

STAT DEGRADERS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims the benefit of U.S. Provisional Appl. No. 63/088,787, filed October 7, 2020 and U.S. Provisional Appl. No. 63/123,337, filed December 9, 2020, the entire content of each of which is herein incorporated by reference.

TECHNICAL FIELD OF THE INVENTION

[002] The present invention relates to compounds and methods useful for the modulation of one or more signal transducers and activators of transcription (“STAT”) via ubiquitination and/or degradation by compounds according to the present invention. The invention also provides pharmaceutically acceptable compositions comprising compounds of the present invention and methods of using said compositions in the treatment of various disorders.

BACKGROUND OF THE INVENTION

[003] Ubiquitin-Proteasome Pathway (UPP) is a critical pathway that regulates key regulator proteins and degrades misfolded or abnormal proteins. UPP is central to multiple cellular processes, and if defective or imbalanced, it leads to pathogenesis of a variety of diseases. The covalent attachment of ubiquitin to specific protein substrates is achieved through the action of E3 ubiquitin ligases.

[004] There are over 600 E3 ubiquitin ligases which facilitate the ubiquitination of different proteins in vivo, which can be divided into four families: HECT-domain E3s, U-box E3s, monomeric RING E3s and multi-subunit E3s. See generally Li et al. (PLOS One, 2008, 3, 1487) titled “Genome-wide and functional annotation of human E3 ubiquitin ligases identifies MULAN, a mitochondrial E3 that regulates the organelle’s dynamics and signaling.”; Bernds et al. (Nat. Struct. Mol. Biol., 2014, 21, 301-307) titled “New insights into ubiquitin E3 ligase mechanism”; Deshaies et al. (Ann. Rev. Biochem., 2009, 78, 399-434) titled “RING domain E3 ubiquitin ligases.”; Spratt et al. (Biochem. 2014, 458, 421-437) titled “RBR E3 ubiquitin ligases: new structures, new insights, new questions.”; and Wang et al. (Nat. Rev. Cancer., 2014, 14, 233-347) titled “Roles of F-box proteins in cancer.”

[005] UPP plays a key role in the degradation of short-lived and regulatory proteins important in a variety of basic cellular processes, including regulation of the cell cycle, modulation of cell surface receptors and ion channels, and antigen presentation. The pathway has been implicated in several forms of malignancy, in the pathogenesis of several genetic diseases (including cystic fibrosis, Angelman’s syndrome, and Liddle syndrome), in immune surveillance/viral pathogenesis, and in the pathology of

muscle wasting. Many diseases are associated with an abnormal UPP and negatively affect cell cycle and division, the cellular response to stress and to extracellular modulators, morphogenesis of neuronal networks, modulation of cell surface receptors, ion channels, the secretory pathway, DNA repair and biogenesis of organelles.

[006] Aberrations in the process have recently been implicated in the pathogenesis of several diseases, both inherited and acquired. These diseases fall into two major groups: (a) those that result from loss of function with the resultant stabilization of certain proteins, and (b) those that result from gain of function, i.e. abnormal or accelerated degradation of the protein target.

[007] The UPP is used to induce selective protein degradation, including use of fusion proteins to artificially ubiquitinate target proteins and synthetic small-molecule probes to induce proteasome-dependent degradation. Bifunctional compounds composed of a target protein-binding ligand and an E3 ubiquitin ligase ligand, induced proteasome-mediated degradation of selected proteins via their recruitment to E3 ubiquitin ligase and subsequent ubiquitination. These drug-like molecules offer the possibility of temporal control over protein expression. Such compounds are capable of inducing the inactivation of a protein of interest upon addition to cells or administration to an animal or human, and could be useful as biochemical reagents and lead to a new paradigm for the treatment of diseases by removing pathogenic or oncogenic proteins (Crews C, *Chemistry & Biology*, 2010, 17(6):551-555; Schnekloth JS Jr., *Chembiochem*, 2005, 6(1):40-46).

[008] An ongoing need exists in the art for effective treatments for disease, especially hyperplasia and cancer, such as breast cancer. However, non-specific effects, and the inability to target and modulate certain classes of proteins altogether, such as transcription factors, remain as obstacles to the development of effective anti-cancer agents. As such, small molecule therapeutic agents that leverage E3 ligase mediated protein degradation to target cancer-associated proteins such as signal transducers and activators of transcription ("STAT") hold promise as therapeutic agents. Accordingly, there remains a need to find compounds that are STAT degraders useful as therapeutic agents.

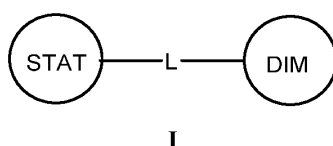
SUMMARY OF THE INVENTION

[009] The present application relates novel bifunctional compounds, which function to recruit STAT proteins to E3 ubiquitin ligase for degradation, and methods of preparation and uses thereof. In particular, the present disclosure provides bifunctional compounds, which find utility as modulators of targeted ubiquitination of STAT proteins, which are then degraded and/or otherwise inhibited by the bifunctional compounds as described herein. Also provided are monovalent compounds, which find utility as inducers of targeted ubiquitination of STAT proteins, which are then degraded and/or otherwise inhibited by the

monovalent compounds as described herein. An advantage of the compounds provided herein is that a broad range of pharmacological activities is possible, consistent with the degradation/inhibition of STAT proteins. In addition, the description provides methods of using an effective amount of the compounds as described herein for the treatment or amelioration of a disease condition, such as cancer, e.g., breast cancer.

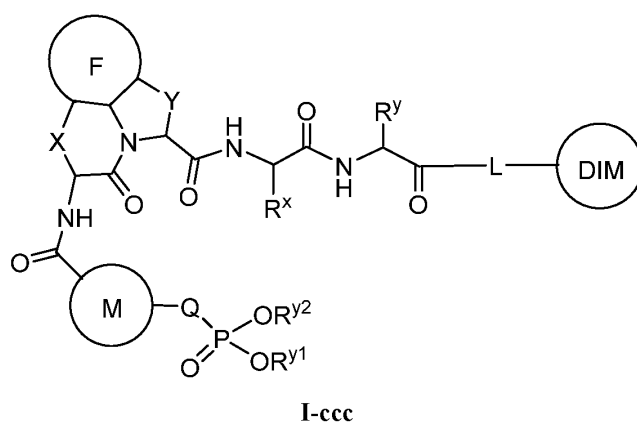
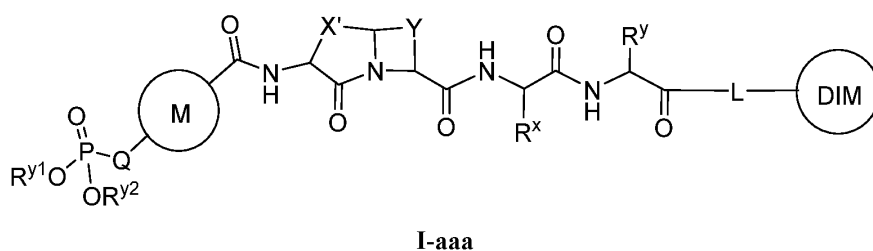
[0010] The present application further relates to targeted degradation of STAT proteins through the use of bifunctional molecules, including bifunctional molecules that link a cereblon-binding moiety to a ligand that binds STAT proteins.

[0011] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are effective as degraders of STAT proteins. Such compounds have the general formula **I**:



or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

[0001] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are effective for the modulation of targeted ubiquitination. Such compounds have the formula **I-aaa** and **I-ccc**:



or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

[0012] Compounds of the present invention, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with regulation of signaling pathways implicating STAT proteins. Such diseases, disorders, or conditions include those described herein.

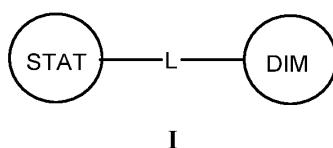
[0013] Compounds provided by this invention are also useful for the study of STAT proteins in biological and pathological phenomena; the study of intracellular signal transduction pathways occurring in bodily tissues; and the comparative evaluation of new STAT inhibitors or STAT degraders or other regulators of cell cycling, metastasis, angiogenesis, and immune cell evasion, *in vitro* or *in vivo*.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Certain Embodiments of the Invention:

[0014] Compounds of the present invention, and compositions thereof, are useful as degraders and/or inhibitors of one or more STAT proteins. In some embodiments, a provided compound degrades and/or inhibits one or more of STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, or STAT6.

[0015] In certain embodiments, the present invention provides a compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:

STAT is a STAT binding moiety capable of binding to one or more of STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, or STAT6, preferably STAT3;

L is a bivalent moiety that connects STAT to DIM; and

DIM is a degradation inducing moiety selected from an E3 ubiquitin ligase binding moiety (LBM), lysine mimetic, and hydrogen.

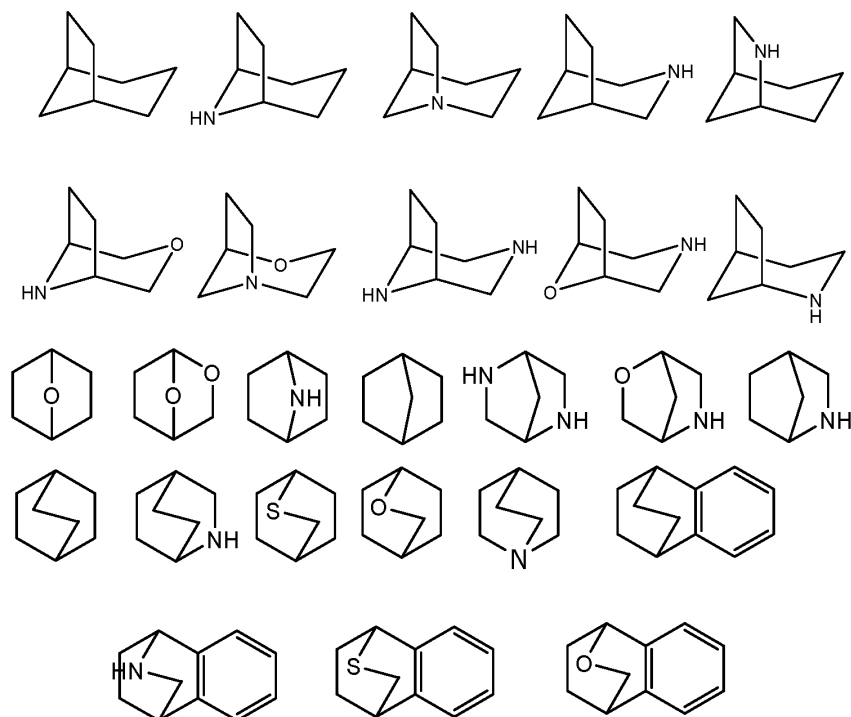
2. Compounds and Definitions:

[0016] Compounds of the present invention include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, 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.

[0017] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle," "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C₃-C₆ hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. In some embodiments, a carbocyclic ring may be a 5-12 membered bicyclic, bridged bicyclic, or spirocyclic ring. A carbocyclic ring may include one or more oxo (=O) or thioxo (=S) substituent. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0018] As used herein, the term "bridged bicyclic" refers to any bicyclic ring system, i.e. carbocyclic or heterocyclic, saturated or partially unsaturated, having at least one bridge. As defined by IUPAC, a "bridge" is an unbranched chain of atoms or an atom or a valence bond connecting two bridgeheads, where a "bridgehead" is any skeletal atom of the ring system which is bonded to three or more skeletal atoms (excluding hydrogen). In some embodiments, a bridged bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Such bridged bicyclic groups are well known in the art and include those groups set forth below where each group is attached to the rest of the molecule at any substitutable carbon or nitrogen atom. Unless otherwise specified, a bridged bicyclic group is optionally substituted with one or more substituents as set forth for aliphatic groups. Additionally or alternatively, any substitutable nitrogen of a bridged bicyclic group is optionally substituted. Exemplary bridged bicyclics include:



[0019] The term “lower alkyl” refers to a C₁₋₄ straight or branched alkyl group. Exemplary lower alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl.

[0020] The term “lower haloalkyl” refers to a C₁₋₄ straight or branched alkyl group that is substituted with one or more halogen atoms.

[0021] The term “heteroatom” means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR⁺ (as in N-substituted pyrrolidinyl)).

[0022] The term “unsaturated,” as used herein, means that a moiety has one or more units of unsaturation.

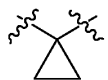
[0023] As used herein, the term “bivalent C₁₋₈ (or C₁₋₆) saturated or unsaturated, straight or branched, hydrocarbon chain”, refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

[0024] The term “alkylene” refers to a bivalent alkyl group. An “alkylene chain” is a polymethylene group, i.e., -(CH₂)_n-, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene

hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0025] The term “alkenylene” refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0026] As used herein, the term “cyclopropylenyl” refers to a bivalent cyclopropyl group of the



following structure:

[0027] The term “halogen” means F, Cl, Br, or I.

[0028] The term “aryl” used alone or as part of a larger moiety as in “aralkyl,” “aralkoxy,” or “aryloxyalkyl,” refers to monocyclic or bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term “aryl” may be used interchangeably with the term “aryl ring.” In certain embodiments of the present invention, “aryl” refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term “aryl,” as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

[0029] The terms “heteroaryl” and “heteroar-,” used alone or as part of a larger moiety, e.g., “heteroaralkyl,” or “heteroaralkoxy,” refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term “heteroatom” refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The terms “heteroaryl” and “heteroar-,” as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*-quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, and pyrido[2,3-*b*]-1,4-oxazin-3(4*H*)-one. A heteroaryl group may be mono- or bicyclic. The term “heteroaryl” may be used interchangeably with the terms “heteroaryl ring,” “heteroaryl

group,” or “heteroaromatic,” any of which terms include rings that are optionally substituted. The term “heteroaralkyl” refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0030] As used herein, the terms “heterocycle,” “heterocyclyl,” “heterocyclic radical,” and “heterocyclic ring” are used interchangeably and refer to a stable 5- to 7-membered monocyclic or 7-10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term “nitrogen” includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl), or ⁺NR (as in *N*-substituted pyrrolidinyl).

[0031] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms “heterocycle,” “heterocyclyl,” “heterocyclyl ring,” “heterocyclic group,” “heterocyclic moiety,” and “heterocyclic radical,” are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*-indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl. In some embodiments, a heterocyclic ring may be a 5-12 membered bicyclic, bridged bicyclic, or spirocyclic ring. A heterocyclic ring may include one or more oxo (=O) or thioxo (=S) substituent. The term “heterocyclylalkyl” refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[0032] As used herein, the term “partially unsaturated” refers to a ring moiety that includes at least one double or triple bond. The term “partially unsaturated” is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0033] As described herein, compounds of the disclosure may contain “substituted” moieties. In general, the term “substituted” means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned

by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term “stable,” as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0034] Suitable monovalent substituents on a substitutable carbon atom of an “optionally substituted” group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$; $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R° ; $-CH=CHPh$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}$ -pyridyl which may be substituted with R° ; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; SiR°_3 ; $-(C_{1-4}$ straight or branched alkylene) $O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene) $C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$ - (5-6 membered heteroaryl ring), or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R° , taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0035] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^\bullet$, $-(haloR^\bullet)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$, $-O(haloR^\bullet)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}SR^\bullet$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^\bullet$, $-(CH_2)_{0-2}NR^\bullet_2$, $-NO_2$, $-SiR^\bullet_3$, $-OSiR^\bullet_3$, $-C(O)SR^\bullet$, $-(C_{1-4}$ straight or branched alkylene) $C(O)OR^\bullet$, or $-SSR^\bullet$ wherein each $R^\bullet$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include $=O$ and $=S$.

[0036] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: $=O$, $=S$, $=NNR^*$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0037] Suitable substituents on the aliphatic group of R^* include halogen, $-R^\bullet$, $-(haloR^\bullet)$, $-OH$, $-OR^\bullet$, $-O(haloR^\bullet)$, $-CN$, $-C(O)OH$, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0038] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $-R^\dagger$, $-NR^\dagger_2$, $-C(O)R^\dagger$, $-C(O)OR^\dagger$, $-C(O)C(O)R^\dagger$, $-C(O)CH_2C(O)R^\dagger$, $-S(O)_2R^\dagger$, $-S(O)_2NR^\dagger_2$, $-C(S)NR^\dagger_2$, $-C(NH)NR^\dagger_2$, or $-N(R^\dagger)S(O)_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted $-OPh$, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0039] Suitable substituents on the aliphatic group of $R^\dagger$ are independently halogen, $-R^\bullet$, $-(haloR^\bullet)$, $-OH$, $-OR^\bullet$, $-O(haloR^\bullet)$, $-CN$, $-C(O)OH$, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0040] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. 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 invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are 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, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

[0041] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. 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, loweralkyl sulfonate and aryl sulfonate. In some embodiments, the provided compounds are purified in salt form for convenience and/or ease of purification, e.g., using an acidic or basic mobile phase during chromatography. Salts forms of the provided compounds formed during chromatographic purification are contemplated herein (e.g., diammonium salts) and are readily apparent to those having skill in the art.

[0042] Unless otherwise stated, structures depicted herein are also 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 invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including 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 invention. Such

compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention

[0043] As used herein, the term “provided compound” refers to any genus, subgenus, and/or species set forth herein.

[0044] The term “prodrug” refers to a compound that is made more active in vivo. The present compounds can also exist as prodrugs, as described in *Hydrolysis in Drug and Prodrug Metabolism: Chemistry, Biochemistry, and Enzymology* (Testa, Bernard and Mayer, Joachim M. Wiley-VHCA, Zurich, Switzerland 2003). Prodrugs of the compounds described herein are structurally modified forms of the compound that readily undergo chemical changes under physiological conditions to provide the compound. Additionally, prodrugs can be converted to the compound by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to a compound when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the compound, or parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the “prodrug”), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound. The term “therapeutically acceptable prodrug,” refers to those prodrugs or zwitterions which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[0045] As used herein, the term “inhibitor” is defined as a compound that binds to and /or inhibits an STAT protein with measurable affinity. In certain embodiments, an inhibitor has an IC₅₀ and/or binding constant of less than about 50 μ M, less than about 1 μ M, less than about 500 nM, less than about 100 nM, less than about 10 nM, or less than about 1 nM.

[0046] As used herein, the term “degrader” is defined as a heterobifunctional compound that binds to and /or inhibits both an STAT protein and an E3 ligase with measurable affinity resulting in the ubiquitination and subsequent degradation of the STAT protein. In certain embodiments, a degrader has an DC₅₀ of less than about 50 μ M, less than about 1 μ M, less than about 500 nM, less than about 100 nM, less than about 10 nM, or less than about 1 nM. As used herein, the term “monovalent” refers to a degrader compound without an appended E3 ligase binding moiety.

[0047] A compound of the present invention may be tethered to a detectable moiety. It will be

appreciated that such compounds are useful as imaging agents. One of ordinary skill in the art will recognize that a detectable moiety may be attached to a provided compound *via* a suitable substituent. As used herein, the term “suitable substituent” refers to a moiety that is capable of covalent attachment to a detectable moiety. Such moieties are well known to one of ordinary skill in the art and include groups containing, e.g., a carboxylate moiety, an amino moiety, a thiol moiety, or a hydroxyl moiety, to name but a few. It will be appreciated that such moieties may be directly attached to a provided compound or *via* a tethering group, such as a bivalent saturated or unsaturated hydrocarbon chain. In some embodiments, such moieties may be attached via click chemistry. In some embodiments, such moieties may be attached via a 1,3-cycloaddition of an azide with an alkyne, optionally in the presence of a copper catalyst. Methods of using click chemistry are known in the art and include those described by Rostovtsev *et al.*, *Angew. Chem. Int. Ed.* 2002, 41, 2596-99 and Sun *et al.*, *Bioconjugate Chem.*, 2006, 17, 52-57.

[0048] As used herein, the term “detectable moiety” is used interchangeably with the term “label” and relates to any moiety capable of being detected, e.g., primary labels and secondary labels. Primary labels, such as radioisotopes (e.g., tritium, ^{32}P , ^{33}P , ^{35}S , or ^{14}C), mass-tags, and fluorescent labels are signal generating reporter groups which can be detected without further modifications. Detectable moieties also include luminescent and phosphorescent groups.

[0049] The term “secondary label” as used herein refers to moieties such as biotin and various protein antigens that require the presence of a second intermediate for production of a detectable signal. For biotin, the secondary intermediate may include streptavidin-enzyme conjugates. For antigen labels, secondary intermediates may include antibody-enzyme conjugates. Some fluorescent groups act as secondary labels because they transfer energy to another group in the process of nonradiative fluorescent resonance energy transfer (FRET), and the second group produces the detected signal.

[0050] The terms “fluorescent label”, “fluorescent dye”, and “fluorophore” as used herein refer to moieties that absorb light energy at a defined excitation wavelength and emit light energy at a different wavelength. Examples of fluorescent labels include, but are not limited to: Alexa Fluor dyes (Alexa Fluor 350, Alexa Fluor 488, Alexa Fluor 532, Alexa Fluor 546, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 633, Alexa Fluor 660 and Alexa Fluor 680), AMCA, AMCA-S, BODIPY dyes (BODIPY FL, BODIPY R6G, BODIPY TMR, BODIPY TR, BODIPY 530/550, BODIPY 558/568, BODIPY 564/570, BODIPY 576/589, BODIPY 581/591, BODIPY 630/650, BODIPY 650/665), Carboxyrhodamine 6G, carboxy-X-rhodamine (ROX), Cascade Blue, Cascade Yellow, Coumarin 343, Cyanine dyes (Cy3, Cy5, Cy3.5, Cy5.5), Dansyl, Dapoxyl, Dialkylaminocoumarin, 4',5'-Dichloro-2',7'-dimethoxy-fluorescein, DM-NERF, Eosin, Erythrosin, Fluorescein, FAM, Hydroxycoumarin, IRDyes (IRD40, IRD 700, IRD 800), JOE, Lissamine rhodamine B, Marina Blue, Methoxycoumarin, Naphthofluorescein, Oregon Green 488, Oregon Green 500,

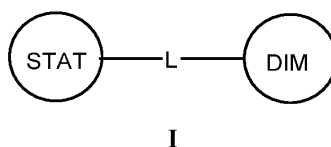
Oregon Green 514, Pacific Blue, PyMPO, Pyrene, Rhodamine B, Rhodamine 6G, Rhodamine Green, Rhodamine Red, Rhodol Green, 2',4',5',7'-Tetra-bromosulfone-fluorescein, Tetramethyl-rhodamine (TMR), Carboxytetramethylrhodamine (TAMRA), Texas Red, Texas Red-X.

[0051] The term “mass-tag” as used herein refers to any moiety that is capable of being uniquely detected by virtue of its mass using mass spectrometry (MS) detection techniques. Examples of mass-tags include electrophore release tags such as N-[3-[4'-(p-Methoxytetrafluorobenzyl)oxy]phenyl]-3-methylglyceronyl]isonipecotic Acid, 4'-[2,3,5,6-Tetrafluoro-4-(pentafluorophenoxy)]methyl acetophenone, and their derivatives. The synthesis and utility of these mass-tags is described in United States Patents 4,650,750, 4,709,016, 5,360,819, 5,516,931, 5,602,273, 5,604,104, 5,610,020, and 5,650,270. Other examples of mass-tags include, but are not limited to, nucleotides, dideoxynucleotides, oligonucleotides of varying length and base composition, oligopeptides, oligosaccharides, and other synthetic polymers of varying length and monomer composition. A large variety of organic molecules, both neutral and charged (biomolecules or synthetic compounds) of an appropriate mass range (100-2000 Daltons) may also be used as mass-tags.

[0052] The terms “measurable affinity” and “measurably inhibit,” as used herein, means a measurable change in a STAT protein activity between a sample comprising a compound of the present invention, or composition thereof, and a STAT protein, and an equivalent sample comprising a STAT protein, in the absence of said compound, or composition thereof.

3. Description of Exemplary Embodiments:

[0053] As described above, in certain embodiments, the present invention provides a compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:

STAT is a STAT protein binding moiety capable of binding to one or more of STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, or STAT6, preferably STAT3;

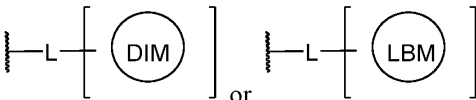
L is a bivalent moiety that connects STAT to DIM; and

DIM is a degradation inducing moiety selected from an E3 ubiquitin ligase binding moiety (LBM), lysine mimetic, and hydrogen.

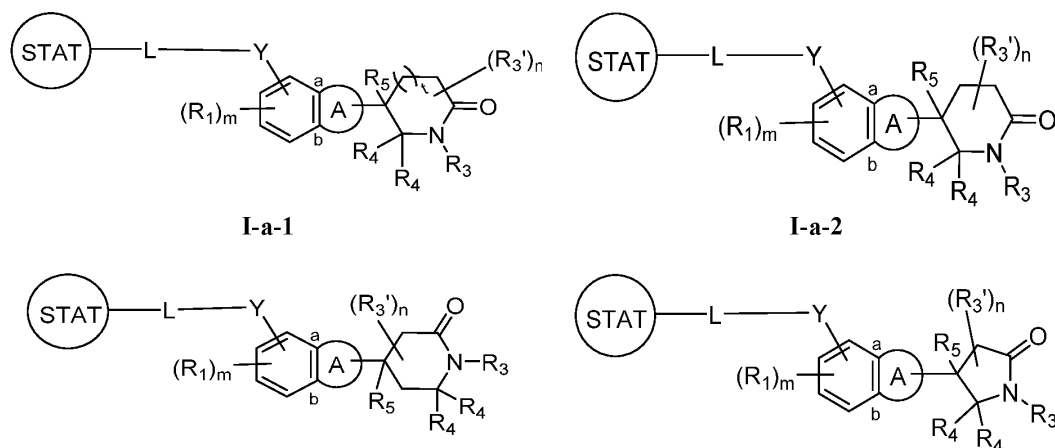
Ligase Binding Moiety (LBM)

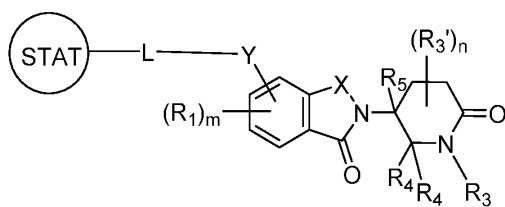
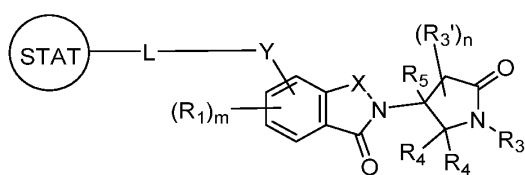
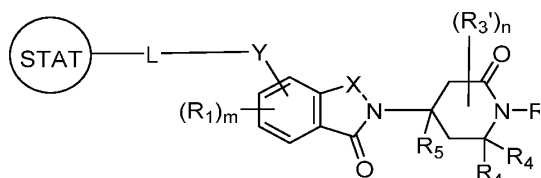
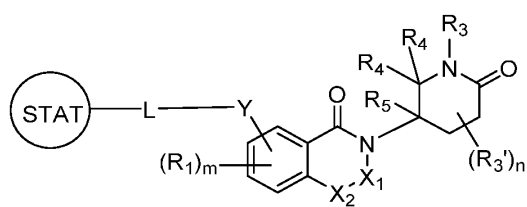
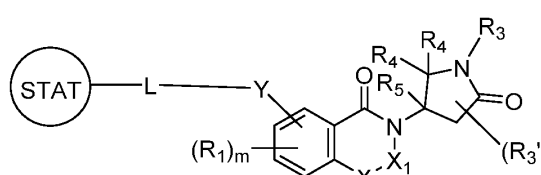
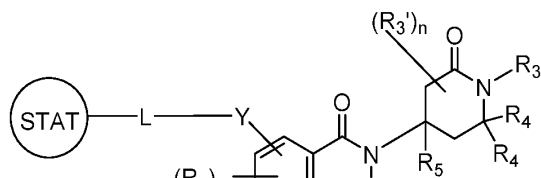
[0054] In some embodiments, LBM is an E3 ligase ligand. Such E3 ligase ligands are well known to one of ordinary skill in the art and include those described in M. Toure, C. M. Crews, *Angew. Chem. Int. Ed.* 2016, 55, 1966, T. Uehara *et al. Nature Chemical Biology* 2017, 13, 675, WO 2017/176708, US 2017/0281784, WO 2017/161119, WO 2017/176957, WO 2017/176958, WO 2015/160845, US 2015/0291562, WO 2016/197032, WO 2016/105518, US 2018/0009779, WO 2017/007612, 2018/0134684, WO 2013/106643, US 2014/0356322, WO 2002/020740, US 2002/0068063, WO 2012/078559, US 2014/0302523, WO 2012/003281, US 2013/0190340, US 2016/0022642, WO 2014/063061, US 2015/0274738, WO 2016/118666, US 2016/0214972, WO 2016/149668, US 2016/0272639, WO 2016/169989, US 2018/0118733, WO 2016/197114, US 2018/0147202, WO 2017/011371, US 2017/0008904, WO 2017/011590, US 2017/0037004, WO 2017/079267, US 2017/0121321, WO 2017/117473, WO 2017/117474, WO 2013/106646, WO 2014/108452, WO 2017/197036, WO 2017/197046, WO 2017/197051, WO 2017/197055, and WO 2017/197056 each of, the entirety of each of which is herein incorporated by reference.

[0055] As defined herein and described below, wherein a formula is depicted using square brackets,

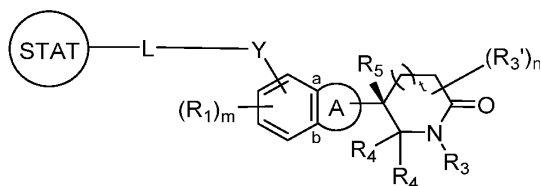
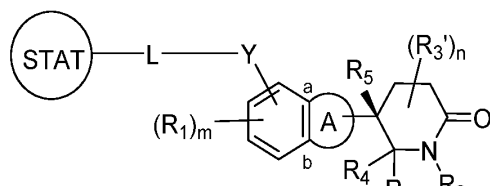
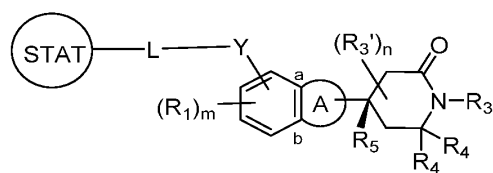
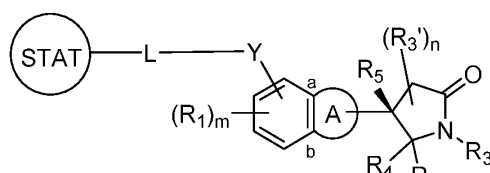
e.g., , L is attached to a modifiable carbon, oxygen, or nitrogen atom within DIM or LBM including substitution or replacement of a defined group in DIM or LBM.

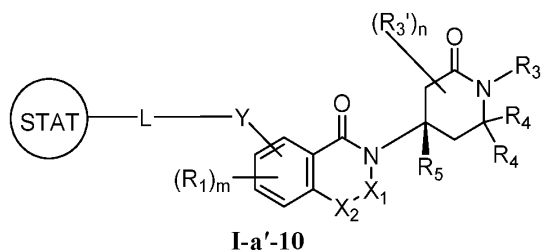
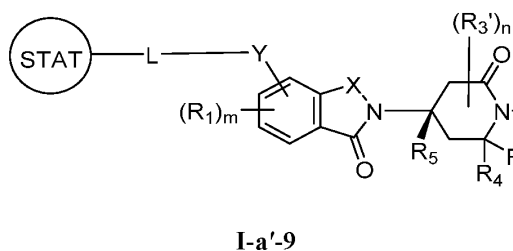
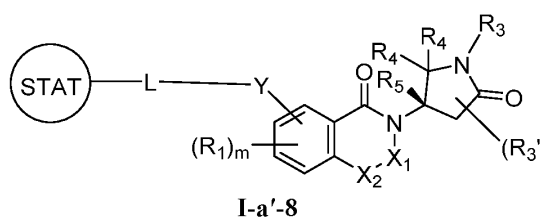
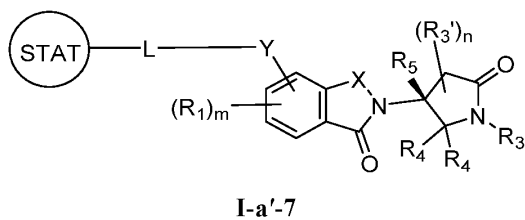
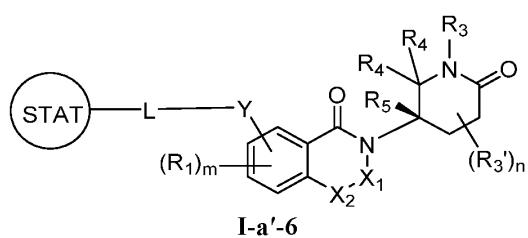
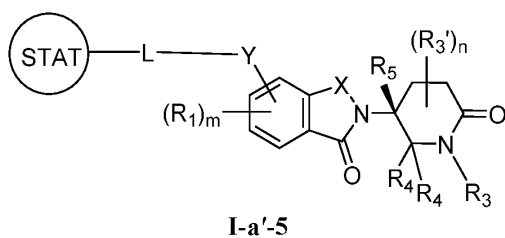
[0056] In certain embodiments, the present invention provides a compound of formula I, wherein LBM is an E3 ubiquitin ligase (cereblon) binding moiety thereby forming a compound of formula I-a-1, I-a-2, I-a-3, I-a-4, I-a-5, I-a-6, I-a-7, I-a-8, I-a-9, or I-a-10 respectively:



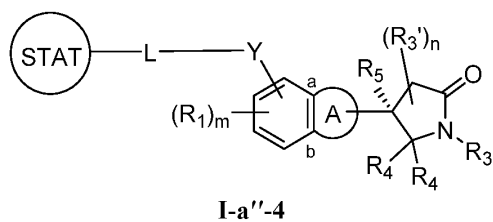
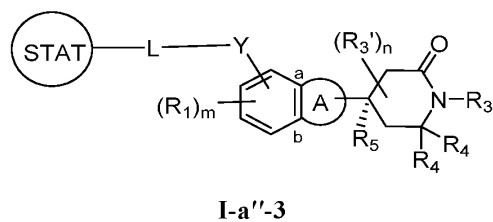
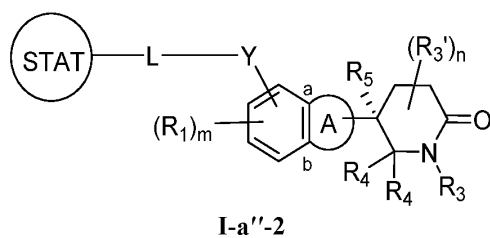
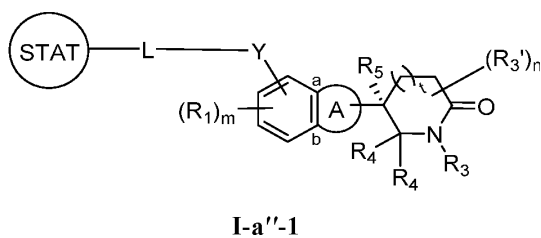
I-a-3**I-a-5****I-a-7****I-a-9****I-a-4****I-a-6****I-a-8****I-a-10**

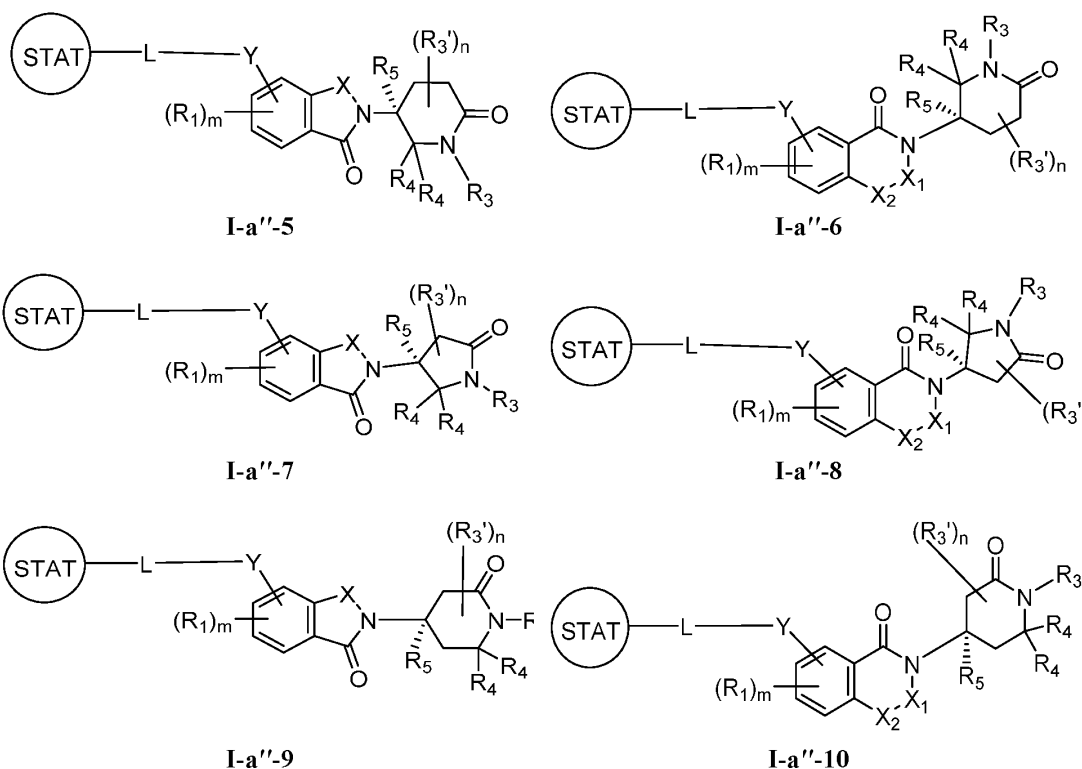
or a compound of formula **I-a'-1**, **I-a'-2**, **I-a'-3**, **I-a'-4**, **I-a'-5**, **I-a'-6**, **I-a'-7**, **I-a'-8**, **I-a'-9**, or **I-a'-10** respectively:

**I-a'-1****I-a'-2****I-a'-3****I-a'-4**

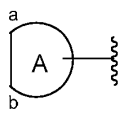


or a compound of formula I-a''-1, I-a''-2, I-a''-3, I-a''-4, I-a''-5, I-a''-6, I-a''-7, I-a''-8, I-a''-9, or I-a''-10 respectively:

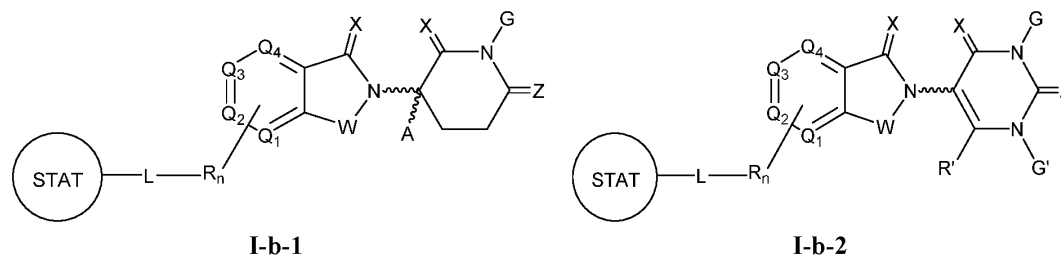


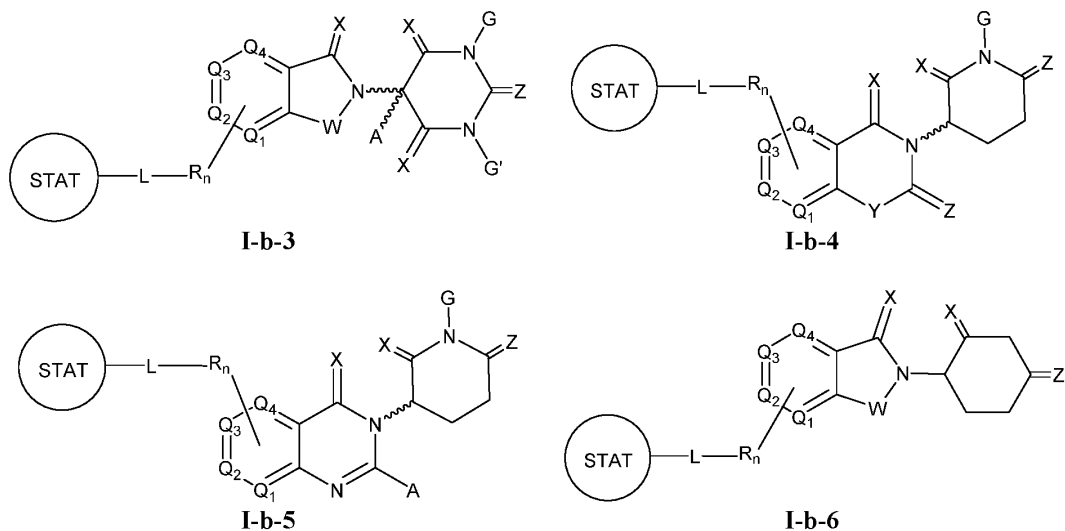


or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in

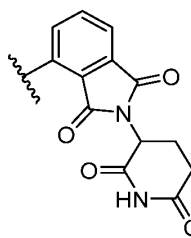
embodiments herein, and wherein each of the variables , X, X₁, X₂, Y, R₁, R₃, R₃', R₄, R₅, t, m and n is as defined and described in WO 2017/007612 and US 2018/0134684, the entirety of each of which is herein incorporated by reference.

[0057] In certain embodiments, the present invention provides a compound of Formula I, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety thereby forming a compound of formula **I-b-1**, **I-b-2**, **I-b-3**, **I-b-4**, **I-b-5**, or **I-b-6** respectively:

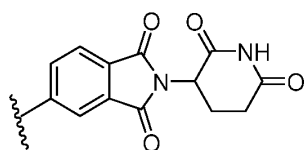




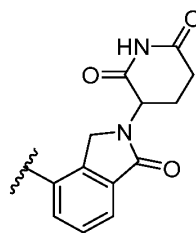
or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein each of the variables A, G, G', Q₁, Q₂, Q₃, Q₄, R, R', W, X, Y, Z, $\sim$, and n is as defined and described in WO 2016/197114 and US 2018/0147202, the entirety of each of which is herein incorporated by reference.



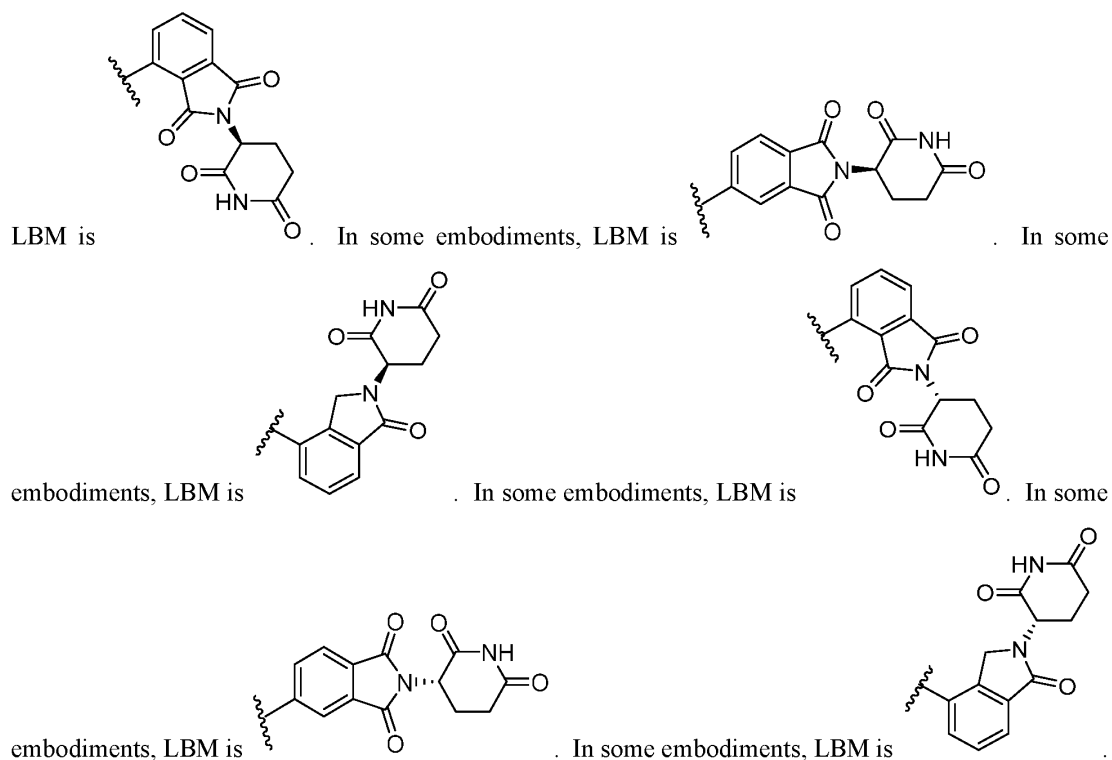
[0058] In some embodiments, LBM is



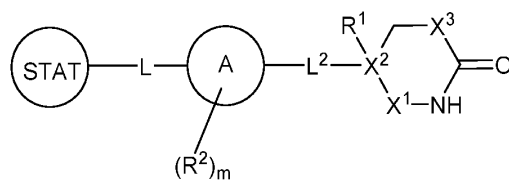
. In some embodiments, LBM is



. In some embodiments,



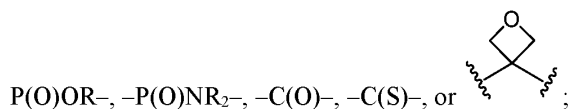
[0059] In certain embodiments, the present invention provides a compound of formula I, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety thereby forming a compound of formula I-c:



I-c

or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described herein, and wherein:

X¹ is a bivalent moiety selected from a covalent bond, -CH₂-, -CHCF₃-, -SO₂-, -S(O)-, -P(O)R-, -



X² is a carbon atom or silicon atom;

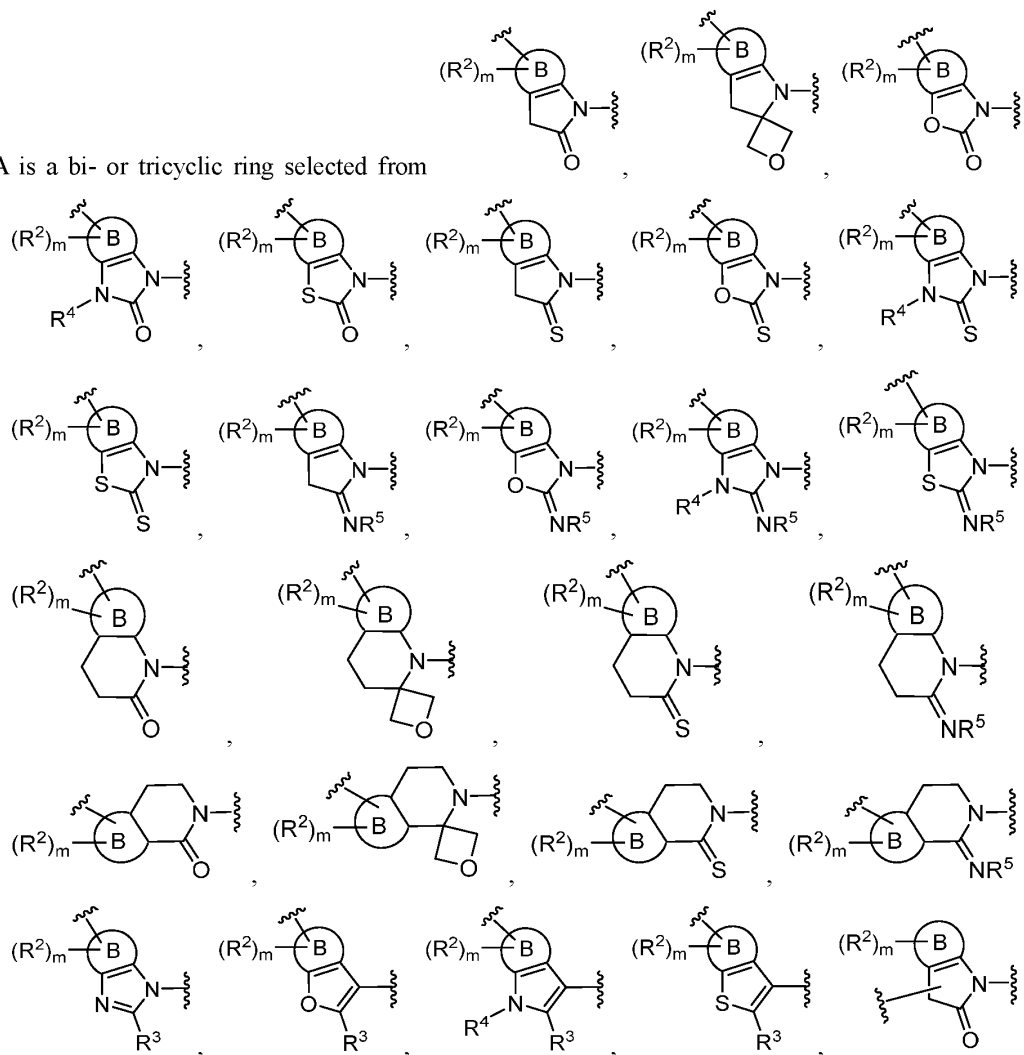
X³ is a bivalent moiety selected from -CR₂-, -NR-, -O-, -S-, or -Si(R₂)-;

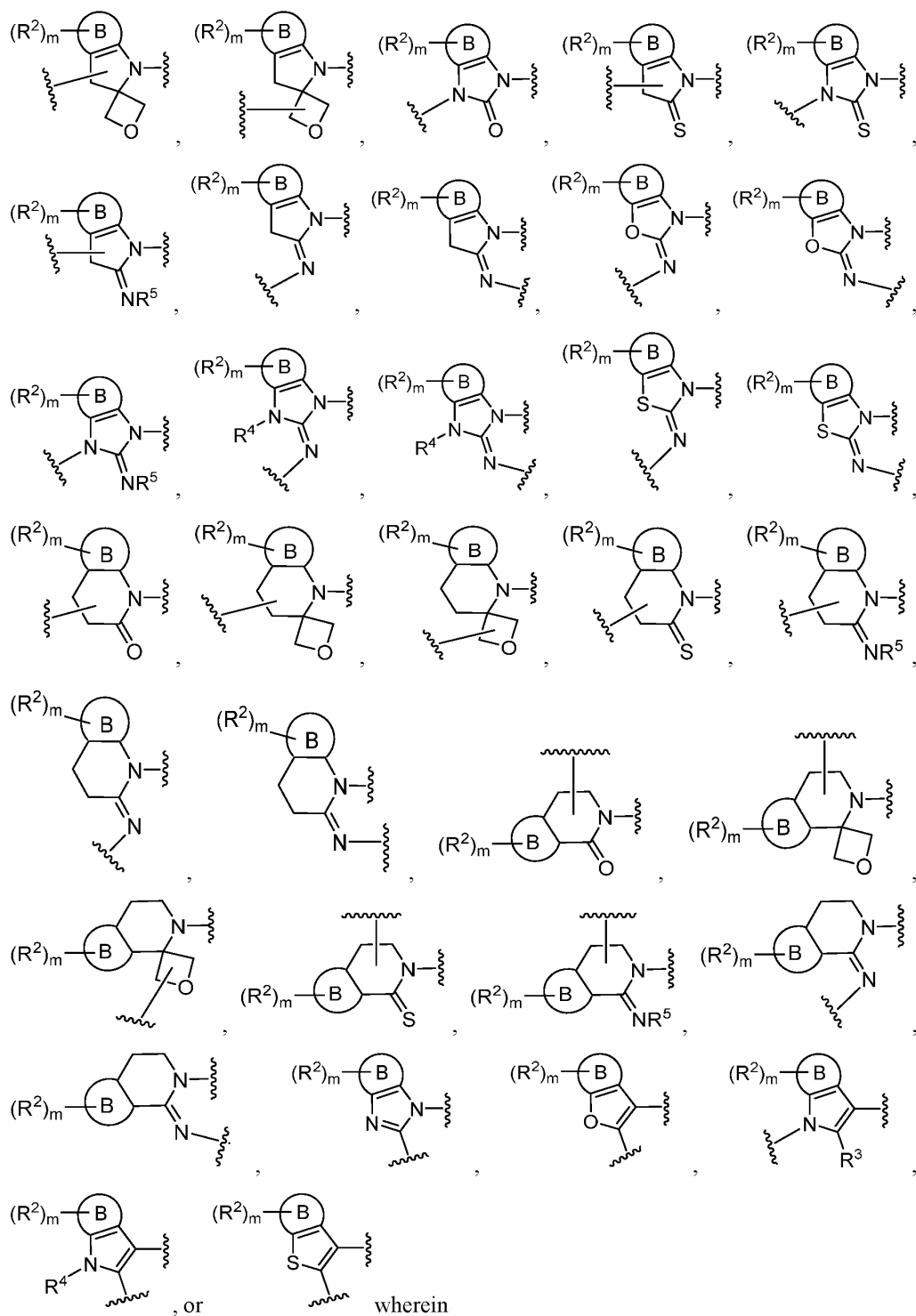
R¹ is hydrogen, deuterium, halogen, -CN, -OR, -SR, -S(O)R, -S(O)₂R, -N(R)₂, -P(O)(OR)₂, -

$P(O)(NR_2)OR$, $-P(O)(NR_2)_2$, $-Si(OH)_2R$, $-Si(OH)(R)_2$, $-Si(R)_3$, or an optionally substituted C_{1-4} aliphatic;

each R^2 is independently hydrogen, deuterium, R^6 , halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-N(R)_2$, $-Si(R)_3$, $-S(O)_2R$, $-S(O)_2N(R)_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $-C(O)N(R)_2$, $-C(O)N(R)OR$, $-C(R)_2N(R)C(O)R$, $-C(R)_2N(R)C(O)N(R)_2$, $-OC(O)R$, $-OC(O)N(R)_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)(NR_2)$, $-OP(O)(NR_2)_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)N(R)_2$, $-N(R)S(O)_2R$, $-NP(O)R_2$, $-N(R)P(O)(OR)_2$, $-N(R)P(O)(OR)(NR_2)$, $-N(R)P(O)(NR_2)_2$, or $-N(R)S(O)_2R$;

Ring A is a bi- or tricyclic ring selected from





Ring B is a fused ring selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;

R^3 is selected from hydrogen, halogen, $-OR$, $-N(R)_2$, or $-SR$;

each R^4 is independently hydrogen, $-R^6$, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

R^5 is hydrogen, C_{1-4} aliphatic, or $-CN$;

each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L^2 is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with $-O-$, $-C(O)-$, $-C(S)-$, $-C(R)_2-$, $-CH(R)-$, $-C(F)_2-$, $-N(R)-$, $-S(O)_2-$ or $-(C)=CH-$;

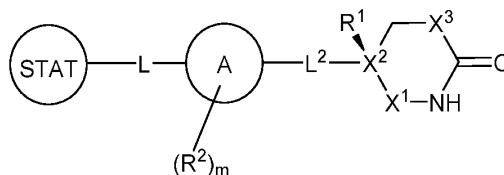
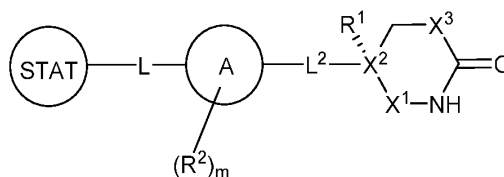
m is 0, 1, 2, 3 or 4;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

[0060] Where a point of attachment of $-(R^2)_m$ is depicted on Ring B, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of $-(R^2)_m$ may be on Ring A and may also be at any available carbon or nitrogen atom on Ring A including the ring to which Ring B is fused. Where $-R^2$ is attached to a nitrogen atom bound to R^4 or R^5 , R^4 or R^5 is absent and $-R^2$ takes the place of the R^4 or R^5 group. Where $-R^2$ is attached to a carbon atom bound to R^3 , R^3 is absent and $-R^2$ takes the place of the R^3 group.

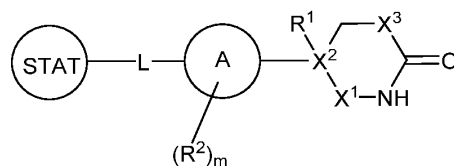
[0061] In some embodiments, a compound of formula **I-c** above is provided as a compound of formula **I-c'** or formula **I-c''**:

**I-c'****I-c''**

or a pharmaceutically acceptable salt thereof, wherein:

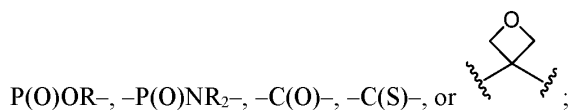
each of STAT, Ring A, L, L², R¹, R², X¹, X², X³, and m is as defined above.

[0062] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety thereby forming a compound of formula **I-d**:

**I-d**

or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein:

X¹ is a bivalent moiety selected from a covalent bond, -CH₂-, -CHCF₃-, -SO₂-, -S(O)-, -P(O)R-, -

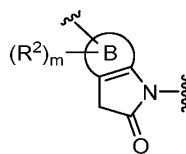


X² is a carbon atom or silicon atom;

X³ is a bivalent moiety selected from -CR₂-, -NR-, -O-, -S-, or -Si(R₂)-;

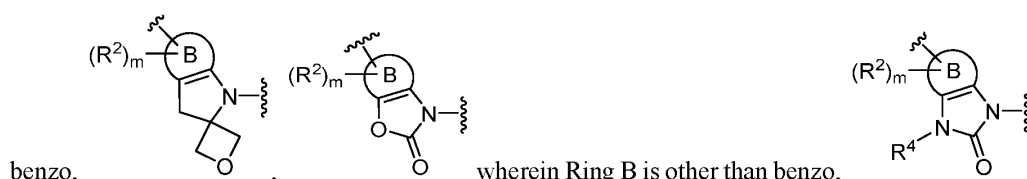
R¹ is hydrogen, deuterium, halogen, -CN, -OR, -SR, -S(O)R, -S(O)₂R, -N(R)₂, -P(O)(OR)₂, -P(O)(NR₂)OR, -P(O)(NR₂)₂, -Si(OH)₂R, -Si(OH)(R)₂, -Si(R)₃, or an optionally substituted C₁₋₄ aliphatic;

each R² is independently hydrogen, deuterium, R⁶, halogen, -CN, -NO₂, -OR, -SR, -N(R)₂, -Si(R)₃, -S(O)₂R, -S(O)₂N(R)₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)N(R)₂, -C(O)N(R)OR, -C(R)₂N(R)C(O)R, -C(R)₂N(R)C(O)N(R)₂, -OC(O)R, -OC(O)N(R)₂, -OP(O)R₂, -OP(O)(OR)₂, -OP(O)(OR)(NR₂), -OP(O)(NR₂)₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -NP(O)R₂, -N(R)P(O)(OR)₂, -N(R)P(O)(OR)(NR₂), -N(R)P(O)(NR₂)₂, or -N(R)S(O)₂R;



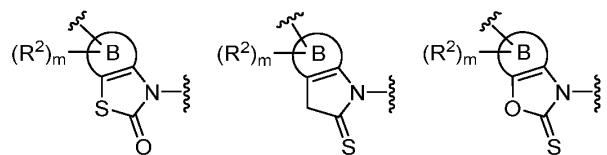
Ring A is a bi- or tricyclic ring selected from

wherein Ring B is other than imidazo or

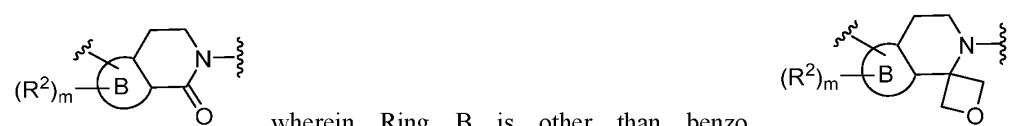
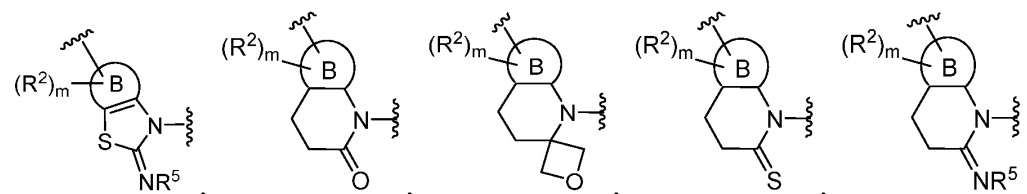
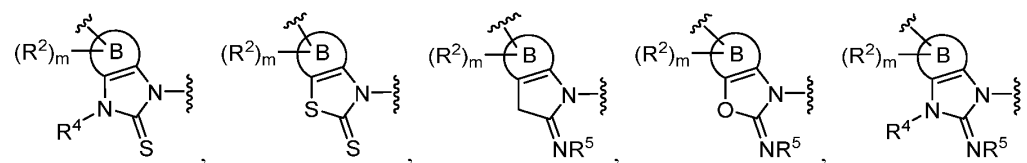


benzo,

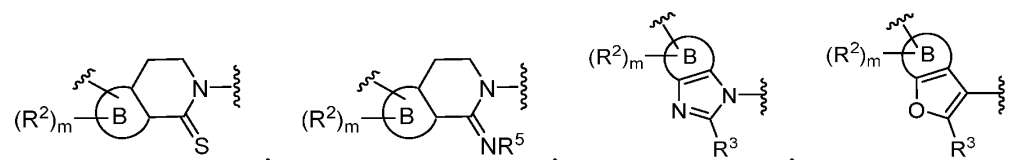
wherein Ring B is other than benzo,

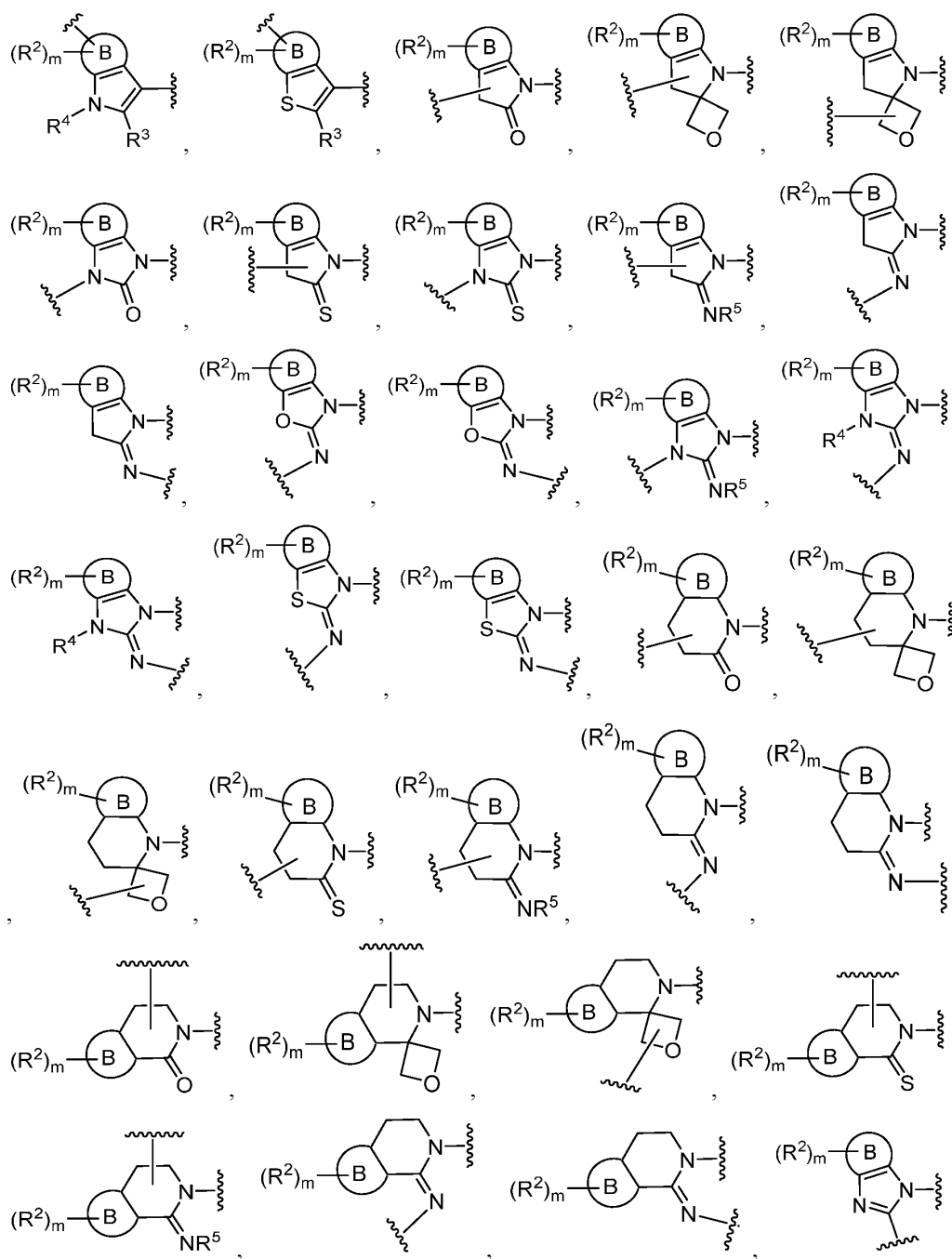


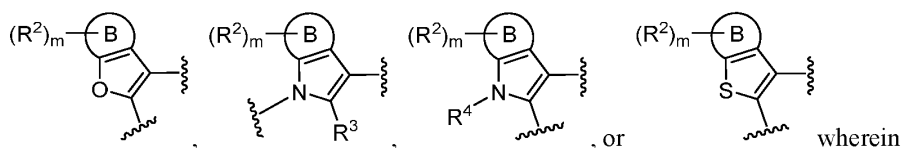
wherein Ring B is other than benzo,



wherein Ring B is other than benzo,







Ring B is a fused ring selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;

R^3 is selected from hydrogen, halogen, $-OR$, $-N(R)_2$, or $-SR$;

each R^4 is independently hydrogen, R^6 , halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

R^5 is hydrogen, C_{1-4} aliphatic, or $-CN$;

each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

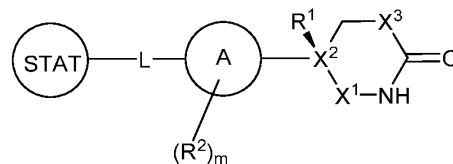
m is 0, 1, 2, 3 or 4; and

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

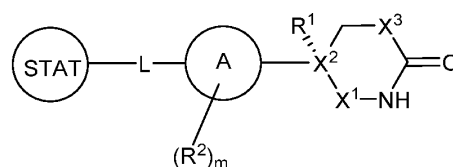
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

[0063] Where a point of attachment of $-(R^2)_m$ is depicted on Ring B, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of $-(R^2)_m$ may be on Ring A and may also be at any available carbon or nitrogen atom on Ring A including the ring to which Ring B is fused. Where $-R^2$ is attached to a nitrogen atom bound to R^4 or R^5 , R^4 or R^5 is absent and $-R^2$ takes the place of the R^4 or R^5 group. Where $-R^2$ is attached to a carbon atom bound to R^3 , R^3 is absent and $-R^2$ takes the place of the R^3 group.

[0064] In some embodiments, the compound of formula I-d above is provided as a compound of formula I-d' or formula I-d'':



I-d'

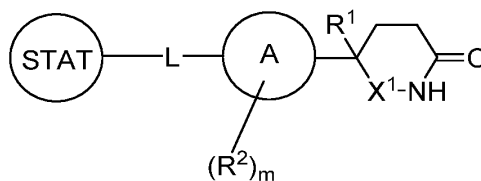


I-d''

or a pharmaceutically acceptable salt thereof, wherein:

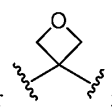
each of STAT, Ring A, L, R¹, R², X¹, X², X³, and m is as defined above.

[0065] In certain embodiments, the present invention provides a compound of formula I, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety thereby forming a compound of formula I-e:



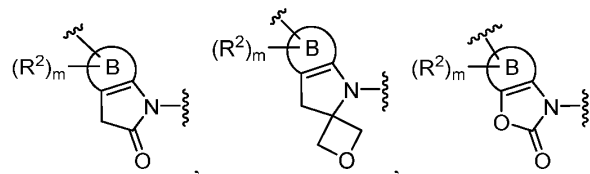
I-e

or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein:

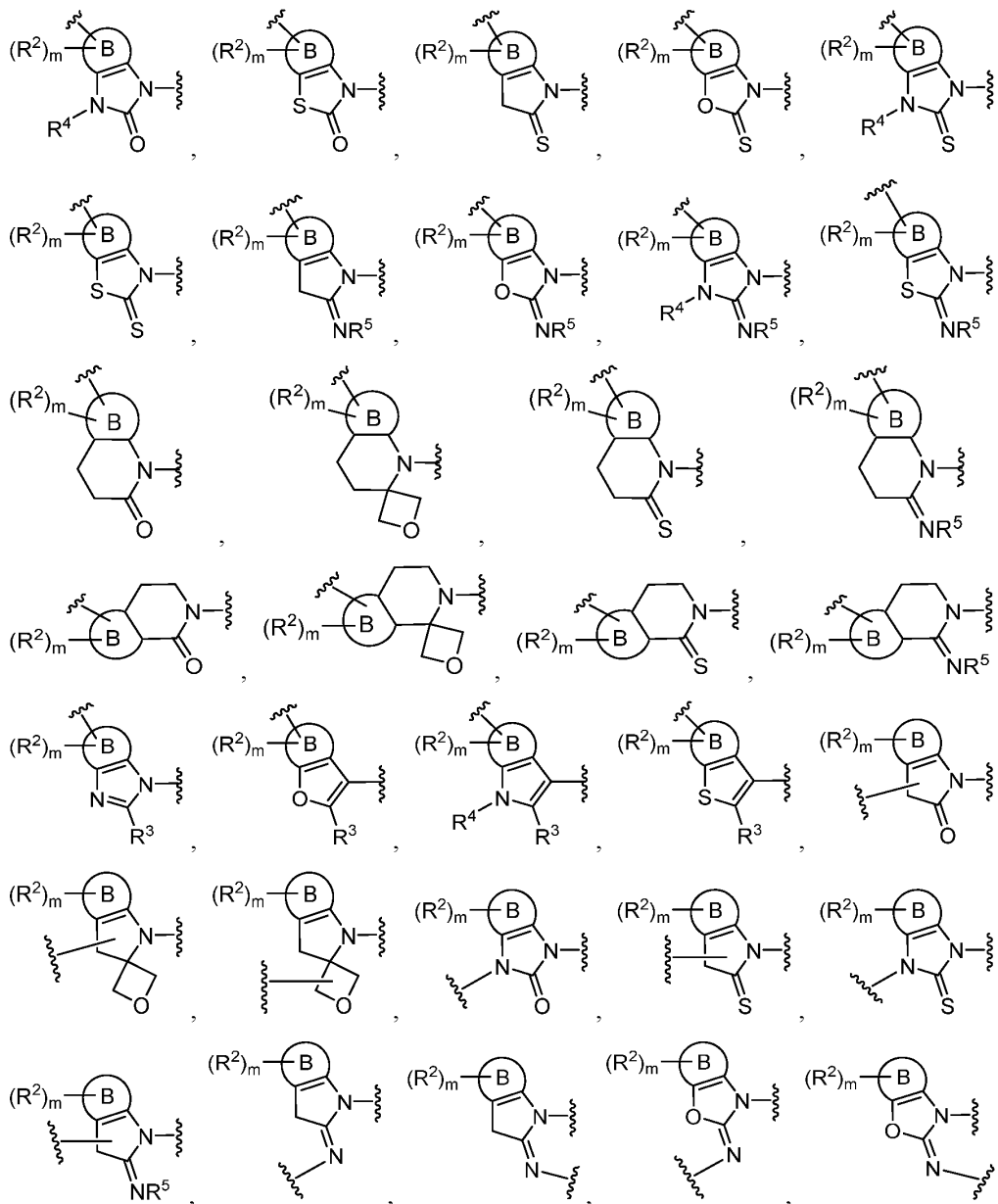
X¹ is a bivalent moiety selected from a covalent bond, -CH₂-, -C(O)-, -C(S)-, or ;

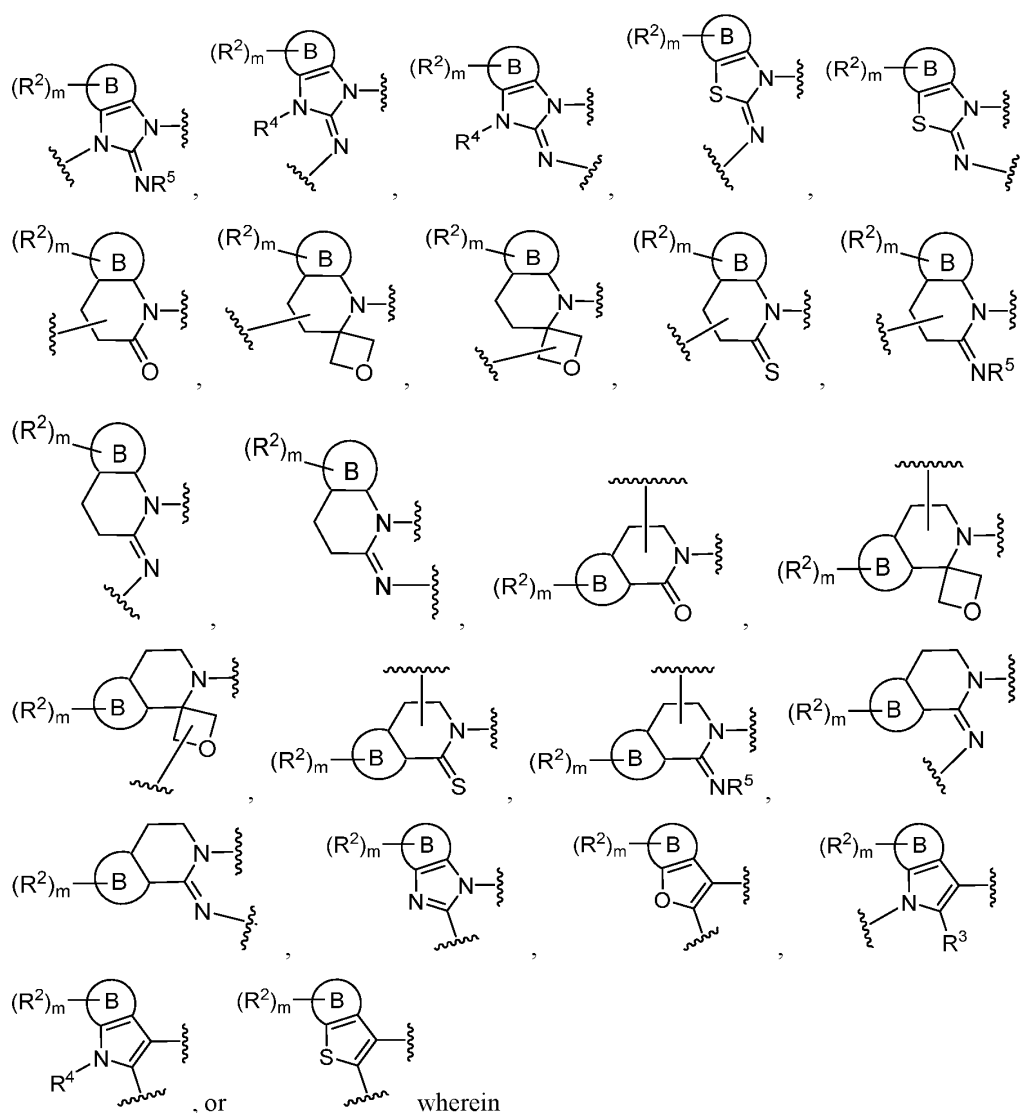
R¹ is hydrogen, deuterium, halogen, -CN, -OR, -SR, -S(O)R, -S(O)₂R, -NR₂, or an optionally substituted C₁₋₄ aliphatic;

each R² is independently hydrogen, R⁶, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, or -N(R)S(O)₂R;



Ring A is a bi- or tricyclic ring selected from





Ring B is a fused ring selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur; R^3 is selected from hydrogen, halogen, $-OR$, $-N(R)_2$, or $-SR$;

each R^4 is independently hydrogen, R^6 , halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $-$

$C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

R^5 is hydrogen, C_{1-4} aliphatic, or $-CN$;

each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

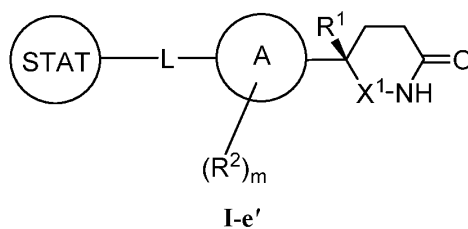
m is 0, 1, 2, 3 or 4; and

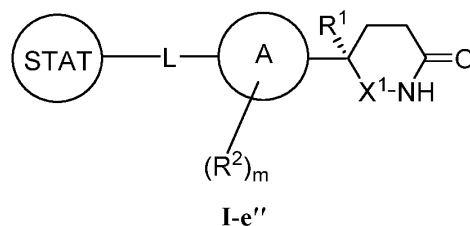
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

[0066] Where a point of attachment of $-(R^2)_m$ is depicted on Ring B, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of $-(R^2)_m$ may be on Ring A and may also be at any available carbon or nitrogen atom on Ring A including the ring to which Ring B is fused. Where $-R^2$ is attached to a nitrogen atom bound to R^4 or R^5 , R^4 or R^5 is absent and $-R^2$ takes the place of the R^4 or R^5 group. Where $-R^2$ is attached to a carbon atom bound to R^3 , R^3 is absent and $-R^2$ takes the place of the R^3 group.

