

3\_Phenomenex Luna C18 75\*30mm\*3um;mobile phase: [water(0.225%FA)-ACN]; B%: 10%-40%, 35 min) to afford 5-[4-[[4-[1,1-difluoro-2-[4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]piperazin-1-yl]ethyl]-1-piperidyl]methyl]-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (33.7 mg, 39.95 umol, 20.00% yield, 99.46% purity) as a yellow solid.

## [00252] Exemplary Synthesis of Exemplary Compound 41

### Step 1

To a mixture of 1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperidine-4-carbaldehyde (200 mg, 541.46 umol, 1 eq) and 4-(2,2-dimethoxyethyl)piperidine (93.81 mg, 541.46 umol, 1 eq) in MeOH (10 mL) was added borane;2-methylpyridine (115.83 mg, 1.08 mmol, 2 eq) and CH<sub>3</sub>COOH (1 mL) in one portion at 20°C under N<sub>2</sub>. The mixture was stirred at 20°C for 2 hours to give yellow solution. LCMS showed there was desired MS. The residue was poured into saturated NaHCO<sub>3</sub> to adjusted the pH=7-8. The aqueous phase was extracted with ethyl acetate (10 mL \* 3). The combined organic phase was washed with brine (10 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (12 g, 0-100% (10 min) of Ethyl acetate in Petroleum ether,1-10% (5 min) of Methanol in Dichloromethane) to give 5-[4-[[4-(2,2-dimethoxyethyl)-1-piperidyl]methyl]-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (210 mg, 338.95 umol, 62.60% yield, 85% purity) as a yellow gum.

### Step 2

To a solution of 5-[4-[[4-(2,2-dimethoxyethyl)-1-piperidyl]methyl]-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (100 mg, 189.89 umol, 1 eq) in THF (5 mL) was added HCl (2 M, 10.22 mL, 107.60 eq) in one portion at 20°C under N<sub>2</sub>. Then the solution was heated to 70°C and stirred for 1 h to give yellow solution. TLC (DCM: MeOH= 10:1, R<sub>f</sub>= 0.06) showed the reaction was completed. The solution was cooled to 20°C. The solution was poured onto water (5 mL) and NaHCO<sub>3</sub> to adjusted the pH=7-8. The aqueous phase was extracted with ethyl acetate (10 mL \* 3). The combined organic phase was washed with brine (10 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum to give 2-[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]acetaldehyde (83 mg, 162.35 umol, 85.50% yield, 94% purity) as a yellow solid.

### Step 3

To a mixture of 2-[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-piperidyl]acetaldehyde (83 mg, 172.72  $\mu$ mol, 1 eq) and 5-isopropoxy-3-(6-piperazin-1-ylpyrimidin-4-yl)-1H-indazole (58.45 mg, 172.72  $\mu$ mol, 1 eq) in MeOH (10 mL) was added CH<sub>3</sub>COOH (10.37 mg, 172.72  $\mu$ mol, 9.88  $\mu$ L, 1 eq) and borane;2-methylpyridine (36.95 mg, 345.43  $\mu$ mol, 2 eq) in one portion at 20°C under N<sub>2</sub>. The mixture was stirred at 30°C for 16 h. LCMS showed there was desired MS. The residue was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL \* 3). The combined organic phase was washed with brine (10 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The crude product was purified by reversed-phase HPLC (Column: 3\_Phenomenex Luna C18 75\*30mm\*3 $\mu$ m; Condition: water(0.225%FA)-ACN; Begin B: 0; End B: 30; FlowRate: 25mL/min; Gradient Time: 35 min; 100%B Hold Time: 3 min) to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[[4-[2-[4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]piperazin-1-yl]ethyl]-1-piperidyl]methyl]-1-piperidyl]isoindoline-1,3-dione (25.5 mg, 30.77  $\mu$ mol, 17.82% yield, 96.9% purity) as a yellow gum.

#### [00253] Exemplary Synthesis of Exemplary Compound 42

##### Step 1

A solution of 2-[(3R)-1-tert-butoxycarbonylpyrrolidin-3-yl]acetic acid (500 mg, 2.18 mmol, 1 eq) in THF (10 mL) was cooled to -10°C. borane;tetrahydrofuran (1 M, 2.62 mL, 1.2 eq) was added slowly to the flask while maintaining the temperature lower than 0°C. The solution was warmed to 20°C and stirred for 1 h. TLC (PE: EtOAc=1:1) showed a new spot. The solution was cooled to 0°C, and a 15% sodium hydroxide solution (10 mL) was added drop-wise over a 5 minute period to control gas evolution. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with brine (30 mL), dried over sodium sulfate and concentrated under reduced pressure to afford tert-butyl (3R)-3-(2-hydroxyethyl)pyrrolidine-1-carboxylate (395 mg, 1.83 mmol, 84.13% yield) as a colorless oil.

##### Step 2

To a solution of tert-butyl (3R)-3-(2-hydroxyethyl)pyrrolidine-1-carboxylate (395 mg, 1.83 mmol, 1 eq) in DCM (5 mL) was added TosCl (699.58 mg, 3.67 mmol, 2 eq) and TEA (371.31 mg, 3.67 mmol, 510.75  $\mu$ L, 2 eq). After addition, the reaction solution was stirred at 20°C for 12h. TLC (PE: EtOAc=1:1) showed several new spots. The reaction was diluted with water (10

mL) and extracted with dichloromethane (3 x 10 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 30% ethyl acetate in petroleum ether) to afford tert-butyl (3R)-3-[2-(p-tolylsulfonyloxy)ethyl]pyrrolidine-1-carboxylate (600 mg, 1.58 mmol, 86.39% yield, 97.6% purity) as a light yellow oil.

### **Step 3**

To a solution of tert-butyl (3R)-3-[2-(p-tolylsulfonyloxy)ethyl]pyrrolidine-1-carboxylate (300 mg, 811.96  $\mu$ mol, 1 eq) and 5-isopropoxy-3-(6-piperazin-1-ylpyrimidin-4-yl)-1H-indazole (274.77 mg, 811.96  $\mu$ mol, 1 eq) in CH<sub>3</sub>CN (5 mL) was added KI (269.57 mg, 1.62 mmol, 2 eq) and DIEA (209.88 mg, 1.62 mmol, 282.86  $\mu$ L, 2 eq). After addition, the reaction mixture was stirred at 95°C for 4h. LCMS showed desired MS. After cooling, the reaction mixture was diluted with ethyl acetate (30 mL) and washed with water (20 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 10% methanol in dichloromethane) to afford tert-butyl (3S)-3-[2-[4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]piperazin-1-yl]ethyl]pyrrolidine-1-carboxylate (210 mg, 376.62  $\mu$ mol, 46.38% yield, 96.07% purity) as a yellow solid.

### **Step 4**

To a solution of tert-butyl (3S)-3-[2-[4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]piperazin-1-yl]ethyl]pyrrolidine-1-carboxylate (210 mg, 392.03  $\mu$ mol, 1 eq) in DCM (5 mL) was added TFA (1.54 g, 13.51 mmol, 1 mL, 34.45 eq). After addition, the reaction mixture was stirred at 20°C for 30 min. LCMS showed desired MS. The reaction was concentrated under reduced pressure. Then the resulting was diluted with dichloromethane (5 mL) and treated with DIEA (1.5 mL). The mixture was concentrated in vacuo to afford 5-isopropoxy-3-[6-[4-[2-[(3R)-pyrrolidin-3-yl]ethyl]piperazin-1-yl]pyrimidin-4-yl]-1H-indazole (170 mg, crude) as a yellow solid. The crude product was used for next step directly.

### **Step 5**

To a solution of 1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isindolin-5-yl]piperidine-4-carbaldehyde (74.63 mg, 202.04  $\mu$ mol, 1.1 eq) in MeOH (3 mL) and HOAc (0.3 mL) was added 5-isopropoxy-3-[6-[4-[2-[(3R)-pyrrolidin-3-yl]ethyl]piperazin-1-yl]pyrimidin-4-yl]-1H-indazole (80 mg, 183.67  $\mu$ mol, 1 eq) and borane;2-methylpyridine (39.29 mg, 367.34  $\mu$ mol, 2 eq). After addition, the reaction solution was stirred at 25°C for 12h. LCMS showed desired MS. The

reaction was diluted with water (5 mL) and extracted with dichloromethane (3 x 10 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by prep.HPLC (column: 3\_Phenomenex Luna C18 75\*30mm\*3um; mobile phase: [water(0.225%FA)-ACN]; B%: 0-30%; 35 min) to afford 2-(2,6-dioxo-3-piperidyl)-5-[4-[[[(3R)-3-[2-[4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]piperazin-1-yl]ethyl]pyrrolidin-1-yl]methyl]-1-piperidyl]isoindoline-1,3-dione (67.7 mg, 85.13 umol, 46.35% yield, 99.20% purity) as a yellow solid.

#### **[00254] Exemplary Synthesis of Exemplary Compound 43**

Compound 43 was prepared in a manner analogous to compound 42 starting with 2-[(3S)-1-tert-butoxycarbonylpyrrolidin-3-yl]acetic acid.

#### **[00255] Exemplary Synthesis of Exemplary Compound 44**

##### **Step 1**

A 3-neck round bottom flask was charged with anhydrous DMF (3 mL) and Zn (1.28 g, 19.51 mmol, 2.5 eq). The mixture was stirred at 20°C. While a mixture of 1,2-DIBROMOETHANE (293.25 mg, 1.56 mmol, 117.77 uL, 0.2 eq) and TMSCl (169.59 mg, 1.56 mmol, 198.12 uL, 0.2 eq) was added at a rate to maintain the temperature below 65°C over 30 min. The resulting slurry was aged for 15 min. A solution of tert-butyl 3-iodoazetidine-1-carboxylate (3 g, 10.60 mmol, 1.36 eq) in DMF (4 mL) was added dropwise over 10min at a rate to maintain the temperature below 65°C and the milky suspension was stirred for 30 min while slowly cooling to 20°C. Another round bottom flask was charged with Pd(dppf)Cl<sub>2</sub>.CH<sub>2</sub>Cl<sub>2</sub> (63.74 mg, 78.05 umol, 0.01 eq) CuI (44.59 mg, 234.15 umol, 0.03 eq) and 4-iodopyridine (1.6 g, 7.81 mmol, 1 eq) in DMF (4 mL) under N<sub>2</sub>. The resulting mixture was degassed with alternate vacuum/N<sub>2</sub> purges. The above prepared zinc iodide reagent of compound in DMF was added as a suspension. The mixture was degassed with vacuum/N<sub>2</sub> twice and then heated to 80°C for 2hr. TLC (Dichloromethane: Methanol=10:1, R<sub>f</sub>=0.5) showed the reaction a new spot. The reaction mixture was filtered and concentrated under reduced pressure. The crude product was poured into H<sub>2</sub>O (50 mL). The mixture was extracted with ethyl acetate (45 mL\*3). The organic phase was washed with brine (30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuum to give a residue. The residue was purified by silica gel column chromatography (0 to 10% Methanol in

Dichloromethane) to give tert-butyl 3-(4-pyridyl)azetidine-1-carboxylate (1.2 g, 4.97 mmol, 63.65% yield, 97% purity) as a yellow oil.

### **Step 2**

To a solution of tert-butyl 3-(4-pyridyl)azetidine-1-carboxylate (1.2 g, 5.12 mmol, 1 eq) in MeCN (10 mL) was added BnBr (892.80 mg, 5.22 mmol, 0.62 mL, 1.02 eq). The mixture was stirred at 80 °C for 1 hr to give yellow suspension. TLC (Dichloromethane: Methanol=10:1, R<sub>f</sub>=0.2) showed the reaction a new spot. The reaction mixture was concentrated in vacuum to give tert-butyl 3-(1-benzylpyridin-1-ium-4-yl)azetidine-1-carboxylate (1.6 g, crude) as a yellow gum.

### **Step 3**

To a solution of tert-butyl 3-(1-benzylpyridin-1-ium-4-yl)azetidine-1-carboxylate (1.6 g, 4.92 mmol, 1 eq) in EtOH (10 mL) was added NaBH<sub>4</sub> (558.03 mg, 14.75 mmol, 3 eq). The mixture was stirred at 0°C for 2h. LCMS showed the formation of the product. TLC (Dichloromethane: Methanol=10:1, R<sub>f</sub>=0.5) showed the reaction a new spot. The crude product was poured into H<sub>2</sub>O (50 mL). The mixture was extracted with ethyl acetate (45 mL\*3). The organic phase was washed with brine (30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuum to give a residue. The residue was purified by silica gel column chromatography (0 to 5% Methanol in Dichloromethane) to give tert-butyl 3-(1-benzyl-3,6-dihydro-2H-pyridin-4-yl)azetidine-1-carboxylate (1.2 g, 2.19 mmol, 44.59% yield, 60% purity) as a colorless gum.

### **Step 4**

To a solution of tert-butyl 3-(1-benzyl-3,6-dihydro-2H-pyridin-4-yl)azetidine-1-carboxylate (1.2 g, 3.65 mmol, 1 eq) in EtOH (15 mL) and EtOAc (15 mL) was added Pd/C (120 mg, 10% purity) and Pd(OH)<sub>2</sub> (120 mg, 85.45 umol, 10% purity, 2.34e-2 eq) under N<sub>2</sub>. The suspension was degassed under vacuum and purged with H<sub>2</sub> several times. The mixture was stirred under H<sub>2</sub> (50 psi) at 60°C for 18 hours. TLC (Dichloromethane: Methanol=10:1, R<sub>f</sub>=0.1) showed the reaction a new spot. The reaction mixture was filtered and concentrated under reduced pressure to afford tert-butyl 3-(4-piperidyl)azetidine-1-carboxylate (900 mg, crude) as a Light Yellow oil.

### **Step 5**

To a solution of tert-butyl 3-(4-piperidyl)azetidine-1-carboxylate (0.4 g, 1.66 mmol, 1 eq) and 2-(2,6-dioxo-3-piperidyl)-5-fluoro-isoindoline-1,3-dione (413.74 mg, 1.50 mmol, 0.9 eq) and DIEA (1.08 g, 8.32 mmol, 1.45 mL, 5 eq) in DMSO (20. mL). Then the mixture was stirred at

100 °C for 16hr under N<sub>2</sub>. TLC (Dichloromethane: Methanol=10:1, R<sub>f</sub>=0.6) showed no start material and a new spot. The residue was diluted with H<sub>2</sub>O (50 mL) extracted with ethyl acetate (70 mL × 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (0 to 10% Methanol in Dichloromethane) to give tert-butyl 3-[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]azetidine-1-carboxylate (800 mg, 1.47 mmol, 88.09% yield, 91% purity) as a yellow solid.

#### **Step 6**

To a solution of tert-butyl 3-[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]azetidine-1-carboxylate (800 mg, 1.61 mmol, 1 eq) in DCM (2 mL) and added TFA (3.08 g, 27.01 mmol, 2 mL, 16.77 eq). Then the mixture was stirred at 20 °C for 1hr under. The residue was concentrated under reduced pressure to give 5-[4-(azetidin-3-yl)-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (1.2 g, crude, 3TFA) as a yellow solid.

#### **Step 7**

To a solution of 5-[4-(azetidin-3-yl)-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (400 mg, 541.63 umol, 1 eq, 3TFA) and 2-chloroacetaldehyde (122.00 mg, 621.68 umol, 0.1 mL, 40% purity, 1.15 eq) in DCM (15 mL) and MeOH (15 mL) was added NaOAc (266.59 mg, 3.25 mmol, 6 eq) and HOAc (3.25 mg, 54.16 umol, 3.10 uL, 0.1 eq). The mixture was stirred at 25 °C for 20 min. Then the NaBH<sub>3</sub>CN (102.11 mg, 1.62 mmol, 3 eq) was added of the solution and was stirred at 25 °C for 2hr. TLC (Dichloromethane: Methanol=10:1, R<sub>f</sub>=0.4) showed no start material and a new spot. The reaction mixture was poured into H<sub>2</sub>O (20 mL). The mixture was extracted with ethyl acetate (30 mL\*3). The organic phase was washed with brine (20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuum to give a residue. The residue was purified by silica gel column chromatography (0-15% Methanol in Dichloromethane) to give 5-[4-[1-(2-chloroethyl)azetidin-3-yl]-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (248 mg, 502.55 umol, 92.78% yield, 93% purity) as a yellow solid.

#### **Step 8**

To a solution of 5-isopropoxy-3-(6-piperazin-1-ylpyrimidin-4-yl)-1H-indazole (79.64 mg, 235.33 umol, 0.9 eq) and 5-[4-[1-(2-chloroethyl)azetidin-3-yl]-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (120 mg, 261.47 umol, 1 eq) and DIEA (168.96 mg, 1.31 mmol,

227.71 uL, 5 eq) and KI (217.02 mg, 1.31 mmol, 5 eq) in MeCN (10 mL). Then the mixture was stirred at 100 °C for 16hr under N<sub>2</sub>. The residue was diluted with H<sub>2</sub>O (20 mL) extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: 3\_Phenomenex Luna C18 75\*30mm\*3um; mobile phase: [water (0.225%FA)-ACN]; B%: 0%-30%, 35 min) to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[1-[2-[4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]piperazin-1-yl]ethyl]azetidin-3-yl]-1-piperidyl]isoindoline-1,3-dione (13.3 mg, 17.43 umol, 6.67% yield, 99.73% purity) as a yellow solid.

## **[00256] Exemplary Synthesis of Exemplary Compound 45**

### **Step 1**

To a solution of tert-butyl 3-(p-tolylsulfonyloxymethyl)azetidine-1-carboxylate (359.10 mg, 1.05 mmol, 1.2 eq) and 2-(2,6-dioxo-3-piperidyl)-5-piperazin-1-yl-isoindoline-1,3-dione (400 mg, 876.48 umol, 1 eq, TFA) and DIEA (566.38 mg, 4.38 mmol, 763.32 uL, 5 eq) and KI (727.48 mg, 4.38 mmol, 5 eq) in MeCN (10 mL). Then the mixture was stirred at 100 °C for 16hr under N<sub>2</sub>. TLC (100% Ethyl acetate, R<sub>f</sub>=0.4) showed no start material and a new spot. The residue was diluted with H<sub>2</sub>O (20 mL) extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (100% Ethyl acetate, R<sub>f</sub>=0.4) to give tert-butyl 3-[[4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazin-1-yl]methyl]azetidine-1-carboxylate (88 mg, 158.26 umol, 18.06% yield, 92% purity) as a yellow solid.

### **Step 2**

To a solution of tert-butyl 3-[[4-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperazin-1-yl]methyl]azetidine-1-carboxylate (88 mg, 172.02 umol, 1 eq) in DCM (1 mL) in TFA (3.39 g, 29.71 mmol, 2.20 mL, 172.73 eq). Then the mixture was stirred at 20°C for 1hr under N<sub>2</sub>. TLC (Dichloromethane: Methanol=10:1, R<sub>f</sub>=0.01) showed no start material and a new spot. The residue was concentrated under reduced pressure to give 5-[4-(azetidin-3-ylmethyl)piperazin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (90 mg, crude, TFA) as a yellow gum.

### **Step 3**



To a solution of 5-isopropoxy-3-(6-piperazin-1-ylpyrimidin-4-yl)-1H-indazole (260 mg, 768.31 umol, 1 eq) and 2-chloroacetaldehyde (301.55 mg, 1.54 mmol, 247.17 uL, 40% purity, 2 eq) in DCM (15 mL) and MeOH (15 mL) was added NaOAc (315.14 mg, 3.84 mmol, 5 eq) and HOAc (4.61 mg, 76.83 umol, 4.39 uL, 0.1 eq) and the mixture was stirred at 25 °C for 20 min. Then the NaBH<sub>3</sub>CN (144.84 mg, 2.30 mmol, 3 eq) was added of the solution and was stirred at 25 °C for 2hr. TLC (Dichloromethane: Methanol= 10:1, R<sub>f</sub>=0.5) was showed the reaction completed. The reaction mixture was poured into H<sub>2</sub>O (20 mL). The mixture was extracted with ethyl acetate (30 mL\*3). The organic phase was washed with brine (20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuum to give a residue. The residue was purified by silica gel column chromatography (0-10% Methanol in Dichloromethane) to give 3-[6-[4-(2-chloroethyl)piperazin-1-yl]pyrimidin-4-yl]-5-isopropoxy-1H-indazole (176 mg, 403.89 umol, 52.57% yield, 92% purity) as a white solid.

#### **Step 4**

To a solution of 5-[4-(azetidin-3-ylmethyl)piperazin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (90 mg, 171.27 umol, 1 eq, TFA) and 3-[6-[4-(2-chloroethyl)piperazin-1-yl]pyrimidin-4-yl]-5-isopropoxy-1H-indazole (68.66 mg, 171.27 umol, 1 eq) and DIEA (110.68 mg, 856.37 umol, 149.16 uL, 5 eq) and KI (142.16 mg, 856.37 umol, 5 eq) in MeCN (10 mL). Then the mixture was stirred at 80 °C for 16hr under N<sub>2</sub>. LCMS showed desired product. The residue was diluted with H<sub>2</sub>O (20 mL) extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: 3\_Phenomenex Luna C18 75\*30mm\*3um;mobile phase: [water(0.225%FA)-ACN];B%: 0%-25%,35min) to afford 2-(2,6-dioxo-3-piperidyl)-5-[4-[[1-[2-[4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]piperazin-1-yl]ethyl]azetidin-3-yl]methyl]piperazin-1-yl]isoindoline-1,3-dione (34 mg, 41.98 umol, 24.51% yield, 95.8% purity) as a yellow solid.

#### **[00257] Exemplary Synthesis of Exemplary Compound 46**

Compound 46 was prepared in a manner analogous to compound 45 starting with tert-butyl 3-(2-hydroxyethyl)azetidine-1-carboxylate.

#### **[00258] Exemplary Synthesis of Exemplary Compound 47**

**Step 1**

To a solution of 1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperidine-4-carbaldehyde (1 g, 2.71 mmol, 1 eq) and tert-butyl piperazine-1-carboxylate (504.24 mg, 2.71 mmol, 1 eq) in MeOH (30 mL) and HOAc (3 mL) was added borane;2-methylpyridine (579.15 mg, 5.41 mmol, 2 eq). After addition, the reaction was stirred at 30°C for 16h. LCMS showed desired mass. The reaction mixture was diluted with water (50 mL) and the solid was collected by filtration to afford tert-butyl 4-[[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazine-1-carboxylate (1.14 g, 1.99 mmol, 73.34% yield, 93.99% purity) as a yellow solid.

**Step 2**

To a solution of tert-butyl 4-[[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazine-1-carboxylate (1.14 g, 2.11 mmol, 1 eq) in DCM (10 mL) was added TFA (7.70 g, 67.53 mmol, 5 mL, 31.97 eq). After addition, the reaction mixture was stirred at 20°C for 2h. LCMS showed desired mass. The reaction solution was concentrated under reduced pressure to afford 2-(2,6-dioxo-3-piperidyl)-5-[4-(piperazin-1-ylmethyl)-1-piperidyl]isoindoline-1,3-dione (2.5 g, crude, TFA) as a yellow gum.

**Step 3**

To a solution of 2-(2,6-dioxo-3-piperidyl)-5-[4-(piperazin-1-ylmethyl)-1-piperidyl]isoindoline-1,3-dione (800 mg, 646.38 umol, 1 eq, TFA) in CH<sub>3</sub>CN (10 mL) was added DIEA (835.40 mg, 6.46 mmol, 1.13 mL, 10 eq), KI (321.90 mg, 1.94 mmol, 3 eq) and tert-butyl (2R)-2-(p-tolylsulfonyloxymethyl)morpholine-4-carboxylate (480.19 mg, 1.29 mmol, 2 eq). After addition, the reaction mixture was stirred at 80°C for 12h. LCMS) showed desired MS. After cooling, the reaction was filtered and filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 10% methanol in chloromethane) to afford tert-butyl (2S)-2-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]morpholine-4-carboxylate (350 mg, 507.83 umol, 78.57% yield, 92.68% purity) as a yellow gum.

**Step 4**

To a solution of tert-butyl (2S)-2-[[4-[[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]methyl]piperazin-1-yl]methyl]morpholine-4-carboxylate (350.00 mg, 547.94 umol, 1 eq) in DCM (5 mL) was added TFA (1.54 g, 13.51 mmol, 1 mL, 24.65 eq). After addition, the

reaction was stirred at 20°C for 1h. LCMS showed desired MS. The reaction mixture was concentrated under reduced pressure to afford 2-(2,6-dioxo-3-piperidyl)-5-[4-[[4-[(2R)-morpholin-2-yl]methyl]piperazin-1-yl]methyl]-1-piperidyl]isoindoline-1,3-dione (600 mg, crude, TFA) as a yellow gum. The crude product was used for next step directly.

#### **Step 5**

To a solution of 3-(6-chloropyrimidin-4-yl)-5-isopropoxy-1H-indazole (80 mg, 277.07  $\mu$ mol, 1 eq) and 2-(2,6-dioxo-3-piperidyl)-5-[4-[[4-[(2R)-morpholin-2-yl]methyl]piperazin-1-yl]methyl]-1-piperidyl]isoindoline-1,3-dione (361.67 mg, 554.14  $\mu$ mol, 2 eq, TFA) in DMSO (2 mL) was added DIEA (179.05 mg, 1.39 mmol, 241.31  $\mu$ L, 5 eq). After addition, the reaction solution was stirred at 100°C for 16h. LCMS showed desired MS. After cooling, the reaction was diluted with water (10 mL) and extracted with dichloromethane (3 x 20 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by prep.HPLC (column: 3\_Phenomenex Luna C18 75\*30mm\*3 $\mu$ m; mobile phase: [water (0.225%FA)-ACN]; B%: 0-30%; 35 min) to afford 2-(2,6-dioxo-3-piperidyl)-5-[4-[[4-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]morpholin-2-yl]methyl]piperazin-1-yl]methyl]-1-piperidyl]isoindoline-1,3-dione (21.4 mg, 26.39  $\mu$ mol, 9.52% yield, 97.52% purity) as a yellow solid.

#### **[00259] Exemplary Synthesis of Exemplary Compound 48**

Compound 48 was prepared in a manner analogous to compound 47 starting with tert-butyl (2S)-2-(p-tolylsulfonyloxymethyl)morpholine-4-carboxylate

#### **[00260] Exemplary Synthesis of Exemplary Compound 49**

##### **Step 1**

To a solution of 2-(4-benzylmorpholin-2-yl)ethanol (1 g, 4.52 mmol, 1 eq) in EtOH (10 mL) was added Pd/C (100 mg, 4.52 mmol, 10% purity, 1 eq) under N<sub>2</sub>. The suspension was degassed under vacuum and purged with H<sub>2</sub> several times. The mixture was stirred under H<sub>2</sub> (45 psi) at 50°C for 4 hours. TLC showed the reaction was completed. The suspension was filtered through a pad of Celite or silica gel and the pad or filter cake was washed with EtOAc (50 mL \* 3), the solution was concentrated in vacuum to give 2-morpholin-2-ylethanol (800 mg, crude) as a yellow oil.

**Step 2**

To a mixture of 2-[[3-(6-chloropyrimidin-4-yl)-5-isopropoxy-indazol-2-yl]methoxy]ethyl-trimethyl-silane (500 mg, 1.19 mmol, 1 eq), 2-morpholin-2-ylethanol (156.53 mg, 1.19 mmol, 1 eq) in DMSO (10 mL) was added Et<sub>3</sub>N (362.26 mg, 3.58 mmol, 498.30  $\mu$ L, 3 eq) in one portion and then was stirred at 100°C for 1 h. TLC showed the starting material was consumed completely. The mixture was cooled to 20°C. Then the residue was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL \* 3). The combined organic phase was washed with brine (10 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (0-10% (10 min) of MeOH in DCM, 10% (5 min) of MeOH in DCM) to give 2-[4-[6-[5-isopropoxy-2-(2-trimethylsilylethoxymethyl)indazol-3-yl]pyrimidin-4-yl]morpholin-2-yl]ethanol (600 mg, 957.75  $\mu$ mol, 80.26% yield, 82% purity) as a yellow oil.

**Step 3**

To a mixture of 2-[4-[6-[5-isopropoxy-2-(2-trimethylsilylethoxymethyl)indazol-3-yl]pyrimidin-4-yl]morpholin-2-yl]ethanol (600 mg, 1.17 mmol, 1 eq) and TsCl (402.26 mg, 2.34 mmol, 2 eq) in DCM (5 mL) was added TEA (118.19 mg, 1.17 mmol, 162.57  $\mu$ L, 1 eq) in one portion at 20°C under N<sub>2</sub>. The mixture was stirred at 20°C for 16 hours. LCMS showed there was desired MS. The residue was poured into water (5 mL). The aqueous phase was extracted with DCM (5 mL \* 3). The combined organic phase was washed with brine (5 mL \* 3), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (0-100% (30 min) of Ethyl acetate in Petroleum ether) to give 2-[4-[6-[5-isopropoxy-2-(2-trimethylsilylethoxymethyl)indazol-3-yl]pyrimidin-4-yl]morpholin-2-yl]ethyl 4-methylbenzenesulfonate (880 mg, crude) as a yellow solid.

**Step 4**

To a mixture of 2-[4-[6-[5-isopropoxy-2-(2-trimethylsilylethoxymethyl)indazol-3-yl]pyrimidin-4-yl]morpholin-2-yl]ethyl 4-methylbenzenesulfonate (880.00 mg, 1.32 mmol, 1 eq) and tert-butyl piperazine-1-carboxylate (490.80 mg, 2.64 mmol, 2 eq) in MeCN (10 mL) was added KI (437.44 mg, 2.64 mmol, 2 eq) and DIPEA (340.57 mg, 2.64 mmol, 458.99  $\mu$ L, 2 eq) in one portion at 20°C under N<sub>2</sub>. The mixture was stirred at 80°C for 2 hours. LCMS showed there was desired MS. The mixture was cooled to 20°C and concentrated in reduced pressure at 20°C. The residue was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (10

mL \* 3). The combined organic phase was washed with brine (10 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (0-40% (15 min) of Ethyl acetate in Petroleum ether, 40% (5 min) of Ethyl acetate in Petroleum ether) to give tert-butyl 4-[2-[4-[6-[5-isopropoxy-1-(2-trimethylsilylethoxymethyl)indazol-3-yl]pyrimidin-4-yl]morpholin-2-yl]ethyl]piperazine-1-carboxylate (550 mg, 709.74 umol, 53.87% yield, 88% purity) as a yellow gum.

### **Step 5**

To a mixture of tert-butyl 4-(2-(4-(6-(5-isopropoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-3-yl)pyrimidin-4-yl)morpholin-2-yl)ethyl)piperazine-1-carboxylate (550 mg, 806.52 umol, 1 eq) in MeOH (5 mL) was added HCl/dioxane (4 M, 4 mL, 19.84 eq) in one portion at 20°C. The mixture was stirred at 65°C for 1 h. LCMS showed the reaction was completed. The residue was adjusted the pH=9-10, the aqueous phase was extracted with DCM (10 mL \* 3). The combined organic phase was washed with brine (10 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (4 g, 0-10% (5 min) of MeOH in DCM, 10% (5 min) of MeOH in DCM) to give 4-(6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl)-2-(2-(piperazin-1-yl)ethyl)morpholine (211 mg, 401.85 umol, 49.82% yield, 86% purity) as a yellow gum.

### **Step 6**

The 4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-(2-piperazin-1-ylethyl)morpholine (211 mg, 467.27 umol, 1 eq) was separated by SFC (Column: DAICEL CHIRALPAK IC(250mm\*30mm,10um); Condition: 0.1%NH<sub>3</sub>H<sub>2</sub>O ETOH; Begin B: 60; End B: 60; FlowRate: 70 mL/min) to give (2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-(2-piperazin-1-ylethyl)morpholine (113 mg, 207.70 umol, 44.45% yield, 83% purity) as a yellow oil. (Rt= 1.770 min, 113 mg) and (2R)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-(2-piperazin-1-ylethyl)morpholine (82 mg, 148.90 umol, 31.87% yield, 82% purity) as a yellow solid. (Rt= 2.224 min, 82 mg).

### **Step 7**

To a mixture of (2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-(2-piperazin-1-ylethyl)morpholine (113 mg, 250.24 umol, 1 eq) and 1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxoisoindolin-5-yl]piperidine-4-carbaldehyde (92.43 mg, 250.24 umol, 1 eq) in MeOH (5 mL) and HOAc (0.5 mL) was added borane;2-methylpyridine (53.53 mg, 500.48 umol, 2 eq) in one

portion at 20°C under N<sub>2</sub>. The mixture was stirred at 30°C for 16 h. LCMS showed there was a desired MS. The residue was poured into water (2 mL). The aqueous phase was extracted with ethyl acetate (2 mL \* 3). The combined organic phase was washed with brine (2 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The crude product was purified by reversed-phase HPLC (Column: 3\_Phenomenex Luna C18 75\*30mm\*3um; Condition: water (0.225%FA)-ACN; Begin B: 0; End B: 35; FlowRate: 25 mL/min; Gradient Time: 35 min; 100%B Hold Time: 3 min) to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[[4-[2-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]morpholin-2-yl]ethyl]piperazin-1-yl]methyl]-1-piperidyl]isoindoline-1,3-dione (64.2 mg, 79.76 umol, 31.87% yield, 100% purity) as a yellow solid.

#### [00261] Exemplary Synthesis of Exemplary Compound 50

Compound 50 was prepared in a manner analogous to compound 49 starting with (2R)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-(2-piperazin-1-ylethyl)morpholine

#### [00262] Exemplary Synthesis of Exemplary Compound 51

##### Step 1

To a solution of tert-butyl 4-methylenepiperidine-1-carboxylate (6.24 g, 31.65 mmol, 1 eq) was added 9-BBN (0.5 M, 63.29 mL, 1 eq) at 25°C. The reaction mixture was stirred at 80°C for 1h under N<sub>2</sub>. After cooling, 4-bromopyridine (5 g, 31.65 mmol, 1 eq), Pd(dppf)Cl<sub>2</sub> (1.39 g, 1.90 mmol, 0.06 eq), K<sub>2</sub>CO<sub>3</sub> (6.56 g, 47.47 mmol, 1.5 eq), DMF (50 mL) and H<sub>2</sub>O (5 mL) were added to the reaction. The resultant mixture was heated to 60°C for 12h. LCMS showed desired MS. After cooling, the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The organic layer was washed with brine (2 x 100 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 40% ethyl acetate in petroleum ether) to afford tert-butyl 4-(4-pyridylmethyl)piperidine-1-carboxylate (3.49 g, 11.66 mmol, 36.83% yield, 92.3% purity) as a pale yellow oil.

##### Step 2

To a solution of tert-butyl 4-(4-pyridylmethyl)piperidine-1-carboxylate (3.49 g, 12.63 mmol, 1 eq) in EtOH (50 mL) and HOAc (758.33 mg, 12.63 mmol, 722.21 uL, 1 eq) was added PtO<sub>2</sub>

(430.12 mg, 1.89 mmol, 0.15 eq) at 25°C. Then the mixture was stirred at 70°C for 24h under H<sub>2</sub> (50 psi). TLC (PE: EA=1:1) showed starting material consumed and a new spot formed. After cooling, the reaction was filtered and filtrate was concentrated under reduced pressure to afford tert-butyl 4-(4-piperidylmethyl)piperidine-1-carboxylate (3.9 g, crude) as a brown oil.

### **Step 3**

To a solution of tert-butyl 4-(4-piperidylmethyl)piperidine-1-carboxylate (3.7 g, 13.10 mmol, 1.21 eq) and 2-(2,6-dioxo-3-piperidyl)-5-fluoro-isoindoline-1,3-dione (3 g, 10.86 mmol, 1 eq) in DMSO (40 mL) was added DIEA (5.61 g, 43.44 mmol, 7.57 mL, 4 eq). After addition, the reaction mixture was stirred at 100°C for 2h. TLC (petroleum ether: ethyl acetate=1:1) showed a new spot. After cooling, the reaction was diluted with ethyl acetate (200 mL) and washed with brine (3 x 100 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 50% ethyl acetate in petroleum ether) to afford tert-butyl 4-[[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]methyl]piperidine-1-carboxylate (2.86 g, 4.41 mmol, 40.58% yield, 83% purity) as a yellow solid.

### **Step 4**

To a solution of tert-butyl 4-[[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]methyl]piperidine-1-carboxylate (2.86 g, 5.31 mmol, 1 eq) in DCM (20 mL) was added TFA (9.24 g, 81.04 mmol, 6 mL, 15.26 eq). After addition, the reaction solution was stirred at 20°C for 3h. LCMS showed desired MS. The reaction was concentrated under reduced pressure to afford 2-(2,6-dioxo-3-piperidyl)-5-[4-(4-piperidylmethyl)-1-piperidyl]isoindoline-1,3-dione (4 g, crude, TFA) as a yellow gum.

### **Step 5**

To a solution of 2-(2,6-dioxo-3-piperidyl)-5-[4-(4-piperidylmethyl)-1-piperidyl]isoindoline-1,3-dione (2 g, 3.62 mmol, 1 eq, TFA) in DCM (10 mL) and MeOH (10 mL) was added NaOAc (2.08 g, 25.34 mmol, 7 eq) and HOAc (217.37 mg, 3.62 mmol, 207.02 uL, 1 eq). Then 2-chloroacetaldehyde (1.67 g, 8.51 mmol, 1.37 mL, 40% purity, 2.35 eq) was added. The mixture was stirred at 20°C for 10 min. Then NaBH<sub>3</sub>CN (454.93 mg, 7.24 mmol, 2 eq) was added. After addition, the reaction was stirred at 20°C for 1.5h. LCMS showed reactant 1 remained and desired MS detected. TLC (dichloromethane: methanol=10:1) showed major two new spots. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 x 40 mL).

The organic layer dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 10% methanol in dichloromethane) to afford 5-[4-[[1-(2-chloroethyl)-4-piperidyl]methyl]-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (1.6 g, 3.11 mmol, 85.99% yield, 97.46% purity) as a yellow gum.

#### **Step 6**

To a solution of 5-isopropoxy-3-(6-piperazin-1-yl)pyrimidin-4-yl)-1H-indazole (88 mg, 260.04  $\mu$ mol, 1 eq) and 5-[4-[[1-(2-chloroethyl)-4-piperidyl]methyl]-1-piperidyl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (250 mg, 498.99  $\mu$ mol, 1.92 eq) in CH<sub>3</sub>CN (3 mL) was added KI (86.34 mg, 520.09  $\mu$ mol, 2 eq) and DIEA (168.04 mg, 1.30 mmol, 226.47  $\mu$ L, 5 eq). After addition, the reaction mixture was stirred at 80°C for 12h. LCMS showed desired MS. After cooling, the reaction mixture was filtered and filtrate was concentrated under reduced pressure. The residue was purified by prep.HPLC (column: 3\_Phenomenex Luna C18 75\*30mm\*3 $\mu$ m; mobile phase: [water (0.225%FA)-ACN]; B%: 0-40%; 35 min) to afford 2-(2,6-dioxo-3-piperidyl)-5-[4-[[1-[2-[4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]piperazin-1-yl]ethyl]-4-piperidyl]methyl]-1-piperidyl]isoindoline-1,3-dione (39.5 mg, 49.06  $\mu$ mol, 18.87% yield, 99.74% purity) as a yellow solid.

#### **Step 7**

To a mixture of benzyl (3S)-4-[2-(4-fluoro-4-piperidyl)ethyl]-3-methyl-piperazine-1-carboxylate (150 mg, 229.32  $\mu$ mol, 73% purity, 1 eq, TFA) and 1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]piperidine-4-carbaldehyde (84.71 mg, 229.32  $\mu$ mol, 1 eq) in MeOH (10 mL) was added borane;2-methylpyridine (49.06 mg, 458.65  $\mu$ mol, 2 eq) and HOAc (1 mL) in one portion at 25°C under N<sub>2</sub>. The mixture was stirred at 25°C for 1 h. TLC (Dichloromethane: Methanol=10:1, R<sub>f</sub>= 0.43) showed the reaction was completed, LCMS showed there was desired MS. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (5 mL \* 3). The combined organic phase was washed with brine (5 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Dichloromethane: Methanol=10:1, R<sub>f</sub>= 0.43, 0-100% (20 min) of Ethyl acetate in Petroleum ether, 100% (10 min) of Ethyl acetate in Petroleum ether) to give benzyl (3S)-4-[2-[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-fluoro-4-piperidyl]ethyl]-3-methyl-piperazine-1-carboxylate (193 mg, crude) as a yellow oil.



**Step 8**

To a mixture of benzyl (3S)-4-[2-[1-[[1-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]-4-piperidyl]methyl]-4-fluoro-4-piperidyl]ethyl]-3-methyl-piperazine-1-carboxylate (193 mg, 269.24  $\mu\text{mol}$ , 1 *eq*) in TFA (2.78 g, 24.39 mmol, 1.81 mL, 90.60 *eq*) in one portion at 20°C under N<sub>2</sub>. The mixture was stirred at 70°C for 1 h to give yellow solution. TLC showed the reaction was completed. The residue was concentrated in vacuum to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[[4-fluoro-4-[2-[(2S)-2-methylpiperazin-1-yl]ethyl]-1-piperidyl]methyl]-1-piperidyl]isoindoline-1,3-dione (150 mg, 131.36  $\mu\text{mol}$ , 48.79% yield, 71% purity, 2TFA) as a yellow gum.

**Step 9**

To a mixture of 2-(2,6-dioxo-3-piperidyl)-5-[4-[[4-fluoro-4-[2-[(2S)-2-methylpiperazin-1-yl]ethyl]-1-piperidyl]methyl]-1-piperidyl]isoindoline-1,3-dione (150 mg, 185.01  $\mu\text{mol}$ , 1.11 *eq*, 2TFA) and 3-(6-chloropyrimidin-4-yl)-5-(1-methylcyclopropoxy)-1H-indazole (50 mg, 166.26  $\mu\text{mol}$ , 1 *eq*) in DMSO (5 mL) was added DIEA (171.89 mg, 1.33 mmol, 231.66  $\mu\text{L}$ , 8 *eq*) in one portion at 20°C under N<sub>2</sub>. The mixture was stirred at 80°C for 16 h. LCMS showed there was desired MS. The mixture was cooled to 20°C and concentrated in reduced pressure at 20°C. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (5 mL \* 3). The combined organic phase was washed with brine (5 mL \* 2), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The crude product was purified by reversed-phase HPLC (Column: 3\_Phenomenex Luna C18 75\*30mm\*3 $\mu\text{m}$ ; Condition: water (0.225%FA)-ACN; Begin B: 0 End B: 40; FlowRate: 25 mL/min; Gradient Time: 40 min; 100%B Hold Time: 3 min) to give 2-(2,6-dioxo-3-piperidyl)-5-[4-[[4-fluoro-4-[2-[(2S)-2-methyl-4-[6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl]piperazin-1-yl]ethyl]-1-piperidyl]methyl]-1-piperidyl]isoindoline-1,3-dione (16.9 mg, 19.45  $\mu\text{mol}$ , 11.70% yield, 97.5% purity) as a yellow solid.

**[00263] Protein Level Control**

**[00264]** This description also provides methods for the control of protein levels within a cell. The method is based on the use of compounds as described herein such that degradation of the

target protein LRRK2 *in vivo* will result in the reducing the amount of the target protein in a biological system, preferably to provide a particular therapeutic benefit.

[00265] The following examples are used to assist in describing the present disclosure, but should not be seen as limiting the present disclosure in any way.

[00266] In certain embodiments, the description provides the following exemplary LRRK2-degrading bifunctional molecules (compounds of Table 1 or exemplary compounds 1-51), including salts, polymorphs, analogs, derivatives, and deuterated forms thereof.

[00267] **Exemplary assay for testing LRRK2 degradation driven by exemplary hetero-bifunctional compounds designed to target LRRK2**

[00268] The assay measures the degradation of wildtype and G2019S LRRK2 tagged with a HiBit tag on the C-terminus of the protein that was expressed from a mammalian expression vector, driven by the ubiquitin promoter in HEK293 cells. Each compound dose-response was repeated on two separate days, on three separate plates each day.

[00269] **Plasmid Preparation.** Transfection mixes were assembled as follows and incubated for 30 minutes at room temperature. In a 15mL tube, 5.25mL Opti-MEM (no additions) was mixed with 17μL Firefly Luciferase plasmid at 1μg/μL and 158μL WT plasmid DNA at 1μg/μL (175μg total DNA) were mixed by flicking. In a new 15mL tube, 5.25mL OptiMEM was mixed with 17μL Firefly Luciferase plasmid at 1μg/μL and 158μL G2019S plasmid DNA at 1μg/μL (175μg total DNA) were mixed by flicking. X-tremeGene HP was mixed thoroughly using a vortex. Next, 175μL was added to each tube and flicked to mix. Both tubes were left to incubate for 30 minutes at room temperature.

[00270] While the transfection mixes were incubating, HEK293 cells (acquired from ATCC ;ATCC CRL-1573) were harvested with trypsin. Once cells are detached, the cells were resuspended in 12mL OptiMEM + 5% FBS and transferred to a 50mL tube. The cells were mixed well and counted. Using OptiMEM + 5% FBS, the cells were diluted in two 250 mL conical tubes at  $0.71 \times 10^6$  cells/mL in 70mL. One tube was labeled “WT” and the other “G2019S”. The WT and G2019S transfection mixes were added dropwise to the corresponding 250mL tubes. The tubes were mixed first by pipetting then by swirling. The tubes were incubated at room temperature for at least 5 minutes.

[00271] Each tube was swirled before dispensing and after every three plates. Seventy microliters of cells were dispensed with WT or G2019S DNA to seven plates each. Three plates

of each were tested with compound plate one (preparation described below) and three plates of each were tested with compound plate two (preparation described below). The first plate from each set served as a “prime” plate and was not used to test compounds. Each plate was incubated in the hood for 10 minutes before placing in the 37°C incubator for 24 hours.

**[00272] Preparation of Compound and Assay Plates.** Two compound plates were made using 96 well polypropylene plates. Compounds were made up at 10mM and were diluted to 1mM in 30µL. Each dose response curve included a well of DMSO, as a negative control and for normalization, and a well of 0.5µM of Exemplary Compound 4 as a positive control. In addition to seven test compounds, each plate also included a dose response of Exemplary Compound 4. The compound plates were spun down along at 1200 rpm for 2 minutes.

**[00273]** The two compound plates were then mixed and 2µL was diluted in intermediate plates having 248µL of Opti-Mem in each well. Next, 10µL diluted compounds from the intermediate plates were added to each test plate (three WT and three G2019S plates per compound plate for a total of 12 assay plates). The plates were incubated for 24 hours at 37°C.

**[00274]** All assay plates and all Nano-Glo Dual-Luciferase Reporter Assay System components (except for the DLR substrate) were equilibrated to room temperature. Next, the luciferase buffer was mixed with the lyophilized amber bottle until fully dissolved, and 75µL of the luciferase mixture was added to each well of each assay plate. The assay plates were incubated for 10 minutes at room temperature with shaking for at least 5 minutes, and then read on a plate reader.

**[00275] Developing Plates and Analyzing Data.** One milliliter of DLR substrate and 1mL LgBiT Protein were added to the Stop and Glo buffer, and 75 µL of the mixture was added to each well of each plate. Optically clear seals were added to each plate and each plate was incubated for 20 minutes with shaking for at least 10 minutes, and then read on a plate reader.

**[00276]** As mentioned above, plates were run in triplicate and assay repeated twice (total of 6 replicates per exemplary compound. Each cell was examined for firefly luciferase for cell number and viability and Nanoluc for the LRRK2-HiBit quantification.

