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(54) Title: BIFUNCTIONAL COMPOUNDS FOR DEGRADING BTK VIA UBIQUITIN PROTEOSOME PATHWAY

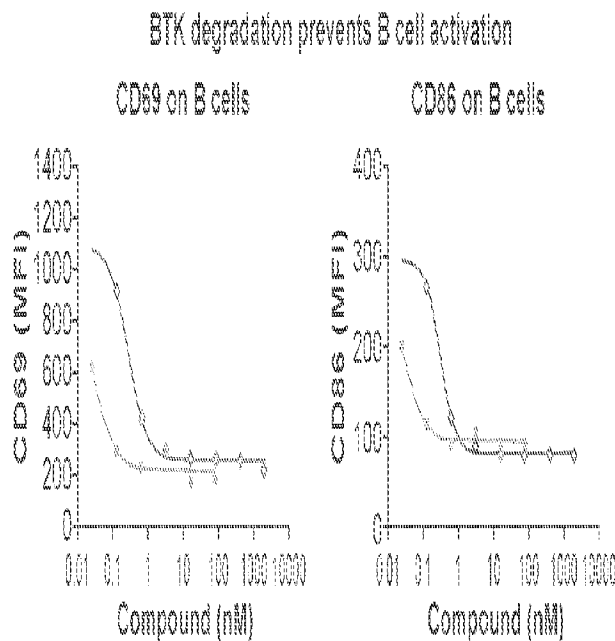


FIG. 5

(57) **Abrégé/Abstract:**

This disclosure relates to compounds useful for degrading BTK via a ubiquitin proteolytic pathway. The description also provides pharmaceutically acceptable compositions comprising said compounds and methods of using the compositions in the treatment of various disease, conditions, or disorders.

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Abstract:

This disclosure relates to compounds useful for degrading BTK via a ubiquitin proteolytic pathway. The description also provides pharmaceutically acceptable compositions comprising said compounds and methods of using the compositions in the treatment of various disease, conditions, or disorders.

BIFUNCTIONAL COMPOUNDS FOR DEGRADING BTK VIA UBIQUITIN PROTEOSOME PATHWAY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/943,720, filed December 4, 2019, U.S. Provisional Application No. 63/010,524, filed April 15, 2020, and incorporates International Application No. PCT/US2019/56112, filed October 14, 2019, each of which is incorporated by reference in their entireties.

FIELD

[0002] This disclosure provides novel bifunctional compounds for proteolytically degrading targeted Bruton's tyrosine kinases (BTK) and methods for treating diseases modulated by BTK.

BACKGROUND

[0003] B cell receptor (BCR) signaling controls B cell development, as well as mature B cell activation, signaling, and survival. Mis-regulation of the BCR signaling pathway is associated with numerous disease indications involving B cell function, and targeting B cells and BCR signaling has clear therapeutic potential (Woyach, *et al.*; *Blood*, 120(6); 1175-1184, 2012). For example, depletion of B cells with monoclonal antibodies targeting CD20 has significant effects in treatment of B cell malignancies and auto-immune and inflammatory diseases (Cang, *et al.*; *J Hematolo Oncol.* 5; 64, 2012.).

[0004] BTK is a member of the TEC family of kinases and is a crucial signaling hub in the BCR pathway. Mutations in BTK result in X-linked agammaglobulinaemia (XLA), in which B cell maturation is impaired, resulting in reduced immunoglobulin production (Hendriks, *et al.*; *Expert Opin Ther Targets* 15; 1002-1021, 2011). The central role of BTK in B cell signaling and function makes BTK an attractive therapeutic target for B cell malignancies as well as autoimmune and inflammatory diseases. Ibrutinib, a covalent inhibitor of BTK, has been approved to treat chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL) and other B cell malignancies, as well as graft-versus-host disease (GvHD) (Miklos, *et al.*; *Blood*, 120(21); 2243-2250, 2017). Currently, ibrutinib and second-generation BTK inhibitors are being investigated for oncology and immune-related indications such as rheumatoid arthritis (Akinleye, *et al.*; *J of Hematolo Oncol.* 6: 59, 2013; Liu, *et al.*; *J Pharm and Exper Ther.* 338(1): 154-163. 2011; Di Paolo, *et al.*; *Nat Chem Biol.* 7(1): 41-50, 2011).

[0005] As an alternative to stoichiometric inhibition, proteolytic degradation of BTK could have dramatic consequences for B cell function by effectively blocking BCR signaling. Removal of BTK protein would eliminate BTK kinase activity as well as any protein interaction or scaffolding function of BTK. Specific degradation of BTK could be accomplished using heterobifunctional small molecules to recruit BTK to a ubiquitin ligase and thus promoting ubiquitylation and proteasomal degradation of BTK. Thalidomide derivatives, such as lenalidomide or pomalidomide, can be used to recruit potential substrates to cereblon (CRBN), a component of a ubiquitin ligase complex. This unique therapeutic approach could present a mechanism of action for interfering with BTK activity and BCR signaling that is distinct from the mechanism of stoichiometric BTK inhibition. Furthermore, this degradative approach could effectively target the C481S mutated form of BTK, which mutation has been clinically observed and confers resistance to inhibition by ibrutinib (Woyach, et al.; *Blood*, 120(6): 1175-1184, 2012.).

[0006] Presently, there remains a need for bifunctional molecules that can induce the *in vivo* proteolytic degradation of BTK via a ubiquitin proteolytic pathway.

SUMMARY

[0007] Provided herein are methods of using bifunctional compounds that induce the proteolytic degradation of BTK via a ubiquitin proteolysis pathway.

[0008] In one aspect, provided herein are methods of treating or preventing cancer in a subject in need thereof. The methods comprise the step of orally administering to the subject an amount of a bifunctional compound capable of inducing proteolytic degradation of Bruton's tyrosine kinase. In certain embodiments, the amount is effective to treat or prevent the cancer.

[0009] In another aspect, provided herein are methods of degrading Bruton's tyrosine kinase in a subject in need thereof. The methods comprise the step of orally administering to the subject an amount of a bifunctional compound capable of inducing proteolytic degradation of Bruton's tyrosine kinase. In certain embodiments, the amount is effective to degrade Bruton's tyrosine kinase in the subject.

[0010] In another aspect, provided herein are methods of preventing B cell activation in a subject in need thereof. The methods comprise the step of orally administering to the subject an amount of a bifunctional compound capable of inducing proteolytic degradation of Bruton's tyrosine kinase. In certain embodiments, the amount is effective to prevent B cell activation.

[0011] In another aspect, provided herein are methods of degrading a mutant Bruton's tyrosine kinase. The methods comprise the step of contacting a cell expressing the mutant Bruton's tyrosine kinase with an amount of a bifunctional compound capable of inducing proteolytic degradation of Bruton's tyrosine kinase. In certain embodiments, the amount is effective to degrade the mutant Bruton's tyrosine kinase. In certain embodiments, the mutant Bruton's tyrosine kinase is a C481 mutant. In certain embodiments, the mutant Bruton's tyrosine kinase is a C481S mutant.

[0012] In the methods, the bifunctional compounds comprise a moiety capable of specifically binding BTK and further comprise a moiety capable of recruiting an ubiquitin ligase to degrade the BTK. Particular compounds are described herein. The compounds can be administered in any form, including pharmaceutically acceptable salts and pharmaceutical compositions.

BRIEF DESCRIPTION OF THE FIGURES

[0013] FIG. 1 provides BTK degradation by a compound herein in B lymphoma cell lines and in primary human B cells.

[0014] FIG. 2 provides degradation of wild-type BTK and ibrutinib-resistant C481S BTK by a compound herein.

[0015] FIG. 3 demonstrates highly selective degradation of BTK by a compound herein.

[0016] FIG. 4 demonstrates increased C481S BTK cell viability sensitivity to a compound herein relative to ibrutinib.

[0017] FIG. 5 demonstrates that a compound herein prevents B cell activation.

[0018] FIG. 6 demonstrates dose proportional degradation of BTK in splenocytes following oral administration of a compound herein to mice.

[0019] FIG. 7 demonstrates dose- and time-proportional reduction of BTK in circulating B cells following oral administration of a compound herein.

[0020] FIG. 8 demonstrates anti-tumor activity of a compound herein following oral administration of a compound herein to mice in a xenograft model of a tumor and an ibrutinib-resistant tumor.

[0021] FIG. 9 demonstrates degradation of BTK neosubstrate Aiolos.

[0022] FIGS. 10A and 10B provide effects of compounds **73**, **72**, **121**, and **44**, and control compounds, on neo-substrate and ITK or BTK levels after twenty-four hours in MOLT4 cells (FIG. 10A) and TMD8 cells (FIG. 10B).

[0023] FIGS. 11A and 11B provide effects of compounds **44**, **72**, and **149**, and control compounds, on CRBN neo-substrate and ITK levels in MOLT4 cells (FIG. 11A) and TMD8 cells (FIG. 11B).

[0024] FIG. 12 provides effects of compounds **130**, **149**, and **44** on ITK levels and IMiD activity.

[0025] FIGS. 13A-D provide TEC degradation by chimeric targeting molecules (CTMs) in K562 cells.

DETAILED DESCRIPTION

[0026] Provided herein are methods of using bifunctional compounds that induce the proteolytic degradation of Bruton's tyrosine kinase (BTK) via a ubiquitin proteolysis pathway.

[0027] As used herein, the following definitions shall apply unless otherwise indicated.

DEFINITIONS

[0028] For purposes herein, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry," Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry," 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0029] As described herein, "protecting group" refers to a moiety or functionality that is introduced into a molecule by chemical modification of a functional group in order to obtain chemoselectivity in a subsequent chemical reaction. Standard protecting groups are provided in Wuts and Greene: "Greene's Protective Groups in Organic Synthesis," 4th Ed, Wuts, P.G.M. and Greene, T.W., Wiley-Interscience, New York: 2006.

[0030] As described herein, compounds herein optionally may be substituted with one or more substituents, such as those illustrated generally herein, or as exemplified by particular classes, subclasses, and species of the description.

[0031] As used herein, the term "hydroxyl" or "hydroxy" refers to an -OH moiety.

[0032] As used herein, the term "aliphatic" encompasses the terms alkyl, alkenyl, and alkynyl, each of which are optionally substituted as set forth below.

[0033] As used herein, an "alkyl" group refers to a saturated aliphatic hydrocarbon group containing 1-12 (e.g., 1-8, 1-6, or 1-4) carbon atoms. An alkyl group can be straight or

branched. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *n*-heptyl, or 2-ethylhexyl. An alkyl group can be substituted (i.e., optionally substituted) with one or more substituents such as halo, phospho, cycloaliphatic (e.g., cycloalkyl or cycloalkenyl), heterocycloaliphatic (e.g., heterocycloalkyl or heterocycloalkenyl), aryl, heteroaryl, alkoxy, aroyl, heteroaroyl, acyl (e.g., (aliphatic)carbonyl, (cycloaliphatic)carbonyl, or (heterocycloaliphatic)carbonyl), nitro, cyano, amido (e.g., (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, alkylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl), amino (e.g., aliphaticamino, cycloaliphaticamino, or heterocycloaliphaticamino), sulfonyl (e.g., aliphatic-SO₂-), sulfinyl, sulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carboxy, carbamoyl, cycloaliphaticoxy, heterocycloaliphaticoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroarylalkoxy, alkoxy, alkylcarbonyloxy, or hydroxy. Without limitation, some examples of substituted alkyls include carboxyalkyl (such as HOOC-alkyl, alkoxyalkyl, and alkylcarbonyloxyalkyl), cyanoalkyl, hydroxyalkyl, alkoxyalkyl, acylalkyl, aralkyl, (alkoxyaryl)alkyl, (sulfonylamino)alkyl (such as (alkyl-SO₂-amino)alkyl), aminoalkyl, amidoalkyl, (cycloaliphatic)alkyl, or haloalkyl.

[0034] As used herein, an "alkenyl" group refers to an aliphatic carbon group that contains 2-8 (e.g., 2-12, 2-6, or 2-4) carbon atoms and at least one double bond. Like an alkyl group, an alkenyl group can be straight or branched. Examples of an alkenyl group include, but are not limited to, allyl, 1- or 2-isopropenyl, 2-butenyl, and 2-hexenyl. An alkenyl group can be optionally substituted with one or more substituents such as halo, phospho, cycloaliphatic (e.g., cycloalkyl or cycloalkenyl), heterocycloaliphatic (e.g., heterocycloalkyl or heterocycloalkenyl), aryl, heteroaryl, alkoxy, aroyl, heteroaroyl, acyl (e.g., (aliphatic)carbonyl, (cycloaliphatic)carbonyl, or (heterocycloaliphatic)carbonyl), nitro, cyano, amido (e.g., (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, alkylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl), amino (e.g., aliphaticamino, cycloaliphaticamino, heterocycloaliphaticamino, or aliphatic-sulfonylamino), sulfonyl (e.g., alkyl-SO₂-,

cycloaliphatic-SO₂-, or aryl-SO₂-), sulfinyl, sulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carboxy, carbamoyl, cycloaliphaticoxy, heterocycloaliphaticoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkoxy, alkoxycarbonyl, alkylcarbonyloxy, or hydroxy. Without limitation, some examples of substituted alkenyls include cyanoalkenyl, alkoxyalkenyl, acylalkenyl, hydroxyalkenyl, aralkenyl, (alkoxyaryl)alkenyl, (sulfonylamino)alkenyl (such as (alkyl-SO₂-amino)alkenyl), aminoalkenyl, amidoalkenyl, (cycloaliphatic)alkenyl, or haloalkenyl.

[0035] As used herein, an "alkynyl" group refers to an aliphatic carbon group that contains 2-8 (e.g., 2-12, 2-6, or 2-4) carbon atoms and has at least one triple bond. An alkynyl group can be straight or branched. Examples of an alkynyl group include, but are not limited to, propargyl and butynyl. An alkynyl group can be optionally substituted with one or more substituents such as aroyl, heteroaroyl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, nitro, carboxy, cyano, halo, hydroxy, sulfo, mercapto, sulfanyl (e.g., aliphaticsulfanyl or cycloaliphaticsulfanyl), sulfinyl (e.g., aliphaticsulfinyl or cycloaliphaticsulfinyl), sulfonyl (e.g., aliphatic-SO₂-, aliphaticamino-SO₂-, or cycloaliphatic-SO₂-), amido (e.g., aminocarbonyl, alkylaminocarbonyl, alkylcarbonylamino, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, cycloalkylcarbonylamino, arylaminocarbonyl, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (cycloalkylalkyl)carbonylamino, heteroaralkylcarbonylamino, heteroarylcarbonylamino, or heteroarylaminocarbonyl), urea, thiourea, sulfamoyl, sulfamide, alkoxycarbonyl, alkylcarbonyloxy, cycloaliphatic, heterocycloaliphatic, aryl, heteroaryl, acyl (e.g., (cycloaliphatic)carbonyl or (heterocycloaliphatic)carbonyl), amino (e.g., aliphaticamino), sulfoxy, oxo, carboxy, carbamoyl, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, or (heteroaryl)alkoxy.

[0036] As used herein, an "amido" encompasses both "aminocarbonyl" and "carbonylamino." These terms when used alone or in connection with another group refer to an amido group such as -N(R^X)-C(O)-R^Y or -C(O)-N(R^X)₂, when used terminally, and -C(O)-N(R^X)- or -N(R^X)-C(O)- when used internally, wherein R^X and R^Y can be aliphatic, cycloaliphatic, aryl, araliphatic, heterocycloaliphatic, heteroaryl, or heteroaraliphatic. Examples of amido groups include alkylamido (such as alkylcarbonylamino or alkylaminocarbonyl), (heterocycloaliphatic)amido, (heteroaralkyl)amido, (heteroaryl)amido, (heterocycloalkyl)alkylamido, arylamido, aralkylamido, (cycloalkyl)alkylamido, or cycloalkylamido.

[0037] As used herein, an "amino" group refers to $-NR^X R^Y$ wherein each of R^X and R^Y is independently hydrogen (H or $-H$), aliphatic, cycloaliphatic, (cycloaliphatic)aliphatic, aryl, araliphatic, heterocycloaliphatic, (heterocycloaliphatic)aliphatic, heteroaryl, carboxy, sulfanyl, sulfinyl, sulfonyl, (aliphatic)carbonyl, (cycloaliphatic)carbonyl, ((cycloaliphatic)aliphatic)carbonyl, arylcarbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, (heteroaryl)carbonyl, or (heteroaraliphatic)carbonyl, each of which being defined herein and being optionally substituted. Examples of amino groups include alkylamino, dialkylamino, or arylamino. When the term "amino" is not the terminal group (e.g., alkylcarbonylamino), it is represented by $-NR^X-$, where R^X has the same meaning as defined above.

[0038] As used herein, an "aryl" group used alone or as part of a larger moiety as in "aralkyl," "aralkoxy," or "aryloxyalkyl" refers to monocyclic (e.g., phenyl); bicyclic (e.g., indenyl, naphthalenyl, tetrahydronaphthyl, or tetrahydroindenyl); and tricyclic (e.g., fluorenyl, tetrahydrofluorenyl, tetrahydroanthracenyl, or anthracenyl) ring systems in which the monocyclic ring system is aromatic or at least one of the rings in a bicyclic or tricyclic ring system is aromatic. The bicyclic and tricyclic groups include benzofused 2-3 membered carbocyclic rings. For example, a benzofused group includes phenyl fused with two or more C_{4-8} carbocyclic moieties. An aryl is optionally substituted with one or more substituents including aliphatic (e.g., alkyl, alkenyl, or alkynyl); cycloaliphatic; (cycloaliphatic)aliphatic; heterocycloaliphatic; (heterocycloaliphatic)aliphatic; aryl; heteroaryl; alkoxy; (cycloaliphatic)oxy; (heterocycloaliphatic)oxy; aryloxy; heteroaryloxy; (araliphatic)oxy; (heteroaraliphatic)oxy; aroyl; heteroaroyl; amino; oxo (on a non-aromatic carbocyclic ring of a benzofused bicyclic or tricyclic aryl); nitro; carboxy; amido; acyl (e.g., (aliphatic)carbonyl; (cycloaliphatic)carbonyl; ((cycloaliphatic)aliphatic)carbonyl; (araliphatic)carbonyl; (heterocycloaliphatic)carbonyl; ((heterocycloaliphatic)aliphatic)carbonyl; or (heteroaraliphatic)carbonyl); sulfonyl (e.g., aliphatic- SO_2- or amino- SO_2-); sulfinyl (e.g., aliphatic-S(O)- or cycloaliphatic-S(O)-); sulfanyl (e.g., aliphatic-S-); cyano; halo; hydroxy; mercapto; sulfoxy; urea; thiourea; sulfamoyl; sulfamide; or carbamoyl. Alternatively, an aryl can be unsubstituted.

[0039] Non-limiting examples of substituted aryls include haloaryl (e.g., mono-, di- (such as *p,m*-dihaloaryl), and (trihalo)aryl); (carboxy)aryl (e.g., (alkoxycarbonyl)aryl, ((aralkyl)carbonyloxy)aryl, and (alkoxycarbonyl)aryl); (amido)aryl (e.g., (aminocarbonyl)aryl, (((alkylamino)alkyl)aminocarbonyl)aryl, (alkylcarbonyl)aminoaryl, (arylamino)carbonyl)aryl,

and (((heteroaryl)amino)carbonyl)aryl; aminoaryl (e.g., ((alkylsulfonyl)amino)aryl or ((dialkyl)amino)aryl); (cyanoalkyl)aryl; (alkoxy)aryl; (sulfamoyl)aryl (e.g., (aminosulfonyl)aryl); (alkylsulfonyl)aryl; (cyano)aryl; (hydroxyalkyl)aryl; ((alkoxy)alkyl)aryl; (hydroxy)aryl, ((carboxy)alkyl)aryl; (((dialkyl)amino)alkyl)aryl; (nitroalkyl)aryl; (((alkylsulfonyl)amino)alkyl)aryl; ((heterocycloaliphatic)carbonyl)aryl; ((alkylsulfonyl)alkyl)aryl; (cyanoalkyl)aryl; (hydroxyalkyl)aryl; (alkylcarbonyl)aryl; alkylaryl; (trihaloalkyl)aryl; *p*-amino-*m*-alkoxycarbonylaryl; *p*-amino-*m*-cyanoaryl; *p*-halo-*m*-aminoaryl; or (*m*-(heterocycloaliphatic)-*o*-(alkyl))aryl.

[0040] As used herein, an "araliphatic" such as an "aralkyl" group refers to an aliphatic group (e.g., a C₁₋₄ alkyl group) that is substituted with an aryl group. "Aliphatic," "alkyl," and "aryl" are defined herein. An example of an araliphatic such as an aralkyl group is benzyl.

[0041] As used herein, an "aralkyl" group refers to an alkyl group (e.g., a C₁₋₄ alkyl group) that is substituted with an aryl group. Both "alkyl" and "aryl" have been defined above. An example of an aralkyl group is benzyl. An aralkyl is optionally substituted with one or more substituents such as aliphatic (e.g., alkyl, alkenyl, or alkynyl, including carboxyalkyl, hydroxyalkyl, or haloalkyl such as trifluoromethyl), cycloaliphatic (e.g., cycloalkyl or cycloalkenyl), (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, amido (e.g., aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, or heteroaralkylcarbonylamino), cyano, halo, hydroxy, acyl, mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0042] As used herein, a "bicyclic ring system" includes 6-12 (e.g., 8-12 or 9-, 10-, or 11-) membered structures that form two rings, wherein the two rings have at least one atom in common (e.g., two atoms in common). Bicyclic ring systems include bicycloaliphatics (e.g., bicycloalkyl or bicycloalkenyl), bicycloheteroaliphatics, bicyclic aryls, and bicyclic heteroaryls.

[0043] As used herein, a "cycloaliphatic" group encompasses a "cycloalkyl" group and a "cycloalkenyl" group, each of which are optionally substituted as set forth below.

[0044] As used herein, a "cycloalkyl" group refers to a saturated carbocyclic mono- or bicyclic (fused or bridged) ring of 3-10 (e.g., 5-10) carbon atoms. Examples of cycloalkyl

groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, norbornyl, cubyl, octahydro-indenyl, decahydro-naphthyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.3.2.]decyl, bicyclo[2.2.2]octyl, adamantyl, or ((aminocarbonyl)cycloalkyl)cycloalkyl.

[0045] A "cycloalkenyl" group, as used herein, refers to a non-aromatic carbocyclic ring of 3-10 (e.g., 4-8) carbon atoms having one or more double bonds. Examples of cycloalkenyl groups include cyclopentenyl, 1,4-cyclohexa-di-enyl, cycloheptenyl, cyclooctenyl, hexahydro-indenyl, octahydro-naphthyl, cyclohexenyl, bicyclo[2.2.2]octenyl, or bicyclo[3.3.1]nonenyl.

[0046] A cycloalkyl or cycloalkenyl group can be optionally substituted with one or more substituents such as phospho, aliphatic (e.g., alkyl, alkenyl, or alkynyl), cycloaliphatic, (cycloaliphatic)aliphatic, heterocycloaliphatic, (heterocycloaliphatic)aliphatic, aryl, heteroaryl, alkoxy, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, aryloxy, heteroaryloxy, (araliphatic)oxy, (heteroaraliphatic)oxy, aroyl, heteroaroyl, amino, amido (e.g., (aliphatic)carbonylamino, (cycloaliphatic)carbonylamino, ((cycloaliphatic)aliphatic)carbonylamino, (aryl)carbonylamino, (araliphatic)carbonylamino, (heterocycloaliphatic)carbonylamino, ((heterocycloaliphatic)aliphatic)carbonylamino, (heteroaryl)carbonylamino, or (heteroaraliphatic)carbonylamino), nitro, carboxy (e.g., HOOC-, alkoxy carbonyl, or alkyl carbonyloxy), acyl (e.g., (cycloaliphatic)carbonyl, ((cycloaliphatic)aliphatic)carbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, or (heteroaraliphatic)carbonyl], cyano, halo, hydroxy, mercapto, sulfonyl (e.g., alkyl-SO₂- and aryl-SO₂-), sulfinyl (e.g., alkyl-S(O)-), sulfanyl (e.g., alkyl-S-), sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0047] As used herein, the term "heterocycloaliphatic" encompasses heterocycloalkyl groups and heterocycloalkenyl groups, each of which being optionally substituted as set forth below.

[0048] As used herein, a "heterocycloalkyl" group refers to a 3-10 membered mono- or bicyclic (fused, bridged, or spiro) (e.g., 5- to 10-membered mono- or bicyclic) saturated ring structure, in which one or more of the ring atoms is a heteroatom (e.g., nitrogen (N), oxygen (O), sulfur (S), or combinations thereof). Non-limiting examples of a heterocycloalkyl group include piperidyl, piperazyl, tetrahydropyranyl, tetrahydrofuryl, 1,4-dioxolanyl, 1,4-dithianyl, 1,3-dioxolanyl, oxazolidyl, isoxazolidyl, morpholiny, thiomorpholiny, octahydrobenzofuryl, octahydrochromenyl, octahydrothiochromenyl, octahydroindolyl, octahydropyrindinyl, decahydroquinolinyl, octahydrobenzo[*b*]thiophenyl, 2-oxa-bicyclo[2.2.2]octyl, 1-aza-bicyclo[2.2.2]octyl, 3-aza-bicyclo[3.2.1]octyl, decahydro-2,7-naphthyridine, 2,8-

diazaspiro[4.5]decane, 2,7-diazaspiro[3.5]nonane, octahydropyrrolo[3,4-c]pyrrole, octahydro-1H-pyrrolo[3,4-b]pyridine, and 2,6-dioxa-tricyclo[3.3.1.0^{3,7}]nonyl. A monocyclic heterocycloalkyl group can be fused with a phenyl moiety to form structures, such as tetrahydroisoquinoline, that would be categorized as heteroaryls.

[0049] A "heterocycloalkenyl" group, as used herein, refers to a mono- or bicyclic (e.g., 5- to 10-membered mono- or bicyclic) non-aromatic ring structure having one or more double bonds, and wherein one or more of the ring atoms is a heteroatom (e.g., N, O, or S). Monocyclic and bicyclic heterocycloaliphatics are numbered according to standard chemical nomenclature.

[0050] A heterocycloalkyl or heterocycloalkenyl group can be optionally substituted with one or more substituents such as phospho, aliphatic (e.g., alkyl, alkenyl, or alkynyl), cycloaliphatic, (cycloaliphatic)aliphatic, heterocycloaliphatic, (heterocycloaliphatic)aliphatic, aryl, heteroaryl, alkoxy, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, aryloxy, heteroaryloxy, (araliphatic)oxy, (heteroaraliphatic)oxy, aroyl, heteroaroyl, amino, amido (e.g., (aliphatic)carbonylamino, (cycloaliphatic)carbonylamino, ((cycloaliphatic)aliphatic)carbonylamino, (aryl)carbonylamino, (araliphatic)carbonylamino, (heterocycloaliphatic)carbonylamino, ((heterocycloaliphatic)aliphatic)carbonylamino, (heteroaryl)carbonylamino, or (heteroaraliphatic)carbonylamino], nitro, carboxy (e.g., HOOC-, alkoxy carbonyl, or alkylcarbonyloxy), acyl (e.g., (cycloaliphatic)carbonyl, ((cycloaliphatic)aliphatic)carbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, or (heteroaraliphatic)carbonyl), nitro, cyano, halo, hydroxy, mercapto, sulfonyl (e.g., alkylsulfonyl or arylsulfonyl), sulfinyl (e.g., alkylsulfinyl), sulfanyl (e.g., alkylsulfanyl), sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0051] A "heteroaryl" group, as used herein, refers to a monocyclic, bicyclic, or tricyclic ring system having four to fifteen ring atoms wherein one or more of the ring atoms is a heteroatom (e.g., N, O, S, or combinations thereof) and in which the monocyclic ring system is aromatic or at least one of the rings in the bicyclic or tricyclic ring systems is aromatic. A heteroaryl group includes a benzofused ring system having two to three rings. For example, a benzofused group includes benzo fused with one or two 4- to 8-membered heterocycloaliphatic moieties (e.g., indolizyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furyl, benzo[b]thiophenyl, quinolinyl, or isoquinolinyl). Some examples of heteroaryl are azetidiny, pyridyl, 1H-indazolyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, tetrazolyl, benzofuryl, isoquinolinyl, benzthiazolyl, xanthene, thioxanthene, phenothiazine, dihydroindole, benzo[1,3]dioxole, benzo[b]furyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl,

benzthiazolyl, puryl, cinnolyl, quinolyl, quinazolyl, phthalazyl, quinazolyl, quinoxalyl, isoquinolyl, 4H-quinolizyl, benzo-1,2,5-thiadiazolyl, or 1,8-naphthyridyl. Other examples of heteroaryls include 1,2,3,4-tetrahydroisoquinoline and 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine.

[0052] Without limitation, monocyclic heteroaryls include furyl, thiophene-yl, 2H-pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4H-pranyl, pyridyl, pyridazyl, pyrimidyl, pyrazolyl, pyrazyl, or 1,3,5-triazyl. Monocyclic heteroaryls are numbered according to standard chemical nomenclature.

[0053] Without limitation, bicyclic heteroaryls include indolizyl, indolyl, isoindolyl, 3H-indolyl, indoliny, benzo[*b*]furyl, benzo[*b*]thiophenyl, quinoliny, isoquinoliny, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizyl, quinolyl, isoquinolyl, cinnolyl, phthalazyl, quinazolyl, quinoxalyl, 1,8-naphthyridyl, or pteridyl. Bicyclic heteroaryls are numbered according to standard chemical nomenclature.

[0054] A heteroaryl is optionally substituted with one or more substituents such as aliphatic (e.g., alkyl, alkenyl, or alkynyl); cycloaliphatic; (cycloaliphatic)aliphatic; heterocycloaliphatic; (heterocycloaliphatic)aliphatic; aryl; heteroaryl; alkoxy; (cycloaliphatic)oxy; (heterocycloaliphatic)oxy; aryloxy; heteroaryloxy; (araliphatic)oxy; (heteroaraliphatic)oxy; aroyl; heteroaroyl; amino; oxo (on a non-aromatic carbocyclic or heterocyclic ring of a bicyclic or tricyclic heteroaryl); carboxy; amido; acyl (e.g., aliphaticcarbonyl; (cycloaliphatic)carbonyl; ((cycloaliphatic)aliphatic)carbonyl; (araliphatic)carbonyl; (heterocycloaliphatic)carbonyl; ((heterocycloaliphatic)aliphatic)carbonyl; or (heteroaraliphatic)carbonyl); sulfonyl (e.g., aliphaticsulfonyl or aminosulfonyl); sulfinyl (e.g., aliphaticsulfinyl); sulfanyl (e.g., aliphatic sulfanyl); nitro; cyano; halo; hydroxy; mercapto; sulfoxy; urea; thiourea; sulfamoyl; sulfamide; or carbamoyl. Alternatively, a heteroaryl can be unsubstituted.

[0055] Non-limiting examples of substituted heteroaryls include (halo)heteroaryl (e.g., mono- and di-(halo)heteroaryl); (carboxy)heteroaryl (e.g., (alkoxycarbonyl)heteroaryl); cyanoheteroaryl; aminoheteroaryl (e.g., ((alkylsulfonyl)amino)heteroaryl and ((dialkyl)amino)heteroaryl); (amido)heteroaryl (e.g., aminocarbonylheteroaryl, ((alkylcarbonyl)amino)heteroaryl, (((((alkyl)amino)alkyl)aminocarbonyl)heteroaryl, (((heteroaryl)amino)carbonyl)heteroaryl, ((heterocycloaliphatic)carbonyl)heteroaryl, and ((alkylcarbonyl)amino)heteroaryl); (cyanoalkyl)heteroaryl; (alkoxy)heteroaryl; (sulfamoyl)heteroaryl (e.g., (aminosulfonyl)heteroaryl); (sulfonyl)heteroaryl (e.g., (alkylsulfonyl)heteroaryl); (hydroxyalkyl)heteroaryl; (alkoxyalkyl)heteroaryl;

(hydroxy)heteroaryl; ((carboxy)alkyl)heteroaryl; (((dialkyl)amino)alkyl)heteroaryl; (heterocycloaliphatic)heteroaryl; (cycloaliphatic)heteroaryl; (nitroalkyl)heteroaryl; (((alkylsulfonyl)amino)alkyl)heteroaryl; ((alkylsulfonyl)alkyl)heteroaryl; (cyanoalkyl)heteroaryl; (acyl)heteroaryl (e.g., (alkylcarbonyl)heteroaryl); (alkyl)heteroaryl; or (haloalkyl)heteroaryl (e.g., trihaloalkylheteroaryl).

[0056] As used herein, a "heteroaraliphatic" (such as a heteroaralkyl group) refers to an aliphatic group (e.g., a C₁₋₄ alkyl group) that is substituted with a heteroaryl group. "Aliphatic," "alkyl," and "heteroaryl" have been defined above.

[0057] As used herein, a "heteroaralkyl" group refers to an alkyl group (e.g., a C₁₋₄ alkyl group) that is substituted with a heteroaryl group. Both "alkyl" and "heteroaryl" have been defined above. A heteroaralkyl is optionally substituted with one or more substituents such as alkyl (including carboxyalkyl, hydroxyalkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, cyano, halo, hydroxy, acyl, mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0058] As used herein, "cyclic moiety" and "cyclic group" refer to mono-, bi-, and tri-cyclic ring systems including cycloaliphatic, heterocycloaliphatic, aryl, or heteroaryl, each of which has been previously defined.

[0059] As used herein, a "bridged bicyclic ring system" refers to a bicyclic heterocyclicalipahitic ring system or bicyclic cycloaliphatic ring system in which the rings are bridged. Examples of bridged bicyclic ring systems include, but are not limited to, adamantanyl, norbornanyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.3.2]decyl, 2-oxabicyclo[2.2.2]octyl, 1-azabicyclo[2.2.2]octyl, 3-azabicyclo[3.2.1]octyl, and 2,6-dioxa-tricyclo[3.3.1.0^{3,7}]nonyl. A bridged bicyclic ring system can be optionally substituted with one or more substituents such as alkyl (including carboxyalkyl, hydroxyalkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy,

heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, cyano, halo, hydroxy, acyl, mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0060] As used herein, an "acyl" group refers to a formyl group or $R^X-C(O)-$ (such as alkyl- $C(O)-$, also referred to as "alkylcarbonyl") where R^X and "alkyl" have been defined previously. Acetyl and pivaloyl are examples of acyl groups.

[0061] As used herein, an "aroyl" or "heteroaroyl" refers to an aryl- $C(O)-$ or a heteroaryl- $C(O)-$. The aryl and heteroaryl portion of the aroyl or heteroaroyl is optionally substituted as previously defined herein.

[0062] As used herein, an "alkoxy" group refers to an alkyl-O- group where "alkyl" has been defined previously herein.

[0063] As used herein, a "carbamoyl" group refers to a group having the structure $-O-CO-NR^X R^Y$ or $-NR^X-CO-O-R^Z$, wherein R^X and R^Y have been defined above and R^Z can be aliphatic, aryl, araliphatic, heterocycloaliphatic, heteroaryl, or heteroaraliphatic.

[0064] As used herein, a "carboxy" group refers to $-COOH$, when used as a terminal group; or $-OC(O)-$ or $-C(O)O-$ when used as an internal group.

[0065] As used herein, an ester refers to $-COOR^X$ when used as a terminal group; or $-COOR^X-$ when used as an internal group, wherein R^X has been defined above.

[0066] As used herein, a formate refers to $-OC(O)H$.

[0067] As used herein, an acetate refers to $-OC(O)R^X$, wherein R^X has been defined above.

[0068] As used herein, a "haloaliphatic" group refers to an aliphatic group substituted with one to three halogen. For instance, the term haloalkyl includes the group $-CF_3$.

[0069] As used herein, a "mercapto" or "sulfhydryl" group refers to $-SH$.

[0070] As used herein, a "sulfo" group refers to $-SO_3H$ or $-SO_3R^X$ when used terminally or $-S(O)_3-$ when used internally.

[0071] As used herein, a "sulfamide" group refers to the structure $-NR^X-S(O)_2-NR^Y R^Z$ when used terminally and $-NR^X-S(O)_2-NR^Y-$ when used internally, wherein R^X , R^Y , and R^Z have been defined above.

[0072] As used herein, a "sulfamoyl" group refers to the structure $-O-S(O)_2-NR^Y R^Z$ wherein R^Y and R^Z have been defined above.

[0073] As used herein, a "sulfonamide" group refers to the structure $-S(O)_2-NR^X R^Y$ or $-NR^X-S(O)_2-R^Z$ when used terminally; or $-S(O)_2-NR^X-$ or $-NR^X-S(O)_2-$ when used internally, wherein R^X , R^Y , and R^Z are defined above.

[0074] As used herein a "sulfanyl" group refers to $-S-R^X$ when used terminally and $-S-$ when used internally, wherein R^X has been defined above. Examples of sulfanyls include aliphatic-S-, cycloaliphatic-S-, aryl-S-, or the like.

[0075] As used herein a "sulfinyl" group refers to $-S(O)-R^X$ when used terminally and $-S(O)-$ when used internally, wherein R^X has been defined above. Examples of sulfinyl groups include aliphatic-S(O)-, aryl-S(O)-, (cycloaliphatic(aliphatic))-S(O)-, cycloalkyl-S(O)-, heterocycloaliphatic-S(O)-, heteroaryl-S(O)-, and/or the like.

[0076] As used herein, a "sulfonyl" group refers to $-S(O)_2-R^X$ when used terminally and $-S(O)_2-$ when used internally, wherein R^X has been defined above. Examples of sulfonyl groups include aliphatic-S(O)₂-, aryl-S(O)₂-, (cycloaliphatic(aliphatic))-S(O)₂-, cycloaliphatic-S(O)₂-, heterocycloaliphatic-S(O)₂-, heteroaryl-S(O)₂-, (cycloaliphatic(amido(aliphatic)))S(O)₂-, and/or the like.

[0077] As used herein, a "sulfoxy" group refers to $-O-S(O)-R^X$ or $-S(O)-O-R^X$, when used terminally and $-O-S(O)-$ or $-S(O)-O-$ when used internally, where R^X has been defined above.

[0078] As used herein, a "halogen" or "halo" group refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I).

[0079] As used herein, an "alkoxycarbonyl," which is encompassed by the term carboxy, used alone or in connection with another group refers to a group such as alkyl-O-C(O)-.

[0080] As used herein, an "alkoxyalkyl" refers to an alkyl group such as alkyl-O-alkyl-, wherein alkyl has been defined above.

[0081] As used herein, a "carbonyl" refers to $-C(O)-$.

[0082] As used herein, an "oxo" refers to $=O$.

[0083] As used herein, the term "phospho" refers to phosphinates and phosphonates. Examples of phosphinates and phosphonates include $-P(O)(R^P)_2$, wherein R^P is aliphatic, alkoxy, aryloxy, heteroaryloxy, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, aryl, heteroaryl, cycloaliphatic or amino.

[0084] As used herein, an "aminoalkyl" refers to the structure $(R^X)_2N$ -alkyl-.

[0085] As used herein, a "cyanoalkyl" refers to the structure (NC) -alkyl-.

[0086] As used herein, a "urea" group refers to the structure $-NR^X-CO-NR^Y R^Z$ and a "thiourea" group refers to the structure $-NR^X-CS-NR^Y R^Z$ each when used terminally and

-NR^X-CO-NR^Y- or -NR^X-CS-NR^Y- each when used internally, wherein R^X, R^Y, and R^Z have been defined above.

[0087] As used herein, a "guanidine" group refers to the structure -N=C(N(R^XR^Y))N(R^XR^Y) or -NR^X-C(=NR^X)NR^XR^Y wherein R^X and R^Y have been defined above.

[0088] As used herein, the term "amidino" group refers to the structure -C=(NR^X)N(R^XR^Y) wherein R^X and R^Y have been defined above.

[0089] As used herein, the term "vicinal" generally refers to the placement of substituents on a group that includes two or more carbon atoms, wherein the substituents are attached to adjacent carbon atoms.

[0090] As used herein, the term "geminal" generally refers to the placement of substituents on a group that includes two or more carbon atoms, wherein the substituents are attached to the same carbon atom.

[0091] The terms "terminally" and "internally" refer to the location of a group within a substituent. A group is terminal when the group is present at the end of the substituent not further bonded to the rest of the chemical structure. Carboxyalkyl (i.e., R^XO(O)C-alkyl) is an example of a carboxy group used terminally. A group is internal when the group is present in the middle of or within the termini of a substituent of the chemical structure. Alkylcarboxy (e.g., alkyl-C(O)O- or alkyl-OC(O)-) and alkylcarboxyaryl (e.g., alkyl-C(O)O-aryl- or alkyl-O(CO)-aryl-) are examples of carboxy groups used internally.

[0092] As used herein, an "aliphatic chain" refers to a branched or straight aliphatic group (e.g., alkyl groups, alkenyl groups, or alkynyl groups). A straight aliphatic chain has the structure -[CH₂]_v-, where v is 1-12. A branched aliphatic chain is a straight aliphatic chain that is substituted with one or more aliphatic groups. A branched aliphatic chain has the structure -[CQQ]_v- where each Q is independently a hydrogen (H or -H) or an aliphatic group; however, Q shall be an aliphatic group in at least one instance. The term aliphatic chain includes alkyl chains, alkenyl chains, and alkynyl chains, where alkyl, alkenyl, and alkynyl are defined above.

[0093] The phrase "optionally substituted" is used herein interchangeably with the phrase "substituted or unsubstituted." As described herein, compounds herein can optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the description. As described herein, the variables R, R¹, R², L, Y, and Z, and other variables contained in Formula (A), (B), (C), (D), (E), (F), (G), (H), (J), (K), (M), (X), (I), (I-A), (I-B), (II), (II-A), (II-B), (III), and (IV) described herein encompass specific groups, such as alkyl and aryl. Unless otherwise

noted, each of the specific groups for the variables **R**, **R¹⁰**, **R^A**, **R¹**, **R²**, **L**, **L¹**, **D**, **W**, **E**, **V**, **G**, **Y**, and **Z**, and other variables contained therein can be optionally substituted with one or more substituents described herein. Each substituent of a specific group is further optionally substituted with one to three of halo, cyano, oxo, alkoxy, hydroxy, amino, nitro, aryl, cycloaliphatic, heterocycloaliphatic, heteroaryl, haloalkyl, and alkyl. For instance, an alkyl group can be substituted with alkylsulfanyl and the alkylsulfanyl can be optionally substituted with one to three of halo, cyano, oxo, alkoxy, hydroxy, amino, nitro, aryl, haloalkyl, and alkyl. As an additional example, the cycloalkyl portion of a (cycloalkyl)carbonylamino can be optionally substituted with one to three of halo, cyano, alkoxy, hydroxy, nitro, haloalkyl, and alkyl. When two alkoxy groups are bound to the same atom or adjacent atoms, the two alkoxy groups can form a ring together with the atom(s) to which they are bound.

[0094] As used herein, the term "substituted," whether preceded by the term "optionally" or not, refers generally to the replacement of hydrogen atoms in a given structure with the radical of a specified substituent. Specific substituents are described above in the definitions and below in the description of compounds and examples thereof. Unless otherwise indicated, an optionally substituted group can have a substituent at each substitutable position of the group, and when more than one position in any given structure can be substituted with more than one substituent selected from a specified group, the substituent can be either the same or different at every position. A ring substituent, such as a heterocycloalkyl, can be bound to another ring, such as a cycloalkyl, to form a spiro-bicyclic ring system, for example, both rings share one common atom. Non-limiting examples of spiro heterocycloalkyls include



2,8-diazaspiro[4.5]decane,



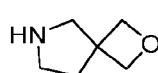
2,7-diazaspiro[3.5]nonane,



3,9-diazaspiro[5.5]undecane,



3-azaspiro[5.5]undecane, and



2-oxa-6-azaspiro[3.4]octane.

[0095] As one of ordinary skill in the art will recognize, combinations of substituents envisioned by this description are those combinations that result in the formation of stable or chemically feasible compounds.

[0096] As used herein, the phrase "stable or chemically feasible" refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and their recovery, purification, and use for one or more of the purposes disclosed

herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[0097] As used herein, an "effective amount" is defined as the amount required to confer a therapeutic effect on the treated patient, and is typically determined based on age, surface area, weight, and condition of the patient. The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described by Freireich *et al.*, Cancer Chemother. Rep., 50: 219 (1966). Body surface area may be approximately determined from height and weight of the patient. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, New York, 537 (1970). As used herein, "patient" refers to a mammal, including a human.

[0098] As used herein, the term "about" means within $\pm 10\%$ of a value. For example, a dose that is about 100 mg/kg provides that the dose can be 90 mg/kg to 110 mg/kg. By way of further example, an amount of an additional therapeutic agent ranging from about 50% to about 100% provides that the amount of additional therapeutic agent ranges from 45-55% to 90-110%. A person of skill in the art will appreciate the scope and application of the term "about" when used to describe other values disclosed herein.

[0099] Unless otherwise stated, structures depicted herein also are meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the (*R*)- and (*S*)- configurations for each asymmetric center, (*Z*)- and (*E*)- double bond isomers, and (*Z*)- and (*E*)- conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the description. Alternatively, as used herein, "enantiomeric excess (ee)" refers to a dimensionless mol ratio describing the purity of chiral substances that contain, for example, a single stereogenic center. For instance, an enantiomeric excess of zero would indicate a racemic (e.g., 50:50 mixture of enantiomers, or no excess of one enantiomer over the other). By way of further example, an enantiomeric excess of ninety-nine would indicate a nearly stereopure enantiomeric compound (i.e., large excess of one enantiomer over the other). The percentage enantiomeric excess, % ee = $\frac{[(R)\text{-compound}] - [(S)\text{-compound}]}{[(R)\text{-compound}] + [(S)\text{-compound}]} \times 100$, where the (*R*)-compound > (*S*)-compound; or % ee = $\frac{[(S)\text{-compound}] - [(R)\text{-compound}]}{[(S)\text{-compound}] + [(R)\text{-compound}]} \times 100$, where the (*S*)-compound > (*R*)-compound. Moreover, as used herein, "diastereomeric excess (de)" refers to a dimensionless mol ratio describing the purity of chiral substances that contain more than one stereogenic center. For example, a

diastereomeric excess of zero would indicate an equimolar mixture of diastereoisomers. By way of further example, diastereomeric excess of ninety-nine would indicate a nearly stereopure diastereomeric compound (i.e., large excess of one diastereomer over the other). Diastereomeric excess may be calculated via a similar method to ee. As would be appreciated by a person of skill, de is usually reported as percent de (% de). % de may be calculated in a similar manner to % ee.

[00100] In certain embodiments, the compounds or inhibitors described herein have an ee, de, % ee, or % de greater than zero. For example, in certain embodiments, the compounds or inhibitors described herein have an ee, de, % ee, or % de of ten. In certain embodiments, the compounds or inhibitors described herein have an ee, de, % ee, or % de of twenty-five. In certain embodiments, the compounds or inhibitors described herein have an ee, de, % ee, or % de of fifty. In certain embodiments, the compounds or inhibitors described herein have an ee, de, % ee, or % de of seventy-five.

[00101] In certain embodiments, the compounds or inhibitors described herein have an ee, de, % ee, or % de range from ninety to one hundred. In certain embodiments, the compounds or inhibitors described herein have an ee, de, % ee, or % de range from ninety-five to one hundred. In certain embodiments, the compounds or inhibitors described herein have an ee, de, % ee, or % de range from ninety-seven to one hundred. In certain embodiments, the compounds or inhibitors described herein have an ee, de, % ee, or % de range from ninety-eight to one hundred. In certain embodiments, the compounds or inhibitors described herein have an ee, de, % ee, or % de range from ninety-nine to one hundred.

[00102] In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is one. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is two. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is three. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is four. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is five. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is six. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is seven. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is eight. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is nine. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is ten. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is eleven. In one embodiment of a

compound or inhibitor described herein, the ee, de, % ee, or % de is twelve. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is thirteen. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is fourteen. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is fifteen. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is sixteen. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is seventeen. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is eighteen. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is nineteen. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is twenty. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is twenty-one. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is twenty-two. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is twenty-three. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is twenty-four. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is twenty-five. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is twenty-six. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is twenty-seven. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is twenty-eight. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is twenty-nine. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is thirty. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is thirty-one. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is thirty-two. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is thirty-three. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is thirty-four. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is thirty-five. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is thirty-six. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is thirty-seven. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is thirty-eight. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is thirty-nine. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is forty. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is forty-

[illegible]

seventy-one. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is seventy-two. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is seventy-three. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is seventy-four. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is seventy-five. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is seventy-six. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is seventy-seven. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is seventy-eight. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is seventy-nine. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is eighty. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is eighty-one. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is eighty-two. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is eighty-three. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is eighty-four. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is eighty-five. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is eighty-six. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is eighty-seven. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is eighty-eight. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is eighty-nine. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is ninety. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is ninety-one. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is ninety-two. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is ninety-three. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is ninety-four. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is ninety-five. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is ninety-six. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is ninety-seven. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is ninety-eight. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is ninety-nine. In one embodiment of a compound or inhibitor described herein, the ee, de, % ee, or % de is one hundred. In certain

embodiments, compounds or inhibitors described within Table 1 herein have an ee, de, % ee, or % de as described within this paragraph. In certain embodiments, compound or inhibitor **32, 34, 44, 57, 72, 121, 130, 149, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218**, as described in the Examples and/or Biological Examples have an ee, de, % ee, or % de as described within this paragraph. Unless otherwise stated, all tautomeric forms of the compounds of the description are within the scope of the description. Additionally, unless otherwise stated, structures depicted herein also are meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this description. Such compounds are useful, for example, as analytical tools or probes in biological assays, or as therapeutic agents.

[00103] As used herein, the term “&1” means that a compound including the “&1” notation at a particular chemical element or atom (e.g., carbon) within the compound was prepared as a mixture of two stereoisomers at the noted chemical element or atom (e.g., a diastereomeric mixture having a de or % de as described above).

[00104] Chemical structures and nomenclature are derived from ChemDraw, version 11.0.1, Cambridge, MA.

[00105] It is noted that the use of the descriptors "first," "second," "third," or the like is used to differentiate separate elements (e.g., solvents, reaction steps, processes, reagents, or the like) and may or may not refer to the relative order or relative chronology of the elements described.

USES OF THE COMPOUNDS AND COMPOSITIONS

[00106] The bifunctional compounds described herein are useful for degrading BTK in biological samples or in patients via an ubiquitin proteolytic pathway. Thus, an embodiment of this disclosure provides a method of treating a BTK-mediated disease or disorder. As used herein, the term "BTK-mediated disease or disorder" means any disease, disorder, or other deleterious condition in which a BTK is known to play a role. In some instances, a BTK-mediated disease or disorder is a proliferative disorder or an autoimmune disorder. Examples of proliferative disorders include cancer.

[00107] In one aspect, provided herein are methods of treating or preventing cancer in a subject in need thereof. In certain embodiments, the methods comprise the step of orally administering to the subject an amount of a bifunctional compound capable of inducing proteolytic

degradation of Bruton's tyrosine kinase. In certain embodiments, the amount is effective to treat or prevent the cancer.

[00108] In certain embodiments, the cancer is any cancer described below. In particular embodiments, the cancer comprises a solid tumor. In certain embodiments, the cancer is a B cell malignancy. In certain embodiments, the cancer is selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), transformed CLL or Richter's transformation, small cell lymphoma, follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), non-Hodgkin lymphoma, mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Waldenstrom macroglobulinemia (WM), and central nervous system (CNS) lymphoma. In certain embodiments, the cancer is chronic lymphocytic leukemia. In certain embodiments, the cancer is small cell lymphoma. In certain embodiments, the cancer is follicular lymphoma. In certain embodiments, the cancer is diffuse large B-cell lymphoma. In certain embodiments, the cancer is non-Hodgkin lymphoma. In certain embodiments, the cancer is mantle cell lymphoma. In certain embodiments, the cancer is marginal zone lymphoma. In certain embodiments, the cancer is Waldenstrom macroglobulinemia. In certain embodiments, the cancer is small lymphocytic lymphoma (SLL). In certain embodiments, the cancer is CNS lymphoma. In certain embodiments, the cancer is transformed CLL or Richter's transformation.

[00109] In certain embodiments, the subject has a mutant Bruton's tyrosine kinase. In certain embodiments, the subject has a C481 mutant Bruton's tyrosine kinase. In certain embodiments, the subject has a C481S mutant Bruton's tyrosine kinase. In certain embodiments, the cancer is resistant to ibrutinib. Those of skill will recognize that certain ibrutinib-resistant cancers express a C481 mutant Bruton's tyrosine kinase, for instance C481S Bruton's tyrosine kinase. For example, in certain embodiments, the subject has a C481 mutant Bruton's tyrosine kinase and the cancer is chronic lymphocytic leukemia (CLL).

[00110] In another aspect, provided herein are methods of degrading Bruton's tyrosine kinase in a subject in need thereof. The methods comprise the step of orally administering to the subject an amount of a bifunctional compound capable of inducing proteolytic degradation of Bruton's tyrosine kinase. In certain embodiments, the amount is effective to degrade Bruton's tyrosine kinase in the subject. The Bruton's tyrosine kinase can be expressed in any cells or tissues of the subject. In certain embodiments, the Bruton's tyrosine kinase is expressed in splenocytes. In certain embodiments, the Bruton's tyrosine kinase is expressed in peripheral blood mononuclear cells.

[00111] In certain embodiments, the Bruton's tyrosine kinase is a mutant form. In certain embodiments, Bruton's tyrosine kinase comprises a C481 mutation. In certain embodiments, the Bruton's tyrosine kinase comprises a C481S mutation. In certain embodiments, the Bruton's tyrosine kinase is resistant to ibrutinib.

[00112] In another aspect, provided herein are methods of preventing B cell activation in a subject in need thereof. The methods comprise the step of orally administering to the subject an amount of a bifunctional compound capable of inducing proteolytic degradation of Bruton's tyrosine kinase. In certain embodiments, the amount is effective to prevent B cell activation. In certain embodiments, the B cell expresses CD69. In certain embodiments, the B cell expresses CD86. In certain embodiments, the B cell expresses CD69 and CD86.

[00113] In another aspect, provided herein are methods of degrading a mutant Bruton's tyrosine kinase. The methods comprise the step of contacting a cell expressing the mutant Bruton's tyrosine kinase with an amount of a bifunctional compound capable of inducing proteolytic degradation of Bruton's tyrosine kinase. In certain embodiments, the amount is effective to degrade the mutant Bruton's tyrosine kinase. In certain embodiments, the mutant Bruton's tyrosine kinase is a C481 mutant. In certain embodiments, the mutant Bruton's tyrosine kinase is a C481S mutant.

[00114] In the methods, the bifunctional compounds comprise a moiety capable of specifically binding BTK and further comprise a moiety capable of recruiting an ubiquitin ligase to degrade the BTK. Particular compounds are described herein. The compounds can be administered in any form, including pharmaceutically acceptable salts and pharmaceutical compositions.

[00115] The bifunctional compound can be administered in any dose deemed suitable by the practitioner of skill. In certain embodiments, the dose is 0.1-1000 mg/kg. In certain embodiments, the dose is 0.1-900 mg/kg. In certain embodiments, the dose is 0.1-800 mg/kg. In certain embodiments, the dose is 0.1-700 mg/kg. In certain embodiments, the dose is 0.1-600 mg/kg. In certain embodiments, the dose is 0.1-500 mg/kg. In certain embodiments, the dose is 0.1-400 mg/kg. In certain embodiments, the dose is 0.1-300 mg/kg. In certain embodiments, the dose is 0.1-200 mg/kg. In certain embodiments, the dose is 0.1-100 mg/kg. In certain embodiments, the dose is selected from the group consisting of 100 mg/kg, 200 mg/kg, 300 mg/kg, 450 mg/kg, 600 mg/kg, 800 mg/kg, and 1000 mg/kg. In certain embodiments, the dose is about 25 mg/kg. In certain embodiments, the dose is about 50 mg/kg. In certain embodiments, the dose is about 75 mg/kg. In certain embodiments, the dose is about 100 mg/kg. In certain embodiments, the dose is about 150 mg/kg. In certain embodiments, the

dose is about 200 mg/kg. In certain embodiments, the dose is about 250 mg/kg. In certain embodiments, the dose is about 300 mg/kg. In certain embodiments, the dose is about 400 mg/kg. In certain embodiments, the dose is about 450 mg/kg. In certain embodiments, the dose is about 500 mg/kg. In certain embodiments, the dose is about 600 mg/kg. In certain embodiments, the dose is about 700 mg/kg. In certain embodiments, the dose is about 750 mg/kg. In certain embodiments, the dose is about 800 mg/kg. In certain embodiments, the dose is about 900 mg/kg. In certain embodiments, the dose is about 1000 mg/kg.

[00116] The dose can be administered on a schedule deemed suitable by the person of skill in the art. In certain embodiments, the dose is administered once per day. In certain embodiments, the dose is administered twice per day. In certain embodiments, the dose is administered three times per day. In certain embodiments, the dose is administered four times per day. In certain embodiments, the dose is administered in divided doses. In certain embodiments, the dose is administered in two divided doses per day. In certain embodiments, the dose is administered in three divided doses per day. In certain embodiments, the dose is administered in four divided doses per day.

[00117] Dosing can continue for any length of time deemed suitable by the person of skill in the art. In certain embodiments, the dose is administered daily for fourteen days. In certain embodiments, the dose is administered daily for thirteen days. In certain embodiments, the dose is administered daily for twelve days. In certain embodiments, the dose is administered daily for eleven days. In certain embodiments, the dose is administered daily for ten days. In certain embodiments, the dose is administered daily for nine days. In certain embodiments, the dose is administered daily for eight days. In certain embodiments, the dose is administered daily for seven days. In certain embodiments, the dose is administered daily for six days. In certain embodiments, the dose is administered daily for five days. In certain embodiments, the dose is administered daily for four days. In certain embodiments, the dose is administered daily for three days. In certain embodiments, the dose is administered daily for two days. In certain embodiments, the dose is administered for one day.

[00118] In the dosing schedule, the doses can be administered on consecutive days or cyclicly, according to the judgment of the practitioner of skill. In certain embodiments, the doses are administered on consecutive days. In certain embodiments, the doses are administered with an interval between doses. In certain embodiments, the interval is one day. In certain embodiments, the interval is two days. In certain embodiments, the interval is three days. In

certain embodiments, the interval is four days. In certain embodiments, the interval is five days. In certain embodiments, the interval is six days.

[00119] In certain embodiments, the dose is administered weekly. In certain embodiments, the dose is administered twice per week. In certain embodiments, the dose is administered three times per week.

[00120] In certain embodiments, the dose(s) are administered for a period of time with a first interval between dose(s), and then the dose(s) are re-administered for a period of time following the first interval between dose(s), wherein this dosing regimen can be repeated (i.e., cyclicly or cyclically, for example, after a second, third, etc. interval between subsequent administrations of dose(s)) according to the judgment of the practitioner of skill. For example, in one embodiment, a first dose is administered for one week, followed by a first interval of one week without the first dose administration; then, a second dose is re-administered for another week, followed by a second interval of one week without the first or second dose administration, and so on cyclicly. Other perturbations for first, second, third, etc. dose(s) followed by perturbations for first, second, third, etc. interval(s), and combinations thereof, are contemplated herein as would be appreciated by the practitioner of skill and the need of the patient. For example, in one embodiment, a first dose is administered daily for one week, followed by a first interval of three weeks without the first daily dose administration; then, a second dose is re-administered biweekly for another week, followed by a second interval of four weeks without the first daily or second biweekly dose administration, and so on cyclicly.

[00121] The compound can be administered by any route of administration deemed suitable by the practitioner of skill. In certain embodiments, the dose is administered orally. Formulations and techniques for administration are described in detail below.

[00122] In certain embodiments, term "cancer" includes, but is not limited to, the following cancers: epidermoid Oral: buccal cavity, lip, tongue, mouth, pharynx, squamous cell carcinoma of the head and neck (HNSCC); Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma, and teratoma; Lung: bronchogenic carcinoma (squamous cell or epidermoid, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma, non-small cell lung cancer (NSCLC); Gastrointestinal: gastric cancer, esophagus (squamous cell carcinoma, larynx, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma,

carcinoid tumors, vipoma), small bowel or small intestines (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel or large intestines (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), colon, colon-rectum, colorectal, microsatellite stable colorectal cancer (MSS CRC), rectum; Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma), metastatic castrate-resistant prostate cancer (mCRPC), muscle-invasive urothelial cancer; Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma, biliary passages; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma (MM), malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical cancer, cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma), breast, triple-negative breast cancer (TNBC), platinum-resistant epithelial ovarian cancer (EOC); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma) hairy cell; lymphoid disorders (e.g., mantle cell lymphoma, Waldenström's macroglobulinemia, Marginal zone lymphoma, and Follicular lymphoma); Skin:

malilymphnant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, keratoacanthoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; Thyroid gland: papillary thyroid carcinoma, follicular thyroid carcinoma; medullary thyroid carcinoma, undifferentiated thyroid cancer, multiple endocrine neoplasia type 2A, multiple endocrine neoplasia type 2B, familial medullary thyroid cancer, pheochromocytoma, paraganglioma; Adrenal glands: neuroblastoma; and metatstaic melanoma.

[00123] Examples of autoimmune disorders include urticaria, graft-versus-host disease (GVHD), acute graft-versus-host disease, pemphigus vulgaris, achalasia, Addison's disease, Adult Still's disease, agammaglobulinemia, alopecia areata, amyloidosis, ankylosing spondylitis, anti-GBM/anti-TBM nephritis, antiphospholipid syndrome, autoimmune angioedema, autoimmune dysautonomia, autoimmune encephalomyelitis, autoimmune hepatitis, autoimmune inner ear disease (AIED), autoimmune myocarditis, autoimmune oophoritis, autoimmune orchitis, autoimmune pancreatitis, autoimmune retinopathy, axonal and neuronal neuropathy (AMAN), Baló disease, Behcet's disease, benign mucosal pemphigoid, bullous pemphigoid, Castleman disease (CD), Celiac disease, Chagas disease, chronic inflammatory demyelinating polyneuropathy (CIDP), chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss Syndrome (CSS) or Eosinophilic Granulomatosis (EGPA), cicatricial pemphigoid, Cogan's syndrome, cold agglutinin disease, congenital heart block, coxsackie myocarditis, CREST syndrome, Crohn's disease, dermatitis herpetiformis, dermatomyositis, Devic's disease (neuromyelitis optica), discoid lupus, Dressler's syndrome, endometriosis, eosinophilic esophagitis (EoE), eosinophilic fasciitis, erythema nodosum, essential mixed cryoglobulinemia, Evans syndrome, fibromyalgia, fibrosing alveolitis, giant cell arteritis (temporal arteritis), giant cell myocarditis, glomerulonephritis, Goodpasture's syndrome, granulomatosis with polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, hemolytic anemia, Henoch-Schonlein purpura (HSP), herpes gestationis or pemphigoid gestationis (PG), hidradenitis suppurativa (HS) (Acne Inversa), hypogammaglobulinemia, IgA nephropathy, IgG4-related sclerosing disease, immune thrombocytopenic purpura (ITP), inclusion body myositis (IBM), interstitial cystitis (IC), juvenile arthritis, juvenile diabetes (Type 1 diabetes), juvenile myositis (JM), Kawasaki disease, Lambert-Eaton syndrome, leukocytoclastic vasculitis, lichen planus, lichen sclerosus, ligneous conjunctivitis, linear IgA disease (LAD), lupus, lyme disease chronic, Meniere's disease, microscopic polyangiitis (MPA), mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multifocal Motor Neuropathy (MMN) or MMNCB,

multiple sclerosis, myasthenia gravis, myositis, narcolepsy, neonatal lupus, neuromyelitis optica, neutropenia, ocular cicatricial pemphigoid, optic neuritis, palindromic rheumatism (PR), PANDAS, paraneoplastic cerebellar degeneration (PCD), paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, pars planitis (peripheral uveitis), Parsonage-Turner syndrome, pemphigus, peripheral neuropathy, perivenous encephalomyelitis, pernicious anemia (PA), POEMS syndrome, polyarteritis nodosa, polyglandular syndromes type I, II, III, polymyalgia rheumatica, polymyositis, postmyocardial infarction syndrome, postpericardiotomy syndrome, primary biliary cirrhosis, primary sclerosing cholangitis, progesterone dermatitis, psoriasis, psoriatic arthritis, pure red cell aplasia (PRCA), pyoderma gangrenosum, Raynaud's phenomenon, reactive Arthritis, reflex sympathetic dystrophy, relapsing polychondritis, restless legs syndrome (RLS), retroperitoneal fibrosis, rheumatic fever, rheumatoid arthritis, sarcoidosis, Schmidt syndrome, scleritis, scleroderma, Sjögren's syndrome, sperm and testicular autoimmunity, stiff person syndrome (SPS), subacute bacterial endocarditis (SBE), Susac's syndrome, sympathetic ophthalmia (SO), Takayasu's arteritis, temporal arteritis (giant cell arteritis), thrombocytopenic purpura (TTP), Tolosa-Hunt syndrome (THS), transverse myelitis, Type 1 diabetes, ulcerative colitis (UC), undifferentiated connective tissue disease (UCTD), uveitis, vasculitis, vitiligo, Vogt-Koyanagi-Harada Disease, and Wegener's granulomatosis (or Granulomatosis with Polyangiitis (GPA)).

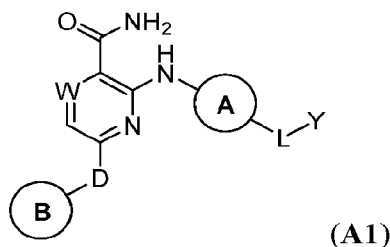
[00124] In certain embodiments, provided herein are methods of degrading a mutant Bruton's tyrosine kinase. The methods comprise the step of contacting a cell expressing the mutant Bruton's tyrosine kinase with an amount of a bifunctional compound capable of inducing proteolytic degradation of Bruton's tyrosine kinase. In certain embodiments, the amount of a bifunctional compound capable of inducing proteolytic degradation of Bruton's tyrosine kinase is the amount effective to degrade the mutant Bruton's tyrosine kinase. In certain embodiments, the mutant Bruton's tyrosine kinase is a C481 mutant. In certain embodiments, the mutant Bruton's tyrosine kinase is a C481S mutant. The contacting can be *in vitro* or *in vivo*. In certain embodiments, the contacting is *in vitro*. In certain embodiments, the contacting is *in vivo*. In certain embodiments, the contacting is in a subject in need thereof.

BIFUNCTIONAL COMPOUNDS

[00125] The methods provided herein comprise administration of a bifunctional compound. The bifunctional compound can be any compound described herein. In certain embodiments,

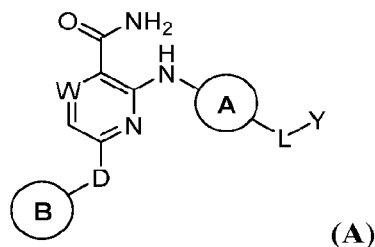
the bifunctional compound comprises at least two moieties. One moiety is capable of specifically binding Bruton's tyrosine kinase (BTK). The other moiety is capable of recruiting an ubiquitin ligase to degrade the BTK. In certain embodiments, the ubiquitin ligase is an E3 ligase. In certain embodiments, the ubiquitin ligase is cereblon (CRBN) or comprises cereblon as a component.

[00126] In the methods, the compound can be a compound of Formula (A1)



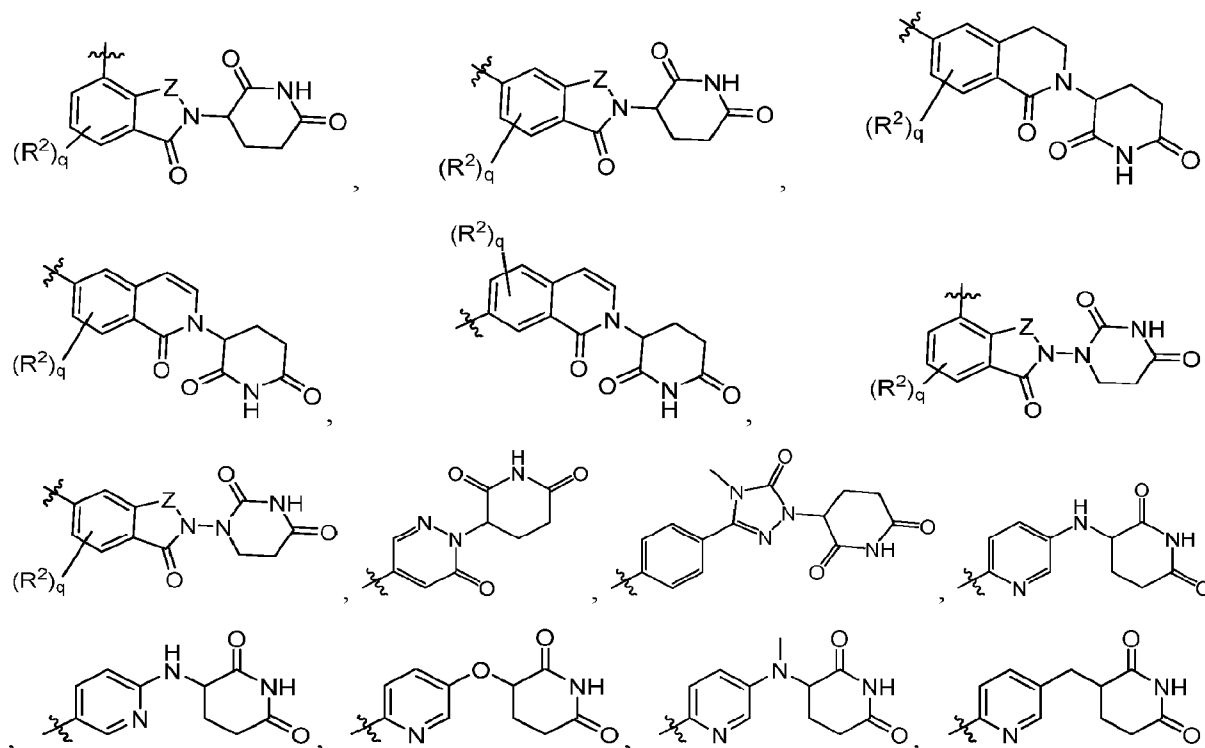
or a pharmaceutically acceptable salt thereof, wherein **W** is CH or N; **D** is a bond or a linker; **Ring A** is aryl or heteroaryl; **Ring B** is aryl or heteroaryl; **L** is a bond or a linker; and **Y** is a moiety capable of binding an ubiquitin ligase.

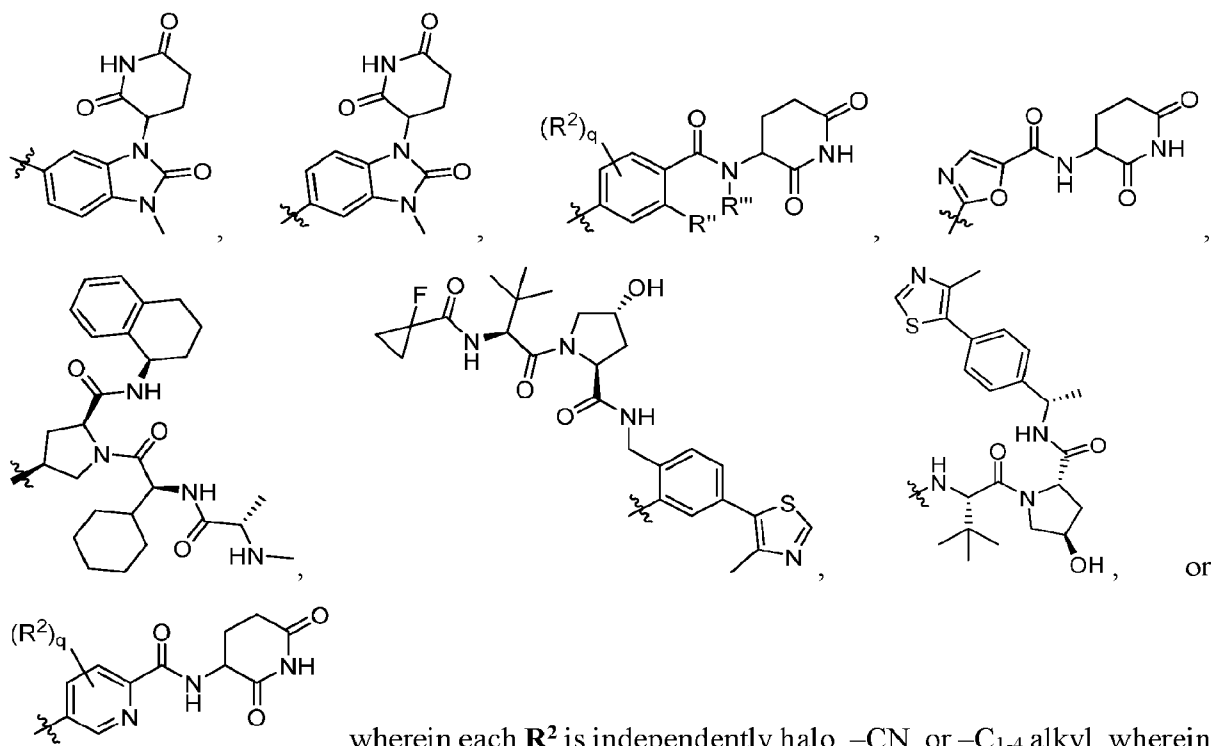
[00127] In the methods, the compound can be a compound of Formula (A)



or a pharmaceutically acceptable salt thereof, wherein **W** is CH or N; **D** is a bond or -NH- ; **Ring A** is phenyl, a 9-10 membered bicyclic aryl, a 5-6 membered partially or fully unsaturated monocyclic heterocycle, or a 9-10 membered bicyclic heteroaryl, wherein the monocyclic heterocycle and bicyclic heteroaryl of **Ring A** each possess one to three heteroatoms independently selected from N, O, or S, wherein **Ring A** is optionally and independently substituted with up to three substituents selected from halo, -CN , -COOH , NH_2 , and optionally substituted C_{1-6} alkyl; **Ring B** is a phenyl, a 5-6 membered heteroaryl, a 4-6 membered heterocycloalkyl, or a 8-10 membered (e.g., 8-9 membered or 9-10 membered) spiro bicyclic heterocycle, wherein **Ring B** is optionally substituted, and wherein the heteroaryl and heterocycloalkyl of **Ring B** has one to three heteroatoms independently selected from N, O, or S; **L** is $\text{-X}^1\text{-X}^2\text{-X}^3\text{-X}^4\text{-X}^5\text{-}$; X^1 is a bond, -C(O)-N(R)- , -N(R)-C(O)- , $\text{-(O-CH}_2\text{-CH}_2\text{)}_m\text{-}$, $\text{-O(C}_6\text{H}_4\text{)-}$, $\text{-(O-CH}_2\text{-CH}_2\text{-CH}_2\text{)}_m\text{-}$, $\text{-C}_{1-5}\text{ alkyl-}$, 7-12 membered spiro or fused bicyclic heterocycloalkyl having one to three heteroatoms independently selected from N, O, or S, or

4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein each of the monocyclic and bicyclic heterocycloalkyl of **X¹** is optionally substituted with $-\text{CH}_3$; **X²** is a bond, $-(\text{O}-\text{CH}_2-\text{CH}_2)_n-$, $-(\text{CH}_2-\text{CH}_2-\text{O})_n-$, $-\text{N}(\text{R})-\text{C}(\text{O})-$, $-\text{N}(\text{R})-$, $-\text{C}(\text{O})-$, $-\text{C}_{1-5}$ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S; **X³** is a bond, $-\text{C}_{1-8}$ alkyl-, $-\text{C}\equiv\text{C}-$, 4-6 membered cycloalkyl, $-\text{N}(\text{R})-$, $-\text{N}(\text{R})-\text{C}(\text{O})-$, $-(\text{O}-\text{CH}_2-\text{CH}_2)_p-$, $-(\text{CH}_2-\text{CH}_2-\text{O})_p-$, 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-\text{CH}_3$; **X⁴** is a bond, $-\text{CH}_2-\text{CH}_2-\text{N}(\text{R})-$, $-\text{N}(\text{R})-$, $-\text{C}_{1-4}$ alkyl-, $-(\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2)_m-$, a 5-6 membered saturated, partially unsaturated, or fully unsaturated carbocycle, or a 5-6 membered saturated, partially unsaturated, or fully unsaturated heterocycle having one to three heteroatoms independently selected from N, O, or S; **X⁵** is a bond, $-\text{C}_{1-4}$ alkyl-, $-\text{N}(\text{R})-$, $-\text{O}-$, $-\text{C}(\text{O})-$, or $-\text{C}(\text{O})-\text{N}(\text{R})-$; each **R** is independently $-\text{H}$ or $-\text{C}_{1-3}$ alkyl (e.g., methyl, ethyl, propyl, or iso-propyl); and each of **m**, **n**, and **p** is independently an integer from one to three (e.g., one, two, or three); and **Y** is

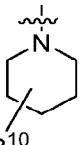


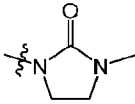
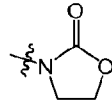


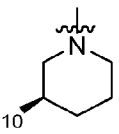
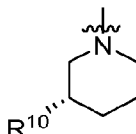
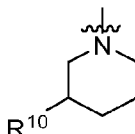
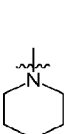
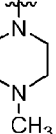
[00128] With the exception of the moieties of group **R**, all moieties of the linking group **L** as defined in the compound of Formula (A) are bivalent moieties unless otherwise specified. For example, any alkyl (e.g., *n*-propyl, *n*-butyl, *n*-hexyl, and the like), aryl (e.g., phenyl), cycloalkyl (e.g., cyclopropyl, cyclohexyl, and the like), heteroaryl, heterocylcoalkyl (e.g., piperidine, piperazine, and the like) that is present in **L** is bivalent unless otherwise specified.

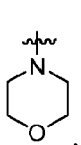
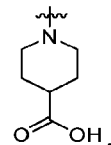
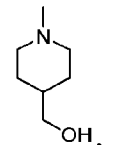
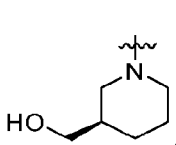
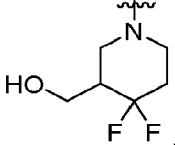
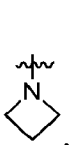
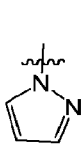
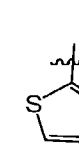
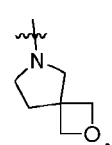
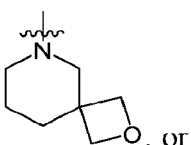
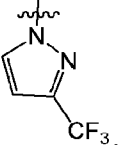
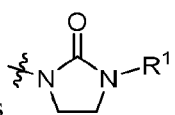
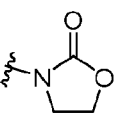
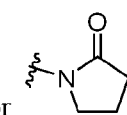
[00129] In some embodiments, **Ring B** is an optionally substituted 5-6 membered heterocycloalkyl having one to two nitrogen atoms. For example, **Ring B** is piperidine-yl, piperazine-yl, or pyrrolidine-yl, any of which is optionally substituted.

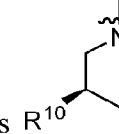
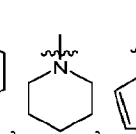
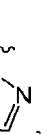
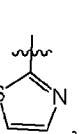
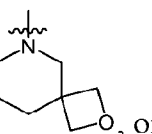
[00130] In some embodiments, **Ring B** is an optionally substituted 5-6 membered heteroaryl having one to two heteroatoms independently selected from N and S. For example, **Ring B** is pyridine-yl, pyrazine-yl, or pyrimidine, any of which is optionally substituted.

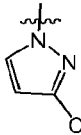
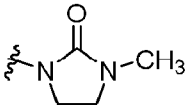
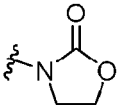
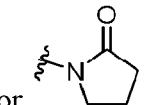
[00131] In some embodiments, **Ring B** is , wherein **R¹⁰** is halo, -H, -C₁₋₅ alkyl (e.g., -C₁₋₃ alkyl), 3-6 membered cycloalkyl, 5-6 membered heterocycloalkyl, -CN, -OH,

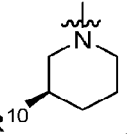
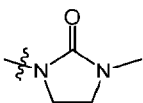
-CF₃, -CH₂OH, -CH₂CH₂OH, -C(O)OH,  or .

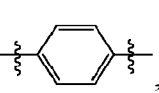
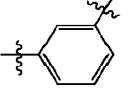
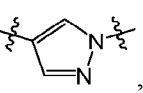
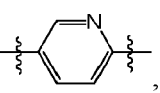
[00132] In some embodiments, **Ring B** is , , , , , ,

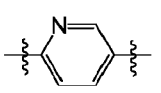
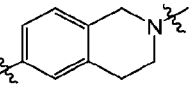
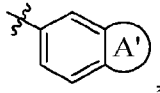
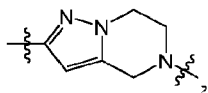
, , , , , , , , , , or , wherein **R¹⁰** is , , or , and wherein **R¹**

is a C₁₋₄ alkyl group. For example, **Ring B** is , , , , , or

, wherein **R¹⁰** is , , or . And, in some instances, **Ring**

B is . In other instances, **R¹⁰** is .

[00133] In some embodiments, **Ring A** is , , , ,

, , , or , wherein **Ring A'** together with the phenyl ring to which **Ring A'** is fused form a 9-10 membered bicyclic aryl or a 9-10 membered bicyclic heteroaryl wherein the bicyclic heteroaryl (i.e., the bicyclic heteroaryl

including **Ring A'**) has one to three heteroatoms independently selected from N, O, or S. For

example, **Ring A** is , or

[00134] In some embodiments, at least one of **X¹**, **X²**, and **X⁵** is **-N(R)-**, **-C(O)-N(R)-**, or **-CH₂-**.

[00135] In some embodiments, **X¹** is $-\text{C}(\text{O})-\text{N}(\text{R})-$.

[00136] In some embodiments, X^2 is $-(O-CH_2-CH_2)_n-$, $-(CH_2-CH_2-O)_n-$, or $-C_{1-5}$ alkyl-.

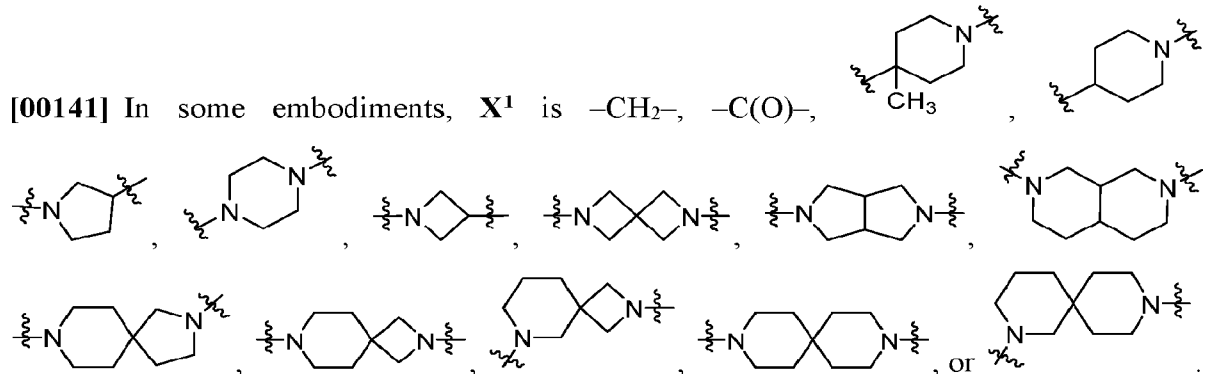
[00137] In some embodiments, X^3 is a bond, $-C\equiv C-$, $-C_{1-4}$ alkyl-, or $-N(R)-$.

[00138] In some embodiments, X^4 is a bond, $-CH_2-$, or $-N(R)-$.

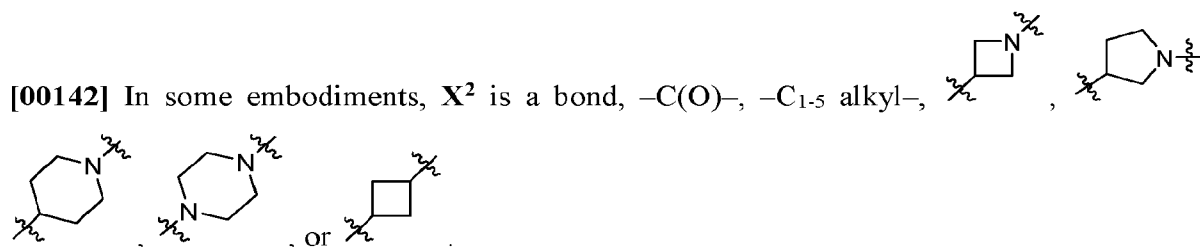
[00139] In some embodiments, X^5 is a bond.

[00140] In some embodiments, $\mathbf{X}^1$ is $-(\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2)_m-$, m is one, and $\mathbf{X}^2$ is $-\text{C}(\text{O})-\text{N}(\mathbf{R})-$.

[00141] In some embodiments, **X¹** is $-\text{CH}_2-$, $-\text{C}(\text{O})-$,

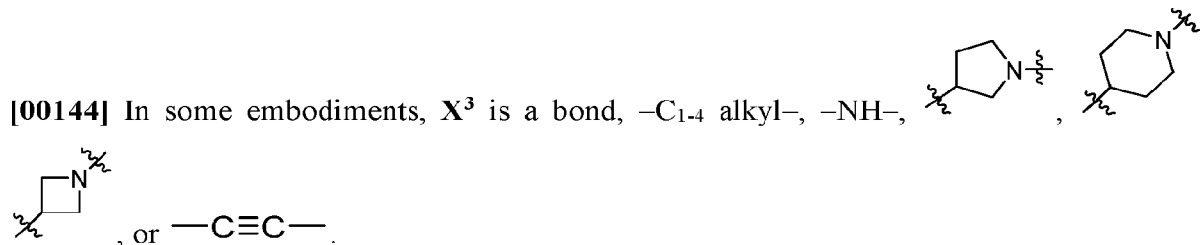


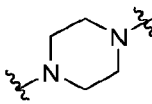
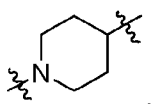
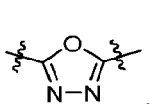
[00142] In some embodiments, X^2 is a bond, $-C(O)-$, $-C_{1-5}$ alkyl-,



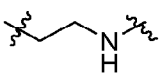
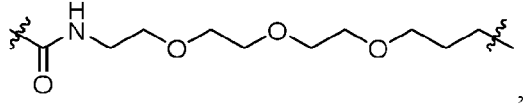
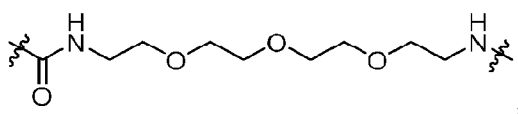
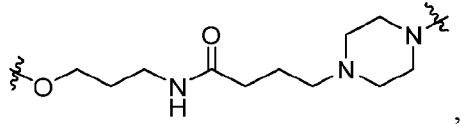
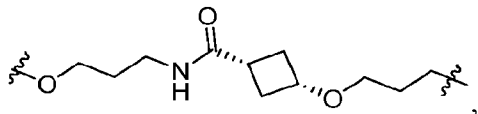
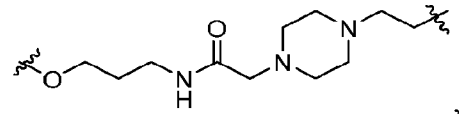
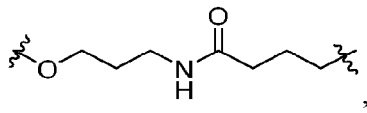
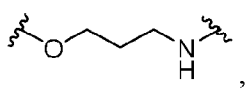
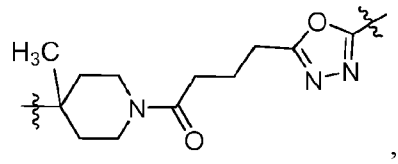
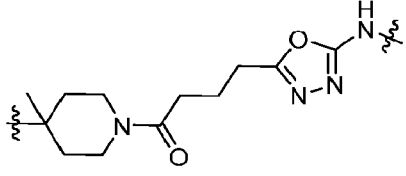
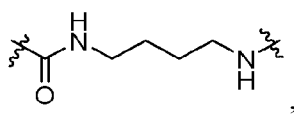
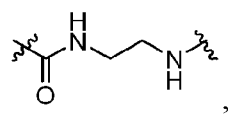
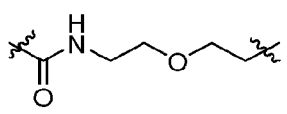
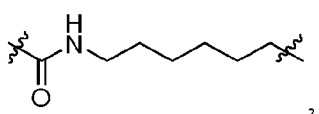
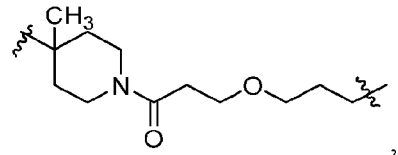
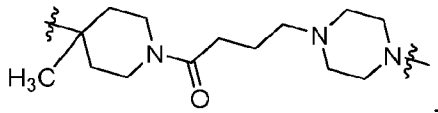
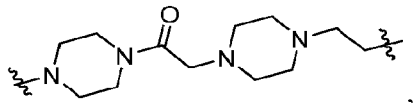
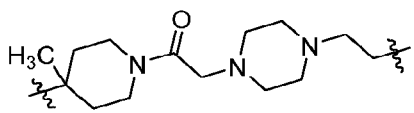
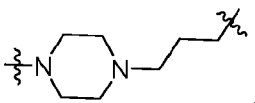
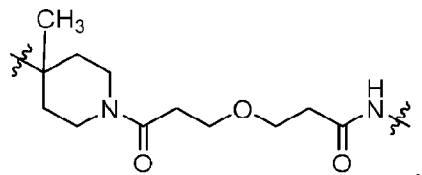
[00143] In some embodiments, **X³** is bond, -C₁₋₄ alkyl-, 4-6 membered cycloalkyl, or -N(**R**)-.