[0067] In some embodiments, the compound of formula I-e above is provided as a compound of formula I-e' or formula I-e'':

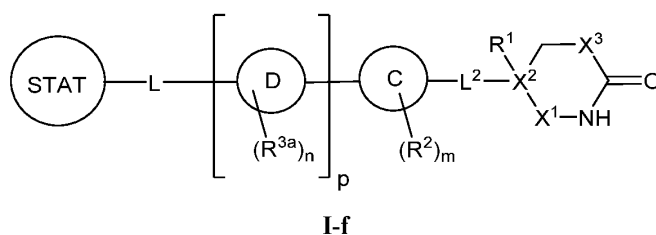




or a pharmaceutically acceptable salt thereof, wherein:

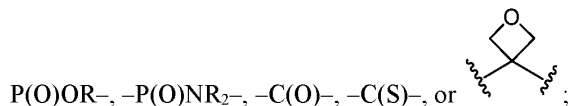
each of STAT, Ring A, L, R¹, R², X¹, and m is as defined above.

[0068] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety thereby forming a compound of formula **I-f**:



or a pharmaceutically acceptable salt thereof, wherein, L and STAT are as defined above and described in embodiments herein, and wherein:

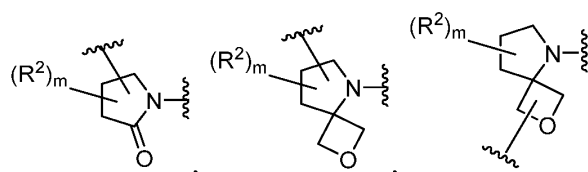
X¹ is a bivalent moiety selected from a covalent bond, -CH₂-, -CHCF₃-, -SO₂-, -S(O)-, -P(O)R-, -



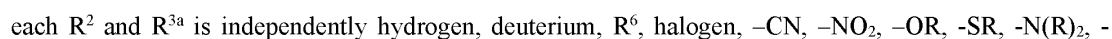
X² is a carbon atom or silicon atom;

X³ is a bivalent moiety selected from -CR₂-, -NR-, -O-, -S-, or -Si(R₂)-

R¹ is hydrogen, deuterium, halogen, -CN, -OR, -SR, -S(O)R, -S(O)₂R, -NR₂, -P(O)(OR)₂, -P(O)(NR₂)OR, -P(O)(NR₂)₂, -Si(OH)₂R, -Si(OH)(R)₂, -Si(R)₃, or an optionally substituted C₁₋₄ aliphatic;



Ring C is a mono- or bicyclic ring selected from



Si(R)₃, -S(O)₂R, -S(O)₂N(R)₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)N(R)₂, -C(O)N(R)OR, -C(R)₂N(R)C(O)R, -C(R)₂N(R)C(O)N(R)₂, -OC(O)R, -OC(O)N(R)₂, -OP(O)R₂, -OP(O)(OR)₂, -OP(O)(OR)(NR₂), -OP(O)(NR₂)₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -NP(O)R₂, -N(R)P(O)(OR)₂, -N(R)P(O)(OR)(NR₂), -N(R)P(O)(NR₂)₂, or -N(R)S(O)₂R;

Ring D is selected from a 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur; each R⁴ is independently hydrogen, R⁶, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, or -N(R)S(O)₂R;

R⁵ is hydrogen, C₁₋₄ aliphatic, or -CN;

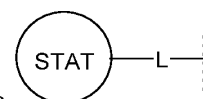
each R⁶ is independently an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L² is a covalent bond or a C₁₋₃ bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, -C(R)₂-, -CH(R)-, -C(F)₂-, -N(R)-, -S(O)₂- or -(C)=CH-;

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

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

p is 0 or 1, wherein when p is 0, the bond connecting Ring C and Ring D is connected to



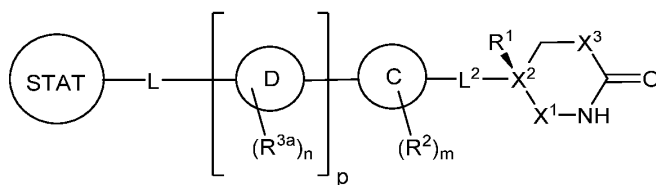
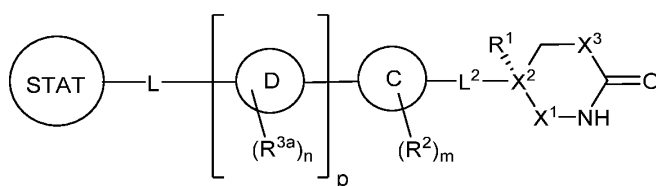
; and

each R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3

heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

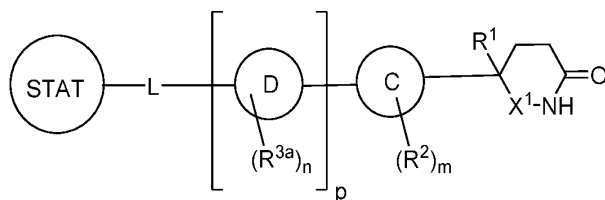
[0069] In some embodiments, a compound of formula **I-f** above is provided as a compound of formula **I-f'** or formula **I-f''**:

**I-f'****I-f''**

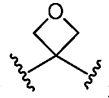
or a pharmaceutically acceptable salt thereof, wherein:

each of STAT, Ring C, Ring D, L, L², R¹, R², R^{3a}, X¹, X², X³, n, m, and p is as defined above.

[0070] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety thereby forming a compound of formula **I-g**:

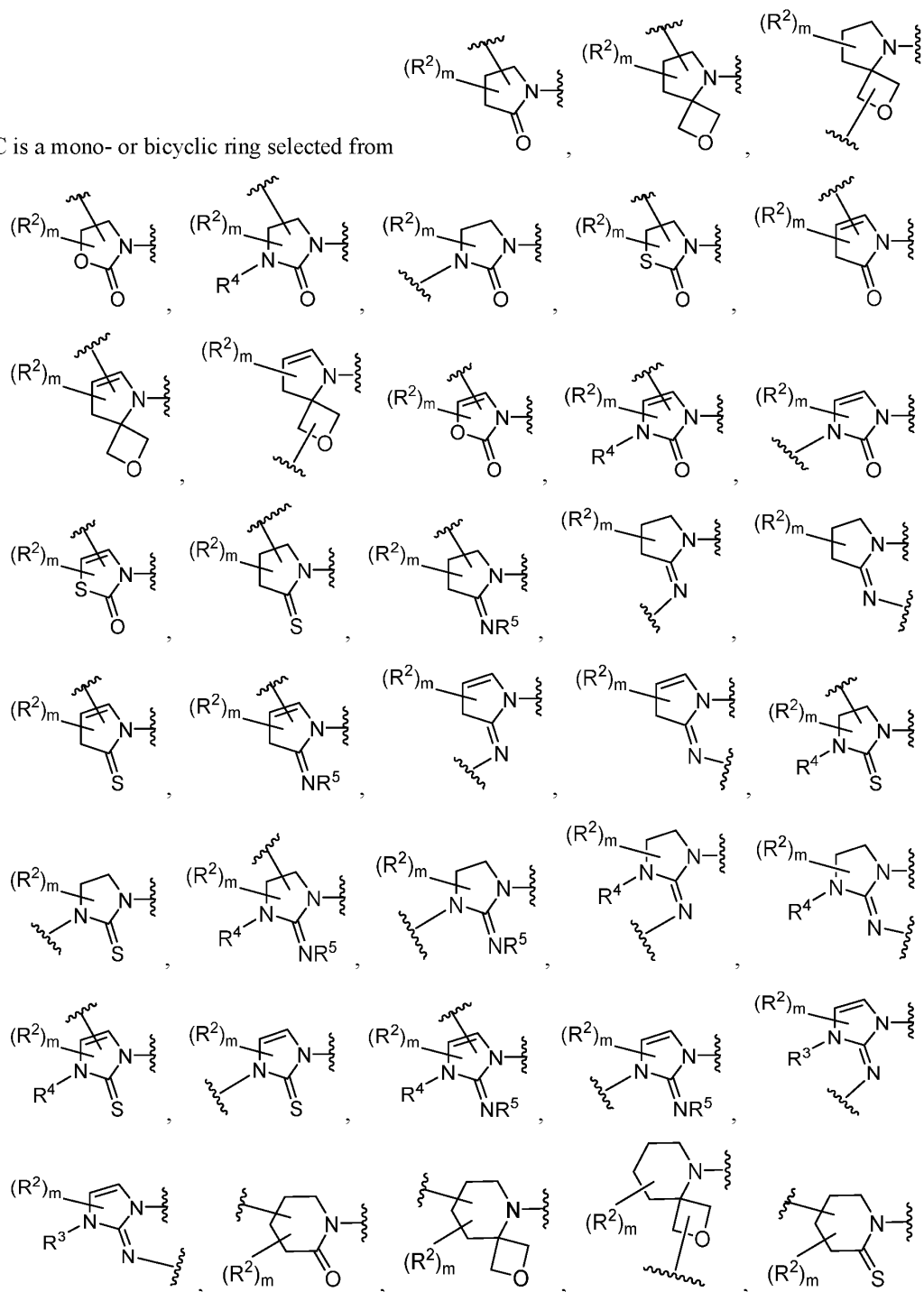
**I-g**

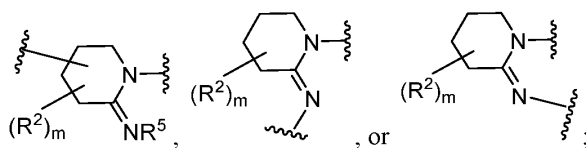
or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein:

X¹ is a bivalent moiety selected from a covalent bond, -CH₂-, -C(O)-, -C(S)-, or ;

R¹ is hydrogen, deuterium, halogen, -CN, -OR, -SR, -S(O)R, -S(O)₂R, -NR₂, or an optionally substituted C₁₋₄ aliphatic;

Ring C is a mono- or bicyclic ring selected from





each R^2 and R^{3a} is independently hydrogen, R^6 , halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}$, $-\text{SR}$, $-\text{NR}_2$, $-\text{S}(\text{O})_2\text{R}$, $-\text{S}(\text{O})_2\text{NR}_2$, $-\text{S}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{OR}$, $-\text{C}(\text{O})\text{NR}_2$, $-\text{C}(\text{O})\text{N}(\text{R})\text{OR}$, $-\text{OC}(\text{O})\text{R}$, $-\text{OC}(\text{O})\text{NR}_2$, $-\text{N}(\text{R})\text{C}(\text{O})\text{OR}$, $-\text{N}(\text{R})\text{C}(\text{O})\text{R}$, $-\text{N}(\text{R})\text{C}(\text{O})\text{NR}_2$, or $-\text{N}(\text{R})\text{S}(\text{O})_2\text{R}$;

Ring D is selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;

each R^4 is independently hydrogen, $-\text{R}^6$, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}$, $-\text{SR}$, $-\text{NR}_2$, $-\text{S}(\text{O})_2\text{R}$, $-\text{S}(\text{O})_2\text{NR}_2$, $-\text{S}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{OR}$, $-\text{C}(\text{O})\text{NR}_2$, $-\text{C}(\text{O})\text{N}(\text{R})\text{OR}$, $-\text{OC}(\text{O})\text{R}$, $-\text{OC}(\text{O})\text{NR}_2$, $-\text{N}(\text{R})\text{C}(\text{O})\text{OR}$, $-\text{N}(\text{R})\text{C}(\text{O})\text{R}$, $-\text{N}(\text{R})\text{C}(\text{O})\text{NR}_2$, or $-\text{N}(\text{R})\text{S}(\text{O})_2\text{R}$;

R^5 is hydrogen, C_{1-4} aliphatic, or $-\text{CN}$;

each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

m is 0, 1, or 2;

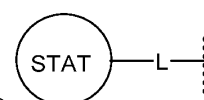
n is 0, 1, 2, 3 or 4;

p is 0 or 1, wherein when p is 0, the bond connecting Ring C and Ring D is connected to

; and

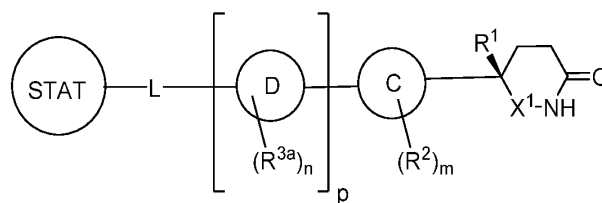
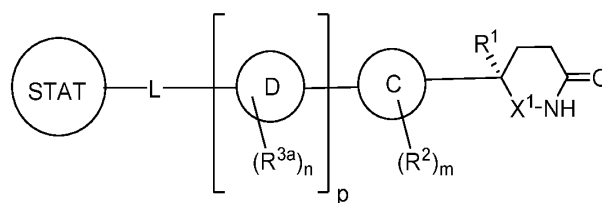
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3



heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

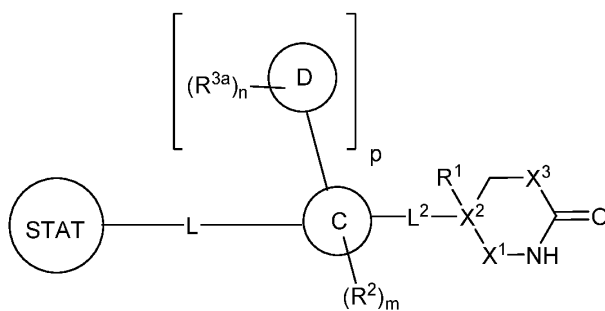
[0071] In some embodiments, a compound of formula **I-g** above is provided as a compound of formula **I-g'** or formula **I-g''**:

**I-g'****I-g''**

or a pharmaceutically acceptable salt thereof, wherein:

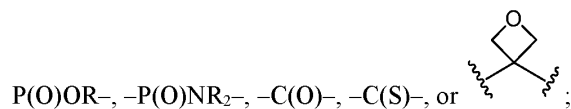
each of STAT, Ring C, Ring D, L, R^1 , R^2 , R^{3a} , X^1 , n, m, and p is as defined above.

[0072] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety thereby forming a compound of formula **I-h**:

**I-h**

or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein:

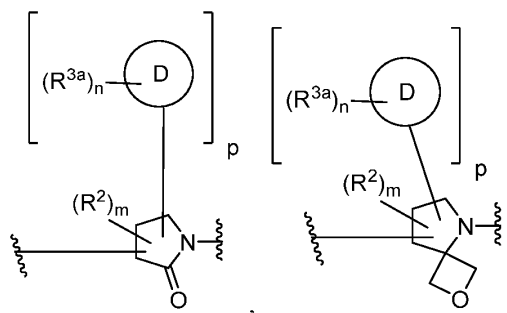
X^1 is a bivalent moiety selected from a covalent bond, $-\text{CH}_2-$, $-\text{CHCF}_3-$, $-\text{SO}_2-$, $-\text{S(O)}-$, $-\text{P(O)R}-$, $-$



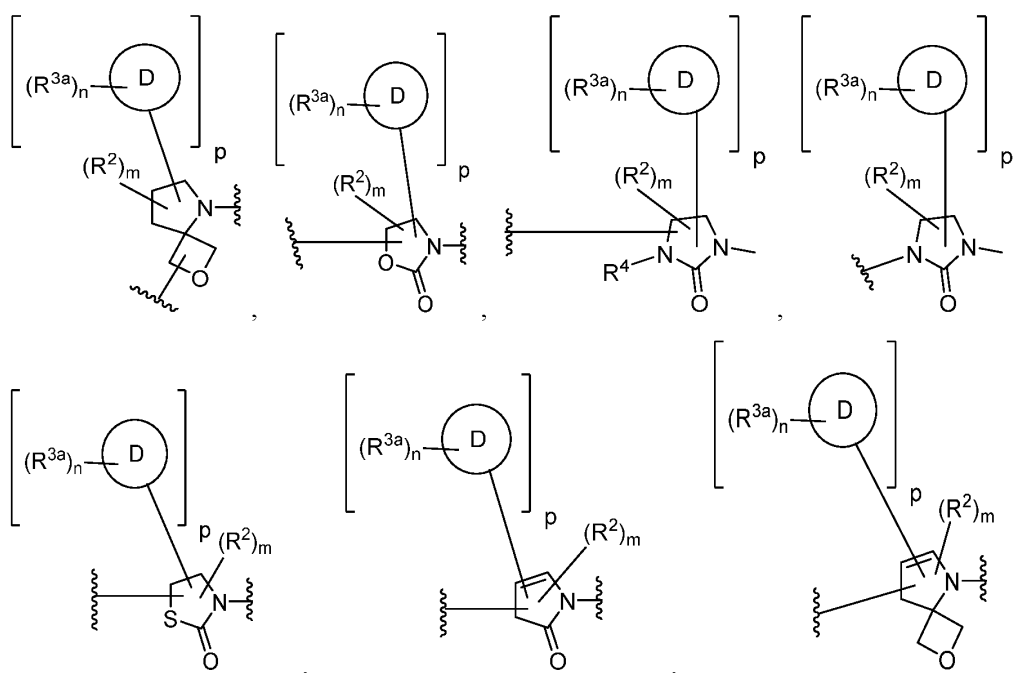
X² is a carbon atom or silicon atom;

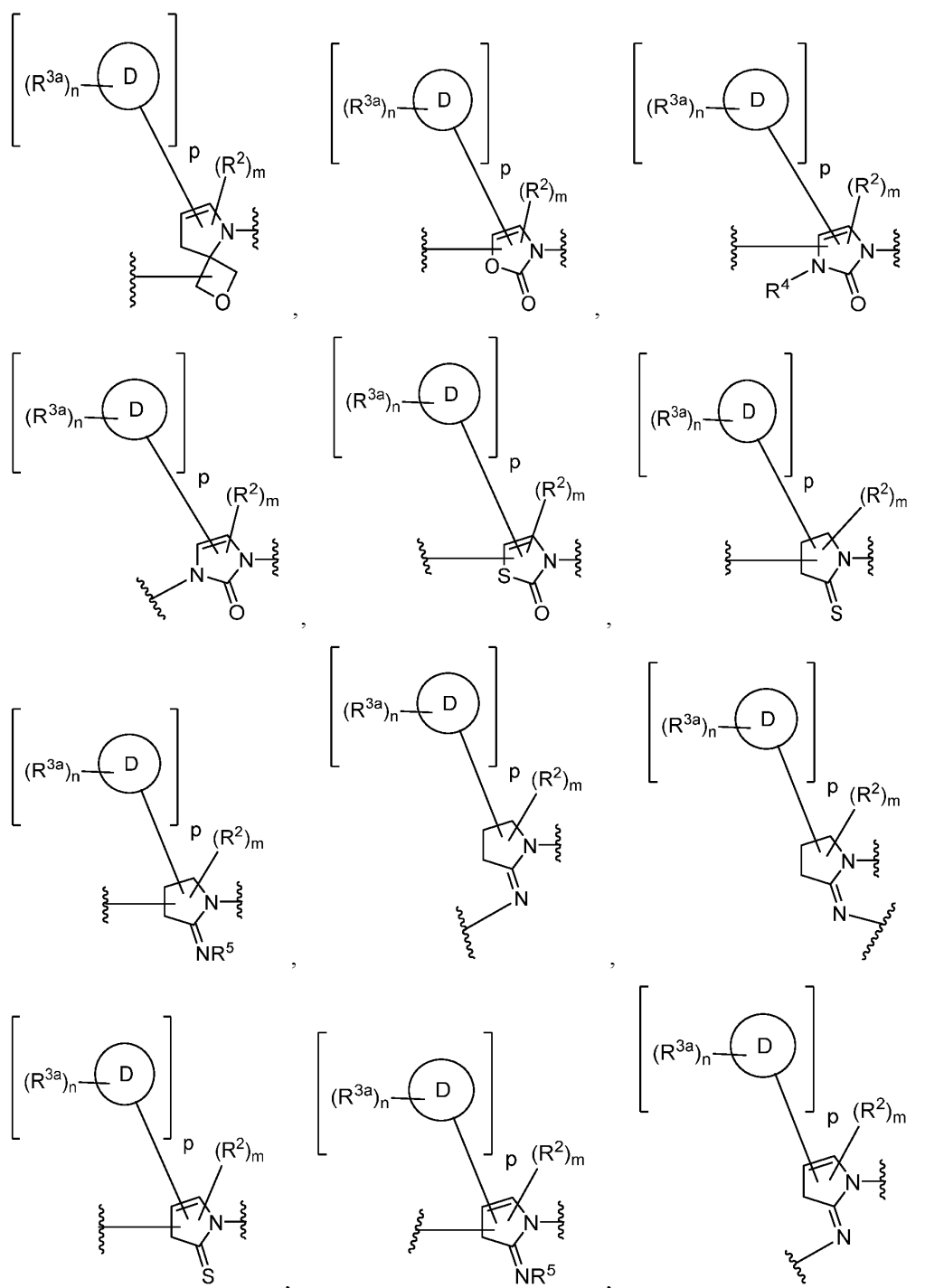
X³ is a bivalent moiety selected from -CR₂-, -NR-, -O-, -S-, or -Si(R₂)-;

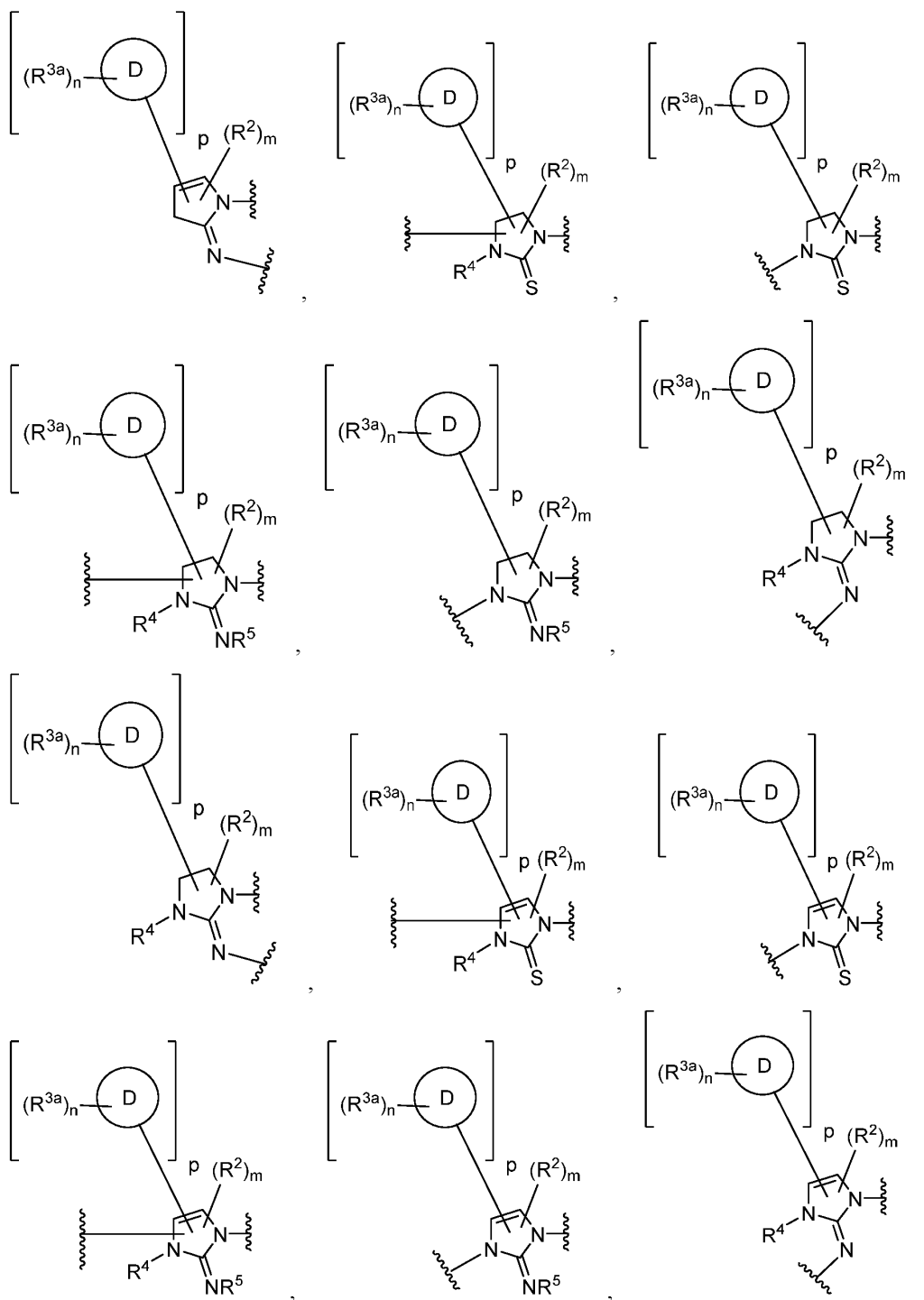
R¹ is hydrogen, deuterium, halogen, -CN, -OR, -SR, -S(O)R, -S(O)₂R, -NR₂, -P(O)(OR)₂, -P(O)(NR₂)OR, -P(O)(NR₂)₂, -Si(OH)₂R, -Si(OH)(R)₂, -Si(R)₃, or an optionally substituted C₁₋₄ aliphatic;

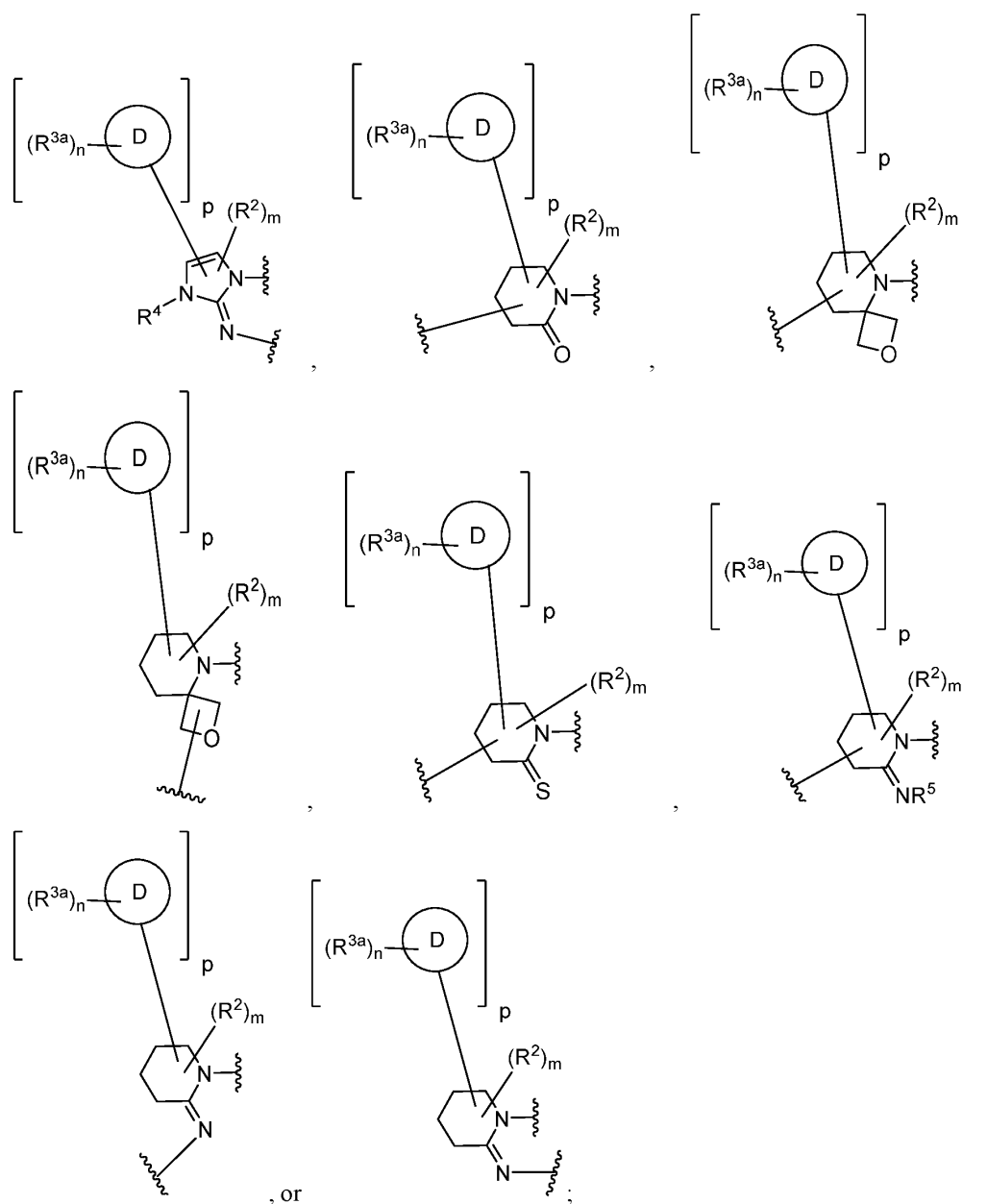


Ring C is a mono- or bicyclic ring selected from









each R^2 and R^{3a} is independently hydrogen, deuterium, R^6 , halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}$, $-\text{SR}$, $-\text{N}(\text{R})_2$, $-\text{Si}(\text{R})_3$, $-\text{S}(\text{O})_2\text{R}$, $-\text{S}(\text{O})_2\text{N}(\text{R})_2$, $-\text{S}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{OR}$, $-\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{C}(\text{O})\text{N}(\text{R})\text{OR}$, $-\text{C}(\text{R})_2\text{N}(\text{R})\text{C}(\text{O})\text{R}$, $-\text{C}(\text{R})_2\text{N}(\text{R})\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{OC}(\text{O})\text{R}$, $-\text{OC}(\text{O})\text{N}(\text{R})_2$, $-\text{OP}(\text{O})\text{R}_2$, $-\text{OP}(\text{O})(\text{OR})_2$, $-\text{OP}(\text{O})(\text{OR})(\text{NR}_2)$, $-\text{OP}(\text{O})(\text{NR}_2)_2$, $-\text{N}(\text{R})\text{C}(\text{O})\text{OR}$, $-\text{N}(\text{R})\text{C}(\text{O})\text{R}$, $-\text{N}(\text{R})\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{S}(\text{O})_2\text{R}$, $-\text{NP}(\text{O})\text{R}_2$, $-\text{N}(\text{R})\text{P}(\text{O})(\text{OR})_2$, $-\text{N}(\text{R})\text{P}(\text{O})(\text{OR})(\text{NR}_2)$, $-\text{N}(\text{R})\text{P}(\text{O})(\text{NR}_2)_2$, or $-\text{N}(\text{R})\text{S}(\text{O})_2\text{R}$;

Ring D is selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur; each R^4 is independently hydrogen, $-R^6$, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

R^5 is hydrogen, C_{1-4} aliphatic, or $-CN$;

each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L^2 is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with $-O-$, $-C(O)-$, $-C(S)-$, $-C(R)_2-$, $-CH(R)-$, $-C(F)_2-$, $-N(R)-$, $-S(O)_2-$ or $-(C)=CH-$;

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

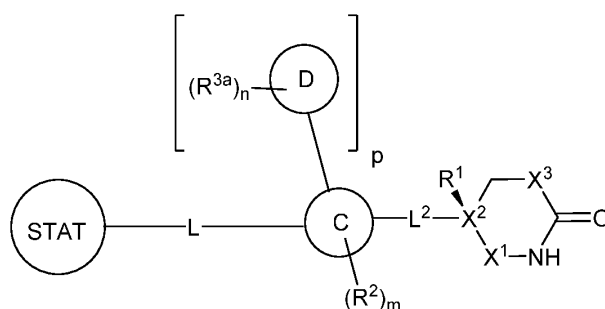
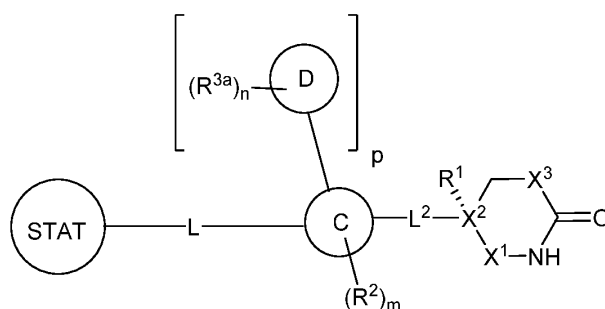
n is 0, 1, 2, 3 or 4;

p is 0 or 1; and

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

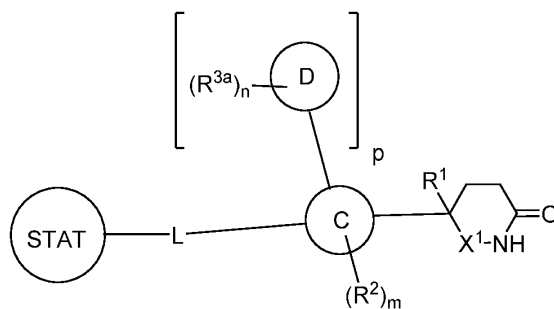
[0073] In some embodiments, a compound of formula **I-h** above is provided as a compound of formula **I-h'** or formula **I-h''**:

**I-h'****I-h''**

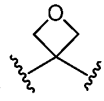
or a pharmaceutically acceptable salt thereof, wherein:

each of STAT, Ring C, Ring D, L, L², R¹, R², R^{3a}, X¹, X², X³, m, n, and p is as defined above.

[0074] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety thereby forming a compound of formula **I-i**:

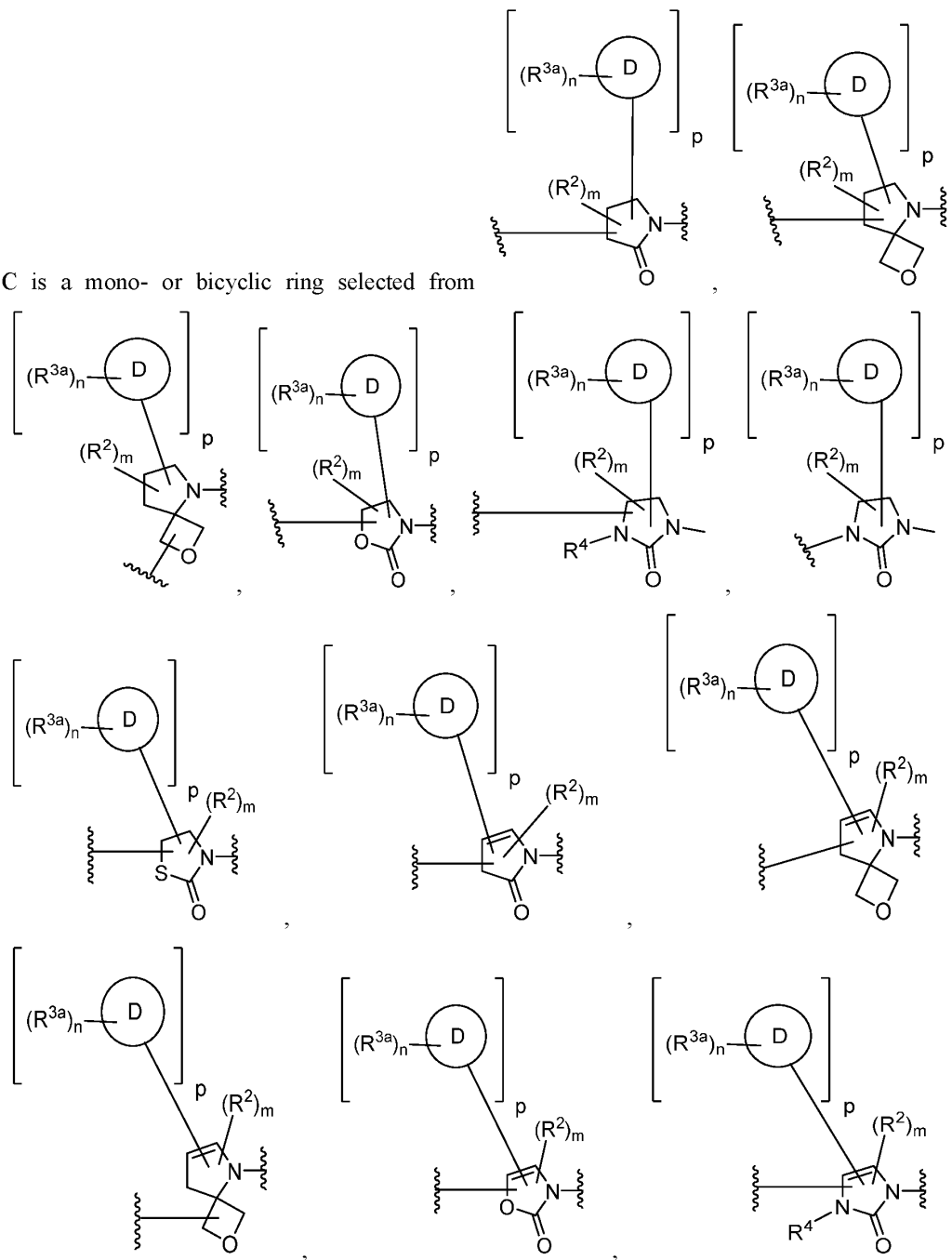
**I-i**

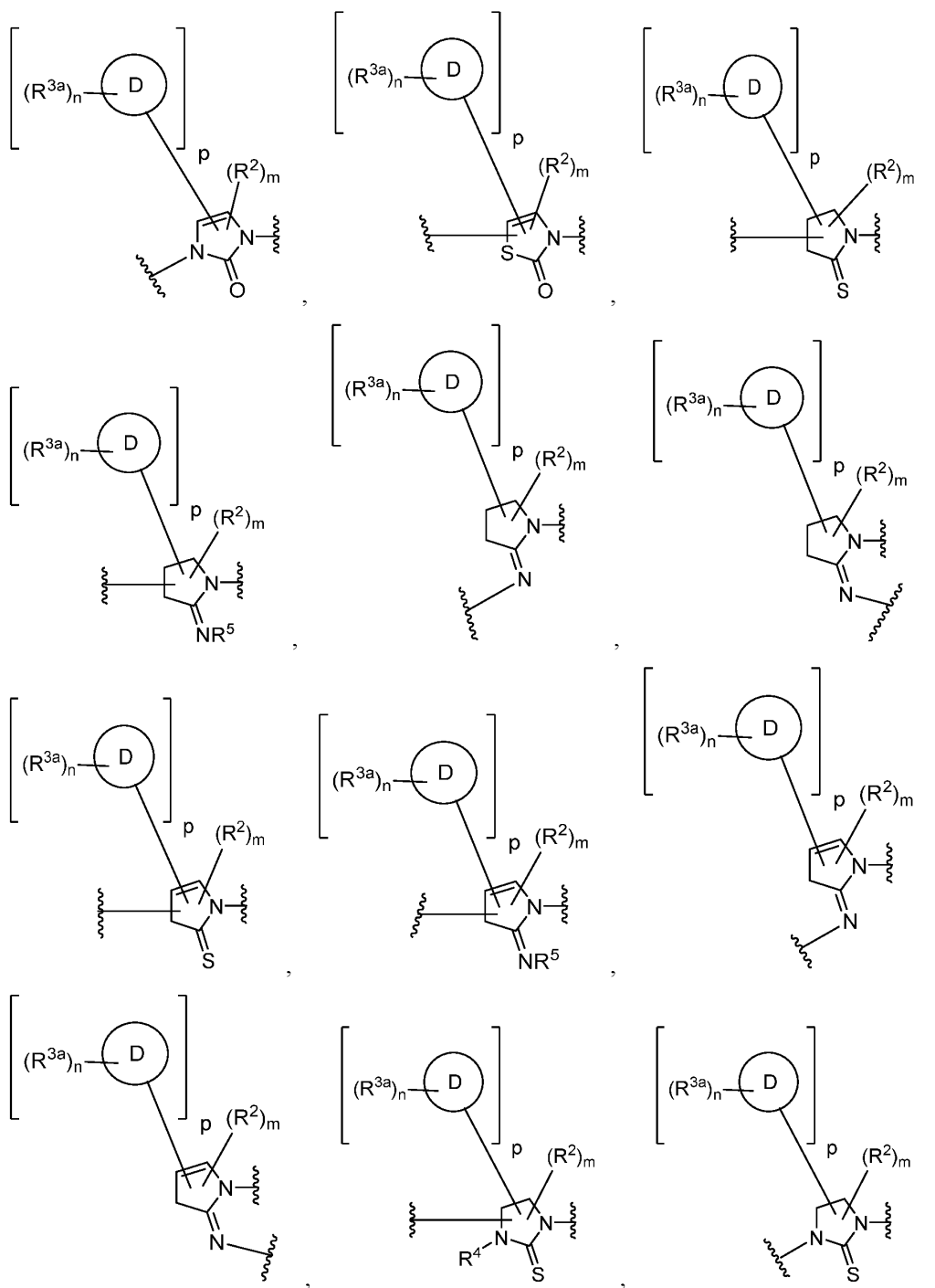
or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein:

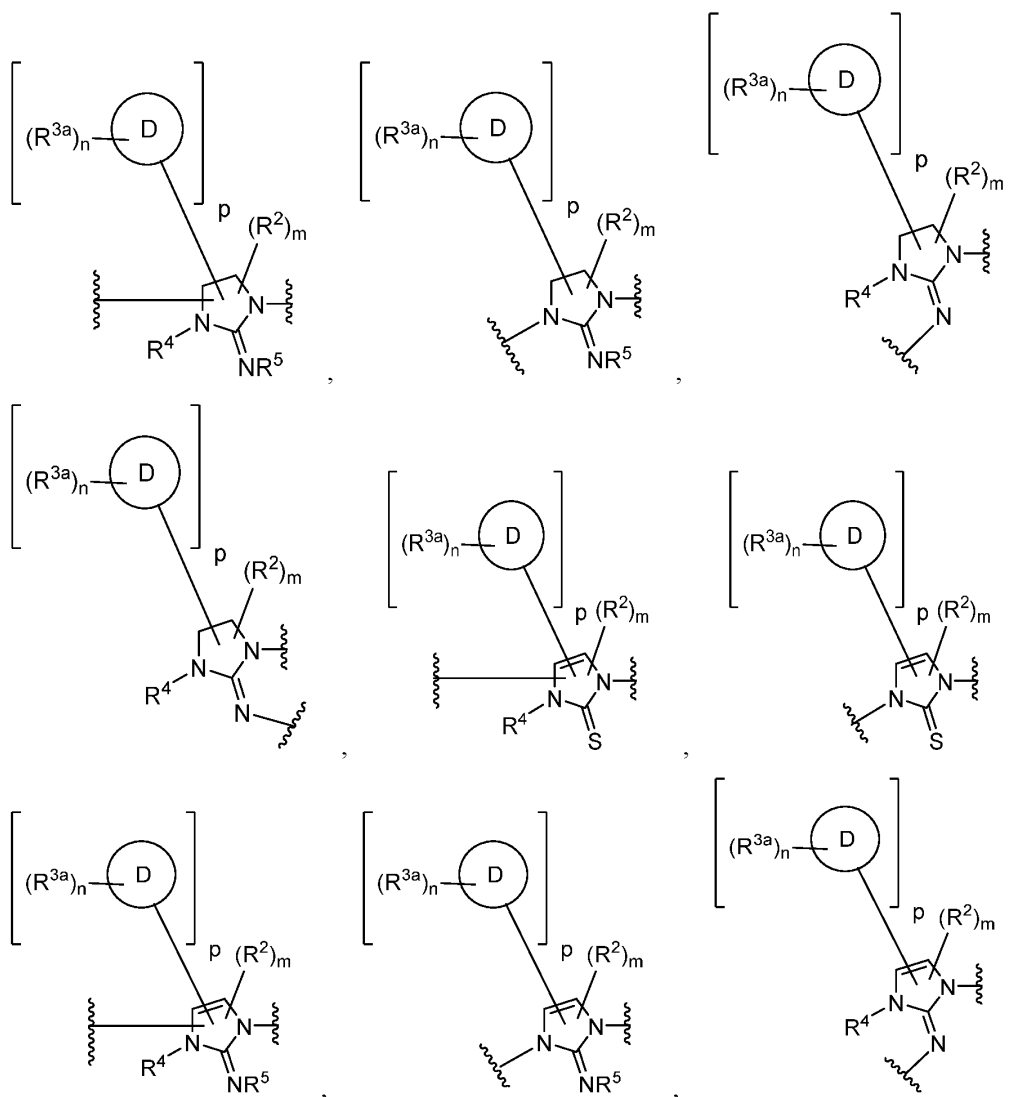
X¹ is a bivalent moiety selected from a covalent bond, -CH₂-, -C(O)-, -C(S)-, or  ;

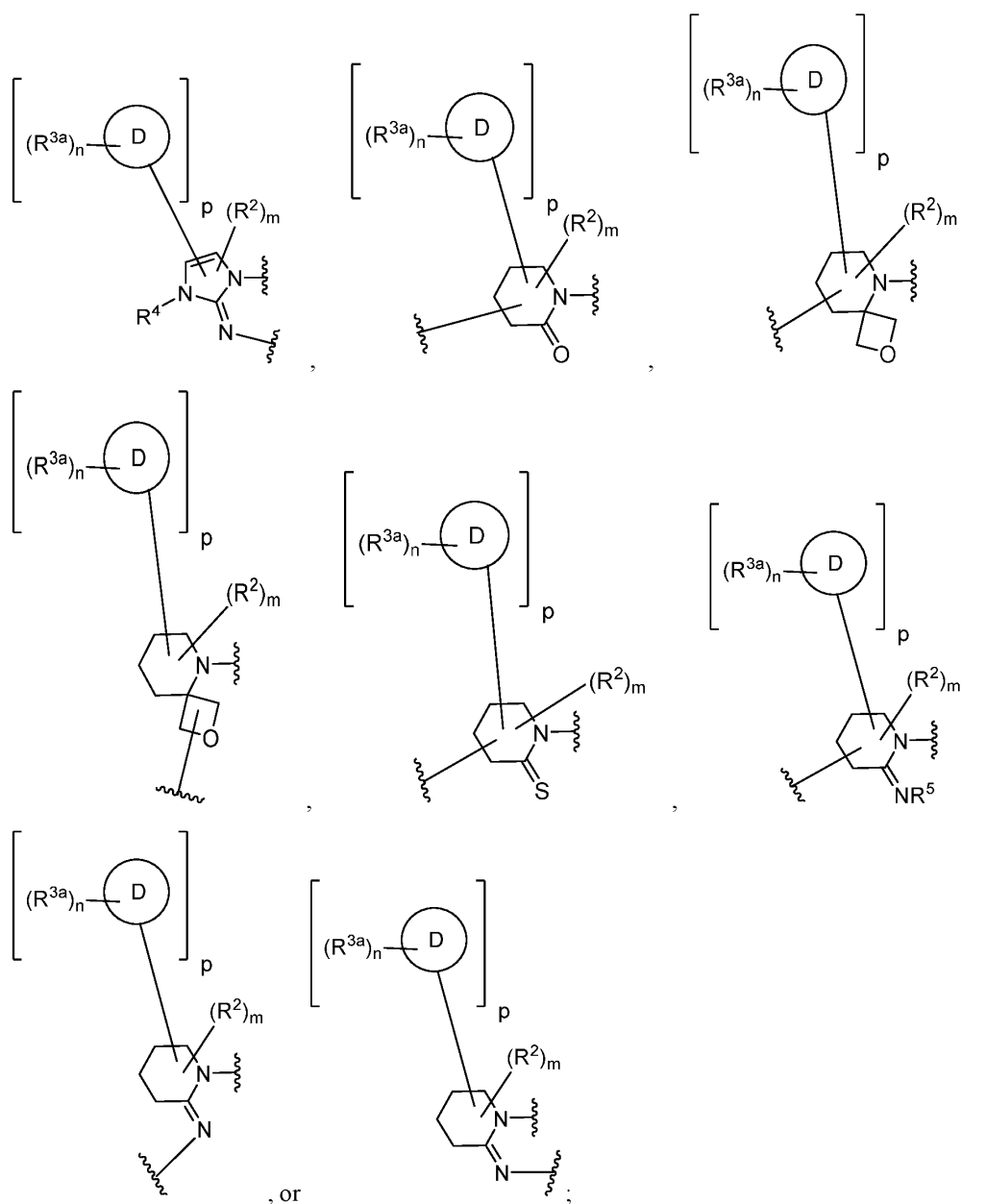
R^1 is hydrogen, deuterium, halogen, $-\text{CN}$, $-\text{OR}$, $-\text{SR}$, $-\text{S(O)R}$, $-\text{S(O)}_2\text{R}$, $-\text{NR}_2$, or an optionally substituted C_{1-4} aliphatic;

Ring C is a mono- or bicyclic ring selected from









each R^2 , R^{3a} , and R^4 is independently hydrogen, R^6 , halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}$, $-\text{SR}$, $-\text{NR}_2$, $-\text{S(O)}_2\text{R}$, $-\text{S(O)}_2\text{NR}_2$, $-\text{S(O)R}$, $-\text{C(O)R}$, $-\text{C(O)OR}$, $-\text{C(O)NR}_2$, $-\text{C(O)N(R)OR}$, $-\text{OC(O)R}$, $-\text{OC(O)NR}_2$, $-\text{N(R)C(O)OR}$, $-\text{N(R)C(O)R}$, $-\text{N(R)C(O)NR}_2$, or $-\text{N(R)S(O)}_2\text{R}$;

Ring D is selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms

independently selected from nitrogen, oxygen, and sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur; R^5 is hydrogen, C_{1-4} aliphatic, or $-CN$;

each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

m is 0, 1, or 2;

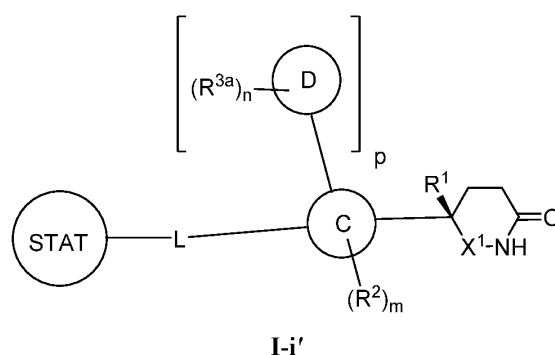
n is 0, 1, 2, 3, or 4;

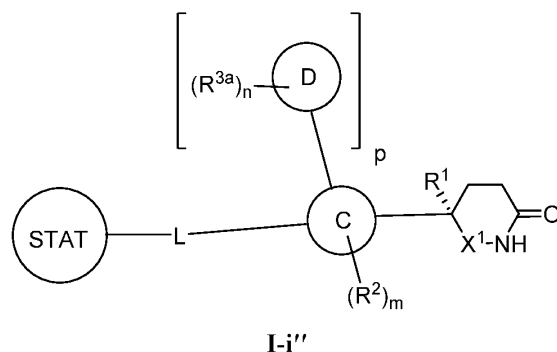
p is 0 or 1; and

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

[0075] In some embodiments, a compound of formula **I-i** above is provided as a compound of formula **I-i'** or formula **I-i''**:

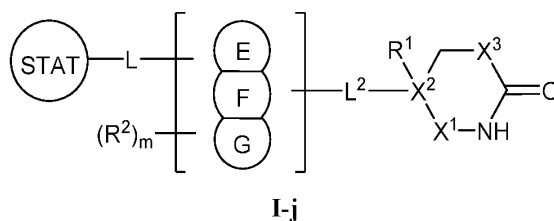




or a pharmaceutically acceptable salt thereof, wherein:

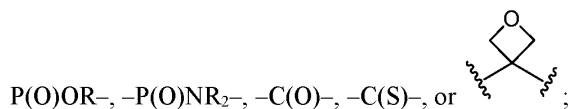
each of STAT, Ring C, Ring D, L, R¹, R², R^{3a}, X¹, m, n, and p is as defined above.

[0076] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety thereby forming a compound of formula **I-j**:



or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein:

X¹ is a bivalent moiety selected from a covalent bond, -CH₂-, -CHCF₃-, -SO₂-, -S(O)-, -P(O)R-, -



X² is a carbon atom or silicon atom;

X³ is a bivalent moiety selected from -CR₂-, -NR-, -O-, -S-, or -Si(R₂)-;

R¹ is hydrogen, deuterium, halogen, -CN, -OR, -SR, -S(O)R, -S(O)₂R, -N(R)₂, -P(O)(OR)₂, -P(O)(NR₂)OR, -P(O)(NR₂)₂, -Si(OH)₂R, -Si(OH)(R)₂, -Si(R)₃, or an optionally substituted C₁₋₄ aliphatic;

each R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7

membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

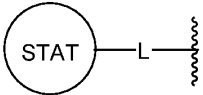
each R^2 is independently hydrogen, deuterium, R^6 , halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-N(R)_2$, $-Si(R)_3$, $-S(O)_2R$, $-S(O)_2N(R)_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $-C(O)N(R)_2$, $-C(O)N(R)OR$, $-C(R)_2N(R)C(O)R$, $-C(R)_2N(R)C(O)N(R)_2$, $-OC(O)R$, $-OC(O)N(R)_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)(NR_2)$, $-OP(O)(NR_2)_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)N(R)_2$, $-N(R)S(O)_2R$, $-NP(O)R_2$, $-N(R)P(O)(OR)_2$, $-N(R)P(O)(OR)(NR_2)$, $-N(R)P(O)(NR_2)_2$, or $-N(R)S(O)_2R$;

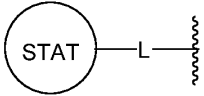
each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each of Ring E, Ring F, and Ring G is independently a fused ring selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur, wherein each of Ring E, Ring F, and Ring G is independently and optionally further substituted with 1-2 oxo groups;

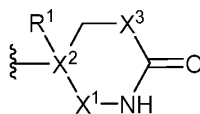
L^2 is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with $-O-$, $-C(O)-$, $-C(S)-$, $-C(R)_2-$, $-CH(R)-$, $-C(F)_2-$, $-N(R)-$, $-S(O)_2-$ or $-(C)=CH-$; and

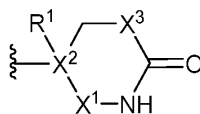
m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16.

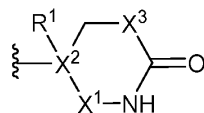
[0077] Where a point of attachment of  is depicted on Ring E, Ring F, or Ring G, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of

 may be on any available carbon or nitrogen atom on Ring E, Ring F, or Ring G, including the ring to which Ring E or Ring G are fused to Ring F.

[0078] Where a point of attachment of $-(R^2)_m$ is depicted on Ring E, Ring F, or Ring G, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of $-(R^2)_m$ may be at any available carbon or nitrogen atom on Ring E, Ring F, or Ring G including the carbon atom to which Ring E or Ring G are fused to Ring F.

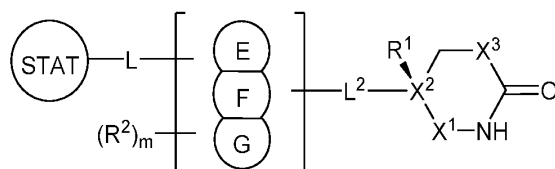


[0079] Where a point of attachment of  is depicted on Ring E, Ring F, or Ring G, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of

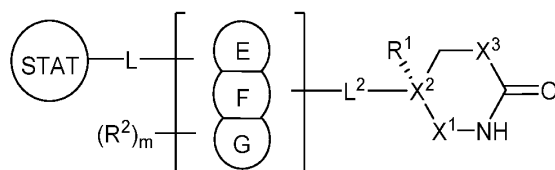


may be on any available carbon or nitrogen atom on Ring E, Ring F, or Ring G, including the carbon atom to which Ring E or Ring G are fused to Ring F.

[0080] In some embodiments, a compound of formula **I-j** above is provided as a compound of formula **I-j'** or formula **I-j''**:



I-j'

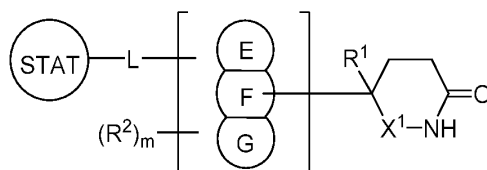


I-j''

or a pharmaceutically acceptable salt thereof, wherein:

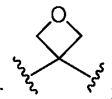
each of STAT, Ring E, Ring F, Ring G, L, L², R¹, R², X¹, X², X³, and m is as defined above.

[0081] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety thereby forming a compound of formula **I-k**:



I-k

or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein:

X^1 is a bivalent moiety selected from a covalent bond, $-\text{CH}_2-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{S})-$, or  ;

R^1 is hydrogen, deuterium, halogen, $-\text{CN}$, $-\text{OR}$, $-\text{SR}$, $-\text{S}(\text{O})\text{R}$, $-\text{S}(\text{O})_2\text{R}$, $-\text{N}(\text{R})_2$, $-\text{Si}(\text{R})_3$, or an optionally substituted C_{1-4} aliphatic;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

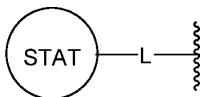
two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

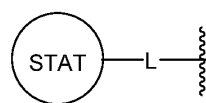
each R^2 is independently hydrogen, deuterium, R^6 , halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}$, $-\text{SR}$, $-\text{N}(\text{R})_2$, $-\text{Si}(\text{R})_3$, $-\text{S}(\text{O})_2\text{R}$, $-\text{S}(\text{O})_2\text{N}(\text{R})_2$, $-\text{S}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{OR}$, $-\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{C}(\text{O})\text{N}(\text{R})\text{OR}$, $-\text{C}(\text{R})_2\text{N}(\text{R})\text{C}(\text{O})\text{R}$, $-\text{C}(\text{R})_2\text{N}(\text{R})\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{OC}(\text{O})\text{R}$, $-\text{OC}(\text{O})\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{C}(\text{O})\text{OR}$, $-\text{N}(\text{R})\text{C}(\text{O})\text{R}$, $-\text{N}(\text{R})\text{C}(\text{O})\text{N}(\text{R})_2$, or $-\text{N}(\text{R})\text{S}(\text{O})_2\text{R}$;

each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each of Ring E, Ring F, and Ring G is independently a fused ring selected from 6-membered aryl containing 0-3 nitrogens, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur, , wherein each of Ring E, Ring F, and Ring G is independently and optionally further substituted with 1-2 oxo groups; and

m is 0, 1, 2, 3, or 4.

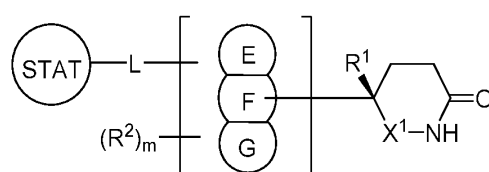
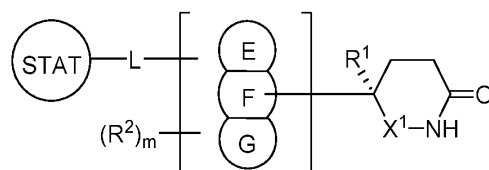
[0082] Where a point of attachment of  is depicted on Ring E, Ring F, or Ring G, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of



may be on any available carbon or nitrogen atom on Ring E, Ring F, or Ring G, including the ring to which Ring E or Ring G are fused to Ring F.

[0083] Where a point of attachment of $-(R^2)_m$ is depicted on Ring E, Ring F, or Ring G, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of $-(R^2)_m$ may be at any available carbon or nitrogen atom on Ring E, Ring F, or Ring G including the carbon atom to which Ring E or Ring G are fused to Ring F.

[0084] In some embodiments, a compound of formula **I-k** above is provided as a compound of formula **I-k'** or formula **I-k''**:

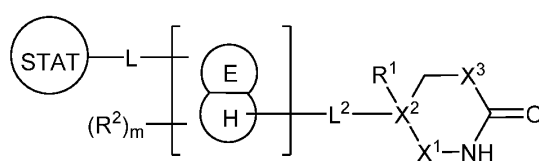
 $I-k'$ 

I-k''

or a pharmaceutically acceptable salt thereof, wherein:

each of STAT, L, Ring E, Ring F, Ring G, L, R^1 , R^2 , X^1 , and m is as defined above.

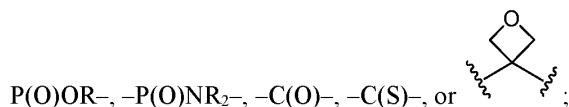
[0085] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is an E3 ubiquitin ligase (cereblon) binding moiety thereby forming a compound of formula **I-I**:



I-1

or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein:

X¹ is a bivalent moiety selected from a covalent bond, -CH₂-, -CHCF₃-, -SO₂-, -S(O)-, -P(O)R-, -



X^2 is a carbon atom or silicon atom;

X^3 is a bivalent moiety selected from $\text{-CR}_2\text{-}$, -NR- , -O- , -S- , or $\text{-Si(R}_2\text{)-}$;

R^1 is hydrogen, deuterium, halogen, -CN , -OR , -SR , -S(O)R , $\text{-S(O)}_2\text{R}$, -N(R)_2 , -P(O)(OR)_2 , $\text{-P(O)(NR}_2\text{)OR}$, $\text{-P(O)(NR}_2\text{)}_2$, $\text{-Si(OH)}_2\text{R}$, -Si(OH)(R)_2 , -Si(R)_3 , or an optionally substituted C_{1-4} aliphatic;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

each R^2 is independently hydrogen, deuterium, R^6 , halogen, -CN , -NO_2 , -OR , -SR , -N(R)_2 , -Si(R)_3 , $\text{-S(O)}_2\text{R}$, $\text{-S(O)}_2\text{N(R)}_2$, -S(O)R , -C(O)R , -C(O)OR , -C(O)N(R)_2 , -C(O)N(R)OR , $\text{-C(R)}_2\text{N(R)C(O)R}$, $\text{-C(R)}_2\text{N(R)C(O)N(R)}_2$, -OC(O)R , -OC(O)N(R)_2 , -OP(O)R_2 , -OP(O)(OR)_2 , $\text{-OP(O)(OR)(NR}_2\text{)}$, $\text{-OP(O)(NR}_2\text{)}_2$, -N(R)C(O)OR , -N(R)C(O)R , -N(R)C(O)N(R)_2 , $\text{-N(R)S(O)}_2\text{R}$, -NP(O)R_2 , -N(R)P(O)(OR)_2 , $\text{-N(R)P(O)(OR)(NR}_2\text{)}$, $\text{-N(R)P(O)(NR}_2\text{)}_2$, or $\text{-N(R)S(O)}_2\text{R}$;

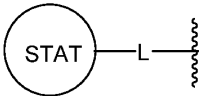
each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

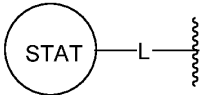
Ring E is a fused ring selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;

Ring H is a fused ring selected from a 7-9 membered saturated or partially unsaturated carbocyclyl or heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, wherein Ring E is optionally further substituted with 1-2 oxo groups;

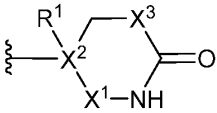
L^2 is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain

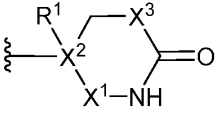
wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, -C(R)₂-, -CH(R)-, -C(F)₂-, -N(R)-, -S(O)₂- or -(C)=CH-;
m is 0, 1, 2, 3, or 4.

[0086] Where a point of attachment of  is depicted on Ring E or Ring H, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of

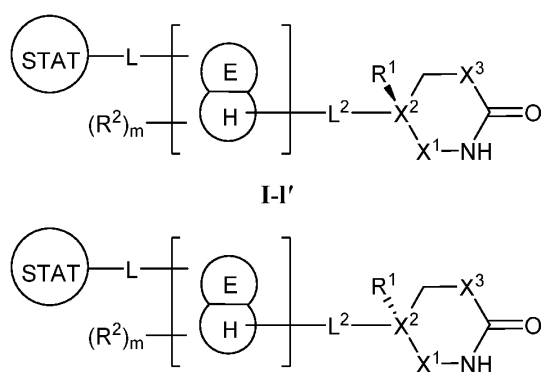
 may be on any available carbon or nitrogen atom on Ring E or Ring H including the carbon atom to which Ring E and Ring H are fused.

[0087] Where a point of attachment of -(R²)_m is depicted on Ring E and Ring H, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of -(R²)_m may be on any available carbon or nitrogen atom on Ring E or Ring H including the carbon atom to which Ring E and Ring H are fused.

[0088] Where a point of attachment of  is depicted on Ring E and Ring H, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of

 may be on any available carbon or nitrogen atom on Ring E or Ring H including the carbon atom to which Ring E and Ring H are fused.

[0089] In some embodiments, a compound of formula I-I above is provided as a compound of formula I-I' or formula I-I'':

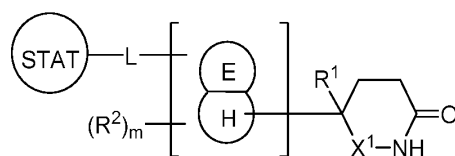


I-I''

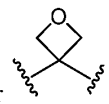
or a pharmaceutically acceptable salt thereof, wherein:

each of STAT, Ring E, Ring H, L, L², R¹, R², X¹, X², X³, and m is as defined above.

[0090] In certain embodiments, the present invention provides a compound of Formula **I**, wherein LBM is an E3 ubiquitin ligase (cereblon) binding moiety thereby forming a compound of formula **I-m**:

**I-m**

or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein:



X¹ is a bivalent moiety selected from a covalent bond, -CH₂-, -C(O)-, -C(S)-, or

R¹ is hydrogen, deuterium, halogen, -CN, -OR, -SR, -S(O)R, -S(O)₂R, -N(R)₂, -Si(R)₃, or an optionally substituted C₁₋₄ aliphatic;

each R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

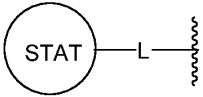
two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

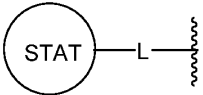
each R² is independently hydrogen, deuterium, R⁶, halogen, -CN, -NO₂, -OR, -SR, -N(R)₂, -Si(R)₃, -S(O)₂R, -S(O)₂N(R)₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)N(R)₂, -C(O)N(R)OR, -C(R)₂N(R)C(O)R, -C(R)₂N(R)C(O)N(R)₂, -OC(O)R, -OC(O)N(R)₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)N(R)₂, or -N(R)S(O)₂R;

each R⁶ is independently an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

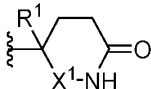
Ring E is a fused ring selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms

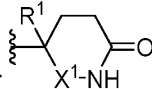
independently selected from nitrogen, oxygen, or sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur; Ring H is a ring selected from a 7-9 membered saturated or partially unsaturated carbocyclyl or heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, wherein Ring E is optionally further substituted with 1-2 oxo groups; and m is 0, 1, 2, 3, or 4.

[0091] Where a point of attachment of  is depicted on Ring E or Ring H, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of

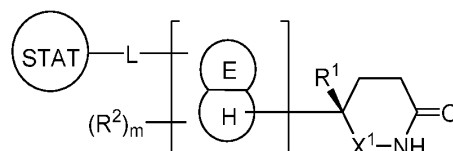
 may be on any available carbon or nitrogen atom on Ring E or Ring H including the carbon atom to which Ring E and Ring H are fused.

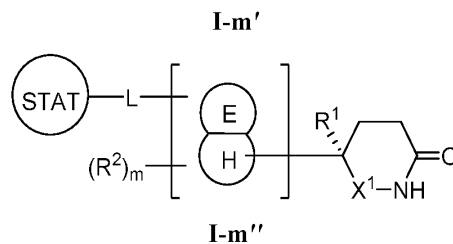
[0092] Where a point of attachment of $-(R^2)_m$ is depicted on Ring E and Ring H, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of $-(R^2)_m$ may be on any available carbon or nitrogen atom on Ring E or Ring H including the carbon atom to which Ring E and Ring H are fused.

[0093] Where a point of attachment of  is depicted on Ring E and Ring H, it is intended,

and one of ordinary skill in the art would appreciate, that the point of attachment of  may be on any available carbon or nitrogen atom on Ring E or Ring H including the carbon atom to which Ring E and Ring H are fused.

[0094] In some embodiments, a compound of formula **I-m** above is provided as a compound of formula **I-m'** or formula **I-m''**:

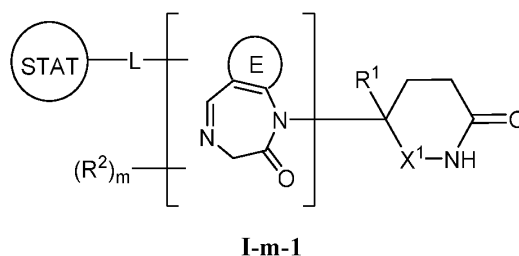




or a pharmaceutically acceptable salt thereof, wherein:

each of STAT, Ring E, Ring H, L, R¹, R², X¹, and m is as defined above.

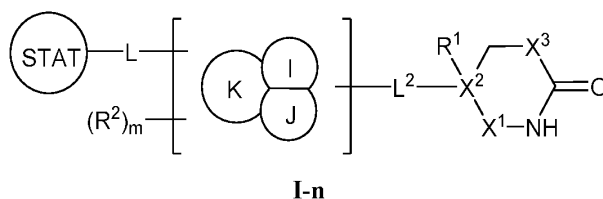
[0095] In some embodiments, a compound of formula **I-m** above is provided as a compound of formula **I-m-1**:



or a pharmaceutically acceptable salt thereof, wherein:

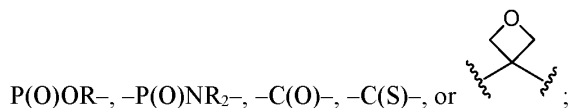
each of STAT, L, Ring E, X¹, R¹, R², and m is as defined above.

[0096] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is an E3 ubiquitin ligase (cereblon) binding moiety thereby forming a compound of formula **I-n**:



or a pharmaceutically acceptable salt thereof, wherein:

X¹ is a bivalent moiety selected from a covalent bond, -CH₂-, -CHCF₃-, -SO₂-, -S(O)-, -P(O)R-, -



X² is a carbon atom or silicon atom;

X³ is a bivalent moiety selected from -CR₂-, -NR-, -O-, -S-, or -Si(R₂)-;

R¹ is hydrogen, deuterium, halogen, -CN, -OR, -SR, -S(O)R, -S(O)₂R, -NR₂, -P(O)(OR)₂, -P(O)(NR₂)OR, -P(O)(NR₂)₂, -Si(OH)₂R, -Si(OH)(R)₂, -Si(R)₃, or an optionally substituted C₁₋₄

aliphatic;

each R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

each R² is independently hydrogen, deuterium, R⁶, halogen, -CN, -NO₂, -OR, -SR, -N(R)₂, -Si(R)₃, -S(O)₂R, -S(O)₂N(R)₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)N(R)₂, -C(O)N(R)OR, -C(R)₂N(R)C(O)R, -C(R)₂N(R)C(O)N(R)₂, -OC(O)R, -OC(O)N(R)₂, -OP(O)R₂, -OP(O)(OR)₂, -OP(O)(OR)(NR₂), -OP(O)(NR₂)₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -NP(O)R₂, -N(R)P(O)(OR)₂, -N(R)P(O)(OR)(NR₂), -N(R)P(O)(NR₂)₂, or -N(R)S(O)₂R;

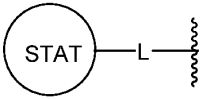
each R⁶ is independently an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

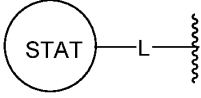
each of Ring I and J is independently a fused ring selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;

Ring K is a fused ring selected from a 6-12 membered saturated or partially unsaturated carbocyclyl or heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, wherein Ring H is optionally further substituted with 1-2 oxo groups;

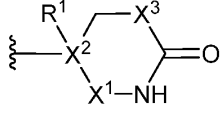
L² is a covalent bond or a C₁₋₃ bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, -C(R)₂-, -CH(R)-, -C(F)₂-, -N(R)-, -S(O)₂- or -(C)=CH-; and

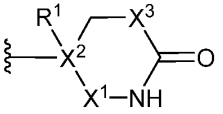
m is 0, 1, 2, 3, or 4.