**[00277]** Ratio of (HiBit/luciferase)\*1000 was determined and the data was normalized to % of DMSO median value. Curve fitting was performed on each individual plate. The data for exemplary compounds of Table 1 below is shown below in Table 2 in the \*G2019S DC50 (nM), \*\*G2019S Dmax (%), \*WT DC50 (nM) and \*\*WT Dmax (%) columns.

**[00278] Exemplary assay for testing LRRK2 degradation driven by exemplary hetero-bifunctional compounds designed to target LRRK2**

**[00279]** The assay measures the degradation of LRRK2 in cells where the C-terminus (3') of the endogenous gene has been tagged with a HiBit sequence in HEK293 cells. The cells also express firefly luciferase, expressed from a Cytomegalovirus promoter and introduced into the HiBit tagged cells and stably expressed. The Nano-Glo® Dual Luciferase Reporter Assay System (Promega™, Madison, WI) was utilized.

**[00280] Day 1 - Preparation of Compound and Assay Plates.** Two sets of plates were prepared: a triplicate set for the HiBit assay in white 384-well plates and a triplicate set of plate in black 384-well plates for the Alamar Blue cell viability assay. Briefly, the growth media (DMEM+Glutamax-10% fetal bovine serum-1% Penicillin-Streptomycin) from two T128 flasks was aspirated from the flasks. Cells were washed with Dulbecco's Phosphate Buffered Saline (dPBS) and aspirated. Trypsin (3 mL per flask) was added and the flasks were incubated for 2-3 minutes.

**[00281]** Ten mL of OptiMEM-10% fetal bovine-1% penicillin-streptomycin (hereinafter, "OptiMEM media") was added to the flask and the cells and transferred to a 50 mL conical tube. A cell count (25ul of cell into Effendorf vial + 25ul of Trypan Blue Stain) was performed and the cell density adjusted to 15,000 cell/45 µl/well ( $3.33 \times 10^5/\text{mL}$ ) in OptiMEM media.

**[00282]** Forty-five microliters of the cell suspension (15,000 cells) was aliquoted to each well of the white 384-well plate. The plates incubated at room temperature for 10 minutes before being placed in the 37°C + 5% CO<sub>2</sub> incubator overnight

**[00283] Day 2 - Compound Treatment.** Exemplary compounds were prepared at a 1 mM starting concentration and 1:3 serial dilution for 11 points CRC prepared and stored in the freezer. The Master Compound Plate was thawed overnight at room temperature. DMSO (20 µL) was added into column 24 of the Master Compound Plate for negative control and 20 µL of 300 µM of Exemplary Compound 4 in column 23 as positive control.

**[00284]** Intermediate Compound Plate with 4% DMSO in OptiMEM Media. DMSO was added to warm OptiMEM media to achieve a 4% DMSO solution (approximately 50 mL/plate). One-hundred microliters of the OptiMEM-4% DMSO was aliquoted to each well of 384-Well Deep Well Microplates.

**[00285]** The Master Compound Plate and the Intermediate Compound Plate were spun down.

**[00286]** One microliter of compound from the Master Compound Plate was transferred into the Intermediate plate (a 1:100 dilution). The diluted mixture was mixed and 5  $\mu$ L transferred into the assay plate (a 1:10 dilution) for the final starting concentration of 1  $\mu$ M. The Treated Assay plates were incubated for 24 hours at 37°C + 5% CO<sub>2</sub>. The Master Compound Plate was sealed and store at room temperature for a second run that was performed within a week.

**[00287] Day 3 - HiBit Assay.** Five microliters of Alamar Blue was added to each well of the black 384-well plates. The plates were incubated for 2 hours in the incubator (37°C + 5% CO<sub>2</sub>) and at room temperature for one hour. Fluorescence of each plate was read on a plated reader for the Alamar Blue viability assay.

**[00288]** One set of white assay plates was warmed to room temperature (45 minute).

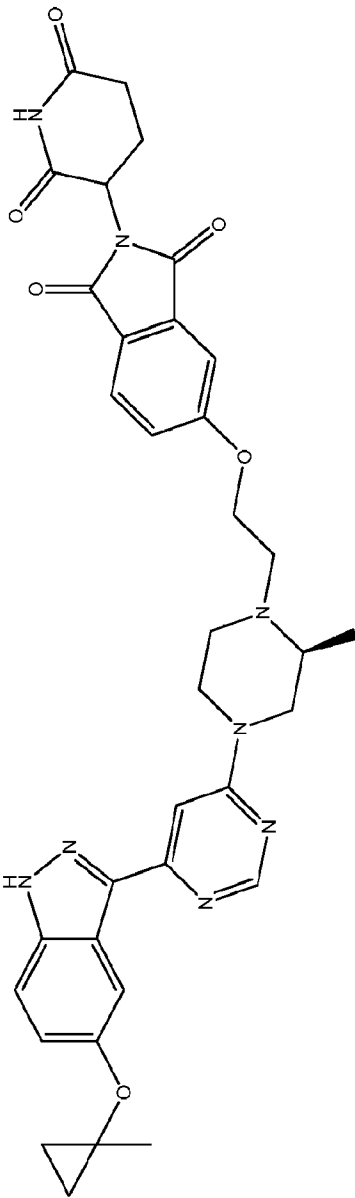
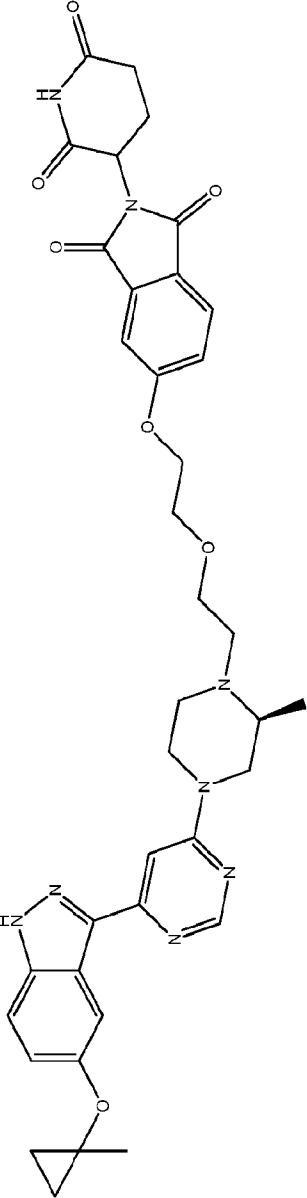
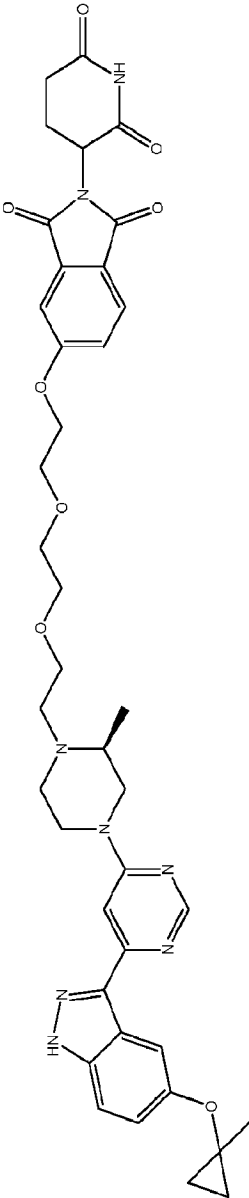
**[00289]** The One Glo luciferase mixture was prepared. The media from white 384-well assay plates was aspirated. Twenty-five  $\mu$ L of the One Glo luciferase mixture was added to each well of the assay plates. The plates were incubated on the bench (room temperature) for 45 minutes, including 10 minutes of shaking at 700 rpm. The luminescence of each plate was read on a plate reader.

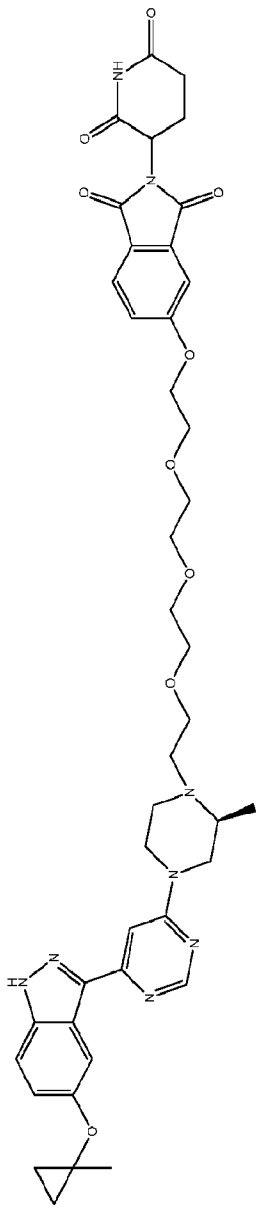
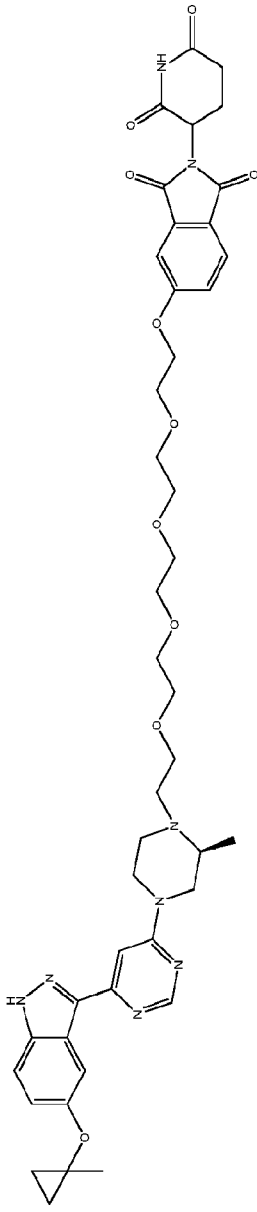
**[00290]** 1:100 DLR substrate and 1:100 LgBiT Protein dilution were added to the Promega Stop and Glo buffer and mixed just before addition to assay plates. Twenty-five microliters of Stop and Glo mixture was added to each well. Assay plates incubated for at least 45 minutes, including 10 minutes of shaking at 700 rpm. The luminescence of each plate was read on a plate reader.

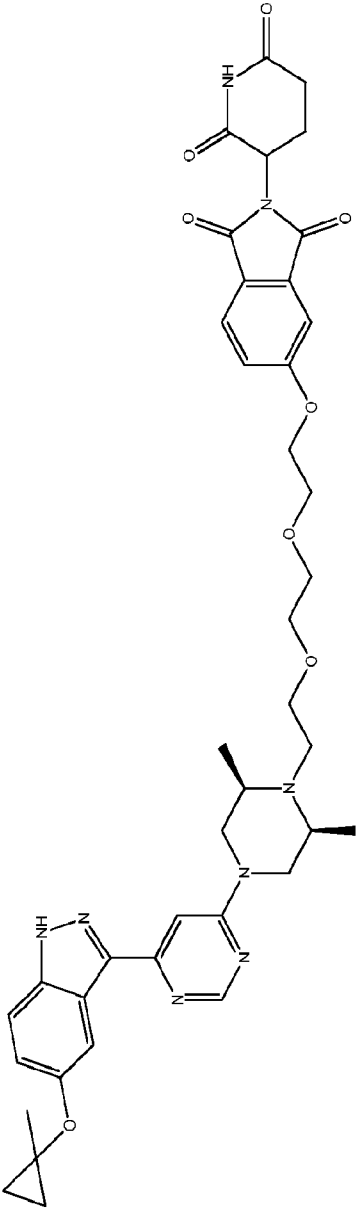
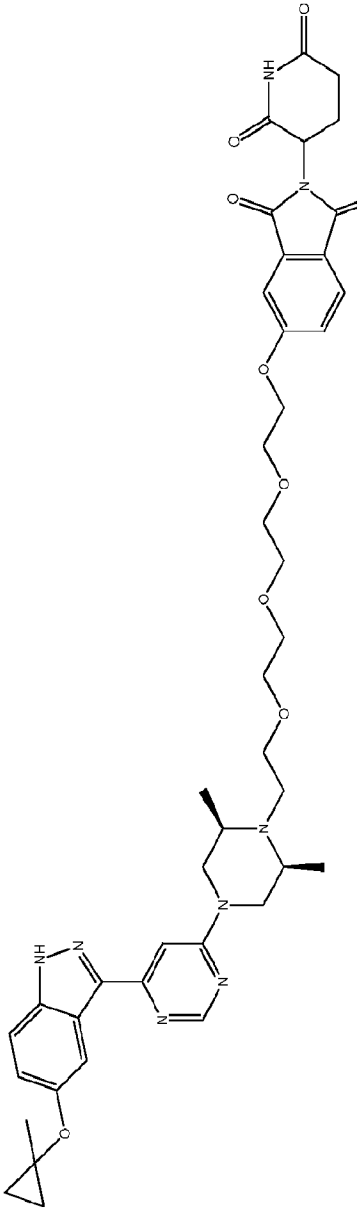
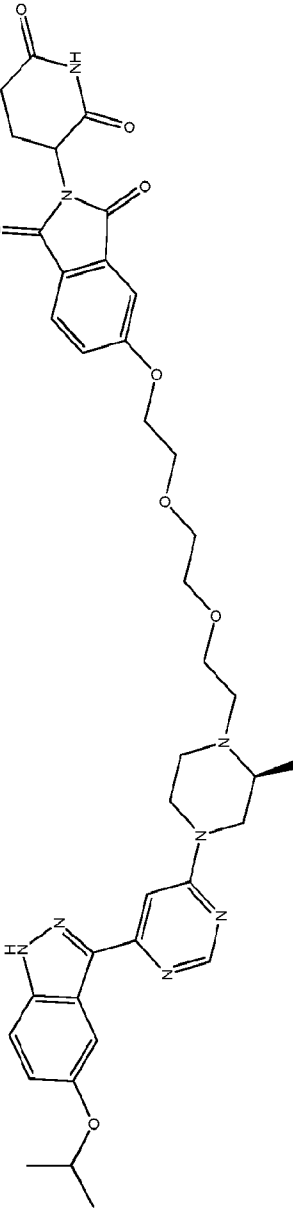
**[00291] Analysis of LRRK2 HiBit Screening assays.** As mentioned above, plates were run in triplicate and the assay repeated twice (total of 6 replicate for exemplary compound). For each treatment, measurements were taken for firefly luciferase for cell number, cell viability (Alamar Blue), and Nanoluc for the LRRK2-HiBit quantification.

**[00292]** The LRRK2 HiBit and alamar blue signal was normalized to % DMSO median value for each plate. Curve fitting was performed on each compound for replicates across three plates. The data for exemplary compounds of Table 1 below is shown below in Table 2 in the Endogenous \*WT DC50 (nM) and \*\*Endogenous WT Dmax columns (%).

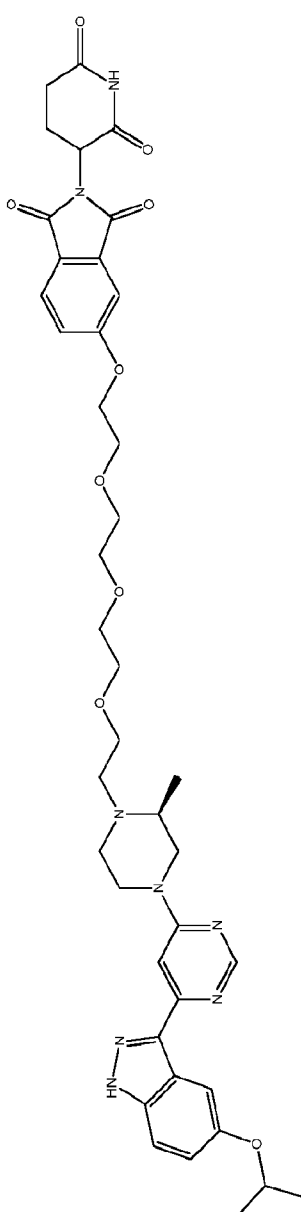
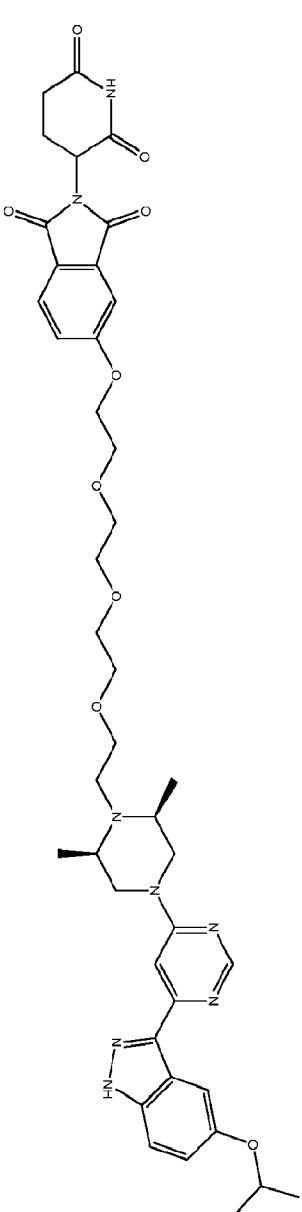
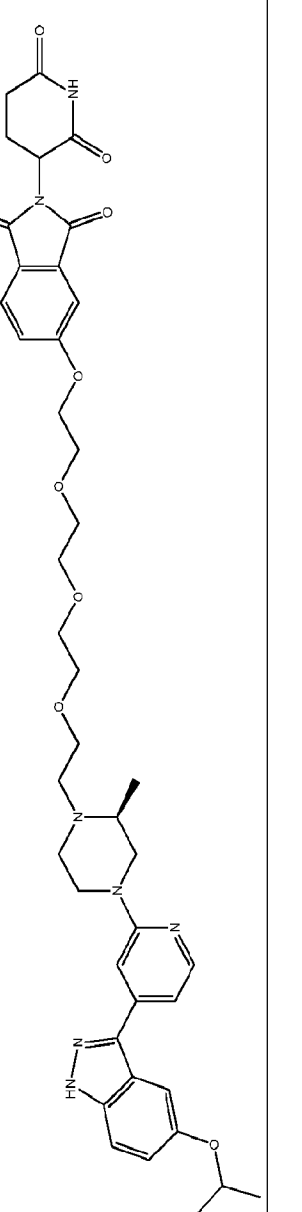
Table 1. Exemplary bifunctional compounds of the present disclosure

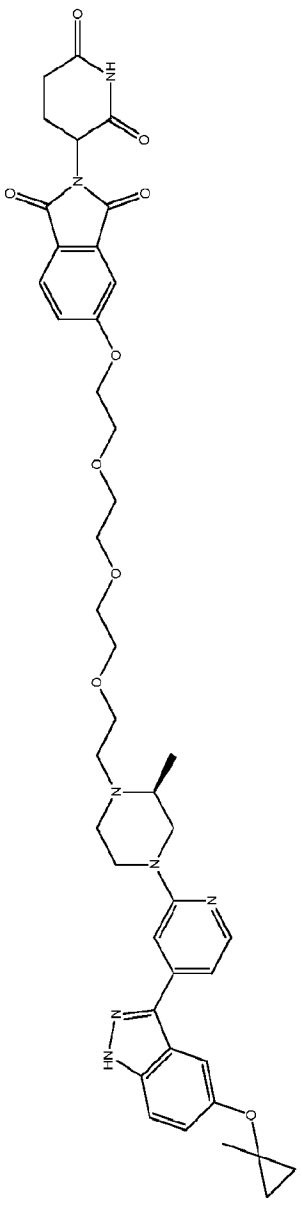
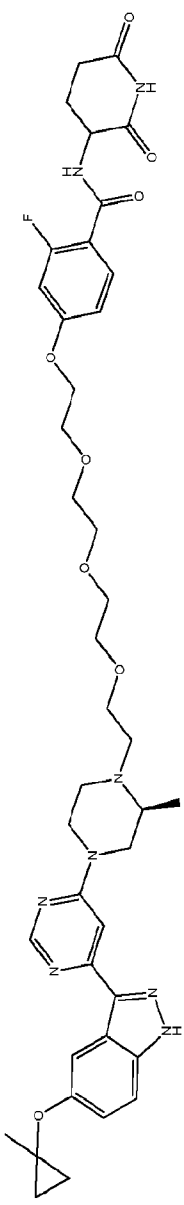
| Ex. No. | Chemical Structure                                                                   | IUPAC Name                                                                                                                                                              |
|---------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1       |    | 2-(2,6-dioxopiperidin-3-yl)-5-{2-[(2S)-2-methyl-4-{6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]ethoxy}-2,3-dihydro-1H-isoindole-1,3-dione |
| 2       |   | 2-(2,6-dioxopiperidin-3-yl)-5-{2-[(2S)-2-methyl-4-{6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]ethoxy}-2,3-dihydro-1H-isoindole-1,3-dione |
| 3       |  | 2-(2,6-dioxopiperidin-3-yl)-5-{2-[(2S)-2-methyl-4-{6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]ethoxy}eth                                 |

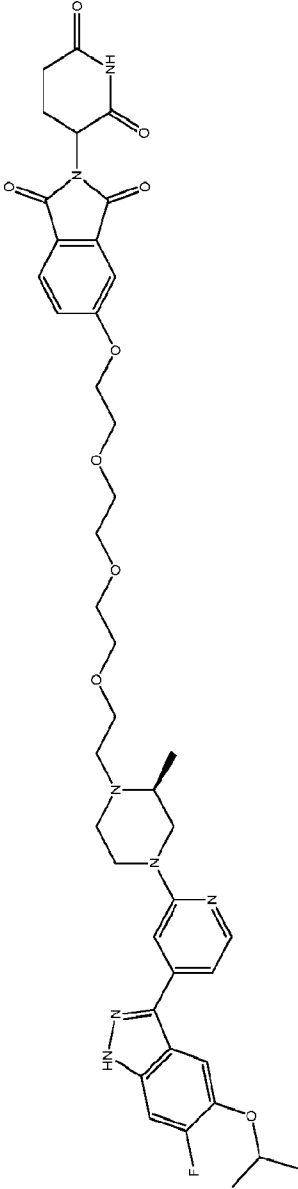
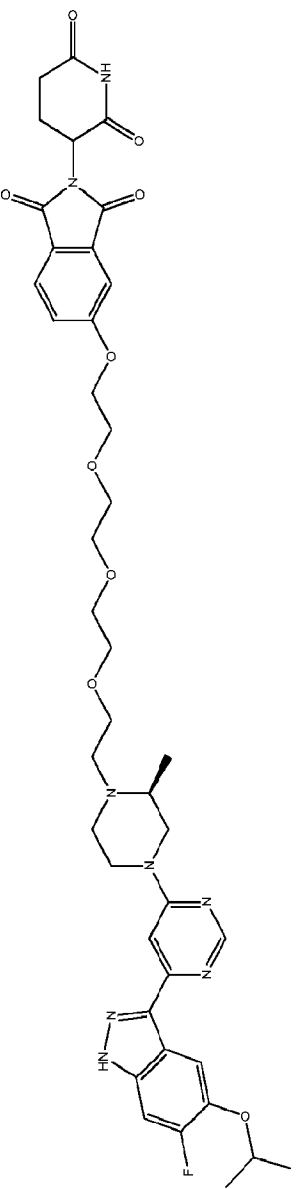
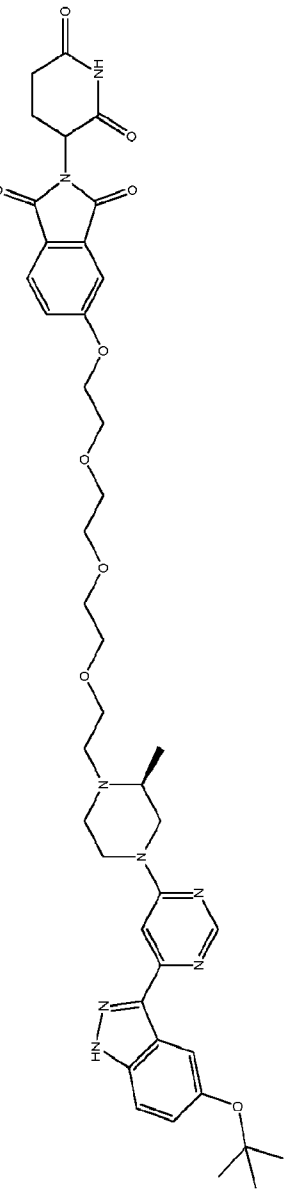
|   |                                                                                     |                                                                                                                                                                                                          |
|---|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|   |                                                                                     | oxy]-2,3-dihydro-1H-isoindole-1,3-dione                                                                                                                                                                  |
| 4 |   | 2-(2,6-dioxopiperidin-3-yl)-5-({2-[2-(2-{2-[(2S)-2-methyl-4-{6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]ethoxy}ethoxy)-2,3-dihydro-1H-isoindole-1,3-dione                 |
| 5 |  | 2-(2,6-dioxopiperidin-3-yl)-5-({14-[(2S)-2-methyl-4-{6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]-3,6,9,12-tetraoxatetradecan-1-yl}oxy)-2,3-dihydro-1H-isoindole-1,3-dione |

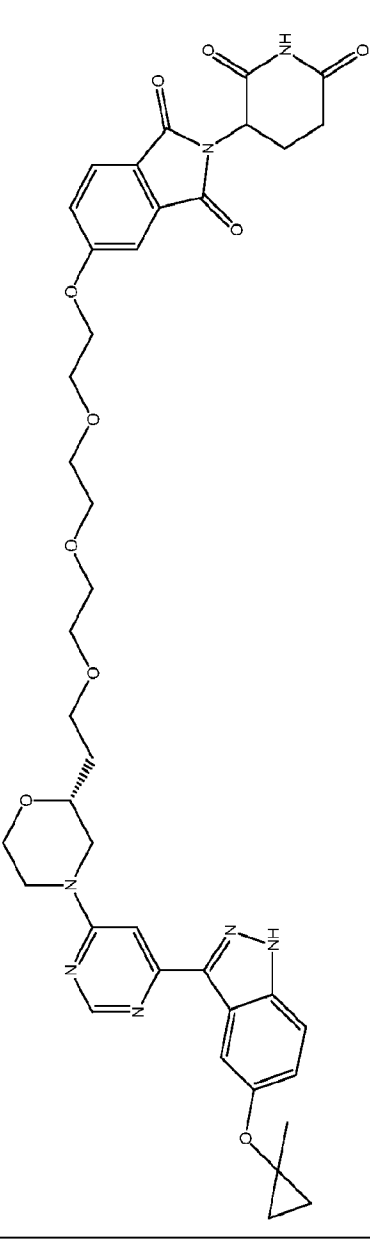
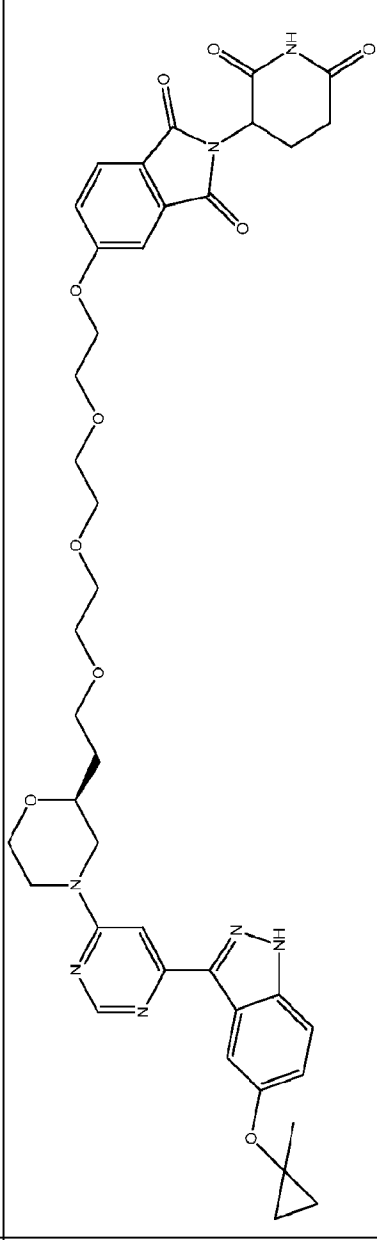
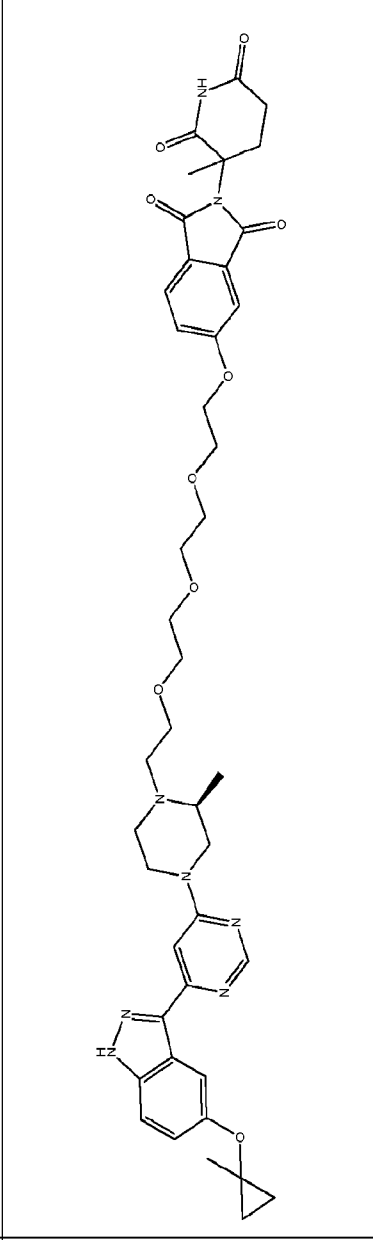
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| 6 |    | 5-[2-(2-{2-[(2R,6S)-2,6-dimethyl-4-{6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]ethoxy}ethoxy)ethoxy]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione    |
| 7 |   | 5-[2-[2-(2-{2-[(2R,6S)-2,6-dimethyl-4-{6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]ethoxy}ethoxy)ethoxy]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione |
| 8 |  | 2-(2,6-dioxopiperidin-3-yl)-5-[2-(2-{2-[(2S)-2-methyl-4-{6-[5-(propan-2-yloxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]ethoxy}ethoxy)ethoxy]-2,3-dihydro-1H-                                    |

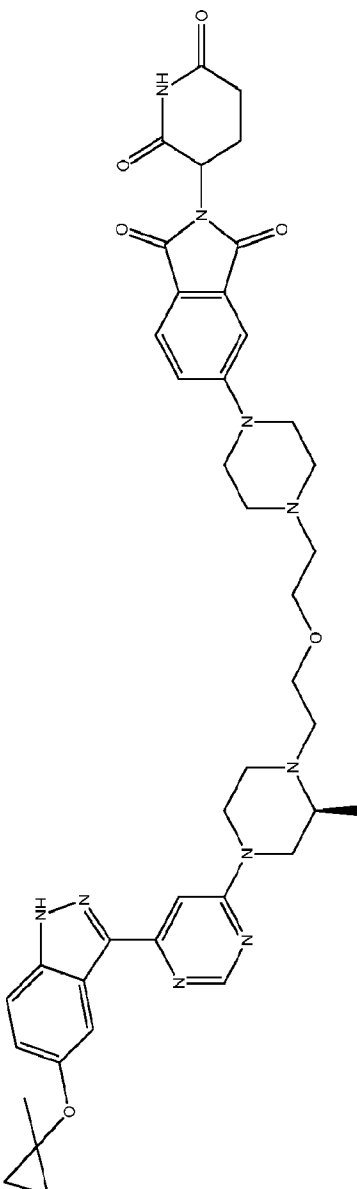
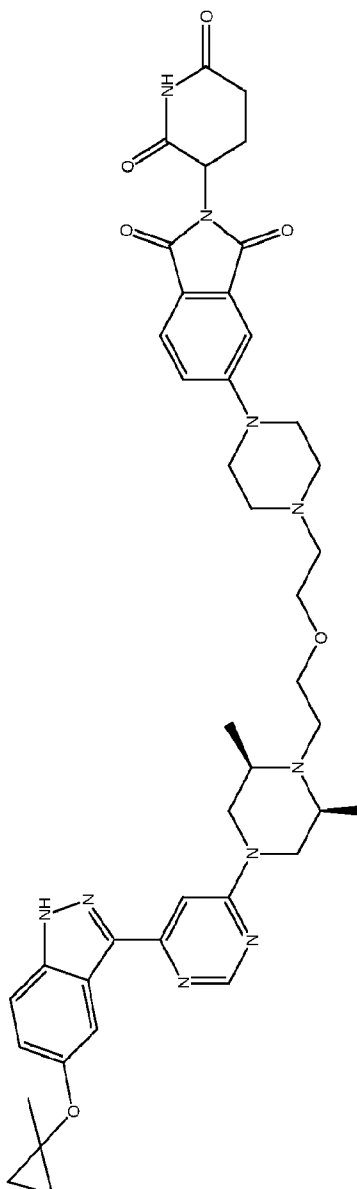


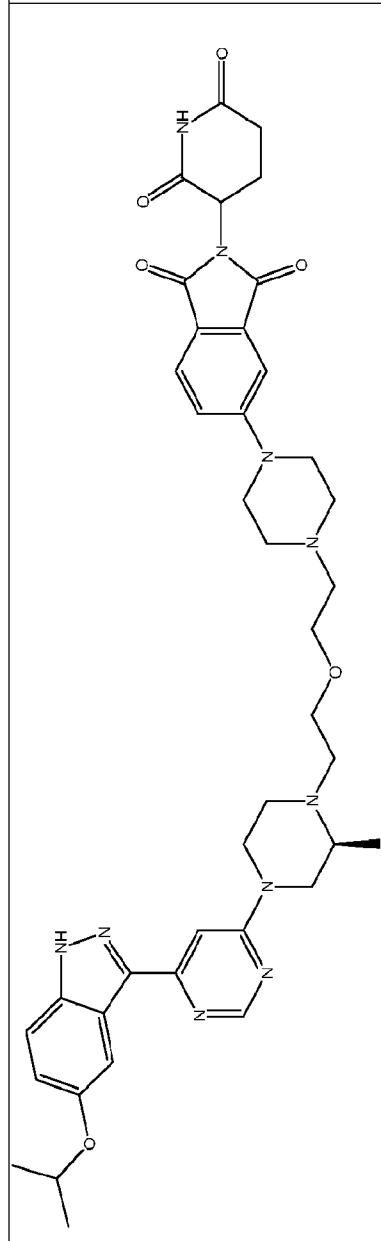
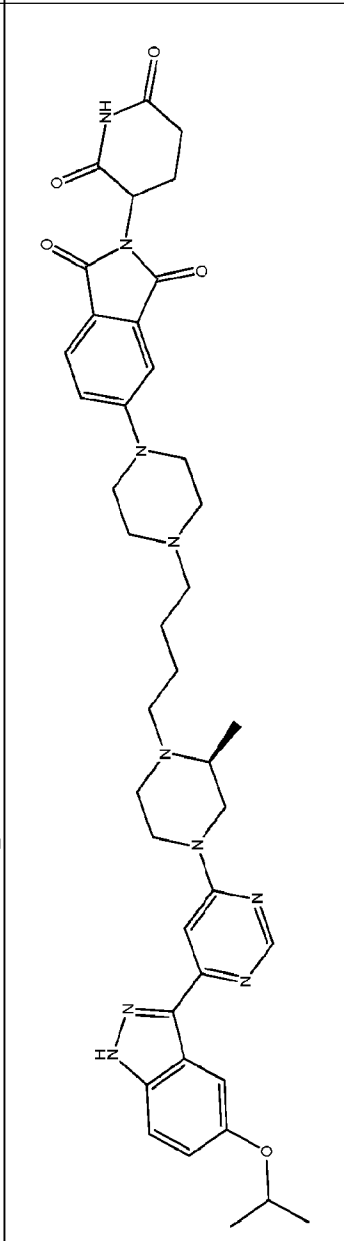
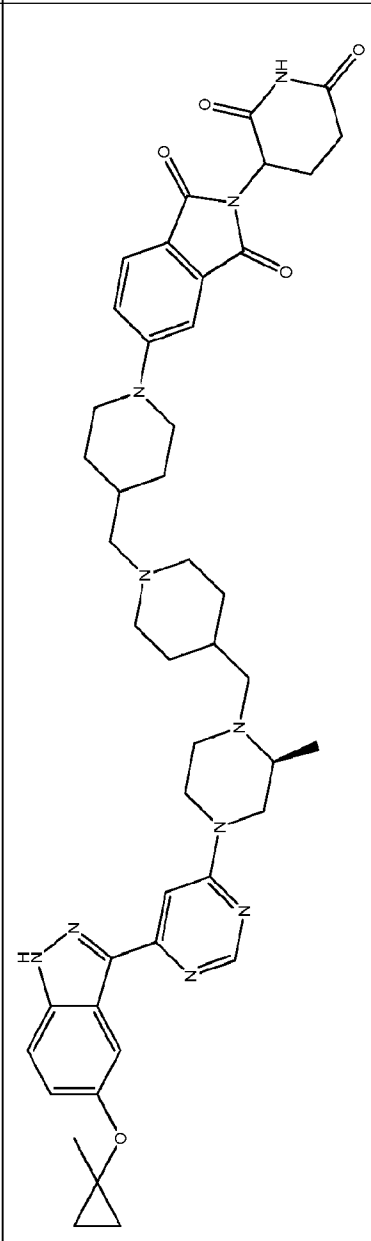
|    |                                                                                      |                                                                                                                                                                                      |
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|    |                                                                                      | isoindole-1,3-dione<br>2-(2,6-dioxopiperidin-3-yl)-5-{2-[2-(2-{2-[5-(propan-2-yloxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl)ethoxy]ethoxy}-2,3-dihydro-1H-isoindole-1,3-dione |
| 9  |    |                                                                                                                                                                                      |
| 10 |    |                                                                                                                                                                                      |
| 11 |  |                                                                                                                                                                                      |

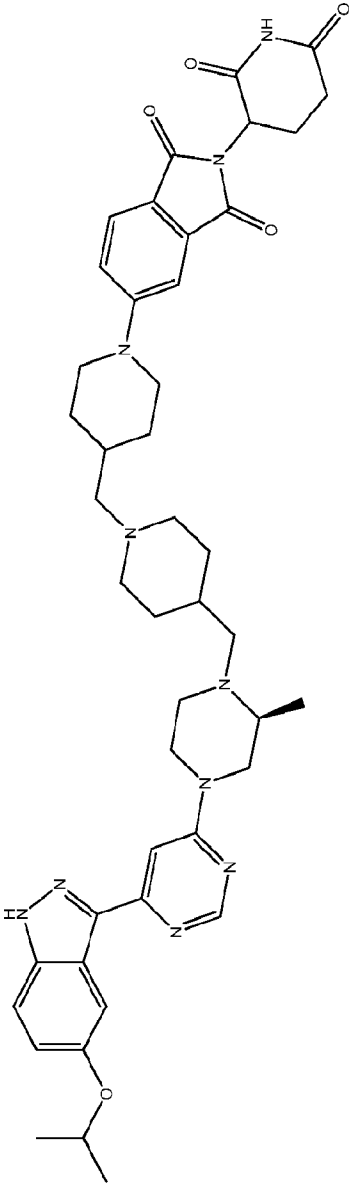
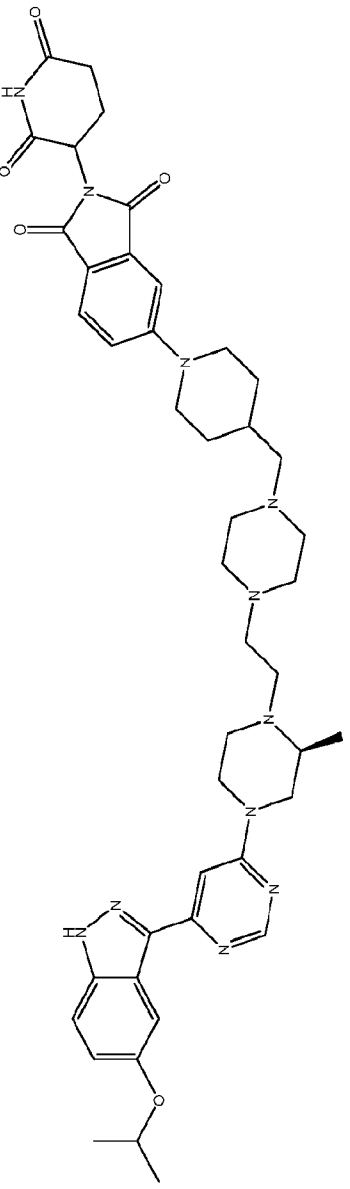
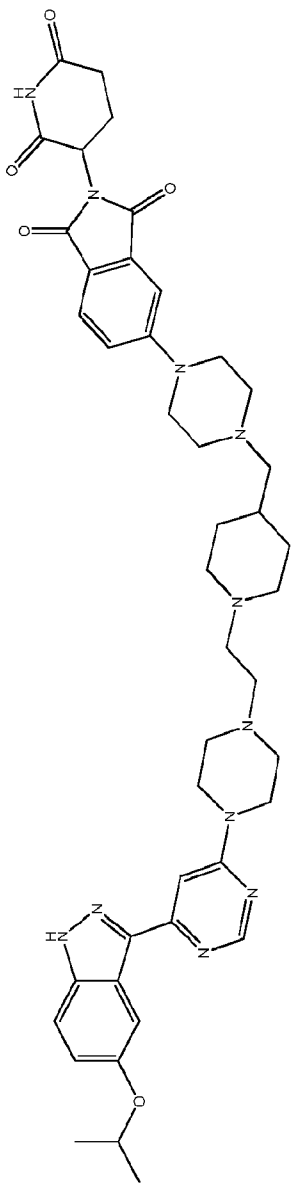
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|  |  | <p>           dihydro-1H-isoindole-1,3-dione<br/>           2-(2,6-dioxopiperidin-3-yl)-5-{2-[2-(2-{2-[(2S)-2-methyl-4-{4-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyridin-2-yl}piperazin-1-yl]ethoxy}ethoxy)ethoxy]ethoxy}-2,3-dihydro-1H-isoindole-1,3-dione         </p>  | 12 |
|  |  | <p>           N-(2,6-dioxopiperidin-3-yl)-2-fluoro-4-{2-[2-(2-{2-[(2S)-2-methyl-4-{4-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]ethoxy}ethoxy)ethoxy]ethoxy}benzamide         </p>                                                               | 13 |

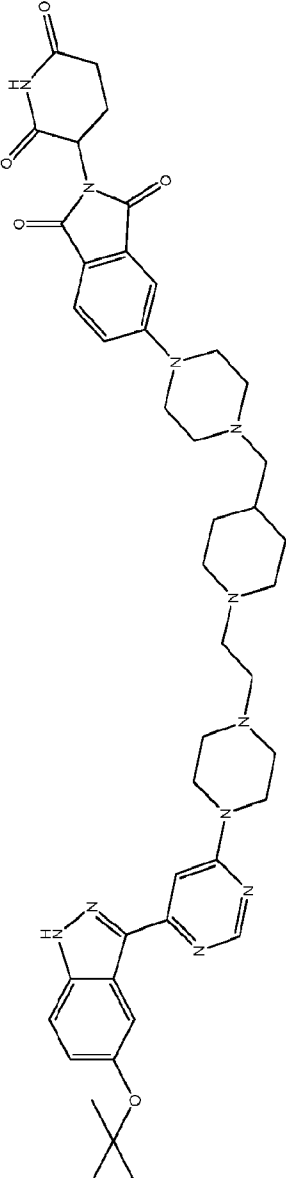
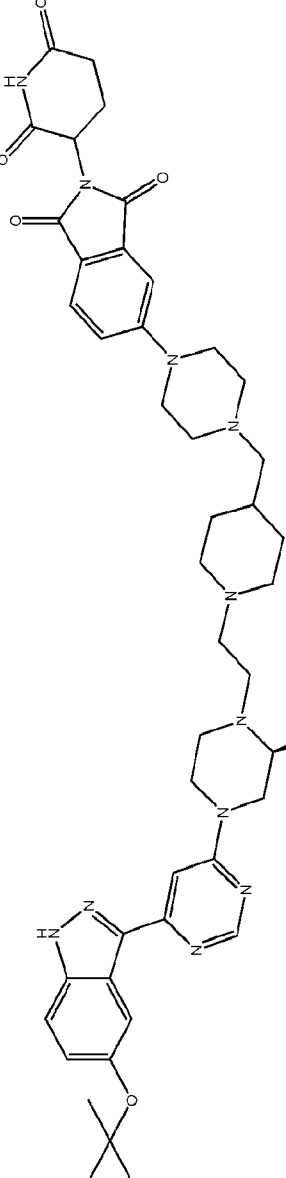
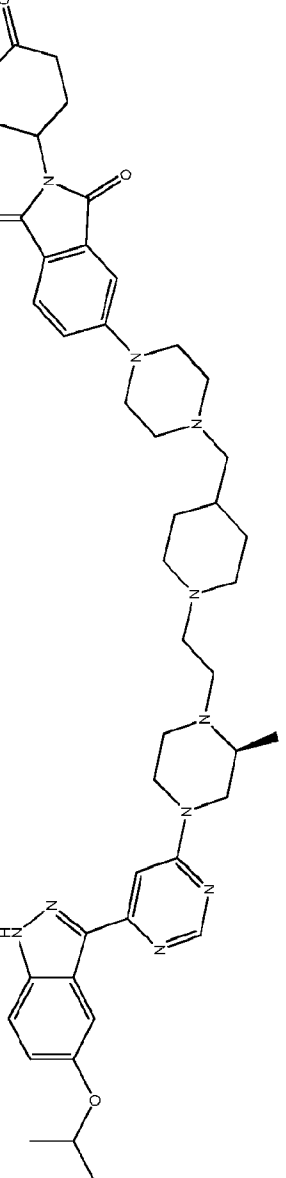
|    |                                                                                      |                                                                                                                                                                                                          |
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| 14 |    | 2-(2,6-dioxopiperidin-3-yl)-5-{2-[2-(2-{2-[(2S)-4-{4-[6-fluoro-5-(propan-2-yloxy)-1H-indazol-3-yl]pyridin-2-yl}-2-methylpiperazin-1-yl]ethoxy}ethoxy)ethoxy]ethoxy}-2,3-dihydro-1H-isoindole-1,3-dione   |
| 15 |    | 2-(2,6-dioxopiperidin-3-yl)-5-{2-[2-(2-{2-[(2S)-4-{4-[6-fluoro-5-(propan-2-yloxy)-1H-indazol-3-yl]pyrimidin-4-yl}-2-methylpiperazin-1-yl]ethoxy}ethoxy)ethoxy]ethoxy}-2,3-dihydro-1H-isoindole-1,3-dione |
| 16 |  | 5-{2-[2-(2-{2-[(2S)-4-{6-[5-(tert-butoxy)-1H-indazol-3-yl]pyrimidin-4-yl}-2-methylpiperazin-1-yl]ethoxy}ethoxy)ethoxy]ethoxy}-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione             |

|    |                                                                                     |                                                                                                                                                                                                                |
|----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 17 |   | 2-(2,6-dioxopiperidin-3-yl)-5-(2-(2-(2-(4-(6-(5-(1-methylcyclopropoxy)-1H-indazol-3-yl)pyrimidin-4-yl)morpholin-2-yl)ethoxy)ethoxy)ethoxy)isoindole-1,3-dione                                                  |
| 18 |   | 2-(2,6-dioxopiperidin-3-yl)-5-{2-[2-(2-{2-[(2S)-4-{6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl}morpholin-2-yl]ethoxy}ethoxy)ethoxy]ethoxy}-2,3-dihydro-1H-isoindole-1,3-dione                   |
| 19 |  | 2-(3-methyl-2,6-dioxopiperidin-3-yl)-5-{2-[2-(2-{2-[(2S)-2-methyl-4-{6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]ethoxy}ethoxy)ethoxy]ethoxy}-2,3-dihydro-1H-isoindole-1,3-dione |