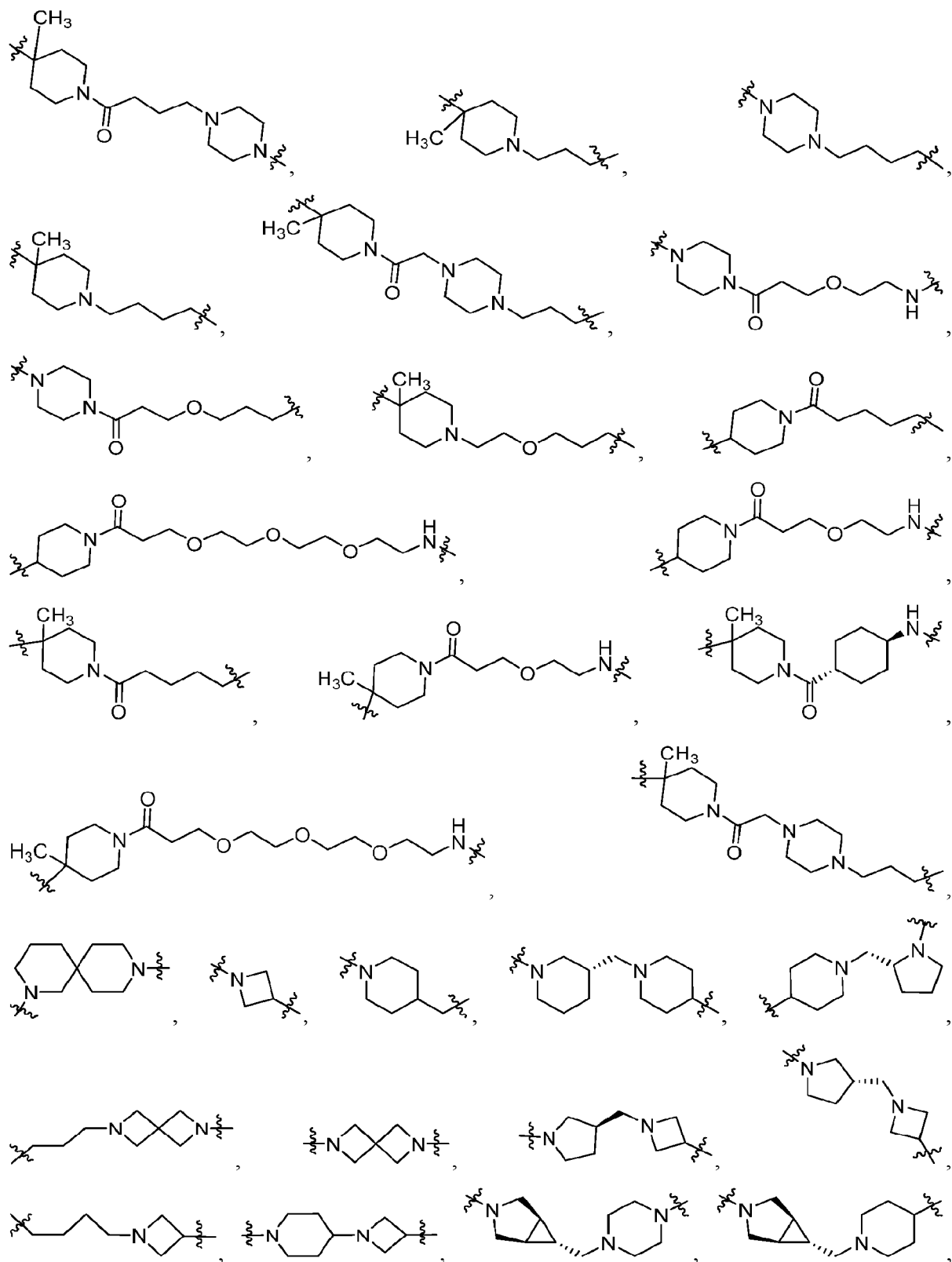
[00144] In some embodiments, X^3 is a bond, $-C_{1-4}$ alkyl-, $-NH-$,

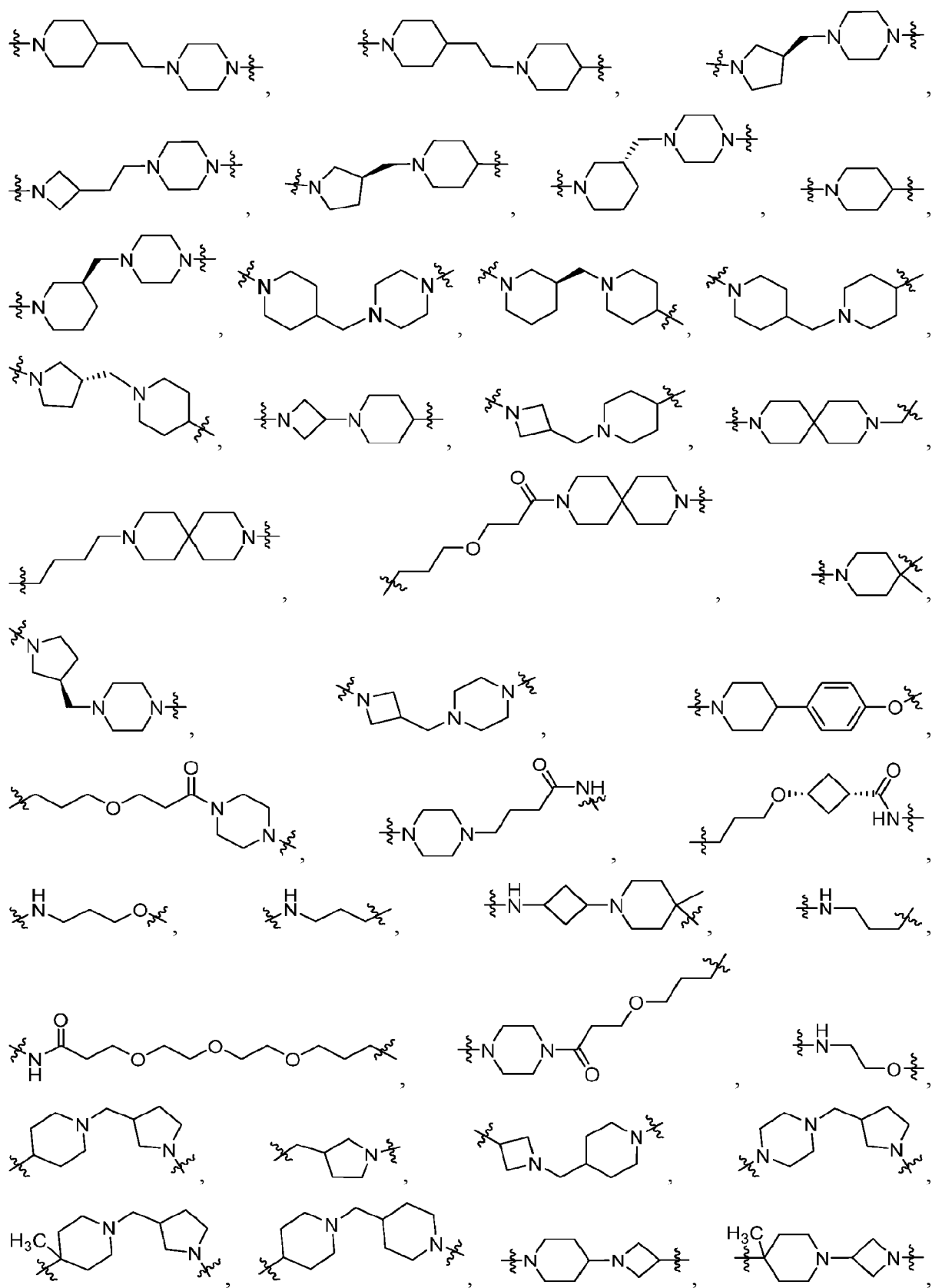


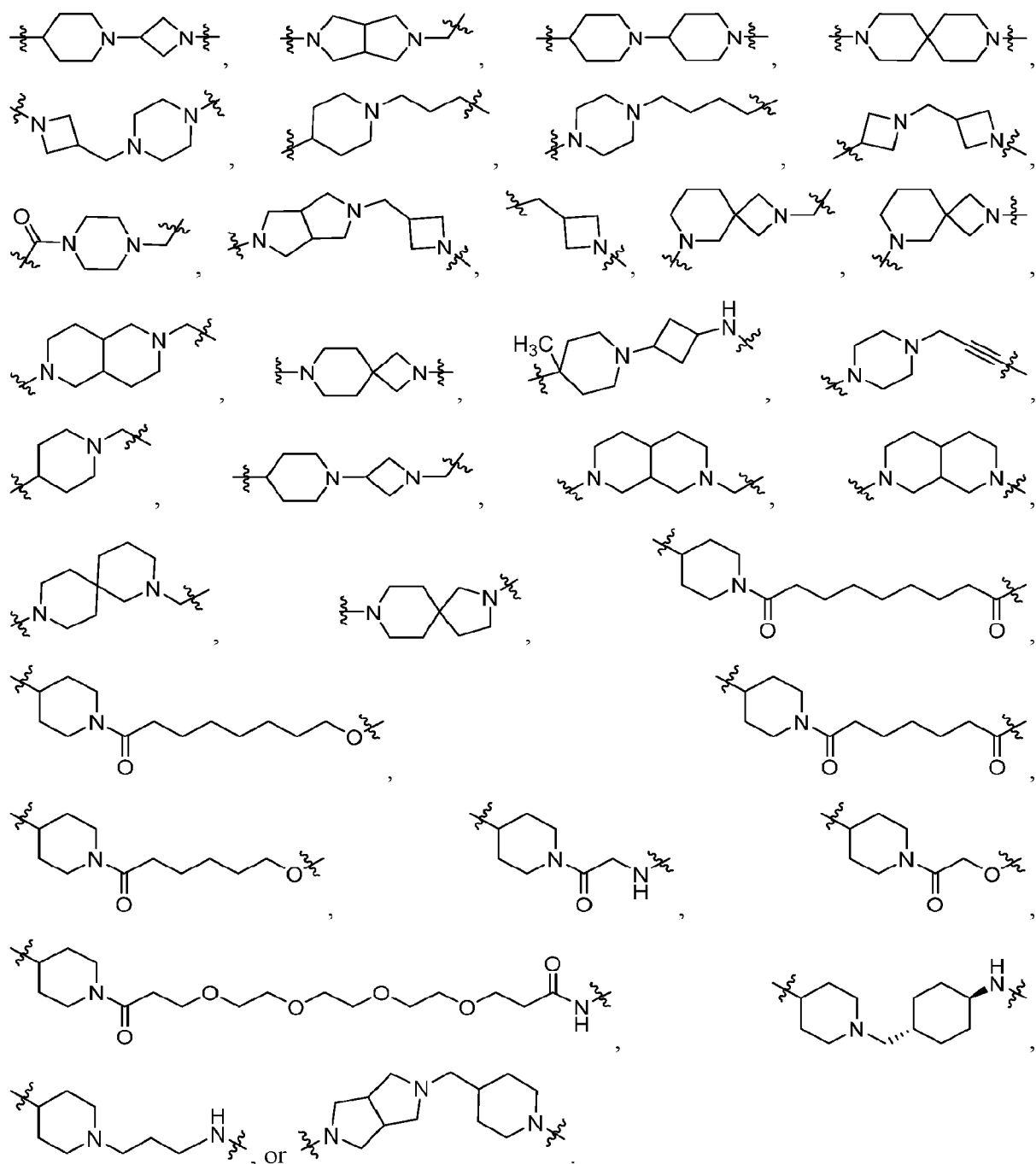
[00145] In some embodiments, X^4 is a bond, , , , $-C_{1-4}$ alkyl-, $-\text{CH}_2-\text{CH}_2-\text{N}(\text{R})-$, or $-\text{N}(\text{R})-$.

[00146] In some embodiments, X^5 is a bond, $-C_{1-4}$ alkyl-, $-\text{N}(\text{R})-$, or $-\text{C}(\text{O})-\text{N}(\text{R})-$.

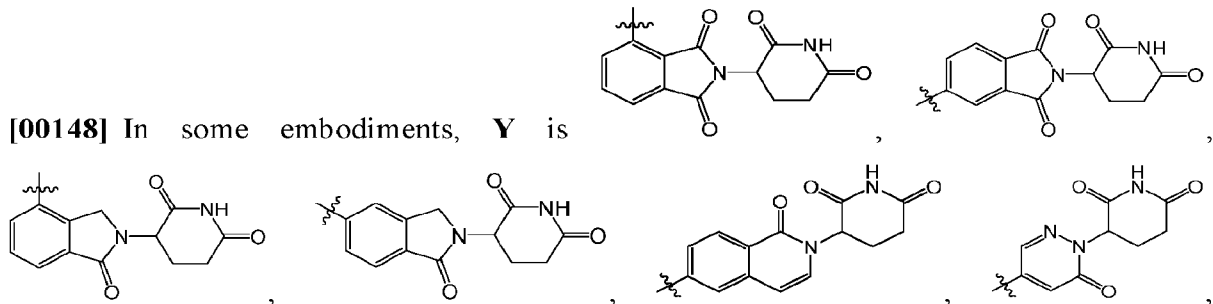
[00147] In some embodiments, L is , , , , , , , , , , , , , , , , , , , 

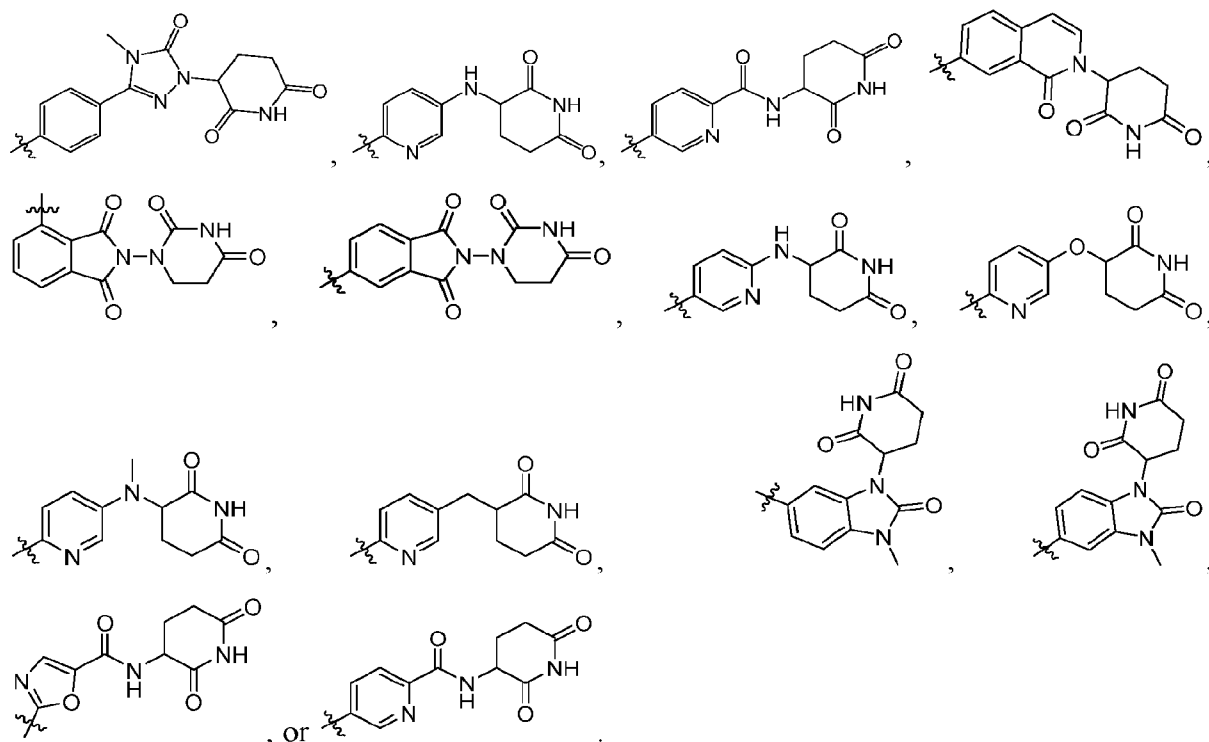






[00148] In some embodiments, **Y** is

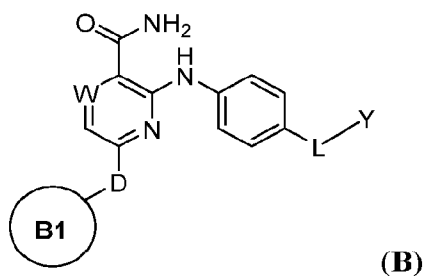




[00149] In some embodiments, **W** is N.

[00150] In some embodiments, **D** is a bond.

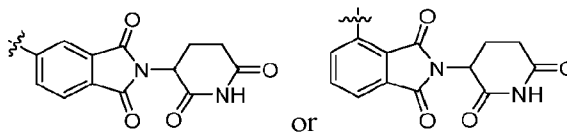
[00151] This disclosure also provides a compound of Formula (**B**)



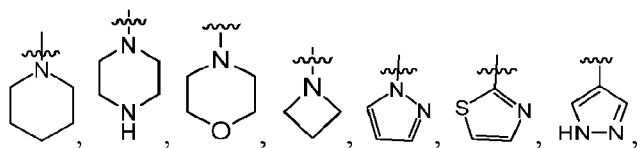
or a pharmaceutically acceptable salt thereof, wherein **W** is CH or N; **D** is a bond or --NH-- ; **Ring B1** is a 4-6 membered, fully saturated, partially unsaturated, or fully unsaturated monocyclic heterocycle or a 8-10 membered, fully saturated, spiro bicyclic heterocycle, wherein **Ring B1** has one to three heteroatoms independently selected from N, O, or S, and is optionally substituted with one to three groups selected from halo, --CH_3 , --CF_3 , --C(O)OH , $\text{--CH}_2\text{OH}$, or a 5-membered heterocycloalkyl optionally substituted with oxo and having one to two heteroatoms independently selected from N or O; **L** is $\text{--X}^1\text{--X}^2\text{--X}^3\text{--}$; **X**¹ is --C(O)--N(R)-- , --N(R)--C(O)-- , $\text{--(O--CH}_2\text{--CH}_2\text{)}_m\text{--}$, $\text{--O(C}_6\text{H}_4\text{)--}$, $\text{--(O--CH}_2\text{--CH}_2\text{--CH}_2\text{)}_m\text{--}$, $\text{--C}_{1-5}\text{ alkyl--}$, 7-12 membered spiro or fused bicyclic heterocycloalkyl having one to three

heteroatoms independently selected from N, O, or S, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein each of the monocyclic and bicyclic heterocycloalkyl of X^1 is optionally substituted with $-CH_3$; X^2 is a bond, $-(O-CH_2-CH_2)_n-$, $-(CH_2-CH_2-O)_n-$, $-N(R)-C(O)-$, $-N(R)-$, $-C(O)-$, $-C_{1-5}$ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S; X^3 is a bond, $-C_{1-4}$ alkyl-, $-C\equiv C-$, 4-6 membered cycloalkyl, $-N(R)-$, $-(O-CH_2-CH_2)_p-$, $-(CH_2-CH_2-O)_p-$, 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-CH_3$; each R is independently $-H$ or $-C_{1-3}$ alkyl; each of m , n , and p is independently an

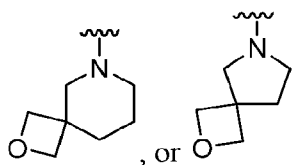
integer from one to three; and Y is



[00152] In some embodiments, **Ring B1** is



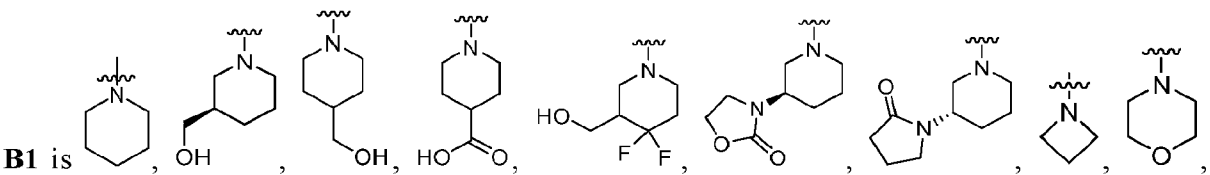
, or



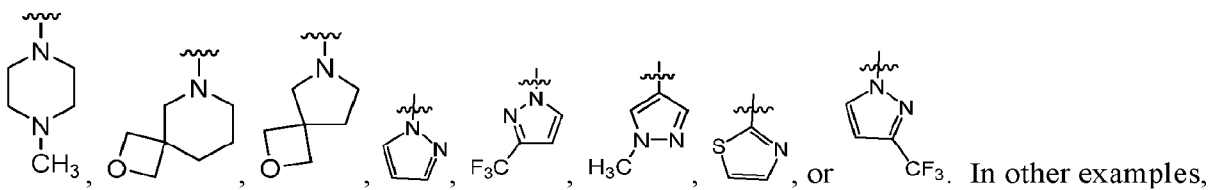
, and **Ring B1** is optionally substituted one to three groups selected from

$-CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-C(O)OH$, $-CF_3$, $-F$, , and . For example, **Ring**

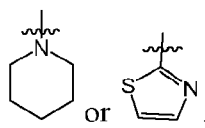
B1 is



, or



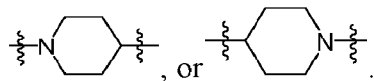
Ring B1 is



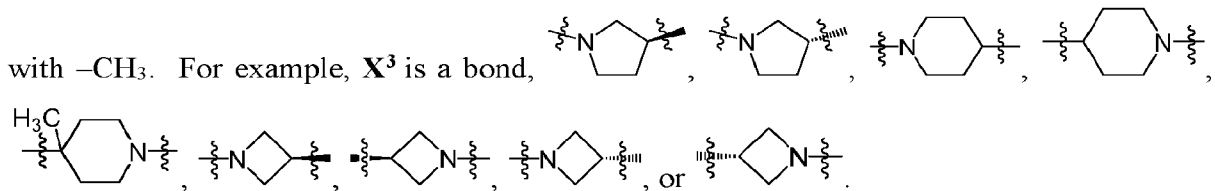
[00153] In some embodiments, X¹ is

The structures shown are: 1) A pyrrolidine ring with wavy bonds at the nitrogen and C2 positions. 2) An N-methylpyrrolidine ring with a methyl group at N1 and wavy bonds at N1 and C2 positions. 3) A piperidine ring with wavy bonds at the nitrogen and C2 positions. 4) An N-methylpiperidine ring with a methyl group at N1 and wavy bonds at N1 and C2 positions. 5) A 2-methylpiperidine ring with a methyl group at C2 and wavy bonds at the nitrogen and C2 positions. 6) A 2-methyl-2-piperidine ring with a methyl group at C2 and wavy bonds at the nitrogen and C2 positions. 7) A 2-methyl-2-pyrrolidine ring with a methyl group at C2 and wavy bonds at the nitrogen and C2 positions. 8) A 2-methyl-2-pyrrolidine ring with a methyl group at C2 and wavy bonds at the nitrogen and C2 positions. 9) A 2-methyl-2-pyrrolidine ring with a methyl group at C2 and wavy bonds at the nitrogen and C2 positions. 10) A 2-methyl-2-pyrrolidine ring with a methyl group at C2 and wavy bonds at the nitrogen and C2 positions. 11) A 1,4-diazabicyclo[2.2.2]octane system with wavy bonds at the two nitrogen atoms.

[00154] In some embodiments, **X²** is a bond, $-C_{1-5}$ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S. For example, **X²** is a bond, $-C_{1-3}$ alkyl-, $-C(O)-$,

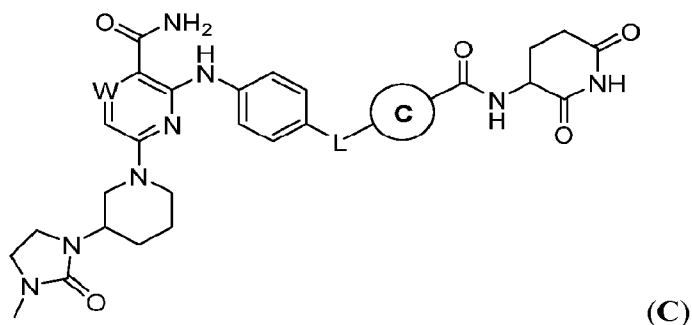


[00155] In some embodiments, **X³** is a bond, -C₁₋₄ alkyl-, -N(**R**)-, -(O-CH₂-CH₂)_p-, -(CH₂-CH₂-O)_p-, or a 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted

[illegible]

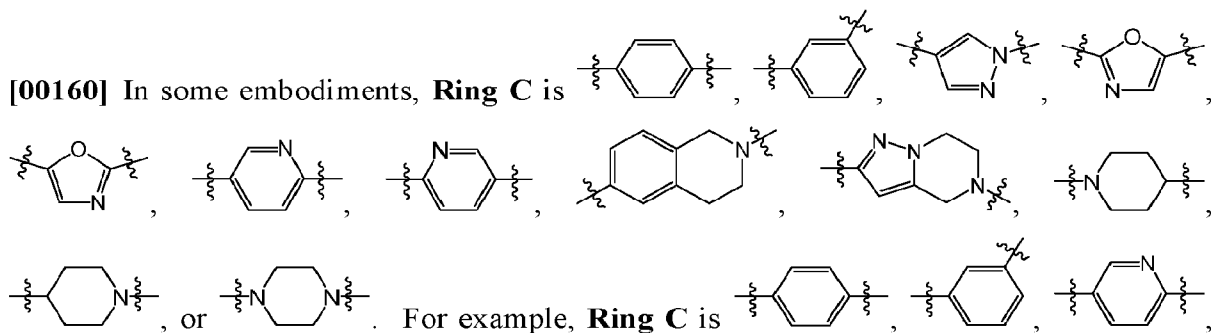
[00157] In some embodiments, **W** is N and **D** is a bond.

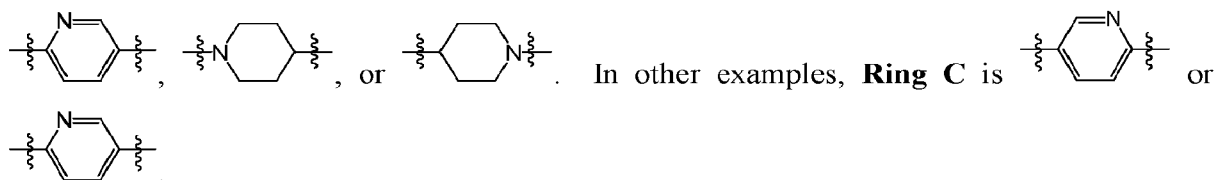
[00158] This disclosure also provides a compound of Formula (C)



or a pharmaceutically acceptable salt thereof, wherein **W** is CH or N; **Ring C** is phenyl or a saturated, partially unsaturated, or fully unsaturated 5-6 membered monocyclic heterocycle having one to two heteroatoms independently selected from N, O, or S, wherein each of the phenyl and heterocycle of **Ring C** is optionally substituted; **L** is $-\mathbf{X}^1-\mathbf{X}^2-\mathbf{X}^3-$; $\mathbf{X}^1$ is $-\text{C}(\text{O})-\text{N}(\mathbf{R})-$, $-\text{N}(\mathbf{R})-\text{C}(\text{O})-$, $-(\text{O}-\text{CH}_2-\text{CH}_2)_m-$, $-\text{O}-(\text{C}_6\text{H}_4)-$, $-(\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2)_m-$, $-\text{C}_{1-5}$ alkyl-, 7-12 membered spiro bicyclic heterocycloalkyl having one to three heteroatoms independently selected from N, O, or S, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein each of the bicyclic heterocycloalkyl and the monocyclic heterocycloalkyl of $\mathbf{X}^1$ is optionally substituted with $-\text{CH}_3$; $\mathbf{X}^2$ is a bond, $-(\text{O}-\text{CH}_2-\text{CH}_2)_n-$, $-(\text{CH}_2-\text{CH}_2-\text{O})_n-$, $-\text{N}(\mathbf{R})-\text{C}(\text{O})-$, $-\text{N}(\mathbf{R})-$, $-\text{C}(\text{O})-$, $-\text{C}_{1-5}$ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S; $\mathbf{X}^3$ is a bond, $-\text{C}_{1-4}$ alkyl-, $-\text{C}\equiv\text{C}-$, 4-6 membered cycloalkyl, $-\text{N}(\mathbf{R})-$, $-(\text{O}-\text{CH}_2-\text{CH}_2)_p-$, $-(\text{CH}_2-\text{CH}_2-\text{O})_p-$, 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-\text{CH}_3$; each **R** is independently $-\text{H}$ or $-\text{C}_{1-3}$ alkyl; and each of **m**, **n**, and **p** is independently an integer from one to three.

[00159] In some embodiments, **W** is N.





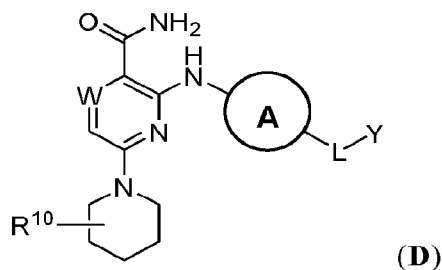
[00161] In some embodiments, **X¹** is a 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S. For example, **X¹** is , , , , , , or . In some examples, **X¹** is or .

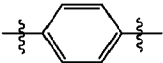
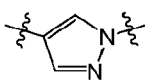
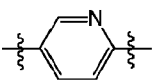
[00162] In some embodiments, **X²** is a bond, $-C_{1-5}$ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S. For example, **X²** is a bond or $-C_{1-3}$ alkyl- (e.g., $-CH_2-$).

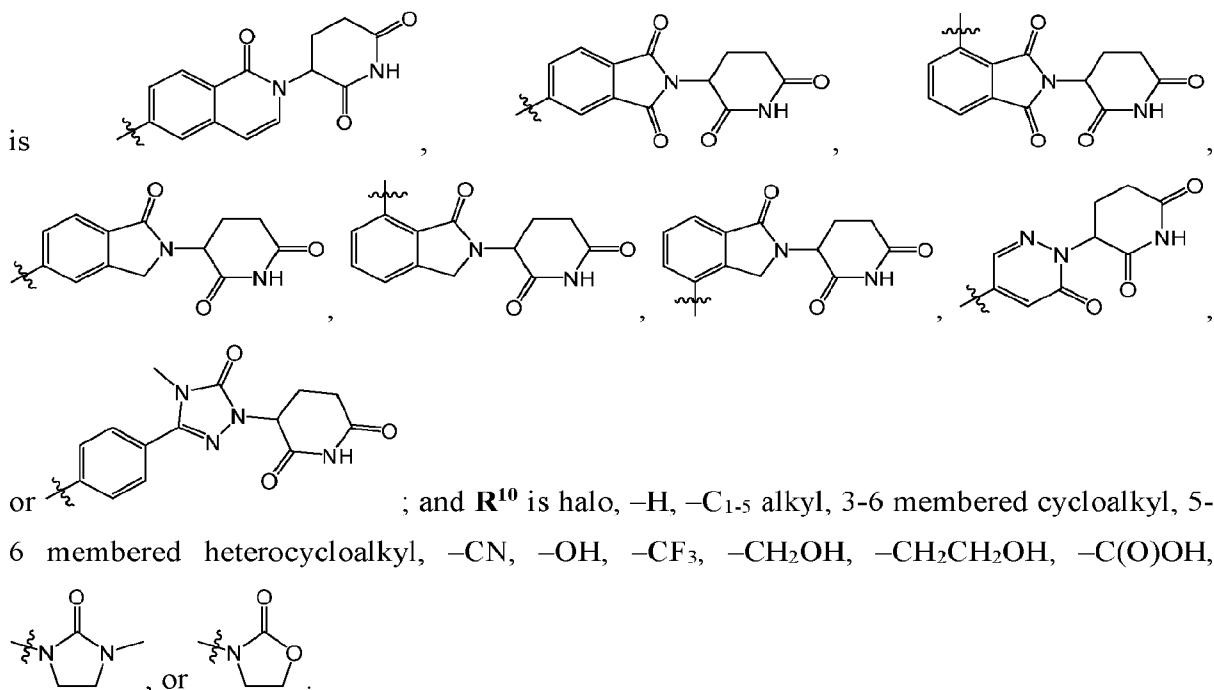
[00163] In some embodiments, **X³** is a 4-6 membered cycloalkyl, $-N(R)-$, or a 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-CH_3$. For example, **X³** is , , , , , or . In other embodiments, **X³** is or .

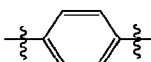
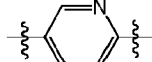
[00164] In some embodiments, **L** is , , , , , or . For example, **L** is or .

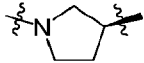
[00165] This disclosure also provides a compound of Formula (**D**)

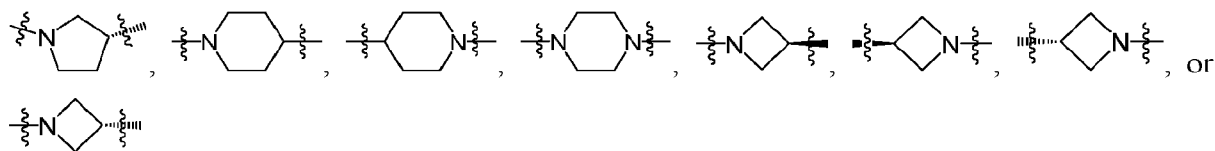


or a pharmaceutically acceptable salt thereof, wherein **W** is CH or N; **Ring A** is , , or ; **L** is $-\mathbf{X}^1-\mathbf{X}^2-\mathbf{X}^3-$; $\mathbf{X}^1$ is $-\text{C}_{1-5}$ alkyl- or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the monocyclic heterocycloalkyl of $\mathbf{X}^1$ is optionally substituted with $-\text{CH}_3$; $\mathbf{X}^2$ is a bond, $-\text{C}_{1-5}$ alkyl-, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the monocyclic heterocycloalkyl of $\mathbf{X}^2$ is optionally substituted with $-\text{CH}_3$; $\mathbf{X}^3$ is a bond, $-\text{C}_{1-4}$ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-\text{CH}_3$; **Y**



[00166] In some embodiments, **Ring A** is  or .

[00167] In some embodiments, $\mathbf{X}^1$ is a 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the monocyclic heterocycloalkyl of $\mathbf{X}^1$ is optionally substituted with $-\text{CH}_3$. For example, $\mathbf{X}^1$ is ,

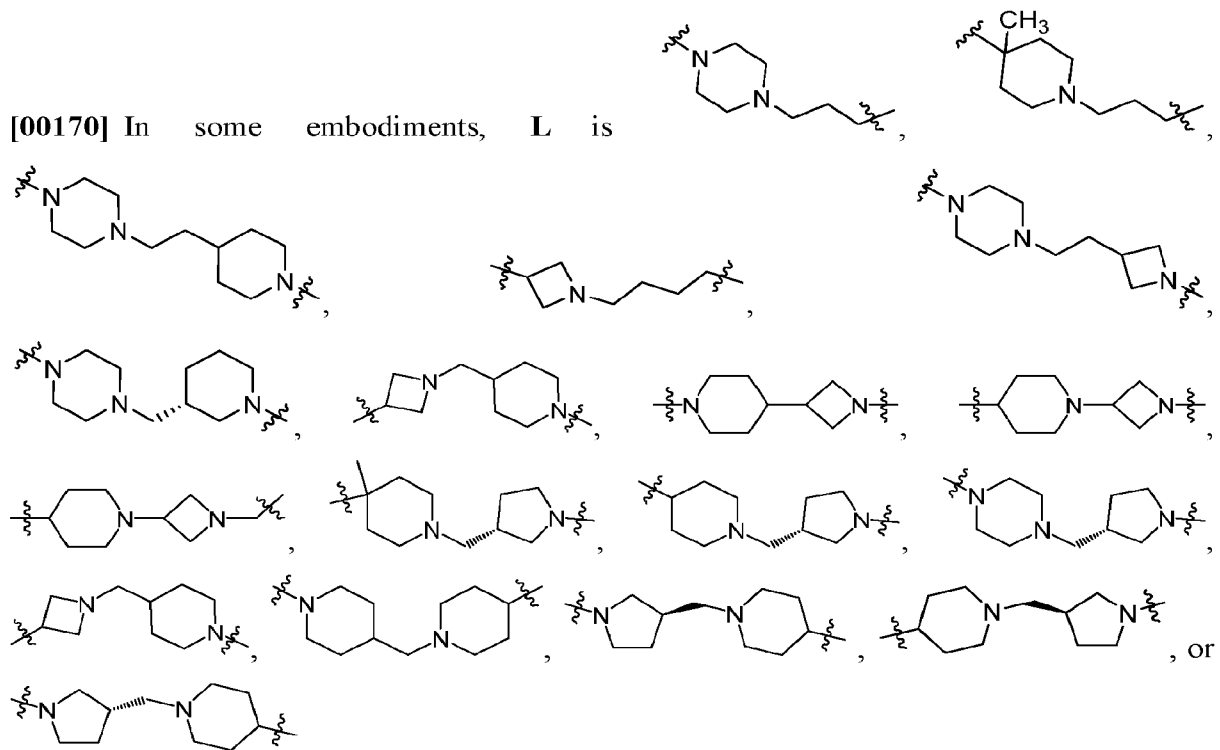


[00168] In some embodiments, **X²** is a bond, $-C_{1-5}$ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S. For example, **X²** is a bond or $-C_{1-4}$ alkyl-.

[00169] In some embodiments, **X³** is a bond, a 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected

from N, O, or S. For example, $\mathbf{X}^3$ is  ,  ,  ,  ,  ,  , or .

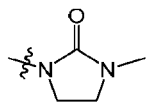
[00170] In some embodiments, L is

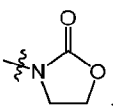


[00171] In some embodiments, **R¹⁰** is halo, -H, -C₁₋₅ alkyl (e.g., -C₁₋₃ alkyl), 3-6 membered cycloalkyl, 5-6 membered heterocycloalkyl, -CN, -OH, -CF₃, -CH₂OH, -C(O)OH, or -CH₂CH₂OH. For instance, **R¹⁰** is halo, -H, C₁₋₃ alkyl, CF₃, -CH₂OH, -C(O)OH, or

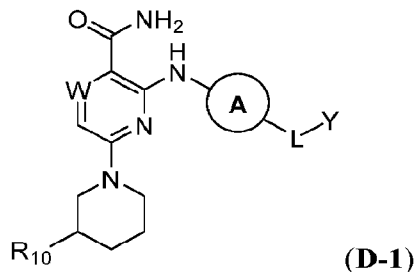
$-\text{CH}_2\text{CH}_2\text{OH}$. In other instances, $\mathbf{R}^{10}$ is
 

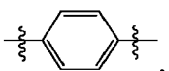
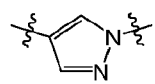
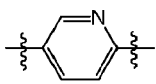
[00172] In some embodiments, $\mathbf{R}^{10}$ is

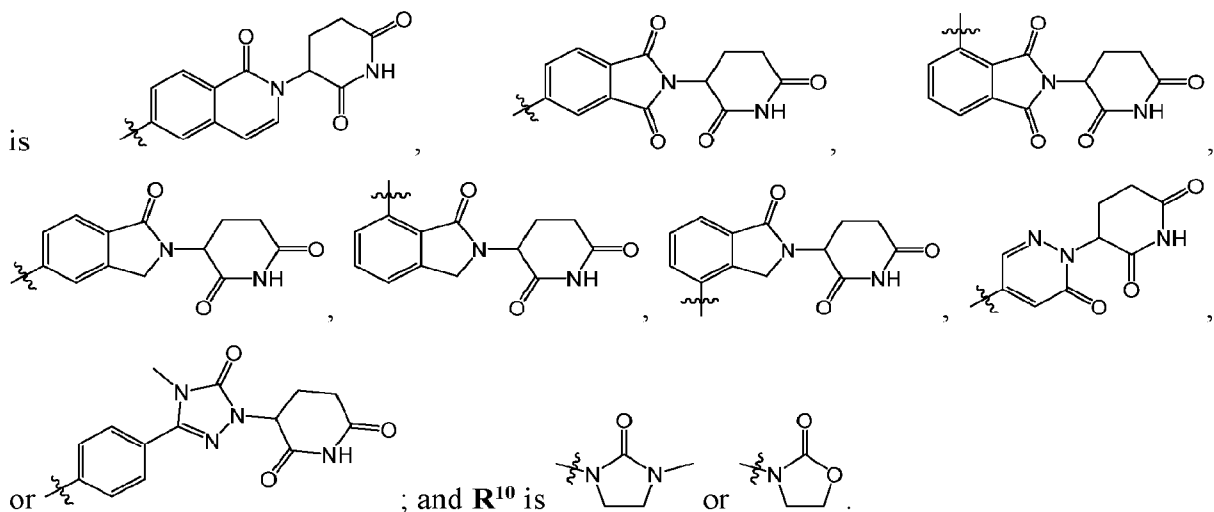


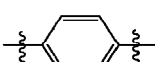
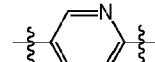
[00173] In some embodiments, R^{10} is .

[00174] In some embodiments, the compound of Formula (D) is a compound of (D-1)

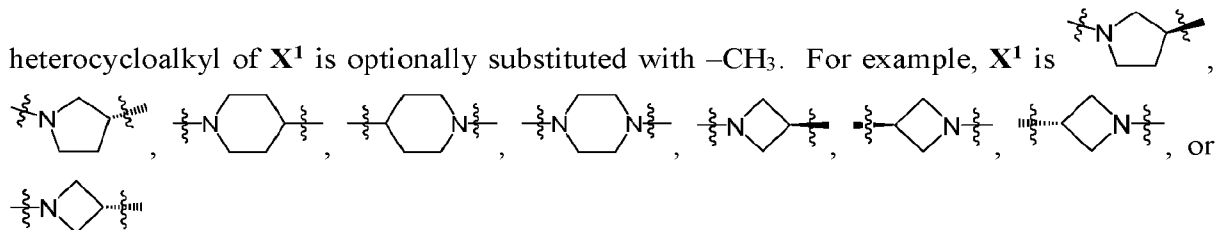


or a pharmaceutically acceptable salt thereof, wherein **W** is CH or N; **Ring A** is , , or ; **L** is $-X^1-X^2-X^3-$; X^1 is $-C_{1-5}$ alkyl- or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the monocyclic heterocycloalkyl of X^1 is optionally substituted with $-CH_3$; X^2 is a bond, $-C_{1-5}$ alkyl-, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the monocyclic heterocycloalkyl of X^1 is optionally substituted with $-CH_3$; X^3 is a bond, $-C_{1-4}$ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-CH_3$; **Y**



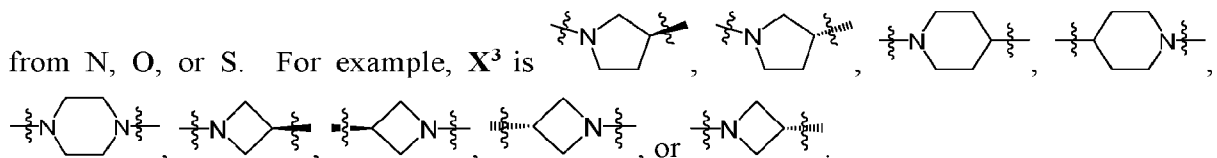
[00175] In some embodiments, **Ring A** is  or .

[00176] In some embodiments, X^1 is a 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the monocyclic

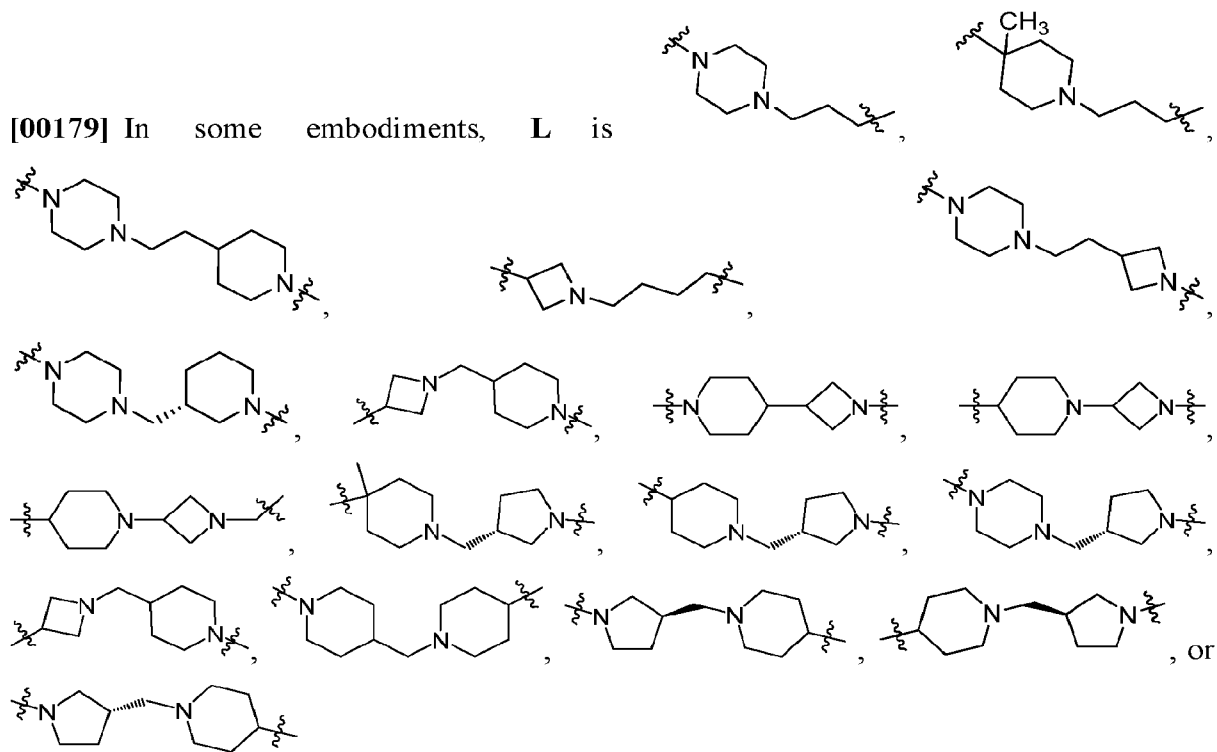
heterocycloalkyl of X^1 is optionally substituted with $-CH_3$. For example, X^1 is , or

[00177] In some embodiments, X^2 is a bond, $-C_{1-5}$ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S. For example, X^2 is a bond or $-C_{1-4}$ alkyl-.

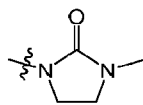
[00178] In some embodiments, X^3 is a bond, a 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected

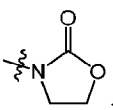
from N, O, or S. For example, X^3 is .

[00179] In some embodiments, L is

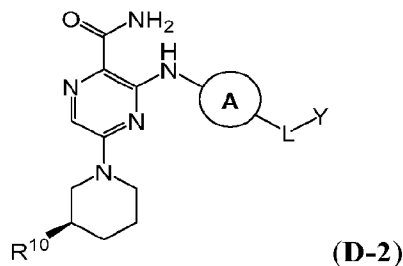


[00180] In some embodiments, R^{10} is

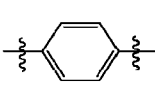
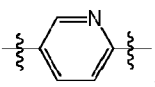


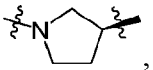
[00181] In some embodiments, R^{10} is .

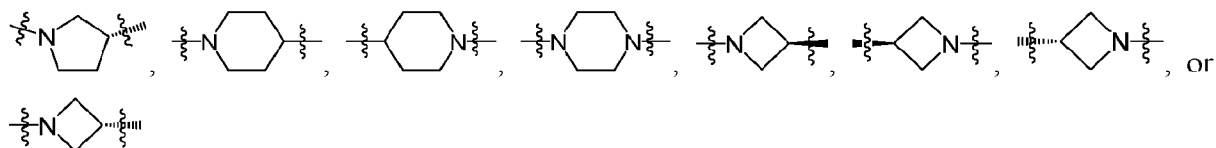
[00182] In some embodiments, the compound of Formula (D) or the compound of Formula (D-1) is a compound of Formula (D-2)



or a pharmaceutically acceptable salt thereof, wherein the terms **Ring A**, **L**, **Y**, and R^{10} are as defined in the compound of Formula (A), the compound of Formula (D), and the compound of Formula (D-1).

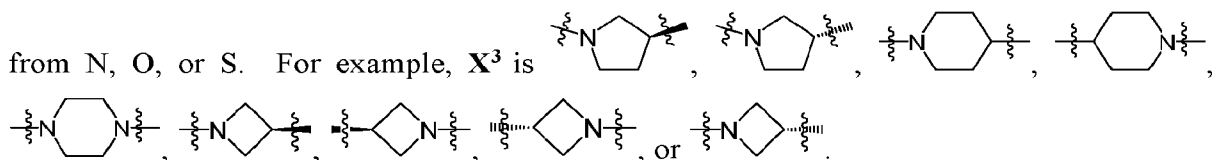
[00183] In some embodiments, **Ring A** is  or .

[00184] In some embodiments, X^1 is a 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the monocyclic heterocycloalkyl of X^1 is optionally substituted with $-CH_3$. For example, X^1 is ,

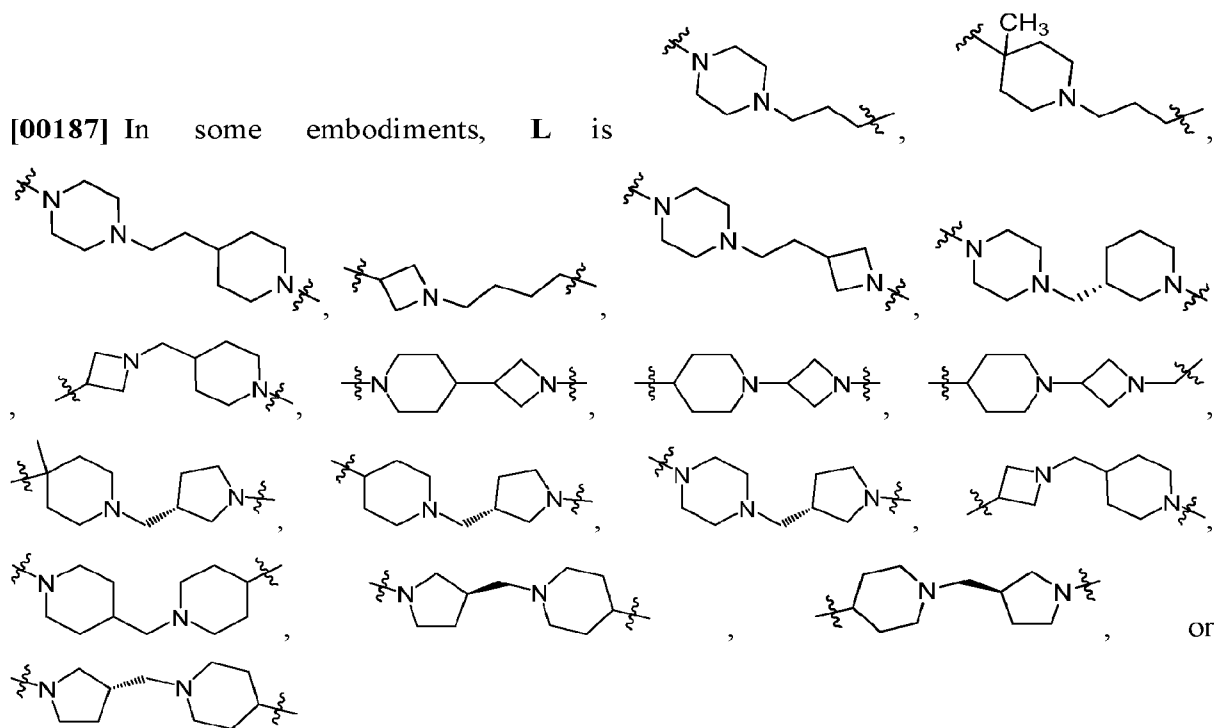


[00185] In some embodiments, X^2 is a bond, $-C_{1-5}$ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S. For example, X^2 is a bond or $-C_{1-4}$ alkyl-.

[00186] In some embodiments, X^3 is a bond, a 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected

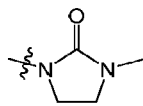


[00187] In some embodiments, **L** is

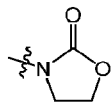


or

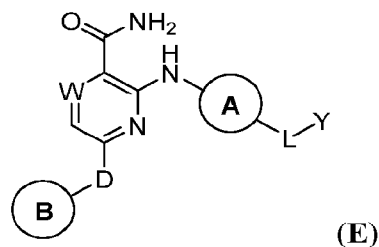
[00188] In some embodiments, **R¹⁰** is



[00189] In some embodiments, **R¹⁰** is



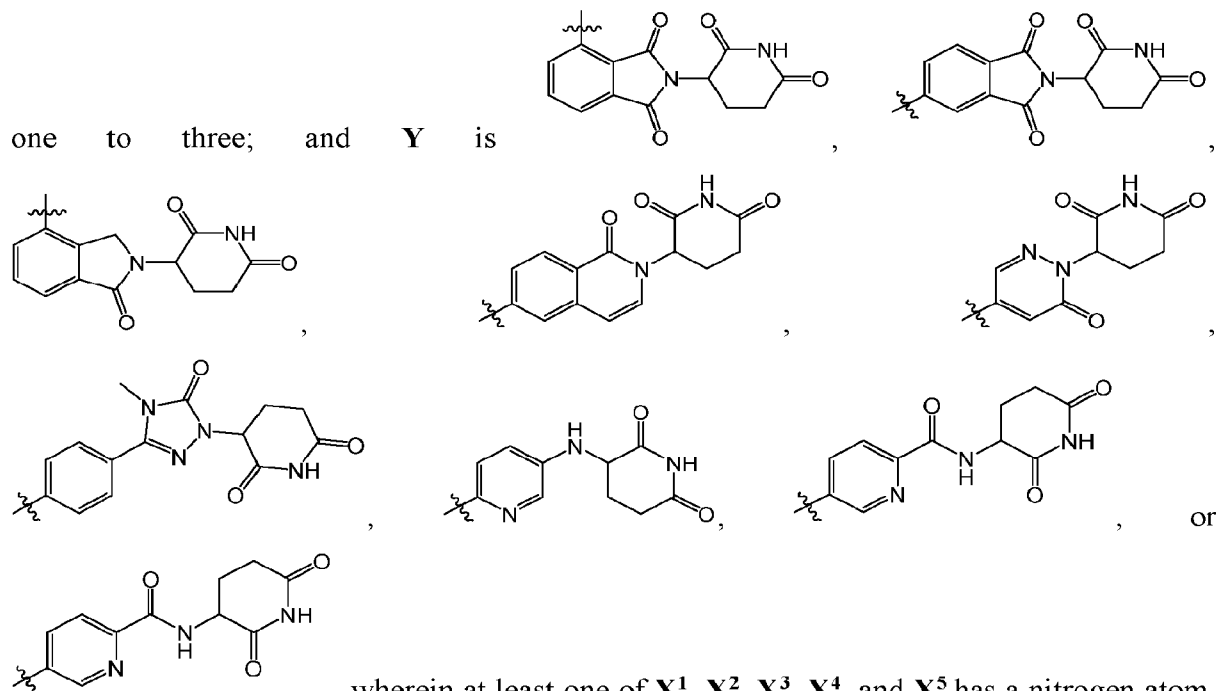
[00190] This disclosure also provides a compound of Formula (**E**)



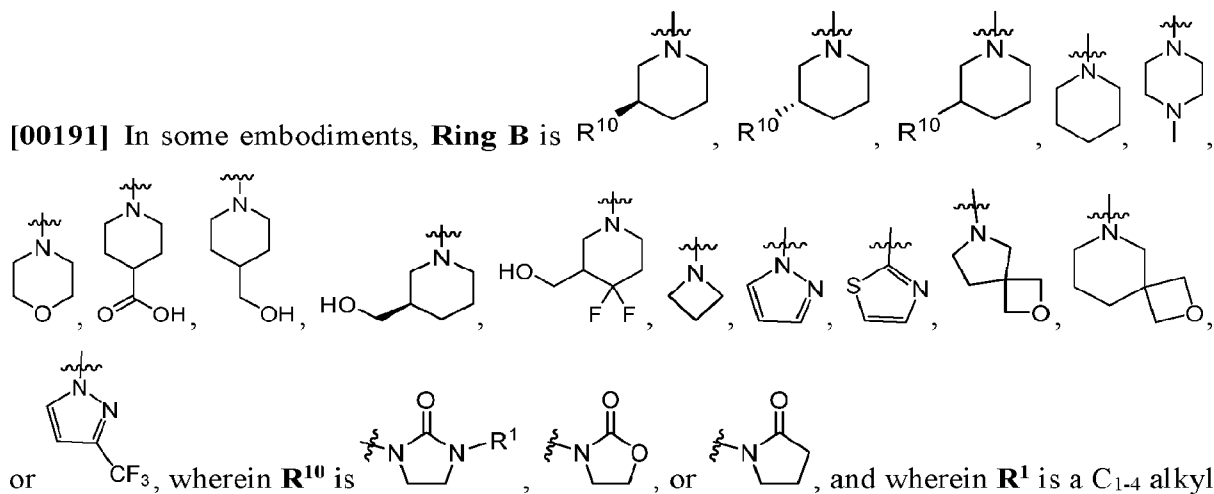
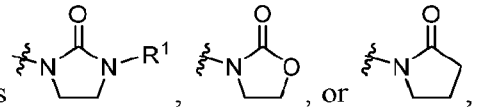
or a pharmaceutically acceptable salt thereof, wherein **D** is a bond or $-\text{NH}-$; **W** is N or CH; **Ring A** is phenyl, a 9-10 membered bicyclic aryl, a 5-6 membered partially or fully unsaturated monocyclic heterocycle, or a 9-10 membered bicyclic heteroaryl, wherein the monocyclic heterocycle and bicyclic heteroaryl of **Ring A** each possess one to three heteroatoms independently selected from N, O, or S; **Ring B** is an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic heterocycle, or an optionally substituted 8-10 membered (e.g., 8-9 membered or 9-10 membered) spiro bicyclic heterocycle,

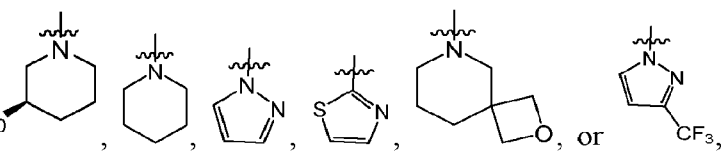
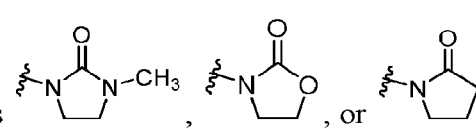
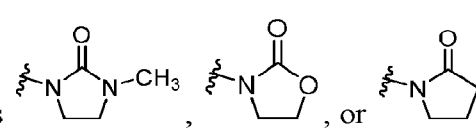
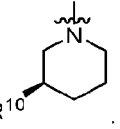
wherein **Ring B** has one to three heteroatoms independently selected from N, O, or S; **L** is —**X**¹—**X**²—**X**³—**X**⁴—**X**⁵—; **X**¹ is a bond, —C(O)—N(**R**)—, —N(**R**)—C(O)—, —(O—CH₂—CH₂)_m—, —O(C₆H₄)—, —(O—CH₂—CH₂—CH₂)_m—, —C₁₋₅ alkyl—, 7-12 membered spiro bicyclic heterocycloalkyl having one to three heteroatoms independently selected from N, O, or S, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein each of the monocyclic and bicyclic heterocycloalkyl of **X**¹ is optionally substituted with —CH₃; **X**² is a bond, —(O—CH₂—CH₂)_n—, —(CH₂—CH₂—O)_n—, —N(**R**)—C(O)—, —N(**R**)—, —C(O)—, —C₁₋₅ alkyl—, 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S; **X**³ is a bond, —C₁₋₄ alkyl—, —C≡C—, 4-6 membered cycloalkyl, —N(**R**)—, —(O—CH₂—CH₂)_p—, —(CH₂—CH₂—O)_p—, 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with —CH₃; **X**⁴ is a bond, —CH₂—CH₂—N(**R**)—, —N(**R**)—, —C₁₋₄ alkyl—, —(O—CH₂—CH₂—CH₂)_m—, a 5-6 membered saturated, partially unsaturated, or fully unsaturated carbocycle, or a 5-6 membered saturated, partially unsaturated, or fully unsaturated heterocycle having one to three heteroatoms independently selected from N, O, or S; **X**⁵ is a bond, —N(**R**)—, or —C(O)—N(**R**)—; each **R** is independently —H or —C₁₋₃ alkyl; each of **m**, **n**, and **p** is independently an integer from

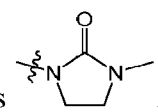
one to three; and **Y** is

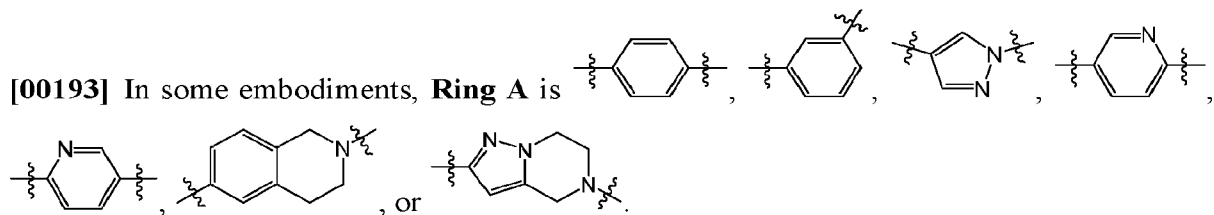



, wherein at least one of **X**¹, **X**², **X**³, **X**⁴, and **X**⁵ has a nitrogen atom, and **Y** is directly bonded to **L** at a nitrogen atom of **X**¹, **X**², **X**³, **X**⁴, or **X**⁵.

[00191] In some embodiments, **Ring B** is , wherein **R**¹⁰ is , and wherein **R**¹ is a C₁₋₄ alkyl

group. For example, **Ring B** is , or , wherein **R**¹⁰ is . In other examples, **Ring B** is .

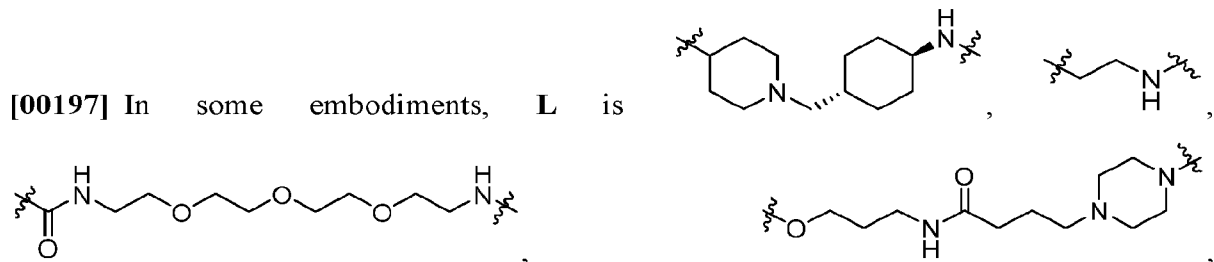
[00192] In some embodiments, **R**¹⁰ is .

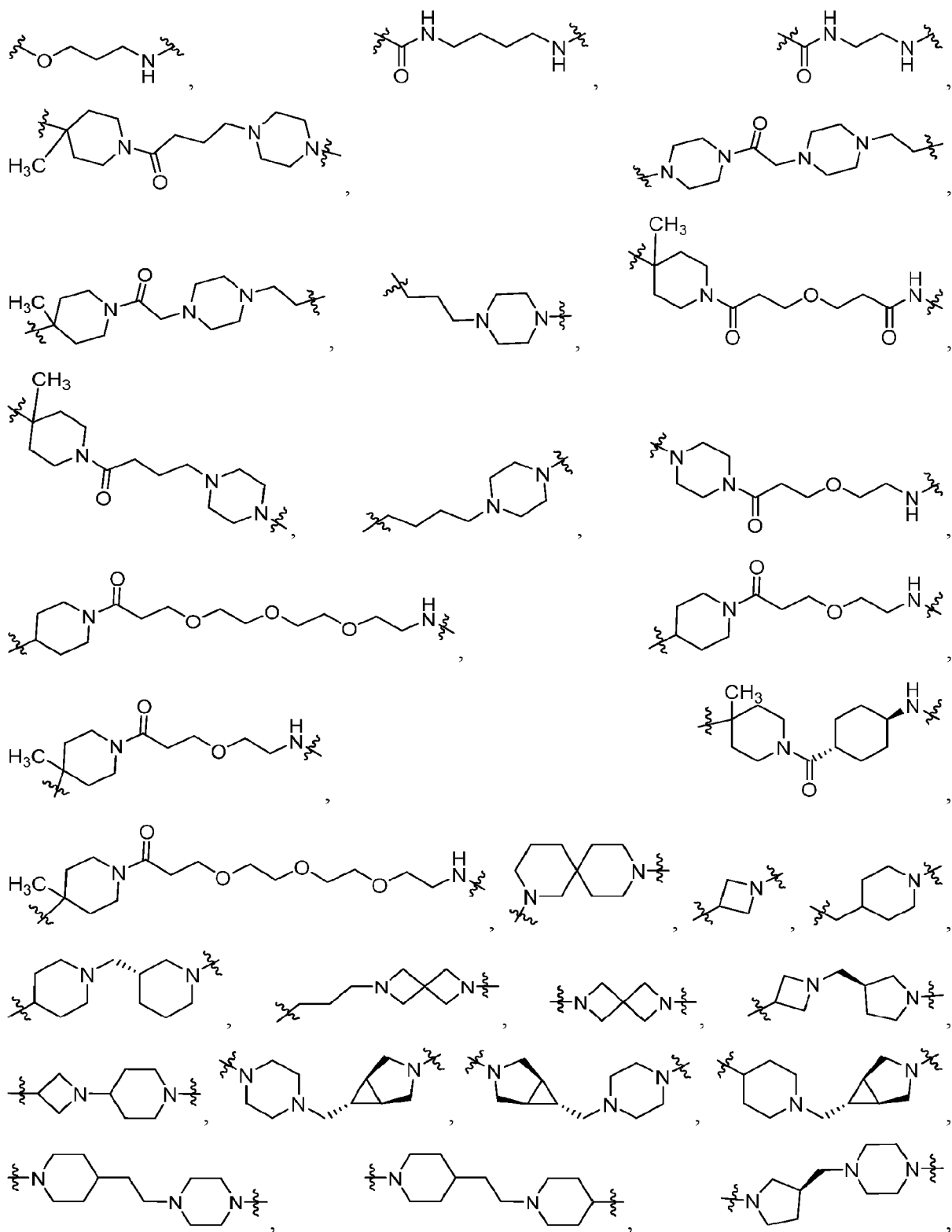
[00193] In some embodiments, **Ring A** is .

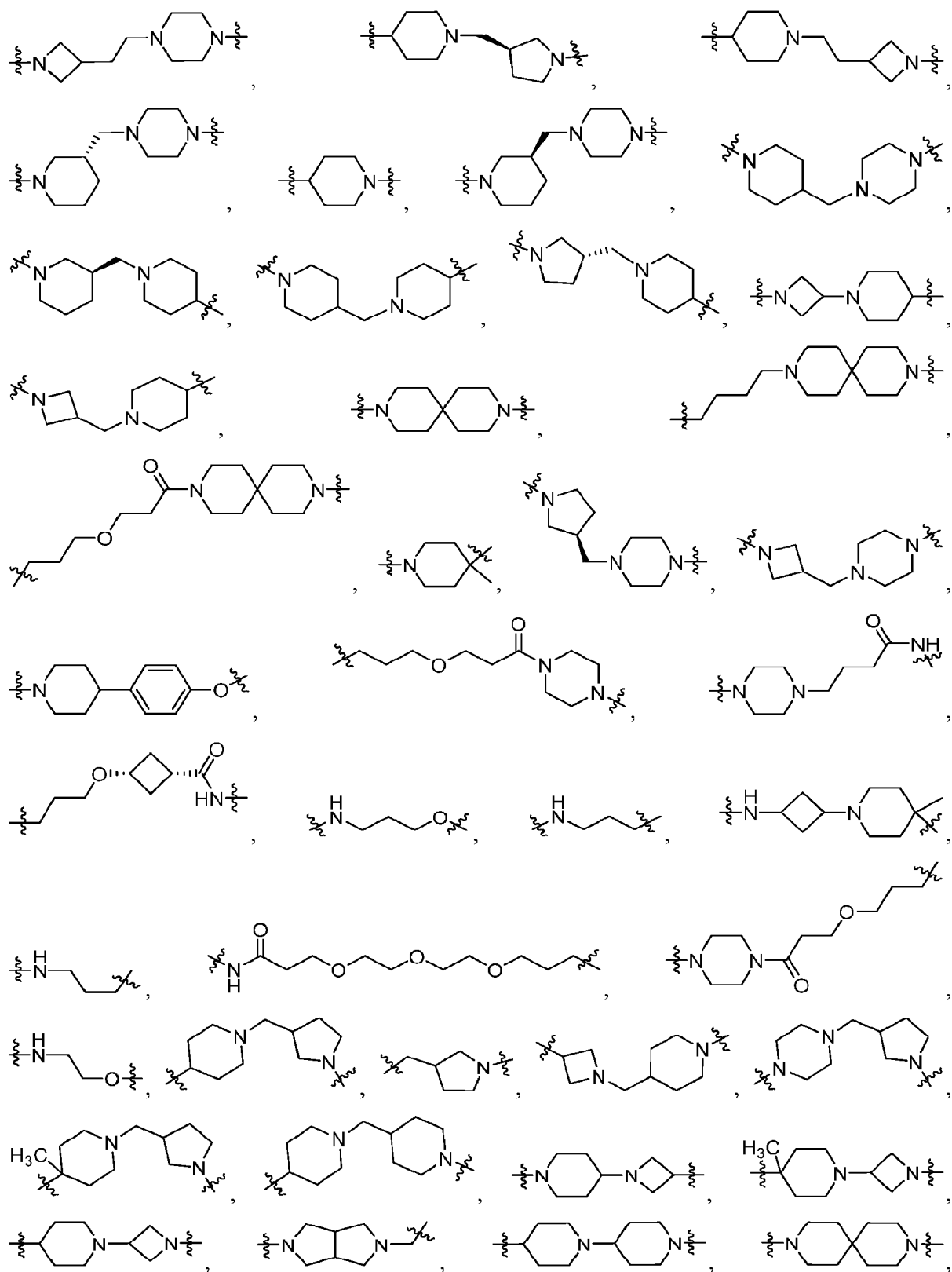
[00194] In some embodiments, **X**⁵ is -N(**R**)-.

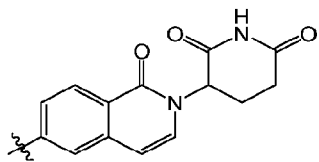
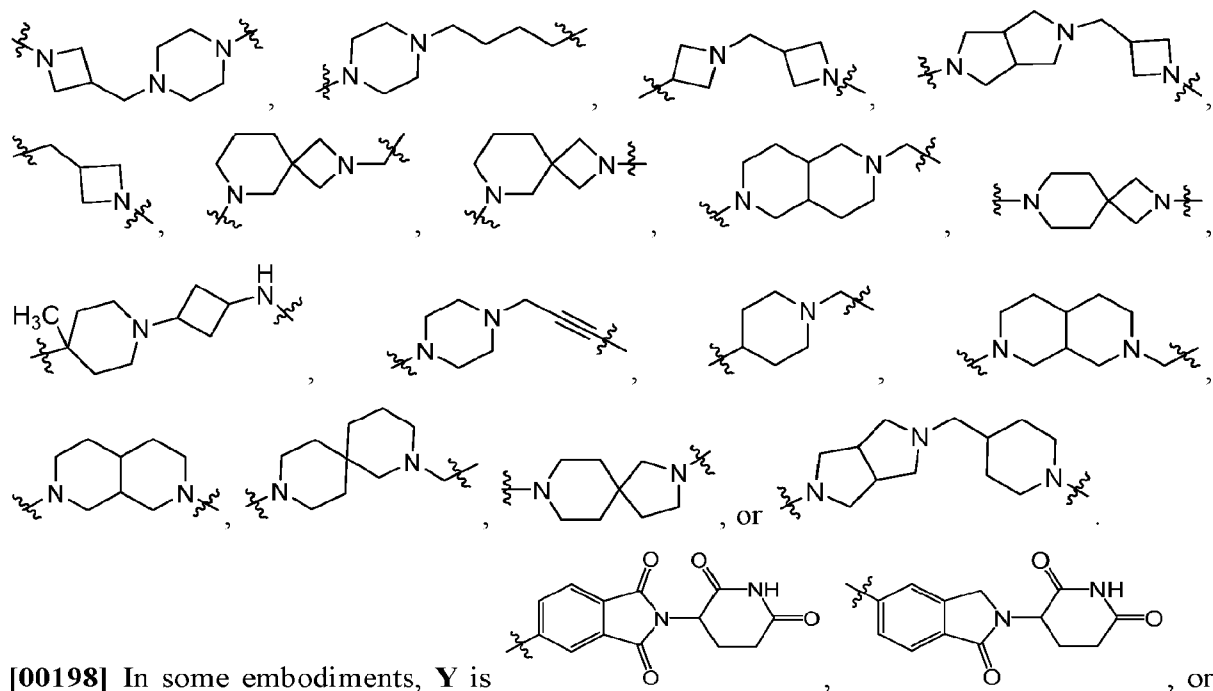
[00195] In some embodiments, **X**⁵ is -C(O)-N(**R**)-.

[00196] In some embodiments, **X**⁵ is a bond.

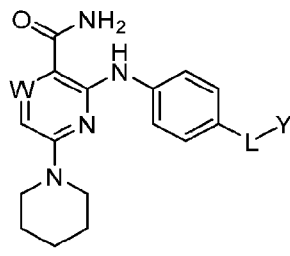
[00197] In some embodiments, **L** is .







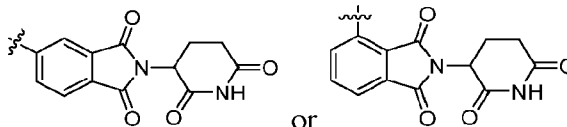
[00199] This disclosure also provides a compound of Formula (F)



(F)

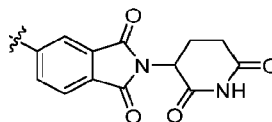
or a pharmaceutically acceptable salt thereof, wherein **W** is CH or N; **L** is $-\mathbf{X}^1-\mathbf{X}^2-\mathbf{X}^3-$; $\mathbf{X}^1$ is $-\text{C}(\text{O})-\text{N}(\mathbf{R})-$, $-\text{N}(\mathbf{R})-\text{C}(\text{O})-$, $-(\text{O}-\text{CH}_2-\text{CH}_2)_m-$, $-\text{O}(\text{C}_6\text{H}_4)-$, $-(\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2)_m-$, $-\text{C}_{1-5}$ alkyl-, 7-12 membered spiro bicyclic heterocycloalkyl having one to three heteroatoms independently selected from N, O, or S, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein each of the monocyclic and bicyclic heterocycloalkyl of $\mathbf{X}^1$ is optionally substituted with $-\text{CH}_3$; $\mathbf{X}^2$ is a bond, $-\text{C}_{1-5}$ alkyl-, $-(\text{O}-\text{CH}_2-\text{CH}_2)_n-$, $-(\text{CH}_2-\text{CH}_2-\text{O})_n-$, $-\text{N}(\mathbf{R})-\text{C}(\text{O})-$, $-\text{N}(\mathbf{R})-$, $-\text{C}(\text{O})-$, $-\text{C}_{1-5}$ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S; $\mathbf{X}^3$ is

a bond, $-C_{1-4}$ alkyl-, $-C\equiv C-$, 4-6 membered cycloalkyl, $-N(\mathbf{R})-$, $-(O-CH_2-CH_2)_p-$, $-(CH_2-CH_2-O)_p-$, 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-CH_3$; each $\mathbf{R}$ is independently $-H$ or $-C_{1-3}$ alkyl; each of $\mathbf{m}$, $\mathbf{n}$, and $\mathbf{p}$ is independently an



integer from one to three; and **Y** is

[00200] In some embodiments, **W** is N.

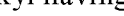


[00201] In some embodiments, **Y** is

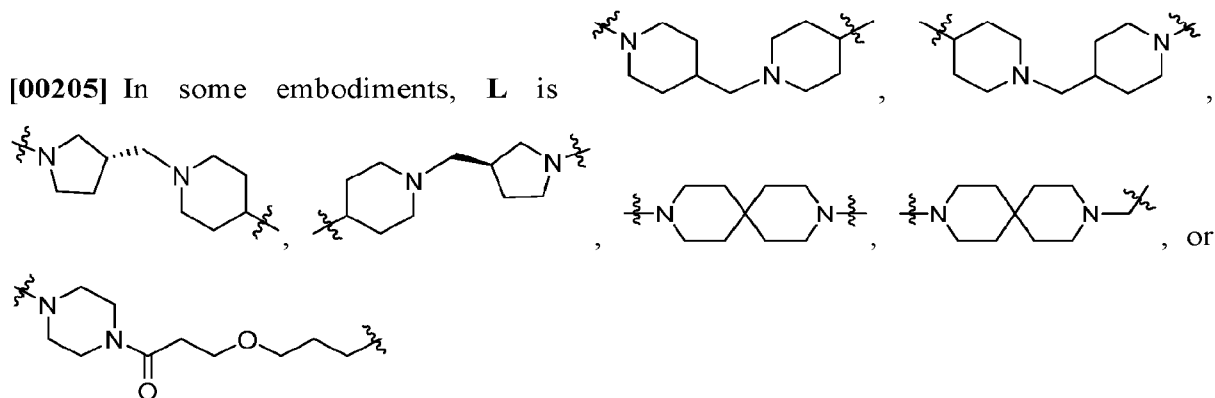
[00202] In some embodiments, **X¹** is a 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein each of the monocyclic

heterocycloalkyl of **X**¹ is optionally substituted with -CH₃. For example, **X**¹ is , , , , , , or . In some instances, **X**¹ is  or .

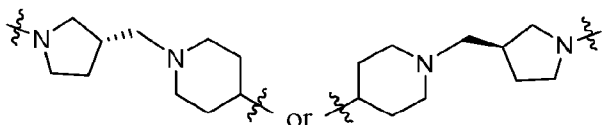
[00203] In some embodiments, X^2 is a bond or $-C_{1-5}$ alkyl—.

[00204] In some embodiments, **X³** is a 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S. For example, **X³** is , , , , , , , or . In some instances, **X³** is  or .

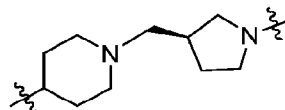
[00205] In some embodiments, L is



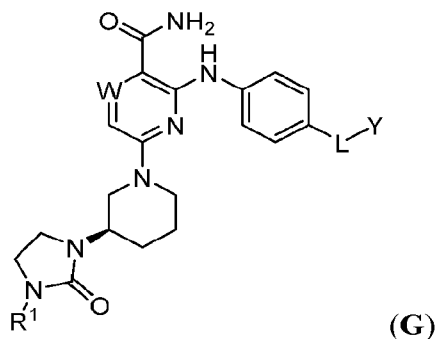
[00206] In some embodiments, **L** is



[00207] In some embodiments, **W** is N; and **L** is



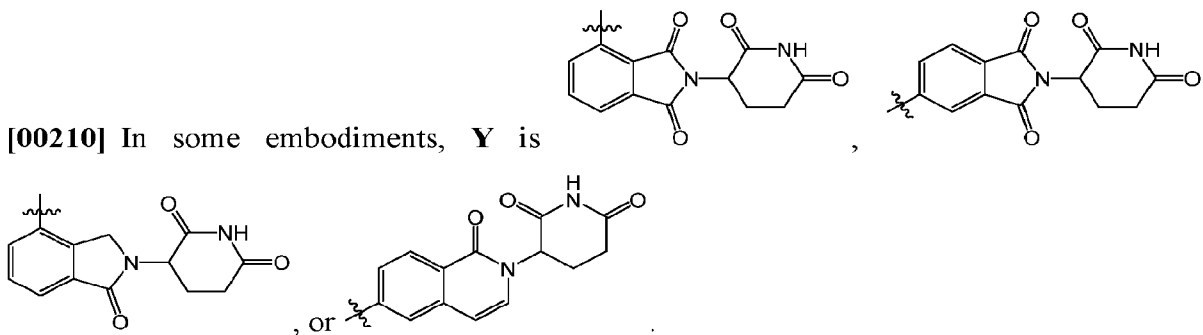
[00208] This disclosure also provides a compound of Formula (**G**)



or a pharmaceutically acceptable salt thereof, wherein **R**¹, **L**, and **Y** are as defined for compounds of Formula (**A**).

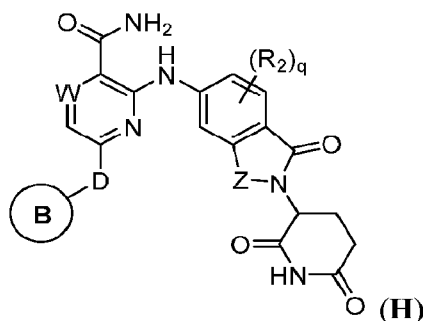
[00209] In some embodiments, **R**¹ is methyl.

[00210] In some embodiments, **Y** is



[00211] In some embodiments, **W** is N.

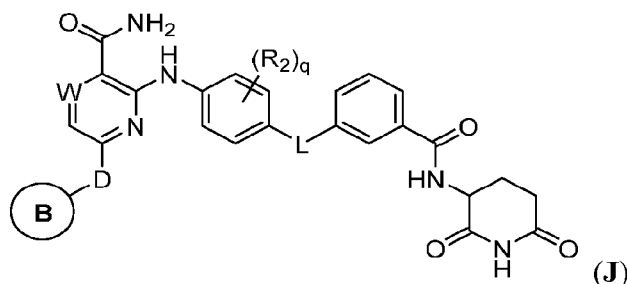
[00212] This disclosure also provides a compound of Formula (**H**)



or a pharmaceutically acceptable salt thereof, wherein **Ring B**, **R²**, **Z**, **W**, **D**, and **q** are as defined in the compound of Formula (A).

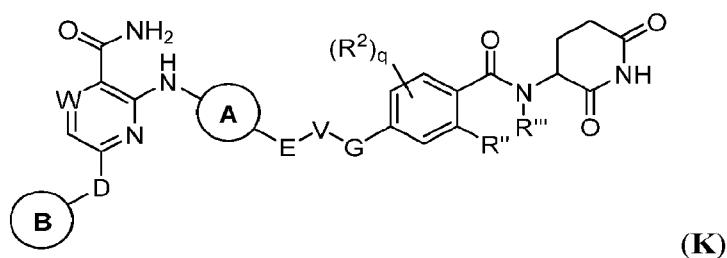
[00213] In some embodiments, **q** is zero.

[00214] This disclosure also provides a compound of Formula (J)

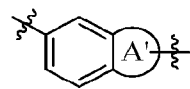


or a pharmaceutically acceptable salt thereof, wherein **Ring B**, **D**, **W**, **R²**, **q**, and **L** are as defined in the compound of Formula (A).

[00215] This disclosure also provides a compound of Formula (K)



or a pharmaceutically acceptable salt thereof, wherein **Ring A** is

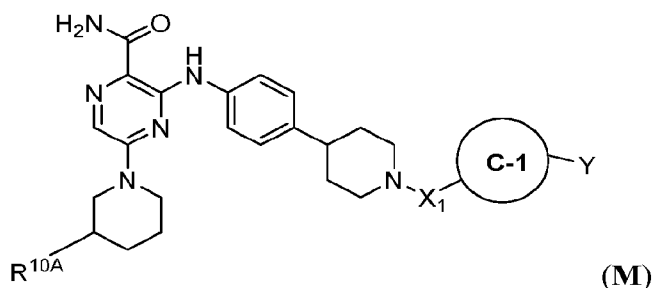


, wherein **Ring A** is optionally and independently substituted with up to three substituents selected from halo, $-\text{CN}$, $-\text{carboxyl}$, $-\text{NH}_2$, and optionally substituted $-\text{C}_{1-6}$ alkyl (e.g., optionally substituted $-\text{C}_{1-3}$ alkyl); **V** is a bond or $-\text{CH}_2-$; and **E** and **G** are each independently a 5-6 membered heterocycloalkyl, wherein each heterocycloalkyl contains at least one nitrogen atom. **Ring B**, **W**, **R²**, **q**, **R''**, **R'''**, and **Ring A'** are as defined in the

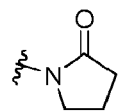
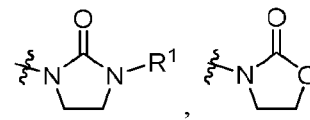
compound of Formula (A). In some embodiments, **Ring A'** together with the phenyl ring to which **Ring A'** is fused form a 9-10 membered bicyclic aryl or a 9-10 membered bicyclic heteroaryl wherein the bicyclic heteroaryl has one to three heteroatoms independently selected from N, O, or S.

[00216] In some embodiments, **D** is a bond and **W** is nitrogen.

[00217] This disclosure also provides a compound of Formula (M)

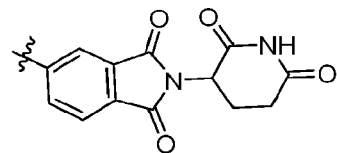
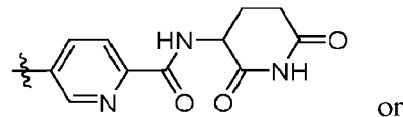


or a pharmaceutically acceptable salt thereof, wherein **R^{10A}** is -H,

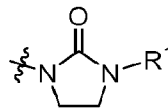


, wherein **R¹** is C₁₋₄ alkyl; **X¹** is -C₁₋₅ alkyl-; **Ring C-1** is a 5-6 membered

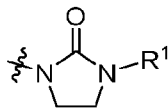
heterocycloalkyl having one nitrogen atom; and **Y** is



[00218] In some embodiments, **R^{10A}** is -H or



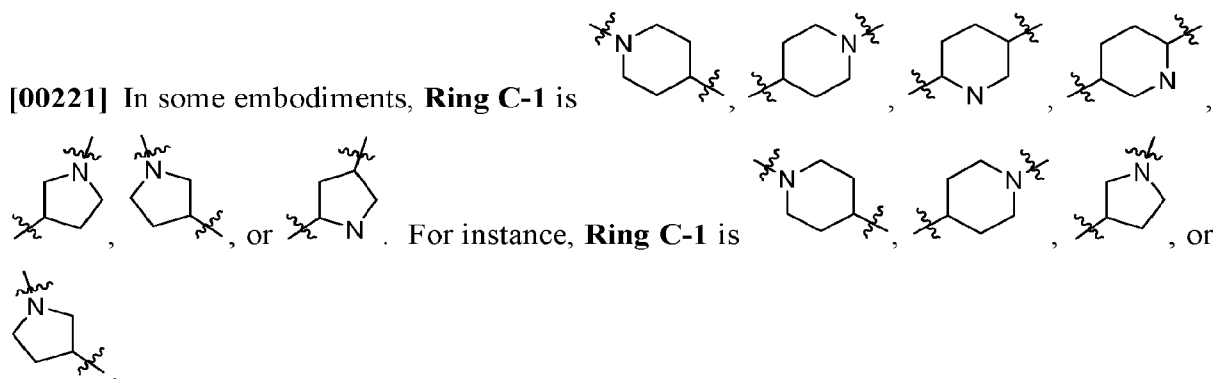
[00219] In some embodiments, **R^{10A}** is



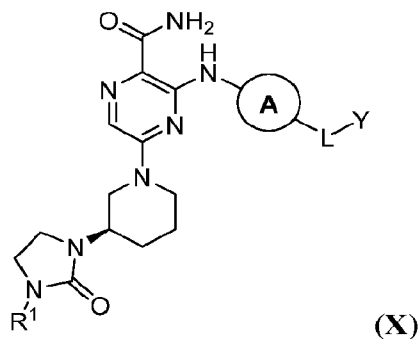
, and **R¹** is methyl, ethyl, propyl, *iso*-propyl, butyl, *sec*-butyl, or *iso*-butyl. For example, **R¹** is methyl.