[0097] Where a point of attachment of  is depicted on Ring I, Ring J, and Ring K, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of

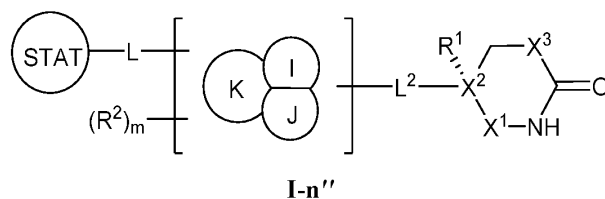
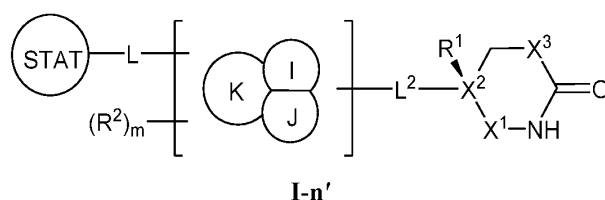
 may be on any available carbon or nitrogen atom on Ring I, Ring J, or Ring K, including the carbon atom to which Ring I, Ring J, and Ring K are fused.

[0098] Where a point of attachment of $-(R^2)_m$ is depicted on Ring I, Ring J, and Ring K, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of $-(R^2)_m$ may be on any available carbon or nitrogen atom on Ring I, Ring J, or Ring K, including the carbon atom to which Ring I, Ring J, and Ring K are fused.

[0099] Where a point of attachment of  is depicted on Ring I, Ring J, and Ring K, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of

 may be on any available carbon or nitrogen atom on Ring I, Ring J, or Ring K, including the carbon atom to which Ring I, Ring J, and Ring K are fused.

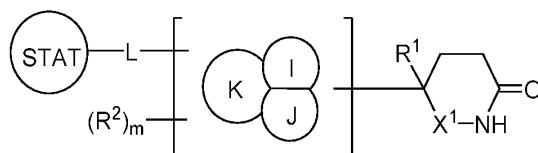
[00100] In some embodiments, a compound of formula **I-n** above is provided as a compound of formula **I-n'** or formula **I-n''**:



or a pharmaceutically acceptable salt thereof, wherein:

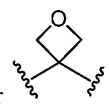
each of STAT, Ring I, Ring J, Ring K, L, L², R¹, R², X¹, X², X³, and m is as defined above.

[00101] In certain embodiments, the present invention provides a compound of formula I, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety thereby forming a compound of formula I-o:



I-o

or a pharmaceutically acceptable salt thereof, wherein:



X¹ is a bivalent moiety selected from a covalent bond, -CH₂-, -C(O)-, -C(S)-, or

R¹ is hydrogen, deuterium, halogen, -CN, -OR, -SR, -S(O)R, -S(O)₂R, -N(R)₂, -Si(R)₃, or an optionally substituted C₁₋₄ aliphatic;

each R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

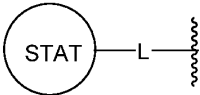
each R² is independently hydrogen, deuterium, R⁶, halogen, -CN, -NO₂, -OR, -SR, -N(R)₂, -Si(R)₃, -S(O)₂R, -S(O)₂N(R)₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)N(R)₂, -C(O)N(R)OR, -C(R)₂N(R)C(O)R, -C(R)₂N(R)C(O)N(R)₂, -OC(O)R, -OC(O)N(R)₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)N(R)₂, or -N(R)S(O)₂R;

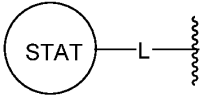
each R⁶ is independently an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each of Ring I and J is independently a fused ring selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected

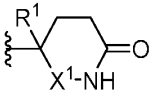
from nitrogen, oxygen or sulfur;

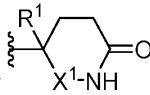
Ring K is a fused ring selected from a 6-12 membered saturated or partially unsaturated carbocyclyl or heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, wherein Ring H is optionally further substituted with 1-2 oxo groups; and m is 0, 1, 2, 3, or 4.

[00102] Where a point of attachment of  is depicted on Ring I, Ring J, and Ring K, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of

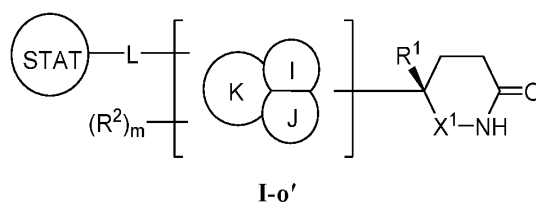
 may be on any available carbon or nitrogen atom on Ring I, Ring J, or Ring K, including the carbon atom to which Ring I, Ring J, and Ring K are fused.

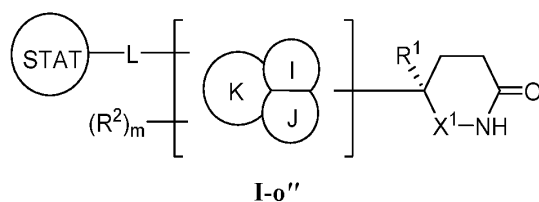
[00103] Where a point of attachment of $-(R^2)_m$ is depicted on Ring I, Ring J, and Ring K, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of $-(R^2)_m$ may be on any available carbon or nitrogen atom on Ring I, Ring J, or Ring K, including the carbon atom to which Ring I, Ring J, and Ring K are fused.

[00104] Where a point of attachment of  is depicted on Ring I, Ring J, and Ring K, it is

intended, and one of ordinary skill in the art would appreciate, that the point of attachment of  may be on any available carbon or nitrogen atom on Ring I, Ring J, or Ring K, including the carbon atom to which Ring I, Ring J, and Ring K are fused.

[00105] In some embodiments, a compound of formula I-o above is provided as a compound of formula I-o' or formula I-o'':

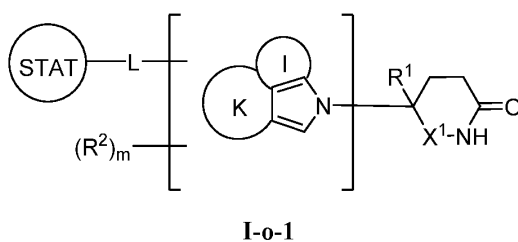




or a pharmaceutically acceptable salt thereof, wherein:

each of STAT, Ring I, Ring J, Ring K, L, R¹, R², X¹, and m is as defined above.

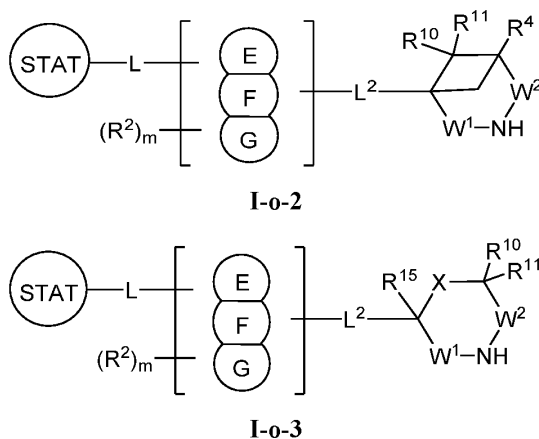
[00106] In some embodiments, a compound of formula **I-o** above is provided as a compound of formula **I-o-1**:



or a pharmaceutically acceptable salt thereof, wherein:

each of STAT, L, Ring I, Ring K, X¹, R¹, R², and m is as defined above.

[00107] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is an E3 ubiquitin ligase (cereblon) binding moiety thereby forming a compound of formula **I-o-2** or **I-o-3**:



or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein:

each R² is independently hydrogen, deuterium, R⁶, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -

SiR₃, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -C(R)₂N(R)C(O)R, -C(R)₂N(R)C(O)N(R)₂, -OC(O)R, -OC(O)N(R)₂, -OP(O)R₂, -OP(O)(OR)₂, -OP(O)(OR)NR₂, -OP(O)(NR₂)₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)S(O)₂R, -NP(O)R₂, -N(R)P(O)(OR)₂, -N(R)P(O)(OR)NR₂, -N(R)P(O)(NR₂)₂, or -N(R)S(O)₂R;

each R⁶ is independently an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each of Ring E, Ring F, and Ring G is independently a fused ring selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur, wherein each of Ring E, Ring F, and Ring G is independently and optionally further substituted with 1-2 oxo groups;

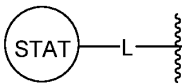
each R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

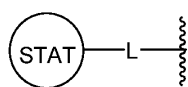
two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

L² is a covalent bond or a C₁₋₃ bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, -C(R)₂-, -CH(R)-, -C(F)₂-, -N(R)-, -S-, -S(O)₂- or -(C)=CH-;

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16; and

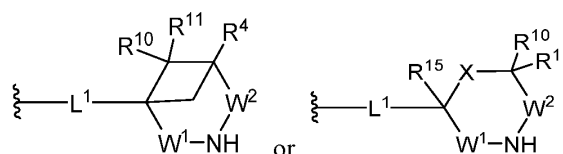
R⁴, R¹⁰, R¹¹, R¹⁵, W¹, W², and X is as defined in WO 2019/099868, the entirety of each of which is herein incorporated by reference.

[00108] Where a point of attachment of  is depicted on Ring E, Ring F, or Ring G, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of

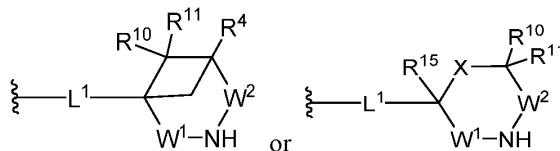


may be on any available carbon or nitrogen atom on Ring E, Ring F, or Ring G, including the ring to which Ring E or Ring G are fused to Ring F.

[00109] Where a point of attachment of $-(R^2)_m$ is depicted on Ring E, Ring F, or Ring G, it is intended, and one of ordinary skill in the art would appreciate, that the point of attachment of $-(R^2)_m$ may be at any available carbon or nitrogen atom on Ring E, Ring F, or Ring G including the carbon atom to which Ring E or Ring G are fused to Ring F.

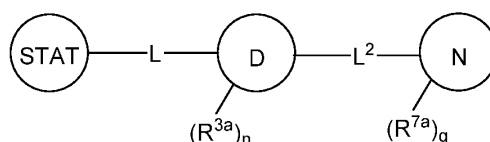


[00110] Where a point of attachment of is depicted on Ring E, Ring F, or Ring G, it is intended, and one of ordinary skill in the art would appreciate,



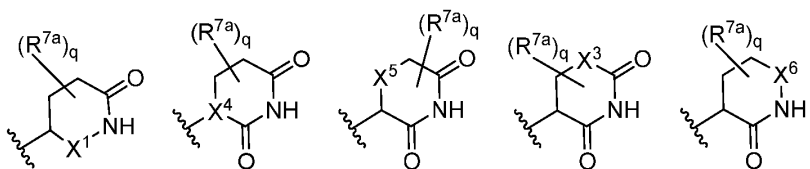
that the point of attachment of may be on any available carbon or nitrogen atom on Ring E, Ring F, or Ring G, including the carbon atom to which Ring E or Ring G are fused to Ring F.

[00111] In certain embodiments, the present invention provides a compound of formula I, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety thereby forming a compound of formula I-o-4:

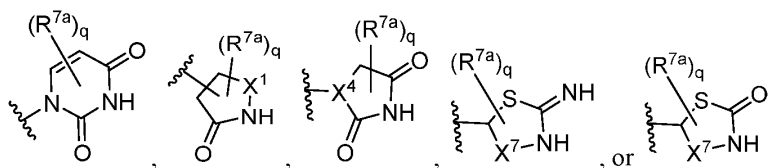


I-o-4

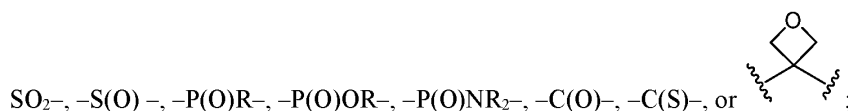
or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein:



Ring N is selected from

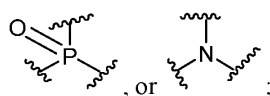


X^1 , X^6 , and X^7 are independently a bivalent moiety selected from a covalent bond, $-\text{CH}_2-$, $-\text{CHCF}_3-$, $-\text{SO}_2-$, $-\text{S(O)}-$, $-\text{P(O)R}-$, $-\text{P(O)OR}-$, $-\text{P(O)NR}_2-$, $-\text{C(O)}-$, $-\text{C(S)}-$, or



X^3 and X^5 are independently a bivalent moiety selected from a covalent bond, $-\text{CR}_2-$, $-\text{NR}-$, $-\text{O}-$, $-\text{S}-$, or $-\text{SiR}_2-$;

X^4 is a trivalent moiety selected from



each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

each R^{3a} is independently hydrogen, deuterium, R^6 , halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}$, $-\text{SR}$, $-\text{NR}_2$, $-\text{SiR}_3$, $-\text{S(O)}_2\text{R}$, $-\text{S(O)}_2\text{NR}_2$, $-\text{S(O)R}$, $-\text{C(O)R}$, $-\text{C(O)OR}$, $-\text{C(O)NR}_2$, $-\text{C(O)N(R)OR}$, $-\text{C(R)}_2\text{N(R)C(O)R}$, $-\text{C(R)}_2\text{N(R)C(O)N(R)}_2$, $-\text{OC(O)R}$, $-\text{OC(O)N(R)}_2$, $-\text{OP(O)R}_2$, $-\text{OP(O)(OR)}_2$, $-\text{OP(O)(OR)NR}_2$, $-\text{OP(O)(NR}_2)_2$, $-\text{N(R)C(O)OR}$, $-\text{N(R)C(O)R}$, $-\text{N(R)C(O)NR}_2$, $-\text{N(R)S(O)}_2\text{R}$, $-\text{NP(O)R}_2$, $-\text{N(R)P(O)(OR)}_2$, $-\text{N(R)P(O)(OR)NR}_2$, $-\text{N(R)P(O)(NR}_2)_2$, or $-\text{N(R)S(O)}_2\text{R}$;

each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^{7a} is independently hydrogen, deuterium, halogen, $-\text{CN}$, $-\text{OR}$, $-\text{SR}$, $-\text{S(O)R}$, $-\text{S(O)}_2\text{R}$, $-\text{NR}_2$, $-\text{P(O)(OR)}_2$, $-\text{P(O)(NR}_2)\text{OR}$, $-\text{P(O)(NR}_2)_2$, $-\text{Si(OH)R}_2$, $-\text{Si(OH)}_2\text{R}$, $-\text{Si(OH)(OR)}_2$, $-\text{Si(OH)(OR)NR}_2$, $-\text{Si(OH)(NR}_2)_2$, or $-\text{Si(OH)(OR)(NR}_2)$;

SiR₃, or an optionally substituted C₁₋₄ aliphatic; or

R^{7a} and X¹ or X³ are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, carbocyclic ring or heterocyclic ring having 1-3 heteroatoms, independently selected from boron, nitrogen, oxygen, silicon, or sulfur;

two R^{7a} groups on the same carbon are optionally taken together with their intervening atoms to form a 3-6 membered spiro fused ring or a 4-7 membered heterocyclic ring having 1-2 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur;

two R^{7a} groups on adjacent carbon atoms are optionally taken together with their intervening atoms to form a 3-7 membered saturated, partially unsaturated, carbocyclic ring or heterocyclic ring having 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or a 7-13 membered saturated, partially unsaturated, bridged heterocyclic ring, or a spiro heterocyclic ring having 1-3 heteroatoms, independently selected from boron, nitrogen, oxygen, silicon, or sulfur;

Ring D is selected from 6 to 10-membered aryl or heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;

L² is a covalent bond or a C₁₋₃ bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, -C(R)₂-, -CH(R)-, -C(F)₂-, -N(R)-, -S-, -S(O)₂- or -(C)=CH-;

q is 0, 1, 2, 3, or 4; and

n is 0, 1, 2, 3, or 4.

[00112] As defined above and described herein, X¹, X⁶, and X⁷ are independently a bivalent moiety selected from a covalent bond, -CH₂-, -C(R)₂-, -C(O)-, -C(S)-, -CH(R)-, -CH(CF₃)-, -P(O)(OR)-, -



P(O)(R)-, -P(O)(NR₂)-, -S(O)-, -S(O)₂-, or

[00113] In some embodiments, one or more of X¹, X⁶, and X⁷ is a covalent bond. In some embodiments, one or more of X¹, X⁶, and X⁷ is -CH₂-. In some embodiments, one or more of X¹, X⁶, and X⁷ is -CR₂-. In some embodiments, one or more of X¹, X⁶, and X⁷ is -C(O)-. In some embodiments, one or more of X¹, X⁶, and X⁷ is -C(S)-. In some embodiments, one or more of X¹, X⁶, and X⁷ is -CH(R)-. In some embodiments, one or more of X¹, X⁶, and X⁷ is -CH(CF₃)-. In some embodiments, one or more of X¹, X⁶,

and X^7 is $-\text{P}(\text{O})(\text{OR})-$. In some embodiments, one or more of X^1 , X^6 , and X^7 is $-\text{P}(\text{O})(\text{R})-$. In some embodiments, one or more of X^1 , X^6 , and X^7 is $-\text{P}(\text{O})\text{NR}_2-$. In some embodiments, one or more of X^1 , X^6 , and X^7 is $-\text{S}(\text{O})-$. In some embodiments, one or more of X^1 , X^6 , and X^7 is $-\text{S}(\text{O})_2-$. In some embodiments,



one or more of X^1 , X^6 , and X^7 is

[00114] In some embodiments, X^1 , X^6 , and X^7 are independently selected from those depicted in **Table 1** below.

[00115] As defined above and described herein, X^2 is a carbon atom, nitrogen atom, or silicon atom.

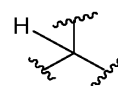
[00116] In some embodiments, X^2 is a carbon atom. In some embodiments, X^2 is a nitrogen atom. In some embodiments, X^2 is a silicon atom.

[00117] In some embodiments, X^2 is selected from those depicted in **Table 1** below.

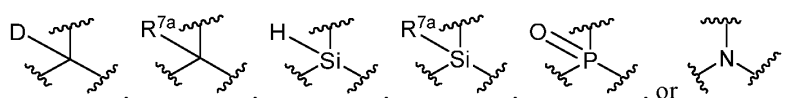
[00118] As defined above and described herein, X^3 and X^5 are independently a bivalent moiety selected from $-\text{CH}_2-$, $-\text{CR}_2-$, $-\text{NR}-$, $-\text{CF}_2-$, $-\text{CHF}-$, $-\text{S}-$, $-\text{CH}(\text{R})-$, $-\text{SiR}_2-$, or $-\text{O}-$.

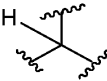
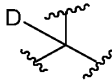
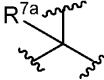
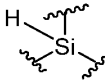
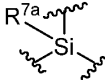
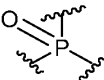
[00119] In some embodiments, one or more of X^3 and X^5 is $-\text{CH}_2-$. In some embodiments, one or more of X^3 and X^5 is $-\text{CR}_2-$. In some embodiments, one or more of X^3 and X^5 is $-\text{NR}-$. In some embodiments, one or more of X^3 and X^5 is $-\text{CF}_2-$. In some embodiments, one or more of X^3 and X^5 is $-\text{CHF}-$. In some embodiments, one or more of X^3 and X^5 is $-\text{S}-$. In some embodiments, one or more of X^3 and X^5 is $-\text{CH}(\text{R})-$. In some embodiments, one or more of X^3 and X^5 is $-\text{SiR}_2-$. In some embodiments, one or more of X^3 and X^5 is $-\text{O}-$.

[00120] In some embodiments, X^3 and X^5 are independently selected from those depicted in **Table 1** below.



[00121] As defined above and described herein, X^4 is a trivalent moiety selected from



[00122] In some embodiments, X^4 is . In some embodiments, X^4 is . In some embodiments, X^4 is . In some embodiments, X^4 is . In some embodiments, X^4 is . In some embodiments, X^4 is . In some embodiments, X^4 is .

[00123] In some embodiments, X^4 is selected from those depicted in **Table 1** below.

[00124] As defined above and described herein, R^1 is hydrogen, deuterium, halogen, $-\text{CN}$, $-\text{OR}$, $-\text{SR}$, $-\text{S(O)R}$, $-\text{S(O)}_2\text{R}$, $-\text{NR}_2$, $-\text{P(O)(OR)}_2$, $-\text{P(O)(NR}_2\text{)OR}$, $-\text{P(O)(NR}_2\text{)}_2$, $-\text{Si(OH)}_2\text{R}$, $-\text{Si(OH)(R)}_2$, $-\text{Si(R)}_3$, an optionally substituted C_{1-4} aliphatic, or R^1 and X^1 or X^4 are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, carbocyclic ring or heterocyclic ring having 1-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur.

[00125] In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is deuterium. In some embodiments, R^1 is halogen. In some embodiments, R^1 is $-\text{CN}$. In some embodiments, R^1 is $-\text{OR}$. In some embodiments, R^1 is $-\text{SR}$. In some embodiments, R^1 is $-\text{S(O)R}$. In some embodiments, R^1 is $-\text{S(O)}_2\text{R}$. In some embodiments, R^1 is $-\text{NR}_2$. In some embodiments, R^1 is $-\text{P(O)(OR)}_2$. In some embodiments, R^1 is $-\text{P(O)(NR}_2\text{)OR}$. In some embodiments, R^1 is $-\text{P(O)(NR}_2\text{)}_2$. In some embodiments, R^1 is $-\text{Si(OH)}_2\text{R}$. In some embodiments, R^1 is $-\text{Si(OH)(R)}_2$. In some embodiments, R^1 is $-\text{Si(R)}_3$. In some embodiments, R^1 is an optionally substituted C_{1-4} aliphatic. In some embodiments, R^1 and X^1 or X^4 are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, carbocyclic ring or heterocyclic ring having 1-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur.

[00126] In some embodiments, R^1 is selected from those depicted in **Table 1**, below.

[00127] As defined above and described herein, each R is independently hydrogen, deuterium, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, and sulfur, or two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from boron, nitrogen, oxygen, silicon, and sulfur.

[00128] In some embodiments, R is hydrogen. In some embodiments, R is deuterium. In some embodiments, R is optionally substituted C₁₋₆ aliphatic. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic having 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, and sulfur. In some embodiments, R is optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, and sulfur. In some embodiments, two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from boron, nitrogen, oxygen, silicon, and sulfur.

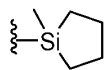
[00129] In some embodiments, R is selected from those depicted in **Table 1**, below.

[00130] As defined above and described herein, each R² and R^{3a} is independently hydrogen, deuterium, -R⁶, halogen, -CN, -NO₂, -OR, -Si(OH)₂R, -Si(OH)₂R₂, -SR, -NR₂, -SiR₃, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -C(R)₂N(R)C(O)R, -C(R)₂N(R)C(O)NR₂, -OC(O)R, -OC(O)NR₂, -OP(O)R₂, -OP(O)(OR)₂, -OP(O)(OR)NR₂, -OP(O)(NR₂)₂-, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)S(O)₂R, -NP(O)R₂, -N(R)P(O)(OR)₂, -N(R)P(O)(OR)NR₂, -N(R)P(O)(NR₂)₂, or -N(R)S(O)₂R.

[00131] In some embodiments, R² and/or R^{3a} is hydrogen. In some embodiments, R² and/or R^{3a} is deuterium. In some embodiments, R² and/or R^{3a} is -R⁶. In some embodiments, R² and/or R^{3a} is halogen. In some embodiments, R² and/or R^{3a} is -CN. In some embodiments, R² and/or R^{3a} is -NO₂. In some embodiments, R² and/or R^{3a} is -OR. In some embodiments, R² and/or R^{3a} is -Si(OH)₂R. In some embodiments, R² and/or R^{3a} is -Si(OH)₂R₂. In some embodiments, R² and/or R^{3a} is -SR. In some embodiments, R² and/or R^{3a} is -NR₂. In some embodiments, R² and/or R^{3a} is -SiR₃. In some embodiments, R² and/or R^{3a} is -S(O)₂R. In some embodiments, R² and/or R^{3a} is -S(O)₂NR₂. In some embodiments, R² and/or R^{3a} is -S(O)R. In some embodiments, R² and/or R^{3a} is -C(O)R. In some embodiments, R² and/or R^{3a} is -C(O)OR. In some embodiments, R² and/or R^{3a} is -C(O)NR₂. In some embodiments, R² and/or R^{3a} is -C(O)N(R)OR. In some embodiments, R² and/or R^{3a} is -C(R)₂N(R)C(O)R. In some embodiments, R² and/or R^{3a} is -C(R)₂N(R)C(O)NR₂. In some embodiments, R² and/or R^{3a} is -OC(O)R. In some embodiments, R² and/or R^{3a} is -OC(O)NR₂. In some embodiments, R² and/or R^{3a} is -OP(O)R₂. In some embodiments, R² and/or R^{3a} is -OP(O)(OR)₂. In some embodiments, R² and/or R^{3a} is -OP(O)(OR)NR₂. In some embodiments, R² and/or R^{3a} is -OP(O)(NR₂)₂-. In some embodiments, R² and/or R^{3a} is -N(R)C(O)OR. In some embodiments, R² and/or R^{3a} is -N(R)C(O)R. In some embodiments, R² and/or R^{3a} is -N(R)C(O)NR₂. In some embodiments, R² and/or R^{3a} is -NP(O)R₂. In some embodiments, R² and/or R^{3a} is -N(R)P(O)(OR)₂. In some

embodiments, R^2 and/or R^{3a} is $-N(R)P(O)(NR_2)_2$. In some embodiments, R^2 and R^{3a} is independently $-N(R)S(O)_2R$.

[00132] In some embodiments, R^2 and/or R^{3a} is $-OH$. In some embodiments, R^2 and/or R^{3a} is $-NH_2$. In some embodiments, R^2 and/or R^{3a} is $-CH_2NH_2$. In some embodiments, R^2 and/or R^{3a} is $-CH_2NHCOMe$. In some embodiments, R^2 and/or R^{3a} is $-CH_2NHCONHMe$. In some embodiments, R^2 and/or R^{3a} is $-NHCOMe$. In some embodiments, R^2 and/or R^{3a} is $-NHCONHMe$. In some embodiments, R^2 and/or R^{3a} is $-SiMe_3$. In some embodiments, R^2 and/or R^{3a} is $-SiMe_2OH$. In some embodiments, R^2 and/or R^{3a} is $-SiMe(OH)_2$. In some embodiments, R^2 and/or R^{3a} is



. In some embodiments, R^2 and/or R^{3a} is Br . In some embodiments, R^2 and/or R^{3a} is Cl . In some embodiments, R^2 and/or R^{3a} is F . In some embodiments, R^2 and/or R^{3a} is Me . In some embodiments, R^2 and/or R^{3a} is $-NHMe$. In some embodiments, R^2 and/or R^{3a} is $-NMe_2$. In some embodiments, R^2 and/or R^{3a} is $-NHCO_2Et$. In some embodiments, R^2 and/or R^{3a} is $-CN$. In some embodiments, R^2 and/or R^{3a} is $-CH_2Ph$. In some embodiments, R^2 and/or R^{3a} is $-NHCO_2tBu$. In some embodiments, R^2 and/or R^{3a} is $-CO_2tBu$. In some embodiments, R^2 and/or R^{3a} is $-OMe$. In some embodiments, R^2 and/or R^{3a} is $-CF_3$.

[00133] In some embodiments, R^2 and R^{3a} are selected from those depicted in **Table 1**, below.

[00134] As defined above and described herein, R^3 is hydrogen, deuterium, halogen, $-CN$, $-NO_2$, $-OR$, $-NR_2$, $-SR$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)NR(OR)$, $-OC(O)R$, $-OC(O)NR_2$, $-OP(O)(OR)_2$, $-OP(O)(NR_2)_2$, $-OP(O)(OR)NR_2$, $-N(R)C(O)R$, $-N(R)C(O)OR$, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-N(R)S(O)_2NR_2$, $-N(R)P(O)(OR)_2$, $-N(R)P(O)(OR)NR_2$, $-P(O)(OR)_2$, $-P(O)(NR_2)OR$, $-P(O)(NR_2)_2$, $-Si(OH)_2R$, $-Si(OH)(R)_2$, or $-Si(R)_3$.

[00135] In some embodiments, R^3 is hydrogen. In some embodiments, R^3 is deuterium. In some embodiments, R^3 is halogen. In some embodiments, R^3 is $-CN$. In some embodiments, R^3 is $-NO_2$. In some embodiments, R^3 is $-OR$. In some embodiments, R^3 is $-NR_2$. In some embodiments, R^3 is $-SR$. In some embodiments, R^3 is $-S(O)_2R$. In some embodiments, R^3 is $-S(O)_2NR_2$. In some embodiments, R^3 is $-S(O)R$. In some embodiments, R^3 is $-C(O)R$. In some embodiments, R^3 is $-C(O)OR$. In some embodiments, R^3 is $-C(O)NR_2$. In some embodiments, R^3 is $-C(O)NR(OR)$. In some embodiments, R^3 is $-OC(O)R$. In some embodiments, R^3 is $-OC(O)NR_2$. In some embodiments, R^3 is $-OP(O)(OR)_2$. In some embodiments, R^3 is $-OP(O)(NR_2)_2$. In some embodiments, R^3 is $-OP(O)(OR)NR_2$. In some embodiments, R^3 is $-N(R)C(O)R$. In some embodiments, R^3 is $-N(R)C(O)OR$. In some embodiments, R^3 is $-N(R)C(O)NR_2$. In some embodiments, R^3 is $-N(R)S(O)_2R$. In some embodiments, R^3 is $-N(R)S(O)_2NR_2$. In some embodiments, R^3 is $-N(R)P(O)(OR)_2$. In some embodiments, R^3 is $-N(R)P(O)(OR)NR_2$. In some embodiments, R^3 is $-P(O)(OR)_2$. In some embodiments, R^3 is $-P(O)(NR_2)OR$. In some embodiments, R^3 is

$-P(O)(NR_2)_2$. In some embodiments, R^3 is $-Si(OH)_2R$. In some embodiments, R^3 is $-Si(OH)(R)_2$. In some embodiments, R^3 is $-Si(R)_3$.

[00136] In some embodiments, R^3 is methyl. In some embodiments, R^3 is $-OCH_3$. In some embodiments, R^3 is chloro.

[00137] In some embodiments, R^3 is selected from those depicted in **Table 1**, below.

[00138] As defined above and described herein, each R^4 is independently hydrogen, deuterium, $-R^6$, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-P(O)(OR)_2$, $-P(O)(NR_2)OR$, or $-P(O)(NR_2)_2$.

[00139] In some embodiments, R^4 is hydrogen. In some embodiments, R^4 is $-R^6$. In some embodiments, R^4 is halogen. In some embodiments, R^4 is $-CN$. In some embodiments, R^4 is $-NO_2$. In some embodiments, R^4 is $-OR$. In some embodiments, R^4 is $-SR$. In some embodiments, R^4 is $-NR_2$. In some embodiments, R^4 is $-S(O)_2R$. In some embodiments, R^4 is $-S(O)_2NR_2$. In some embodiments, R^4 is $-S(O)R$. In some embodiments, R^4 is $-C(O)R$. In some embodiments, R^4 is $-C(O)OR$. In some embodiments, R^4 is $-C(O)NR_2$. In some embodiments, R^4 is $-C(O)N(R)OR$. In some embodiments, R^4 is $-OC(O)R$. In some embodiments, R^4 is $-OC(O)NR_2$. In some embodiments, R^4 is $-N(R)C(O)OR$. In some embodiments, R^4 is $-N(R)C(O)R$. In some embodiments, R^4 is $-N(R)C(O)NR_2$. In some embodiments, R^4 is $-N(R)S(O)_2R$. In some embodiments, R^4 is $-P(O)(OR)_2$. In some embodiments, R^4 is $-P(O)(NR_2)OR$. In some embodiments, R^4 is $-P(O)(NR_2)_2$.

[00140] In some embodiments, R^4 is methyl. In some embodiments, R^4 is ethyl. In some embodiments, R^4 is cyclopropyl.

[00141] In some embodiments, R^4 is selected from those depicted in **Table 1**, below.

[00142] As defined above and described herein, R^5 is hydrogen, deuterium, an optionally substituted C_{1-4} aliphatic, or $-CN$.

[00143] In some embodiments, R^5 is hydrogen. In some embodiments, R^5 is deuterium. In some embodiments, R^5 is an optionally substituted C_{1-4} aliphatic. In some embodiments, R^5 is $-CN$.

[00144] In some embodiments, R^5 is selected from those depicted in **Table 1**, below.

[00145] As defined above and described herein, each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, and sulfur.

[00146] In some embodiments, R^6 is an optionally substituted C_{1-6} aliphatic. In some embodiments, R^6 is an optionally substituted phenyl. In some embodiments, R^6 is an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, and sulfur. In some embodiments, R^6 is an optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, and sulfur.

[00147] In some embodiments, R^6 is selected from those depicted in **Table 1**, below.

[00148] As defined generally above, each R^{7a} is independently hydrogen, deuterium, halogen, $-CN$, $-OR$, $-SR$, $-S(O)R$, $-S(O)_2R$, $-N(R)_2$, $-P(O)(R)_2$, $-P(O)(OR)_2$, $-P(O)(NR_2)OR$, $-P(O)(NR_2)_2$, $-Si(OH)R_2$, $-Si(OH)_2R$, $-SiR_3$, or an optionally substituted C_{1-4} aliphatic, or R^{7a} and X^1 or X^3 are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, carbocyclic ring or heterocyclic ring having 1-3 heteroatoms, independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or two R^{7a} groups on the same carbon are optionally taken together with their intervening atoms to form a 3-6 membered spiro fused ring or a 4-7 membered heterocyclic ring having 1-2 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or two R^{7a} groups on adjacent carbon atoms are optionally taken together with their intervening atoms to form a 3-7 membered saturated, partially unsaturated, carbocyclic ring or heterocyclic ring having 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or a 7-13 membered saturated, partially unsaturated, bridged heterocyclic ring, or a spiro heterocyclic ring having 1-3 heteroatoms, independently selected from boron, nitrogen, oxygen, silicon, or sulfur.

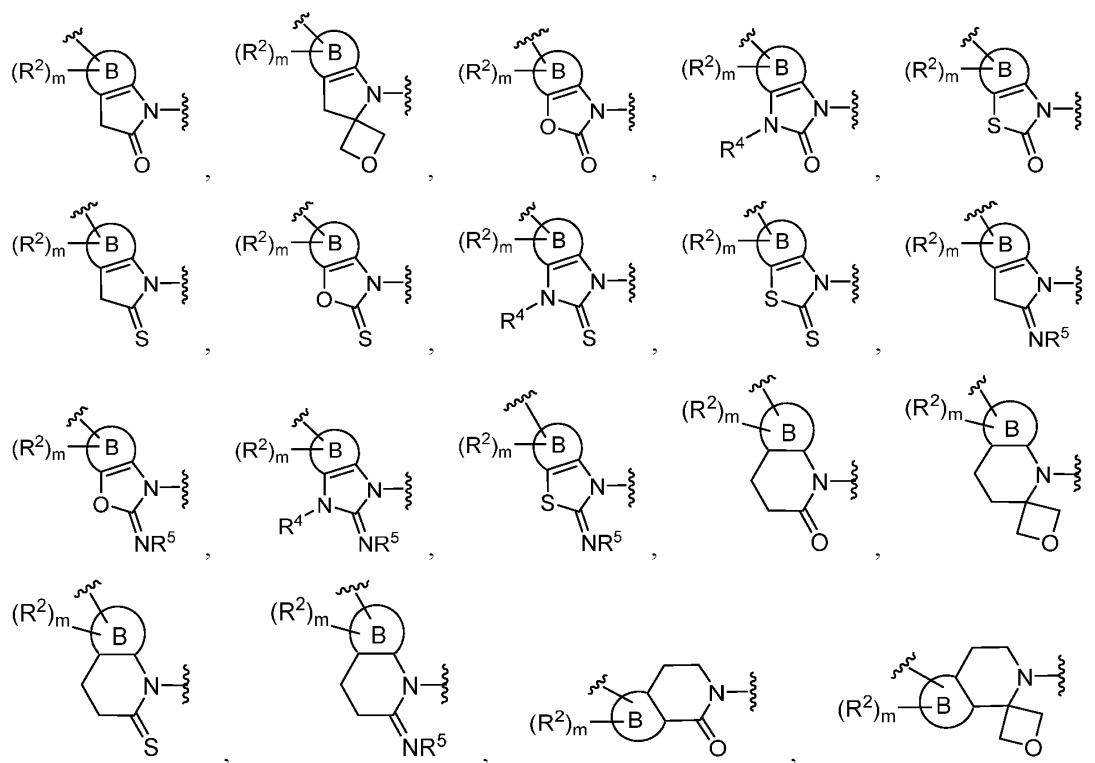
[00149] In some embodiments, R^{7a} is hydrogen. In some embodiments, R^{7a} is deuterium. In some embodiments, R^{7a} is halogen. In some embodiments, R^{7a} is $-CN$. In some embodiments, R^{7a} is $-OR$. In some embodiments, R^{7a} is $-SR$. In some embodiments, R^{7a} is $-S(O)R$. In some embodiments, R^{7a} is $-S(O)_2R$. In some embodiments, R^{7a} is $-NR_2$. In some embodiments, R^{7a} is $-Si(R)_3$. In some embodiments, R^{7a} is $-P(O)(R)_2$. In some embodiments, R^{7a} is $-P(O)(OR)_2$. In some embodiments, R^{7a} is $-P(O)(NR_2)OR$. In some embodiments, R^{7a} is $-P(O)(NR_2)_2$. In some embodiments, R^{7a} is $-Si(OH)R_2$. In some embodiments, R^{7a} is $-Si(OH)_2R$. In some embodiments, R^{7a} is an optionally substituted C_{1-4} aliphatic. In some embodiments, R^{7a} and X^1 or X^3 are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, carbocyclic ring or heterocyclic ring having 1-3 heteroatoms, independently selected from boron, nitrogen, oxygen, silicon, or sulfur. In some embodiments, two R^{7a} groups on the same carbon are optionally taken together with their intervening atoms to form a 3-6 membered spiro fused ring or a 4-7 membered heterocyclic ring having 1-2 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur. In some embodiments, two R^{7a} groups on adjacent carbon atoms are

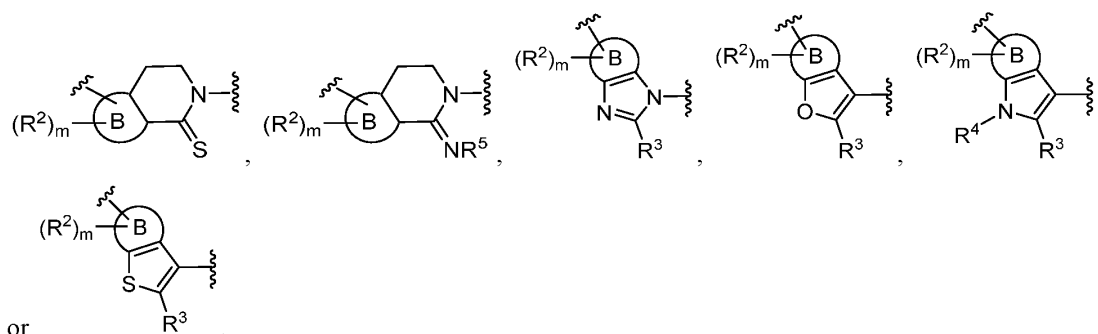
optionally taken together with their intervening atoms to form a 3-7 membered saturated, partially unsaturated, carbocyclic ring or heterocyclic ring having 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur. In some embodiments, two R^{7a} groups on adjacent carbon atoms are optionally taken together with their intervening atoms to form a 7-13 membered saturated, partially unsaturated, bridged heterocyclic ring, or a spiro heterocyclic ring having 1-3 heteroatoms, independently selected from boron, nitrogen, oxygen, silicon, or sulfur.

[00150] In some embodiments, R^{7a} is selected from hydrogen, halogen, -CN, -OR, -NR₂, or C₁₋₄ alkyl. In some embodiments, R^{7a} is selected from hydrogen, halogen, -CN, or C₁₋₄ alkyl. In some embodiments, R^{7a} is fluoro. In some embodiments, two R^{7a} groups on the same carbon are optionally taken together with their intervening atoms to form a 3- or 4-membered spiro fused ring.

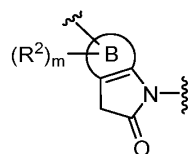
[00151] In some embodiments, R^{7a} is selected from those depicted in **Table 1** below.

[00152] As defined above and described herein, Ring A is a bi- or tricyclic ring selected from

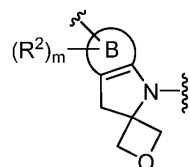




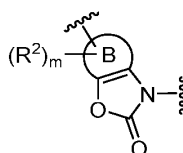
[00153] In some embodiments, Ring A is



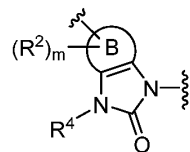
In some embodiments, Ring A is



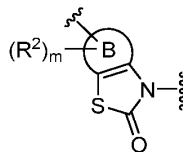
In some embodiments, Ring A is



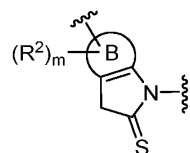
In some embodiments, Ring A is



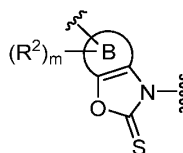
In some embodiments, Ring A is



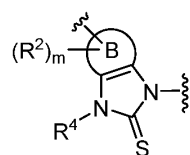
In some embodiments, Ring A is



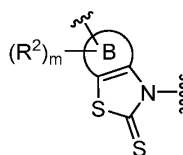
In some embodiments, Ring A is



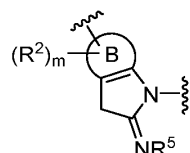
In some embodiments, Ring A is



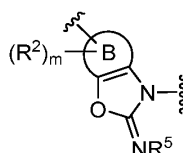
In some embodiments, Ring A is



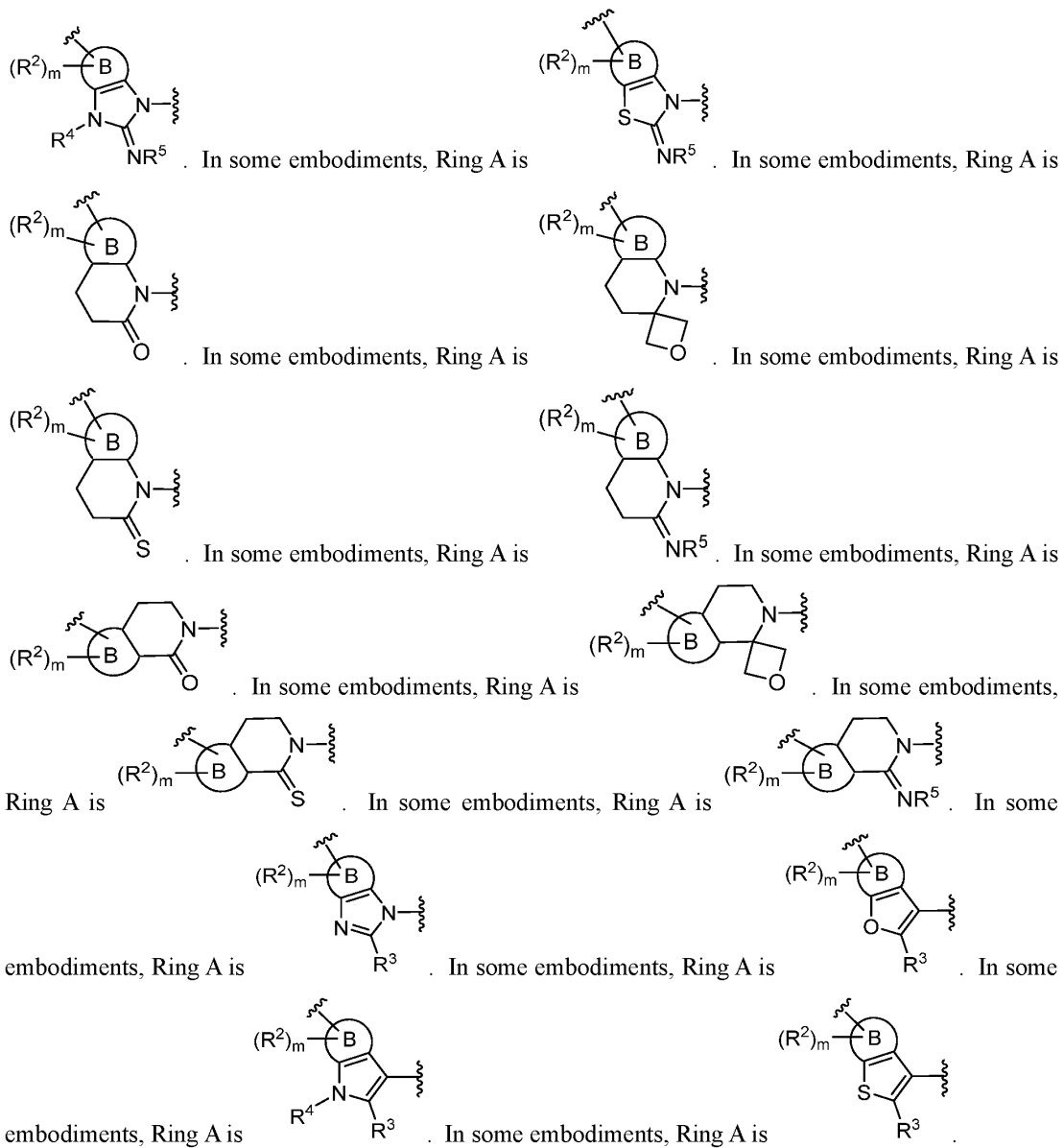
In some embodiments, Ring A is



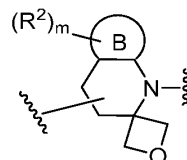
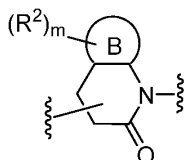
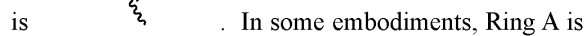
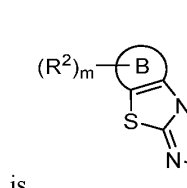
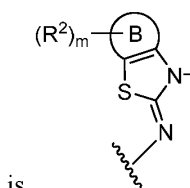
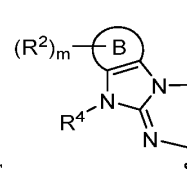
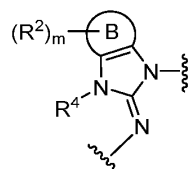
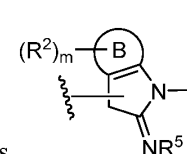
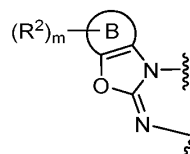
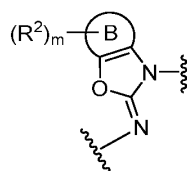
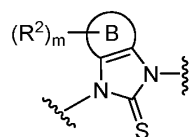
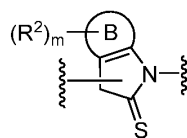
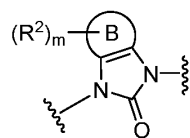
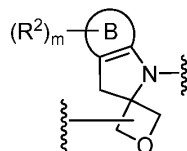
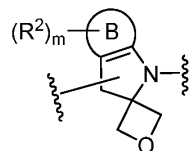
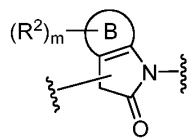
In some embodiments, Ring A is

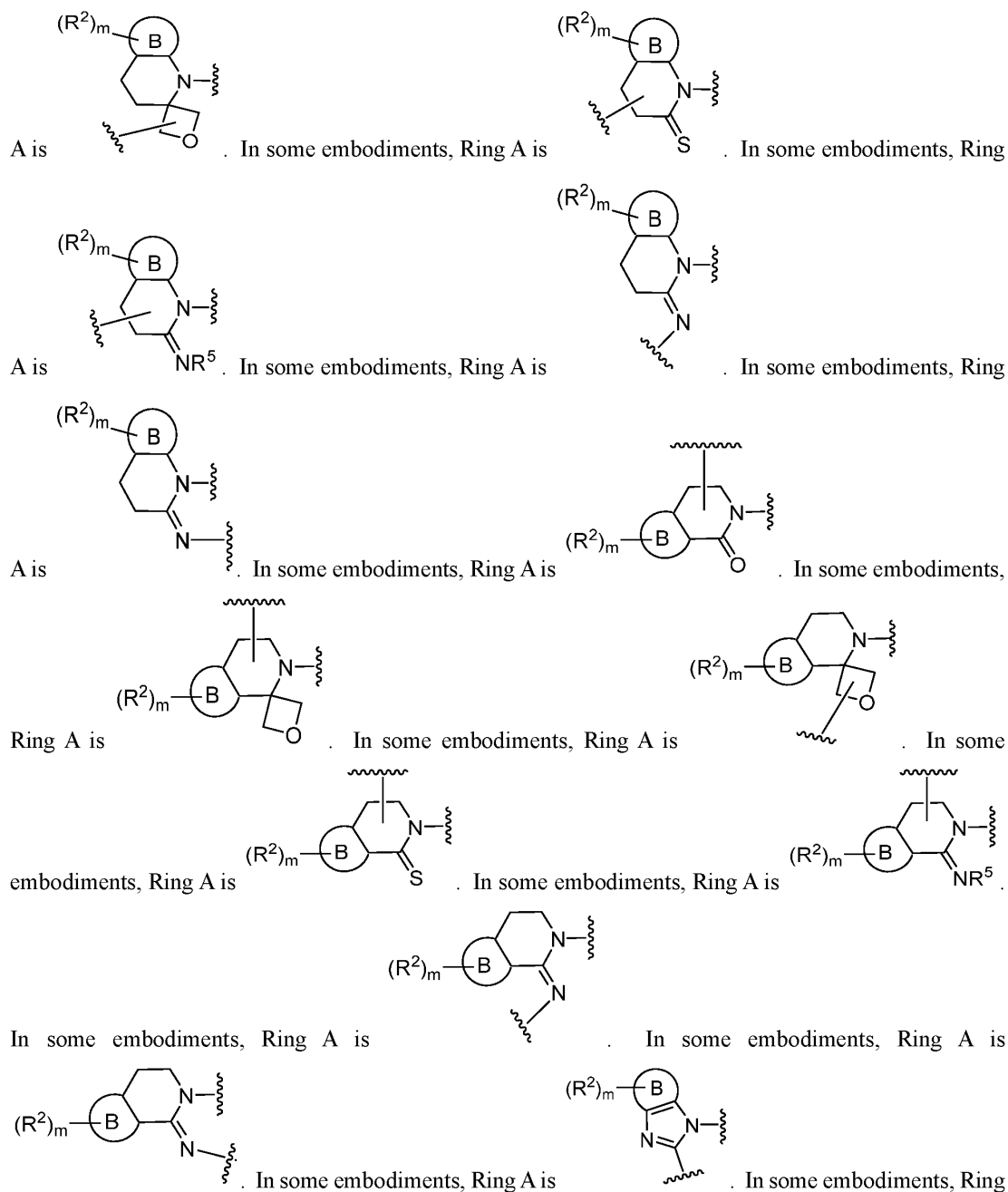


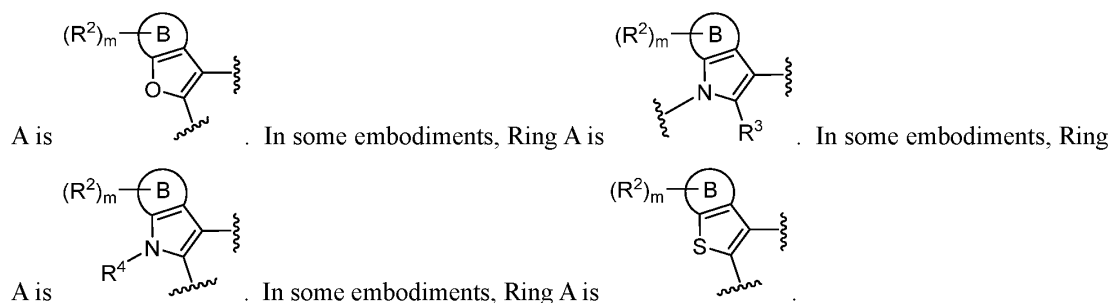
In some embodiments, Ring A is



[00154] In some embodiments, Ring A is



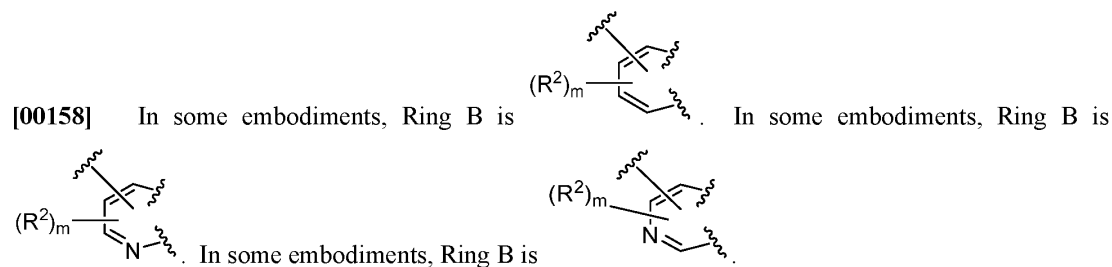




[00155] In some embodiments, Ring A is selected from those depicted in **Table 1**, below.

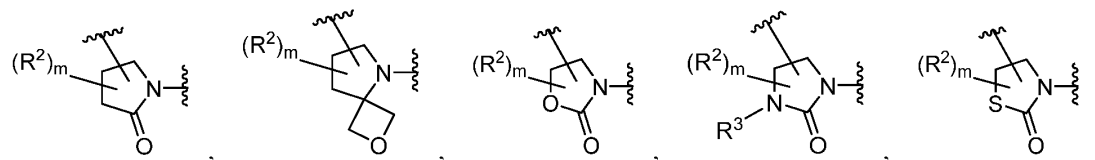
[00156] As defined above and described herein, Ring B is a fused ring selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;

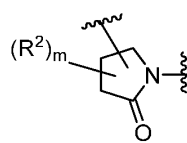
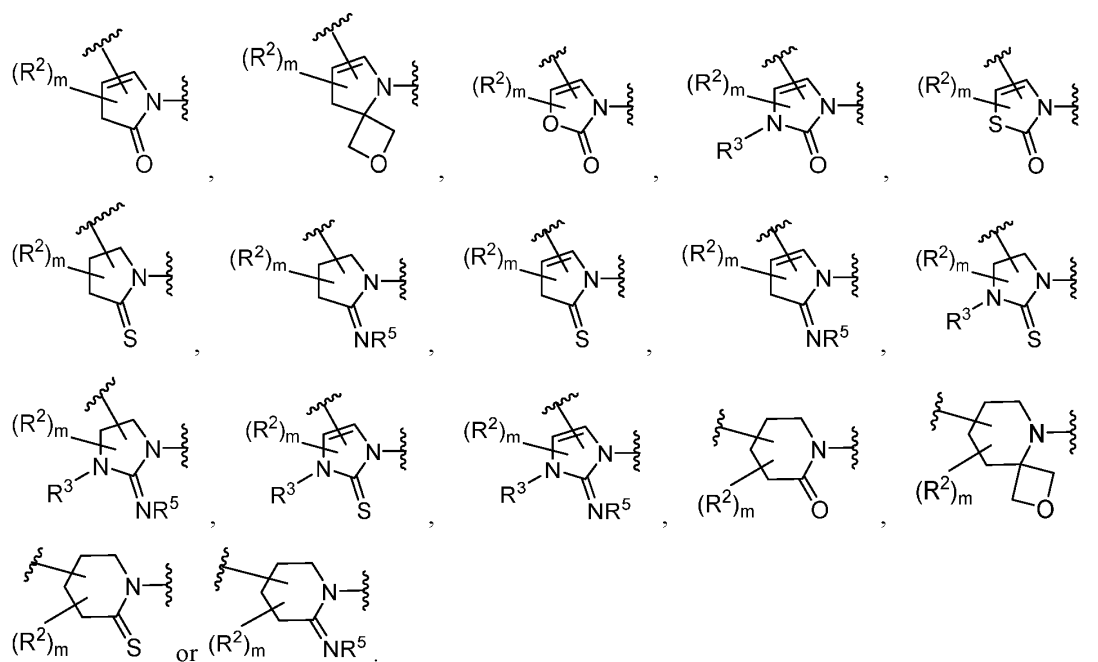
[00157] In some embodiments, Ring B is a fused 6-membered aryl. In some embodiments, Ring B is a fused 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring B is a fused 5 to 7-membered saturated or partially unsaturated carbocyclyl. In some embodiments, Ring B is fused 5 to 7-membered saturated or partially saturated heterocyclyl with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur. In some embodiments, Ring B is fused 5-membered heteroaryl with 1-4 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur.



[00159] In some embodiments, Ring B is selected from those depicted in **Table 1**, below.

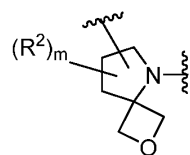
[00160] As defined above and described herein, Ring C is a mono- or bicyclic ring selected from



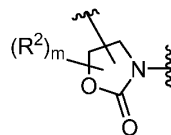


[00161] In some embodiments, Ring C is

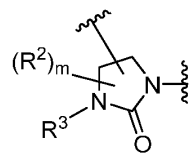
. In some embodiments, Ring C is



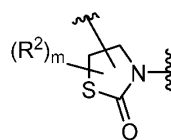
. In some embodiments, Ring C is



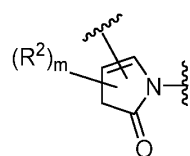
. In some embodiments, Ring C is



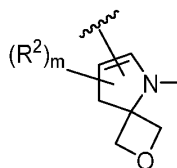
. In some embodiments, Ring C is



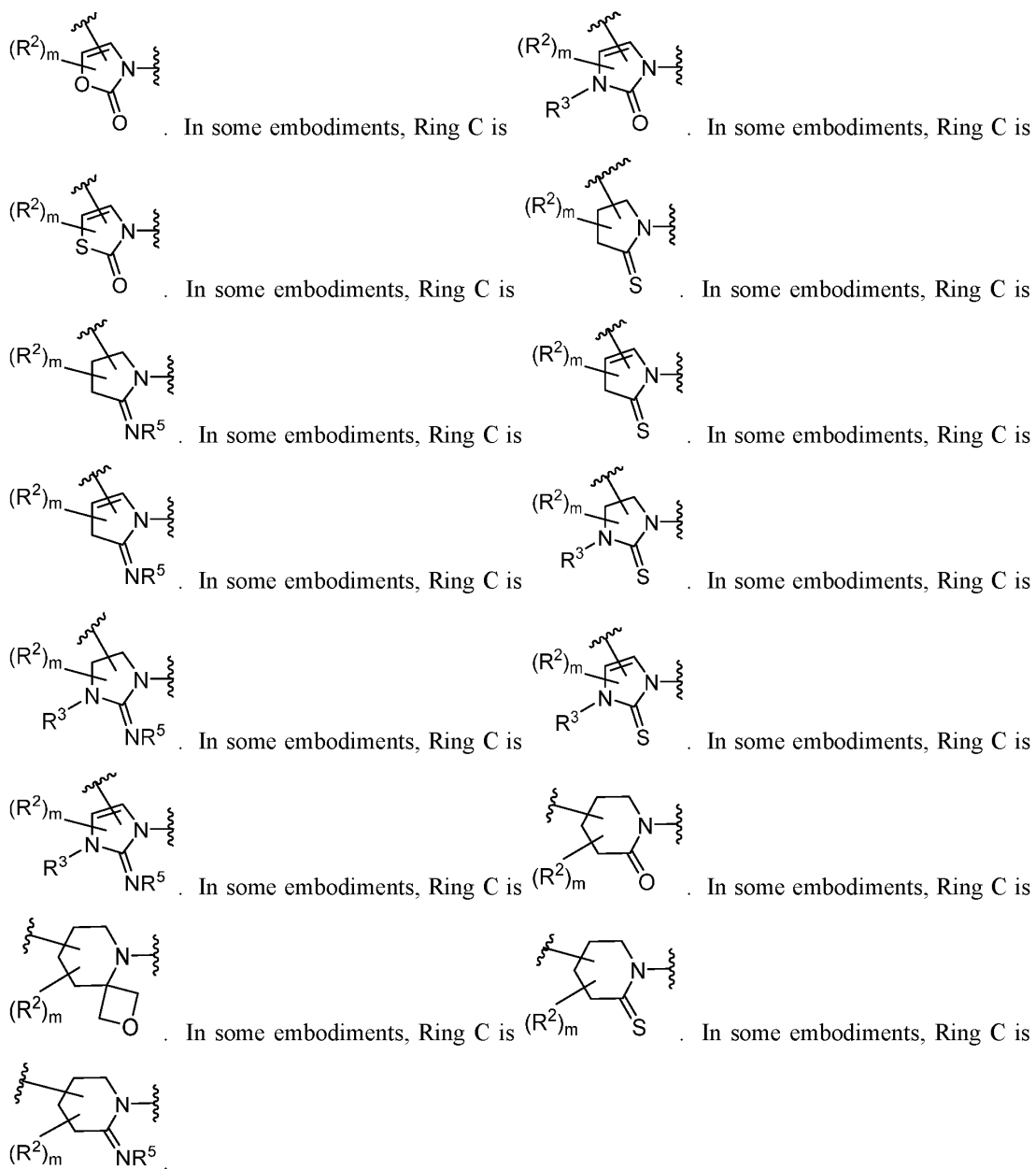
. In some embodiments, Ring C is

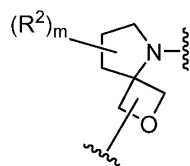


. In some embodiments, Ring C is



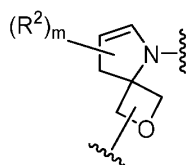
. In some embodiments, Ring C is



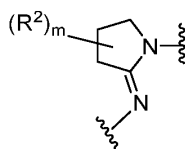


[00162] In some embodiments, Ring C is

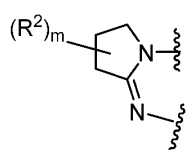
. In some embodiments, Ring C is



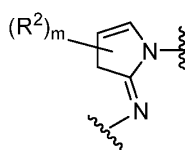
. In some embodiments, Ring C is



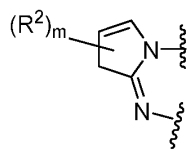
. In some embodiments, Ring C is



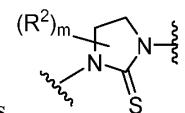
. In some embodiments, Ring C is



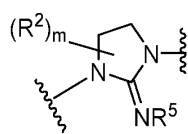
. In some embodiments, Ring C is



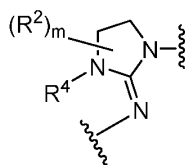
. In some embodiments, Ring C is



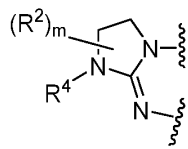
. In some embodiments, Ring C is



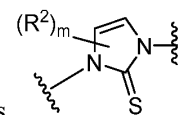
. In some embodiments, Ring C is



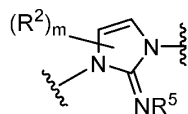
. In some embodiments, Ring C is



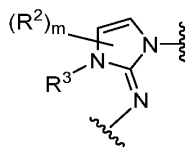
. In some embodiments, Ring C is



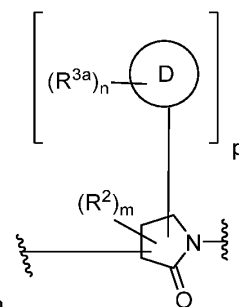
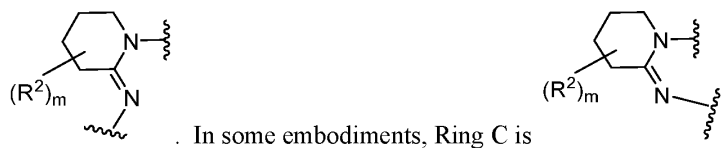
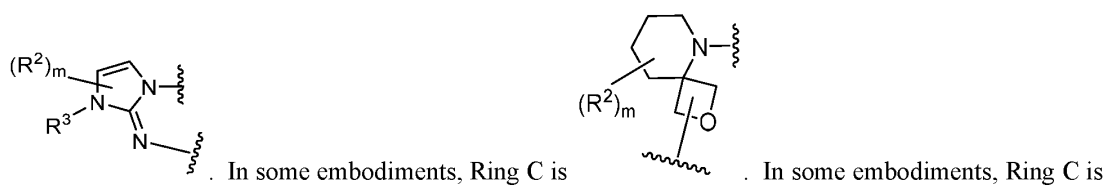
. In some embodiments, Ring C is



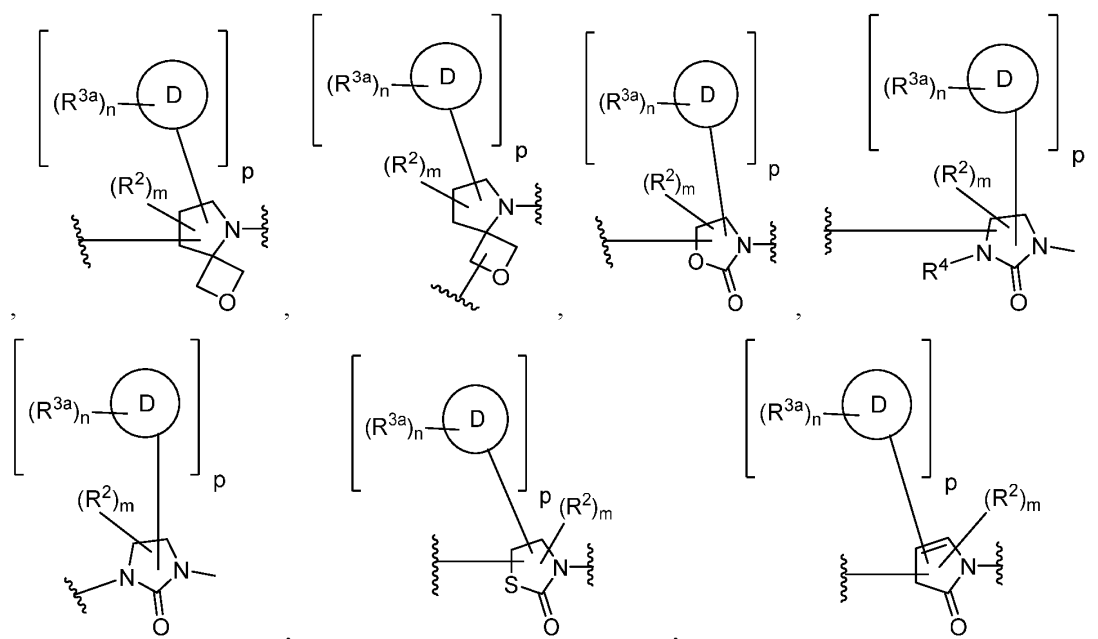
. In some embodiments, Ring C is

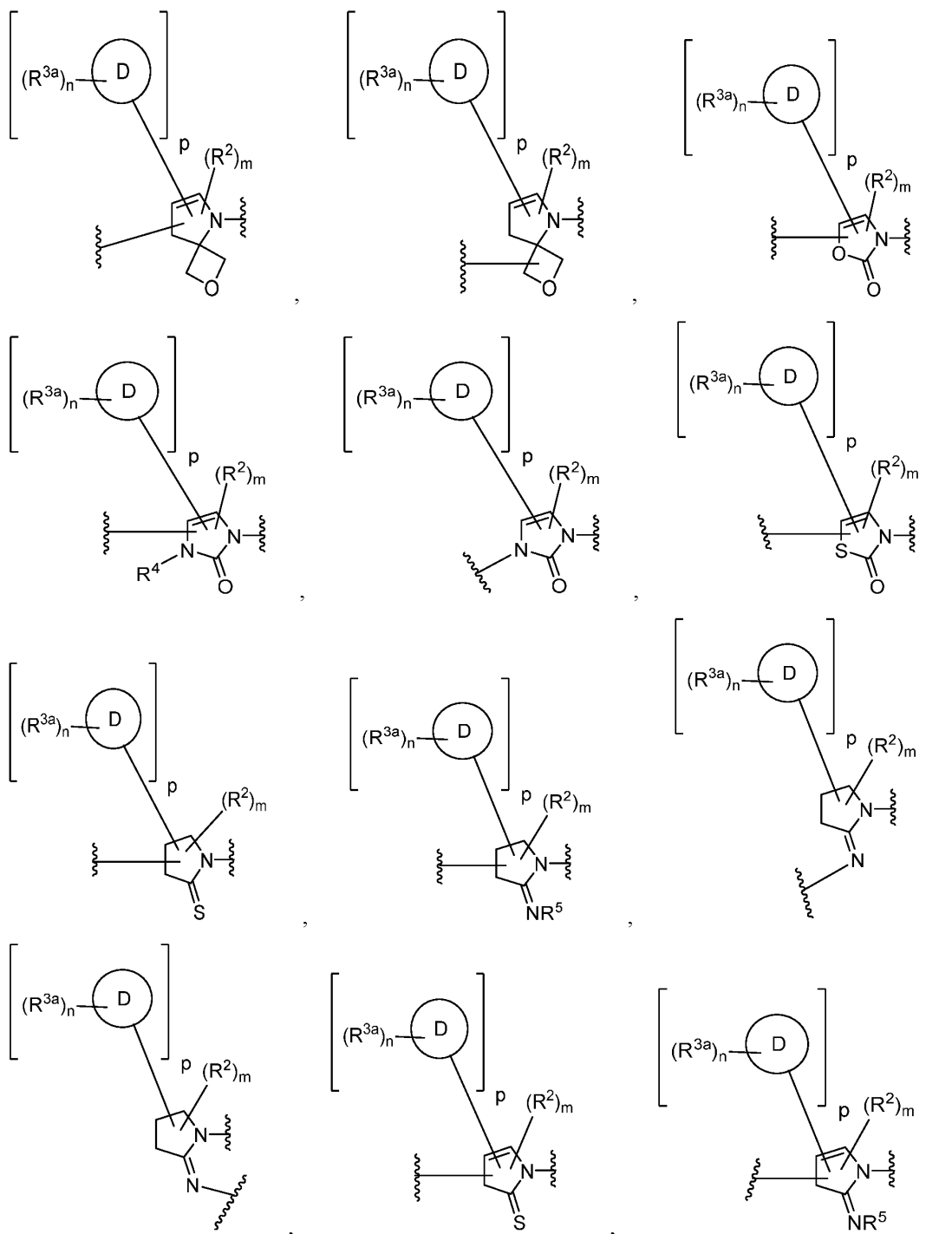


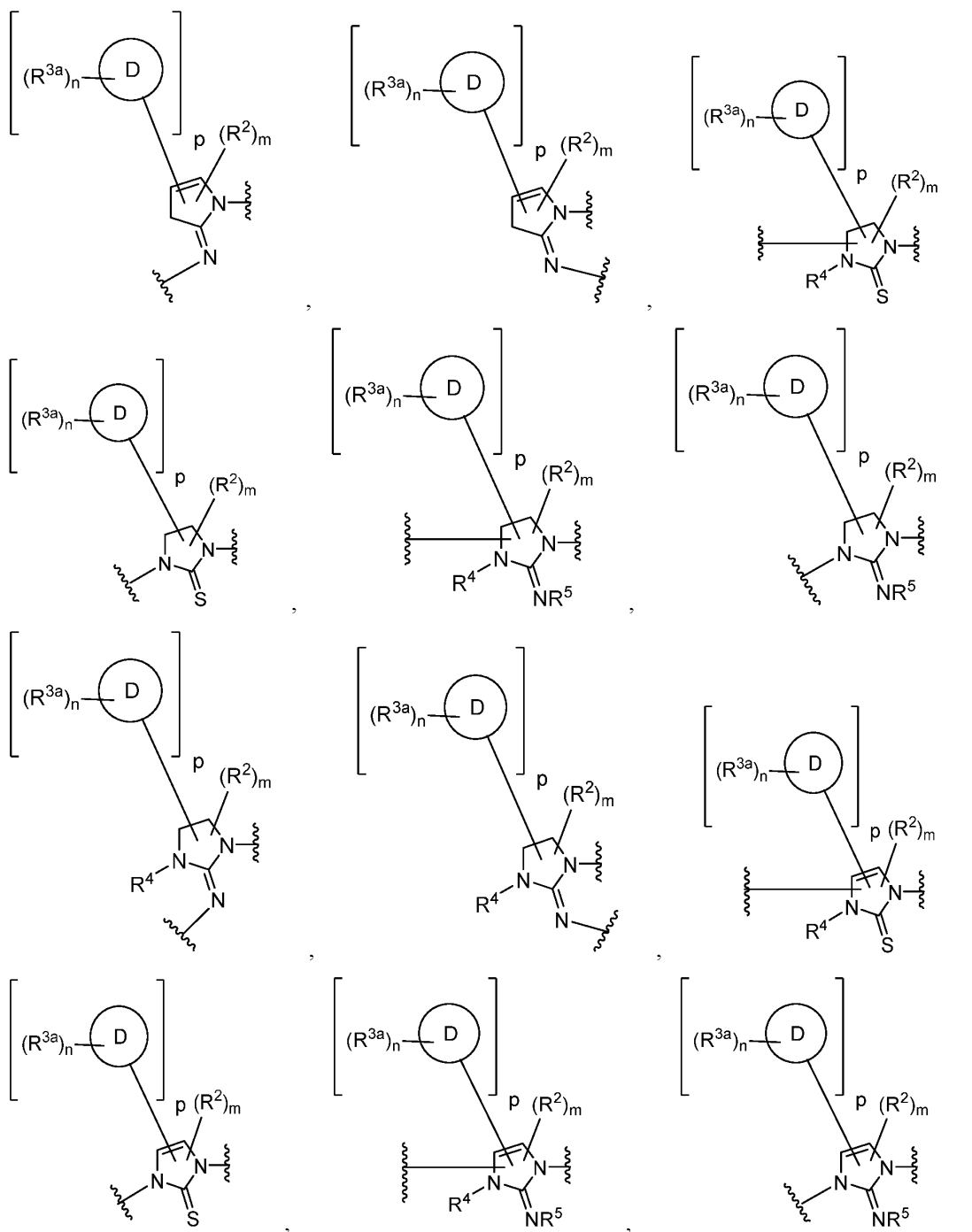
. In some embodiments, Ring C is

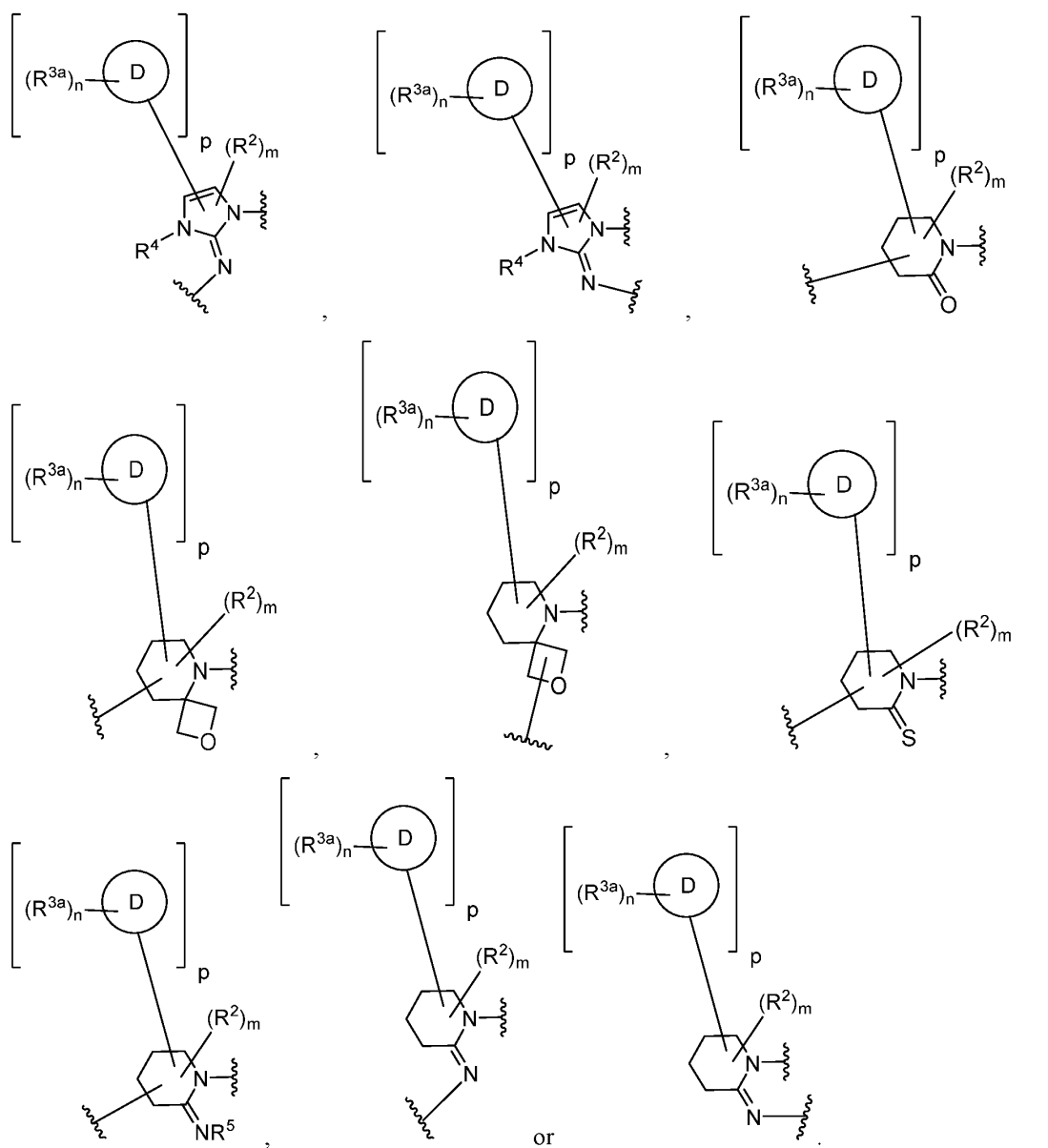


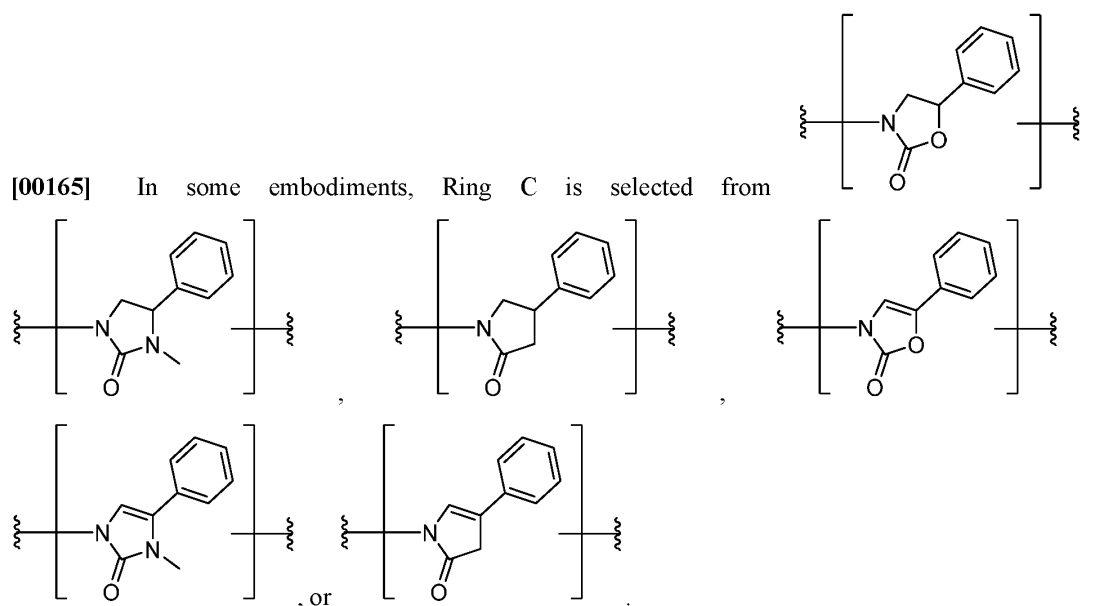
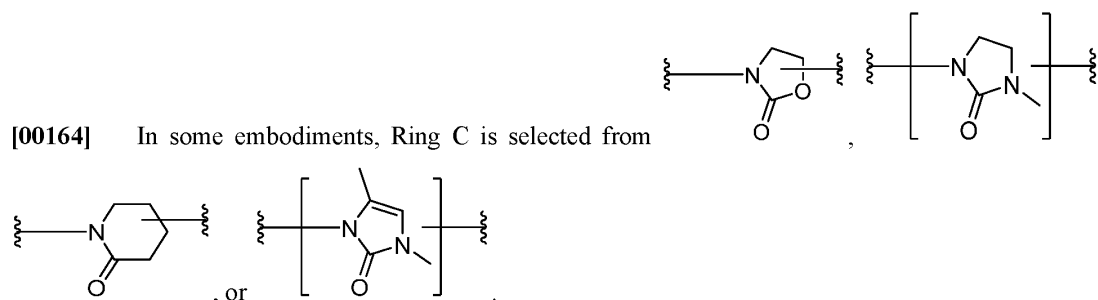
[00163] In some embodiments, Ring C is a mono- or bicyclic ring selected from











[00166] In some embodiments, Ring C is selected from those depicted in **Table 1**, below.