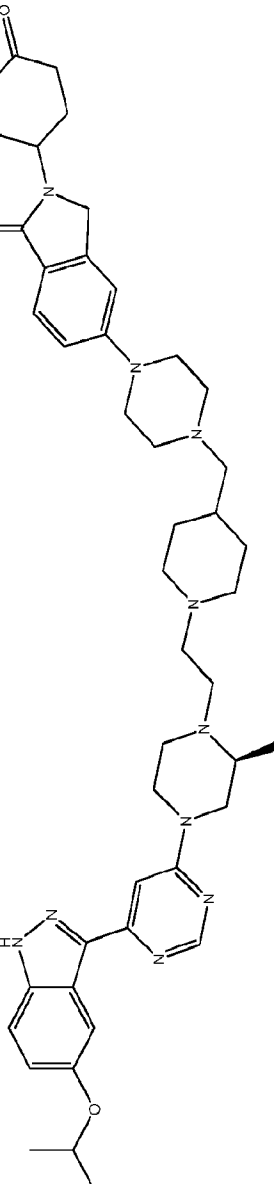
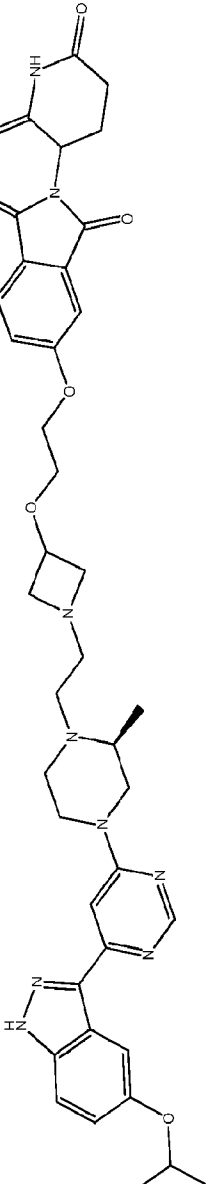
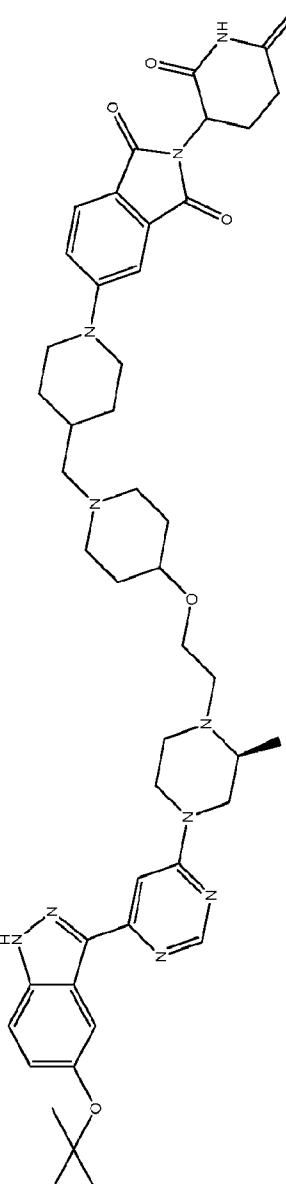
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|    |                                                                                     | 1,3-dione<br>2-(2,6-dioxopiperidin-3-yl)-5-[4-(2-{2-[(2S)-2-methyl-4-{6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]ethoxy}ethyl)piperazin-1-yl]-2,3-dihydro-1H-isoindole-1,3-dione |
| 20 |   |                                                                                                                                                                                                                 |
| 21 |  |                                                                                                                                                                                                                 |

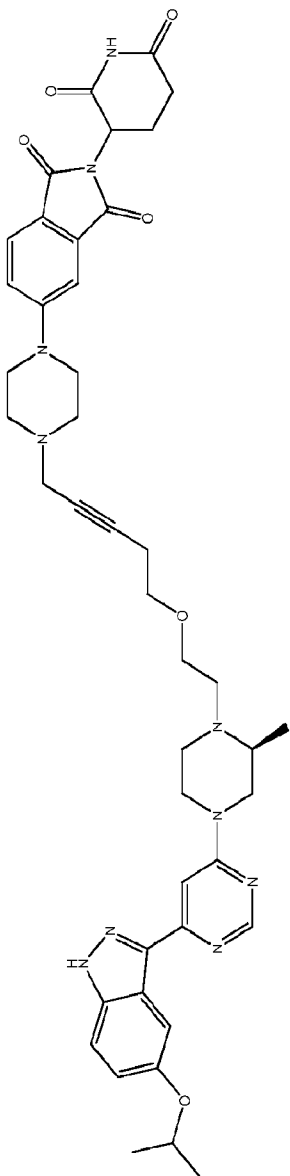
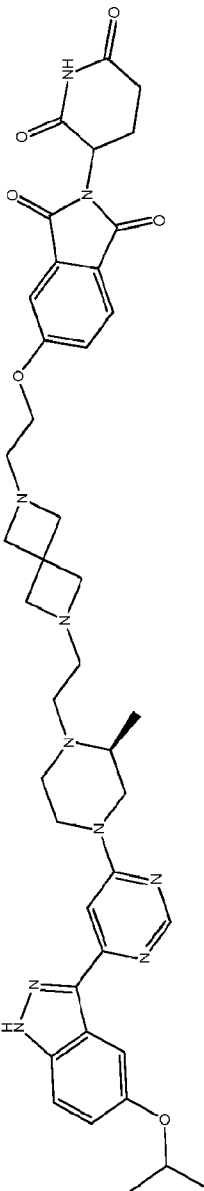
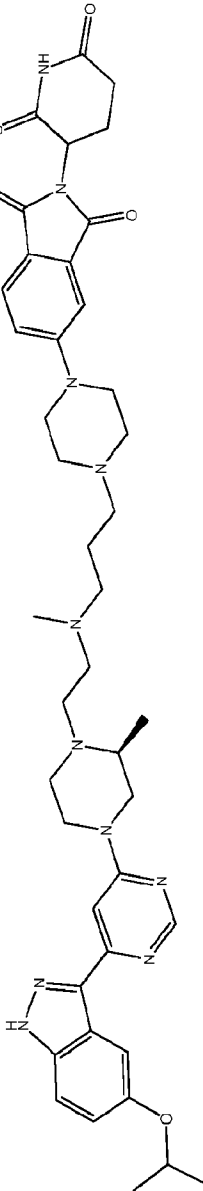
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| <p>2-(2,6-dioxo-3-piperidyl)-5-[4-[2-[(2S)-4-[6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethoxy]ethyl]piperazin-1-yl]isoindoline-1,3-dione</p>                                            |   | 22 |
| <p>2-(2,6-dioxopiperidin-3-yl)-5-(4-{4-[(2S)-2-methyl-4-{6-[5-(propan-2-yloxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]butyl}piperazin-1-yl)-2,3-dihydro-1H-isoindole-1,3-dione</p>                              |   | 23 |
| <p>2-(2,6-dioxopiperidin-3-yl)-5-[4-{4-[(2S)-2-methyl-4-{6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]methyl}piperidin-1-yl)methyl]piperidin-1-yl]-2,3-dihydro-1H-isoindole-1,3-dione</p> |  | 24 |

|                                                                                               |                                                                                                                                                                                                       |
|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>25</p>   | <p>2-(2,6-dioxopiperidin-3-yl)-5-[4-[(2S)-2-methyl-4-{6-[5-(propan-2-yloxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl)methyl]piperidin-1-yl]-2,3-dihydro-1H-isoindole-1,3-dione</p>               |
| <p>26</p>   | <p>2-(2,6-dioxopiperidin-3-yl)-5-[4-[(2S)-2-methyl-4-{6-[5-(propan-2-yloxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl)ethyl]piperidin-1-yl]-2,3-dihydro-1H-isoindole-1,3-dione</p>                |
| <p>27</p>  | <p>2-(2,6-dioxopiperidin-3-yl)-5-[4-[(1-[2-(4-{6-[5-(propan-2-yloxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl)ethyl]piperidin-4-yl)methyl]piperazin-1-yl]-2,3-dihydro-1H-isoindole-1,3-dione</p> |

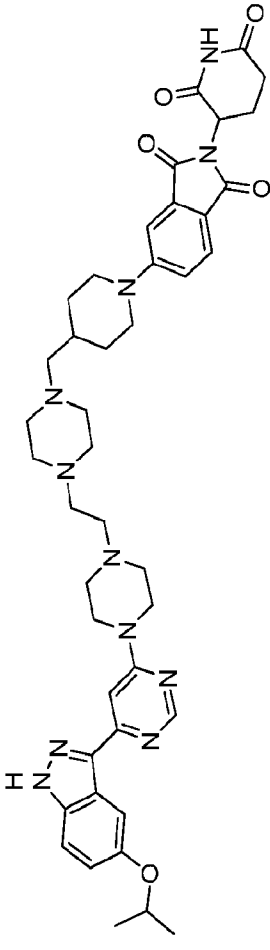
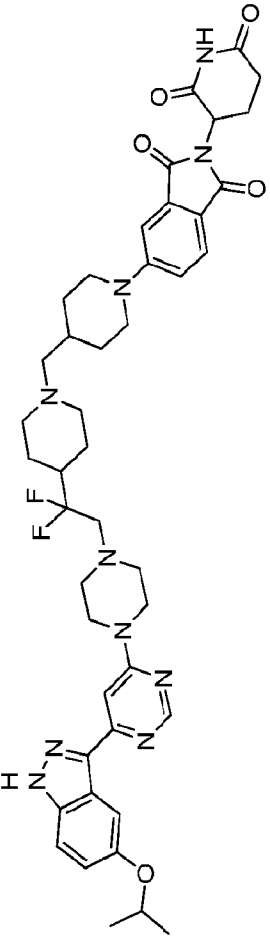
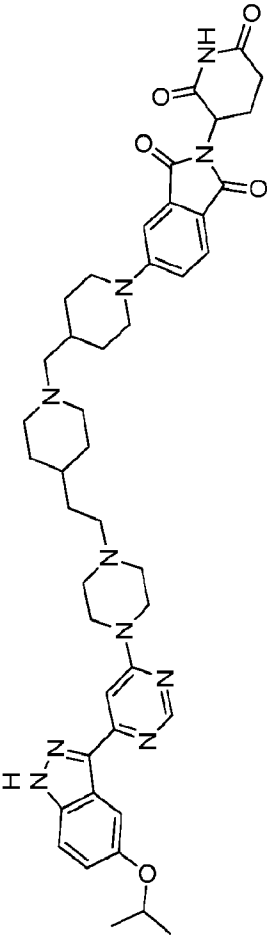
|                                                                                                                                                                                                                           |                                                                                      |    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----|
| <p>2-(2,6-dioxopiperidin-3-yl)-5-[4-({1-[2-(4-{6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl)ethyl]piperidin-4-yl)methyl]piperazin-1-yl]-2,3-dihydro-1H-isoindole-1,3-dione</p>               |    | 28 |
| <p>2-(2,6-dioxopiperidin-3-yl)-5-[4-({1-[2-[(2S)-2-methyl-4-{6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]ethyl]piperidin-4-yl)methyl]piperazin-1-yl]-2,3-dihydro-1H-isoindole-1,3-dione</p> |    | 29 |
| <p>2-(2,6-dioxopiperidin-3-yl)-5-[4-({1-[2-[(2S)-2-methyl-4-{6-[5-(propan-2-yloxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]ethyl]piperidin-4-yl)methyl]piperazin-1-yl]-2,3-dihydro-1H-isoindole-1,3-dione</p>       |  | 30 |

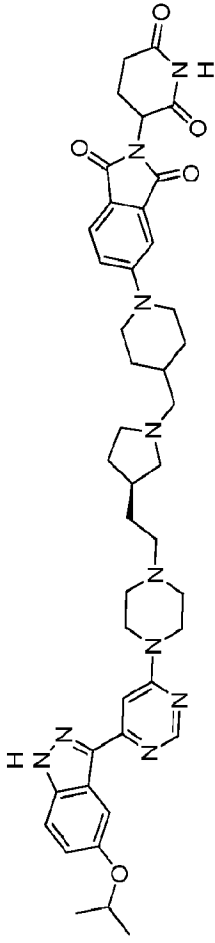
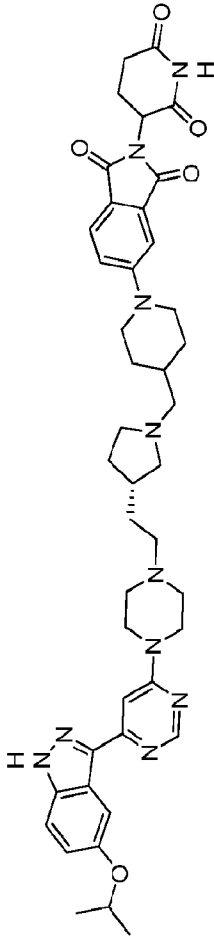
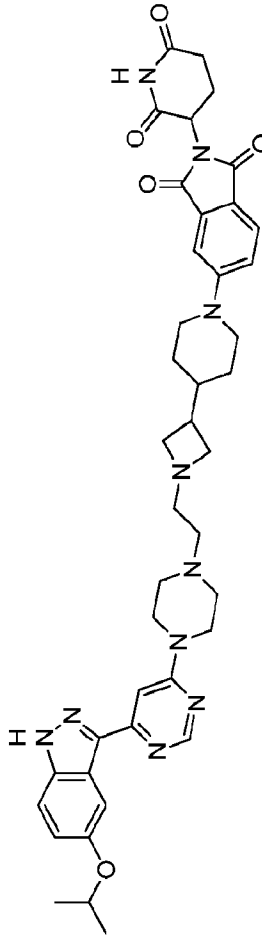


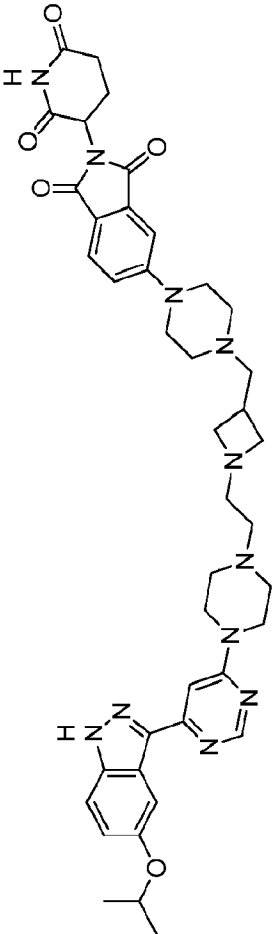
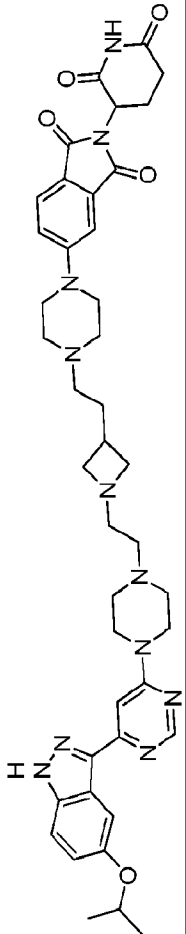
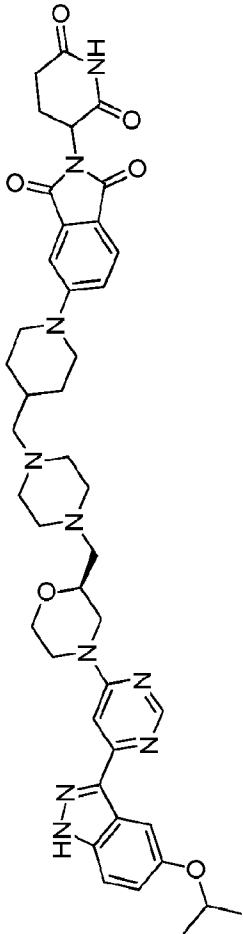
|    |                                                                                      |                                                                                                                                                                                                                                            |
|----|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |    | <p>isoindole-1,3-dione</p> <p>3-(5-{4-[(1-{2-[(2S)-2-methyl-4-{6-[5-(propan-2-yloxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]ethyl}piperidin-4-yl)methyl]piperazin-1-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione</p> |
| 31 |                                                                                      |                                                                                                                                                                                                                                            |
|    |    | <p>2-(2,6-dioxopiperidin-3-yl)-5-{2-[(1-{2-[(2S)-2-methyl-4-{6-[5-(propan-2-yloxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]ethyl}azetidin-3-yl)oxy]ethoxy}-2,3-dihydro-1H-isoindole-1,3-dione</p>                                    |
| 32 |                                                                                      |                                                                                                                                                                                                                                            |
|    |  | <p>2-(2,6-dioxopiperidin-3-yl)-5-{4-[(4-{2-[(2S)-2-methyl-4-{6-[5-(1-methylcyclopropoxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]ethoxy}piperidin-2-yl)ethoxy]piperidin-2-yl}piperidine-2,6-dione</p>                                |
| 33 |                                                                                      |                                                                                                                                                                                                                                            |

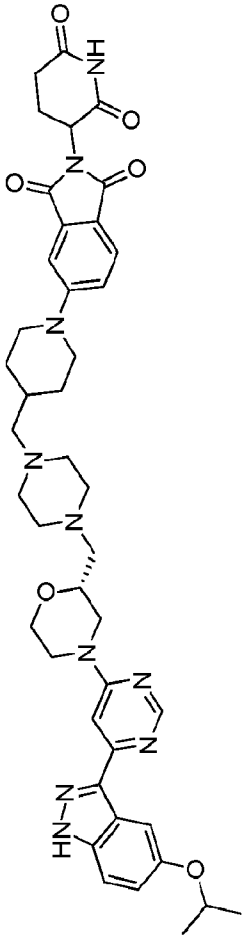
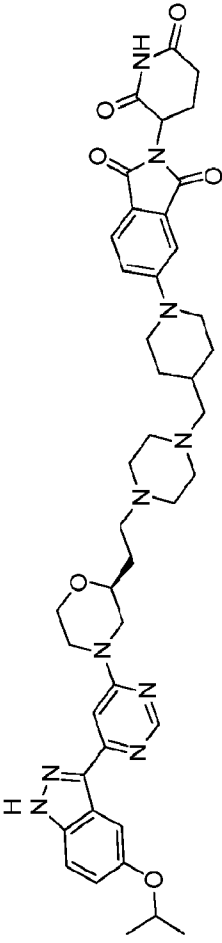
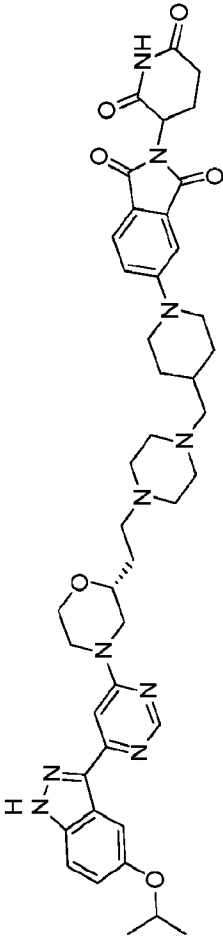
|    |                                                                                      |                                                                                                                                                                                                                 |
|----|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |                                                                                      | 1-yl)methyl]piperidin-1-yl}-2,3-dihydro-1H-isoindole-1,3-dione                                                                                                                                                  |
| 34 |    | 2-(2,6-dioxopiperidin-3-yl)-5-[4-(5-{2-[2-(2S)-2-methyl-4-{6-[5-(propan-2-yloxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]ethoxy}pent-2-yn-1-yl)piperazin-1-yl]-2,3-dihydro-1H-isoindole-1,3-dione         |
| 35 |   | 2-(2,6-dioxopiperidin-3-yl)-5-[2-(6-{2-[2-(2S)-2-methyl-4-{6-[5-(propan-2-yloxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl]ethyl}-2,6-diazaspiro[3.3]heptan-2-yl)ethoxy]-2,3-dihydro-1H-isoindole-1,3-dione |
| 36 |  | 2-(2,6-dioxopiperidin-3-yl)-5-(4-{3-[methyl(2-{2-(2S)-2-methyl-4-{6-[5-(propan-2-yloxy)-1H-indazol-3-yl]pyrimidin-4-                                                                                            |

|    |  |                                                                                                                                                                                                                 |
|----|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |  | <p>yl}piperazin-1-yl}ethyl}amino]propyl}piperazin-1-yl)-2,3-dihydro-1H-indole-1,3-dione</p>                                                                                                                     |
| 37 |  | <p>2-(2,6-dioxopiperidin-3-yl)-5-(4-{2-[methyl({2-[(2S)-2-methyl-4-{6-[5-(propan-2-yloxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl}ethyl}amino]ethyl}piperazin-1-yl)-2,3-dihydro-1H-indole-1,3-dione</p>   |
| 38 |  | <p>2-(2,6-dioxopiperidin-3-yl)-5-(4-{3-[methyl({3-[(2S)-2-methyl-4-{6-[5-(propan-2-yloxy)-1H-indazol-3-yl]pyrimidin-4-yl}piperazin-1-yl}propyl}amino]propyl}piperazin-1-yl)-2,3-dihydro-1H-indole-1,3-dione</p> |

|                                                                                                                                                                                                  |                                                                                      |    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----|
| <p>2-(2,6-dioxopiperidin-3-yl)-5-(4-(2-(4-(6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl)piperazin-1-yl)ethyl)piperidin-1-yl)methyl)piperidin-1-yl)isoindoline-1,3-dione</p>                    |    | 39 |
| <p>5-(4-(2-(4-(1,1-difluoro-2-(4-(6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl)piperazin-1-yl)ethyl)piperidin-1-yl)methyl)piperidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione</p> |    | 40 |
| <p>2-(2,6-dioxopiperidin-3-yl)-5-(4-(2-(4-(6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl)piperazin-1-yl)ethyl)piperidin-1-yl)methyl)piperidin-1-yl)isoindoline-1,3-dione</p>                    |  | 41 |

|    |                                                                                     |                                                                                                                                                                                 |
|----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 42 |   | 2-(2,6-dioxopiperidin-3-yl)-5-(4-(((R)-3-(2-(4-(6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl)piperazin-1-yl)ethyl)pyrrolidin-1-yl)methyl)piperidin-1-yl)isoindoline-1,3-dione |
| 43 |   | 2-(2,6-dioxopiperidin-3-yl)-5-(4-(((S)-3-(2-(4-(6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl)piperazin-1-yl)ethyl)pyrrolidin-1-yl)methyl)piperidin-1-yl)isoindoline-1,3-dione |
| 44 |  | 2-(2,6-dioxopiperidin-3-yl)-5-(4-(1-(2-(4-(6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl)piperazin-1-yl)ethyl)azetidin-3-yl)piperidin-1-yl)isoindoline-1,3-dione               |

|    |                                                                                      |                                                                                                                                                                              |
|----|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 45 |    | 2-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(2-(4-(6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl)piperazin-1-yl)ethyl)azetidin-3-yl)methyl)piperazin-1-yl)isoindoline-1,3-dione    |
| 46 |    | 2-(2,6-dioxopiperidin-3-yl)-5-(4-(2-(1-(2-(4-(6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl)piperazin-1-yl)ethyl)azetidin-3-yl)methyl)piperazin-1-yl)isoindoline-1,3-dione  |
| 47 |  | 2-(2,6-dioxopiperidin-3-yl)-5-(4-((4-((S)-4-(6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl)morpholin-2-yl)methyl)piperazin-1-yl)methyl)piperidin-1-yl)isoindoline-1,3-dione |

|    |                                                                                      |                                                                                                                                                                          |
|----|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 48 |    | 2-(2,6-dioxopiperidin-3-yl)-5-(4-((R)-4-(6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl)morpholin-2-yl)methyl)piperazin-1-yl)methyl)piperidin-1-yl)isoindoline-1,3-dione |
| 49 |    | 2-(2,6-dioxopiperidin-3-yl)-5-(4-((S)-4-(6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl)morpholin-2-yl)ethyl)piperazin-1-yl)methyl)piperidin-1-yl)isoindoline-1,3-dione  |
| 50 |  | 2-(2,6-dioxopiperidin-3-yl)-5-(4-((R)-4-(6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl)morpholin-2-yl)ethyl)piperazin-1-yl)methyl)piperidin-1-yl)isoindoline-1,3-dione  |

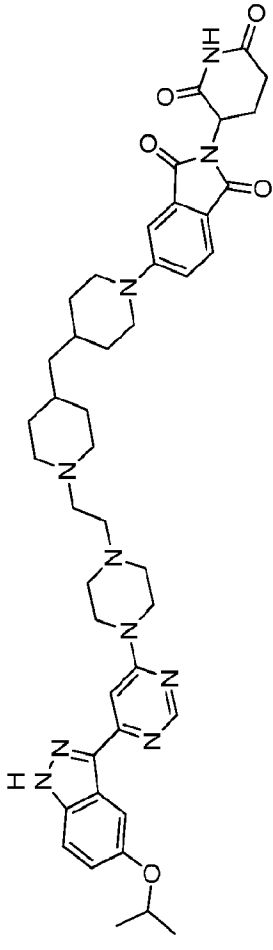
|                                                                                                                                                                                   |                                                                                    |    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|----|
| <p>2-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(2-(4-(6-(5-isopropoxy-1H-indazol-3-yl)pyrimidin-4-yl)piperazin-1-yl)ethyl)piperidin-4-yl)methyl)piperidin-1-yl)isoindoline-1,3-dione</p> |  | 51 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|----|



Table 2. Degradation and characterization of exemplary bifunctional compounds of the present disclosure

| Ex. No. | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Mol Weight (Exact Mass) | Mean Observed Mass | *G2019S DC50 (nM) | **G2019S Dmax (%) | *WT DC50 (nM) | **WT Dmax (%) | *Endogenous WT DC50 (nM) | **Endogenous Dmax (%) |
|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|--------------------|-------------------|-------------------|---------------|---------------|--------------------------|-----------------------|
| 1       | <sup>1</sup> H NMR (400MHz, MeOD) $\delta$ : 8.63 (s, 1 H), 8.10 (s, 1 H), 7.82 (d, $J$ =8.28 Hz, 1 H), 7.35 - 7.53 (m, 4 H), 7.08 (dd, $J$ =9.03, 2.26 Hz, 1 H), 5.11 (dd, $J$ =12.55, 5.52 Hz, 1 H), 4.34 (s, 2 H), 4.20 (d, $J$ =10.79 Hz, 2 H), 3.35 - 3.46 (m, 1 H), 3.13 (s, 3 H), 2.73 (s, 6 H), 2.05 - 2.16 (m, 1 H), 1.61 (s, 3 H), 1.24 (d, $J$ =6.27 Hz, 3 H), 1.01 (s, 2 H), 0.78 (d, $J$ =1.51 Hz, 2 H).                                                    | 664.72 (664.28)         | 665.38             | A                 | C                 | A             | C             |                          |                       |
| 2       | <sup>1</sup> H NMR (400MHz, MeOD) $\delta$ : 8.62 (s, 1 H), 8.10 (s, 1 H), 7.77 (d, $J$ =8.28 Hz, 1 H), 7.42 - 7.48 (m, 2 H), 7.37 (s, 1 H), 7.31 (dd, $J$ =8.53, 2.26 Hz, 1 H), 7.09 (dd, $J$ =9.29, 2.26 Hz, 1 H), 5.07 (dd, $J$ =12.67, 5.40 Hz, 1 H), 4.30 - 4.38 (m, 2 H), 4.16 (s, 2 H), 3.83 - 3.89 (m, 2 H), 3.74 (s, 2 H), 3.00 (s, 4 H), 2.52 - 2.84 (m, 6 H), 2.01 - 2.12 (m, 1 H), 1.61 (s, 3 H), 1.17 (d, $J$ =6.27 Hz, 3 H), 1.02 (s, 2 H), 0.78 (s, 2 H). | 708.78 (708.30)         | 709.41             | A                 | C                 | A             | B             |                          |                       |
| 3       | <sup>1</sup> H NMR (400MHz, MeOD) $\delta$ : 8.60 (s, 1 H), 8.08 (s, 1 H), 7.73 (d, $J$ =8.03 Hz, 1 H), 7.25 - 7.51 (m, 4 H), 7.08 (dd, $J$ =9.03, 2.26 Hz, 1 H), 5.05 (d, $J$ =12.30 Hz, 1 H), 4.24 - 4.32 (m, 2 H), 4.18 (s, 2 H), 3.84 - 3.93 (m, 2 H), 3.58 - 3.76 (m, 6 H), 3.26 (s, 1 H), 3.02                                                                                                                                                                     | 752.83 (752.33)         | 753.44             | B                 | B                 | A             | A             |                          |                       |

[illegible]

|   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                    |        |   |   |   |   |  |  |  |
|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------|---|---|---|---|--|--|--|
|   | H), 7.06 (dd, $J=9.07$ , 2.06 Hz, 1 H), 5.06 (dd, $J=12.69$ , 5.44 Hz, 1 H), 4.59 (s, 1 H), 4.33 (d, $J=10.63$ Hz, 1 H), 4.15 - 4.21 (m, 2 H), 3.79 - 3.86 (m, 2 H), 3.66 - 3.62 (m, 2 H), 3.59 (d, $J=5.38$ Hz, 4 H), 3.02 - 3.01 (m, 2 H), 2.66 - 2.93 (m, 7 H), 2.04 - 2.14 (m, 1 H), 1.60 (s, 3 H), 1.20 (d, $J=6.00$ Hz, 6 H), 1.01 (s, 2 H), 0.77 (s, 2 H).                                                                                                                       |                    |        |   |   |   |   |  |  |  |
| 7 | <sup>1</sup> H NMR (400MHz, MeOD) $\delta$ : 8.61 (s, 1 H), 8.09 (s, 1 H), 7.70 (d, $J=8.38$ Hz, 1 H), 7.30 - 7.47 (m, 3 H), 7.21 (dd, $J=8.32$ , 2.19 Hz, 1 H), 7.03 - 7.11 (m, 1 H), 5.07 (dd, $J=12.44$ , 5.57 Hz, 1 H), 4.60 (s, 4 H), 4.35 (d, $J=9.76$ Hz, 2 H), 4.14 - 4.21 (m, 2 H), 3.75 - 3.82 (m, 2 H), 3.54 - 3.64 (m, 7 H), 3.05 (s, 2 H), 2.64 - 2.92 (m, 6 H), 2.06 - 2.13 (m, 1 H), 1.60 (s, 3 H), 1.22 (d, $J=6.13$ Hz, 6 H), 1.01 (s, 2 H), 0.78 (s, 2 H).            | 810.91<br>(810.37) | 811.37 | A | B | A | A |  |  |  |
| 8 | <sup>1</sup> H NMR (400MHz, MeOD) $\delta$ : ppm 8.63 (s, 1 H), 8.36 (br s, 1 H), 7.91 (s, 1 H), 7.72 (d, $J=8.25$ Hz, 1 H), 7.46 (d, $J=9.01$ Hz, 1 H), 7.40 (s, 2 H), 7.28 (dd, $J=8.32$ , 2.06 Hz, 1 H), 7.07 (dd, $J=9.01$ , 2.13 Hz, 1 H), 5.01 - 5.07 (m, 1 H), 4.62 - 4.69 (m, 1 H), 4.20 - 4.31 (m, 4 H), 3.84 - 3.91 (m, 2 H), 3.64 - 3.81 (m, 7 H), 3.40 - 3.54 (m, 1 H), 3.26 - 3.27 (m, 1 H), 3.20 - 3.27 (m, 2 H), 3.05 - 3.15 (m, 1 H), 2.87 - 2.98 (m, 2 H), 2.60 - 2.82 | 740.82<br>(740.33) | 741.20 | D | C | D | C |  |  |  |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                    |        |   |   |   |   |  |  |  |
|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------|---|---|---|---|--|--|--|
|    | (m, 3 H), 2.00 - 2.10 (m, 1 H), 1.36 (d, $J=6.00$ Hz, 6 H), 1.28 (d, $J=6.25$ Hz, 3 H)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                    |        |   |   |   |   |  |  |  |
| 9  | <sup>1</sup> H NMR (400MHz, MeOD) $\delta$ : ppm 8.65 (s, 1 H), 8.38 (s, 1 H), 7.93 (d, $J=2.13$ Hz, 1 H), 7.69 (d, $J=8.38$ Hz, 1 H), 7.48 (d, $J=9.01$ Hz, 1 H), 7.42 (s, 1 H), 7.36 (d, $J=2.13$ Hz, 1 H), 7.25 (dd, $J=8.25$ , 2.25 Hz, 1 H), 7.09 (dd, $J=9.07$ , 2.31 Hz, 1 H), 4.98 - 5.07 (m, 1 H), 4.68 (dt, $J=12.04$ , 6.05 Hz, 1 H), 4.24 - 4.33 (m, 4 H), 3.86 - 3.91 (m, 2 H), 3.74 - 3.84 (m, 2 H), 3.65 - 3.74 (m, 9 H), 3.48 - 3.55 (m, 1 H), 3.41 (br d, $J=12.38$ Hz, 1 H), 3.24 (br s, 1 H), 3.15 (br d, $J=1.63$ Hz, 1 H), 2.92 - 3.03 (m, 2 H), 2.76 - 2.88 (m, 1 H), 2.60 - 2.75 (m, 2 H), 2.01 - 2.11 (m, 2.63 Hz, 1 H), 1.39 (d, $J=6.00$ Hz, 6 H), 1.32 (d, $J=6.38$ Hz, 3 H) | 784.87<br>(784.35) | 785.20 | D | C | D | C |  |  |  |
| 10 | <sup>1</sup> H NMR (400MHz, CDCl <sub>3</sub> ) $\delta$ : 11.00 (s, 1H), 8.71 (s, 1H), 8.16 (s, 1H), 7.76 (d, $J = 8.4$ Hz, 1H), 7.33-7.51 (m, 3H), 7.26 - 7.22 (m, 1H), 7.09 (dd, $J = 8.8$ , 2.0 Hz, 1H), 5.03 (dd, $J = 12.0$ , 5.2 Hz, 1H), 4.71 (dt, $J = 12.0$ , 6.0 Hz, 1H), 4.20-4.48 (m, 4H), 3.86-3.94 (m, 2H), 3.54-3.76 (m, 9H), 3.43 (s, 2H), 2.60-3.02 (m, 8H), 2.16-2.24 (m, 1H), 1.40 (d, $J=6.0$ Hz, 6H), 0.92-1.19 ppm (m, 6H).                                                                                                                                                                                                                                                      | 798.90<br>(798.37) | 799.20 | B | B | B | B |  |  |  |
| 11 | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) $\delta$ : 8.12 (d, $J= 6.8$ Hz, 1H), 7.80 -                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 783.88<br>(783.36) | 784.30 | B | B | D | B |  |  |  |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                    |        |   |   |   |   |  |  |  |  |
|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------|---|---|---|---|--|--|--|--|
|    | 7.74 (m, 2H), 7.62 (dd, $J=8.4, 12.4$ Hz, 2H), 7.47 (d, $J=1.6$ Hz, 1H), 7.26 (s, 1H), 7.21 - 7.18 (m, 2H), 5.04 (dd, $J=5.6, 12.8$ Hz, 1H), 4.77 - 4.71 (m, 1H), 4.46 (d, $J=14.8$ Hz, 2H), 4.28 (s, 2H), 3.90 (s, 5H), 3.75 (s, 4H), 3.72 (d, $J=3.6$ Hz, 7H), 3.58 - 3.48 (m, 2H), 2.86 - 2.58 (m, 4H), 2.06 - 2.03 (m, 1H), 1.55 (s, 3H), 1.38 (d, $J=6.0$ Hz, 6H).                                                                                                                                                                                                  |                    |        |   |   |   |   |  |  |  |  |
| 12 | <sup>1</sup> H NMR (400MHz, MeOD) $\delta$ : 8.24 (d, $J=4.0$ Hz, 1 H), 7.64 (d, $J=8.2$ Hz, 1 H), 7.54 (d, $J=2.0$ Hz, 1 H), 7.49 (d, $J=8.0$ Hz, 1 H), 7.30 (d, $J=2.0$ Hz, 2 H), 7.26 (d, $J=5.2$ Hz, 1 H), 7.20 (dd, $J=8.0, 2.2$ Hz, 1 H), 7.14 (dd, $J=12.0, 2.0$ Hz, 1 H), 4.98 - 5.08 (m, 1 H), 4.76 - 4.79 (m, 1 H), 4.13 - 4.29 (m, 4 H), 3.75 - 3.92 (m, 4 H), 3.64 - 3.73 (m, 8 H), 3.37 - 3.61 (m, 3 H), 3.03 - 3.25 (m, 3 H), 2.56 - 2.86 (m, 3 H), 1.96 - 2.05 (m, 1 H), 1.59 (s, 3 H), 1.34 - 1.40 (m, 3 H), 1.00 - 1.06 (m, 2 H), 0.77 - 0.82 (m, 2 H). | 795.89<br>(795.36) | 796.20 | A | A | A | A |  |  |  |  |
| 13 | <sup>1</sup> H NMR (400MHz, MeOD) $\delta$ : 8.66 (s, 1 H), 8.11 (d, $J=2.00$ Hz, 1 H), 7.76 (t, $J=8.80$ Hz, 1 H), 7.51 - 7.40 (m, 2 H), 7.10 (dd, $J=9.20, 2.40$ Hz, 1 H), 6.87 - 6.75 (m, 2 H), 4.74 (dd, $J=12.80, 5.60$ Hz, 1 H), 4.27 (t, $J=11.60$ Hz, 2 H), 4.20 - 4.15 (m, 2 H), 3.89 - 3.82 (m, 2 H), 3.80 - 3.71 (m, 2 H), 3.70 -                                                                                                                                                                                                                             | 788.88<br>(788.37) | 789.30 | B | C | B | C |  |  |  |  |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                 |        |   |   |   |   |  |  |  |
|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|--------|---|---|---|---|--|--|--|
|    | 3.62 (m, 8 H), 3.55 - 3.46 (m, 1 H), 3.42-3.36 (m, 1 H), 3.29 - 3.23 (m, 2 H), 3.18 - 3.05 (m, 1 H), 2.01 - 3.86 (m, 2 H), 2.83 - 2.61 (m, 2 H), 2.30 - 2.19 (m, 1 H), 2.16 - 2.02 (m, 1 H), 1.60 (s, 3 H), 1.30 (d, $J=6.40$ Hz, 3 H), 106 - 0.99 (m, 2 H), 0.81 - 0.75 (m, 2 H).                                                                                                                                                                                                                                                                                    |                 |        |   |   |   |   |  |  |  |
| 14 | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) $\delta$ : 8.50 (s, 1H), 8.22 (d, $J = 5.2$ Hz, 1H), 7.65 (d, $J = 8.4$ Hz, 1H), 7.52 (d, $J = 7.6$ Hz, 1H), 7.37 - 7.29 (m, 2H), 7.26 (s, 1H), 7.22 (d, $J = 5.6$ Hz, 2H), 5.04 (ddd, $J = 1.6, 5.6, 12.8$ Hz, 1H), 4.66 - 4.59 (m, 2H), 4.24 (d, $J = 4.4$ Hz, 2H), 4.12 (d, $J = 10.4$ Hz, 2H), 3.89 - 3.84 (m, 2H), 3.80 - 3.66 (m, 7H), 3.65 (s, 4H), 3.06 (s, 2H), 2.91 (d, $J=6.0$ Hz, 2H), 2.84 - 2.51 (m, 4H), 2.05 (dtd, $J = 2.8, 5.6, 12.8$ Hz, 1H), 1.38 (d, $J = 6.0$ Hz, 6H), 1.29 (d, $J=2.4$ Hz, 3H) | 801.87 (801.35) | 802.20 | D | B | D | A |  |  |  |
| 15 | <sup>1</sup> H NMR (400MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ : 13.50 (br s, 1H), 11.12 (br s, 1H), 8.64 (s, 1H), 8.20 (s, 1H), 8.14 (d, $J = 8.0$ Hz, 1H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.45 - 7.43 (m, 2H), 7.37 - 7.34 (m, 2H), 5.13 - 5.10 (m, 1H), 4.59 - 4.56 (m, 1H), 4.29 (br s, 2H), 4.07 (br s, 2H), 3.78 (br s, 2H), 3.58 - 3.51 (m, 14H), 2.92 - 2.81 (m, 5H), 2.05 (br s, 1H), 1.34 (d, $J = 4.0$ Hz, 6H), 1.05 (d, $J = 8.0$ Hz, 3H)                                                                                                                | 802.86 (802.35) | 803.20 | D | C | D | C |  |  |  |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                    |        |   |   |   |   |  |  |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------|---|---|---|---|--|--|
| 16 | <sup>1</sup> H NMR (400MHz, CDCl <sub>3</sub> ) δ: 11.54 (s, 1 H), 10.71 - 11.03 (m, 1 H), 8.70 (s, 1 H), 8.33 (d, <i>J</i> =2.0 Hz, 1 H), 7.79 (d, <i>J</i> =8.4 Hz, 1 H), 7.39 - 7.50 (m, 3 H), 7.26 (d, <i>J</i> =2.0 Hz, 1 H), 7.15 (dd, <i>J</i> =8.0, 2.2 Hz, 1 H), 4.93 - 5.11 (m, 1 H), 4.19 - 4.34 (m, 4 H), 3.90-3.95 (m, 2 H), 3.72 - 3.77 (m, 2 H), 3.65 - 3.71 (m, 4 H), 3.57 - 3.62 (m, 2 H), 3.47-3.52 (m, 2 H), 3.13 - 3.29 (m, 1 H), 2.79 - 3.04 (m, 6 H), 2.28 - 2.43 (m, 3 H), 2.17 - 2.25 (m, 1 H), 1.41 (s, 9 H), 0.98-0.95 (m, 3 H). | 798.90<br>(798.37) | 799.20 | D | C | D | C |  |  |
| 17 | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ: 8.63 (s, 1 H), 8.08 (s, 1 H), 7.68 (d, <i>J</i> =8.0 Hz, 1 H), 7.28 - 7.48 (m, 3 H), 7.03 - 7.25 (m, 2 H), 5.06 (dd, <i>J</i> =12.0, 8.0 Hz, 1 H), 4.26 - 4.41 (m, 2 H), 4.15 - 4.22 (m, 2 H), 4.00 (d, <i>J</i> =4.0 Hz, 1 H), 3.77 - 3.92 (m, 2 H), 3.55 - 3.74 (m, 12 H), 3.03 - 3.14 (m, 1 H), 2.61 - 2.87 (m, 4 H), 2.05 - 2.14 (m, 1 H), 1.74 - 1.87 (m, 2 H), 1.60 (s, 3 H), 0.96 - 1.05 (m, 2 H), 0.73 - 0.81 (m, 2 H).                                                                         | 783.84<br>(783.32) | 784.2  | C | A | B | A |  |  |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                    |        |   |   |   |   |   |   |
|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------|---|---|---|---|---|---|
| 18 | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ: 8.63 (s, 1 H), 8.08 (s, 1 H), 7.68 (d, J=8.0 Hz, 1 H), 7.28 - 7.48 (m, 3 H), 7.03 - 7.25 (m, 2 H), 5.06 (dd, J=12.0, 8.0 Hz, 1 H), 4.26 - 4.41 (m, 2 H), 4.15 - 4.22 (m, 2 H), 4.00 (d, J=4.0 Hz, 1 H), 3.77 - 3.92 (m, 2 H), 3.55 - 3.74 (m, 12 H), 3.03 - 3.14 (m, 1 H), 2.61 - 2.87 (m, 4 H), 2.05 - 2.14 (m, 1 H), 1.74 - 1.87 (m, 2 H), 1.60 (s, 3 H), 0.96 - 1.05 (m, 2 H), 0.73 - 0.81 (m, 2 H).                                   | 783.84<br>(783.32) | 784.20 | A | A | A | A | A | A |
| 19 | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ: 8.61 (s, 1H), 8.08 (s, 1H), 7.62 (d, J=8.4 Hz, 1H), 7.45 (d, J=9.0 Hz, 1H), 7.37 (s, 1H), 7.28 (d, J=2.1 Hz, 1H), 7.21 (dd, J=2.1, 8.3 Hz, 1H), 7.08 (dd, J=2.2, 9.1 Hz, 1H), 4.31 - 4.15 (m, 4H), 3.89 - 3.80 (m, 2H), 3.73 - 3.61 (m, 10H), 3.43 - 3.34 (m, 1H), 3.24 - 3.02 (m, 3H), 2.86 - 2.53 (m, 6H), 2.07 - 1.99 (m, 1H), 1.95 (d, J=1.4 Hz, 3H), 1.60 (s, 3H), 1.22 (d, J=6.3 Hz, 3H), 1.04 - 0.99 (m, 2H), 0.82 - 0.74 (m, 2H). | 810.91<br>(810.37) | 811.20 | B | C | D | C | C | C |
| 20 | <sup>1</sup> H NMR (400MHz, CHLOROFORM- <i>d</i> ) δ: 8.72 (s, 1H), 8.28 (br s, 1H), 7.67 (d, J=8.4 Hz, 1H), 7.42 - 7.32 (m, 2H), 7.28 (br s, 1H), 7.13 (dd, J=2.4, 9.2 Hz, 1H), 7.06 - 6.99 (m, 1H), 5.00 - 4.91 (m, 1H), 4.29 - 4.11 (m, 2H), 3.64 - 3.55 (m, 4H), 3.49 (br s, 4H), 3.30 (br s, 1H), 3.03 - 2.86                                                                                                                                                                           | 776.90<br>(776.38) | 777.37 | A | B | A | B | B | B |