[00220] In some embodiments, **X¹** is methylene (-CH₂-), ethylene (-CH₂CH₂-), or propylene (-CH₂CH₂CH₂-). For instance, **X¹** is methylene (-CH₂-).

[00221] In some embodiments, **Ring C-1** is

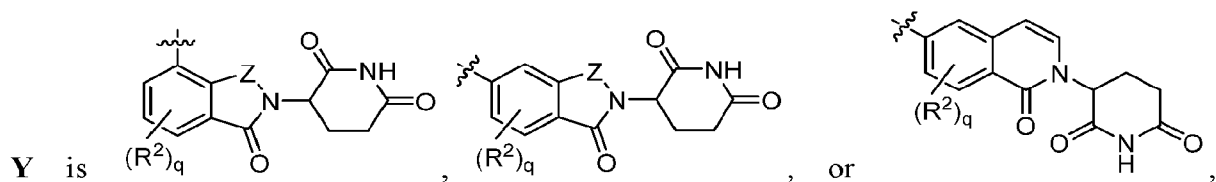


[00222] This disclosure provides a compound of Formula (X)



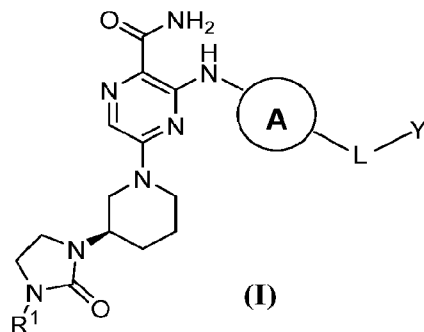
or a pharmaceutically acceptable salt thereof, wherein **R**¹ is C₁₋₃ alkyl; **Ring A** is phenyl, 5-6 membered partially or fully unsaturated monocyclic heterocycle, 9-10 membered bicyclic aryl, or 9-10 membered bicyclic heteroaryl, wherein the heterocycle and the bicyclic heteroaryl of **Ring A** each independently have one to three heteroatoms independently selected from N, O, or S; **L** is -**X**¹-**X**²-**X**³-**X**⁴-**X**⁵-; **X**¹ is -C(O)-N(**R**)-, -N(**R**)-C(O)-, -(O-CH₂-CH₂)_m-, -O(C₆H₄)-, -(O-CH₂-CH₂-CH₂)_m-, -C₁₋₅ alkyl-, 7-12 membered spiro bicyclic heterocycloalkyl having one to three heteroatoms independently selected from N, O, or S, wherein the bicyclic heterocycloalkyl of **X**¹ is optionally substituted with -CH₃, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the monocyclic heterocycloalkyl of **X**¹ is optionally substituted with -CH₃; **X**² is a bond, -(O-CH₂-CH₂)_n-, -(CH₂-CH₂-O)_n-, -N(**R**)-C(O)-, -N(**R**)-, -C(O)-, -C₁₋₅ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S; **X**³ is a bond, -C₁₋₄ alkyl-, -C≡C-, 4-6 membered cycloalkyl, -N(**R**)-, -(O-CH₂-CH₂)_p-, -(CH₂-CH₂-O)_p-, 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with -CH₃; **X**⁴ is a bond, -CH₂-CH₂-N(**R**)-, -N(**R**)-, -C₁₋₄ alkyl-,

–(O-CH₂-CH₂-CH₂)_m–, or 5-6 membered saturated, partially unsaturated, or fully unsaturated carbocycle having zero to three heteroatoms independently selected from N, O, or S; **X**⁵ is a bond, –C₁₋₄ alkyl–, –N(**R**)–, or –C(O)-N(**R**)–; each **R** is independently –H or –C₁₋₃ alkyl; each of **m**, **n**, and **p** is independently an integer from one to three;



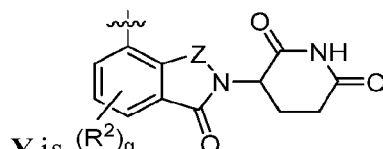
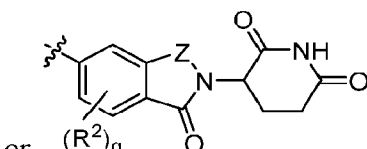
wherein each **R**² is independently halo or C₁₋₄ alkyl; each **Z** is –C(**R**^A)₂– or –C(O)–; each **R**^A is independently –H or C₁₋₄ alkyl; and **q** is zero, one, or two.

[00223] In some instances, the compound of Formula (**X**) is a compound of Formula (**I**)



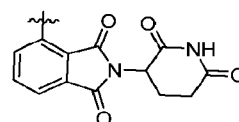
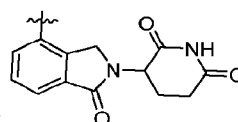
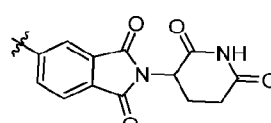
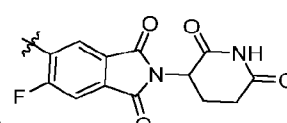
or a pharmaceutically acceptable salt thereof, wherein **R**¹ is C₁₋₃ alkyl; **Ring A** is phenyl, 9-10 membered bicyclic aryl, or 9-10 membered bicyclic heteroaryl having one to three heteroatoms independently selected from N, O, or S; **L** is –**X**¹–**X**²–**X**³–**X**⁴–**X**⁵–; **X**¹ is –C(O)-N(**R**)–, –N(**R**)-C(O)–, –(O-CH₂-CH₂)_m–, –O(C₆H₄)–, –(O-CH₂-CH₂-CH₂)_m–, –C₁₋₅ alkyl–, 7-12 membered spiro bicyclic heterocycloalkyl having one to three heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with –CH₃, or 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with –CH₃; **X**² is a bond, –(O-CH₂-CH₂)_n–, –(CH₂-CH₂-O)_n–, –N(**R**)-C(O)–, –N(**R**)–, –C(O)–, –C₁₋₅ alkyl–, 4-6 membered cycloalkyl, or 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S; **X**³ is a bond, –C₁₋₄ alkyl–, 4-6 membered cycloalkyl, –N(**R**)–, –(O-CH₂-CH₂)_p–, –(CH₂-CH₂-O)_p–, 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with –CH₃; **X**⁴ is a bond, –CH₂-CH₂-N(**R**)–, –N(**R**)–, –C₁₋₄ alkyl–, –(O-CH₂-CH₂-CH₂)_m–, or 5-6 membered saturated, partially unsaturated, or fully unsaturated

heterocycle having one to three heteroatoms independently selected from N, O, or S; $\mathbf{X}^5$ is a bond, $-\text{C}_{1-4}$ alkyl-, $-\text{N}(\mathbf{R})-$, or $-\text{C}(\text{O})-\text{N}(\mathbf{R})-$; each $\mathbf{R}$ is independently $-\text{H}$ or $-\text{C}_{1-3}$ alkyl; each of $\mathbf{m}$, $\mathbf{n}$, and $\mathbf{p}$ is independently an integer from one to three (e.g., one, two, or three);

$\mathbf{Y}$ is  or , wherein each $\mathbf{R}^2$ is independently halo or $-\text{C}_{1-4}$ alkyl; each $\mathbf{Z}$ is $-\text{C}(\mathbf{R}^A)_2-$ or $-\text{C}(\text{O})-$; each $\mathbf{R}^A$ is independently $-\text{H}$ or $-\text{C}_{1-4}$ alkyl; and $\mathbf{q}$ is zero, one, or two.

[00224] In some embodiments, $\mathbf{q}$ is zero. In other embodiments, $\mathbf{q}$ is one and $\mathbf{R}^2$ is $-\text{F}$.

[00225] In some embodiments, $\mathbf{Z}$ is $-\text{CH}_2-$ or $-\text{C}(\text{O})-$.

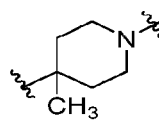
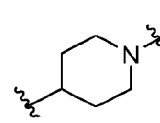
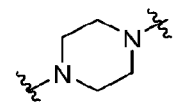
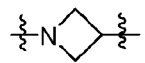
[00226] In some embodiments, $\mathbf{Y}$ is  or  or  or .

[00227] In other embodiments, $\mathbf{Y}$ is

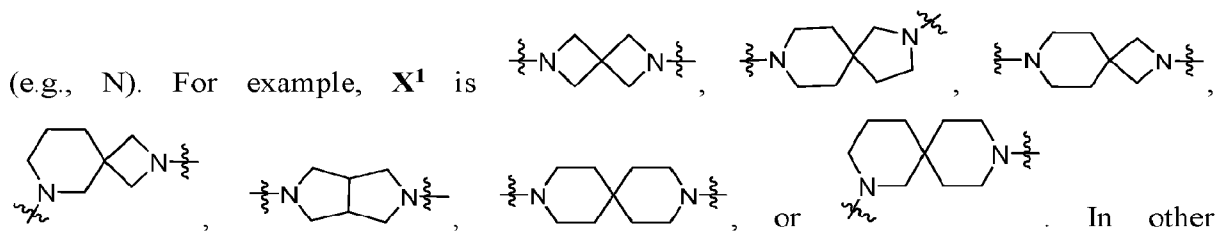
[00228] In some embodiments, $\mathbf{R}^1$ is $-\text{C}_{1-3}$ alkyl. For example, $\mathbf{R}^1$ is methyl, ethyl, propyl, or *iso*-propyl. In other embodiments, $\mathbf{R}^1$ is methyl.

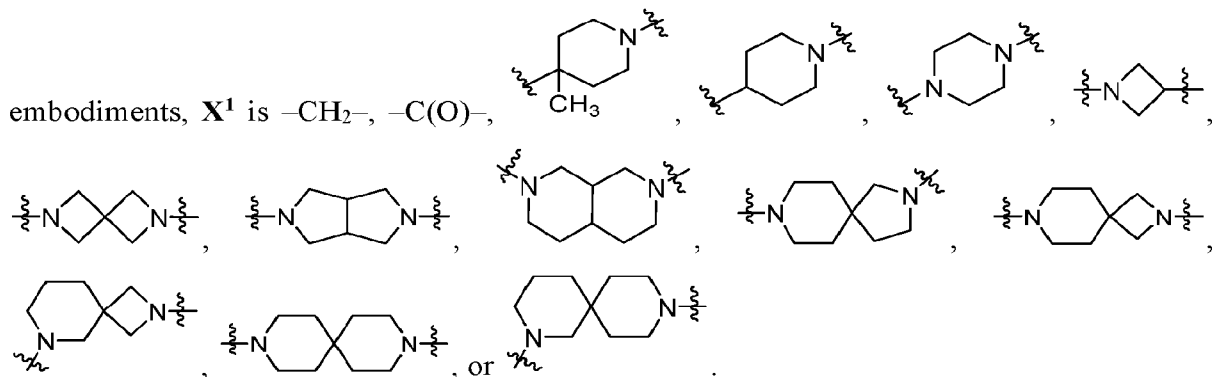
[00229] In some embodiments, each $\mathbf{R}$ is independently $-\text{H}$ or $-\text{CH}_3$. For instance, each $\mathbf{R}$ is $-\text{H}$.

[00230] In some embodiments, $\mathbf{X}^1$ is $-\text{C}(\text{O})-\text{N}(\mathbf{R})-$, $-\text{N}(\mathbf{R})-\text{C}(\text{O})-$, $-(\text{O}-\text{CH}_2-\text{CH}_2)_m-$, $-\text{O}(\text{C}_6\text{H}_4)-$, $-(\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2)_m-$, $-\text{C}_{1-5}$ alkyl-, 7-12 membered spiro bicyclic heterocycloalkyl having one to three heteroatoms independently selected from N, O, or S, or 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-\text{CH}_3$. In some embodiments, $\mathbf{X}^1$ is $-\text{C}(\text{O})-\text{N}(\mathbf{R})-$. For example, $\mathbf{X}^1$ is $-\text{C}(\text{O})-\text{N}(\text{H})-$, $-\text{C}(\text{O})-\text{N}(\text{CH}_3)-$, or $-\text{C}(\text{O})-\text{N}(\text{CH}_2\text{CH}_3)-$. In other embodiments, $\mathbf{X}^1$ is a 5-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl

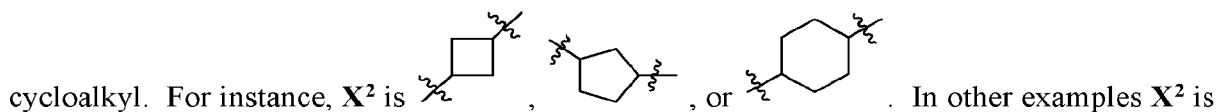
is optionally substituted with $-\text{CH}_3$. For example, $\mathbf{X}^1$ is, , , , or . In other examples, $\mathbf{X}^1$ is a 7-10 membered spiro bicyclic

heterocycloalkyl ring having one to three heteroatoms independently selected from N, O, or S

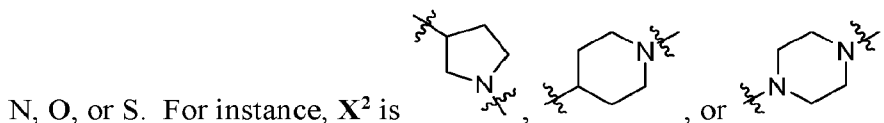
(e.g., N). For example, **X¹** is . In other embodiments, **X¹** is $-(O-CH_2-CH_2)_m-$ or $-(O-CH_2-CH_2-CH_2)_m-$, wherein **m** is one, two, three. For example, **X¹** is $-(O-CH_2-CH_2)_m-$ or $-(O-CH_2-CH_2-CH_2)_m-$, and **m** is one. In another example, **X¹** is $-(O-CH_2-CH_2)_m-$ or $-(O-CH_2-CH_2-CH_2)_m-$, and **m** is two. In some embodiments, **X¹** is $-C_{1-5}$ alkyl-. For example, **X¹** is methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), butylene ($-CH_2CH_2CH_2CH_2-$), or the like. In some

embodiments, **X¹** is $-CH_2-$, $-C(O)-$, .

[00231] In some embodiments, **X²** is a bond, $-(O-CH_2-CH_2)_n-$, $-(CH_2-CH_2-O)_n-$, $-N(R)-C(O)-$, $-N(R)-$, $-C(O)-$, $-C_{1-5}$ alkyl-, 4-6 membered cycloalkyl, or 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S. In some embodiments, **X²** is a bond. In some embodiments, **X²** is $-(O-CH_2-CH_2)_n-$, $-(CH_2-CH_2-O)_n-$, or $-C_{1-5}$ alkyl-, wherein **n** is one, two, or three. For example, **X¹** is $-C(O)-N(R)-$, and **X²** is $-(O-CH_2-CH_2)_n-$, $-(CH_2-CH_2-O)_n-$, or $-C_{1-5}$ alkyl-. In some examples, **X²** is $-(O-CH_2-CH_2)_n-$ or $-(CH_2-CH_2-O)_n-$, where **n** is one or two. In other examples, **X²** is $-C_{1-5}$ alkyl-. For instance, **X²** is methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), butylene ($-CH_2CH_2CH_2CH_2-$), or the like. In other examples, **X²** is a bond, $-CH_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$. In some examples, **X²** is 4-6 membered

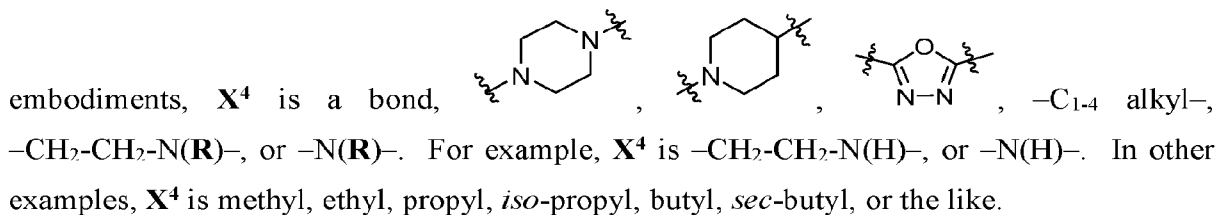
cycloalkyl. For instance, **X²** is . In other examples **X²** is

4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from

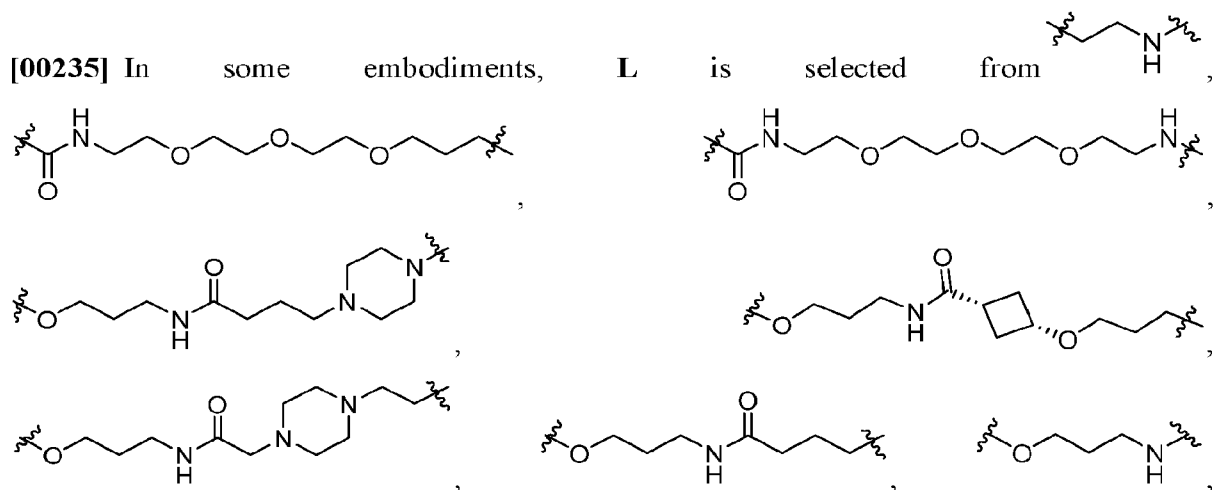


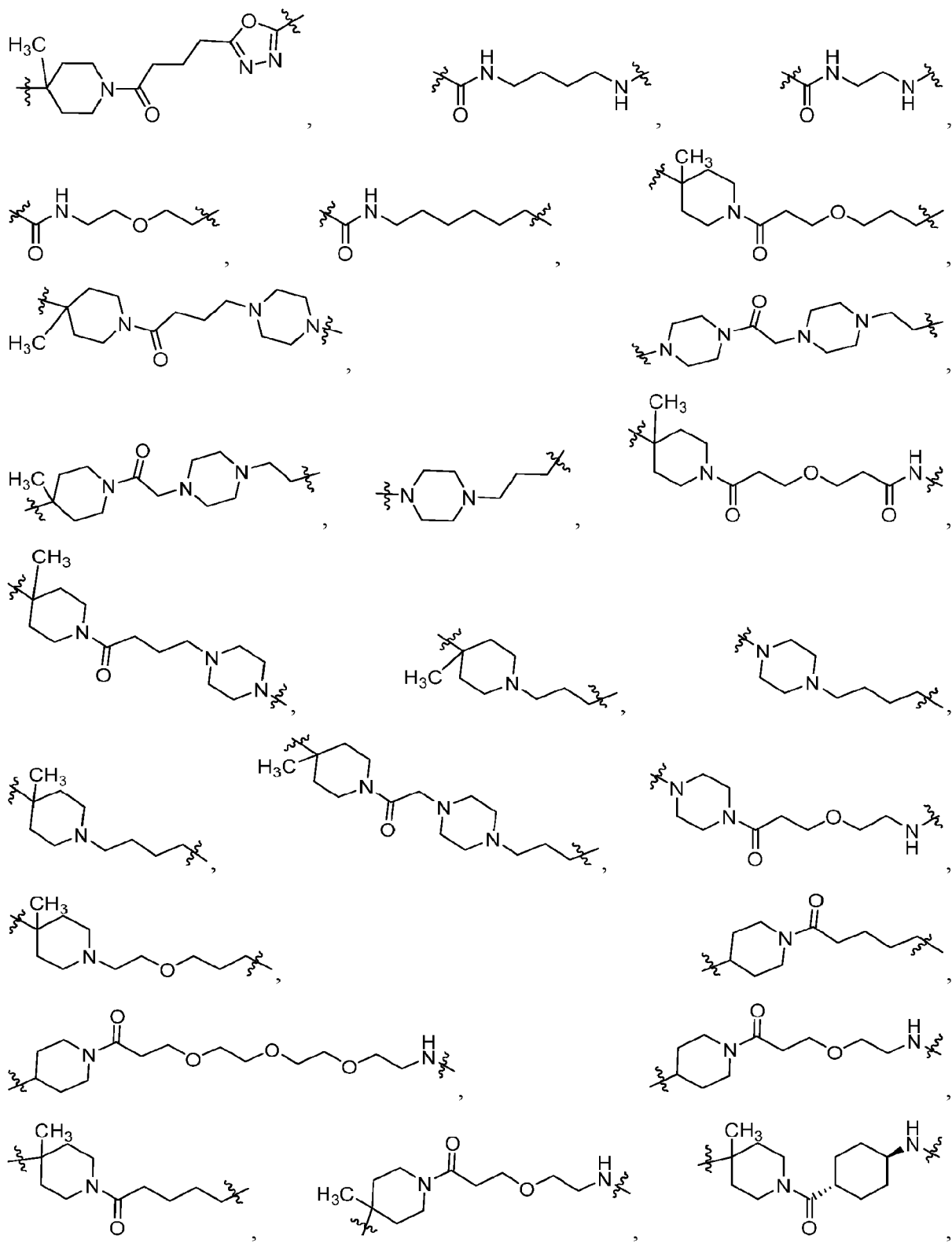
[00232] In some embodiments, X^3 is a bond, $-C_{1-4}$ alkyl-, 4-6 membered cycloalkyl-, $-N(R)-$, $-(O-CH_2-CH_2)_p-$, $-(CH_2-CH_2-O)_p-$, 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-CH_3$. In some embodiments, X^3 is a bond. In some embodiments, X^3 is methyl, ethyl, propyl, *iso*-propyl, butyl, or the like. In some embodiments, X^3 is cyclopentyl or cyclohexyl. In some embodiments, X^3 $-N(H)-$. And, in other embodiments, X^3 is $-(O-CH_2-CH_2)_p-$ or $-(CH_2-CH_2-O)_p-$, wherein p is one or two.

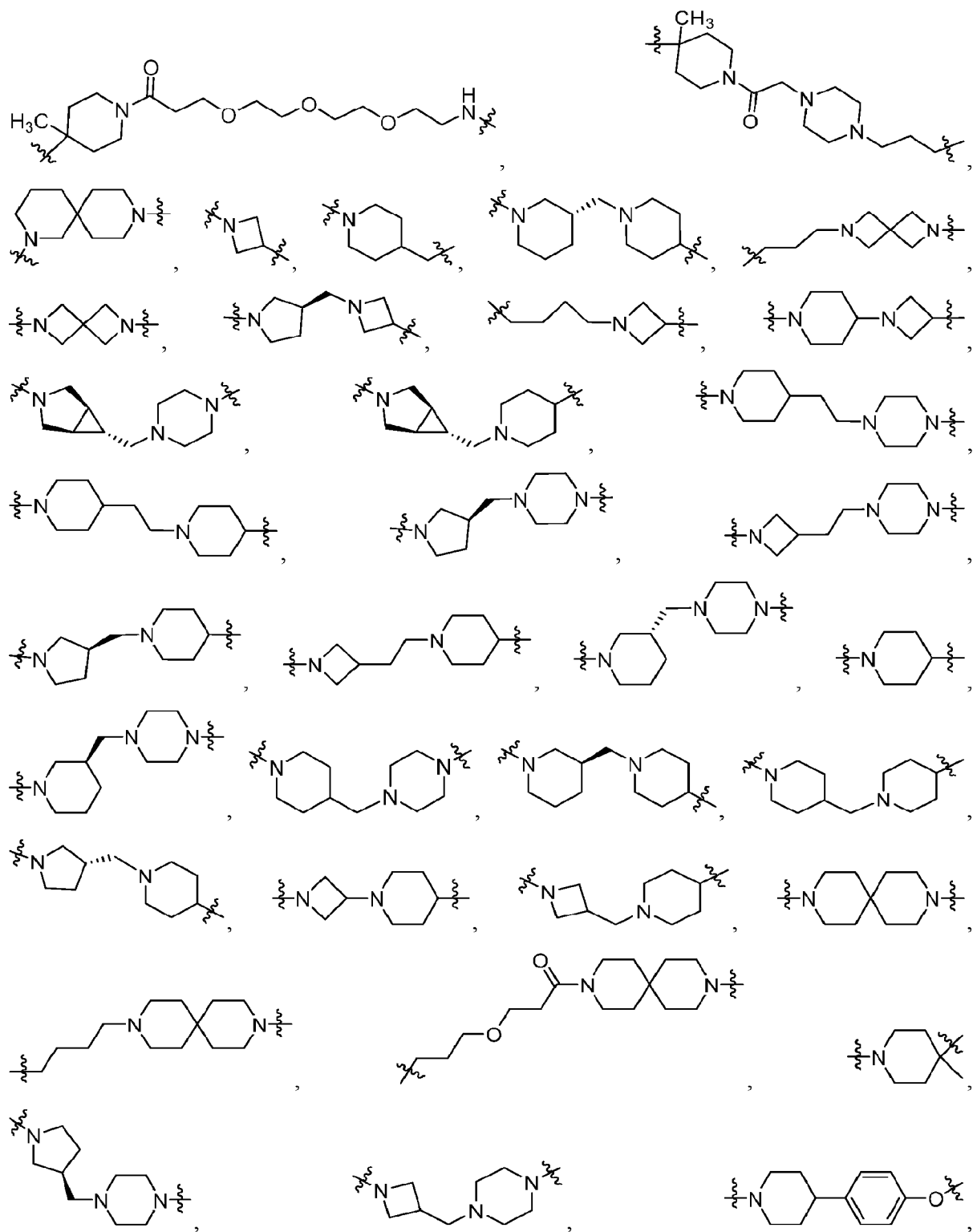
[00233] In some embodiments, X^4 is a bond, $-CH_2-CH_2-N(R)-$, $-N(R)-$, $-C_{1-4}$ alkyl-, $-(O-CH_2-CH_2-CH_2)_m-$, or 5-6 membered saturated, partially unsaturated, or fully unsaturated heterocycle having one to three heteroatoms independently selected from N, O, or S. In some

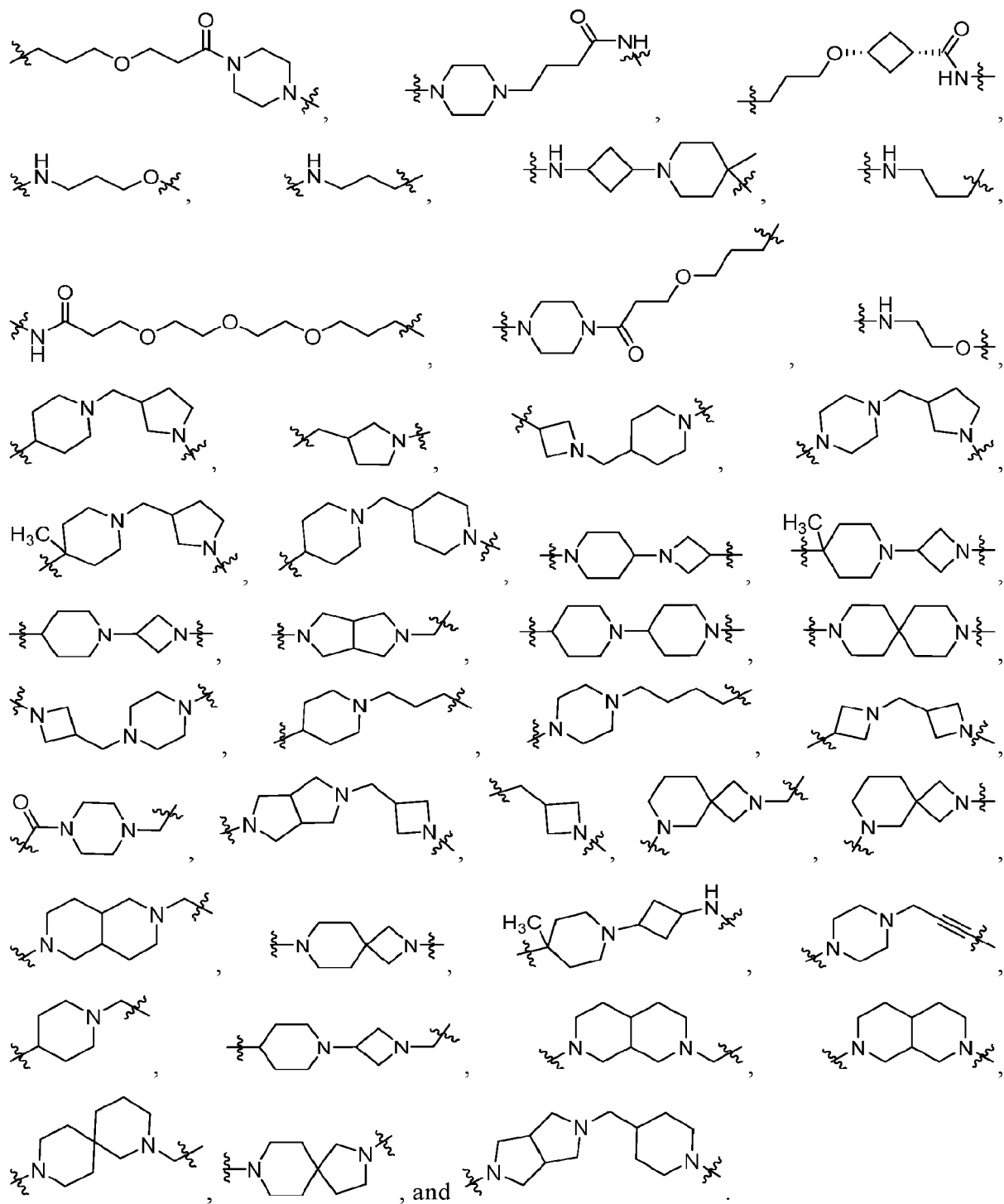


[00234] In some embodiments, X^5 is a bond, $-C_{1-4}$ alkyl-, $-N(R)-$, or $-C(O)-N(R)-$. In some embodiments, X^5 is a bond. In some embodiments, X^5 is methyl, ethyl, propyl, *iso*-propyl, butyl, or the like. In some embodiments, X^5 is $-N(H)-$ or $-C(O)-N(H)-$.

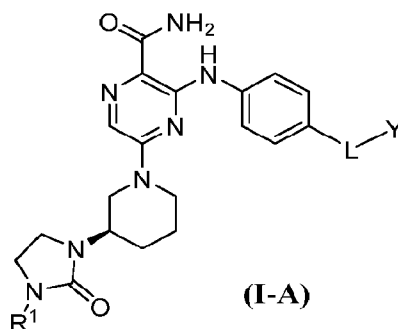








[00236] This disclosure also provides a compound of Formula (I-A):

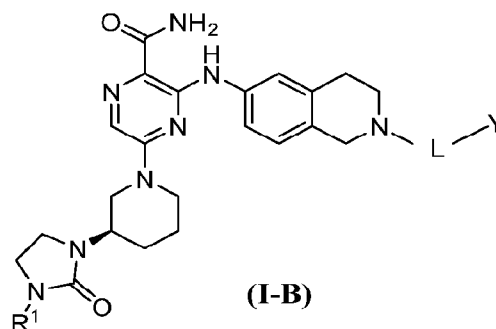


or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R}^1$ is C_{1-3} alkyl; $\mathbf{L}$ is $-\mathbf{X}^1-\mathbf{X}^2-\mathbf{X}^3-\mathbf{X}^4-\mathbf{X}^5-$; $\mathbf{X}^1$ is $-\text{C}(\text{O})-\text{N}(\mathbf{R})-$, $-\text{N}(\mathbf{R})-\text{C}(\text{O})-$, $-(\text{O}-\text{CH}_2-\text{CH}_2)_m-$, $-\text{O}(\text{C}_6\text{H}_4)-$, $-(\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2)_m-$, $-\text{C}_{1-5}$ alkyl-, 7-12 membered spiro bicyclic heterocycloalkyl having one to three heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-\text{CH}_3$, or 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-\text{CH}_3$; $\mathbf{X}^2$ is a bond, $-(\text{O}-\text{CH}_2-\text{CH}_2)_n-$, $-(\text{CH}_2-\text{CH}_2-\text{O})_n-$, $-\text{N}(\mathbf{R})-\text{C}(\text{O})-$, $-\text{N}(\mathbf{R})-$, $-\text{C}(\text{O})-$, $-\text{C}_{1-5}$ alkyl-, 4-6 membered cycloalkyl, or 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S; $\mathbf{X}^3$ is a bond, $-\text{C}_{1-4}$ alkyl-, 4-6 membered cycloalkyl, $-\text{N}(\mathbf{R})-$, $-(\text{O}-\text{CH}_2-\text{CH}_2)_p-$, $-(\text{CH}_2-\text{CH}_2-\text{O})_p-$, or 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-\text{CH}_3$; $\mathbf{X}^4$ is a bond, $-\text{CH}_2-\text{CH}_2-\text{N}(\mathbf{R})-$, $-\text{N}(\mathbf{R})-$, $-\text{C}_{1-4}$ alkyl-, $-(\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2)_m-$, or 5-6 membered saturated, partially unsaturated, or fully unsaturated heterocycle having one to three heteroatoms independently selected from N, O, or S; $\mathbf{X}^5$ is a bond, $-\text{C}_{1-4}$ alkyl-, $-\text{N}(\mathbf{R})-$, or $-\text{C}(\text{O})-\text{N}(\mathbf{R})-$; each $\mathbf{R}$ is independently $-\text{H}$ or $-\text{C}_{1-3}$ alkyl; each of m , n , and p is independently an integer from

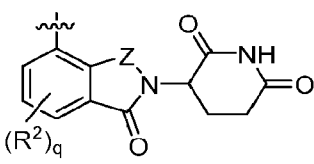
one to three; $\mathbf{Y}$ is $(\text{R}^2)_q$ or $(\text{R}^2)_q$, wherein each $\mathbf{R}^2$ is independently halo or $-\text{C}_{1-4}$ alkyl; each $\mathbf{Z}$ is $-\text{C}(\mathbf{R}^A)_2-$ or $-\text{C}(\text{O})-$; each $\mathbf{R}^A$ is independently $-\text{H}$ or $-\text{C}_{1-4}$ alkyl; and q is zero, one, or two.

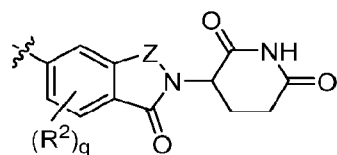
[00237] In other embodiments, each of the variables in Formula (I-A) is as defined herein for the compound of Formula (X) or (I).

[00238] This disclosure also provides a compound of Formula (I-B)



or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R}^1$ is C_{1-3} alkyl; $\mathbf{L}$ is $-\mathbf{X}^1-\mathbf{X}^2-\mathbf{X}^3-\mathbf{X}^4-\mathbf{X}^5-$; $\mathbf{X}^1$ is $-\text{C}(\text{O})-\text{N}(\mathbf{R})-$, $-\text{N}(\mathbf{R})-\text{C}(\text{O})-$, $-(\text{O}-\text{CH}_2-\text{CH}_2)_m-$, $-\text{O}(\text{C}_6\text{H}_4)-$, $-(\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2)_m-$, $-\text{C}_{1-5}$ alkyl-, 7-12 membered spiro bicyclic heterocycloalkyl ring having one to three heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-\text{CH}_3$, or 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-\text{CH}_3$; $\mathbf{X}^2$ is a bond, $-(\text{O}-\text{CH}_2-\text{CH}_2)_n-$, $-(\text{CH}_2-\text{CH}_2-\text{O})_n-$, $-\text{N}(\mathbf{R})-\text{C}(\text{O})-$, $-\text{N}(\mathbf{R})-$, $-\text{C}(\text{O})-$, $-\text{C}_{1-5}$ alkyl-, 4-6 membered cycloalkyl, or 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S; $\mathbf{X}^3$ is a bond, $-\text{C}_{1-4}$ alkyl-, 4-6 membered cycloalkyl, $-\text{N}(\mathbf{R})-$, $-(\text{O}-\text{CH}_2-\text{CH}_2)_p-$, $-(\text{CH}_2-\text{CH}_2-\text{O})_p-$, or 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-\text{CH}_3$; $\mathbf{X}^4$ is a bond, $-\text{CH}_2-\text{CH}_2-\text{N}(\mathbf{R})-$, $-\text{N}(\mathbf{R})-$, $-\text{C}_{1-4}$ alkyl-, $-(\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2)_m-$, or 5-6 membered saturated, partially unsaturated, or fully unsaturated heterocycle having one to three heteroatoms independently selected from N, O, or S; $\mathbf{X}^5$ is a bond, $-\text{C}_{1-4}$ alkyl-, $-\text{N}(\mathbf{R})-$, or $-\text{C}(\text{O})-\text{N}(\mathbf{R})-$; each $\mathbf{R}$ is independently $-\text{H}$ or $-\text{C}_{1-3}$ alkyl; each of m , n , and p is

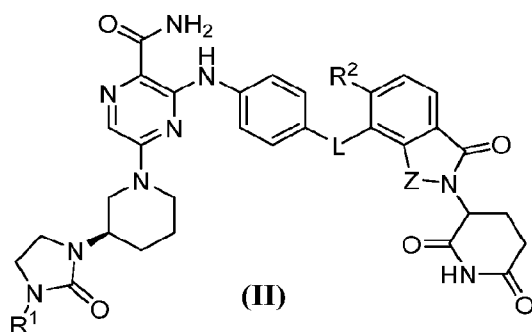
independently an integer from one to three; $\mathbf{Y}$ is  or



, wherein each $\mathbf{R}^2$ is independently halo or C_{1-4} alkyl; each $\mathbf{Z}$ is $-\text{C}(\mathbf{R}^A)_2-$ or $-\text{C}(\text{O})-$; each $\mathbf{R}^A$ is independently $-\text{H}$ or C_{1-4} alkyl; and q is zero, one, or two.

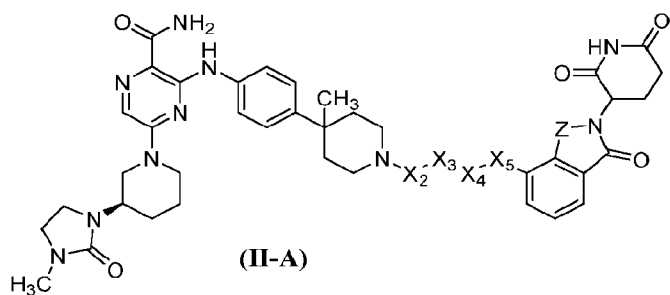
[00239] In other embodiments, each of the variables in Formula (I-B) is as defined herein for the compound of Formula (X) or (I).

[00240] This disclosure also provides a compound of Formula (II)

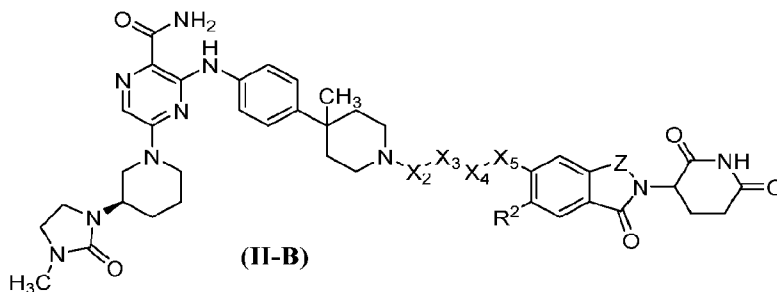


or a pharmaceutically acceptable salt thereof, wherein each of **R**¹, **R**², **L**, and **Z** are as defined herein for the compound of Formula (X), (I), (I-A), or (I-B).

[00241] In some embodiments, the compound of Formula (II) is a compound of Formulae (II-A) or (II-B)

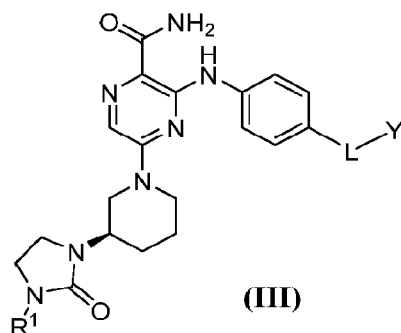


or

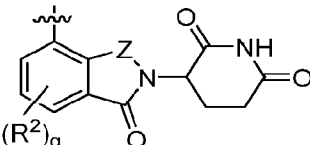
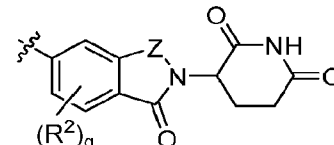


or a pharmaceutically acceptable salt thereof, wherein each of **X**², **X**³, **X**⁴, and **X**⁵ are as defined herein for the compound of Formula (X), (I), (I-A), (I-B), or (II).

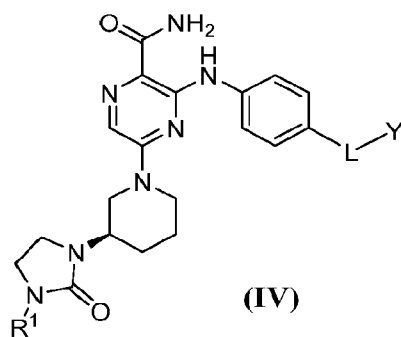
[00242] This disclosure also provides a compound of Formula (III)



or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-3} alkyl; L is $-X^1-X^2-X^3-$; X^1 is 7-12 membered spiro bicyclic heterocycloalkyl having one to three heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-CH_3$, or 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-CH_3$; X^2 is a bond or $-C_{1-5}$ alkyl-; X^3 is a bond, $-C_{1-4}$ alkyl-, 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally

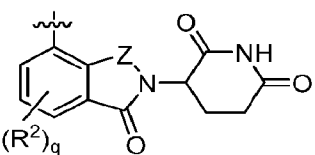
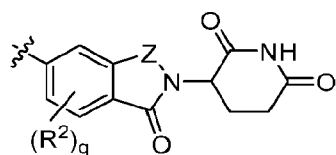
substituted with $-CH_3$; Y is  or , wherein each R^2 is independently halo or $-C_{1-4}$ alkyl; each Z is $-C(R^A)_2-$ or $-C(O)-$; each R^A is independently $-H$; and q is zero, one, or two.

[00243] This disclosure also provides a compound of Formula (IV)



or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-3} alkyl; L is $-X^1-X^2-X^3-X^4-X^5-$; X^1 is $-C(O)-N(R)-$, $-N(R)-C(O)-$, $-(O-CH_2-CH_2)_m-$, $-O(C_6H_4)-$, $-(O-CH_2-CH_2-CH_2)_m-$, $-C_{1-5}$ alkyl-, 7-12 membered spiro bicyclic heterocycloalkyl having one to three heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-CH_3$, or 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally

substituted with $-\text{CH}_3$; X^2 is a bond, $-(\text{O}-\text{CH}_2-\text{CH}_2)_n-$, $-(\text{CH}_2-\text{CH}_2-\text{O})_n-$, $-\text{N}(\text{R})-\text{C}(\text{O})-$, $-\text{N}(\text{R})-$, $-\text{C}(\text{O})-$, $-\text{C}_{1-5}$ alkyl-, 4-6 membered cycloalkyl, or 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S; X^3 is a bond, $-\text{C}_{1-4}$ alkyl-, 4-6 membered cycloalkyl, $-\text{N}(\text{R})-$, $-(\text{O}-\text{CH}_2-\text{CH}_2)_p-$, $-(\text{CH}_2-\text{CH}_2-\text{O})_p-$, or 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-\text{CH}_3$; X^4 is a bond, $-\text{CH}_2-\text{CH}_2-\text{N}(\text{R})-$, $-\text{N}(\text{R})-$, $-\text{C}_{1-4}$ alkyl-, $-(\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2)_m-$, or 5-6 membered saturated, partially unsaturated, or fully unsaturated heterocycle having one to three heteroatoms independently selected from N, O, or S; X^5 is a bond, $-\text{C}_{1-4}$ alkyl-, $-\text{N}(\text{R})-$, or $-\text{C}(\text{O})-\text{N}(\text{R})-$; each R is independently $-\text{H}$ or $-\text{C}_{1-3}$ alkyl; each of m , n , and p is independently an integer from

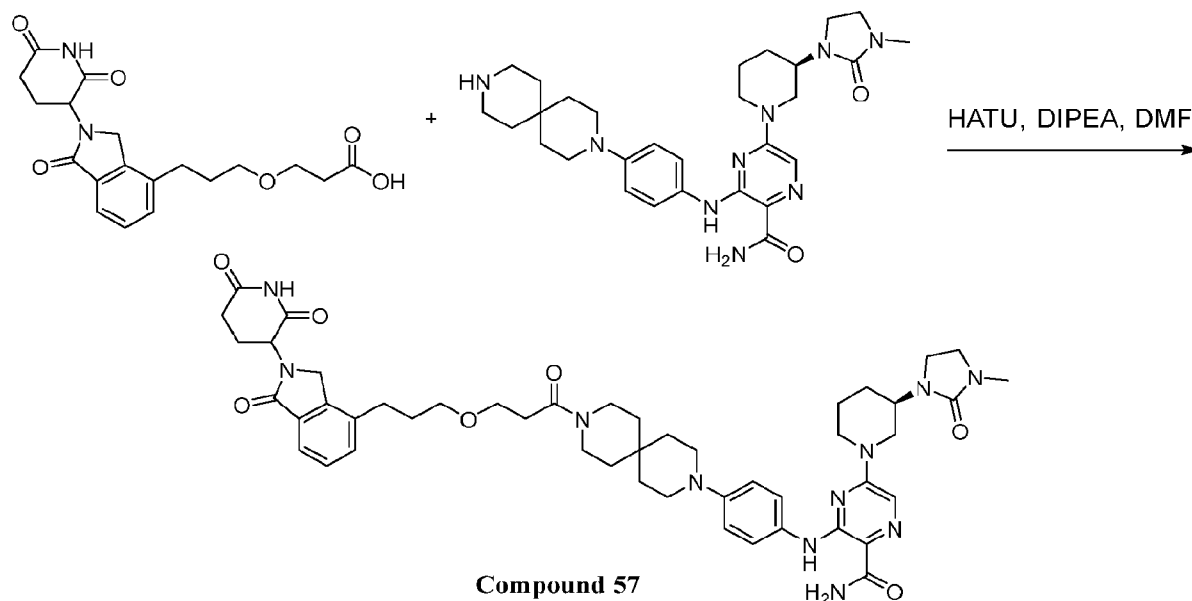
one to three; Y is  or , wherein each R^2 is independently halo or $-\text{C}_{1-4}$ alkyl; each Z is $-\text{C}(\text{R}^{\text{A}})_2-$ or $-\text{C}(\text{O})-$; each R^{A} is independently $-\text{H}$ or $-\text{C}_{1-4}$ alkyl; and q is zero, one, or two.

[00244] General Synthetic Schemes

[00245] Compounds can be prepared or synthesized according to any technique deemed suitable by the person of skill in the art. In certain embodiments, compounds are prepared according to International Application No. PCT/US2019/56112, filed October 14, 2019, incorporated by reference herein in its entirety. Exemplary synthetic schemes are described below.

[00246] General Procedure 1: Amide Coupling

[00247] A mixture of amine (0.03 mmol), acid (0.03 mmol), HATU (0.04 mmol), DIPEA (0.15 mmol) and DMF was allowed to stir at room temperature for thirty minutes. The mixture was purified by HPLC (H₂O/MeCN with 0.1% TFA) to afford the amide product. An exemplary amide coupling is provided in Scheme 1 below where 3-(3-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)propoxy)propanoic acid, and (*R*)-3-((4-(3,9-diazaspiro[5.5]undecan-3-yl)phenyl)amino)-5-(3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl)pyrazine-2-carboxamide were reacted as described above to provide 3-((4-(9-(3-(3-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)propoxy)propanoyl)-3,9-diazaspiro[5.5]undecan-3-yl)phenyl)amino)-5-((*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl)pyrazine-2-carboxamide (Compound 57).

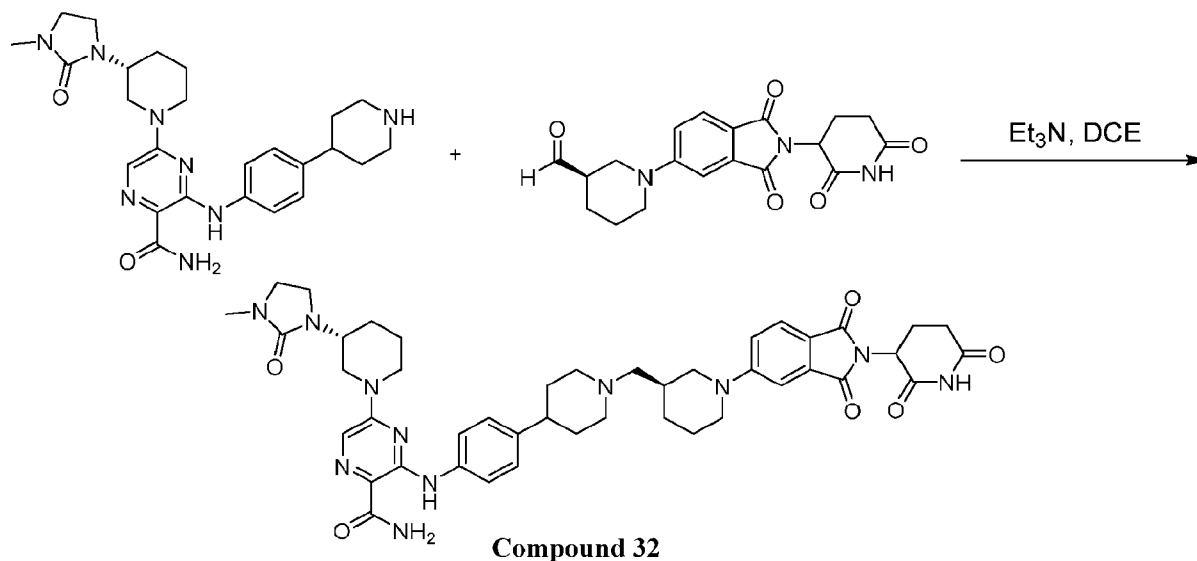
[00248] Scheme 1: Synthesis of Compound 57 via Amide Formation

[00249] Other amide containing compounds of this description synthesized using General Procedure 1 were Compounds 2-9, 10-14, 19, 20, 22-28, 61, 62, 63, and 67.

[00250] General Procedure 2: Reductive Amination

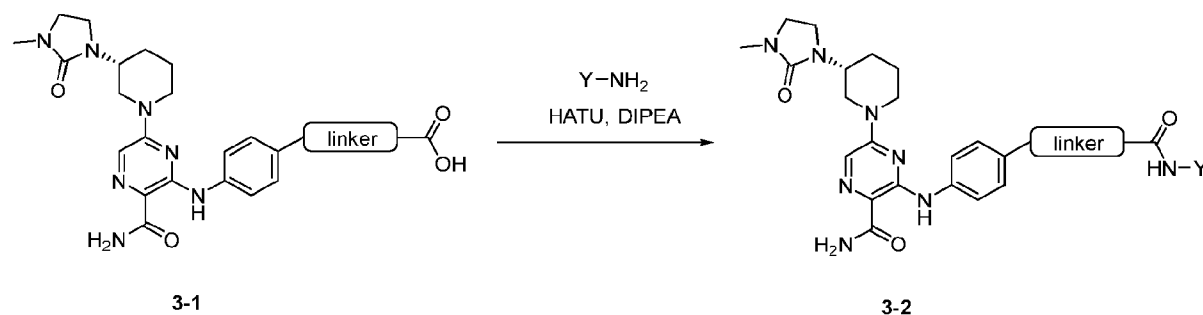
[00251] A mixture of amine TFA salt (0.07 mmol), aldehyde (0.1 mmol), triethylamine (0.28 mmol), and DCE were allowed to stir at room temperature for ten minutes. NaBH(OAc)₃ (0.14 mmol) was added and the mixture was allowed to stir at room temperature for 2 h. The mixture was filtered through celite, washed with CH₂Cl₂, concentrated, and purified by HPLC (H₂O/MeCN with 0.1% TFA) to afford the amine product. An exemplary reductive amination is provided in Scheme 2 where (*R*)-5-(3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl)-3-((4-(piperidin-4-yl)phenyl)amino)pyrazine-2-carboxamide was treated as described above with (3*R*)-1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)piperidine-3-carbaldehyde to provide 3-((4-(1-(((3*S*)-1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)piperidin-3-yl)methyl)piperidin-4-yl)phenyl)amino)-5-((*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl)pyrazine-2-carboxamide (Compound 32).

[00252] Scheme 2: Synthesis of Compound 32 via Reductive Amination



[00253] Other amine containing compounds of this description synthesized using General Procedure 2 were Compounds 33, 46, 56, 15-18, 21, 31, 48-52, 54, 59, 60, 35, 36, and 38-45.

[00254] Scheme 3: Synthesis of Compounds of This Disclosure

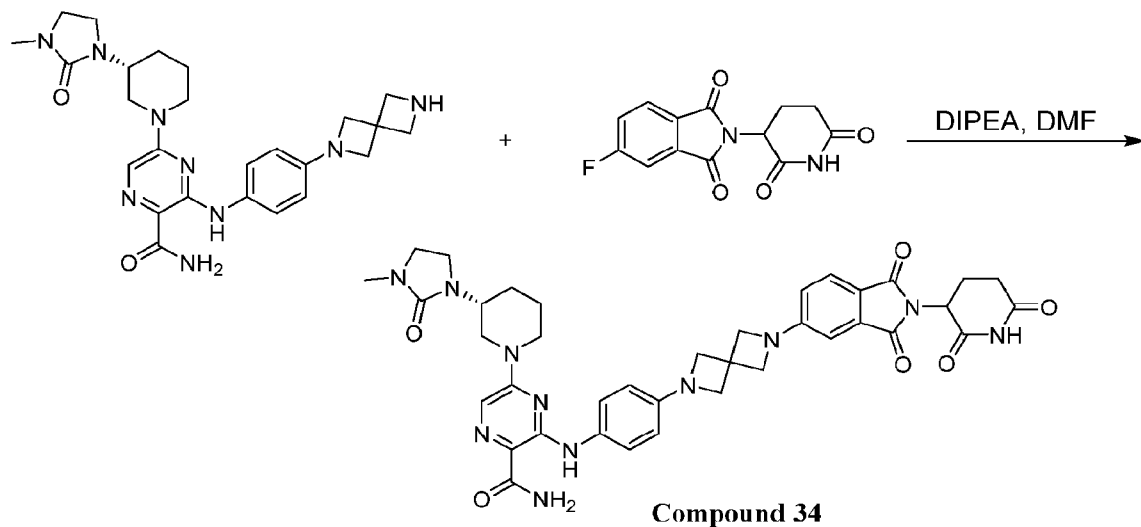


[00255] Intermediate (3-1), which can be generated by de-esterifying intermediate (1-6), is treated with amine, Y-NH₂, under coupling conditions to generate compounds of this disclosure (3-2), wherein the terminal linking group of L is an amide.

[00256] General Procedure 3: Aryl fluoride displacement

[00257] A mixture of amine (0.22 mmol), aryl fluoride (0.22 mmol), DIPEA (0.88 mmol) and DMF (1 mL) was allowed to stir at 90 °C for 16 h. The mixture was purified by HPLC (H₂O/MeCN with 0.1% TFA) to afford the desired product. An exemplary aryl fluoride displacement is provided in Scheme 3, where (R)-3-((4-(2,6-diazaspiro[3.3]heptan-2-yl)phenyl)amino)-5-(3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl)pyrazine-2-carboxamide is treated as described above with 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisindoline-1,3-dione to provide 3-((4-(6-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)-2,6-diazaspiro[3.3]heptan-2-yl)phenyl)amino)-5-((R)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl)pyrazine-2-carboxamide (Compound 34).

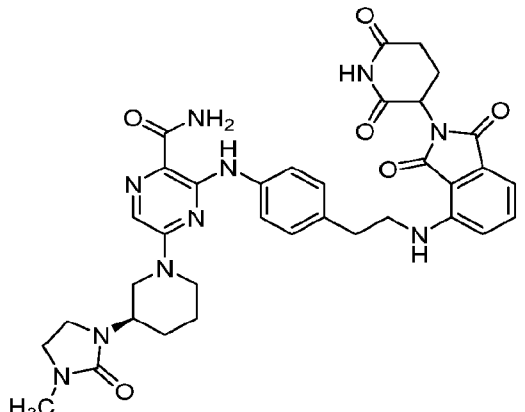
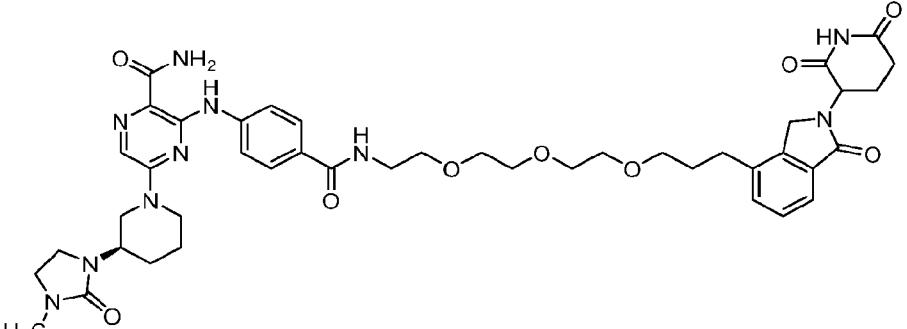
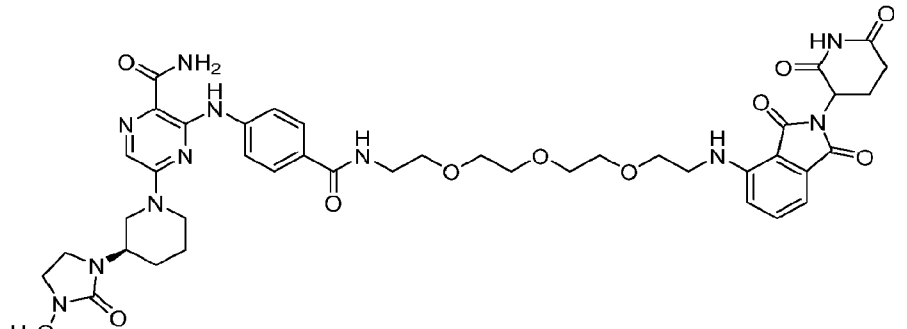
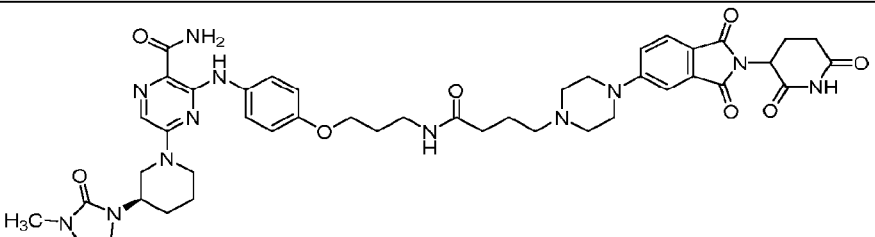
[00258] Scheme 3: Synthesis of Compound 34 via Aryl Fluoride Displacement



Other aryl amine containing compounds of this description synthesized using General Procedure 3 are Compounds 55, 29, 47, 53, 58, 64-66, 37, and 30.

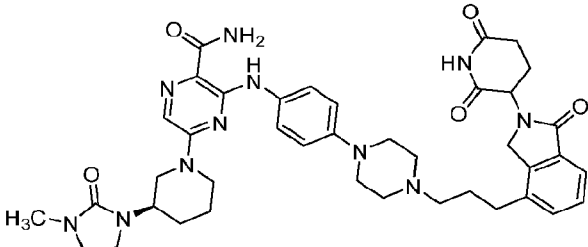
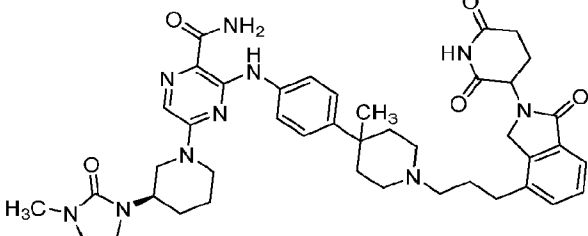
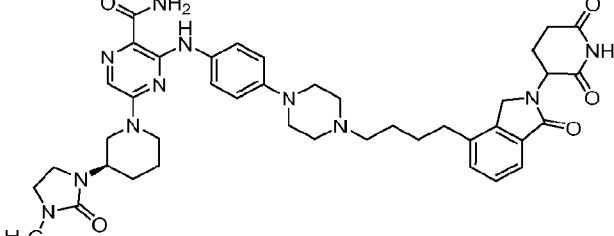
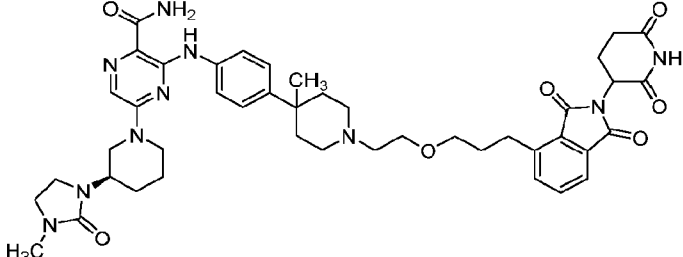
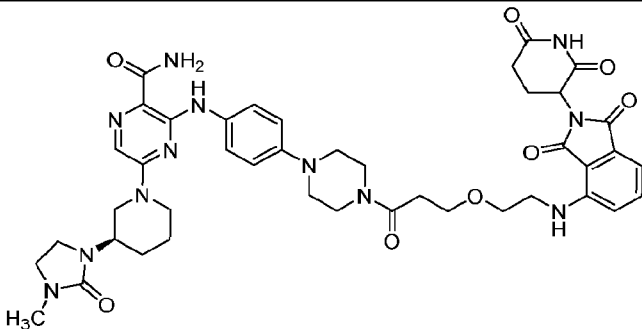
[00259] The abovementioned synthetic schemes were used to synthesize the compounds in Table 1.

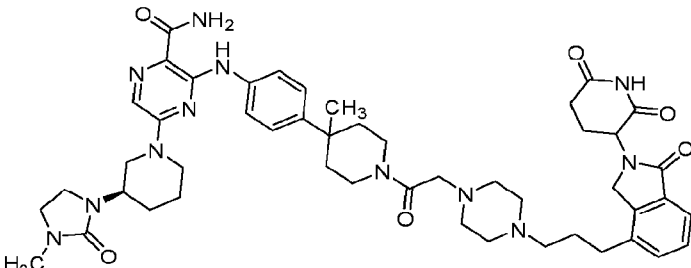
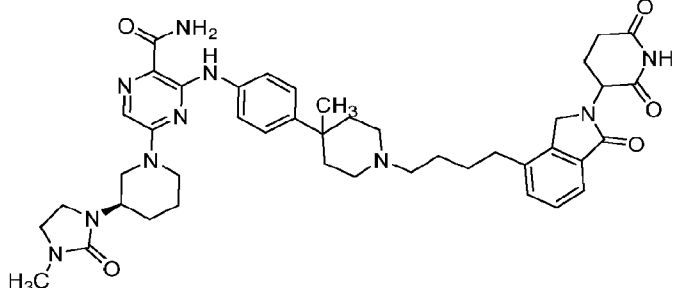
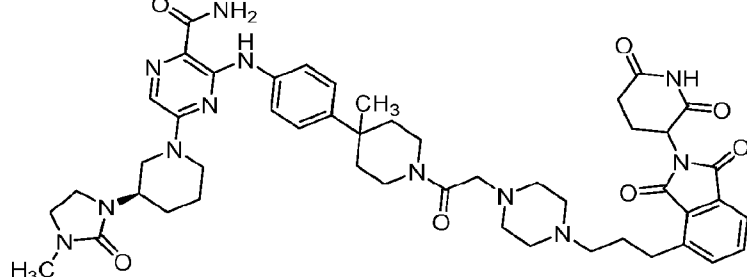
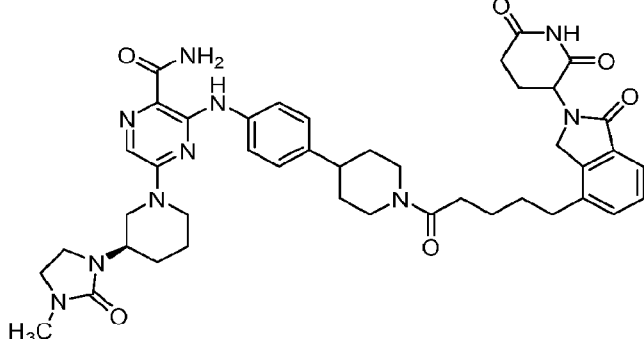
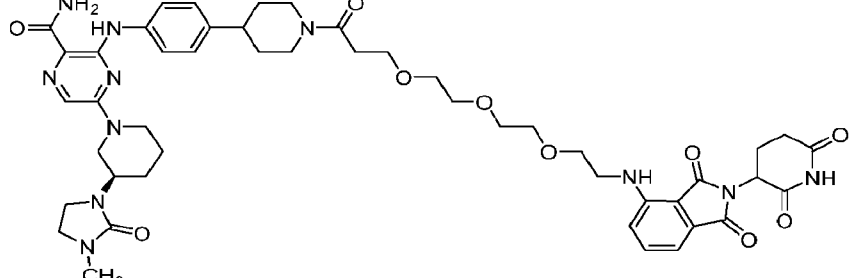
[00260] Table 1: Example compounds and/or pharmaceutically acceptable salts thereof for use in the methods described herein.

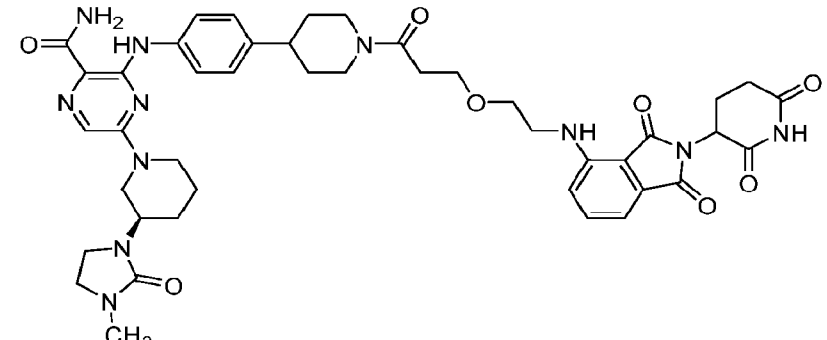
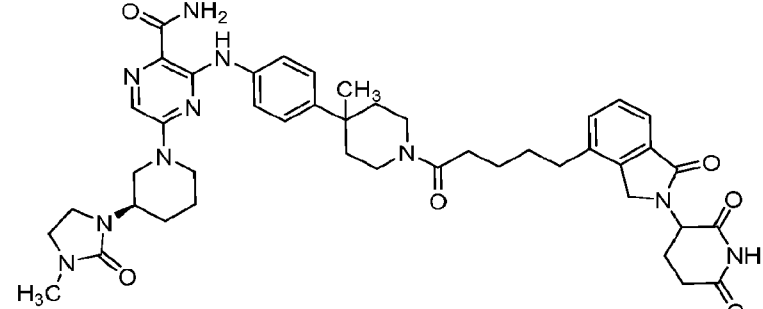
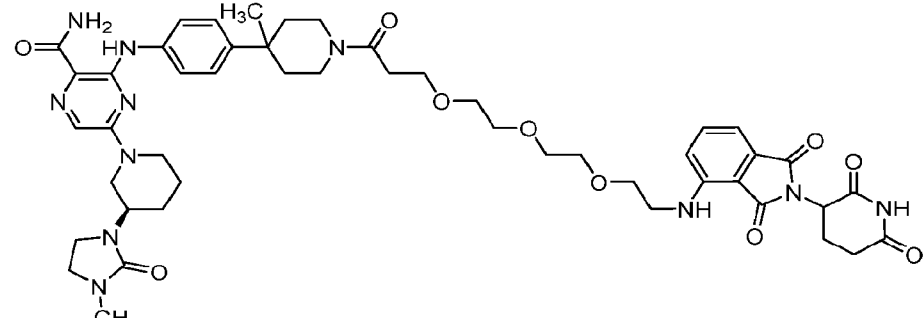
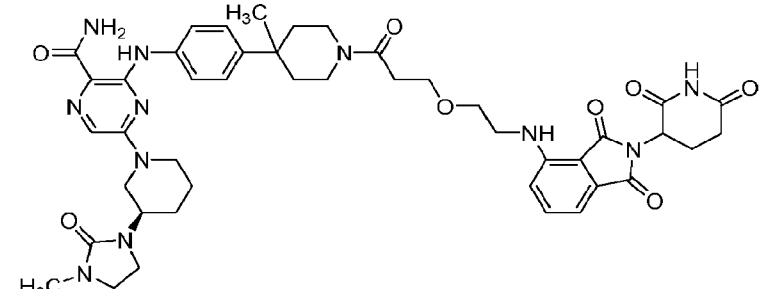
Compound Number	Structure
1	 Chemical structure of Compound 1: A complex molecule featuring a 4-aminopyrimidin-2(1H)-one ring substituted with a (4-((2-methyl-1,3-dioxol-2-yl)methyl)phenyl)amino group and a (4-((2-methyl-1,3-dioxol-2-yl)methyl)phenyl)amino group. The pyrimidine ring is also substituted with a (4-((2-methyl-1,3-dioxol-2-yl)methyl)phenyl)amino group. The molecule includes a 2-methyl-1,3-dioxol-2-yl group and a 2-methyl-1,3-dioxol-2-yl group.
2	 Chemical structure of Compound 2: A complex molecule featuring a 4-aminopyrimidin-2(1H)-one ring substituted with a (4-((2-methyl-1,3-dioxol-2-yl)methyl)phenyl)amino group and a (4-((2-methyl-1,3-dioxol-2-yl)methyl)phenyl)amino group. The pyrimidine ring is also substituted with a (4-((2-methyl-1,3-dioxol-2-yl)methyl)phenyl)amino group. The molecule includes a 2-methyl-1,3-dioxol-2-yl group and a 2-methyl-1,3-dioxol-2-yl group.
3	 Chemical structure of Compound 3: A complex molecule featuring a 4-aminopyrimidin-2(1H)-one ring substituted with a (4-((2-methyl-1,3-dioxol-2-yl)methyl)phenyl)amino group and a (4-((2-methyl-1,3-dioxol-2-yl)methyl)phenyl)amino group. The pyrimidine ring is also substituted with a (4-((2-methyl-1,3-dioxol-2-yl)methyl)phenyl)amino group. The molecule includes a 2-methyl-1,3-dioxol-2-yl group and a 2-methyl-1,3-dioxol-2-yl group.
4	 Chemical structure of Compound 4: A complex molecule featuring a 4-aminopyrimidin-2(1H)-one ring substituted with a (4-((2-methyl-1,3-dioxol-2-yl)methyl)phenyl)amino group and a (4-((2-methyl-1,3-dioxol-2-yl)methyl)phenyl)amino group. The pyrimidine ring is also substituted with a (4-((2-methyl-1,3-dioxol-2-yl)methyl)phenyl)amino group. The molecule includes a 2-methyl-1,3-dioxol-2-yl group and a 2-methyl-1,3-dioxol-2-yl group.

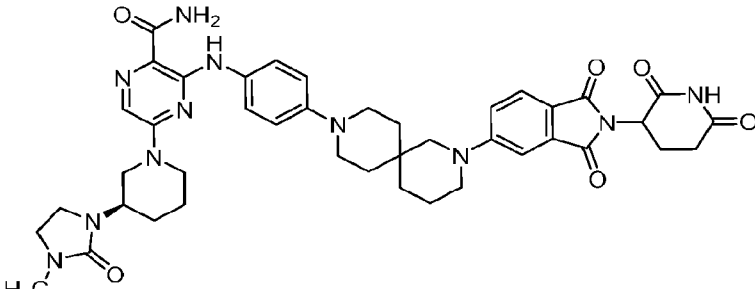
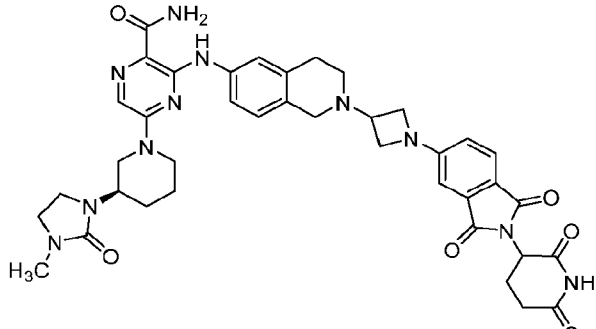
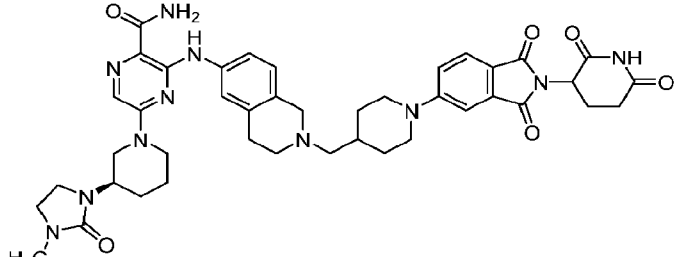
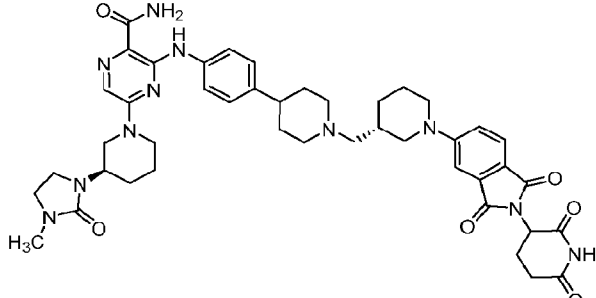
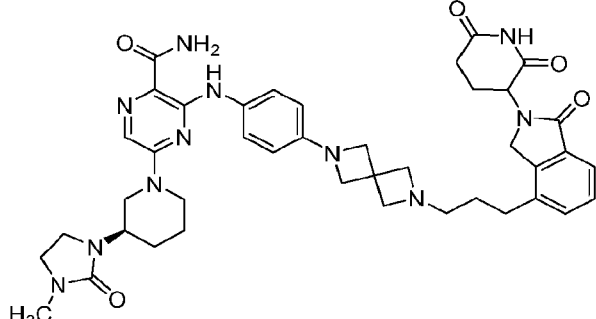
Compound Number	Structure
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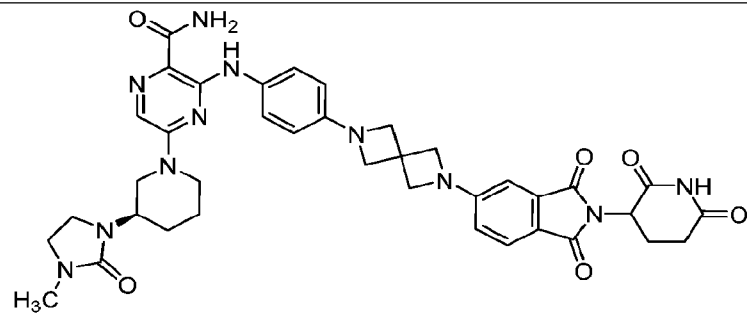
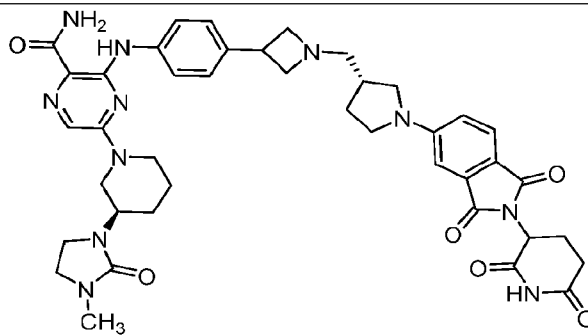
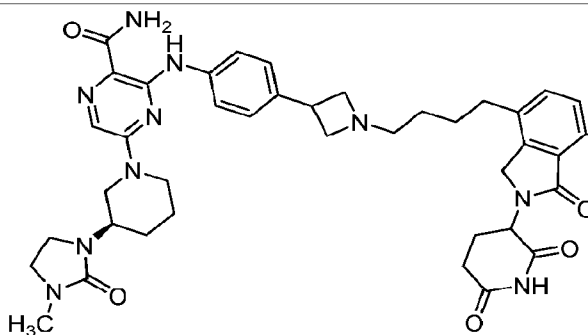
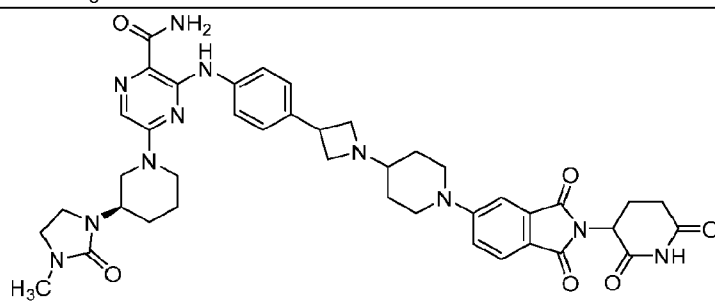
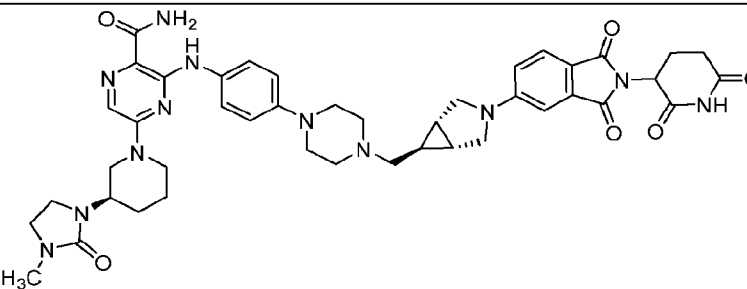
Compound Number	Structure
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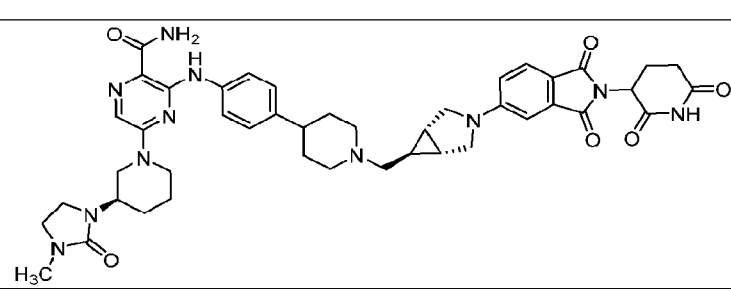
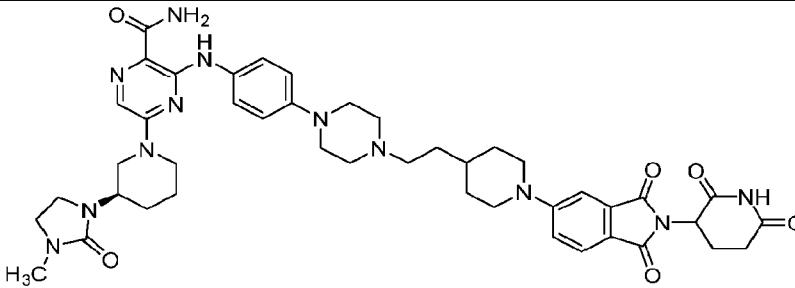
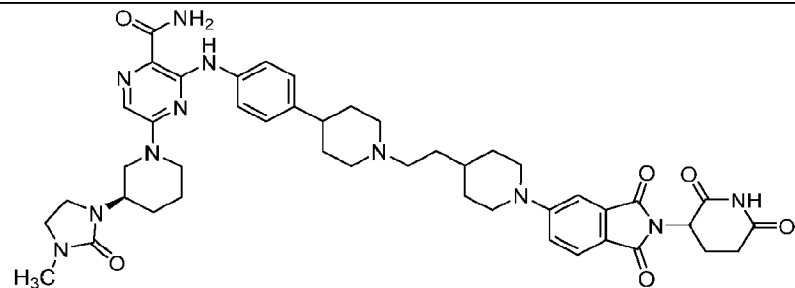
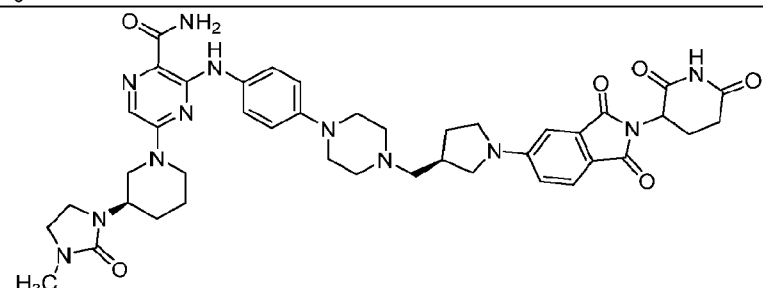
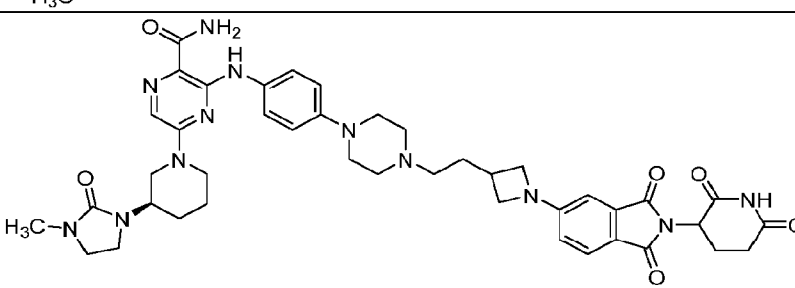
Compound Number	Structure
15	 Chemical structure of compound 15: A complex molecule featuring a central benzene ring substituted with a guanidine group (NH₂ and NH-C(=O)-NH₂), a piperidine ring, and a 1,4-bis(methylamino)phenyl group. The piperidine ring is further substituted with a methyl group and a carbonyl group. The 1,4-bis(methylamino)phenyl group is connected to a 1,4-bis(methylamino)phenyl group, which is in turn connected to a 1,4-bis(methylamino)phenyl group.
16	 Chemical structure of compound 16: A complex molecule featuring a central benzene ring substituted with a guanidine group (NH₂ and NH-C(=O)-NH₂), a piperidine ring, and a 1,4-bis(methylamino)phenyl group. The piperidine ring is further substituted with a methyl group and a carbonyl group. The 1,4-bis(methylamino)phenyl group is connected to a 1,4-bis(methylamino)phenyl group, which is in turn connected to a 1,4-bis(methylamino)phenyl group.
17	 Chemical structure of compound 17: A complex molecule featuring a central benzene ring substituted with a guanidine group (NH₂ and NH-C(=O)-NH₂), a piperidine ring, and a 1,4-bis(methylamino)phenyl group. The piperidine ring is further substituted with a methyl group and a carbonyl group. The 1,4-bis(methylamino)phenyl group is connected to a 1,4-bis(methylamino)phenyl group, which is in turn connected to a 1,4-bis(methylamino)phenyl group.
18	 Chemical structure of compound 18: A complex molecule featuring a central benzene ring substituted with a guanidine group (NH₂ and NH-C(=O)-NH₂), a piperidine ring, and a 1,4-bis(methylamino)phenyl group. The piperidine ring is further substituted with a methyl group and a carbonyl group. The 1,4-bis(methylamino)phenyl group is connected to a 1,4-bis(methylamino)phenyl group, which is in turn connected to a 1,4-bis(methylamino)phenyl group.
19	 Chemical structure of compound 19: A complex molecule featuring a central benzene ring substituted with a guanidine group (NH₂ and NH-C(=O)-NH₂), a piperidine ring, and a 1,4-bis(methylamino)phenyl group. The piperidine ring is further substituted with a methyl group and a carbonyl group. The 1,4-bis(methylamino)phenyl group is connected to a 1,4-bis(methylamino)phenyl group, which is in turn connected to a 1,4-bis(methylamino)phenyl group.