[00167] As defined above and described herein, Ring D is a ring selected from 6 to 10-membered aryl or heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;

[00168] In some embodiments, Ring D is a 6 to 10-membered aryl. In some embodiments, Ring D is a 6 to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring D is a 5 to 7-membered saturated or partially unsaturated carbocyclyl. In some embodiments, Ring D is 5 to 7-membered saturated or partially saturated heterocyclyl with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur. In some embodiments,

Ring D is 5-membered heteroaryl with 1-4 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur.

[00169] In some embodiments, Ring D is isoquinoline. In some embodiments, Ring D is imidazo[1,2-a]pyridine.

[00170] In some embodiments, Ring D is selected from those depicted in **Table 1**, below.

[00171] As defined above and described herein, each of Ring E, Ring F, and Ring G is independently a fused ring selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur, wherein each of Ring E, Ring F, and Ring G is independently and optionally further substituted with 1-2 oxo groups.

[00172] In some embodiments, each Ring E, Ring F, and Ring G is independently a 6-membered aryl. In some embodiments, each Ring E, Ring F, and Ring G is independently a 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, each Ring E, Ring F, and Ring G is independently a 5 to 7-membered saturated or partially unsaturated carbocyclyl. In some embodiments, each Ring E, Ring F, and Ring G is independently a 5 to 7-membered saturated or partially unsaturated heterocyclyl with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur. In some embodiments, each Ring E, Ring F, and Ring G is independently a 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur. In some embodiments, each of Ring E, Ring F, and Ring G is independently and optionally further substituted with 1-2 oxo groups.

[00173] In some embodiments, Ring E, Ring F, and Ring G is selected from those depicted in **Table 1**, below.

[00174] As defined above and described herein, Ring H is a ring selected from a 7-9 membered saturated or partially unsaturated carbocyclyl or heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, wherein Ring E is optionally further substituted with 1-2 oxo groups.

[00175] In some embodiments, Ring H is a ring selected from a 7-9 membered saturated or partially unsaturated carbocyclyl or heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, wherein Ring H is optionally further substituted with 1-2 oxo groups.

[00176] In some embodiments, Ring E and Ring H is selected from those depicted in **Table 1**, below.

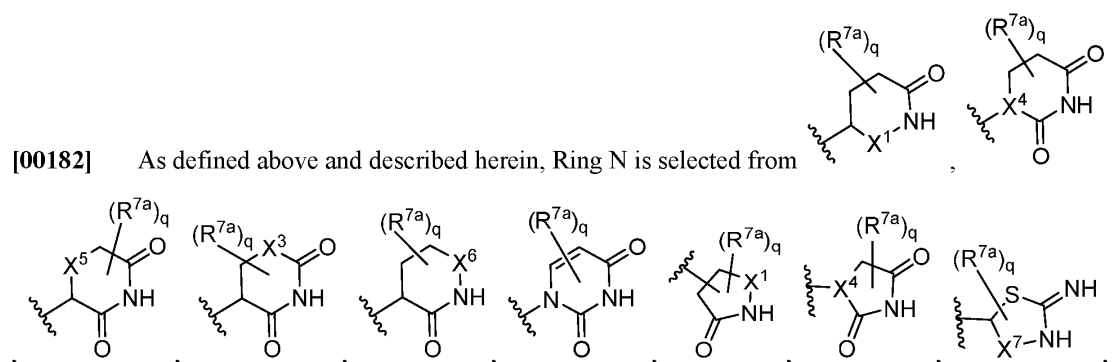
[00177] As defined above and described herein, each of Ring I and Ring J is independently a fused ring selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur

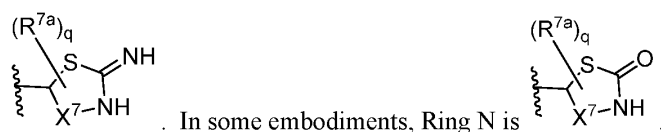
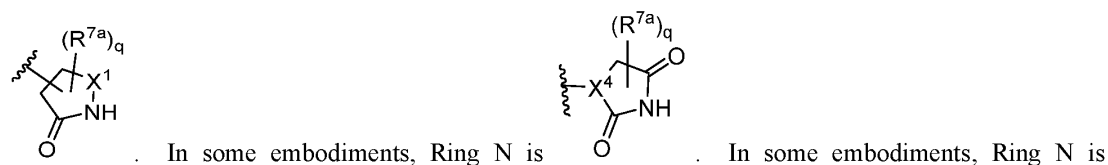
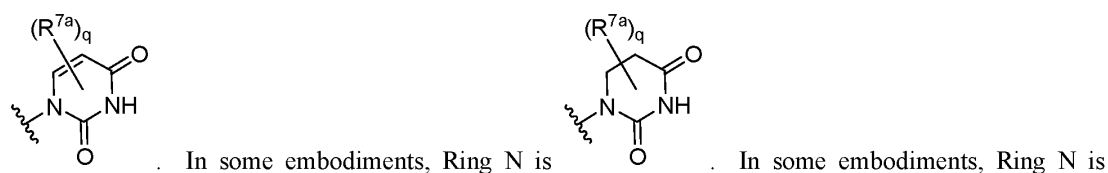
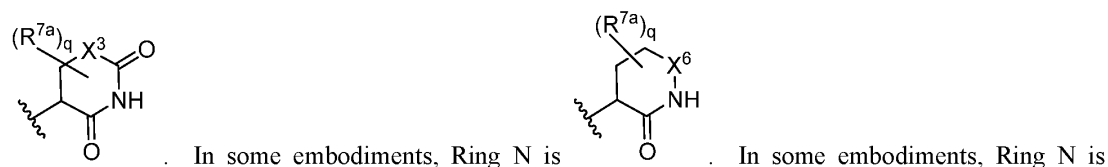
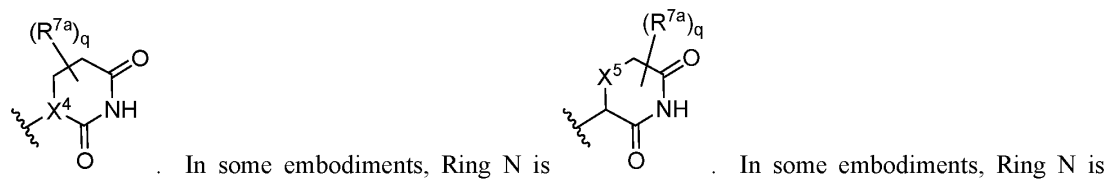
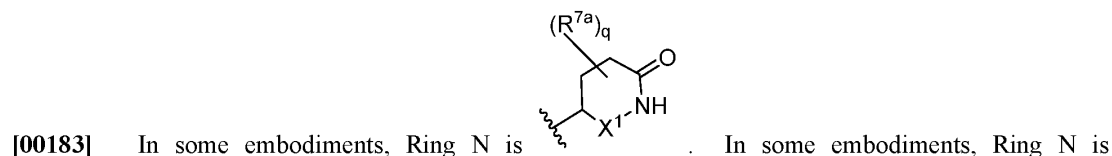
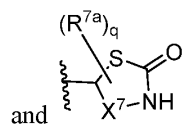
[00178] In some embodiments, each of Ring I and Ring J is independently a 6-membered aryl. In some embodiments, each of Ring I and Ring J is independently a 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, each of Ring I and Ring J is independently a 5 to 7-membered saturated or partially unsaturated carbocyclyl. In some embodiments, each of Ring I and Ring J is independently a 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur. In some embodiments, each of Ring I and Ring J is independently a 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur.

[00179] As defined above and described herein, Ring K is a fused ring selected from a 6-12 membered saturated or partially unsaturated carbocyclyl or heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, wherein Ring H is optionally further substituted with 1-2 oxo groups.

[00180] In some embodiments, Ring K is a fused ring selected from a 6-12 membered saturated or partially unsaturated carbocyclyl. In some embodiments, Ring K is a 6-12 membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur. In some embodiments, Ring K is optionally further substituted with 1-2 oxo groups.

[00181] In some embodiments, Ring I, Ring J, and Ring K is selected from those depicted in **Table 1**, below.





[00184] In some embodiments, Ring N is selected from those depicted in **Table 1** below.

[00185] As defined above and described here, L^2 is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, -C(R)₂-, -CH(R)-, -C(F)₂-, -N(R)-, -S(O)₂- or -(C)=CH-;

[00186] In some embodiments, L^2 is a covalent bond. In some embodiments, L^2 is a C_{1-3} aliphatic. In some embodiments, L^2 is $-CH_2-$. In some embodiments, L^2 is $-C(D)(H)-$. In some embodiments, L^2 is $-C(D)_2-$. In some embodiments, L^2 is $-CH_2CH_2-$. In some embodiments, L^2 is $-NR-$. In some embodiments, L^2 is $-CH_2NR-$. In some embodiments, L^2 is or $-O-$. In some embodiments, L^2 is $-CH_2O-$. In some embodiments, L^2 is $-S-$. In some embodiments, L^2 is $-OC(O)-$. In some embodiments, L^2 is $-C(O)O-$. In some embodiments, L^2 is $-C(O)-$. In some embodiments, L^2 is $-S(O)-$. In some embodiments, L^2 is $-S(O)_2-$. In some embodiments, L^2 is $-NRS(O)_2-$. In some embodiments, L^2 is $-S(O)_2NR-$. In some embodiments, L^2 is $-NRC(O)-$. In some embodiments, L^2 is $-C(O)NR-$.

[00187] In some embodiments, Ring L^2 is selected from those depicted in **Table 1**, below.

[00188] As defined above and described herein, $==$ is a single or double bond.

[00189] In some embodiments, $==$ is a single bond. In some embodiments, $==$ is a double bond.

[00190] In some embodiments, $==$ is selected from those depicted in **Table 1**, below.

[00191] As defined above and described herein, m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16.

[00192] In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 4. In some embodiments, m is 5. In some embodiments, m is 6. In some embodiments, m is 7. In some embodiments, m is 8. In some embodiments, m is 9. In some embodiments, m is 10. In some embodiments, m is 11. In some embodiments, m is 12. In some embodiments, m is 13. In some embodiments, m is 14. In some embodiments, m is 15. In some embodiments, m is 16.

[00193] In some embodiments, m is selected from those depicted in **Table 1**, below.

[00194] As defined above and described herein, n is 0, 1, 2, 3 or 4.

[00195] In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

[00196] In some embodiments, n is selected from those depicted in **Table 1**, below.

[00197] As defined above and described herein, p is 0 or 1.

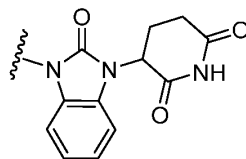
[00198] In some embodiments, p is 0. In some embodiments, p is 1.

[00199] In some embodiments, p is selected from those depicted in **Table 1**, below.

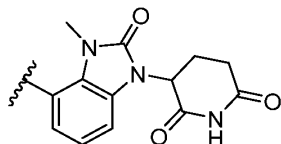
[00200] As defined above and described herein, q is 0, 1, 2, 3 or 4.

[00201] In some embodiments, q is 0. In some embodiments, q is 1. In some embodiments, q is 2. In some embodiments, q is 3. In some embodiments, q is 4.

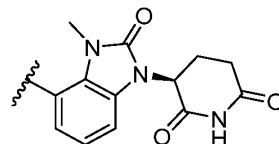
[00202] In some embodiments, q is selected from those depicted in **Table 1** below.



[00203] In some embodiments, LBM is . In some embodiments, LBM is

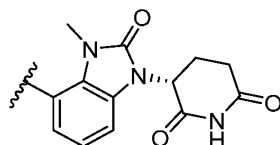


. In some embodiments, LBM is

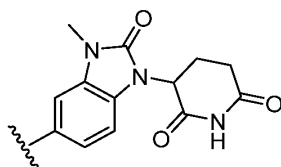


. In some

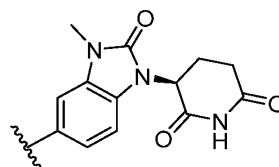
embodiments, LBM is



. In some embodiments, LBM is

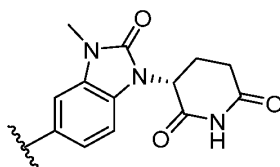


. In some embodiments, LBM is

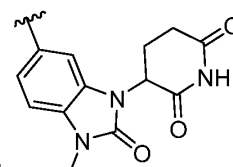


. In some

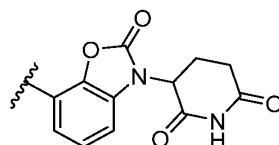
embodiments, LBM is



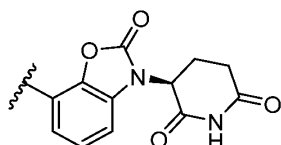
. In some embodiments, LBM is



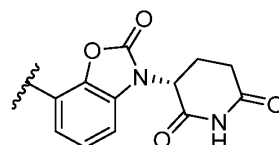
. In some embodiments, LBM is



. In some embodiments, LBM is

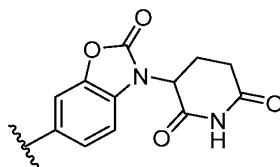


. In some embodiments, LBM is

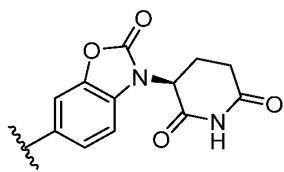


. In some

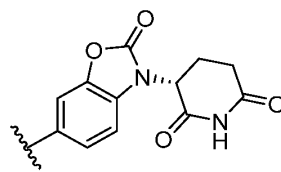
embodiments, LBM is



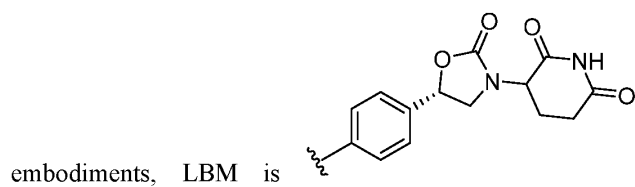
. In some embodiments, LBM is



. In some embodiments, LBM is

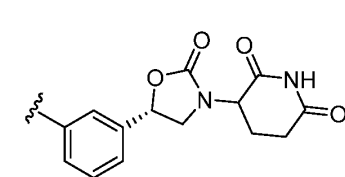
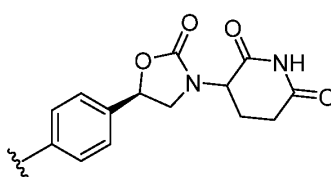


. In some

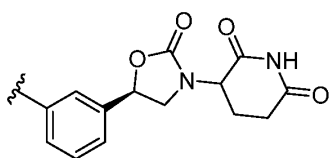


embodiments, LBM is

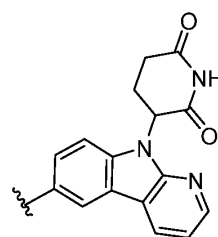
. In some embodiments, LBM is



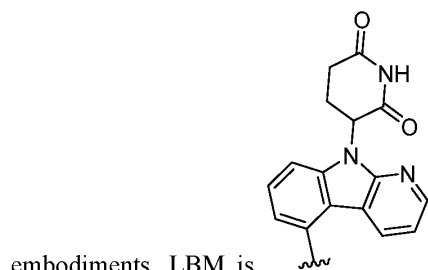
. In some embodiments, LBM is



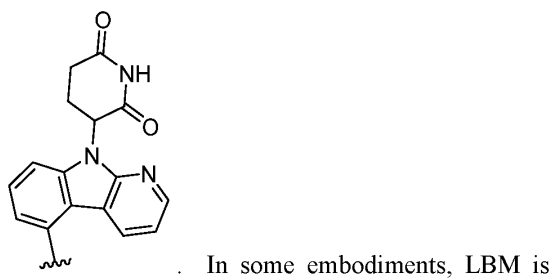
. In some embodiments, LBM is



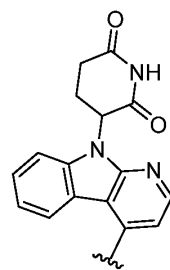
. In some



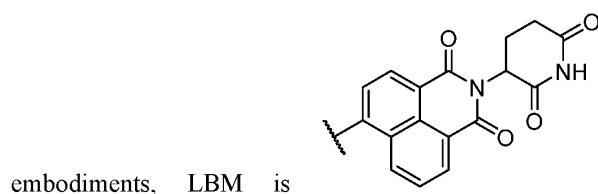
embodiments, LBM is



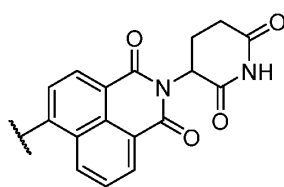
. In some embodiments, LBM is



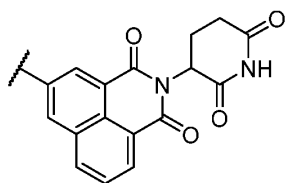
. In some



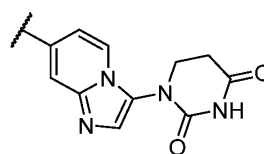
embodiments, LBM is



. In some embodiments, LBM is

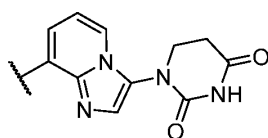


In some embodiments, LBM is

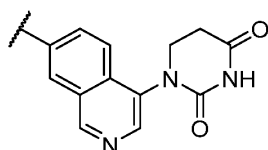


In some

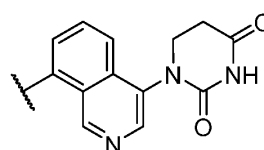
embodiments, LBM is



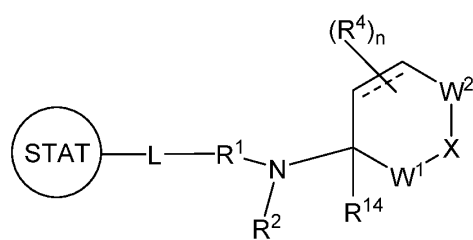
In some embodiments, LBM is



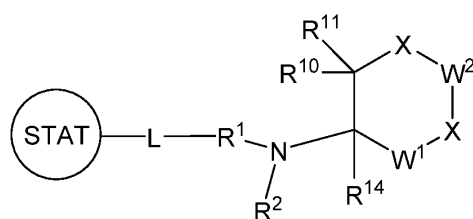
In some embodiments, LBM is



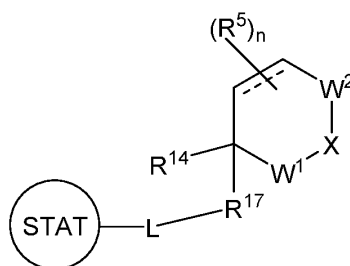
[00204] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is an E3 ubiquitin ligase (cereblon) binding moiety thereby forming a compound of formula **I-p-1**, **I-p-2**, or **I-p-3** respectively:



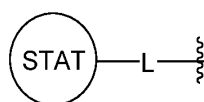
I-p-1



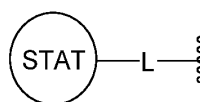
I-p-2

**I-p-3**

or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described herein, and wherein each of the variables R^1 , R^2 , R^4 , R^5 , R^{10} , R^{11} , R^{14} , R^{17} , W^1 , W^2 , X, $\equiv$, and n is as defined in WO 2017/197051 which is herein incorporated by reference in its entirety and wherein



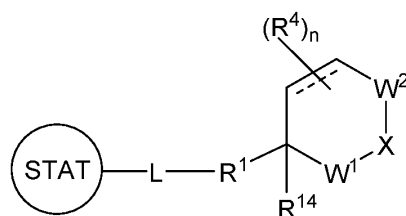
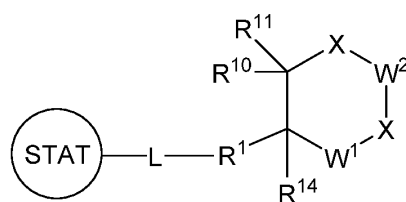
is attached to R^1 , the ring formed by combining R^1 and R^2 , or R^{17} at the site of

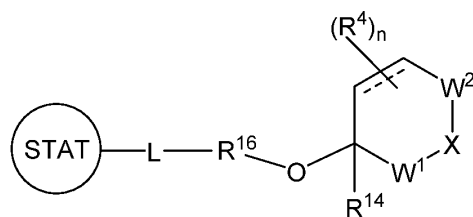


attachment of R^{12} as defined in WO 2017/197051 such that

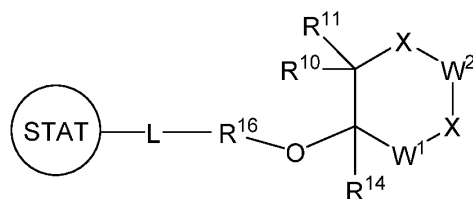
takes the place of the R^{12} substituent.

[00205] In some embodiments, the present invention provides a compound of formula I, wherein LBM is an E3 ubiquitin ligase (cereblon) binding moiety thereby forming a compound of formula **I-q-1**, **I-q-2**, **I-q-3**, or **I-q-4**, respectively:

**I-q-1****I-q-2**

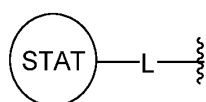


I-q-3

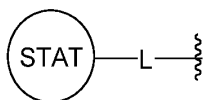


I-q-4

or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described herein, and wherein each of the variables R^1 , R^4 , R^{10} , R^{11} , R^{14} , R^{16} , W^1 , W^2 , X, $\equiv$, and n is as defined in WO 2018/237026, the entirety of each of which is herein incorporated by reference, and wherein

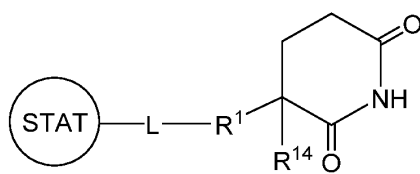


is attached to R^1 or R^{16} at the site of attachment of R^{12} as defined in WO 2018/237026,

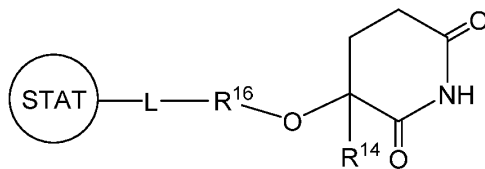


such that takes the place of the R^{12} substituent.

[00206] In some embodiments, the present invention provides a compound of formula I, wherein LBM is an E3 ubiquitin ligase (cereblon) binding moiety thereby forming a compound of formula I-r-1 or I-r-3, respectively:

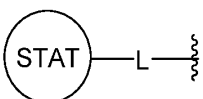


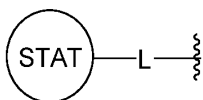
I-r-1



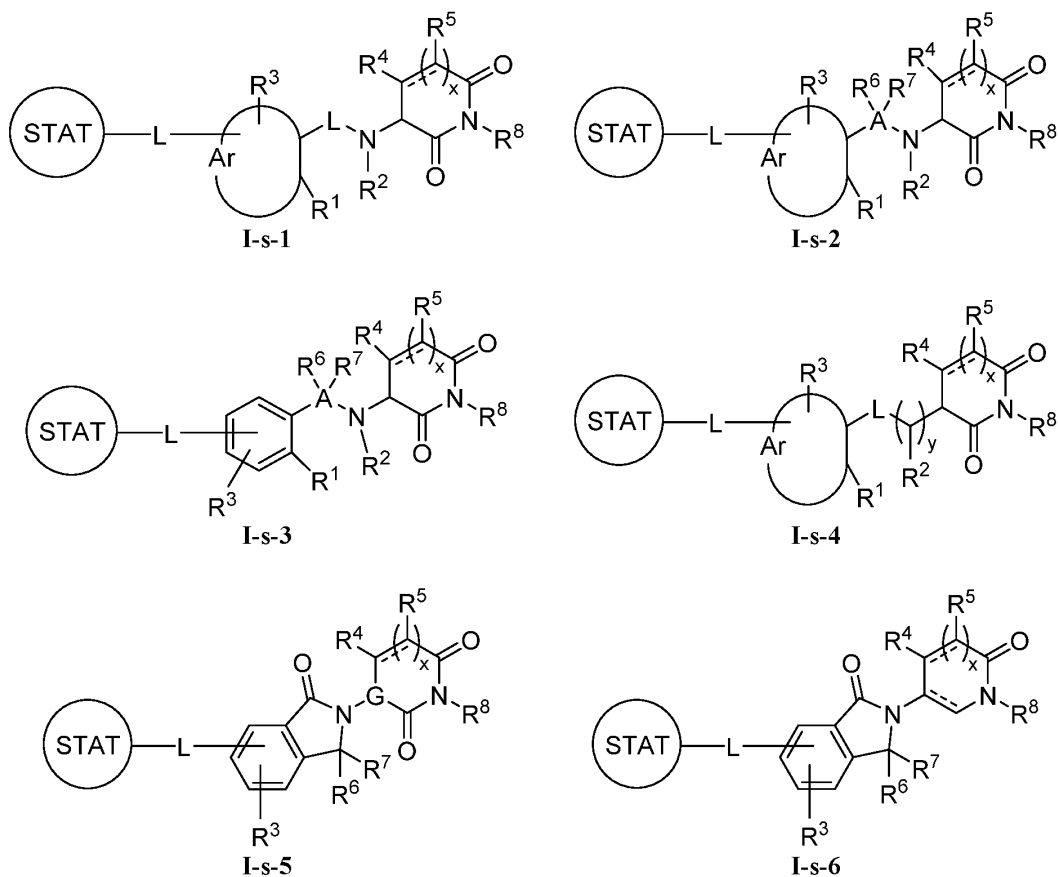
I-r-3

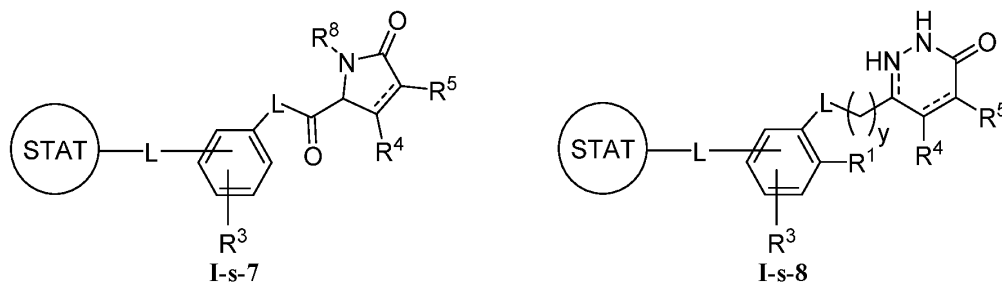
or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described herein, and wherein each of the variables R^1 , R^{14} , and R^{16} is as defined in WO 2018/237026, the entirety of

each of which is herein incorporated by reference, and wherein  is attached to R^1 or R^{16}

at the site of attachment of R^{12} as defined in WO 2018/237026, such that  takes the place of the R^{12} substituent.

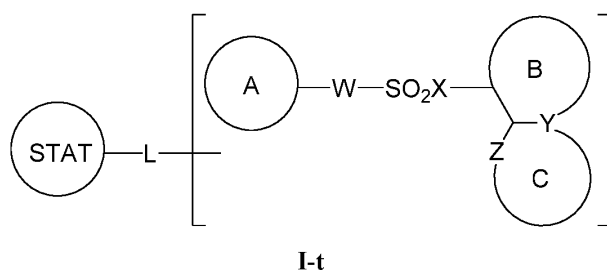
[00207] In certain embodiments, the present invention provides a compound of formula I, wherein LBM is an E3 ubiquitin ligase (cereblon) binding moiety thereby forming a compound of formula I-s-1, I-s-2, I-s-3, I-s-4, I-s-5, I-s-6, I-s-7, or I-s-8:





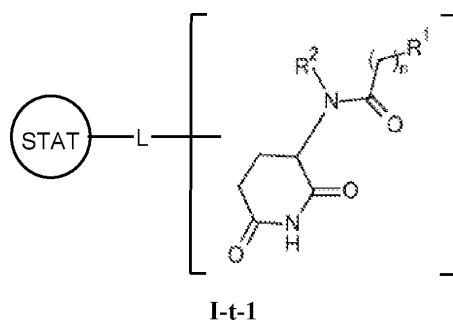
or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein each of the variables Ar, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, A, L, x, y, and --- is as described and defined in WO 2017/161119, the entirety of each of which is herein incorporated by reference.

[00208] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is an E3 ubiquitin ligase (cereblon) binding moiety thereby forming a compound of formula **I-t**:



or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein each of the variables A, B, C, W, X, Y, and Z is as described and defined in US 5,721,246, the entirety of each of which is herein incorporated by reference.

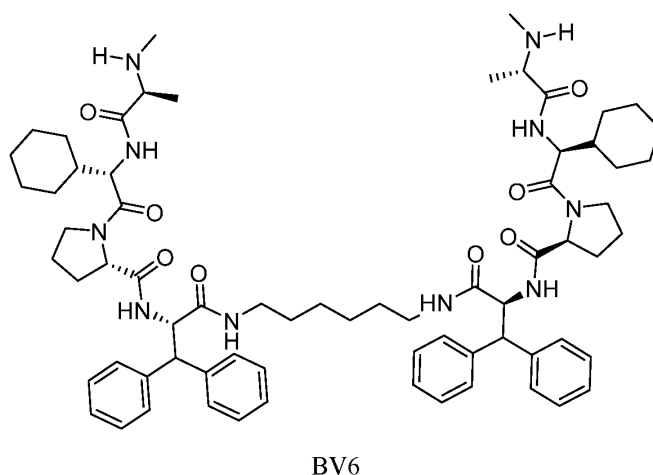
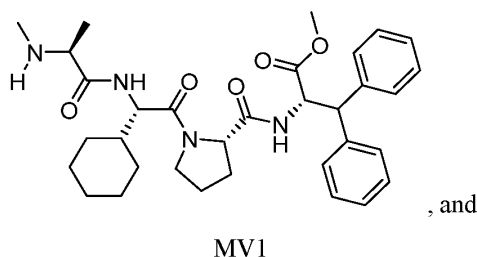
[00209] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is an E3 ubiquitin ligase (cereblon) binding moiety thereby forming a compound of formula **I-t-1**:



or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in

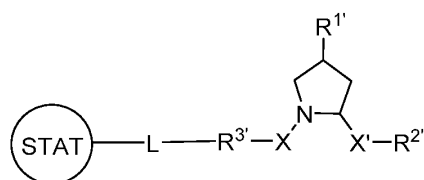
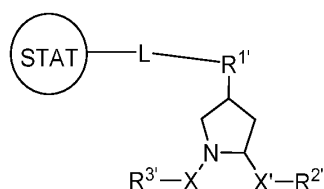
embodiments herein, and wherein each of the variables R_1 , R_2 , and n is as described and defined in WO 2019/043214, the entirety of each of which is herein incorporated by reference.

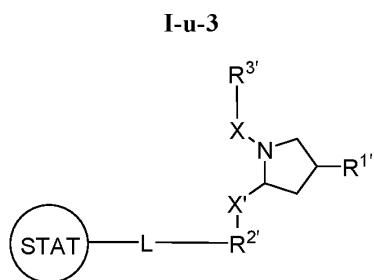
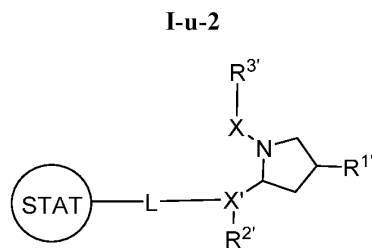
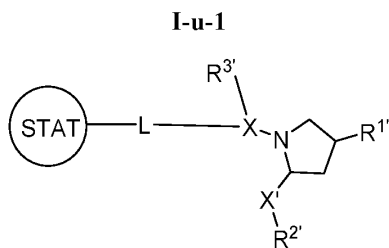
[00210] In some embodiments, LBM is a IAP E3 Ubiquitin ligase binding moiety recited in Varfolomeev, E. *et al.*, *IAP Antagonists Induce Autoubiquitination of c-IAPs, NF- κ B activation, and TNF α -Dependent Apoptosis*, Cell, 2007, 131(4): 669-81, such as, for example:



wherein —L— is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

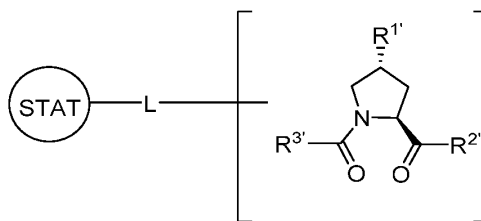
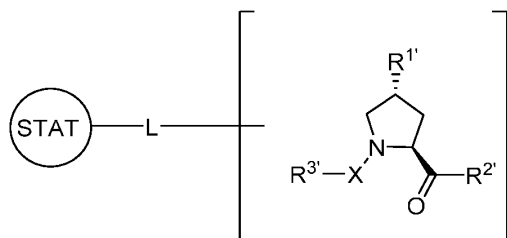
[00211] In certain embodiments, the present invention provides a compound of formula I, wherein LBM is a VHL E3 ubiquitin ligase binding moiety thereby forming a compound of formula I-u-1, I-u-2, I-u-3, I-u-4, or I-u-5 respectively:

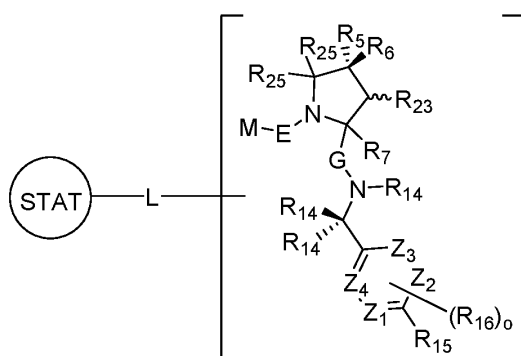


**I-u-4****I-u-5**

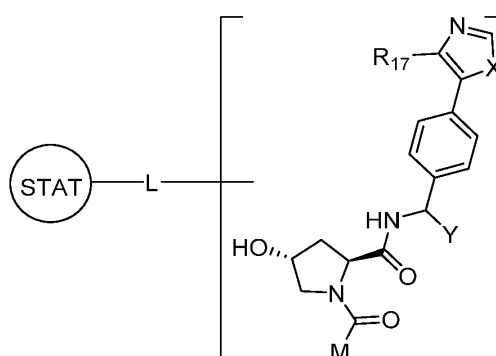
or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein each of the variables $R^{1'}$, $R^{2'}$, $R^{3'}$, X, and X' is as defined and described in WO 2013/106643 and US 2014/0356322, the entirety of each of which is herein incorporated by reference.

[00212] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a VHL E3 ubiquitin ligase binding moiety thereby forming a compound of formula **I-v-1**, **I-v-2**, **I-v-3**, **I-v-4**, **I-v-5** or **I-v-6** respectively:

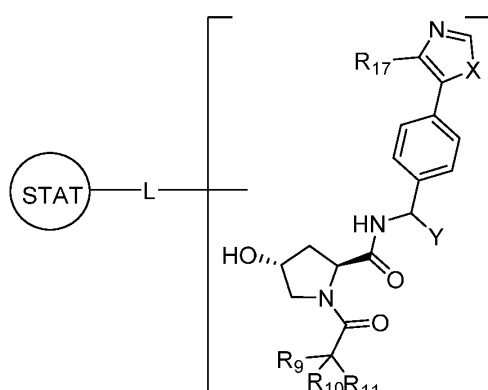




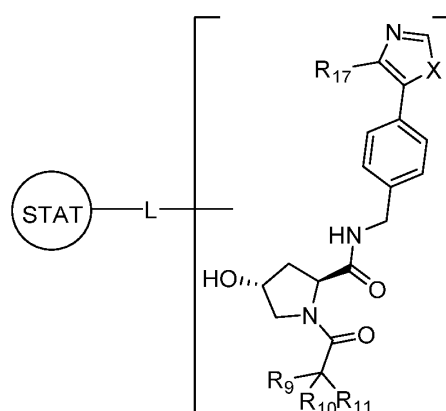
I-v-3



I-v-4

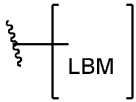


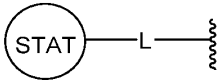
I-v-5

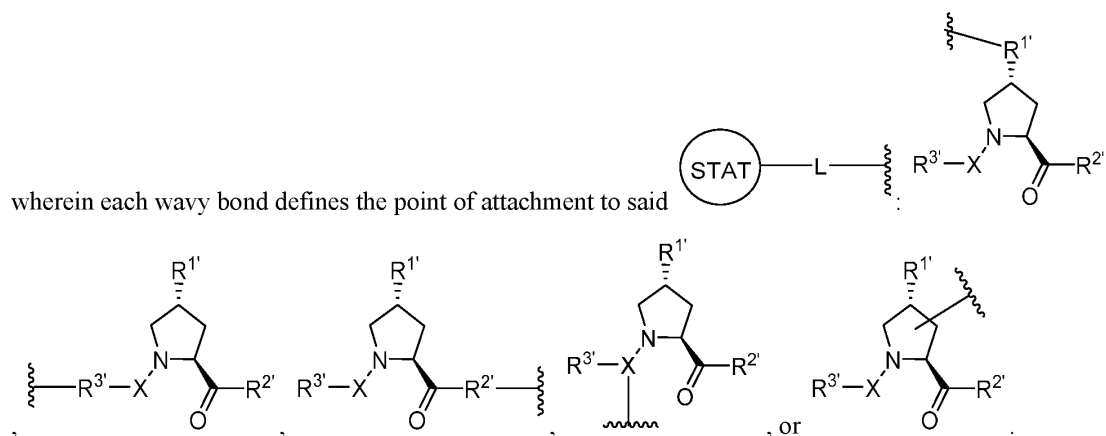


I-v-6

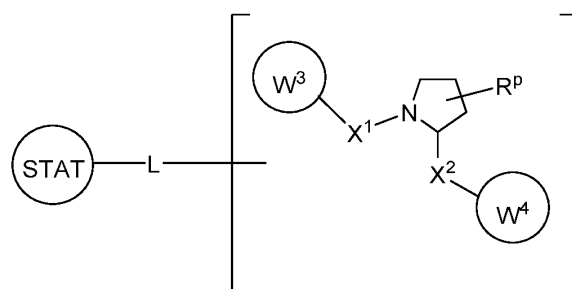
or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein each of the variables R^1 , R^2 , R^3 , R_5 , R_6 , R_7 , R_9 , R_{10} , R_{11} , R_{14} , R_{15} , R_{16} , R_{17} , R_{23} , R_{25} , E, G, M, X, X', Y, Z₁, Z₂, Z₃, Z₄, and o is as defined and described in WO 2016/149668 and US 2016/0272639, the entirety of each of which is herein incorporated by reference.

[00213] As used herein, depiction of brackets around any LBM  means that the

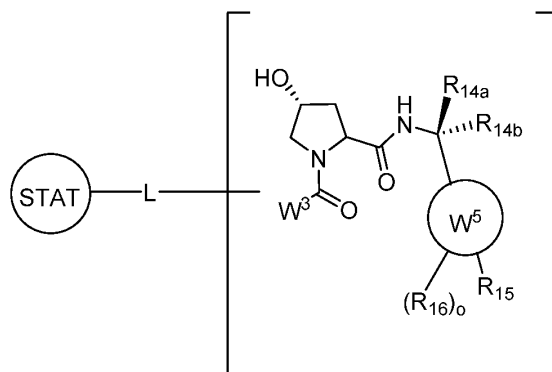
 moiety is covalently attached to said LBM at any available modifiable carbon, nitrogen, oxygen, or sulfur atom. For purposes of clarity and by way of example, such available modifiable carbon, nitrogen, oxygen, or sulfur atoms in the following LBM compound structure are depicted below,



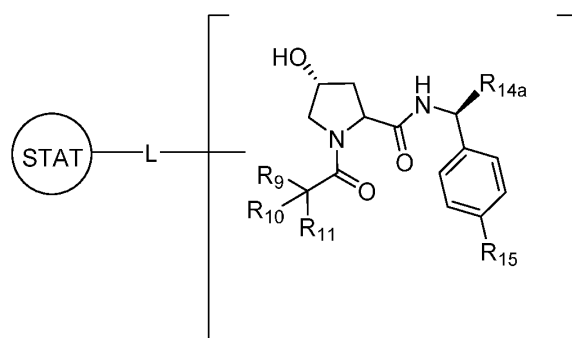
[00214] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a VHL E3 ubiquitin ligase binding moiety thereby forming a compound of formula **I-w-1**, **I-w-2**, or **I-w-3** respectively:



I-w-1

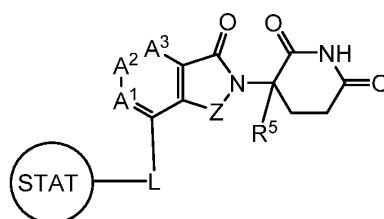
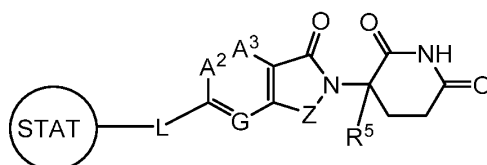
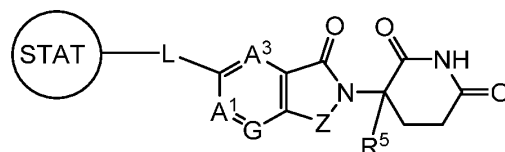


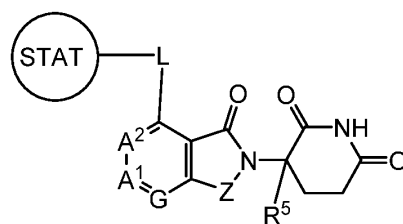
I-w-2

**I-w-3**

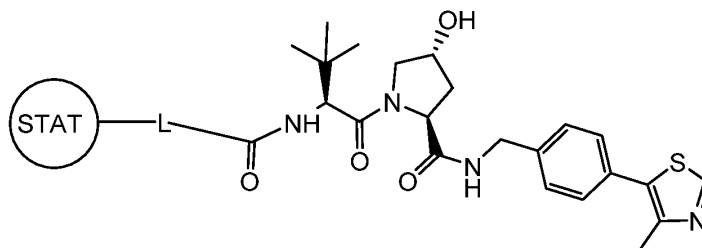
or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein each of the variables R^p , R_9 , R_{10} , R_{11} , R_{14a} , R_{14b} , R_{15} , R_{16} , W^3 , W^4 , W^5 , X^1 , X^2 , and o is as defined and described in WO 2016/118666 and US 2016/0214972, the entirety of each of which is herein incorporated by reference.

[00215] In certain embodiments, the present invention provides a compound of formula I, wherein LBM is a cereblon or VHL E3 ubiquitin ligase binding moiety thereby forming a compound of formula I-x-1, I-x-2, I-x-3, I-x-4, I-x-5, I-x-6, or I-x-7 respectively:

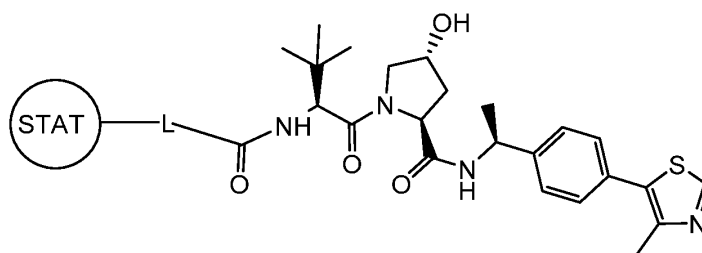
**I-x-1****I-x-2****I-x-3**



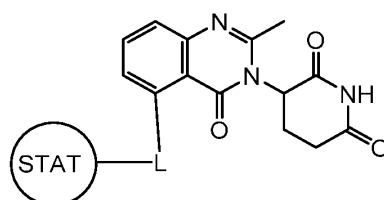
I-x-4



I-x-5



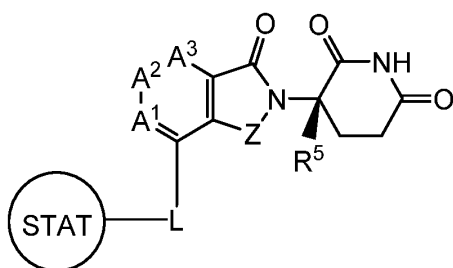
I-x-6



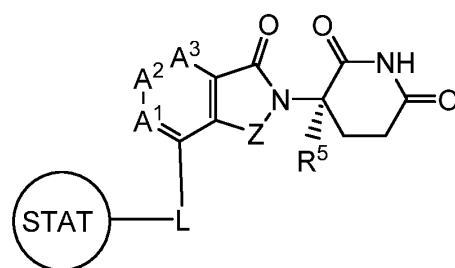
I-x-7

or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein each of the variables A¹, A², A³, R⁵, G and Z is as defined and described in WO 2017/176958.

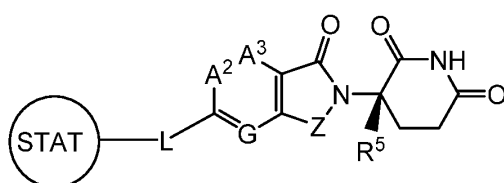
[00216] In certain embodiments, the present invention provides a compound of formula I, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety thereby forming a compound of formula I-x'-1, I-x''-1, I-x'-2, I-x''-2, I-x'-3, I-x''-3, I-x'-4, I-x''-4, I-x'-7 or I-x''-7 respectively:



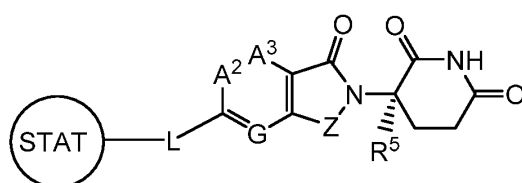
I-x'-1



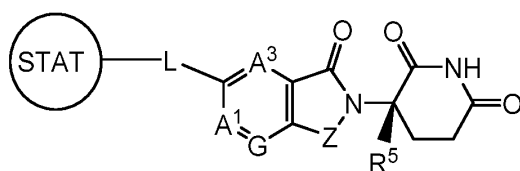
I-x''-1



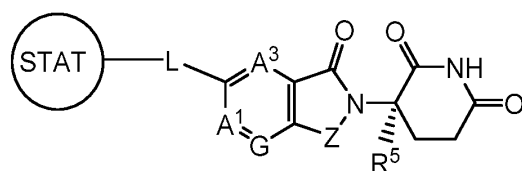
I-x'-2



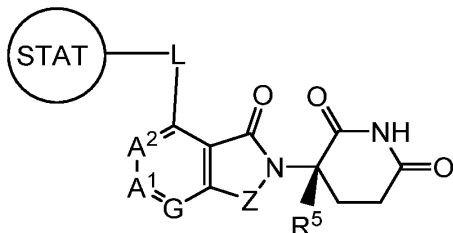
I-x''-2



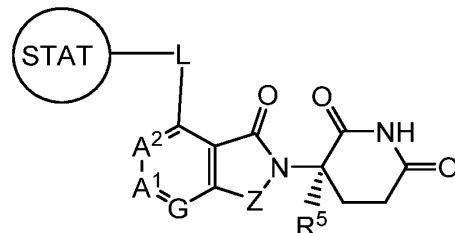
I-x'-3



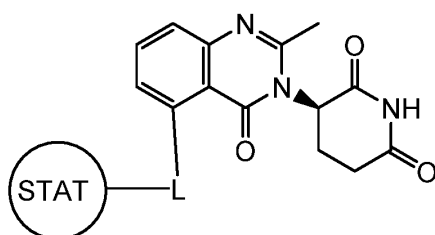
I-x''-3



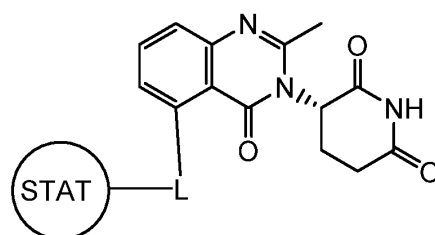
I-x'-4



I-x''-4



I-x'-7

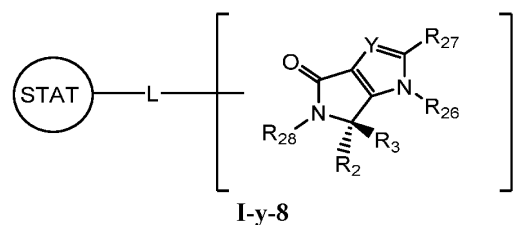
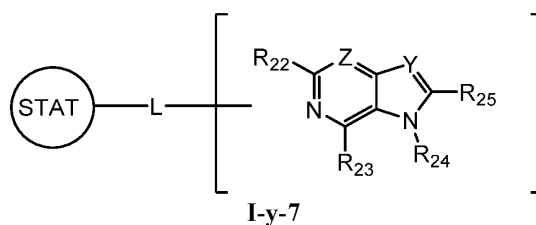
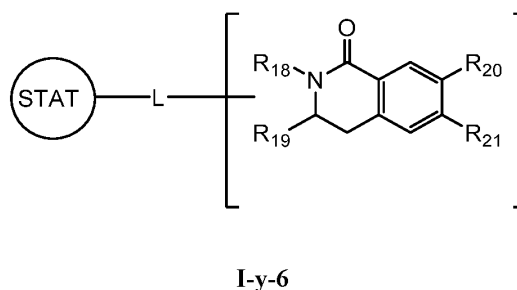
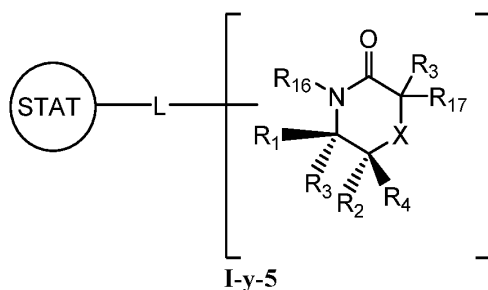
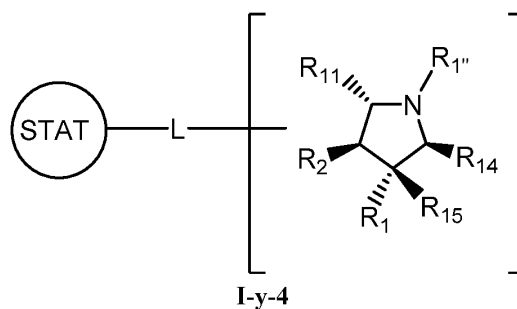
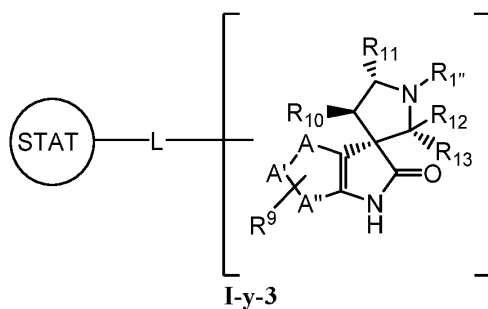
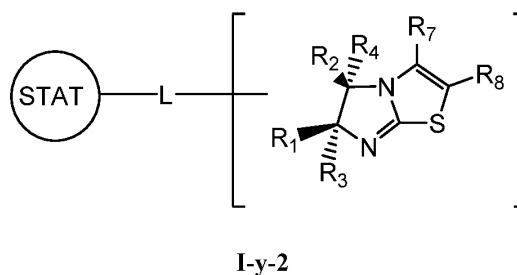
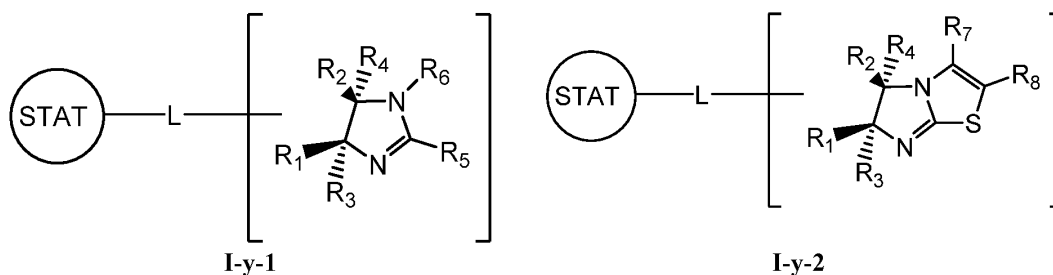


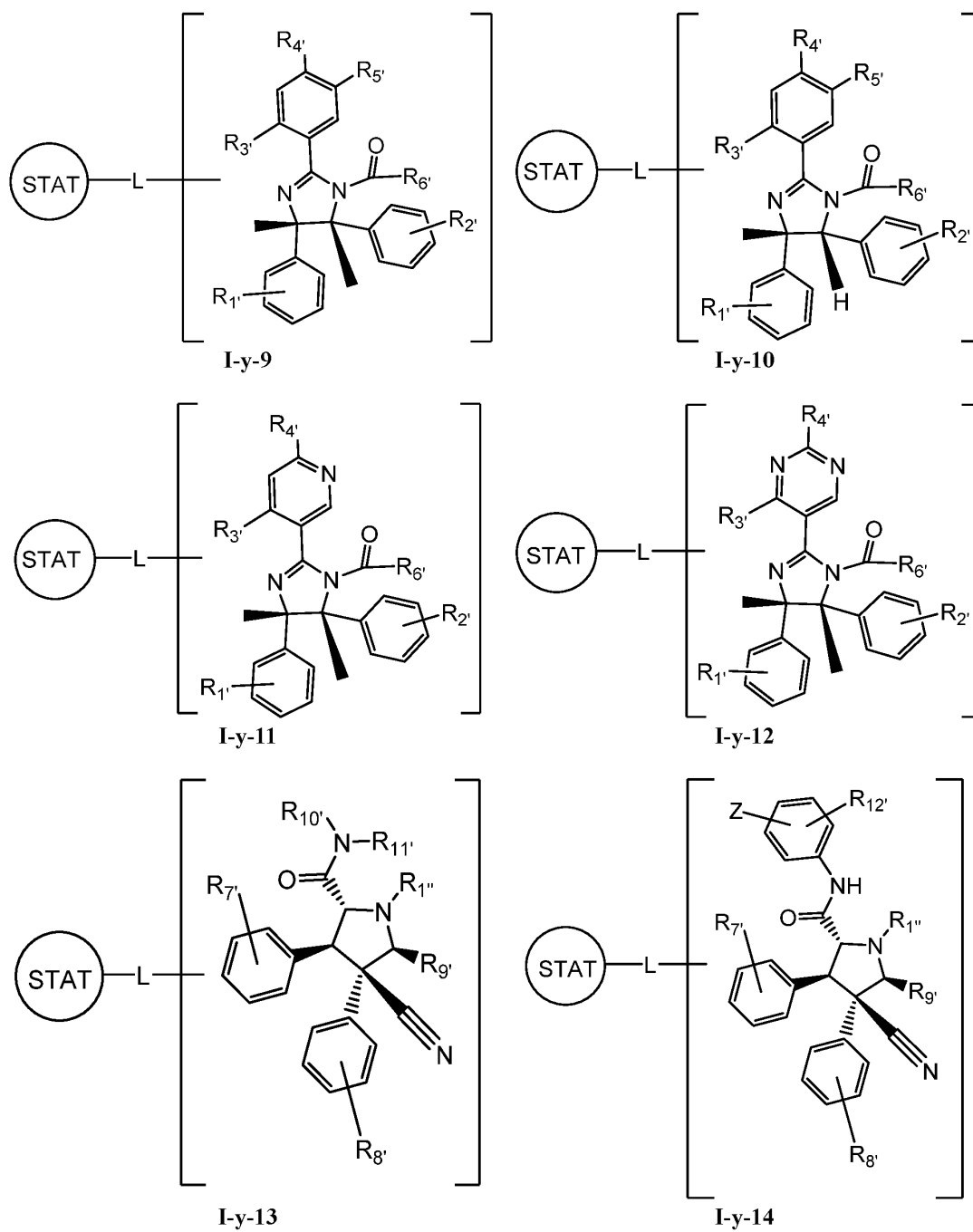
I-x''-7

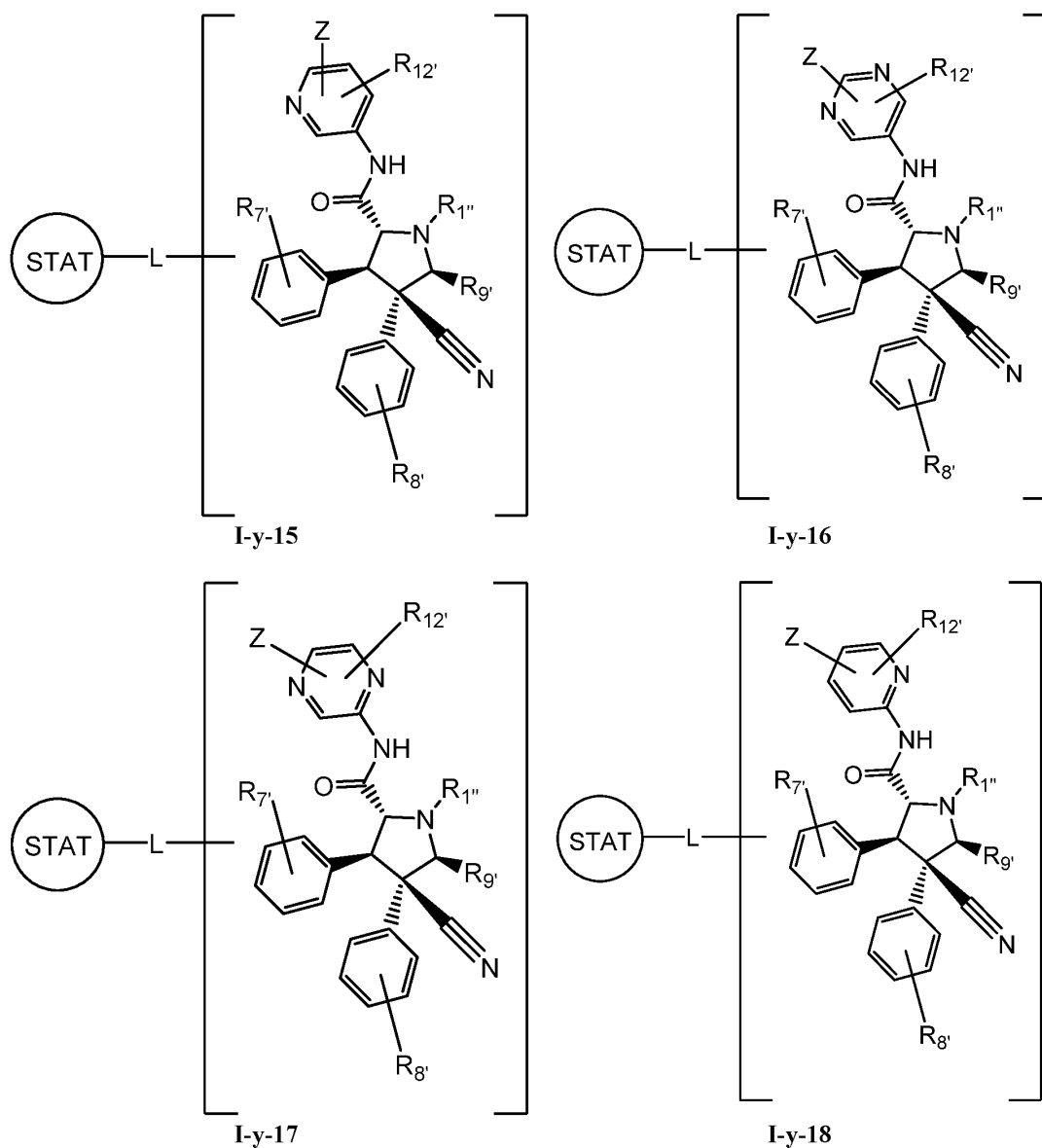
or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein each of the variables A¹, A², A³, R⁵, G and Z is as defined and described

in WO 2017/176958, the entirety of which is herein incorporated by reference.

[00217] In certain embodiments, the present invention provides a compound of formula I, wherein LBM is a MDM2 (i.e. human double minute 2 or HDM2) E3 ligase binding moiety thereby forming a compound of formula I-y-1, I-y-2, I-y-3, I-y-4, I-y-5, I-y-6, I-y-7, I-y-8, I-y-9, I-y-10, I-y-11, I-y-12, I-y-13, I-y-14, I-y-15, I-y-16, I-y-17, or I-y-18 respectively:



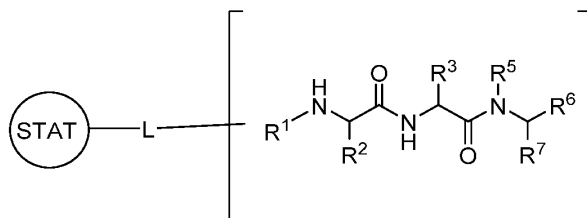
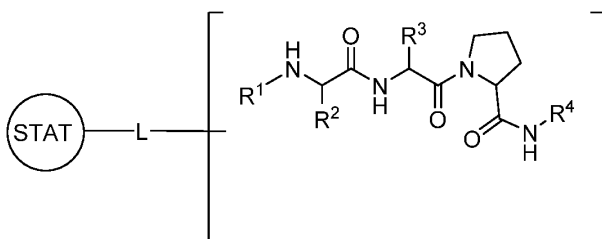
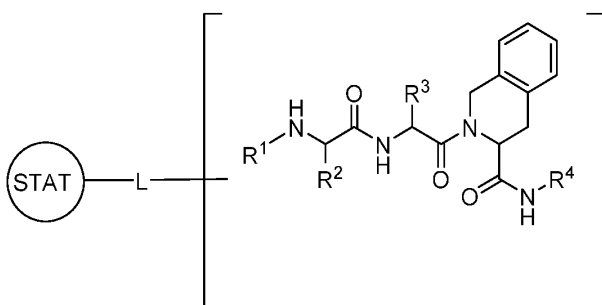
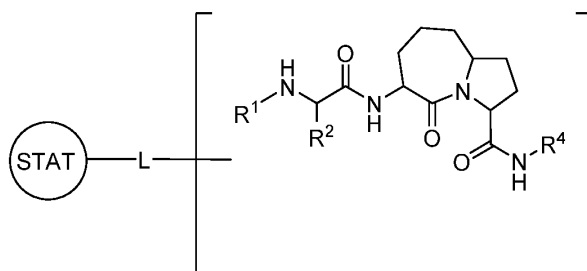




or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein each of the variables R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄, R₂₅, R₂₆, R₂₇, R₂₈, R_{1'}, R_{2'}, R_{3'}, R_{4'}, R_{5'}, R_{6'}, R_{7'}, R_{8'}, R_{9'}, R_{10'}, R_{11'}, R_{12'}, R_{1''}, A, A', A'', X, Y, and Z is as defined and described in WO 2017/011371 and US 2017/0008904, the entirety of each of which is herein incorporated by reference.

[00218] In certain embodiments, the present invention provides a compound of formula I, wherein

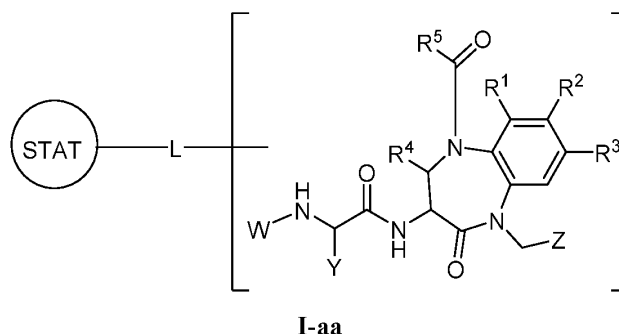
LBM is an IAP E3 ubiquitin ligase binding moiety thereby forming a compound of formula **I-z-1**, **I-z-2**, **I-z-3**, or **I-z-4** respectively:

**I-z-1****I-z-2****I-z-3****I-z-4**

or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein each of the variables R¹, R², R³, R⁴, R⁵, R⁶, and R⁷, is as defined and

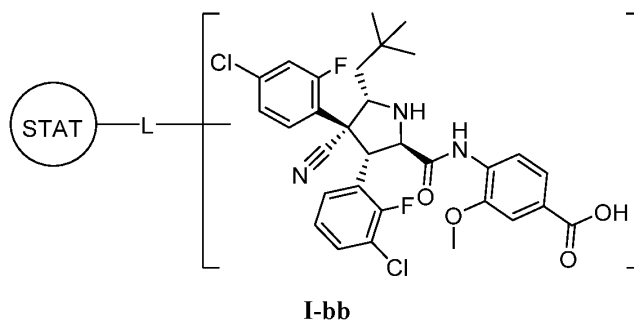
described in WO 2017/011590 and US 2017/0037004, the entirety of each of which is herein incorporated by reference.

[00219] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is an IAP binding moiety thereby forming a compound of formula **I-aa**:



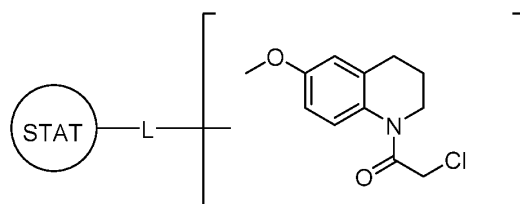
or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein each of the variables W, Y, Z, R¹, R², R³, R⁴, and R⁵ is as described and defined in WO 2014/044622, US 2015/0225449, WO 2015/071393, and US 2016/0272596, the entirety of each of which is herein incorporated by reference.

[00220] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a MDM2 binding moiety thereby forming a compound of formula **I-bb**:



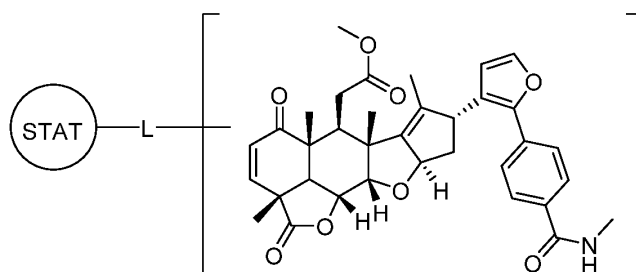
or a pharmaceutically acceptable salt thereof, as described and defined in Hines, J. et al., *Cancer Res.* (DOI: 10.1158/0008-5472.CAN-18-2918), the entirety of each of which is herein incorporated by reference.

[00221] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a DCAF16 binding moiety thereby forming a compound of formula **I-cc**:

**I-cc**

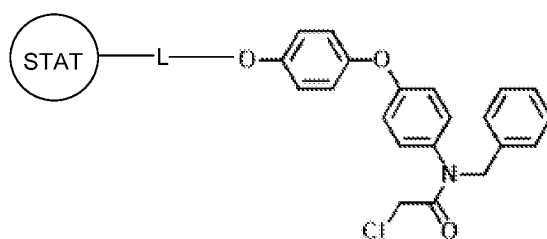
or a pharmaceutically acceptable salt thereof, as described and defined in Zhang, X. et al., *bioRxiv* (doi: <https://doi.org/10.1101/443804>), the entirety of each of which is herein incorporated by reference.