|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                    |        |   |   |   |   |  |  |  |  |  |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------|---|---|---|---|--|--|--|--|--|
|    | (m, 5H), 2.69 (br s, 6H), 2.61 - 2.43 (m, 3H), 2.15 (br d, J=5.2 Hz, 1H), 1.63 (s, 4H), 1.26 (s, 2H), 1.11 - 1.04 (m, 5H), 0.82 - 0.73 (m, 2H)                                                                                                                                                                                                                                                                                                                                                                          |                    |        |   |   |   |   |  |  |  |  |  |
| 21 | <sup>1</sup> H NMR (400MHz, MeOD) δ: 8.60 (s, 1 H), 8.07 (d, J=2.40 Hz, 1 H), 7.37 - 7.54 (m, 3 H), 7.21 (d, J=2.00 Hz, 1 H), 7.04 (m, 2 H), 5.01 (m, 1 H), 4.38 (d, J=9.60 Hz, 2 H), 3.62 (dd, J=9.60 Hz, 5.60 Hz, 4 H), 3.32 - 3.37 (m, 4 H), 3.06 - 3.17 (m, 2 H), 3.01 (s, 2 H), 2.68 - 2.87 (m, 5 H), 2.62 (m, 6 H), 2.06 - 2.16 (m, 1 H), 1.59 (s, 3 H), 1.25 (d, J=6.00 Hz, 6 H), 1.01 (s, 2 H), 0.72 - 0.82 (m, 2 H).                                                                                           | 790.93<br>(790.39) | 791.38 | A | B | A | A |  |  |  |  |  |
| 22 | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ: 13.38 (s, 1H), 11.07 (s, 1H), 8.63 (s, 1H), 8.27 (s, 1H), 7.96 (d, J=6.4 Hz, 1H), 7.64 (d, J=8.8 Hz, 1H), 7.50 (d, J=8.8 Hz, 1H), 7.38 (s, 1H), 7.32 (s, 1H), 7.22 (d, J=8.8 Hz, 1H), 7.05 (dd, J=2.4, 8.8 Hz, 1H), 5.06 (dd, J=5.2, 13.2 Hz, 1H), 4.64 - 4.55 (m, 1H), 4.07 (s, 2H), 3.60 - 3.50 (m, 4H), 2.99 - 2.81 (m, 9H), 2.73 (s, 2H), 2.56 (d, J=4.4 Hz, 8H), 2.01 (d, J=10.4 Hz, 1H), 2.05 - 1.95 (m, 1H), 1.30 (d, J=6.0 Hz, 6H), 1.07 (d, J=6.0 Hz, 3H) | 764.89<br>(764.38) | 765.40 | B | C | B | C |  |  |  |  |  |
| 23 | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ: 13.40 (br s, 1H), 11.09 (s, 1H), 8.64 (s, 1H), 8.16 (s, 2H), 7.97 (s, 1H), 7.68 (d, J=8.5 Hz, 1H), 7.50                                                                                                                                                                                                                                                                                                                                                            | 748.89<br>(748.38) | 749.50 | A | B | A | B |  |  |  |  |  |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                    |        |   |   |   |   |   |   |   |  |
|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------|---|---|---|---|---|---|---|--|
| 24 | (d, $J=8.9$ Hz, 1H), 7.36 (br d, $J=18.0$ Hz, 2H), 7.26 (br d, $J=8.6$ Hz, 1H), 7.05 (dd, $J=2.1$ , 9.1 Hz, 1H), 5.07 (br dd, $J=5.4$ , 12.9 Hz, 1H), 4.60 (td, $J=5.9$ , 12.0 Hz, 1H), 4.07 (br s, 2H), 3.55 - 3.44 (m, 8H), 3.05 - 2.81 (m, 5H), 2.75 - 2.64 (m, 2H), 2.35 - 2.18 (m, 3H), 2.06 - 1.98 (m, 1H), 1.46 (br s, 4H), 1.30 (d, $J=6.0$ Hz, 8H), 1.06 (br d, $J=6.0$ Hz, 3H)                                                                                                                                                | 814.99<br>(814.43) | 815.42 | A | A | A | A | A | B | A |  |
| 25 | <sup>1</sup> H NMR (400MHz, MeOD) $\delta$ : 8.62 (s, 1 H), 8.38 (s, 1 H), 8.10 (d, $J=2.00$ Hz, 1 H), 7.66 (d, $J=8.40$ Hz, 1 H), 7.47 (d, $J=8.80$ Hz, 1 H), 7.40 (s, 1 H), 7.10 (dd, $J=8.80$ , 2.00 Hz, 1 H), 6.84 (dd, $J=8.40$ , 2.00 Hz, 1 H), 5.06 (dd, $J=12.40$ , 5.20 Hz, 1 H), 4.09 (s, 2 H), 3.59 (s, 3 H), 3.46 (s, 2 H), 3.21 (s, 5 H), 3.01-2.98 (m, 3 H), 2.54 - 2.90 (m, 5 H), 2.36 (s, 3 H), 2.25-1.75 (m, 8 H), 1.61 (s, 3 H), 1.45 (s, 2 H), 1.15 (d, $J=6.00$ Hz, 3 H), 1.04-0.97 (m, 2 H), 0.73 - 0.82 (m, 2 H). | 802.98<br>(802.43) | 803.30 | A | A | A | A | A | A |   |  |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                    |        |   |   |   |   |  |  |  |
|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------|---|---|---|---|--|--|--|
|    | - 3.02 (m, 8H), 2.94 - 2.64 (m, 7H), 2.35 - 2.18 (m, 2H), 2.14 - 1.96 (m, 5H), 1.93 - 1.85 (m, 2H), 1.80 - 1.68 (m, 1H), 1.60 (s, 3H), 1.27 (d, J=6.4 Hz, 3H), 1.04 - 0.97 (m, 2H), 0.80 - 0.75 (m, 2H)                                                                                                                                                                                                                                                                                                                                                                                |                    |        |   |   |   |   |  |  |  |
| 26 | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ: 8.64 (s, 1H), 8.37 (s, 1H), 7.92 (d, J=1.6 Hz, 1H), 7.61 (d, J=8.4 Hz, 1H), 7.50 - 7.37 (m, 2H), 7.08 (d, J=9.2 Hz, 1H), 6.94 (d, J=1.2 Hz, 1H), 6.78 (br d, J=8.8 Hz, 1H), 5.05 (dd, J=5.6, 12.4 Hz, 1H), 4.65 (td, J=6.4, 12.0 Hz, 1H), 4.14 (d, J=12.4 Hz, 2H), 3.63 - 3.48 (m, 3H), 3.43 - 3.36 (m, 1H), 3.25 - 3.10 (m, 3H), 3.10 - 2.94 (m, 8H), 2.93 - 2.78 (m, 7H), 2.76 - 2.65 (m, 4H), 2.42 - 2.31 (m, 1H), 2.25 (d, J=6.4 Hz, 1H), 2.15 - 2.04 (m, 1H), 1.88 - 1.68 (m, 3H), 1.36 (d, J=6.4 Hz, 6H), 1.26 - 1.20 (m, 3H) | 818.00<br>(817.44) | 818.30 | B | A | B | A |  |  |  |
| 27 | <sup>1</sup> H NMR (400MHz, CDCl <sub>3</sub> ) δ: 8.74 (br s, 1 H), 8.41 (br s, 1 H), 8.08 (br s, 1 H), 7.70 (d, J=8.4 Hz, 1 H), 7.35 - 7.50 (m, 2 H), 7.34 (s, 1 H), 7.28 (d, J=2.4 Hz, 2 H), 7.10 (dd, J=9.2, 2.4 Hz, 1 H), 7.04 - 7.08 (m, 1 H), 4.95 (dd, J=12.4, 5.6 Hz, 1 H), 4.71 (dt, J=12.0, 6.4 Hz, 1 H), 3.76 (br s, 4 H), 3.48 (br d, J=12.0 Hz, 2 H), 3.40 (br d, J=5.2 Hz, 4 H), 2.70 - 3.00 (m, 8 H), 2.62 (br s, 4 H), 2.57 (br d, J=5.2 Hz, 4 H), 2.50 (br t, J=11.6 Hz, 2 H), 2.29 (d, J=6.8 Hz, 2 H),                                                              | 803.97<br>(803.42) | 804.30 | A | A | A | A |  |  |  |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                    |        |   |   |   |   |   |   |  |  |  |  |  |  |  |  |  |  |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------|---|---|---|---|---|---|--|--|--|--|--|--|--|--|--|--|
|    | 2.13 (br d, $J=5.2$ Hz, 1 H), 1.90 (br s, 2 H), 1.48 - 1.53 (m, 2 H), 1.40 (d, $J=6.2$ Hz, 6 H)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                    |        |   |   |   |   |   |   |  |  |  |  |  |  |  |  |  |  |
| 28 | <sup>1</sup> H NMR (400MHz, CDCl <sub>3</sub> ) $\delta$ : 8.73 (br s, 1 H), 8.48 (br s, 1 H), 8.24 (br s, 1 H), 7.70 (d, $J=8.4$ Hz, 1 H), 7.36 - 7.50 (m, 2 H), 7.30 - 7.35 (m, 2 H), 7.28 (br d, $J=2.4$ Hz, 1 H), 7.14 (dd, $J=9.2, 2.0$ Hz, 1 H), 7.05 (dd, $J=8.8, 2.4$ Hz, 1 H), 4.95 (dd, $J=12.4, 5.6$ Hz, 1 H), 3.75 (br s, 4 H), 3.47 (br d, $J=12.0$ Hz, 2 H), 3.39 - 3.44 (m, 4 H), 2.83 - 3.00 (m, 4 H), 2.71 - 2.82 (m, 4 H), 2.60 - 2.65 (m, 4 H), 2.55 - 2.59 (m, 4 H), 2.49 (br t, $J=11.2$ Hz, 3 H), 2.29 (br d, $J=6.8$ Hz, 2 H), 2.14 (br dd, $J=7.8, 5.2$ Hz, 1 H), 1.63 (s, 3 H), 1.58 (br d, $J=11.2$ Hz, 3 H), 1.05 - 1.11 (m, 2 H), 0.76 - 0.81 (m, 2 H) | 815.98<br>(815.42) | 816.30 | A | A | A | A | A | A |  |  |  |  |  |  |  |  |  |  |
| 29 | <sup>1</sup> H NMR (400MHz, METHANOL-d <sub>4</sub> ) $\delta$ : 8.63 (d, $J=0.9$ Hz, 1H), 8.45 (br s, 1H), 8.11 (d, $J=2.1$ Hz, 1H), 7.69 (d, $J=8.5$ Hz, 1H), 7.47 (d, $J=9.0$ Hz, 1H), 7.42 (s, 1H), 7.37 (d, $J=2.3$ Hz, 1H), 7.24 (dd, $J=2.3, 8.6$ Hz, 1H), 7.10 (dd, $J=2.3, 9.1$ Hz, 1H), 5.07 (dd, $J=5.5, 12.5$ Hz, 1H), 4.03 (br d, $J=11.3$ Hz, 2H), 3.61 (br t, $J=12.0$ Hz, 3H), 3.50 - 3.44 (m, 4H), 3.36 (br d, $J=7.4$ Hz, 1H), 3.27 - 3.11 (m, 3H), 3.07 - 2.98 (m, 3H), 2.91 - 2.81 (m, 1H), 2.79 - 2.67 (m, 4H), 2.65 - 2.60 (m, 4H), 2.50 (br                                                                                                                 | 830.01<br>(829.44) | 830.30 | A | A | A | A | A | A |  |  |  |  |  |  |  |  |  |  |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                    |        |   |   |   |   |  |  |  |  |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------|---|---|---|---|--|--|--|--|
|    | t, J=8.5 Hz, 1H), 2.35 (d, J=7.3 Hz, 2H), 2.15 - 2.04 (m, 3H), 1.94 (br d, J=4.3 Hz, 1H), 1.61 (s, 3H), 1.52 (br d, J=13.9 Hz, 2H), 1.20 (d, J=6.3 Hz, 3H), 1.05 - 0.99 (m, 2H), 0.80 - 0.76 (m, 2H)                                                                                                                                                                                                                                                                                                                                                 |                    |        |   |   |   |   |  |  |  |  |
| 30 | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) □: 13.42 (br s, 1H), 11.10 (s, 1H), 8.64 (s, 1H), 7.98 (s, 1H), 7.68 (d, J=8.5 Hz, 1H), 7.51 (d, J=8.9 Hz, 1H), 7.39 (s, 1H), 7.34 (s, 1H), 7.25 (br d, J=8.6 Hz, 1H), 7.06 (dd, J=2.3, 8.9 Hz, 1H), 5.07 (dd, J=5.3, 12.9 Hz, 1H), 4.60 (td, J=6.0, 11.9 Hz, 1H), 4.04 (br s, 2H), 2.97 (br d, J=4.1 Hz, 3H), 2.94 - 2.79 (m, 6H), 2.44 - 2.36 (m, 11H), 2.23 - 1.93 (m, 5H), 1.71 (br d, J=10.9 Hz, 2H), 1.55 (br s, 1H), 1.31 (d, J=6.0 Hz, 6H), 1.29 - 1.09 (m, 4H), 1.07 (br d, J=6.1 Hz, 3H) | 818.00<br>(817.44) | 818.40 | A | A | A | A |  |  |  |  |
| 31 | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ: 8.63 (d, J=0.9 Hz, 1H), 8.37 (br s, 1H), 7.93 (d, J=2.1 Hz, 1H), 7.64 (d, J=8.6 Hz, 1H), 7.50 - 7.41 (m, 2H), 7.12 - 7.05 (m, 3H), 5.10 (dd, J=5.1, 13.4 Hz, 1H), 4.66 (td, J=6.1, 12.1 Hz, 2H), 4.46 - 4.33 (m, 2H), 4.03 (br d, J=12.5 Hz, 2H), 3.67 - 3.56 (m, 3H), 3.37 (br d, J=6.0 Hz, 4H), 3.30 - 3.15 (m, 3H), 3.10 - 2.98 (m, 3H), 2.96 - 2.84 (m, 1H), 2.82 - 2.68 (m, 3H), 2.67 - 2.61 (m, 4H), 2.56 - 2.33 (m, 4H), 2.20 - 1.90 (m, 4H), 1.61                                         | 804.01<br>(803.46) | 804.40 | B | A | A | A |  |  |  |  |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                    |        |   |   |   |   |  |  |  |
|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------|---|---|---|---|--|--|--|
|    | - 1.45 (m, 2H), 1.37 (d, J=6.0 Hz, 6H), 1.20 (d, J=6.3 Hz, 3H)                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                    |        |   |   |   |   |  |  |  |
| 32 | <sup>1</sup> H NMR (400MHz, MeOD) δ: 8.72 (s, 1H), 7.84 (d, J=8.4 Hz, 1H), 7.69 - 7.55 (m, 2H), 7.49 (s, 2H), 7.39 (dd, J=2.1, 8.4 Hz, 1H), 7.25 (dd, J=1.9, 9.1 Hz, 1H), 5.09 (dd, J=5.4, 12.6 Hz, 1H), 4.81 - 4.76 (m, 1H), 4.62 (s, 4H), 4.39 - 4.33 (m, 2H), 4.24 (s, 3H), 4.03 - 3.92 (m, 2H), 3.90-3.71 (m, 2H), 3.69 - 3.46 (m, 4H), 3.29 - 3.16 (m, 3H), 2.90 - 2.63 (m, 3H), 2.17 - 2.06 (m, 1H), 1.55 - 1.41 (m, 3H), 1.38 (d, J=6.0 Hz, 6H)                                                              | 751.85<br>(751.34) | 752.40 | D | C | D | C |  |  |  |
| 33 | <sup>1</sup> H NMR (400MHz, METHANOL- <i>d</i> 4) δ: 8.65 (s, 1H), 8.10 (d, J=2.0 Hz, 1H), 7.61 (d, J=8.4 Hz, 1H), 7.47 - 7.41 (m, 2H), 7.11 - 7.06 (m, 1H), 6.92 (s, 1H), 6.76 (br d, J=7.2 Hz, 1H), 5.10 - 5.00 (m, 1H), 4.27 (br t, J=12.0 Hz, 2H), 3.73 (br d, J=4.4 Hz, 3H), 3.61 - 3.36 (m, 5H), 3.24 - 3.02 (m, 8H), 2.94 - 2.64 (m, 7H), 2.35 - 2.18 (m, 2H), 2.14 - 1.96 (m, 5H), 1.93 - 1.85 (m, 2H), 1.80 - 1.68 (m, 1H), 1.60 (s, 3H), 1.27 (d, J=6.4 Hz, 3H), 1.04 - 0.97 (m, 2H), 0.80 - 0.75 (m, 2H) | 845.02<br>(844.44) | 845.43 | A | A | B | A |  |  |  |
| 34 | <sup>1</sup> H NMR (400MHz, METHANOL- <i>d</i> 4) δ: 8.64 (s, 1H), 8.30 (s, 1H), 7.90 (d, J=2.1 Hz, 1H), 7.57 (d, J=8.4 Hz, 1H), 7.47 - 7.41 (m, 2H), 7.27 (d, J=2.1 Hz, 1H), 7.09 (ddd, J=2.3, 8.8, 17.7                                                                                                                                                                                                                                                                                                           | 802.94<br>(802.39) | 803.30 | D | B | C | A |  |  |  |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                    |        |   |   |   |   |  |  |
|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------|---|---|---|---|--|--|
|    | Hz, 2H), 5.03 (dd, J=3.3, 5.3, 12.4 Hz, 1H), 4.68 (br s, 1H), 4.34 - 4.24 (m, 2H), 3.73 (br t, J=5.3 Hz, 2H), 3.59 (t, J=6.2 Hz, 2H), 3.48 - 3.37 (m, 6H), 3.22 - 3.11 (m, 3H), 2.99 (br d, J=4.0 Hz, 2H), 2.95 - 2.72 (m, 4H), 2.72 - 2.62 (m, 6H), 2.51 (br t, J=6.2 Hz, 2H), 2.12 - 2.02 (m, 1H), 1.36 (d, J=6.1 Hz, 6H), 1.27 (d, J=6.3 Hz, 3H)                                                                                                                                                                                                                                                                                                                 |                    |        |   |   |   |   |  |  |
| 35 | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ: 13.36 (br s, 1H), 11.08 (br s, 1H), 8.59 (s, 1H), 8.17 (s, 2H), 7.92 (d, J=2.3 Hz, 1H), 7.79 (d, J=8.4 Hz, 1H), 7.46 (d, J=9.0 Hz, 1H), 7.37 (d, J=2.0 Hz, 1H), 7.34 (s, 1H), 7.29 (dd, J=2.1, 8.3 Hz, 1H), 7.01 (dd, J=2.3, 8.9 Hz, 1H), 5.07 (dd, J=5.3, 12.8 Hz, 1H), 4.55 (td, J=6.0, 12.0 Hz, 1H), 4.08 (br t, J=4.9 Hz, 2H), 3.97 (br s, 2H), 3.25 (s, 8H), 2.98 - 2.88 (m, 2H), 2.83 (br d, J=11.9 Hz, 2H), 2.70 (br s, 2H), 2.63 (br d, J=1.8 Hz, 1H), 2.60 - 2.51 (m, 4H), 2.41 - 2.37 (m, 1H), 2.31 - 2.15 (m, 2H), 2.01 (br dd, J=5.4, 10.9 Hz, 1H), 1.26 (d, J=6.0 Hz, 6H), 0.99 (d, J=6.1 Hz, 3H) | 776.90<br>(776.38) | 777.40 | C | C | C | C |  |  |
| 36 | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ: 8.62 (d, J=2.0 Hz, 1 H), 7.91 (d, J=2.0 Hz, 1 H), 7.64 (d, J=8.0 Hz, 1 H), 7.41 - 7.47 (m, 2 H), 7.33 (d, J=4.0 Hz, 1 H), 7.17 (dd, J=8.0, 2.0 Hz, 1 H), 7.07 (dd, J=8.0, 2.0 Hz, 1 H), 5.06 (dd, J=12.0, 4.0 Hz,                                                                                                                                                                                                                                                                                                                                                                                                | 791.96<br>(791.42) | 792.30 | B | A | B | A |  |  |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                    |        |   |   |   |   |  |  |  |  |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------|---|---|---|---|--|--|--|--|
|    | 1 H), 4.53 - 4.71 (m, 1 H), 4.12 - 4.25 (m, 2 H), 3.39 - 3.48 (m, 5 H), 2.92 - 3.18 (m, 3 H), 2.69 - 2.90 (m, 3 H), 2.41 - 2.68 (m, 13 H), 2.32 (s, 3 H), 2.07 - 2.15 (m, 1 H), 1.72 - 1.82 (m, 2 H), 1.36 (d, J=8.0 Hz, 6 H), 1.19 (d, J=8.0 Hz, 3 H).                                                                                                                                                                                                                                                                                  |                    |        |   |   |   |   |  |  |  |  |
| 37 | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ:<br>8.62 (d, J=1.0 Hz, 1 H), 7.91 (d, J=2.0 Hz, 1 H), 7.66 (d, J=8.0 Hz, 1 H), 7.47 (d, J=8.0 Hz, 1 H), 7.41 (s, 1 H), 7.37 (d, J=2.0 Hz, 1 H), 7.24 (dd, J=8.0, 2.0 Hz, 1 H), 7.09 (dd, J=8.0, 2.0 Hz, 1 H), 5.04 (dd, J=12.0, 4.0 Hz, 1 H), 4.67 (t, J=12.0, 4.0 Hz, 1 H), 4.00 (d, J=12.0 Hz, 2 H), 3.64 - 3.73 (m, 1 H), 3.41 - 3.57 (m, 9 H), 3.08 - 3.25 (m, 2 H), 2.98 (s, 3 H), 2.61 - 2.91 (m, 12 H), 2.01 - 2.10 (m, 1 H), 1.37 (d, J=4.0 Hz, 6 H), 1.23 (d, J=6.0 Hz, 3 H). | 777.93<br>(777.41) | 778.40 | C | B | D | B |  |  |  |  |
| 38 | <sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD) δ:<br>8.63 (s, 1 H), 7.92 (s, 1 H), 7.67 (d, J=8.00 Hz, 1 H), 7.47 (d, J=9.01 Hz, 1 H), 7.42 (s, 1 H), 7.36 (s, 1 H), 7.23 (d, J=8.00 Hz, 1 H), 7.05 - 7.13 (m, 1 H), 5.06 (dd, J=12.00, 4.00 Hz, 1 H), 4.66 (t, J=12.00, 4.00 Hz, 1 H), 4.11 (d, J=11.51 Hz, 2 H), 3.41 - 3.53 (m, 5 H), 3.15 - 3.26 (m, 6 H), 3.04 (d, J=12.00 Hz, 1 H), 2.81 - 2.94 (m, 5 H), 2.64 - 2.78 (m, 7 H), 2.58 (t, J=6.38 Hz, 2 H), 2.42 - 2.52 (m, 2                                                       | 805.99<br>(805.44) | 806.40 | D | A | C | A |  |  |  |  |



|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                    |       |   |   |   |   |  |  |  |
|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-------|---|---|---|---|--|--|--|
| 39 | <p>H), 2.03 - 2.14 (m, 1 H), 1.95 (s, 3 H), 1.37 (d, <math>J=4.00</math> Hz, 6 H), 1.19 (d, <math>J=4.00</math> Hz, 3 H).</p> <p><sup>1</sup>H NMR: (400MHz, MeOD-d<sub>4</sub>) <math>\delta</math>: 8.76 (s, 1H), 7.74 (d, <math>J=8.5</math> Hz, 1H), 7.64 - 7.61 (m, 2H), 7.66 (s, 1H), 7.52 (s, 1H), 7.49 (d, <math>J=2.0</math> Hz, 1H), 7.37 (dd, <math>J=2.1, 8.5</math> Hz, 1H), 7.26 (dd, <math>J=2.0, 9.1</math> Hz, 1H), 5.09 (dd, <math>J=5.6, 12.6</math> Hz, 1H), 4.85 - 4.82 (m, 1H), 4.68 (br d, <math>J=12.1</math> Hz, 1H), 4.44 (br s, 1H), 4.38 - 4.23 (m, 1H), 4.08 (br d, <math>J=13.1</math> Hz, 2H), 3.68 (br s, 4H), 3.57 (br s, 4H), 3.24 - 3.12 (m, 6H), 2.92 - 2.83 (m, 2H), 2.76 (br d, <math>J=2.6</math> Hz, 1H), 2.74 - 2.65 (m, 2H), 2.30 (br d, <math>J=15.4</math> Hz, 1H), 2.15 - 2.07 (m, 2H), 2.03 (br d, <math>J=12.5</math> Hz, 2H), 1.62 - 1.43 (m, 4H), 1.38 (d, <math>J=6.0</math> Hz, 8H)</p> | 803.97<br>(803.42) | 804.6 | B | A | A | A |  |  |  |
| 40 | <p><sup>1</sup>H NMR: (400MHz, DMSO-d<sub>6</sub>) <math>\delta</math>: 13.41 (br s, 1H), 11.08 (s, 1H), 8.66 (d, <math>J=1.0</math> Hz, 1H), 8.16 (s, 1H), 7.98 (d, <math>J=2.1</math> Hz, 1H), 7.65 (d, <math>J=8.6</math> Hz, 1H), 7.51 (d, <math>J=9.0</math> Hz, 1H), 7.39 (s, 1H), 7.31 (d, <math>J=1.9</math> Hz, 1H), 7.23 (dd, <math>J=2.1, 8.7</math> Hz, 1H), 7.06 (dd, <math>J=2.4, 8.9</math> Hz, 1H), 5.07 (dd, <math>J=5.3, 12.9</math> Hz, 1H), 4.66 - 4.56 (m, 1H), 4.04 (br d, <math>J=12.4</math> Hz, 2H), 3.69 (br s, 3H), 3.02 - 2.87 (m, 6H), 2.85 - 2.76 (m, 2H), 2.71 - 2.59 (m, 5H), 2.58 - 2.54 (m, 1H), 2.15 (br d, <math>J=6.5</math> Hz, 2H), 2.01 (br dd, <math>J=5.2, 10.3</math></p>                                                                                                                                                                                                                       | 838.96<br>(838.41) | 839.6 | B | B | B | A |  |  |  |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                    |       |   |   |   |   |   |  |  |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-------|---|---|---|---|---|--|--|
| 41 | <p>Hz, 2H), 1.91 - 1.70 (m, 7H), 1.50 - 1.39 (m, 2H), 1.31 (d, <math>J=6.1</math> Hz, 6H), 1.14 (br d, <math>J=9.8</math> Hz, 2H)</p> <p><math>^1\text{H}</math> NMR: (400MHz, <math>\text{CDCl}_3</math>) <math>\delta</math>: 8.76 (s, 1H), 8.10 (d, <math>J=2.1</math> Hz, 1H), 7.67 (d, <math>J=8.5</math> Hz, 1H), 7.44 - 7.35 (m, 2H), 7.26 (d, <math>J=2.1</math> Hz, 1H), 7.09 (dd, <math>J=2.4</math>, 9.0 Hz, 1H), 7.03 (dd, <math>J=2.1</math>, 8.6 Hz, 1H), 4.95 (dd, <math>J=5.4</math>, 12.3 Hz, 1H), 4.70 (td, <math>J=6.1</math>, 12.1 Hz, 1H), 3.93 (d, <math>J=13.1</math> Hz, 2H), 3.79 (s, 4H), 3.30 - 3.21 (m, 2H), 3.03 - 2.74 (m, 5H), 2.59 (t, <math>J=4.6</math> Hz, 4H), 2.54 (d, <math>J=6.3</math> Hz, 2H), 2.46 (t, <math>J=7.3</math> Hz, 2H), 2.29 (t, <math>J=11.0</math> Hz, 2H), 2.19 - 2.09 (m, 1H), 2.03 - 1.90 (m, 3H), 1.77 (d, <math>J=12.3</math> Hz, 2H), 1.62 - 1.49 (m, 5H), 1.39 (d, <math>J=6.0</math> Hz, 8H).</p> | 802.98<br>(802.43) | 803.4 | B | B | B | B | B |  |  |
| 42 | <p><math>^1\text{H}</math> NMR: 400MHz, CHLOROFORM-d) <math>\delta</math>: 8.76 (s, 1H), 8.40 (s, 1H), 8.09 (d, <math>J=2.1</math> Hz, 1H), 7.67 (d, <math>J=8.5</math> Hz, 1H), 7.42 (d, <math>J=9.0</math> Hz, 1H), 7.37 (s, 1H), 7.25 (d, <math>J=2.3</math> Hz, 1H), 7.10 (dd, <math>J=2.4</math>, 9.0 Hz, 1H), 7.03 (dd, <math>J=2.1</math>, 8.6 Hz, 1H), 4.95 (dd, <math>J=5.3</math>, 12.3 Hz, 1H), 4.71 (quind, <math>J=6.1</math>, 12.1 Hz, 1H), 3.95 (br d, <math>J=13.1</math> Hz, 2H), 3.78 (br s, 4H), 3.65 - 3.41 (m, 1H), 3.41 - 3.14 (m, 3H), 3.02 - 2.69 (m, 8H), 2.66 - 2.55 (m, 4H), 2.54 - 2.39 (m, 3H), 2.25 (br dd, <math>J=5.4</math>, 12.4 Hz, 1H), 2.19 - 2.12 (m, 1H), 2.11 -</p>                                                                                                                                                                                                                                                      | 788.95<br>(788.41) | 789.2 | B | B | B | B | B |  |  |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                    |       |   |   |   |   |   |  |
|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-------|---|---|---|---|---|--|
|    | 1.92 (m, 3H), 1.79 - 1.64 (m, 3H),<br>1.40 (d, J=6.0 Hz, 7H)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                    |       |   |   |   |   |   |  |
| 43 | <sup>1</sup> H NMR: (400MHz,<br>METHANOL-d <sub>4</sub> ) δ: 8.66 (s, 1H),<br>8.22 (s, 1H), 7.92 (d, J=2.1 Hz,<br>1H), 7.67 (d, J=8.6 Hz, 1H), 7.50 -<br>7.42 (m, 2H), 7.36 (d, J=2.1 Hz,<br>1H), 7.24 (dd, J=2.1, 8.6 Hz, 1H),<br>7.09 (dd, J=2.3, 9.0 Hz, 1H), 5.07<br>(dd, J=5.5, 12.5 Hz, 1H), 4.67<br>(quind, J=6.0, 12.1 Hz, 1H), 4.10<br>(br d, J=13.0 Hz, 2H), 3.84 (br s,<br>4H), 3.75 - 3.63 (m, 1H), 3.51 -<br>3.38 (m, 2H), 3.19 - 3.13 (m, 2H),<br>3.04 (br t, J=11.8 Hz, 3H), 2.92 -<br>2.81 (m, 1H), 2.79 - 2.68 (m, 6H),<br>2.60 (br t, J=7.0 Hz, 2H), 2.55 -<br>2.44 (m, 1H), 2.38 - 2.28 (m, 1H),<br>2.16 - 2.04 (m, 2H), 1.93 (br d,<br>J=12.1 Hz, 2H), 1.86 - 1.73 (m,<br>3H), 1.49 - 1.39 (m, 2H), 1.37 (d,<br>J=6.0 Hz, 6H) | 788.95<br>(788.41) | 789.5 | B | B | B | B | A |  |
| 44 | <sup>1</sup> H NMR: (400MHz, MeOD-d <sub>4</sub> ) δ:<br>8.64 (s, 1H), 8.52 (s, 1H), 7.92 (s,<br>1H), 7.67 (d, J=8.5 Hz, 1H), 7.47<br>(d, J=9.0 Hz, 1H), 7.42 (s, 1H),<br>7.35 (d, J=2.3 Hz, 1H), 7.22 (br d,<br>J=8.5 Hz, 1H), 7.08 (dd, J=2.1, 9.0<br>Hz, 1H), 5.06 (dd, J=5.4, 12.4 Hz,<br>1H), 4.66 (td, J=6.1, 12.1 Hz, 2H),<br>4.58 (br s, 3H), 4.20 - 4.04 (m,<br>4H), 3.89 - 3.83 (m, 1H), 3.80 (br<br>s, 4H), 3.00 (br t, J=13.3 Hz, 2H),<br>2.89 - 2.80 (m, 1H), 2.76 (br d,<br>J=2.6 Hz, 1H), 2.73 - 2.67 (m,<br>2H), 2.63 (br s, 4H), 2.10 (br d,                                                                                                                                                                                     | 760.90<br>(760.38) | 761.4 | B | B | B | B | B |  |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                    |       |   |   |   |   |  |  |  |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-------|---|---|---|---|--|--|--|
|    | $J=10.5$ Hz, 1H), 1.89 (br s, 1H), 1.80 (br d, $J=13.0$ Hz, 2H), 1.36 (d, $J=6.0$ Hz, 6H), 1.29 - 1.19 (m, 2H)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                    |       |   |   |   |   |  |  |  |
| 45 | <sup>1</sup> H NMR: (400MHz, MeOD-d <sub>4</sub> ) $\delta$ : 8.64 (s, 1H), 7.93 (d, $J=1.9$ Hz, 1H), 7.69 (d, $J=8.5$ Hz, 1H), 7.47 (d, $J=9.1$ Hz, 1H), 7.42 (s, 1H), 7.37 (d, $J=2.1$ Hz, 1H), 7.24 (dd, $J=2.3$ , 8.6 Hz, 1H), 7.09 (dd, $J=2.3$ , 9.1 Hz, 1H), 5.07 (dd, $J=5.4$ , 12.3 Hz, 1H), 4.66 (td, $J=6.1$ , 12.1 Hz, 2H), 4.60 (br s, 2H), 4.20 - 4.16 (m, 1H), 3.80 (br d, $J=4.3$ Hz, 6H), 3.52 - 3.45 (m, 4H), 3.19 - 3.11 (m, 1H), 2.88 - 2.80 (m, 1H), 2.78 - 2.74 (m, 2H), 2.74 - 2.71 (m, 2H), 2.69 (br d, $J=4.5$ Hz, 1H), 2.64 (br d, $J=4.4$ Hz, 10H), 2.13 - 2.06 (m, 1H), 1.37 (d, $J=6.0$ Hz, 6H) | 775.92<br>(775.39) | 776.4 | D | C | B | C |  |  |  |
| 46 | <sup>1</sup> H NMR: (400MHz, MeOD-d <sub>4</sub> ) $\delta$ : 8.65 (s, 1H), 8.45 (s, 2H), 7.93 (d, $J=2.1$ Hz, 1H), 7.81 - 7.77 (m, 1H), 7.53 - 7.50 (m, 1H), 7.47 (s, 1H), 7.44 (s, 1H), 7.39 (dd, $J=2.4$ , 8.5 Hz, 1H), 7.09 (dd, $J=5.4$ , 12.6 Hz, 1H), 4.67 (td, $J=6.0$ , 12.1 Hz, 1H), 4.07 (br dd, $J=7.5$ , 12.0 Hz, 1H), 3.91 - 3.85 (m, 2H), 3.82 (br s, 7H), 3.77 (br d, $J=3.9$ Hz, 2H), 3.72 (br s, 2H), 3.54 - 3.38 (m, 2H), 3.08 - 3.01 (m, 4H), 2.93 - 2.81 (m, 2H), 2.77 (br d, $J=2.4$ Hz, 1H), 2.73 (br d, $J=6.1$ Hz,                                                                                  | 789.94<br>(789.41) | 790.6 |   |   | A | B |  |  |  |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                    |       |   |   |   |   |  |  |  |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-------|---|---|---|---|--|--|--|
| 47 | <p>2H), 2.68 (br d, <math>J = 5.5</math> Hz, 4H), 2.56 - 2.46 (m, 2H), 2.15 - 2.04 (m, 2H), 1.38 (s, 3H), 1.37 (s, 3H)</p> <p><sup>1</sup>H NMR: (400MHz, CHLOROFORM-d) <math>\delta</math>: 8.77 (s, 1H), 8.11 (d, <math>J=2.3</math> Hz, 1H), 7.68 (d, <math>J=8.5</math> Hz, 1H), 7.41 (d, <math>J=9.0</math> Hz, 1H), 7.38 (d, <math>J=1.5</math> Hz, 1H), 7.28 (br s, 1H), 7.11 (dd, <math>J=2.4</math>, 9.0 Hz, 1H), 7.05 (dd, <math>J=2.3</math>, 8.6 Hz, 1H), 4.96 (dd, <math>J=5.3</math>, 12.1 Hz, 1H), 4.72 (spt, <math>J=6.1</math> Hz, 1H), 4.42 - 4.20 (m, 2H), 4.03 (br d, <math>J=11.6</math> Hz, 1H), 3.96 (br d, <math>J=13.0</math> Hz, 2H), 3.78 (dt, <math>J=3.5</math>, 6.9 Hz, 1H), 3.71 - 3.60 (m, 1H), 3.11 (br t, <math>J=11.3</math> Hz, 1H), 3.03 - 2.91 (m, 3H), 2.91 - 2.76 (m, 4H), 2.70 - 2.51 (m, 9H), 2.33 (br d, <math>J=6.5</math> Hz, 2H), 2.19 - 2.10 (m, 1H), 1.94 - 1.77 (m, 3H), 1.40 (d, <math>J=6.1</math> Hz, 8H)</p> | 790.93<br>(790.39) | 791.3 | B | B | A | B |  |  |  |
| 48 | <p><sup>1</sup>H NMR: (400MHz, METHANOL-d<sub>4</sub>) <math>\delta</math>: 8.67 (d, <math>J=0.9</math> Hz, 1H), 8.39 (s, 1H), 7.94 (d, <math>J=2.1</math> Hz, 1H), 7.67 (d, <math>J=8.5</math> Hz, 1H), 7.50 - 7.43 (m, 2H), 7.35 (d, <math>J=2.1</math> Hz, 1H), 7.22 (dd, <math>J=2.3</math>, 8.7 Hz, 1H), 7.09 (dd, <math>J=2.4</math>, 9.0 Hz, 1H), 5.07 (dd, <math>J=5.4</math>, 12.4 Hz, 1H), 4.67 (td, <math>J=6.0</math>, 12.1 Hz, 1H), 4.46 (br d, <math>J=13.4</math> Hz, 1H), 4.31 (br d, <math>J=11.8</math> Hz, 1H), 4.07 (br d, <math>J=11.0</math> Hz, 3H), 3.87 (br s, 1H), 3.71 (dt, <math>J=2.5</math>, 11.6 Hz, 1H), 3.23 - 3.07 (m, 2H), 3.07 - 2.65 (m,</p>                                                                                                                                                                                                                                                                                 | 790.93<br>(790.39) | 791.3 | A | B | A | B |  |  |  |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                    |       |   |   |   |   |  |  |   |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-------|---|---|---|---|--|--|---|
|    | 15H), 2.56 (br s, 2H), 2.16 - 2.05 (m, 1H), 2.04 - 1.86 (m, 3H), 1.37 (d, J=6.1 Hz, 8H)                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                    |       |   |   |   |   |  |  |   |
| 49 | <sup>1</sup> H NMR: (400MHz, CDCl <sub>3</sub> ) δ:<br>8.77 (s, 1H), 8.41 (s, 1H), 8.11 (d, J=2.0 Hz, 1H), 7.68 (d, J=8.5 Hz, 1H), 7.41 (d, J=8.9 Hz, 1H), 7.35 (s, 1H), 7.10 (dd, J=2.1, 9.0 Hz, 1H), 7.04 (dd, J=2.1, 8.6 Hz, 1H), 4.95 (dd, J=5.3, 12.3 Hz, 1H), 4.72 (t, J=6.0 Hz, 1H), 4.35 (d, J=11.8 Hz, 1H), 4.26 (d, J=12.9 Hz, 1H), 4.04 - 3.90 (m, 3H), 3.70 - 3.54 (m, 2H), 3.12 (t, J=10.9 Hz, 1H), 3.02 - 2.66 (m, 16H), 2.31 (d, J=6.9 Hz, 2H), 2.19 - 2.10 (m, 1H), 1.94 - 1.80 (m, 5H), 1.40 (d, J=6.0 Hz, 6H), 1.35 - 1.25 (m, 2H). | 804.95<br>(804.41) | 805.4 | A | B | A | A |  |  |   |
| 50 | <sup>1</sup> H NMR: (400MHz, CDCl <sub>3</sub> ) δ:<br>8.77 (s, 1H), 8.41 (s, 1H), 8.11 (d, J=2.0 Hz, 1H), 7.68 (d, J=8.5 Hz, 1H), 7.41 (d, J=8.9 Hz, 1H), 7.35 (s, 1H), 7.10 (dd, J=2.1, 9.0 Hz, 1H), 7.04 (dd, J=2.1, 8.6 Hz, 1H), 4.95 (dd, J=5.3, 12.3 Hz, 1H), 4.72 (t, J=6.0 Hz, 1H), 4.35 (d, J=11.8 Hz, 1H), 4.26 (d, J=12.9 Hz, 1H), 4.04 - 3.90 (m, 3H), 3.70 - 3.54 (m, 2H), 3.12 (t, J=10.9 Hz, 1H), 3.02 - 2.66 (m, 16H), 2.31 (d, J=6.9 Hz, 2H), 2.19 - 2.10 (m, 1H), 1.94 - 1.80 (m, 5H), 1.40 (d, J=6.0 Hz, 6H), 1.35 - 1.25 (m, 2H). | 804.95<br>(804.41) | 805.4 | A | A | A | A |  |  |   |
| 51 | <sup>1</sup> H NMR: (400MHz,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 802.98             | 803.4 | R | R | R | R |  |  | R |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |          |  |  |  |  |  |  |  |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|--|--|--|--|--|--|--|--|
| CHLOROFORM-d) $\delta$ : 8.76 (s, 1H), 8.53 (s, 1H), 8.22 (br s, 1H), 8.10 (d, $J=2.3$ Hz, 1H), 7.68 (d, $J=8.6$ Hz, 1H), 7.41 (d, $J=9.0$ Hz, 1H), 7.35 (s, 1H), 7.10 (dd, $J=2.4$ , 9.0 Hz, 1H), 7.04 (dd, $J=2.3$ , 8.7 Hz, 1H), 4.99 - 4.90 (m, 1H), 4.71 (spt, $J=6.1$ Hz, 1H), 3.94 (br d, $J=13.1$ Hz, 2H), 3.76 (br s, 4H), 3.38 (br d, $J=11.3$ Hz, 2H), 3.00 - 2.68 (m, 12H), 2.61 (br t, $J=4.8$ Hz, 4H), 2.40 (br t, $J=10.5$ Hz, 2H), 2.17 - 2.10 (m, 1H), 1.77 (br d, $J=12.8$ Hz, 4H), 1.63 (br d, $J=3.6$ Hz, 1H), 1.40 (d, $J=6.0$ Hz, 6H), 1.31 - 1.18 (m, 4H) | (802.43) |  |  |  |  |  |  |  |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|--|--|--|--|--|--|--|--|

\*DC<sub>50</sub> Ranges: A<10; 10≤B<50; 50≤C<100; D≥100.

**\*\*D<sub>Max</sub> Ranges: A≥70; 50≤B<70; C<50**

**[00293]** A novel bifunctional molecule, which contains a LRRK2 recruiting moiety and an E3 ubiquitin ligase recruiting moiety is described. The bifunctional molecules of the present disclosure actively degrades LRRK2, leading to robust cellular proliferation suppression and apoptosis induction. Protein degradation mediated by the bifunctional compounds of the present disclosure provides a promising strategy in targeting the “undruggable” pathological proteins by traditional approaches.

**[00294]** 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 disclosure may be utilized in numerous combinations, all of which are expressly contemplated by the present description. These additional aspects 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 disclosure, and in particular cases, to provide additional details respecting the practice, are incorporated by reference.

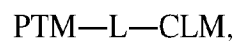
**[00295]** Thus, those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the disclosure described herein. Such equivalents are intended to be encompassed by the following claims. It is understood that 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 disclosure. 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 disclosure described herein. Such equivalents are intended to be encompassed by the following claims.