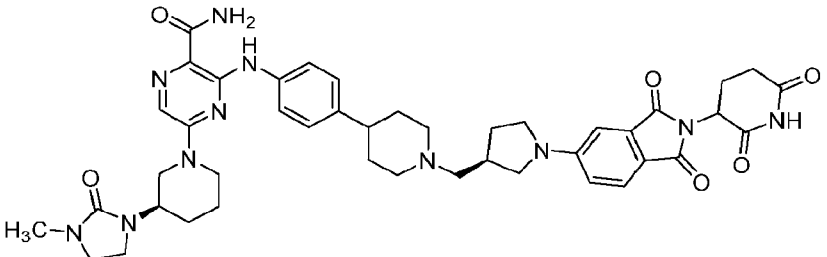
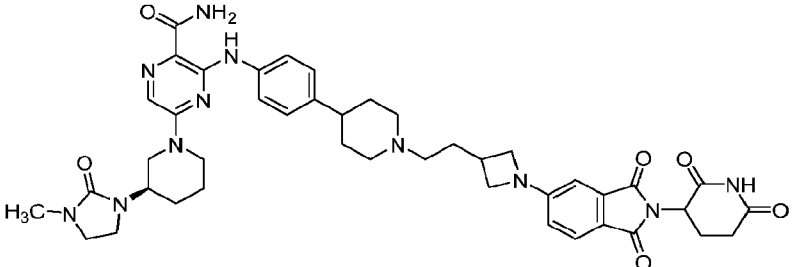
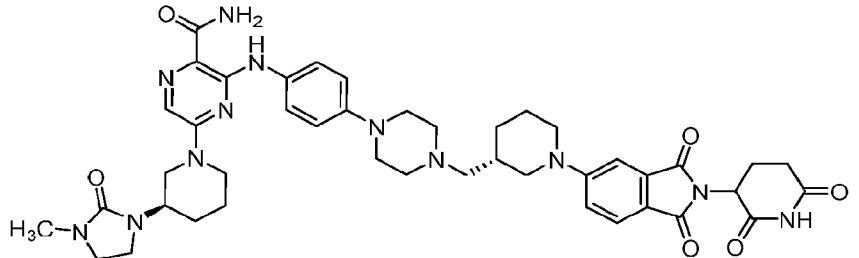
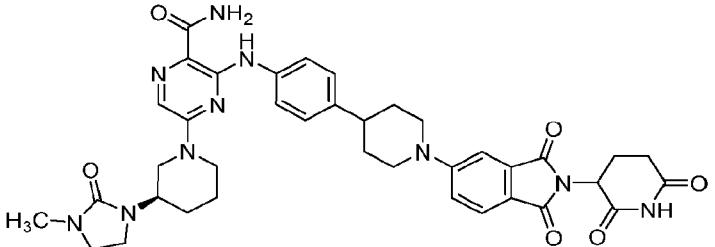
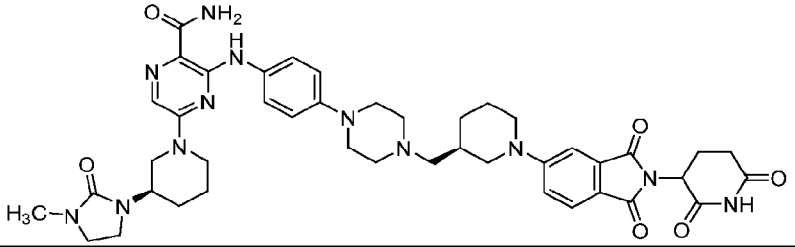
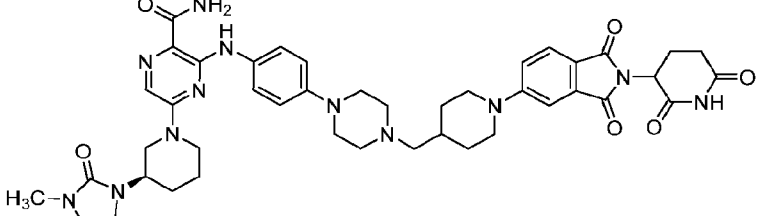
Compound Number	Structure
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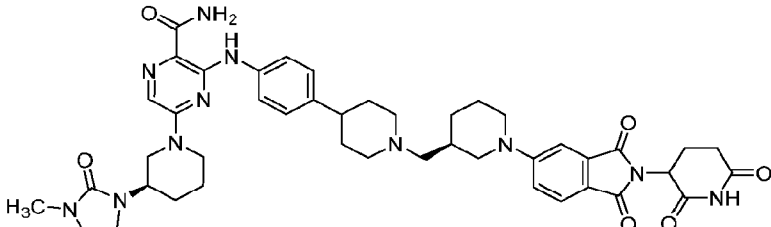
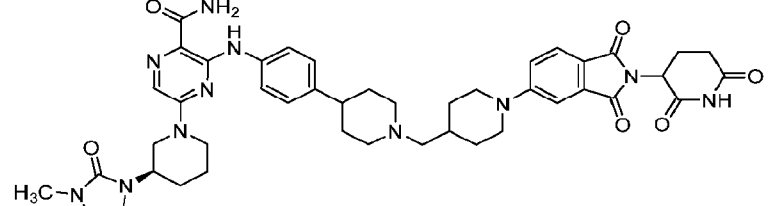
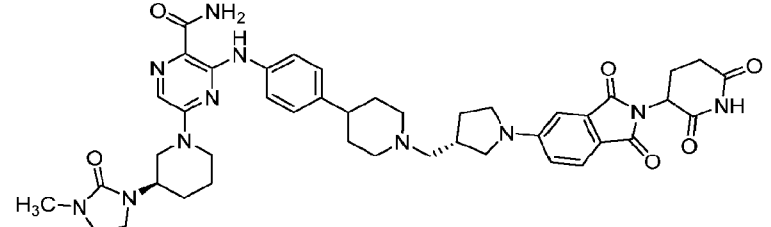
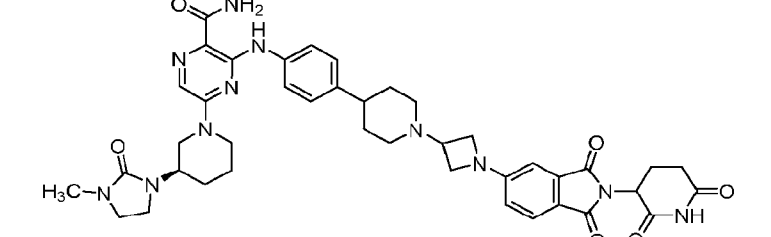
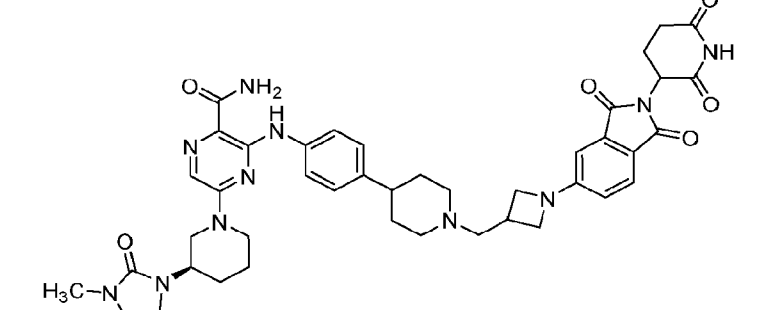
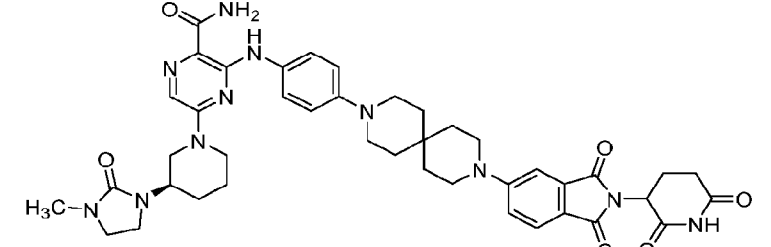
Compound Number	Structure
25	 Chemical structure of Compound 25: A complex molecule featuring a pyrimidine ring substituted with an amino group (NH₂) and a piperidine ring. The piperidine ring is further substituted with a methyl group and a carbonyl group. The pyrimidine ring is connected via an amine group to a benzene ring, which is linked to a piperidine ring. This piperidine ring is connected via a carbonyl group to a chain containing an ether linkage and a terminal amine group. The terminal amine group is part of a bicyclic system, specifically a benzimidazole derivative, which is further substituted with a carbonyl group and a piperidine ring.
26	 Chemical structure of Compound 26: A complex molecule featuring a pyrimidine ring substituted with an amino group (NH₂) and a piperidine ring. The piperidine ring is further substituted with a methyl group and a carbonyl group. The pyrimidine ring is connected via an amine group to a benzene ring, which is linked to a piperidine ring. This piperidine ring is connected via a carbonyl group to a chain containing a carbonyl group and a terminal amine group. The terminal amine group is part of a bicyclic system, specifically a benzimidazole derivative, which is further substituted with a carbonyl group and a piperidine ring.
27	 Chemical structure of Compound 27: A complex molecule featuring a pyrimidine ring substituted with an amino group (NH₂) and a piperidine ring. The piperidine ring is further substituted with a methyl group and a carbonyl group. The pyrimidine ring is connected via an amine group to a benzene ring, which is linked to a piperidine ring. This piperidine ring is connected via a carbonyl group to a chain containing an ether linkage and a terminal amine group. The terminal amine group is part of a bicyclic system, specifically a benzimidazole derivative, which is further substituted with a carbonyl group and a piperidine ring.
28	 Chemical structure of Compound 28: A complex molecule featuring a pyrimidine ring substituted with an amino group (NH₂) and a piperidine ring. The piperidine ring is further substituted with a methyl group and a carbonyl group. The pyrimidine ring is connected via an amine group to a benzene ring, which is linked to a piperidine ring. This piperidine ring is connected via a carbonyl group to a chain containing an ether linkage and a terminal amine group. The terminal amine group is part of a bicyclic system, specifically a benzimidazole derivative, which is further substituted with a carbonyl group and a piperidine ring.

Compound Number	Structure
29	 Chemical structure of compound 29: A complex molecule featuring a 4-aminopyrimidin-2-yl group connected via an amine bridge to a 4-phenylpiperidine ring. This piperidine ring is further connected to a 4-phenylpiperidine ring, which is linked to a 4-phenylisoindolin-1-one ring. The isoindolinone ring is connected to a 4-phenylpiperidine ring, which is finally linked to a 4-phenylpiperidine ring. The molecule also includes a 4-phenylpiperidine ring and a 4-phenylpiperidine ring.
30	 Chemical structure of compound 30: A complex molecule featuring a 4-aminopyrimidin-2-yl group connected via an amine bridge to a 4-phenylpiperidine ring. This piperidine ring is further connected to a 4-phenylpiperidine ring, which is linked to a 4-phenylisoindolin-1-one ring. The isoindolinone ring is connected to a 4-phenylpiperidine ring, which is finally linked to a 4-phenylpiperidine ring. The molecule also includes a 4-phenylpiperidine ring and a 4-phenylpiperidine ring.
31	 Chemical structure of compound 31: A complex molecule featuring a 4-aminopyrimidin-2-yl group connected via an amine bridge to a 4-phenylpiperidine ring. This piperidine ring is further connected to a 4-phenylpiperidine ring, which is linked to a 4-phenylisoindolin-1-one ring. The isoindolinone ring is connected to a 4-phenylpiperidine ring, which is finally linked to a 4-phenylpiperidine ring. The molecule also includes a 4-phenylpiperidine ring and a 4-phenylpiperidine ring.
32	 Chemical structure of compound 32: A complex molecule featuring a 4-aminopyrimidin-2-yl group connected via an amine bridge to a 4-phenylpiperidine ring. This piperidine ring is further connected to a 4-phenylpiperidine ring, which is linked to a 4-phenylisoindolin-1-one ring. The isoindolinone ring is connected to a 4-phenylpiperidine ring, which is finally linked to a 4-phenylpiperidine ring. The molecule also includes a 4-phenylpiperidine ring and a 4-phenylpiperidine ring.
33	 Chemical structure of compound 33: A complex molecule featuring a 4-aminopyrimidin-2-yl group connected via an amine bridge to a 4-phenylpiperidine ring. This piperidine ring is further connected to a 4-phenylpiperidine ring, which is linked to a 4-phenylisoindolin-1-one ring. The isoindolinone ring is connected to a 4-phenylpiperidine ring, which is finally linked to a 4-phenylpiperidine ring. The molecule also includes a 4-phenylpiperidine ring and a 4-phenylpiperidine ring.

Compound Number	Structure
34	
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Compound Number	Structure
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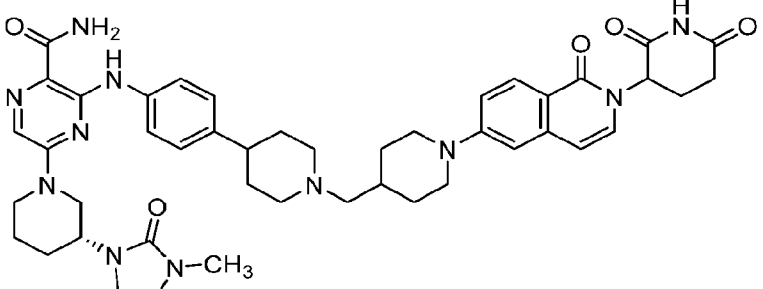
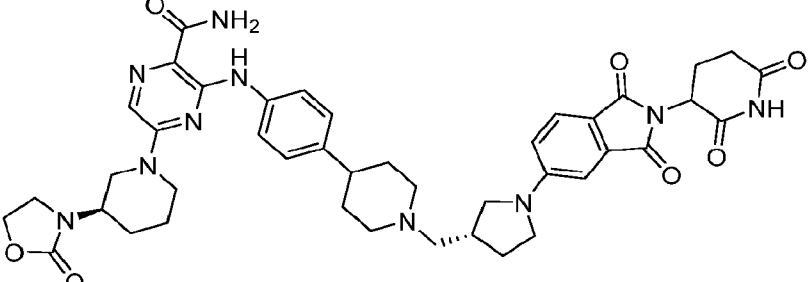
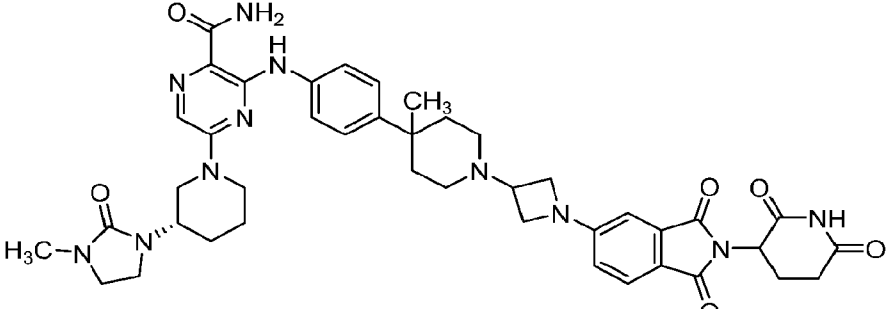
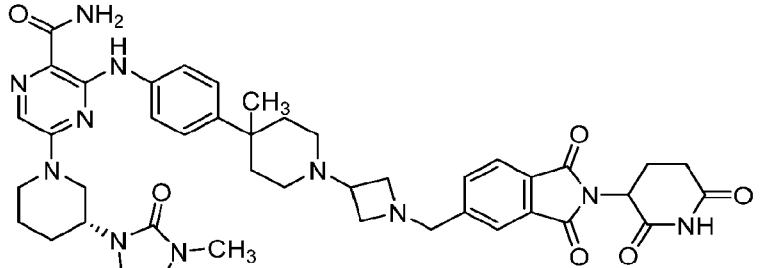
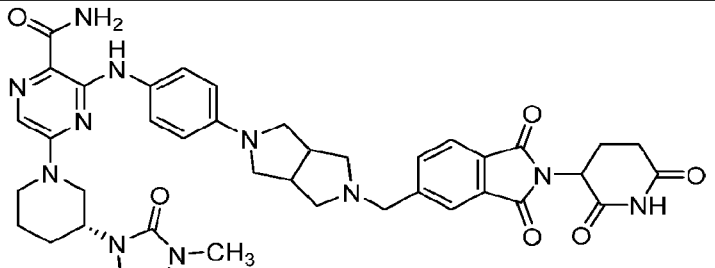
Compound Number	Structure
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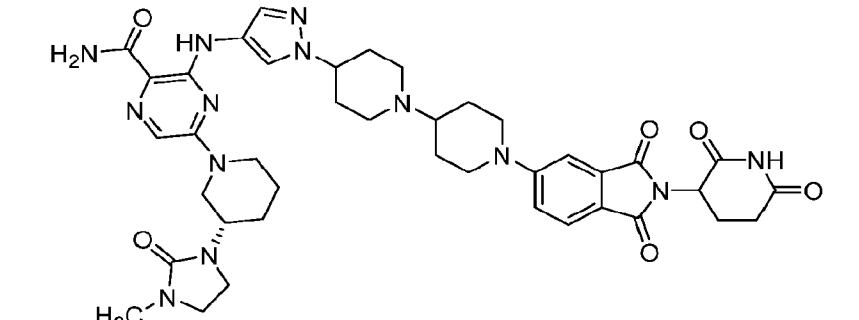
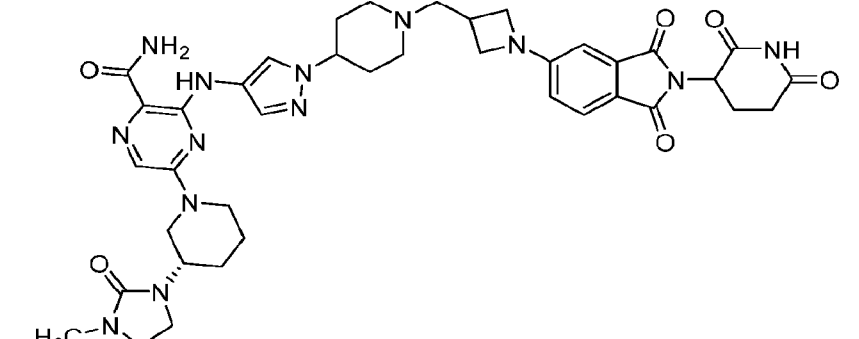
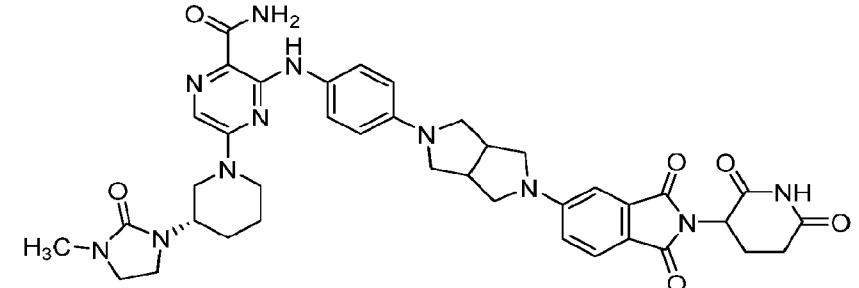
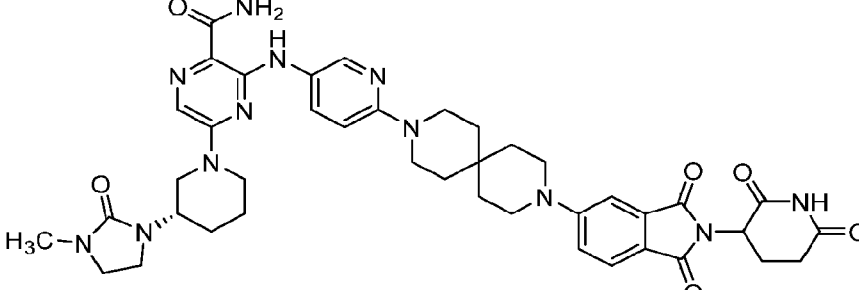
Compound Number	Structure
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Compound Number	Structure
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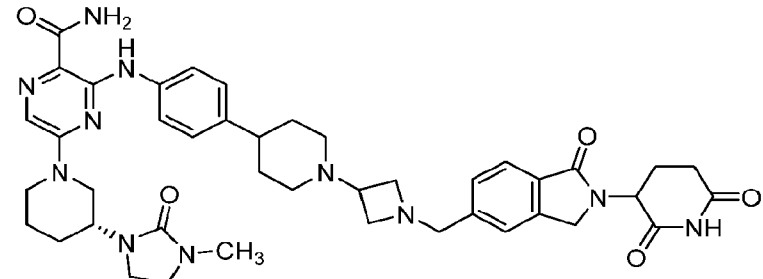
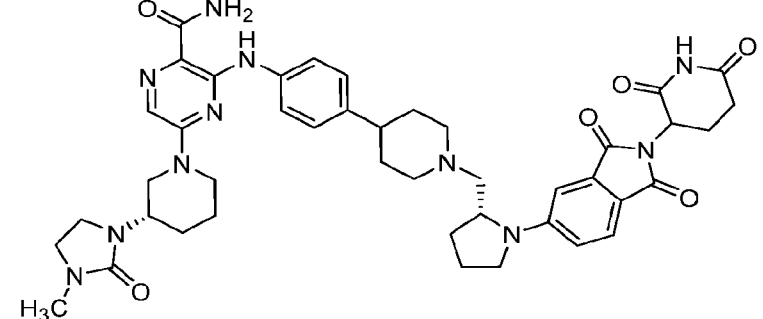
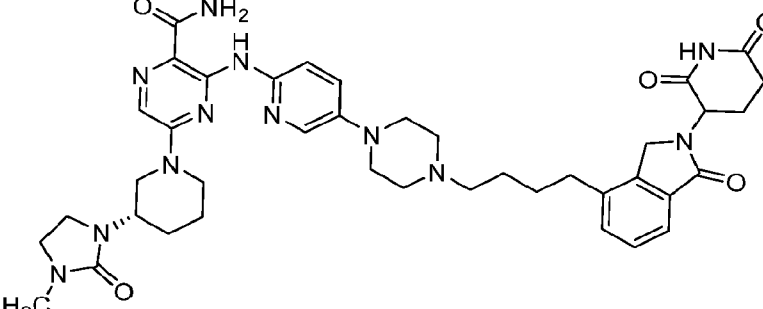
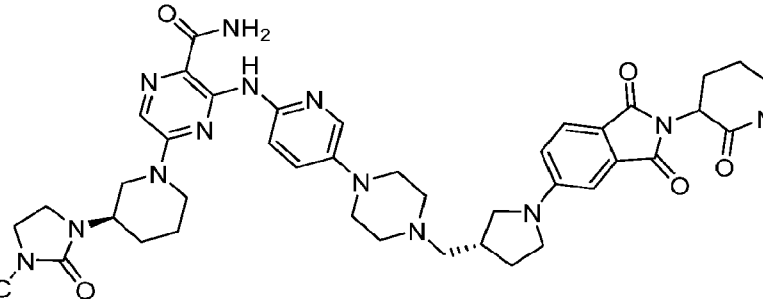
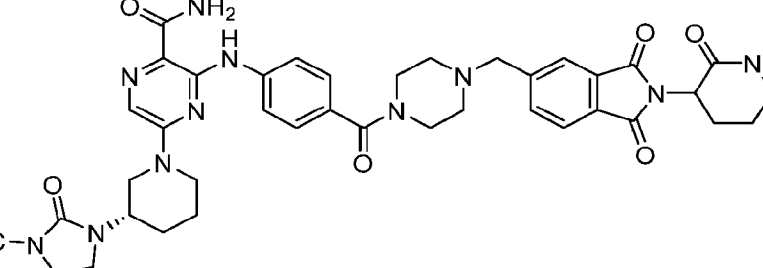
Compound Number	Structure
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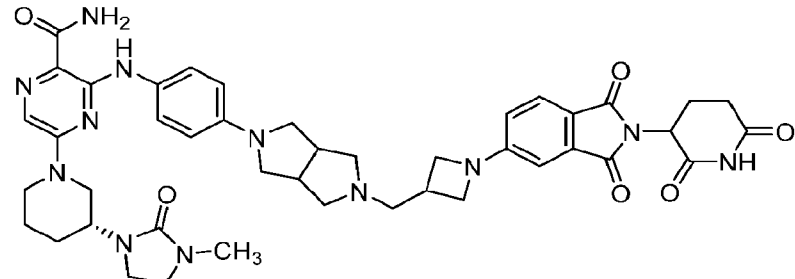
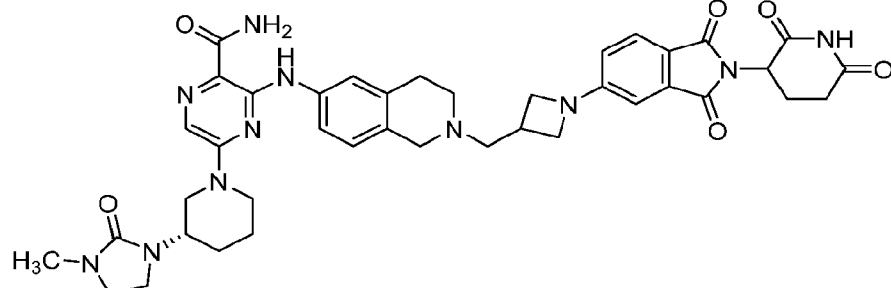
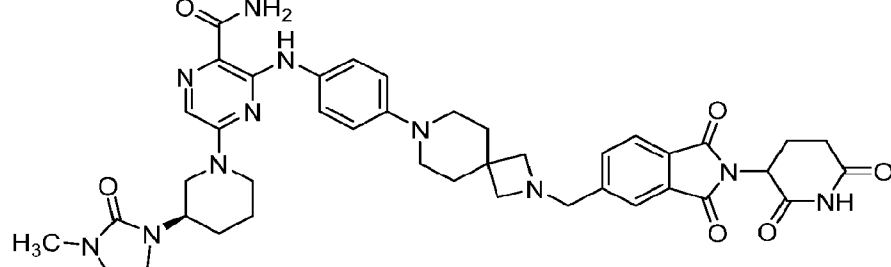
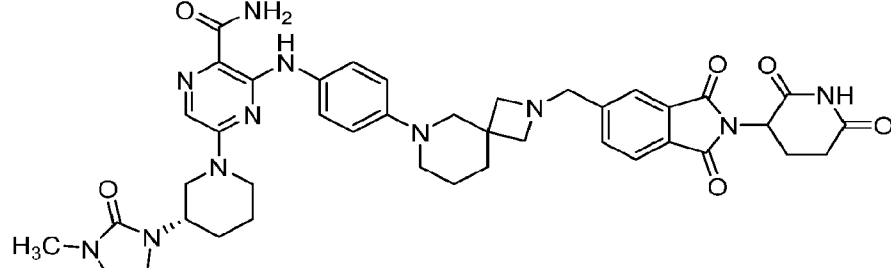
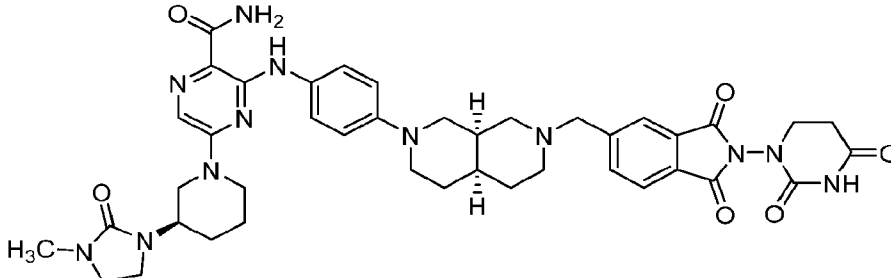
Compound Number	Structure
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Compound Number	Structure
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Compound Number	Structure
77	 Chemical structure of compound 77: A complex molecule featuring a pyrimidine ring substituted with a carboxamide group (H₂N-C(=O)-), a piperidine ring, and a 1-methyl-2-oxo-1,3-dihydroisindol-4-yl group. The pyrimidine ring is also substituted with a 1H-pyrazol-4-yl group, which is further linked via a piperidine ring to another piperidine ring, which is in turn linked to a 1,3-dioxo-1,3-dihydro-2H-indol-2-yl group.
78	 Chemical structure of compound 78: A complex molecule featuring a pyrimidine ring substituted with a carboxamide group (NH₂-C(=O)-), a piperidine ring, and a 1-methyl-2-oxo-1,3-dihydroisindol-4-yl group. The pyrimidine ring is also substituted with a 1H-pyrazol-4-yl group, which is further linked via a piperidine ring to a 1,3-dioxo-1,3-dihydro-2H-indol-2-yl group.
79	 Chemical structure of compound 79: A complex molecule featuring a pyrimidine ring substituted with a carboxamide group (NH₂-C(=O)-), a piperidine ring, and a 1-methyl-2-oxo-1,3-dihydroisindol-4-yl group. The pyrimidine ring is also substituted with a 1H-pyrazol-4-yl group, which is further linked via a piperidine ring to a 1,3-dioxo-1,3-dihydro-2H-indol-2-yl group.
80	 Chemical structure of compound 80: A complex molecule featuring a pyrimidine ring substituted with a carboxamide group (NH₂-C(=O)-), a piperidine ring, and a 1-methyl-2-oxo-1,3-dihydroisindol-4-yl group. The pyrimidine ring is also substituted with a 1H-pyrazol-4-yl group, which is further linked via a piperidine ring to a 1,3-dioxo-1,3-dihydro-2H-indol-2-yl group.

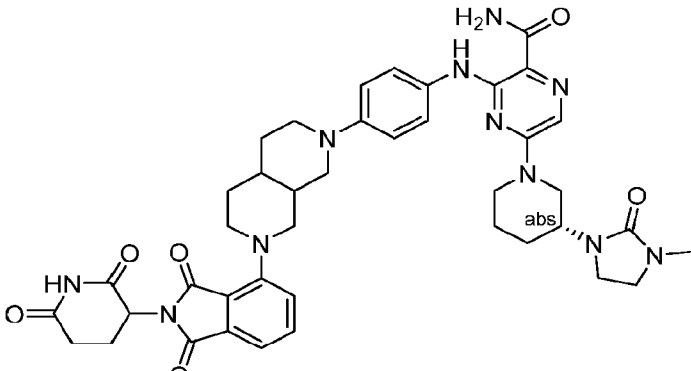
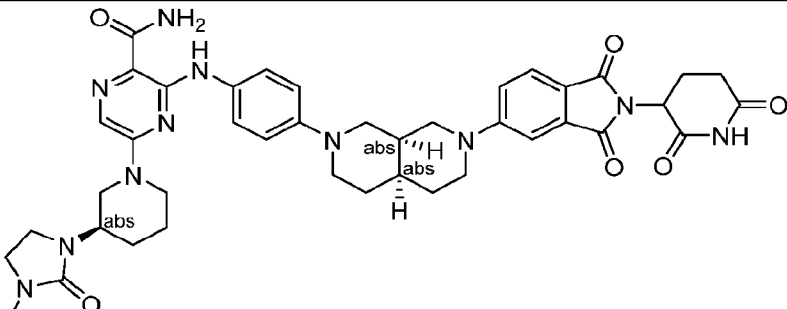
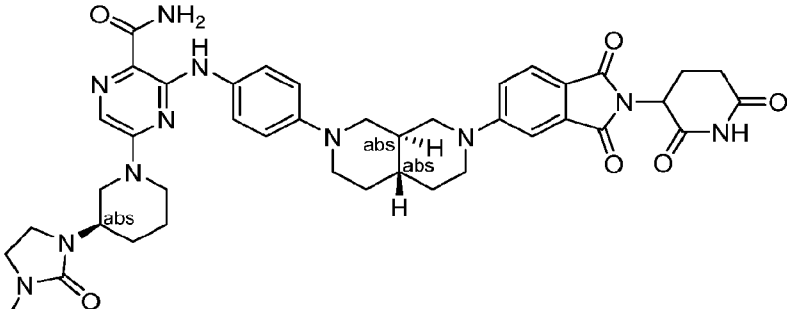
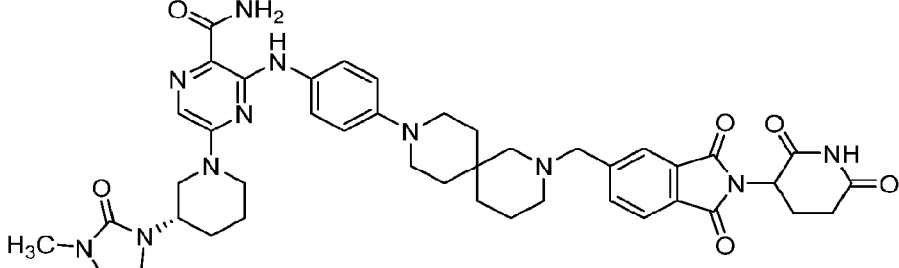
Compound Number	Structure
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Compound Number	Structure
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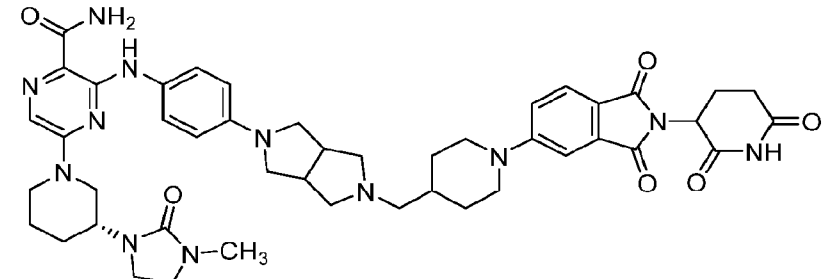
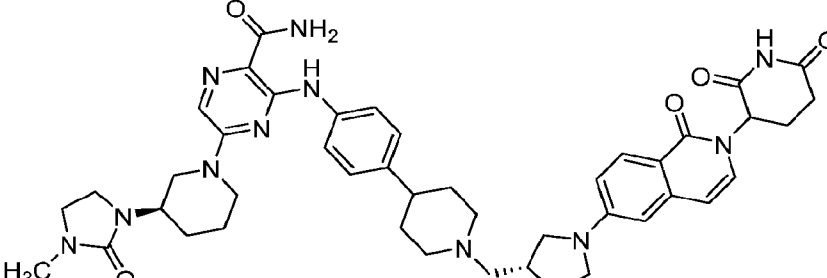
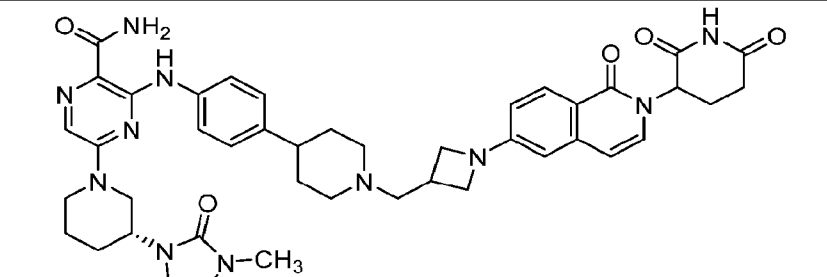
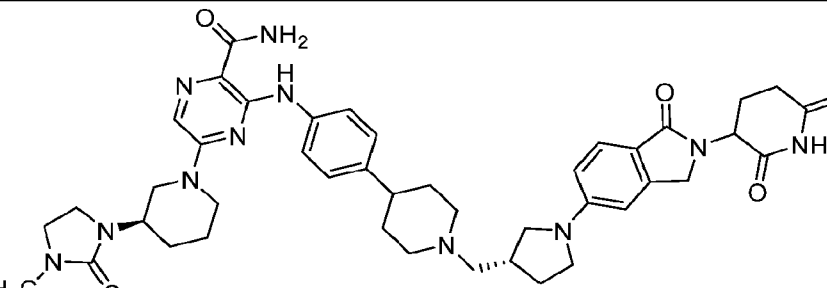
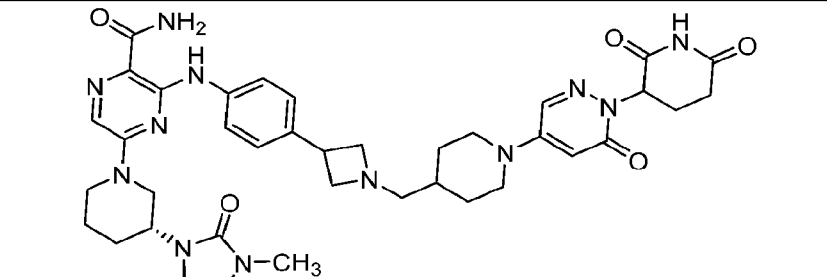
Compound Number	Structure
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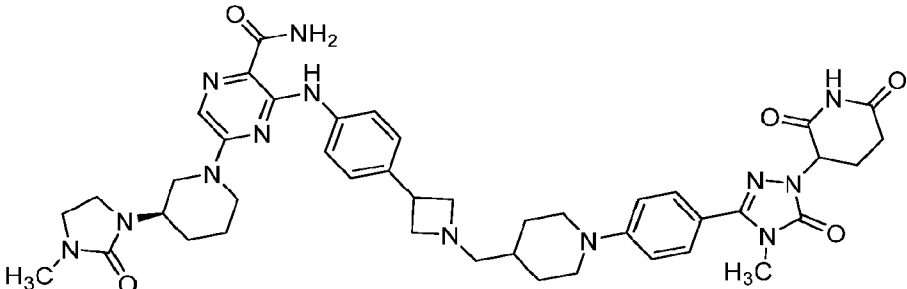
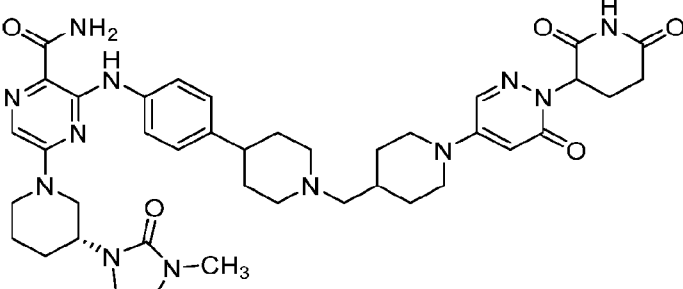
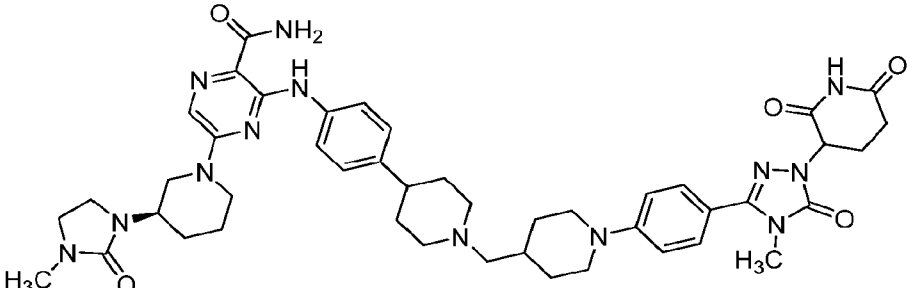
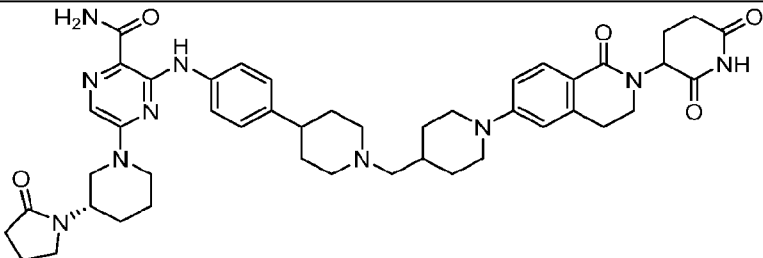
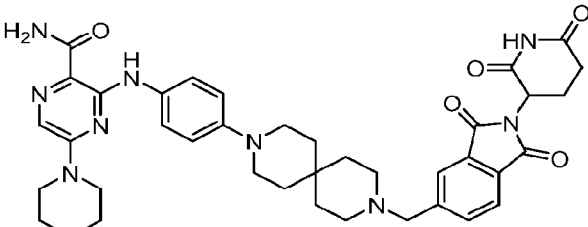
Compound Number	Structure
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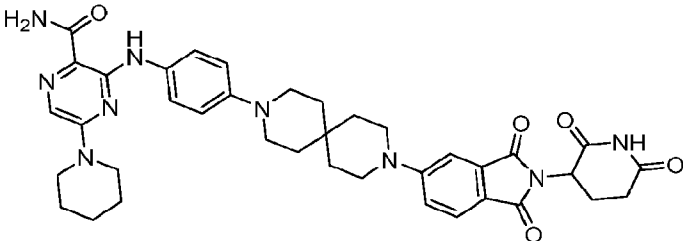
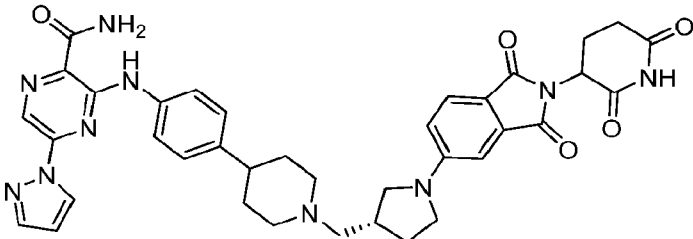
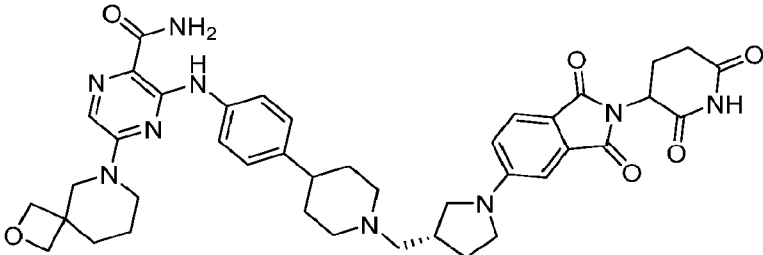
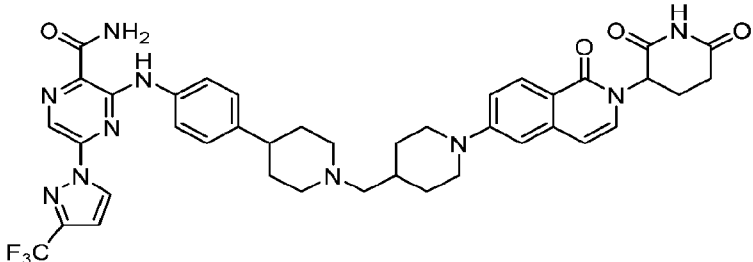
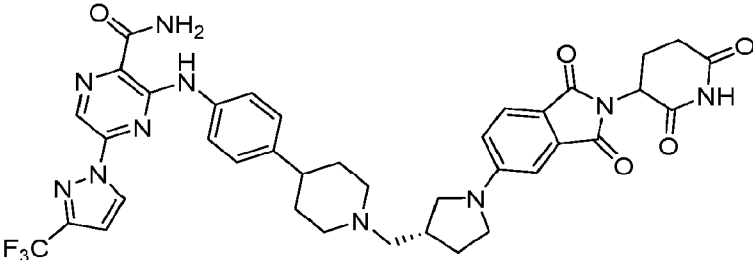
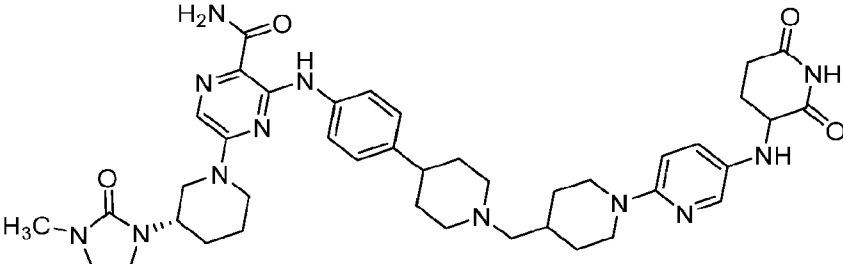
Compound Number	Structure
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Compound Number	Structure
105	 Chemical structure of compound 105: A complex molecule featuring a 1,2,3,4-tetrahydroquinolin-5(1H)-one core. This core is linked via its nitrogen atom to a 1,4-bis(piperidin-1-yl)benzene moiety. The second piperidine ring of this moiety is further connected to a 4-aminophenyl group. This phenyl group is linked via its nitrogen atom to a 1,2,4-triazine-3-carboxamide ring. The 1-position of the triazine is substituted with a 1-methyl-2-oxo-1,3-dihydroisindol-4-yl group. Stereochemistry is indicated with 'abs' (arbitrary) at the chiral center of the isindole ring.
106	 Chemical structure of compound 106: A complex molecule featuring a 1,2,3,4-tetrahydroquinolin-5(1H)-one core. This core is linked via its nitrogen atom to a 1,4-bis(piperidin-1-yl)benzene moiety. The second piperidine ring of this moiety is further connected to a 4-aminophenyl group. This phenyl group is linked via its nitrogen atom to a 1,2,4-triazine-3-carboxamide ring. The 1-position of the triazine is substituted with a 1-methyl-2-oxo-1,3-dihydroisindol-4-yl group. Stereochemistry is indicated with 'abs' (arbitrary) at the chiral center of the isindole ring and 'H' (hydrogen) at the chiral center of the piperidine ring.
107	 Chemical structure of compound 107: A complex molecule featuring a 1,2,3,4-tetrahydroquinolin-5(1H)-one core. This core is linked via its nitrogen atom to a 1,4-bis(piperidin-1-yl)benzene moiety. The second piperidine ring of this moiety is further connected to a 4-aminophenyl group. This phenyl group is linked via its nitrogen atom to a 1,2,4-triazine-3-carboxamide ring. The 1-position of the triazine is substituted with a 1-methyl-2-oxo-1,3-dihydroisindol-4-yl group. Stereochemistry is indicated with 'abs' (arbitrary) at the chiral center of the isindole ring and 'H' (hydrogen) at the chiral center of the piperidine ring.
108	 Chemical structure of compound 108: A complex molecule featuring a 1,2,3,4-tetrahydroquinolin-5(1H)-one core. This core is linked via its nitrogen atom to a 1,4-bis(piperidin-1-yl)benzene moiety. The second piperidine ring of this moiety is further connected to a 4-aminophenyl group. This phenyl group is linked via its nitrogen atom to a 1,2,4-triazine-3-carboxamide ring. The 1-position of the triazine is substituted with a 1-methyl-2-oxo-1,3-dihydroisindol-4-yl group. Stereochemistry is indicated with 'H₃C' (methyl) at the chiral center of the isindole ring and 'H' (hydrogen) at the chiral center of the piperidine ring.

Compound Number	Structure
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Compound Number	Structure
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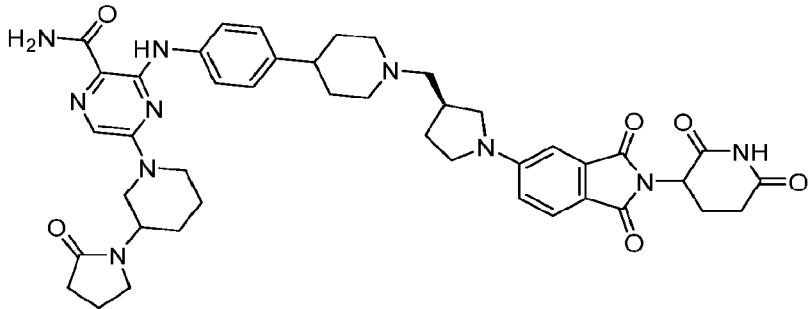
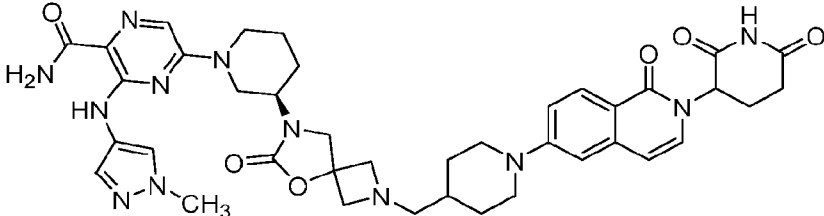
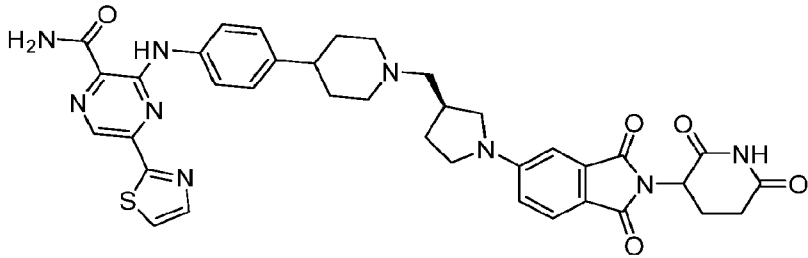
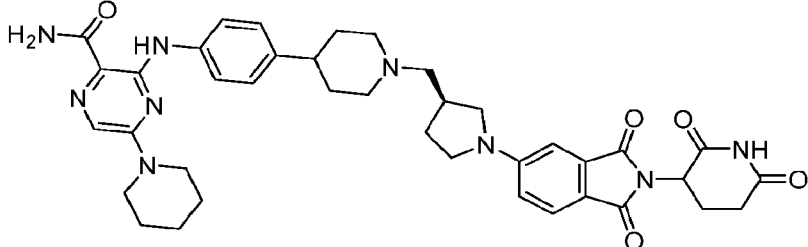
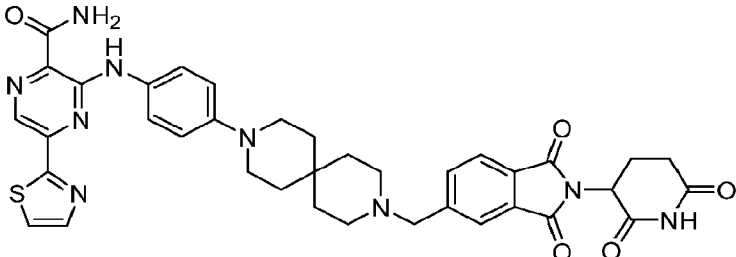
Compound Number	Structure
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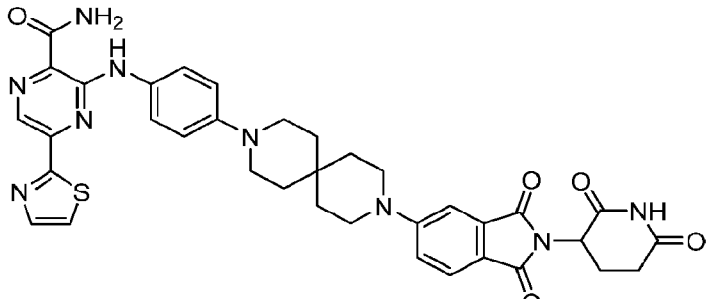
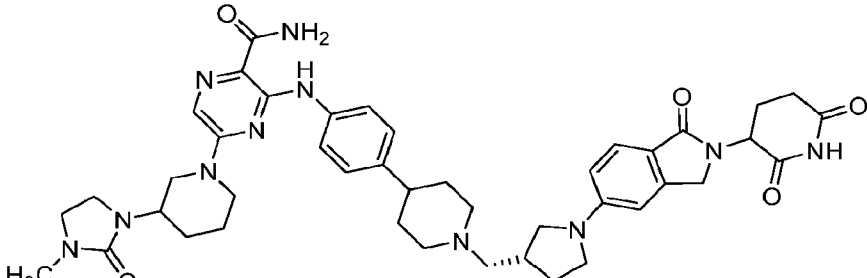
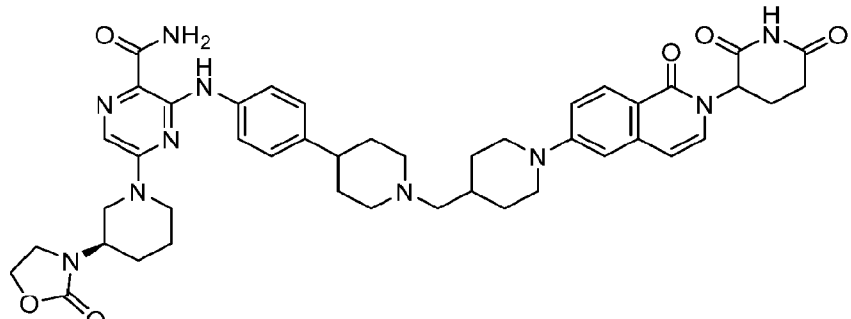
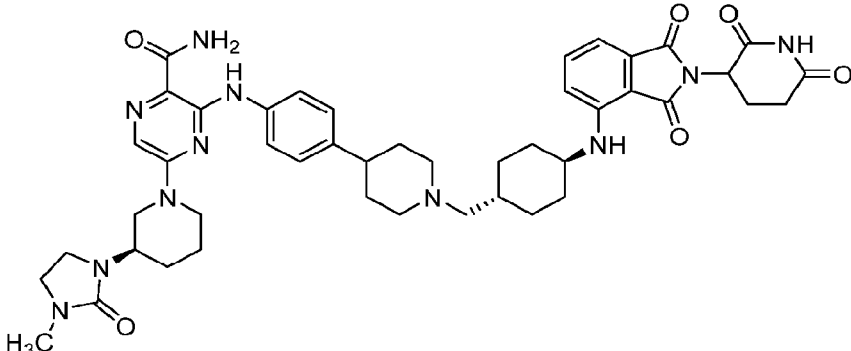
Compound Number	Structure
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Compound Number	Structure
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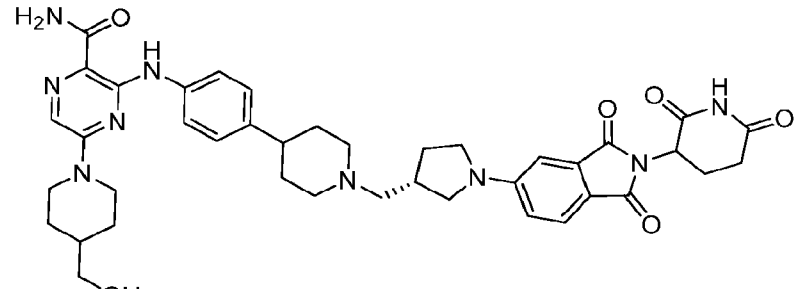
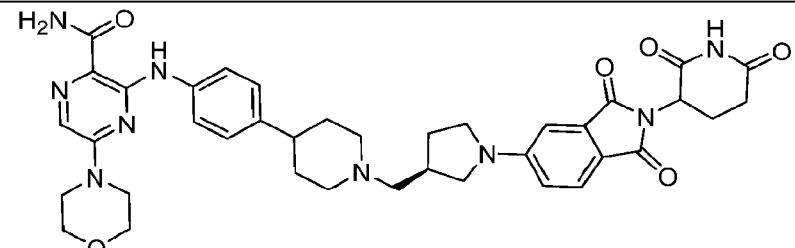
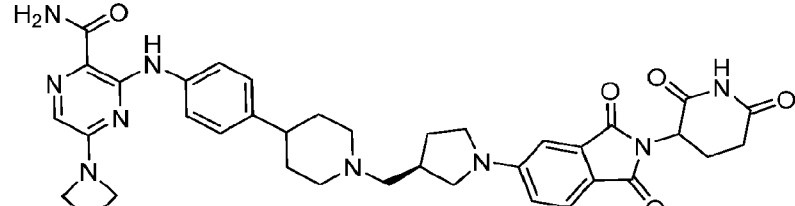
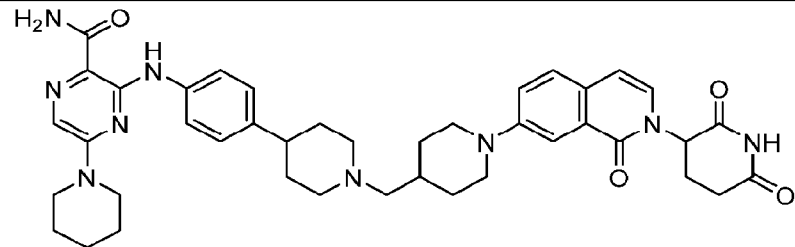
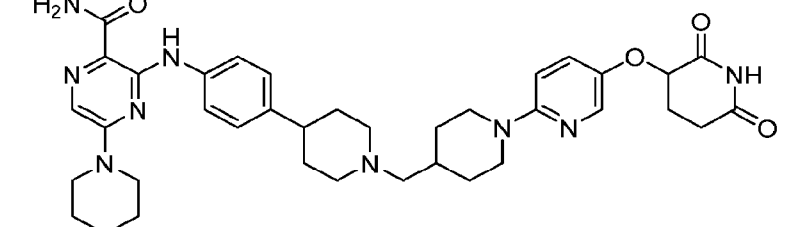
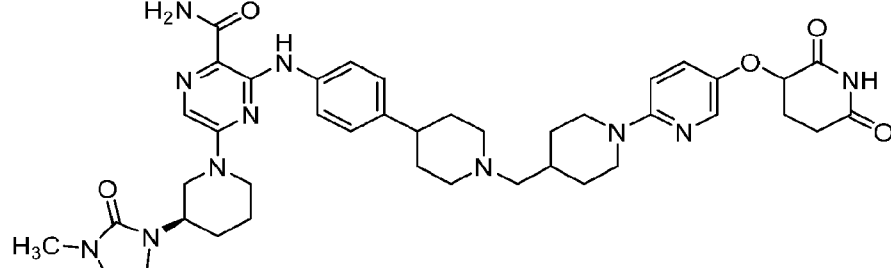
Compound Number	Structure
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Compound Number	Structure
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Compound Number	Structure
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Compound Number	Structure
151	 Chemical structure of compound 151: A thiazole ring substituted with a pyrimidin-2-ylideneamino group and a 4-(4,4'-bipiperidin-1-yl)phenyl group, connected via a methylene bridge to a 1,2,3,4-tetrahydroquinolin-5(1H)-one ring, which is further substituted with a 2,6-pyridinedione moiety.
152	 Chemical structure of compound 152: A thiazole ring substituted with a pyrimidin-2-ylideneamino group and a 4-(4-(4-methyl-1,3-dioxol-2-yl)piperidin-1-yl)phenyl group, connected via a methylene bridge to a 1,2,3,4-tetrahydroquinolin-5(1H)-one ring, which is further substituted with a 2,6-pyridinedione moiety.
153	 Chemical structure of compound 153: A thiazole ring substituted with a pyrimidin-2-ylideneamino group and a 4-(4-(4-methyl-1,3-dioxol-2-yl)piperidin-1-yl)phenyl group, connected via a methylene bridge to a 1,2,3,4-tetrahydroquinolin-5(1H)-one ring, which is further substituted with a 2,6-pyridinedione moiety.
154	 Chemical structure of compound 154: A thiazole ring substituted with a pyrimidin-2-ylideneamino group and a 4-(4-(4-methyl-1,3-dioxol-2-yl)piperidin-1-yl)phenyl group, connected via a methylene bridge to a 1,2,3,4-tetrahydroquinolin-5(1H)-one ring, which is further substituted with a 2,6-pyridinedione moiety.

Compound Number	Structure
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Compound Number	Structure
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Compound Number	Structure
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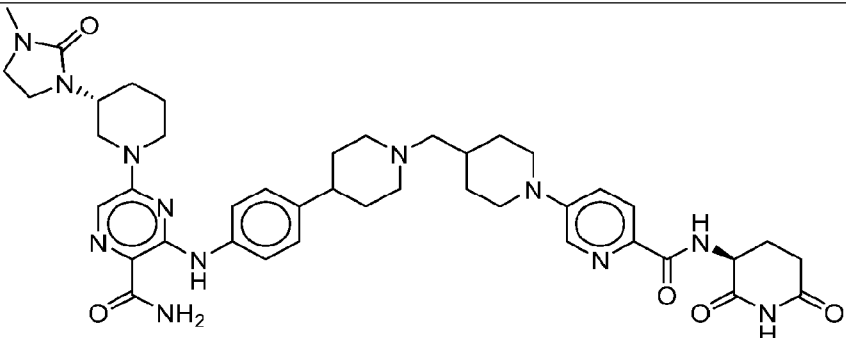
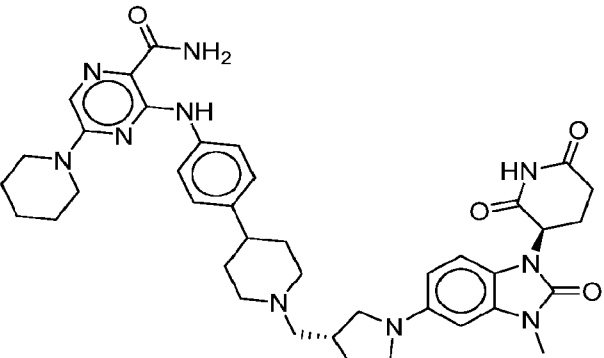
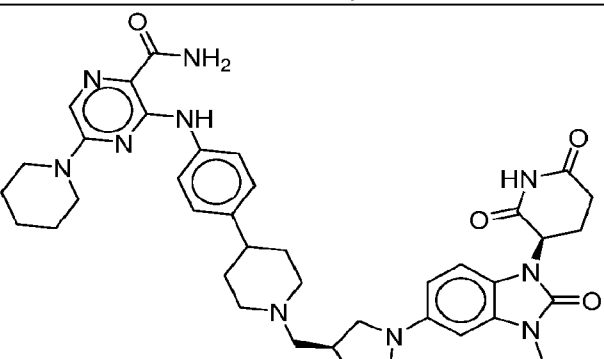
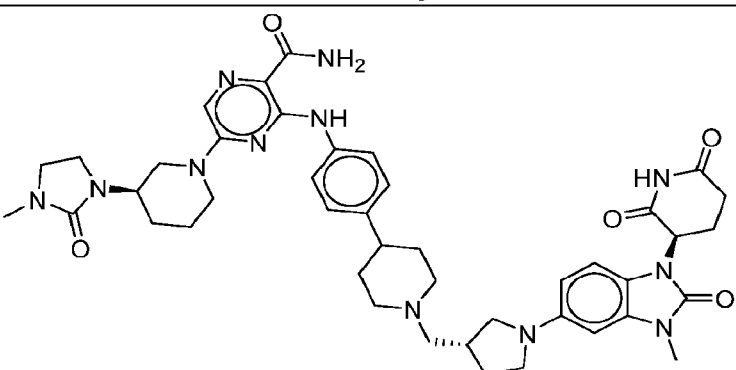
Compound Number	Structure
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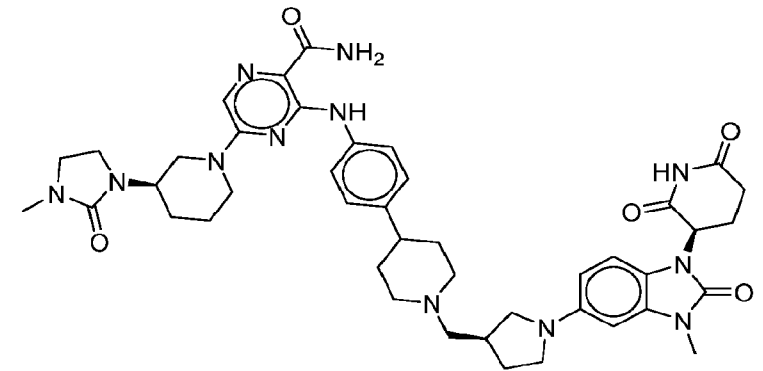
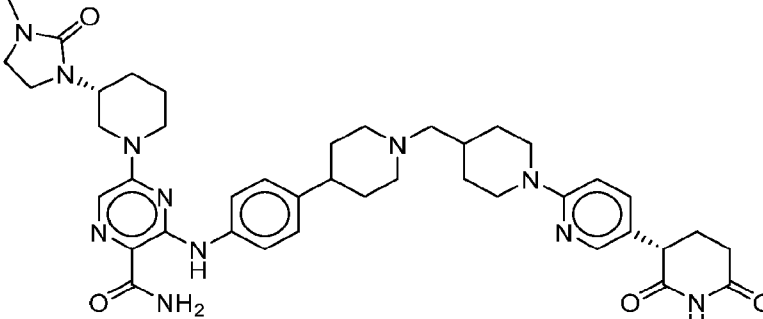
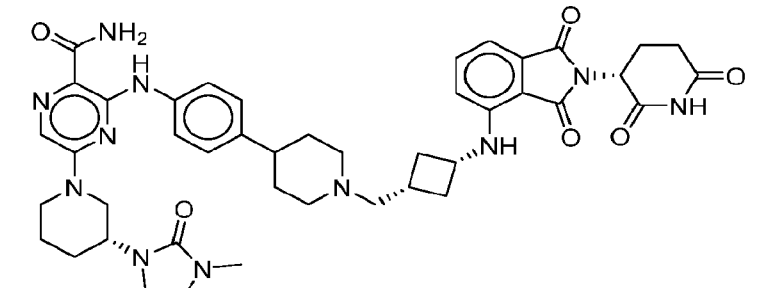
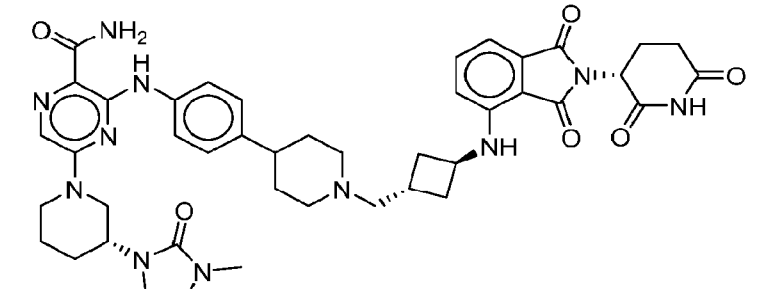
Compound Number	Structure
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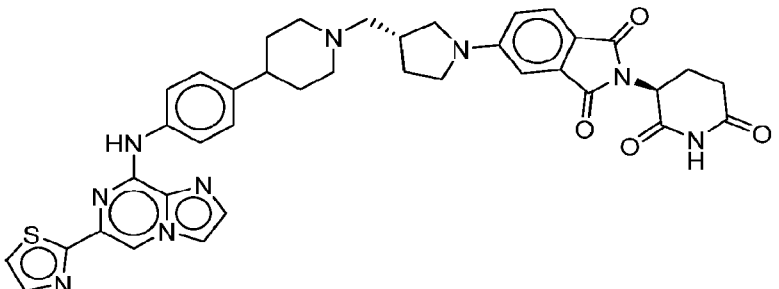
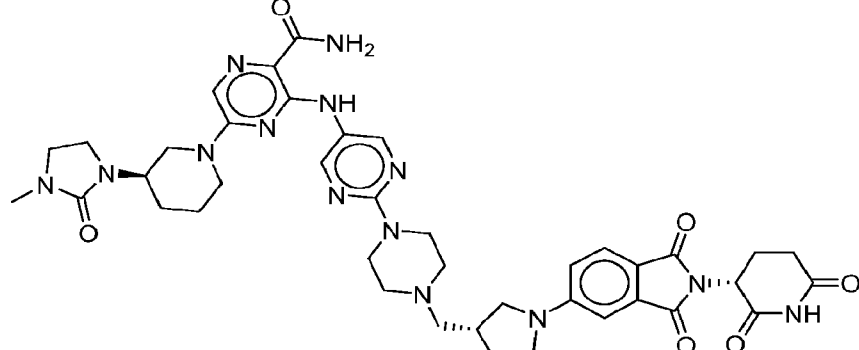
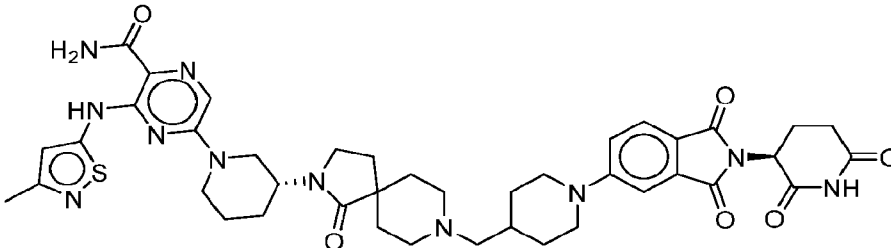
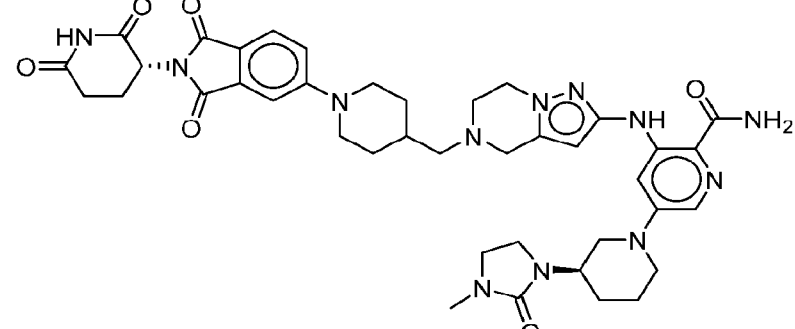
Compound Number	Structure
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Compound Number	Structure
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Compound Number	Structure
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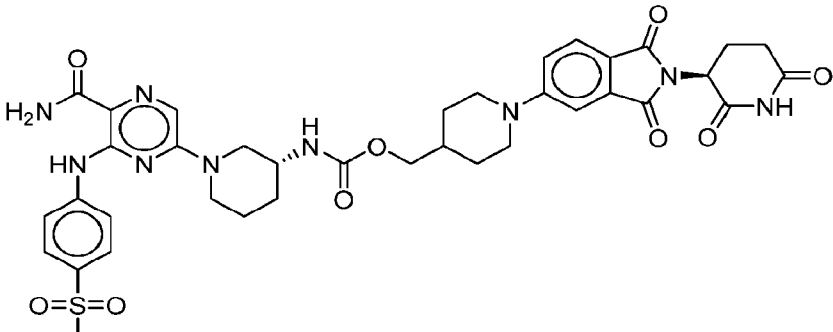
Compound Number	Structure
195	 Chemical structure of compound 195: A complex molecule featuring a central benzene ring connected to a pyrimidine ring (with an amide group) and a pyridine ring (with an amide group). The pyrimidine ring is also connected to a morpholine ring, which is further connected to a morpholine ring. The pyridine ring is connected to a morpholine ring, which is further connected to a morpholine ring. The molecule also includes a morpholine ring and a morpholine ring.
196	 Chemical structure of compound 196: A complex molecule featuring a central benzene ring connected to a pyrimidine ring (with an amide group) and a pyridine ring (with an amide group). The pyrimidine ring is also connected to a morpholine ring, which is further connected to a morpholine ring. The pyridine ring is connected to a morpholine ring, which is further connected to a morpholine ring. The molecule also includes a morpholine ring and a morpholine ring.
197	 Chemical structure of compound 197: A complex molecule featuring a central benzene ring connected to a pyrimidine ring (with an amide group) and a pyridine ring (with an amide group). The pyrimidine ring is also connected to a morpholine ring, which is further connected to a morpholine ring. The pyridine ring is connected to a morpholine ring, which is further connected to a morpholine ring. The molecule also includes a morpholine ring and a morpholine ring.
198	 Chemical structure of compound 198: A complex molecule featuring a central benzene ring connected to a pyrimidine ring (with an amide group) and a pyridine ring (with an amide group). The pyrimidine ring is also connected to a morpholine ring, which is further connected to a morpholine ring. The pyridine ring is connected to a morpholine ring, which is further connected to a morpholine ring. The molecule also includes a morpholine ring and a morpholine ring.

Compound Number	Structure
199	 Chemical structure of compound 199: A complex molecule featuring a central pyrimidine ring substituted with an amide group (NH₂) and an amine group (NH). The amine group is linked to a phenyl ring, which is further connected to a piperidine ring. This piperidine ring is linked to a cyclohexane ring, which is in turn linked to a pyrrolidine ring. The pyrrolidine ring is substituted with a methyl group and a carbonyl group. The cyclohexane ring is also linked to a piperidine ring, which is connected to a phenyl ring. This phenyl ring is linked to a piperidine ring, which is connected to a pyrrolidine ring. The pyrrolidine ring is substituted with a methyl group and a carbonyl group. The cyclohexane ring is also linked to a piperidine ring, which is connected to a phenyl ring. This phenyl ring is linked to a piperidine ring, which is connected to a pyrrolidine ring. The pyrrolidine ring is substituted with a methyl group and a carbonyl group.
200	 Chemical structure of compound 200: A complex molecule featuring a central pyrimidine ring substituted with an amide group (NH₂) and an amine group (NH). The amine group is linked to a phenyl ring, which is further connected to a piperidine ring. This piperidine ring is linked to a cyclohexane ring, which is in turn linked to a pyrrolidine ring. The pyrrolidine ring is substituted with a methyl group and a carbonyl group. The cyclohexane ring is also linked to a piperidine ring, which is connected to a phenyl ring. This phenyl ring is linked to a piperidine ring, which is connected to a pyrrolidine ring. The pyrrolidine ring is substituted with a methyl group and a carbonyl group. The cyclohexane ring is also linked to a piperidine ring, which is connected to a phenyl ring. This phenyl ring is linked to a piperidine ring, which is connected to a pyrrolidine ring. The pyrrolidine ring is substituted with a methyl group and a carbonyl group.
201	 Chemical structure of compound 201: A complex molecule featuring a central pyrimidine ring substituted with an amide group (NH₂) and an amine group (NH). The amine group is linked to a phenyl ring, which is further connected to a piperidine ring. This piperidine ring is linked to a cyclohexane ring, which is in turn linked to a pyrrolidine ring. The pyrrolidine ring is substituted with a methyl group and a carbonyl group. The cyclohexane ring is also linked to a piperidine ring, which is connected to a phenyl ring. This phenyl ring is linked to a piperidine ring, which is connected to a pyrrolidine ring. The pyrrolidine ring is substituted with a methyl group and a carbonyl group. The cyclohexane ring is also linked to a piperidine ring, which is connected to a phenyl ring. This phenyl ring is linked to a piperidine ring, which is connected to a pyrrolidine ring. The pyrrolidine ring is substituted with a methyl group and a carbonyl group.
202	 Chemical structure of compound 202: A complex molecule featuring a central pyrimidine ring substituted with an amide group (NH₂) and an amine group (NH). The amine group is linked to a phenyl ring, which is further connected to a piperidine ring. This piperidine ring is linked to a cyclohexane ring, which is in turn linked to a pyrrolidine ring. The pyrrolidine ring is substituted with a methyl group and a carbonyl group. The cyclohexane ring is also linked to a piperidine ring, which is connected to a phenyl ring. This phenyl ring is linked to a piperidine ring, which is connected to a pyrrolidine ring. The pyrrolidine ring is substituted with a methyl group and a carbonyl group. The cyclohexane ring is also linked to a piperidine ring, which is connected to a phenyl ring. This phenyl ring is linked to a piperidine ring, which is connected to a pyrrolidine ring. The pyrrolidine ring is substituted with a methyl group and a carbonyl group.

Compound Number	Structure
203	 Chemical structure of compound 203: A complex molecule featuring a thiazole ring substituted with a pyrazole ring, which is further substituted with a benzyl group. This benzyl group is connected via a piperidine ring to a cyclopentyl ring, which is in turn connected to a phthalimide ring. The phthalimide ring is substituted with a 2,6-pyridinedicarboxamide group.
204	 Chemical structure of compound 204: A complex molecule featuring a thiazole ring substituted with a pyrazole ring, which is further substituted with a benzyl group. This benzyl group is connected via a piperidine ring to a cyclopentyl ring, which is in turn connected to a phthalimide ring. The phthalimide ring is substituted with a 2,6-pyridinedicarboxamide group.
205	 Chemical structure of compound 205: A complex molecule featuring a thiazole ring substituted with a pyrazole ring, which is further substituted with a benzyl group. This benzyl group is connected via a piperidine ring to a cyclopentyl ring, which is in turn connected to a phthalimide ring. The phthalimide ring is substituted with a 2,6-pyridinedicarboxamide group.
206	 Chemical structure of compound 206: A complex molecule featuring a thiazole ring substituted with a pyrazole ring, which is further substituted with a benzyl group. This benzyl group is connected via a piperidine ring to a cyclopentyl ring, which is in turn connected to a phthalimide ring. The phthalimide ring is substituted with a 2,6-pyridinedicarboxamide group.

Compound Number	Structure
207	
208	
209	
210	
211	

Compound Number	Structure
212	
213	
214	
215	
216	
217	

Compound Number	Structure
218	

FORMULATIONS AND ADMINISTRATION

[00261] Pharmaceutical Compositions

[00262] The compounds described herein can be formulated into pharmaceutical compositions that further comprise a pharmaceutically acceptable carrier, diluent, adjuvant, or vehicle. In one embodiment, this disclosure provides a pharmaceutical composition comprising a compound described above, and a pharmaceutically acceptable carrier, diluent, adjuvant, or vehicle. In one embodiment, this disclosure is a pharmaceutical composition comprising an effective amount of a compound of this disclosure or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent, adjuvant, or vehicle. Pharmaceutically acceptable carriers include, for example, pharmaceutical diluents, excipients, or carriers suitably selected with respect to the intended form of administration, and consistent with conventional pharmaceutical practices.

[00263] According to another embodiment, the description provides a composition comprising a compound herein or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. Pharmaceutical compositions of this description comprise a therapeutically effective amount of a compound of Formula (A1), (A), (B), (C), (D), (D-1), (D-2), (E), (F), (G), (H), (J), (K), (M), (I), (I-A), (I-B), (II), (II-A), (II-B), (III), (IV), and/or (X) wherein a "therapeutically effective amount" is an amount that is (a) effective to measurably degrade BTK (or reduce the amount of BTK) in a biological sample or in a patient; or (b) effective in treating and/or ameliorating a disease or disorder that is mediated by BTK.

[00264] The term "patient," as used herein, means an animal, alternatively a mammal, and alternatively a human.

[00265] It also will be appreciated that certain compounds of this disclosure can exist in free

form for treatment, or where appropriate, as a pharmaceutically acceptable derivative (e.g., a salt) thereof. According to this disclosure, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable prodrugs, salts, esters, salts of such esters, or any other adduct/educt or derivative that upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[00266] As used herein, the term "pharmaceutically acceptable salt" refers to those salts that are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like.

[00267] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* **1977**, *66*, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this description include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts include salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid; or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid; or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4} \text{ alkyl})_4$ salts. This description also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such

as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[00268] A pharmaceutically acceptable carrier may contain inert ingredients that do not unduly inhibit the biological activity of the compounds. The pharmaceutically acceptable carriers should be biocompatible, for example, non-toxic, non-inflammatory, non-immunogenic, or devoid of other undesired reactions or side-effects upon the administration to a subject. Standard pharmaceutical formulation techniques can be employed.

[00269] The pharmaceutically acceptable carrier, adjuvant, or vehicle, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants, and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds described herein, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, the use of such conventional carrier medium is contemplated to be within the scope of this description. As used herein, the phrase "side effects" encompasses unwanted and adverse effects of a therapy (e.g., a prophylactic or therapeutic agent). Side effects are always unwanted, but unwanted effects are not necessarily adverse. An adverse effect from a therapy (e.g., prophylactic or therapeutic agent) might be harmful, uncomfortable, or risky. Side effects include, but are not limited to, fever, chills, lethargy, gastrointestinal toxicities (including gastric and intestinal ulcerations and erosions), nausea, vomiting, neurotoxicities, nephrotoxicities, renal toxicities (including such conditions as papillary necrosis and chronic interstitial nephritis), hepatic toxicities (including elevated serum liver enzyme levels), myelotoxicities (including leukopenia, myelosuppression, thrombocytopenia and anemia), dry mouth, metallic taste, prolongation of gestation, weakness, somnolence, pain (including muscle pain, bone pain, and headache), hair loss, asthenia, dizziness, extra-pyramidal symptoms, akathisia, cardiovascular disturbances, and sexual dysfunction.

[00270] Some examples of materials that can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins (such as human serum albumin), buffer substances (such as tween 80, phosphates,

glycine, sorbic acid, or potassium sorbate), partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes (such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, or zinc salts), colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, methylcellulose, hydroxypropyl methylcellulose, wool fat, sugars such as lactose, glucose, and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; glycols such as propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring, and perfuming agents. Preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[00271] As used herein, the term "measurably degrade," means a measurable reduction in (a) BTK activity, between a sample comprising a compound of this description and a BTK and an equivalent sample comprising a BTK in the absence of said compound; or (b) the concentration of the BTK in a sample over time.

ADMINISTRATION

[00272] The compositions of this disclosure are administered orally. The pharmaceutically acceptable compositions of this description 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 commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring, or coloring agents also may be added.

[00273] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and

elixirs. In addition to the active compounds herein, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions also can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00274] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound herein is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay; and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets, and pills, the dosage form also may comprise buffering agents.

[00275] Solid compositions of a similar type also may be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. Solid dosage forms optionally may contain opacifying agents. These solid dosage forms also can be of a composition such that they release the active ingredient(s) only, for example, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type also may be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00276] The active compounds herein also can be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings, and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms also may comprise, as is normal practice, additional substances other than inert diluents, for example, tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms also may comprise buffering agents. They may optionally contain opacifying agents and also can be of a composition such that they release the active ingredient(s) only, for example, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00277] The compounds of the description are formulated in dosage unit form for ease of administration and uniformity of dosage. As used herein, the phrase "dosage unit form" refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of this disclosure will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts.

[00278] The amount of the compounds of this disclosure that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration, and other factors. The compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the compound or inhibitor can be administered to a patient receiving these compositions.

[00279] Depending upon the particular condition, or disease, to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that condition, also may be present in the compositions of this disclosure. As used herein, additional

therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated."

[00280] For example, chemotherapeutic agents or other anti-proliferative agents may be combined with the compounds of this disclosure to treat proliferative diseases and cancer. Examples of known chemotherapeutic agents include, but are not limited to, PI3K inhibitors (e.g., idelalisib and copanlisib), BCL-2 inhibitors (e.g., venetoclax), BTK inhibitors (e.g., ibrutinib and acalabrutinib), etoposide, CD20 antibodies (e.g., rituximab, ocrelizumab, obinutuzumab, ofatumumab, ibritumomab tiuxetan, tositumomab, and ublituximab), aletuzumab, bendamustine, cladribine, doxorubicin, chlorambucil, prednisone, midostaurin, lenalidomide, pomalidomide, checkpoint inhibitors (e.g., ipilimumab, nivolumab, pembolizumab, atezolizumab, avelumab, durvalumab), engineered cell therapy (e.g., CAR-T therapy - Kymriah®, Yescarta®), Gleevec™, adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, and platinum derivatives.

[00281] And, in some instances, radiation therapy is administered during the treatment course wherein a compound of this disclosure (or a pharmaceutically acceptable salt thereof) is administered to a patient in need thereof.

[00282] Other examples of agents with which the compounds or inhibitors of this disclosure also may be combined include, without limitation, treatments for Alzheimer's Disease such as Aricept® and Exelon®; treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating Multiple Sclerosis (MS) such as beta interferon (e.g., Avonex® and Rebif®), Copaxone®, and mitoxantrone; treatments for asthma such as albuterol and Singulair®; agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophosphamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as

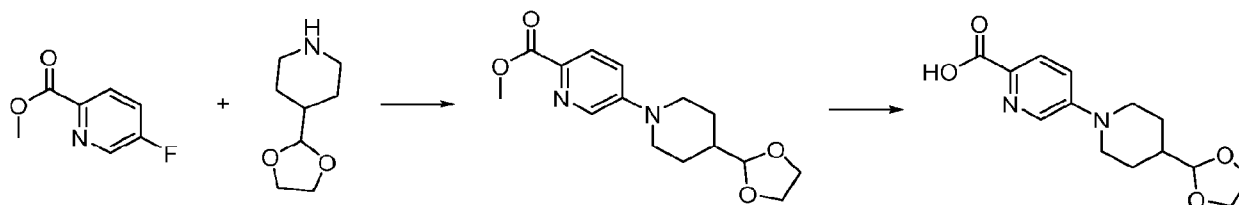
corticosteroids, anti-leukemic agents, and growth factors; and agents for treating immunodeficiency disorders such as gamma globulin.

[00283] The amount of additional therapeutic agent present in the compositions of this disclosure will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. The amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

EXAMPLES

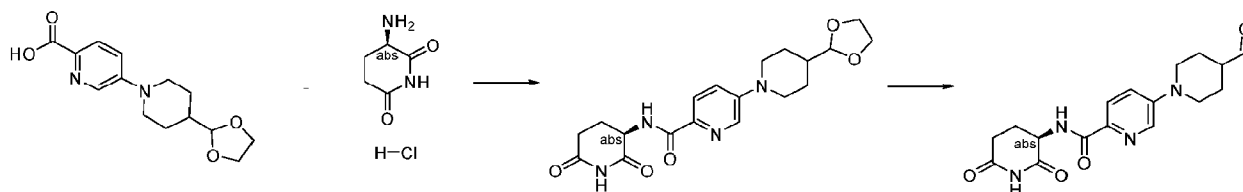
[00284] Additional embodiments are disclosed in further detail in the following examples, which are not in any way intended to limit the scope of the claims.

Example 1



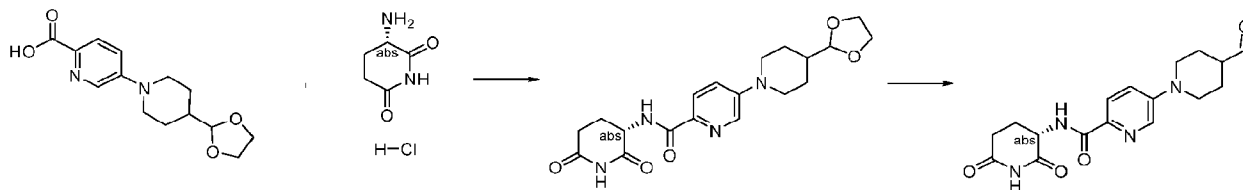
[00285] Synthesis of methyl 5-(4-(1,3-dioxolan-2-yl)piperidin-1-yl)picolinate: A mixture of methyl 5-fluoropyridine-2-carboxylate (1020 mg, 6.58 mmol), 4-(1,3-dioxolan-2-yl)piperidine (1033 mg, 6.58 mmol), *N,N*-diisopropylethylamine (2.29 mL, 13.15 mmol) and DMSO (6.5 mL) was allowed to stir at 100 °C overnight. The mixture was cooled to room temperature. H₂O (8.1 mL) was added and the mixture was filtered. The solids were collected and dried to afford methyl 5-[4-(1,3-dioxolan-2-yl)piperidin-1-yl]pyridine-2-carboxylate (1.90 g, 98.8%). LCMS: C₁₅H₂₀N₂O₄ requires: 292, found: *m/z* = 293 [M+H]⁺.

[00286] Synthesis of 5-(4-(1,3-dioxolan-2-yl)piperidin-1-yl)picolinic acid: A mixture of methyl 5-[4-(1,3-dioxolan-2-yl)piperidin-1-yl]pyridine-2-carboxylate (1.90 g, 6.50 mmol), sodium hydroxide (324.95 mg, 8.12 mmol), THF (8.4 mL) and water (8.4 mL) were allowed to stir at rt for 2 h. The volatiles were removed. MeCN (11.8 mL) was added and the mixture was stirred at rt for 20 min. The mixture was filtered and the solids were collected to yield 5-[4-(1,3-dioxolan-2-yl)piperidin-1-yl]pyridine-2-carboxylic acid (1.68 g, 92.9%). LCMS: C₁₄H₁₈N₂O₄ requires: 278, found: *m/z* = 279 [M+H]⁺.

Example 2

[00287] Synthesis of (R)-5-(4-(1,3-dioxolan-2-yl)piperidin-1-yl)-N-(2,6-dioxopiperidin-3-yl)picolinamide: A mixture of 5-[4-(1,3-dioxolan-2-yl)piperidin-1-yl]pyridine-2-carboxylic acid (196 mg, 0.70 mmol), (3R)-3-aminopiperidine-2,6-dione hydrochloride (115 mg, 0.70 mmol), [(dimethylamino)({[1,2,3]triazolo[4,5-b]pyridin-3-yl}oxy)methylidene]dimethylazanium; hexafluoro-lambda5-phosphanuide (535 mg, 1.41 mmol), *N,N*-diisopropylethylamine (0.31 mL, 1.76 mmol), and DMF (2 mL) was allowed to stir at rt for 30 min. 0.1 M HCl (1 mL) in water was added and the mixture was allowed to stir at rt for 15 min. The mixture was filtered, washing with cold H₂O. The solids were collected to afford 5-[4-(1,3-dioxolan-2-yl)piperidin-1-yl]-*N*-[(3R)-2,6-dioxopiperidin-3-yl]pyridine-2-carboxamide (0.272 g, 99.4%). LCMS: C₁₉H₂₄N₄O₅ requires: 388, found: *m/z* = 389 [M+H]⁺.

[00288] Synthesis of (R)-N-(2,6-dioxopiperidin-3-yl)-5-(4-formylpiperidin-1-yl)picolinamide: A mixture of 5-[4-(1,3-dioxolan-2-yl)piperidin-1-yl]-*N*-[(3R)-2,6-dioxopiperidin-3-yl]pyridine-2-carboxamide (259 mg, 0.67 mmol), THF (3 mL) and 2 M HCl (3 mL) was allowed to stir at 50 °C for 1 h. Saturated aq. NaHCO₃ was added until pH~7-8. CHCl₃/iPrOH was added, and the organic layer was dried with MgSO₄, filtered, and concentrated. MeCN was added and the mixture was sonicated for ~10 min. The mixture was filtered and the solids were collected to afford (R)-*N*-(2,6-dioxopiperidin-3-yl)-5-(4-formylpiperidin-1-yl)picolinamide (0.155g, 68%). LCMS: C₁₇H₂₀N₄O₄ requires: 344, found: *m/z* = 345 [M+H]⁺.

Example 3

[00289] Synthesis of (S)-5-(4-(1,3-dioxolan-2-yl)piperidin-1-yl)-N-(2,6-dioxopiperidin-3-yl)picolinamide: A mixture of (3S)-3-aminopiperidine-2,6-dione hydrochloride (118.28 mg, 0.72 mmol), 5-[4-(1,3-dioxolan-2-yl)piperidin-1-yl]pyridine-2-carboxylic acid (200 mg, 0.72

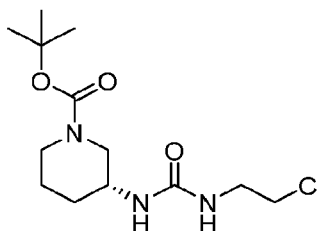
mmol), [(dimethylamino)({[1,2,3]triazolo[4,5-b]pyridin-3-yloxy})methylidene]dimethylazanium; hexafluoro-lambda5-phosphanuide (546 mg, 1.44 mmol), *N,N*-diisopropylethylamine (0.32 mL, 1.80 mmol), and DMF (2 mL) was allowed to stir at rt for 30 min. Aq. 1M HCl was added and the mixture was stirred at rt for 15 min. The mixture was filtered and the solids were collected as 5-[4-(1,3-dioxolan-2-yl)piperidin-1-yl]-*N*-[(3*S*)-2,6-dioxopiperidin-3-yl]pyridine-2-carboxamide (0.2750 g, 99%). LCMS: C₁₉H₂₄N₄O₅ requires: 388, found: *m/z* = 389 [M+H]⁺.

[00290] Synthesis of (*S*)-*N*-(2,6-dioxopiperidin-3-yl)-5-(4-formylpiperidin-1-yl)picolinamide: A mixture of 5-[4-(1,3-dioxolan-2-yl)piperidin-1-yl]-*N*-[(3*S*)-2,6-dioxopiperidin-3-yl]pyridine-2-carboxamide (332 mg, 0.85 mmol), THF (3 mL), and 2M HCl (3 mL) was allowed to stir at 50 °C for 1 h. Saturated aq. NaHCO₃ was added until pH~7-8. CHCl₃/iPrOH was added, and the organic layer was dried with MgSO₄, filtered, and concentrated. MeCN was added and the mixture was sonicated for ~10 min. The mixture was filtered and the solids were collected to afford (*S*)-*N*-(2,6-dioxopiperidin-3-yl)-5-(4-formylpiperidin-1-yl)picolinamide (175 mg, 60%). LCMS: C₁₇H₂₀N₄O₄ requires: 344, found: *m/z* = 345 [M+H]⁺.