[00222] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a RNF114 binding moiety thereby forming a compound of formula **I-dd**:

**I-dd**

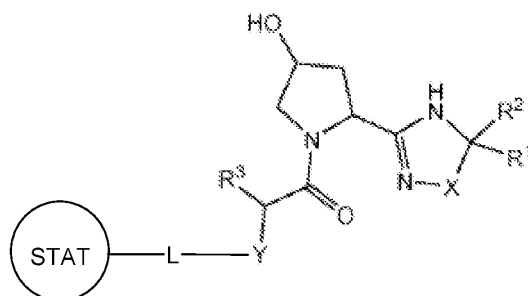
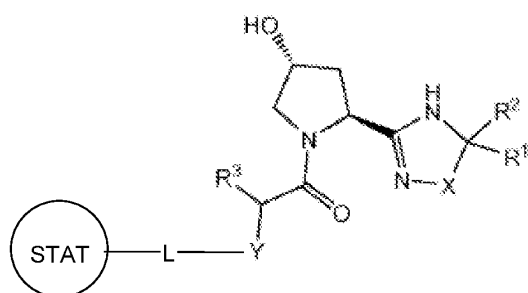
or a pharmaceutically acceptable salt thereof, as described and defined in Spradin, J.N. et al., *bioRxiv* (doi: <https://doi.org/10.1101/436998>), the entirety of each of which is herein incorporated by reference.

[00223] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a RNF4 binding moiety thereby forming a compound of formula **I-ee**:

**I-ee**

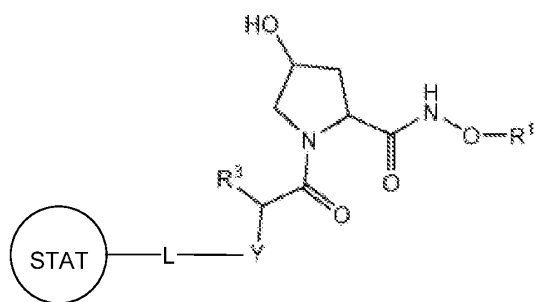
or a pharmaceutically acceptable salt thereof, as described and defined in Ward, C.C., et al., *bioRxiv* (doi: <https://doi.org/10.1101/439125>), the entirety of each of which is herein incorporated by reference.

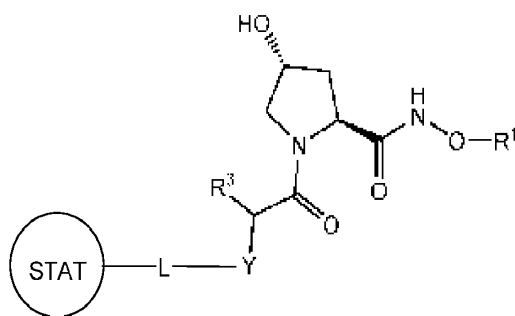
[00224] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a VHL binding moiety thereby forming a compound of formula **I-ff-1** or **I-ff-2**:

**I-ff-1****I-ff-2**

or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein each of the variables R^1 , R^2 , R^3 , X, and Y is as defined and described in WO 2019/084026, the entirety of each of which is herein incorporated by reference.

[00225] In certain embodiments, the present invention provides a compound of formula I, wherein LBM is a VHL binding moiety thereby forming a compound of formula **I-gg-1** or **I-gg-2**:

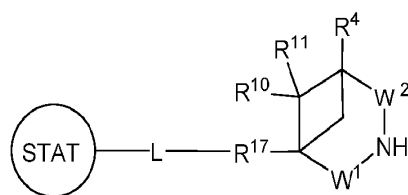
**I-gg-1**



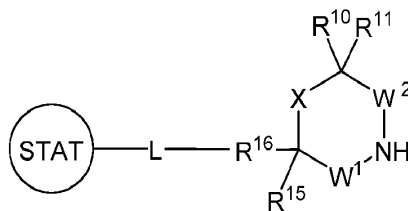
I-gg-2

or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein each of the variables R¹, R³, and Y is as defined and described in WO 2019/084030, the entirety of each of which is herein incorporated by reference.

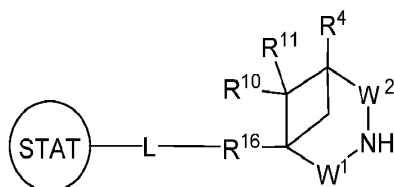
[00226] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a E3 ubiquitin ligase (cereblon) binding moiety thereby forming a compound of formula **I-hh-1**, **I-hh-2**, **I-hh-3**, or **I-hh-4**:



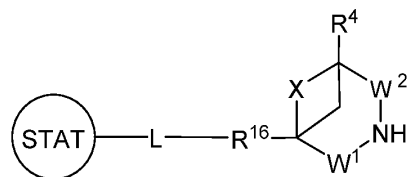
I-hh-1



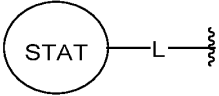
I-hh-2

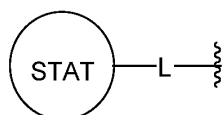


I-hh-3

**I-hh-4**

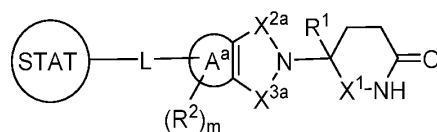
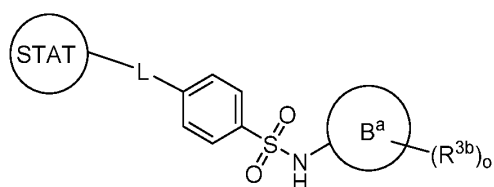
or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described herein, and wherein each of the variables R^4 , R^{10} , R^{11} , R^{15} , R^{16} , R^{17} , W^1 , W^2 , and X is as defined in WO

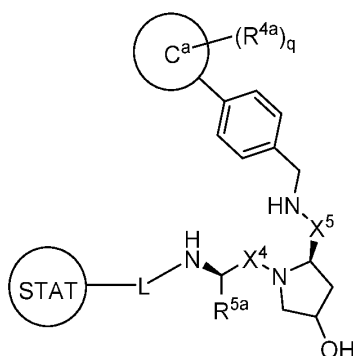
2019/099868 which is herein incorporated by reference in its entirety, and wherein  is attached to R^{17} or R^{16} at the site of attachment of R^{12} as defined in WO 2018/237026, such that



takes the place of the R^{12} substituent.

[00227] In certain embodiments, the present invention provides a compound of formula I, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety, a DCAF15 E3 ubiquitin ligase binding moiety, or a VHL E3 ubiquitin ligase binding moiety; thereby forming a compound of formula I-ii-1, I-ii-2, or I-ii-3:

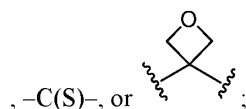
**I-ii-1****I-ii-2**



I-ii-3

or a pharmaceutically acceptable salt thereof, wherein L and STAT is as defined above and described in embodiments herein, and wherein:

each of X^1 , X^{2a} , and X^{3a} is independently a bivalent moiety selected from a covalent bond, $-\text{CH}_2-$, $-\text{C}(\text{O})-$



each of X^4 and X^5 is independently a bivalent moiety selected from $-\text{CH}_2-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{S})-$, and



R^1 is hydrogen, deuterium, halogen, $-\text{CN}$, $-\text{OR}$, $-\text{SR}$, $-\text{S}(\text{O})\text{R}$, $-\text{S}(\text{O})_2\text{R}$, $-\text{NR}_2$, or an optionally substituted C_{1-4} aliphatic;

each of R^2 , R^{3b} , and R^{4a} is independently hydrogen, R^6 , halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}$, $-\text{SR}$, $-\text{NR}_2$, $-\text{S}(\text{O})_2\text{R}$, $-\text{S}(\text{O})_2\text{NR}_2$, $-\text{S}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{OR}$, $-\text{C}(\text{O})\text{NR}_2$, $-\text{C}(\text{O})\text{N}(\text{R})\text{OR}$, $-\text{OC}(\text{O})\text{R}$, $-\text{OC}(\text{O})\text{NR}_2$, $-\text{N}(\text{R})\text{C}(\text{O})\text{OR}$, $-\text{N}(\text{R})\text{C}(\text{O})\text{R}$, $-\text{N}(\text{R})\text{C}(\text{O})\text{NR}_2$, or $-\text{N}(\text{R})\text{S}(\text{O})_2\text{R}$;

R^{5a} is hydrogen or C_{1-6} aliphatic;

each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring A^a is a fused ring selected from 6-membered aryl containing 0-2 nitrogen atoms, 5 to 7-membered partially saturated carbocyclyl, 5 to 7-membered partially saturated heterocyclyl with 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, or 5-membered heteroaryl with

1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur;

Ring B^a is selected from 6-membered aryl containing 0-2 nitrogen atoms or a 8-10 membered bicyclic heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring C^a is selected from 6-membered aryl containing 0-2 nitrogen atoms or a 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur;

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

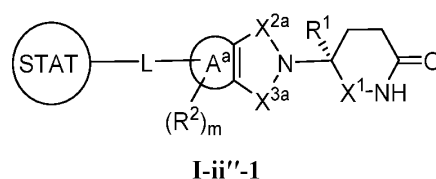
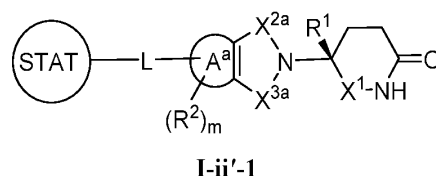
o is 0, 1, 2, 3 or 4;

q is 0, 1, 2, 3 or 4; and

each R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

[00228] In certain embodiments, the present invention provides a compound of formula I-ii, wherein LBM is an E3 ubiquitin ligase (cereblon) binding moiety thereby forming a compound of formula I-ii'-1 or I-ii''-1:



or a pharmaceutically acceptable salt thereof, wherein STAT, L, Ring A^a, X¹, X^{2a}, X^{3a}, R¹, R² and m are as described above.

[00229] As defined above and described herein, each of X¹, X^{2a}, and X^{3a} is independently a bivalent

C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, or -N(R)S(O)₂R.

[00245] In some embodiments, R² is hydrogen, -R⁶, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, or -N(R)S(O)₂R.

[00246] In some embodiments, R² is selected from those depicted in **Table 1**, below.

[00247] In some embodiments, R^{3b} is hydrogen, -R⁶, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, or -N(R)S(O)₂R.

[00248] In some embodiments, R^{3b} is methyl.

[00249] In some embodiments, R^{3b} is selected from those depicted in **Table 1**, below.

[00250] In some embodiments, R^{4a} is hydrogen, -R⁶, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, or -N(R)S(O)₂R.

[00251] In some embodiments, R^{4a} is methyl.

[00252] In some embodiments, R^{4a} is selected from those depicted in **Table 1**, below.

[00253] As defined above and described herein, R^{5a} is hydrogen or C₁₋₆ aliphatic.

[00254] In some embodiments, R^{5a} is *t*-butyl.

[00255] In some embodiments, R^{5a} is selected from those depicted in **Table 1**, below.

[00256] As defined above and described herein, each R⁶ is independently an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00257] In some embodiments, R⁶ is an optionally substituted C₁₋₆ aliphatic group. In some embodiments, R⁶ is an optionally substituted phenyl. In some embodiments, R⁶ is an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R⁶ is an optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00258] In some embodiments, R⁶ is selected from those depicted in **Table 1**, below.

[00259] As defined above and described herein, Ring A^a is a fused ring selected from 6-membered aryl containing 0-2 nitrogen atoms, 5 to 7-membered partially saturated carbocyclyl, 5 to 7-membered partially saturated heterocyclyl with 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, or 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur.

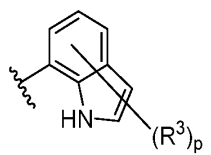
[00260] In some embodiments Ring A^a is a fused 6-membered aryl containing 0-2 nitrogen atoms. In some embodiments Ring A^a is a fused 5 to 7-membered partially saturated carbocyclyl. In some embodiments Ring A^a is a fused 5 to 7-membered partially saturated heterocyclyl with 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur. In some embodiments Ring A^a is a fused 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur.

[00261] In some embodiments, Ring A^a is a fused phenyl.

[00262] In some embodiments, Ring A^a is selected from those depicted in **Table 1**, below.

[00263] As defined above and described herein, Ring B^a is selected from 6-membered aryl containing 0-2 nitrogen atoms or a 8-10 membered bicyclic heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00264] In some embodiments, Ring B^a is a 6-membered aryl containing 0-2 nitrogen atoms. In some embodiments, Ring B^a is a 8-10 membered bicyclic heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

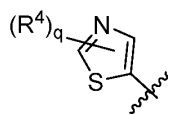


[00265] In some embodiments, Ring B^a is

[00266] In some embodiments, Ring B^a is selected from those depicted in **Table 1**, below.

[00267] As defined above and described herein, Ring C^a is selected from 6-membered aryl containing 0-2 nitrogen atoms or a 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur.

[00268] In some embodiments, Ring C^a is a 6-membered aryl containing 0-2 nitrogen atoms. In some embodiments, Ring C^a is a 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur.



[00269] In some embodiments, Ring C^a is

[00270] In some embodiments, Ring C^a is selected from those depicted in **Table 1**, below.

[00271] As defined above and described herein, m is 0, 1, 2, 3 or 4.

[00272] In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 4.

[00273] In some embodiments, m is selected from those depicted in **Table 1**, below.

[00274] In some embodiments, o is selected from those depicted in **Table 1**, below.

[00275] As defined above and described herein, o is 0, 1, 2, 3 or 4.

[00276] In some embodiments, o is 0. In some embodiments, o is 1. In some embodiments, o is 2. In some embodiments, o is 3. In some embodiments, o is 4.

[00277] In some embodiments, o is selected from those depicted in **Table 1**, below.

[00278] As defined above and described herein, q is 0, 1, 2, 3 or 4.

[00279] In some embodiments, q is 0. In some embodiments, q is 1. In some embodiments, q is 2. In some embodiments, q is 3. In some embodiments, q is 4.

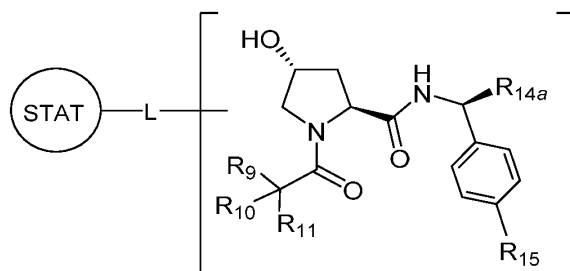
[00280] In some embodiments, q is selected from those depicted in **Table 1**, below.

[00281] As defined above and described herein, each R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or: two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

[00282] In some embodiments, R is hydrogen. In some embodiments, R is phenyl. In some embodiments, R is a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

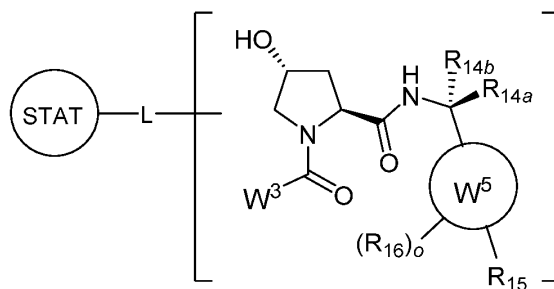
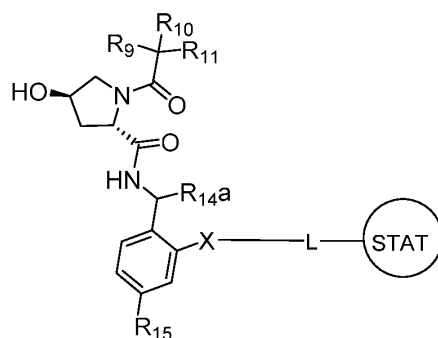
[00283] In some embodiments, R is selected from those depicted in **Table 1**, below.

[00284] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a VHL binding moiety thereby forming a compound of formula **I-jj**:

**I-jj**

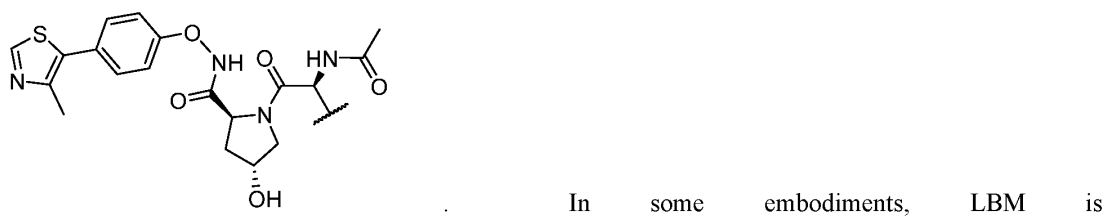
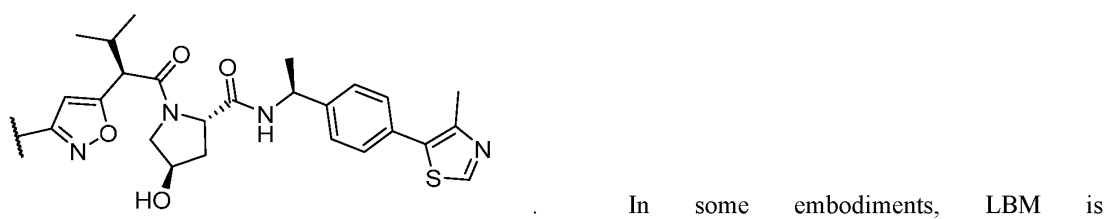
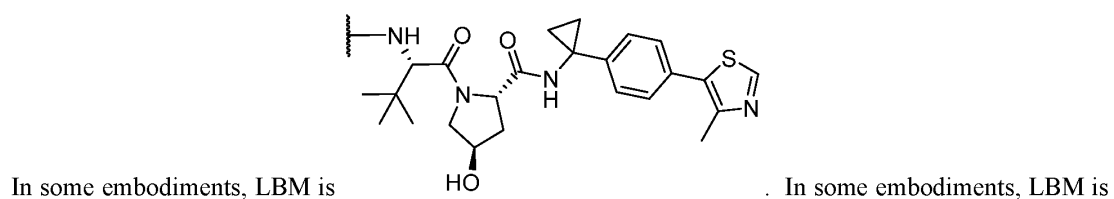
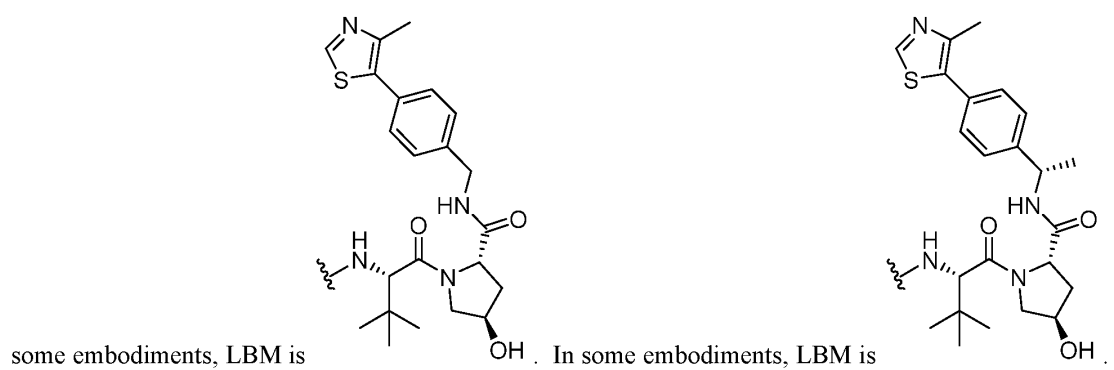
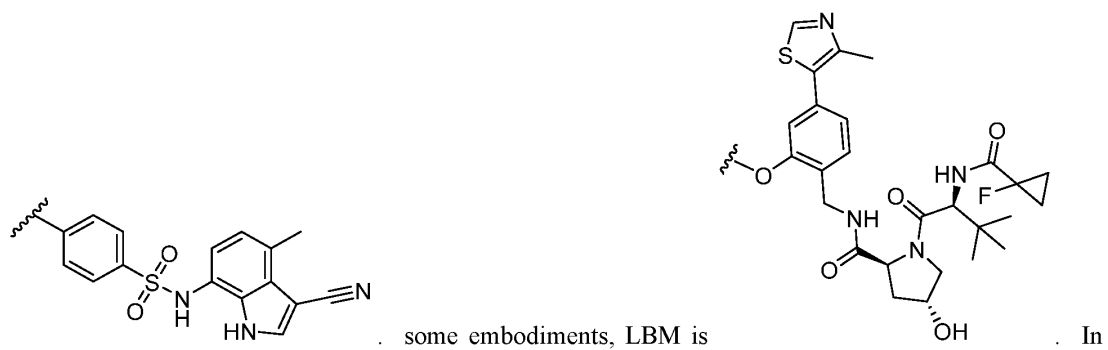
or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein each of the variables R_9 , R_{10} , R_{11} , R_{14a} , and R_{15} is as described and defined in WO 2017/030814, WO 2016/118666, and US 2017/0327469, the entirety of each of which is herein incorporated by reference.

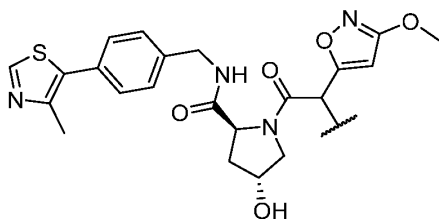
[00285] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a VHL binding moiety thereby forming a compound of formula **I-kk-1** or **I-kk-2**:

**I-kk-1****I-kk-2**

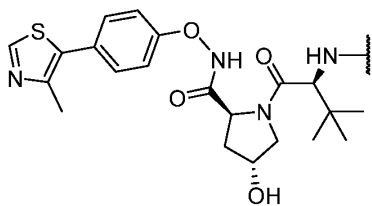
[00286] or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein each of the variables X , W^3 , W^5 , R_9 , R_{10} , R_{11} , R_{14a} , R_{14b} , R_{15} , R_{16} , and o is as described and defined in WO 2017/030814, WO 2016/118666, and US 2017/0327469, the

entirety of each of which is herein incorporated by reference. In some embodiments, LBM is

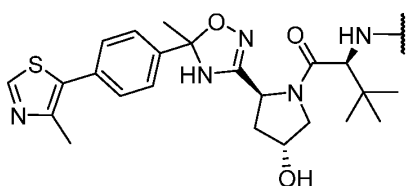




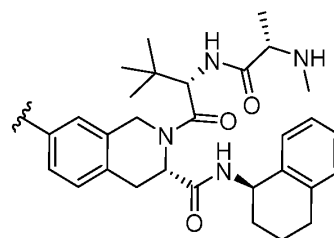
In some embodiments, LBM is



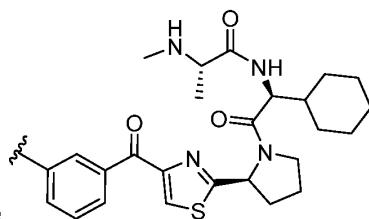
In some embodiments, LBM is



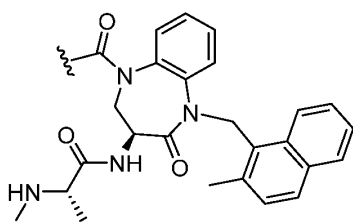
In some embodiments, LBM is



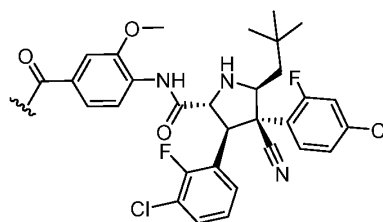
In some embodiments, LBM is



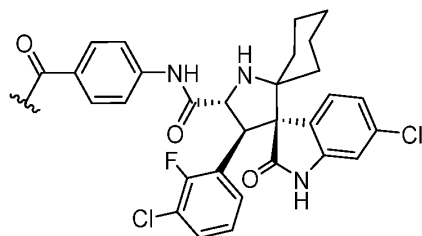
In some embodiments, LBM is



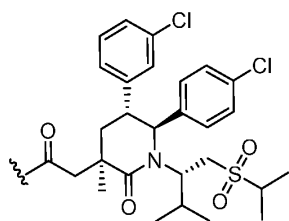
In some embodiments, LBM is



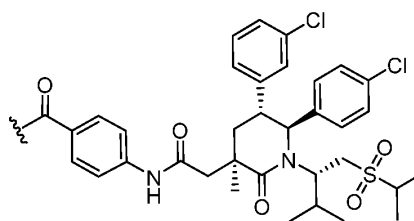
In some embodiments, LBM is



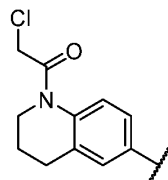
In some embodiments, LBM is



. In some embodiments, LBM is

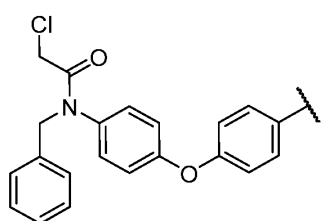


. In

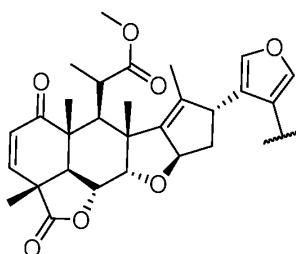


some embodiments, LBM is

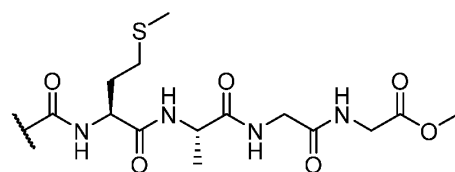
In some embodiments, LBM is



. In some embodiments, LBM is

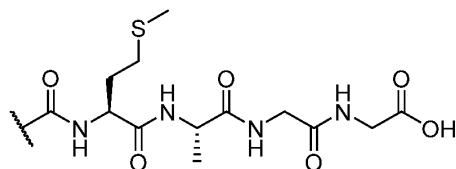


. In some

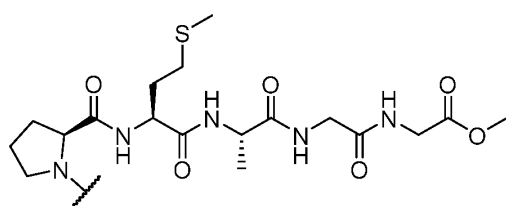


embodiments, LBM is

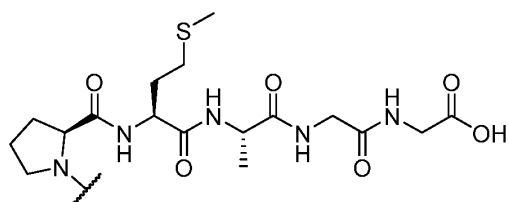
. In some embodiments, LBM is



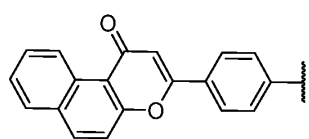
In some embodiments, LBM is



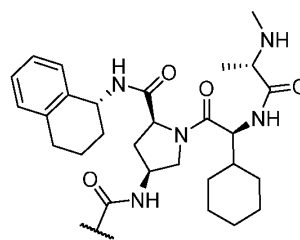
In some embodiments, LBM is



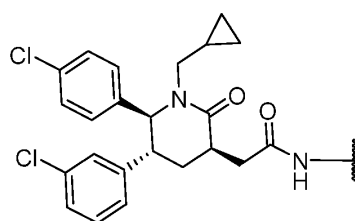
In some embodiments, LBM is



In some embodiments, LBM is

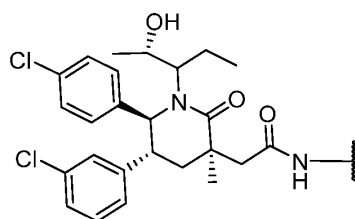


In some

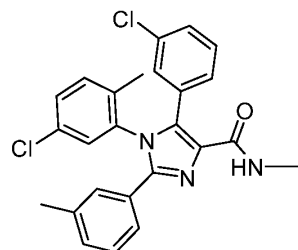


embodiments, LBM is

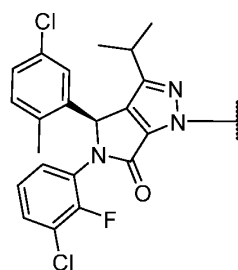
In some embodiments, LBM is



In some embodiments, LBM is

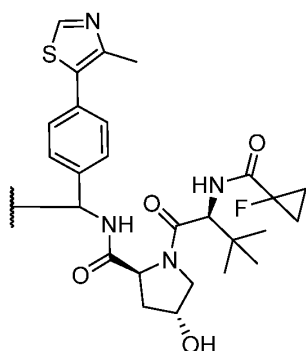


In some

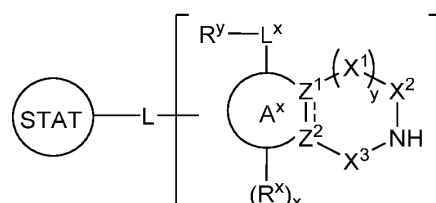


embodiments, LBM is

In some embodiments, LBM is

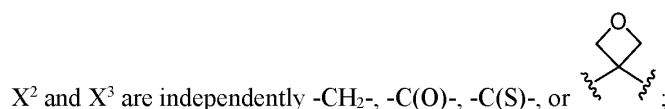
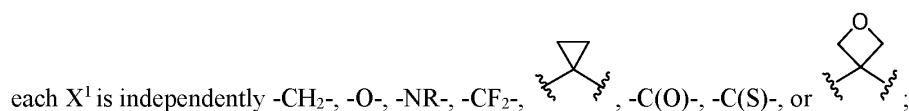


[00287] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a E3 ubiquitin ligase (cereblon) binding moiety thereby forming a compound of formula formula **I-II**:



I-II

or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, wherein:



Z^1 and Z^2 are independently a carbon atom or a nitrogen atom;

Ring A^x is a fused ring selected from benzo or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L^x is a covalent bond or a C₁₋₃ bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -S-, -C(O)-, -C(S)-, -CR₂-, -CRF-, -CF₂-, -NR-, or -S(O)₂-;

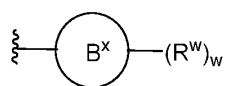
each R^x is independently selected from hydrogen, deuterium, R^z, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -CF₂R, -CF₃, -CR₂(OR), -CR₂(NR₂), -C(O)R, -C(O)OR, -

C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -C(S)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)S(O)₂R, -OP(O)R₂, -OP(O)(OR)₂, -OP(O)(OR)NR₂, -OP(O)(NR₂)₂, -Si(OR)R₂, and -SiR₃; or

two R^x groups are optionally taken together to form an optionally substituted 5-8 membered partially unsaturated or aryl fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently selected from hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the carbon or nitrogen, independently selected from nitrogen, oxygen, and sulfur;



R^y is selected from or hydrogen;

Ring B^x is phenyl, a 4-10 membered saturated or partially unsaturated mono- or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring B^x is further optionally substituted with 1-2 oxo groups;

each R^w is independently selected from hydrogen, deuterium, R^z, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -CF₂R, -CF₃, -CR₂(OR), -CR₂(NR₂), -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)S(O)₂R, -OP(O)R₂, -OP(O)(OR)₂, -OP(O)(OR)NR₂, -OP(O)(NR₂)₂, and -SiR₃;

each R^z is independently selected from an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

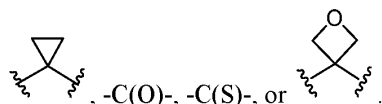
=== is a single or double bond;

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

y is 0, 1 or 2; and

w is 0, 1, 2, 3 or 4.

[00288] As defined above and described herein, each X^1 is independently $-\text{CH}_2-$, $-\text{O}-$, $-\text{NR}-$, $-\text{CF}_2-$,



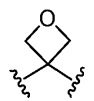
[00289] In some embodiments, X^1 is a covalent bond. In some embodiments, X^1 is $-\text{CH}_2-$. In some embodiments, X^1 is $-\text{O}-$. In some embodiments, X^1 is $-\text{NR}-$. In some embodiments, X^1 is $-\text{CF}_2-$. In some

embodiments, X^1 is . In some embodiments, X^1 is $-\text{C}(\text{O})-$. In some embodiments, X^1 is $-\text{C}(\text{S})-$.

In some embodiments, X^1 is .

[00290] In certain embodiments, X^1 is selected from those shown in the compounds of **Table 1**.

[00291] As defined above and described herein, X^2 and X^3 are independently $-\text{CH}_2-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{S})-$, or



[00292] In some embodiments, X^2 and X^3 are independently $-\text{CH}_2-$. In some embodiments, X^2 and X^3 are independently $-\text{C}(\text{O})-$. In some embodiments, X^2 and X^3 are independently $-\text{C}(\text{S})-$. In some

embodiments, X^2 and X^3 are independently .

[00293] In certain embodiments, X^2 and X^3 are independently selected from those shown in the compounds of **Table 1**.

[00294] As define above and described herein, Z^1 and Z^2 are independently a carbon atom or a nitrogen atom.

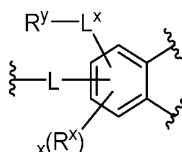
[00295] In some embodiments, Z^1 and Z^2 are independently a carbon atom. In some embodiments, Z^1 and Z^2 are independently a carbon atom.

[00296] In certain embodiments, Z^1 and Z^2 are independently selected from those shown in the compounds of **Table 1**.

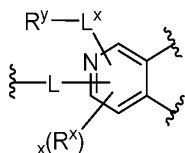
[00297] As defined above and described herein, Ring A^x is fused ring selected from benzo or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00298] In some embodiments, Ring A^x is benzo. In some embodiments, Ring A^x is a 5-6 membered

heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.



[00299] In some embodiments, Ring A^x is . In some embodiments, Ring A^x is



[00300] In certain embodiments, Ring A^x is selected from those shown in the compounds of **Table 1**.

[00301] As defined above and described herein, L^x is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with $-O-$, $-S-$, $-C(O)-$, $-C(S)-$, $-CR_2-$, $-CRF-$, $-CF_2-$, $-NR-$, or $-S(O)_2-$.

[00302] In some embodiments, L^x is a covalent bond. In some embodiments, L^x is a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with $-O-$, $-S-$, $-C(O)-$, $-C(S)-$, $-CR_2-$, $-CRF-$, $-CF_2-$, $-NR-$, or $-S(O)_2-$.

[00303] In some embodiments, L^x is $-C(O)-$.

[00304] In certain embodiments, L^x is selected from those shown in the compounds of **Table 1**.

[00305] As defined above and described herein, each R^x is independently selected from hydrogen, deuterium, R^z , halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-C(S)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-Si(OR)R_2$, and $-SiR_3$, or two R^x groups are optionally taken together to form an optionally substituted 5-8 membered partially unsaturated or aryl fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

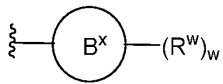
[00306] In some embodiments, R^x is hydrogen. In some embodiments, R^x is deuterium. In some embodiments, R^x is R^z . In some embodiments, R^x is halogen. In some embodiments, R^x is $-CN$. In some embodiments, R^x is $-NO_2$. In some embodiments, R^x is $-OR$. In some embodiments, R^x is $-SR$. In some embodiments, R^x is $-NR_2$. In some embodiments, R^x is $-S(O)_2R$. In some embodiments, R^x is $-S(O)_2NR_2$. In some embodiments, R^x is $-S(O)R$. In some embodiments, R^x is $-CF_2R$. In some embodiments, R^x is $-CF_3$. In some embodiments, R^x is $-CR_2(OR)$. In some embodiments, R^x is $-CR_2(NR_2)$. In some

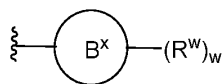
embodiments, R^x is $-C(O)R$. In some embodiments, R^x is $-C(O)OR$. In some embodiments, R^x is $-C(O)NR_2$. In some embodiments, R^x is $-C(O)N(R)OR$. In some embodiments, R^x is $-OC(O)R$. In some embodiments, R^x is $-OC(O)NR_2$. In some embodiments, R^x is $-C(S)NR_2$. In some embodiments, R^x is $-N(R)C(O)OR$. In some embodiments, R^x is $-N(R)C(O)R$. In some embodiments, R^x is $-N(R)C(O)NR_2$. In some embodiments, R^x is $-N(R)S(O)_2R$. In some embodiments, R^x is $-OP(O)R_2$. In some embodiments, R^x is $-OP(O)(OR)_2$. In some embodiments, R^x is $-OP(O)(OR)NR_2$. In some embodiments, R^x is $-OP(O)(NR_2)_2$. In some embodiments, R^x is $-Si(OR)R_2$. In some embodiments, R^x is $-SiR_3$. In some embodiments, two R^x groups are optionally taken together to form an optionally substituted 5-8 membered partially unsaturated or aryl fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

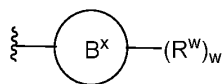
[00307] In certain embodiments, each R^x is independently selected from those shown in the compounds of **Table 1**.

[00308] As defined above and described here, each R is independently selected from hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the carbon or nitrogen, independently selected from nitrogen, oxygen, and sulfur.

[00309] In some embodiments, R is hydrogen. In some embodiments, R is an optionally substituted C_{1-6} aliphatic. In some embodiments, R is an optionally substituted phenyl. In some embodiments, R is an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the carbon or nitrogen, independently selected from nitrogen, oxygen, and sulfur.

[00310] As defined above and described herein, R^y is selected from  or hydrogen.



[00311] In some embodiments R^y is . In some embodiments, R^y is hydrogen.

[00312] In certain embodiments, R^y is selected from those shown in the compounds of **Table 1**.

[00313] As defined above and described herein, Ring B^x is phenyl, a 4-10 membered saturated or partially unsaturated mono- or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring B^x is further optionally substituted with 1-2 oxo groups.

[00314] In some embodiments, Ring B^x is phenyl. In some embodiments, Ring B^x is a 4-10 membered saturated or partially unsaturated mono- or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring B^x is a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring B^x is further optionally substituted with 1-2 oxo groups.

[00315] In certain embodiments, Ring B^x is selected from those shown in the compounds of **Table 1**.

[00316] As defined above and described herein, each R^w is independently selected from hydrogen, deuterium, R^z, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -CF₂R, -CF₃, -CR₂(OR), -CR₂(NR₂), -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)S(O)₂R, -OP(O)R₂, -OP(O)(OR)₂, -OP(O)(OR)NR₂, -OP(O)(NR₂)₂, and -SiR₃.

[00317] In some embodiments, R^w is hydrogen. In some embodiments, R^w is deuterium. In some embodiments, R^w is R^z. In some embodiments, R^w is halogen. In some embodiments, R^w is -CN. In some embodiments, R^w is -NO₂. In some embodiments, R^w is -OR. In some embodiments, R^w is -SR. In some embodiments, R^w is -NR₂. In some embodiments, R^w is -S(O)₂R. In some embodiments, R^w is -S(O)₂NR₂. In some embodiments, R^w is -S(O)R. In some embodiments, R^w is -CF₂R. In some embodiments, R^w is -CF₃. In some embodiments, R^w is -CR₂(OR). In some embodiments, R^w is -CR₂(NR₂). In some embodiments, R^w is -C(O)R. In some embodiments, R^w is -C(O)OR. In some embodiments, R^w is -C(O)NR₂. In some embodiments, R^w is -C(O)N(R)OR. In some embodiments, R^w is -OC(O)R. In some embodiments, R^w is -OC(O)NR₂. In some embodiments, R^w is -N(R)C(O)OR. In some embodiments, R^w is -N(R)C(O)R. In some embodiments, R^w is -N(R)C(O)NR₂. In some embodiments, R^w is -N(R)S(O)₂R. In some embodiments, R^w is -OP(O)R₂. In some embodiments, R^w is -OP(O)(OR)₂. In some embodiments, R^w is -OP(O)(OR)NR₂. In some embodiments, R^w is -OP(O)(NR₂)₂. In some embodiments, R^w is -SiR₃.

[00318] In certain embodiments, R^w is selected from those shown in the compounds of **Table 1**.

[00319] As defined above and described herein, each R^z is independently an optionally substituted

group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00320] In some embodiments, R^z is an optionally substituted C₁₋₆ aliphatic. In some embodiments, R^z is an optionally substituted phenyl. In some embodiments, R^z is an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^z is an optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00321] In certain embodiments, R^z is selected from those shown in the compounds of **Table 1**.

[00322] As defined above and described herein, --- is a single or double bond.

[00323] In some embodiments, --- is a single bond. In some embodiments, --- is a double bond.

[00324] In certain embodiments, --- is selected from those shown in the compounds of **Table 1**.

[00325] As defined above and described herein, w is 0, 1, 2, 3 or 4.

[00326] In some embodiments, w is 0. In some embodiments, w is 1. In some embodiments, w is 2. In some embodiments, w is 3. In some embodiments, w is 4.

[00327] In certain embodiments, w is selected from those shown in the compounds of **Table 1**.

[00328] As defined above and described herein, x is 0, 1, 2, 3 or 4.

[00329] In some embodiments, x is 0. In some embodiments, x is 1. In some embodiments, m is 2. In some embodiments, x is 3. In some embodiments, x is 4.

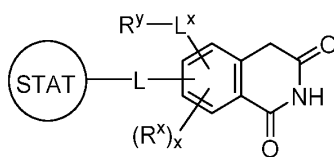
[00330] In certain embodiments, x is selected from those shown in the compounds of **Table 1**.

[00331] As defined above and described herein, y is 0, 1 or 2.

[00332] In some embodiments, y is 0. In some embodiments, y is 1. In some embodiments, y is 2.

[00333] In certain embodiments, y is selected from those shown in the compounds of **Table 1**.

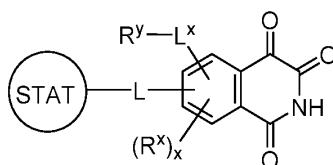
[00334] In some embodiments, the present invention provides a compound of formula **I-ii**, wherein Ring A^x is benzo, y is 1, X¹ is -CH₂-, X² and X³ are -C(O)-, and Z¹ and Z² are carbon atoms as shown, to provide a compound of formula **I-II-1**:



I-II-1

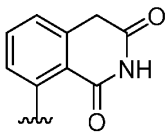
or a pharmaceutically acceptable salt thereof, wherein each of STAT, L, L^x, R^x, R^y, and x is as defined above and described in embodiments herein, both singly and in combination.

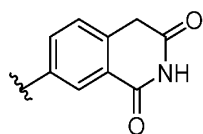
[00335] In some embodiments, the present invention provides a compound of formula **I-II**, wherein Ring A is benzo, y is 1, X¹, X² and X³ are -C(O)-, and Z¹ and Z² are carbon atoms as shown, to provide a compound of formula **I-II-2**:



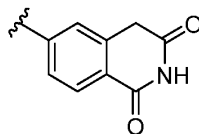
I-II-2

or a pharmaceutically acceptable salt thereof, wherein each of STAT, L, L^x, R^x, R^y, and x is as defined above and described in embodiments herein, both singly and in combination.

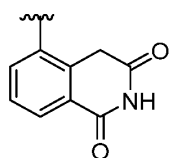
[00336] In some embodiments, LBM is . In some embodiments, LBM is



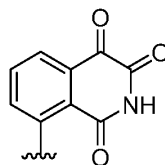
. In some embodiments, LBM is



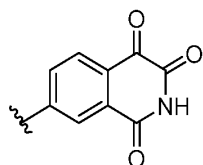
. In some embodiments, LBM is



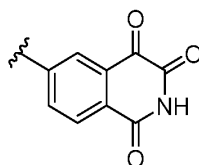
. In some embodiments, LBM is



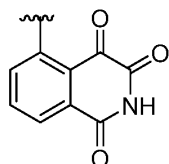
. In some embodiments, LBM is



. In some embodiments, LBM is



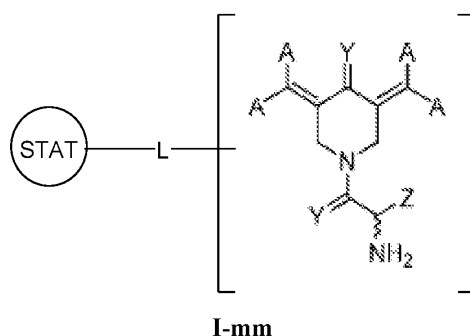
. In some embodiments, LBM is



[00337] In some embodiments, LBM is selected from those in **Table 1**.

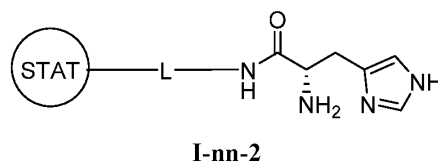
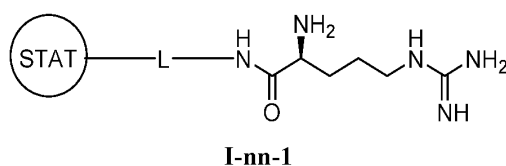
[00338] In certain embodiments, the present invention provides a compound of formula **I**, wherein

LBM is a RPN13 binding moiety thereby forming a compound of formula **I-mm**:



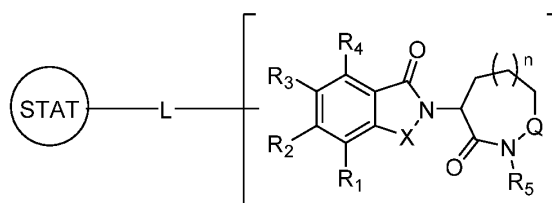
or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein each of the variables A, Y, and Z is as described and defined in WO 2019/165229, the entirety of each of which is herein incorporated by reference.

[00339] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a Ubr1 binding moiety as described in Shanmugasundaram, K. et al, J. Bio. Chem. 2019, doi: 10.1074/jbc.AC119.010790, the entirety of each of which is herein incorporated by reference, thereby forming a compound of formula **I-nn-1** or **I-nn-2**:



or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein.

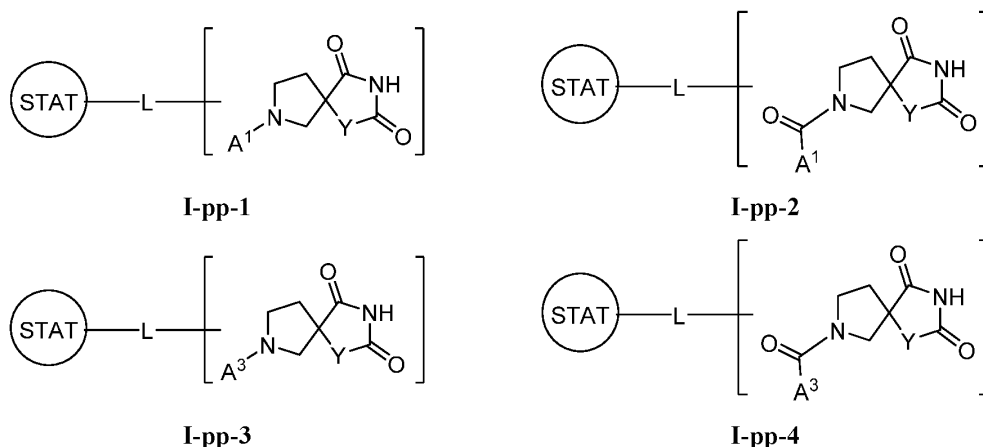
[00340] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is a cereblon binding moiety thereby forming a compound of formula **I-oo**:



I-oo

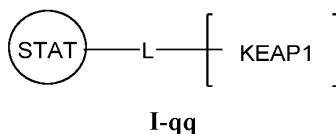
or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein each of the variables R₁, R₂, R₃, R₄, R₅, Q, X, and n is as described and defined in US 2019/276474, the entirety of each of which is herein incorporated by reference.

[00341] In certain embodiments, the present invention provides a compound of formula I, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety thereby forming a compound of formula **I-pp-1**, **I-pp-2**, **I-pp-3** or **I-pp-4**:



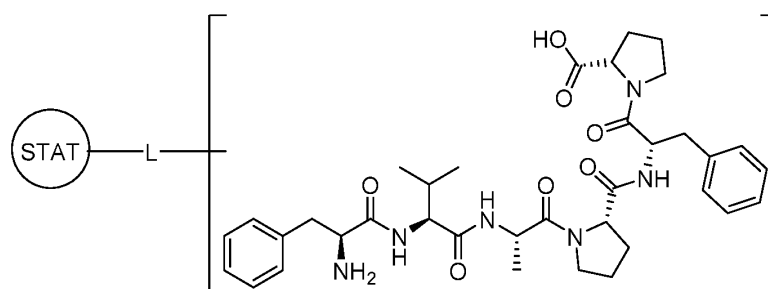
or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein each of the variables Y, A¹, and A³ is as described and defined in WO 2019/236483, the entirety of each of which is herein incorporated by reference.

[00342] In certain embodiments, the present invention provides a compound of formula I, wherein LBM is human kelch-like ECH-associated protein 1 (KEAP1) of formula **I-qq**:



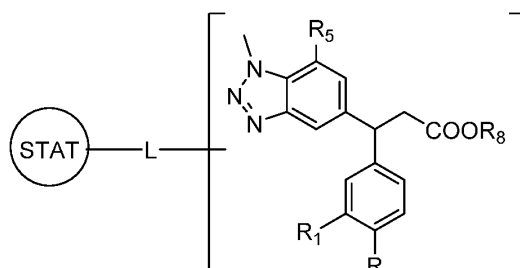
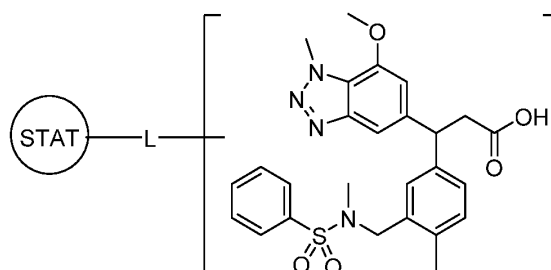
or a pharmaceutically acceptable salt thereof.

[00343] In certain embodiments, the present invention provides a compound of formula I, wherein LBM is KEAP1 binding moiety as recited in Lu et al., Euro. J. Med. Chem., 2018, 146:251-9, thereby forming a compound of formula **I-rr**:

**I-rr**

or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein.

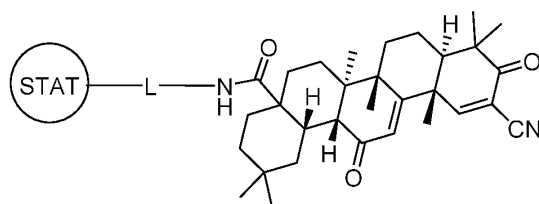
[00344] In certain embodiments, the present invention provides a compound of formula I, wherein LBM is KEAP1-NRF2 binding moiety thereby forming a compound of formula I-ss-1 or I-ss-2:

**I-ss-1****I-ss-2**

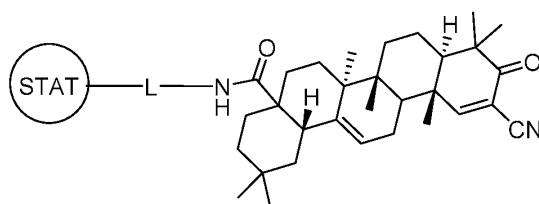
or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, wherein each of the variables R, R₁, R₅, and R₈ is as described and defined in WO 2020/018788, the entirety of each of which is herein incorporated by reference.

[00345] In certain embodiments, the present invention provides a compound of formula I, wherein LBM is KEAP1-NRF2 binding moiety as recited in Tong et al., "Targeted Protein Degradation via a Covalent Reversible Degradation Based on Bardoxolone", ChemRxiv 2020, thereby forming a compound of

formula **I-tt-1** or **I-tt-2**:



I-tt-1



I-tt-2

or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein.

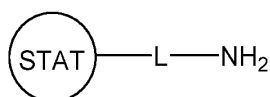
Lysine Mimetic

[00346] In some embodiments, DIM is LBM as described above and herein. In some embodiments, DIM is a lysine mimetic. In some embodiments, the covalent attachment of ubiquitin to one or more members of the STAT protein family (*i.e.*, STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, or STAT6) is achieved through the action of a lysine mimetic. In some embodiments, upon the binding of a compound of formula **I** to STAT3, the DIM moiety that mimics a lysine undergoes ubiquitination thereby marking STAT3 for degradation via the Ubiquitin-Proteasome Pathway (UPP).

[00347] In some embodiments, DIM is ---NH_2 . In some embodiments, DIM is ---NH_2 . In some embodiments, DIM is ---NH_2 .

[00348] In some embodiments, DIM is selected from those depicted in **Table 1**, below.

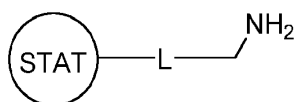
[00349] In some embodiments, the present invention provides the compound of formula **I** as a compound of formula **I-uu-1**:



I-uu-1

or a pharmaceutically acceptable salt thereof, wherein each of STAT and L is as defined above and described in embodiments herein, both singly and in combination.

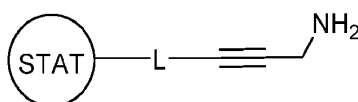
[00350] In some embodiments, the present invention provides the compound of formula I as a compound of formula I-uu-2:



I-uu-2

or a pharmaceutically acceptable salt thereof, wherein each of STAT and L is as defined above and described in embodiments herein, both singly and in combination.

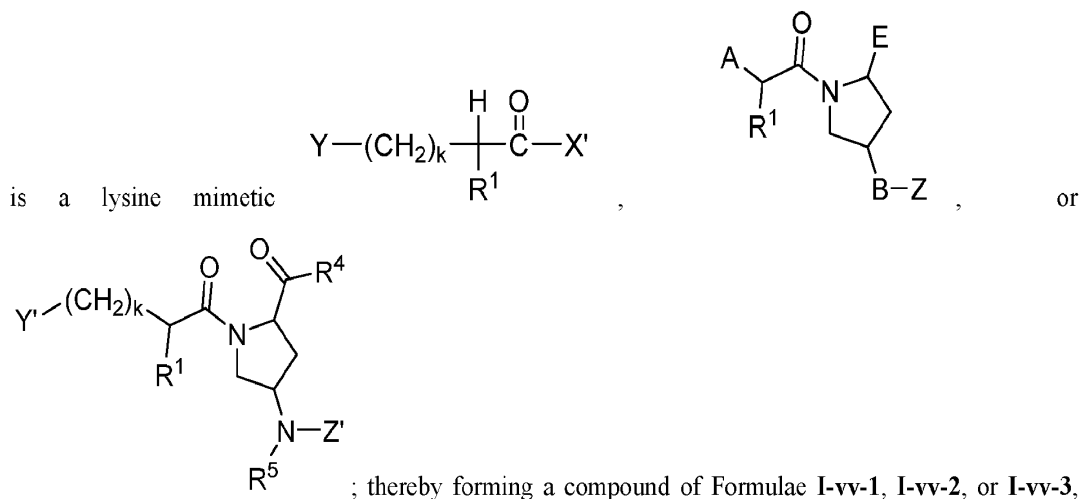
[00351] In some embodiments, the present invention provides the compound of formula I as a compound of formula I-uu-3:



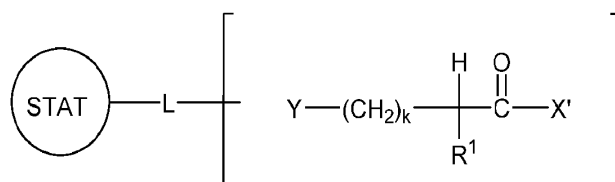
I-uu-3

or a pharmaceutically acceptable salt thereof, wherein each of STAT and L is as defined above and described in embodiments herein, both singly and in combination.

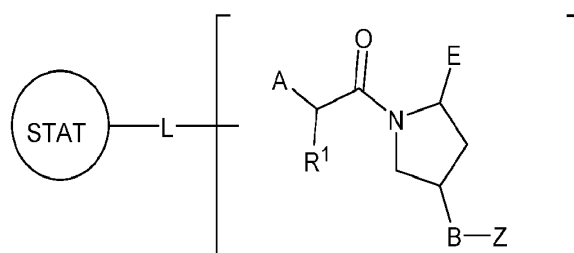
[00352] In certain embodiments, the present invention provides a compound of formula I, wherein DIM



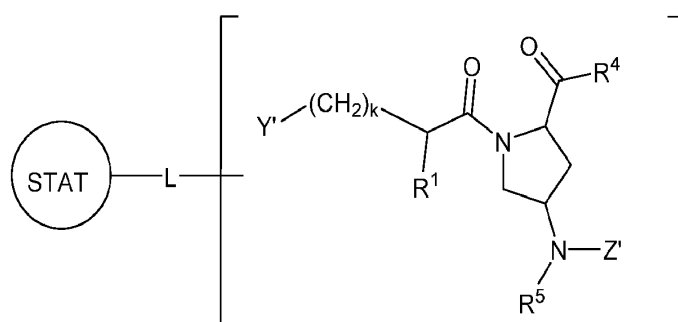
respectively:



I-vv-1



I-vv-2



I-vv-3

or a pharmaceutically acceptable salt thereof, wherein L and STAT are as defined above and described in embodiments herein, and wherein each of the variables R^1 , R^4 , R^5 , A, B, E, Y, Y' , Z, Z' , and k are as defined and described in U.S. Pat. No. 7,622,496, the entirety of each of which is herein incorporated by reference.

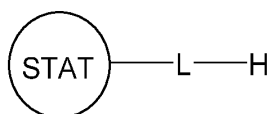
Hydrogen Atom

[00353] In some embodiments, DIM is a hydrogen atom. In some embodiments, the covalent attachment of ubiquitin to one or more members of the STAT protein family (*i.e.*, STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, or STAT6) is achieved through a provided compound wherein DIM is a hydrogen atom. In some embodiments, upon the binding of a compound of formula I to STAT3, the DIM moiety being hydrogen effectuates ubiquitination thereby marking STAT3 for degradation via the Ubiquitin-Proteasome Pathway (UPP).

[00354] In some embodiments, DIM is selected from those depicted in Table 1, below.

[00355] In some embodiments, the present invention provides the compound of formula I wherein DIM

is a hydrogen atom, thereby forming a compound of formula **I-ww**:



I-ww

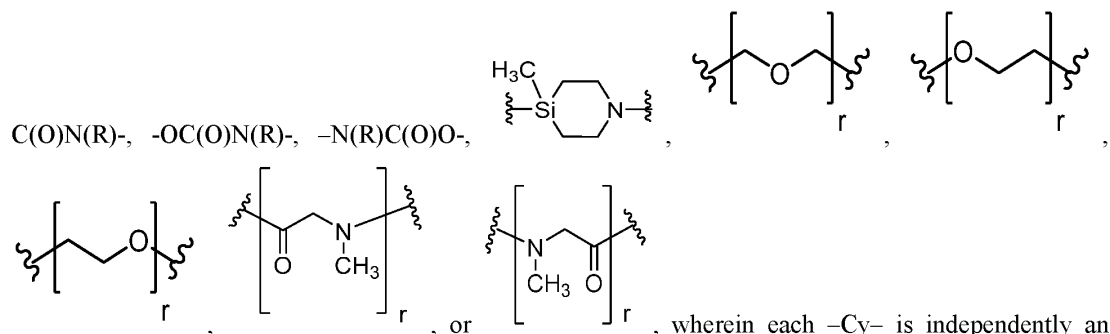
or a pharmaceutically acceptable salt thereof, wherein each of STAT and L is as defined above and described in embodiments herein, both singly and in combination.

Linker (L)

[00356] As defined above and described herein, L is a bivalent moiety that connects to STAT to DIM.

[00357] In some embodiments, L is a bivalent moiety that connects STAT to DIM. In some embodiments, L is a bivalent moiety that connects STAT to LBM. In some embodiments, L is a bivalent moiety that connects STAT to a lysine mimetic.

[00358] In some embodiments, L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C₁₋₅₀ hydrocarbon chain, wherein 0-10 methylene units of L are independently replaced by -C(D)(H)-, -C(D)₂-, -C_y-, -O-, -N(R)-, -Si(R)₂-, -Si(OH)(R)-, -Si(OH)₂-, -P(O)(OR)-, -P(O)(R)-, -P(O)(NR₂)-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -S(O)₂-, -N(R)S(O)₂-, -S(O)₂N(R)-, -N(R)C(O)-, -



optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl

having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

[00359] In some embodiments, each -Cy- is independently an optionally substituted bivalent phenylenyl. In some embodiments, each -Cy- is independently an optionally substituted 8-10 membered bicyclic arylene. In some embodiments, each -Cy- is independently an optionally substituted 4-7 membered saturated or partially unsaturated carbocyclylenyl. In some embodiments, each -Cy- is independently an optionally substituted 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl. In some embodiments, each -Cy- is independently an optionally substituted 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl. In some embodiments, each -Cy- is independently an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each -Cy- is independently an optionally substituted 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each -Cy- is independently an optionally substituted 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each -Cy- is independently an optionally substituted 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each -Cy- is independently an optionally substituted 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00360] In some embodiments, L is -NR-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-NR-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-NR-(CH₂CH₂O)₁₋₁₀CH₂CH₂-. In some embodiments, L is -Cy-NR-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-NR-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-NR-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-Cy-NR-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-Cy-(C₁₋₁₀ aliphatic)-NR-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-Cy-(C₁₋₁₀ aliphatic)-NR-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-Cy-NR-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-NR-Cy-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-Cy-NR-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-NR-Cy-(C₁₋₁₀ aliphatic)-.

[00361] In some embodiments, L is -CONR-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-CONR-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-CONR-(CH₂CH₂O)₁₋₁₀CH₂CH₂-. In some embodiments, L is -Cy-CONR-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-CONR-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-CONR-(C₁₋₁₀ aliphatic)-. In some

embodiments, L is -(C₁₋₁₀ aliphatic)-Cy-CONR-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-Cy-(C₁₋₁₀ aliphatic)-CONR-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-Cy-(C₁₋₁₀ aliphatic)-CONR-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-Cy-CONR-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-CONR-Cy-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-CONR-Cy-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-CONR-Cy-(C₁₋₁₀ aliphatic)-.

[00362] In some embodiments, L is -NRCO-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-NRCO-(C₁₋₁₀aliphatic)-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-NRCO-(CH₂CH₂O)₁₀CH₂CH₂-. In some embodiments, L is -Cy-NRCO-(C₁₋₁₀aliphatic)-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-NRCO-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-NRCO-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-Cy-NRCO-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-Cy-(C₁₋₁₀ aliphatic)-NRCO-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-Cy-(C₁₋₁₀ aliphatic)-NRCO-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-Cy-NRCO-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-NRCO-Cy-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-Cy-NRCO-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-NRCO-Cy-(C₁₋₁₀ aliphatic)-.

[00363] In some embodiments, L is -O-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-O-(C₁₋₁₀aliphatic)-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-O-(CH₂CH₂O)₁₋₁₀CH₂CH₂-. In some embodiments, L is -Cy-O-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-O-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-O-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-Cy-O-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-Cy-(C₁₋₁₀ aliphatic)-O-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-Cy-(C₁₋₁₀ aliphatic)-O-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-Cy-O-.In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-O-Cy-.In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-Cy-O-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-O-Cy-(C₁₋₁₀ aliphatic)-.

[00364] In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-Cy-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-Cy-(CH₂CH₂O)₁₋₁₀CH₂CH₂-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-Cy-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-Cy-(C₁₋₁₀ aliphatic)-. In some embodiments, L is -Cy-(C₁₋₁₀ aliphatic)-Cy-(C₁₋₁₀ aliphatic)-Cy-. In some embodiments, L is -(C₁₋₁₀ aliphatic)-Cy-(C₁₋₁₀ aliphatic)-Cy-(C₁₋₁₀ aliphatic)-.

[00365] In some embodiments, L is -NR-(CH₂)₁₋₁₀-. In some embodiments, L is -(CH₂)₁₋₁₀-NR-(CH₂)₁₋₁₀-. In some embodiments, L is -(CH₂)₁₋₁₀-NR-(CH₂CH₂O)₁₋₁₀CH₂CH₂-. In some embodiments, L is -Cy-NR-(CH₂)₁₋₁₀-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-NR-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-NR-(CH₂)₁₋₁₀-. In some embodiments, L is -(CH₂)₁₋₁₀-Cy-NR-(CH₂)₁₋₁₀-. In some embodiments, L is -(CH₂)₁₋₁₀-Cy-(CH₂)₁₋₁₀-NR-. In some embodiments, L is -(CH₂)₁₋₁₀-Cy-(CH₂)₁₋₁₀-NR-(CH₂)₁₋₁₀-. In some

embodiments, L is -Cy-(CH₂)₁₋₁₀-Cy-NR-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-NR-Cy-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-Cy-NR-(CH₂)₁₋₁₀-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-NR-Cy-(CH₂)₁₋₁₀-.

[00366] In some embodiments, L is -CONR-(CH₂)₁₋₁₀-. In some embodiments, L is -(CH₂)₁₋₁₀-CONR-(CH₂)₁₋₁₀-. In some embodiments, L is -(CH₂)₁₋₁₀-CONR-(CH₂CH₂O)₁₋₁₀CH₂CH₂-. In some embodiments, L is -Cy-CONR-(CH₂)₁₋₁₀-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-CONR-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-CONR-(CH₂)₁₋₁₀-. In some embodiments, L is -(CH₂)₁₋₁₀-Cy-CONR-(CH₂)₁₋₁₀-. In some embodiments, L is -(CH₂)₁₋₁₀-Cy-(CH₂)₁₋₁₀-CONR-(CH₂)₁₋₁₀-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-Cy-CONR-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-CONR-Cy-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-Cy-CONR-(CH₂)₁₋₁₀-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-CONR-Cy-(CH₂)₁₋₁₀-.

[00367] In some embodiments, L is -NRCO-(CH₂)₁₋₁₀-. In some embodiments, L is -(CH₂)₁₋₁₀-NRCO-(CH₂)₁₋₁₀-. In some embodiments, L is -(CH₂)₁₋₁₀-NRCO-(CH₂CH₂O)₁₋₁₀CH₂CH₂-. In some embodiments, L is -Cy-NRCO-(CH₂)₁₋₁₀-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-NRCO-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-NRCO-(CH₂)₁₋₁₀-. In some embodiments, L is -(CH₂)₁₋₁₀-Cy-NRCO-(CH₂)₁₋₁₀-. In some embodiments, L is -(CH₂)₁₋₁₀-Cy-(CH₂)₁₋₁₀-NRCO-(CH₂)₁₋₁₀-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-Cy-NRCO-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-NRCO-Cy-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-Cy-NRCO-(CH₂)₁₋₁₀-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-NRCO-Cy-(CH₂)₁₋₁₀-.

[00368] In some embodiments, L is $-\text{O}-(\text{CH}_2)_{1-10}-$. In some embodiments, L is $-(\text{CH}_2)_{1-10}-\text{O}-(\text{CH}_2)_{1-10}-$. In some embodiments, L is $-(\text{CH}_2)_{1-10}-\text{O}-(\text{CH}_2\text{CH}_2\text{O})_{1-10}\text{CH}_2\text{CH}_2-$. In some embodiments, L is $-\text{Cy}-\text{O}-(\text{CH}_2)_{1-10}-$. In some embodiments, L is $-\text{Cy}-(\text{CH}_2)_{1-10}-\text{O}-$. In some embodiments, L is $-\text{Cy}-(\text{CH}_2)_{1-10}-\text{O}-(\text{CH}_2)_{1-10}-$. In some embodiments, L is $-(\text{CH}_2)_{1-10}-\text{Cy}-\text{O}-(\text{CH}_2)_{1-10}-$. In some embodiments, L is $-(\text{CH}_2)_{1-10}-\text{Cy}-(\text{CH}_2)_{1-10}-\text{O}-(\text{CH}_2)_{1-10}-$. In some embodiments, L is $-(\text{CH}_2)_{1-10}-\text{Cy}-(\text{CH}_2)_{1-10}-\text{O}-(\text{CH}_2)_{1-10}-$. In some embodiments, L is $-\text{Cy}-(\text{CH}_2)_{1-10}-\text{Cy}-\text{O}-$. In some embodiments, L is $-\text{Cy}-(\text{CH}_2)_{1-10}-\text{O}-\text{Cy}-$. In some embodiments, L is $-\text{Cy}-(\text{CH}_2)_{1-10}-\text{Cy}-\text{O}-(\text{CH}_2)_{1-10}-$. In some embodiments, L is $-\text{Cy}-(\text{CH}_2)_{1-10}-\text{O}-\text{Cy}-(\text{CH}_2)_{1-10}-$.

[00369] In some embodiments, L is -Cy-(CH₂)₁₋₁₀-. In some embodiments, L is -(CH₂)₁₋₁₀-Cy-(CH₂)₁₋₁₀-. In some embodiments, L is -(CH₂)₁₋₁₀-Cy-(CH₂CH₂O)₁₋₁₀CH₂CH₂-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-Cy-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-Cy-(CH₂)₁₋₁₀-. In some embodiments, L is -Cy-(CH₂)₁₋₁₀-Cy-(CH₂)₁₋₁₀-Cy-. In some embodiments, L is -(CH₂)₁₋₁₀-Cy-(CH₂)₁₋₁₀-Cy-(CH₂)₁₋₁₀-.

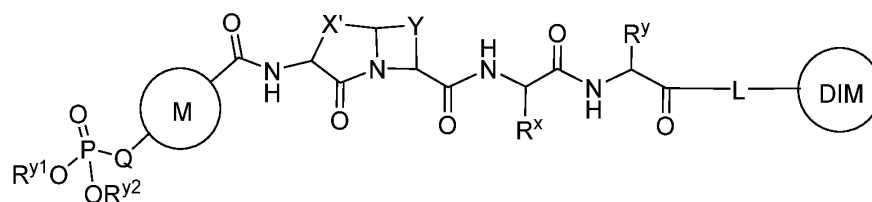
[00370] In some embodiments, L is selected from those depicted in **Table 1**, below.

STAT Binding Moiety (STAT)

[00371] As defined above and described herein, STAT is a STAT binding moiety capable of binding to one or more of STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, or STAT6.

[00372] In some embodiments, STAT is a STAT binding moiety capable of binding to STAT3.

[00373] In certain embodiments, the present invention provides a compound of formula **I-aaa**:



I-aaa

or a pharmaceutically acceptable salt thereof, wherein L and DIM are as defined above and described in embodiments herein, and wherein:

X' is an optionally substituted $-(CH_2)_x-$, wherein 1-2 methylenes of X is optionally replaced with a bivalent group selected from $-NR-$, $-N(COR)-$, $-N(CO_2R)-$, $-N(SO_2R)-$, $-N(CONR_2)-$, and $-N(SO_2NR_2)-$, wherein:

x is 1, 2, 3, 4, or 5;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

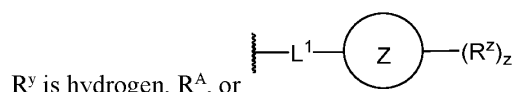
two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in addition to the carbon or nitrogen from which the two R groups are attached, independently selected from nitrogen, oxygen, and sulfur;

Y is an optionally substituted $-(CH_2)_y-$, wherein:

y is 1, 2, or 3;

R^x is hydrogen, R^A , $-(CR_2)_{1-3}OCONR_2$, or $-(CR_2)_{1-3}CONR_2$;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;



L^1 is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-5} hydrocarbon chain, wherein 0-3 methylene units of L^1 are independently replaced by $-O-$, $-NR-$, $-CRF-$, $-CF_2-$, $-C(O)-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

Ring Z is a ring selected from phenyl, naphthyl, a 5-10 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

$R^{z'}$ is hydrogen, R^A , halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)NROR$, $-CR_2NRC(O)R$, $-CR_2NRC(O)NR_2$, $-OC(O)R$, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-NRC(O)OR$, $-NRC(O)R$, $-NRC(O)NR_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, or $-NRS(O)_2R$;

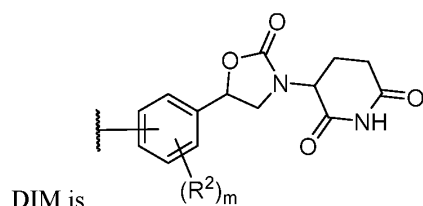
z is 0, 1, 2, 3, or 4;

Ring M is an optionally substituted bivalent ring selected from phenylenyl, naphthylenyl, a 5-10 membered heteroarylenyl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclylenyl or heterocyclylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

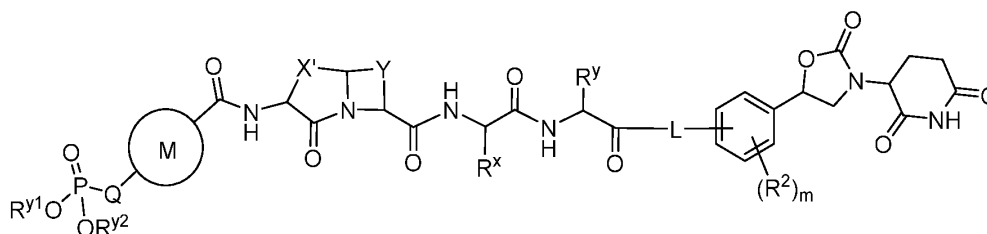
Q is a bivalent moiety selected from $-O-$, $-CR_2-$, $-CF_2-$, $-CFR-$, $-C(O)-$, $-OCR_2-$, and $-C(S)-$; and

R^{y1} and R^{y2} are each independently hydrogen, R^A , $-CH_2CO_2R$, or $-CH_2OCO_2R$.