## CLAIMS

## What Is Claimed Is:

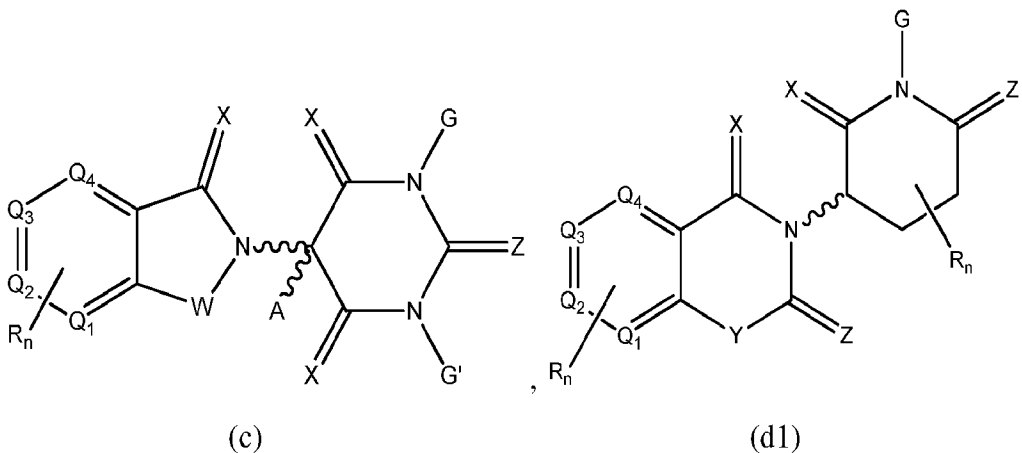
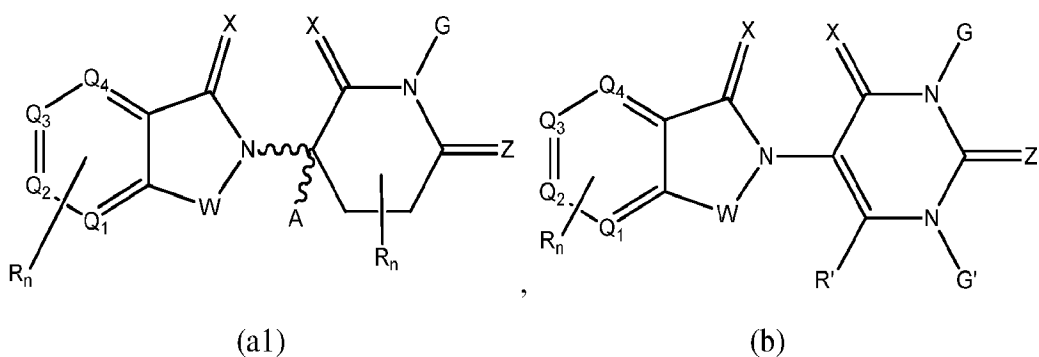
1. A hetero-bifunctional compound having the chemical structure:

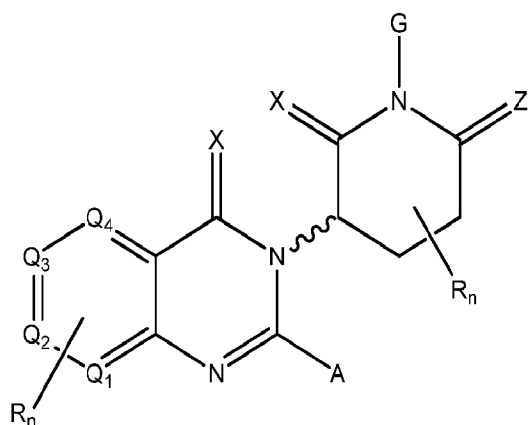


or a pharmaceutically acceptable salt or solvate thereof,

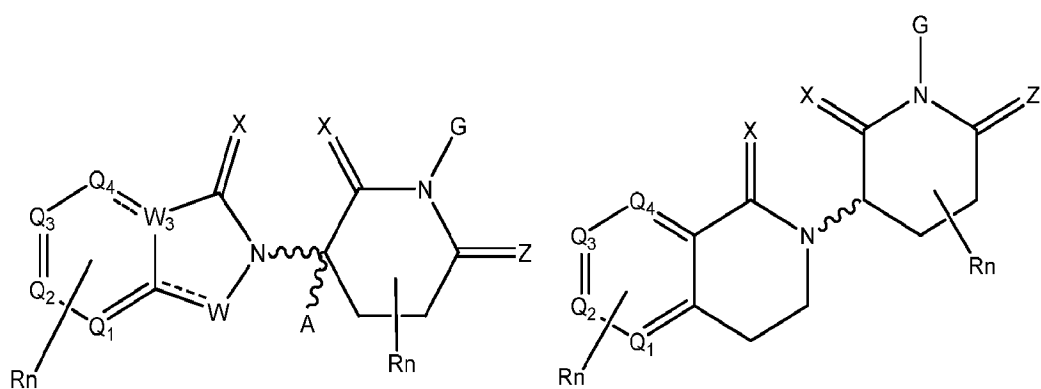
wherein:

- (a) the CLM is a small molecule E3 ubiquitin ligase binding moiety that binds a cereblon E3 ubiquitin ligase and represented by the chemical structure:



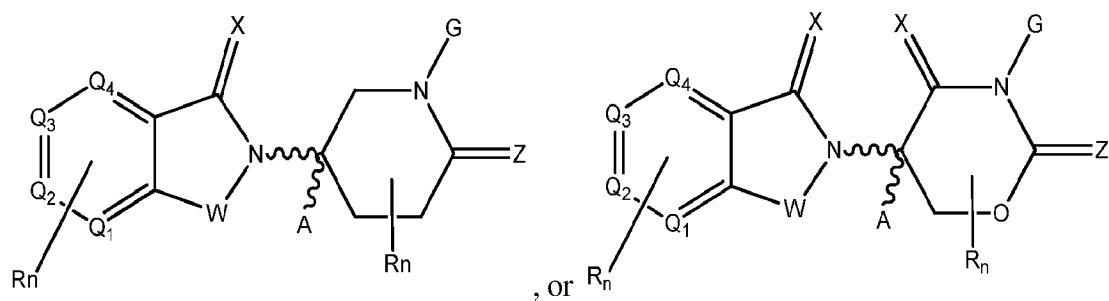


(e)



(a2)

(d2)



(a3)

(a4)

wherein:

W is selected from the group consisting of CH<sub>2</sub>, O, CHR, C=O, SO<sub>2</sub>, NH, N, optionally substituted cyclopropyl group, optionally substituted cyclobutyl group, and N-alkyl;

W<sub>3</sub> is selected from C or N;

each X is independently selected from the group consisting of absent, O, S, and CH<sub>2</sub>;

Y is selected from the group consisting of CH<sub>2</sub>, -C=CR', NH, N-alkyl, N-aryl, N-heteroaryl, N-cycloalkyl, N-heterocyclyl, O, and S;

Z is selected from the group consisting of absent, O, S, and CH<sub>2</sub>;

G and G' are independently selected from the group consisting of H, unsubstituted or substituted linear or branched alkyl, OH, R'OCOOR, R'OCONRR'', CH<sub>2</sub>-heterocyclyl optionally substituted with R', and benzyl optionally substituted with R';

Q<sub>1</sub>, Q<sub>2</sub>, Q<sub>3</sub>, and Q<sub>4</sub> represent a carbon C or N substituted with a group independently selected from H, R, N or N-oxide;

A is independently selected from the group H, unsubstituted or substituted linear or branched alkyl, cycloalkyl, Cl and F;

n is an integer from 1 to 10 (e.g., 1-4, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10);

R comprises H, -CONR'R'', -C(=O)R', -OR', -NR'R'', -SR', -SO<sub>2</sub>R', -SO<sub>2</sub>NR'R'', -CR'R''-, -CR'NR'R''-, (-CR'O)<sub>n</sub>R'', optionally substituted heterocyclyl, aryl (e.g., an optionally substituted C<sub>5</sub>-C<sub>7</sub> aryl), optionally substituted alkyl-aryl (e.g., an alkyl-aryl comprising at least one of an optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, an optionally substituted C<sub>5</sub>-C<sub>7</sub> aryl, or combinations thereof), hetaryl, unsubstituted or substituted linear or branched alkyl (e.g., a C<sub>1</sub>-C<sub>6</sub> linear or branched alkyl optionally substituted with one or more halogen, cycloalkyl (e.g., a C<sub>3</sub>-C<sub>6</sub> cycloalkyl), or aryl (e.g., C<sub>5</sub>-C<sub>7</sub> aryl)), optionally substituted alkoxy group (e.g., a methoxy, ethoxy, butoxy, propoxy, pentoxy, or hexoxy; wherein the alkoxy may be substituted with one or more halogen, alkyl, haloalkyl, fluoroalkyl, cycloalkyl (e.g., a C<sub>3</sub>-C<sub>6</sub> cycloalkyl), or aryl (e.g., C<sub>5</sub>-C<sub>7</sub> aryl)), optionally substituted heterocyclyl, -P(O)(OR')R'', -P(O)R'R'', -OP(O)(OR')R'', -OP(O)R'R'', -Cl, -F, -Br, -I, -CF<sub>3</sub>, -CN, -NR'SO<sub>2</sub>NR'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<sub>2</sub>)NR'R'', -SO<sub>2</sub>NR'COR'', -NO<sub>2</sub>, -CO<sub>2</sub>R', -C(C=N-OR')R'', -CR'=CR'R'', -CCR', -S(C=O)(C=N-R')R'', -SF<sub>5</sub> and -OCF<sub>3</sub>, wherein at least one R or W is modified to be covalently joined to the PTM or the L;

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

R' and R'' are independently selected from the group consisting of H, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aryl,

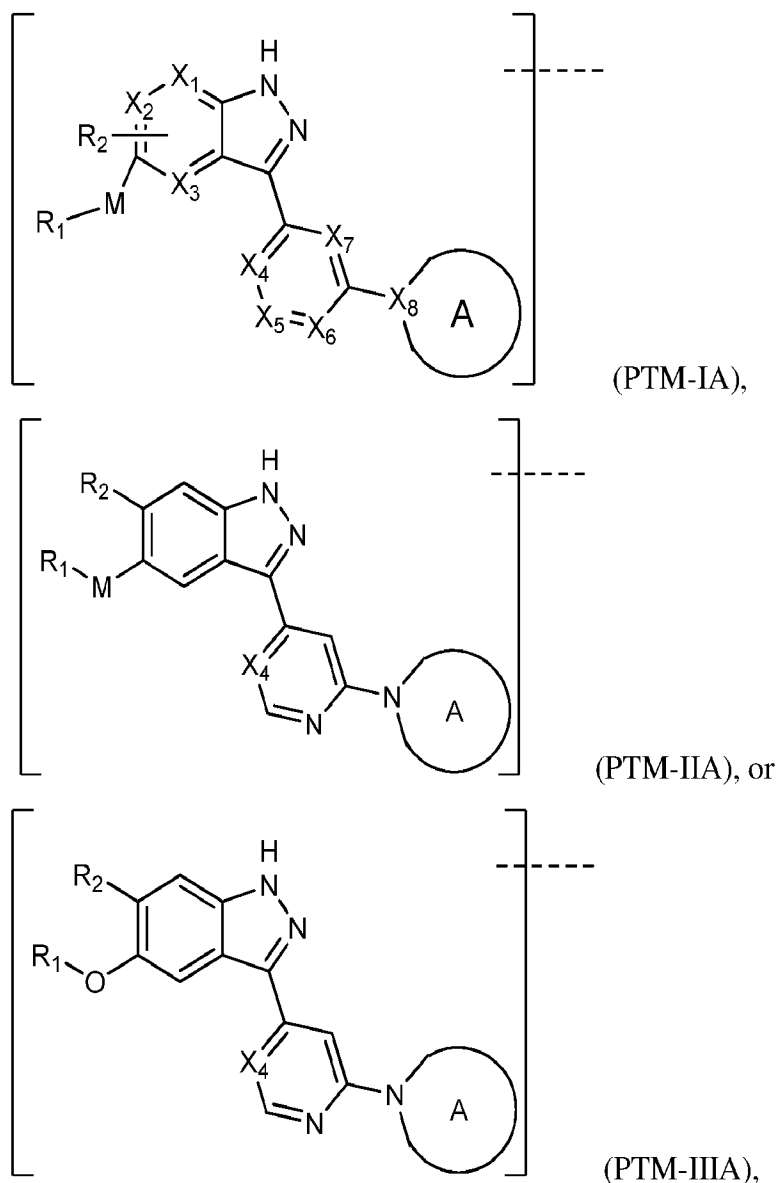
optionally substituted heteroaryl, optionally substituted heterocyclic, and optionally substituted heterocyclyl;

$n'$  is an integer from 1-10 (e.g., 1-4, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10);

 represents a single bond or a double bond; and

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

(b) the PTM is a small molecule leucine-rich repeat kinase 2 (LRRK2) targeting moiety that binds to LRRK2 or a mutant form thereof, represented by the chemical structure:



wherein:

$R_1$  is a linear or branched C1-C6 alkyl (e.g., isopropyl or tert-butyl), an optionally substituted C3-C6 cycloalkyl (e.g., an optionally substituted C3-C5 cycloalkyl, a

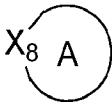
methylenated C3-C5 cycloalkyl, or , wherein the dashed line is the point of attachment to the M or the oxygen atom of the PTM), linear or branched C1-C6 haloalkyl (e.g., linear or branched C1-C4 haloalkyl), an optionally substituted C3-C6 halocycloalkyl (e.g., C3-C5 halocycloalkyl), an optionally substituted alkyl nitrile (e.g., a C1-C4 alkyl nitrile), an optionally substituted C3-C6 cyclonitrile (e.g., a C3-C5 cyclonitrile);

R<sub>2</sub> is hydrogen, halogen (e.g., F, Cl, or Br), C1-C3 alkyl, or C1-C3 fluoroalkyl;

X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub>, X<sub>6</sub>, and X<sub>7</sub> are each independently CH or N, wherein X<sub>1</sub>, X<sub>2</sub>, and X<sub>3</sub> are each optionally substituted with R<sub>2</sub> when CH;

X<sub>8</sub> is CH, S, or N;

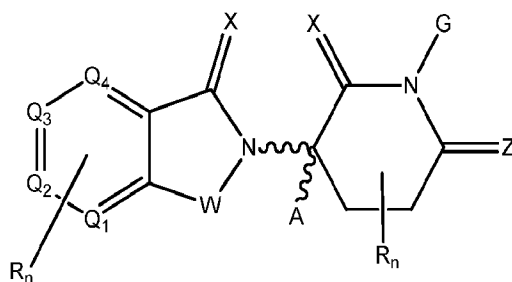
M is a CH<sub>2</sub>, NH, or O;

 or  is an optionally substituted 3-10 membered cycloalkyl or heterocycloalkyl containing 1-4 (e.g., 1, 2, 3, or 4) heteroatoms selected from N, O, and S (e.g., optionally substituted with one or more (e.g., 1, 2, 3, or 4) substitutions; and

 of the PTM indicates the point of attachment with the L or the CLM; and

(c) the L is a bond or a chemical linker group that covalently couples the CLM to the PTM.

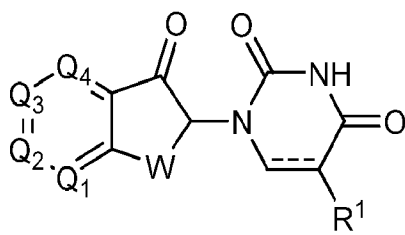
2. The compound according to claim 1, wherein the CLM has the chemical structure:



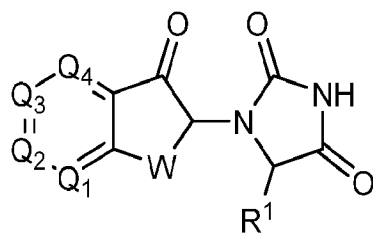
3. A hetero-bifunctional compound having the chemical structure:  
PTM—L—CLM,

or a pharmaceutically acceptable salt or solvate thereof,  
wherein:

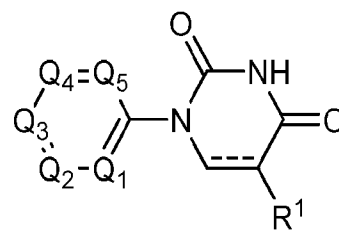
(a) the CLM is a small molecule E3 ubiquitin ligase binding moiety that binds a cereblon E3 ubiquitin ligase and represented by the chemical structure:



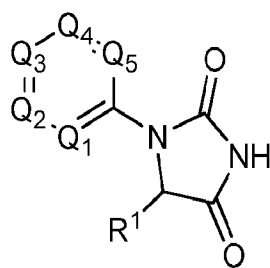
(h)



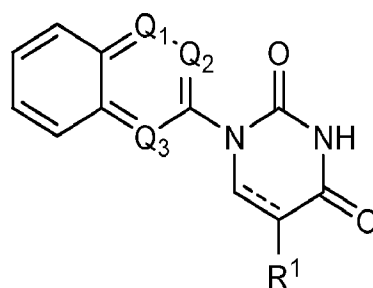
(i)



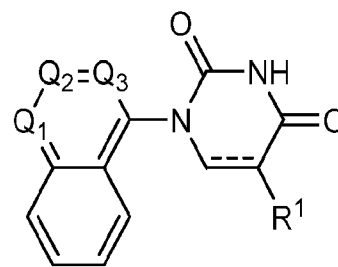
(j)



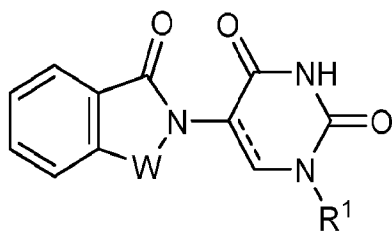
(k)



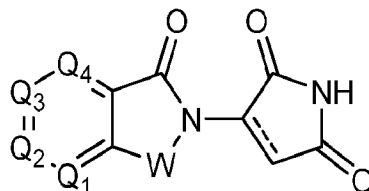
(l)



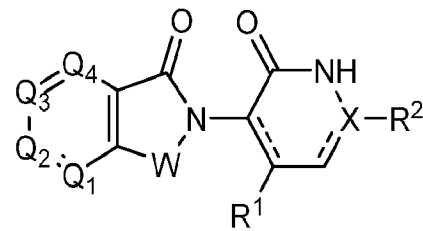
(m)



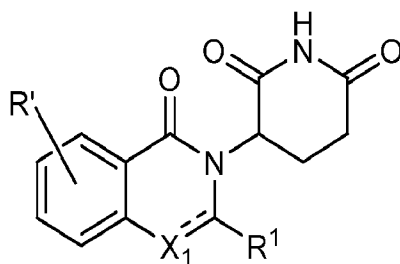
(n)



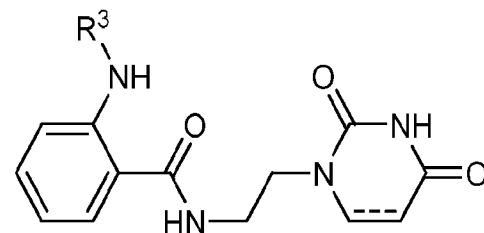
(o)



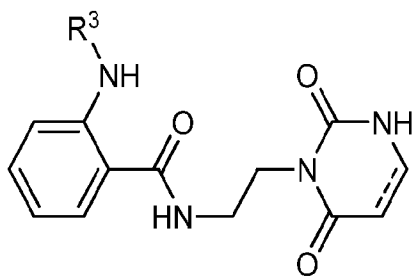
(p)



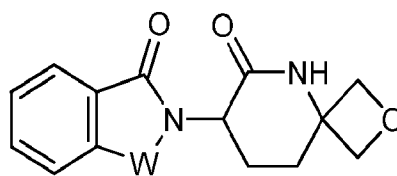
(q)



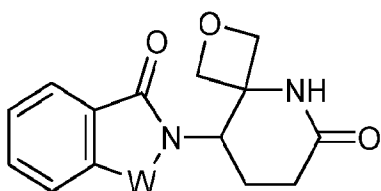
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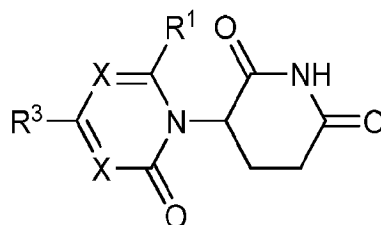
(s)



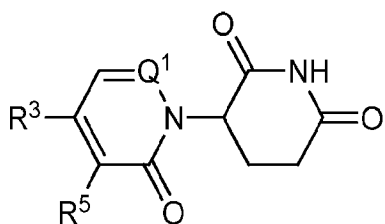
(t)



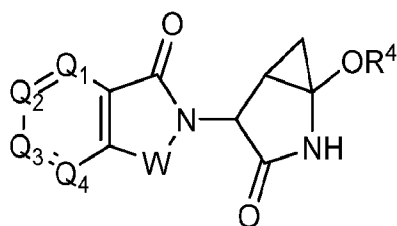
(u)



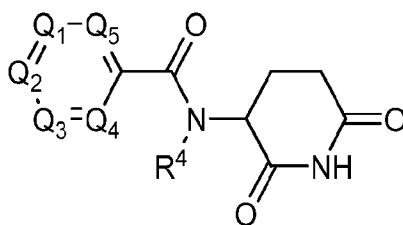
(v)



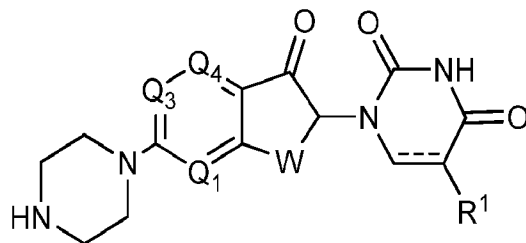
(w)



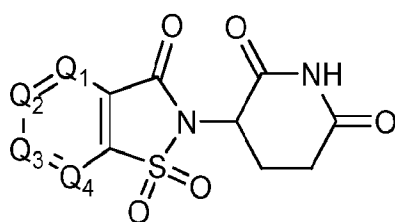
(x)



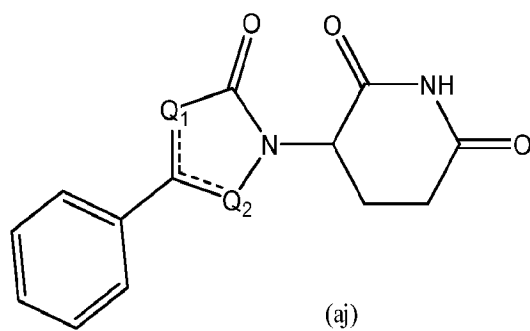
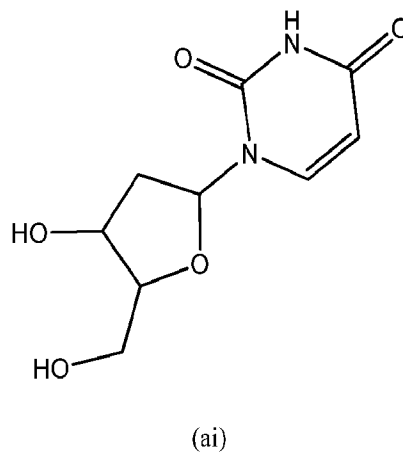
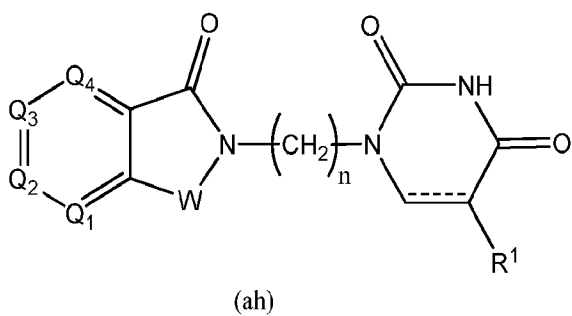
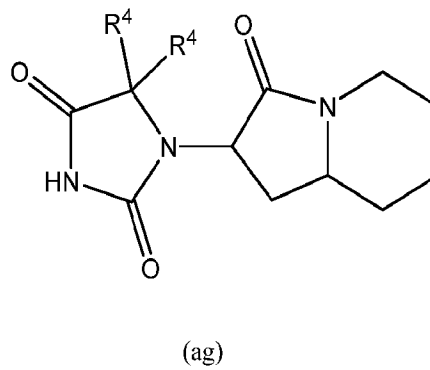
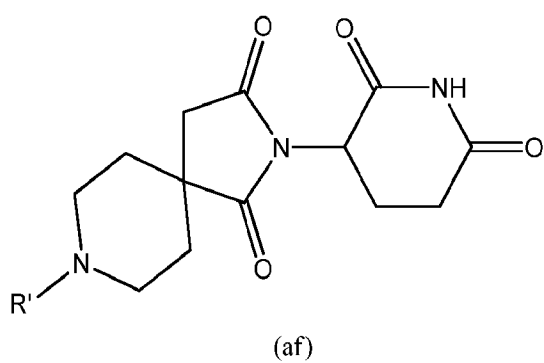
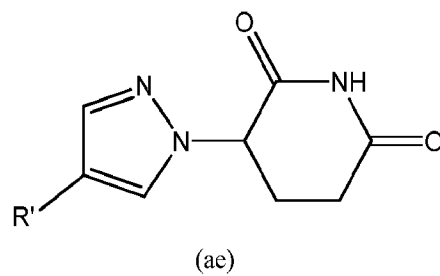
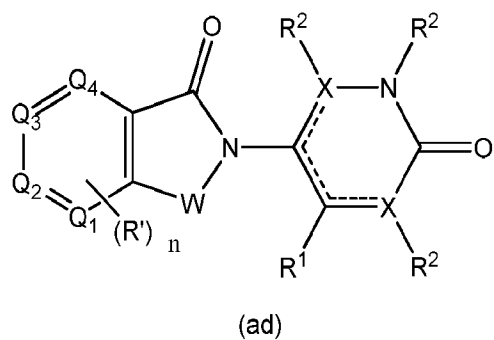
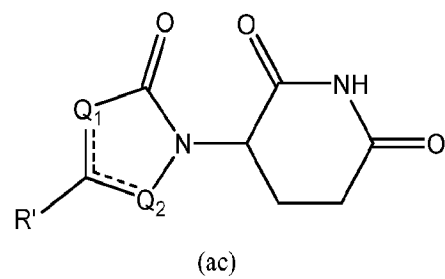
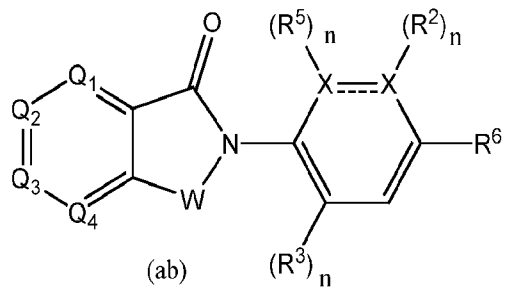
(y)



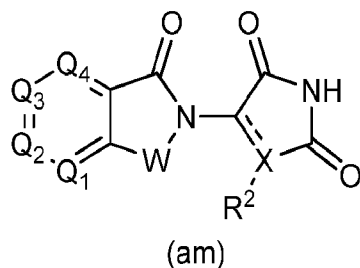
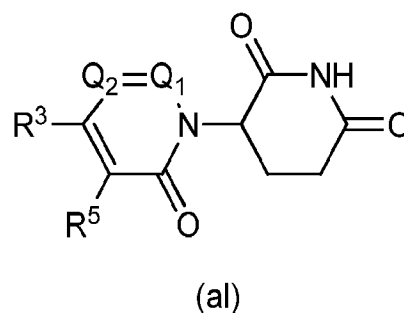
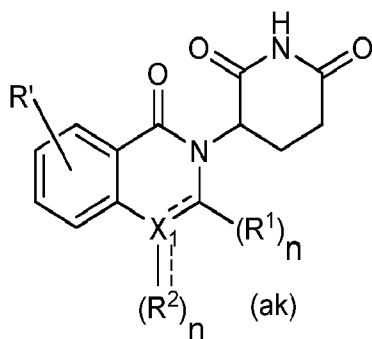
(z)



(aa)







wherein:

W is selected from the group consisting of CH<sub>2</sub>, O, CHR, C=O, SO<sub>2</sub>, NH, N, optionally substituted cyclopropyl group, optionally substituted cyclobutyl group, and N-alkyl;

Q<sub>1</sub>, Q<sub>2</sub>, Q<sub>3</sub>, Q<sub>4</sub>, Q<sub>5</sub> each independently represent a carbon C or N substituted with a group independently selected from R', N or N-oxide;

R<sup>1</sup> is selected from absent, H, OH, CN, C1-C3 alkyl, C=O;

R<sup>2</sup> is selected from the group absent, H, OH, CN, C1-C3 alkyl, CHF<sub>2</sub>, CF<sub>3</sub>, CHO, C(=O)NH<sub>2</sub>;

R<sup>3</sup> is selected from H, alkyl (e.g., C1-C6 or C1-C3 alkyl), substituted alkyl (e.g., substituted C1-C6 or C1-C3 alkyl), alkoxy (e.g., C1-C6 or C1-C3 alkoxy), substituted alkoxy (e.g., substituted C1-C6 or C1-C3 alkoxy);

R<sup>4</sup> is selected from H, alkyl, substituted alkyl;

R<sup>5</sup> and R<sup>6</sup> are each independently H, halogen, C(=O)R', CN, OH, CF<sub>3</sub>;

X is C, CH, C=O, or N;

X<sub>1</sub> is C=O, N, CH, or CH<sub>2</sub>;

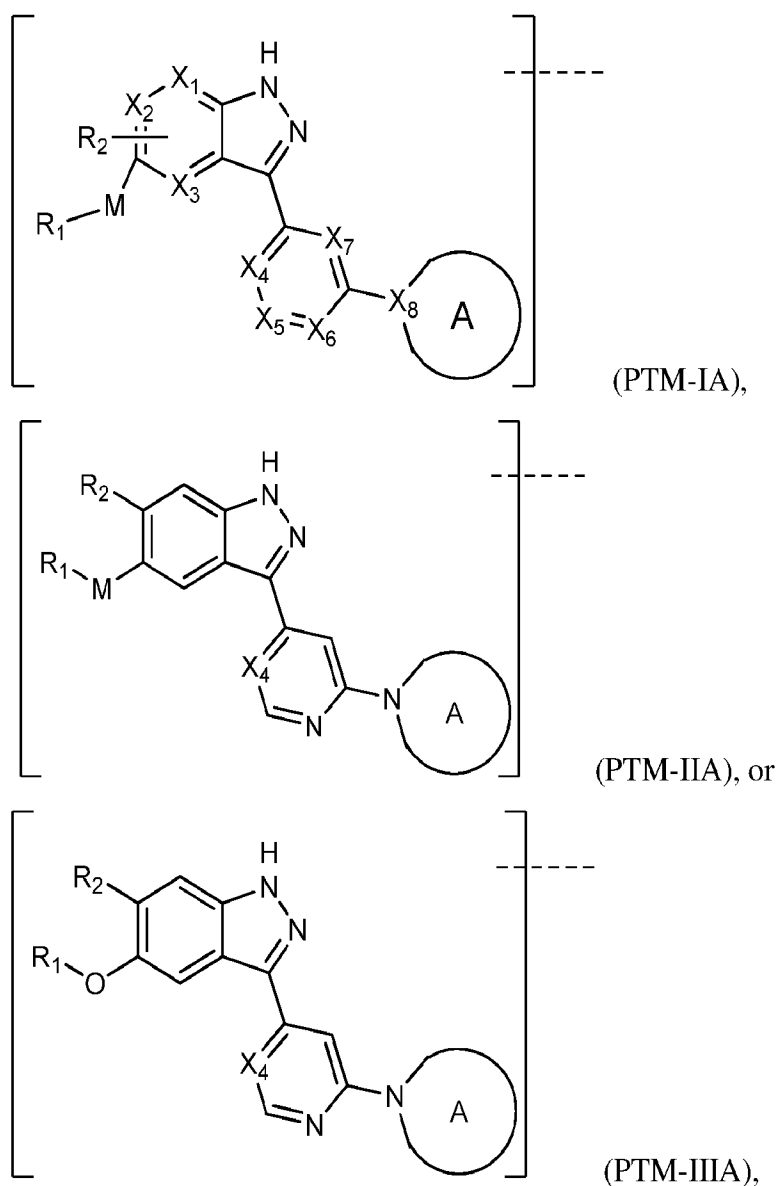
R' is selected from H, halogen, amine, alkyl (e.g., C1-C3 alkyl), substituted alkyl (e.g., substituted C1-C3 alkyl), alkoxy (e.g., C1-C3 alkoxy), substituted alkoxy (e.g., substituted C1-C3 alkoxy), NR<sup>2</sup>R<sup>3</sup>, C(=O)OR<sup>2</sup>, optionally substituted phenyl;

n is 0-4;

$\diagup$  is a single or double bond; and

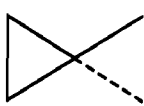
the CLM is covalently joined to the PTM or the L;

(b) the PTM is a small molecule leucine-rich repeat kinase 2 (LRRK2) targeting moiety that binds to LRRK2 or a mutant form thereof, represented by the chemical structure:



wherein:

$R_1$  is a linear or branched C1-C6 alkyl (e.g., isopropyl or tert-butyl), an optionally substituted C3-C6 cycloalkyl (e.g., an optionally substituted C3-C5 cycloalkyl, a

methylated C3-C5 cycloalkyl, or , wherein the dashed line is the point of attachment to the M or the oxygen atom of the PTM), linear or branched C1-C6

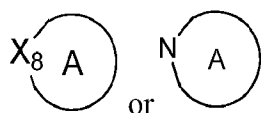
haloalkyl (e.g., linear or branched C1-C4 haloalkyl), an optionally substituted C3-C6 halocycloalkyl (e.g., C3-C5 halocycloalkyl), an optionally substituted alkyl nitrile (e.g., a C1-C4 alkyl nitrile), an optionally substituted C3-C6 cyclonitrile (e.g., a C3-C5 cyclonitrile);

R<sub>2</sub> is hydrogen, halogen (e.g., F, Cl, or Br), C1-C3 alkyl, or C1-C3 fluoroalkyl;

X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub>, X<sub>6</sub>, and X<sub>7</sub> are each independently CH or N, wherein X<sub>1</sub>, X<sub>2</sub>, and X<sub>3</sub> are each optionally substituted with R<sub>2</sub> when CH;

X<sub>8</sub> is CH, S, or N;

M is a CH<sub>2</sub>, NH, or O;

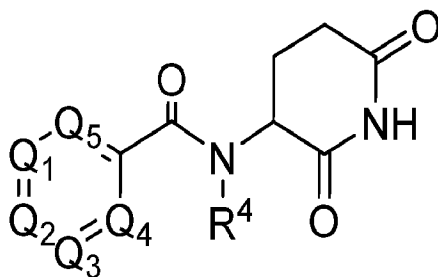


is an optionally substituted 3-10 membered cycloalkyl or heterocycloalkyl containing 1-4 (e.g., 1, 2, 3, or 4) heteroatoms selected from N, O, and S (e.g., optionally substituted with one or more (e.g., 1, 2, 3, or 4) substitutions; and

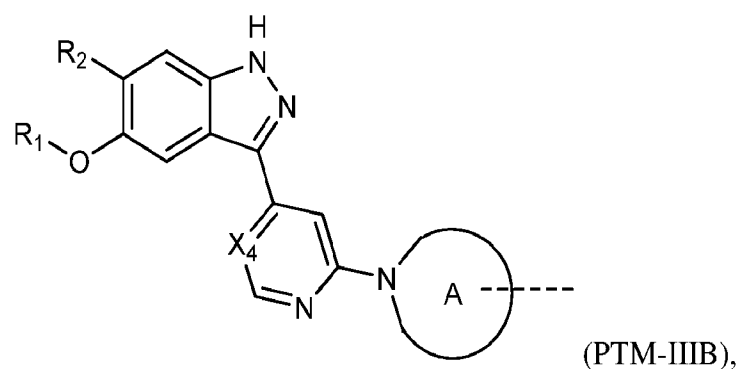
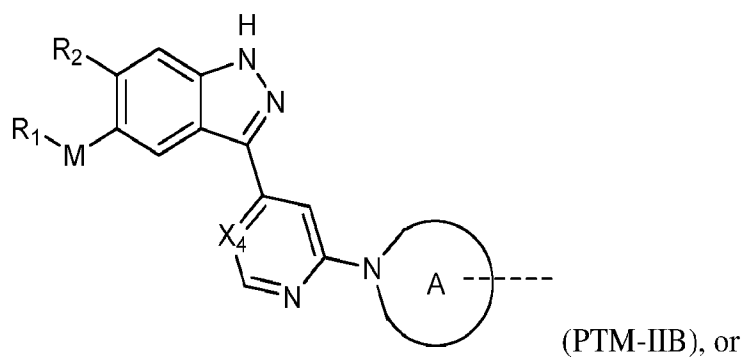
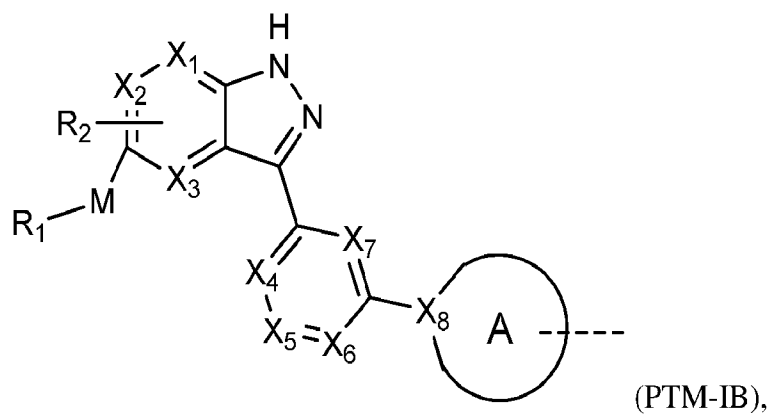
--- of the PTM indicates the point of attachment with the L or the CLM; and

(c) the L is a bond or a chemical linker group that covalently couples the CLM to the PTM.

4. The compound according to claim 3, wherein the CLM is represented by the chemical structure:



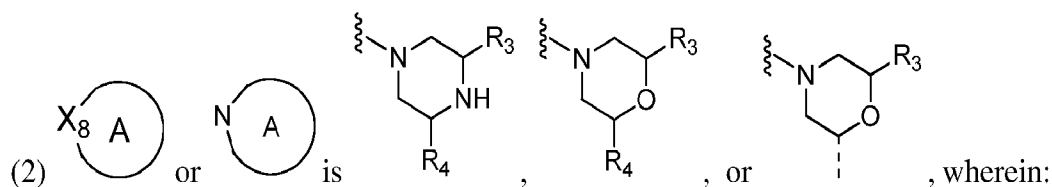
5. The compound according to any of claims 1-4, wherein the PTM is represented by:



wherein  $\text{---}$  of the PTM indicates the point of attachment with the L or the CLM.

6. The compound according to any of claim 1-5, wherein:

- (1)  $\text{X}_8$  A or N A includes 1-4 substitution, each independently selected from a halogen, OH, NH<sub>2</sub>, N(C1-C3 alkyl)<sub>2</sub>, linear or branched C1-C4 alkyl (e.g., methyl or ethyl), linear or branched C1-C4 hydroxyalkyl, linear or branched C1-C4 alkoxy, and linear or branched C1-C4 haloalkyl)



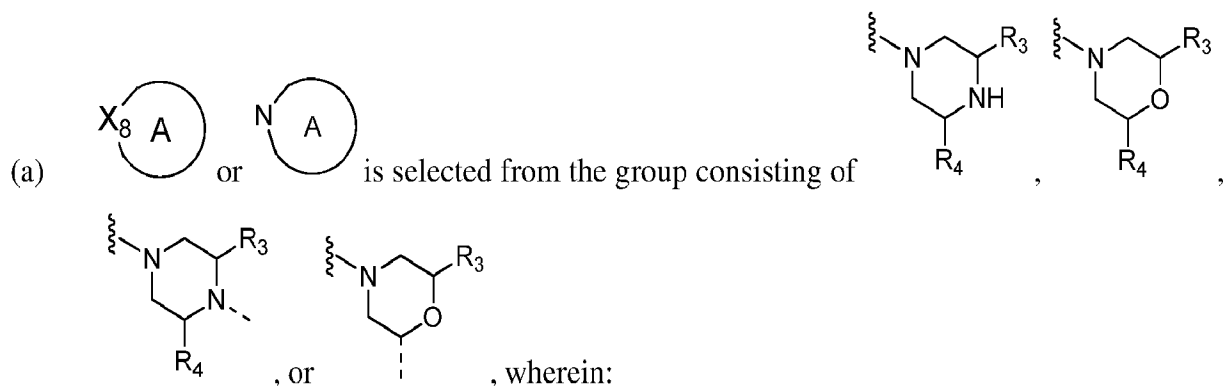
$R_3$  and  $R_4$  are each independently selected from a H, halogen, OH,  $NH_2$ ,  $N(C1-C3 \text{ alkyl})_2$ , linear or branched C1-C4 alkyl, linear or branched C1-C4 hydroxyalkyl, linear or branched C1-C4 alkoxy, and linear or branched C1-C4 haloalkyl;

 indicates the point of attachment of the  or  (i.e., the point of attachment with the 6-membered heteroaryl to the PTM); and

 indicates the point of attachment with the L or the CLM, and where not present, the  or  is attached to the L or the CLM via an atom of the 6-membered heterocycloalkyl or cycloalkyl (e.g., a carbon or nitrogen),  $R_3$ , or  $R_4$ ; or

(3) a combination thereof.

7. The compound according to any of claims 1-6, wherein:

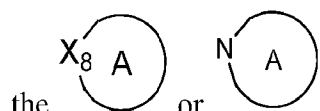


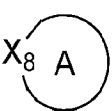
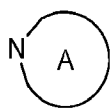
$R_3$  is H or linear or branched C1-C3 alkyl (e.g., methyl);

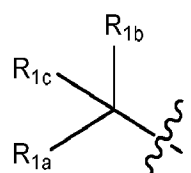
$R_4$  is H or linear or branched C1-C3 alkyl (e.g., methyl);

 indicates the point of attachment of the  or  (i.e., the point of attachment with the 6-membered heteroaryl of the PTM); and

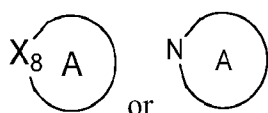
-- indicates the point of attachment with the L or the CLM, and where not present,



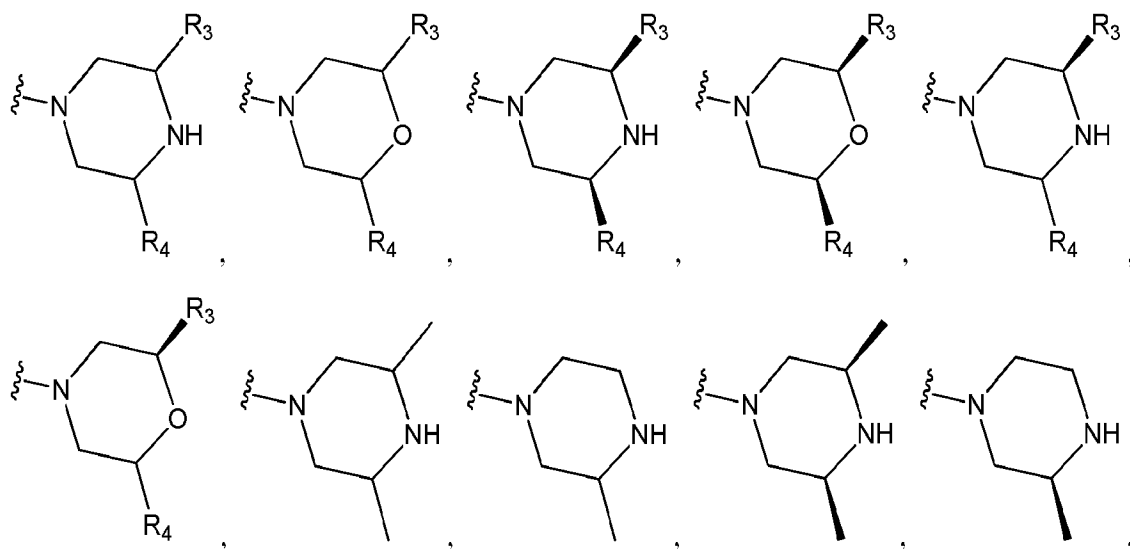
the  or  is attached to the L or the CLM via an atom of the 6-membered heterocycloalkyl (e.g., a carbon or nitrogen of the 6-membered heterocycloalkyl), R<sub>3</sub>, or R<sub>4</sub>;

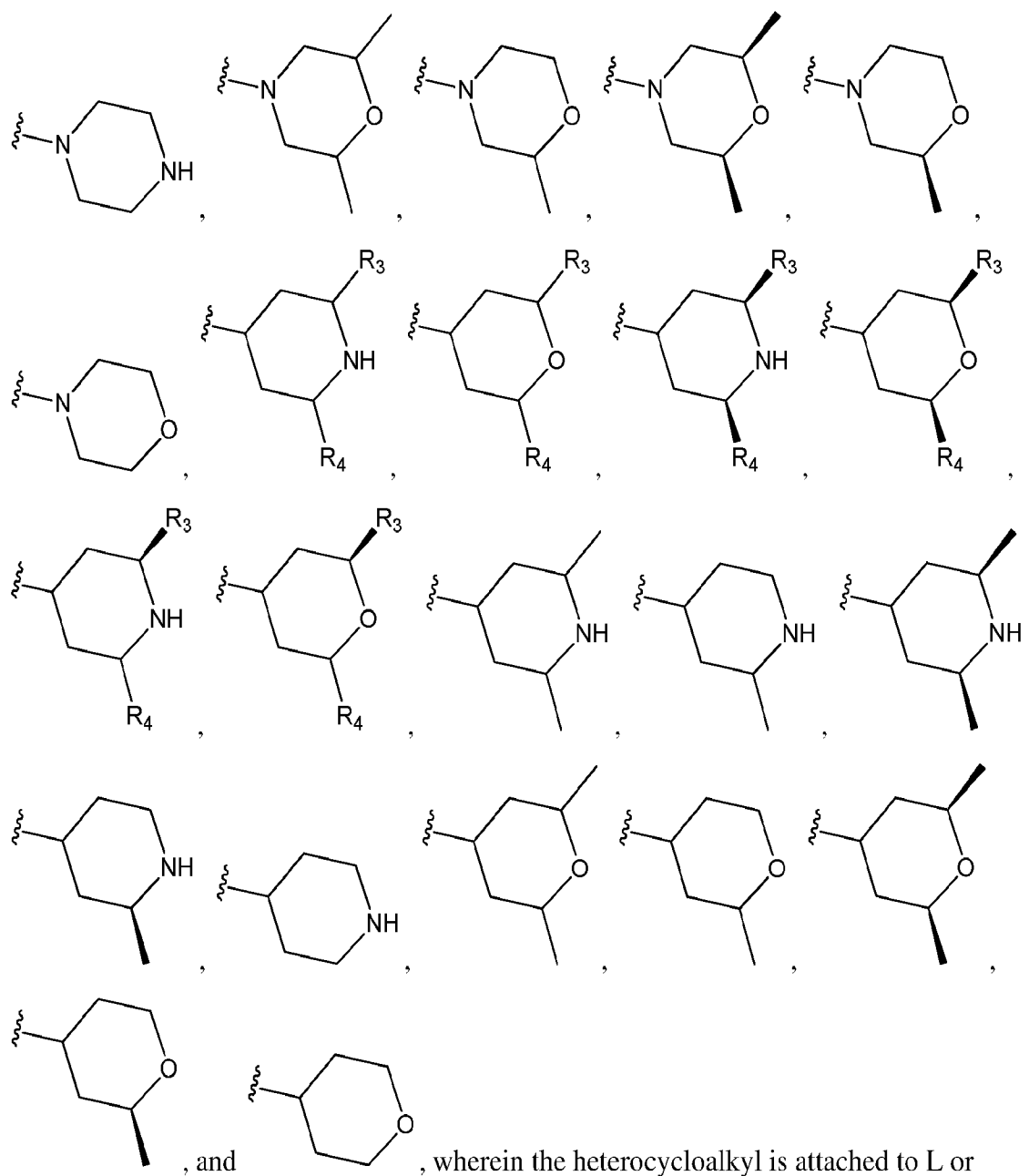
- (b) R<sub>1</sub> is , wherein: R<sub>1a</sub>, R<sub>1b</sub>, and R<sub>1c</sub> are each independently a H, or a linear or branched C1-C2 alkyl, each optionally substituted with one or more halogen or nitrile group; or R<sub>1a</sub> or R<sub>1b</sub> together with the carbon to which they are attached form a C3-C6 cycloalkyl that is optionally substituted with one or more C1-C3 alkyl, nitrile group, or halogen; or
- (c) R<sub>2</sub> is H or F; or
- (d) a combination thereof.

8. The compound according to any of claims 1-7, wherein



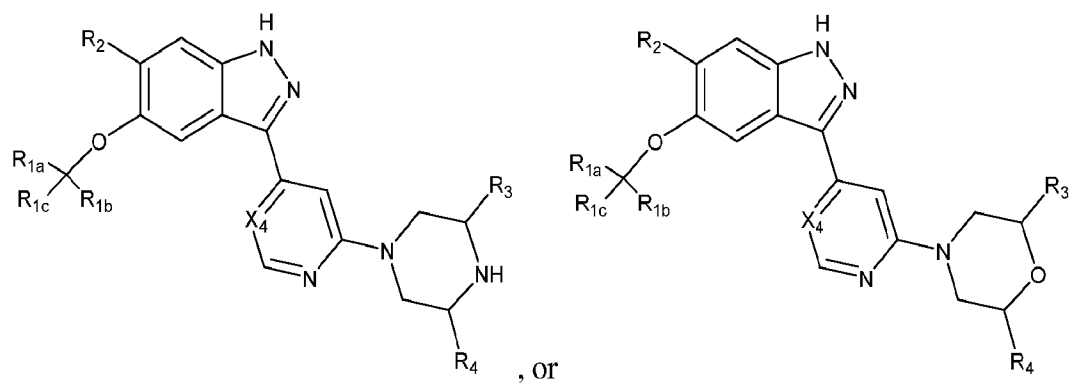
is selected from the group consisting of:



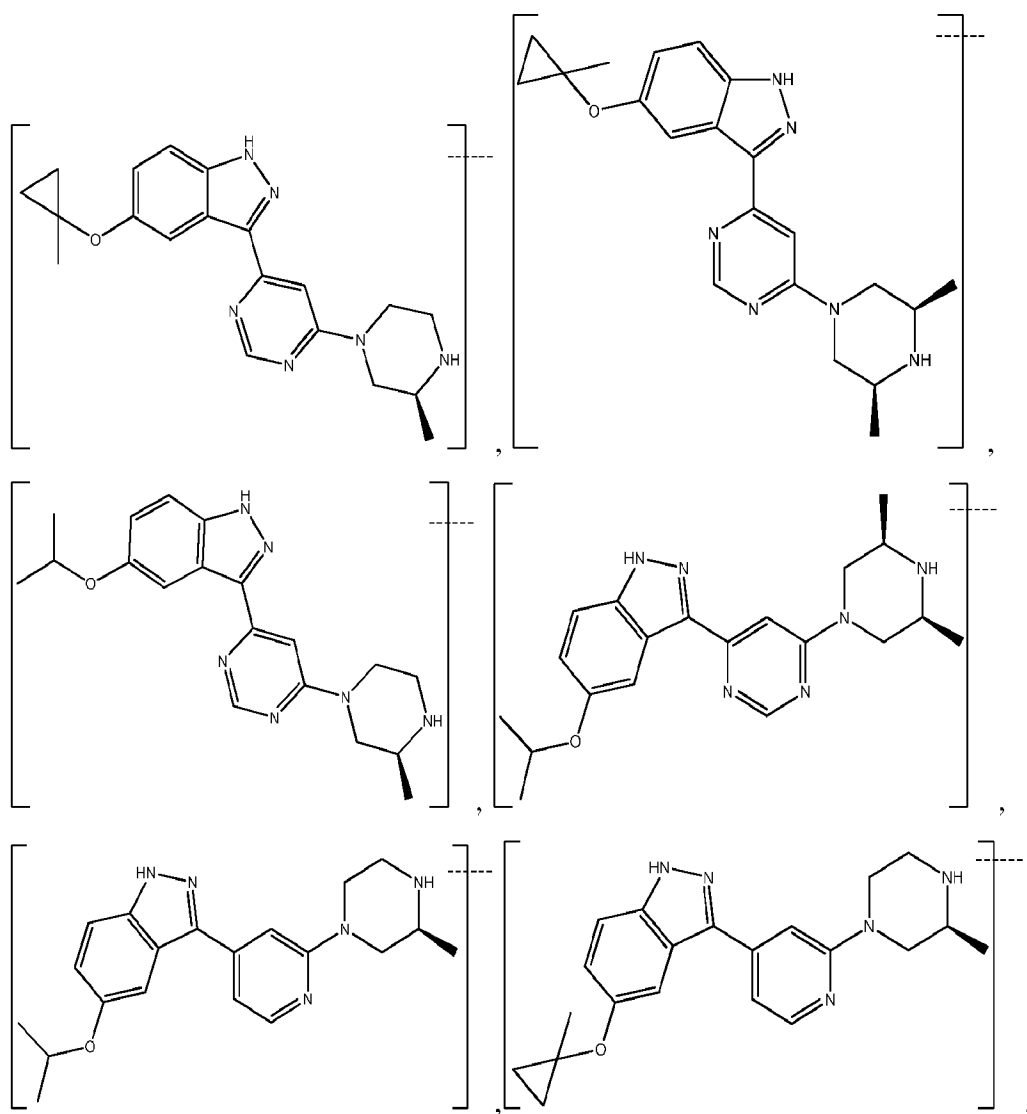


PTM via an atom of the heterocycloalkyl or a substituent thereof.