Example 4

Synthesis of 5-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]-3-{[4-(piperazin-1-yl)phenyl]amino}pyrazine-2-carboxamide:

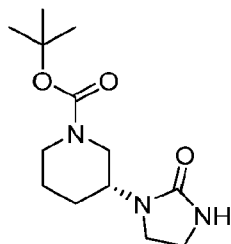
[00291] *tert*-butyl (3*R*)-3-[[2-(chloroethyl)carbamoyl]amino]piperidine-1-carboxylate



[00292] To a mixture of *tert*-butyl (3*R*)-3-aminopiperidine-1-carboxylate (25.0 g, 125 mmol) and triethylamine (34.8 mL, 25.3 g, 250 mmol) in DCM (250 mL) was added 1-chloro-2-isocyanatoethane (12.8 mL, 15.8 g, 150 mmol) over 25 minutes. A mild exotherm was observed. After four hours, 100 mL water was added. The layers were separated. The organic layer was dried over Na₂SO₄ and concentrated. The mixture was dissolved in ethyl acetate and filtered through 1000 cc of silica gel in a 2000 mL Buchner funnel eluted with ethyl acetate. The resulting solution was concentrated *in vacuo* to provide *tert*-butyl (3*R*)-3-[[2-

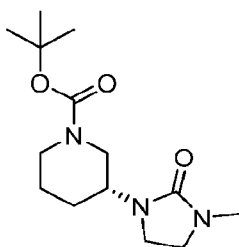
chloroethyl)carbamoyl]amino}piperidine-1-carboxylate (40.6 g, 106%) which was used without further purification. LCMS: $C_{13}H_{24}ClN_3O_3$ requires 305, found: $m/z = 306 [M+H]^+$.

[00293] *tert*-butyl (3*R*)-3-(2-oxoimidazolidin-1-yl)piperidine-1-carboxylate



[00294] To an ice cooled mixture of *tert*-butyl (3*R*)-3-[(2-chloroethyl)carbamoyl]amino}piperidine-1-carboxylate (40.3 g, 132 mmol) in THF (400 mL) was added 60% sodium hydride (10.6 g, 264 mmol) in portions. The cooling bath was allowed to melt and the reaction was stirred at room temperature overnight. Another portion of 60% sodium hydride (5.65 g, 141 mmol) was added. The mixture bubbled. After ten minutes, a mild exotherm was observed. After two hours, the reaction was quenched by the addition of 75 mL water. The layers were separated. The aqueous layer was extracted with two 50 mL portions of DCM. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The resulting material was partitioned between acetonitrile and hexanes. The acetonitrile layer was concentrated *in vacuo* to provide *tert*-butyl (3*R*)-3-(2-oxoimidazolidin-1-yl)piperidine-1-carboxylate (33.9 g, 95.4%). LCMS: $C_{13}H_{23}N_3O_3$ requires 269, found: $m/z = 270 [M+H]^+$.

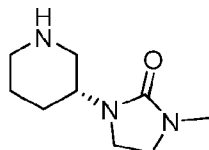
[00295] *tert*-butyl (3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidine-1-carboxylate



[00296] To an ice cooled mixture of *tert*-butyl (3*R*)-3-(2-oxoimidazolidin-1-yl)piperidine-1-carboxylate (33.8 g, 126 mmol) in THF (300 mL) was added 60% sodium hydride (10.1 g, 251 mmol) in portions. After five minutes, the cooling bath was removed. The mixture bubbled for one hour. The mixture was cooled in an ice bath. Methyl iodide (11.7 mL, 26.7 g, 188 mmol) was added over five minutes. The mixture bubbled. The cooling bath was allowed to warm to room temperature. After stirring for 16 hours at room temperature, the reaction was quenched with water (75 mL). The layers were separated. The organic layer was washed with

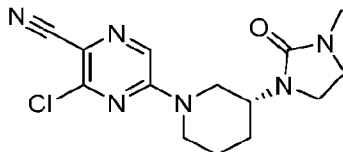
brine. The combined aqueous layers were extracted twice with DCM. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The resulting material was partitioned between acetonitrile and hexane. The acetonitrile layer was filtered and concentrated *in vacuo* to provide *tert*-butyl (3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidine-1-carboxylate (38.4 g, 108%) which was used crude without further purification. LCMS: $\text{C}_{14}\text{H}_{25}\text{N}_3\text{O}_3$ requires 283, found: $m/z = 306 [\text{M}+\text{Na}]^+$.

[00297] 1-methyl-3-[(3*R*)-piperidin-3-yl]imidazolidin-2-one hydrochloride



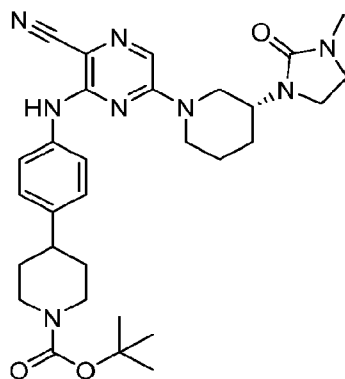
[00298] *tert*-butyl (3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidine-1-carboxylate (35.1 g, 124 mmol) was stirred in hydrogen chloride 4M solution in dioxane (310 mL, 1.24 mol) for two hours. The mixture was concentrated *in vacuo* to provide 1-methyl-3-[(3*R*)-piperidin-3-yl]imidazolidin-2-one hydrochloride (35.0 g, 128%) which was used crude without further purification.. LCMS: $\text{C}_9\text{H}_{17}\text{N}_3\text{O}$ requires 183, found: $m/z = 184 [\text{M}+\text{H}]^+$.

[00299] 3-chloro-5-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyrazine-2-carbonitrile



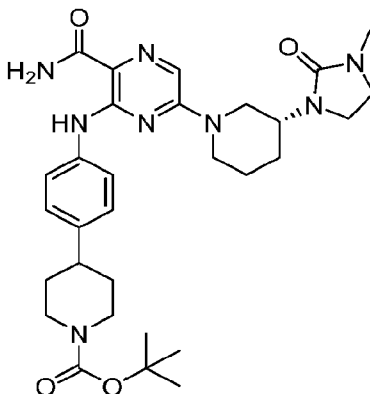
[00300] 3,5-dichloropyrazine-2-carbonitrile (21.6 g, 124 mmol) was added to an ice-cold mixture of 1-methyl-3-[(3*R*)-piperidin-3-yl]imidazolidin-2-one hydrochloride (27.2 g, 124 mmol) and *N,N*-diisopropylethylamine (86.3 mL, 495 mmol) in DMF (300 mL). After 15 minutes, the cooling bath was removed. After stirring for 16 hours, the mixture was diluted with 800 mL water. The mixture was extracted with ethyl acetate. The organic layer was washed twice with water and washed once with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography on a 330 g silica gel column eluted with zero to 3% MeOH/DCM gradient to provide 3-chloro-5-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyrazine-2-carbonitrile (22.1 g, 55.6%). LCMS: $\text{C}_{14}\text{H}_{17}\text{ClN}_6\text{O}$ requires 320, found: $m/z = 320 [\text{M}+\text{H}]^+$.

[00301] *tert*-butyl 4-[4-({3-cyano-6-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyrazin-2-yl}amino)phenyl]piperidine-1-carboxylate



[00302] A mixture of 3-chloro-5-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyrazine-2-carbonitrile (244 mg, 0.76 mmol), *tert*-butyl 4-(4-aminophenyl)piperidine-1-carboxylate (211 mg, 0.76 mmol), Pd(OAc)₂ (56.4 mg, 0.25 mmol), BINAP (156.3 mg, 0.25 mmol), and Cs₂CO₃ (7434 mg, 2.28 mmol) was degassed and backfilled with N₂ five times. The mixture was allowed to stir at 100 °C for 90 min. The mixture was filtered through celite washing with MeOH/EtOAc, concentrated, and purified by MPLC (0-100% EtOAc in CH₂Cl₂) to afford *tert*-butyl 4-[4-({3-cyano-6-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyrazin-2-yl}amino)phenyl]piperidine-1-carboxylate (259 mg, 60.7%). LCMS: C₃₀H₄₀N₈O₃ requires 560, found *m/z* = 561 [M+H]⁺.

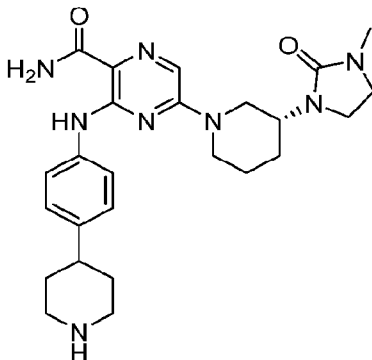
[00303] *tert*-butyl 4-[4-({3-carbamoyl-6-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyrazin-2-yl}amino)phenyl]piperidine-1-carboxylate



[00304] H₂O₂ (30% in water, 2.50 mL, 0.24 mmol) was added to a mixture of *tert*-butyl 4-[4-({3-cyano-6-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyrazin-2-yl}amino)phenyl]piperidine-1-carboxylate (259 mg, 0.46 mmol), Cs₂CO₃ (150.5 mg, 0.46 mmol), MeOH (9 mL), and DMSO (0.5 mL). The mixture was allowed to stir at rt for 30 min. The mixture was concentrated. EtOAc was added and the organic phase was washed with H₂O and brine. The organic layer was dried with MgSO₄, filtered, concentrated, and purified by

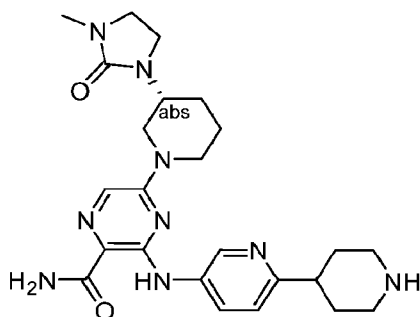
MPLC (0-10% MeOH in CH₂Cl₂) to afford *tert*-butyl 4-[4-({3-carbamoyl-6-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyrazin-2-yl}amino)phenyl]piperidine-1-carboxylate (252 mg, 94%). LCMS: C₃₀H₄₂N₈O₄ requires 578, found *m/z* = 579 [M+H]⁺.

[00305] 5-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]-3-{[4-(piperazin-1-yl)phenyl]amino}pyrazine-2-carboxamide

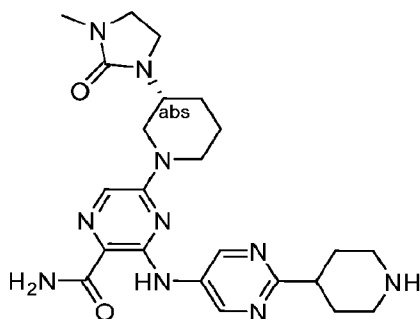


[00306] A mixture of *tert*-butyl 4-[4-({3-carbamoyl-6-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyrazin-2-yl}amino)phenyl]piperidine-1-carboxylate (252 mg, 0.44 mmol), hydrogen chloride (4M in dioxane, 2.72 mL, 10.89 mmol), and THF (2 mL) was allowed to stir at room temperature for 2 h. The volatiles were removed to afford 5-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]-3-{[4-(piperidin-4-yl)phenyl]amino}pyrazine-2-carboxamide (209 mg, quant).

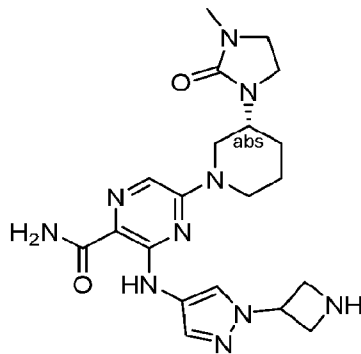
Example 5



[00307] Synthesis of (R)-5-(3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl)-3-((6-(piperidin-4-yl)pyridin-3-yl)amino)pyrazine-2-carboxamide: Prepared in a manner analogous to the preparation of 5-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]-3-{[4-(piperidin-4-yl)phenyl]amino}pyrazine-2-carboxamide with *tert*-butyl 4-(5-aminopyridin-2-yl)piperidine-1-carboxylate in place of *tert*-butyl 4-(4-aminophenyl)piperidine-1-carboxylate.

Example 6

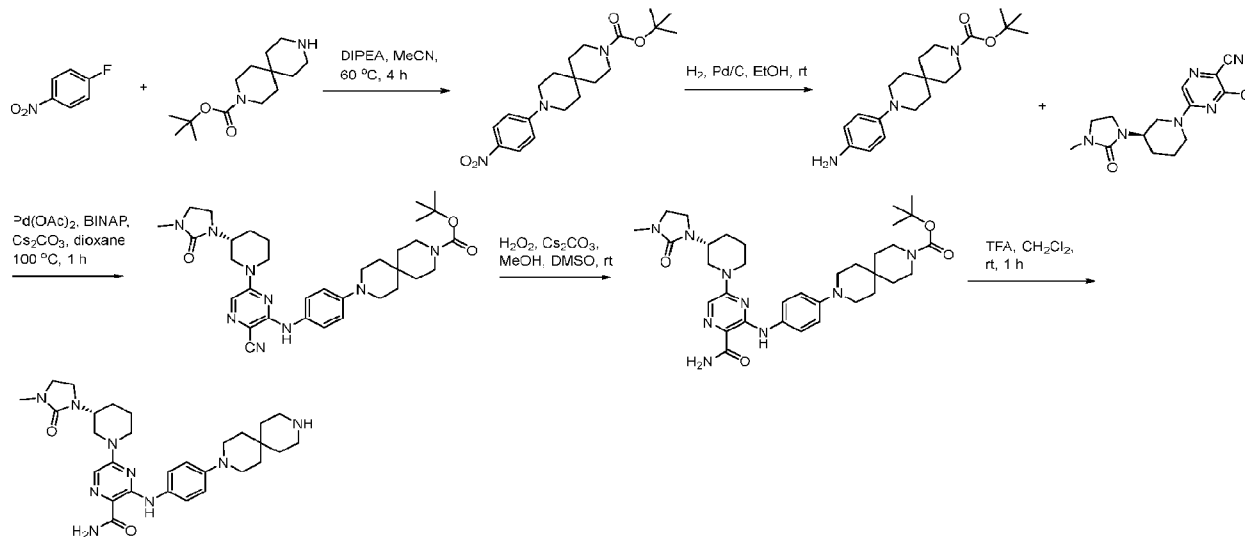
[00308] **Synthesis of (R)-5-(3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl)-3-((piperidin-4-yl)pyrimidin-5-yl)amino)pyrazine-2-carboxamide:** Prepared in a manner analogous to the preparation of 5-[(3R)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]-3-{[4-(piperidin-4-yl)phenyl]amino}pyrazine-2-carboxamide with *tert*-butyl 4-(5-aminopyrimidin-2-yl)piperidine-1-carboxylate in place of *tert*-butyl 4-(4-aminophenyl)piperidine-1-carboxylate.

Example 7

[00309] **Synthesis of (R)-3-((1-(azetidin-3-yl)-1H-pyrazol-4-yl)amino)-5-(3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl)pyrazine-2-carboxamide:** Prepared in a manner analogous to the preparation of 5-[(3R)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]-3-{[4-(piperidin-4-yl)phenyl]amino}pyrazine-2-carboxamide with *tert*-butyl 3-(4-amino-1H-pyrazol-1-yl)azetidine-1-carboxylate in place of *tert*-butyl 4-(4-aminophenyl)piperidine-1-carboxylate.

Example 8

[00310] Synthesis of (*R*)-3-((4-(3,9-diazaspiro[5.5]undecan-3-yl)phenyl)amino)-5-(3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl)pyrazine-2-carboxamide:



[00311] Synthesis of *tert*-butyl 9-(4-nitrophenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate:

[00312] A mixture of 4-fluoronitrobenzene (554.7 mg, 3.93 mmol), DMF (20 mL), ethylbis(propan-2-yl)amine (2.74 mL, 15.7 mmol) and *tert*-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (1000 mg, 3.93 mmol) was allowed to stir at 90 °C overnight. EtOAc and H₂O were added. The organic layer was dried with MgSO₄, filtered, concentrated, and purified by MPLC (0-50% EtOAc in hexanes) to afford *tert*-butyl 9-(4-nitrophenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (1287.00 mg, 87.2%). C₂₀H₂₉N₃O₄ requires 375, found: *m/z* = 376 [M+H]⁺.

[00313] Synthesis of *tert*-butyl 9-(4-aminophenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate:

[00314] A mixture of *tert*-butyl 9-(4-nitrophenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (1.29 g, 3.43 mmol), Pd/C (36 mg, 0.34 mmol), and EtOH (30 mL) was evacuated and backfilled with H₂ five times. The mixture was allowed to stir at room temperature for 2 h.

[00315] The mixture was filtered through celite washing with EtOAc/MeOH and concentrated to afford *tert*-butyl 9-(4-aminophenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (871 mg, 73.5%). LCMS: C₂₀H₃₁N₃O₂ requires 345, found: *m/z* = 346 [M+H]⁺.

[00316] Synthesis of *tert*-butyl (*R*)-9-(4-((3-cyano-6-(3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl)pyrazin-2-yl)amino)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate:

[00317] A mixture of *tert*-butyl 9-(4-aminophenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (162.6 mg, 0.47 mmol), 3-chloro-5-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyrazine-2-carbonitrile (151 mg, 0.47 mmol), Pd(OAc)₂ (34.9 mg, 0.16 mmol), [2'-(diphenylphosphanyl)-[1,1'-binaphthalen]-2-yl]diphenylphosphane (96.7 mg, 0.16 mmol), and cesium carbonate (460 mg, 1.41 mmol) was degassed and backfilled with N₂ five times. The mixture was allowed to stir at 100 °C for 90 min. The mixture was filtered through celite washing with MeOH/EtOAc, concentrated, and purified by MPLC (0-100% EtOAc in CH₂Cl₂) to afford *tert*-butyl 9-[4-({3-cyano-6-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyrazin-2-yl}amino)phenyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate (204 mg, 68.8%). LCMS: C₃₄H₄₇N₉O₃ requires 629, found: m/z = 630 [M+H]⁺.

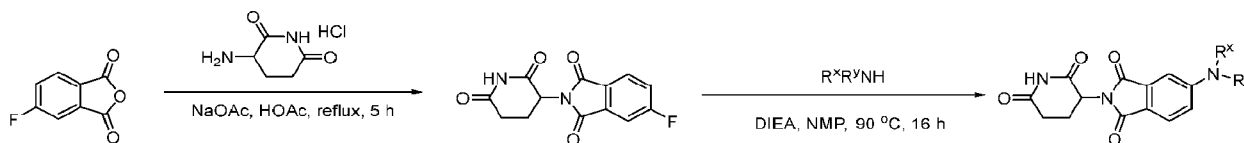
[00318] Synthesis of *tert*-butyl (*R*)-9-(4-((3-carbamoyl-6-(3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl)pyrazin-2-yl)amino)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate:

[00319] H₂O₂ (30% in H₂O, 0.55 mL, 0.05 mmol) was added to a mixture of *tert*-butyl 9-[4-({3-cyano-6-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyrazin-2-yl}amino)phenyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate (204 mg, 0.32 mmol), cesium carbonate (106 mg, 0.32 mmol), MeOH (6 mL), and DMSO (0.3 mL). The mixture was allowed to stir at room temperature for 30 min. The mixture was concentrated. EtOAc was added and the organic phase was washed with H₂O and brine. The organic layer was dried with MgSO₄, filtered, concentrated, and purified by MPLC (0-10% MeOH in CH₂Cl₂) to afford *tert*-butyl 9-[4-({3-carbamoyl-6-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyrazin-2-yl}amino)phenyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate (95.00 mg, 45%). LCMS: C₃₄H₄₉N₉O₄ requires 647, found: m/z = 648 [M+H]⁺.

[00320] Synthesis of (*R*)-3-((4-(3,9-diazaspiro[5.5]undecan-3-yl)phenyl)amino)-5-(3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl)pyrazine-2-carboxamide:

[00321] A mixture of *tert*-butyl 9-[4-({3-carbamoyl-6-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyrazin-2-yl}amino)phenyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate (25 mg, 0.04 mmol), CH₂Cl₂ (1 mL), and TFA (0.2 mL) was allowed to stir at room temperature for 1 h. The volatiles were removed to afford 3-[(4-{3,9-diazaspiro[5.5]undecan-3-yl}phenyl)amino]-5-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyrazine-2-carboxamide (21.00 mg, 99.4%). LCMS: C₂₉H₄₁N₉O₂ requires 547, found: m/z = 548 [M+H]⁺.

Example 9

General Procedure B**[00322] Step 1: Synthesis of 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisindoline-1,3-dione:**

[00323] A mixture of 5-fluoro-1,3-dihydro-2-benzofuran-1,3-dione (5.0 g, 30.10 mmol), 3-aminopiperidine-2,6-dione hydrochloride (6.9 g, 42.14 mmol), and NaOAc (4.2 g, 51.17 mmol) in HOAc (50 mL) was stirred at 120 °C for 5 h before concentration under vacuum. The residue was washed with water and the solid was collected by filtration. The crude product was washed with water twice, ethyl acetate twice, and dried in an oven to afford 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisindoline-1,3-dione (7.7 g, 92%) as a light brown solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.16 (s, 1H), 8.03 – 8.00 (m, 1H), 7.87 – 7.85 (m, 1H), 7.75 – 7.70 (m, 1H), 5.19 – 5.15 (m, 1H), 2.94 – 2.86 (m, 1H), 2.63 – 2.48 (m, 2H), 2.12 – 2.06 (m, 1H). ¹⁹F NMR (300 MHz, DMSO-*d*₆) δ -102.078.

[00324] Step 2: Amine displacement of aryl fluoride

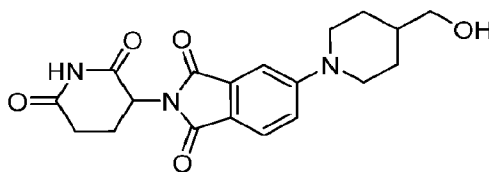
[00325] To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-fluoro-2,3-dihydro-1H-isindole-1,3-dione (1.0 g, 3.62 mmol) in *N*-methyl pyrrolidone (10 mL) were added **R^xR^yNH** (3.60 mmol) and DIEA (1.4 g, 10.83 mmol). The resulting solution was stirred at 80 °C for 16 h. The reaction mixture was cooled to room temperature and purified by reverse phase flash chromatography to afford the corresponding final product. **R^xR^y** correspond to any amine **R** groups defined elsewhere herein.

[00326] Step 3: Alcohol oxidation

[00327] Dess-Martin periodinane (1.54 mmol) was added to a mixture of the alkyl alcohol (0.77 mmol) and CH₂Cl₂ (10 mL). The mixture was allowed to stir at room temperature for one hour. CH₂Cl₂ and aqueous Na₂SO₃ were added. The organic layer was dried with MgSO₄, filtered, concentrated, and purified by MPLC (20-100% EtOAc in hexanes) to afford the aldehyde.

Example 10

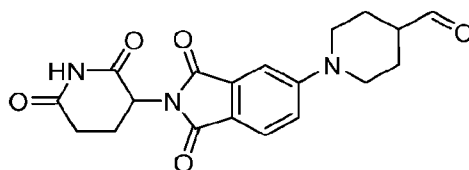
[00328] Synthesis of 2-(2,6-dioxopiperidin-3-yl)-5-(4-(hydroxymethyl)piperidin-1-yl)isindoline-1,3-dione:



[00329] General Procedure B was used with piperidin-4-ylmethanol to afford 2-(2,6-dioxopiperidin-3-yl)-5-(4-(hydroxymethyl)piperidin-1-yl)isoindoline-1,3-dione (938.7 mg, 70%) as a yellow solid. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 11.09 (s, 1H), 7.65 (d, $J = 8.4$ Hz, 1H), 7.30 (d, $J = 2.4$ Hz, 1H), 7.23 (dd, $J = 8.4, 2.4$ Hz, 1H), 5.07 (dd, $J = 12.6, 5.4$ Hz, 1H), 4.51 (t, $J = 5.1$ Hz, 1H), 4.07 (d, $J = 13.2$ Hz, 2H), 3.27 (t, $J = 5.7$ Hz, 2H), 2.99 – 2.80 (m, 3H), 2.62 – 2.55 (m, 2H), 2.17 – 1.95 (m, 1H), 1.76 – 1.67 (m, 3H), 1.24 – 1.12 (m, 2H). MS (ESI) calc'd for ($\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_5$) $[\text{M}+\text{H}]^+$, 372.1; found 372.2.

Example 11

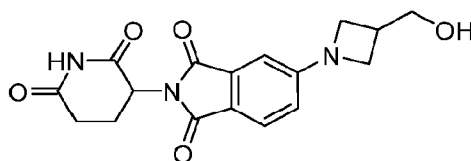
[00330] Synthesis of 1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)piperidine-4-carbaldehyde:



[00331] General Procedure B was used with 2-(2,6-dioxopiperidin-3-yl)-5-(4-(hydroxymethyl)piperidin-1-yl)isoindoline-1,3-dione to afford 1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)piperidine-4-carbaldehyde. MS (ESI) calc'd for ($\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_5$) $[\text{M}+\text{H}]^+$, 370; found 370.

Example 12

[00332] Synthesis of 2-(2,6-dioxopiperidin-3-yl)-5-(3-(hydroxymethyl)azetidin-1-yl)isoindoline-1,3-dione:

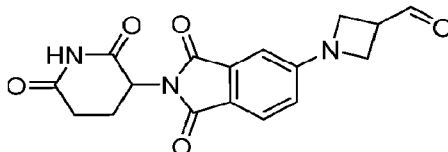


[00333] General Procedure B was used with azetidin-3-ylmethanol hydrochloride to afford 2-(2,6-dioxopiperidin-3-yl)-5-(3-(hydroxymethyl)azetidin-1-yl)isoindoline-1,3-dione (1.85 g, 68%) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.09 (s, 1H), 7.63 (d, $J = 8.4$ Hz,

1H), 6.76 (d, $J = 2.0$ Hz, 1H), 6.62 (dd, $J = 8.4, 2.0$ Hz, 1H), 5.06 (dd, $J = 12.4, 5.2$ Hz, 1H), 4.86 (t, $J = 5.2$ Hz, 1H), 4.05 (t, $J = 8.4$ Hz, 2H), 3.77 (dd, $J = 8.4, 5.2$ Hz, 2H), 3.60 (t, $J = 5.2$ Hz, 2H), 3.00 – 2.81 (m, 2H), 2.65 – 2.53 (m, 2H), 2.06 – 1.96 (m, 1H). MS (ESI) calc'd for (C₁₇H₁₇N₃O₅) [M+H]⁺, 344.1; found 344.4.

[00334] Example 13

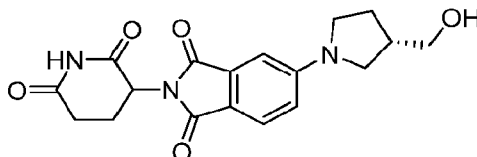
[00335] Synthesis of 1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)azetidine-3-carbaldehyde:



[00336] General Procedure B was used with 2-(2,6-dioxopiperidin-3-yl)-5-(3-(hydroxymethyl)azetidin-1-yl)isoindoline-1,3-dione to afford 1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)azetidine-3-carbaldehyde. MS (ESI) calc'd for (C₁₇H₁₅N₃O₅) [M+H]⁺, 342; found 342.

Example 14

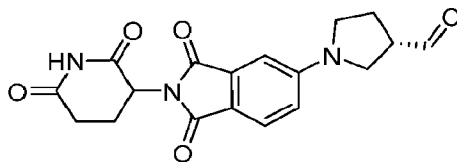
[00337] Synthesis of 2-(2-(2,6-dioxopiperidin-3-yl)-5-((S)-3-(hydroxymethyl)pyrrolidin-1-yl)isoindoline-1,3-dione:



[00338] General Procedure B was used with (S)-pyrrolidin-3-ylmethanol to afford 2-(2-(2,6-dioxopiperidin-3-yl)-5-((S)-3-(hydroxymethyl)pyrrolidin-1-yl)isoindoline-1,3-dione (643.1 mg, 33%) as a yellow solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.08 (s, 1H), 7.64 (d, $J = 8.4$ Hz, 1H), 6.89 (d, $J = 2.1$ Hz, 1H), 6.80 (dd, $J = 8.4, 2.1$ Hz, 1H), 5.06 (dd, $J = 12.9, 5.4$ Hz, 1H), 4.78 (t, $J = 5.4$ Hz, 1H), 3.59 – 3.41 (m, 5H), 3.22 – 3.17 (m, 1H), 2.95 – 2.83 (m, 1H), 2.67 – 2.44 (m, 3H), 2.12 – 1.88 (m, 2H), 1.87 – 1.76 (m, 1H). MS (ESI) calc'd for (C₁₈H₁₉N₃O₅) [M+H]⁺, 358.1; found 358.1.

Example 15

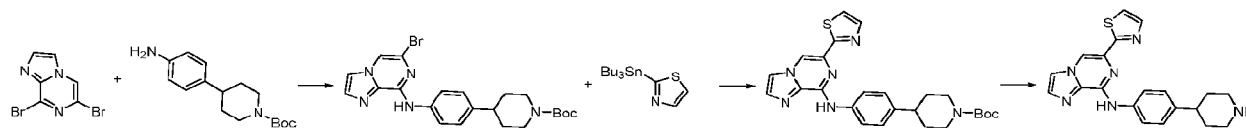
[00339] Synthesis of (3S)-1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)pyrrolidine-3-carbaldehyde:



[00340] General Procedure B was used with (2,6-dioxopiperidin-3-yl)-5-((S)-3-(hydroxymethyl)pyrrolidin-1-yl)isoindoline-1,3-dione to afford (3S)-1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)pyrrolidine-3-carbaldehyde. MS (ESI) calc'd for (C₁₈H₁₇N₃O₅) [M+H]⁺, 356; found 356.

Example 16

[00341] Synthesis of *N*-(4-(piperidin-4-yl)phenyl)-6-(thiazol-2-yl)imidazo[1,2-*a*]pyrazin-8-amine:



[00342] Synthesis of *tert*-butyl 4-(4-((6-bromoimidazo[1,2-*a*]pyrazin-8-yl)amino)phenyl)piperidine-1-carboxylate: A mixture of 6,8-dibromoimidazo[1,2-*a*]pyrazine (1 g), *tert*-butyl 4-(4-aminophenyl)piperidine-1-carboxylate (1.1 g), DIEA (1.3 mL), and *i*PrOH (10 mL) was allowed to stir at 80 °C overnight. The mixture was poured into water, and the mixture was filtered. After washing with water and Et₂O, *tert*-butyl 4-(4-((6-bromoimidazo[1,2-*a*]pyrazin-8-yl)amino)phenyl)piperidine-1-carboxylate (0.70g, 41%) was obtained. LCMS: C₂₂H₂₆BrN₅O₂ requires 471, found: *m/z* = 472 [M+H]⁺.

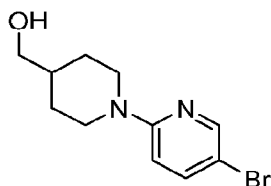
[00343] Synthesis of *tert*-butyl 4-(4-((6-(thiazol-2-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)phenyl)piperidine-1-carboxylate:

[00344] A mixture of *tert*-butyl 4-[4-((6-bromoimidazo[1,2-*a*]pyrazin-8-yl)amino)phenyl]piperidine-1-carboxylate (50 mg), tetrakis(triphenylphosphine)palladium(0) (25 mg), sodium carbonate (23 mg), 2-(tributylstannyl)-1,3-thiazole (40 mg) and 1,4-dioxane (1 mL) was allowed to stir at 50 °C overnight. EtOAc and H₂O were added, and the organic layer was dried with MgSO₄, filtered, concentrated, and purified by HPLC (5-95 MeCN in H₂O) to afford *tert*-butyl 4-(4-((6-(thiazol-2-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)phenyl)piperidine-1-carboxylate (24 mg, 48%).

[00345] Synthesis of *N*-(4-(piperidin-4-yl)phenyl)-6-(thiazol-2-yl)imidazo[1,2-*a*]pyrazin-8-amine: A mixture of *tert*-butyl 4-(4-((6-(thiazol-2-yl)imidazo[1,2-*a*]pyrazin-8-yl)amino)phenyl)piperidine-1-carboxylate (24 mg), TFA (0.5 mL) and CH₂Cl₂ (0.5 mL) was

allowed to stir at rt for one hour. The volatiles were removed to afford *N*-(4-(piperidin-4-yl)phenyl)-6-(thiazol-2-yl)imidazo[1,2-*a*]pyrazin-8-amine.

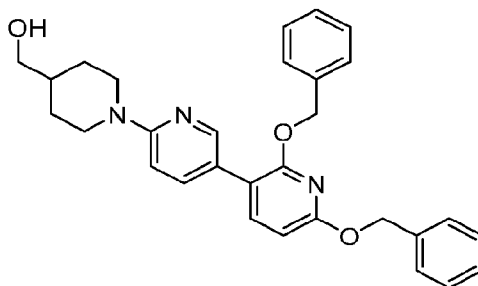
Example 17



[00346] [1-(5-bromopyridin-2-yl)piperidin-4-yl]methanol

[00347] To a mixture of 5-bromo-2-fluoropyridine (559 mg, 3.18 mmol) in DMF (7.00 mL) was added piperidin-4-ylmethanol (366 mg, 3.18 mmol) and potassium carbonate (0.88 g, 6.35 mmol). The mixture was stirred at 90 °C overnight. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on a 40 g column eluted with zero to 10% MeOH/DCM to provide [1-(5-bromopyridin-2-yl)piperidin-4-yl]methanol (0.841 g, 97.6%). LCMS: C₁₁H₁₅BrN₂O requires 270, found: *m/z* = 271 [M+H]⁺.

Example 18

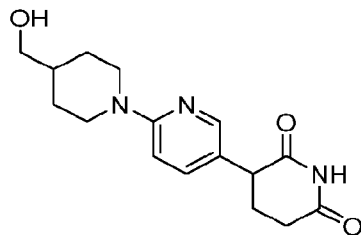


[00348] {1-[2',6'-bis(benzyloxy)-[3,3'-bipyridin]-6-yl]piperidin-4-yl}methanol

[00349] [1-(5-bromopyridin-2-yl)piperidin-4-yl]methanol (93.0 mg, 0.34 mmol), 2,6-bis(benzyloxy)pyridin-3-ylboronic acid (172 mg, 0.51 mmol), tetrakis(triphenylphosphine)palladium(0) (39.6 mg, 0.03 mmol), and potassium carbonate (94.8 mg, 0.69 mmol) were deposited in a microwave vial in THF (3.00 mL) and water (1.00 mL). The mixture was microwaved at 120 °C for 40 minutes. The organic layer was loaded

directly onto a silica gel cartridge and the mixture was purified by flash chromatography on a 24 g column eluted with zero to 10% MeOH/DCM. The resulting material was repurified by flash chromatography on a 24 g column eluted with zero to 50% ethylacetate/DCM to provide {1-[2',6'-bis(benzyloxy)-[3,3'-bipyridin]-6-yl]piperidin-4-yl}methanol (0.097 g, 58.7%). LCMS: $C_{30}H_{31}N_3O_3$ requires 481, found: $m/z = 482 [M+H]^+$.

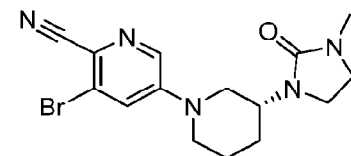
Example 19



[00350] 3-{6-[4-(hydroxymethyl)piperidin-1-yl]pyridin-3-yl}piperidine-2,6-dione

[00351] To a mixture of {1-[2',6'-bis(benzyloxy)-[3,3'-bipyridin]-6-yl]piperidin-4-yl}methanol (97.0 mg, 0.20 mmol) in ethanol (3.00 mL) was added 10% palladium on carbon (97.0 mg). The mixture was stirred under an atmosphere of H_2 for three hours. The mixture was filtered through a pad of celite which was washed with 50 mL DCM. The resulting solution was concentrated then purified by flash chromatography on a 24 g column eluted with zero to 20% MeOH/DCM to provide 3-{6-[4-(hydroxymethyl)piperidin-1-yl]pyridin-3-yl}piperidine-2,6-dione (0.0214 g, 34.3%). LCMS: $C_{16}H_{21}N_3O_3$ requires 303, found: $m/z = 304 [M+H]^+$.

Example 20

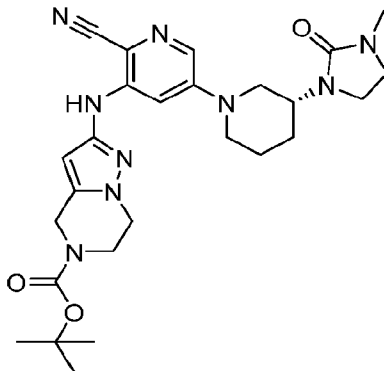


[00352] 3-bromo-5-[(3R)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyridine-2-carbonitrile

[00353] 1-methyl-3-[(3R)-piperidin-3-yl]imidazolidin-2-one trifluoroacetate (1.40 g, 4.72 mmol), 3-bromo-5-fluoropyridine-2-carbonitrile (948 mg, 4.72 mmol), and *N,N*-diisopropylethylamine (2.46 mL, 1.83 g, 14.2 mmol) were stirred in DMF (12.00 mL) at 90 °C for two hours. The mixture was poured into ice water. The mixture was extracted with ethyl

acetate. The organic layer was washed twice with water, dried over Na₂SO₄, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on a 40 g column eluted with zero to 10% MeOH/DCM to provide 3-bromo-5-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyridine-2-carbonitrile (828 mg, 48.2%). LCMS: C₁₅H₁₈BrN₅O requires 363, found: *m/z* = 364 [M+H]⁺.

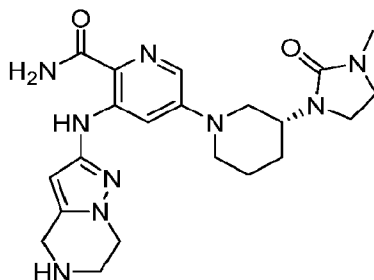
Example 21



[00354] 3-bromo-5-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyridine-2-carbonitrile

[00355] 3-bromo-5-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyridine-2-carbonitrile (283 mg, 0.78 mmol), *tert*-butyl 2-amino-4*H*,6*H*,7*H*-pyrazolo[1,5-*a*]pyrazine-5-carboxylate (185 mg, 0.78 mmol), and cesium carbonate (1.01 g, 3.11 mmol) were suspended in dioxane (6.00 mL). A vacuum was applied on the vial until the contents bubbled, and the headspace was backfilled with argon for five cycles. (Acetyloxy)palladio acetate (34.89 mg, 0.16 mmol) and BINAP (96.8 mg, 0.16 mmol) were added. A vacuum was applied on the vial until the contents bubbled, and the headspace was backfilled with argon for five cycles. The mixture was heated at 90 °C overnight. The mixture was cooled, diluted with DCM, and filtered. The resulting solution was concentrated *in vacuo* then purified by flash chromatography on a 40 g column eluted with zero to 10% MeOH/DCM to provide *tert*-butyl 2-({2-cyano-5-[(3*R*)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyridin-3-yl}amino)-4*H*,6*H*,7*H*-pyrazolo[1,5-*a*]pyrazine-5-carboxylate (253 mg, 62.4%). LCMS: C₂₆H₃₅N₉O₃ requires 521, found: *m/z* = 522 [M+H]⁺.

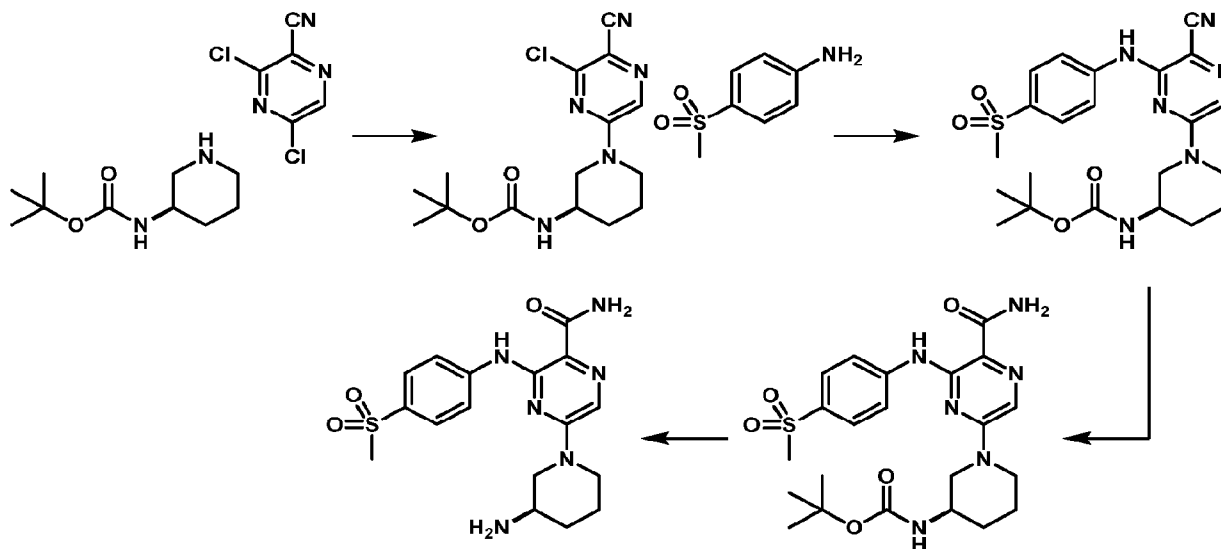
Example 22



[00356] 5-[(3R)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]-3-{4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-ylamino}pyridine-2-carboxamide trifluoroacetate

[00357] *tert*-butyl 2-({2-carbamoyl-5-[(3R)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]pyridin-3-yl}amino)-4H,6H,7H-pyrazolo[1,5-a]pyrazine-5-carboxylate (20.00 mg, 0.04 mmol) was stirred in DCM (1.00 mL) and hydrogen chloride (4M in dioxane, 1.00 mL, 0.15 g, 4.00 mmol) for one hour. The mixture was concentrated to provide 5-[(3R)-3-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]-3-{4H,5H,6H,7H-pyrazolo[1,5-a]pyrazin-2-ylamino}pyridine-2-carboxamide trifluoroacetate (0.021 g, 100%). LCMS: $C_{21}H_{29}N_9O_2$ requires 439, found: $m/z = 440 [M+H]^+$.

Example 23



[00358] A: A mixture of 3,5-dichloropyrazine-2-carbonitrile (1.5 g, 8.62 mmol), *t*-butyl *N*-piperidinylcarbamate (2.07 g, 10.4 mmol), and *i*-Pr₂NEt (3 mL, 17.2 mmol) was dissolved in DMF (10 mL) and stirred for 1.5 h at rt. The reaction mixture was diluted with EtOAc (20 mL) and washed with H₂O (2 x 30 mL) before being concentrated to a yellow oil. Flash

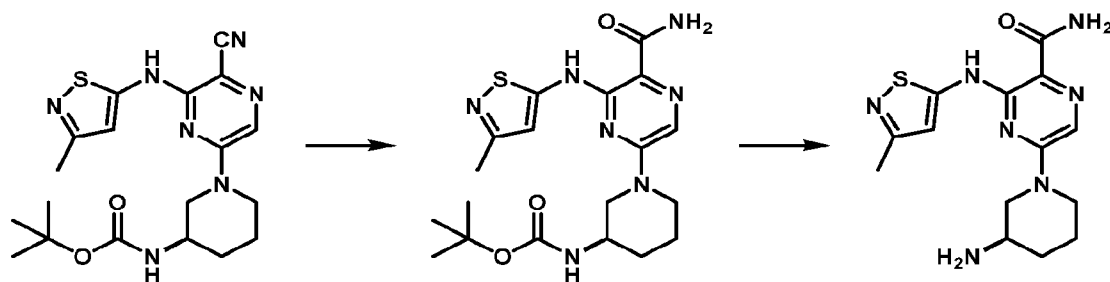
chromatography (SiO₂, 10→15% CH₂Cl₂/EtOAc) afforded *tert*-butyl (*R*)-(1-(6-chloro-5-cyanopyrazin-2-yl)piperidin-3-yl)carbamate (2.5 g, 86%) as a white solid. LCMS: C₁₅H₂₀ClN₅O₂ requires: 338, found: *m/z* = 339 [M+H]⁺.

[00359] B: A mixture of *tert*-butyl (*R*)-(1-(6-chloro-5-cyanopyrazin-2-yl)piperidin-3-yl)carbamate (800 mg, 2.37 mmol), 4-methylsulfonylaniline (405 mg, 2.37 mmol), (acetyloxy)palladio acetate (106 mg, 0.47 mmol), BINAP (295 mg, 0.47 mmol), and Cs₂CO₃ (3.09 g, 9.47 mmol) were suspended in DCE (35 mL) and the mixture was degassed under a stream of N₂ for five min. The reaction mixture was heated to 110 °C for 2.5 h before being cooled and diluted with EtOAc (50 mL), filtered over celite, and concentrated. Purification (SiO₂, 10→65% EtOAc/CH₂Cl₂) afforded *tert*-butyl (*R*)-(1-(5-cyano-6-((4-(methylsulfonyl)phenyl)amino)pyrazin-2-yl)piperidin-3-yl)carbamate (760 mg, 68%). LCMS: C₂₂H₂₈N₆O₄S requires: 472, found: *m/z* = 473 [M+H]⁺.

[00360] C: *tert*-butyl *N*-[(3*R*)-1-{5-cyano-6-[(4-methanesulfonylphenyl)amino]pyrazin-2-yl}piperidin-3-yl]carbamate (760 mg, 1.61 mmol) was dissolved in MeOH (5 mL) and NaOH (100 mg) and H₂O₂ (33% aq, one mL) were added. The reaction mixture was stirred for 20 min before being diluted with ACN (2 mL) and stirred for an additional 10 min. An exotherm was observed upon ACN addition. The mixture was concentrated before being diluted with 50 mL EtOAc and the organic phase was washed with H₂O (2 x 15 mL). The combined organic extracts were dried (MgSO₄), filtered, and concentrated to afford *tert*-butyl (*R*)-(1-(5-carbamoyl-6-((4-(methylsulfonyl)phenyl)amino)pyrazin-2-yl)piperidin-3-yl)carbamate after purification (SiO₂, 0→10% MeOH/CH₂Cl₂). LCMS: C₂₂H₃₀N₆O₅S requires: 490, found: *m/z* = 491 [M+H]⁺.

[00361] D: *tert*-butyl *N*-[(3*R*)-1-{5-carbamoyl-6-[(4-methanesulfonylphenyl)amino]pyrazin-2-yl}piperidin-3-yl]carbamate was dissolved in CH₂Cl₂ (5 mL) and TFA (2 mL) was added at rt. After one h the reaction mixture was concentrated to a thick oil before being dissolved in ACN/H₂O and lyophilized to afford (*R*)-5-(3-aminopiperidin-1-yl)-3-((4-(methylsulfonyl)phenyl)amino)pyrazine-2-carboxamide (402 mg, 44%, 3 steps) as a TFA salt. LCMS: C₁₇H₂₂N₆O₃S requires: 390, found: *m/z* = 391 [M+H]⁺.

Example 24

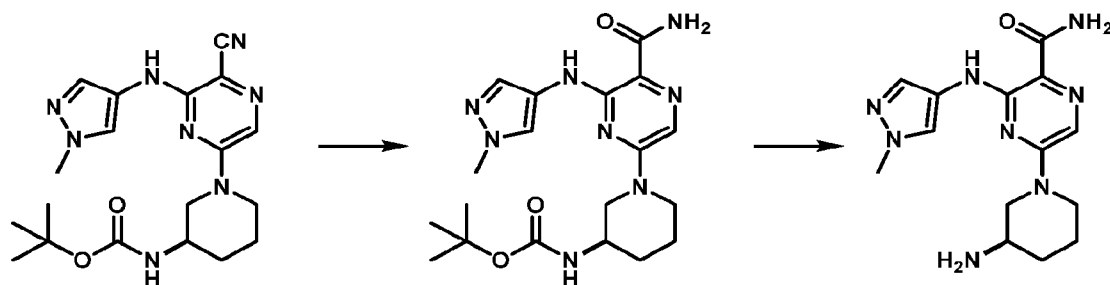


[00362] Procedure **B** was followed to afford *tert*-butyl (*R*)-(1-(5-cyano-6-((3-methylisothiazol-5-yl)amino)pyrazin-2-yl)piperidin-3-yl)carbamate (5.6 g, 89%). LCMS: $C_{19}H_{25}N_7O_2S$ requires: 415, found: $m/z = 416 [M+H]^+$.

[00363] Procedure **C** was followed to afford *tert*-butyl (*R*)-(1-(5-carbamoyl-6-((3-methylisothiazol-5-yl)amino)pyrazin-2-yl)piperidin-3-yl)carbamate (850 mg, 82%). LCMS: $C_{19}H_{27}N_7O_3S$ requires: 433, found: $m/z = 434 [M+H]^+$.

[00364] Procedure **D** was followed to afford (*R*)-5-(3-aminopiperidin-1-yl)-3-((3-methylisothiazol-5-yl)amino)pyrazine-2-carboxamide (600 mg, 74%). LCMS: $C_{14}H_{19}N_7OS$ requires: 333, found: $m/z = 334 [M+H]^+$.

Example 25



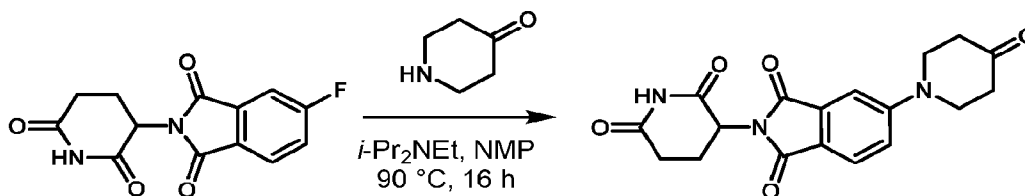
[00365] Procedure **B** was followed to afford *tert*-butyl (*R*)-(1-(5-cyano-6-((1-methyl-1H-pyrazol-4-yl)amino)pyrazin-2-yl)piperidin-3-yl)carbamate (941 mg, 80%). LCMS: $C_{19}H_{26}N_8O_2$ requires: 398, found: $m/z = 399 [M+H]^+$.

[00366] Procedure **C** was followed to afford *tert*-butyl (*R*)-(1-(5-carbamoyl-6-((1-methyl-1H-pyrazol-4-yl)amino)pyrazin-2-yl)piperidin-3-yl)carbamate (297 mg, 95%). LCMS: $C_{19}H_{28}N_8O_3$ requires: 416, found: $m/z = 417 [M+H]^+$.

[00367] Procedure **D** was followed to afford (*R*)-5-(3-aminopiperidin-1-yl)-3-((1-methyl-1H-pyrazol-4-yl)amino)pyrazine-2-carboxamide. LCMS: $C_{14}H_{20}N_8O$ requires: 316, found: $m/z = 317 [M+H]^+$.

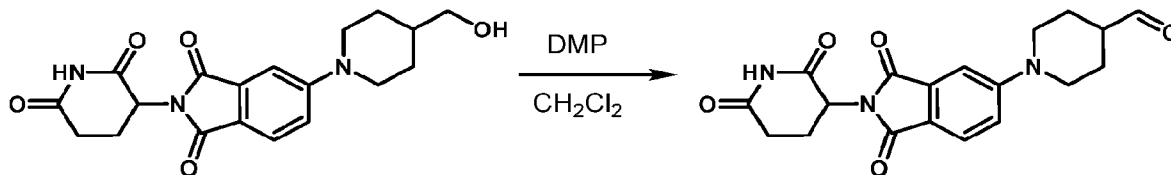
[00368] Procedure **D** was followed to afford (*R*)-5-(3-aminopiperidin-1-yl)-3-((1-methyl-1H-pyrazol-4-yl)amino)pyrazine-2-carboxamide. LCMS: $C_{14}H_{20}N_8O$ requires: 4=316, found: $m/z = 317 [M+H]^+$.

Example 26



[00369] E: 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindole-1,3-dione (500 mg, 1.81 mmol) and 4-piperidinone hydrochloride (245 mg, 1.81 mmol) were dissolved in NMP (3 mL) and $i\text{-Pr}_2\text{NEt}$ (703 mg, 5.43 mmol) was added. The mixture was heated at $90\text{ }^\circ\text{C}$ for 16 h before being diluted with EtOAc. The organic phase was washed (2 x H_2O , sat. aq. NaCl), dried (Na_2SO_4), concentrated, and purified (SiO_2 , 10→100% EtOAc/hexanes) to provide 2-(2,6-dioxopiperidin-3-yl)-5-(4-oxopiperidin-1-yl)isoindole-1,3-dione (131 mg, 20%). LCMS: $C_{18}H_{17}N_3O_5$ requires 355, found: $m/z = 356 [M+H]^+$.

Example 27

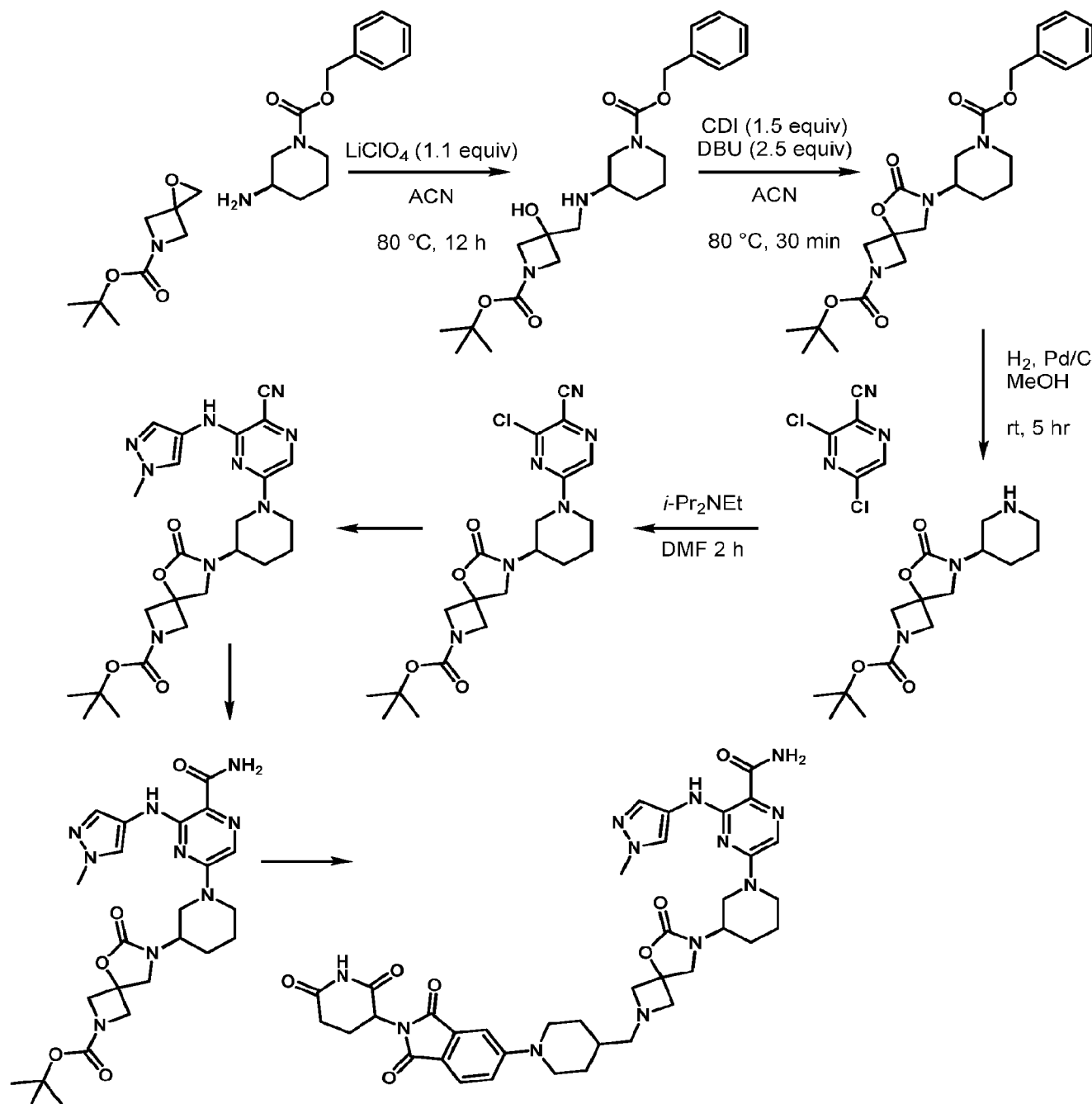


[00370] Procedure **E** was used with piperidin-4-ylmethanol to afford 2-(2,6-dioxopiperidin-3-yl)-5-(4-(hydroxymethyl)piperidin-1-yl)isoindoline-1,3-dione (939 mg, 70%) as a yellow solid. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 11.09 (s, 1H), 7.65 (d, $J = 8.4$ Hz, 1H), 7.30 (d, $J = 2.4$ Hz, 1H), 7.23 (dd, $J = 8.4, 2.4$ Hz, 1H), 5.07 (dd, $J = 12.6, 5.4$ Hz, 1H), 4.51 (t, $J = 5.1$ Hz, 1H), 4.07 (d, $J = 13.2$ Hz, 2H), 3.27 (t, $J = 5.7$ Hz, 2H), 2.99 – 2.80 (m, 3H), 2.62 – 2.55 (m, 2H), 2.17 – 1.95 (m, 1H), 1.76 – 1.67 (m, 3H), 1.24 – 1.12 (m, 2H). LCMS: $C_{19}H_{21}N_3O_5$ requires: 371, found: $m/z = 372 [M+H]^+$.

[00371] F: 2-(2,6-dioxopiperidin-3-yl)-5-[4-(hydroxymethyl)piperidin-1-yl]isoindole-1,3-dione (1.50 g, 4.04 mmol) was dissolved in CH_2Cl_2 (15 mL) and 1,1-bis(acetyloxy)-3-oxo-11lambda5,2-benziodaoxol-1-yl acetate (1.88 g, 4.44 mmol) was added in one portion at rt. After five hours, the reaction mixture was diluted with NaHCO_3 (2 mL sat. aq.), $\text{Na}_2\text{S}_2\text{O}_3$ (sat. aq.) was added, and the mixture was stirred for 30 min. The organic phase was removed. The

aqueous layer was extracted (2 x 20 mL CH₂Cl₂) and the combined organic phases were dried (Na₂SO₄), filtered, and concentrated. Purification (SiO₂, 2→6% MeOH in CH₂Cl₂) afforded 1-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]piperidine-4-carbaldehyde (1.20 g, 80%). LCMS: C₁₉H₁₉N₃O₅ requires: 369, found: m/z = 370 [M+H]⁺.

Example 28



[00372] (*R*)-3-amino-1-*N*-Cbz-piperidine (253 mg, 1.08 mmol) and LiClO₄ (126 mg, 1.19 mmol) were added sequentially to a solution of *tert*-butyl 1-oxa-5-azaspiro[2.3]hexane-5-carboxylate (200 mg, 1.08 mmol) in ACN (10 mL). After stirring at 80 °C for 16 h the reaction mixture was concentrated under reduced pressure. Purification (SiO₂, 0→5% MeOH/CH₂Cl₂) afforded the desired product (441 mg, 97%). LCMS: C₂₂H₃₃N₃O₅ requires: 419, found: *m/z* = 420 [M+H]⁺.

[00373] CDI (255 mg, 1.57 mmol) and DBU (392 μL, 2.62 mmol) were added sequentially to a solution of benzyl (3*R*)-3-({[1-(*tert*-butoxycarbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)piperidine-1-carboxylate (440 mg, 1.05 mmol) in ACN (2.6 mL). After stirring at 80 °C for 30 min, the reaction mixture was concentrated under reduced pressure. Purification (SiO₂, 0→5% MeOH/CH₂Cl₂) afforded the desired product (363 mg, 78%). LCMS: C₂₃H₃₁N₃O₆ requires: 445, found: *m/z* = 446 [M+H]⁺.

[00374] A solution of *tert*-butyl 7-[(3*R*)-1-[(benzyloxy)carbonyl]piperidin-3-yl]-6-oxo-5-oxa-2,7-diazaspiro[3.4]octane-2-carboxylate (363 mg, 0.81 mmol, 1 equiv) in MeOH (8.1 mL) was stirred with Pd/C (36.3 mg, 10 wt%) under a balloon of H₂. After stirring for 2 h, the reaction mixture was filtered through Celite and concentrated under reduced pressure to afford *tert*-butyl (*R*)-6-oxo-7-(piperidin-3-yl)-5-oxa-2,7-diazaspiro[3.4]octane-2-carboxylate. LCMS: C₁₅H₂₅N₃O₄ requires: 311, found: *m/z* = 312 [M+H]⁺.

[00375] Procedure A was followed to afford *tert*-butyl 7-[(3*R*)-1-(6-chloro-5-cyanopyrazin-2-yl)piperidin-3-yl]-6-oxo-5-oxa-2,7-diazaspiro[3.4]octane-2-carboxylate (364 mg, 95%, 2 steps). LCMS: C₂₀H₂₅ClN₆O₄ requires: 448, found: *m/z* = 449 [M+H]⁺.

[00376] Procedure B was followed to afford *tert*-butyl (*R*)-7-(1-(5-cyano-6-((1-methyl-1H-pyrazol-4-yl)amino)pyrazin-2-yl)piperidin-3-yl)-6-oxo-5-oxa-2,7-diazaspiro[3.4]octane-2-carboxylate (131 mg, 56%). LCMS: C₂₄H₃₁N₉O₄ requires: 509, found: *m/z* = 510 [M+H]⁺.

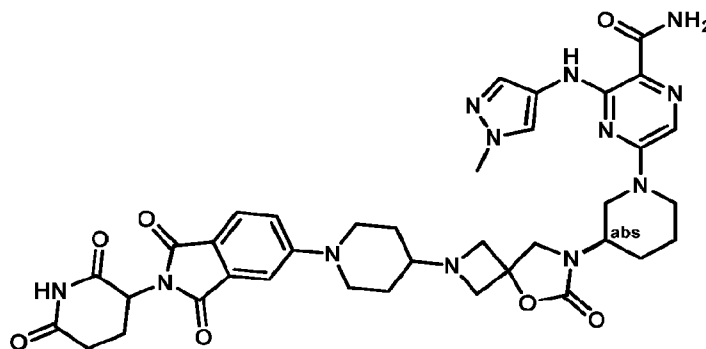
[00377] Procedure C was followed to afford *tert*-butyl (*R*)-7-(1-(5-carbamoyl-6-((1-methyl-1H-pyrazol-4-yl)amino)pyrazin-2-yl)piperidin-3-yl)-6-oxo-5-oxa-2,7-diazaspiro[3.4]octane-2-carboxylate (121 mg, 89%). LCMS: C₂₄H₃₃N₉O₅ requires: 527, found: *m/z* = 528 [M+H]⁺.

[00378] Compound 211: Procedure D was followed to afford a crude amine that was subjected to Procedure Q to afford 5-[(3*R*)-3-[2-({1-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]piperidin-4-yl}methyl)-6-oxo-5-oxa-2,7-diazaspiro[3.4]octan-7-yl]piperidin-1-yl]-3-[(1-methylpyrazol-4-yl)amino]pyrazine-2-carboxamide (13.8 mg, 49%, 2 steps). ¹H NMR (500 MHz, Acetonitrile-*d*₃) δ 10.74 (s, 1H), 8.94 (s, 1H), 7.87 (s, 1H), 7.65 (d, *J* = 8.6 Hz, 1H), 7.50 (s, 1H), 7.47 (d, *J* = 0.8 Hz, 1H), 7.37 (s, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.17 (dd, *J* = 8.7, 2.4

Hz, 1H), 5.79 (s, 1H), 5.07 – 4.88 (m, 1H), 4.50 (d, $J = 12.8$ Hz, 1H), 4.19 (d, $J = 13.6$ Hz, 1H), 4.00 (d, $J = 13.1$ Hz, 2H), 3.84 (s, 3H), 3.78 (dd, $J = 19.2, 10.2$ Hz, 2H), 3.45 (d, $J = 8.1$ Hz, 1H), 3.39 (d, $J = 8.1$ Hz, 1H), 3.34 (d, $J = 8.1$ Hz, 1H), 3.31 – 3.25 (m, 1H), 3.17 (dd, $J = 12.9, 10.4$ Hz, 1H), 3.14 – 3.07 (m, 1H), 2.97 (td, $J = 12.8, 2.7$ Hz, 2H), 2.87 – 2.63 (m, 3H), 2.39 (d, $J = 6.9$ Hz, 2H), 2.31 – 2.26 (m, 1H), 2.15 – 2.08 (m, 1H), 1.91 (dt, $J = 13.3, 3.5$ Hz, 1H), 1.88 – 1.84 (m, 1H), 1.81 (dd, $J = 12.1, 3.6$ Hz, 3H), 1.70 (tt, $J = 11.1, 3.9$ Hz, 1H), 1.61 (dtd, $J = 11.6, 7.4, 4.0$ Hz, 1H), 0.90 (dq, $J = 7.8, 6.0, 5.5$ Hz, 3H). LCMS: $C_{38}H_{44}N_{12}O_7$ requires: 780, found: $m/z = 781$ $[M+H]^+$.

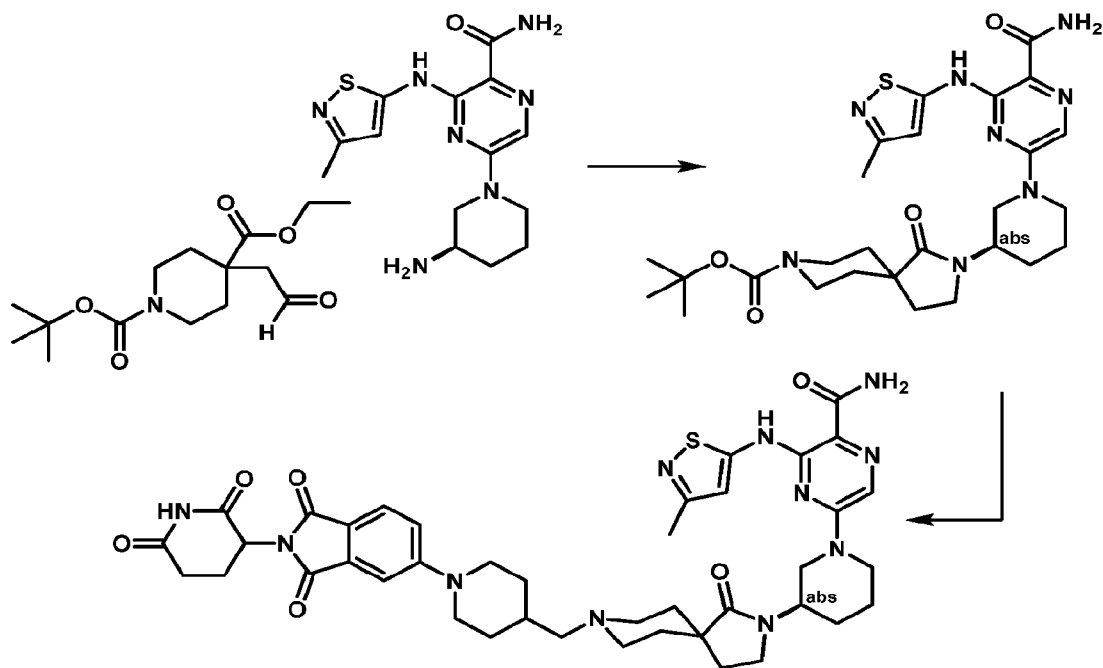
Example 29

[00379] Compound 212



[00380] Procedure D was followed to afford a crude amine that was subjected to Procedure Q to afford 5-[(3*R*)-3-(2-{1-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]piperidin-4-yl}-6-oxo-5-oxa-2,7-diazaspiro[3.4]octan-7-yl)piperidin-1-yl]-3-[(1-methylpyrazol-4-yl)amino]pyrazine-2-carboxamide (9.5 mg, 34%, 2 steps). ^1H NMR (500 MHz, Acetonitrile- d_3) δ 10.71 (s, 1H), 8.90 (s, 1H), 7.84 (s, 1H), 7.63 (d, $J = 8.5$ Hz, 1H), 7.47 (s, 1H), 7.44 (s, 1H), 7.34 (s, 1H), 7.28 (d, $J = 2.4$ Hz, 1H), 7.15 (dd, $J = 8.6, 2.4$ Hz, 1H), 5.75 (s, 1H), 4.93 (dd, $J = 12.3, 5.4$ Hz, 1H), 4.50 (dd, $J = 13.1, 4.1$ Hz, 1H), 4.18 (d, $J = 13.6$ Hz, 1H), 3.81 (s, 3H), 3.81 – 3.66 (m, 3H), 3.44 (d, $J = 8.0$ Hz, 1H), 3.40 (d, $J = 8.0$ Hz, 1H), 3.34 (d, $J = 7.9$ Hz, 1H), 3.31 (d, $J = 7.8$ Hz, 1H), 3.17 – 3.00 (m, 4H), 2.83 – 2.60 (m, 3H), 2.36 (tt, $J = 8.3, 3.7$ Hz, 1H), 2.12 – 2.05 (m, 2H), 1.96 (s, 1H), 1.87 (dq, $J = 13.4, 3.3$ Hz, 1H), 1.79 (ddd, $J = 16.5, 10.2, 4.2$ Hz, 3H), 1.70 – 1.59 (m, 1H), 1.33 (qd, $J = 9.6, 5.0$ Hz, 1H), 0.87 (dt, $J = 11.1, 5.7$ Hz, 2H). LCMS: $C_{37}H_{42}N_{12}O_7$ requires: 766, found: $m/z = 767$ $[M+H]^+$.

Example 30

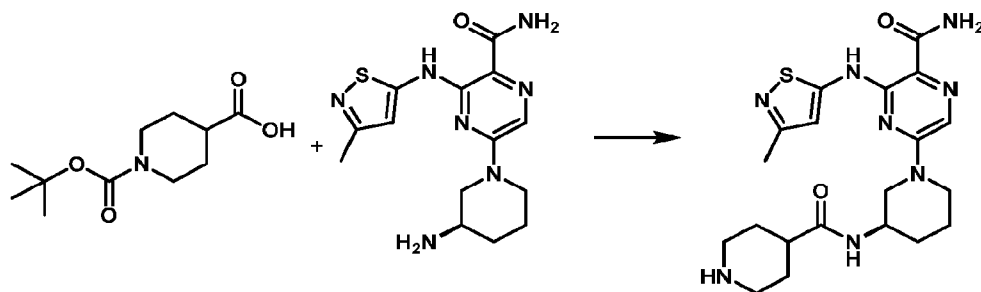


[00381] Q: A mixture of 4-(2-oxoethyl)-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester (23.7 mg, 79 μ mol) and (*R*)-5-(3-aminopiperidin-1-yl)-3-((3-methylisothiazol-5-yl)amino)pyrazine-2-carboxamide (41 mg, 103 μ mol, TFA salt) was dissolved in DCE (1 mL) and stirred at rt for 5 min before $\text{NaBH}(\text{OAc})_3$ (33 mg, 160 μ mol) was added in one portion. After 16 h the mixture was diluted with CH_2Cl_2 and NaHCO_3 (sat. aq.) and the aqueous phase was extracted (3 x 5 mL CH_2Cl_2). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified (RP-HPLC) to afford *tert*-butyl 2-[(3*R*)-1-{5-carbamoyl-6-[(3-methyl-1,2-thiazol-5-yl)amino]pyrazin-2-yl}piperidin-3-yl]-1-oxo-2,8-diazaspiro[4.5]decane-8-carboxylate (40 mg, 68%). LCMS: $\text{C}_{27}\text{H}_{38}\text{N}_8\text{O}_4\text{S}$ requires: 570, found: $m/z = 571$.

[00382] Compound 205: Procedure **D** was followed to afford a crude amine that was subjected to Procedure **Q** to afford 5-[(3*R*)-3-[8-({1-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]piperidin-4-yl}methyl)-1-oxo-2,8-diazaspiro[4.5]decan-2-yl]piperidin-1-yl]-3-[(3-methyl-1,2-thiazol-5-yl)amino]pyrazine-2-carboxamide (29.7 mg, 49%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 12.29 (s, 1H), 11.08 (s, 1H), 7.92 (s, 1H), 7.84 (s, 1H), 7.66 (d, $J = 8.5$ Hz, 1H), 7.58 (s, 1H), 7.32 (d, $J = 2.3$ Hz, 1H), 7.24 (dd, $J = 8.8, 2.3$ Hz, 1H), 6.86 (s, 1H), 5.07 (dd, $J = 12.8, 5.4$ Hz, 1H), 4.46 (s, 2H), 4.05 (d, $J = 13.0$ Hz, 2H), 3.83 (d, $J = 10.9$ Hz, 1H), 3.12 (t, $J = 12.6$ Hz, 1H), 2.98 (t, $J = 12.4$ Hz, 2H), 2.89 (t, $J = 12.9$ Hz, 1H), 2.76 (d, $J = 9.1$ Hz, 2H), 2.71 – 2.55 (m, 3H), 2.30 (s, 3H), 2.15 (d, $J = 6.9$ Hz, 2H), 2.09 – 1.94 (m, 3H), 1.94 – 1.69 (m, 9H),

1.62 (d, $J = 13.1$ Hz, 1H), 1.36 (dd, $J = 25.7, 12.6$ Hz, 2H), 1.25 (s, 1H), 1.15 (d, $J = 12.5$ Hz, 2H). LCMS: $C_{41}H_{49}N_{11}O_6S$ requires: 823, found: $m/z = 824$.

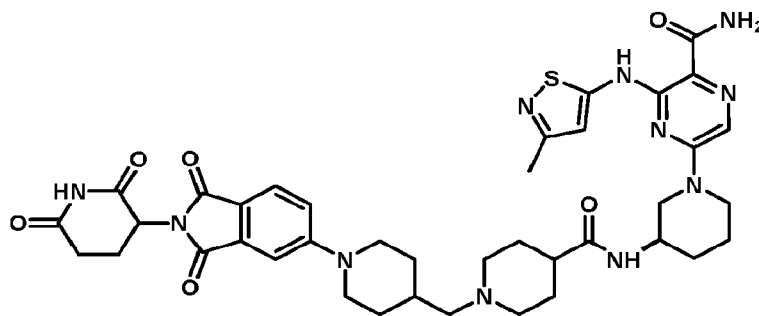
Example 31



[00383] R: A mixture of 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (22.35 mg, 100 μ mol) and (1,2,3-benzotriazol-1-yloxy)tris(dimethylamino)phosphonium; hexafluoro-lambda5-phosphanuide (50 mg, 110 μ mol), and *i*-Pr₂NEt (65 μ L, 370 μ mol) was added at rt. After 5 min 5-[(3*R*)-3-aminopiperidin-1-yl]-3-[(3-methyl-1,2-thiazol-5-yl)amino]pyrazine-2-carboxamide (25.00 mg, 70 μ mol) was added and the mixture was stirred for 20 min. The reaction mixture was diluted with H₂O and extracted (3 x 5 mL CH₂Cl₂). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated. The crude residue was purified (SiO₂, 0→10% MeOH/CH₂Cl₂) to afford *tert*-butyl 4-[(3*R*)-1-[(5-carbamoyl-6-[(3-methyl-1,2-thiazol-5-yl)amino]pyrazin-2-yl)piperidin-3-yl]carbamoyl]piperidine-1-carboxylate (25 mg, 61%). The product was dissolved in a mixture of CH₂Cl₂ (1 mL) and TFA (1 mL) and stirred for 30 min before being concentrated to dryness. LCMS: $C_{25}H_{36}N_8O_4S$ requires: 544, found: $m/z = 546$.

Example 32

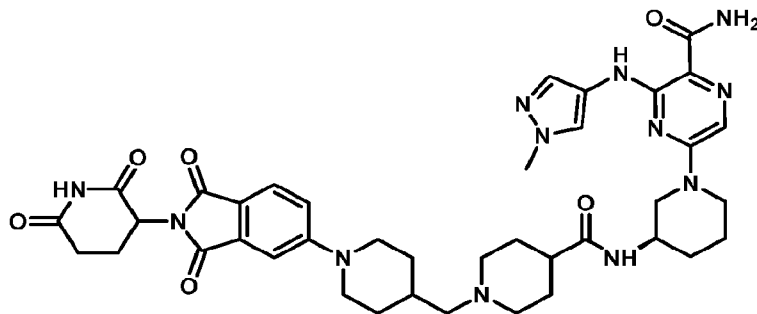
[00384] Compound 217



[00385] Procedure **Q** was followed to afford 5-[(3*R*)-3-[1-({1-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]piperidin-4-yl}methyl)piperidine-4-amido]piperidin-1-yl]-3-[(3-methyl-1,2-thiazol-5-yl)amino]pyrazine-2-carboxamide (18 mg, 19%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.27 (d, *J* = 32.4 Hz, 1H), 11.06 (s, 1H), 8.01 (s, 1H), 7.84 (d, *J* = 18.1 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.58 – 7.43 (m, 2H), 7.28 (s, 1H), 7.20 (d, *J* = 9.1 Hz, 1H), 6.85 (d, *J* = 22.5 Hz, 1H), 5.05 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.17 (s, 1H), 4.00 (d, *J* = 14.4 Hz, 2H), 3.74 (d, *J* = 14.2 Hz, 1H), 3.57 (s, 1H), 3.48 – 3.35 (m, 3H), 3.09 – 2.77 (m, 3H), 2.72 – 2.54 (m, 2H), 2.28 (s, 3H), 2.22 – 2.05 (m, 2H), 2.05 – 1.90 (m, 3H), 1.80 (s, 3H), 1.70 (d, *J* = 11.6 Hz, 3H), 1.64 – 1.28 (m, 5H), 1.23 (s, 1H), 1.20 – 0.96 (m, 3H). LCMS: C₃₈H₄₆N₁₂O₆S requires: 798, found: *m/z* = 799 [M+H]⁺.

Example 33

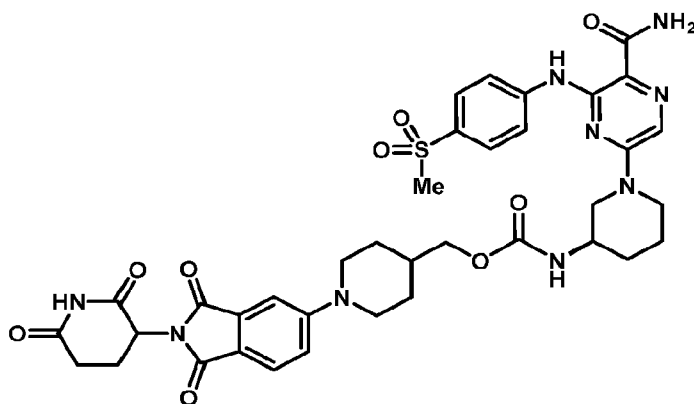
[00386] Compound **215**



[00387] Procedure **Q** was followed to afford 5-((3*R*)-3-(1-((1-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl]piperidin-4-yl)methyl)piperidine-4-carboxamido)piperidin-1-yl)-3-((1-methyl-1H-pyrazol-4-yl)amino)pyrazine-2-carboxamide (9.7 mg, 33%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.07 (s, 1H), 10.87 (s, 1H), 7.98 (s, 1H), 7.81 (d, *J* = 6.9 Hz, 1H), 7.66 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.55 (s, 1H), 7.48 (s, 1H), 7.30 (d, *J* = 2.1 Hz, 1H), 7.28 – 7.19 (m, 2H), 5.06 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.29 (s, 1H), 4.04 (d, *J* = 13.0 Hz, 2H), 3.94 (d, *J* = 13.0 Hz, 1H), 3.86 (s, 3H), 3.70 (s, 1H), 3.08 (t, *J* = 10.9 Hz, 1H), 3.01 – 2.92 (m, 2H), 2.90 – 2.78 (m, 3H), 2.09 (h, *J* = 6.3 Hz, 3H), 2.00 (dd, *J* = 11.8, 6.0 Hz, 1H), 1.92 – 1.71 (m, 8H), 1.59 (d, *J* = 24.4 Hz, 7H), 1.12 (d, *J* = 12.5 Hz, 3H). LCMS: C₃₉H₄₈N₁₂O₆ requires: 780, found: *m/z* = 781 [M+H]⁺.

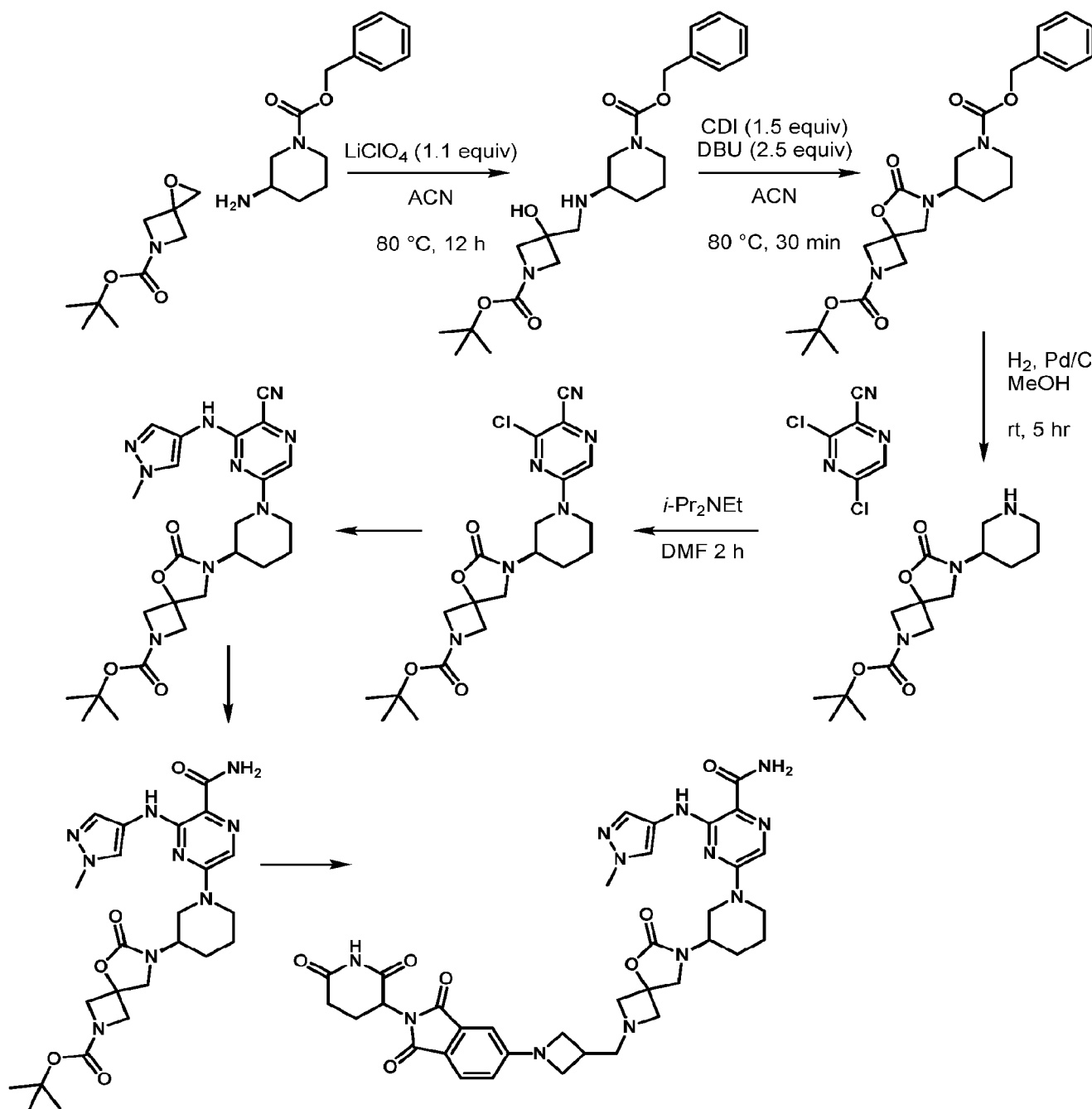
Example 34

[00388] Compound **218**



[00389] A solution of 2-(2,6-dioxopiperidin-3-yl)-5-(4-(hydroxymethyl)piperidin-1-yl)isoindoline-1,3-dione (37.1 mg, 100 μ M) and Et₃N (18.1 μ L, 13 mg, 130 μ mol) in a mixture of CH₂Cl₂ (1 mL) and NMP (0.1 mL) was cooled to 0 °C before a 100 μ L solution of 4-nitrophenyl chloroformate (20.2 mg, 0.10 mmol) was added. After 10 min the ice bath was removed and the reaction mixture was stirred for one hour, diluted with H₂O (1 mL) and extracted (2 x 3 mL CH₂Cl₂). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated. The crude nitrophenyl carbonate and 5-[(3*R*)-3-aminocyclohexyl]-3-[(4-methanesulfonylphenyl)amino]pyrazine-2-carboxamide (19.5 mg, 50 μ mol) was dissolved in DMF (0.5 mL) and Et₃N (18.1 μ L, 13.1 mg, 130 μ mol) was added. The mixture was stirred for one hour at rt before being filtered and purified (RP-HPLC) to afford (1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)piperidin-4-yl)methyl ((*R*)-1-(5-carbamoyl-6-((4-(methanesulfonyl)phenyl)amino)pyrazin-2-yl)piperidin-3-yl)carbamate (17 mg, 39%). ¹H NMR (500 MHz, chloroform-*d*) δ 11.60 (s, 1H), 7.99 (d, *J* = 13.7 Hz, 1H), 7.94 – 7.75 (m, 4H), 7.55 (s, 0H), 5.30 (s, 2H), 4.96 (dd, *J* = 12.2, 5.8 Hz, 1H), 4.39 – 3.12 (m, 13H), 2.89 (t, *J* = 19.6 Hz, 1H), 2.84 – 2.65 (m, 1H), 2.20 – 2.10 (m, 1H), 2.10 – 1.98 (m, 1H), 1.59 (s, 15H). LCMS: C₃₇H₄₁N₉O₉S requires: 787, found: *m/z* = 788 [M+H]⁺.

Example 35



[00390] (*R*)-3-amino-1-*N*-Cbz-piperidine (253 mg, 1.08 mmol) and LiClO₄ (126 mg, 1.19 mmol) were added sequentially to a solution of *tert*-butyl 1-oxa-5-azaspiro[2.3]hexane-5-carboxylate (200 mg, 1.08 mmol) in ACN (10 mL). After stirring at 80 °C for 16 h the reaction mixture was concentrated under reduced pressure. Purification (SiO₂, 0→5% MeOH/CH₂Cl₂) afforded the desired product (441 mg, 97%). LCMS: C₂₂H₃₃N₃O₅ requires: 419, found: *m/z* = 420 [M+H]⁺.

[00391] CDI (255 mg, 1.57 mmol) and DBU (392 μ L, 2.62 mmol) were added sequentially to a solution of benzyl (3*R*)-3-([1-(*tert*-butoxycarbonyl)-3-hydroxyazetidin-3-yl]methyl)amino)piperidine-1-carboxylate (440 mg, 1.05 mmol) in ACN (2.6 mL). After stirring at 80 °C for 30 min, the reaction mixture was concentrated under reduced pressure. Purification (SiO₂, 0→5% MeOH/CH₂Cl₂) afforded the desired product (363 mg, 78%). LCMS: C₂₃H₃₁N₃O₆ requires: 445, found: m/z = 446 [M+H]⁺.

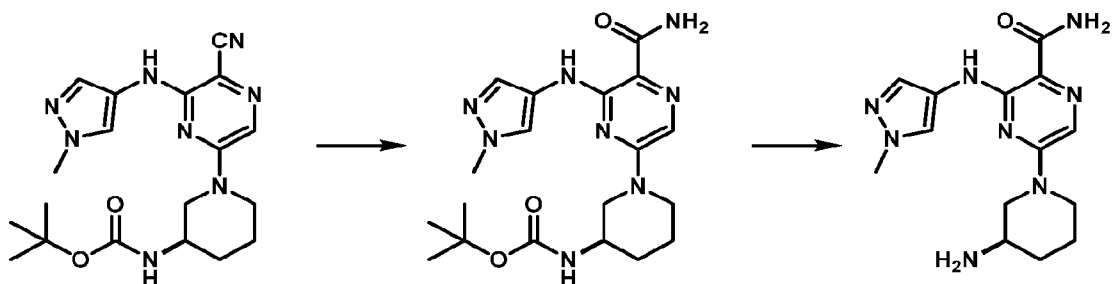
[00392] A solution of *tert*-butyl 7-[(3*R*)-1-[(benzyloxy)carbonyl]piperidin-3-yl]-6-oxo-5-oxa-2,7-diazaspiro[3.4]octane-2-carboxylate (363 mg, 0.81 mmol, 1 equiv) in MeOH (8.1 mL) was stirred with Pd/C (36.3 mg, 10 wt%) under a balloon of H₂. After stirring for 2 h, the reaction mixture was filtered through Celite and concentrated under reduced pressure to afford *tert*-butyl (*R*)-6-oxo-7-(piperidin-3-yl)-5-oxa-2,7-diazaspiro[3.4]octane-2-carboxylate. LCMS: C₁₅H₂₅N₃O₄ requires: 311, found: m/z = 312 [M+H]⁺.