[00374] In some embodiments, the present invention provides a compound of formula **I-aaa**, wherein



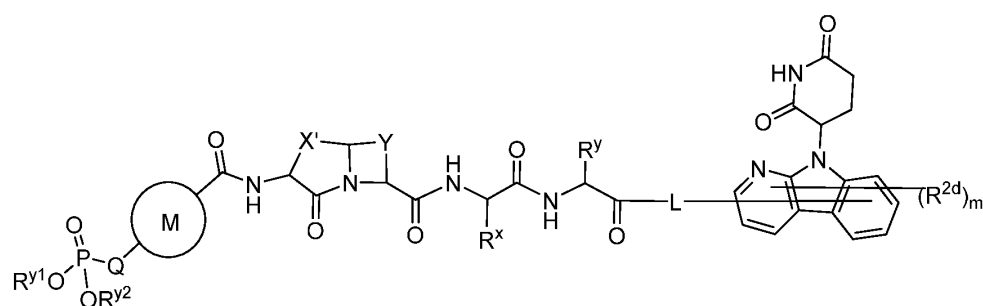
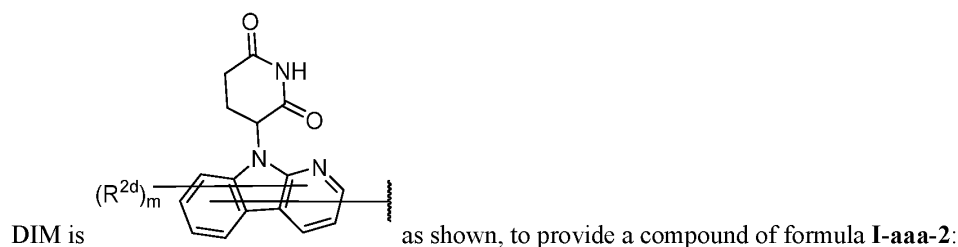
as shown, to provide a compound of formula **I-aaa-1**:



I-aaa-1

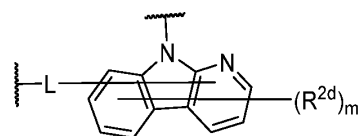
or a pharmaceutically acceptable salt thereof, wherein each of R^2 , m , L , Ring M, X' , R^x , R^y , R^{y1} , and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00375] In some embodiments, the present invention provides a compound of formula **I-aaa**, wherein

**I-aaa-2**

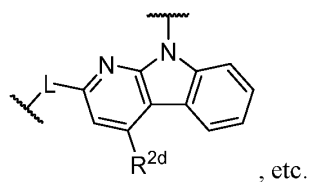
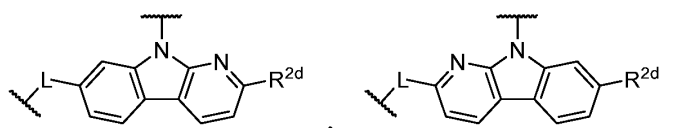
or a pharmaceutically acceptable salt thereof, wherein each of R^{2d} , m , L , Ring M, X' , R^x , R^y , R^{y1} , and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00376] In some embodiments herein, structures depicted as

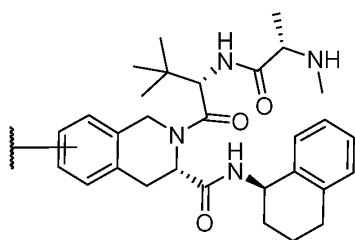


can

include, for example structures

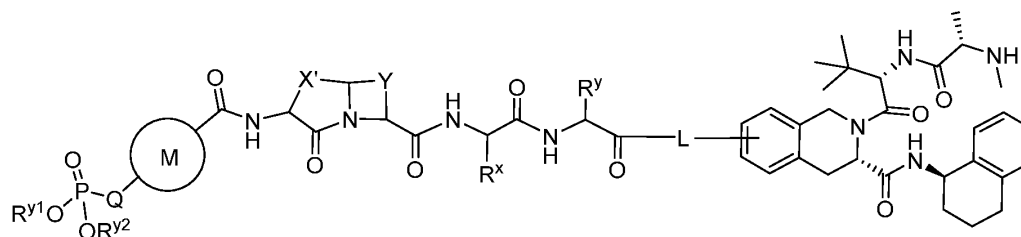


[00377] In some embodiments, the present invention provides a compound of formula **I-aaa**, wherein



DIM is

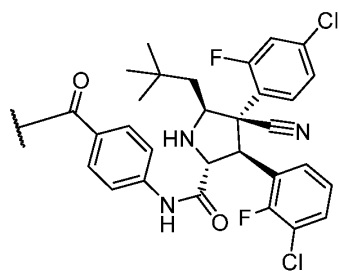
as shown, to provide a compound of formula **I-aaa-3**:



I-aaa-3

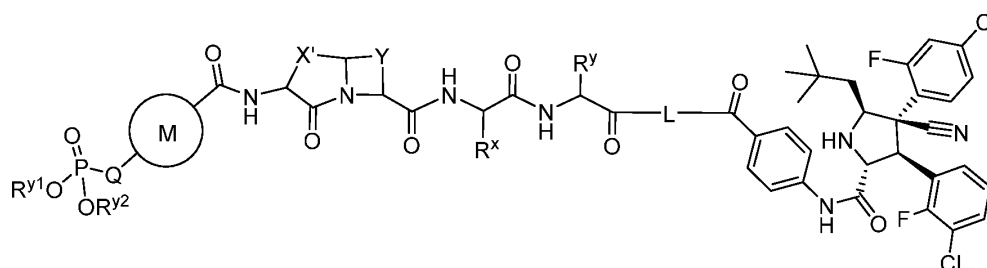
or a pharmaceutically acceptable salt thereof, wherein each of L, Ring M, X^z, R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00378] In some embodiments, the present invention provides a compound of formula **I-aaa**, wherein



DIM is

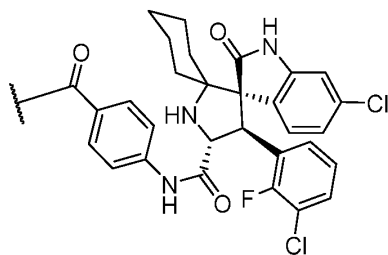
as shown, to provide a compound of formula **I-aaa-4**:



I-aaa-4

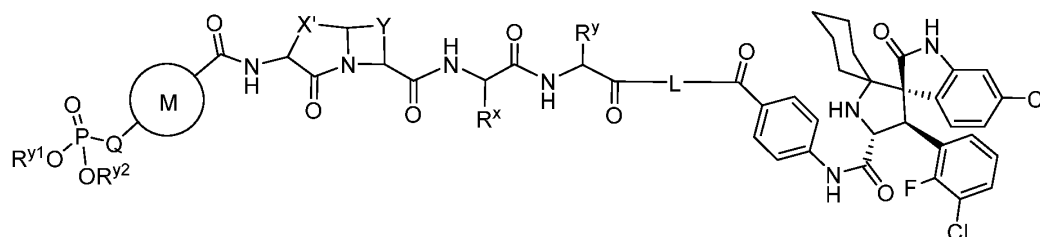
or a pharmaceutically acceptable salt thereof, wherein each of L, Ring M, X', R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00379] In some embodiments, the present invention provides a compound of formula **I-aaa**, wherein



DIM is

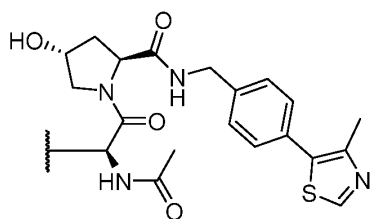
as shown, to provide a compound of formula **I-aaa-5**:



I-aaa-5

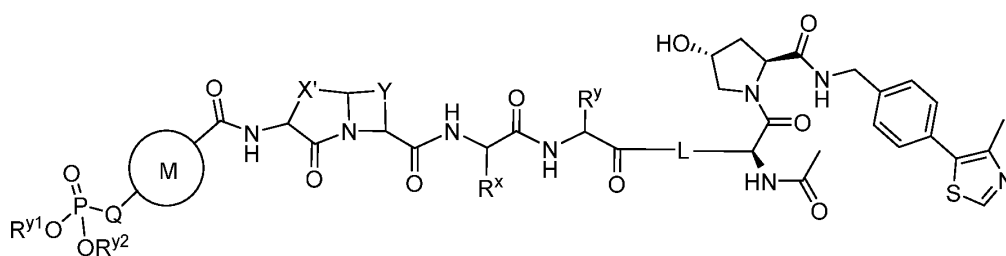
or a pharmaceutically acceptable salt thereof, wherein each of L, Ring M, X', R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00380] In some embodiments, the present invention provides a compound of formula **I-aaa**, wherein



DIM is

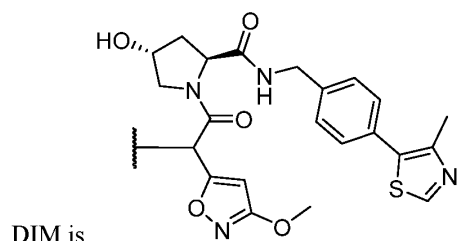
as shown, to provide a compound of formula **I-aaa-6**:



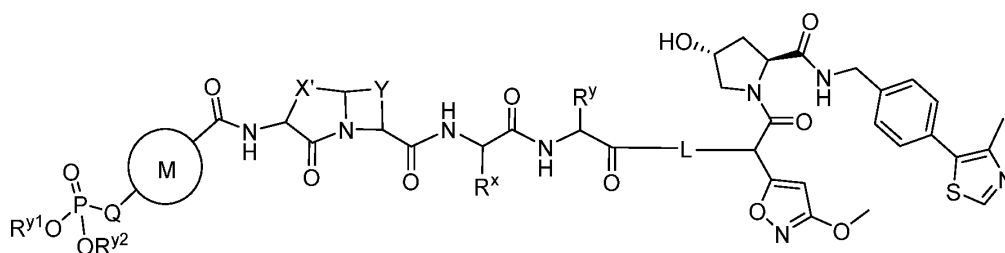
I-aaa-6

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring M, X', R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00381] In some embodiments, the present invention provides a compound of formula **I-aaa**, wherein



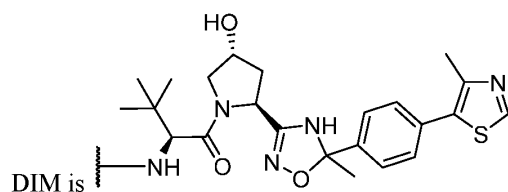
as shown, to provide a compound of formula **I-aaa-7**:



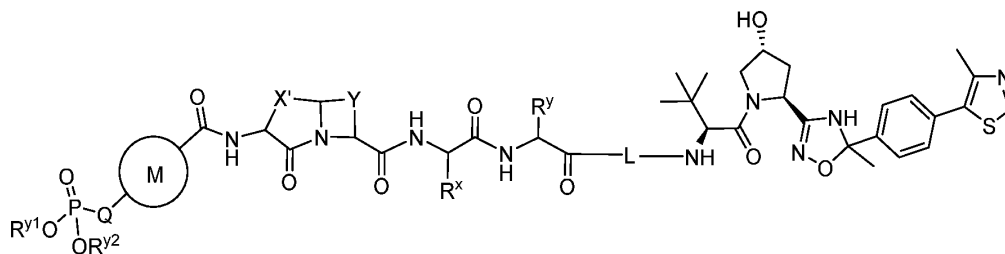
I-aaa-7

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring M, X', R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00382] In some embodiments, the present invention provides a compound of formula **I-aaa**, wherein



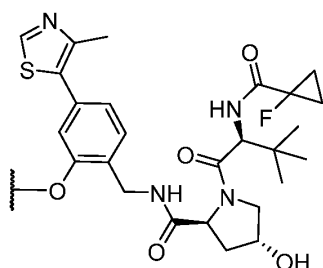
as shown, to provide a compound of formula **I-aaa-8**:



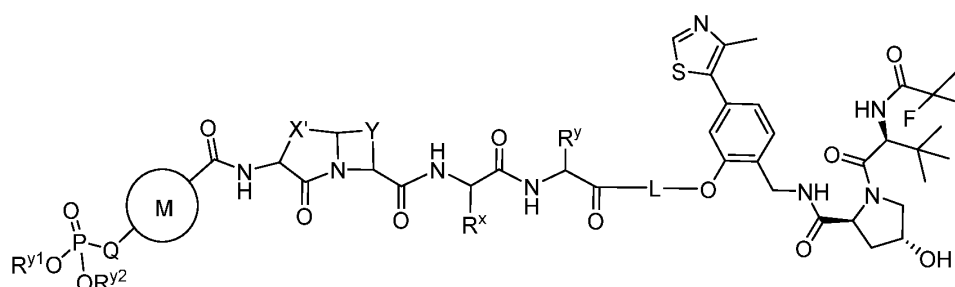
I-aaa-8

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring M, X', R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00383] In some embodiments, the present invention provides a compound of formula **I-aaa**, wherein



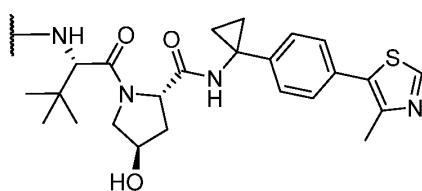
DIM is as shown, to provide a compound of formula **I-aaa-9**:



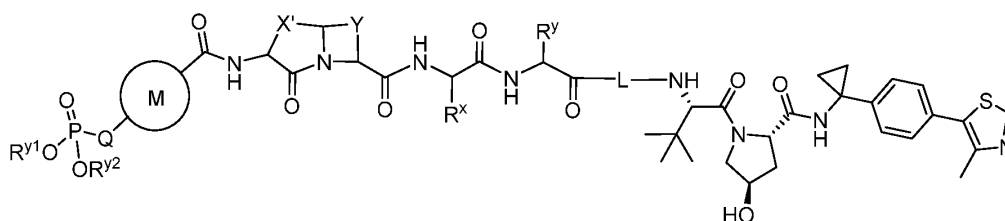
I-aaa-9

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring M, X', R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00384] In some embodiments, the present invention provides a compound of formula **I-aaa**, wherein



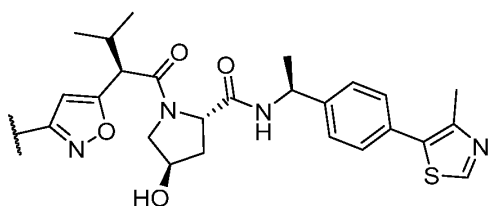
DIM is as shown, to provide a compound of formula **I-aaa-10**:



I-aaa-10

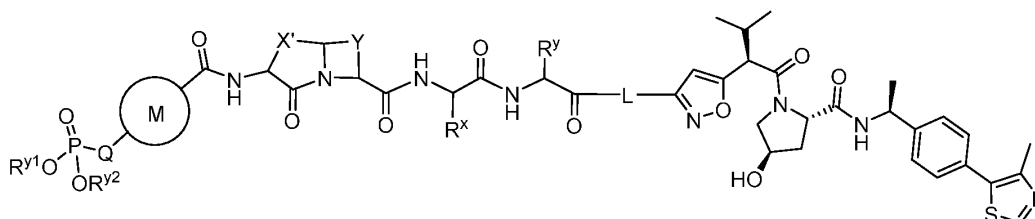
or a pharmaceutically acceptable salt thereof, wherein each of L, Ring M, X', R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00385] In some embodiments, the present invention provides a compound of formula **I-aaa**, wherein



DIM is
aaa-11:

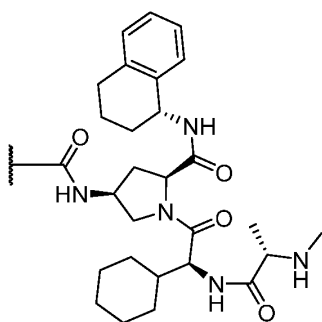
as shown, to provide a compound of formula I-



I-aaa-11

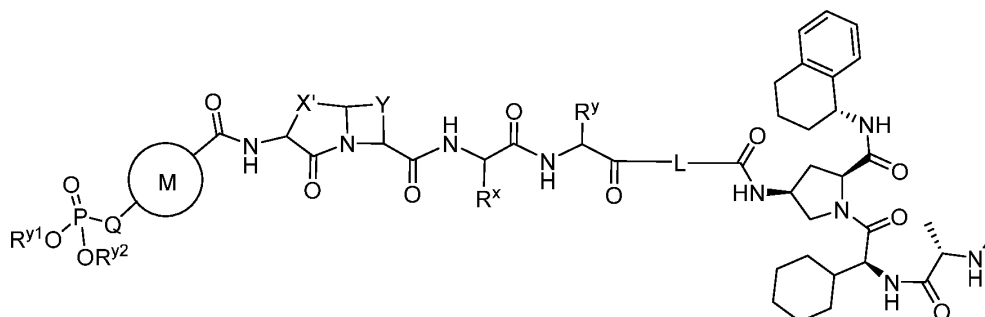
or a pharmaceutically acceptable salt thereof, wherein each of L, Ring M, X', R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00386] In some embodiments, the present invention provides a compound of formula I-aaa, wherein



DIM is

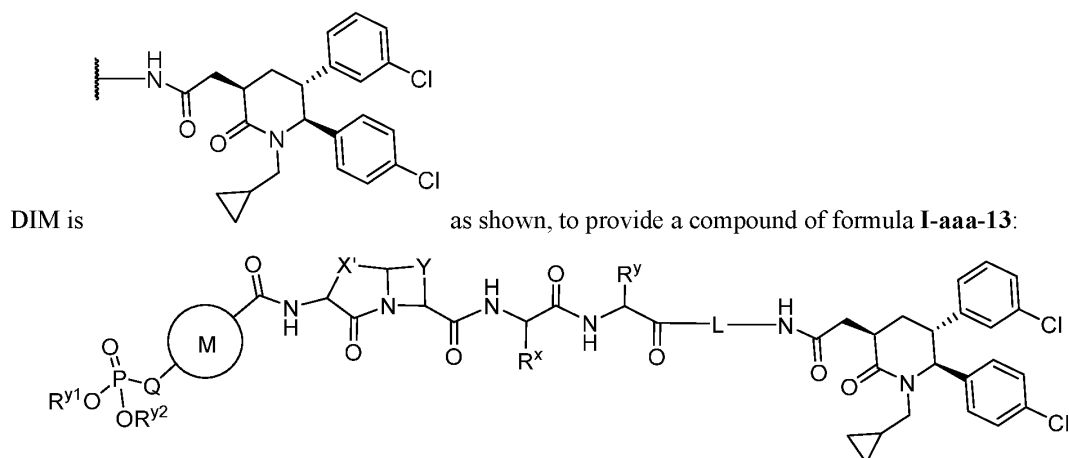
as shown, to provide a compound of formula I-aaa-12:



I-aaa-12

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring M, X', R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

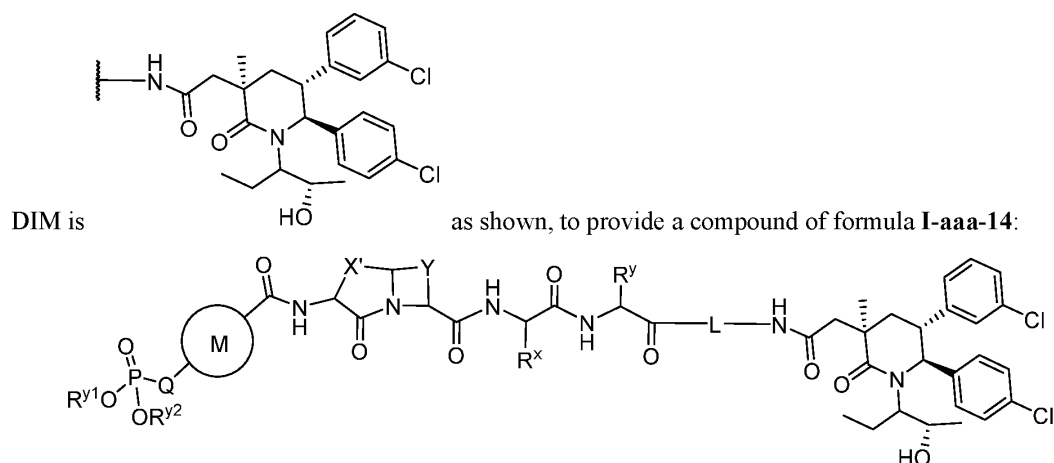
[00387] In some embodiments, the present invention provides a compound of formula **I-aaa**, wherein



I-aaa-13

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring M, X', R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

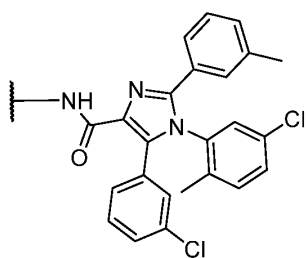
[00388] In some embodiments, the present invention provides a compound of formula **I-aaa**, wherein



I-aaa-14

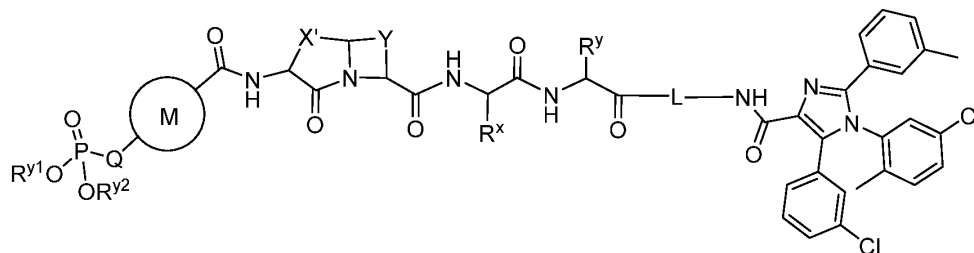
or a pharmaceutically acceptable salt thereof, wherein each of L, Ring M, X', R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00389] In some embodiments, the present invention provides a compound of formula **I-aaa**, wherein



DIM is

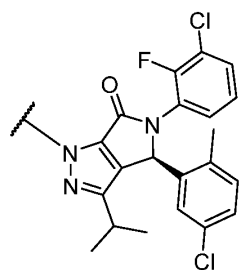
as shown, to provide a compound of formula **I-aaa-15**:



I-aaa-15

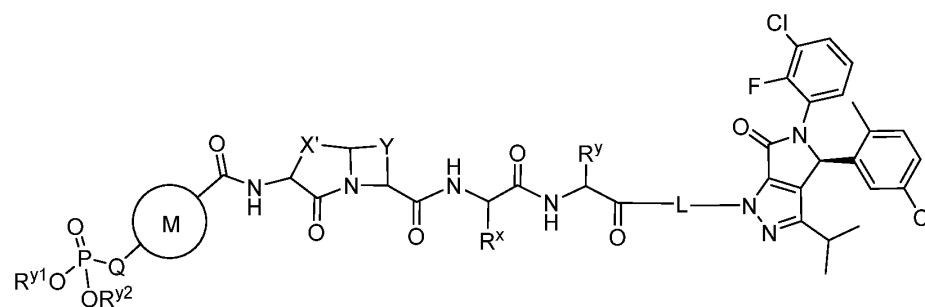
or a pharmaceutically acceptable salt thereof, wherein each of L, Ring M, X', R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00390] In some embodiments, the present invention provides a compound of formula **I-aaa**, wherein



DIM is

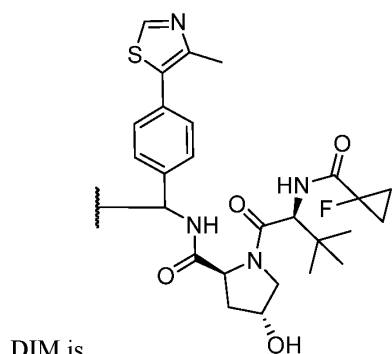
as shown, to provide a compound of formula **I-aaa-16**:



I-aaa-16

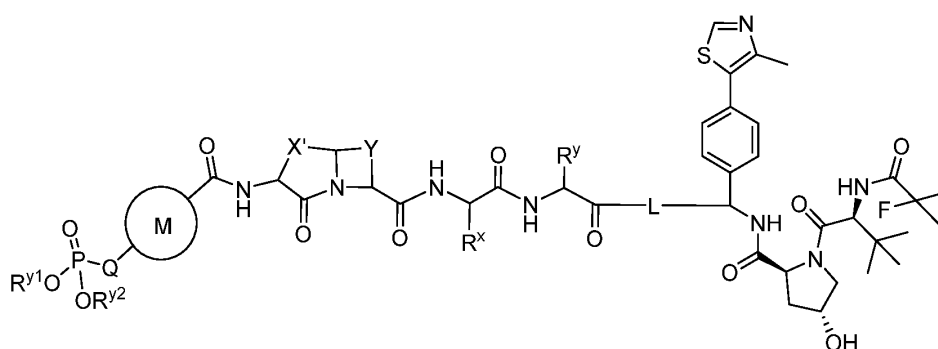
or a pharmaceutically acceptable salt thereof, wherein each of L, Ring M, X', R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00391] In some embodiments, the present invention provides a compound of formula **I-aaa**, wherein



DIM is

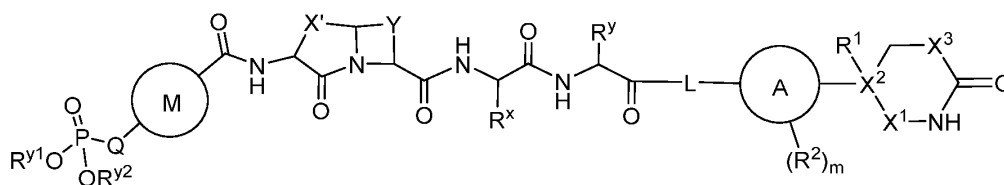
as shown, to provide a compound of formula **I-aaa-17**:



I-aaa-17

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring M, X', R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

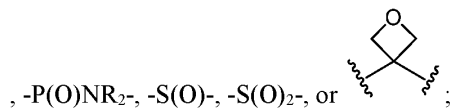
[00392] In certain embodiments, the present invention provides a compound of formula **I-bbb**:



I-bbb

or a pharmaceutically acceptable salt thereof, wherein:

X¹ is a bivalent moiety selected from a covalent bond, -CR₂-, -C(O)-, -C(S)-, -CR(CF₃)-, -P(O)OR-, -P(O)R-



X² is a carbon atom or silicon atom;

X^3 is a bivalent moiety selected from $-CR_2-$, $-NR-$, $-O-$, $-S-$, or $-SiR_2-$;

R^1 is hydrogen, halogen, $-CN$, $-OR$, $-SR$, $-S(O)R$, $-S(O)_2R$, $-NR_2$, $-P(O)(OR)_2$, $-P(O)NR_2OR$, $-P(O)(NR_2)_2$, $-Si(OH)_2R$, $-Si(OH)R_2$, $-SiR_3$, or an optionally substituted C_{1-4} aliphatic;

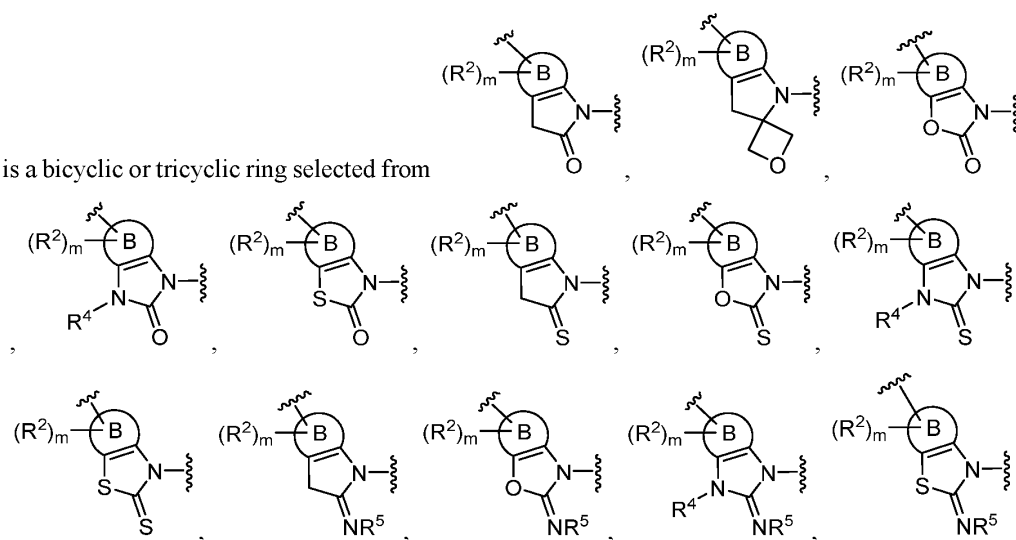
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

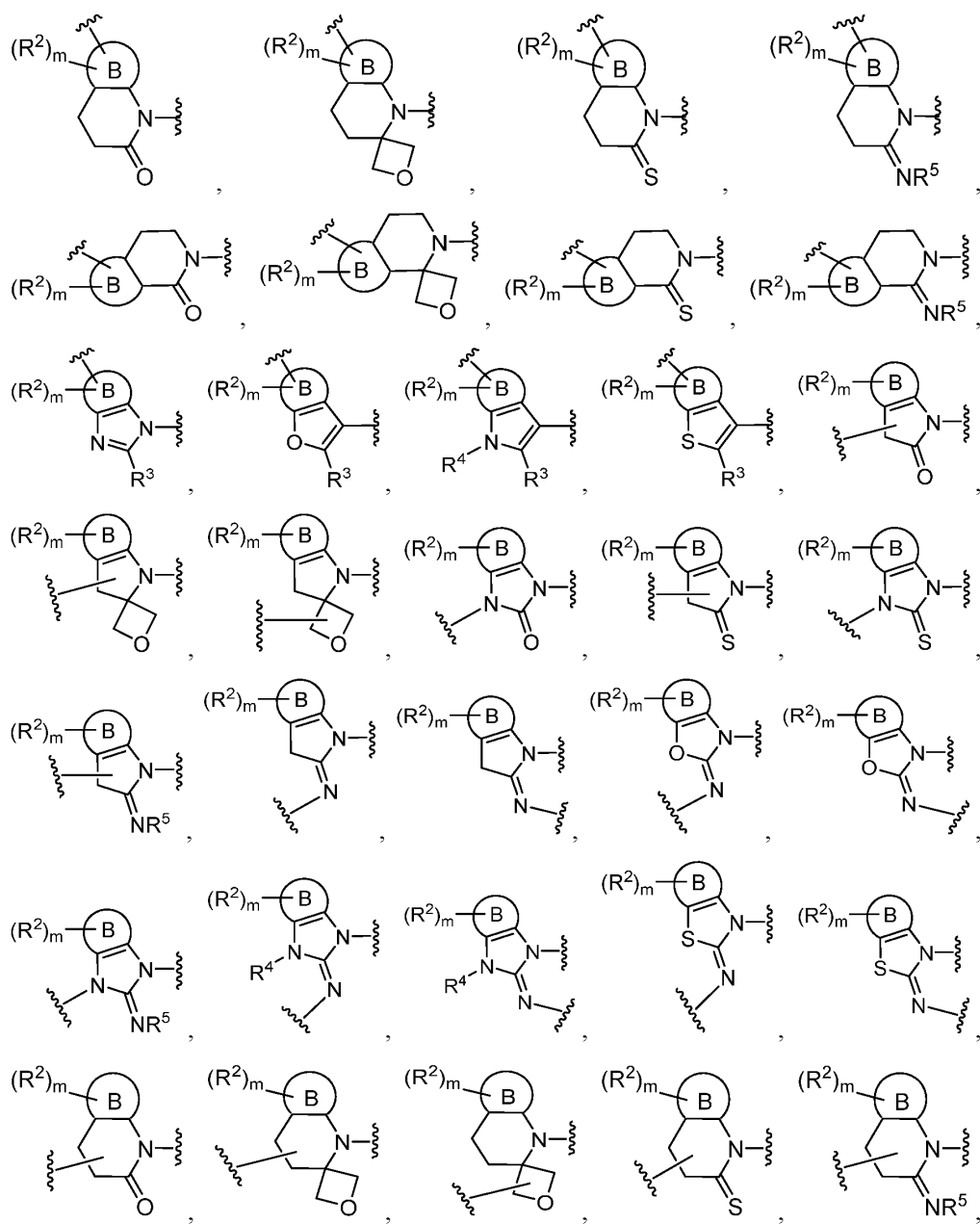
two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in addition to the carbon or nitrogen from which the two R groups are attached, independently selected from nitrogen, oxygen, and sulfur;

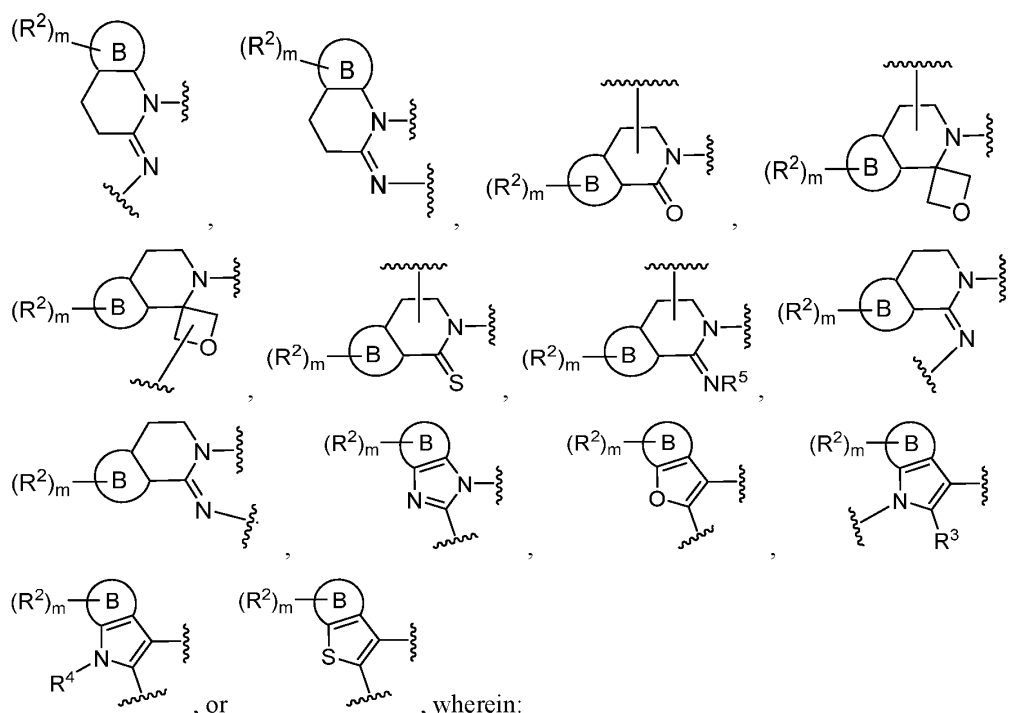
each R^2 is independently hydrogen, R^6 , halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)NROR$, $-CR_2NRC(O)R$, $-CR_2NRC(O)NR_2$, $-OC(O)R$, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-NRC(O)OR$, $-NRC(O)R$, $-NRC(O)NR_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, or $-NRS(O)_2R$;

each R^6 and R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring A is a bicyclic or tricyclic ring selected from







Ring B is a fused ring selected from benzo, 5-6 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5 to 7-membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is selected from hydrogen, halogen, -OR, -NR₂, or -SR;

each R^4 is independently hydrogen, R^6 , halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)NROR, -OC(O)R, -OC(O)NR₂, -NRC(O)OR, -NRC(O)R, -NRC(O)NR₂, or -NRS(O)₂R;

R^5 is hydrogen, C₁₋₄ aliphatic, or -CN;

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

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C₁₋₂₀ hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, -CRF-, -CF₂-, -C(O)-, -S-, -S(O)-, -S(O)₂-, -SiR₂-, -Si(OH)R-, -Si(OH)₂-, -P(O)OR-, -P(O)R-, or -P(O)NR₂-, wherein:

each -Cy- is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylene, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a

4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

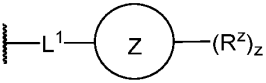
X' is an optionally substituted $-(CH_2)_x-$, wherein 1-2 methylenes of X is optionally replaced with a bivalent group selected from $-NR-$, $-N(COR)-$, $-N(CO_2R)-$, $-N(SO_2R)-$, $-N(CONR_2)-$, and $-N(SO_2NR_2)-$, wherein:

x is 1, 2, 3, 4, or 5;

Y is an optionally substituted $-(CH_2)_y-$, wherein:

y is 1, 2, or 3;

R^x is hydrogen, R^A, $-(CR_2)_{1-3}OCONR_2$, or $-(CR_2)_{1-3}CONR_2$;

R^y is hydrogen, R^A, or 

L¹ is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C₁₋₅ hydrocarbon chain, wherein 0-3 methylene units of L¹ are independently replaced by $-O-$, $-NR-$, $-CRF-$, $-CF_2-$, $-C(O)-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

Ring Z is a ring selected from phenyl, naphthyl, a 5-10 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^z is hydrogen, R^A, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)NROR$, $-CR_2NRC(O)R$, $-CR_2NRC(O)NR_2$, $-OC(O)R$, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-NRC(O)OR$, $-NRC(O)R$, $-NRC(O)NR_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, or $-NRS(O)_2R$;

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

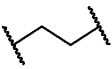
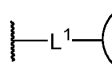
Ring M is an optionally substituted bivalent ring selected from phenylenyl, naphthylenyl, a 5-10 membered

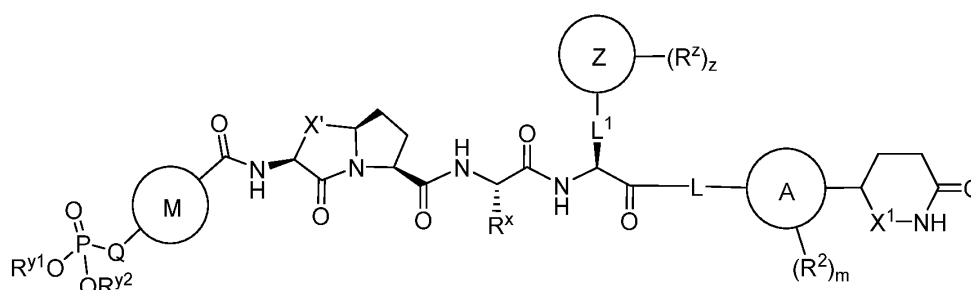
heteroarylenyl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;
 a 5-11 membered saturated or partially unsaturated carbocyclylenyl or heterocyclylenyl with 1-4
 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Q is a bivalent moiety selected from -O-, -CR₂-, -CF₂-, -CFR-, -C(O)-, -OCR₂-, and -C(S)-; and

R^{y1} and R^{y2} are each independently hydrogen, R^A, -CH₂CO₂R, or -CH₂OCO₂R.

[00393] In some embodiments, the present invention provides a compound of formula **I-bbb**, wherein

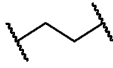
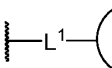
X² and X³ are carbon atoms, R¹ is hydrogen, Y is , and Ry is  as shown, to provide a compound of formula **I-bbb-1**:

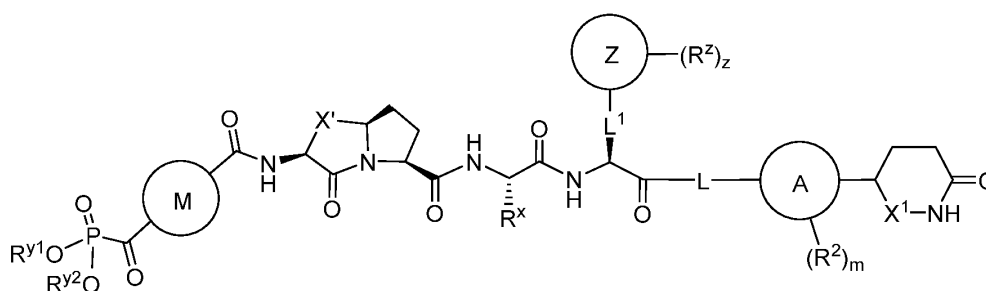


I-bbb-1

or a pharmaceutically acceptable salt thereof, wherein each of R², m, L, L¹, X¹, Ring A, Ring M, Ring Z, Q, X', R^x, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00394] In some embodiments, the present invention provides a compound of formula **I-bbb**, wherein

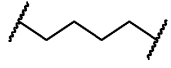
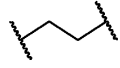
X² and X³ are carbon atoms, R¹ is hydrogen, Y is , Q is -C(O)-, and Ry is  as shown, to provide a compound of formula **I-bbb-2**:

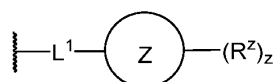


I-bbb-2

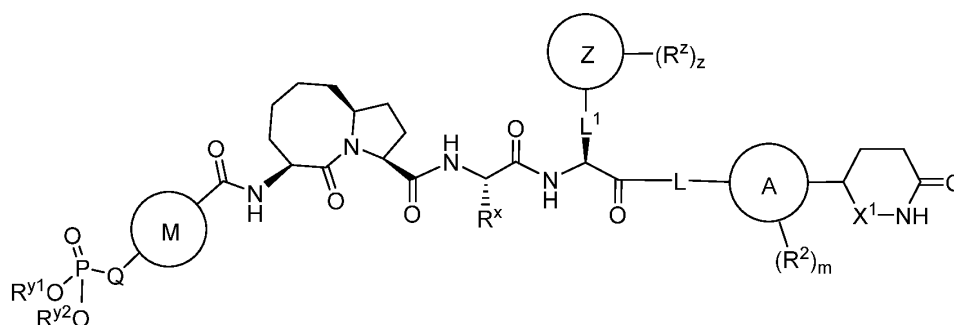
or a pharmaceutically acceptable salt thereof, wherein each of R^2 , m , L , L^1 , X^1 , Ring A, Ring M, Ring Z, X , R^x , R^{y1} , and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00395] In some embodiments, the present invention provides a compound of formula **I-bbb**, wherein

X^2 and X^3 are carbon atoms, R^1 is hydrogen, X' is , Y is , and R_y is



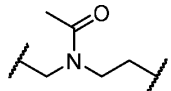
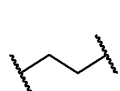
as shown, to provide a compound of formula **I-bbb-3**:

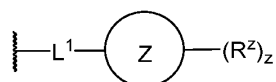


I-bbb-3

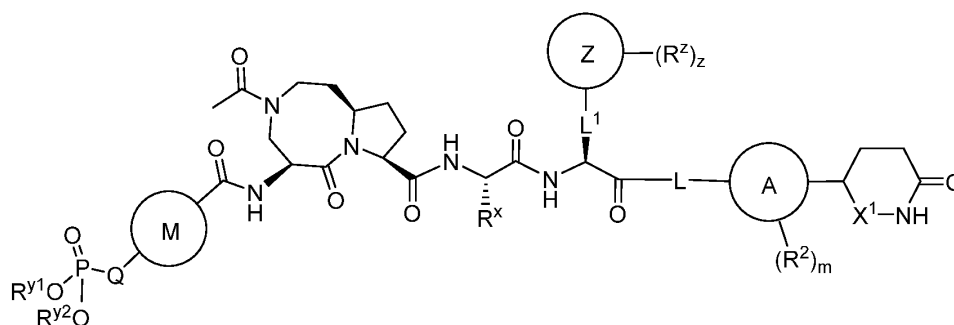
or a pharmaceutically acceptable salt thereof, wherein each of R^2 , m , L , L^1 , Ring A, Ring M, Ring Z, Q , R^x , R^{y1} , and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00396] In some embodiments, the present invention provides a compound of formula **I-bbb**, wherein

X^2 and X^3 are carbon atoms, R^1 is hydrogen, X' is , Y is , and R_y is



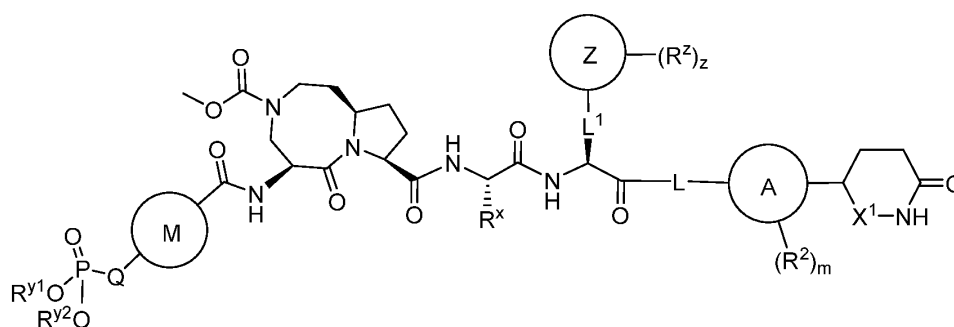
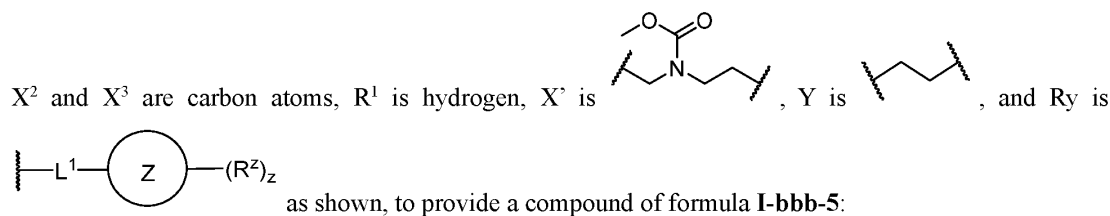
as shown, to provide a compound of formula **I-bbb-4**:



I-bbb-4

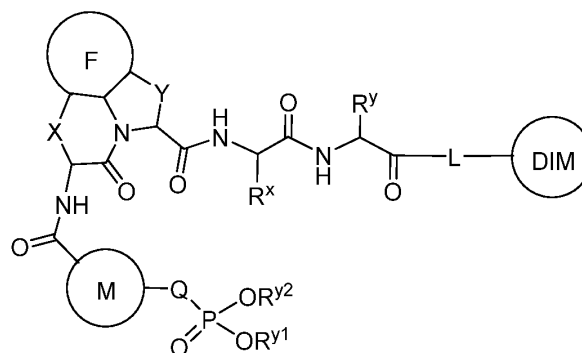
or a pharmaceutically acceptable salt thereof, wherein each of R^2 , m , L , L^1 , Ring A, Ring M, Ring Z, Q, R^x , R^{y1} , and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00397] In some embodiments, the present invention provides a compound of formula **I-bbb**, wherein

**I-bbb-5**

or a pharmaceutically acceptable salt thereof, wherein each of R^2 , m , L , L^1 , Ring A, Ring M, Ring Z, Q, R^x , R^{y1} , and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00398] In certain embodiments, the present invention provides a compound of formula **I-ccc**:

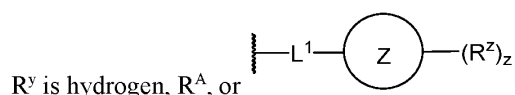
**I-ccc**

or a pharmaceutically acceptable salt thereof, wherein L and DIM are as defined above and described in embodiments herein, and wherein:

R^x is hydrogen, R^A , $-(CR_2)_{1-3}OCONR_2$, or $-(CR_2)_{1-3}CONR_2$;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in addition to the carbon or nitrogen from which the two R groups are attached, independently selected from nitrogen, oxygen, and sulfur;



L^1 is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-5} hydrocarbon chain, wherein 0-3 methylene units of L^1 are independently replaced by -O-, -NR-, -CRF-, -CF₂-, -C(O)-, -S-, -S(O)-, or -S(O)₂-;

Ring Z is a ring selected from phenyl, naphthyl, a 5-10 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^z is hydrogen, R^A , halogen, -CN, -NO₂, -OR, -SR, -NR₂, -SiR₃, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)NROR, -CR₂NRC(O)R, -CR₂NRC(O)NR₂, -OC(O)R, -OC(O)NR₂, -OP(O)R₂, -OP(O)(OR)₂, -OP(O)(OR)NR₂, -OP(O)(NR₂)₂, -NRC(O)OR, -NRC(O)R, -NRC(O)NR₂, -NRS(O)₂R, -NP(O)R₂, -NRP(O)(OR)₂, -NRP(O)(OR)NR₂, -NRP(O)(NR₂)₂, or -NRS(O)₂R;

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

Ring F is an optionally substituted fused ring selected from a 6-membered aryl, a 5-6 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

X is an optionally substituted -(CH₂)_x-, wherein:

x is 0, 1, 2, or 3;

Y is an optionally substituted $-(CH_2)_y-$, wherein:

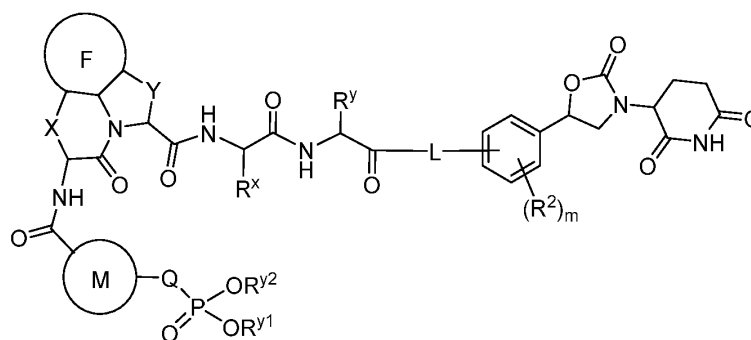
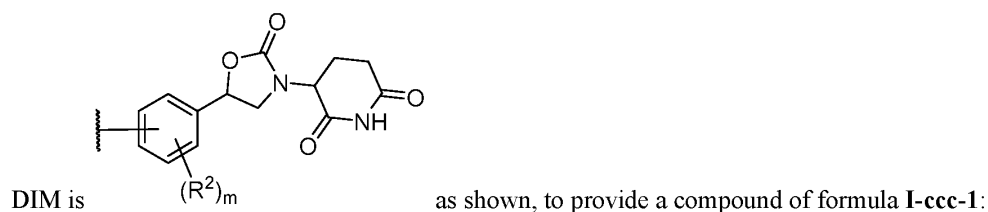
y is 0, 1, 2, or 3;

Ring M is an optionally substituted bivalent ring selected from phenylenyl, naphthylenyl, a 5-10 membered heteroarylenyl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclylenyl or heterocyclylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Q is a bivalent moiety selected from $-O-$, $-CR_2-$, $-CF_2-$, $-CFR-$, $-C(O)-$, $-OCR_2-$, and $-C(S)-$; and

R^{y1} and R^{y2} are each independently hydrogen, R^A , $-CH_2CO_2R$, or $-CH_2OCO_2R$.

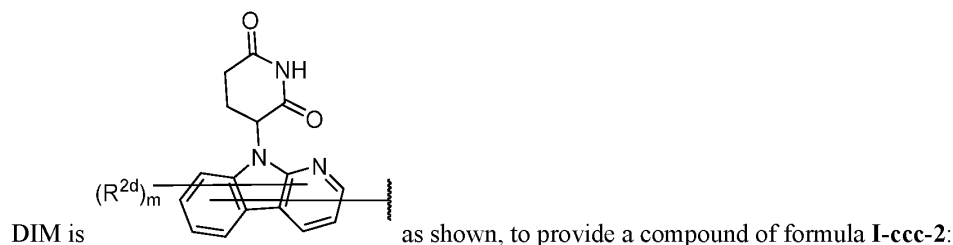
[00399] In some embodiments, the present invention provides a compound of formula I-ccc, wherein

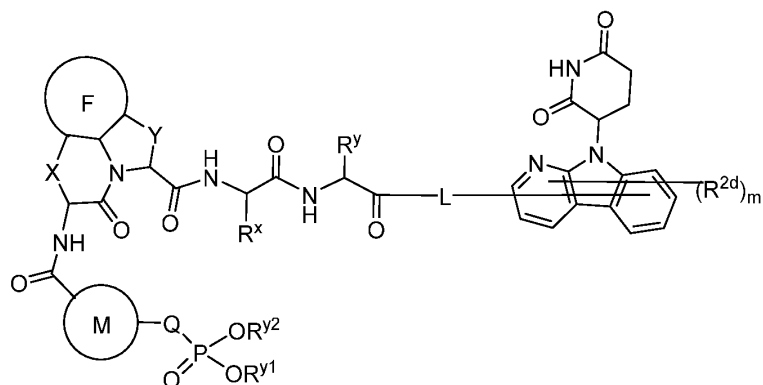


I-ccc-1

or a pharmaceutically acceptable salt thereof, wherein each of R^2 , m, L, Ring F, Ring M, X, Y, R^x , R^y , R^{y1} , and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

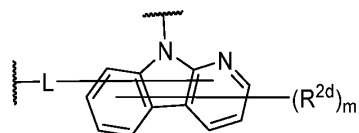
[00400] In some embodiments, the present invention provides a compound of formula I-ccc, wherein



**I-ccc-2**

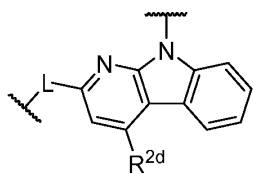
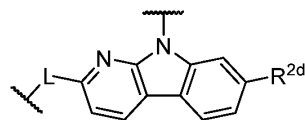
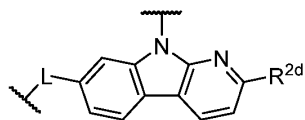
or a pharmaceutically acceptable salt thereof, wherein each of R^{2d} , m , L , Ring F, Ring M, X , Y , R^x , R^y , R^{y1} , and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00401] In some embodiments herein, structures depicted as



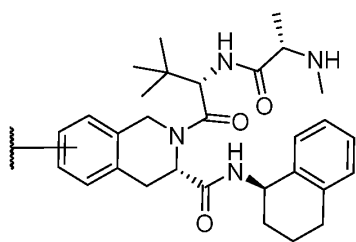
can

include, for example structures



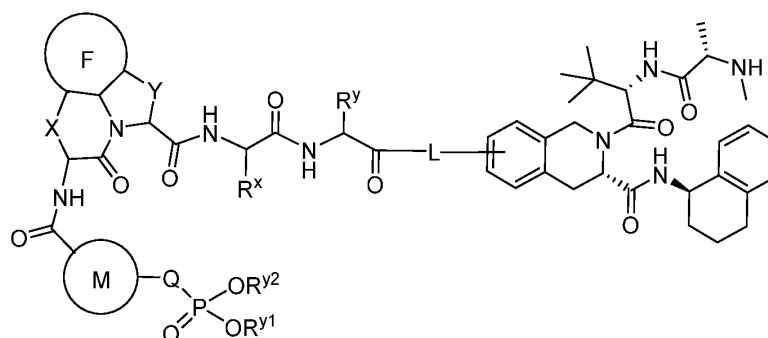
, etc.

[00402] In some embodiments, the present invention provides a compound of formula **I-ccc**, wherein



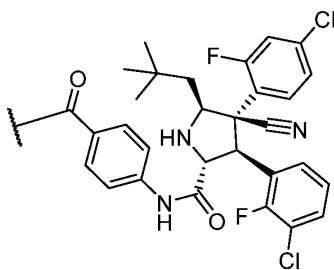
DIM is

as shown, to provide a compound of formula **I-ccc-3**:

**I-ccc-3**

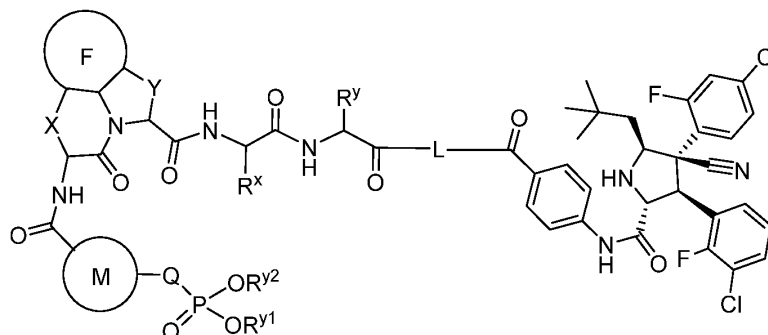
or a pharmaceutically acceptable salt thereof, wherein each of L, Ring F, Ring M, X, Y, R^x , R^y , R^{y1} , and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00403] In some embodiments, the present invention provides a compound of formula I-ccc, wherein



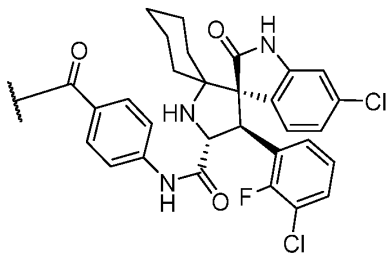
DIM is

as shown, to provide a compound of formula I-ccc-4:

**I-ccc-4**

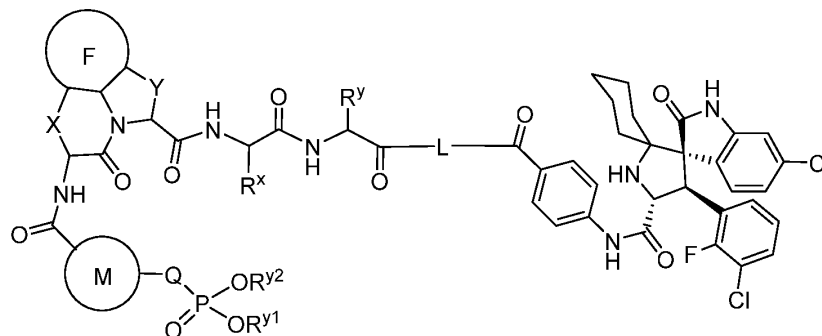
or a pharmaceutically acceptable salt thereof, wherein each of L, Ring F, Ring M, X, Y, R^x , R^y , R^{y1} , and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00404] In some embodiments, the present invention provides a compound of formula I-ccc, wherein



DIM is

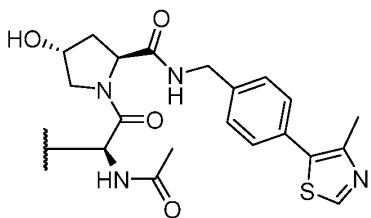
as shown, to provide a compound of formula **I-ccc-5**:



I-ccc-5

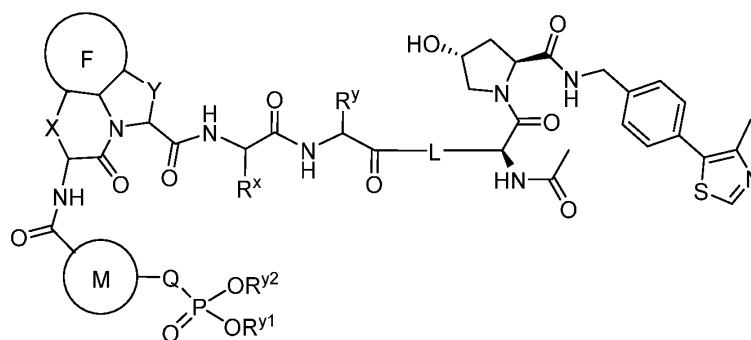
or a pharmaceutically acceptable salt thereof, wherein each of L, Ring F, Ring M, X, Y, R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00405] In some embodiments, the present invention provides a compound of formula **I-ccc**, wherein



DIM is

as shown, to provide a compound of formula **I-ccc-6**:

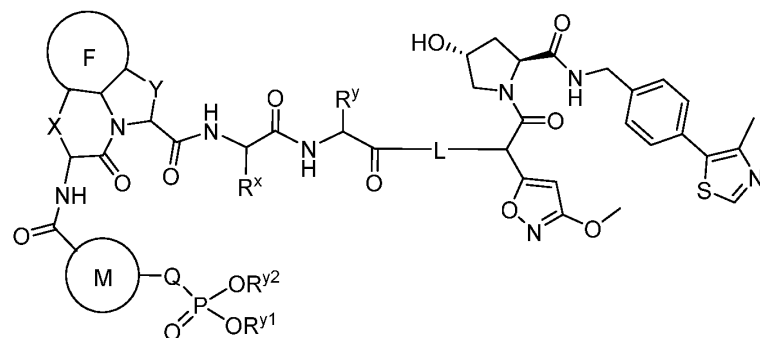
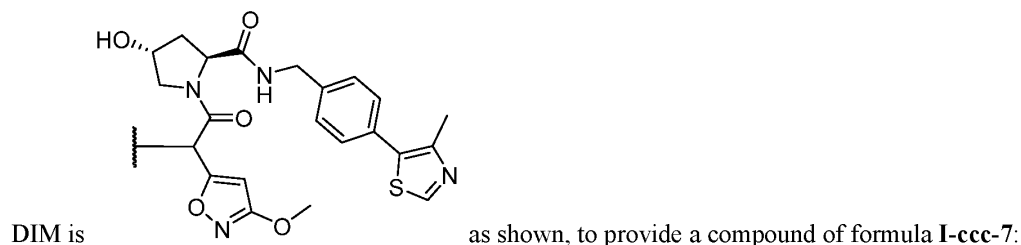


I-ccc-6

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring F, Ring M, X, Y, R^x, R^y, R^{y1}, and R^{y2}

is as defined above and described in embodiments herein, both singly and in combination.

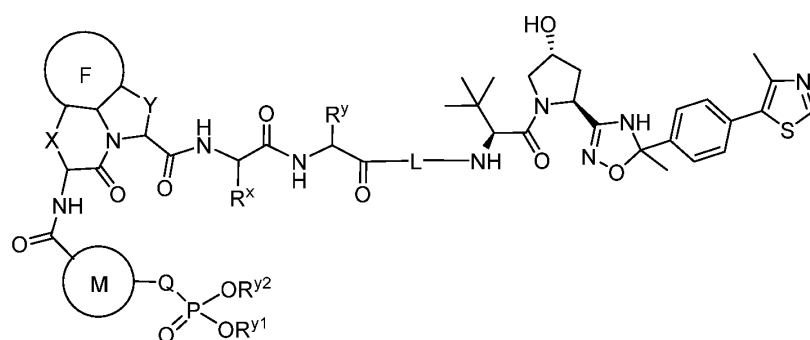
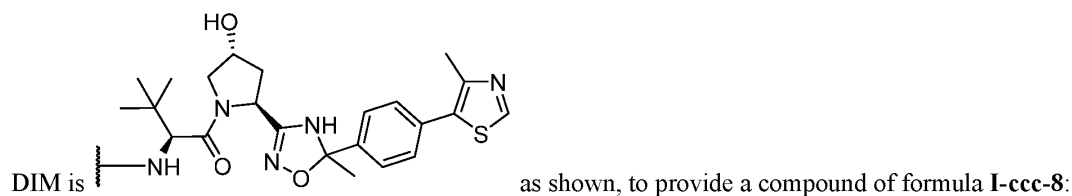
[00406] In some embodiments, the present invention provides a compound of formula **I-aaa**, wherein



I-ccc-7

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring F, Ring M, X, Y, R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00407] In some embodiments, the present invention provides a compound of formula **I-ccc**, wherein

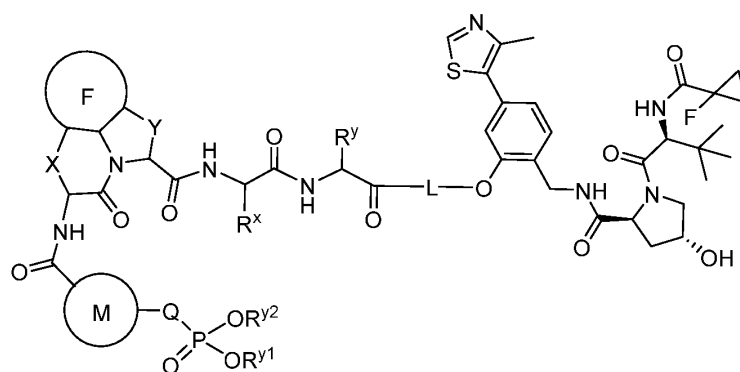
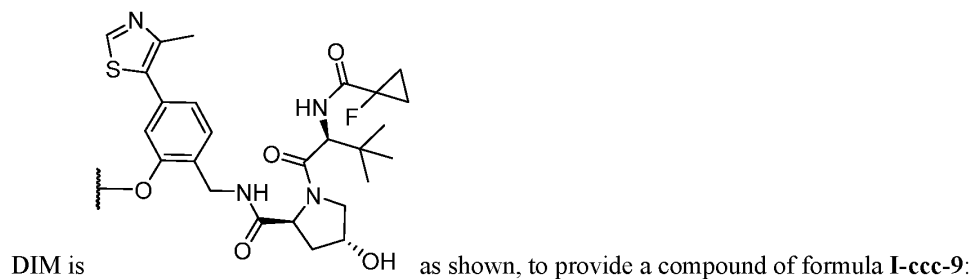


I-ccc-8

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring F, Ring M, X, Y, R^x, R^y, R^{y1}, and R^{y2}

is as defined above and described in embodiments herein, both singly and in combination.

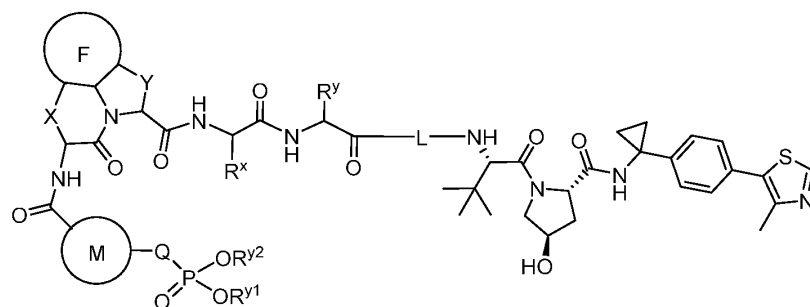
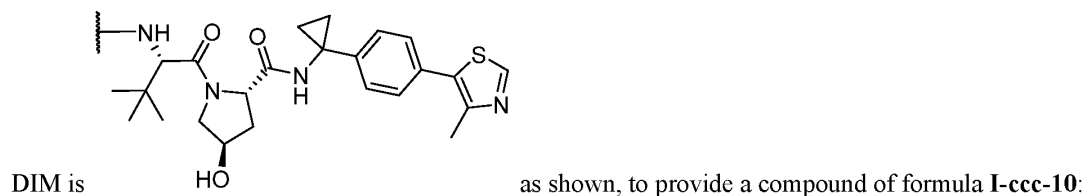
[00408] In some embodiments, the present invention provides a compound of formula I-ccc, wherein



I-ccc-9

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring F, Ring M, X, Y, R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

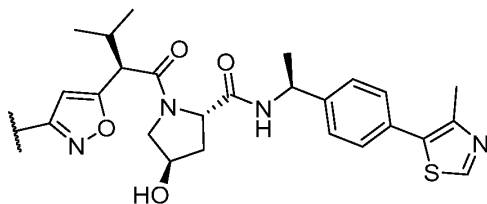
[00409] In some embodiments, the present invention provides a compound of formula I-ccc, wherein



I-ccc-10

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring F, Ring M, X, Y, R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

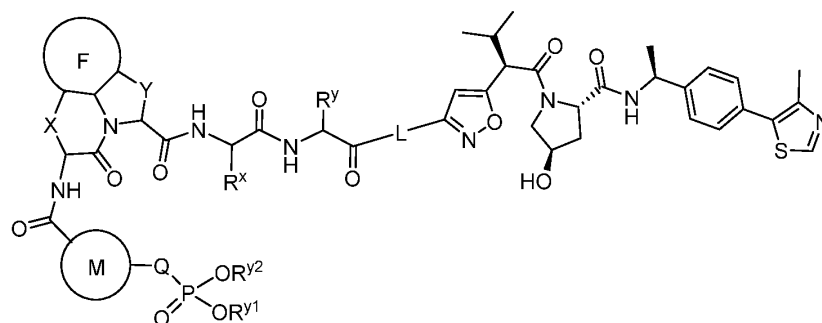
[00410] In some embodiments, the present invention provides a compound of formula I-ccc, wherein



DIM is

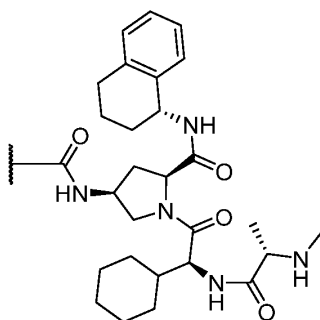
as shown, to provide a compound of formula I-

aaa-11:

**I-ccc-11**

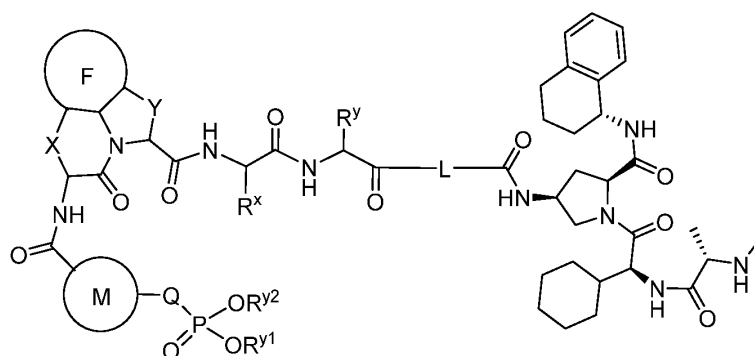
or a pharmaceutically acceptable salt thereof, wherein each of L, Ring F, Ring M, X, Y, R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00411] In some embodiments, the present invention provides a compound of formula I-ccc, wherein



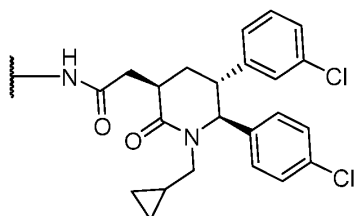
DIM is

as shown, to provide a compound of formula I-ccc-12:

**I-ccc-12**

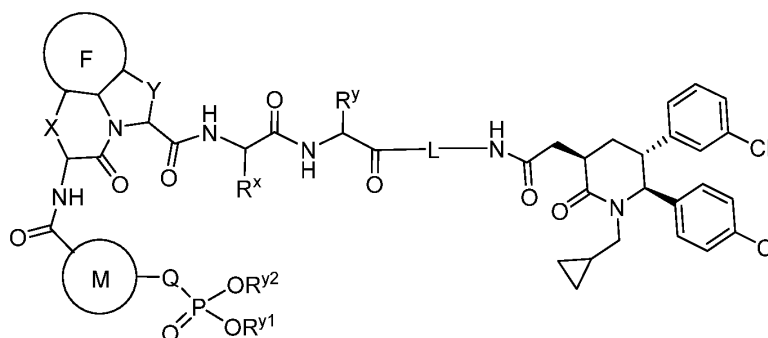
or a pharmaceutically acceptable salt thereof, wherein each of L, Ring F, Ring M, X, Y, R^x , R^y , R^{y1} , and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00412] In some embodiments, the present invention provides a compound of formula I-ccc, wherein



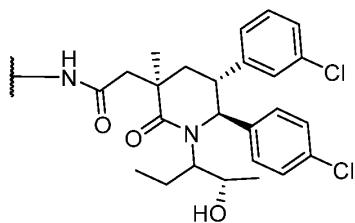
DIM is

as shown, to provide a compound of formula I-ccc-13:

**I-ccc-13**

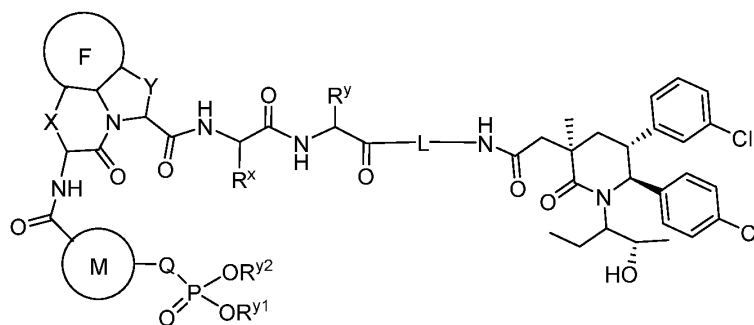
or a pharmaceutically acceptable salt thereof, wherein each of L, Ring F, Ring M, X, Y, R^x , R^y , R^{y1} , and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00413] In some embodiments, the present invention provides a compound of formula I-ccc, wherein



DIM is

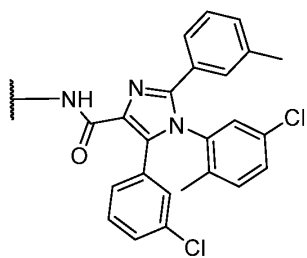
as shown, to provide a compound of formula I-ccc-14:



I-ccc-14

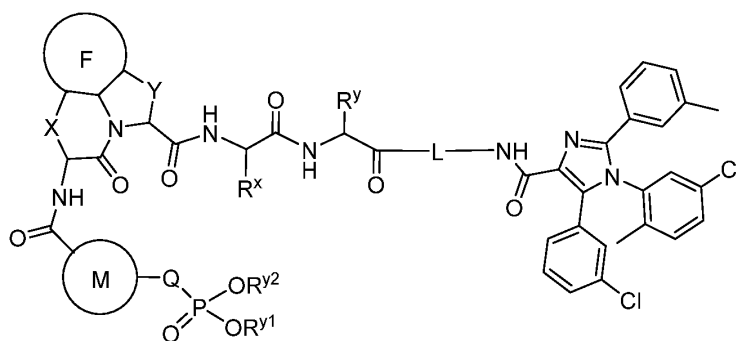
or a pharmaceutically acceptable salt thereof, wherein each of L, Ring F, Ring M, X, Y, R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00414] In some embodiments, the present invention provides a compound of formula I-ccc, wherein



DIM is

as shown, to provide a compound of formula I-ccc-15:

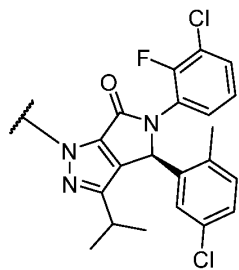


I-ccc-15

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring F, Ring M, X, Y, R^x, R^y, R^{y1}, and R^{y2}

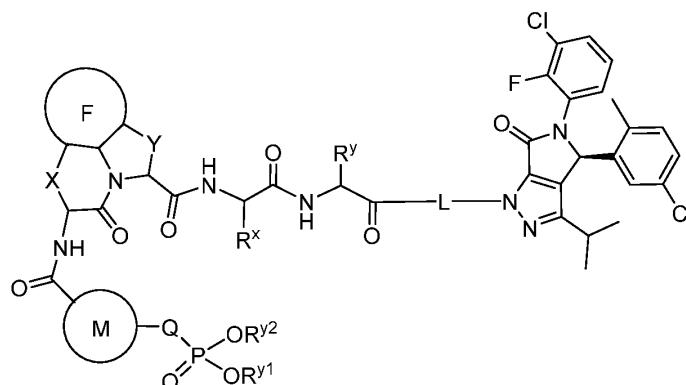
is as defined above and described in embodiments herein, both singly and in combination.