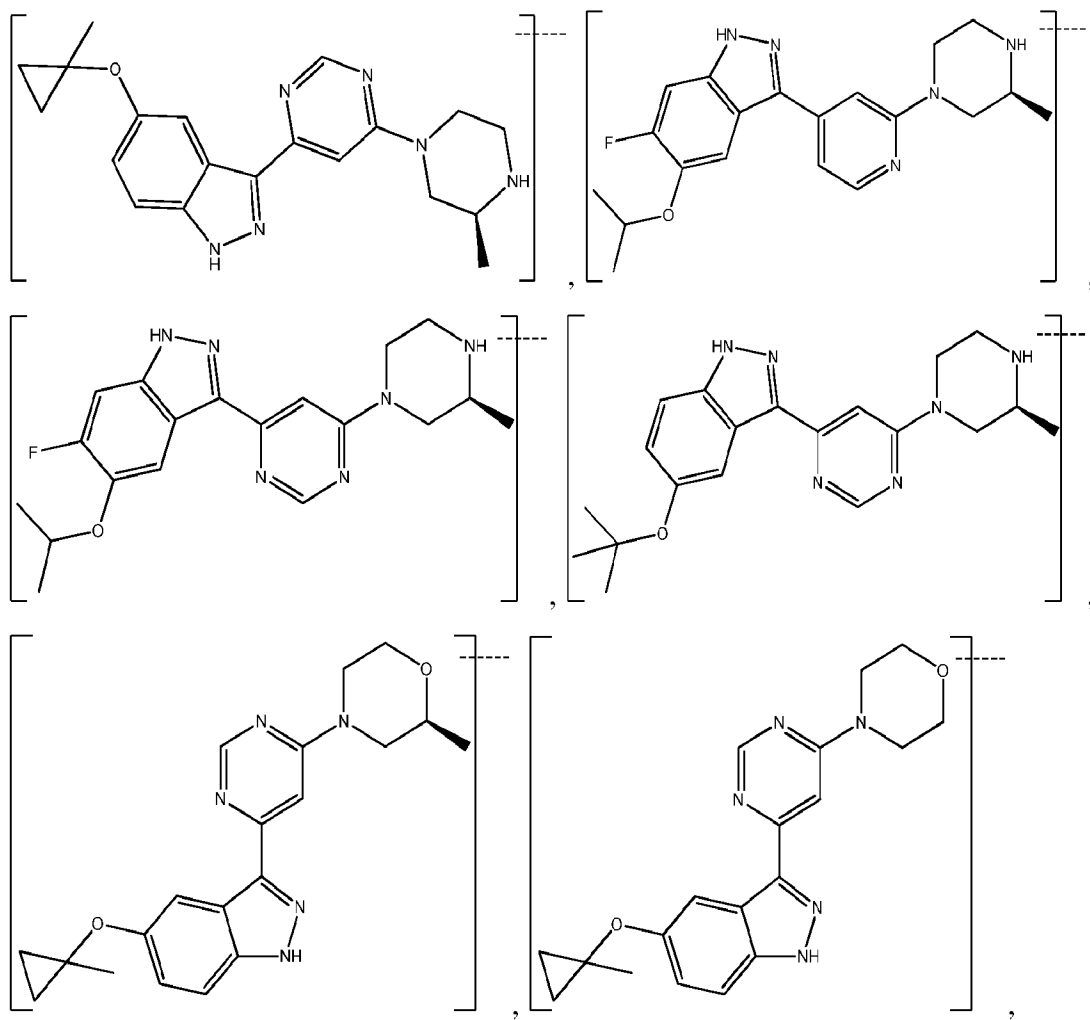
9. The compound according to any of claims 1-8, wherein the PTM is represented by the chemical structure:



10. The compound according to any of claims 1-9, wherein the PTM is represented by chemical structure:







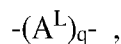


wherein:

the dashed line indicates a site of attachment of the L or the CLM; and

each PTM is coupled to at least one L or CLM.

11. The compound of any one of claims 1-10, wherein the L comprises a chemical structural unit represented by the formula:



wherein:

$-(A^L)_q-$  is a group which is connected to the CLM and the PTM;

q is an integer greater than or equal to 1;

each  $A^L$  is independently selected from the group consisting of  $CR^{L1}R^{L2}$ , O, S, SO, SO<sub>2</sub>, NR<sup>L3</sup>, SO<sub>2</sub>NR<sup>L3</sup>, SONR<sup>L3</sup>, CONR<sup>L3</sup>, NR<sup>L3</sup>CONR<sup>L4</sup>, NR<sup>L3</sup>SO<sub>2</sub>NR<sup>L4</sup>, CO, CR<sup>L1</sup>=CR<sup>L2</sup>, C≡C, SiR<sup>L1</sup>R<sup>L2</sup>, P(O)R<sup>L1</sup>, P(O)OR<sup>L1</sup>, NR<sup>L3</sup>C(=NCN)NR<sup>L4</sup>, NR<sup>L3</sup>C(=NCN), NR<sup>L3</sup>C(=CNO<sub>2</sub>)NR<sup>L4</sup>, C<sub>3-11</sub>cycloalkyl optionally substituted with 1-6 R<sup>L1</sup> and/or R<sup>L2</sup> groups, C<sub>5-13</sub>spirocycloalkyl optionally substituted with 1-9 R<sup>L1</sup> and/or R<sup>L2</sup> groups, C<sub>3-11</sub>heteocyclyl optionally substituted with 1-6 R<sup>L1</sup> and/or R<sup>L2</sup> groups, C<sub>5-13</sub>spiroheterocyclyl optionally substituted with 1-8 R<sup>L1</sup> and/or R<sup>L2</sup> groups, aryl optionally substituted with 0-6 R<sup>L1</sup> and/or R<sup>L2</sup> groups, and heteroaryl optionally substituted with 1-6 R<sup>L1</sup> and/or R<sup>L2</sup> groups, where R<sup>L1</sup> or R<sup>L2</sup>, each independently are optionally linked to other groups to form cycloalkyl and/or heterocyclyl moiety, optionally substituted with 1-4 R<sup>L5</sup> groups; and

R<sup>L1</sup>, R<sup>L2</sup>, R<sup>L3</sup>, R<sup>L4</sup> and R<sup>L5</sup> are, each independently, H, halogen, C<sub>1-8</sub>alkyl, OC<sub>1-8</sub>alkyl, SC<sub>1-8</sub>alkyl, NHC<sub>1-8</sub>alkyl, N(C<sub>1-8</sub>alkyl)<sub>2</sub>, C<sub>3-11</sub>cycloalkyl, aryl, heteroaryl, C<sub>3-11</sub>heterocyclyl, OC<sub>3-8</sub>cycloalkyl, SC<sub>3-8</sub>cycloalkyl, NHC<sub>3-8</sub>cycloalkyl, N(C<sub>3-8</sub>cycloalkyl)<sub>2</sub>, N(C<sub>3-8</sub>cycloalkyl)(C<sub>1-8</sub>alkyl), OH, NH<sub>2</sub>, SH, SO<sub>2</sub>C<sub>1-8</sub>alkyl, P(O)(OC<sub>1-8</sub>alkyl)(C<sub>1-8</sub>alkyl), P(O)(OC<sub>1-8</sub>alkyl)<sub>2</sub>, CC-C<sub>1-8</sub>alkyl, CCH, CH=CH(C<sub>1-8</sub>alkyl), C(C<sub>1-8</sub>alkyl)=CH(C<sub>1-8</sub>alkyl), C(C<sub>1-8</sub>alkyl)=C(C<sub>1-8</sub>alkyl)<sub>2</sub>, Si(OH)<sub>3</sub>, Si(C<sub>1-8</sub>alkyl)<sub>3</sub>, Si(OH)(C<sub>1-8</sub>alkyl)<sub>2</sub>, COC<sub>1-8</sub>alkyl, CO<sub>2</sub>H, CN, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, NO<sub>2</sub>, SF<sub>5</sub>, SO<sub>2</sub>NHC<sub>1-8</sub>alkyl, SO<sub>2</sub>N(C<sub>1-8</sub>alkyl)<sub>2</sub>, SONHC<sub>1-8</sub>alkyl, SON(C<sub>1-8</sub>alkyl)<sub>2</sub>, CONHC<sub>1-8</sub>alkyl, CON(C<sub>1-8</sub>alkyl)<sub>2</sub>, N(C<sub>1-8</sub>alkyl)CONH(C<sub>1-8</sub>alkyl), N(C<sub>1-8</sub>alkyl)CON(C<sub>1-8</sub>alkyl)<sub>2</sub>, NHCONH(C<sub>1-8</sub>alkyl), NHCON(C<sub>1-8</sub>alkyl)<sub>2</sub>, NHCONH<sub>2</sub>, N(C<sub>1-8</sub>alkyl)SO<sub>2</sub>NH(C<sub>1-8</sub>alkyl), N(C<sub>1-8</sub>alkyl)SO<sub>2</sub>N(C<sub>1-8</sub>alkyl)<sub>2</sub>, NH SO<sub>2</sub>NH(C<sub>1-8</sub>alkyl), NH SO<sub>2</sub>N(C<sub>1-8</sub>alkyl)<sub>2</sub>, or NH SO<sub>2</sub>NH<sub>2</sub>.

12. The compound according to any one of claim 1-11, wherein the linker (L) includes an optionally substituted C<sub>1</sub>-C<sub>50</sub> alkyl (e.g., C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, C<sub>6</sub>, C<sub>7</sub>, C<sub>8</sub>, C<sub>9</sub>, C<sub>10</sub>, C<sub>11</sub>,

C<sub>12</sub>, C<sub>13</sub>, C<sub>14</sub>, C<sub>15</sub>, C<sub>16</sub>, C<sub>17</sub>, C<sub>18</sub>, C<sub>19</sub>, C<sub>20</sub>, C<sub>21</sub>, C<sub>22</sub>, C<sub>23</sub>, C<sub>24</sub>, C<sub>25</sub>, C<sub>26</sub>, C<sub>27</sub>, C<sub>28</sub>, C<sub>29</sub>, C<sub>30</sub>, C<sub>31</sub>, C<sub>32</sub>, C<sub>33</sub>, C<sub>34</sub>, C<sub>35</sub>, C<sub>36</sub>, C<sub>37</sub>, C<sub>38</sub>, C<sub>39</sub>, C<sub>40</sub>, C<sub>41</sub>, C<sub>42</sub>, C<sub>43</sub>, C<sub>44</sub>, C<sub>45</sub>, C<sub>46</sub>, C<sub>47</sub>, C<sub>48</sub>, C<sub>49</sub>, or C<sub>50</sub> alkyl), wherein each carbon is optionally substituted or replaced with (1) a heteroatom selected from N, O, S, P, or Si atoms that has an appropriate number of hydrogens, substitutions, or both to complete valency, (2) an optionally substituted cycloalkyl or bicyclic cycloalkyl, (3) an optionally substituted heterocycloalkyl or bicyclic heterocycloalkyl, (4) an optionally substituted aryl or bicyclic aryl, or (5) optionally substituted heteroaryl or bicyclic heteroaryl, with the proviso that there is no heteroatom-heteroatom bonding (e.g., no heteroatoms are covalently linked or adjacently located).

13. The compound according to any one of claim 1-11, wherein the linker (L) includes an optionally substituted C<sub>1</sub>-C<sub>50</sub> alkyl (e.g., C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, C<sub>6</sub>, C<sub>7</sub>, C<sub>8</sub>, C<sub>9</sub>, C<sub>10</sub>, C<sub>11</sub>, C<sub>12</sub>, C<sub>13</sub>, C<sub>14</sub>, C<sub>15</sub>, C<sub>16</sub>, C<sub>17</sub>, C<sub>18</sub>, C<sub>19</sub>, C<sub>20</sub>, C<sub>21</sub>, C<sub>22</sub>, C<sub>23</sub>, C<sub>24</sub>, C<sub>25</sub>, C<sub>26</sub>, C<sub>27</sub>, C<sub>28</sub>, C<sub>29</sub>, C<sub>30</sub>, C<sub>31</sub>, C<sub>32</sub>, C<sub>33</sub>, C<sub>34</sub>, C<sub>35</sub>, C<sub>36</sub>, C<sub>37</sub>, C<sub>38</sub>, C<sub>39</sub>, C<sub>40</sub>, C<sub>41</sub>, C<sub>42</sub>, C<sub>43</sub>, C<sub>44</sub>, C<sub>45</sub>, C<sub>46</sub>, C<sub>47</sub>, C<sub>48</sub>, C<sub>49</sub>, or C<sub>50</sub> alkyl), wherein:

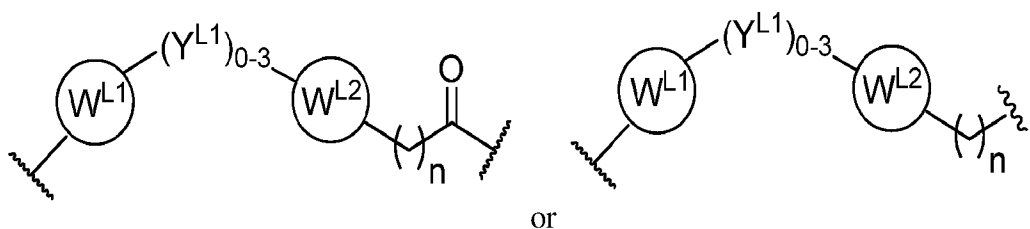
each carbon is optionally substituted or replaced with CR<sup>L1</sup>R<sup>L2</sup>, O, S, SO, SO<sub>2</sub>, NR<sup>L3</sup>, SO<sub>2</sub>NR<sup>L3</sup>, SONR<sup>L3</sup>, CONR<sup>L3</sup>, NR<sup>L3</sup>CONR<sup>L4</sup>, NR<sup>L3</sup>SO<sub>2</sub>NR<sup>L4</sup>, CO, CR<sup>L1</sup>=CR<sup>L2</sup>, C≡C, SiR<sup>L1</sup>R<sup>L2</sup>, P(O)R<sup>L1</sup>, P(O)OR<sup>L1</sup>, NR<sup>L3</sup>C(=NCN)NR<sup>L4</sup>, NR<sup>L3</sup>C(=NCN), NR<sup>L3</sup>C(=CNO<sub>2</sub>)NR<sup>L4</sup>, C<sub>3-11</sub>cycloalkyl optionally substituted with 1-6 R<sup>L1</sup> and/or R<sup>L2</sup> groups, C<sub>5-13</sub>spirocycloalkyl optionally substituted with 1-9 R<sup>L1</sup> and/or R<sup>L2</sup> groups, C<sub>3-11</sub>heterocyclyl optionally substituted with 1-6 R<sup>L1</sup> and/or R<sup>L2</sup> groups, C<sub>5-13</sub>spiroheterocyclyl optionally substituted with 1-8 R<sup>L1</sup> and/or R<sup>L2</sup> groups, aryl optionally substituted with 1-6 R<sup>L1</sup> and/or R<sup>L2</sup> groups, or heteroaryl optionally substituted with 1-6 R<sup>L1</sup> and/or R<sup>L2</sup> groups, where R<sup>L1</sup> or R<sup>L2</sup>, each independently are optionally linked to other groups to form cycloalkyl and/or heterocyclyl moiety, optionally substituted with 1-4 R<sup>L5</sup> groups; and R<sup>L1</sup>, R<sup>L2</sup>, R<sup>L3</sup>, R<sup>L4</sup> and R<sup>L5</sup> are, each independently, H, halogen, C<sub>1-8</sub>alkyl, OC<sub>1-8</sub>alkyl, SC<sub>1-8</sub>alkyl, NHC<sub>1-8</sub>alkyl, N(C<sub>1-8</sub>alkyl)<sub>2</sub>, C<sub>3-11</sub>cycloalkyl, aryl, heteroaryl, C<sub>3-11</sub>heterocyclyl, OC<sub>3-8</sub>cycloalkyl, SC<sub>3-8</sub>cycloalkyl, NHC<sub>3-8</sub>cycloalkyl, N(C<sub>3-8</sub>cycloalkyl)<sub>2</sub>, N(C<sub>3-8</sub>cycloalkyl)(C<sub>1-8</sub>alkyl), OH, NH<sub>2</sub>, SH, SO<sub>2</sub>C<sub>1-8</sub>alkyl, P(O)(OC<sub>1-8</sub>alkyl)(C<sub>1-8</sub>alkyl), P(O)(OC<sub>1-8</sub>alkyl)<sub>2</sub>, CC-C<sub>1-8</sub>alkyl, CCH, CH=CH(C<sub>1-8</sub>alkyl), C(C<sub>1-8</sub>alkyl)=CH(C<sub>1-8</sub>alkyl), C(C<sub>1-8</sub>alkyl)=C(C<sub>1-8</sub>alkyl)<sub>2</sub>, Si(OH)<sub>3</sub>, Si(C<sub>1-8</sub>alkyl)<sub>3</sub>, Si(OH)(C<sub>1-8</sub>alkyl)<sub>2</sub>, COC<sub>1-8</sub>alkyl,

CO<sub>2</sub>H, CN, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, NO<sub>2</sub>, SF<sub>5</sub>, SO<sub>2</sub>NHC<sub>1-8</sub>alkyl, SO<sub>2</sub>N(C<sub>1-8</sub>alkyl)<sub>2</sub>, SONHC<sub>1-8</sub>alkyl, SON(C<sub>1-8</sub>alkyl)<sub>2</sub>, CONHC<sub>1-8</sub>alkyl, CON(C<sub>1-8</sub>alkyl)<sub>2</sub>, N(C<sub>1-8</sub>alkyl)CONH(C<sub>1-8</sub>alkyl), N(C<sub>1-8</sub>alkyl)CON(C<sub>1-8</sub>alkyl)<sub>2</sub>, NHCONH(C<sub>1-8</sub>alkyl), NHCON(C<sub>1-8</sub>alkyl)<sub>2</sub>, NHCONH<sub>2</sub>, N(C<sub>1-8</sub>alkyl)SO<sub>2</sub>NH(C<sub>1-8</sub>alkyl), N(C<sub>1-8</sub>alkyl) SO<sub>2</sub>N(C<sub>1-8</sub>alkyl)<sub>2</sub>, NH SO<sub>2</sub>NH(C<sub>1-8</sub>alkyl), NH SO<sub>2</sub>N(C<sub>1-8</sub>alkyl)<sub>2</sub>, or NH SO<sub>2</sub>NH<sub>2</sub>.

14. The compound according to any one of claim 1-11, wherein the L includes an optionally substituted C<sub>6</sub>-C<sub>30</sub> alkyl (e.g., C<sub>6</sub>, C<sub>7</sub>, C<sub>8</sub>, C<sub>9</sub>, C<sub>10</sub>, C<sub>11</sub>, C<sub>12</sub>, C<sub>13</sub>, C<sub>14</sub>, C<sub>15</sub>, C<sub>16</sub>, C<sub>17</sub>, C<sub>18</sub>, C<sub>19</sub>, C<sub>20</sub>, C<sub>21</sub>, C<sub>22</sub>, C<sub>23</sub>, C<sub>24</sub>, C<sub>25</sub>, C<sub>26</sub>, C<sub>27</sub>, C<sub>28</sub>, C<sub>29</sub>, or C<sub>30</sub> alkyl), wherein each carbon is optionally substituted or replaced with (1) a heteroatom selected from O, N, S, P, or Si atoms that has an appropriate number of hydrogens, substitutions, or both to complete valency, (2) an optionally substituted cycloalkyl or bicyclic cycloalkyl, (3) an optionally substituted heterocyloalkyl or bicyclic heterocyloalkyl, (4) an optionally substituted aryl or bicyclic aryl, or (5) optionally substituted heteroaryl or bicyclic heteroaryl, with the proviso that there is no heteroatom-heteroatom bonding (e.g., no heteroatoms are covalently linked or adjacently located).

15. The compound according to any one of claim 1-11, wherein the 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 6-20 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20), and wherein L is covalently bound to both the PTM and the ULM, and provides for binding of the PTM to the protein target and the ULM to an E3 ubiquitin ligase in sufficient proximity to result in target protein ubiquitination.

16. The compound according to any of claims 1-15, wherein the L comprises the following chemical structure:



wherein:

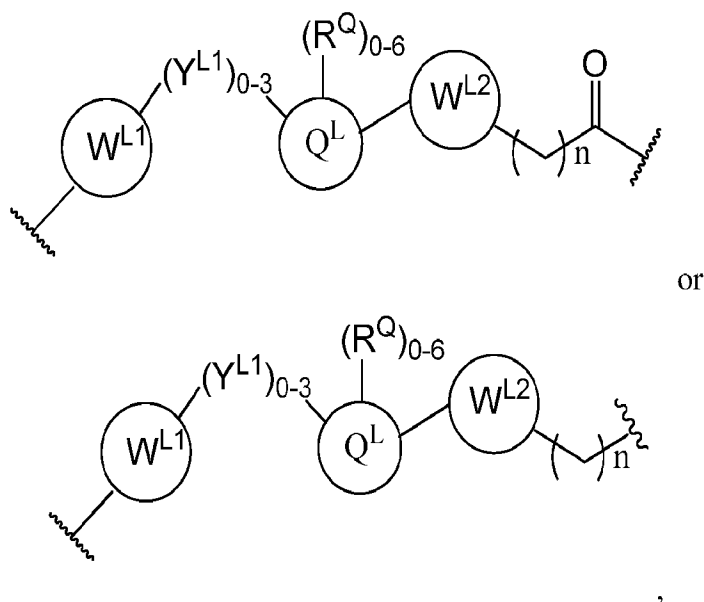
$W^{L1}$  and  $W^{L2}$  are each independently absent, a 4-8 membered ring with 0-4 heteroatoms, optionally substituted with  $R^Q$ , each  $R^Q$  is independently a H, halo, OH, CN,  $CF_3$ , unsubstituted or substituted linear or branched C1-C6, unsubstituted or substituted linear or branched C1-C6 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, unsubstituted or substituted linear or branched C1-C6 alkyl and optionally one or more C atoms are replaced with O; or unsubstituted or substituted linear or branched C1-C6 alkoxy;

n is 0-10; and

 and  indicate the attachment point to the PTM or the CLM.

17. The compound according to any of claims 1-15, wherein the L comprises the following chemical structure:



wherein:

$W^{L1}$  and  $W^{L2}$  are each independently absent, aryl, heteroaryl, cyclic, heterocyclic, C<sub>1-6</sub> alkyl and optionally one or more C atoms are replaced with O, C<sub>1-6</sub> alkene and optionally one or more C atoms are replaced with O, C<sub>1-6</sub> 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<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, unsubstituted or substituted linear or branched C<sub>1-6</sub>

alkyl, unsubstituted or substituted linear or branched C<sub>1</sub>-C<sub>6</sub> alkoxy, OC<sub>1-3</sub>alkyl optionally substituted by 1 or more -F, OH, NH<sub>2</sub>, NR<sup>Y1</sup>R<sup>Y2</sup>, CN, or 2 R<sup>Q</sup> groups taken together with the atom they are attached to, form a 4-8 membered ring system containing 0-4 heteroatoms;

Y<sup>L1</sup> is each independently: a bond; NR<sup>YL1</sup>; O; S; NR<sup>YL2</sup>; CR<sup>YL1</sup>R<sup>YL2</sup>; C=O; C=S; SO; SO<sub>2</sub>; unsubstituted or substituted linear or branched C<sub>1</sub>-C<sub>6</sub> alkyl with one or more C atoms are optionally replaced with O; unsubstituted or substituted linear or branched C<sub>1</sub>-C<sub>6</sub> alkoxy;

Q<sup>L</sup> is a 3-6 membered alicyclic or aromatic ring with 0-4 heteroatoms, optionally bridged, optionally substituted with 1-6 R<sup>Q</sup>, each R<sup>Q</sup> is independently H, linear or branched C<sub>1-6</sub> alkyl optionally substituted by 1 or more halo or C<sub>1-6</sub> alkoxy, or 2 R<sup>Q</sup> groups taken together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms;

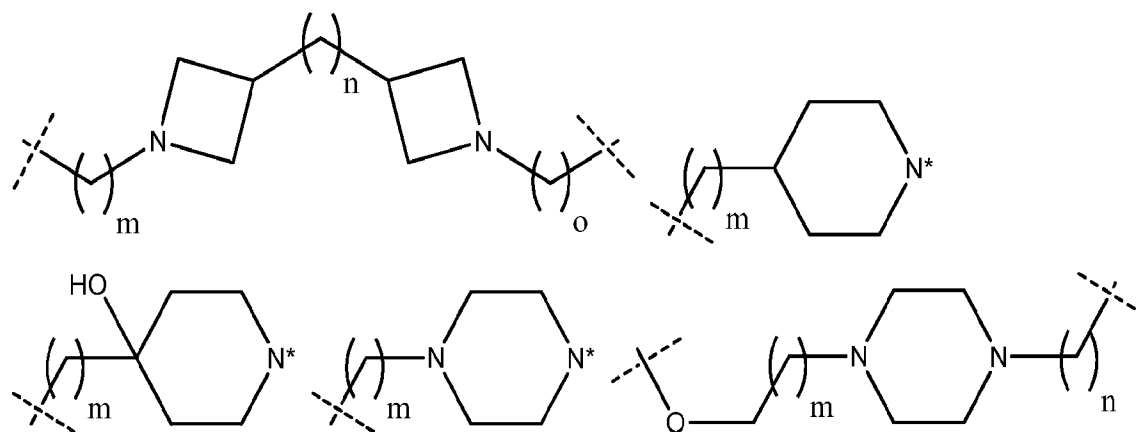
R<sup>YL1</sup>, R<sup>YL2</sup> are each independently: H; OH; linear or branched C<sub>1-6</sub> alkyl optionally substituted by 1 or more halo or C<sub>1-6</sub> alkoxy; or R<sup>YL1</sup>, R<sup>YL2</sup> together with the atom they are attached to, form a 3-8 membered ring system containing 0-2 heteroatoms;

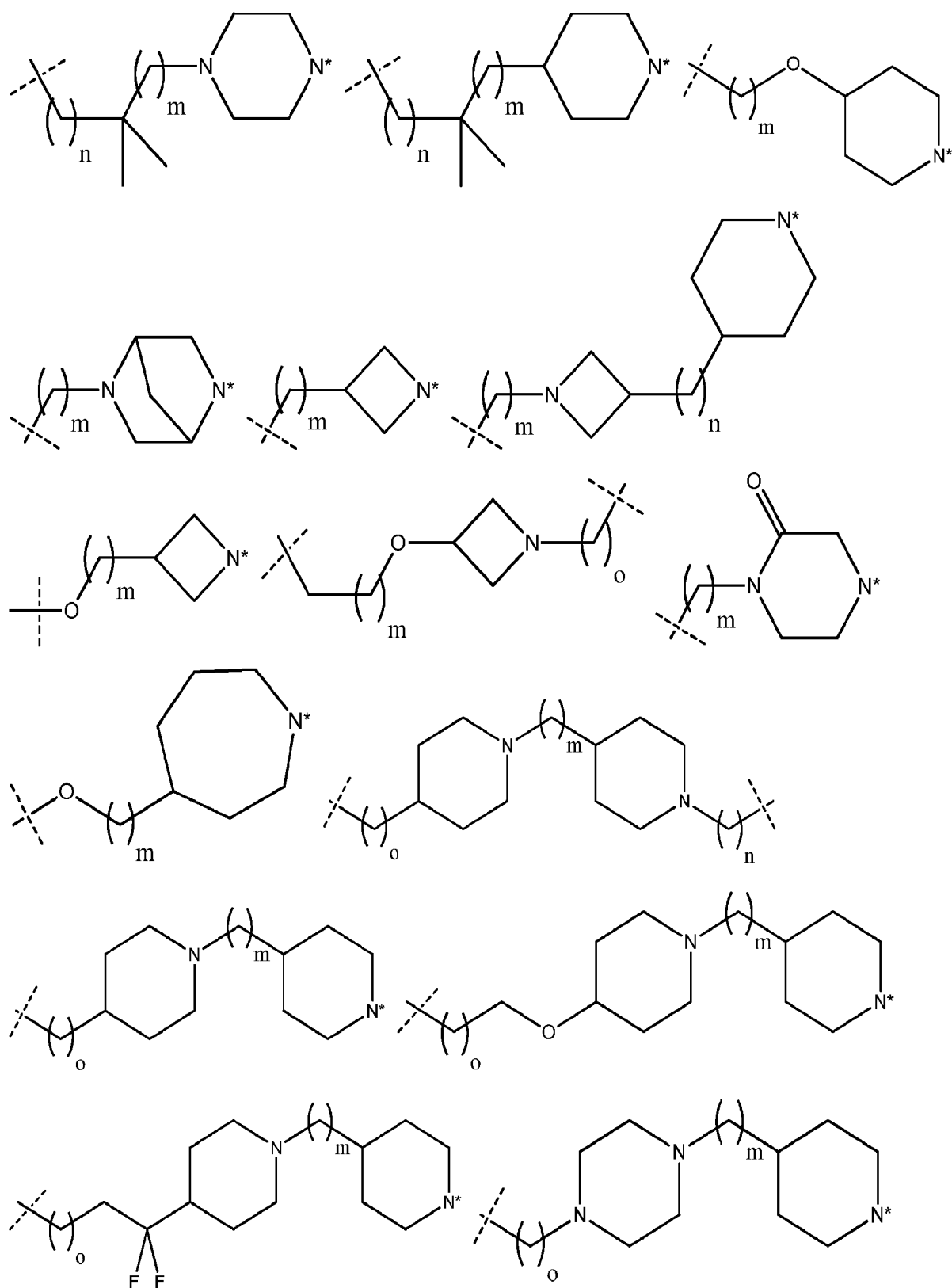
n is 0-10; and

 and  indicate the attachment point to the PTM or the CLM.

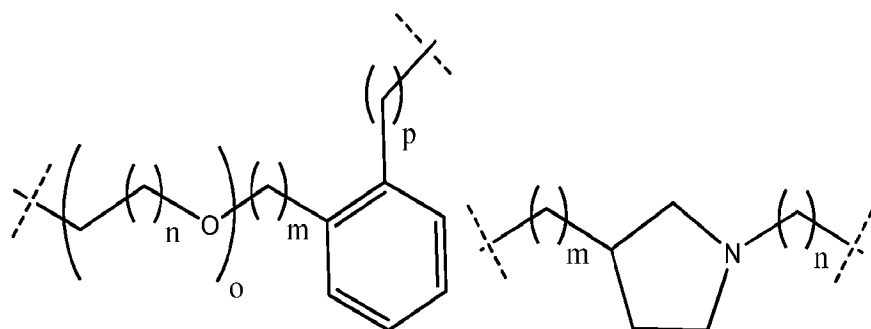
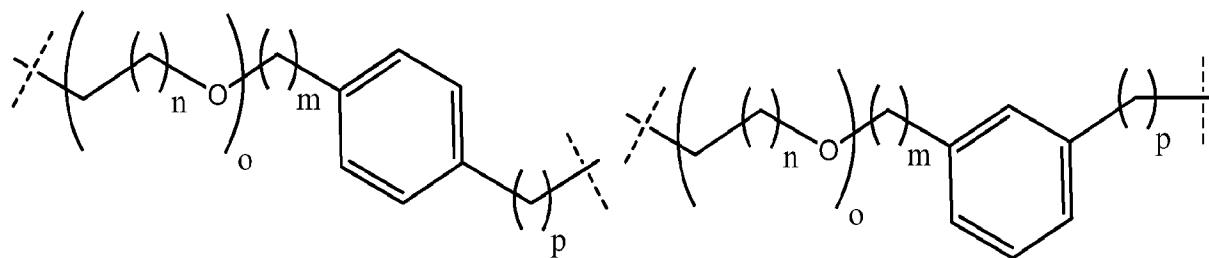
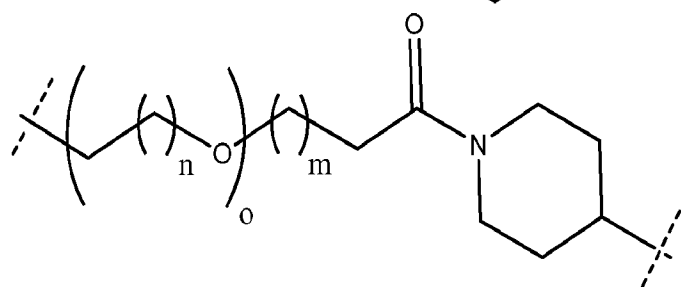
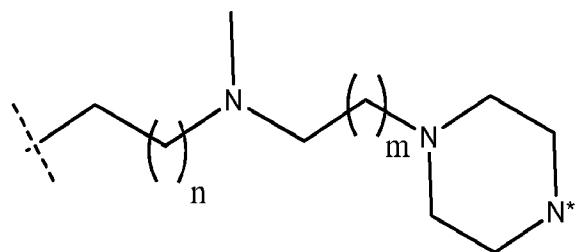
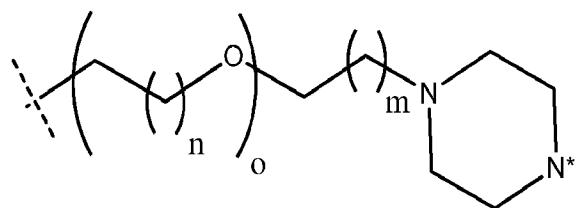
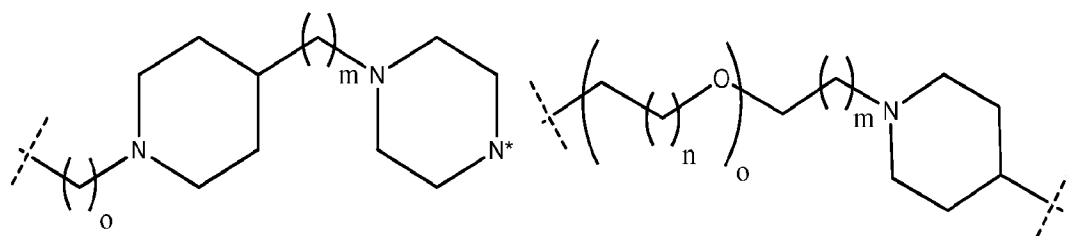
18. The compound according to any of claims 1-17, wherein L is a means for covalently coupling the PTM to the CLM.

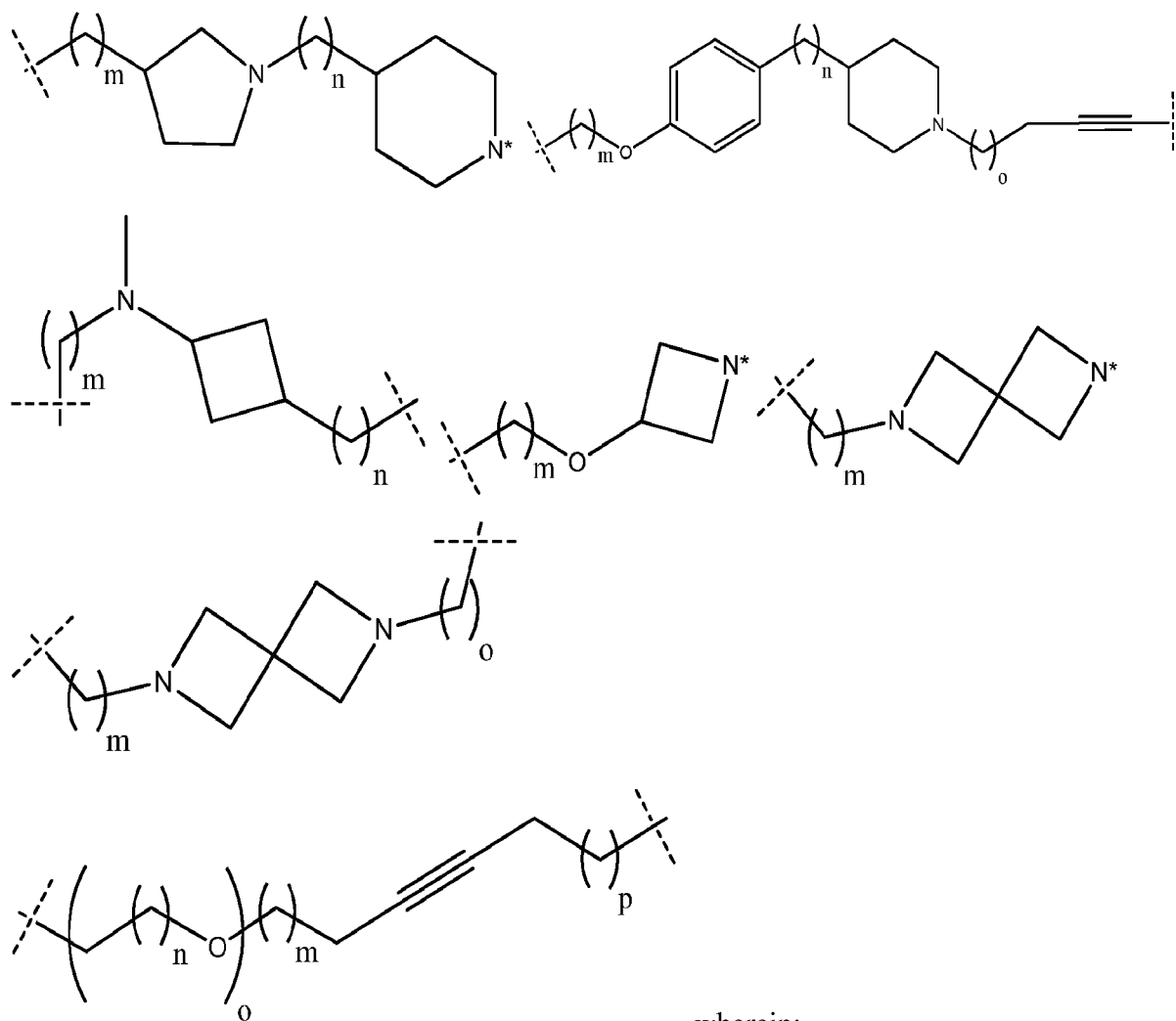
19. The compound according to any of claims 1-18, wherein the L is selected from the group consisting of:









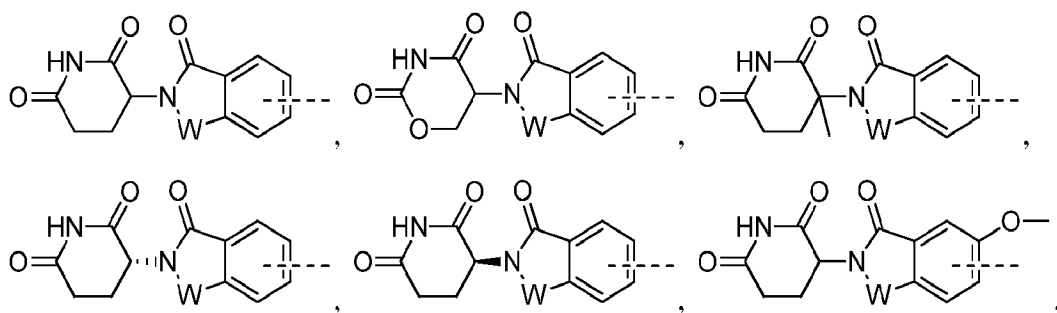


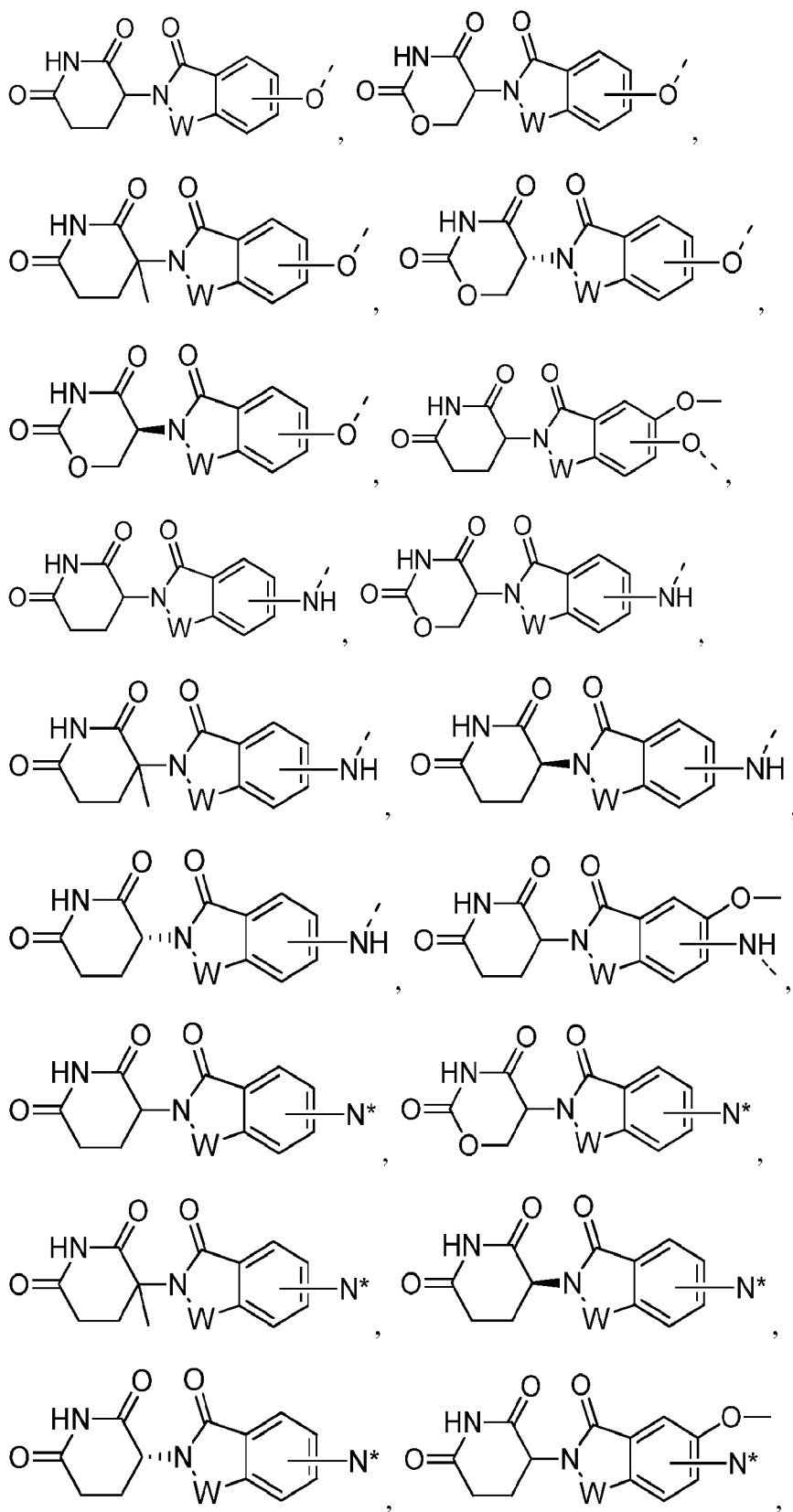
, wherein:

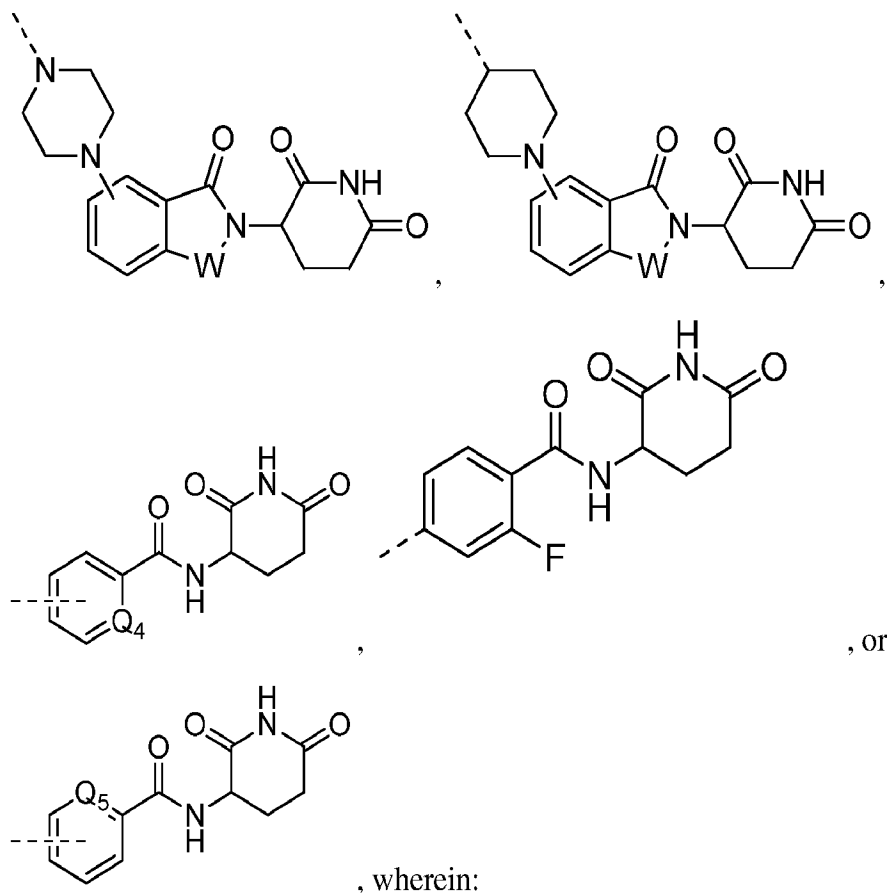
N\* is a nitrogen atom that is covalently linked to the CLM or the PTM, or that is shared with the CLM or the PTM; and  
 each m, n, o, p, q, and r is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

20. The compound according to any of claims 1-19, wherein at least one of:

(a) the CLM is represented by:



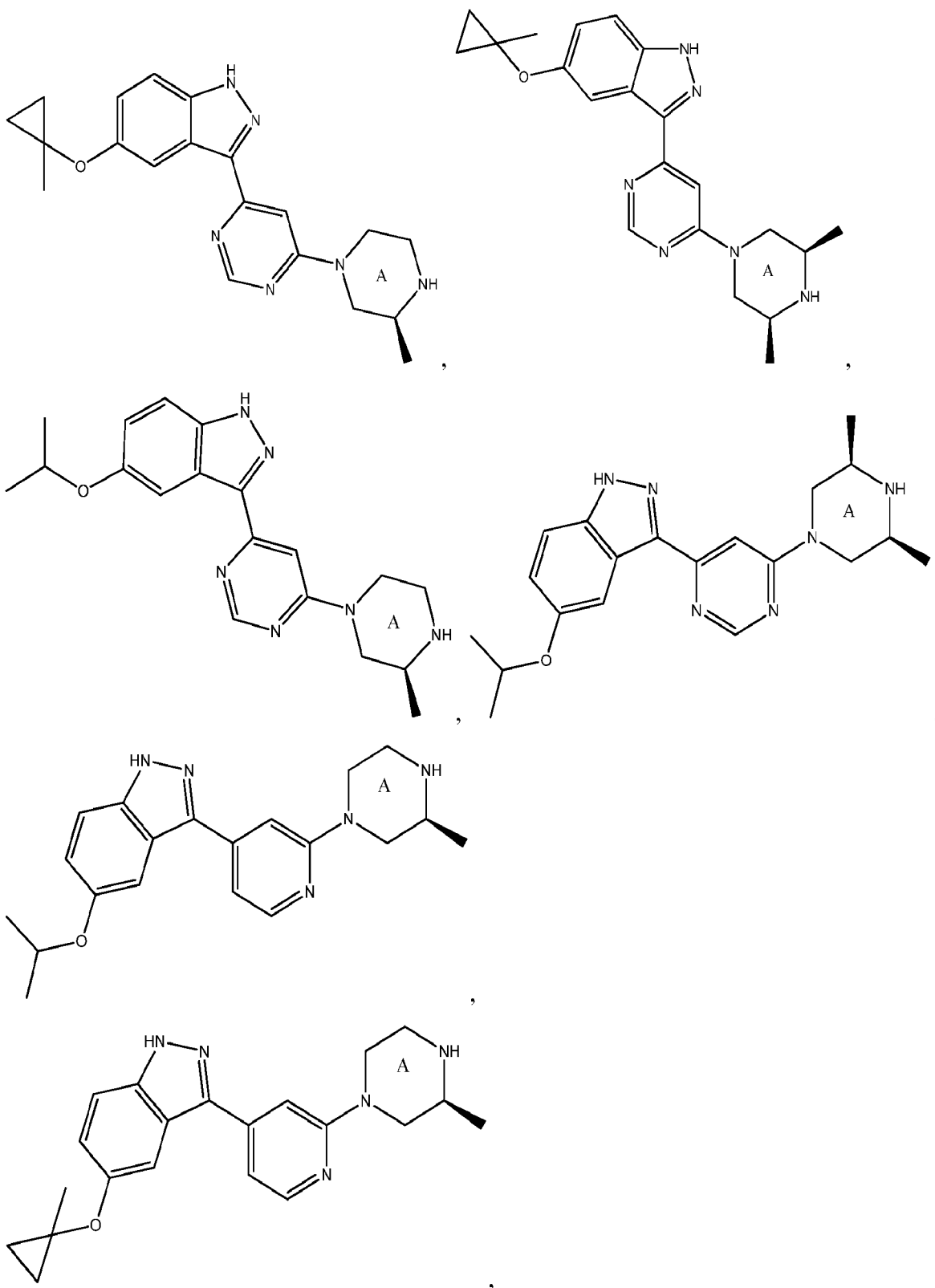


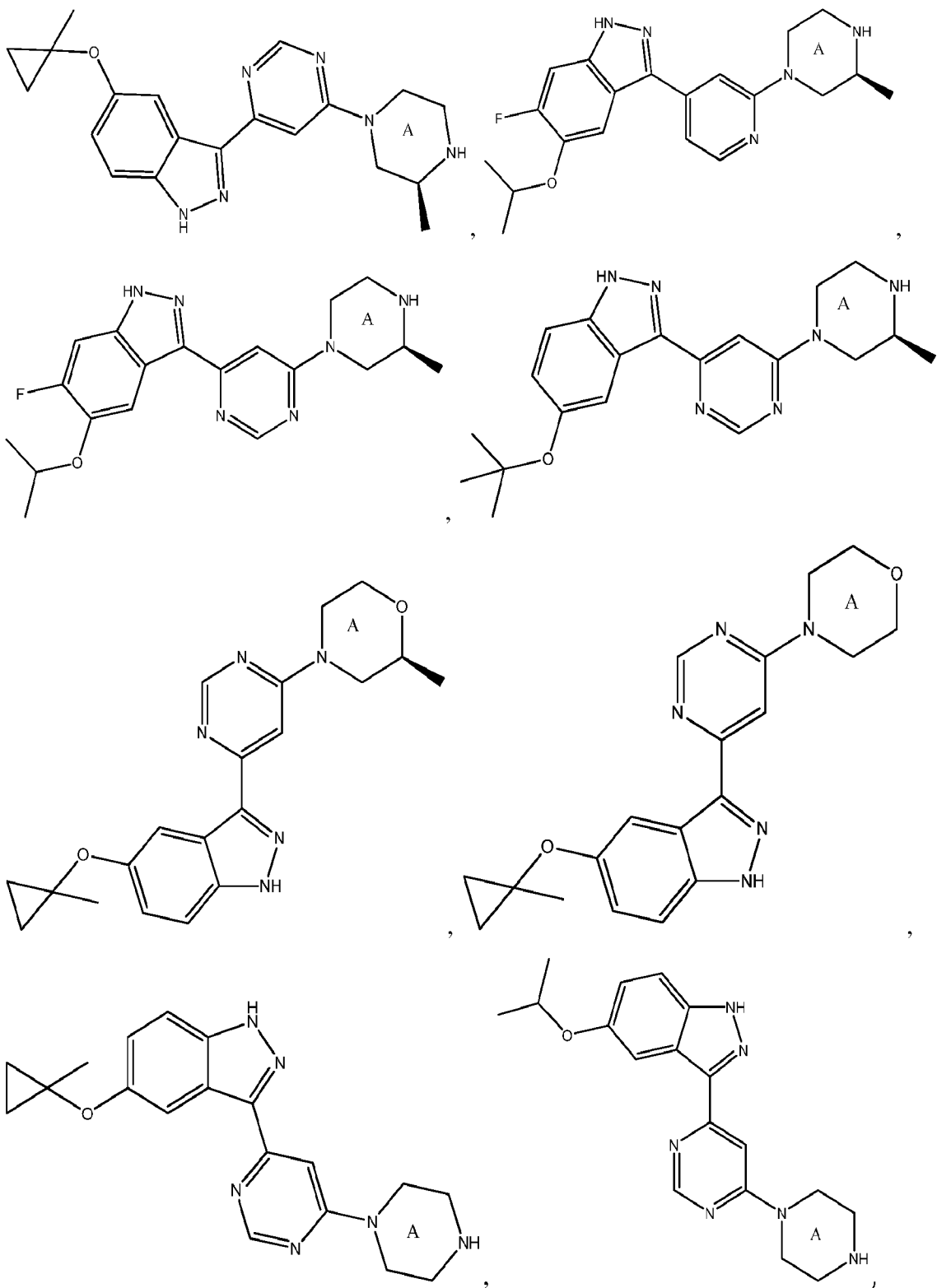


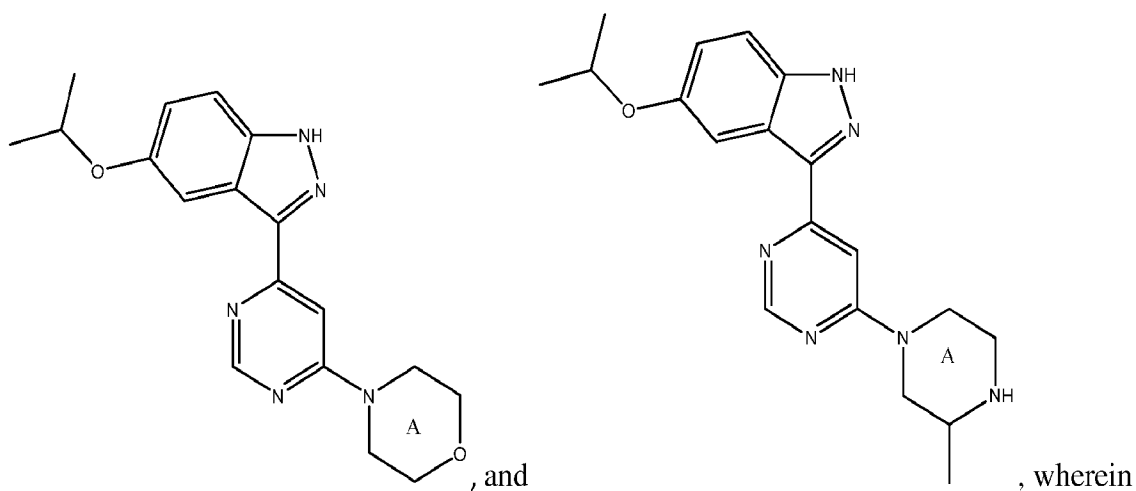
--- of the ULM indicates the point of attachment with the L or the PTM; and

N\* is a nitrogen atom that is shared with the L or the PTM;

(b) the PTM is represented by:

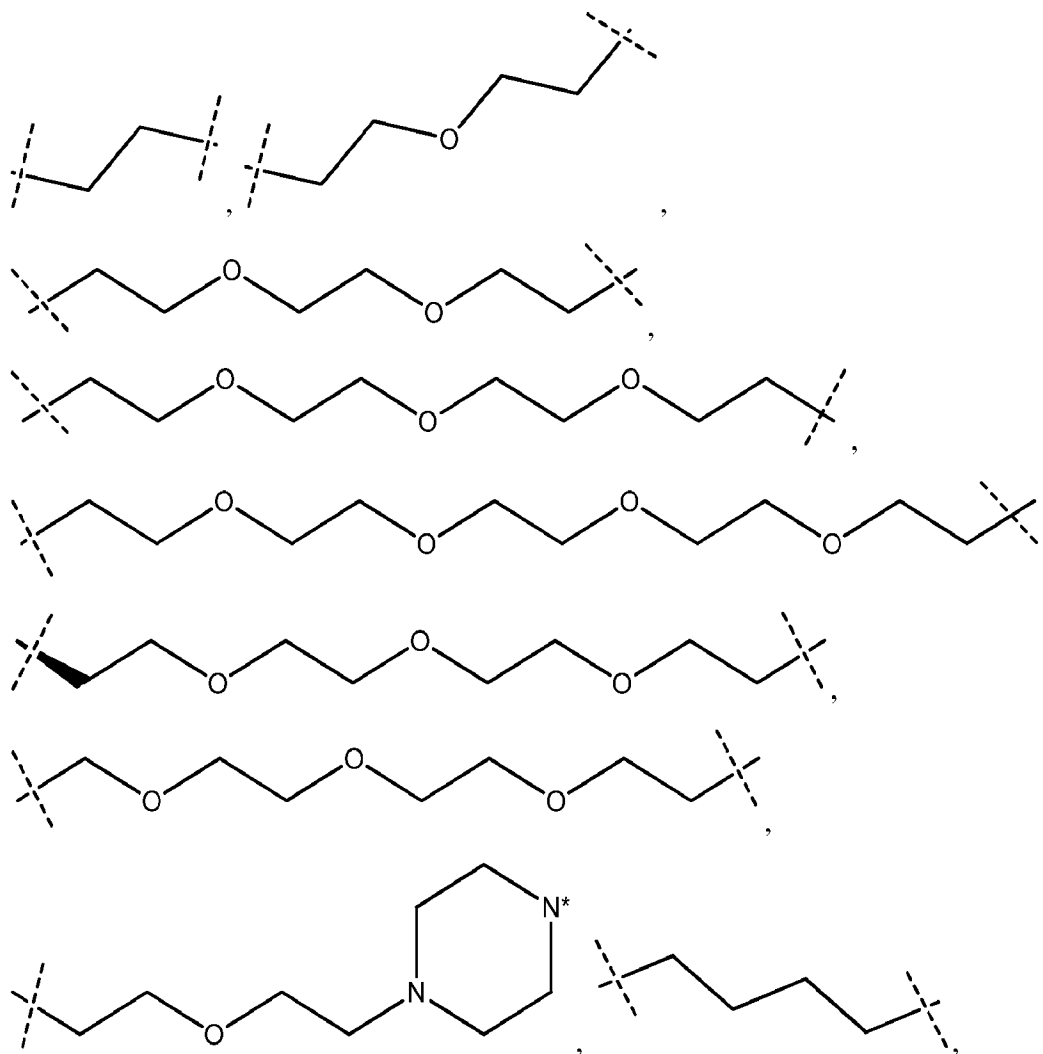


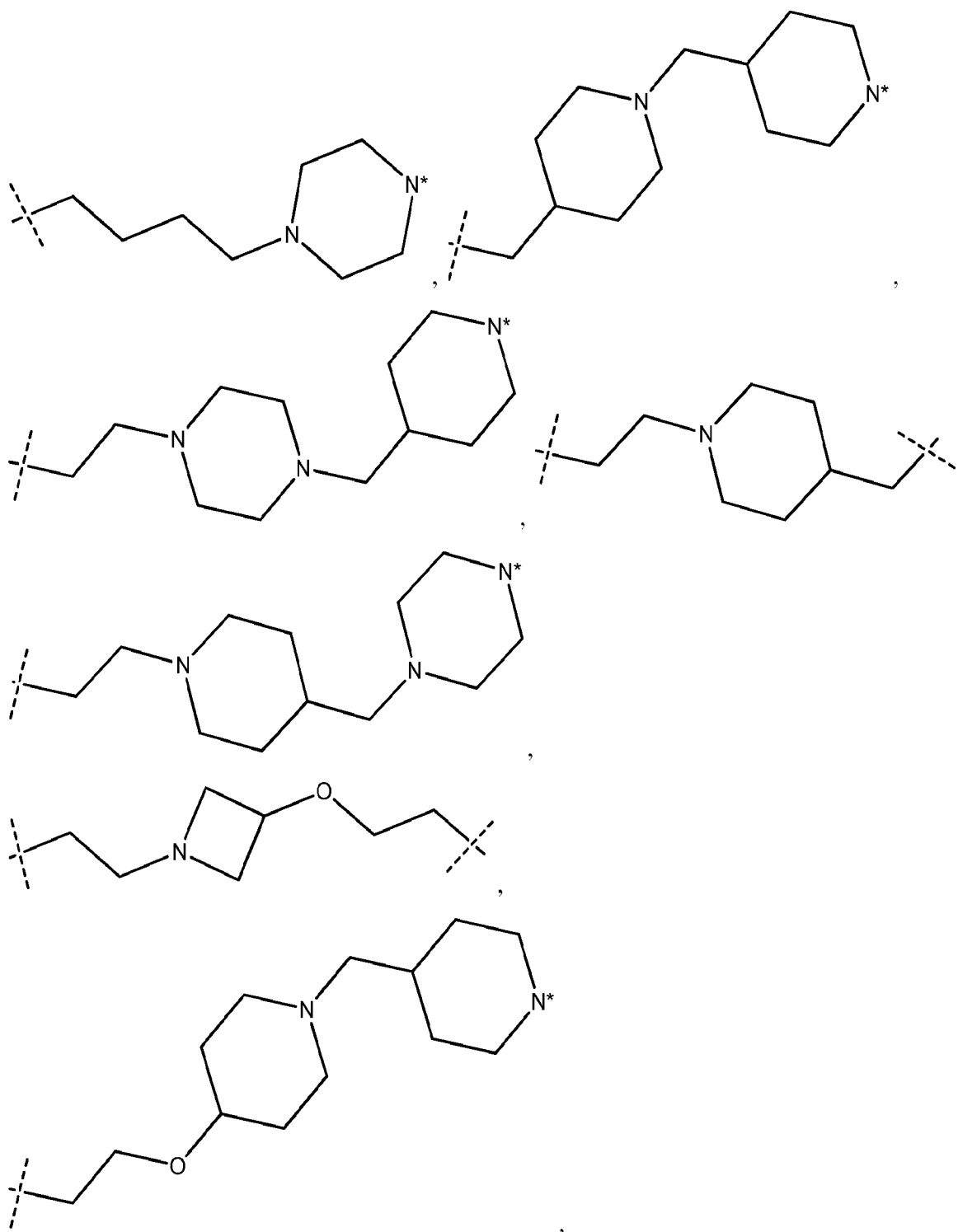




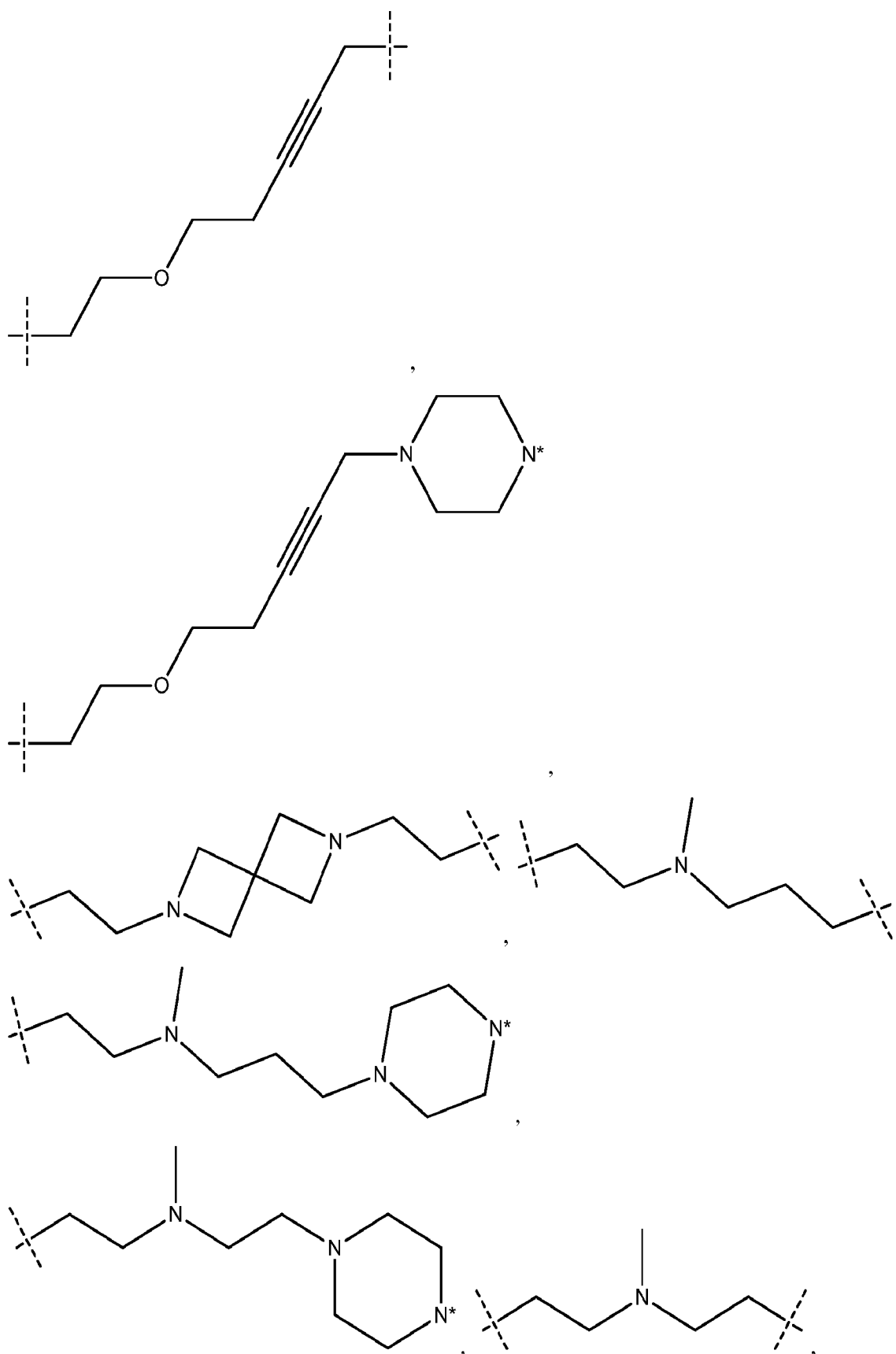
the PTM is covalently linked to the L or the CLM via an atom of heterocycloalkyl A or a substituent thereof;

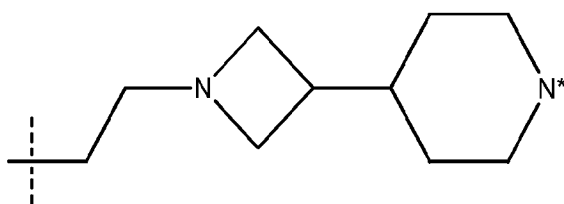
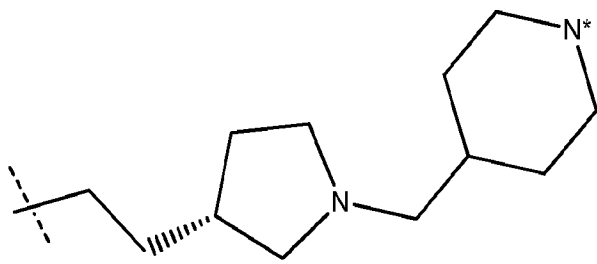
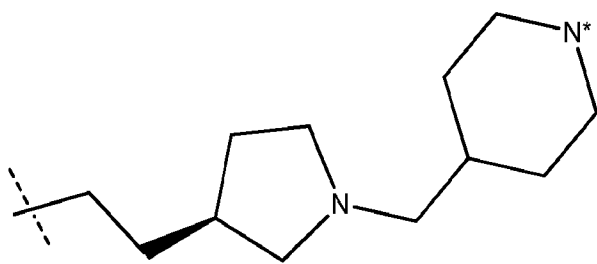
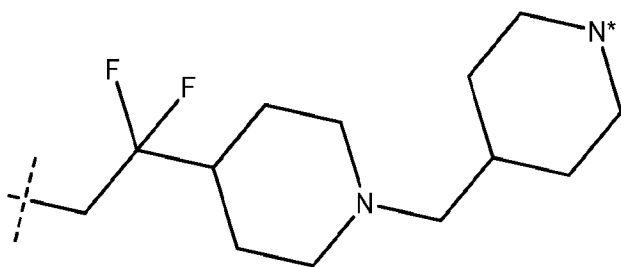
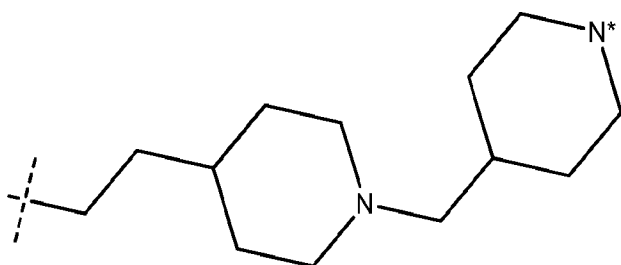
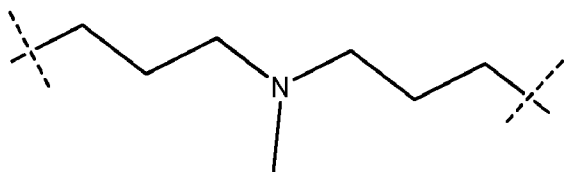
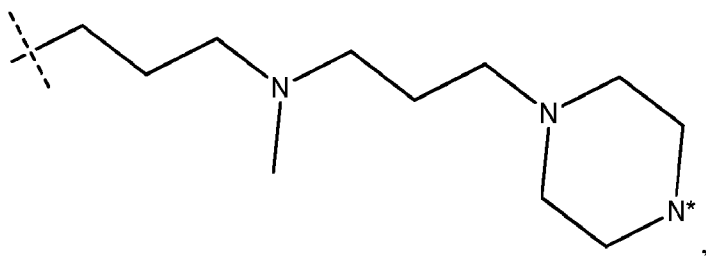
(c) the L is a linker group (L) selected from:

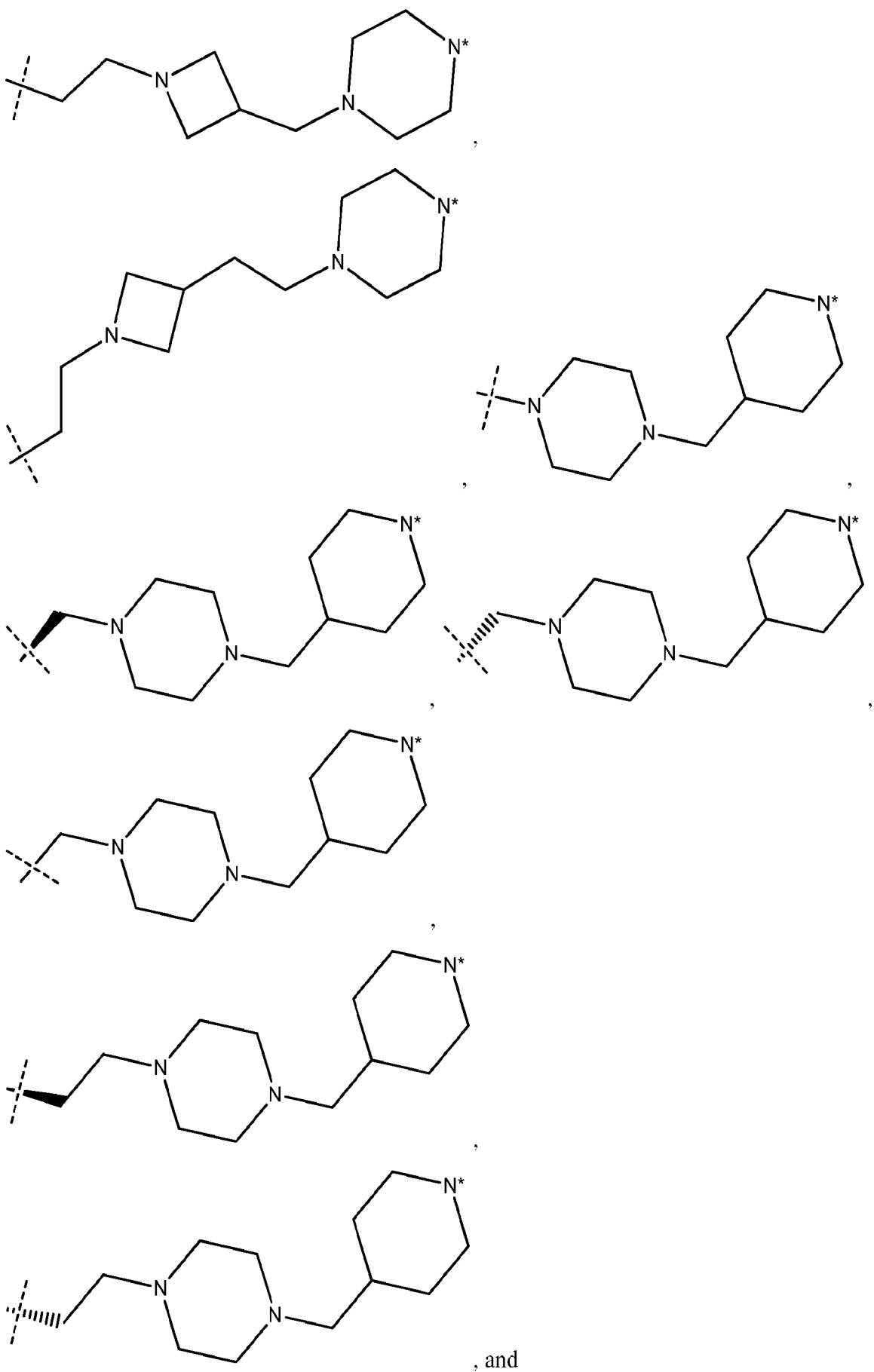


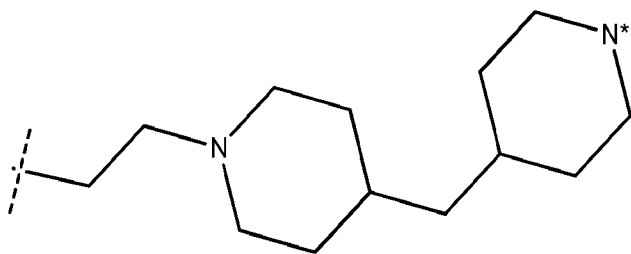












, wherein N\* is a nitrogen atom that is covalently linked to the CLM or the PTM, or that is shared with the CLM or the PTM; or (d) a combination thereof.

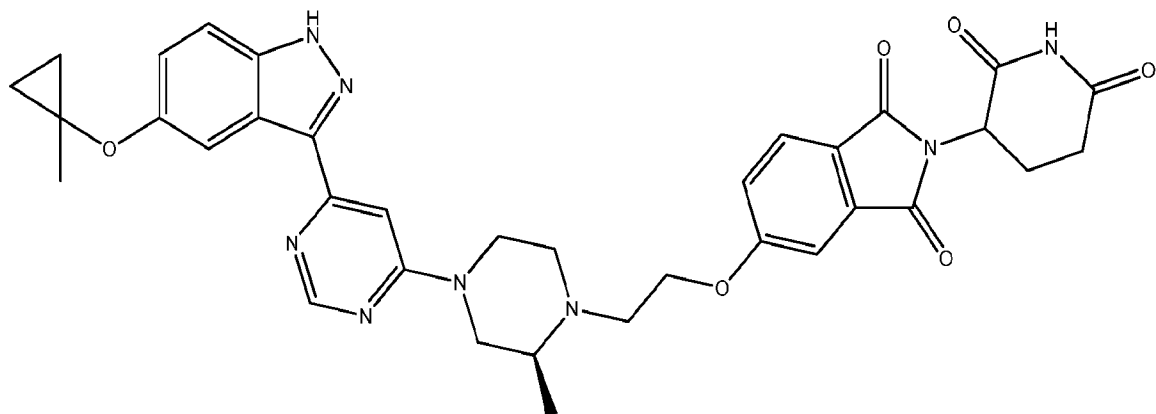
21. The compound according to claim 1, wherein at least one of:

the PTM is a PTM selected from a compound of Table 1;

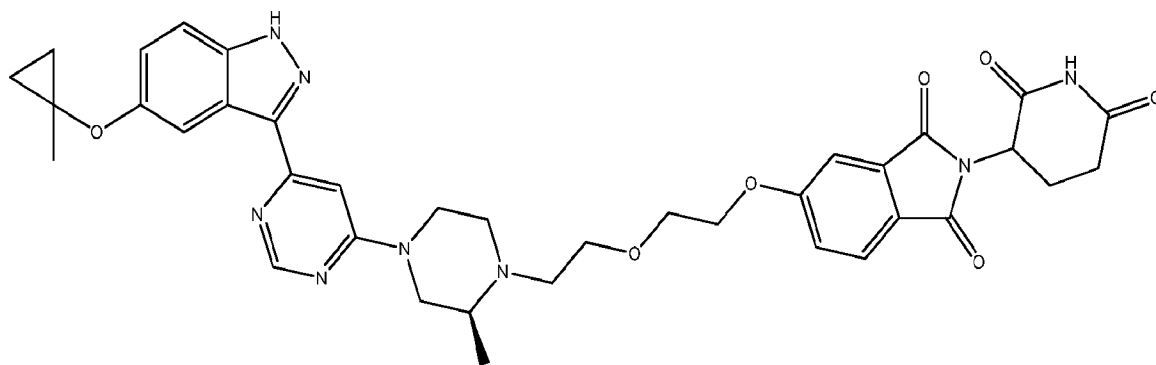
the CLM is a CLM selected from a compound of Table 1; and

the L is an L selected from a compound of Table 1.

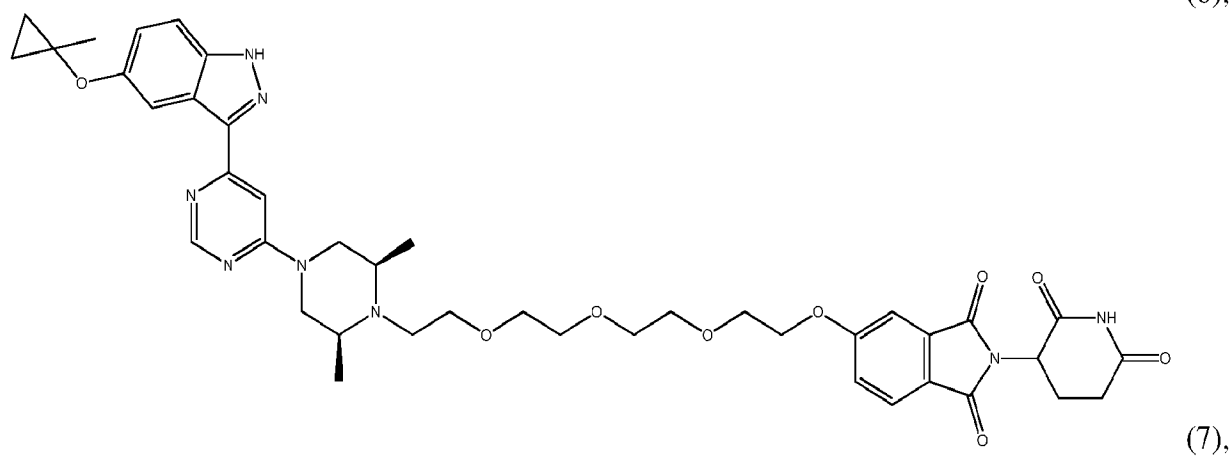
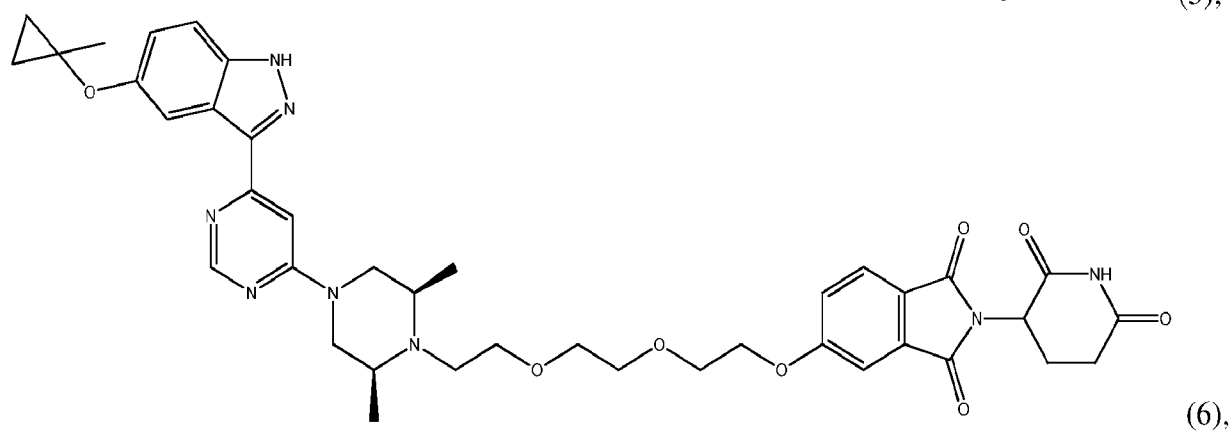
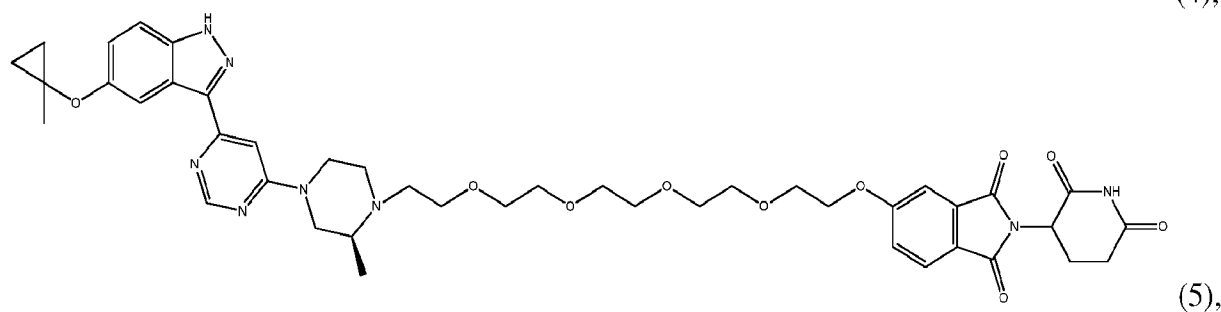
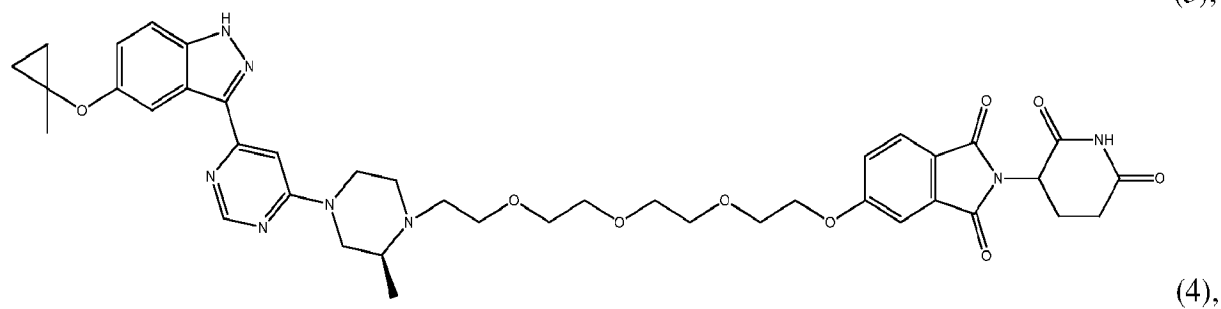
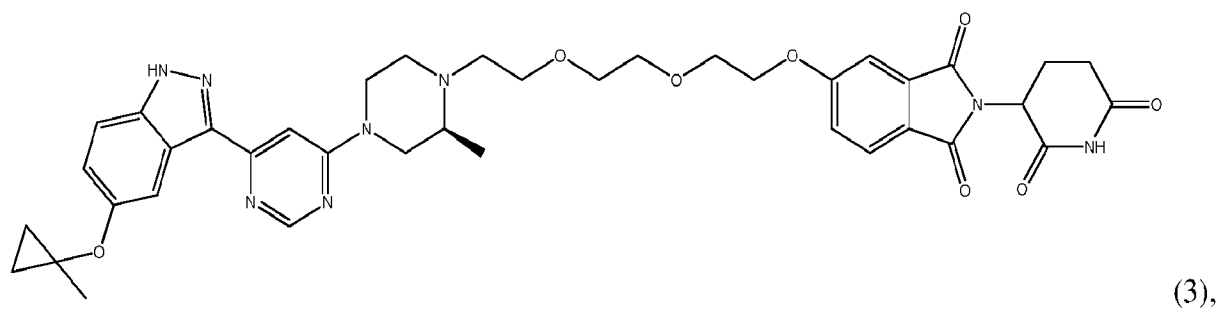
22. The compound of claim 1, wherein the compound is selected from the group consisting of compounds 1-51 of Table 1:

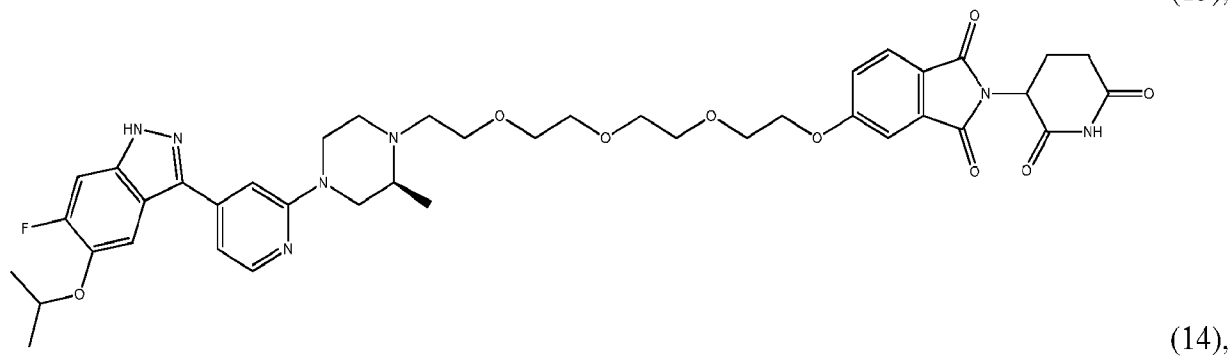
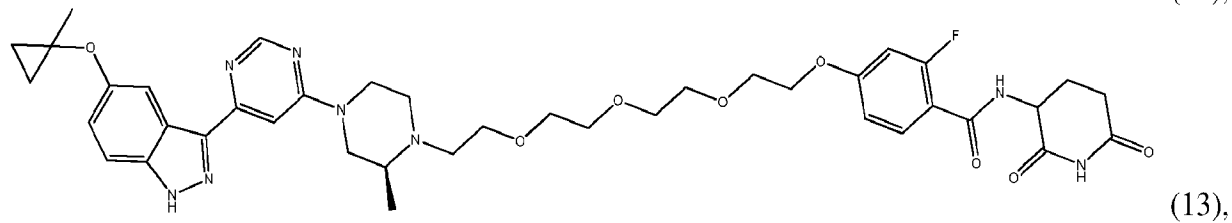
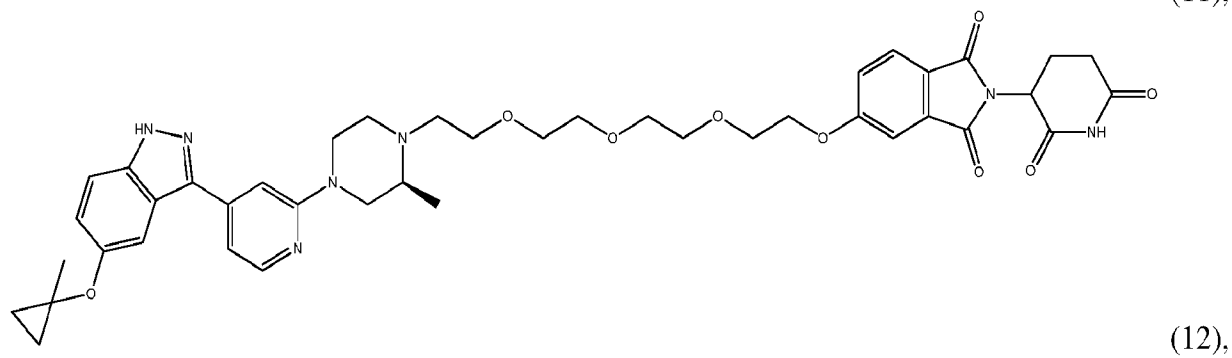
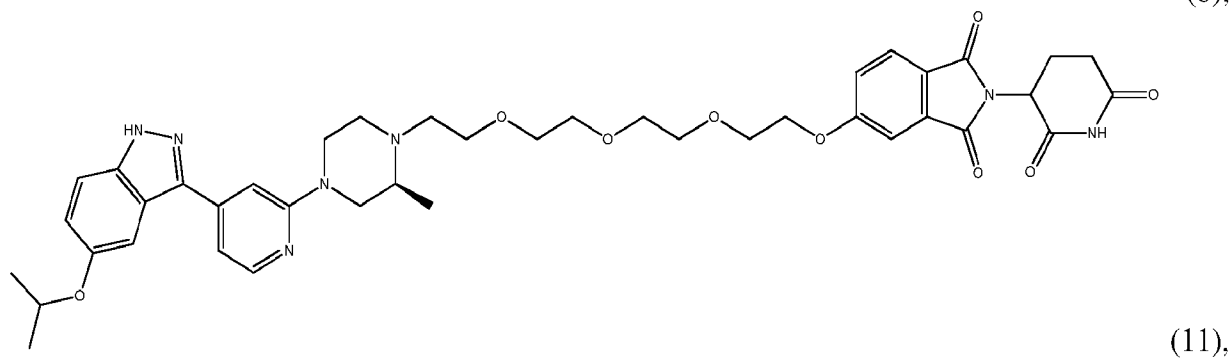
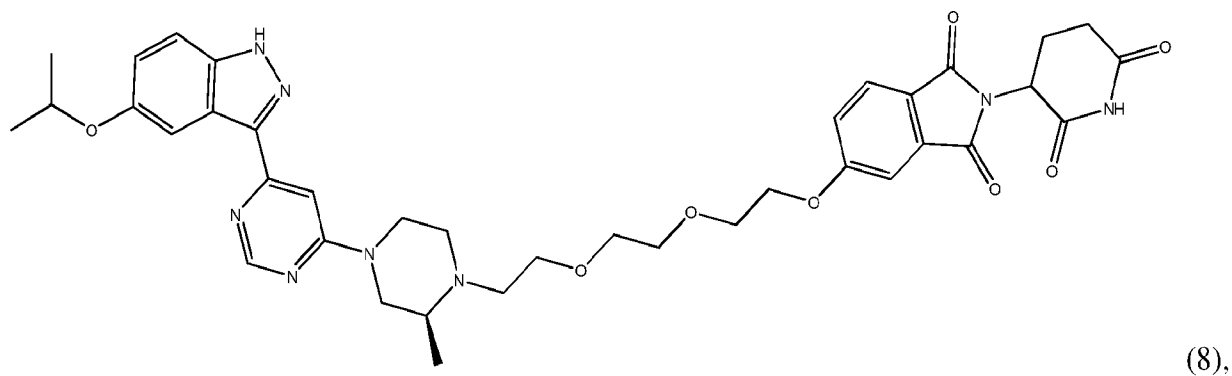


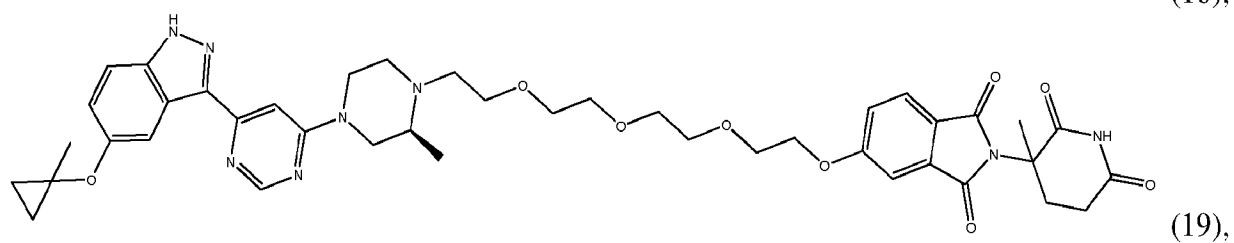
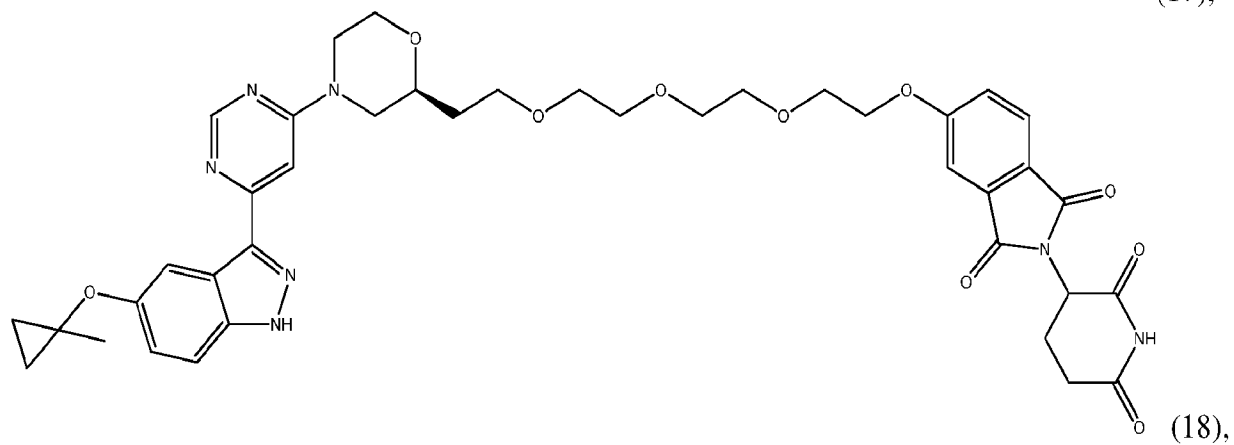
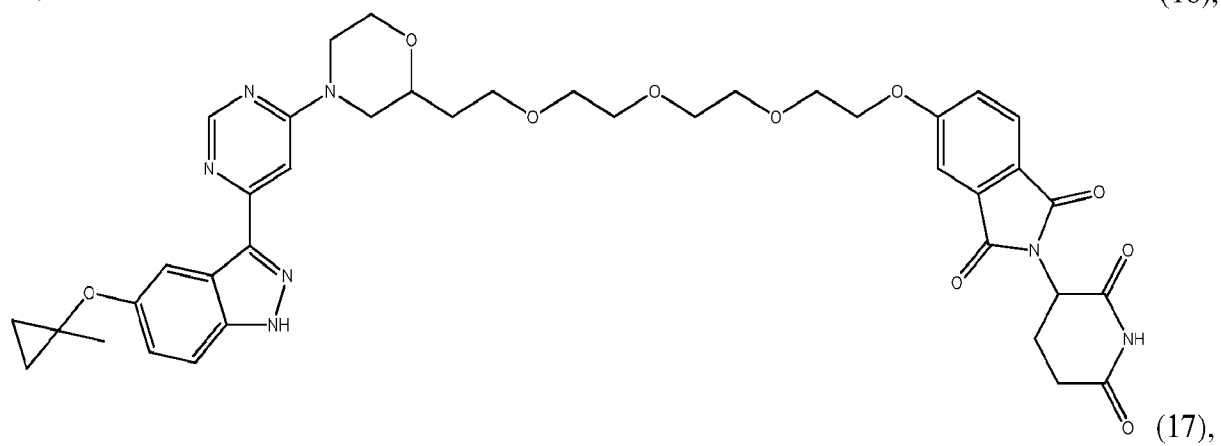
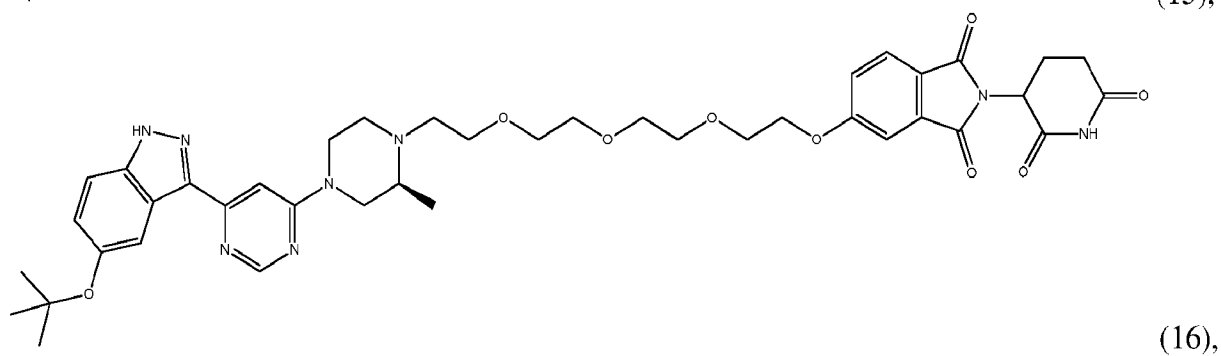
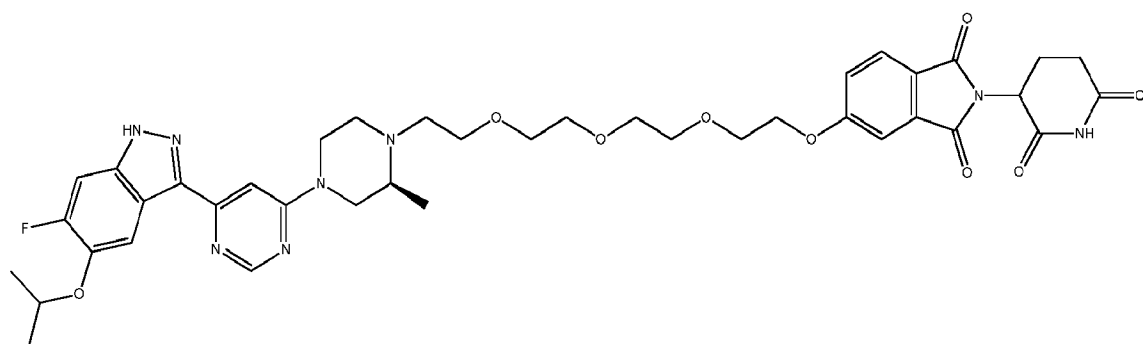
(1),