[00393] Procedure **A** was followed to afford *tert*-butyl 7-[(3*R*)-1-(6-chloro-5-cyanopyrazin-2-yl)piperidin-3-yl]-6-oxo-5-oxa-2,7-diazaspiro[3.4]octane-2-carboxylate (364 mg, 95%, 2 steps). LCMS: C₂₀H₂₅ClN₆O₄ requires: 448, found: m/z = 449 [M+H]⁺.

[00394] Procedure **B** was followed to afford *tert*-butyl (*R*)-7-(1-(5-cyano-6-((1-methyl-1H-pyrazol-4-yl)amino)pyrazin-2-yl)piperidin-3-yl)-6-oxo-5-oxa-2,7-diazaspiro[3.4]octane-2-carboxylate (131 mg, 56%). LCMS: C₂₄H₃₁N₉O₄ requires: 509, found: m/z = 510 [M+H]⁺.

[00395] Procedure **C** was followed to afford *tert*-butyl (*R*)-7-(1-(5-carbamoyl-6-((1-methyl-1H-pyrazol-4-yl)amino)pyrazin-2-yl)piperidin-3-yl)-6-oxo-5-oxa-2,7-diazaspiro[3.4]octane-2-carboxylate (121 mg, 89%). LCMS: C₂₄H₃₃N₉O₅ requires: 527, found: m/z = 528 [M+H]⁺.

[00396] Compound **213**: Procedure **D** was followed to afford a crude amine that was subjected to Procedure **Q** to afford 5-((3*R*)-3-(2-((1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)azetidin-3-yl)methyl)-6-oxo-5-oxa-2,7-diazaspiro[3.4]octan-7-yl)piperidin-1-yl)-3-((1-methyl-1H-pyrazol-4-yl)amino)pyrazine-2-carboxamide (8.4 mg, 30%, 2 steps). ¹H NMR (500 MHz, acetonitrile-*d*₃) δ 10.72 (s, 1H), 8.91 – 8.84 (m, 1H), 7.84 (s, 1H), 7.60 (d, J = 8.3 Hz, 1H), 7.46 (d, J = 17.7 Hz, 2H), 7.34 (s, 1H), 6.76 (s, 1H), 6.59 (d, J = 8.5 Hz, 1H), 5.75 (s, 1H), 4.92 (dd, J = 12.2, 5.3 Hz, 1H), 4.49 (dd, J = 12.6, 4.2 Hz, 1H), 4.18 (d, J = 13.7 Hz, 1H), 4.08 (t, J = 7.7 Hz, 2H), 3.83 – 3.66 (m, 6H), 3.47 – 3.33 (m, 4H), 3.16 – 3.03 (m, 2H), 2.81 – 2.62 (m, 5H), 2.08 (d, J = 17.1 Hz, 2H), 2.01 – 1.96 (m, 1H), 1.92 – 1.75 (m, 1H), 1.66 (qt, J = 11.5, 4.0 Hz, 1H). LCMS: C₃₆H₄₀N₁₂O₇ requires: 752, found: m/z = 753 [M+H]⁺.

Example 36

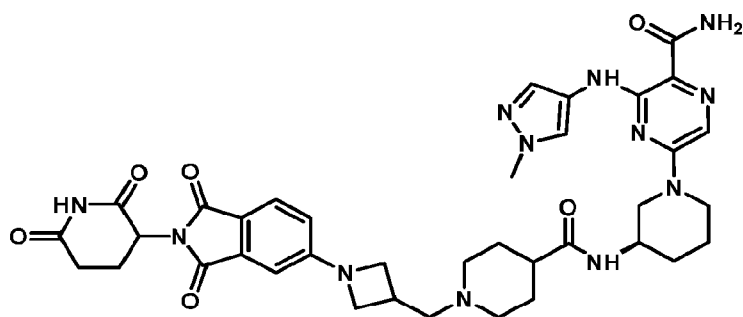
[00397] Procedure **B** was followed to afford *tert*-butyl (*R*)-(1-(5-cyano-6-((1-methyl-1H-pyrazol-4-yl)amino)pyrazin-2-yl)piperidin-3-yl)carbamate (941 mg, 80%). LCMS: $C_{19}H_{26}N_8O_2$ requires: 398, found: $m/z = 399$ $[M+H]^+$.

[00398] Procedure **C** was followed to afford *tert*-butyl (*R*)-(1-(5-carbamoyl-6-((1-methyl-1H-pyrazol-4-yl)amino)pyrazin-2-yl)piperidin-3-yl)carbamate (297 mg, 95%). LCMS: $C_{19}H_{28}N_8O_3$ requires: 416, found: $m/z = 417$ $[M+H]^+$.

[00399] Procedure **D** was followed to afford (*R*)-5-(3-aminopiperidin-1-yl)-3-((1-methyl-1H-pyrazol-4-yl)amino)pyrazine-2-carboxamide. LCMS: $C_{14}H_{20}N_8O$ requires: 4=316, found: $m/z = 317$ $[M+H]^+$.

Example 37

[00400] Compound **216**



[00401] Procedure **R** was followed to afford (*R*)-3-((1-methyl-1H-pyrazol-4-yl)amino)-5-(3-(piperidine-4-carboxamido)piperidin-1-yl)pyrazine-2-carboxamide (199 mg, 75%). LCMS: $C_{20}H_{29}N_9O_2$ requires: 427, found: $m/z = 428$ $[M+H]^+$.

[00402] Procedure **Q** was followed to afford 5-[(3*R*)-3-[1-((1-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]azetidin-3-yl)methyl)piperidine-4-amido]piperidin-1-yl]-3-[(1-methylpyrazol-4-yl)amino]pyrazine-2-carboxamide (8.4 mg, 10%). ^1H NMR (500 MHz, acetonitrile- d_3) δ 10.74 (s, 1H), 8.87 (s, 1H), 7.92 (s, 1H), 7.59 (d, $J = 8.3$ Hz, 1H), 7.45 (d, J

= 7.4 Hz, 2H), 7.38 – 7.22 (m, 1H), 6.76 (d, $J = 2.1$ Hz, 1H), 6.59 (dd, $J = 8.3, 2.2$ Hz, 1H), 6.34 (d, $J = 7.2$ Hz, 1H), 5.72 (s, 1H), 4.92 (dd, $J = 12.3, 5.3$ Hz, 1H), 4.24 – 4.16 (m, 1H), 4.11 (t, $J = 8.1$ Hz, 2H), 3.87 (s, 3H), 3.85 – 3.78 (m, 2H), 3.68 (dd, $J = 8.2, 5.4$ Hz, 2H), 3.45 (td, $J = 9.0, 8.5, 4.4$ Hz, 1H), 3.35 (dd, $J = 13.1, 7.8$ Hz, 1H), 3.28 (s, 1H), 2.97 (ddt, $J = 10.1, 7.8, 4.2$ Hz, 1H), 2.90 – 2.79 (m, 2H), 2.70 (dddt, $J = 21.8, 13.4, 7.8, 4.3$ Hz, 3H), 2.57 (d, $J = 7.4$ Hz, 2H), 2.11 – 2.01 (m, 3H), 1.87 – 1.77 (m, 2H), 1.71 – 1.49 (m, 6H). LCMS: $C_{37}H_{44}N_{12}O_6$ requires: 752, found: $m/z = 753$.

Example 38

[00403] General Procedure 1: Amide Coupling

[00404] A mixture of amine (0.03 mmol), acid (0.03 mmol), HATU (0.04 mmol), DIPEA (0.15 mmol), and DMF was allowed to stir at room temperature for 30 minutes. The mixture was purified by HPLC ($H_2O/MeCN$ with 0.1% TFA) to afford the amide product.

[00405] General Procedure 2: Reductive Amination

[00406] A mixture of amine TFA salt (0.07 mmol), aldehyde (0.1 mmol), triethylamine (0.28 mmol), and DCE were allowed to stir at room temperature for 10 minutes. $NaBH(OAc)_3$ (0.14 mmol) was added and the mixture was allowed to stir at room temperature for 2 h. The mixture was filtered through celite, washed with CH_2Cl_2 , concentrated, and purified by HPLC ($H_2O/MeCN$ with 0.1% TFA) to afford the amine product.

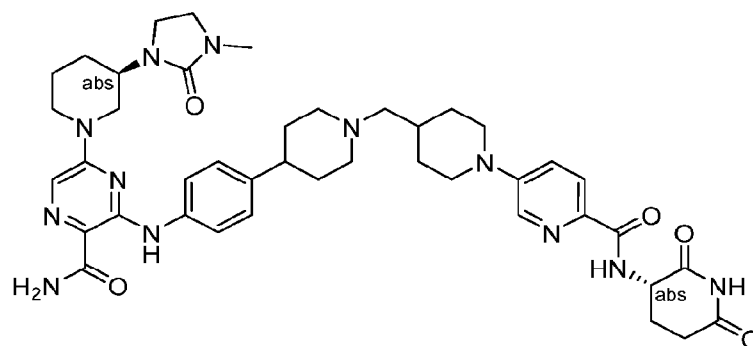
[00407] General Procedure 3: Aryl Fluoride Displacement

[00408] A mixture of amine (0.22 mmol), aryl fluoride (0.22 mmol), DIPEA (0.88 mmol), and DMF (1 mL) was allowed to stir at 90 °C for 16 h. The mixture was purified by HPLC ($H_2O/MeCN$ with 0.1% TFA) to afford the desired product.

Example 39

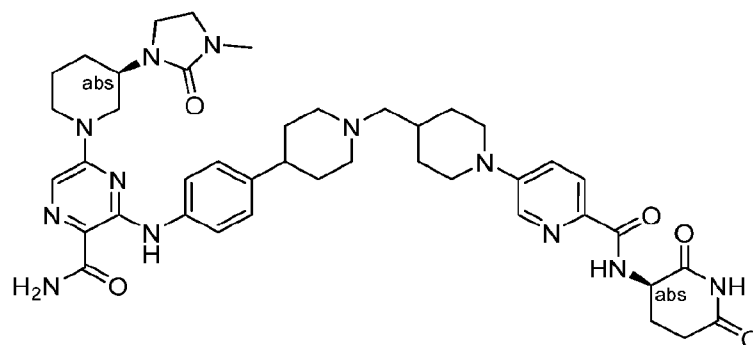
[00409] Prepared according to General Procedure 2

[00410] Compound 195



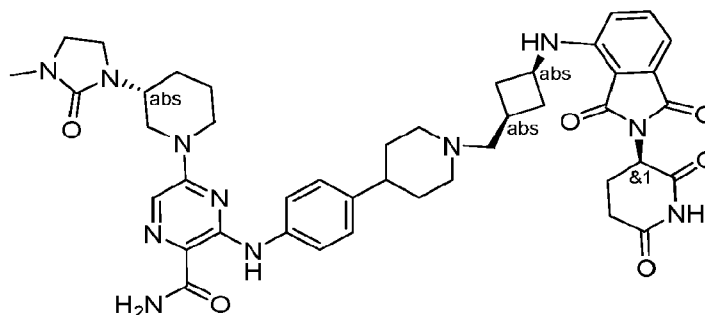
[00411] ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 11.19 (s, 1H), 10.85 (s, 1H), 8.71 (d, $J = 8.2$ Hz, 1H), 8.32 (d, $J = 2.9$ Hz, 1H), 7.85 (d, $J = 8.8$ Hz, 1H), 7.76 (s, 1H), 7.67 (s, 1H), 7.51 (d, $J = 8.1$ Hz, 2H), 7.42 (dd, $J = 8.9, 2.9$ Hz, 1H), 7.34 (s, 1H), 7.18 (d, $J = 8.2$ Hz, 2H), 4.75 (ddd, $J = 13.2, 8.2, 5.4$ Hz, 1H), 4.34 (dd, $J = 39.7, 12.8$ Hz, 2H), 3.96 (d, $J = 12.5$ Hz, 2H), 3.62 (d, $J = 11.0$ Hz, 1H), 3.28 (dd, $J = 14.4, 7.4$ Hz, 5H), 3.11 – 2.76 (m, 8H), 2.73 (s, 3H), 2.19 (dd, $J = 10.7, 5.3$ Hz, 3H), 2.08 – 1.93 (m, 3H), 1.89 – 1.71 (m, 8H), 1.59 (d, $J = 29.1$ Hz, 4H), 1.23 (d, $J = 14.3$ Hz, 5H). LCMS: $\text{C}_{42}\text{H}_{54}\text{N}_{12}\text{O}_5$ requires: 806, found: $m/z = 807$ $[\text{M}+\text{H}]^+$.

[00412] Compound 194



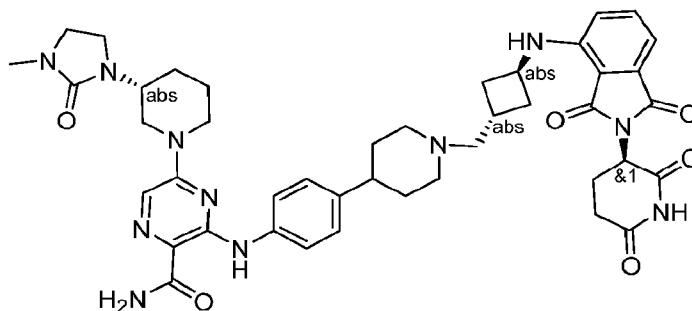
[00413] ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 11.30 (s, 1H), 10.86 (s, 1H), 8.71 (d, $J = 8.1$ Hz, 1H), 8.36 (s, 1H), 7.88 (d, $J = 8.7$ Hz, 1H), 7.79 (s, 1H), 7.69 (s, 1H), 7.58 (d, $J = 7.9$ Hz, 2H), 7.46 (d, $J = 8.8$ Hz, 1H), 7.36 (s, 1H), 7.19 (d, $J = 8.2$ Hz, 2H), 4.75 (ddd, $J = 13.1, 8.2, 5.4$ Hz, 1H), 4.42 – 4.25 (m, 2H), 4.01 (d, $J = 12.9$ Hz, 2H), 3.65 (dd, $J = 13.8, 7.9$ Hz, 3H), 3.27 (t, $J = 8.3$ Hz, 3H), 3.17 – 2.87 (m, 6H), 2.86 – 2.70 (m, 5H), 2.27 – 2.10 (m, 2H), 2.11 – 1.69 (m, 12H), 1.68 – 1.47 (m, 2H), 1.30 (d, $J = 52.1$ Hz, 3H). LCMS: $\text{C}_{42}\text{H}_{54}\text{N}_{12}\text{O}_5$ requires: 806, found: $m/z = 807$ $[\text{M}+\text{H}]^+$.

[00414] Compound 201



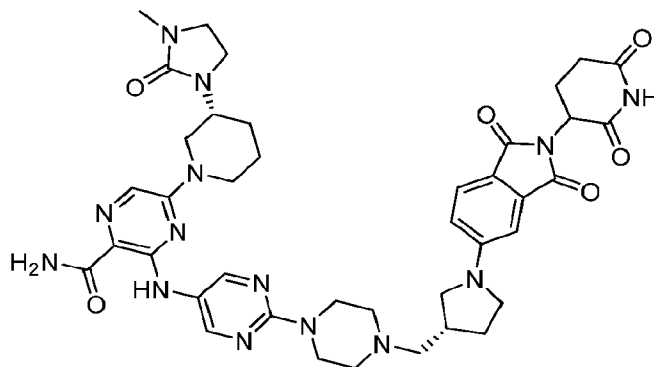
[00415] ^1H NMR (500 MHz, acetonitrile- d_3) δ 11.13 (s, 1H), 8.92 (s, 1H), 7.67 – 7.55 (m, 5H), 7.43 (s, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 7.4 Hz, 1H), 6.99 (d, J = 8.5 Hz, 1H), 6.37 (s, 1H), 5.81 (s, 1H), 5.01 – 4.92 (m, 1H), 4.43 (d, J = 12.4 Hz, 1H), 4.31 (d, J = 13.2 Hz, 1H), 4.11 (d, J = 8.5 Hz, 1H), 3.71 (s, 1H), 3.63 – 3.54 (m, 2H), 3.45 – 3.23 (m, 5H), 3.19 (s, 2H), 3.14 – 2.92 (m, 4H), 2.76 (d, J = 14.2 Hz, 9H), 1.93 – 1.63 (m, 5H). LCMS: $\text{C}_{43}\text{H}_{51}\text{N}_{11}\text{O}_6$ requires: 817, found: m/z = 818 $[\text{M}+\text{H}]^+$.

[00416] Compound **202**



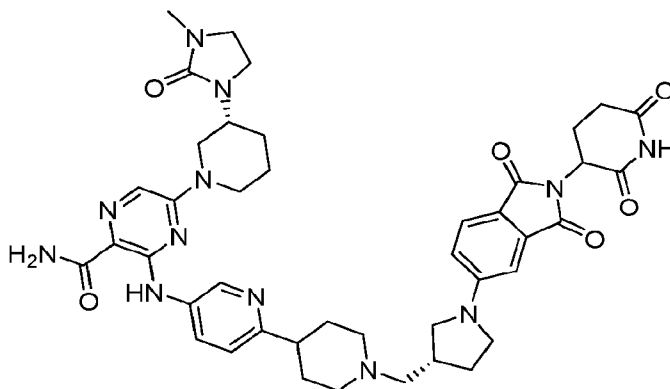
[00417] ^1H NMR (500 MHz, acetonitrile- d_3) δ 11.13 (s, 1H), 8.93 (s, 1H), 8.65 (s, 1H), 7.60 (dd, J = 17.5, 6.7 Hz, 5H), 7.43 (s, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 7.0 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 6.46 (s, 1H), 5.83 (s, 1H), 4.98 (dd, J = 12.5, 5.2 Hz, 1H), 4.51 – 4.16 (m, 4H), 3.72 (s, 1H), 3.60 (d, J = 12.4 Hz, 2H), 3.46 – 3.26 (m, 7H), 3.03 (tt, J = 30.3, 14.5 Hz, 6H), 2.89 – 2.63 (m, 8H), 2.42 (d, J = 8.7 Hz, 2H), 2.31 (d, J = 12.7 Hz, 2H), 2.05 (d, J = 17.6 Hz, 3H), 1.94 – 1.59 (m, 4H). LCMS: $\text{C}_{43}\text{H}_{51}\text{N}_{11}\text{O}_6$ requires: 817, found: m/z = 818 $[\text{M}+\text{H}]^+$.

[00418] Compound **204**



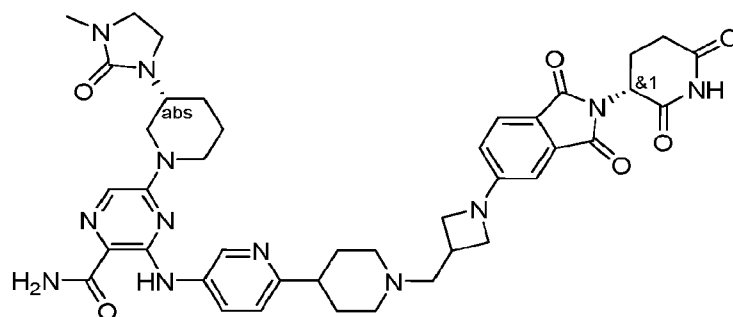
[00419] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.07 (s, 1H), 10.72 (s, 1H), 8.57 (s, 2H), 7.75 (s, 1H), 7.66 (d, $J = 8.8$ Hz, 2H), 7.34 (s, 1H), 6.92 (d, $J = 2.1$ Hz, 1H), 6.84 (dd, $J = 8.4, 2.1$ Hz, 1H), 5.06 (dd, $J = 12.9, 5.4$ Hz, 1H), 4.22 (dd, $J = 37.3, 13.0$ Hz, 2H), 3.79 – 3.40 (m, 9H), 3.28 – 3.05 (m, 16H), 2.97 – 2.82 (m, 2H), 2.67 (s, 4H), 2.24 – 1.95 (m, 2H), 1.78 (q, $J = 5.6, 5.1$ Hz, 5H), 1.52 (s, 2H), 1.25 (s, 4H). LCMS: $\text{C}_{40}\text{H}_{48}\text{N}_{14}\text{O}_6$ requires: 820, found: $m/z = 821$ $[\text{M}+\text{H}]^+$.

[00420] Compound **207**



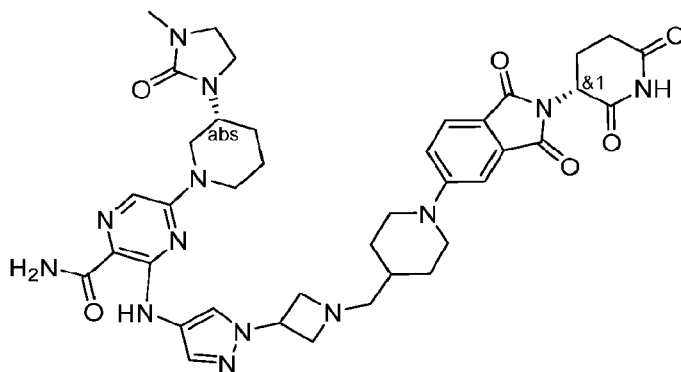
[00421] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.27 (s, 1H), 11.07 (s, 1H), 8.55 (d, $J = 2.4$ Hz, 1H), 8.13 – 8.05 (m, 1H), 7.84 – 7.78 (m, 1H), 7.73 (s, 1H), 7.65 (d, $J = 8.4$ Hz, 1H), 7.40 (d, $J = 2.5$ Hz, 1H), 7.22 (d, $J = 8.6$ Hz, 1H), 6.92 (d, $J = 2.2$ Hz, 1H), 6.83 (dd, $J = 8.7, 2.2$ Hz, 1H), 5.06 (dd, $J = 12.9, 5.4$ Hz, 1H), 4.31 (s, 2H), 3.67 – 3.38 (m, 4H), 3.30 – 2.81 (m, 8H), 2.72 (s, 3H), 2.69 – 2.55 (m, 1H), 2.43 – 2.33 (m, 2H), 2.23 – 1.46 (m, 11H), 1.25 (s, 3H). LCMS: $\text{C}_{42}\text{H}_{50}\text{N}_{12}\text{O}_6$ requires: 818, found: $m/z = 819$ $[\text{M}+\text{H}]^+$.

[00422] Compound **208**



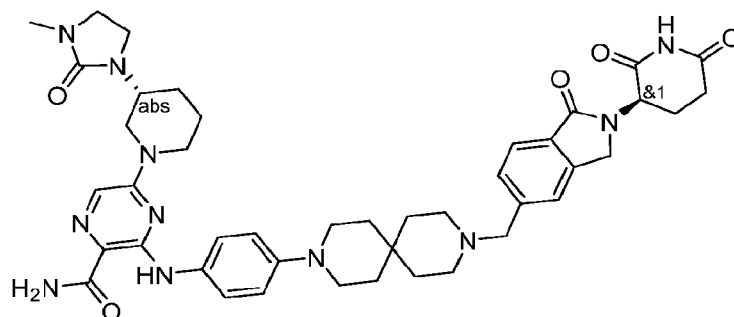
[00423] ^1H NMR (500 MHz, DMSO- d_6) δ 11.28 (s, 1H), 11.08 (s, 1H), 8.55 (d, $J = 2.6$ Hz, 1H), 8.10 (d, $J = 8.4$ Hz, 1H), 7.81 (s, 1H), 7.73 (s, 1H), 7.65 (d, $J = 8.2$ Hz, 1H), 7.40 (d, $J = 2.6$ Hz, 1H), 7.21 (d, $J = 8.6$ Hz, 1H), 6.79 (d, $J = 2.1$ Hz, 1H), 6.66 (dd, $J = 8.4, 2.1$ Hz, 1H), 5.06 (dd, $J = 12.8, 5.4$ Hz, 1H), 4.31 (d, $J = 12.8$ Hz, 2H), 4.16 (t, $J = 8.2$ Hz, 2H), 3.77 – 3.55 (m, 4H), 3.27 (dd, $J = 11.3, 4.9$ Hz, 2H), 3.16 – 2.81 (m, 6H), 2.74 – 2.55 (m, 7H), 2.16 – 1.97 (m, 3H), 1.91 – 1.42 (m, 9H), 1.25 (s, 5H). LCMS: $\text{C}_{41}\text{H}_{48}\text{N}_{12}\text{O}_6$ requires: 818, found: $m/z = 819$ $[\text{M}+\text{H}]^+$.

[00424] Compound 209



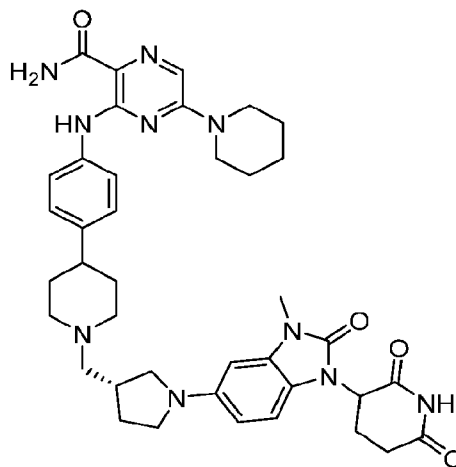
[00425] ^1H NMR (500 MHz, DMSO- d_6) δ 11.08 (s, 1H), 10.89 (s, 1H), 8.10 (s, 1H), 7.71 (d, $J = 2.8$ Hz, 1H), 7.66 (d, $J = 8.5$ Hz, 1H), 7.61 (d, $J = 4.5$ Hz, 2H), 7.31 (dd, $J = 7.8, 2.5$ Hz, 2H), 7.24 (dd, $J = 8.8, 2.3$ Hz, 1H), 5.12 – 4.94 (m, 2H), 4.43 (d, $J = 12.5$ Hz, 1H), 4.30 (d, $J = 13.2$ Hz, 1H), 4.05 (d, $J = 12.9$ Hz, 2H), 3.75 – 3.56 (m, 3H), 3.28 (t, $J = 8.2$ Hz, 2H), 3.10 – 2.83 (m, 5H), 2.73 (s, 3H), 2.67 – 2.53 (m, 2H), 2.40 (d, $J = 6.8$ Hz, 2H), 2.02 (ddd, $J = 12.9, 5.7, 3.2$ Hz, 1H), 1.90 – 1.69 (m, 6H), 1.68 – 1.48 (m, 2H), 1.20 (qd, $J = 14.1, 12.4, 4.3$ Hz, 2H). LCMS: $\text{C}_{39}\text{H}_{47}\text{N}_{13}\text{O}_6$ requires: 793, found: $m/z = 794$ $[\text{M}+\text{H}]^+$.

[00426] Compound 210



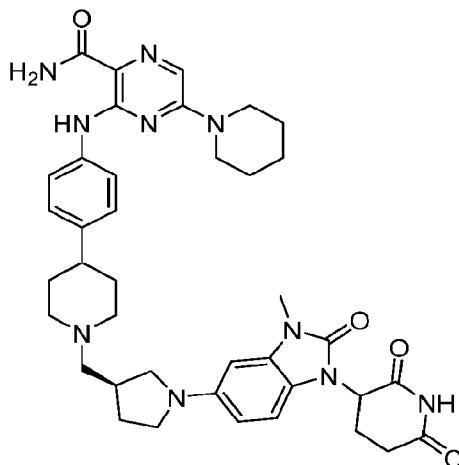
[00427] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.15 (s, 2H), 11.03 (s, 1H), 9.46 (d, $J = 28.8$ Hz, 1H), 7.87 (d, $J = 7.8$ Hz, 1H), 7.75 (d, $J = 9.7$ Hz, 2H), 7.65 (d, $J = 7.3$ Hz, 2H), 7.53 (s, 2H), 7.33 (s, 1H), 7.09 (s, 2H), 5.16 (dd, $J = 13.2, 5.2$ Hz, 1H), 4.41 (dtd, $J = 57.1, 31.0, 29.6, 15.4$ Hz, 7H), 3.62 (tt, $J = 9.7, 4.2$ Hz, 1H), 3.43 – 2.85 (m, 16H), 2.71 (s, 3H), 2.67 – 2.58 (m, 1H), 2.09 – 1.70 (m, 9H), 1.66 – 1.42 (m, 6H). LCMS: $\text{C}_{43}\text{H}_{53}\text{N}_{11}\text{O}_5$ requires: 793, found: $m/z = 794$ $[\text{M}+\text{H}]^+$.

[00428] Compound **196**



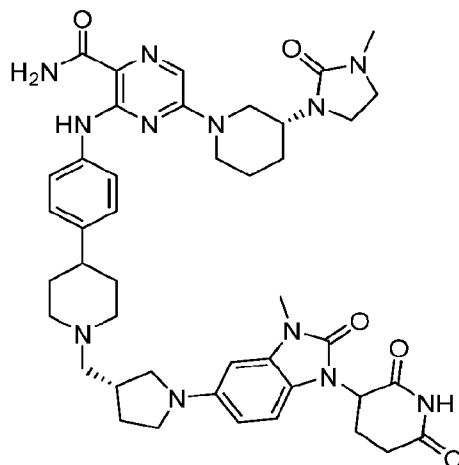
[00429] ^1H NMR (500 MHz, acetonitrile- d_3) δ 11.17 (s, 1H), 8.91 (s, 1H), 7.65 (d, $J = 8.2$ Hz, 2H), 7.58 (s, 1H), 7.41 (s, 1H), 7.24 (d, $J = 8.2$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 1H), 6.41 (s, 1H), 6.33 (d, $J = 8.7$ Hz, 1H), 5.79 (s, 1H), 5.14 (dd, $J = 12.9, 5.3$ Hz, 1H), 3.81 – 3.65 (m, 5H), 3.61 (t, $J = 8.3$ Hz, 1H), 3.49 – 3.39 (m, 2H), 3.38 – 3.31 (m, 4H), 3.27 – 3.20 (m, 2H), 3.20 – 3.12 (m, 1H), 3.10 – 2.96 (m, 2H), 2.95 – 2.80 (m, 3H), 2.80 – 2.67 (m, 2H), 2.54 – 2.01 (m, 6H), 1.92 – 1.80 (m, 1H), 1.78 – 1.70 (m, 2H), 1.70 – 1.65 (m, 4H). LCMS: $\text{C}_{39}\text{H}_{48}\text{N}_{10}\text{O}_4$ requires 720, found: $m/z = 721$ $[\text{M}+\text{H}]^+$.

[00430] Compound **197**



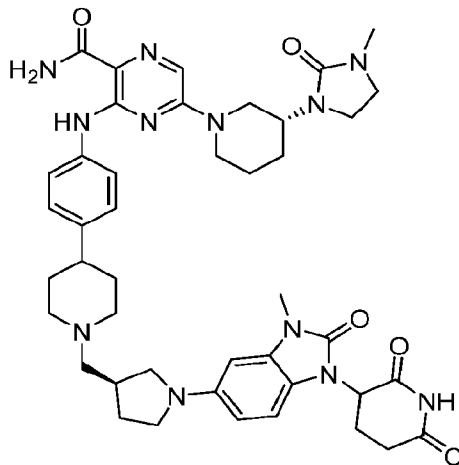
[00431] ^1H NMR (500 MHz, acetonitrile- d_3) δ 11.18 (s, 1H), 9.77 (s, 1H), 8.91 (s, 1H), 7.65 (d, $J = 8.2$ Hz, 2H), 7.58 (s, 1H), 7.41 (s, 1H), 7.24 (d, $J = 8.2$ Hz, 2H), 6.85 (d, $J = 8.5$ Hz, 1H), 6.41 (s, 1H), 6.33 (d, $J = 8.5$ Hz, 1H), 5.80 (s, 1H), 5.15 (dd, $J = 12.8, 5.4$ Hz, 1H), 3.78 – 3.70 (m, 5H), 3.61 (t, $J = 8.5$ Hz, 1H), 3.49 – 3.39 (m, 2H), 3.38 – 3.31 (m, 4H), 3.28 – 3.20 (m, 2H), 3.20 – 3.13 (m, 1H), 3.12 – 2.96 (m, 2H), 2.92 – 2.84 (m, 3H), 2.80 – 2.71 (m, 2H), 2.57 – 2.03 (m, 6H), 1.92 – 1.79 (m, 1H), 1.80 – 1.71 (m, 2H), 1.71 – 1.65 (m, 4H). LCMS: $\text{C}_{39}\text{H}_{48}\text{N}_{10}\text{O}_4$ requires 720, found: $m/z = 721$ $[\text{M}+\text{H}]^+$.

[00432] Compound 198

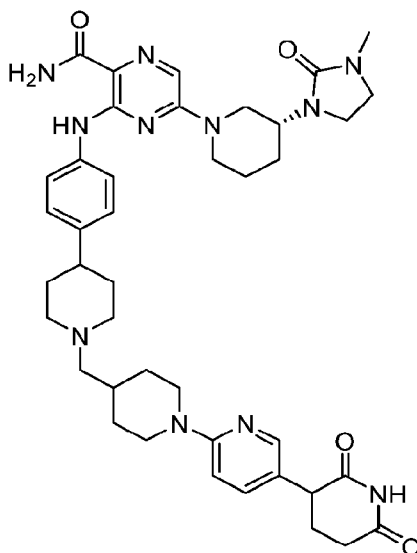


[00433] ^1H NMR (500 MHz, acetonitrile- d_3) δ 11.14 (s, 1H), 8.99 (s, 1H), 8.93 (s, 1H), 7.66 – 7.56 (m, 3H), 7.43 (s, 1H), 7.23 (d, J = 8.2 Hz, 2H), 6.86 (d, J = 8.4 Hz, 1H), 6.45 (s, 1H), 6.37 (s, 1H), 5.84 (s, 1H), 5.15 (dd, J = 12.8, 5.4 Hz, 1H), 4.42 (d, J = 12.8 Hz, 1H), 4.31 (d, J = 13.7 Hz, 1H), 3.77 – 3.67 (m, 3H), 3.63 – 3.59 (m, 1H), 3.50 – 3.13 (m, 10H), 3.13 – 2.96 (m,

[00434] Compound 199

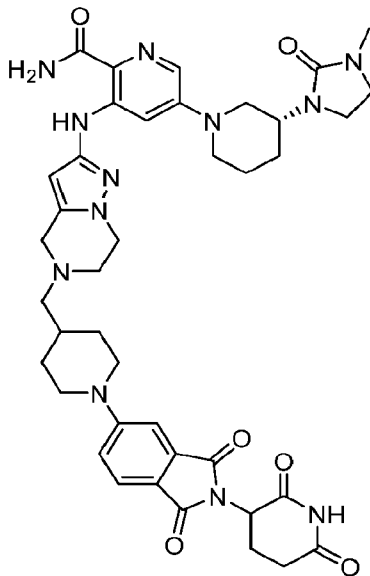


[00436] Compound 200



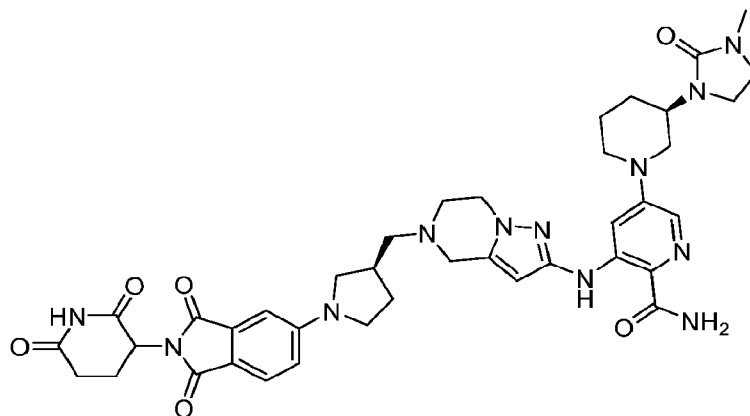
[00437] ^1H NMR (500 MHz, DMSO- d_6) δ 11.30 (s, 1H), 10.82 (s, 1H), 7.97 (d, $J = 2.5$ Hz, 1H), 7.79 (d, $J = 2.7$ Hz, 1H), 7.69 (s, 1H), 7.57 (d, $J = 8.2$ Hz, 2H), 7.43 – 7.34 (m, 2H), 7.22 – 7.14 (m, 2H), 6.86 (d, $J = 8.8$ Hz, 1H), 4.31 (d, $J = 14.0$ Hz, 4H), 3.75 (dd, $J = 12.2, 4.9$ Hz, 1H), 3.65 – 3.56 (m, 3H), 3.40 – 3.21 (m, 3H), 3.13 – 2.94 (m, 6H), 2.90 – 2.62 (m, 6H), 2.27 – 2.10 (m, 3H), 2.10 – 1.94 (m, 5H), 1.88 – 1.76 (m, 6H), 1.61 – 1.55 (m, 1H), 1.35 – 1.14 (m, 3H). LCMS: $\text{C}_{41}\text{H}_{53}\text{N}_{11}\text{O}_4$ requires 763, found: $m/z = 764$ $[\text{M}+\text{H}]^+$.

[00438] Compound 206



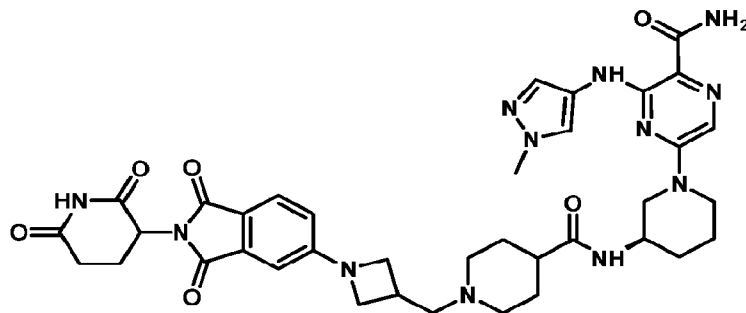
[00439] ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.08 (s, 1H), 10.93 (s, 1H), 7.89 – 7.84 (m, 2H), 7.75 (d, *J* = 2.6 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.35 – 7.18 (m, 3H), 5.83 (s, 1H), 5.77 (s, 1H), 5.06 (dd, *J* = 13.0, 5.4 Hz, 1H), 4.12 – 3.95 (m, 5H), 3.83 (d, *J* = 13.2 Hz, 1H), 3.74 (t, *J* = 12.2 Hz, 1H), 3.70 – 3.55 (m, 3H), 3.28 – 3.21 (m, 2H), 3.04 – 2.95 (m, 3H), 2.93 – 2.82 (m, 4H), 2.67 (s, 3H), 2.62 – 2.35 (m, 3H), 2.05 – 1.98 (m, 1H), 1.94 – 1.90 (m, 1H), 1.87 – 1.76 (m, 5H), 1.75 – 1.66 (m, 1H), 1.63 – 1.53 (m, 1H), 1.26 – 1.15 (m, 3H). LCMS: C₄₀H₄₈N₁₂O₆ requires 792, found: *m/z* = 793 [M+H]⁺.

[00440] Compound 214



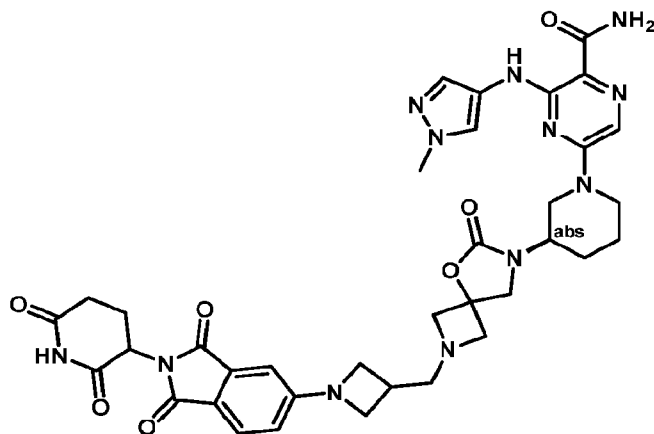
[00441] ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.07 (s, 1H), 10.93 (s, 1H), 7.89 – 7.82 (m, 2H), 7.75 (d, J = 2.6 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 3.2 Hz, 1H), 6.93 (d, J = 2.2 Hz, 1H), 6.84 (dd, J = 8.7, 2.2 Hz, 1H), 5.83 (s, 1H), 5.05 (dd, J = 13.3, 5.3 Hz, 1H), 4.02 (t, J = 5.7 Hz, 2H), 3.83 (d, J = 13.2 Hz, 1H), 3.78 – 3.58 (m, 4H), 3.56 – 3.38 (m, 2H), 3.27 – 3.16 (m, 3H), 3.05 – 2.82 (m, 4H), 2.71 (q, J = 7.4 Hz, 1H), 2.66 (s, 3H), 2.62 – 2.40 (m, 6H), 2.22 – 2.14 (m, 1H), 2.02 – 1.98 (m, 1H), 1.86 – 1.66 (m, 4H), 1.62 – 1.53 (m, 1H), 1.36 – 1.08 (m, 2H). LCMS: $\text{C}_{39}\text{H}_{46}\text{N}_{12}\text{O}_6$ requires 778, found: m/z = 779 $[\text{M}+\text{H}]^+$.

[00442] Compound 216



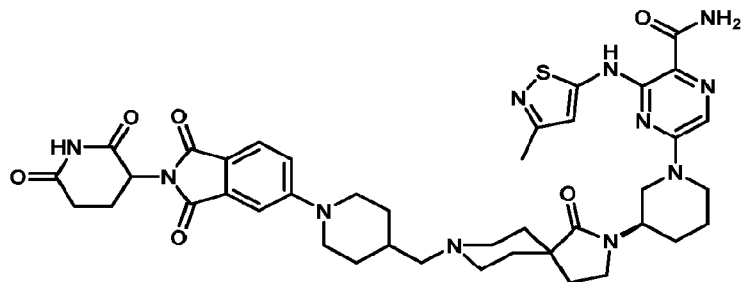
[00443] ^1H NMR (500 MHz, acetonitrile- d_3) δ 10.74 (s, 1H), 8.87 (s, 1H), 7.92 (s, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 7.4 Hz, 2H), 7.38 – 7.22 (m, 1H), 6.76 (d, J = 2.1 Hz, 1H), 6.59 (dd, J = 8.3, 2.2 Hz, 1H), 6.34 (d, J = 7.2 Hz, 1H), 5.72 (s, 1H), 4.92 (dd, J = 12.3, 5.3 Hz, 1H), 4.24 – 4.16 (m, 1H), 4.11 (t, J = 8.1 Hz, 2H), 3.87 (s, 3H), 3.85 – 3.78 (m, 2H), 3.68 (dd, J = 8.2, 5.4 Hz, 2H), 3.45 (td, J = 9.0, 8.5, 4.4 Hz, 1H), 3.35 (dd, J = 13.1, 7.8 Hz, 1H), 3.28 (s, 1H), 2.97 (ddt, J = 10.1, 7.8, 4.2 Hz, 1H), 2.90 – 2.79 (m, 2H), 2.70 (dddt, J = 21.8, 13.4, 7.8, 4.3 Hz, 3H), 2.57 (d, J = 7.4 Hz, 2H), 2.11 – 2.01 (m, 3H), 1.87 – 1.77 (m, 2H), 1.71 – 1.49 (m, 6H). LCMS: $\text{C}_{37}\text{H}_{44}\text{N}_{12}\text{O}_6$ requires: 753, found: m/z = 754.

[00444] Compound 213



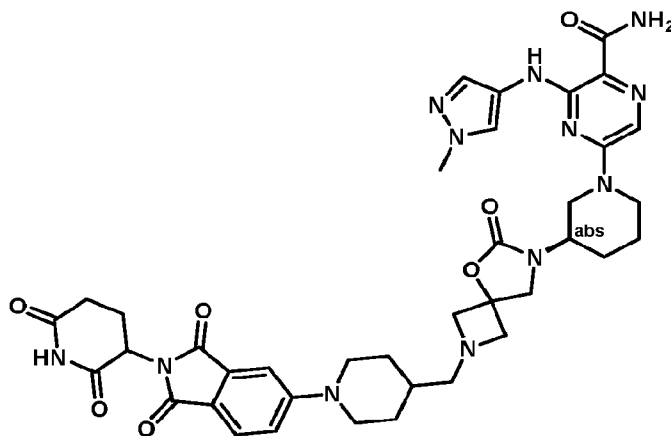
[00445] ^1H NMR (500 MHz, acetonitrile- d_3) δ 10.75 (s, 1H), 8.90 (s, 1H), 7.87 (s, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.50 (s, 1H), 7.47 (s, 1H), 7.37 (s, 1H), 6.79 (d, J = 2.1 Hz, 1H), 6.62 (dd, J = 8.3, 2.1 Hz, 1H), 5.78 (s, 1H), 4.95 (dd, J = 12.3, 5.4 Hz, 1H), 4.52 (d, J = 13.0 Hz, 1H), 4.21 (d, J = 13.6 Hz, 1H), 4.11 (t, J = 7.7 Hz, 2H), 3.85 (s, 3H), 3.80 (q, J = 9.1 Hz, 2H), 3.73 (ddd, J = 12.7, 8.2, 4.7 Hz, 3H), 3.48 (d, J = 8.0 Hz, 1H), 3.45 – 3.35 (m, 3H), 3.20 – 3.05 (m, 2H), 2.86 – 2.63 (m, 6H), 2.05 – 1.99 (m, 1H), 1.93 – 1.78 (m, 2H), 1.76 – 1.59 (m, 1H), 0.97 – 0.81 (m, 1H). LCMS: $\text{C}_{36}\text{H}_{40}\text{N}_{12}\text{O}_7$ requires: 753, found: m/z = 754.

[00446] Compound **205**



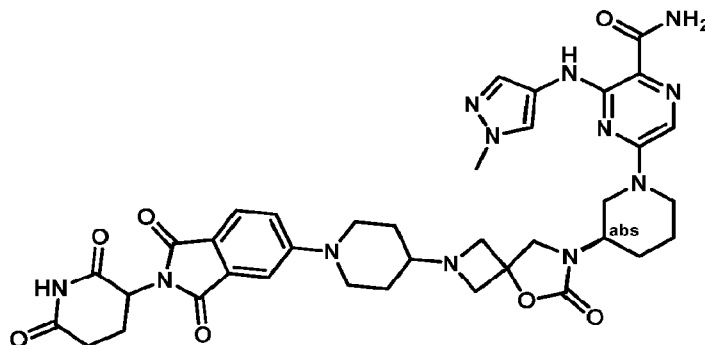
[00447] ^1H NMR (500 MHz, DMSO- d_6) δ 12.29 (s, 1H), 11.08 (s, 1H), 7.92 (s, 1H), 7.84 (s, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.58 (s, 1H), 7.32 (d, J = 2.3 Hz, 1H), 7.24 (dd, J = 8.8, 2.3 Hz, 1H), 6.86 (s, 1H), 5.07 (dd, J = 12.8, 5.4 Hz, 1H), 4.46 (s, 2H), 4.05 (d, J = 13.0 Hz, 2H), 3.83 (d, J = 10.9 Hz, 1H), 3.12 (t, J = 12.6 Hz, 1H), 2.98 (t, J = 12.4 Hz, 2H), 2.89 (t, J = 12.9 Hz, 1H), 2.76 (d, J = 9.1 Hz, 2H), 2.71 – 2.55 (m, 3H), 2.30 (s, 3H), 2.15 (d, J = 6.9 Hz, 2H), 2.09 – 1.94 (m, 3H), 1.94 – 1.69 (m, 9H), 1.62 (d, J = 13.1 Hz, 1H), 1.36 (dd, J = 25.7, 12.6 Hz, 2H), 1.25 (s, 1H), 1.15 (d, J = 12.5 Hz, 2H). LCMS: $\text{C}_{41}\text{H}_{49}\text{N}_{11}\text{O}_6\text{S}$ requires: 823, found: m/z = 824.

[00448] Compound **211**



[00449] ^1H NMR (500 MHz, acetonitrile- d_3) δ 10.74 (s, 1H), 8.94 (s, 1H), 7.87 (s, 1H), 7.65 (d, J = 8.6 Hz, 1H), 7.50 (s, 1H), 7.47 (d, J = 0.8 Hz, 1H), 7.37 (s, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.17 (dd, J = 8.7, 2.4 Hz, 1H), 5.79 (s, 1H), 5.07 – 4.88 (m, 1H), 4.50 (d, J = 12.8 Hz, 1H), 4.19 (d, J = 13.6 Hz, 1H), 4.00 (d, J = 13.1 Hz, 2H), 3.84 (s, 3H), 3.78 (dd, J = 19.2, 10.2 Hz, 2H), 3.45 (d, J = 8.1 Hz, 1H), 3.39 (d, J = 8.1 Hz, 1H), 3.34 (d, J = 8.1 Hz, 1H), 3.31 – 3.25 (m, 1H), 3.17 (dd, J = 12.9, 10.4 Hz, 1H), 3.14 – 3.07 (m, 1H), 2.97 (td, J = 12.8, 2.7 Hz, 2H), 2.87 – 2.63 (m, 3H), 2.39 (d, J = 6.9 Hz, 2H), 2.31 – 2.26 (m, 1H), 2.15 – 2.08 (m, 1H), 1.91 (dt, J = 13.3, 3.5 Hz, 1H), 1.88 – 1.84 (m, 1H), 1.81 (dd, J = 12.1, 3.6 Hz, 3H), 1.70 (tt, J = 11.1, 3.9 Hz, 1H), 1.61 (dtd, J = 11.6, 7.4, 4.0 Hz, 1H), 0.90 (dq, J = 7.8, 6.0, 5.5 Hz, 3H). LCMS: $\text{C}_{38}\text{H}_{44}\text{N}_{12}\text{O}_7$ requires: 780, found: m/z = 781.

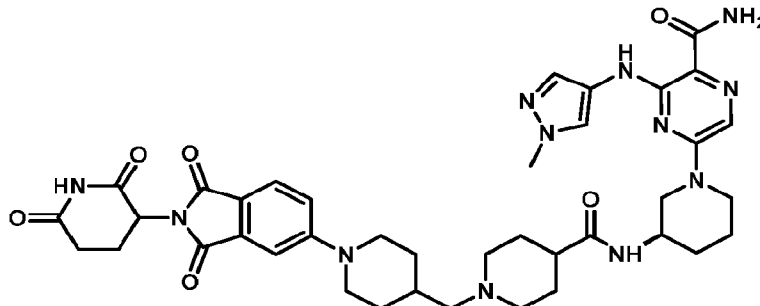
[00450] Compound **212**



[00451] ^1H NMR (500 MHz, acetonitrile- d_3) δ 10.71 (s, 1H), 8.90 (s, 1H), 7.84 (s, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.47 (s, 1H), 7.44 (s, 1H), 7.34 (s, 1H), 7.28 (d, J = 2.4 Hz, 1H), 7.15 (dd, J = 8.6, 2.4 Hz, 1H), 5.75 (s, 1H), 4.93 (dd, J = 12.3, 5.4 Hz, 1H), 4.50 (dd, J = 13.1, 4.1 Hz, 1H), 4.18 (d, J = 13.6 Hz, 1H), 3.81 (s, 3H), 3.81 – 3.66 (m, 3H), 3.44 (d, J = 8.0 Hz, 1H), 3.40 (d, J = 8.0 Hz, 1H), 3.34 (d, J = 7.9 Hz, 1H), 3.31 (d, J = 7.8 Hz, 1H), 3.17 – 3.00 (m, 4H), 2.83 – 2.60 (m, 3H), 2.36 (tt, J = 8.3, 3.7 Hz, 1H), 2.12 – 2.05 (m, 2H), 1.96 (s, 1H), 1.87 (dq,

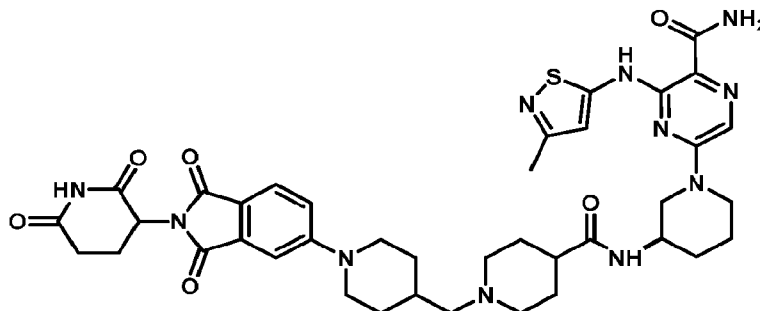
$J = 13.4, 3.3$ Hz, 1H), 1.79 (ddd, $J = 16.5, 10.2, 4.2$ Hz, 3H), 1.70 – 1.59 (m, 1H), 1.33 (qd, $J = 9.6, 5.0$ Hz, 1H), 0.87 (dt, $J = 11.1, 5.7$ Hz, 2H). LCMS: $C_{37}H_{42}N_{12}O_7$ requires: 766, found: $m/z = 767$.

[00452] Compound 215



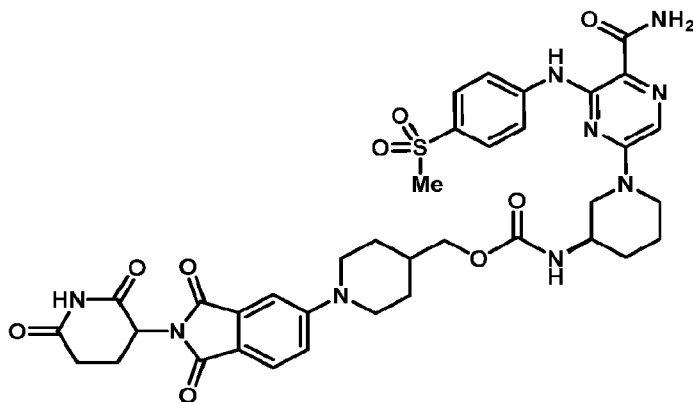
[00453] ^1H NMR (500 MHz, DMSO- d_6) δ 11.07 (s, 1H), 10.87 (s, 1H), 7.98 (s, 1H), 7.81 (d, J = 6.9 Hz, 1H), 7.66 (s, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.55 (s, 1H), 7.48 (s, 1H), 7.30 (d, J = 2.1 Hz, 1H), 7.28 – 7.19 (m, 2H), 5.06 (dd, J = 12.8, 5.4 Hz, 1H), 4.29 (s, 1H), 4.04 (d, J = 13.0 Hz, 2H), 3.94 (d, J = 13.0 Hz, 1H), 3.86 (s, 3H), 3.70 (s, 1H), 3.08 (t, J = 10.9 Hz, 1H), 3.01 – 2.92 (m, 2H), 2.90 – 2.78 (m, 3H), 2.09 (h, J = 6.3 Hz, 3H), 2.00 (dd, J = 11.8, 6.0 Hz, 1H), 1.92 – 1.71 (m, 8H), 1.59 (d, J = 24.4 Hz, 7H), 1.12 (d, J = 12.5 Hz, 3H). LCMS: $\text{C}_{39}\text{H}_{48}\text{N}_{12}\text{O}_6$ requires: 780, found: m/z = 781.

[00454] Compound 217



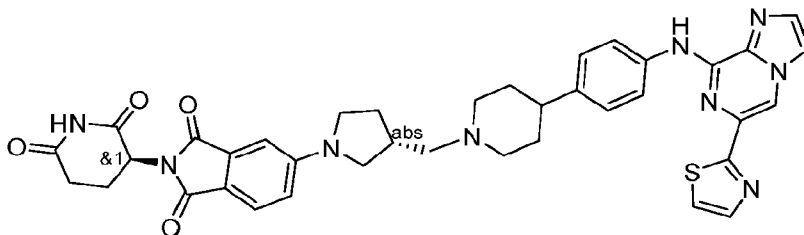
[00455] ^1H NMR (500 MHz, DMSO- d_6) δ 12.27 (d, $J = 32.4$ Hz, 1H), 11.06 (s, 1H), 8.01 (s, 1H), 7.84 (d, $J = 18.1$ Hz, 1H), 7.63 (d, $J = 8.4$ Hz, 1H), 7.58 – 7.43 (m, 2H), 7.28 (s, 1H), 7.20 (d, $J = 9.1$ Hz, 1H), 6.85 (d, $J = 22.5$ Hz, 1H), 5.05 (dd, $J = 12.9, 5.4$ Hz, 1H), 4.17 (s, 1H), 4.00 (d, $J = 14.4$ Hz, 2H), 3.74 (d, $J = 14.2$ Hz, 1H), 3.57 (s, 1H), 3.48 – 3.35 (m, 3H), 3.09 – 2.77 (m, 3H), 2.72 – 2.54 (m, 2H), 2.28 (s, 3H), 2.22 – 2.05 (m, 2H), 2.05 – 1.90 (m, 3H), 1.80 (s, 3H), 1.70 (d, $J = 11.6$ Hz, 3H), 1.64 – 1.28 (m, 5H), 1.23 (s, 1H), 1.20 – 0.96 (m, 3H). LCMS: $\text{C}_{38}\text{H}_{46}\text{N}_{12}\text{O}_6\text{S}$ requires: 798, found: $m/z = 799$.

[00456] Compound 218



[00457] ^1H NMR (500 MHz, chloroform-*d*) δ 11.60 (s, 1H), 7.99 (d, J = 13.7 Hz, 1H), 7.94 – 7.75 (m, 4H), 7.55 (s, 1H), 5.30 (s, 2H), 4.96 (dd, J = 12.2, 5.8 Hz, 1H), 4.39 – 3.12 (m, 13H), 2.89 (t, J = 19.6 Hz, 1H), 2.84 – 2.65 (m, 1H), 2.20 – 2.10 (m, 1H), 2.10 – 1.98 (m, 1H), 1.59 (s, 15H). LCMS: $\text{C}_{37}\text{H}_{41}\text{N}_9\text{O}_9\text{S}$ requires: 787, found: m/z = 788.

[00458] Compound 203



[00459] LCMS: $\text{C}_{38}\text{H}_{37}\text{N}_9\text{O}_4\text{S}$ requires: 715, found: m/z = 716.

[00460] **Biological Example 1**

[00461] **Cell Culture**

[00462] Ramos cells (CRL-1596) were obtained from American Type Culture Collection. TMD8 cells were obtained from Tokyo Medical and Dental University. Ramos cells were grown in RPMI-1640 media (ATCC, 30-2001) supplemented with 10% heat-inactivated FBS (Corning Premium Fetal Bovine Serum from Fisher, MT35015CV). TMD8 cells were grown in MEM alpha media (Fisher, 12571063) supplemented with 10% heat-inactivated FBS (Corning Premium Fetal Bovine Serum from Fisher, MT35015CV). All cells were cultured at 37 °C and 5% CO_2 .

[00463] Human peripheral blood mononuclear cells (PBMC) were obtained either: 1) by using Ficoll-Paque™ (GE Healthcare) for separation of peripheral blood hematopoietic cells from buffy coats of healthy human donors; or 2) directly from LeukoPak donations. PBMCs were

grown at 37 °C and 5% CO₂ in RPMI supplemented with 10% heat-inactivated FBS (Corning Premium Fetal Bovine Serum from Fisher, MT35015CV), 1X Penicillin/Streptomycin, and 2 mM Glutamine.

[00464] Generation of BTK^{C481S} knock-in cell lines

[00465] To generate cell lines expressing BTK^{C481S}, Cas9 RNP with a specific gRNA was introduced into cells by electroporation. Gene editing was assessed in polyclonal cell populations by sequencing. Monoclonal cell lines were made by diluting single cells into single wells, and mutation was confirmed by sequencing.

[00466] Western Blot Time-course Assays

[00467] *Determine the kinetics of CTM-induced BTK degradation*

[00468] Cells were plated in 6-well plates and treated with DMSO or CTM with a final DMSO concentration of >0.2%. At indicated timepoints after treatment, cells were harvested, washed once with PBS and lysed. Western blot analysis was performed using a BTK-specific antibody (Cell Signaling, 8547).

[00469] Biological Example 2

[00470] Cellular BTK Degradation Assay

[00471] *In vitro cellular screening to determine potency as measured by DC₅₀ values after four hour incubation*

[00472] BTK CTMs were added to cells in round-bottom 96-well plates with a final DMSO concentration of >0.2% and were incubated at 37 °C and 5% CO₂ for four hours. BTK levels were determined using Cisbio Total-BTK HTRF (Homologous Time-Resolved Fluorescence) kit (63ADK064PEG) according to the manufacturer's protocol. Briefly, cells were incubated in 1X supplied lysis buffer for 30 minutes. In an opaque white low volume 96-well plate (Cisbio, 66PL96005), cell lysate was combined with two different specific BTK antibodies, one conjugated with Eu³⁺-Cryptate FRET donor and one conjugated with d2 FRET acceptor. Assay controls include wells containing cell lysate with only the Eu³⁺-Cryptate FRET donor antibody and wells containing both HTRF antibodies and lysis buffer without cells or control lysate provided by Cisbio. HTRF ratio was calculated as (acceptor signal at 665 nm / donor signal at 620 nm) x 10⁴. Background HTRF levels were determined from the control well containing the donor, but no acceptor, antibody. Background HTRF levels were subtracted from all samples. Readouts were reported as HTRF levels relative to HTRF levels of DMSO-

treated cells. Four-parameter non-linear regressions were performed in GraphPad Prism 7.02 to obtain DC50 values.

[00473] As shown in FIG. 1, robust, time-dependent degradation of BTK was observed in multiple cell lines and primary human B cells in the presence of a compound provided herein. As shown in FIG. 2, several compounds provided herein induced degradation of BTK in Ramos cells expressing wild-type BTK or ibrutinib-resistant C481S mutant BTK.

[00474] **Biological Example 3**

[00475] **Proteomics**

[00476] *Determine global effects of BTK CTM treatment on the proteome*

[00477] TMD8 cells were treated with DMSO or 50 nM CTM in triplicate. After six hours, cells were harvested, washed twice with PBS, and stored as frozen cell pellets. Proteomic analysis, including sample preparation, tandem mass tag (TMT) labeling, fraction, mass spectrometry, and data processing, was performed by MS Bioworks.

[00478] As shown in FIG. 3, a compound provided herein selectively degraded BTK in TMD8 cells.

[00479] **Biological Example 4**

[00480] **Cellular Viability Assay**

[00481] *Evaluate effects of BTK degradation in BTK-dependent cell lines*

[00482] Cell viability was determined using CellTiter-Glo 2.0 Luminescent Cell Viability Assay (Promega, G9242), which quantitates the amount of ATP present as a proxy for the number of viable cells in culture. Cells were plated with densities between 2000-4000 cells per well in 96-well plates. Serial dilutions of BTK CTMs or comparator compounds were added with a final DMSO concentration of >0.3% and were incubated at 37 °C and 5% CO₂ for seventy-two hours. CellTiter-Glo reagent was added to cells at a dilution of 1:20, and the plate was incubated ten minutes at room temperature prior to reading the luminescence signal using an EnVision plate reader. Controls included cells treated with DMSO and wells that contained no cells, only media. Background luminescence signal was determined by control wells containing no cells, only media, and was then subtracted from all sample wells. Luminescence values were then normalized to DMSO-treated wells and reported at proportion viable cells.

[00483] As shown in FIG. 4, wild-type BTK cells were sensitive to a compound provided herein and to ibrutinib. Mutant C4813 BTK cells retained sensitivity to the compound provided herein but were less sensitive to ibrutinib.

[00484] **Biological Example 5**

[00485] **B Cell Activation Assay**

[00486] *Evaluate effects of BTK degradation on B cell receptor signaling*

[00487] Frozen human peripheral blood mononuclear cells (PBMCs) were thawed and treated with DMSO or compound for four hours and then stimulated for 18 hours with 10 µg/ml anti-IgM (Jackson ImmunoResearch 109-006-129), and an additional DMSO-treated sample was left unstimulated. Compound was present throughout the stimulation. Cells were stained with Live/Dead dye (Fisher L34976) and then fluorophore-conjugated antibodies against CD20 (Biolegend 302330), CD3 (BD Pharmingen 557705), CD86 (Biolegend 305416) and CD69 (Biolegend 310906). Stained cells were fixed in PFA and run on an Attune NxT Acoustic Focusing Flow Cytometer (Thermo-Fisher A29004), and data was analyzed using FlowJo (v10.5.3) and GraphPad Prism (v7.00) software. Single live lymphocytes were gated for B cells (CD20+CD3-) and T cells (CD3+CD20-), and the geometric mean fluorescence intensity (MFI) of CD86 and CD69 was calculated for each population. The MFI of the unstimulated sample was used to quantify baseline activation.

[00488] As shown in FIG. 5, compound-mediated degradation of BTK prevented anti-IgM-induced upregulation of activation markers CD69 and CD86 on B cells.

[00489] **Biological Example 6**

[00490] **Cellular Aiolos Degradation Assay**

[00491] *In vitro cellular screening to determine IMiD activity*

[00492] Frozen human peripheral blood mononuclear cells (PBMCs) were thawed and treated with DMSO or compound for twenty-four hours and then fixed and permeabilized using a Foxp3/Transcription Factor Fixation/Permeabilization Kit (eBioscience, 00-5523). Cells were stained with fluorophore-conjugated antibodies against CD20 (Biolegend 302330), CD3 (BD Pharmingen 552127), and Aiolos (Biolegend 371106). An additional set of DMSO-treated PBMCs was stained for CD20, CD3, and an AlexaFluor 647-conjugated mouse IgG1 isotype control antibody (Biolegend 400136). Stained cells were run on an Attune NxT Acoustic Focusing Flow Cytometer (Thermo-Fisher A29004), and data was analyzed using FlowJo

(v10.5.3) and GraphPad Prism (v7.00) software. Single lymphocytes were gated for B cells (CD20+CD3-) and T cells (CD3+CD20-), and the geometric mean fluorescence intensity (MFI) of Aiolos was calculated for each population. The MFI of the isotype control was calculated for each population and used to quantify background staining. Percent Aiolos degradation was calculated for each compound-treated sample using the following equation:

$$\% \text{Degradation} = 100 * (\text{Sample MFI} - \text{Isotype MFI}) / (\text{DMSO MFI} - \text{Isotype MFI}).$$

[00493] Exemplary results are shown in FIG. 9.

[00494] **Biological Example 7**

[00495] **Mouse PD assays**

[00496] *Determine whether CTMs catalyze BTK degradation* in vivo

[00497] A method of determining the pharmacodynamic profile of BTK degraders was performed by dosing either CD-1 or BALB/c mice with CTM. The CTM was prepared in a suitable formulation and was administered via oral gavage (PO) at a suitable dose level and frequency as informed by prior pharmacokinetic and tolerability studies. Following administration of CTM, BTK levels in blood or splenocytes are measured using flow cytometry or HTRF. For assessment of BTK levels via flow cytometry, either whole blood or splenocytes were first treated with ACK RBC lysis buffer to facilitate lysing of red blood cells. Remaining cells were then stained with fluorophore-conjugated antibodies against CD45, TCR beta and CD45R (B220). Cell pellets were washed with 1x PBS, fixed, and permeabilized for twenty-four hours with Foxp3/Transcription Factor Fixation/Permeabilization Kit. Cells were then stained intracellularly with unconjugated BTK antibody and detected with a fluorophore-conjugated secondary antibody. Stained cells were run on an Attune NxT Acoustic Focusing Flow Cytometer (Thermo-Fisher A29004), and data was analyzed using FlowJo (v10.5.3) and GraphPad Prism (v7.00) software. Lymphocytes were gated for B cells defined as CD45+ TCR beta- B220+ and T cells as CD45+ TCR beta+ B220-. The BTK geometric mean fluorescence intensity (MFI) was calculated for B and T cells. Percent BTK degradation for each compound-treated sample was calculated using the equation described below:

$$\% \text{ Degradation} = 100 * (\text{Treated sample B cell BTK MFI} - \text{treated sample T cell BTK MFI}) / (\text{Vehicle B cell BTK MFI} - \text{Vehicle T cell BTK MFI})$$

[00498] As shown in FIG. 6, a dose-proportional decrease in BTK levels was observed in splenocytes after six hours of treatment and was associated with compound exposure in plasma.

As shown in FIG. 7, dose- and time-dependent reduction in BTK levels were observed in circulating murine B cells after a single oral dose.

[00499] Biological Example 8

[00500] TMD8 Xenograft Efficacy Studies

[00501] *Evaluate anti-tumor effects of BTK degradation in vivo*

[00502] The anti-tumor activity of CTM and Ibrutinib was evaluated in CB.17 SCID female mice bearing either TMD8 or TMD8 BTK^{C481S} tumor cells. Mice were inoculated subcutaneously with either TMD8 or TMD8 BTK^{C481S} cells and were randomized when tumors reached the predetermined size into treatment groups, vehicle control, CTM (30 mg/kg) or ibrutinib (30 mg/kg). Tumor bearing mice received either once a day (QD) or twice daily (BID) oral dose of CTM or ibrutinib.

[00503] Tumor and body weights were measured three times per week over a duration of twenty-one days. Tumor growth inhibition (% TGI) were calculated on the final day of measurement using the equation $[1 - (T - T_0 / C - T_0)] \times 100$, where T and C represent the mean size of tumors in the treated (T) and control (C) groups, and T₀ refers to the tumor size at randomization.

[00504] As shown in FIG. 8, treatment with a compound herein caused tumor growth inhibition in a wild-type BTK xenograft model and in an ibrutinib-resistant C481S xenograft model.

[00505] Biological Example 9

[00506] Cellular BTK Degradation Assay

[00507] Cellular BTK degradation was measured as above for four hours in TMD8 cells for two diastereomers of compound **130**. DC₅₀ and EC₅₀ values are the concentration at which the response is halfway between the top and bottom of the fitted non-linear regression curve.

Compound	Treatment Time (h)	Cells	DC ₅₀ (μM)
195	4	TMD8	0.00026
194	4	TMD8	0.0043

[00508] Biological Example 10

[00509] *BTK degradation (Total BTK HTRF) at twenty-four hours in TMD8 cells*

[00510] The present example evaluates whether potency of BTK CTMs shifts with longer timepoints. DC₅₀ values are typically calculated with a 4-hour timepoint. Most CTMs tested were slightly more potent at twenty-four hours compared to four hours.

Compound ID	Treatment Time (h)	Cells	DC ₅₀ (μM)
44	24	TMD8	0.00036
148	24	TMD8	0.00068
149	24	TMD8	0.0023
150	24	TMD8	0.0047
72	24	TMD8	0.00021
121	24	TMD8	0.0010

[00511] **Biological Example 11**

[00512] *BTK degradation (Total BTK HTRF) at four hours in TMD8 cells expressing BTK-C481S*

[00513] This example evaluates the potency of CTM in degrading BTK-C481S. The BTK binding moieties utilized in CTMs bind to the BTK active site. This example evaluates whether the active site mutation C481S affects CTM-induced degradation of BTK. The CTMs are potent towards Bruton's tyrosine kinase-C481S, but they are generally two- to three-fold more potent towards WT BTK compared to BTK-C481S.

Compound ID	Treatment Time (h)	Cells	DC ₅₀ (μM)
55	4	TMD8 BTK-C481S (clone2C3)	0.0058
53	4	TMD8 BTK-C481S (clone2C3)	0.0080
44	4	TMD8 BTK-C481S (clone2C3)	0.0018
37	4	TMD8 BTK-C481S (clone2C3)	0.0027
101	4	TMD8 BTK-C481S (clone2C3)	0.0043
83	4	TMD8 BTK-C481S (clone2C3)	0.0027
121	4	TMD8 BTK-C481S (clone2C3)	0.0041

Compound ID	Treatment Time (h)	Cells	DC ₅₀ (μM)
73	4	TMD8 BTK- C481S (clone2C3)	0.0012
72	4	TMD8 BTK- C481S (clone2C3)	0.0020
70	4	TMD8 BTK- C481S (clone2C3)	0.0031
69	4	TMD8 BTK- C481S (clone2C3)	0.0008
149	4	TMD8 BTK- C481S (clone2C3)	0.0144
148	4	TMD8 BTK- C481S (clone2C3)	0.0097
133	4	TMD8 BTK- C481S (clone2C3)	0.0083
130	4	TMD8 BTK- C481S (clone2C3)	0.0018
129	4	TMD8 BTK- C481S (clone2C3)	0.0053
126	4	TMD8 BTK- C481S (clone2C3)	0.0077
166	4	TMD8 BTK- C481S (clone2C3)	0.0081
182	4	TMD8 BTK- C481S (clone2C3)	0.0145
156	4	TMD8 BTK- C481S (clone2C3)	0.0004

[00514] Biological Example 12

[00515] *BTK degradation (Total BTK HTRF) at four hours in Mino cells*

[00516] This example evaluates the potency of CTMs in a model of Mantle Cell Lymphoma (MCL). To evaluate potential therapeutic indications, BTK CTMs were assayed in models of Mantle Cell Lymphoma as with the TMD8 cells (ABC-DLBCL) above. Tested CTMs had similar potencies for BTK degradation in the MCL cell lines (Mino and Rec-1) and TMD8 cells.

Compound ID	Treatment Time (h)	Cells	DC ₅₀ (μM)
44	4	Mino	0.00056
149	4	Mino	0.0059
130	4	Mino	0.00058
44	4	Rec-1	0.001
149	4	Rec-1	0.004
130	4	Rec-1	0.002

[00517] Biological Example 13

[00518] *BTK degradation in human PBMCs (BTK Flow Cytometry)*

[00519] This example evaluates the potency of CTMs in primary human B cells, rather than transformed or immortalized cancer cell lines. Primary cells are believed to be a physiologically relevant model. Thus, this example confirms the potency, kinetics, and level of BTK degradation in these cells in addition to the cell line models. Furthermore, this assay establishes that it is possible to monitor BTK degradation in primary human B cells, which can serve as a clinical biomarker.

Compound ID	Treatment Time (h)	DC ₅₀ (μM)
44	4	0.00051
149	4	0.0019
130	4	0.00013
44	2	0.003
44	1	0.006

[00520] Biological Example 14

[00521] *Ikaros and Aiolos degradation in Mantle Cell Lymphoma lines (Ikaros and Aiolos Flow Cytometry)*

[00522] This example evaluates the IMiD activity of CTMs in cellular models of Mantle Cell Lymphoma (MCL). Currently approved treatments for MCL include ibrutinib and lenalidomide, suggesting that targeting BTK and engaging CRBN are both viable therapeutic approaches in this indication. These assays are to determine potency of CTMs for degrading IMiD neo-substrates in cellular models of MCL and to generate data to inform efficacy studies in MCL xenografts. These data demonstrate IMiD activity for some compounds (e.g., compound **149**) and not others (e.g., compound **130**) and shows that IMiD neo-substrates are

more potently degraded in Rec-1 cells compared to Mino cells, supporting us of Rec-1 cells in subsequent *in vitro* and *in vivo* studies.

Compound ID	Treatment Time (h)	Cells	Aiolos DC ₅₀ (μM)	Ikaros DC ₅₀ (μM)
44	24	Mino	0.1	1.4
44	24	Rec-1	0.07	0.072
149	24	Mino	0.087	0.13
149	24	Rec-1	0.081	0.061
130	24	Mino	>2	>2
130	24	Rec-1	>2	>2
30	24	Mino	0.01	1.1
30	24	Rec-1	0.034	1.0
25	24	Mino	0.01	0.029
25	24	Rec-1	0.031	0.063
Lenalidomide	24	Rec-1	0.394	1.904
Pomalidomide	24	Rec-1	0.033	0.056
Lenalidomide	24	Mino	0.91	>2
Pomalidomide	24	Mino	0.049	0.244

[00523] As shown in FIGS. 10A and 10B, compound **44** has some effects on neo-substrate and ITK levels after twenty-four hours in TMD8 and/or MOLT4 cells.

[00524] As shown in FIGS. 10A and 10B, compound **72** does not effect CRBN neo-substrates but does affect ITK levels at twenty-four hours.

[00525] As shown in FIGS. 10A and 10B, compound **121** has minimal effects on CRBN neo-substrates and ITK at twenty-four hours.

[00526] As shown in FIGS. 11A and 11B, compounds **44** and **149** have some effect on CRBN neo-substrate and ITK levels in cells.

[00527] As shown in FIG. 12, other CTMs tested had slight effects on ITK levels but did not have IMiD activity, including compounds **72** and **130**.

Biological Example 15

[00528] TEC Kinase Degradation

[00529] This example assesses whether CTM treatment affects levels of off-target protein TEC kinase.

[00530] BTK and TEC kinase are two members of the TEC kinase family, and BTK inhibitors, such as ibrutinib, have been shown to affect TEC activity. This off-target effect of ibrutinib on TEC kinase has been implicated in the bleeding effects observed clinically with ibrutinib treatment. To determine effects of BTK CTMs on TEC levels in cells, K562 cells were treated for four hours with CTMs at concentrations between 0.026 – 2000 nM. TEC levels in cell lysate was assessed by western blot.

[00531] Tested CTMs have mild to moderate effects on TEC kinase levels in K562 cells but exhibit more potent degradation of BTK than TEC as shown in FIGS. 13A-13D. The CTMs include compounds **44**, **72**, **149**, and **130**.

[00532] Biological Example 16

[00533] *B cell activation assay (Flow Cytometry)*

[00534] This example evaluates whether CTM treatment affects B cell receptor (BCR) signaling. BTK is activated downstream of the B cell receptor and leads to upregulation of activation markers CD86 and CD69 on the surface of B cells. These data illustrate that degradation of BTK can block this signaling pathway similar to inhibition of BTK with ibrutinib.

Compound ID	Treatment Time (h)	IgM Stimulation Time (h)	Cells	CD86 EC ₅₀ (μM)	CD69 EC ₅₀ (μM)
44	4	18	Mouse B cells	0.0004	0.0002
37	4	18	Mouse B cells	0.0002	0.0001
83	4	18	Mouse B cells	0.0001	0.00008
69	4	18	Mouse B cells	0.0003	0.0001
121	4	18	Mouse B cells	0.0009	0.0005
72	4	18	Mouse B cells	0.0002	0.00007
73	4	18	Mouse B cells	0.0002	~0.0002
71	4	18	Mouse B cells	0.002	0.001
Ibrutinib	4	18	Mouse B cells	0.001	0.0007
Acalabrutinib	4	18	Mouse B cells	0.003	0.001
ARQ531	4	18	Mouse B cells	0.07	0.05
44	4	18	Human B cells	0.0005	0.0005
149	4	18	Human B cells	0.005	0.004
130	4	18	Human B cells	0.0005	0.0004
Ibrutinib	4	18	Human B cells	0.0002	0.0002
Acalabrutinib	4	18	Human B cells	0.003	0.002

[00535] Biological Example 17**[00536] *T cell activation assay (ELISA and Flow Cytometry)***

[00537] This example evaluates whether CTMs with IMiD activity affect T cell activation. Activation of T cells is thought to be one way in which IMiDs, such as Lenalidomide and Pomalidomide can modulate the immune system. These assays were performed to assess whether BTK CTMs with and without IMiD activity affected activation of primary human T cells after stimulation of the T cell receptor with anti-CD3/anti-CD28 stimulation. T cell activation was measured by IL-2 secretion (ELISA assay) and upregulation of activation markers CD25 and CD69 on the surface of T cells (flow cytometry). Data are presented as the fold-change of response relative to baseline (stimulation with anti-CD3/anti-CD28 stimulation in the absence of compound).

[00538] Lenalidomide and Pomalidomide induce IL-2 secretion and increase expression of CD25 and CD69 above the baseline level (anti-CD3/anti-CD28 stimulation alone).

[00539] Ibrutinib treatment results in decreases in IL-2 secretion and expression of CD25 and CD69 compared to baseline. As BTK is not present in T cells, this could be due to ibrutinib's off-target effects on other kinases such as ITK.

[00540] CTMs with IMiD activity (such as compounds **44**, **149**, **30**, and **25**) increased IL-2 secretion but not to the level observed with IMiDs. Treatment with these CTMs resulted in unchanged or decreased levels of CD25 and CD69, potentially due to non-IMiD effects of the CTM, like affecting ITK.

[00541] These data suggest there is a correlation between IMiD neo-substrate degradation activity of certain CTMs and their phenotypic effects on T cell activation in terms of IL-2 secretion.

Compound ID	IL-2 Secretion Anti-CD3/Anti-CD28 Stimulation			CD25 Staining Anti-CD3/Anti-CD28 Stimulation			CD69 Staining Anti-CD3/Anti-CD28 Stimulation		
	333 nM	37 nM	1.4 nM	333 nM	37 nM	1.4 nM	333 nM	37 nM	1.4 nM
Ibrutinib	0.34	0.85	0.84	0.22	0.74	0.92	0.22	0.74	0.89
Lenalidomide	8.67	4.48	1.63	1.93	1.73	1.26	1.81	1.49	1.20
Pomalidomide	5.50	4.80	1.31	1.63	1.39	1.03	1.77	1.33	1.01
25	3.86	3.35	2.42	1.39	1.30	1.25	1.39	1.33	1.18
17	2.92	3.14	1.59	1.11	1.34	1.06	1.12	1.23	1.05
64	1.48	1.80	1.28	0.34	1.04	1.17	0.64	1.14	1.14

Compound ID	IL-2 Secretion Anti-CD3/Anti-CD28 Stimulation			CD25 Staining Anti-CD3/Anti-CD28 Stimulation			CD69 Staining Anti-CD3/Anti-CD28 Stimulation		
	333 nM	37 nM	1.4 nM	333 nM	37 nM	1.4 nM	333 nM	37 nM	1.4 nM
53	2.53	2.08	1.22	0.84	1.14	1.09	0.83	1.07	1.06
51	2.12	1.99	1.19	0.38	0.62	0.86	0.39	0.62	0.91
44	3.75	3.49	1.43	0.52	0.86	1.25	0.60	0.85	1.21
38	1.81	1.58	1.21	0.86	1.02	1.05	0.90	0.99	1.02
37	1.64	2.06	1.16	0.43	0.79	1.11	0.45	0.77	1.08
34	1.58	1.66	1.48	1.25	1.31	1.21	1.23	1.21	1.14
31	3.59	2.45	1.23	1.32	1.34	1.15	1.26	1.24	1.12
30	3.95	3.82	1.59	1.17	1.14	1.01	1.16	1.10	1.01
92	1.63	2.19	1.53	1.06	1.21	1.14	1.35	1.29	1.09
78	1.20	1.17	1.00	0.44	0.73	0.99	0.43	0.66	1.00
149	4.24	3.63	1.86	0.61	1.02	1.31	0.63	0.93	1.22
130	2.02	1.42	1.19	0.55	0.98	1.02	0.55	0.96	1.00
155	3.11	3.13	1.62	1.21	1.46	1.31	1.20	1.34	1.25
154	3.45	3.38	1.77	1.13	1.36	1.23	1.16	1.29	1.18

[00542] Biological Example 18**[00543] Cell viability assay (CellTiter-Glo)**

[00544] This example evaluates effects of CTM-mediated degradation on cell viability. Certain B cell malignancies have been shown to be dependent on BCR signaling and thus BTK for survival. Here, the ability of CTMs to affect viability in BTK-dependent cell lines was assessed. Mino and Rec-1 are models of Mantle Cell Lymphoma, which is sensitive to IMiDs. In these MCL cell lines, BTK CTMs affected degradation, and CTMs with IMiD activity (compounds **44** and **149**) were more potent than a CTM with minimal IMiD activity (compound **130**).

Compound ID	Treatment Time (h)	Cells	EC ₅₀ (μM)	EMAX (% viable cells)
44	72	Mino	11.7	61
149	72	Mino	3.4	50
130	72	Mino	176	78
Ibrutinib	72	Mino	498	79
Acalabrutinib	72	Mino	1,241	84
Ibrutinib	72	Rec-1	268	68

Compound ID	Treatment Time (h)	Cells	EC ₅₀ (μM)	E _{MAX} (% viable cells)
Acalabrutinib	72	Rec-1	582	76
44	72	Rec-1	0.82	37
149	72	Rec-1	0.17	24
130	72	Rec-1	155	63

[00545] Biological Example 19

[00546] This example evaluates the effects of CTM-mediated degradation on cell viability. Certain B cell malignancies have been shown to be dependent on BCR signaling and thus BTK for survival. Here, the ability of CTMs to affect viability in BTK-dependent cell lines was assessed. The ABC-DLBCL cell line TMD8 was very sensitive to BTK degradation or inhibition, while the TMD8 cell line expressing the ibrutinib-resistant mutant BTK-C481S retained sensitivity to BTK degradation (~2-5 fold less sensitive than WT) but were not sensitive to BTK inhibition.

Compound ID	Treatment Time (h)	Cells	EC ₅₀ (μM)	E _{MAX} (% viable cells)
21	72	TMD8	0.001600	19
17	72	TMD8	0.000600	7
60	72	TMD8	0.000970	20
59	72	TMD8	0.000150	31
55	72	TMD8	0.002405	15
54	72	TMD8	0.000610	13
53	72	TMD8	0.002240	16
51	72	TMD8	0.000320	20
49	72	TMD8	0.000610	28
47	72	TMD8	0.003831	39
44	72	TMD8	0.003728	15
42	72	TMD8	0.000217	40
37	72	TMD8	0.021090	10
31	72	TMD8	0.015884	27
101	72	TMD8	0.093380	27
86	72	TMD8	0.000670	27
83	72	TMD8	0.001660	38
80	72	TMD8	0.045160	45
78	72	TMD8	0.009040	41

Compound ID	Treatment Time (h)	Cells	EC ₅₀ (μM)	E _{MAX} (% viable cells)
212	72	TMD8	0.015080	42
211	72	TMD8	0.011700	30
121	72	TMD8	0.001542	28
210	72	TMD8	0.005610	32
209	72	TMD8	0.007410	49
208	72	TMD8	0.000007	24
206	72	TMD8	0.000005	43
73	72	TMD8	0.000004	25
72	72	TMD8	0.000429	26
149	72	TMD8	0.009615	7
148	72	TMD8	0.003265	2
115	72	TMD8	0.002743	13
133	72	TMD8	0.006981	15
130	72	TMD8	0.001496	27
129	72	TMD8	0.003174	16
Acalabrutinib	72	TMD8	0.012	35
ARQ531	72	TMD8	0.10	16
Ibrutinib	72	TMD8	0.003	16
Vecabrutinib	72	TMD8	0.256	38
17	72	TMD8 C481S	0.003710	15
60	72	TMD8 C481S	0.008370	26
59	72	TMD8 C481S	0.002030	52
55	72	TMD8 C481S	0.016840	19
54	72	TMD8 C481S	0.007110	6
53	72	TMD8 C481S	0.016060	24
51	72	TMD8 C481S	0.001950	49
49	72	TMD8 C481S	0.003860	23
47	72	TMD8 C481S	0.043520	61
44	72	TMD8 C481S	0.008104	25
42	72	TMD8 C481S	0.001960	57
37	72	TMD8 C481S	0.051657	16
31	72	TMD8 C481S	0.059425	33
101	72	TMD8 C481S	0.431100	27
86	72	TMD8 C481S	0.004780	30
83	72	TMD8 C481S	0.004315	52
80	72	TMD8 C481S	0.124800	78

Compound ID	Treatment Time (h)	Cells	EC ₅₀ (μM)	E _{MAX} (% viable cells)
78	72	TMD8 C481S	0.007190	37
212	72	TMD8 C481S	0.062955	44
211	72	TMD8 C481S	0.112690	28
121	72	TMD8 C481S	0.004943	31
210	72	TMD8 C481S	0.005290	40
209	72	TMD8 C481S	0.055200	44
208	72	TMD8 C481S	0.000038	16
207	72	TMD8 C481S	0.000009	54
206	72	TMD8 C481S	0.000102	46
73	72	TMD8 C481S	0.000054	19
72	72	TMD8 C481S	0.001158	21
149	72	TMD8 C481S	0.037184	18
148	72	TMD8 C481S	0.009176	4
115	72	TMD8 C481S	0.001931	16
133	72	TMD8 C481S	0.006829	9
130	72	TMD8 C481S	0.004829	33
129	72	TMD8 C481S	0.004356	14
Acalabrutinib	72	TMD8 C481S	>2	96
ARQ531	72	TMD8 C481S	0.10	17
Ibrutinib	72	TMD8 C481S	1.044	46
Vecabrutinib	72	TMD8 C481S	0.530	51

[00547] Biological Example 20

[00548] *In vivo degradation of BTK in mouse PD experiments with oral dosing*

[00549] This example evaluates *in vivo* activity of BTK CTMs via a direct mouse PD measurement following oral dosing

[00550] Various BTK CTMs demonstrate robust BTK degradation activity *in vivo*; activity varies from inactive compounds to compounds with sustained BTK degradation even twenty-four hours after a single oral dose; this data helped understand BTK degradation/resynthesis rates *in vivo*. Screens were completed at 90 mg/kg for six hours, and then changed to lower doses/longer time points after seeing strong BTK degradation activity with an initial set of compounds. This assay was useful in selecting compounds for *in vivo* efficacy experiments. The assay showed a good correlation between mouse PD results and *in vivo* efficacy in mouse tumor models.