[00415] In some embodiments, the present invention provides a compound of formula I-ccc, wherein



DIM is

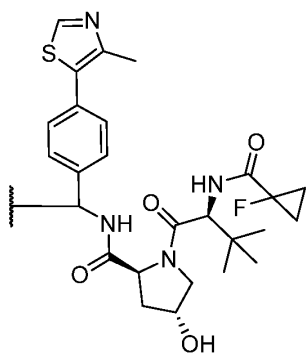
as shown, to provide a compound of formula I-ccc-16:



I-ccc-16

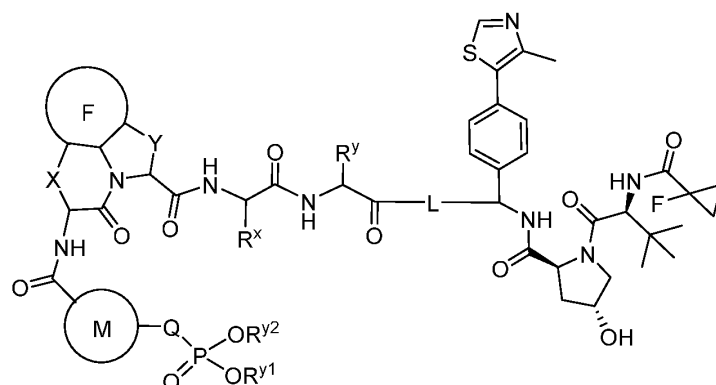
or a pharmaceutically acceptable salt thereof, wherein each of L, Ring F, Ring M, X, Y, R^x, R^y, R^{y1}, and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00416] In some embodiments, the present invention provides a compound of formula I-ccc, wherein



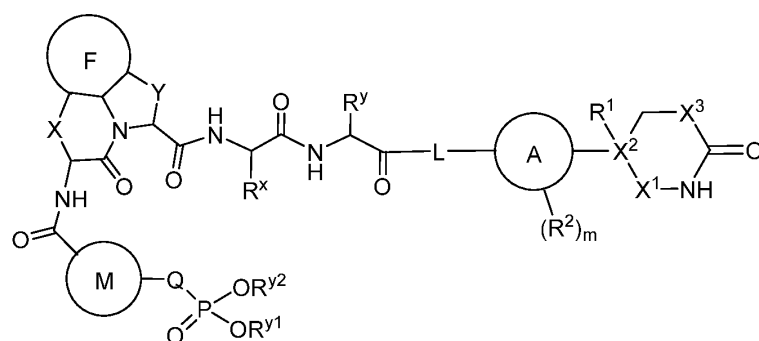
DIM is

as shown, to provide a compound of formula **I-ccc-17**:

**I-ccc-17**

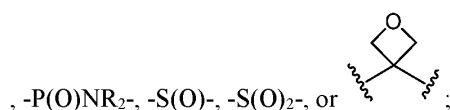
or a pharmaceutically acceptable salt thereof, wherein each of L, Ring F, Ring M, X, Y, R^x , R^y , R^{y1} , and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00417] In certain embodiments, the present invention provides a compound of formula **I-ddd**:

**I-ddd**

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is a bivalent moiety selected from a covalent bond, $-CR_2-$, $-C(O)-$, $-C(S)-$, $-CR(CF_3)-$, $-P(O)OR-$, $-P(O)R-$



X^2 is a carbon atom or silicon atom;

X^3 is a bivalent moiety selected from $-CR_2-$, $-NR-$, $-O-$, $-S-$, or $-SiR_2-$;

R^1 is hydrogen, halogen, $-CN$, $-OR$, $-SR$, $-S(O)R$, $-S(O)_2R$, $-NR_2$, $-P(O)(OR)_2$, $-P(O)NR_2OR$, $-P(O)(NR_2)_2$, $-Si(OH)_2R$, $-Si(OH)R_2$, $-SiR_3$, or an optionally substituted C_{1-4} aliphatic;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms

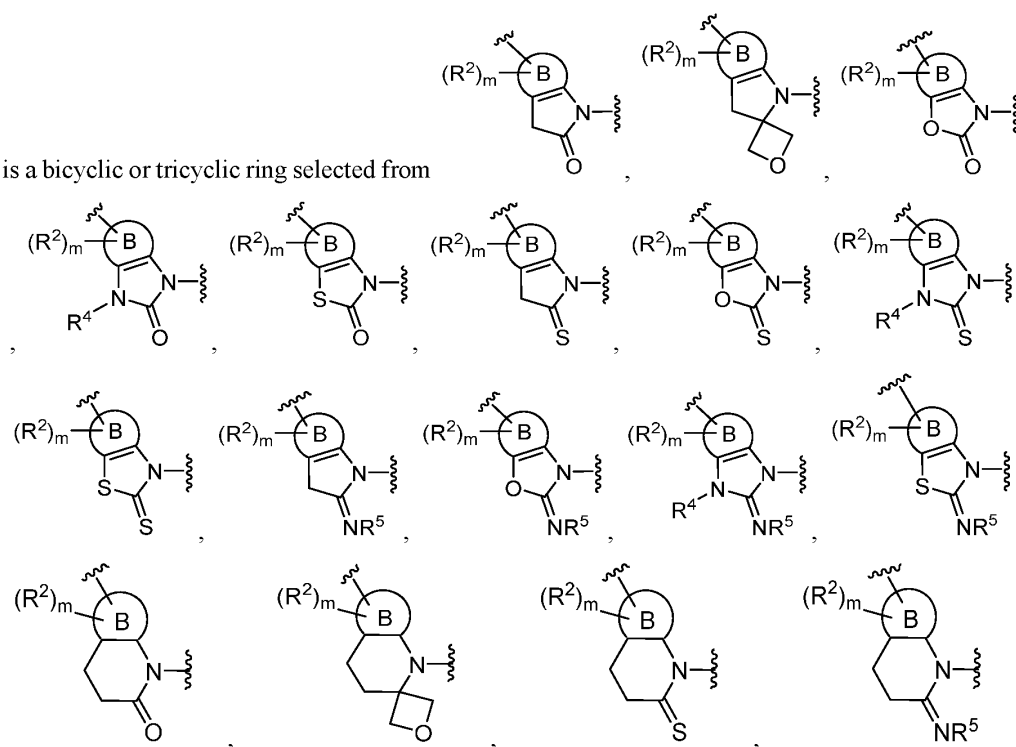
independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

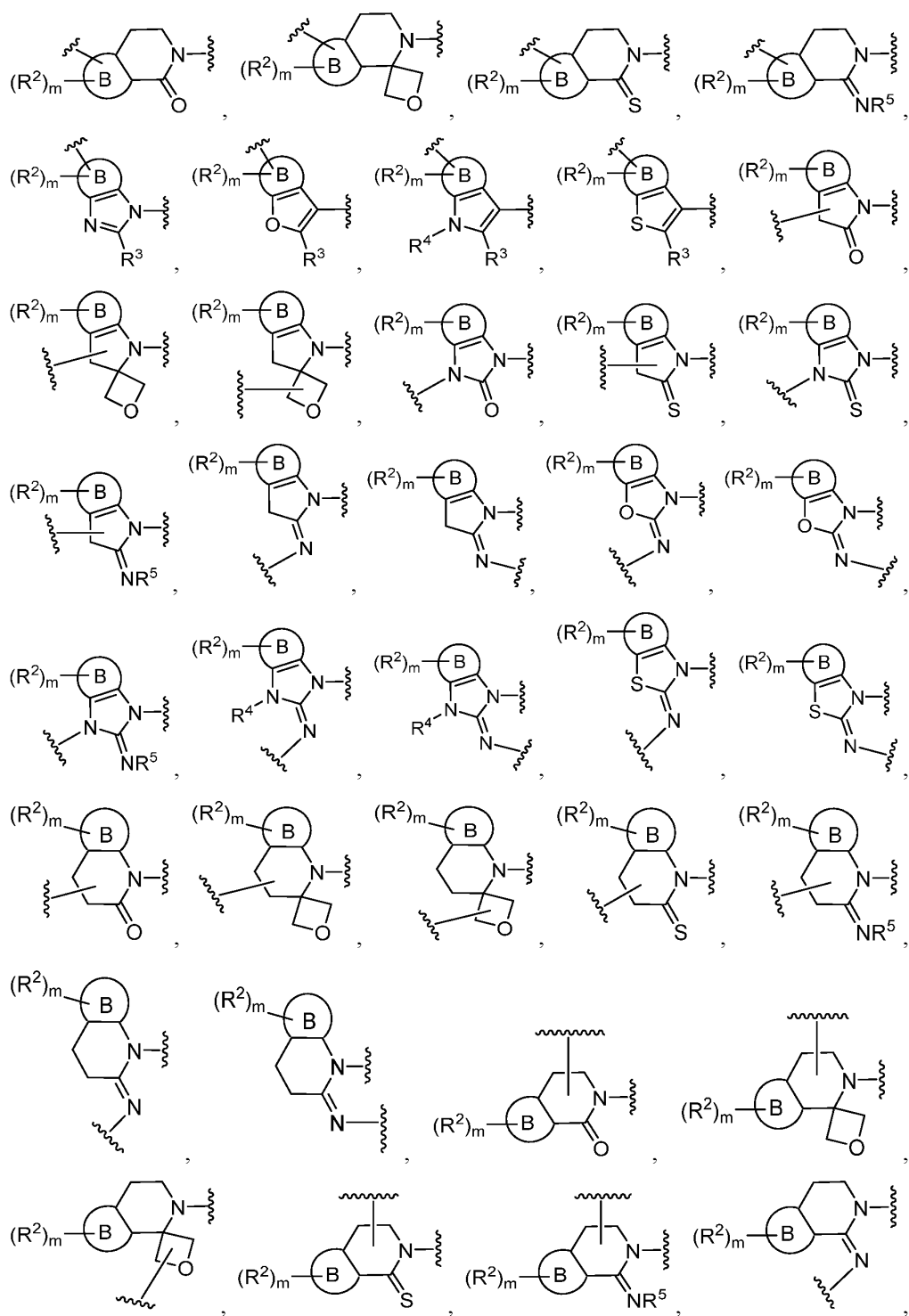
two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in addition to the carbon or nitrogen from which the two R groups are attached, independently selected from nitrogen, oxygen, and sulfur;

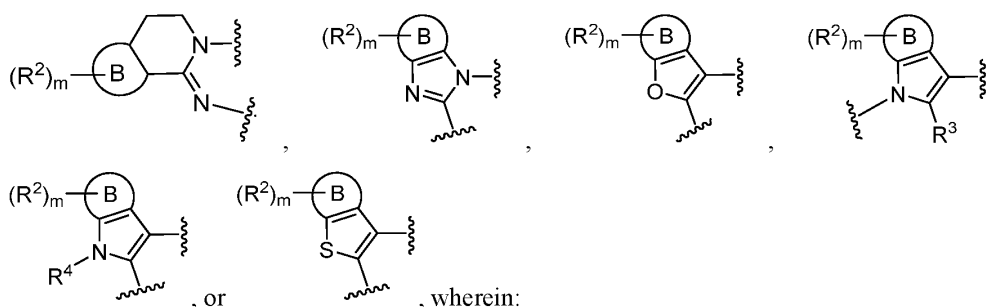
each R^2 is independently hydrogen, R^6 , halogen, -CN, -NO₂, -OR, -SR, -NR₂, -SiR₃, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)NROR, -CR₂NRC(O)R, -CR₂NRC(O)NR₂, -OC(O)R, -OC(O)NR₂, -OP(O)R₂, -OP(O)(OR)₂, -OP(O)(OR)NR₂, -OP(O)(NR₂)₂, -NRC(O)OR, -NRC(O)R, -NRC(O)NR₂, -NRS(O)₂R, -NP(O)R₂, -NRP(O)(OR)₂, -NRP(O)(OR)NR₂, -NRP(O)(NR₂)₂, or -NRS(O)₂R;

each R^6 and R^A is independently an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring A is a bicyclic or tricyclic ring selected from







Ring B is a fused ring selected from benzo, 5-6 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5 to 7-membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is selected from hydrogen, halogen, -OR, -NR₂, or -SR;

each R^4 is independently hydrogen, R^6 , halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)NROR, -OC(O)R, -OC(O)NR₂, -NRC(O)OR, -NRC(O)R, -NRC(O)NR₂, or -NRS(O)₂R;

R^5 is hydrogen, C₁₋₄ aliphatic, or -CN;

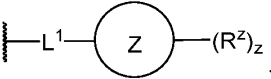
m is 0, 1, 2, 3 or 4;

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C₁₋₂₀ hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, -CRF-, -CF₂-, -C(O)-, -S-, -S(O)-, -S(O)₂-, -SiR₂-, -Si(OH)R-, -Si(OH)₂-, -P(O)OR-, -P(O)R-, or -P(O)NR₂-, wherein:

each -Cy- is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclenyl, a 4-7 membered saturated or partially unsaturated heterocyclenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or

sulfur;

R^x is hydrogen, R^A , $-(CR_2)_{1-3}OCONR_2$, or $-(CR_2)_{1-3}CONR_2$;

R^y is hydrogen, R^A , or ;

L^1 is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-5} hydrocarbon chain, wherein 0-3 methylene units of L^1 are independently replaced by $-O-$, $-NR-$, $-CRF-$, $-CF_2-$, $-C(O)-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

Ring Z is a ring selected from phenyl, naphthyl, a 5-10 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^z is hydrogen, R^A , halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)NROR$, $-CR_2NRC(O)R$, $-CR_2NRC(O)NR_2$, $-OC(O)R$, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-NRC(O)OR$, $-NRC(O)R$, $-NRC(O)NR_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, or $-NRS(O)_2R$;

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

Ring F is an optionally substituted fused ring selected from a 6-membered aryl, a 5-6 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

X is an optionally substituted $-(CH_2)_x-$, wherein:

x is 0, 1, 2, or 3;

Y is an optionally substituted $-(CH_2)_y-$, wherein:

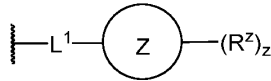
y is 0, 1, 2, or 3;

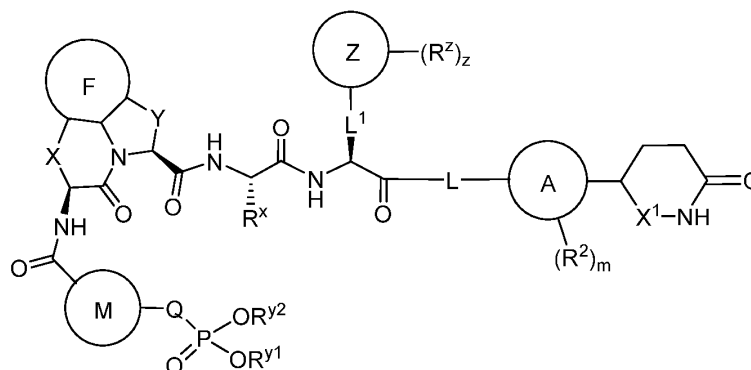
Ring M is an optionally substituted bivalent ring selected from phenylenyl, naphthylene, a 5-10 membered heteroarylene containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclenyl or heterocyclenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Q is a bivalent moiety selected from $-O-$, $-CR_2-$, $-CF_2-$, $-CFR-$, $-C(O)-$, $-OCR_2-$, and $-C(S)-$; and

R^{y1} and R^{y2} are each independently hydrogen, R^A , $-CH_2CO_2R$, or $-CH_2OCO_2R$.

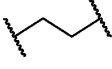
[00418] In some embodiments, the present invention provides a compound of formula **I-ddd**, wherein

X^2 and X^3 are carbon atoms, R^1 is hydrogen, and R_y is  as shown, to provide a compound of formula **I-ddd-1**:

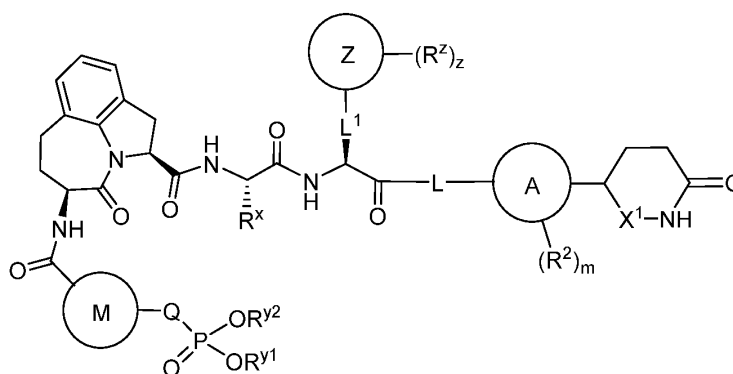
**I-ddd-1**

or a pharmaceutically acceptable salt thereof, wherein each of R^2 , m , L , L^1 , X^1 , Ring A, Ring F, Ring M, Ring Z, Q, X, Y, R^x , R^{y1} , and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00419] In some embodiments, the present invention provides a compound of formula **I-ddd**, wherein

X^2 and X^3 are carbon atoms, R^1 is hydrogen, X' is , Y is $-\text{CH}_2-$, Ring F is a 6-member aryl, and

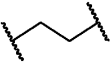
R_y is  as shown, to provide a compound of formula **I-ddd-2**:

**I-ddd-2**

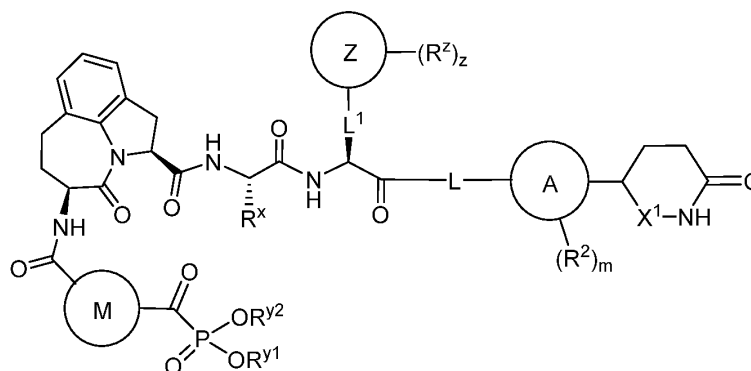
or a pharmaceutically acceptable salt thereof, wherein each of R^2 , m , L , L^1 , X^1 , Ring A, Ring M, Ring Z, Q, R^x , R^{y1} , and R^{y2} is as defined above and described in embodiments herein, both singly and in

combination.

[00420] In some embodiments, the present invention provides a compound of formula **I-ddd**, wherein

X^2 and X^3 are carbon atoms, R^1 is hydrogen, X' is , Y is $-\text{CH}_2-$, Ring F is a 6-member aryl, Q is

$-\text{C}(\text{O})-$, and R_y is  as shown, to provide a compound of formula **I-ddd-3**:



I-ddd-3

or a pharmaceutically acceptable salt thereof, wherein each of R^2 , m, L, L^1 , X^1 , Ring A, Ring M, Ring Z, R^x , R^{y1} , and R^{y2} is as defined above and described in embodiments herein, both singly and in combination.

[00421] As defined above and described herein, R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00422] In some embodiments, R^A is an optionally substituted C_{1-6} aliphatic. In some embodiments, R^A is an optionally substituted phenyl. In some embodiments, R^A is an optionally substituted 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^A is an optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^A is $-\text{CH}_2\text{CO}_2\text{R}$. In some embodiments, R^A is $-\text{CH}_2\text{OCO}_2\text{R}$. In some embodiments, R^A is $-\text{CH}_2\text{C}(\text{O})\text{NR}_2$.

[00423] In some embodiments, R^A is selected from those depicted in **Table 1**, below.

[00424] As defined above and described herein, each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated

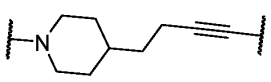
heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in addition to the carbon or nitrogen from which the two R groups are attached, independently selected from nitrogen, oxygen, and sulfur.

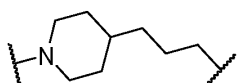
[00425] In some embodiments, R is hydrogen. In some embodiments, R is an optionally substituted C₁₋₆ aliphatic. In some embodiments, R is an optionally substituted phenyl. In some embodiments, R is an optionally substituted 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in addition to the carbon or nitrogen from which the two R groups are attached, independently selected from nitrogen, oxygen, and sulfur.

[00426] In some embodiments, R is selected from those depicted in **Table 1**, below.

[00427] As defined above and described herein, L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C₁₋₂₀ hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, -CRF-, -CF₂-, -C(O)-, -S-, -S(O)-, -S(O)₂-, -SiR₂-, -Si(OH)R-, -Si(OH)₂-, -P(O)OR-, -P(O)R-, or -P(O)NR₂-.

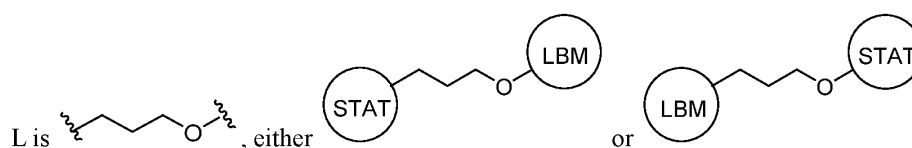
[00428] In some embodiments, L is a covalent bond. In some embodiments, L is a bivalent, saturated or partially unsaturated, straight or branched C₁₋₂₀ hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, -CRF-, -CF₂-, -C(O)-, -S-, -S(O)-, -S(O)₂-, -SiR₂-, -Si(OH)R-, -Si(OH)₂-, -P(O)OR-, -P(O)R-, or -P(O)NR₂-.

[00429] In some embodiments, L is . In some embodiments, L is



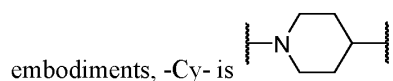
[00430] In some embodiments, L is selected from those depicted in **Table 1**, below.

[00431] Without limitation, the point of attachment of L to STAT and LBM can be, for example when



[00432] As defined above and described herein, each -Cy- is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylene, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00433] In some embodiments, -Cy- is an optionally substituted phenylenyl. In some embodiments, -Cy- is an optionally substituted 8-10 membered bicyclic arylene. In some embodiments, -Cy- is an optionally substituted 4-7 membered saturated or partially unsaturated carbocyclylenyl. In some embodiments, -Cy- is an optionally substituted 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl. In some embodiments, -Cy- is an optionally substituted 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl. In some embodiments, -Cy- is an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, -Cy- is an optionally substituted 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, -Cy- is an optionally substituted 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, -Cy- is an optionally substituted 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, -Cy- is an optionally substituted 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some



[00434] In some embodiments, -Cy- is selected from those depicted in **Table 1**, below.

[00435] As defined above and described herein, L^1 is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-5} hydrocarbon chain, wherein 0-3 methylene units of L^1 are independently replaced by -O-, -NR-, -CRF-, -CF₂-, -C(O)-, -S-, -S(O)-, or -S(O)₂-.

[00436] In some embodiments, L^1 is covalent bond. In some embodiments, L^1 is a bivalent, saturated or partially unsaturated, straight or branched C_{1-5} hydrocarbon chain, wherein 0-3 methylene units of L^1 are independently replaced by -O-, -NR-, -CRF-, -CF₂-, -C(O)-, -S-, -S(O)-, or -S(O)₂-. In some embodiments, L^1 is -CH₂-.

[00437] In some embodiments, L^1 is selected from those depicted in **Table 1**, below.

[00438] As defined above and described herein, Q is a bivalent moiety selected from -O-, -CR₂-, -CF₂-, -CFR-, -C(O)-, -OCR₂-, and -C(S)-.

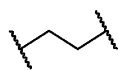
[00439] In some embodiments, Q is -O-. In some embodiments, Q is -CR₂-. In some embodiments, Q is -OCR₂-. In some embodiments, Q is -CF₂-. In some embodiments, Q is -CFR-. In some embodiments, Q is -C(O)-. In some embodiments, Q is -C(S)-.

[00440] In some embodiments, Q is selected from those depicted in **Table 1**, below.

[00441] As defined above and described herein, Y is an optionally substituted -(CH₂)_y-.

[00442] In some embodiments, Y is an optionally substituted -(CH₂)_y-. In some embodiments, Y is -

CH₂-. In some embodiments, Y is



[00443] In some embodiments, Y is selected from those depicted in **Table 1**, below.

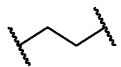
[00444] As defined above and described herein, y is 0, 1, 2, or 3.

[00445] In some embodiments, y is 0. In some embodiments, y is 1. In some embodiments, y is 2. In some embodiments, y is 3.

[00446] In some embodiments, y is selected from those depicted in **Table 1**, below.

[00447] As defined above and described herein, X is an optionally substituted -(CH₂)_x-.

[00448] In some embodiments, X is an optionally substituted -(CH₂)_x-. In some embodiments, X is

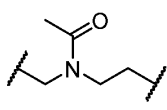
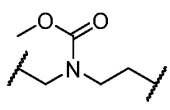


[00449] In some embodiments, X is selected from those depicted in **Table 1**, below.

[00450] As defined above and described herein, X' is an optionally substituted -(CH₂)_x-, wherein 1-2 methylenes of X' is optionally replaced with a bivalent group selected from -NR-, -N(COR)-, -N(CO₂R)-, -N(SO₂R)-, -N(CONR₂)-, and -N(SO₂NR₂)-.

[00451] In some embodiments, X' is an optionally substituted -(CH₂)_x-, wherein 1-2 methylenes of X' is optionally replaced with a bivalent group selected from -NR-, -N(COR)-, -N(CO₂R)-, -N(SO₂R)-, -

$N(CONR_2)-$, and $-N(SO_2NR_2)-$.

[00452] In some embodiments, X^* is . In some embodiments, X^* is .

[00453] In some embodiments, X^* is selected from those depicted in **Table 1**, below.

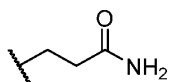
[00454] As defined above and described herein, x is 0, 1, 2, 3, 4, or 5.

[00455] In some embodiments, x is 0. In some embodiments, x is 1. In some embodiments, x is 2. In some embodiments, x is 3. In some embodiments, x is 4. In some embodiments, x is 5.

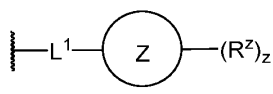
[00456] In some embodiments, x is selected from those depicted in **Table 1**, below.

[00457] As defined above and described herein, R^x is R^x is hydrogen, R^A , $-(CR_2)_{1-3}OCONR_2$, or $-(CR_2)_{1-3}CONR_2$.

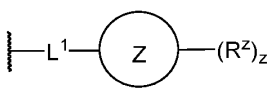
[00458] In some embodiments, R^x is hydrogen. In some embodiments, R^x is R^A . In some embodiments, R^x is $-(CR_2)_{1-3}OCONR_2$. In some embodiments, R^x is $-(CR_2)_{1-3}CONR_2$. In some embodiments, R^x is



[00459] In some embodiments, R^x is selected from those depicted in **Table 1**, below.

[00460] As defined above and described herein, R^y is hydrogen, R^A , or .

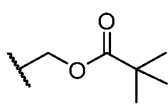
[00461] In some embodiments, R^y is hydrogen. In some embodiments, R^y is R^A . In some embodiments,

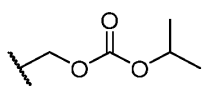
R^y is .

[00462] In some embodiments, R^y is selected from those depicted in **Table 1**, below.

[00463] As defined above and described herein, R^{y1} and R^{y2} are each independently hydrogen, R^A , $-CH_2CO_2R$, or $-CH_2OCO_2R$.

[00464] In some embodiments, R^{y1} is hydrogen. In some embodiments, R^{y1} is R^A . In some embodiments, R^{y1} is $-CH_2CO_2R$. In some embodiments, R^{y1} is $-CH_2OCO_2R$. In some embodiments, R^{y2} is hydrogen. In some embodiments, R^{y2} is R^A . In some embodiments, R^{y2} is $-CH_2CO_2R$. In some

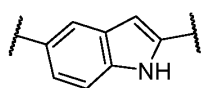
embodiments, R^{y2} is $-CH_2OCO_2R$. In some embodiments, R^x is . In some embodiments,

R^x is .

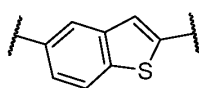
[00465] In some embodiments, R^{y1} and R^{y2} are selected from those depicted in **Table 1**, below.

[00466] As defined above and described herein, Ring M is an optionally substituted bivalent ring selected from phenylenyl, naphthylenyl, a 5-10 membered heteroarylenyl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclylenyl or heterocyclylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

[00467] In some embodiments, Ring M is an optionally substituted phenylenyl. In some embodiments, Ring M is an optionally substituted naphthylenyl. In some embodiments, Ring M is an optionally substituted 5-10 membered heteroarylenyl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring M is an optionally substituted 5-11 membered saturated or partially unsaturated carbocyclylenyl. In some embodiments, Ring M is an optionally substituted 5-11 membered saturated or partially unsaturated heterocyclylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring M is



. In some embodiments, Ring M is



[00468] In some embodiments, Ring M is selected from those depicted in **Table 1**, below.

[00469] As defined above and described herein, Ring Z is a ring selected from phenyl, naphthyl, a 5-10 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00470] In some embodiments, Ring Z is phenyl. In some embodiments, Ring Z is naphthyl. In some embodiments, Ring Z is a 5-10 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring Z is a 5-11 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring Z is cyclohexyl.

[00471] In some embodiments, Ring Z is selected from those depicted in **Table 1**, below.

[00472] As defined above and described herein, R^z is hydrogen, R^A , halogen, -CN, -NO₂, -OR, -SR, -NR₂, -SiR₃, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)NROR, -CR₂NRC(O)R, -CR₂NRC(O)NR₂, -OC(O)R, -OC(O)NR₂, -OP(O)R₂, -OP(O)(OR)₂, -OP(O)(OR)NR₂, -OP(O)(NR₂)₂, -NRC(O)OR, -NRC(O)R, -NRC(O)NR₂, -NRS(O)₂R, -NP(O)R₂, -NRP(O)(OR)₂, -NRP(O)(OR)NR₂, -NRP(O)(NR₂)₂, or -NRS(O)₂R.

[00473] In some embodiments, R^z is hydrogen. In some embodiments, R^z is R^A . In some embodiments, R^z is halogen. In some embodiments, R^z is -CN. In some embodiments, R^z is -NO₂. In some embodiments,

R^z is -OR. In some embodiments, R^z is -SR. In some embodiments, R^z is -NR₂. In some embodiments, R^z is -SiR₃. In some embodiments, R^z is -S(O)₂R. In some embodiments, R^z is -S(O)₂NR₂. In some embodiments, R^z is -S(O)R, -C(O)R. In some embodiments, R^z is -C(O)OR. In some embodiments, R^z is -C(O)NR₂. In some embodiments, R^z is -C(O)NROR. In some embodiments, R^z is -CR₂NRC(O)R. In some embodiments, R^z is -CR₂NRC(O)NR₂. In some embodiments, R^z is -OC(O)R. In some embodiments, R^z is -OC(O)NR₂. In some embodiments, R^z is -OP(O)R₂. In some embodiments, R^z is -OP(O)(OR)₂. In some embodiments, R^z is -OP(O)(OR)NR₂. In some embodiments, R^z is -OP(O)(NR₂)₂. In some embodiments, R^z is -NRC(O)OR. In some embodiments, R^z is -NRC(O)R. In some embodiments, R^z is -NRC(O)NR₂. In some embodiments, R^z is -NRS(O)₂R. In some embodiments, R^z is -NP(O)R₂. In some embodiments, R^z is -NRP(O)(OR)₂. In some embodiments, R^z is -NRP(O)(OR)NR₂. In some embodiments, R^z is -NRP(O)(NR₂)₂. In some embodiments, R^z is -NRS(O)₂R. In some embodiments, R^z is fluoro.

[00474] In some embodiments, R^z is selected from those depicted in **Table 1**, below.

[00475] As defined above and described herein, z is 0, 1, 2, 3 or 4.

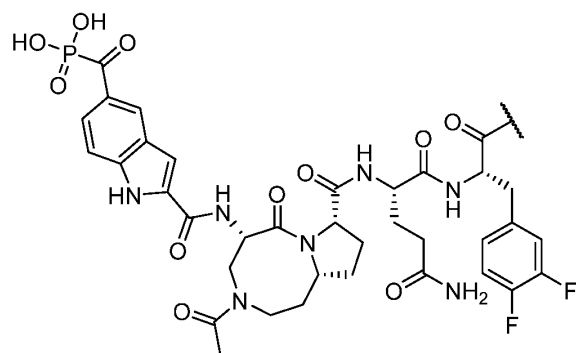
[00476] In some embodiments, z is 0. In some embodiments, z is 1. In some embodiments, z is 2. In some embodiments, z is 3. In some embodiments, z is 4.

[00477] In some embodiments, z is selected from those depicted in **Table 1**, below.

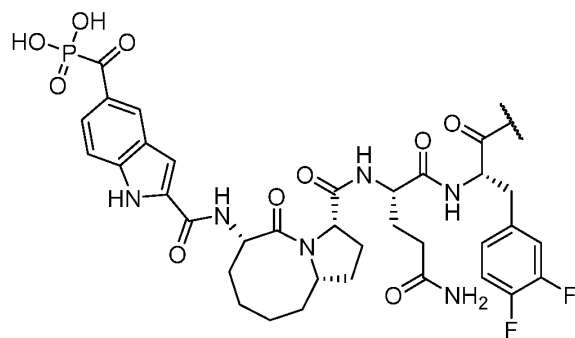
[00478] As defined above and described herein, Ring F is an optionally substituted fused ring selected from a 6-membered aryl, a 5-6 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00479] In some embodiments, Ring F is an optionally substituted 6-membered aryl. In some embodiments, Ring F is an optionally substituted 5-6 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring F is an optionally substituted 5-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring F is a 6-membered aryl.

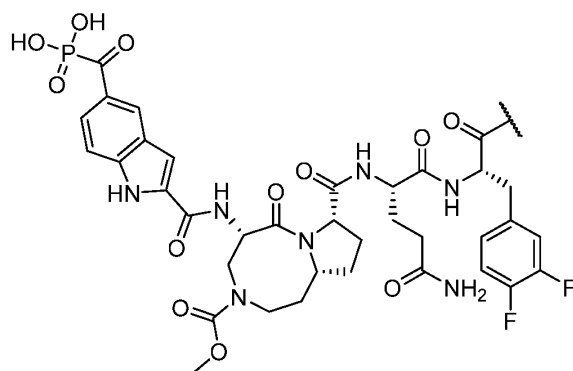
[00480] In some embodiments, Ring F is selected from those depicted in **Table 1**, below.



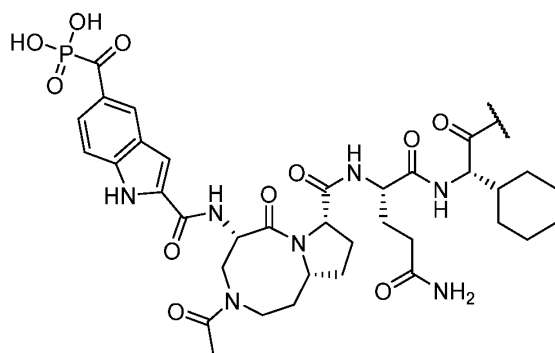
[00481] In some embodiments, STAT is . In



some embodiments, STAT is . In some

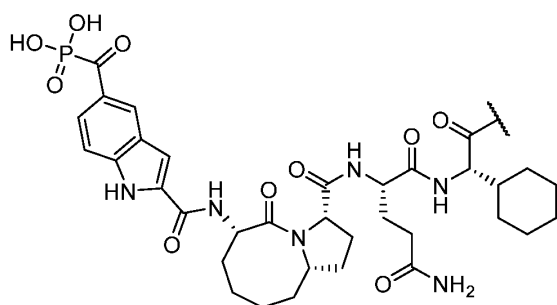


embodiments, STAT is . In some embodiments,

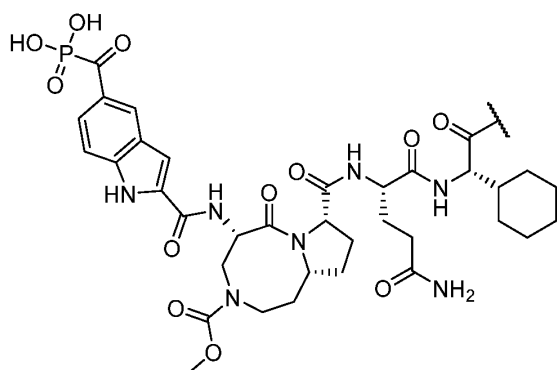


STAT is

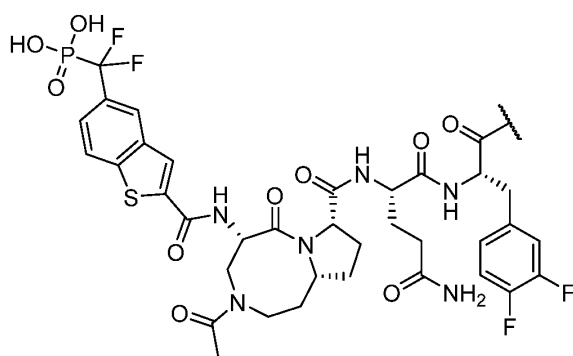
In some embodiments, STAT is



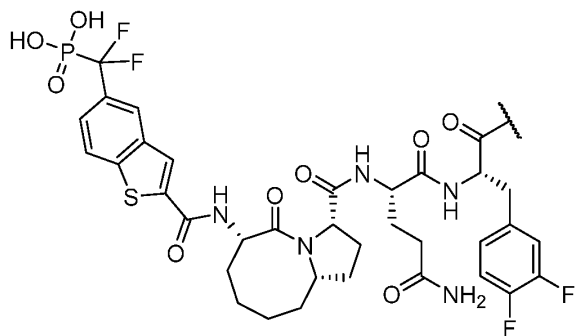
In some embodiments, STAT is



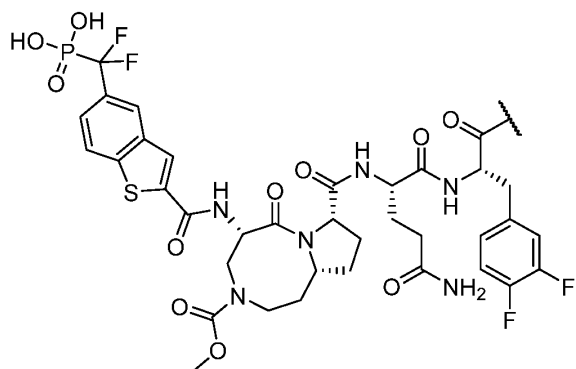
In some embodiments, STAT is



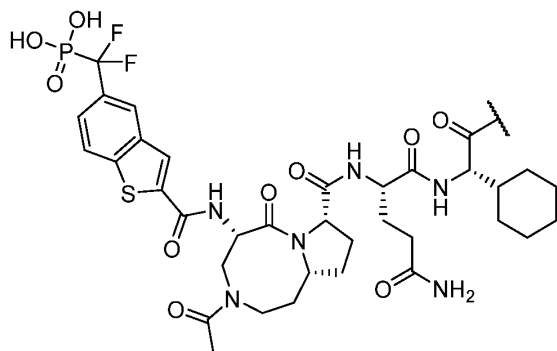
In some embodiments, STAT is



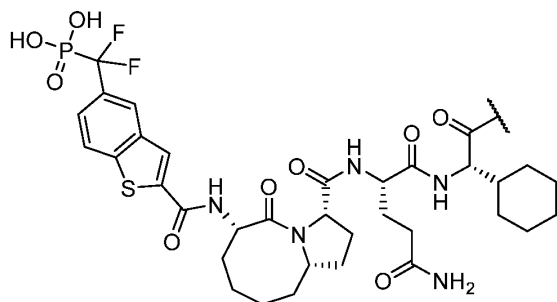
In some embodiments, STAT is



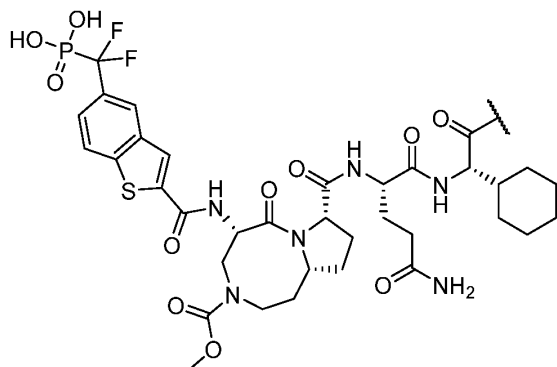
In some embodiments, STAT is



In some embodiments, STAT is



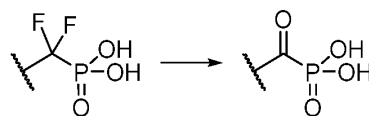
In some embodiments, STAT is



. In some embodiments, STAT is selected from those depicted in **Table 1**, below.

[00482] Without being limited to any particular theory, prodrugs of compounds of formula **I** are included in the present invention. It is well established that a prodrug approach, wherein a compound is derivatized into a form suitable for formulation and/or administration, then released as a drug in vivo, has been successfully employed to transiently (e.g., bioreversibly) alter the physicochemical properties of the compound (see, H. Bundgaard, Ed., “Design of Prodrugs,” Elsevier, Amsterdam, (1985); R. B. Silverman, “The Organic Chemistry of Drug Design and Drug Action,” Academic Press, San Diego, chapter 8, (1992); K. M. Hillgren et al., *Med. Res. Rev.*, 15, 83 (1995)).

[00483] One of ordinary skill in the art will appreciate that the difluoro phosphonate moiety described

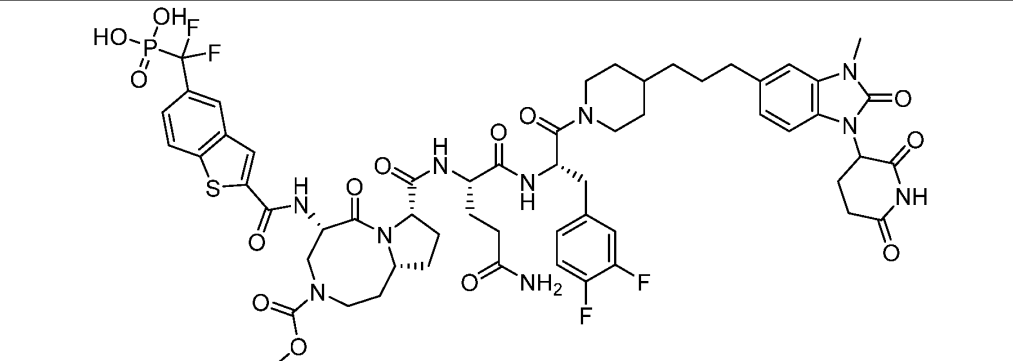
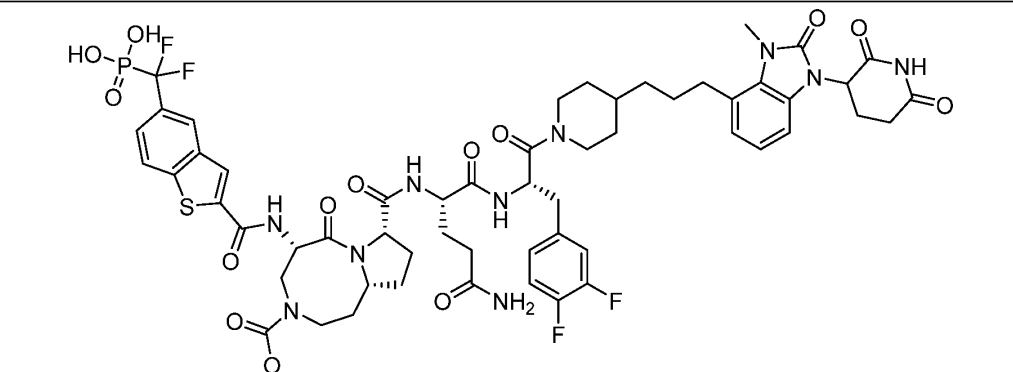
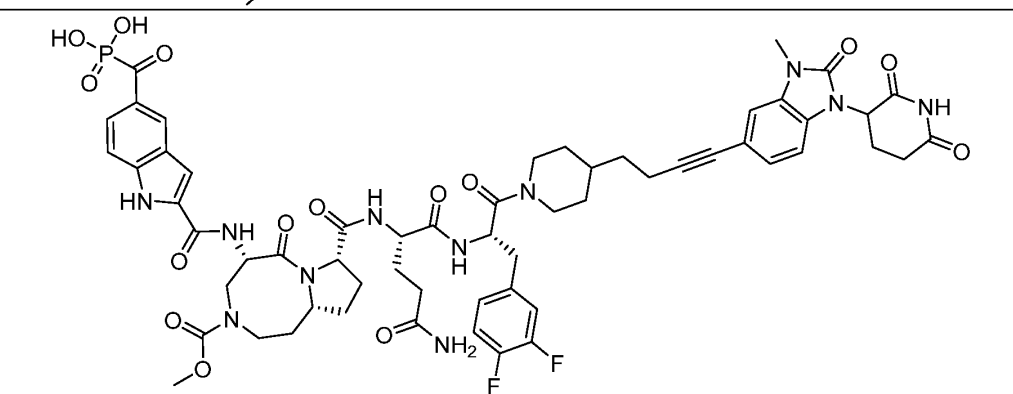


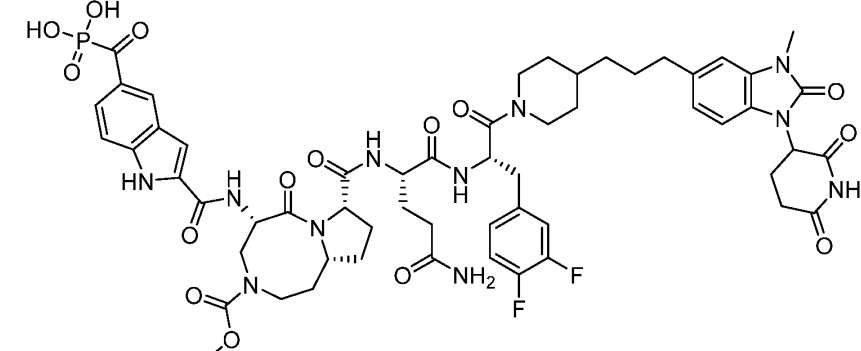
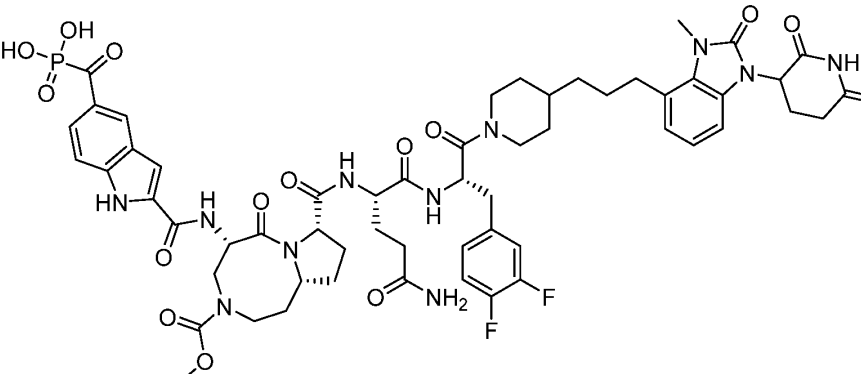
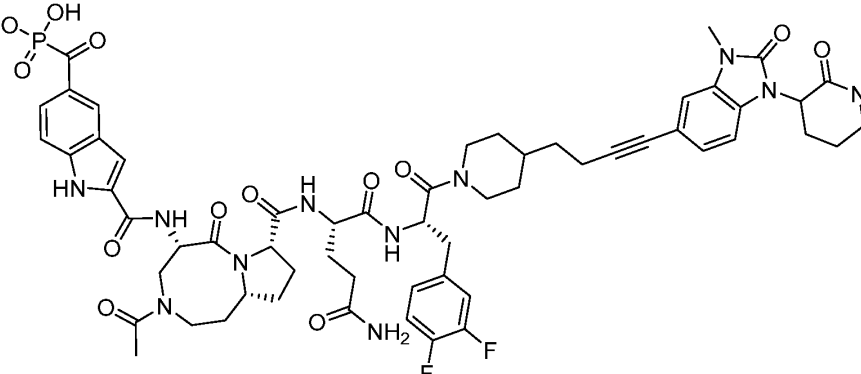
above may convert in vivo to a ketone phosphonate moiety, e.g.,

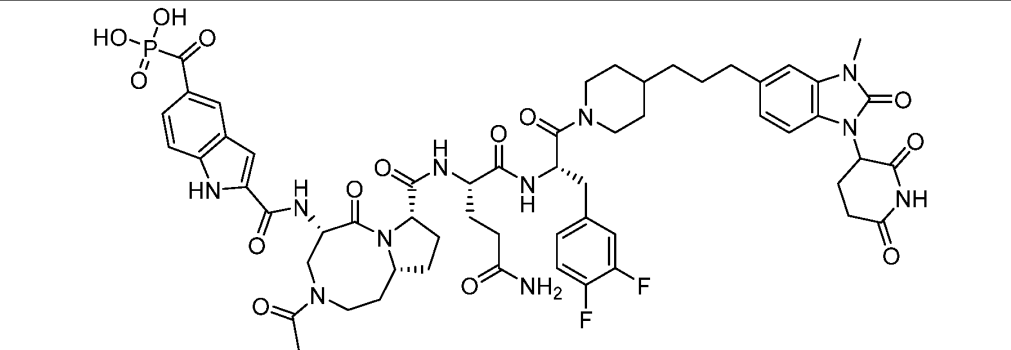
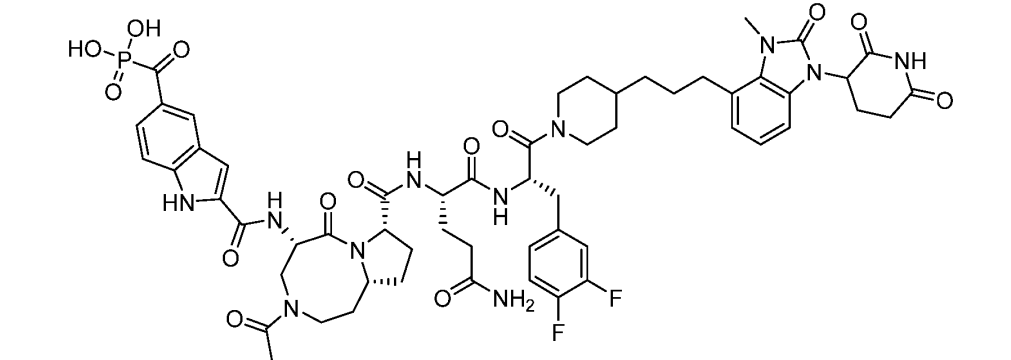
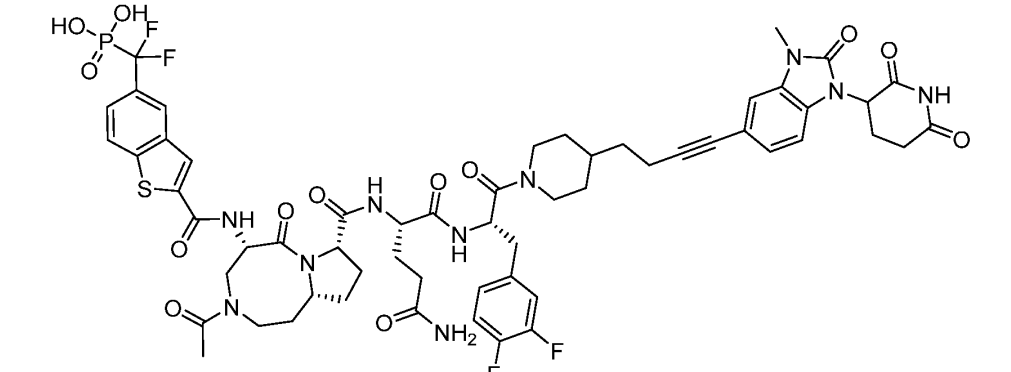
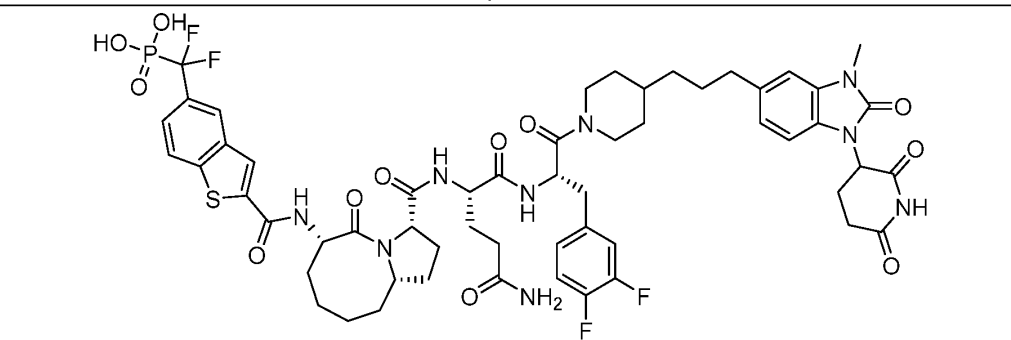
[00484] Exemplary compounds of the invention are set forth in **Table 1**, below.

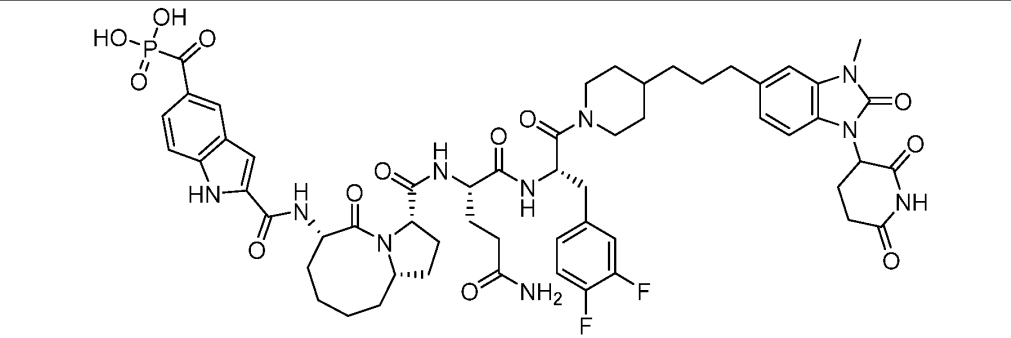
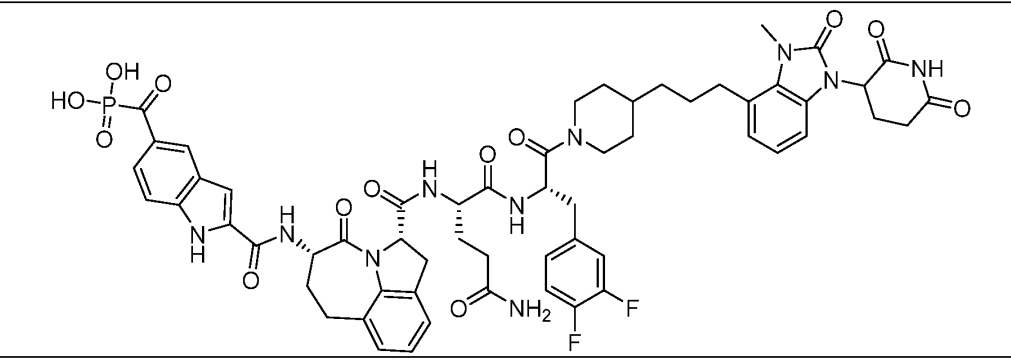
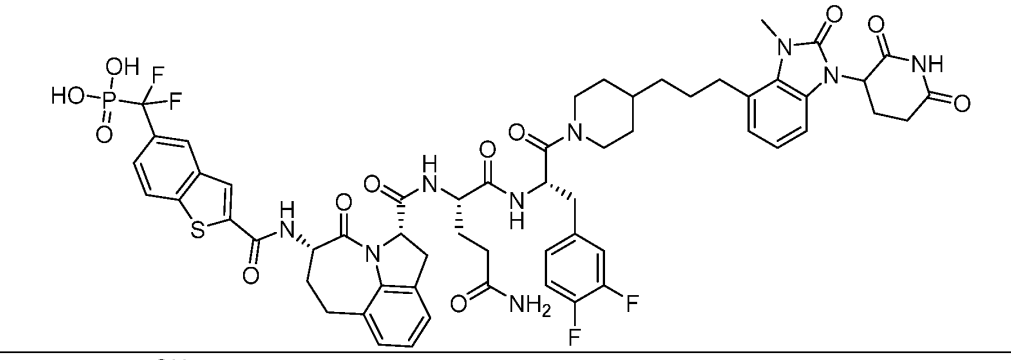
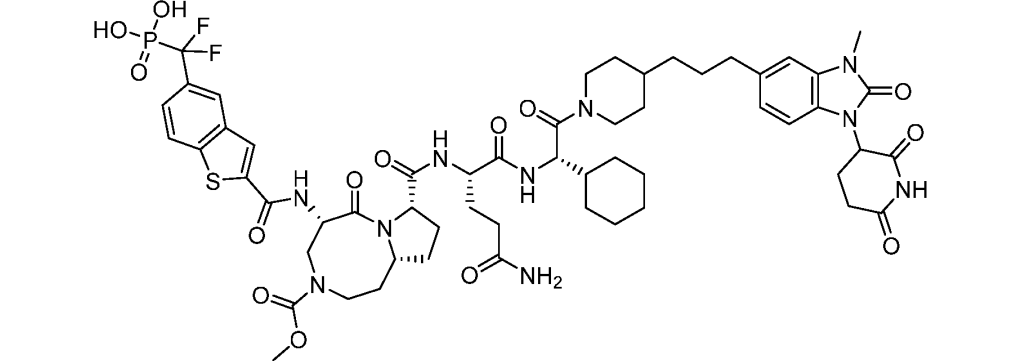
Table 1. Exemplary Compounds

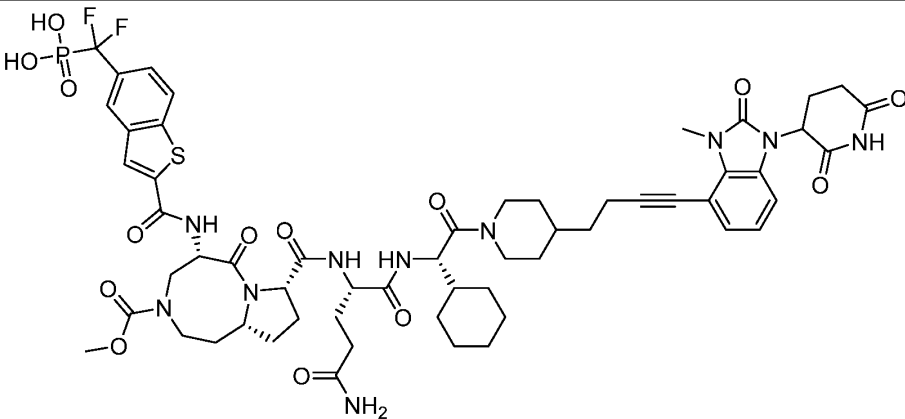
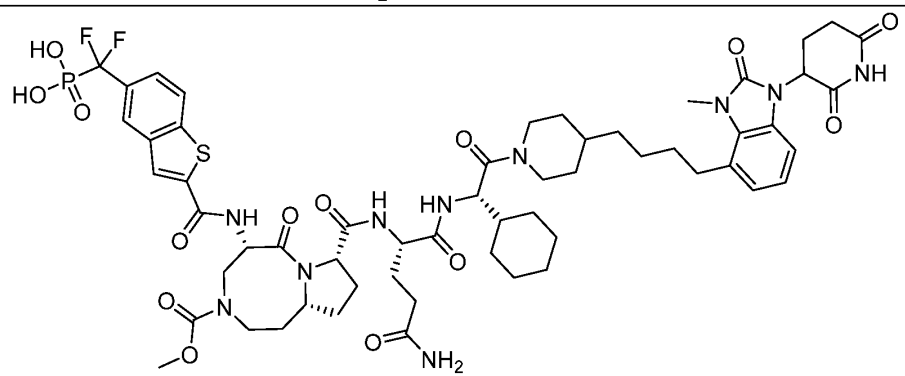
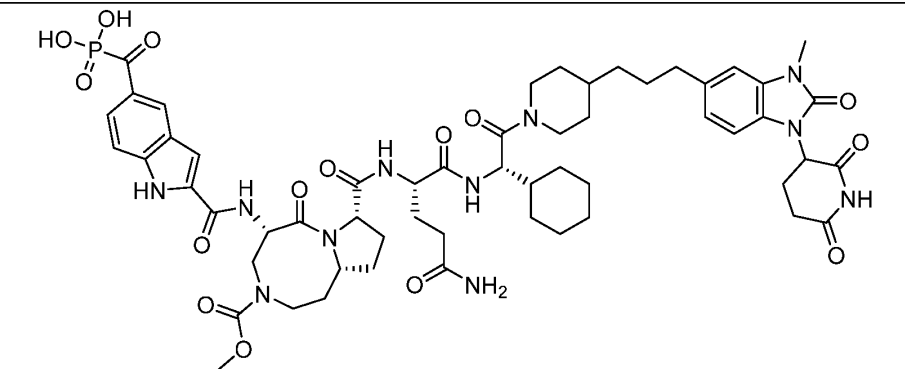
I-#	Structure
I-1	

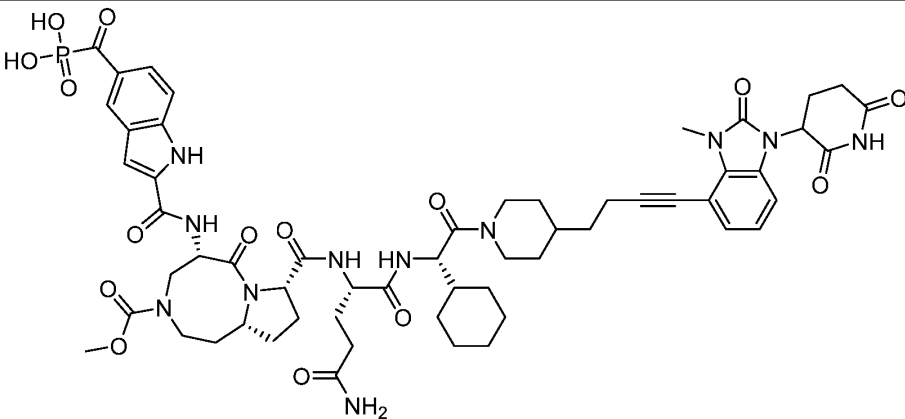
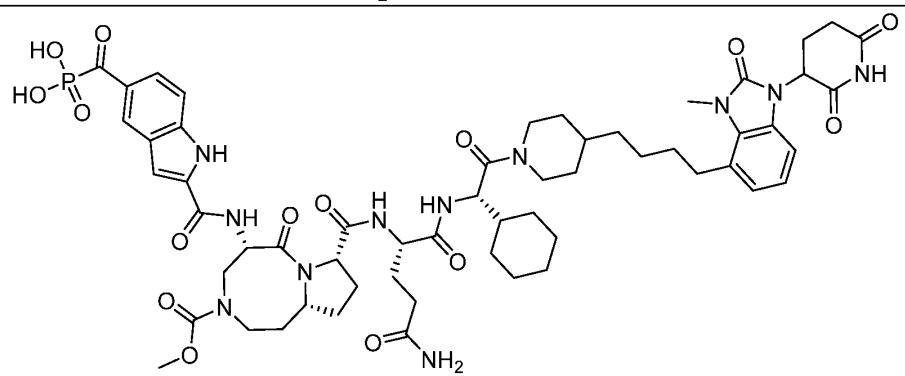
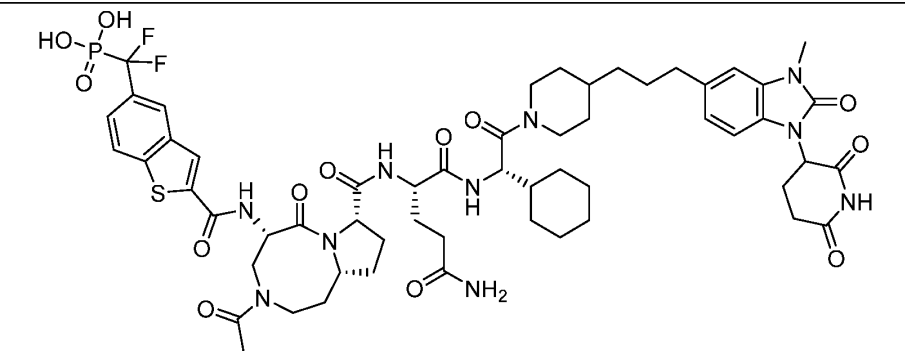
I-2	
I-3	
I-4	

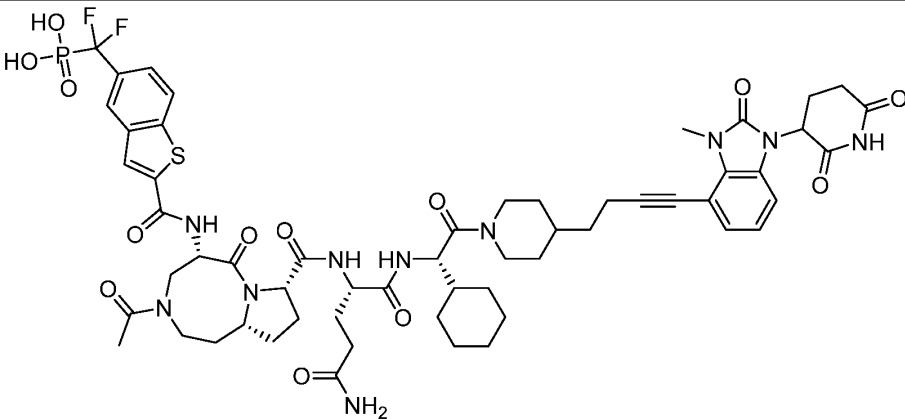
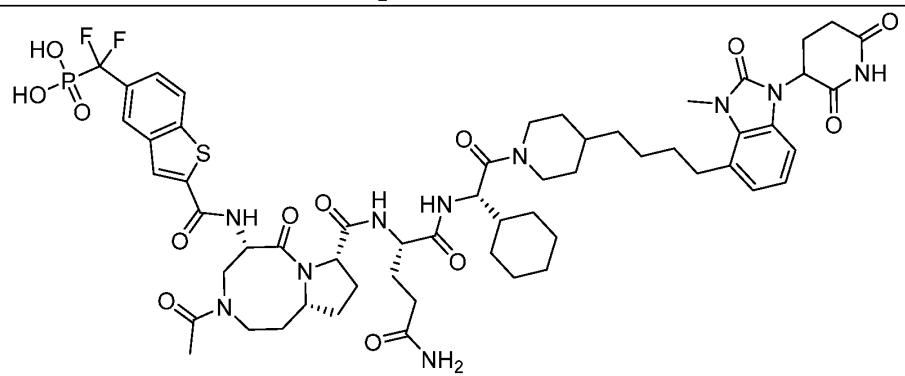
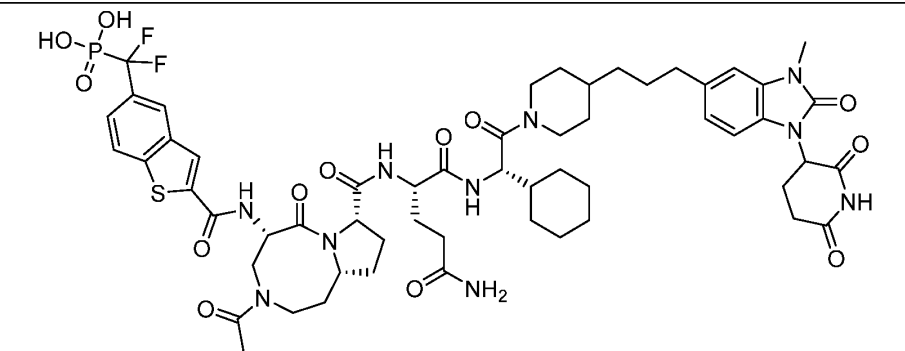
I-5	
I-6	
I-7	

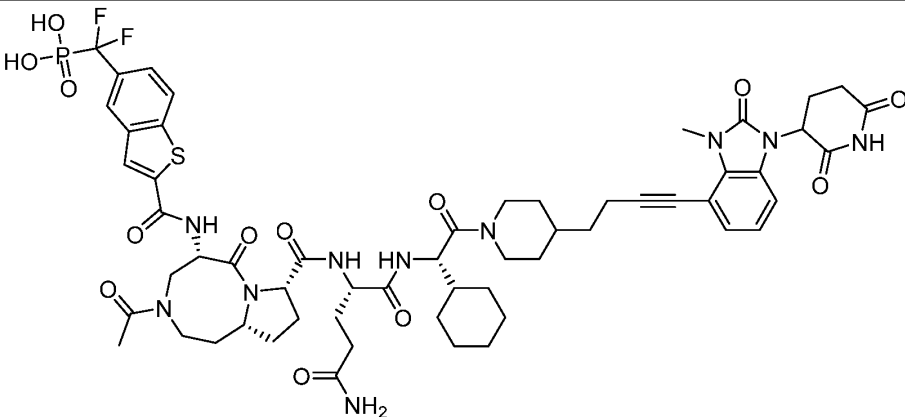
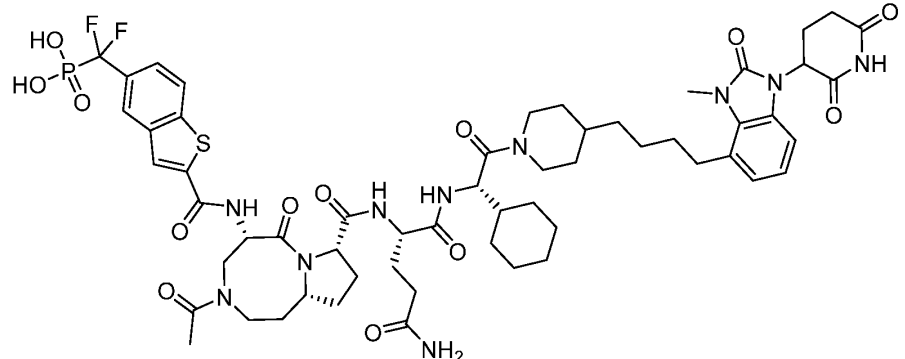
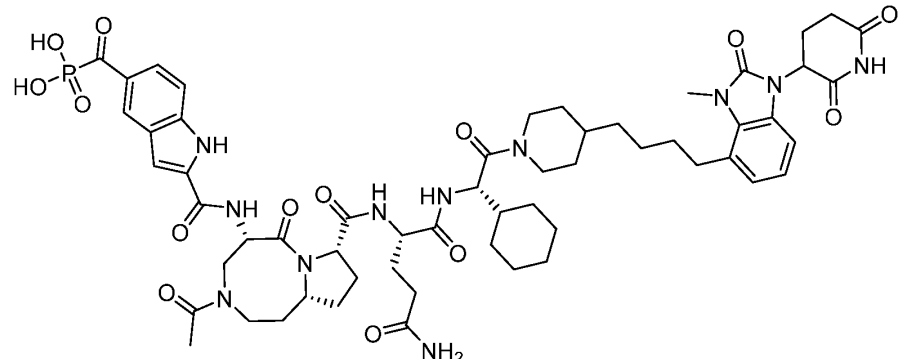
I-8	
I-9	
I-10	
I-11	

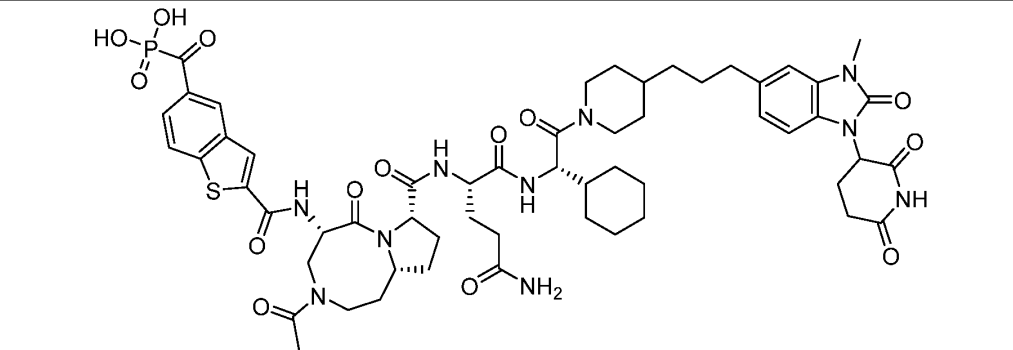
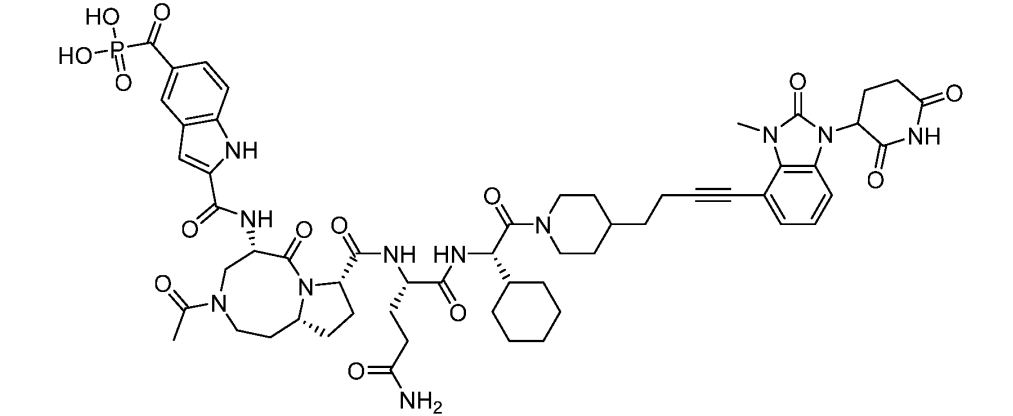
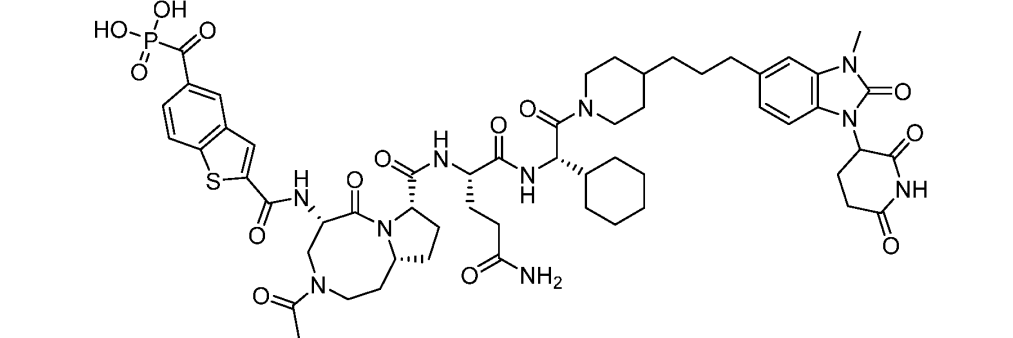
I-12	
I-13	
I-14	
I-15	

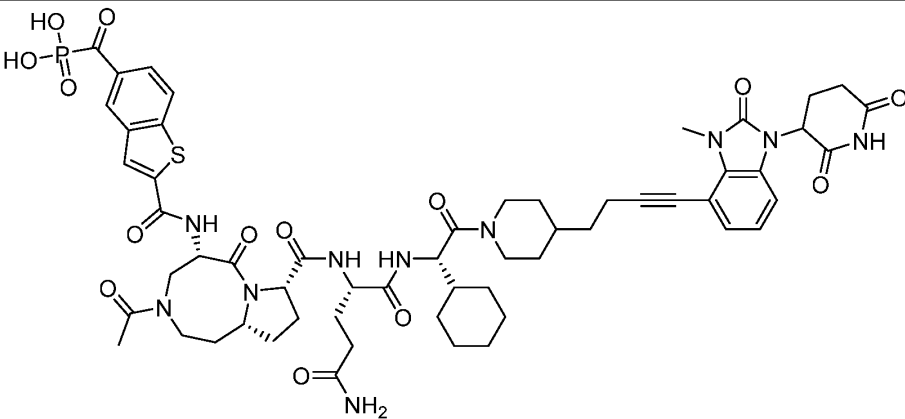
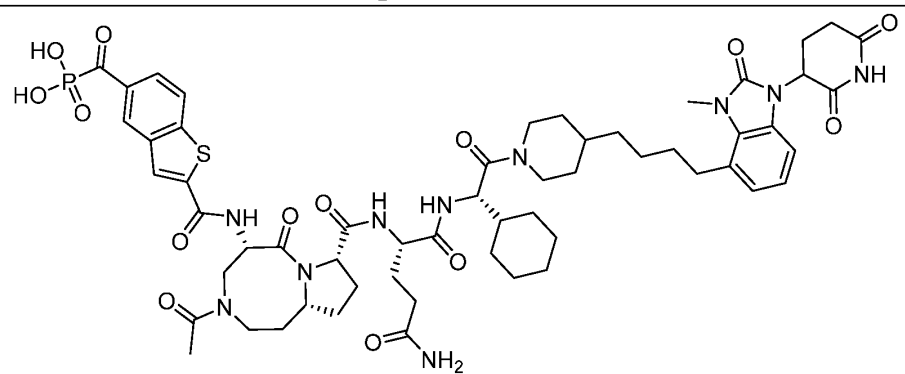
I-16	 Chemical structure of compound I-16. It features a central core consisting of a 1,4-dioxane ring substituted with a methoxycarbonyl group and a 2-aminoethyl group. This core is linked via amide bonds to a thienothiopyran derivative (with a 2,2-difluoro-1-hydroxyethyl phosphonate group) and a cyclohexylmethyl amide. The cyclohexylmethyl amide is further connected to a 1,2,3,4-tetrahydropyridine ring, which is substituted with a 1-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-yl group.
I-17	 Chemical structure of compound I-17. It features a central core consisting of a 1,4-dioxane ring substituted with a methoxycarbonyl group and a 2-aminoethyl group. This core is linked via amide bonds to a thienothiopyran derivative (with a 2,2-difluoro-1-hydroxyethyl phosphonate group) and a cyclohexylmethyl amide. The cyclohexylmethyl amide is further connected to a 1,2,3,4-tetrahydropyridine ring, which is substituted with a 1-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-yl group.
I-18	 Chemical structure of compound I-18. It features a central core consisting of a 1,4-dioxane ring substituted with a methoxycarbonyl group and a 2-aminoethyl group. This core is linked via amide bonds to a thienothiopyran derivative (with a 2,2-difluoro-1-hydroxyethyl phosphonate group) and a cyclohexylmethyl amide. The cyclohexylmethyl amide is further connected to a 1,2,3,4-tetrahydropyridine ring, which is substituted with a 1-methyl-2-oxo-3,4-dihydro-1H-pyridine-5-yl group.