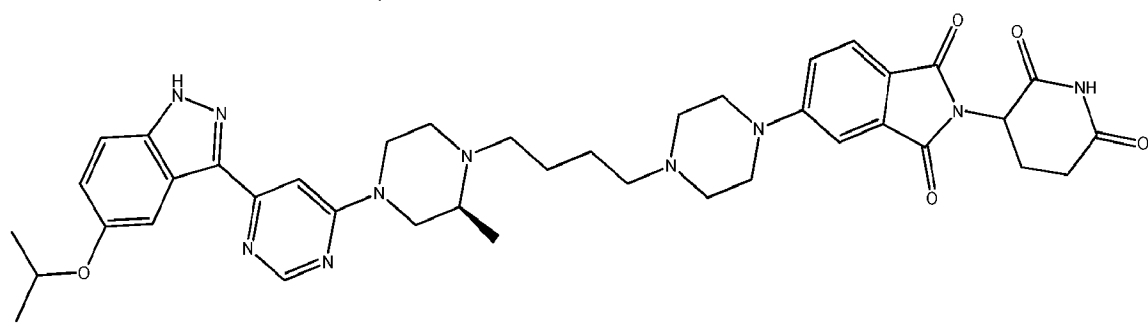
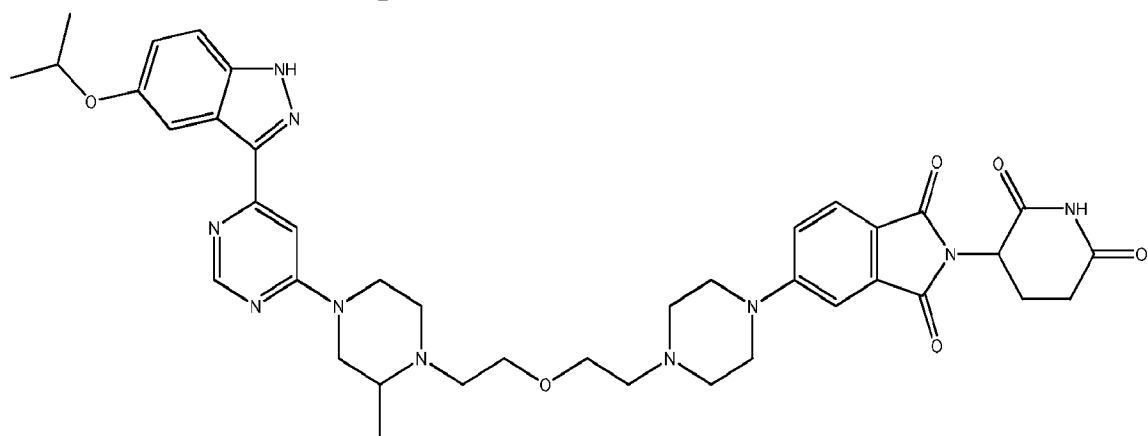
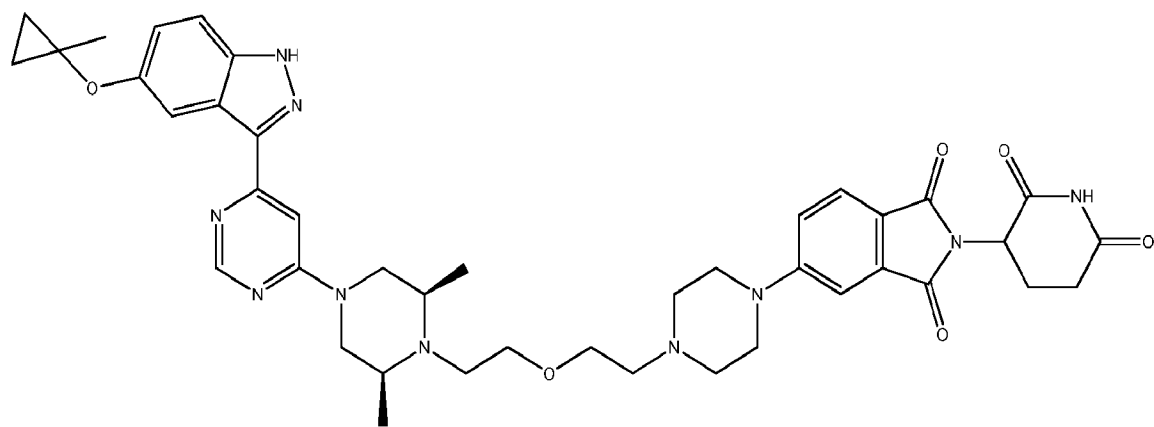
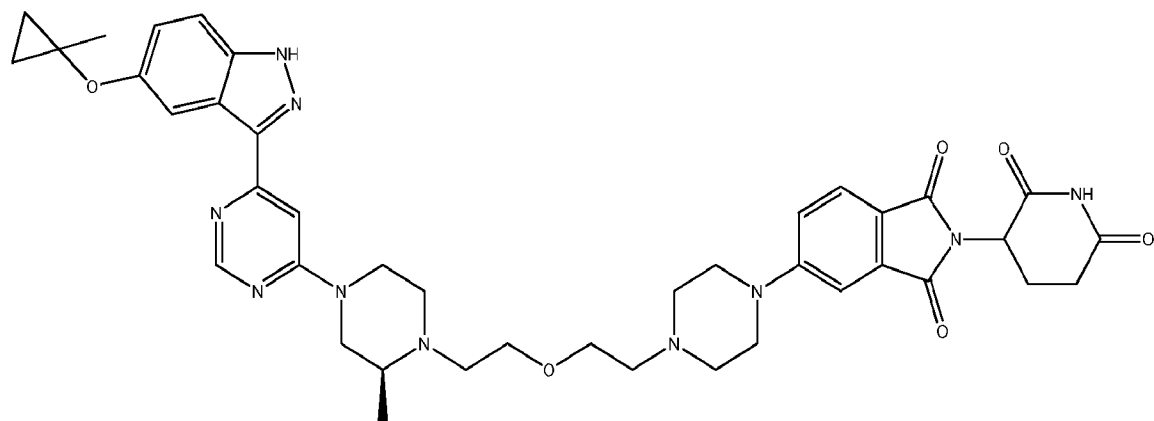


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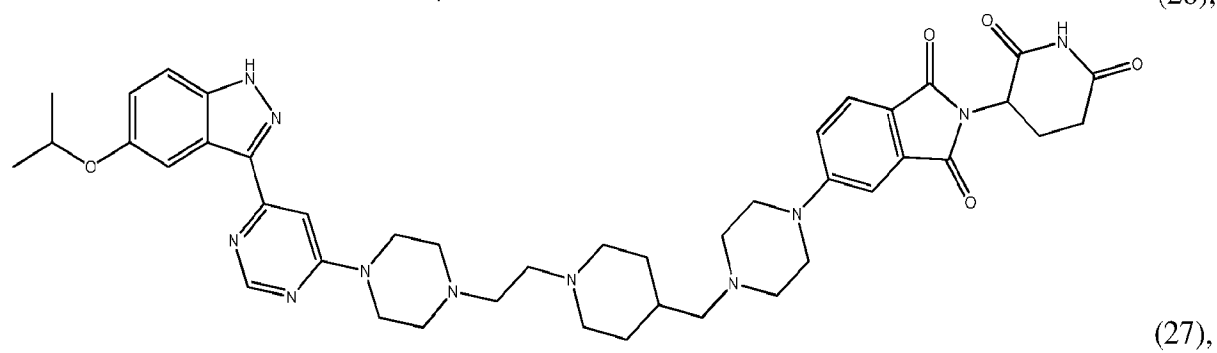
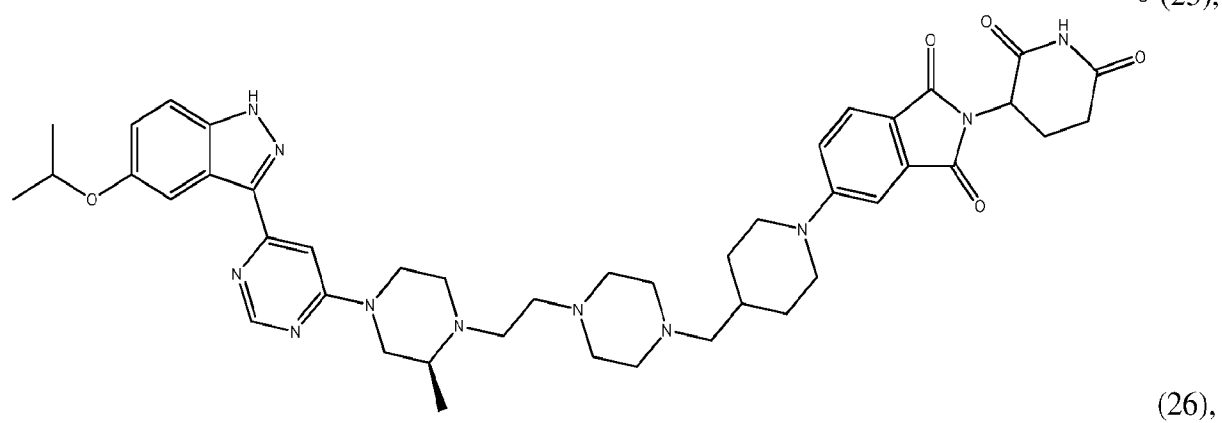
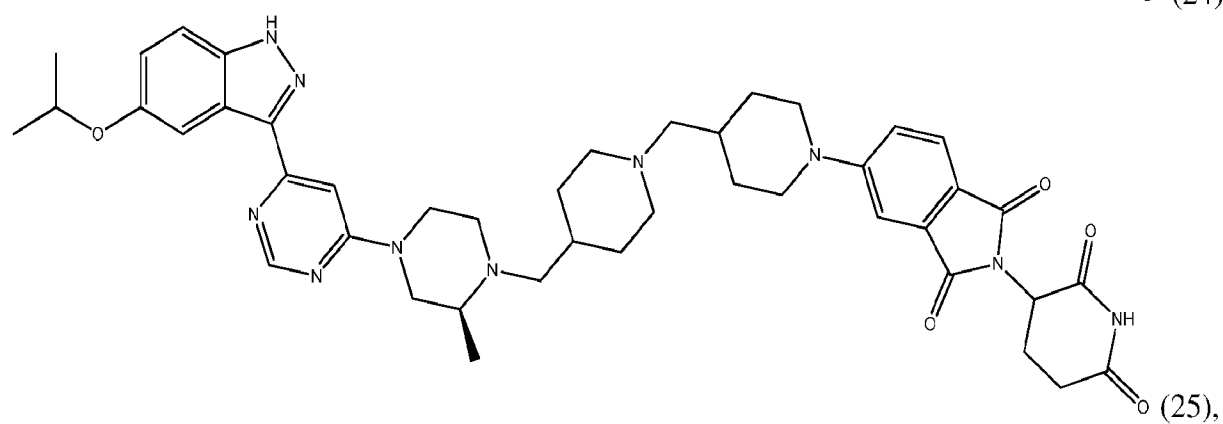
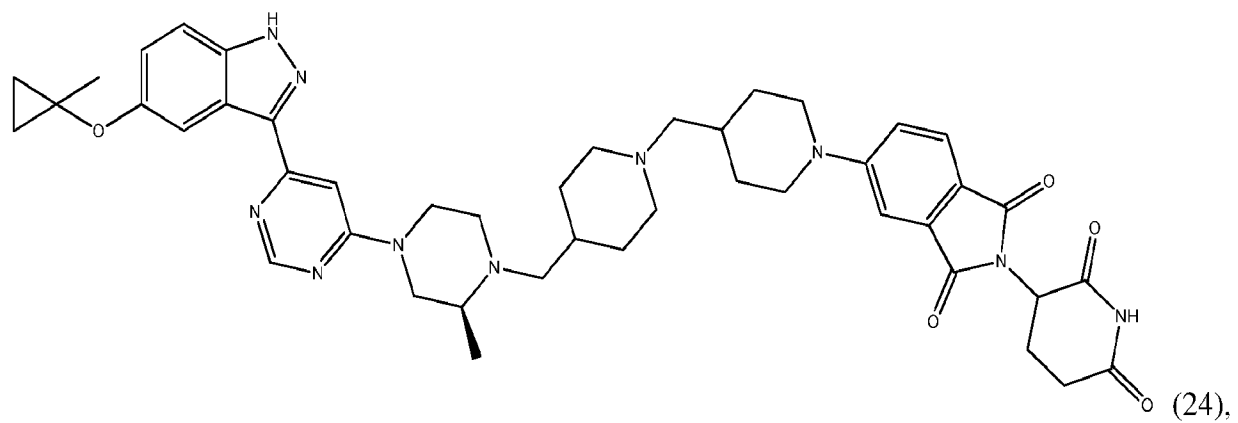


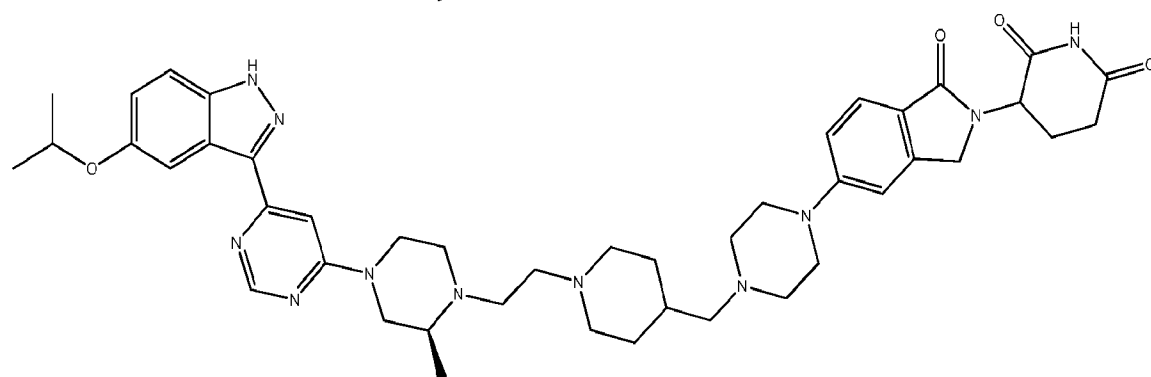
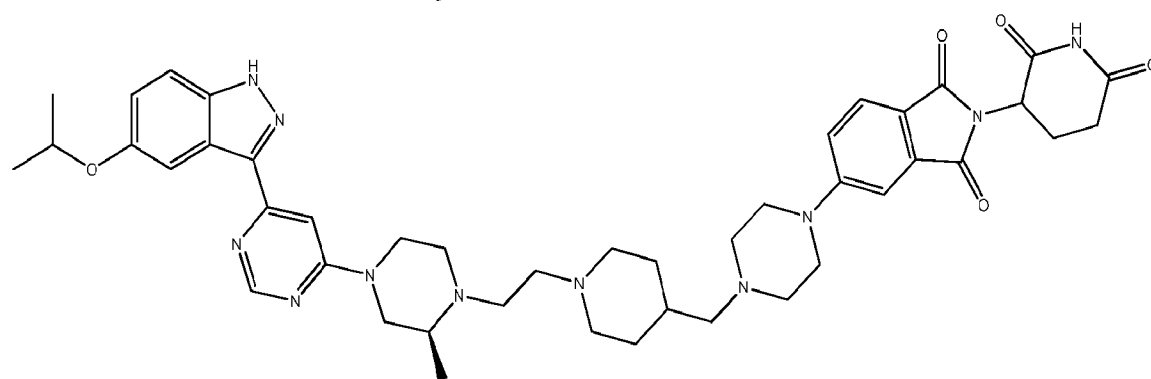
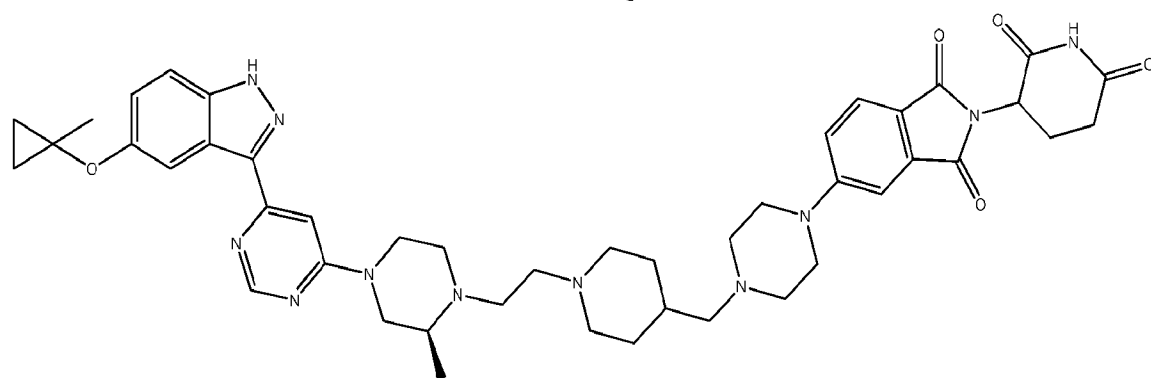
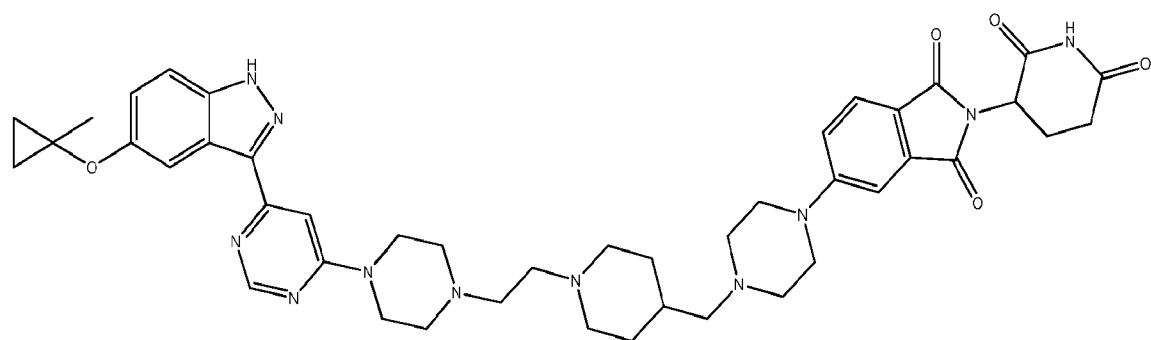


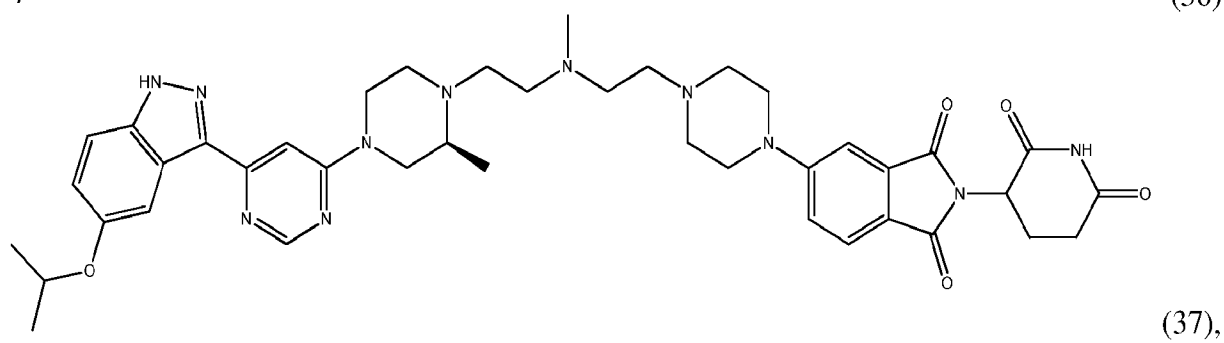
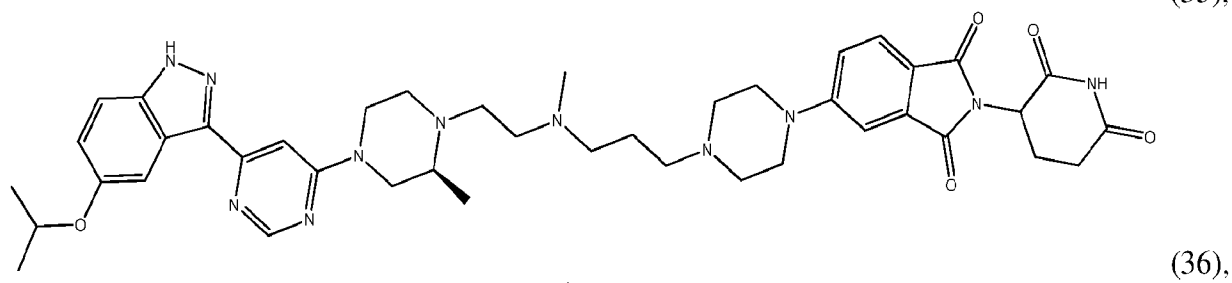
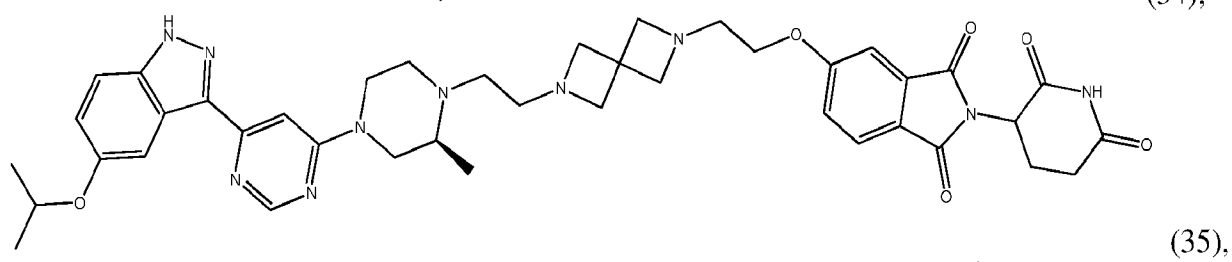
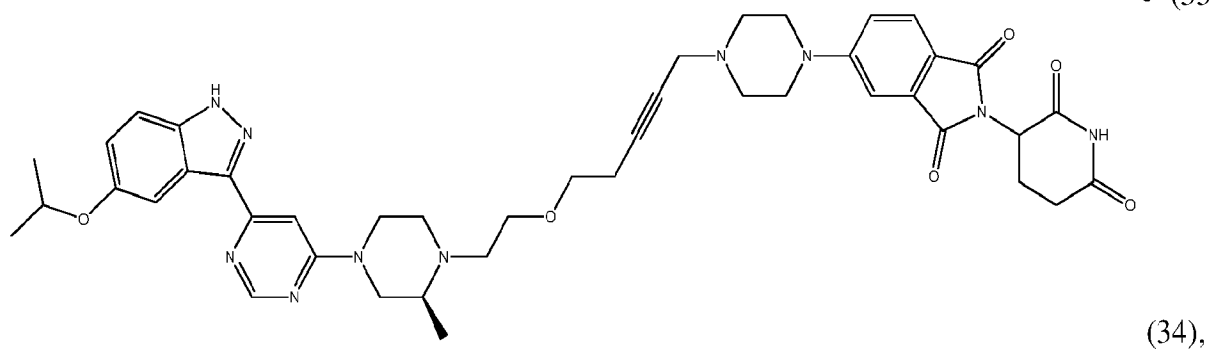
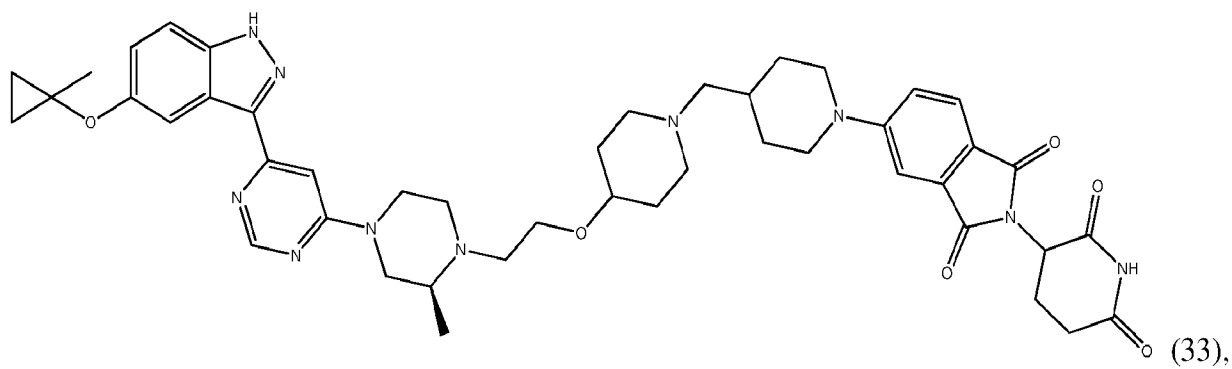


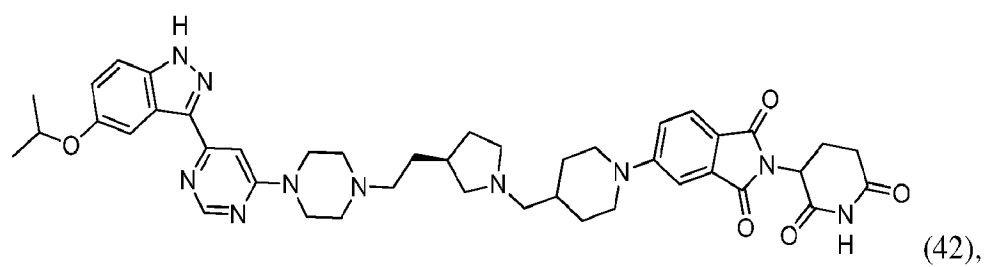
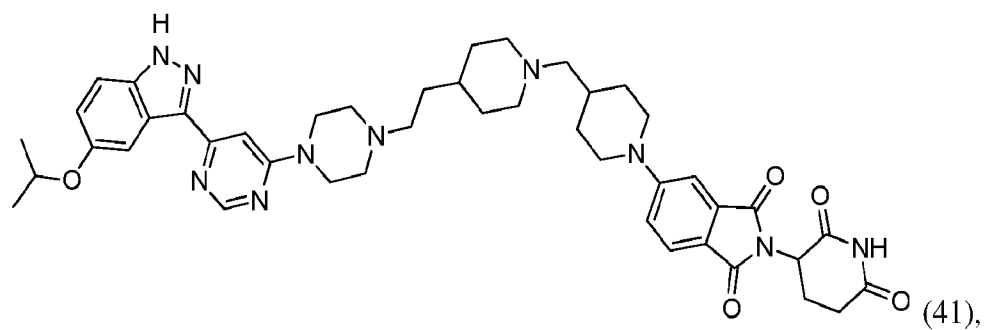
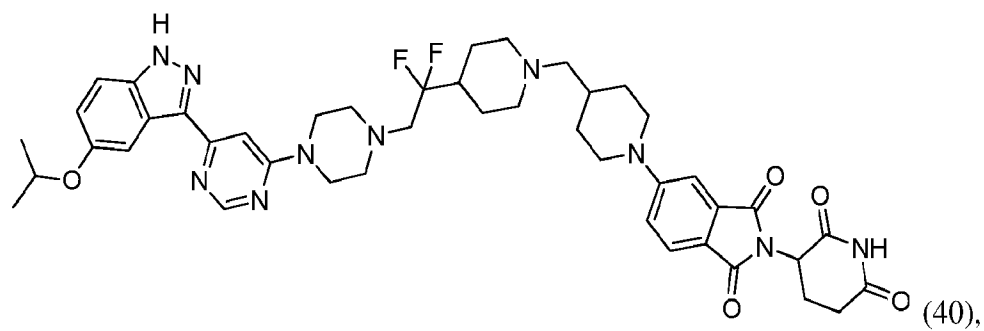
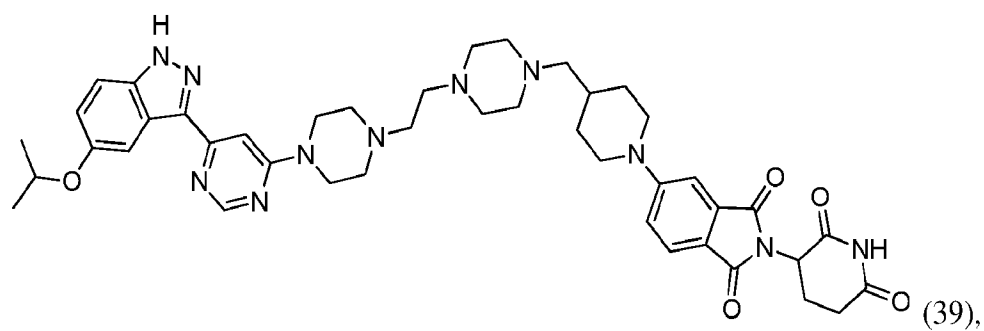
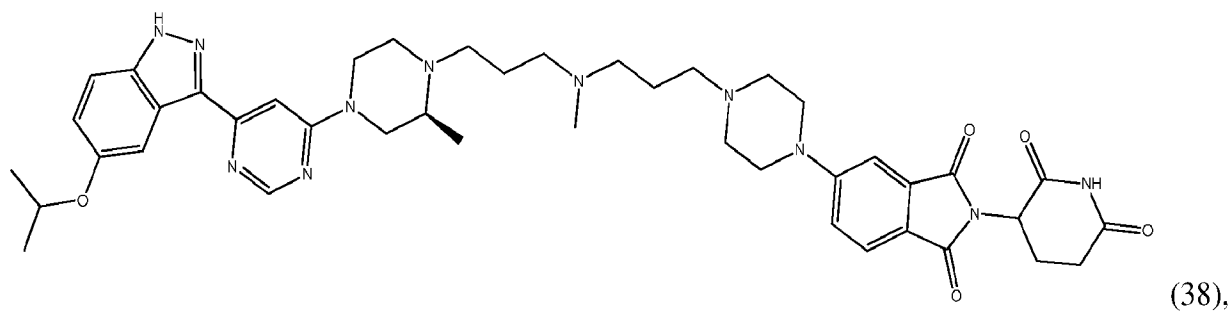


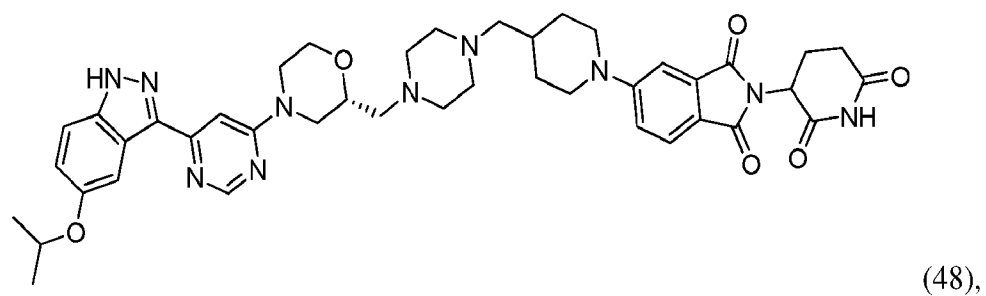
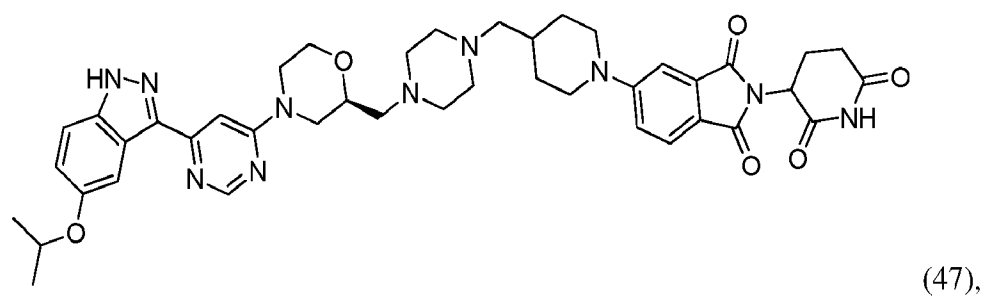
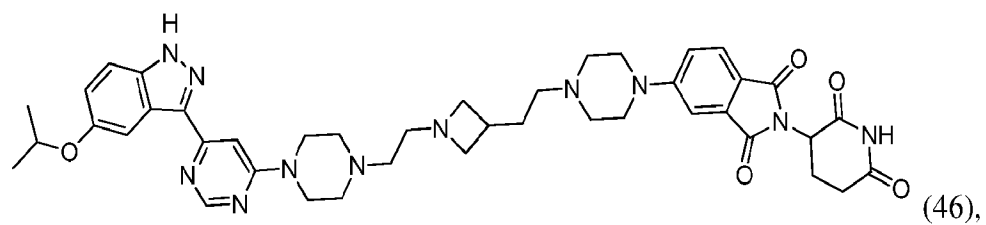
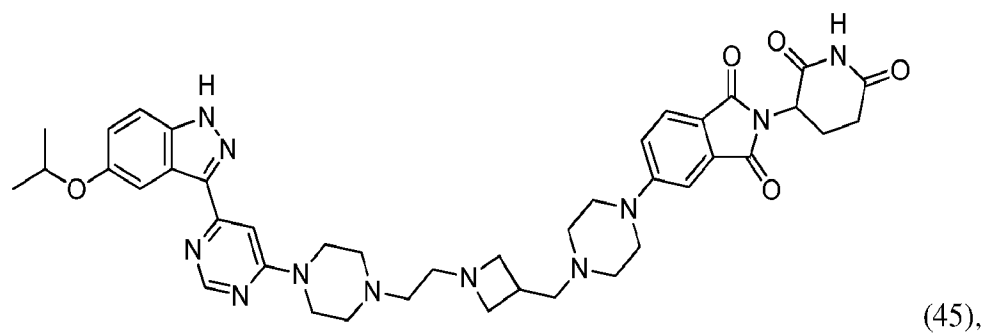
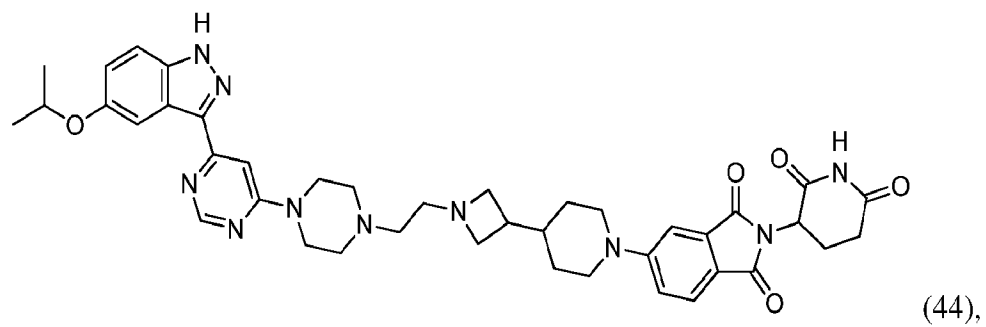
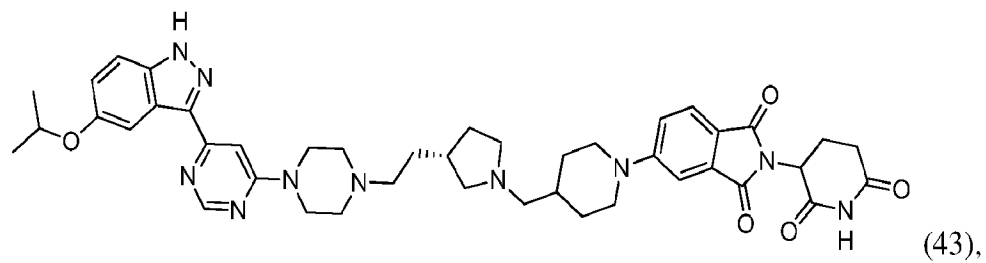


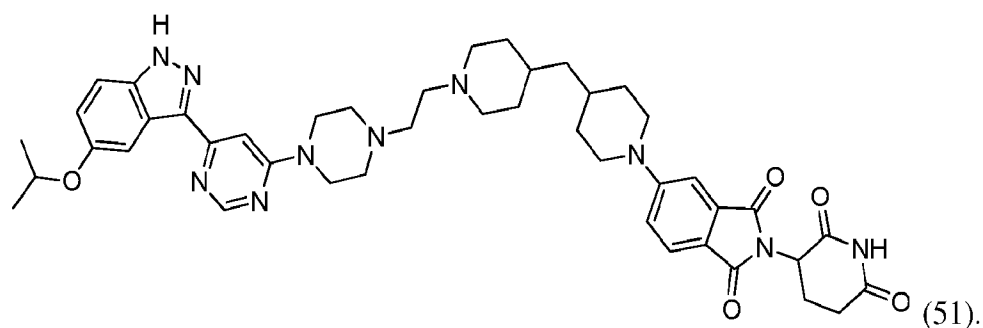
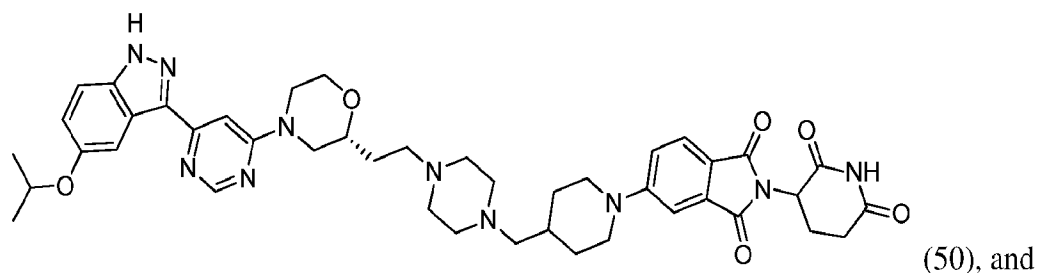
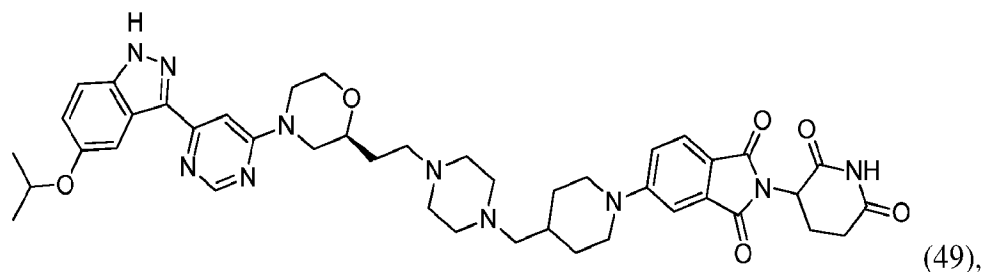












23. A composition comprising an effective amount of a bifunctional compound of any of claims 1-22, and a pharmaceutically acceptable carrier.

24. The composition of claim 23, wherein the composition further comprises at least one of additional bioactive agent or a second bifunctional compound of any of claims 1-22.

25. The composition of claim 24, wherein the additional bioactive agent is an anti-inflammatory, a chemotherapy agent, or an immunomodulatory agent.

26. A composition comprising a pharmaceutically acceptable carrier and an effective amount of at least one compound of any of claims 1-22 for treating a disease, a disorder or a symptom casually related to LRRK2 in a subject, wherein the composition is effective in treating or ameliorating the disease, disorder, or at least one symptom of the disease or disorder.

27. The composition of claim 26, wherein the disease or disorder is idiopathic Parkinson's disease (PD), LRRK2 mutation associated PD, primary tauopathies, lewy body dementia, Crohn's Disease, Leprosy, and/or neuroinflammation.

28. A method of treating or preventing a disease, a disorder, or symptom associated with LRRK2 comprising, providing a patient in need thereof, and administering an effective amount of a compound as described herein or composition comprising the same to the patient, wherein the compound or composition is effective in treating or ameliorating the disease, disorder, or at least one symptom of the disease or disorder.

FIG. 1A

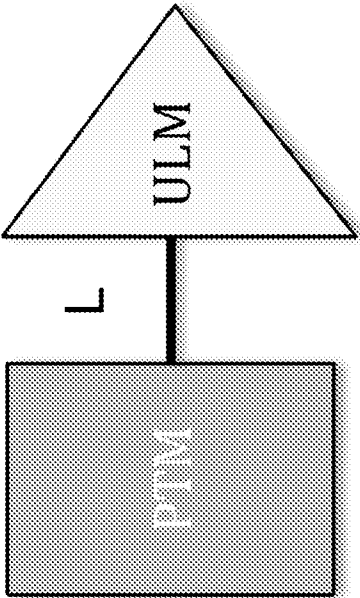
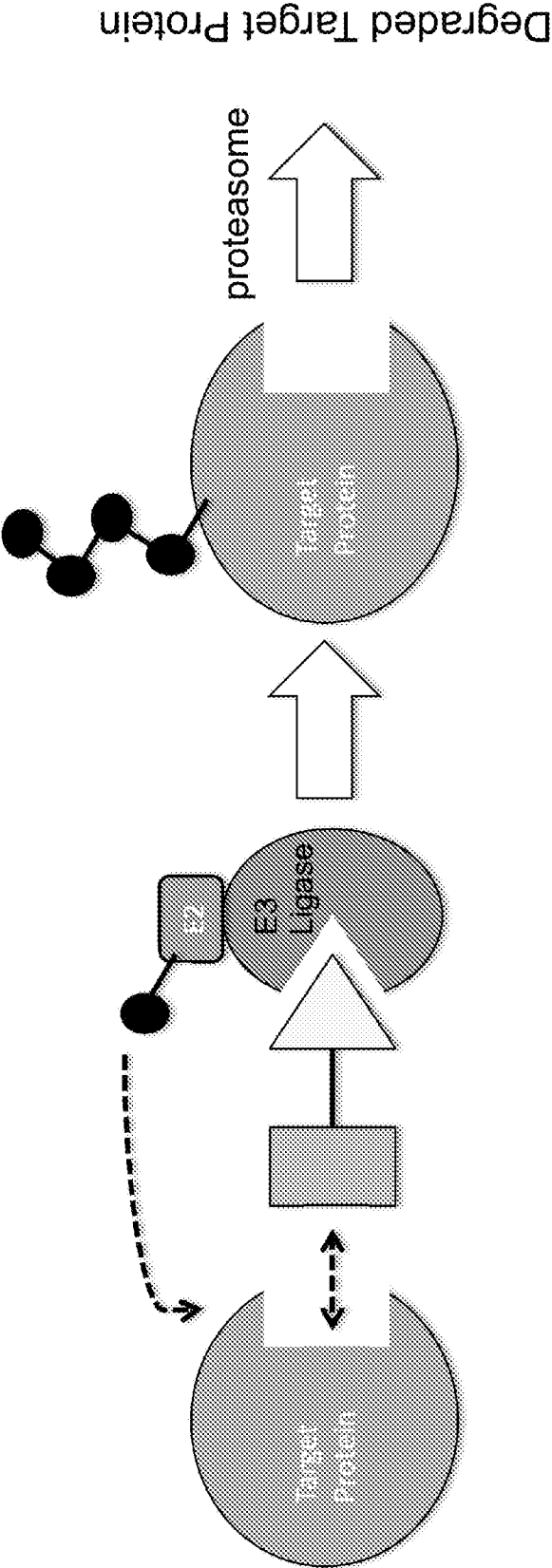


FIG. 1B





## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2021/023183

## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/14 C07D413/14 A61K31/506 A61P25/00 A61P35/00  
A61P37/00

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 A61K 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,P       | WO 2020/081682 A1 (DANA FARBER CANCER INST INC [US]) 23 April 2020 (2020-04-23)<br>claims 1-23; figures 1-20; examples 1-13,16-32; tables 1,2; compounds 8-13<br>----- | 1-20,<br>23-28        |
| Y         | WO 2018/148443 A1 (DANA FARBER CANCER INST INC [US]) 16 August 2018 (2018-08-16)<br>page 169 to page 170;<br>page 108 - page 128; claims 1,31,61<br>-----              | 1-28                  |
| Y         | WO 2014/134774 A1 (MERCK SHARP & DOHME [US]; MILLER MICHAEL [US] ET AL.)<br>12 September 2014 (2014-09-12)<br>claims 1-19; tables 1-15<br>-----<br>-/-                 | 1-28                  |



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

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## INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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| Y         | WO 2014/134776 A1 (MERCK SHARP & DOHME<br>[US]; MILLER MICHAEL [US] ET AL.)<br>12 September 2014 (2014-09-12)<br>Examples;<br>claims 1-10; tables A,B<br>----- | 1-28                  |

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Information on patent family members

International application No

PCT/US2021/023183

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s)                                                                                                      | Publication<br>date                                                                            |
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