Compound ID	Oral Dose (mg/kg)	Time (h)	Tissue	%BTK Remaining	Analysis Method
60	90	6	Splenocytes	3%	HTRF
59	90	6	Splenocytes	7%	HTRF
54	90	6	Splenocytes	1%	HTRF
58	90	6	Splenocytes	89%	HTRF
47	90	6	Splenocytes	80%	HTRF
44	90	6	Splenocytes	4%	HTRF
44	1	6	Splenocytes	58%	HTRF
44	3	6	Splenocytes	32%	HTRF
44	10	6	Splenocytes	11%	HTRF
44	30	6	Splenocytes	4%	HTRF
44	10	24	Splenocytes	34%	HTRF
44	30	24	Splenocytes	23%	HTRF
44	1 (IV)	24	Splenocytes	58%	HTRF
45	90	6	Splenocytes	8%	HTRF
46	90	6	Splenocytes	14%	HTRF
48	90	6	Splenocytes	7%	HTRF
49	90	6	Splenocytes	<1%	HTRF
50	90	6	Splenocytes	9%	HTRF
51	90	6	Splenocytes	2%	HTRF
52	90	6	Splenocytes	2%	HTRF
43	90	6	Splenocytes	4%	HTRF
42	90	6	Splenocytes	5%	HTRF
41	90	6	Splenocytes	15%	HTRF
40	1	6	Splenocytes	82%	HTRF
39	1	6	Splenocytes	79%	HTRF
38	1	6	Splenocytes	68%	HTRF
38	1	6	Splenocytes	76%	HTRF
38	3	6	Splenocytes	38%	HTRF
32	1	6	Splenocytes	93%	HTRF
34	1	6	Splenocytes	75%	HTRF
35	1	6	Splenocytes	74%	HTRF
55	1	6	Splenocytes	80%	HTRF
55	1	6	Splenocytes	66%	HTRF
55	3	6	Splenocytes	18%	HTRF
55	0.3	24	Blood	83%	Flow cytometry

Compound ID	Oral Dose (mg/kg)	Time (h)	Tissue	%BTK Remaining	Analysis Method
55	3	24	Blood	55%	Flow cytometry
55	10	24	Blood	47%	Flow cytometry
55	30	24	Blood	39%	Flow cytometry
55	90	24	Blood	23%	Flow cytometry
55	0.3	24	Splenocytes	114%	Flow cytometry
55	3	24	Splenocytes	72%	Flow cytometry
55	10	24	Splenocytes	45%	Flow cytometry
55	30	24	Splenocytes	36%	Flow cytometry
55	90	24	Splenocytes	48%	Flow cytometry
108	1	6	Splenocytes	116%	HTRF
113	1	6	Splenocytes	70%	HTRF
113	30	24	blood	59%	
113	30	24	splenocytes	52%	HTRF
76	1	6	Splenocytes	100%	HTRF
79	1	6	Splenocytes	102%	HTRF
105	1	6	Splenocytes	85%	HTRF
101	1	6	Splenocytes	18%	HTRF
101	1	6	Splenocytes	55%	HTRF
218	1	6	Splenocytes	97%	HTRF
86	3	6	blood	56%	Flow cytometry
86	3	24	blood	70%	Flow cytometry
83	3	6	blood	48%	Flow cytometry
83	3	24	blood	63%	Flow cytometry
217	3	6	blood	97%	Flow cytometry
217	3	24	blood	97%	Flow cytometry
37	3	6	blood	26%	Flow cytometry
37	3	24	blood	51%	Flow cytometry
53	3	6	blood	35%	Flow cytometry
53	3	24	blood	56%	Flow cytometry
31	3	6	blood	67%	Flow cytometry
31	3	24	blood	69%	Flow cytometry
216	3	6	blood	100%	Flow cytometry
215	3	6	blood	88%	Flow cytometry
214	3	6	blood	100%	Flow cytometry
80	3	6	blood	96%	Flow cytometry
80	0.3	24	blood	88%	Flow cytometry

Compound ID	Oral Dose (mg/kg)	Time (h)	Tissue	%BTK Remaining	Analysis Method
80	3	24	blood	77%	Flow cytometry
80	10	24	blood	59%	Flow cytometry
80	30	24	blood	52%	Flow cytometry
80	90	24	blood	48%	Flow cytometry
80	0.3	24	Splenocytes	115%	Flow cytometry
80	3	24	Splenocytes	111%	Flow cytometry
80	10	24	Splenocytes	74%	Flow cytometry
80	30	24	Splenocytes	69%	Flow cytometry
80	90	24	Splenocytes	65%	Flow cytometry
213	3	6	blood	97%	Flow cytometry
78	3	6	blood	74%	Flow cytometry
212	3	6	blood	78%	Flow cytometry
211	3	6	blood	74%	Flow cytometry
71	30	24	splenocytes	27%	HTRF
73	30	24	splenocytes	26%	HTRF
206	30	24	splenocytes	59%	HTRF
207	30	24	splenocytes	46%	HTRF
72	30	24	splenocytes	20%	HTRF
121	30	24	splenocytes	33%	HTRF
121	0.3	24	blood	102%	Flow cytometry
121	3	24	blood	68%	Flow cytometry
121	30	24	blood	28%	Flow cytometry
120	30	24	splenocytes	59%	HTRF
70	30	24	splenocytes	42%	HTRF
204	30	24	splenocytes	87%	HTRF
119	30	24	splenocytes	77%	HTRF
69	30	24	splenocytes	33%	HTRF
69	0.3	24	blood	112%	Flow cytometry
69	3	24	blood	43%	Flow cytometry
69	30	24	blood	30%	Flow cytometry
118	30	24	splenocytes	85%	HTRF
205	30	24	splenocytes	66%	HTRF
153	30	24	blood	33%	Flow cytometry
117	30	24	blood	49%	Flow cytometry
146	30	24	blood	37%	Flow cytometry
144	30	24	blood	29%	Flow cytometry

Compound ID	Oral Dose (mg/kg)	Time (h)	Tissue	%BTK Remaining	Analysis Method
143	30	24	blood	37%	Flow cytometry
116	30	24	blood	39%	Flow cytometry
142	30	24	blood	43%	Flow cytometry
148	30	24	blood	24%	Flow cytometry
149	10	24	blood	27%	Flow cytometry
149	30	24	blood	11%	Flow cytometry
149	90	24	blood	1%	Flow cytometry
149	10	24	splenocytes	21%	HTRF
149	30	24	splenocytes	8%	HTRF
149	90	24	splenocytes	1%	HTRF
145	30	24	blood	100%	Flow cytometry
150	30	24	blood	25%	Flow cytometry
203	30	24	blood	95%	Flow cytometry
115	30	24	blood	30%	Flow cytometry
133	30	24	blood	10%	Flow cytometry
130	30	24	blood	5%	Flow cytometry
129	30	24	blood	16%	Flow cytometry
126	30	24	blood	33%	Flow cytometry
176	30	24	splenocytes	48%	HTRF
175	30	24	splenocytes	62%	HTRF
168	30	24	splenocytes	84%	HTRF
166	30	24	splenocytes	19%	HTRF
164	30	24	splenocytes	29%	HTRF
165	30	24	splenocytes	29%	HTRF
182	30	24	splenocytes	12%	HTRF
196	30	24	blood	33%	Flow cytometry
197	30	24	blood	13%	Flow cytometry
198	30	24	blood	25%	Flow cytometry
199	30	24	blood	20%	Flow cytometry
200	30	24	blood	23%	Flow cytometry
202	30	24	blood	79%	Flow cytometry
201	30	24	blood	71%	Flow cytometry
195	3	24	Blood	40%	Flow cytometry
194	3	24	blood	90%	Flow cytometry
195	10	24	Blood	25%	Flow cytometry
194	10	24	blood	63%	Flow cytometry

Compound ID	Oral Dose (mg/kg)	Time (h)	Tissue	%BTK Remaining	Analysis Method
195	3	24	splenocytes	39%	Flow cytometry
194	3	24	splenocytes	95%	Flow cytometry
195	10	24	splenocytes	23%	Flow cytometry
194	10	24	splenocytes	57%	Flow cytometry

[00551] Biological Example 21

[00552] *PD data from rat, dog, and cyno*

[00553] In this example, compounds were profiled for activity in non-mouse species. These data were used to assess likelihood of BTK degradation activity in humans and to estimate an efficacious human dose

[00554] Multiple BTK CTMs demonstrated potent BTK degradation activity across rat, dog, and cyno species. Human dose projections based upon this data suggest an efficacious human dose of <500 mg/day.

Compound ID	Dose (mg/kg)	Route of Administration	Time (h)	Species	Tissue	%BTK Remaining
44	10	PO	2	cyno	blood	82%
44	10	PO	4	cyno	blood	42%
44	10	PO	8	cyno	blood	27%
44	10	PO	24	cyno	blood	29%
44	30	PO	2	cyno	blood	83%
44	30	PO	4	cyno	blood	47%
44	30	PO	8	cyno	blood	22%
44	30	PO	24	cyno	blood	17%
44	1	IV	2	cyno	blood	6%
44	1	IV	4	cyno	blood	6%
44	1	IV	8	cyno	blood	7%
44	1	IV	24	cyno	blood	9%
44	10	PO	2	dog	blood	88%
44	10	PO	4	dog	blood	56%
44	10	PO	8	dog	blood	35%
44	10	PO	24	dog	blood	19%
44	30	PO	2	dog	blood	87%
44	30	PO	4	dog	blood	58%
44	30	PO	8	dog	blood	28%
44	30	PO	24	dog	blood	14%

Compound ID	Dose (mg/kg)	Route of Administration	Time (h)	Species	Tissue	%BTK Remaining
44	1	PO	2	cyno	blood	85%
44	1	PO	4	cyno	blood	65%
44	1	PO	8	cyno	blood	52%
44	1	PO	24	cyno	blood	40%
44	10	PO	2	cyno	blood	59%
44	10	PO	4	cyno	blood	35%
44	10	PO	8	cyno	blood	22%
44	10	PO	24	cyno	blood	15%
44	100	PO	2	cyno	blood	48%
44	100	PO	4	cyno	blood	27%
44	100	PO	8	cyno	blood	12%
44	100	PO	24	cyno	blood	8%
130	10	PO	4	rat	blood	<1%
130	30	PO	4	rat	blood	<1%
130	10	PO	24	rat	blood	<1%
130	30	PO	24	rat	blood	<1%
130	1	IV	4	rat	blood	<1%
130	1	IV	24	rat	blood	<1%
130	1	IV	2	Cyno	blood	8
130	1	IV	4	cyno	blood	6
130	1	IV	8	Cyno	blood	5
130	1	IV	24	cyno	blood	13
130	10	PO	2	Cyno	blood	4
130	10	PO	4	cyno	blood	<1
130	10	PO	8	Cyno	blood	<3
130	10	PO	24	cyno	blood	<1
130	30	PO	2	Cyno	blood	6
130	30	PO	4	cyno	blood	<1
130	30	PO	8	Cyno	blood	<1
130	30	PO	24	cyno	blood	1
149	1	IV	2	Cyno	blood	24
149	1	IV	4	cyno	blood	9
149	1	IV	8	Cyno	blood	4
149	1	IV	24	cyno	blood	7
149	10	PO	2	Cyno	blood	81
149	10	PO	4	cyno	blood	39

Compound ID	Dose (mg/kg)	Route of Administration	Time (h)	Species	Tissue	%BTK Remaining
149	10	PO	8	Cyno	blood	17
149	10	PO	24	cyno	blood	12
149	30	PO	2	Cyno	blood	89
149	30	PO	4	cyno	blood	51
149	30	PO	8	Cyno	blood	26
149	30	PO	24	cyno	blood	19
149	100	PO	2	Cyno	blood	97
149	100	PO	4	cyno	blood	56
149	100	PO	8	Cyno	blood	20
149	100	PO	24	cyno	blood	12
149	1	IV	2	dog	blood	43
149	1	IV	4	dog	blood	22
149	1	IV	8	dog	blood	10
149	1	IV	24	dog	blood	11
149	10	PO	2	dog	blood	61
149	10	PO	4	dog	blood	47
149	10	PO	8	dog	blood	29
149	10	PO	24	dog	blood	17

[00555] Biological Example 22

[00556] *Non-human primate (cyno) DRF PD data*

[00557] This example evaluates potency and tolerability of BTK CTMs following multiple, consecutive days of dosing and examines potency of compounds for BTK and Aiolos degradation.

[00558] Compounds were generally well tolerated, even at high doses. All compounds demonstrated potent BTK degradation. Compound **149** demonstrated Aiolos degradation after fourteen days of dosing, whereas the other CTMs tested did not demonstrate Aiolos degradation.

[00559] The data in the table below is from a study in which animals were dosed daily with the designated oral dose. Analysis for BTK and Aiolos levels was performed twenty-four hours following the previous dose.

Compound ID	Dose (mg/kg)	Route of Administration	Days of Dosing	Species	Tissue	%BTK Remaining in B cells	% Aiolos Remaining in T cells
44	10	PO	1	cyno	blood	35	96
44	30	PO	1	cyno	blood	31	99
44	100	PO	1	cyno	blood	14	96
44	10	PO	14	cyno	blood	16	71
44	30	PO	14	cyno	blood	10	69
44	100	PO	14	cyno	blood	6	63
149	10	PO	1	cyno	blood	9	79
149	30	PO	1	cyno	blood	4	74
149	100	PO	1	cyno	blood	3	77
149	10	PO	14	cyno	blood	7	76
149	30	PO	14	cyno	blood	6	55
149	100	PO	14	cyno	blood	6	43
130	10	PO	1	cyno	blood	6	102
130	30	PO	1	cyno	blood	3	98
130	100	PO	1	cyno	blood	4	106
130	10	PO	14	cyno	blood	5	96
130	30	PO	14	cyno	blood	5	108
130	100	PO	14	cyno	blood	4	99

[00560] Biological Example 23**[00561] *Mouse DRF PD data***

[00562] This example evaluates potency and tolerability of BTK CTMs following multiple, consecutive days of dosing and evaluates potency of compounds for BTK degradation.

[00563] Compounds were generally well tolerated, even at high doses. All compounds tested demonstrated potent BTK degradation

[00564] The data in the table below is from a study in which animals were dosed daily with the designated oral dose. Analysis for BTK levels was performed twenty-four hours following the previous dose.

Compound ID	Dose (mg/kg)	Route of Administration	Days of Dosing	Species	Tissue	%BTK Remaining in B cells
44	30	PO	1	mouse	blood	16
44	100	PO	1	mouse	blood	10
44	300	PO	1	mouse	blood	8

Compound ID	Dose (mg/kg)	Route of Administration	Days of Dosing	Species	Tissue	%BTK Remaining in B cells
44	30	PO	14	mouse	blood	16
44	100	PO	14	mouse	blood	11
44	300	PO	14	mouse	blood	10
149	30	PO	1	mouse	blood	11
149	100	PO	1	mouse	blood	10
149	300	PO	1	mouse	blood	6
149	30	PO	14	mouse	blood	8
149	100	PO	14	mouse	blood	5
149	300	PO	14	mouse	blood	2
130	30	PO	1	mouse	blood	11
130	100	PO	1	mouse	blood	3
130	300	PO	1	mouse	blood	2
130	30	PO	14	mouse	blood	6
130	100	PO	14	mouse	blood	2
130	300	PO	14	mouse	blood	<1

[00565] Biological Example 24

[00566] *Compound plasma exposure in cyno DRF study*

[00567] This example evaluates compound plasma concentration which results in *in vivo* BTK and/or Aiolos degradation in cyno.

[00568] Plasma concentrations were determined and this data indicates dose and efficacious compound concentrations in human.

[00569] The data in the table below is from a study in which animals were dosed daily with the designated oral dose. Analysis for compound concentration in plasma was performed twenty-four hours following the previous dose.

Compd	Species	Strain	Dose (mg/kg)	Route of Administration	Days of Dosing	C _{max} (μM)	AUC (hr*μM)
44	Monkey	Cynomolgus	10	PO	1	0.0106	0.1477
44	Monkey	Cynomolgus	30	PO	1	0.0180	0.2683
44	Monkey	Cynomolgus	100	PO	1	0.0226	0.2939
44	Monkey	Cynomolgus	10	PO	14	0.0340	0.4672
44	Monkey	Cynomolgus	30	PO	14	0.0555	0.7940
44	Monkey	Cynomolgus	100	PO	14	0.0942	1.5197

Compd	Species	Strain	Dose (mg/kg)	Route of Administration	Days of Dosing	C _{max} (μM)	AUC (hr*μM)
44	Mouse	CD-1	30	PO	1	0.23	2.32
44	Mouse	CD-1	100	PO	1	0.40	4.15
44	Mouse	CD-1	300	PO	1	0.74	9.53
44	Mouse	CD-1	30	PO	14	0.25	2.22
44	Mouse	CD-1	100	PO	14	0.59	8.07
44	Mouse	CD-1	300	PO	14	0.94	12.84
149	Monkey	Cynomolgus	10	PO	1	0.042	0.386
149	Monkey	Cynomolgus	30	PO	1	0.051	0.720
149	Monkey	Cynomolgus	100	PO	1	0.076	0.714
149	Monkey	Cynomolgus	10	PO	14	0.049	0.763
149	Monkey	Cynomolgus	30	PO	14	0.088	1.481
149	Monkey	Cynomolgus	100	PO	14	0.159	2.664
149	Mouse	CD-1	30	PO	1	0.94	12.24
149	Mouse	CD-1	100	PO	1	2.05	27.69
149	Mouse	CD-1	300	PO	1	2.61	38.65
149	Mouse	CD-1	30	PO	14	1.64	22.81
149	Mouse	CD-1	100	PO	14	2.41	33.40
149	Mouse	CD-1	300	PO	14	4.10	64.24
130	Monkey	Cynomolgus	10	PO	1	0.020	0.172
130	Monkey	Cynomolgus	30	PO	1	0.055	0.582
130	Monkey	Cynomolgus	100	PO	1	0.096	1.404
130	Monkey	Cynomolgus	10	PO	14	0.028	0.387
130	Monkey	Cynomolgus	30	PO	14	0.054	0.844
130	Monkey	Cynomolgus	100	PO	14	0.177	3.839
130	Mouse	CD-1	30	PO	1	2.2	23.2
130	Mouse	CD-1	100	PO	1	3.8	51.3
130	Mouse	CD-1	300	PO	1	5.1	67.0
130	Mouse	CD-1	30	PO	14	1.7	21.1
130	Mouse	CD-1	100	PO	14	3.4	49.8
130	Mouse	CD-1	300	PO	14	5.2	72.2

[00570] Biological Example 25**[00571]** *Efficacy in mouse xenograft models*

[00572] This example examines the activity of various BTK CTMs in relevant disease models, including the WT and C481S TMD8 model, which models B cell malignancies with/without inhibitor-driven BTK mutations at C481.

[00573] BTK CTMs demonstrate significant efficacy in both WT and C481S tumor models.

Compd	Model	Route of Admin.	Dose (mg/kg)	Dosing Frequency	Days of Dosing	Tumor Growth Inhibition (relative to vehicle)	BTK Remaining (% relative to vehicle)
17	TMD8 WT	IP	10	QD	14	14%	20
17	TMD8 WT	IP	30	QD	14	66%	15
44	TMD8 WT	PO	30	QD	23	83%	Not determined
44	TMD8 WT	PO	90	QD	23	93%	Not determined
44	TMD8 WT	PO	30	BID	23	99%	Not determined
44	TMD8 WT	PO	90	BID	23	100%	Not determined
Ibrutinib	TMD8 WT	PO	30	QD	23	80%	Not determined
Ibrutinib	TMD8 WT	PO	90	QD	23	99%	Not determined
Ibrutinib	TMD8 WT	PO	30	BID	23	100%	Not determined
Ibrutinib	TMD8 WT	PO	90	BID	23	100%	Not determined
17	TMD8 WT	IP	30	QD	21	81%	7
44	TMD8 WT	PO	30	QD	21	49%	32
Ibrutinib	TMD8 WT	PO	25	QD	21	43%	109
55	TMD8 WT	PO	30	QD	21	17%	27
53	TMD8 WT	PO	30	QD	21	27%	19
37	TMD8 WT	PO	30	QD	21	41%	16
83	TMD8 WT	PO	30	QD	21	39%	22
44	TMD8 WT	PO	30	QD	21	54%	20
44	TMD8 WT	PO (water bottle)	15	QD (water bottle)	21	29%	7
Ibrutinib	TMD8 WT	PO	30	QD	21	56%	42
44	TMD8 C481S	PO	30	QD	23	48%	51
44	TMD8 C481S	PO	30	BID	23	70%	39

Compd	Model	Route of Admin.	Dose (mg/kg)	Dosing Frequency	Days of Dosing	Tumor Growth Inhibition (relative to vehicle)	BTK Remaining (% relative to vehicle)
Ibrutinib	TMD8 C481S	PO	30	QD	23	26%	69
Ibrutinib	TMD8 C481S	PO	30	BID	23	10%	102
44	TMD8 C481S	PO	5	BID	23	65%	44
44	TMD8 C481S	PO	10	QD	23	48%	38
44	TMD8 C481S	PO	15	BID	23	62%	25
44	TMD8 C481S	PO	30	QD	23	51%	42
44	TMD8 C481S	PO	30	BID	23	78%	35
44	TMD8 C481S	PO	60	QD	23	70%	36
44	TMD8 WT	PO (water bottle)	35	QD (water bottle)	23	89%	18
Ibrutinib	TMD8 C481S	PO	30	QD	23	15%	73
44	1:1 TMD8 WT:TMD8 C481S	PO	30	BID	21	54%	Not determined
44/ ibrutinib	1:1 TMD8 WT:TMD8 C481S	PO	30/30	QD/QD	21	55%	Not determined
44/ ibrutinib	1:1 TMD8 WT:TMD8 C481S	PO	15/30	QD/QD	21	47%	Not determined
44/ ibrutinib	1:1 TMD8 WT:TMD8 C481S	PO	7.5/30	QD/QD	21	41%	Not determined

Compd	Model	Route of Admin.	Dose (mg/kg)	Dosing Frequency	Days of Dosing	Tumor Growth Inhibition (relative to vehicle)	BTK Remaining (% relative to vehicle)
Ibrutinib	1:1 TMD8 WT:TMD8 C481S	PO	30	QD	21	-8%	Not determined
ibrutinib	1:1 TMD8 WT:TMD8 C481S	PO	30	BID	21	21%	Not determined
149	TMD8 C481S	PO	10	QD	23	27%	Not determined
149	TMD8 C481S	PO	30	QD	23	29%	Not determined
130	TMD8 C481S	PO	10	QD	23	58%	Not determined
130	TMD8 C481S	PO	30	QD	23	79%	Not determined
44	TMD8 C481S	PO	10	QD	23	23%	Not determined
44	TMD8 C481S	PO	30	QD	23	36%	Not determined
ibrutinib	TMD8 C481S	PO	30	QD	23	0%	Not determined
149	TMD8 C481S	PO	10	QD	24	17%	Not determined
149	TMD8 C481S	PO	30	QD	24	43%	Not determined
149	TMD8 C481S	PO	90	QD	24	59%	Not determined
130	TMD8 C481S	PO	10	QD	24	90%	Not determined
130	TMD8 C481S	PO	30	QD	24	100%	Not determined
130	TMD8 C481S	PO	90	QD	24	100%	Not determined
Ibrutinib	TMD8 C481S	PO	30	QD	24	8%	Not determined

Compd	Model	Route of Admin.	Dose (mg/kg)	Dosing Frequency	Days of Dosing	Tumor Growth Inhibition (relative to vehicle)	BTK Remaining (% relative to vehicle)
44	TMD8 WT	PO	7.5	BID	21	100	Not determined
44	TMD8 WT	PO	15	BID	21	100	Not determined
44	TMD8 WT	PO	30	QD	21	100	Not determined
44/ ibrutinib	TMD8 WT	PO	7.5/7.5	QD/QD	21	97	Not determined
44/ ibrutinib	TMD8 WT	PO	15/15	QD/QD	21	71	Not determined
Ibrutinib	TMD8 WT	PO	7.5	BID	21	68	Not determined
ibrutinib	TMD8 WT	PO	15	BID	21	100	Not determined
ibrutinib	TMD8 WT	PO	30	QD	21	90	Not determined

[00574] % TGI is defined as $(1 - (\text{mean volume of treated tumors})/(\text{mean volume of control tumors})) \times 100\%$.

[00575] **Biological Example 26**

[00576] *PK data for BTK CTMs*

[00577] The present example evaluates *in vivo* plasma concentrations of BTK CTMs to develop PK-PD-efficacy relationship and predict human exposure.

[00578] *In vivo* PK properties of BTK CTMs varied among the various compounds tested. Molecules with moderate-to-low *in vivo* clearance were identified. Suitable exposure to enable potent BTK degradation was demonstrated with multiple compounds and enabled prediction of human dose and human PK.

Compd	Species	Strain	Dose (mg/kg)	Route of Admin.	Cl (mL/min/kg)	Volume of Distribution (L/kg)	AUC (hr* μ M)	%F
55	Mouse	Balb/c	1	IV	2.4	0.48	8.64	
55	Mouse	Balb/c	30	PO			74.3	29
53	Mouse	Balb/c	1	IV	7.5	0.88	2.75	
53	Mouse	Balb/c	30	PO			96	113
53	Rat	Sprague-Dawley	1	IV	75	5.9	0.31	
53	Rat	Sprague-Dawley	10	PO			2.3	97
44	Mouse	Balb/c	1	IV	5.1	0.69	4.07	
44	Mouse	Balb/c	10	PO			4.0	10
37	Mouse	Balb/c	1	IV	12.0	1.2	1.77	

Compd	Species	Strain	Dose (mg/kg)	Route of Admin.	Cl (mL/min/kg)	Volume of Distribution (L/kg)	AUC (hr* μ M)	%F
37	Mouse	Balb/c	30	PO			1.79	5
37	Rat	Sprague-Dawley	1	IV	36.3	4.6	0.59	
37	Rat	Sprague-Dawley	10	PO			0.027	1
86	Mouse	Balb/c	1	IV	35.0	7.7	0.50	
86	Mouse	Balb/c	30	PO			0.34	2
83	Mouse	Balb/c	1	IV	68.3	4.0	0.29	
83	Mouse	Balb/c	30	PO			0.81	9
121	Mouse	Balb/c	1	IV	6.6	0.77	2.87	
121	Mouse	Balb/c	30	PO			2.22	11
121	Rat	Sprague-Dawley	1	IV	20	3.12	0.919	
121	Rat	Sprague-Dawley	10	PO			0.083	1
121	Rat	Sprague-Dawley	30	PO			0.73	
73	Mouse	Balb/c	1	IV	33.8	3.4	0.6	
73	Mouse	Balb/c	10	PO			2.9	47
72	Mouse	Balb/c	1	IV	5.1	0.68	3.96	
72	Mouse	Balb/c	10	PO			2.9	7
69	Mouse	Balb/c	1	IV	31.4	2.2	0.68	
69	Mouse	Balb/c	10	PO			0.078	1
149	Mouse	Balb/c	1	IV	5.2	1.0	4.5	
149	Mouse	Balb/c	10	PO			16	35
149	Mouse	Balb/c	30	PO			27.7	1
149	Mouse	Balb/c	90	PO			37.5	1
149	Mouse	CD-1	1	IV	12.6	1.5	1.8	
149	Mouse	CD-1	10	PO			11.5	64
149	Rat	Sprague-Dawley	1	IV	19	2.8	1.2	
149	Rat	Sprague-Dawley	10	PO			0.88	7
149	Dog	Beagle	1	IV	18.4	7.0	1.2	
149	Dog	Beagle	10	PO			0.11	0.9
149	Monkey	cynomolgus	1	IV	22.2	7.5	1.0	
149	Monkey	cynomolgus	10	PO			0.09	0.8
149	Monkey	cynomolgus	30	PO			0.08	
130	Mouse	Balb/c	1	IV	6.0	0.72	3.4	
130	Mouse	Balb/c	10	PO			5.81	17
130	Mouse	Balb/c	30	PO			2.3	
130	Mouse	CD-1	1	IV	11.6	1.4	1.7	
130	Mouse	CD-1	10	PO			5.2	33
130	Rat	Sprague-Dawley	1	IV	99.5	32	0.18	
130	Rat	Sprague-Dawley	10	PO			0.69	32
130	Rat	Sprague-Dawley	30	PO			1.62	7
130	Dog	Beagle	1	IV	118	56	0.16	
130	Dog	Beagle	10	PO			0.17	10

Compd	Species	Strain	Dose (mg/kg)	Route of Admin.	Cl (mL/min/kg)	Volume of Distribution (L/kg)	AUC (hr*μM)	%F
130	Dog	Beagle	30	PO			0.23	
130	Monkey	cynomolgus	0.75	IV	90.9	16	0.17	
130	Monkey	cynomolgus	10	PO			0.028	1
130	Monkey	cynomolgus	30	PO			0.45	

[00579] $\%F = (AUC_{inf\ PO} * IV_{dose}) / (AUC_{inf\ IV} * PO_{dose}) * 100$

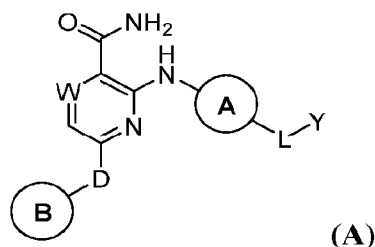
OTHER EMBODIMENTS

[00580] It is to be understood that the foregoing description is intended to illustrate and not limit the scope of this disclosure, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A method of treating or preventing an autoimmune disease or cancer in a subject in need thereof, comprising the step of orally administering to the subject an amount of a bifunctional compound, wherein said bifunctional compound is capable of inducing proteolytic degradation of Bruton's tyrosine kinase, and wherein said amount is effective to treat or prevent the autoimmune disease or the cancer.
2. The method of claim 1, wherein the cancer comprises a solid tumor.
3. The method of claim 1, wherein the cancer is a B cell malignancy.
4. The method of claim 1, wherein the cancer is selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), transformed CLL or Richter's transformation, small cell lymphoma, follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), non-Hodgkin lymphoma, mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Waldenstrom macroglobulinemia (WM), central nervous system (CNS) lymphoma, metastatic melanoma, squamous cell carcinoma of the head and neck (HNSCC), non-small cell lung cancer (NSCLC), platinum-resistant epithelial ovarian cancer (EOC), gastric cancer, metastatic castrate-resistant prostate cancer (mCRPC), triple-negative breast cancer (TNBC), muscle-invasive urothelial cancer, mesothelioma, cervical cancer, microsatellite stable colorectal cancer (MSS CRC), and multiple myeloma (MM).
5. The method of claim 1, wherein the autoimmune disease is selected from the group consisting of graft-versus-host disease (GVHD), acute graft-versus-host disease, and immune thrombocytopenic purpura (ITP).
6. The method of any of the previous claims, wherein the subject has a C481 mutant Bruton's tyrosine kinase.
7. The method of any of the previous claims, wherein the cancer is ibrutinib-resistant.
8. The method of any of the previous claims, wherein the subject has a C481 mutant Bruton's tyrosine kinase and the cancer is chronic lymphocytic leukemia (CLL).
9. A method of degrading splenocyte Bruton's tyrosine kinase in a subject in need thereof, comprising the step of orally administering to the subject an amount of a bifunctional compound, wherein said bifunctional compound is capable of inducing proteolytic degradation of Bruton's tyrosine kinase, and wherein said amount is effective to degrade splenocyte Bruton's tyrosine kinase in the subject.

10. The method of claim 9, wherein the Bruton's tyrosine kinase is a C481 mutant Bruton's tyrosine kinase.
11. A method of preventing B cell activation in a subject in need thereof, comprising the step of orally administering to the subject an amount of a bifunctional compound, wherein said bifunctional compound is capable of inducing proteolytic degradation of Bruton's tyrosine kinase, and wherein said amount is effective to prevent B cell activation.
12. The method of claim 11, wherein the B cell expresses CD69 and/or CD86.
13. The method of any of the previous claims, wherein the bifunctional compound is administered to the subject at a dose of 0.1-500 mg/kg.
14. The method of any of the previous claim, wherein the bifunctional compound is administered to the subject at a dose selected from the group consisting of 100 mg/kg, 200 mg/kg, 300 mg/kg, 450 mg/kg, 600 mg/kg, 800 mg/kg, and 1000 mg/kg.
15. The method of any of the previous claims, wherein the bifunctional compound is administered one, two, three, or four times per day.
16. The method of any of the previous claims, wherein the bifunctional compound is administered daily for one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, or fourteen days.
17. The method of any of the previous claims, wherein the bifunctional compound is administered cyclically.
18. A method of degrading C481S Bruton's tyrosine kinase, comprising the step of contacting a cell expressing the C481S Bruton's tyrosine kinase with an amount of a bifunctional compound effective to degrade the C481S Bruton's tyrosine kinase.
19. The method of claim 18, wherein the method is *in vitro*.
20. The method of claim 18, wherein the method is *in vivo*.
21. The method of claim 18, wherein contacting a cell expressing the C481S Bruton's tyrosine kinase with an amount of a bifunctional compound effective to degrade the C481S Bruton's tyrosine kinase is in a subject in need thereof.
22. The method of any of the previous claims, wherein the bifunctional compound is a compound of Formula (A)



or a pharmaceutically acceptable salt thereof, wherein

W is CH or N;

D is a bond or —NH— ;

Ring A is phenyl, a 9-10 membered bicyclic aryl, a 5-6 membered partially or fully unsaturated monocyclic heterocycle, or a 9-10 membered bicyclic heteroaryl, wherein the monocyclic heterocycle and bicyclic heteroaryl of **Ring A** each possess one to three heteroatoms independently selected from N, O, or S, wherein **Ring A** is optionally and independently substituted with up to three substituents selected from halo, —CN , —COOH , NH_2 , and optionally substituted C_{1-6} alkyl;

Ring B is a phenyl, a 5-6 membered heteroaryl, a 4-6 membered heterocycloalkyl, or a 8-10 membered spiro bicyclic heterocycle, wherein **Ring B** is optionally substituted, and wherein the heteroaryl and heterocycloalkyl of **Ring B** has one to three heteroatoms independently selected from N, O, or S;

L is $\text{—X}^1\text{—X}^2\text{—X}^3\text{—X}^4\text{—X}^5\text{—}$;

X¹ is a bond, —C(O)—N(R)— , —N(R)—C(O)— , $\text{—(O—CH}_2\text{—CH}_2\text{)}_m\text{—}$, $\text{—O(C}_6\text{H}_4\text{)—}$, $\text{—(O—CH}_2\text{—CH}_2\text{—CH}_2\text{)}_m\text{—}$, —C_{1-5} alkyl—, 7-12 membered spiro or fused bicyclic heterocycloalkyl having one to three heteroatoms independently selected from N, O, or S, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein each of the monocyclic and bicyclic heterocycloalkyl of **X**¹ is optionally substituted with —CH_3 ;

X² is a bond, $\text{—(O—CH}_2\text{—CH}_2\text{)}_n\text{—}$, $\text{—(CH}_2\text{—CH}_2\text{—O)}_n\text{—}$, —N(R)—C(O)— , —N(R)— , —C(O)— , —C_{1-5} alkyl—, 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S;

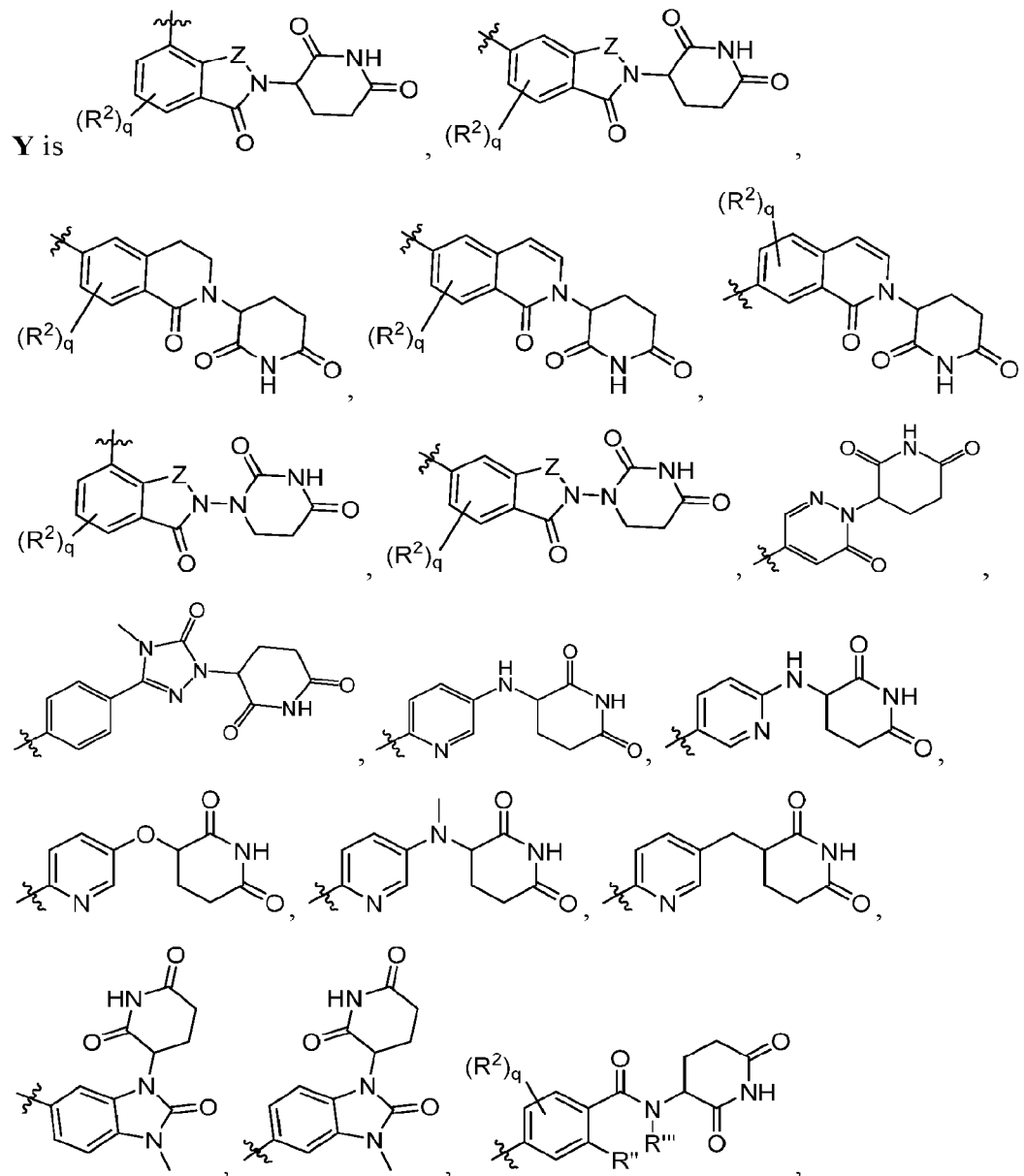
X³ is a bond, —C_{1-8} alkyl—, $\text{—C}\equiv\text{C—}$, 4-6 membered cycloalkyl, —N(R)— , —N(R)—C(O)— , $\text{—(O—CH}_2\text{—CH}_2\text{)}_p\text{—}$, $\text{—(CH}_2\text{—CH}_2\text{—O)}_p\text{—}$, 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with —CH_3 ;

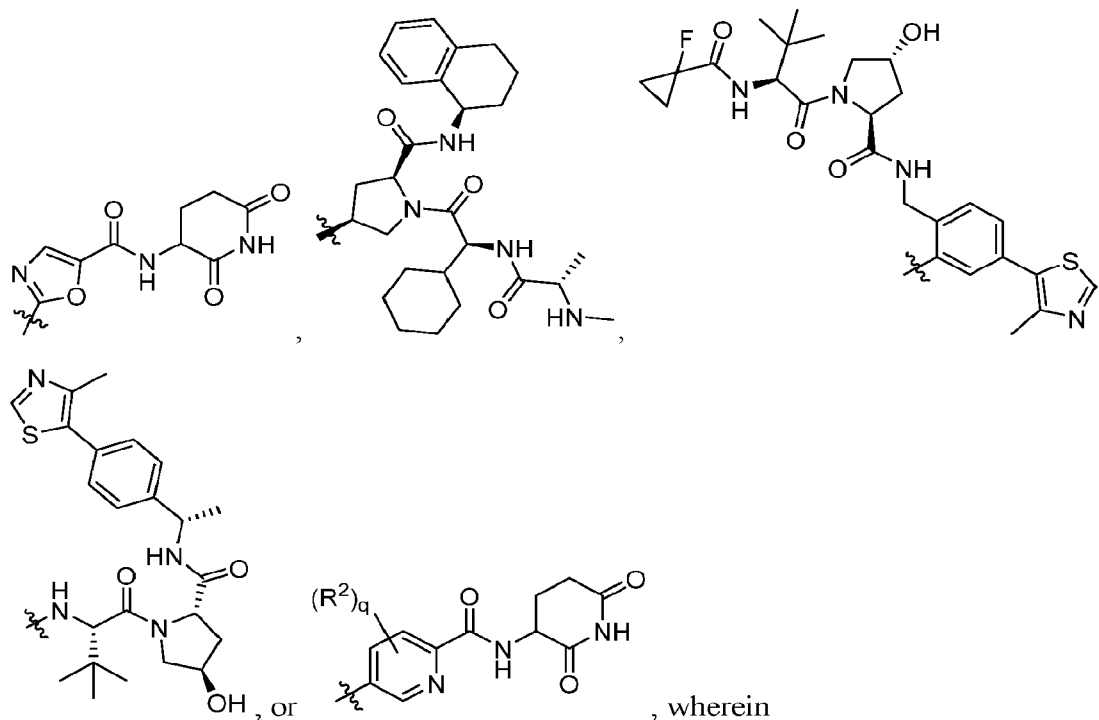
X⁴ is a bond, $-\text{CH}_2\text{CH}_2\text{N}(\mathbf{R})-$, $-\text{N}(\mathbf{R})-$, $-\text{C}_{1-4}$ alkyl-, $-(\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2)_m-$, a 5-6 membered saturated, partially unsaturated, or fully unsaturated carbocycle, or a 5-6 membered saturated, partially unsaturated, or fully unsaturated heterocycle having one to three heteroatoms independently selected from N, O, or S;

X⁵ is a bond, $-\text{C}_{1-4}$ alkyl-, $-\text{N}(\mathbf{R})-$, $-\text{O}-$, $-\text{C}(\text{O})-$, or $-\text{C}(\text{O})\text{N}(\mathbf{R})-$;

each **R** is independently hydrogen or $-\text{C}_{1-3}$ alkyl; and

each of **m**, **n**, and **p** is independently an integer from one to three; and





each R^2 is independently halo, $-\text{CN}$, or C_{1-4} alkyl, wherein each C_{1-4} alkyl is optionally and independently substituted with up to three instances of halo, $-\text{CN}$, $-\text{COOH}$, $-\text{COONH}_2$, $-\text{NH}_2$, or $-\text{CF}_3$;

each R'' and R''' are independently hydrogen or, together with the atoms to which they are attached, form a 5-6 membered partially unsaturated or fully unsaturated benzofused heterocycle;

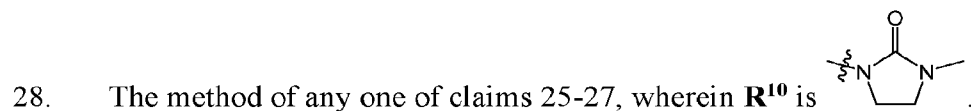
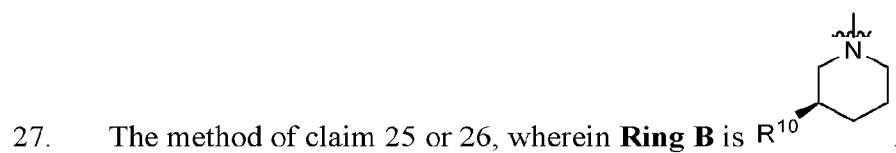
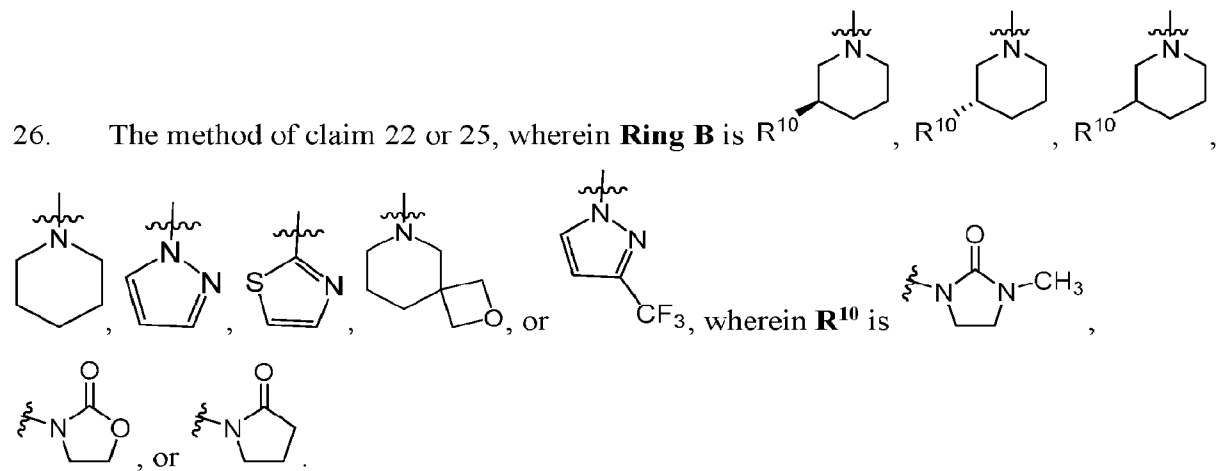
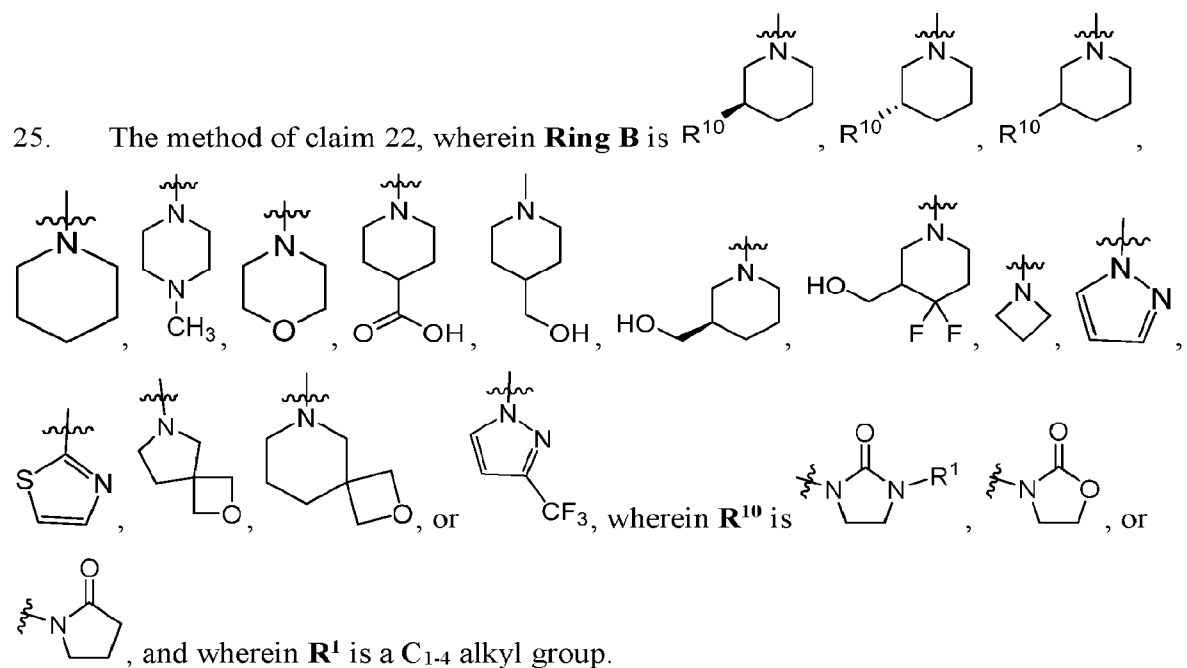
each Z is $-\text{C}(R^A)_2-$ or $-\text{C}(\text{O})-$;

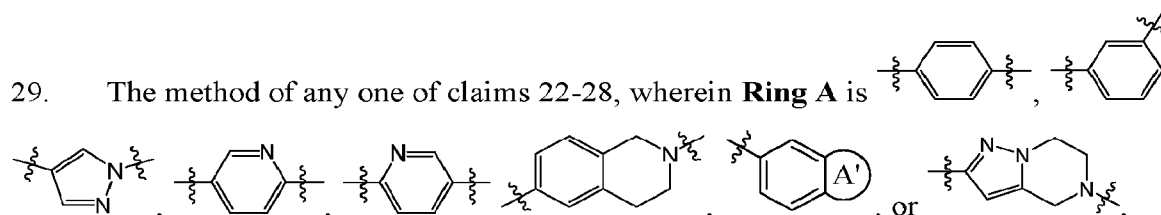
each R^A is independently hydrogen or $-\text{C}_{1-4}$ alkyl; and

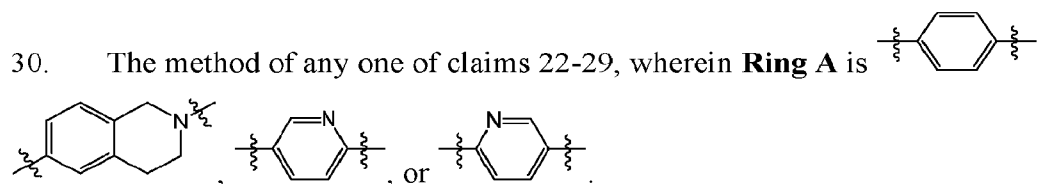
q is zero, one, or two.

23. The method of claim 22, wherein **Ring B** is an optionally substituted 5-6 membered heterocycloalkyl having one to two nitrogen atoms.

24. The method of claim 22, wherein **Ring B** is an optionally substituted 5-6 membered heteroaryl having one to two heteroatoms independently selected from N and S.



29. The method of any one of claims 22-28, wherein **Ring A** is ,
 wherein **Ring A'** together with the phenyl ring to which **Ring A'** is fused forms a 9-10 membered bicyclic aryl or a 9-10 membered bicyclic heteroaryl wherein the bicyclic heteroaryl has one to three heteroatoms independently selected from N, O, or S.

30. The method of any one of claims 22-29, wherein **Ring A** is .

31. The method of any one of claims 22-30, or a pharmaceutically acceptable salt thereof, wherein at least one of **X¹**, **X²**, and **X⁵** is $-\text{N}(\text{R})-$, $-\text{C}(\text{O})-\text{N}(\text{R})-$, or $-\text{CH}_2-$.

32. The method of any one of claims 22-31, wherein **X¹** is $-\text{C}(\text{O})-\text{N}(\text{R})-$.

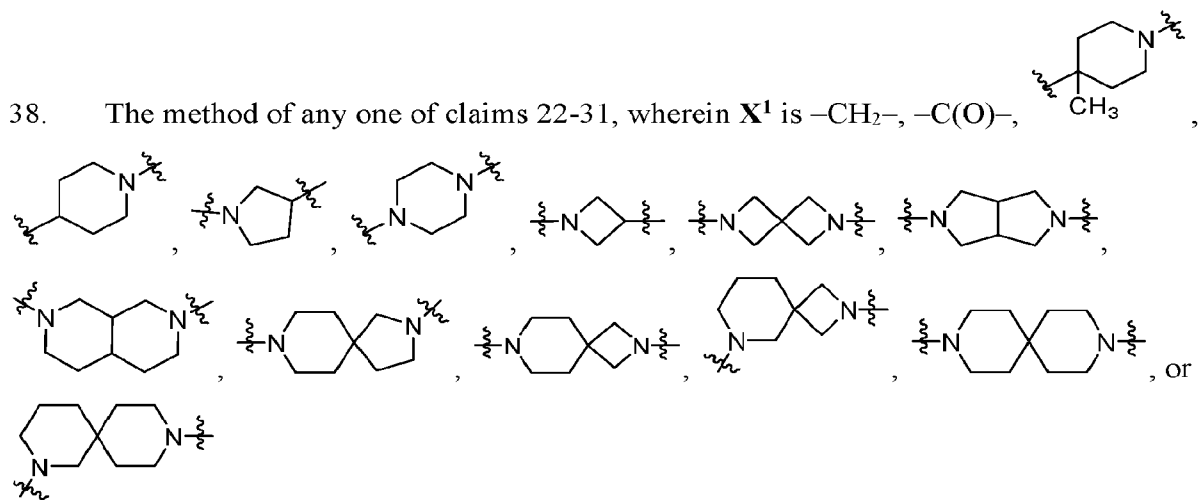
33. The method of any one of claims 22-32, or a pharmaceutically acceptable salt thereof, wherein **X²** is $-(\text{O}-\text{CH}_2-\text{CH}_2)_n-$, $-(\text{CH}_2-\text{CH}_2-\text{O})_n-$, or $-\text{C}_{1-5}$ alkyl-.

34. The method of any one of claims 22-33, wherein **X³** is a bond, $-\text{C}\equiv\text{C}-$, $-\text{C}_{1-4}$ alkyl-, or $-\text{N}(\text{R})-$.

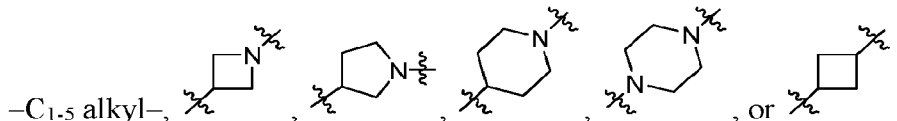
35. The method of any one of claims 22-34, wherein **X⁴** is a bond, $-\text{CH}_2-$, or $-\text{N}(\text{R})-$.

36. The compound or pharmaceutically acceptable salt of any one of claims 1-17, wherein **X⁵** is a bond.

37. The method of any one of claims 22-31, wherein **X¹** is $-(\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2)_m-$, **m** is one, and **X²** is $-\text{C}(\text{O})-\text{N}(\text{R})-$.

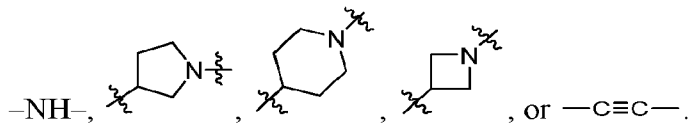


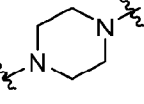
39. The method of any one of claims 22-31, 37, or 38, wherein $\mathbf{X}^2$ is a bond, $-\text{C}(\text{O})-$,

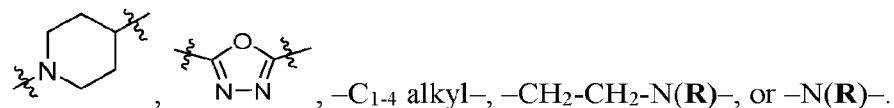


40. The method of any one of claims 22-31 or 37-39, wherein $\mathbf{X}^3$ is bond, $-\text{C}_{1-4}$ alkyl-, 4-6 membered cycloalkyl, or $-\text{N}(\mathbf{R})-$.

41. The method of any one of claims 22-31 or 37-40, wherein $\mathbf{X}^3$ is a bond, $-\text{C}_{1-4}$ alkyl-,

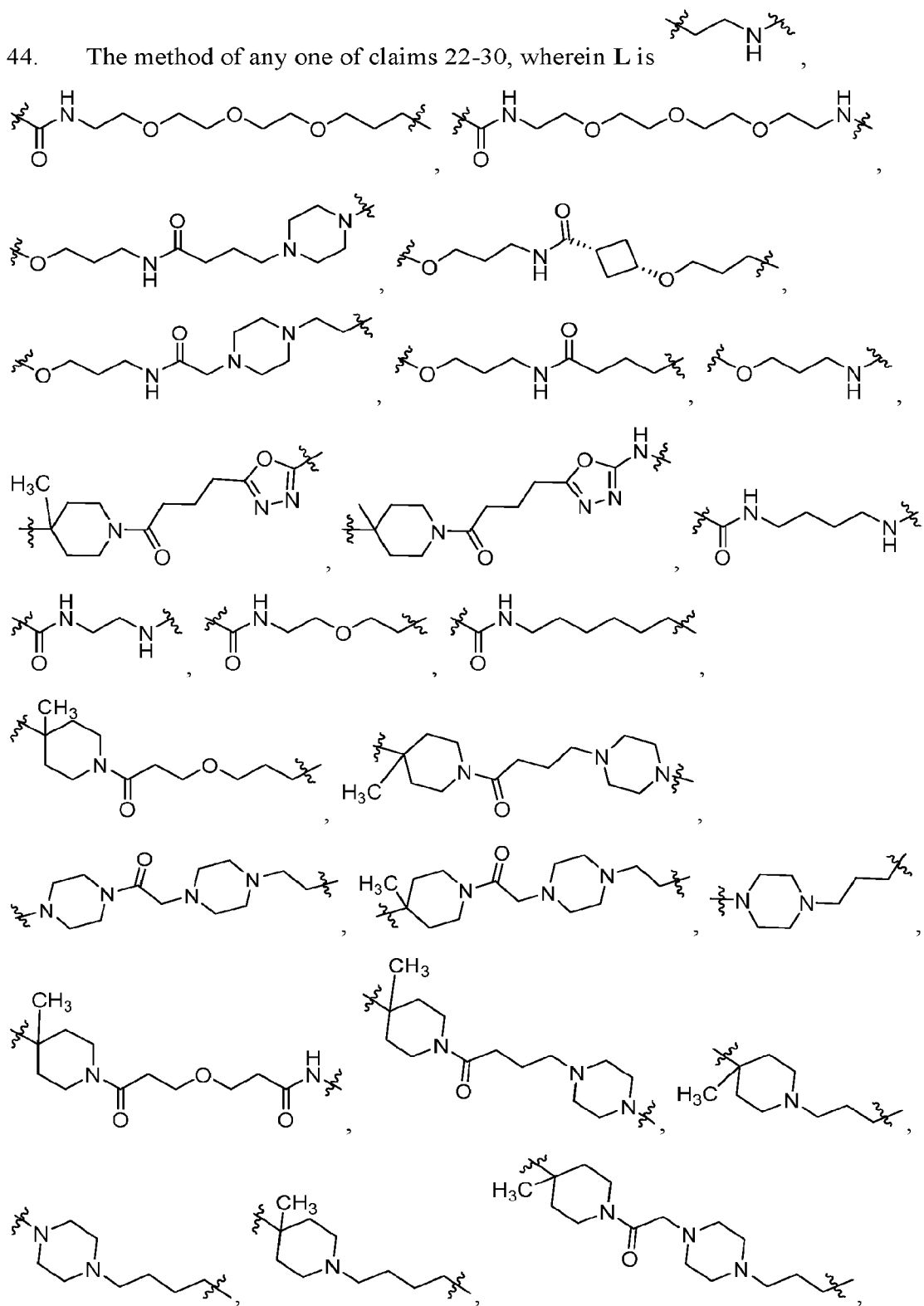


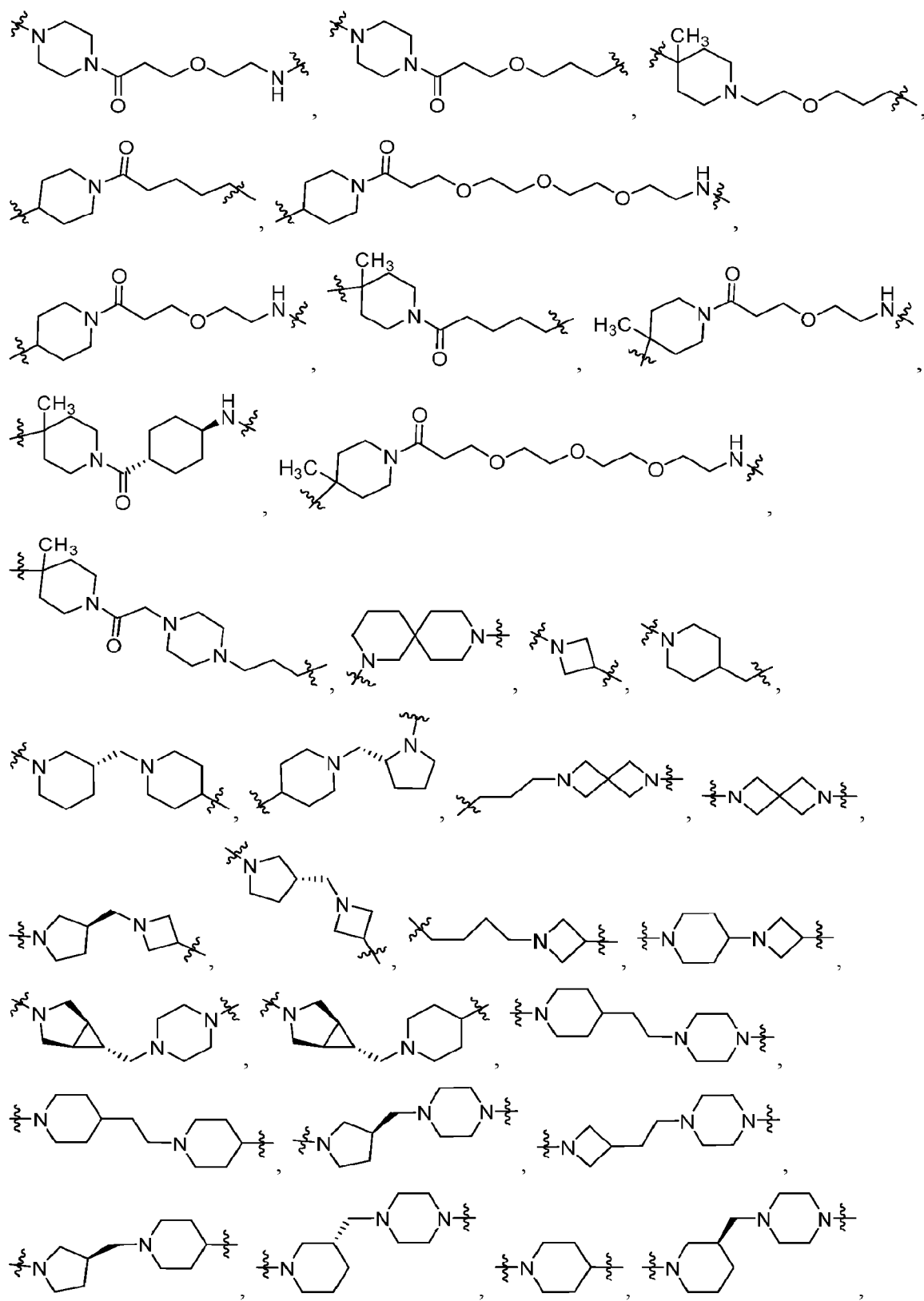
42. The method of any one of claims 22-31 or 37-41, wherein $\mathbf{X}^4$ is a bond, ,

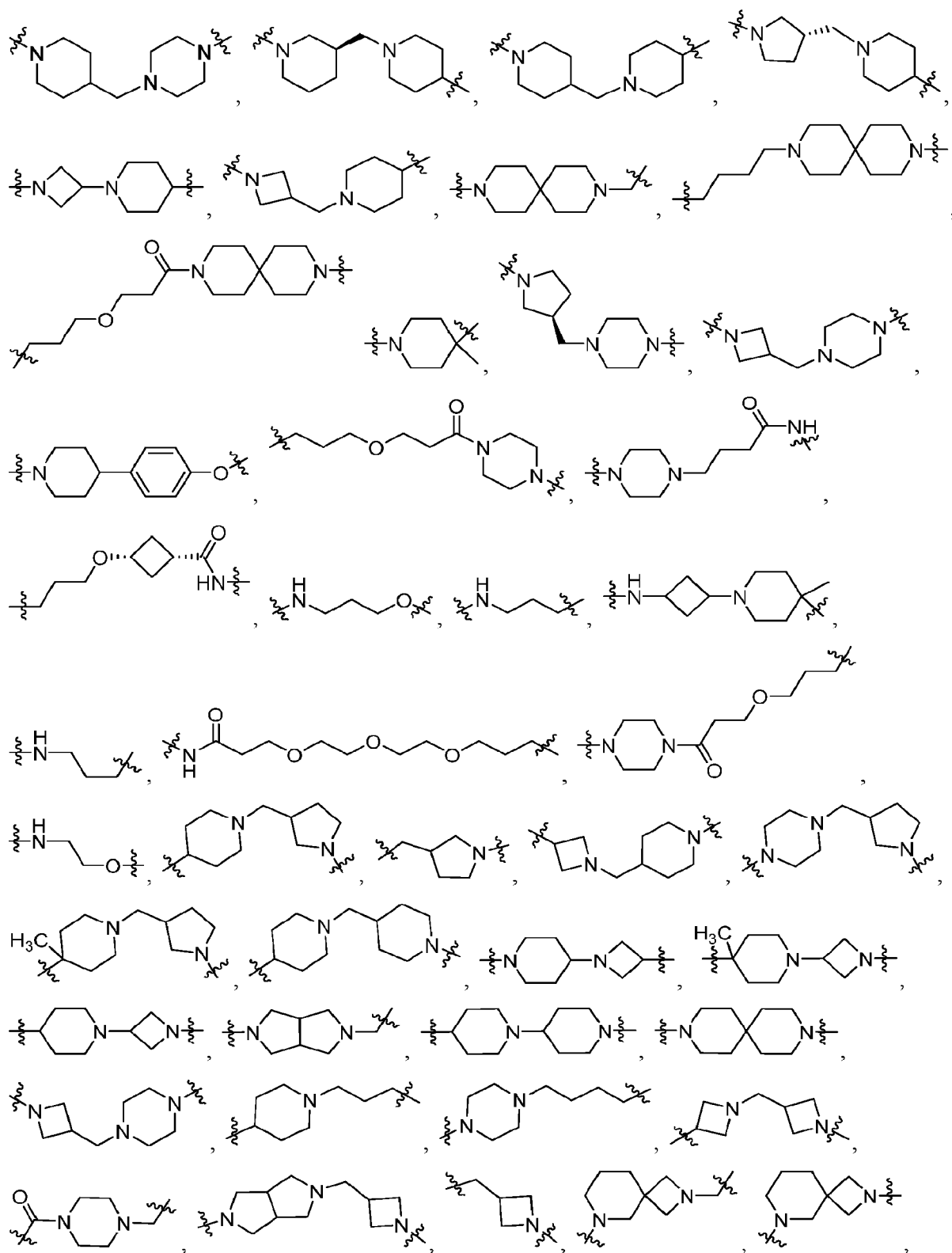


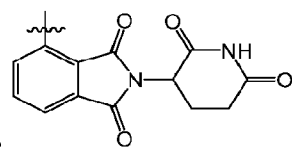
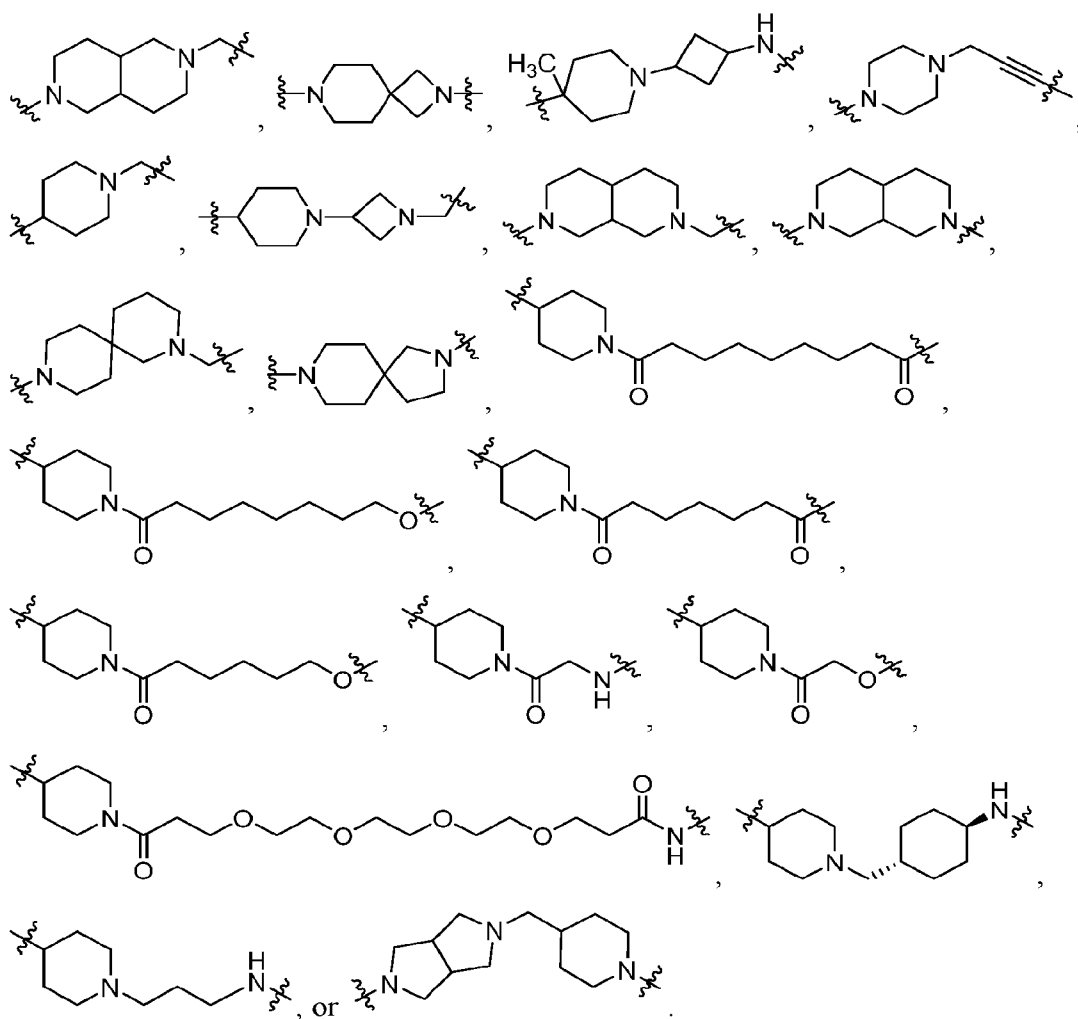
43. The method of any one of claims 22-31 or 37-42, wherein $\mathbf{X}^5$ is a bond, $-\text{C}_{1-4}$ alkyl-, $-\text{N}(\mathbf{R})-$, or $-\text{C}(\text{O})-\text{N}(\mathbf{R})-$.

44. The method of any one of claims 22-30, wherein L is

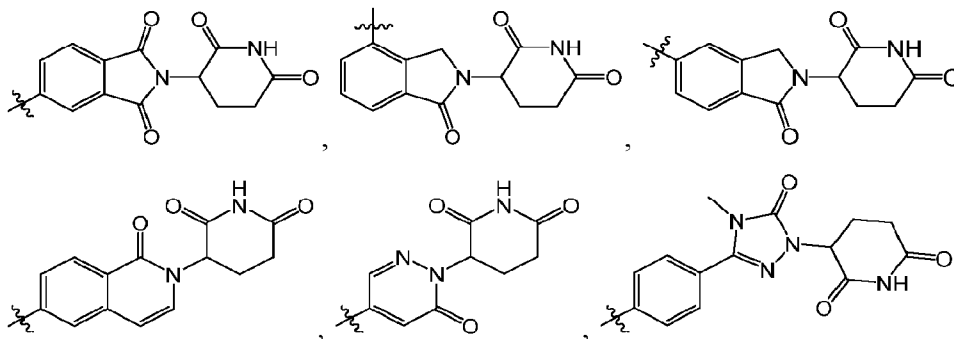


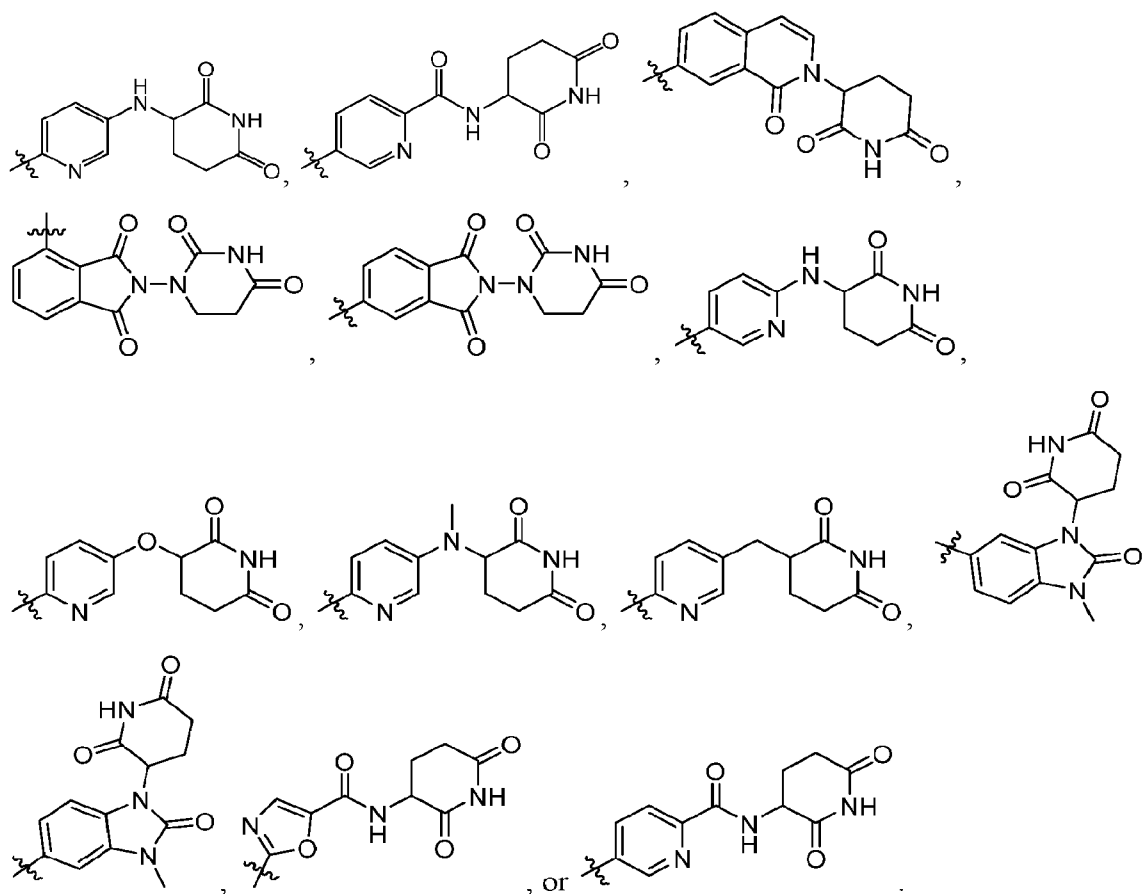




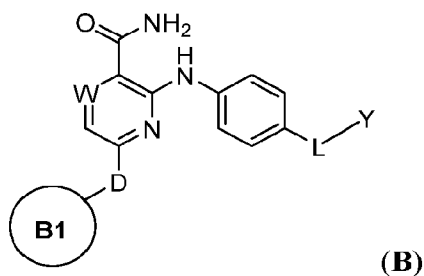


45. The method of any one of claims 22-44, wherein **Y** is





46. The method of any one of claims 22-45, wherein **W** is N.
47. The method of any one of claims 22-46, wherein **D** is a bond.
48. The method of claim 22, wherein the compound of Formula (**A**) is a compound of Formula (**B**)



or a pharmaceutically acceptable salt thereof, wherein

W is CH or N;

D is a bond or —NH— ;

Ring B1 is a 4-6 membered, fully saturated, partially unsaturated, or fully unsaturated monocyclic heterocycle or a 8-10 membered, fully saturated, spiro bicyclic heterocycle, wherein **Ring B1** has one to three heteroatoms independently selected from N, O, or S, and is optionally substituted with one to three groups selected from halo, —CH_3 , —CF_3 , —C(O)OH , $\text{—CH}_2\text{OH}$, or a five membered heterocycloalkyl optionally substituted with oxo and having one to two heteroatoms independently selected from N or O;

L is $\text{—X}^1\text{—X}^2\text{—X}^3\text{—}$;

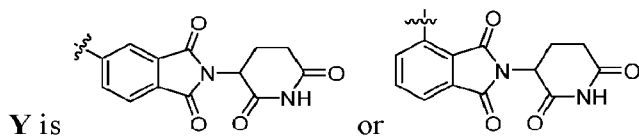
X¹ is —C(O)—N(R)— , —N(R)—C(O)— , $\text{—(O—CH}_2\text{—CH}_2\text{)—}_m\text{—}$, $\text{—O(C}_6\text{H}_4\text{)—}$, $\text{—(O—CH}_2\text{—CH}_2\text{—CH}_2\text{)—}_m\text{—}$, $\text{—C}_{1-5}\text{ alkyl—}$, 7-12 membered spiro or fused bicyclic heterocycloalkyl having one to three heteroatoms independently selected from N, O, or S, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein each of the monocyclic and bicyclic heterocycloalkyl of **X**¹ is optionally substituted with —CH_3 ;

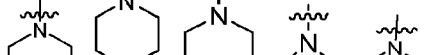
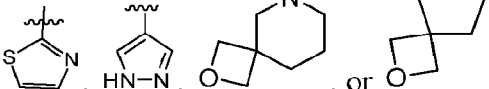
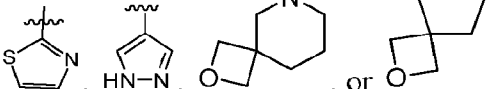
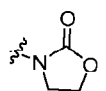
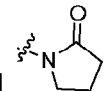
X² is a bond, $\text{—(O—CH}_2\text{—CH}_2\text{)—}_n\text{—}$, $\text{—(CH}_2\text{—CH}_2\text{—O)—}_n\text{—}$, —N(R)—C(O)— , —N(R)— , —C(O)— , $\text{—C}_{1-5}\text{ alkyl—}$, 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S;

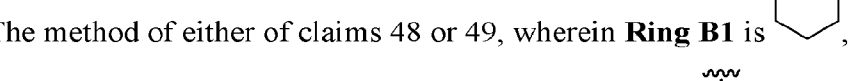
X³ is a bond, $\text{—C}_{1-4}\text{ alkyl—}$, $\text{—C}\equiv\text{C—}$, 4-6 membered cycloalkyl, —N(R)— , $\text{—(O—CH}_2\text{—CH}_2\text{)—}_p\text{—}$, $\text{—(CH}_2\text{—CH}_2\text{—O)—}_p\text{—}$, 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with —CH_3 ;

each **R** is independently hydrogen or $\text{—C}_{1-3}\text{ alkyl}$;

each of **m**, **n**, and **p** is independently an integer from one to three; and



49. The method of claim 48, wherein **Ring B1** is , , or , and **Ring B1** is optionally substituted one to three groups selected from $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, $-\text{C}(\text{O})\text{OH}$, $-\text{CF}_3$, fluorine, , and .

50. The method of either of claims 48 or 49, wherein **Ring B1** is , 

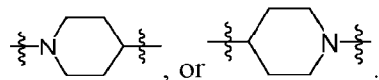
51. The method of any one of claims 48-50, wherein **Ring B1** is  or .

52. The method of any one of claims 48-51, wherein **X**¹ is

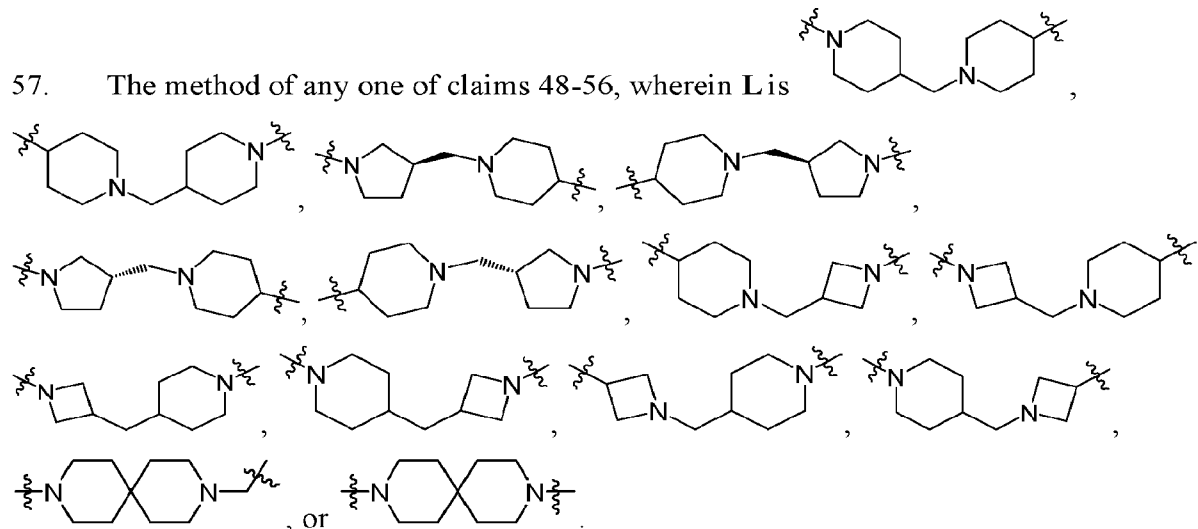
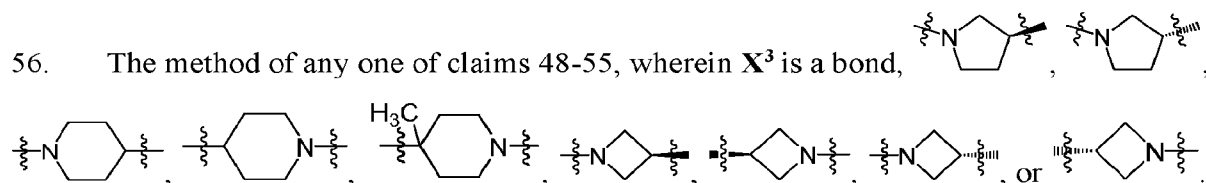
Chemical structures for **X**¹ include: pyrrolidine, 2-methylpyrrolidine, 1,4-dioxane, 1,4-dioxane with a methyl group at position 2, 1,4-dioxane with a methyl group at position 3, 1,4-dioxane with a methyl group at position 4, 1,4-dioxane with a methyl group at position 5, 1,4-dioxane with a methyl group at position 6, 1,4-dioxane with a methyl group at position 7, 1,4-dioxane with a methyl group at position 8, or 1,4-dioxane with a methyl group at position 9.

53. The method of any one of claims 48-52, wherein X^2 is a bond, $-C_{1-5}$ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S.

54. The method of any one of claims 48-53, wherein X^2 is a bond, $-C_{1-3}$ alkyl-, $-C(O)-$,

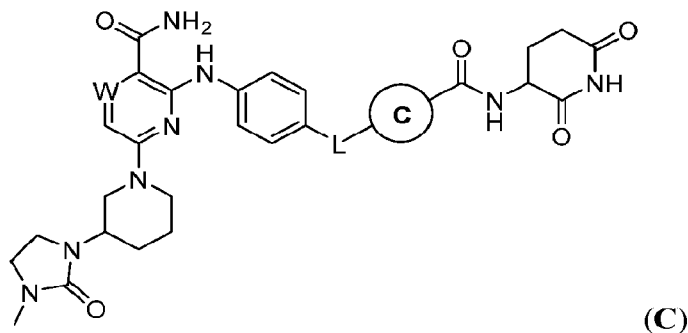


55. The method of any one of claims 48-54, wherein X^3 is a bond, $-C_{1-4}$ alkyl-, $-N(R)-$, $-(O-CH_2-CH_2)_p-$, $-(CH_2-CH_2-O)_p-$, or a 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-CH_3$.



58. The method of any one of claims 48-57, wherein W is N and D is a bond.

59. The method of claim 22, wherein the compound of Formula (A) is a compound of Formula (C)



or a pharmaceutically acceptable salt thereof, wherein

W is CH or N;

Ring C is phenyl or a saturated, partially unsaturated, or fully unsaturated 5-6 membered monocyclic heterocycle having one to two heteroatoms independently selected from N, O, or S, wherein each of the phenyl and heterocycle of **Ring C** is optionally substituted;

L is $-\text{X}^1-\text{X}^2-\text{X}^3-$;

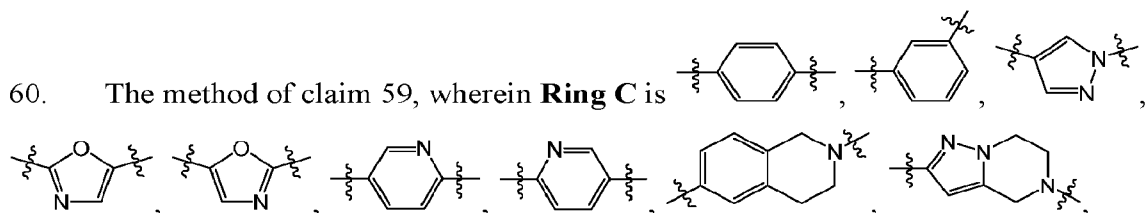
X¹ is $-\text{C}(\text{O})-\text{N}(\text{R})-$, $-\text{N}(\text{R})-\text{C}(\text{O})-$, $-(\text{O}-\text{CH}_2-\text{CH}_2)_m-$, $-\text{O}-(\text{C}_6\text{H}_4)-$, $-(\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2)_m-$, $-\text{C}_{1-5}$ alkyl-, 7-12 membered spiro bicyclic heterocycloalkyl having one to three heteroatoms independently selected from N, O, or S, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein each of the bicyclic heterocycloalkyl and the monocyclic heterocycloalkyl of **X¹** is optionally substituted with $-\text{CH}_3$;

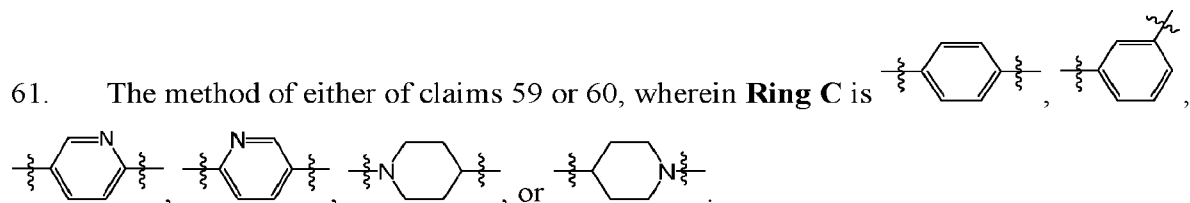
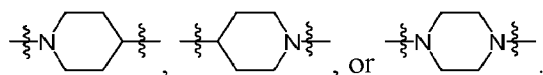
X² is a bond, $-(\text{O}-\text{CH}_2-\text{CH}_2)_n-$, $-(\text{CH}_2-\text{CH}_2-\text{O})_n-$, $-\text{N}(\text{R})-\text{C}(\text{O})-$, $-\text{N}(\text{R})-$, $-\text{C}(\text{O})-$, $-\text{C}_{1-5}$ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S;

X³ is a bond, $-\text{C}_{1-4}$ alkyl-, $-\text{C}\equiv\text{C}-$, 4-6 membered cycloalkyl, $-\text{N}(\text{R})-$, $-(\text{O}-\text{CH}_2-\text{CH}_2)_p-$, $-(\text{CH}_2-\text{CH}_2-\text{O})_p-$, 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-\text{CH}_3$;

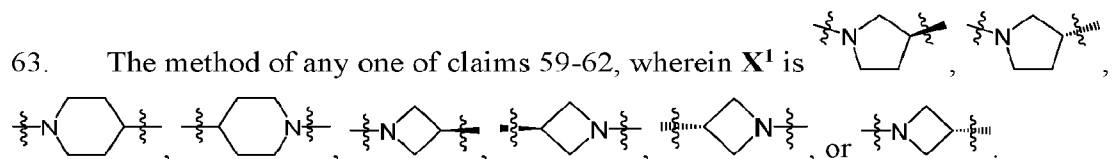
each **R** is independently hydrogen or $-\text{C}_{1-3}$ alkyl; and

each of **m**, **n**, and **p** is independently an integer from one to three.





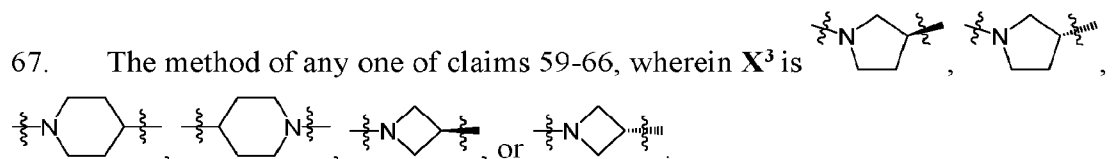
62. The method of any one of claims 59-61, wherein **X¹** is a 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S.



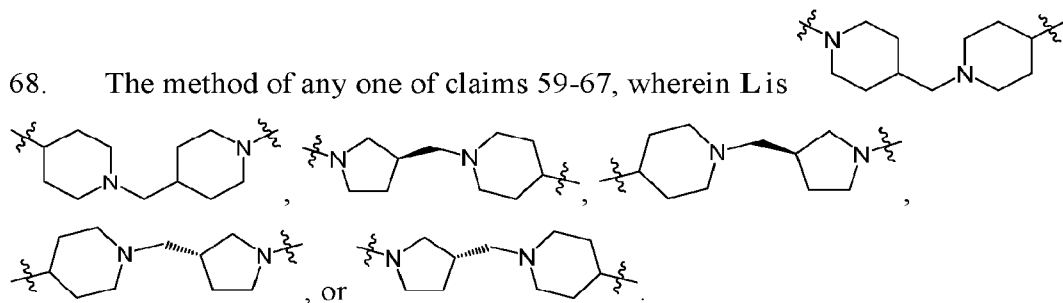
64. The method of any one of claims 59-63, wherein **X²** is a bond, $-C_{1-5}$ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S.

65. The compound or pharmaceutically acceptable salt of any one of claims 41-46, wherein **X²** is a bond or $-C_{1-3}$ alkyl-.

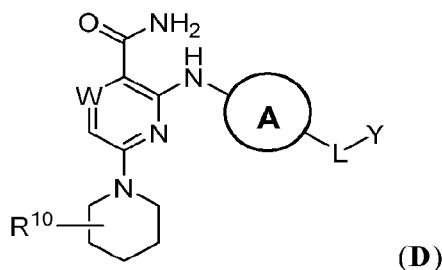
66. The method of any one of claims 59-65, wherein **X³** is a 4-6 membered cycloalkyl, $-N(R)-$, or a 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-CH_3$.



68. The method of any one of claims 59-67, wherein **L** is

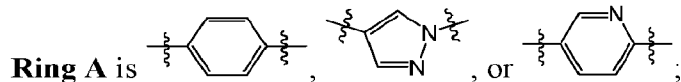


69. The method of claim 22, wherein the compound of Formula (**A**) is a compound of Formula (**D**)



or a pharmaceutically acceptable salt thereof, wherein

W is CH or N;

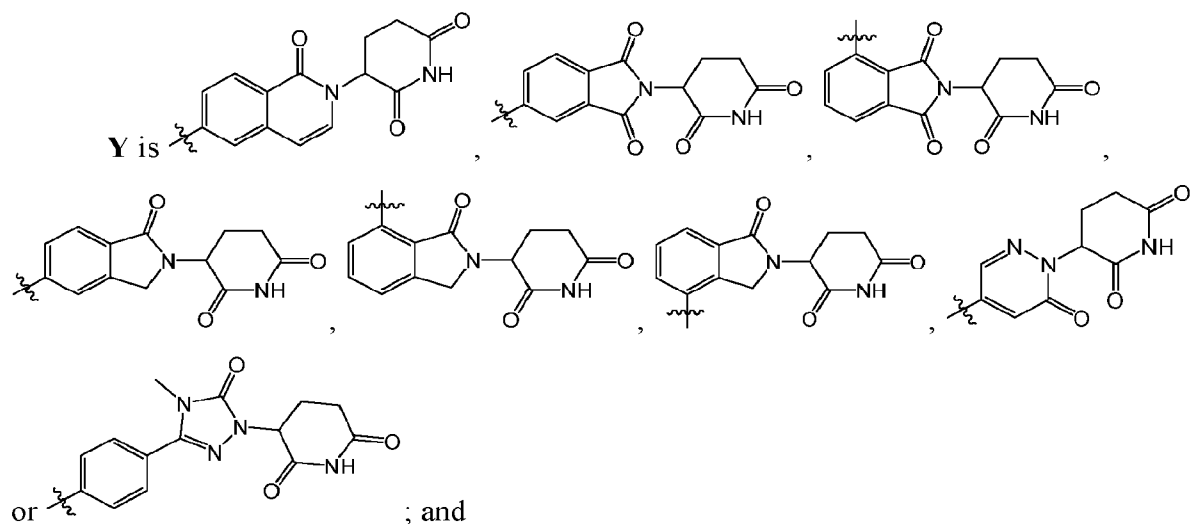


L is $-\text{X}^1-\text{X}^2-\text{X}^3-$;

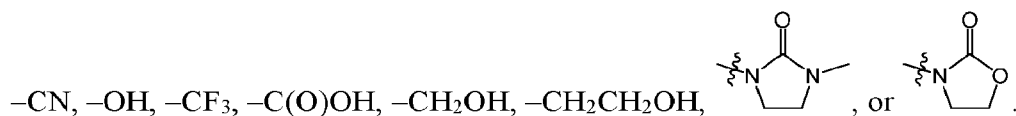
X¹ is $-\text{C}_{1-5}$ alkyl- or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the monocyclic heterocycloalkyl of **X¹** is optionally substituted with $-\text{CH}_3$;

X² is a bond, $-\text{C}_{1-5}$ alkyl-, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the monocyclic heterocycloalkyl of **X¹** is optionally substituted with $-\text{CH}_3$;

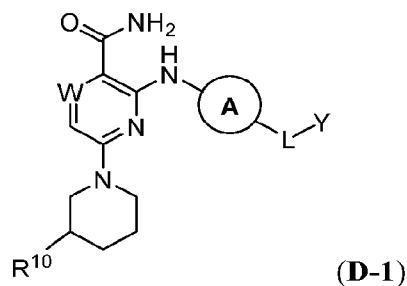
X³ is a bond, $-\text{C}_{1-4}$ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-\text{CH}_3$;



R¹⁰ is halo, -C₁₋₅ alkyl, 3-6 membered cycloalkyl, 5-6 membered heterocycloalkyl,

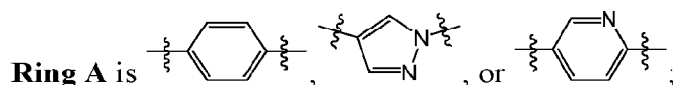


70. The method of claim 69, wherein the compound of Formula (D) is a compound of Formula (D-1)



or a pharmaceutically acceptable salt thereof, wherein

W is CH or N;

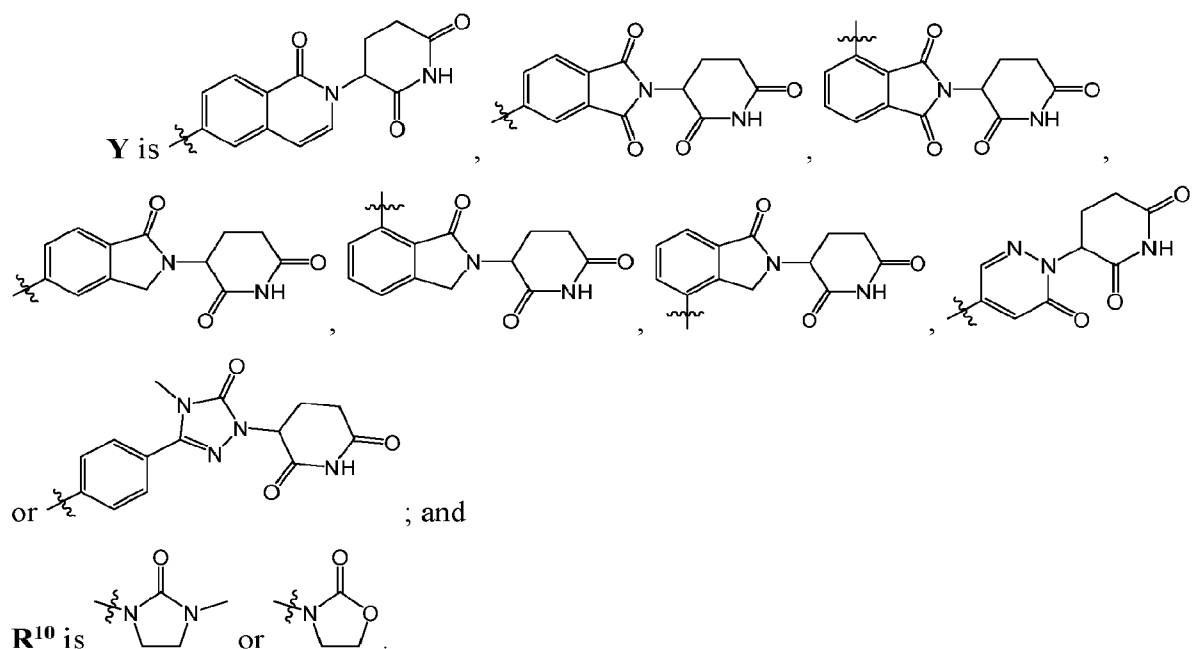


L is $-X^1-X^2-X^3-$;

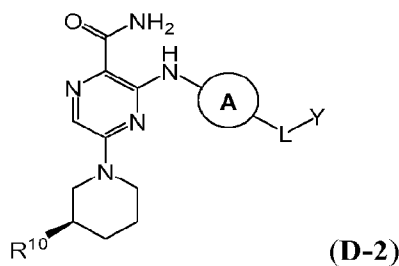
X¹ is $-C_{1-5}$ alkyl- or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the monocyclic heterocycloalkyl of **X¹** is optionally substituted with $-CH_3$;

X² is a bond, $-C_{1-5}$ alkyl-, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the monocyclic heterocycloalkyl of **X¹** is optionally substituted with $-CH_3$;

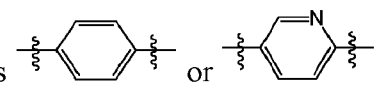
X³ is a bond, $-C_{1-4}$ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-CH_3$;



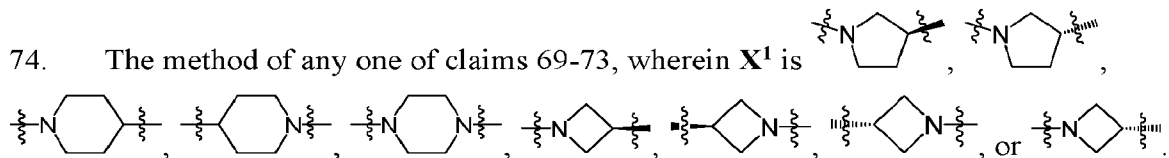
71. The method of claim 69, wherein the compound of Formula (**D**) is a compound of Formula (**D-2**)



or a pharmaceutically acceptable salt thereof.

72. The method any one of claims 69-71, wherein **Ring A** is .

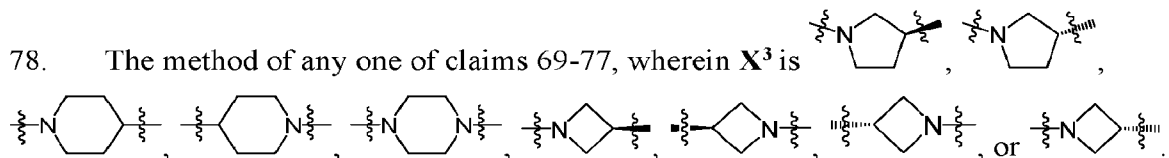
73. The method of any one of claims 69-72, wherein X^1 is a 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the monocyclic heterocycloalkyl of X^1 is optionally substituted with $-CH_3$.

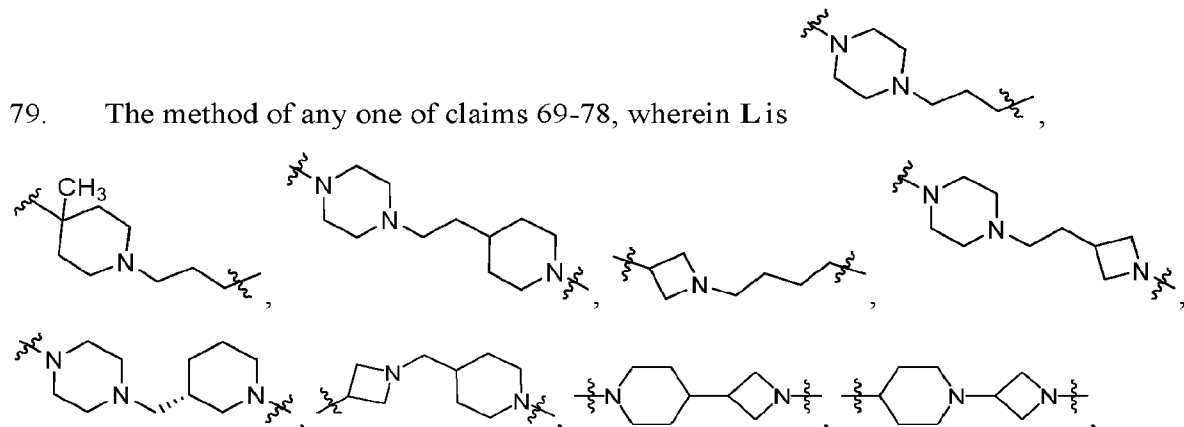
74. The method of any one of claims 69-73, wherein X^1 is 

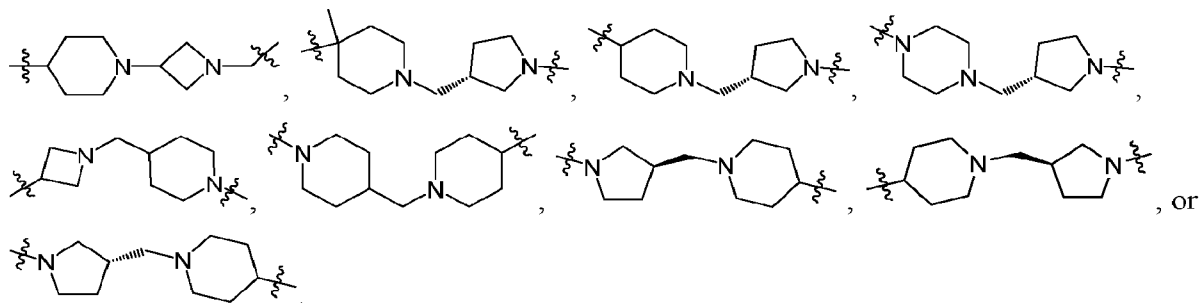
75. The method of any one of claims 69-74, wherein X^2 is a bond, $-C_{1-5}$ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S.

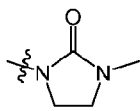
76. The method of any one of claims 69-75, wherein X^2 is a bond or $-C_{1-4}$ alkyl-.

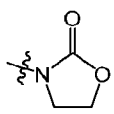
77. The method of any one of claims 69-76, wherein X^3 is a bond, a 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S.

78. The method of any one of claims 69-77, wherein X^3 is 

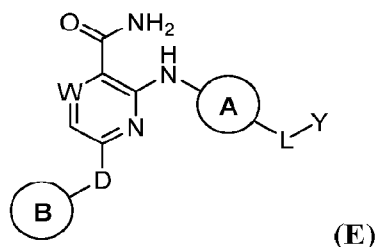
79. The method of any one of claims 69-78, wherein L is 



80. The method of any one of claims 69-79, wherein **R**¹⁰ is .

81. The method of any one of claims 69-79, wherein **R**¹⁰ is .

82. The method of claim 22, wherein the compound of Formula (A) is a compound of Formula (E)



or a pharmaceutically acceptable salt thereof, wherein

D is a bond or —NH— ;

W is N or CH;

Ring A is phenyl, a 9-10 membered bicyclic aryl, a 5-6 membered partially or fully unsaturated monocyclic heterocycle, or a 9-10 membered bicyclic heteroaryl, wherein the monocyclic heterocycle and bicyclic heteroaryl of **Ring A** each possess one to three heteroatoms independently selected from N, O, or S;

Ring B is an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic heterocycle, or an optionally substituted 8-10 membered spiro bicyclic heterocycle, wherein **Ring B** has one to three heteroatoms independently selected from N, O, or S;

L is $\text{—X}^1\text{—X}^2\text{—X}^3\text{—X}^4\text{—X}^5\text{—}$;

X¹ is a bond, $-\text{C}(\text{O})-\text{N}(\text{R})-$, $-\text{N}(\text{R})-\text{C}(\text{O})-$, $-(\text{O}-\text{CH}_2-\text{CH}_2)_m-$, $-\text{O}(\text{C}_6\text{H}_4)-$, $-(\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2)_m-$, $-\text{C}_{1-5}$ alkyl-, 7-12 membered spiro bicyclic heterocycloalkyl having one to three heteroatoms independently selected from N, O, or S, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein each of the monocyclic and bicyclic heterocycloalkyl of **X¹** is optionally substituted with $-\text{CH}_3$;

X² is a bond, $-(O-CH_2-CH_2)_n-$, $-(CH_2-CH_2-O)_n-$, $-N(R)-C(O)-$, $-N(R)-$, $-C(O)-$, $-C_{1-5}$ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S;

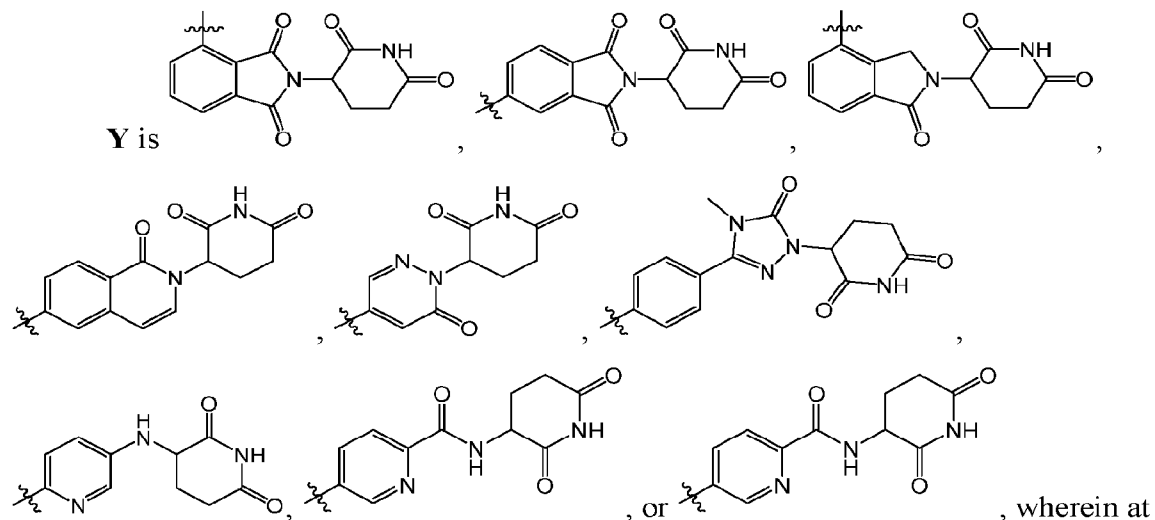
X³ is a bond, $\text{—C}_{1-4}\text{ alkyl—}$, $\text{—C}\equiv\text{C—}$, 4-6 membered cycloalkyl, —N(R)— , $\text{—(O—CH}_2\text{—CH}_2\text{)—}_p\text{—}$, $\text{—(CH}_2\text{—CH}_2\text{—O)—}_p\text{—}$, 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with —CH_3 ;

X⁴ is a bond, $-\text{CH}_2-\text{CH}_2-\text{N}(\text{R})-$, $-\text{N}(\text{R})-$, $-\text{C}_{1-4}$ alkyl-, $-(\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2)_m-$, a 5-6 membered saturated, partially unsaturated, or fully unsaturated carbocycle, or a 5-6 membered saturated, partially unsaturated, or fully unsaturated heterocycle having one to three heteroatoms independently selected from N, O, or S;

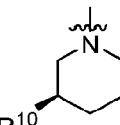
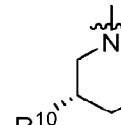
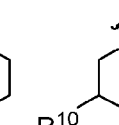
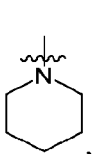
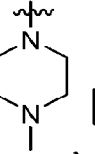
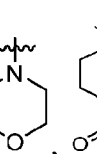
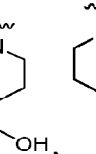
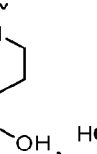
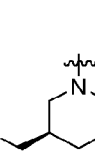
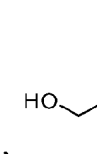
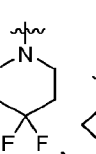
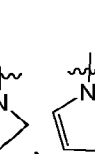
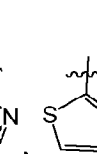
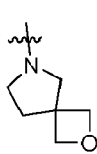
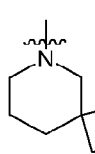
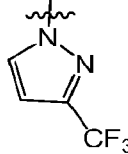
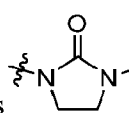
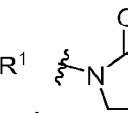
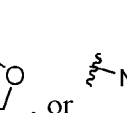
X⁵ is a bond, -N(**R**)-, or -C(O)-N(**R**-;

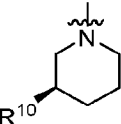
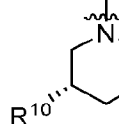
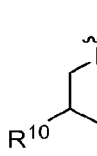
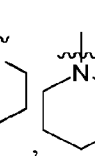
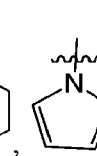
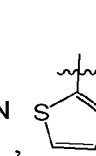
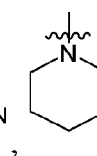
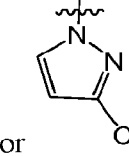
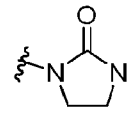
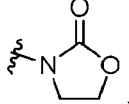
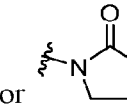
each **R** is independently hydrogen or $-C_{1-3}$ alkyl;

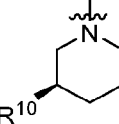
each of **m**, **n**, and **p** is independently an integer from one to three; and

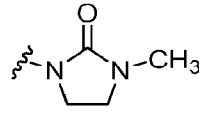


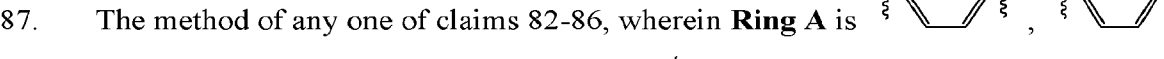
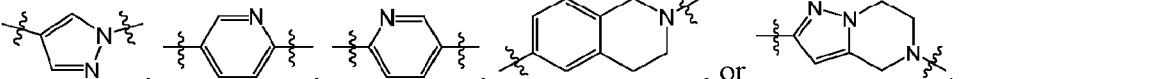
least one of **X**¹, **X**², **X**³, **X**⁴, and **X**⁵ has a nitrogen atom, and **Y** is directly bonded to **L** at a nitrogen atom of **X**¹, **X**², **X**³, **X**⁴, or **X**⁵.

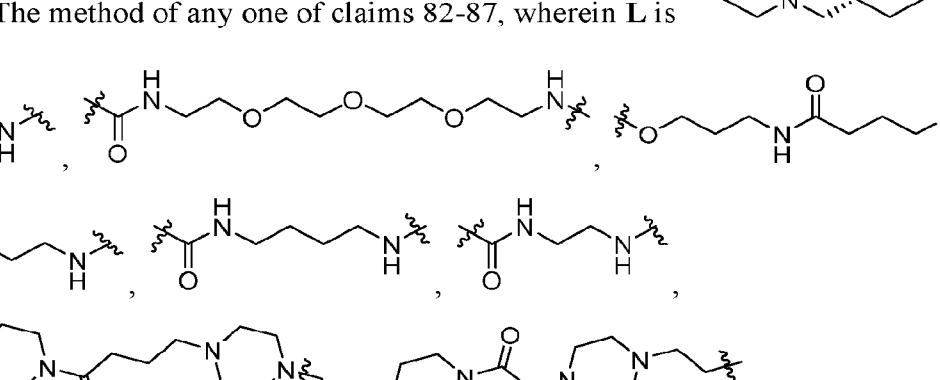
83. The method of claim 82, wherein **Ring B** is , , ,
- , , , , , , , , , ,
- , , or , wherein **R¹⁰** is , , or , and wherein **R¹** is a C₁₋₄ alkyl group.

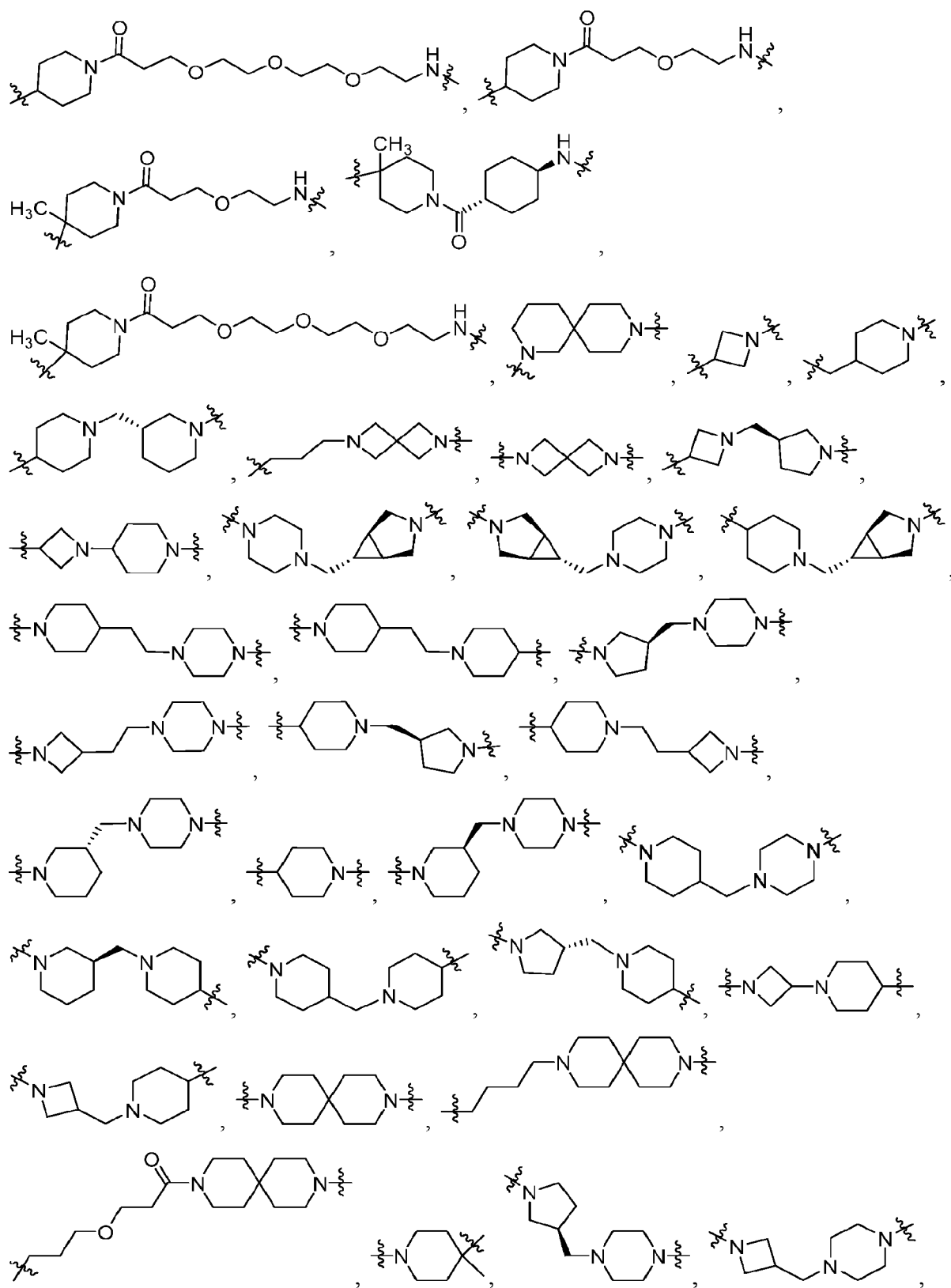
84. The method either of claims 82 or 83, wherein **Ring B** is , ,
- , , , , , or , wherein **R¹⁰** is ,
- , or .

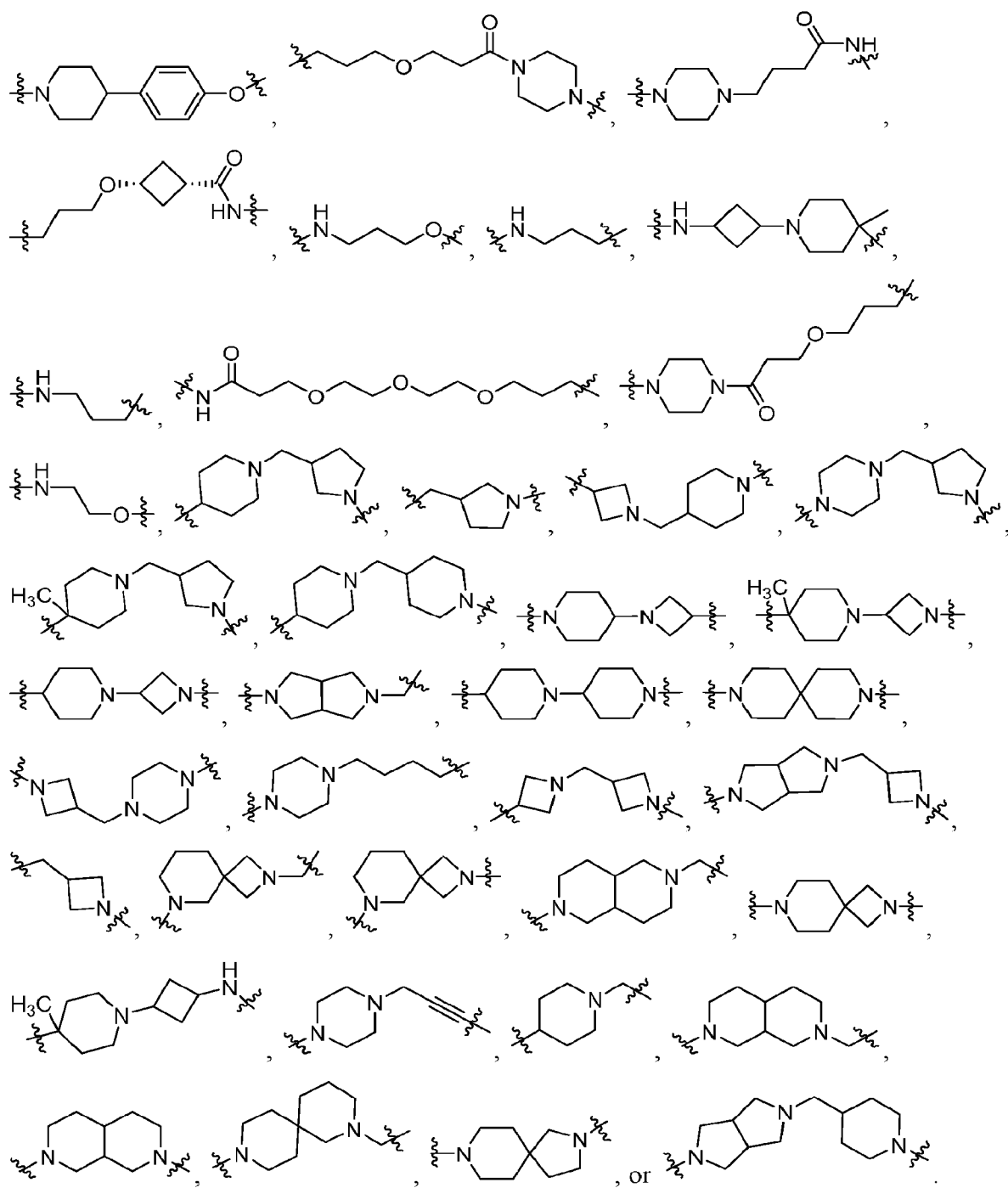
85. The method of any one of claims 82-84, wherein **Ring B** is .

86. The method of any one of claims 82-85, wherein **R¹⁰** is .

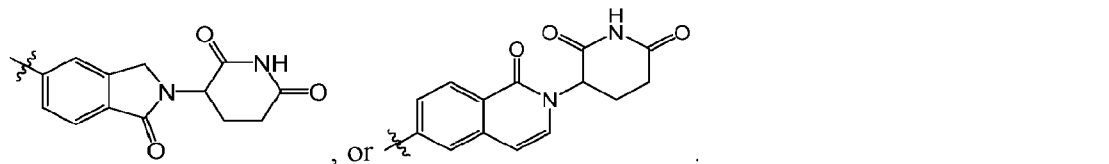
87. The method of any one of claims 82-86, wherein **Ring A** is , 
88. The method of any one of claims 82-87, wherein **X⁵** is --N(R)-- .
89. The method of any one of claims 82-87, wherein **X⁵** is --C(O)--N(R)-- .
90. The method of any one of claims 82-87, wherein **X⁵** is a bond.

91. The method of any one of claims 82-87, wherein **L** is
- 

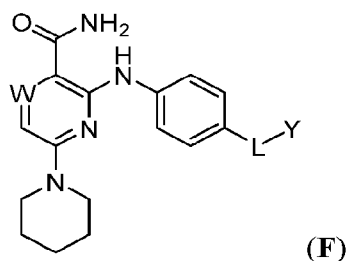




92. The method of any one of claims 82-91, wherein **Y** is



93. The method of claim 22, wherein the compound of Formula (**A**) is a compound of Formula (**F**)



or a pharmaceutically acceptable salt thereof, wherein

W is CH or N;

L is $-X^1-X^2-X^3-$;

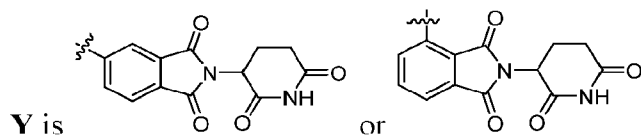
X¹ is $-C(O)-N(R)-$, $-N(R)-C(O)-$, $-(O-CH_2-CH_2)_m-$, $-O(C_6H_4)-$, $-(O-CH_2-CH_2-CH_2)_m-$, $-C_{1-5}$ alkyl-, 7-12 membered spiro bicyclic heterocycloalkyl having one to three heteroatoms independently selected from N, O, or S, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein each of the monocyclic and bicyclic heterocycloalkyl of **X¹** is optionally substituted with $-CH_3$;

X² is a bond, $-C_{1-5}$ alkyl-, $-(O-CH_2-CH_2)_n-$, $-(CH_2-CH_2-O)_n-$, $-N(R)-C(O)-$, $-N(R)-$, $-C(O)-$, $-C_{1-5}$ alkyl-, 4-6 membered monocyclic cycloalkyl, or 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S;

X³ is a bond, $-C_{1-4}$ alkyl-, $-C\equiv C-$, 4-6 membered cycloalkyl, $-N(R)-$, $-(O-CH_2-CH_2)_p-$, $-(CH_2-CH_2-O)_p-$, 4-6 membered heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein the heterocycloalkyl is optionally substituted with $-CH_3$;

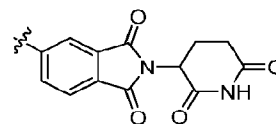
each **R** is independently hydrogen or $-C_{1-3}$ alkyl;

each of **m**, **n**, and **p** is independently an integer from one to three; and

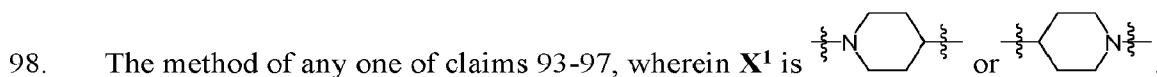
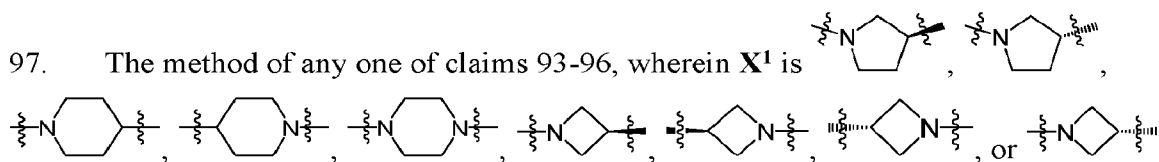


94. The method of claim 93, wherein **W** is N.

95. The method of either of claims 93 or 94, wherein **Y** is

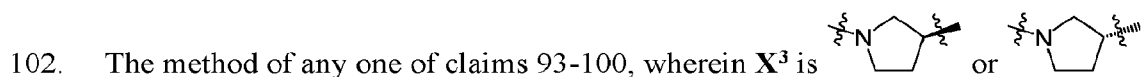
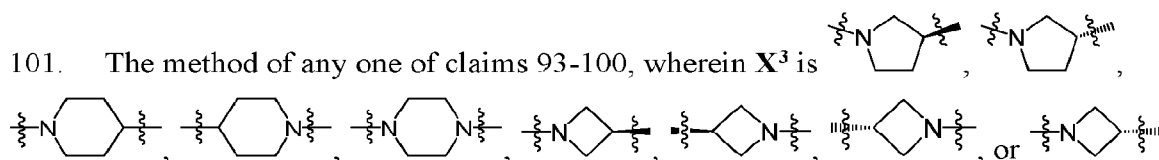


96. The method of any one of claims 93-95, wherein **X¹** is a 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S, wherein each of the monocyclic heterocycloalkyl of **X¹** is optionally substituted with $-\text{CH}_3$.

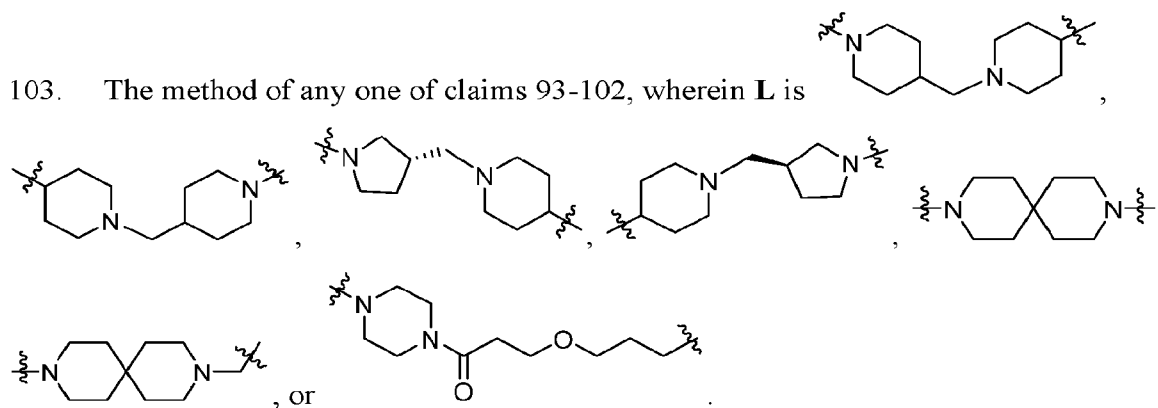


99. The method of any one of claims 93-98, wherein **X²** is a bond or $-\text{C}_{1-5}$ alkyl-.

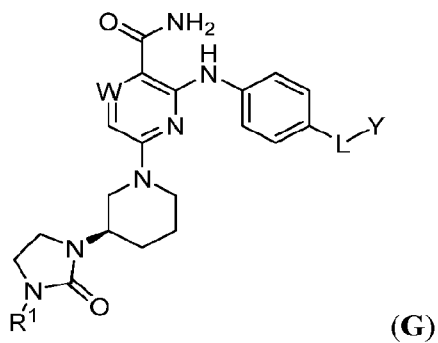
100. The method of any one of claims 93-99, wherein **X³** is a 4-6 membered monocyclic heterocycloalkyl having one to two heteroatoms independently selected from N, O, or S.



103. The method of any one of claims 93-102, wherein **L** is



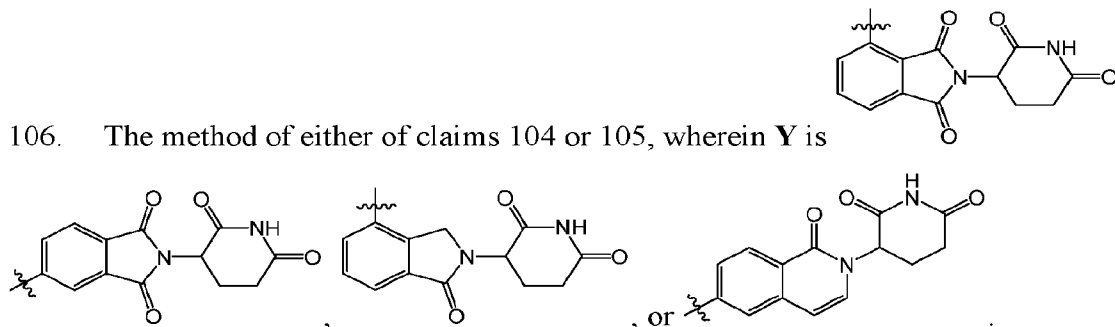
104. The method of claim 22, wherein the compound of Formula (**A**) is a compound of Formula (**G**)



or a pharmaceutically acceptable salt thereof.

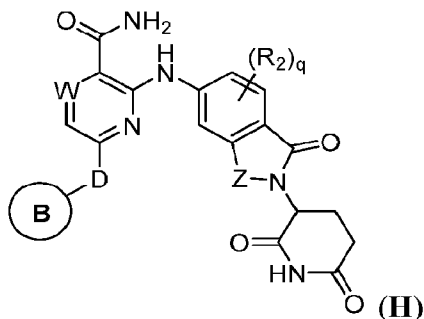
105. The method of claim 104, wherein **R**¹ is methyl.

106. The method of either of claims 104 or 105, wherein **Y** is



107. The method of any one of claims 104-106, wherein **W** is N.

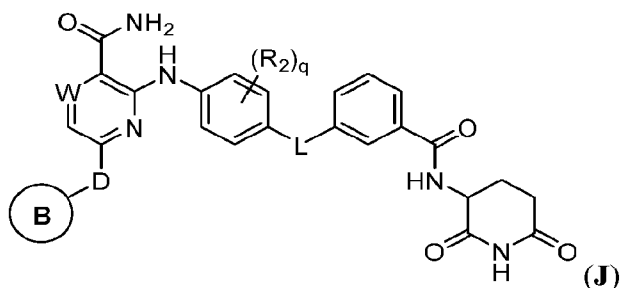
108. The method of claim 22, wherein the compound of Formula (A) is a compound of Formula (H)



or a pharmaceutically acceptable salt thereof.

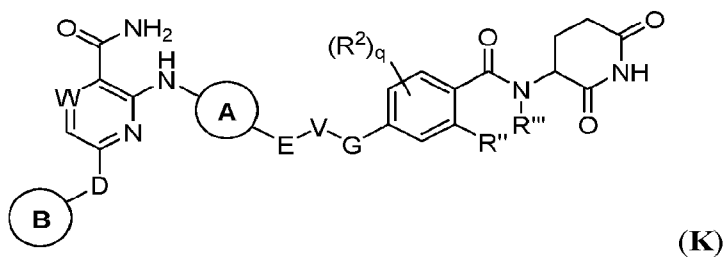
109. The method of claim 108, wherein **q** is zero.

110. The method of claim 22, wherein the compound of Formula (A) is a compound of Formula (J)

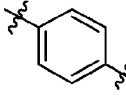
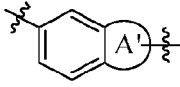


or a pharmaceutically acceptable salt thereof.

111. The method of claim 22, wherein the compound of Formula (A) is a compound of Formula (K)



or a pharmaceutically acceptable salt thereof, wherein

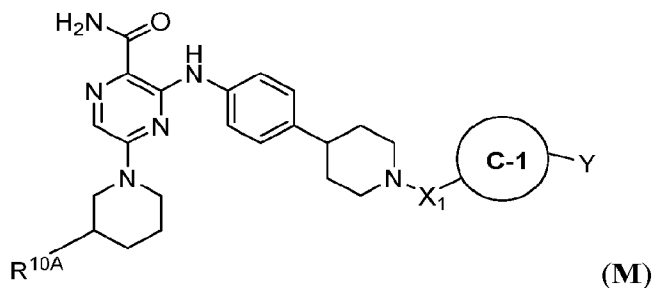
Ring A is  or , wherein **Ring A** is optionally and independently substituted with up to three substituents selected from halo, CN, carboxyl, NH₂, and optionally substituted C₁₋₆ alkyl;

V is a bond or -CH₂-; and

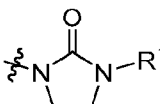
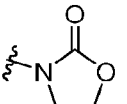
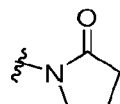
E and **G** are each independently a 5-6 membered heterocycloalkyl, wherein each heterocycloalkyl contains at least one nitrogen atom.

112. The method of claim 111, wherein **D** is a bond and **W** is a nitrogen atom.

113. The method of claim 22, wherein the compound of Formula (**A**) is a compound of Formula (**M**)



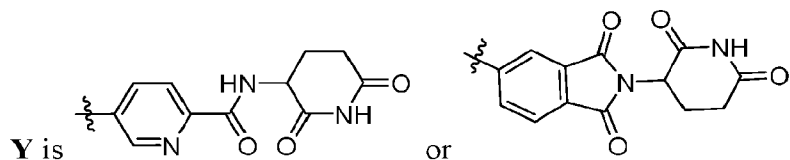
or a pharmaceutically acceptable salt thereof, wherein

R^{10A} is hydrogen, , , or , wherein

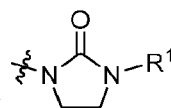
R¹ is C₁₋₄ alkyl;

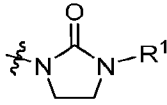
X¹ is -C₁₋₅ alkyl-;

Ring C-1 is a 5-6 membered heterocycloalkyl having one nitrogen atom; and



114. The method of claim 113, wherein **R**^{10A} is hydrogen or

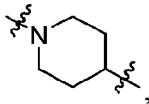
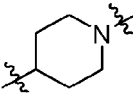
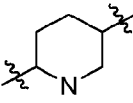
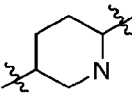
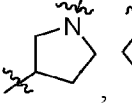
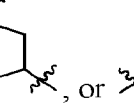
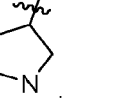


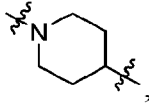
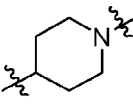
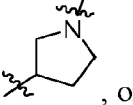
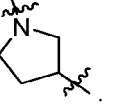
115. The method of either of claims 113 or 114, wherein **R**^{10A} is , and **R**¹ is methyl, ethyl, propyl, iso-propyl, butyl, sec-butyl, or iso-butyl.

116. The method of any one of claims 113-115, wherein **R**¹ is methyl.

117. The method of any one of claims 113-116, wherein **X**¹ is -CH₂-, -CH₂CH₂-, or -CH₂CH₂CH₂-.

118. The method of any one of claims 113-117, wherein **X**¹ is -CH₂-.

119. The method of any one of claims 113-118, wherein **Ring C-1** is , , , , , , or .

120. The method of any one of claims 113-119, wherein **Ring C-1** is , , , or .

121. The method of claim 1 wherein the compound is selected from Table 1, or a pharmaceutically acceptable salt thereof.

122. The method of any of the previous claims, wherein the compound is administered in the form of a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, vehicle, or adjuvant.

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**BTK CTMs induced BTK degradation in
B lymphoma cell lines and primary human B cells**

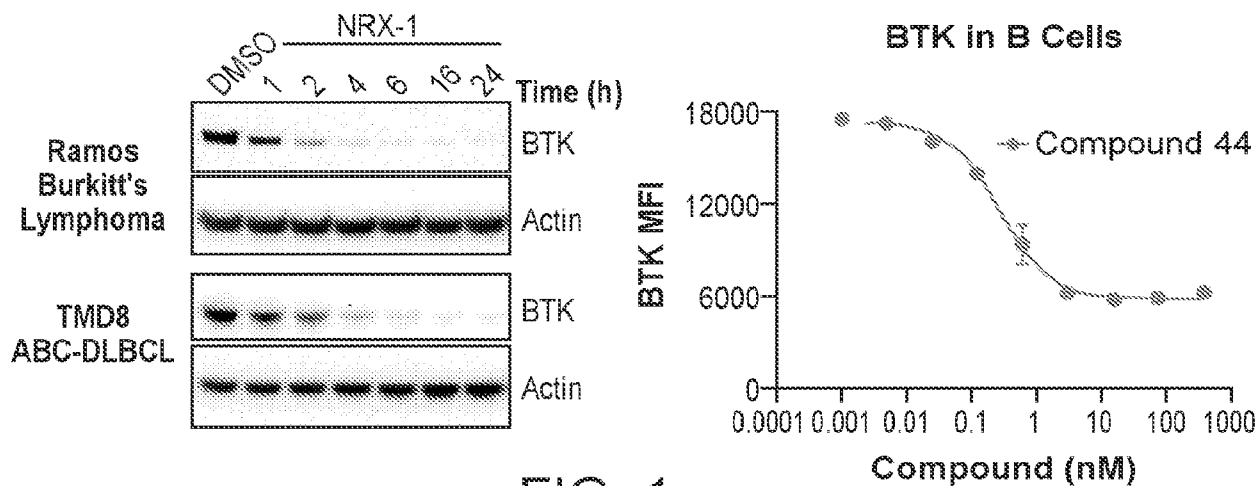


FIG. 1

**BTK CTMs induce degradation of wild-type BTK
and ibrutinib-resistant mutant BTK^{C481S}**

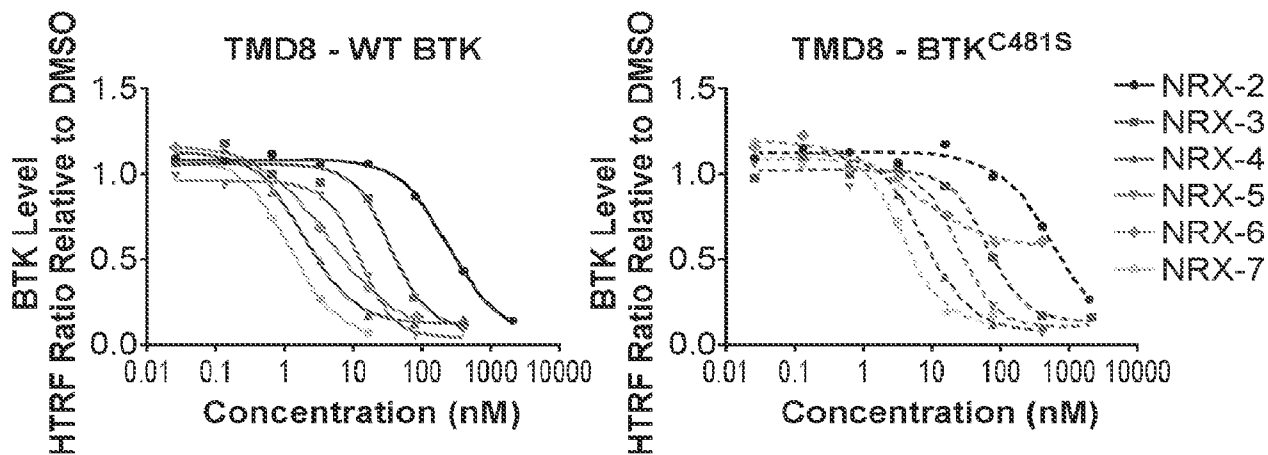


FIG. 2

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CTM-mediated degradation
of BTK is highly selective

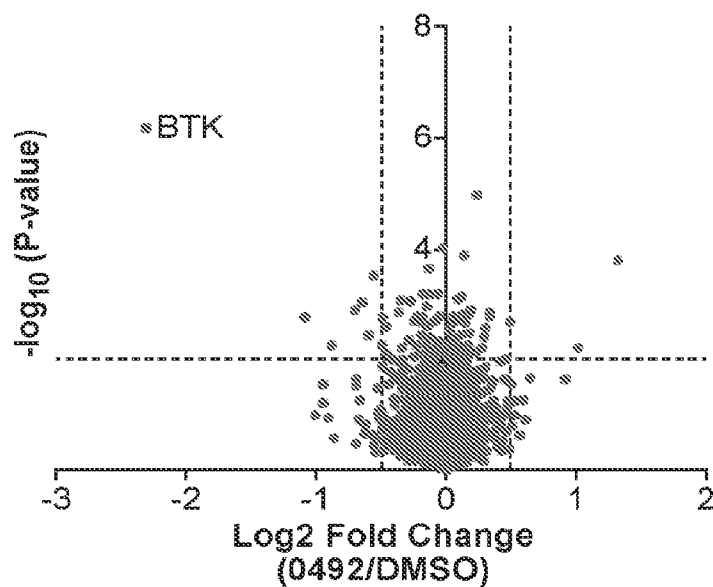


FIG. 3

BTK CTM differentiates from BTK kinase inhibitors in
ibrutinib-resistant BTK^{C481S} cell viability assays

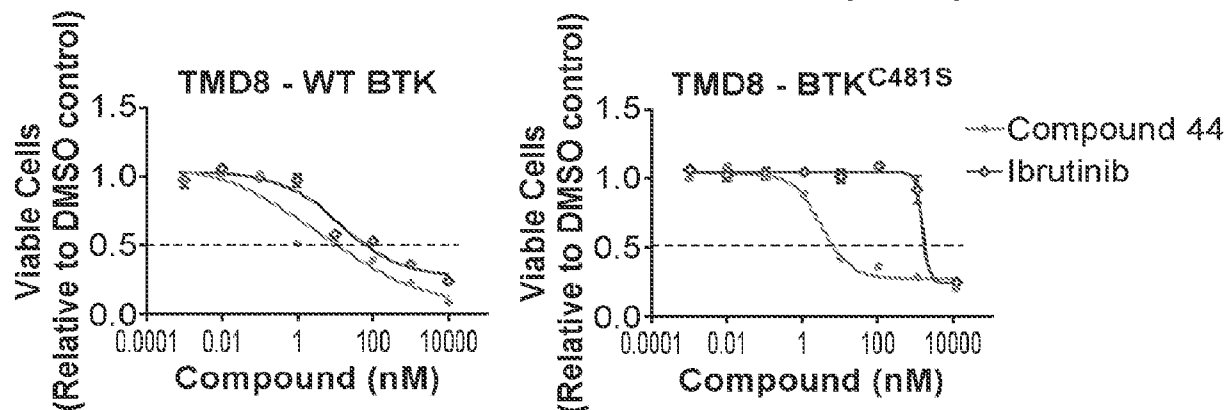


FIG. 4

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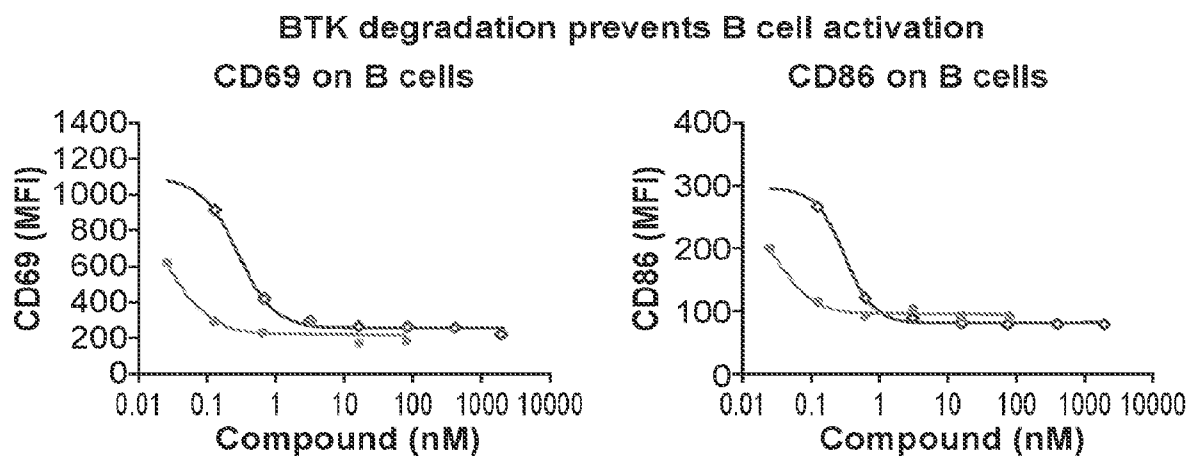


FIG. 5

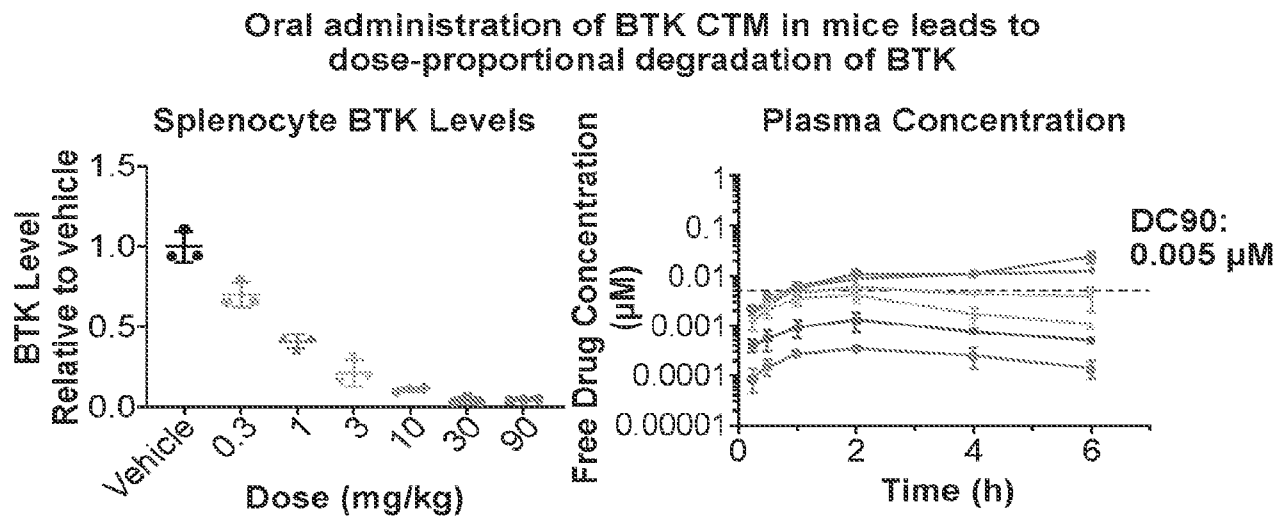


FIG. 6

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Orally dosed BTK CTM confers dose- and time-proportional reduction in BTK in circulating B cells

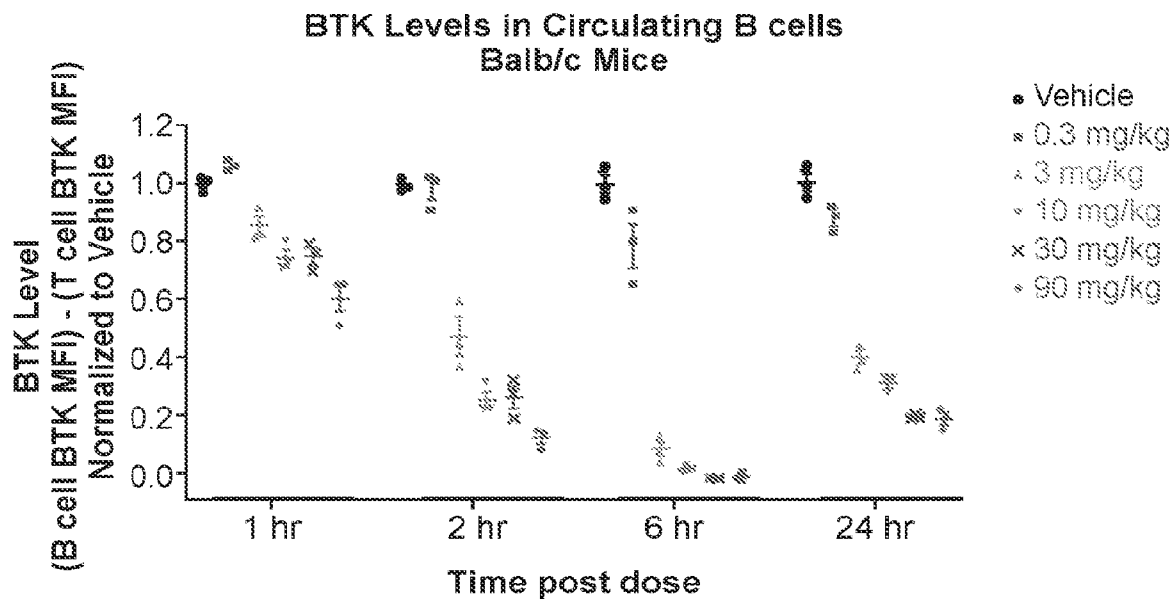


FIG. 7

Anti-tumor activity associated with BTK degradation in a xenograft model of acquired resistance to ibrutinib

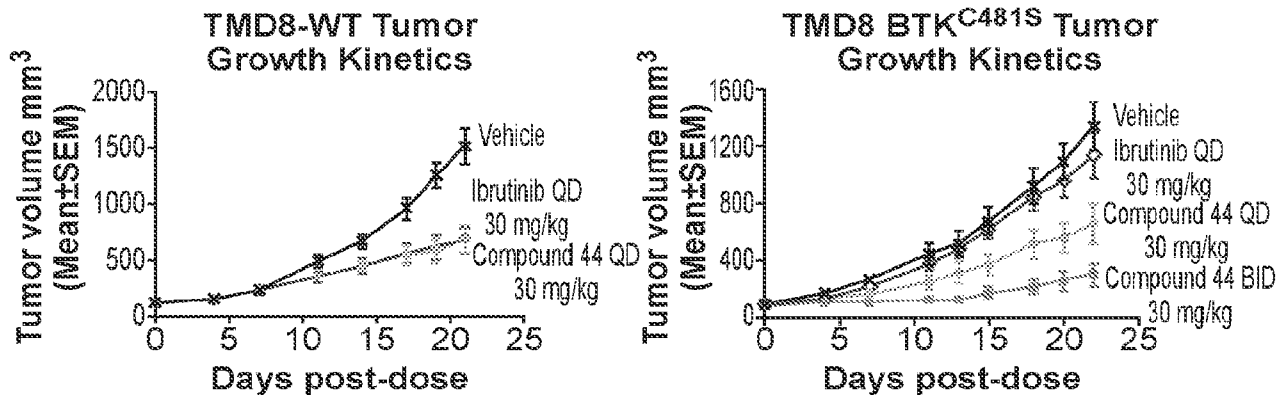


FIG. 8

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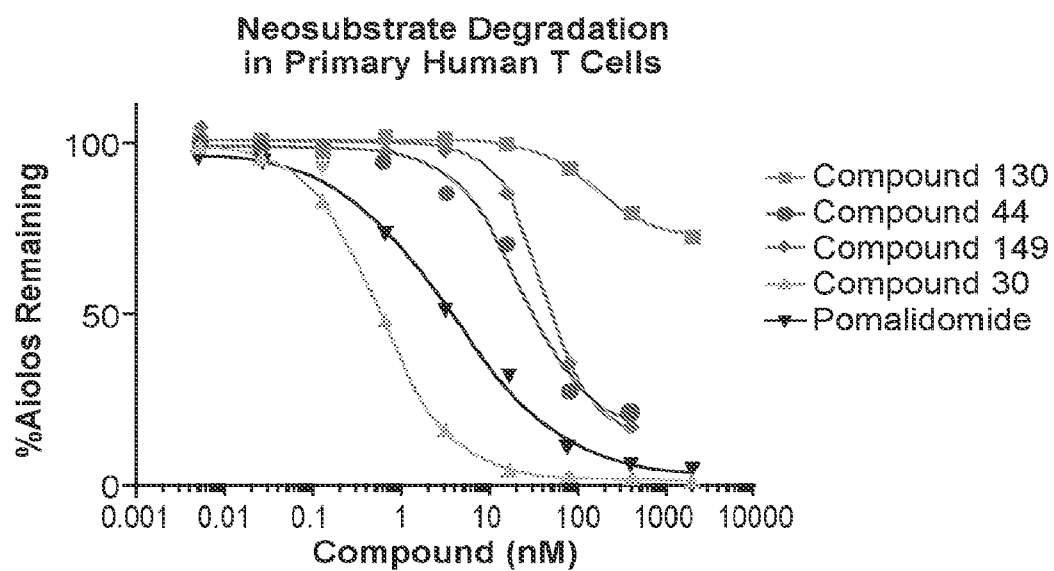
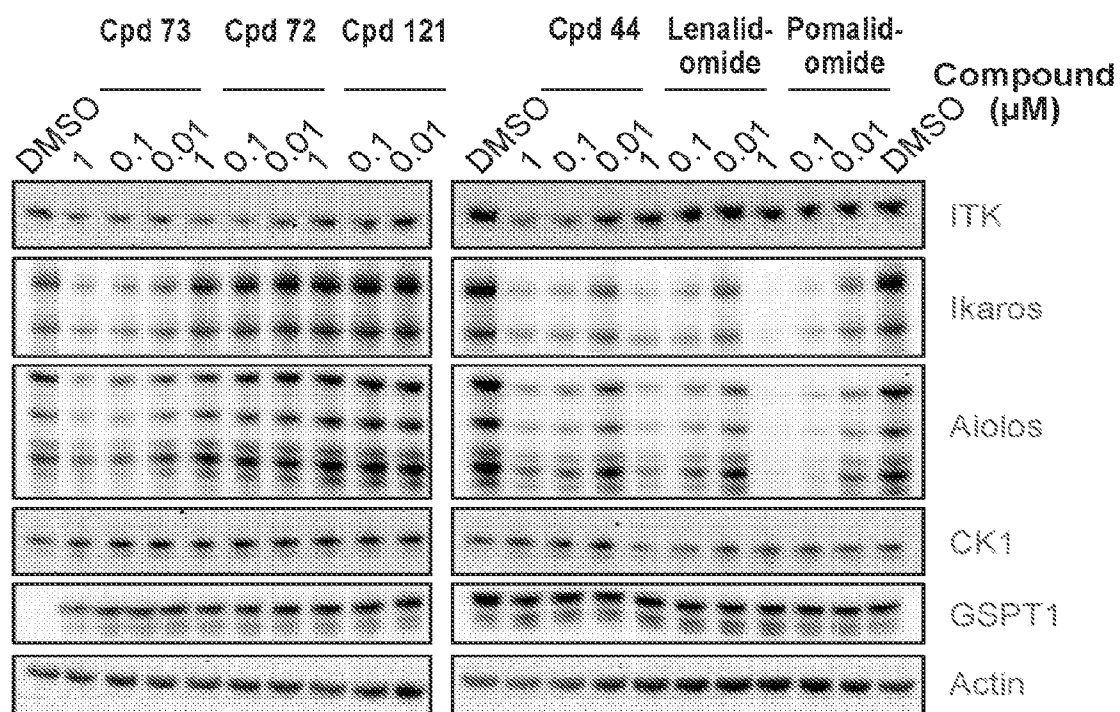


FIG. 9

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MOLT4 Cells

FIG. 10A

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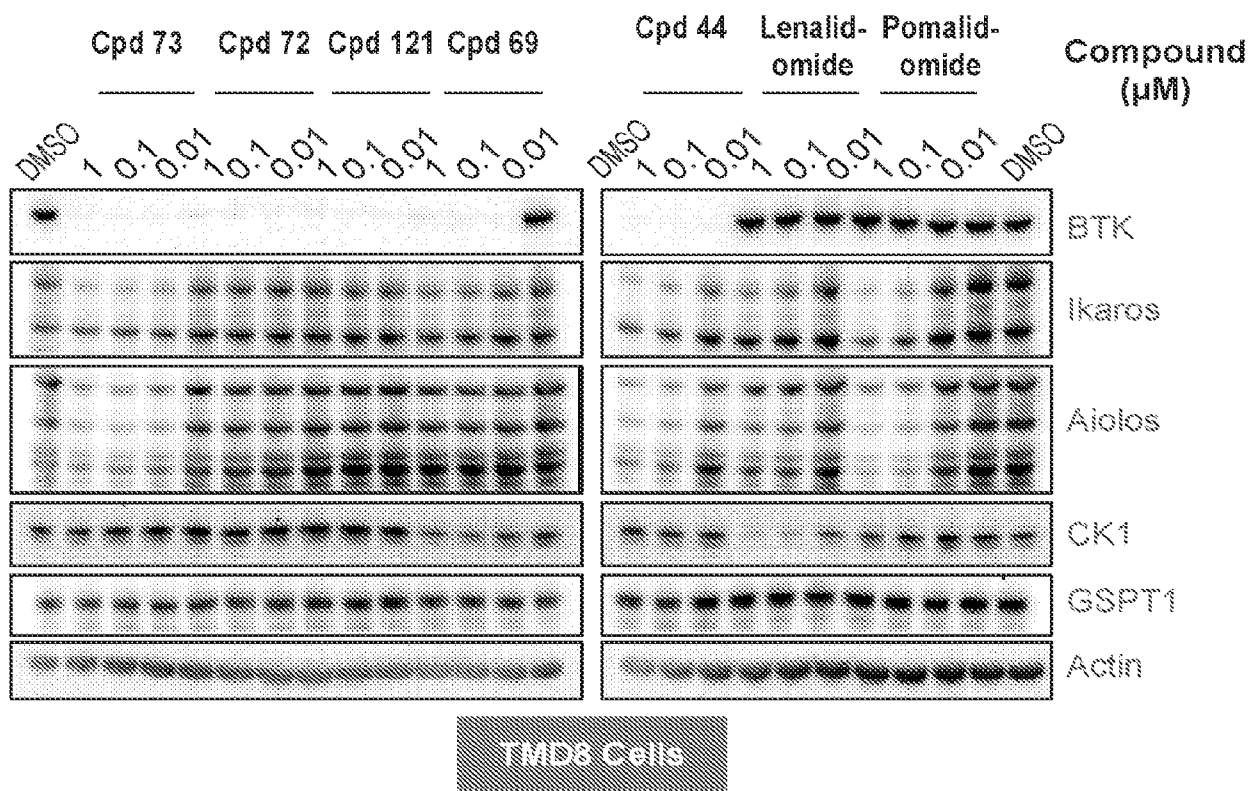


FIG. 10B

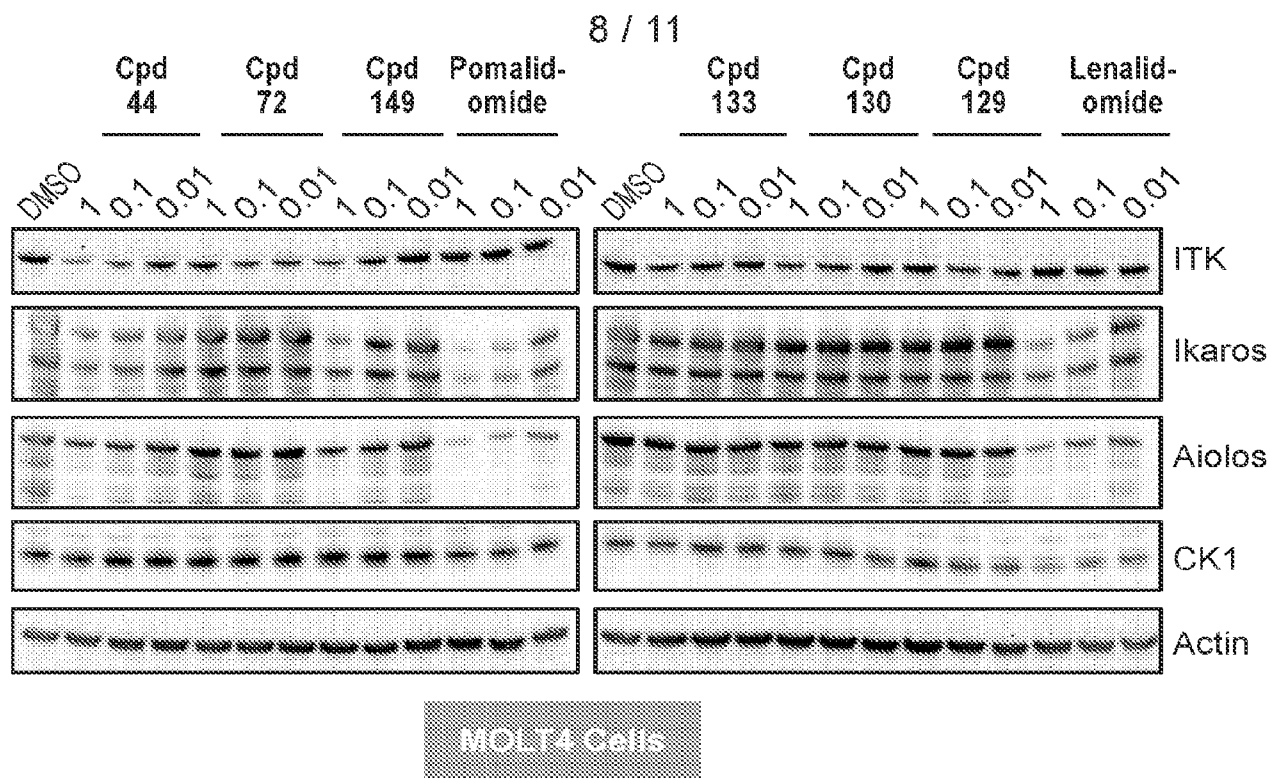


FIG. 11A

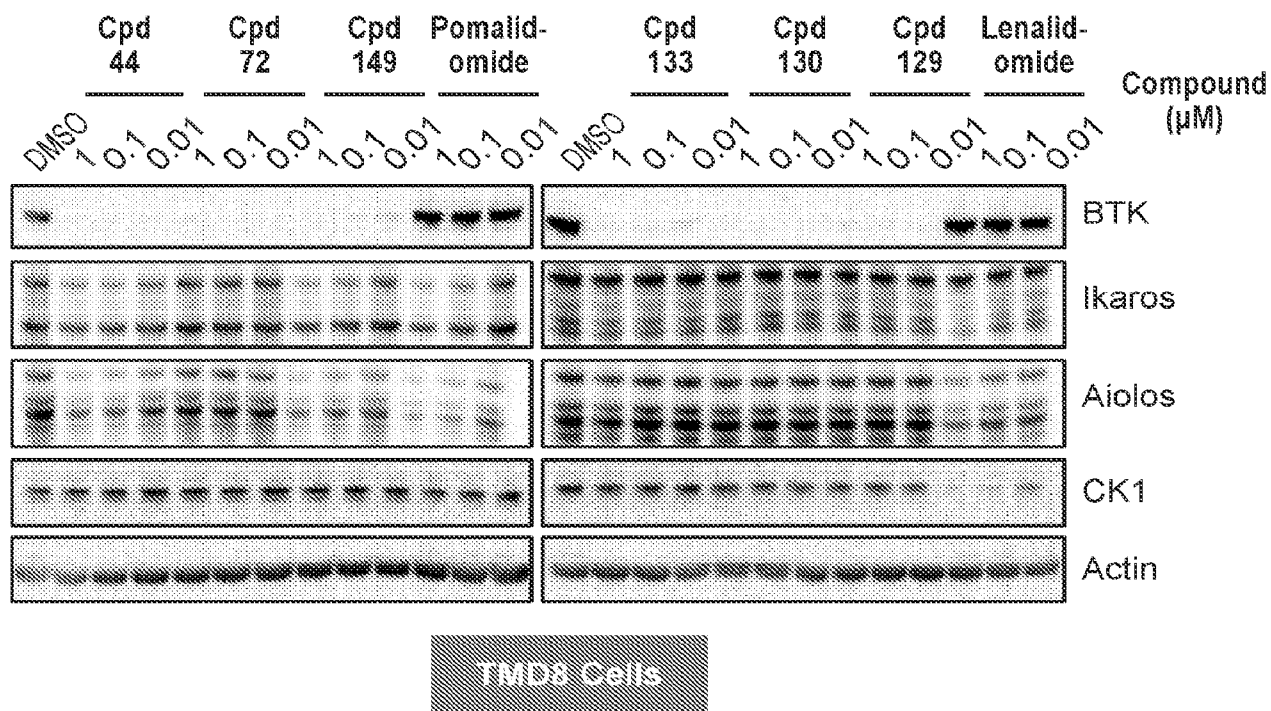


FIG. 11B

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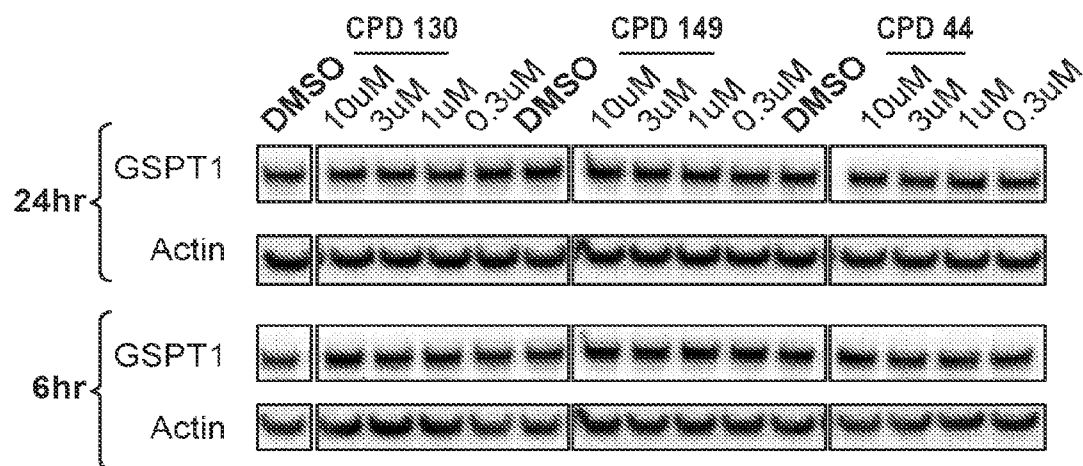


FIG. 12

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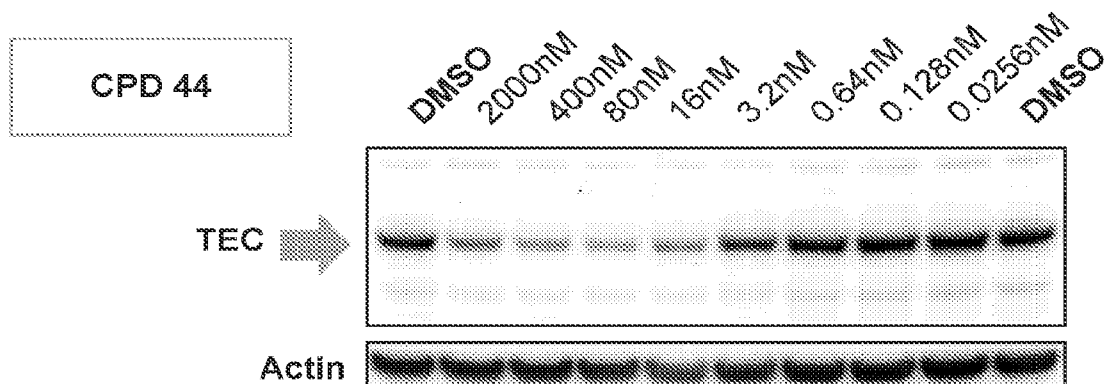


FIG. 13A

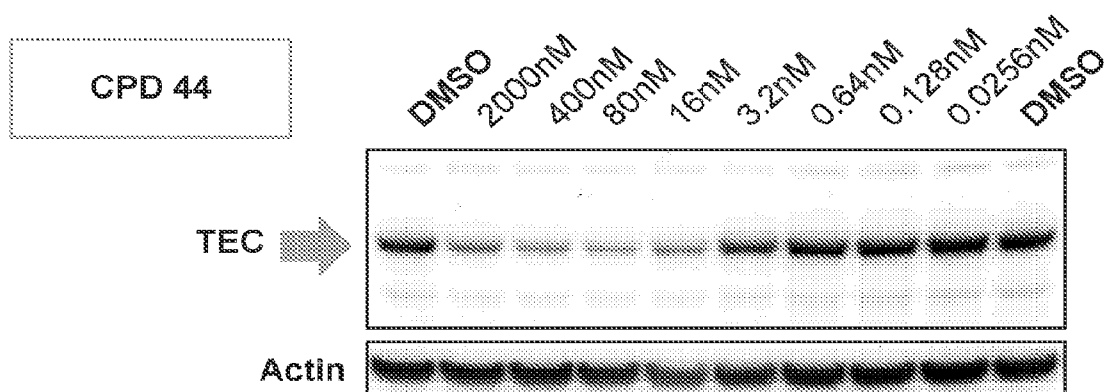


FIG. 13B

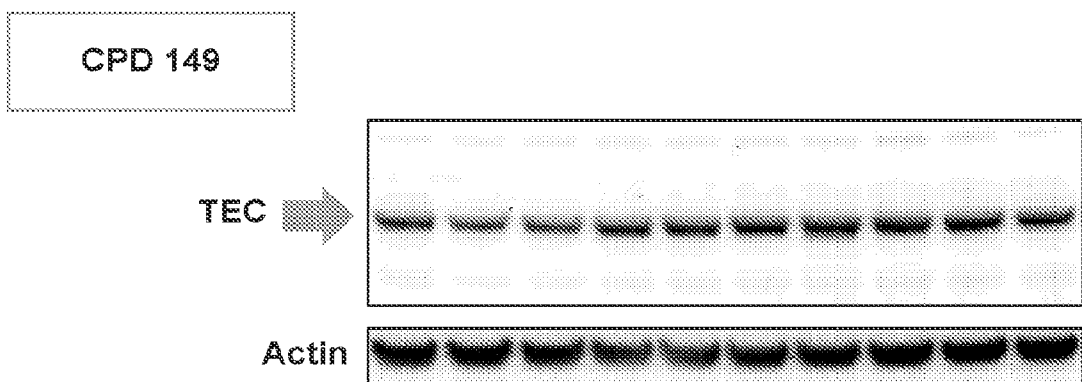


FIG. 13C

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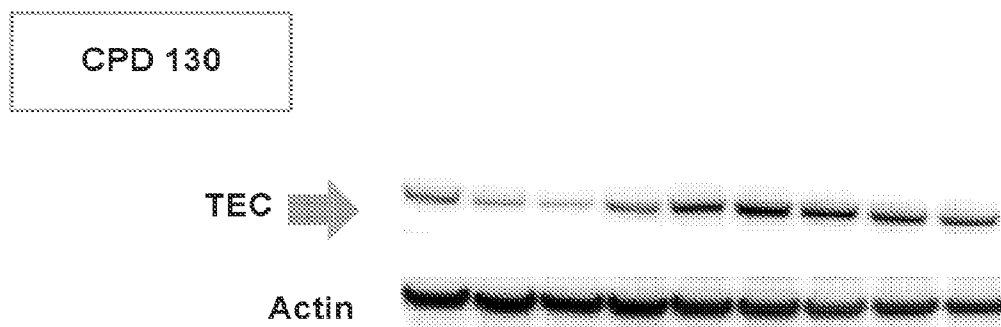
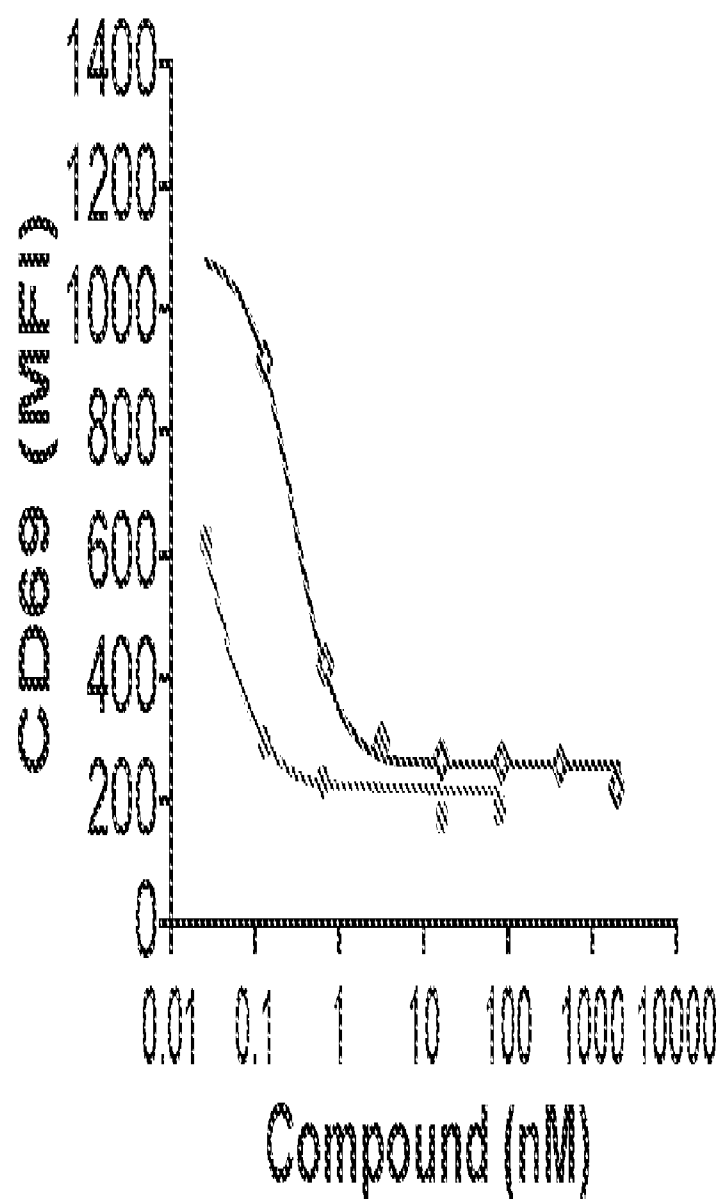


FIG. 13D

BTK degradation prevents B cell activation

CD69 on B cells



CD86 on B cells

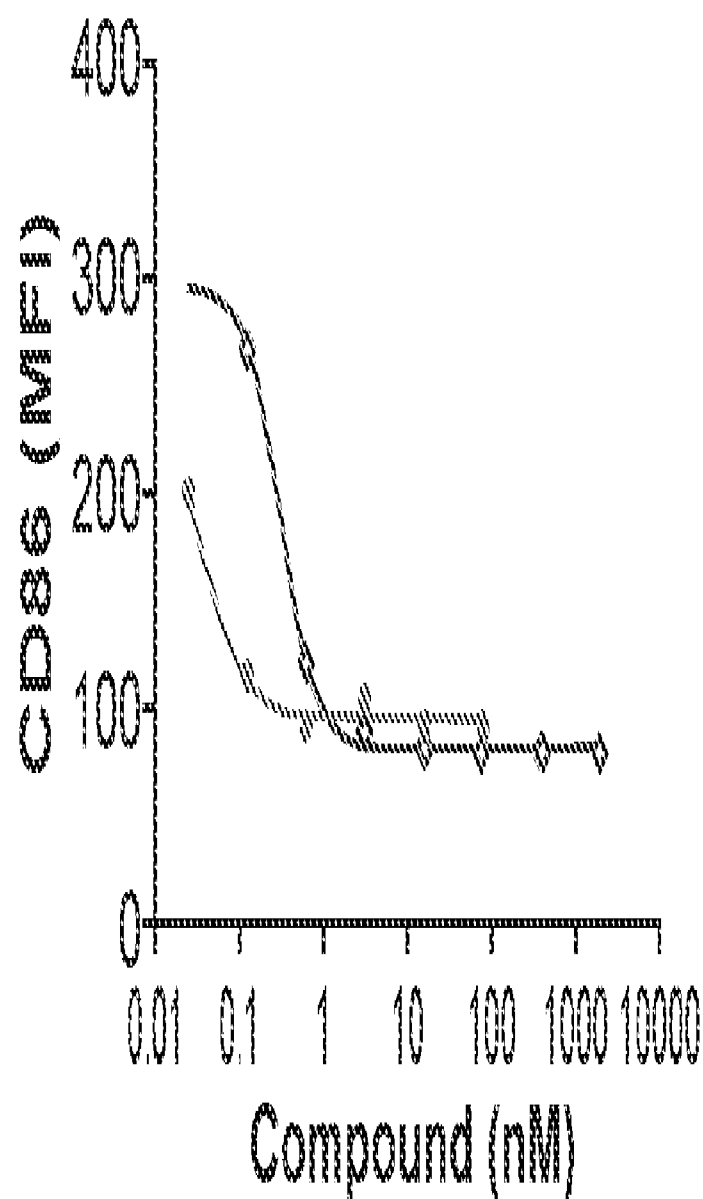


FIG. 5