I-19	
I-20	
I-21	

I-22	
I-23	
I-24	

I-25	 Chemical structure of compound I-25. It features a central bicyclic amide core (a 10-membered ring fused to a 5-membered ring). The 10-membered ring has a methyl group and a carbonyl group. The 5-membered ring has a carbonyl group and a side chain. The side chain consists of a 2-aminoethyl group, a cyclohexylmethyl group, and a piperidin-4-ylmethyl group. The piperidine ring is connected to a 4-ethynylphenyl group, which is further connected to a 1-methyl-2-(2-oxo-2,3-dihydro-1H-pyridin-4-yl)pyrrolidine group. The 10-membered ring also has a side chain consisting of a carbonyl group and a 2-(2,2,2-trifluoro-1-hydroxyethyl)thiophen-5-yl group.
I-26	 Chemical structure of compound I-26. It features a central bicyclic amide core (a 10-membered ring fused to a 5-membered ring). The 10-membered ring has a methyl group and a carbonyl group. The 5-membered ring has a carbonyl group and a side chain. The side chain consists of a 2-aminoethyl group, a cyclohexylmethyl group, and a piperidin-4-ylmethyl group. The piperidine ring is connected to a 4-(4-(1-methyl-2-(2-oxo-2,3-dihydro-1H-pyridin-4-yl)pyrrolidin-2-yl)phenyl)butyl group. The 10-membered ring also has a side chain consisting of a carbonyl group and a 2-(2,2,2-trifluoro-1-hydroxyethyl)thiophen-5-yl group.
I-27	 Chemical structure of compound I-27. It features a central bicyclic amide core (a 10-membered ring fused to a 5-membered ring). The 10-membered ring has a methyl group and a carbonyl group. The 5-membered ring has a carbonyl group and a side chain. The side chain consists of a 2-aminoethyl group, a cyclohexylmethyl group, and a piperidin-4-ylmethyl group. The piperidine ring is connected to a 4-(4-(1-methyl-2-(2-oxo-2,3-dihydro-1H-pyridin-4-yl)pyrrolidin-2-yl)phenyl)butyl group. The 10-membered ring also has a side chain consisting of a carbonyl group and a 2-(2,2,2-trifluoro-1-hydroxyethyl)thiophen-5-yl group.

I-28	
I-29	
I-30	

I-31	
I-32	

[00485] In some embodiments, the present invention provides a compound set forth in **Table 1**, above, or a pharmaceutically acceptable salt thereof. In some embodiments, the present invention provides a compound set forth in **Table 1** as a diammonium salt.

4. General Methods of Providing the Present Compounds

[00486] The compounds of this invention may be prepared or isolated in general by synthetic and/or semi-synthetic methods known to those skilled in the art for analogous compounds and by methods described in detail in the Examples, herein.

[00487] In the Schemes below, where a particular protecting group, leaving group, or transformation condition is depicted, one of ordinary skill in the art will appreciate that other protecting groups, leaving groups, and transformation conditions are also suitable and are contemplated. Such groups and transformations are described in detail in *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, M. B. Smith and J. March, 5th Edition, John Wiley & Sons, 2001, *Comprehensive Organic Transformations*, R. C. Larock, 2nd Edition, John Wiley & Sons, 1999, and *Protecting Groups in Organic*

Synthesis, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of each of which is hereby incorporated herein by reference.

[00488] As used herein, the phrase “oxygen protecting group” includes, for example, carbonyl protecting groups, hydroxyl protecting groups, etc. Hydroxyl protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of each of which is herein incorporated by reference. Examples of suitable hydroxyl protecting groups include, but are not limited to, esters, allyl ethers, ethers, silyl ethers, alkyl ethers, arylalkyl ethers, and alkoxyalkyl ethers. Examples of such esters include formates, acetates, carbonates, and sulfonates. Specific examples include formate, benzoyl formate, chloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, p-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate, 4,4-(ethylenedithio)pentanoate, pivaloate (trimethylacetyl), crotonate, 4-methoxy-crotonate, benzoate, p-benylbenzoate, 2,4,6-trimethylbenzoate, carbonates such as methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl)ethyl, 2-(phenylsulfonyl)ethyl, vinyl, allyl, and p-nitrobenzyl. Examples of such silyl ethers include trimethylsilyl, triethylsilyl, t-butyl dimethylsilyl, t-butyl diphenylsilyl, triisopropylsilyl, and other trialkylsilyl ethers. Alkyl ethers include methyl, benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, trityl, t-butyl, allyl, and allyloxycarbonyl ethers or derivatives. Alkoxyalkyl ethers include acetals such as methoxymethyl, methylthiomethyl, (2-methoxyethoxy)methyl, benzyloxymethyl, beta-(trimethylsilyl)ethoxymethyl, and tetrahydropyranyl ethers. Examples of arylalkyl ethers include benzyl, p-methoxybenzyl (MPM), 3,4-dimethoxybenzyl, O-nitrobenzyl, p-nitrobenzyl, p-halobenzyl, 2,6-dichlorobenzyl, p-cyanobenzyl, and 2- and 4-picolyl.

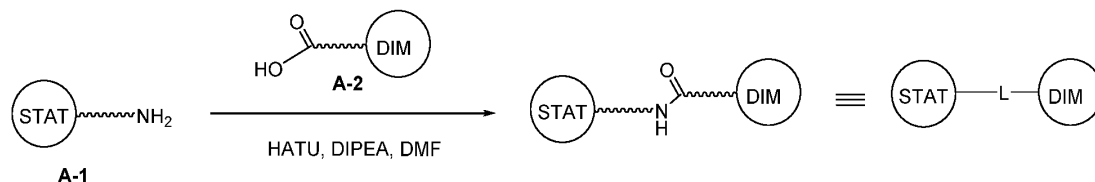
[00489] Amino protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of each of which is herein incorporated by reference. Suitable amino protecting groups include, but are not limited to, aralkylamines, carbamates, cyclic imides, allyl amines, amides, and the like. Examples of such groups include t-butyloxycarbonyl (BOC), ethyloxycarbonyl, methyloxycarbonyl, trichloroethyloxycarbonyl, allyloxycarbonyl (Alloc), benzyloxycarbonyl (CBZ), allyl, phthalimide, benzyl (Bn), fluorenylmethylcarbonyl (Fmoc), formyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, phenylacetyl, trifluoroacetyl, benzoyl, and the like.

[00490] In the schemes below, where a final degrader is formed having a free amine DIM moiety, it is not shown but it is generally appreciated and well known by those having ordinary skill in the art that the reactivity of said free amine may be masked by employing a suitable amino protecting group that can thereafter be removed in situ or during a separate synthetic step to form the final degrader product.

[00491] In certain embodiments, compounds of the present invention are generally prepared according

to Scheme 1 set forth below:

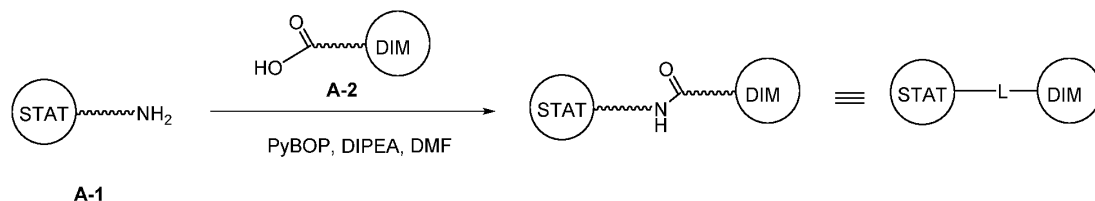
Scheme 1: Synthesis of Compounds of the Invention



[00492] As depicted in Scheme 1, above, amine **A-1** is coupled to acid **A-2** using the coupling agent HATU in the presence of the base DIPEA in DMF to form a compound of the invention with a linker comprising an amide bond. The squiggly bond, , represents the portion of the linker between STAT and the terminal amino group of **A-1** or the portion of the linker between DIM and the terminal carboxyl group of **A-2**, respectively. Additionally, an amide bond can be formed using coupling reagents known in the art such as, but not limited to DCC, DIC, EDC, HBTU, HCTU, PyAOP, PyBrOP, BOP, BOP-Cl, DEPBT, T3P, TATU, TBTU, TNTU, TOTU, TPTU, TSTU, or TDBTU.

[00493] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 2 set forth below:

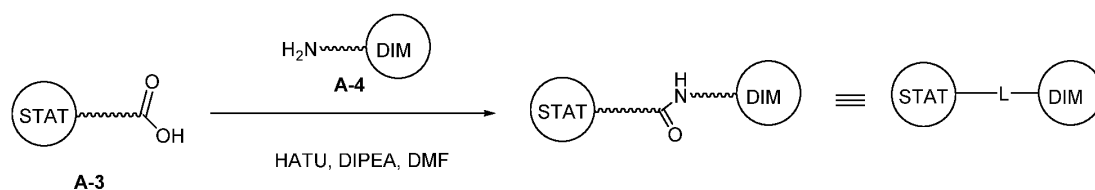
Scheme 2: Synthesis of Compounds of the Invention



[00494] As depicted in Scheme 2, above, amine **A-1** is coupled to acid **A-2** using the coupling agent PyBOP in the presence of the base DIPEA in DMF to form a compound of the invention with a linker comprising an amide bond. The squiggly bond, , represents the portion of the linker between STAT and the terminal amino group of **A-1** or the portion of the linker between DIM and the terminal carboxyl group of **A-2**, respectively. Additionally, an amide bond can be formed using coupling reagents known in the art such as, but not limited to DCC, DIC, EDC, HBTU, HCTU, PyAOP, PyBrOP, BOP, BOP-Cl, DEPBT, T3P, TATU, TBTU, TNTU, TOTU, TPTU, TSTU, or TDBTU.

[00495] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 3 set forth below:

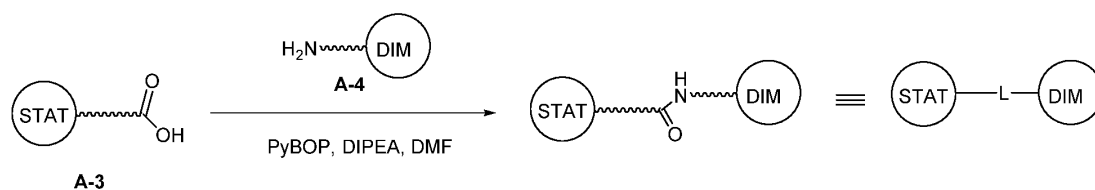
Scheme 3: Synthesis of Compounds of the Invention



[00496] As depicted in Scheme 3, above, acid **A-3** is coupled to amine **A-4** using the coupling agent HATU in the presence of the base DIPEA in DMF to form a compound of the invention with a linker comprising an amide bond. The squiggly bond, $\sim$, represents the portion of the linker between STAT and the terminal carboxyl group of **A-3** or the portion of the linker between DIM and the terminal amino group of **A-4**, respectively. Additionally, an amide bond can be formed using coupling reagents known in the art such as, but not limited to DCC, DIC, EDC, HBTU, HCTU, PyAOP, PyBrOP, BOP, BOP-Cl, DEPBT, T3P, TATU, TBTU, TNTU, TOTU, TPTU, TSTU, or TDBTU.

[00497] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 4 set forth below:

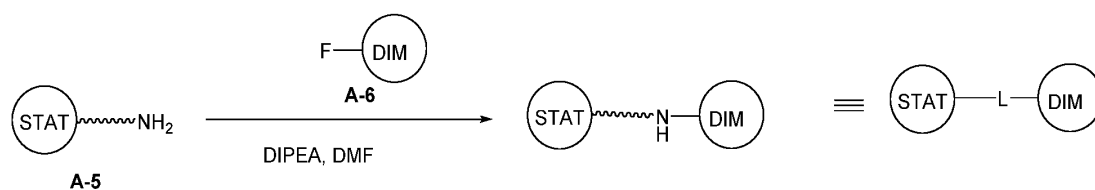
Scheme 4: Synthesis of Compounds of the Invention



[00498] As depicted in Scheme 4, above, acid **A-3** is coupled to amine **A-4** using the coupling agent PyBOP in the presence of the base DIPEA in DMF to form a compound of the invention with a linker comprising an amide bond. The squiggly bond, $\sim$, represents the portion of the linker between STAT and the terminal carboxyl group of **A-3** or the portion of the linker between DIM and the terminal amino group of **A-4**, respectively. Additionally, an amide bond can be formed using coupling reagents known in the art such as, but not limited to DCC, DIC, EDC, HBTU, HCTU, PyAOP, PyBrOP, BOP, BOP-Cl, DEPBT, T3P, TATU, TBTU, TNTU, TOTU, TPTU, TSTU, or TDBTU.

[00499] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 5 set forth below:

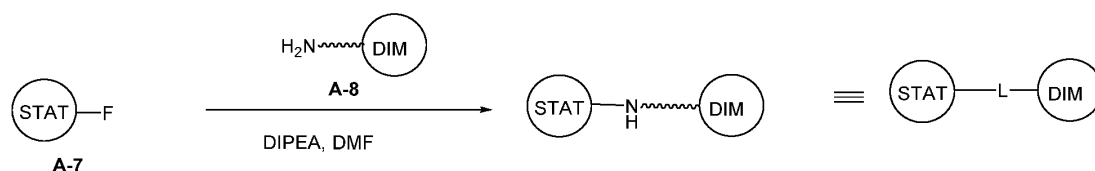
Scheme 5: Synthesis of Compounds of the Invention



[00500] As depicted in Scheme 5, above, an $\text{S}_{\text{N}}\text{Ar}$ displacement of fluoride A-6 by amine A-5 is effected in the presence of the base DIPEA in DMF to form a compound of the invention with a linker comprising a secondary amine. The squiggly bond, --- , represents the portion of the linker between STAT and the terminal amino group of A-5.

[00501] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 6 set forth below:

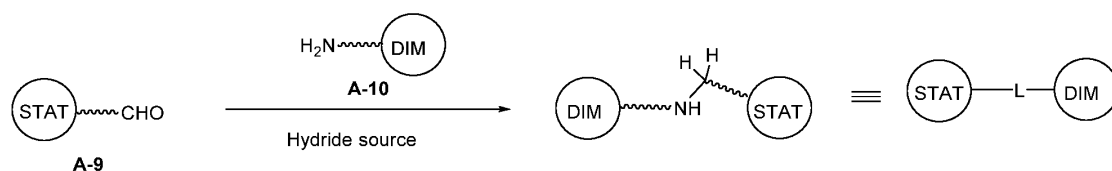
Scheme 6: Synthesis of Compounds of the Invention



[00502] As depicted in Scheme 6, above, an $\text{S}_{\text{N}}\text{Ar}$ displacement of fluoride A-7 by amine A-8 is effected in the presence of the base DIPEA in DMF to form a compound of the invention with a linker comprising a secondary amine. The squiggly bond, --- , represents the portion of the linker between DIM and the terminal amino group of A-8.

[00503] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 7 set forth below:

Scheme 7: Synthesis of Compounds of the Invention

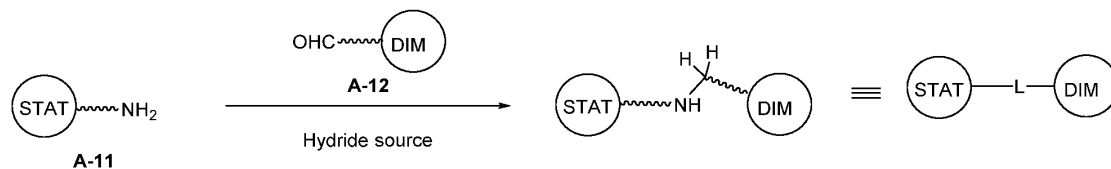


[00504] As depicted in Scheme 7, above, reductive alkylation of aldehyde A-9 by amine A-10 is effected in the presence of a mild hydride source (*e.g.*, sodium cyanoborohydride or sodium triacetoxyborohydride) to form a provided compound with a linker comprising a secondary amine. The squiggly bond, --- , represents the portion of the linker between DIM and the terminal amino group of A-10.

[00505] In certain embodiments, compounds of the present invention are generally prepared according

to Scheme 8 set forth below:

Scheme 8: Synthesis of Compounds of the Invention



[00506] As depicted in Scheme 8, above, reductive alkylation of aldehyde **A-12** by amine **A-11** is effected in the presence of a mild hydride source (*e.g.*, sodium cyanoborohydride or sodium triacetoxyborohydride) to form a provided compound with a linker comprising a secondary amine. The squiggly bond, --- , represents the portion of the linker between STAT and the terminal amino group of **A-11**.

[00507] One of skill in the art will appreciate that various functional groups present in compounds of the invention such as aliphatic groups, alcohols, carboxylic acids, esters, amides, aldehydes, halogens and nitriles can be interconverted by techniques well known in the art including, but not limited to reduction, oxidation, esterification, hydrolysis, partial oxidation, partial reduction, halogenation, dehydration, partial hydration, and hydration. See for example, “March’s Advanced Organic Chemistry”, 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entirety of each of which is herein incorporated by reference. Such interconversions may require one or more of the aforementioned techniques, and certain methods for synthesizing compounds of the invention are described below in the Exemplification.

5. Uses, Formulation and Administration

Pharmaceutically acceptable compositions

[00508] According to another embodiment, the invention provides a composition comprising a compound of this invention or a pharmaceutically acceptable derivative thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of compound in compositions of this invention is such that is effective to measurably degrade and/or inhibit a STAT protein, or a mutant thereof, in a biological sample or in a patient. In certain embodiments, the amount of compound in compositions of this invention is such that is effective to measurably degrade and/or inhibit an STAT protein, or a mutant thereof, in a biological sample or in a patient. In certain embodiments, a composition of this invention is formulated for administration to a patient in need of such composition. In some embodiments, a composition of this invention is formulated for oral administration to a patient.

[00509] The term “patient,” as used herein, means an animal, preferably a mammal, and most preferably

a human.

[00510] The term “pharmaceutically acceptable carrier, adjuvant, or vehicle” refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[00511] A “pharmaceutically acceptable derivative” means any non-toxic salt, ester, salt of an ester or other derivative of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily or degradingly active metabolite or residue thereof.

[00512] As used herein, the term “inhibitorily active metabolite or residue thereof” means that a metabolite or residue thereof is also an inhibitor of a STAT protein, or a mutant thereof.

[00513] As used herein, the term “degradingly active metabolite or residue thereof” means that a metabolite or residue thereof is also a degrader of an STAT protein, or a mutant thereof.

[00514] In certain embodiments, a provided compound is administered as a prodrug.

[00515] The term “prodrug” refers to a compound that is made more active in vivo. A provided compound can also exist as prodrugs, as described in *Hydrolysis in Drug and Prodrug Metabolism: Chemistry, Biochemistry, and Enzymology* (Testa, Bernard and Mayer, Joachim M. Wiley-VHCA, Zurich, Switzerland 2003). Prodrugs of the provided compounds described herein are structurally modified forms of the compound that readily undergo chemical changes under physiological conditions to provide the compound. Additionally, prodrugs can be converted to the compound by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to a compound when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the compound, or parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound which is administered as

a phosphonate ester (the "prodrug"), but then is metabolically hydrolyzed to the phosphonic acid or a conjugate base thereof, the active entity. Additional examples include peptidyl derivatives of a compound. The term "therapeutically acceptable prodrug," refers to those prodrugs or zwitterions which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[00516] Compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[00517] For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[00518] Pharmaceutically acceptable compositions of this invention 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 may also be added.

[00519] Alternatively, pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[00520] Pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[00521] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[00522] For topical applications, provided pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, provided pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[00523] For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[00524] Pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[00525] Most preferably, pharmaceutically acceptable compositions of this invention are formulated for oral administration. Such formulations may be administered with or without food. In some embodiments,

pharmaceutically acceptable compositions of this invention are administered without food. In other embodiments, pharmaceutically acceptable compositions of this invention are administered with food.

[00526] The amount of compounds of the present invention 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. Preferably, provided compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the compound can be administered to a patient receiving these compositions.

[00527] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

Uses of Compounds and Pharmaceutically Acceptable Compositions

[00528] Compounds and compositions described herein are generally useful for the degradation and/or inhibition of STAT protein activity.

[00529] Examples of STAT protein that are degraded and/or inhibited by the compounds and compositions described herein and against which the methods described herein are useful include those of the signal transducer and activators of transcription (STAT) family of proteins, the members of which include STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, or STAT6, or a mutant thereof. Yu et al., "Crosstalk between cancer and immune cells: Role of STAT3 in the tumour microenvironment" Nat. Rev. Immunol. 2007, 7, 41-51., Levy et al., "STATs: Transcriptional control and biological impact" Nat. Rev. Mol. Cell Biol. 2002, 3, 651-662, the entirety of each of which is herein incorporated by reference.

[00530] The activity of a compound utilized in this invention as a degrader and/or inhibitor of STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, or STAT6, or a mutant thereof, may be assayed *in vitro*, *in vivo* or in a cell line. *In vitro* assays include assays that determine inhibition of either the activity and/or the subsequent functional consequences of activated STAT protein, or a mutant thereof. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to a STAT protein. Inhibitor binding may be measured by radiolabeling the inhibitor prior to binding, isolating the inhibitor/STAT complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with a STAT protein bound to known radioligands. Representative *in vitro* and *in vivo* assays useful in assaying a STAT inhibitor include those described and

disclosed in, *e.g.*, Schust et al., “A high-throughput fluorescence polarization assay for signal transducer and activator of transcription 3” *Anal. Biochem.* 2004, 333(1):114; Müller et al., “A high-throughput assay for signal transducer and activator of transcription 5b based on fluorescence polarization” *Anal. Biochem.* 2008, 375(2):249. Detailed conditions for assaying a compound utilized in this invention as a degrader and/or inhibitor of STAT proteins, or a mutant thereof, are set forth in the Examples below.

[00531] The STAT family of proteins are cytoplasmic transcription factors with important roles in mediating responses to cytokines and growth factors, including promoting cell growth and differentiation, and inflammation and immune responses (Bromberg et al., *Breast Cancer Res.* 2000, 2:86-90; Darnell et al., *Nat. Rev. Cancer* 2002, 2:740-749). STAT proteins are classically activated by tyrosine (Tyr) kinases, such as Janus kinases (JAKs) and Src family kinases, in response to the binding of cytokine and growth factors to their cognate receptors (Darnell et al., *Science* 1994, 264:1415). The Tyr phosphorylation (pTyr) promotes dimerization between two activated STAT:STAT monomers through a reciprocal pTyr-Src homology SH2 domain interactions. Active STAT:STAT dimers translocate to the nucleus to induce gene transcription by binding to specific DNA-response elements in the promoters of target genes to regulate gene expression. By contrast, aberrantly-active STAT3, one of the STAT family members, has been implicated in many human tumors and represents an attractive target for drug discovery. Persistently activated STAT3 and, to some extent, STAT5 increase tumour cell proliferation, survival and invasion while suppressing anti-tumour immunity. The persistent activation of STAT3 also mediates tumour-promoting inflammation. This aberrant activation of STAT3 occurs in glioma, breast, prostate, ovarian, and many other human cancers, whereby it promotes malignant progression (Yu & Jove, *Nat. Rev. Cancer* 2004, 4:97-105). JAKs, Src, and epidermal growth factor receptor (EGFR) are STAT3 upstream regulators (Bromberg et al., *Mol. Cell. Biol.* 1998, 18:2553; Sartor et al., *Cancer Res.* 1997, 57:978; Garcia et al., *Oncogene* 2001, 20:2499). Mechanisms by which constitutively-active STAT3 mediates tumorigenesis include dysregulation of gene expression that leads to uncontrolled growth and survival of tumor cells, enhanced tumor angiogenesis, and metastasis and the suppression of tumor immune surveillance (Yu & Jove 2004; Bromberg & Darnell, *Oncogene* 2000, 19:2468-2473; Bowman et al., *Oncogene* 2000, 19:2474-2488; Turkson & Jove, *Oncogene* 2000, 19:6613-6626; Turkson, *Expert Opin. Ther. Targets* 2004, 8:409-422; Wang et al., *Nat. Med.* 2004, 10:48-54).

[00532] The main domains of STAT3 protein include the tetramerization and leucine zipper at the N-terminus, the DNA binding domain, and the SH2 transactivation domain at the carboxy-terminal end. The SH2 region is responsible for the binding of STAT3 to the tyrosine-phosphorylated receptors and for the dimerization which is necessary for DNA binding and gene expression (Zhong et al., *Science* 1994, 264:95). STAT3 is activated by phosphorylation at Y-705, which leads to dimer formation, nuclear translocation,

recognition of STAT3-specific DNA binding elements, and activation of target gene transcription (Darnell 1994; Zhong 1994).

[00533] The constitutive activation of STAT3 is frequently detected in breast carcinoma cell lines but not in normal breast epithelial cells (Garcia et al., *Cell. Growth. Differ.* 1997, 8:1267; Bowman 2000). It has been reported that approximately 60 percent of breast tumors contain persistently activated STAT3 (Dechow et al., *Proc. Natl. Acad. Sci. USA* 2004, 101:10602). STAT3 has been classified as a proto-oncogene because activated STAT3 can mediate oncogenic transformation in cultured cells and tumor formation in nude mice (Bromberg et al., *Cell* 1999, 98:295). STAT3 may participate in oncogenesis by stimulating cell proliferation, promoting angiogenesis, and conferring resistance to apoptosis induced by conventional therapies (Catlett-Falcone et al., *Curr. Opin. Oncol.* 1999, 11:1; Catlett-Falcone et al., *Immunity* 1999, 10:105; Alas et al., *Clin. Cancer Res.* 2003, 9:316; Wei et al., *Oncogene* 2003, 22:1517). Possible downstream targets through which STAT3 promotes oncogenesis include up-regulation of anti-apoptotic factors (Bcl-2, survivin, Mcl-1, and Bcl-X_L), cell-cycle regulators (cyclin D1, MEK5, and c-myc), and inducer of tumor angiogenesis (VEGF) (Bromberg et al., *Cell* 1999, 98:295; Wei et al., *Oncogene* 2003, 22:1517; Real et al., *Oncogene* 2002, 21:7611; Puthier et al., *Eur. J. Immunol.* 1999, 29:3945; Niu et al., *Oncogene* 2002, 21:2000; Kiuchi et al., *J. Exp. Med.* 1999, 189:63; Song et al., *Oncogene* 2004, 23:8301). Activated STAT3 signaling directly contributes to malignant progression of cancer. STAT3 oncogenic function acts through the pro-survival proteins such as survivin, Mcl-1, Bcl-2, and Bcl-X_L and results in the prevention of apoptosis (Real et al., *Oncogene* 2002, 21:7611; Aoki et al., *Blood* 2003, 101:1535; Epling-Burnette et al., *J. Clin. Invest.* 2001, 107:351; Nielsen et al., *Leukemia* 1999, 13:735). Blockade of STAT3 signaling inhibits cancer cell growth, demonstrating that STAT3 is essential to the survival or growth of tumor cells (Alas et al., *Clin. Cancer Res.* 2003, 9:316; Aoki et al., *Blood* 2003, 101:1535; Epling-Burnette et al., *J. Clin. Invest.* 2001, 107:351; Burke et al., *Oncogene* 2001, 20:7925; Mora et al., *Cancer Res.* 2002, 62:6659; Ni et al., *Cancer Res.* 2000, 60:1225; Rahaman et al., *Oncogene* 2002, 21:8404).

[00534] Recent evidence also reveals the role of STAT3 in modulating mitochondrial functions and STAT3 crosstalk with other proteins, such as NF- κ B, that promotes the malignant phenotype. Many human tumors harbor aberrantly-active STAT3 signaling, and studies in experimental models indicate tumor cells and tumors harboring constitutively-active STAT3 are responsive to STAT3 signaling modulators (Gough et al., *Science* 2009, 324:1713; Yu et al., *Nat. Rev. Cancer* 2009, 9:798; Grivennikov & Karin, *Cytokine & Growth Factor Rev.* 2010, 21:11).

[00535] Representative STAT inhibitors include those described and disclosed in e.g., Morlacchi et al. *Future Med. Chem.* 2014, 6(7):1909; Sgrignani et al. *Int. J. Mol. Sci.* 2018, 19:1591, Botta et al. *Mol. Inf.*

2015, 34:689; Leung et al. *Methods* 2015, 71:38; Lavecchia et al. *Cur. Med. Chem.* 2011, 18:1; Chun et al. *Can. Lett.* 2015, 357:393; Zhang et al. *Eur. J. Med. Chem.* 2017, 125:538; Yesylevskyy et al. *J. Chem. Inf. Model.* 2016, 56:1588; Huang et al. *Bioorg. Med. Chem. Lett.* 2016, 26:5172; Gao et al. *Bioorg. Med. Chem.* 2016, 24:2549; Daka et al. *Bioorg. Med. Chem.* 2015, 23:1348; Ji et al. *Bioorg. Med. Chem.* 2016, 24:6174; Zhou et al. *Bioorg. Med. Chem.* 2017, 25:2995; and Yu et al. *J. Med. Chem.* 2017, 60:2718; Chen et al. *Med. Chem. Lett.* 2010, 1:85; the entirety of each of which is herein incorporated by reference.

[00536] As used herein, the terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

[00537] Provided compounds are degraders and/or inhibitors of one or more STAT protein and are therefore useful for treating one or more disorders associated with activity of one or more of STAT protein. Thus, in certain embodiments, the present invention provides a method for treating a STAT1-mediated, STAT2-mediated, STAT3-mediated, STAT4-mediated, STAT5A-mediated, STAT5B-mediated, or STAT6-mediated disorder comprising the step of administering to a patient in need thereof a compound of the present invention, or pharmaceutically acceptable composition thereof.

[00538] As used herein, the terms “STAT1-mediated”, “STAT2-mediated”, “STAT3-mediated”, “STAT4-mediated”, “STAT5A-mediated”, “STAT5B-mediated”, and/or “STAT6-mediated” disorders, diseases, and/or conditions as used herein means any disease or other deleterious condition in which one or more STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, or STAT6, or a mutant thereof, are known to play a role. Accordingly, another embodiment of the present invention relates to treating or lessening the severity of one or more diseases in which one or more STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, or STAT6, or a mutant thereof, are known to play a role.

[00539] In some embodiments, the present invention provides a method for treating one or more disorders, diseases, and/or conditions wherein the disorder, disease, or condition is a cancer, a neurodegenerative disorder, a viral disease, an autoimmune disease, an inflammatory disorder, a hereditary disorder, a hormone-related disease, a metabolic disorder, conditions associated with organ transplantation, immunodeficiency disorders, a destructive bone disorder, a proliferative disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, liver disease, pathologic immune conditions involving T cell activation, a cardiovascular disorder, or a CNS disorder.

[00540] Diseases and conditions treatable according to the methods of this invention include, but are not limited to, cancer (*see, e.g.,* Turkson & Jove, *Oncogene* 2000, 19:6613-6626), diabetes (*see, e.g.,* Gurzov et al., *FEBS* 2016, 283:3002), cardiovascular disease (*see, e.g.,* Grote et al., *Vasc. Pharmacol.* 2005, 43:2005), viral disease (*see, e.g.,* Gao et al., *J. Hepatol.* 2012, 57(2):430), autoimmune diseases such as lupus (*see, e.g.,* Goropevšek et al., *Clin. Rev. Alleg. & Immun.* 2017, 52(2):164), and rheumatoid arthritis (*see, e.g.,* Walker & Smith, *J. Rheumat.* 2005, 32(9):1650), autoinflammatory syndromes (*see, e.g.,* Rauch et al., *Jak-Stat* 2013, 2(1):e23820), atherosclerosis (*see, e.g.,* Ortiz-Muñoz et al., *Arterio., Thrombo., Vasc. Bio.* 2009, 29:525), psoriasis (*see, e.g.,* Andrés et al., *Exp. Derm.* 2013, 22(5):323), allergic disorders (*see, e.g.,* Oh et al., *Eur. Respir. Rev.* 2019, 19(115):46), inflammatory bowel disease (*see, e.g.,* Sugimoto, *World J. Gastroenterol.* 2008, 14(33):5110), inflammation (*see, e.g.,* Tamiya et al., *Arterio., Thrombo., Vasc. Bio.* 2011, 31:980), acute and chronic gout and gouty arthritis, neurological disorders (*see, e.g.,* Campbell, *Brain Res. Rev.* 2005, 48(2):166), metabolic syndrome, immunodeficiency disorders such as AIDS and HIV (*see, e.g.,* O'Shea et al., *N. Engl. J. Med.* 2013, 368:161), destructive bone disorders (*see, e.g.,* Jatiani et al., *Genes & Can.* 2011, 1(10):979), osteoarthritis, proliferative disorders, Waldenström's Macroglobulinemia (*see, e.g.,* Hodge et al., *Blood* 2014, 123(7):1055) infectious diseases, conditions associated with cell death, pathologic immune conditions involving T cell activation, and CNS disorders in a patient. In one embodiment, a human patient is treated with a compound of the current invention and a pharmaceutically acceptable carrier, adjuvant, or vehicle, wherein said compound is present in an amount to measurably degrade and/or inhibit one or more STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, or STAT6, or a mutant thereof

[00541] Compounds of the current invention are useful in the treatment of a proliferative disease selected from a benign or malignant tumor, solid tumor, liquid tumor, carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina, cervix, testis, genitourinary tract, esophagus, larynx, skin, bone or thyroid, sarcoma, glioblastomas, neuroblastomas, multiple myeloma, gastrointestinal cancer, especially colon carcinoma or colorectal adenoma, a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, adenoma, adenocarcinoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small-cell lung carcinoma, lymphomas, Hodgkins and Non-Hodgkins, a mammary carcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, an IL-1 driven disorder, an MyD88 driven disorder, Smoldering of indolent multiple myeloma, or hematological malignancies (including leukemia, diffuse large B-cell lymphoma (DLBCL), ABC DLBCL, chronic lymphocytic leukemia (CLL), chronic lymphocytic lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia,

lymphoplasmacytic lymphoma, Waldenström's macroglobulinemia (WM), splenic marginal zone lymphoma, multiple myeloma, plasmacytoma, intravascular large B-cell lymphoma).

[00542] In some embodiments, the aberrant activation of STAT3 which can be treated according to the methods of this invention is a human cancer. In some embodiments, the human cancer which can be treated according to the methods of this invention is selected from glioma, breast cancer, prostate cancer, head and neck squamous cell carcinoma, skin melanomas, and ovarian cancer. In some embodiments, abnormal STAT3 activation also correlates with the progression of diverse hematopoietic malignancies, such as various leukemias and lymphomas, and STAT3 is frequently activated in both multiple myeloma cell lines and tumor cell lines derived from patient bone marrows.

[00543] In some embodiments, the present invention provides a method of treating a cancer selected from glioma, breast cancer, prostate cancer, head and neck squamous cell carcinoma, skin melanomas, ovarian cancer, malignant peripheral nerve sheath tumors (MPNST), pancreatic cancer, non-small cell lung cancer, urothelial cancer, liver cancer, bile duct cancer, kidney cancer, colon cancer, esophageal cancer, gastric cancer, gastrointestinal stromal tumors, and hematological malignancies include lymphomas, leukemias, myelomas, myeloproliferative neoplasms and myelodysplastic syndromes.

[00544] In some embodiments, the present invention provides a method of treating a JAK-associated disease. In some embodiments, the JAK-associated disease is cancer including those characterized by solid tumors (e.g., prostate cancer, renal cancer, hepatic cancer, pancreatic cancer, gastric cancer, breast cancer, lung cancer, cancers of the head and neck, thyroid cancer, glioblastoma, Kaposi's sarcoma, Castleman's disease, uterine leiomyosarcoma, melanoma etc.), hematological cancers (e.g., lymphoma, leukemia Such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML) or multiple myeloma), and skin cancer such as cutaneous T-cell lymphoma (CTCL) and cutaneous B-cell lymphoma. Example CTCLs include Sezary syndrome and mycosis fungoides.

[00545] In some embodiments, the present invention provides a method of treating triple negative breast cancer in a patient in need thereof, comprising administering a compound of the present invention, or a pharmaceutically acceptable salt thereof.

[00546] In some embodiments, the present invention provides a method of treating malignant peripheral nerve sheath tumors (MPNST) in a patient in need thereof, comprising administering a compound of the present invention, or a pharmaceutically acceptable salt thereof.

[00547] In some embodiments, the present invention provides a method of treating lung cancer, in a patient in need thereof, comprising administering a compound of the present invention, or a pharmaceutically acceptable salt thereof.

[00548] In some embodiments, the present invention provides a method of treating colorectal cancer,

in a patient in need thereof, comprising administering a compound of the present invention, or a pharmaceutically acceptable salt thereof.

[00549] In some embodiments, the present invention provides a method of treating peripheral T-cell lymphoma, in a patient in need thereof, comprising administering a compound of the present invention, or a pharmaceutically acceptable salt thereof.

[00550] In some embodiments, the present invention provides a method of treating pancreatic cancer in a patient in need thereof, comprising administering a compound of the present invention, or a pharmaceutically acceptable salt thereof.

[00551] Compounds according to the invention are useful in the treatment of inflammatory or obstructive airways diseases, resulting, for example, in reduction of tissue damage, airways inflammation, bronchial hyperreactivity, remodeling or disease progression. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics.

[00552] Compounds according to the invention are useful in the treatment of heteroimmune diseases. Examples of such heteroimmune diseases include, but are not limited to, graft versus host disease, transplantation, transfusion, anaphylaxis, allergies (e.g., allergies to plant pollens, latex, drugs, foods, insect poisons, animal hair, animal dander, dust mites, or cockroach calyx), type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, and atopic dermatitis.

[00553] Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, such as therapy for or intended to restrict or abort symptomatic attack when it occurs, for example antiinflammatory or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognized asthmatic syndrome, common to a substantial percentage of asthmatics and characterized by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant from any previously administered symptomatic asthma therapy.

[00554] Compounds of the current invention can be used for other inflammatory or obstructive airways

diseases and conditions to which the present invention is applicable and include acute lung injury (ALI), adult/acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, but not limited to, acute, arachidic, catarrhal, croupus, chronic or phthinoïd bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

[00555] With regard to their anti-inflammatory activity, in particular in relation to inhibition of eosinophil activation, compounds of the invention are also useful in the treatment of eosinophil related disorders, e.g. eosinophilia, in particular eosinophil related disorders of the airways (e.g. involving morbid eosinophilic infiltration of pulmonary tissues) including hypereosinophilia as it effects the airways and/or lungs as well as, for example, eosinophil- related disorders of the airways consequential or concomitant to Löffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma and eosinophil-related disorders affecting the airways occasioned by drug-reaction.

[00556] Compounds of the invention are also useful in the treatment of inflammatory or allergic conditions of the skin, for example psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, systemic lupus erythematosus, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acne vulgaris, and other inflammatory or allergic conditions of the skin.

[00557] Compounds of the invention may also be used for the treatment of other diseases or conditions, such as diseases or conditions having an inflammatory component, for example, treatment of diseases and conditions of the eye such as ocular allergy, conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or etiology, including autoimmune hematological disorders (e.g. hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia), systemic lupus erythematosus, rheumatoid arthritis, polychondritis,

scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), irritable bowel syndrome, celiac disease, periodontitis, hyaline membrane disease, kidney disease, glomerular disease, alcoholic liver disease, multiple sclerosis, endocrine ophthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), Sjogren's syndrome, keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, cryopyrin-associated periodic syndrome, nephritis, vasculitis, diverticulitis, interstitial cystitis, glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy), chronic granulomatous disease, endometriosis, leptospirosis renal disease, glaucoma, retinal disease, ageing, headache, pain, complex regional pain syndrome, cardiac hypertrophy, musclewasting, catabolic disorders, obesity, fetal growth retardation, hypercholesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ectodermal dysplasia, Behcet's disease, incontinentia pigmenti, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma (allergic and non-allergic, mild, moderate, severe, bronchitic, and exercise-induced), acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, nasal sinusitis, ocular allergy, silica induced diseases, COPD (reduction of damage, airways inflammation, bronchial hyperreactivity, remodeling or disease progression), pulmonary disease, cystic fibrosis, acid-induced lung injury, pulmonary hypertension, polyneuropathy, cataracts, muscle inflammation in conjunction with systemic sclerosis, inclusion body myositis, myasthenia gravis, thyroiditis, Addison's disease, lichen planus, Type 1 diabetes, or Type 2 diabetes, appendicitis, atopic dermatitis, asthma, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, Crohn's disease, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, ulcerative colitis, uveitis, vaginitis, vasculitis, or vulvitis.

[00558] In some embodiments, the present invention provides a method of treating an autoimmune disease selected from systemic sclerosis, idiopathic pulmonary fibrosis, inflammatory bowel disease, atopic dermatitis, rheumatoid arthritis, graft versus host disease (acute and chronic), and other tissue fibrosis

diseases.

[00559] In some embodiments, the present invention provides a method of treating a hematologic malignancy selected from LGL leukemia (T and NK cell), cutaneous T cell lymphoma (CTCL), peripheral T cell lymphomas (PTCL, all subtypes including ALCL), diffuse large B cell lymphoma (DLBCL), acute myelogenous leukemia, multiple myeloma, and myelofibrosis

[00560] In some embodiments, the present invention provides a method of treating tissue fibrosis or chronic tissue disease, including liver and kidney fibrosis, in a patient in need thereof, comprising administering a compound of the present invention, or a pharmaceutically acceptable salt thereof.

[00561] In some embodiments, the present invention provides a method of treating idiopathic interstitial pneumonia(s) (IIPs), including any type of lung fibrosis, either interstitial lung disease associated with rheumatoid disease (including SSc) or IPF itself, in a patient in need thereof, comprising administering a compound of the present invention, or a pharmaceutically acceptable salt thereof.

[00562] In some embodiments the inflammatory disease which can be treated according to the methods of this invention is an disease of the skin. In some embodiments, the inflammatory disease of the skin is selected from contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, and other inflammatory or allergic conditions of the skin.

[00563] In some embodiments the inflammatory disease which can be treated according to the methods of this invention is selected from acute and chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, Juvenile rheumatoid arthritis, Systemic juvenile idiopathic arthritis (SJIA), Cryopyrin Associated Periodic Syndrome (CAPS), and osteoarthritis.

[00564] In some embodiments the inflammatory disease which can be treated according to the methods of this invention is a TH17 mediated disease. In some embodiments the TH17 mediated disease is selected from Systemic lupus erythematosus, Multiple sclerosis, and inflammatory bowel disease (including Crohn's disease or ulcerative colitis).

[00565] In some embodiments the inflammatory disease which can be treated according to the methods of this invention is selected from Sjogren's syndrome, allergic disorders, osteoarthritis, conditions of the eye such as ocular allergy, conjunctivitis, keratoconjunctivitis sicca and vernal conjunctivitis, and diseases affecting the nose such as allergic rhinitis.

[00566] Cardiovascular diseases which can be treated according to the methods of this invention include, but are not limited to, restenosis, cardiomegaly, atherosclerosis, myocardial infarction, ischemic stroke, congestive heart failure, angina pectoris, reocclusion after angioplasty, restenosis after angioplasty,

reocclusion after aortocoronary bypass, restenosis after aortocoronary bypass, stroke, transitory ischemia, a peripheral arterial occlusive disorder, pulmonary embolism, and deep venous thrombosis.

[00567] In some embodiments, the neurodegenerative disease which can be treated according to the methods of this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia, and neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity, hypoxia, epilepsy, treatment of diabetes, metabolic syndrome, obesity, organ transplantation and graft versus host disease.

[00568] In some embodiments the invention provides a method of treating, preventing or lessening the severity of Alzheimer's disease comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt or composition thereof.

[00569] In some embodiments the invention provides a method of treating a disease or condition commonly occurring in connection with transplantation. In some embodiments, the disease or condition commonly occurring in connection with transplantation is selected from organ transplantation, organ transplant rejection, and graft versus host disease.

[00570] In some embodiments the invention provides a method of treating a metabolic disease. In some embodiments the metabolic disease is selected from Type 1 diabetes, Type 2 diabetes, metabolic syndrome, and obesity.

[00571] In some embodiments the invention provides a method of treating a viral disease. In some embodiments, the viral infection is HIV infection.

[00572] Furthermore, the invention provides the use of a compound according to the definitions herein, or a pharmaceutically acceptable salt, or a hydrate or solvate thereof for the preparation of a medicament for the treatment of a proliferative disease, an inflammatory disease, an obstructive respiratory disease, a cardiovascular disease, a metabolic disease, a neurological disease, a neurodegenerative disease, a viral disease, or a disorder commonly occurring in connection with transplantation.

Combination Therapies

[00573] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents, which are normally administered to treat that condition, may be administered in combination with compounds and compositions of this invention. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated."

[00574] In certain embodiments, a provided combination, or composition thereof, is administered in combination with another therapeutic agent.

[00575] In some embodiments, the present invention provides a method of treating a disclosed disease or condition comprising administering to a patient in need thereof an effective amount of a compound disclosed herein or a pharmaceutically acceptable salt thereof and co-administering simultaneously or sequentially an effective amount of one or more additional therapeutic agents, such as those described herein. In some embodiments, the method includes co-administering one additional therapeutic agent. In some embodiments, the method includes co-administering two additional therapeutic agents. In some embodiments, the combination of the disclosed compound and the additional therapeutic agent or agents acts synergistically.

[00576] Examples of agents the combinations of this invention may also be combined with include, without limitation: treatments for Alzheimer's Disease such as Aricept® and Exelon®; treatments for HIV such as ritonavir; 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; agents that prolong or improve pharmacokinetics such as cytochrome P450 inhibitors (i.e., inhibitors of metabolic breakdown) and CYP3A4 inhibitors (e.g., ketokenazole and ritonavir), and agents for treating immunodeficiency disorders such as gamma globulin.

[00577] In certain embodiments, combination therapies of the present invention, or a pharmaceutically acceptable composition thereof, are administered in combination with a monoclonal antibody or an siRNA therapeutic.

[00578] Those additional agents may be administered separately from a provided combination therapy, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of

time from one another normally within five hours from one another.

[00579] As used herein, the term “combination,” “combined,” and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a combination of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form.

[00580] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably 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.

[00581] One or more other therapeutic agent may be administered separately from a compound or composition of the invention, as part of a multiple dosage regimen. Alternatively, one or more other therapeutic agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as a multiple dosage regime, one or more other therapeutic agent and a compound or composition of the invention may be administered simultaneously, sequentially or within a period of time from one another, for example within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 hours from one another. In some embodiments, one or more other therapeutic agent and a compound or composition of the invention are administered as a multiple dosage regimen within greater than 24 hours apart.

[00582] In one embodiment, the present invention provides a composition comprising a provided compound and one or more additional therapeutic agents. The therapeutic agent may be administered together with a provided compound, or may be administered prior to or following administration of a provided compound. Suitable therapeutic agents are described in further detail below. In certain embodiments, a provided compound may be administered up to 5 minutes, 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, or 18 hours before the therapeutic agent. In other embodiments, a provided compound may be administered up to 5 minutes, 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, or 18 hours following the therapeutic agent.

[00583] In another embodiment, the present invention provides a method of treating an inflammatory disease, disorder or condition by administering to a patient in need thereof a provided compound and one or more additional therapeutic agents. Such additional therapeutic agents may be small molecules or

recombinant biologic agents and include, for example, acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, colchicine (Colcrys®), corticosteroids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and the like, probenecid, allopurinol, febuxostat (Uloric®), sulfasalazine (Azulfidine®), antimalarials such as hydroxychloroquine (Plaquenil®) and chloroquine (Aralen®), methotrexate (Rheumatrex®), gold salts such as gold thioglucose (Solganal®), gold thiomalate (Myochrysine®) and auranofin (Ridaura®), D-penicillamine (Depen® or Cuprimine®), azathioprine (Imuran®), cyclophosphamide (Cytoxan®), chlorambucil (Leukeran®), cyclosporine (Sandimmune®), leflunomide (Arava®) and “anti-TNF” agents such as etanercept (Enbrel®), infliximab (Remicade®), golimumab (Simponi®), certolizumab pegol (Cimzia®) and adalimumab (Humira®), “anti-IL-1” agents such as anakinra (Kineret®) and rilonacept (Arcalyst®), canakinumab (Ilaris®), anti-Jak inhibitors such as tofacitinib, antibodies such as rituximab (Rituxan®), “anti-T-cell” agents such as abatacept (Orencia®), “anti-IL-6” agents such as tocilizumab (Actemra®), diclofenac, cortisone, hyaluronic acid (Synvisc® or Hyalgan®), monoclonal antibodies such as tanezumab, anticoagulants such as heparin (Calcinparine® or Liquaemin®) and warfarin (Coumadin®), antidiarrheals such as diphenoxylate (Lomotil®) and loperamide (Imodium®), bile acid binding agents such as cholestyramine, alosetron (Lotronex®), lubiprostone (Amitiza®), laxatives such as Milk of Magnesia, polyethylene glycol (MiraLax®), Dulcolax®, Correctol® and Senokot®, anticholinergics or antispasmodics such as dicyclomine (Bentyl®), Singulair®, beta-2 agonists such as albuterol (Ventolin® HFA, Proventil® HFA), levalbuterol (Xopenex®), metaproterenol (Alupent®), pirbuterol acetate (Maxair®), terbutaline sulfate (Brethaire®), salmeterol xinafoate (Serevent®) and formoterol (Foradil®), anticholinergic agents such as ipratropium bromide (Atrovent®) and tiotropium (Spiriva®), inhaled corticosteroids such as beclomethasone dipropionate (Beclovent®, Qvar®, and Vanceril®), triamcinolone acetonide (Azmecort®), mometasone (Asthmanex®), budesonide (Pulmocort®), and flunisolide (Aerobid®), Afviar®, Symbicort®, Dulera®, cromolyn sodium (Intal®), methylxanthines such as theophylline (Theo-Dur®, Theolair®, Slo-bid®, Uniphyll®, Theo-24®) and aminophylline, IgE antibodies such as omalizumab (Xolair®), nucleoside reverse transcriptase inhibitors such as zidovudine (Retrovir®), abacavir (Ziagen®), abacavir/lamivudine (Epzicom®), abacavir/lamivudine/zidovudine (Trizivir®), didanosine (Videx®), emtricitabine (Emtriva®), lamivudine (Epivir®), lamivudine/zidovudine (Combivir®), stavudine (Zerit®), and zalcitabine (Hivid®), non-nucleoside reverse transcriptase inhibitors such as delavirdine (Rescriptor®), efavirenz (Sustiva®), nevirapine (Viramune®) and etravirine (Intelence®), nucleotide reverse transcriptase inhibitors such as tenofovir (Viread®), protease inhibitors such as amprenavir (Agenerase®), atazanavir (Reyataz®), darunavir (Prezista®), fosamprenavir (Lexiva®), indinavir (Crixivan®), lopinavir and ritonavir (Kaletra®), nelfinavir (Viracept®), ritonavir

(Norvir®), saquinavir (Fortovase® or Invirase®), and tipranavir (Aptivus®), entry inhibitors such as enfuvirtide (Fuzeon®) and maraviroc (Selzentry®), integrase inhibitors such as raltegravir (Isentress®), doxorubicin (Hydrodaunorubicin®), vincristine (Oncovin®), bortezomib (Velcade®), and dexamethasone (Decadron®) in combination with lenalidomide (Revlimid®), or any combination(s) thereof.

[00584] In another embodiment, the present invention provides a method of treating gout comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, colchicine (Colcrys®), corticosteroids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and the like, probenecid, allopurinol and febuxostat (Uloric®).

[00585] In another embodiment, the present invention provides a method of treating rheumatoid arthritis comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, corticosteroids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and the like, sulfasalazine (Azulfidine®), antimalarials such as hydroxychloroquine (Plaquenil®) and chloroquine (Aralen®), methotrexate (Rheumatrex®), gold salts such as gold thioglucose (Solganal®), gold thiomalate (Myochrysine®) and auranofin (Ridaura®), D-penicillamine (Depen® or Cuprimine®), azathioprine (Imuran®), cyclophosphamide (Cytosan®), chlorambucil (Leukeran®), cyclosporine (Sandimmune®), leflunomide (Arava®) and “anti-TNF” agents such as etanercept (Enbrel®), infliximab (Remicade®), golimumab (Simponi®), certolizumab pegol (Cimzia®) and adalimumab (Humira®), “anti-IL-1” agents such as anakinra (Kineret®) and rilonacept (Arcalyst®), antibodies such as rituximab (Rituxan®), “anti-T-cell” agents such as abatacept (Orencia®) and “anti-IL-6” agents such as tocilizumab (Actemra®).

[00586] In some embodiments, the present invention provides a method of treating osteoarthritis comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, diclofenac, cortisone, hyaluronic acid (Synvisc® or Hyalgan®) and monoclonal antibodies such as tanezumab.

[00587] In some embodiments, the present invention provides a method of treating lupus comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, corticosteroids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and the like, antimalarials such as hydroxychloroquine (Plaquenil®)

and chloroquine (Aralen®), cyclophosphamide (Cytoxan®), methotrexate (Rheumatrex®), azathioprine (Imuran®) and anticoagulants such as heparin (Calcinparine® or Liquaemin®) and warfarin (Coumadin®).

[00588] In some embodiments, the present invention provides a method of treating inflammatory bowel disease comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from mesalamine (Asacol®) sulfasalazine (Azulfidine®), antidiarrheals such as diphenoxylate (Lomotil®) and loperamide (Imodium®), bile acid binding agents such as cholestyramine, alosetron (Lotronex®), lubiprostone (Amitiza®), laxatives such as Milk of Magnesia, polyethylene glycol (MiraLax®), Dulcolax®, Correctol® and Senokot® and anticholinergics or antispasmodics such as dicyclomine (Bentyl®), anti-TNF therapies, steroids, and antibiotics such as Flagyl or ciprofloxacin.

[00589] In some embodiments, the present invention provides a method of treating asthma comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from Singulair®, beta-2 agonists such as albuterol (Ventolin® HFA, Proventil® HFA), levalbuterol (Xopenex®), metaproterenol (Alupent®), pirbuterol acetate (Maxair®), terbutaline sulfate (Brethaire®), salmeterol xinafoate (Serevent®) and formoterol (Foradil®), anticholinergic agents such as ipratropium bromide (Atrovent®) and tiotropium (Spiriva®), inhaled corticosteroids such as prednisone, prednisolone, beclomethasone dipropionate (Beclovent®, Qvar®, and Vanceril®), triamcinolone acetonide (Azmecort®), mometasone (Asthmanex®), budesonide (Pulmocort®), flunisolide (Aerobid®), Afviar®, Symbicort®, and Dulera®, cromolyn sodium (Intal®), methylxanthines such as theophylline (Theo-Dur®, Theolair®, Slo-bid®, Uniphyll®, Theo-24®) and aminophylline, and IgE antibodies such as omalizumab (Xolair®).

[00590] In some embodiments, the present invention provides a method of treating COPD comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from beta-2 agonists such as albuterol (Ventolin® HFA, Proventil® HFA), levalbuterol (Xopenex®), metaproterenol (Alupent®), pirbuterol acetate (Maxair®), terbutaline sulfate (Brethaire®), salmeterol xinafoate (Serevent®) and formoterol (Foradil®), anticholinergic agents such as ipratropium bromide (Atrovent®) and tiotropium (Spiriva®), methylxanthines such as theophylline (Theo-Dur®, Theolair®, Slo-bid®, Uniphyll®, Theo-24®) and aminophylline, inhaled corticosteroids such as prednisone, prednisolone, beclomethasone dipropionate (Beclovent®, Qvar®, and Vanceril®), triamcinolone acetonide (Azmecort®), mometasone (Asthmanex®), budesonide (Pulmocort®), flunisolide (Aerobid®), Afviar®, Symbicort®, and Dulera®,

[00591] In some embodiments, the present invention provides a method of treating HIV comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic

agents selected from nucleoside reverse transcriptase inhibitors such as zidovudine (Retrovir®), abacavir (Ziagen®), abacavir/lamivudine (Epzicom®), abacavir/lamivudine/zidovudine (Trizivir®), didanosine (Videx®), emtricitabine (Emtriva®), lamivudine (Epivir®), lamivudine/zidovudine (Combivir®), stavudine (Zerit®), and zalcitabine (Hivid®), non-nucleoside reverse transcriptase inhibitors such as delavirdine (Rescriptor®), efavirenz (Sustiva®), nevirapine (Viramune®) and etravirine (Intelence®), nucleotide reverse transcriptase inhibitors such as tenofovir (Viread®), protease inhibitors such as amprenavir (Agenerase®), atazanavir (Reyataz®), darunavir (Prezista®), fosamprenavir (Lexiva®), indinavir (Crixivan®), lopinavir and ritonavir (Kaletra®), nelfinavir (Viracept®), ritonavir (Norvir®), saquinavir (Fortovase® or Invirase®), and tipranavir (Aptivus®), entry inhibitors such as enfuvirtide (Fuzeon®) and maraviroc (Selzentry®), integrase inhibitors such as raltegravir (Isentress®), and combinations thereof.

[00592] In another embodiment, the present invention provides a method of treating a hematological malignancy comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from rituximab (Rituxan®), cyclophosphamide (Cytosan®), doxorubicin (Hydrodaunorubicin®), vincristine (Oncovin®), prednisone, a hedgehog signaling inhibitor, a BTK inhibitor, a JAK/pan-JAK inhibitor, a TYK2 inhibitor, a PI3K inhibitor, a SYK inhibitor, and combinations thereof.

[00593] In another embodiment, the present invention provides a method of treating a solid tumor comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from rituximab (Rituxan®), cyclophosphamide (Cytosan®), doxorubicin (Hydrodaunorubicin®), vincristine (Oncovin®), prednisone, a hedgehog signaling inhibitor, a BTK inhibitor, a JAK/pan-JAK inhibitor, a TYK2 inhibitor, a PI3K inhibitor, a SYK inhibitor, and combinations thereof.

[00594] In another embodiment, the present invention provides a method of treating a hematological malignancy comprising administering to a patient in need thereof a provided compound and a Hedgehog (Hh) signaling pathway inhibitor. In some embodiments, the hematological malignancy is DLBCL (Ramirez *et al* "Defining causative factors contributing in the activation of hedgehog signaling in diffuse large B-cell lymphoma" Leuk. Res. (2012), published online July 17, and incorporated herein by reference in its entirety).

[00595] In another embodiment, the present invention provides a method of treating diffuse large B-cell lymphoma (DLBCL) comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from rituximab (Rituxan®), cyclophosphamide (Cytosan®), doxorubicin (Hydrodaunorubicin®), vincristine (Oncovin®), prednisone, a hedgehog

signaling inhibitor, and combinations thereof.

[00596] In another embodiment, the present invention provides a method of treating multiple myeloma comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from bortezomib (Velcade®), and dexamethasone (Decadron®), a hedgehog signaling inhibitor, a BTK inhibitor, a JAK/pan-JAK inhibitor, a TYK2 inhibitor, a PI3K inhibitor, a SYK inhibitor in combination with lenalidomide (Revlimid®).

[00597] In another embodiment, the present invention provides a method of treating Waldenström's macroglobulinemia comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from chlorambucil (Leukeran®), cyclophosphamide (Cytosan®, Neosar®), fludarabine (Fludara®), cladribine (Leustatin®), rituximab (Rituxan®), a hedgehog signaling inhibitor, a BTK inhibitor, a JAK/pan-JAK inhibitor, a TYK2 inhibitor, a PI3K inhibitor, and a SYK inhibitor.

[00598] In some embodiments, one or more other therapeutic agent is an antagonist of the hedgehog pathway. Approved hedgehog pathway inhibitors which may be used in the present invention include sonidegib (Odomzo®, Sun Pharmaceuticals); and vismodegib (Erivedge®, Genentech), both for treatment of basal cell carcinoma.

[00599] In some embodiments, one or more other therapeutic agent is a Poly ADP ribose polymerase (PARP) inhibitor. In some embodiments, a PARP inhibitor is selected from olaparib (Lynparza®, AstraZeneca); rucaparib (Rubraca®, Clovis Oncology); niraparib (Zejula®, Tesaro); talazoparib (MDV3800/BMN 673/LT00673, Medivation/Pfizer/Biomarin); veliparib (ABT-888, AbbVie); and BGB-290 (BeiGene, Inc.).

[00600] In some embodiments, one or more other therapeutic agent is a histone deacetylase (HDAC) inhibitor. In some embodiments, an HDAC inhibitor is selected from vorinostat (Zolinza®, Merck); romidepsin (Istodax®, Celgene); panobinostat (Farydak®, Novartis); belinostat (Beleodaq®, Spectrum Pharmaceuticals); entinostat (SNDX-275, Syndax Pharmaceuticals) (NCT00866333); and chidamide (Epidaza®, HBI-8000, Chipscreen Biosciences, China).

[00601] In some embodiments, one or more other therapeutic agent is a CDK inhibitor, such as a CDK4/CDK6 inhibitor. In some embodiments, a CDK 4/6 inhibitor is selected from palbociclib (Ibrance®, Pfizer); ribociclib (Kisqali®, Novartis); abemaciclib (Ly2835219, Eli Lilly); and trilaciclib (G1T28, G1 Therapeutics).

[00602] In some embodiments, one or more other therapeutic agent is a folic acid inhibitor. Approved folic acid inhibitors useful in the present invention include pemetrexed (Alimta®, Eli Lilly).

[00603] In some embodiments, one or more other therapeutic agent is a CC chemokine receptor 4 (CCR4) inhibitor. CCR4 inhibitors being studied that may be useful in the present invention include mogamulizumab (Poteligeo®, Kyowa Hakko Kirin, Japan).

[00604] In some embodiments, one or more other therapeutic agent is an isocitrate dehydrogenase (IDH) inhibitor. IDH inhibitors being studied which may be used in the present invention include AG120 (Celgene; NCT02677922); AG221 (Celgene, NCT02677922; NCT02577406); BAY1436032 (Bayer, NCT02746081); IDH305 (Novartis, NCT02987010).

[00605] In some embodiments, one or more other therapeutic agent is an arginase inhibitor. Arginase inhibitors being studied which may be used in the present invention include AEB1102 (pegylated recombinant arginase, Aeglea Biotherapeutics), which is being studied in Phase 1 clinical trials for acute myeloid leukemia and myelodysplastic syndrome (NCT02732184) and solid tumors (NCT02561234); and CB-1158 (Calithera Biosciences).

[00606] In some embodiments, one or more other therapeutic agent is a glutaminase inhibitor. Glutaminase inhibitors being studied which may be used in the present invention include CB-839 (Calithera Biosciences).

[00607] In some embodiments, one or more other therapeutic agent is an antibody that binds to tumor antigens, that is, proteins expressed on the cell surface of tumor cells. Approved antibodies that bind to tumor antigens which may be used in the present invention include rituximab (Rituxan®, Genentech/BiogenIdec); ofatumumab (anti-CD20, Arzerra®, GlaxoSmithKline); obinutuzumab (anti-CD20, Gazyva®, Genentech); ibritumomab (anti-CD20 and Yttrium-90, Zevalin®, Spectrum Pharmaceuticals); daratumumab (anti-CD38, Darzalex®, Janssen Biotech), dinutuximab (anti-glycolipid GD2, Unituxin®, United Therapeutics); trastuzumab (anti-HER2, Herceptin®, Genentech); ado-trastuzumab emtansine (anti-HER2, fused to emtansine, Kadcyla®, Genentech); and pertuzumab (anti-HER2, Perjeta®, Genentech); and brentuximab vedotin (anti-CD30-drug conjugate, Adcetris®, Seattle Genetics).

[00608] In some embodiments, one or more other therapeutic agent is a topoisomerase inhibitor. Approved topoisomerase inhibitors useful in the present invention include irinotecan (Onivyde®, Merrimack Pharmaceuticals); topotecan (Hycamtin®, GlaxoSmithKline). Topoisomerase inhibitors being studied which may be used in the present invention include pixantrone (Pixuvri®, CTI Biopharma).

[00609] In some embodiments, one or more other therapeutic agent is an inhibitor of anti-apoptotic proteins, such as BCL-2. Approved anti-apoptotics which may be used in the present invention include venetoclax (Venclexta®, AbbVie/Genentech); and blinatumomab (Blincyto®, Amgen). Other therapeutic

agents targeting apoptotic proteins which have undergone clinical testing and may be used in the present invention include navitoclax (ABT-263, Abbott), a BCL-2 inhibitor (NCT02079740).

[00610] In some embodiments, one or more other therapeutic agent is an androgen receptor inhibitor. Approved androgen receptor inhibitors useful in the present invention include enzalutamide (Xtandi®, Astellas/Medivation); approved inhibitors of androgen synthesis include abiraterone (Zytiga®, Centocor/Ortho); approved antagonist of gonadotropin-releasing hormone (GnRH) receptor (degarelix, Firmagon®, Ferring Pharmaceuticals).

[00611] In some embodiments, one or more other therapeutic agent is a selective estrogen receptor modulator (SERM), which interferes with the synthesis or activity of estrogens. Approved SERMs useful in the present invention include raloxifene (Evista®, Eli Lilly).

[00612] In some embodiments, one or more other therapeutic agent is an inhibitor of bone resorption. An approved therapeutic which inhibits bone resorption is Denosumab (Xgeva®, Amgen), an antibody that binds to RANKL, prevents binding to its receptor RANK, found on the surface of osteoclasts, their precursors, and osteoclast-like giant cells, which mediates bone pathology in solid tumors with osseous metastases. Other approved therapeutics that inhibit bone resorption include bisphosphonates, such as zoledronic acid (Zometa®, Novartis).

[00613] In some embodiments, one or more other therapeutic agent is an inhibitor of interaction between the two primary p53 suppressor proteins, MDMX and MDM2. Inhibitors of p53 suppression proteins being studied which may be used in the present invention include ALRN-6924 (Aileron), a stapled peptide that equipotently binds to and disrupts the interaction of MDMX and MDM2 with p53. ALRN-6924 is currently being evaluated in clinical trials for the treatment of AML, advanced myelodysplastic syndrome (MDS) and peripheral T-cell lymphoma (PTCL) (NCT02909972; NCT02264613).

[00614] In some embodiments, one or more other therapeutic agent is an inhibitor of transforming growth factor-beta (TGF-beta or TGFβ). Inhibitors of TGF-beta proteins being studied which may be used in the present invention include NIS793 (Novartis), an anti-TGF-beta antibody being tested in the clinic for treatment of various cancers, including breast, lung, hepatocellular, colorectal, pancreatic, prostate and renal cancer (NCT 02947165). In some embodiments, the inhibitor of TGF-beta proteins is fresolimumab (GC1008; Sanofi-Genzyme), which is being studied for melanoma (NCT00923169); renal cell carcinoma (NCT00356460); and non-small cell lung cancer (NCT02581787). Additionally, in some embodiments, the additional therapeutic agent is a TGF-beta trap, such as described in Connolly et al. (2012) *Int'l J. Biological Sciences* 8:964-978. One therapeutic compound currently in clinical trials for treatment of solid tumors is M7824 (Merck KgaA - formerly MSB0011459X), which is a bispecific, anti-PD-L1/TGFβ trap compound (NCT02699515); and (NCT02517398). M7824 is comprised of a fully human IgG1 antibody

against PD-L1 fused to the extracellular domain of human TGF-beta receptor II, which functions as a TGFβ “trap.”

[00615] In some embodiments, one or more other therapeutic agent is selected from glembatumumab vedotin-monomethyl auristatin E (MMAE) (Celldex), an anti-glycoprotein NMB (gpNMB) antibody (CR011) linked to the cytotoxic MMAE. gpNMB is a protein overexpressed by multiple tumor types associated with cancer cells' ability to metastasize.

[00616] In some embodiments, one or more other therapeutic agent is an antiproliferative compound. Such antiproliferative compounds include, but are not limited to aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active compounds; alkylating compounds; histone deacetylase inhibitors; compounds which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibitors; mTOR inhibitors; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; matrix metalloproteinase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; compounds used in the treatment of hematologic malignancies; compounds which target, decrease or inhibit the activity of Flt-3; Hsp90 inhibitors such as 17-AAG (17-allylaminogeldanamycin, NSC330507), 17-DMAG (17-dimethylaminoethylamino-17-demethoxy-geldanamycin, NSC707545), IPI-504, CNF1010, CNF2024, CNF1010 from Conforma Therapeutics; temozolomide (Temodal®); kinesin spindle protein inhibitors, such as SB715992 or SB743921 from GlaxoSmithKline, or pentamidine/chlorpromazine from CombinatoRx; MEK inhibitors such as ARRY142886 from Array BioPharma, AZd₆244 from AstraZeneca, PD181461 from Pfizer and leucovorin.

[00617] In some embodiments, the present invention provides a method of treating Alzheimer's disease comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from donepezil (Aricept®), rivastigmine (Exelon®), galantamine (Razadyne®), tacrine (Cognex®), and memantine (Namenda®).

[00618] In some embodiments, one or more other therapeutic agent is a taxane compound, which causes disruption of microtubules, which are essential for cell division. In some embodiments, a taxane compound is selected from paclitaxel (Taxol®, Bristol-Myers Squibb), docetaxel (Taxotere®, Sanofi-Aventis; Docefrez®, Sun Pharmaceutical), albumin-bound paclitaxel (Abraxane®; Abraxis/Celgene), cabazitaxel (Jevtana®, Sanofi-Aventis), and SID530 (SK Chemicals, Co.) (NCT00931008).

[00619] In some embodiments, one or more other therapeutic agent is a nucleoside inhibitor, or a

therapeutic agent that interferes with normal DNA synthesis, protein synthesis, cell replication, or will otherwise inhibit rapidly proliferating cells.

[00620] In some embodiments, a nucleoside inhibitor is selected from trabectedin (guanidine alkylating agent, Yondelis®, Janssen Oncology), mechlorethamine (alkylating agent, Valchlor®, Aktelion Pharmaceuticals); vincristine (Oncovin®, Eli Lilly; Vincasar®, Teva Pharmaceuticals; Marqibo®, Talon Therapeutics); temozolomide (prodrug to alkylating agent 5-(3-methyltriazene-1-yl)-imidazole-4-carboxamide (MTIC) Temodar®, Merck); cytarabine injection (ara-C, antimetabolic cytidine analog, Pfizer); lomustine (alkylating agent, CeeNU®, Bristol-Myers Squibb; Gleostine®, NextSource Biotechnology); azacitidine (pyrimidine nucleoside analog of cytidine, Vidaza®, Celgene); omacetaxine mepesuccinate (cephalotaxine ester) (protein synthesis inhibitor, Synribo®; Teva Pharmaceuticals); asparaginase *Erwinia chrysanthemi* (enzyme for depletion of asparagine, Elspar®, Lundbeck; Erwinaze®, EUSA Pharma); eribulin mesylate (microtubule inhibitor, tubulin-based antimetabolic, Halaven®, Eisai); cabazitaxel (microtubule inhibitor, tubulin-based antimetabolic, Jevtana®, Sanofi-Aventis); capacetrine (thymidylate synthase inhibitor, Xeloda®, Genentech); bendamustine (bifunctional mechlorethamine derivative, believed to form interstrand DNA cross-links, Treanda®, Cephalon/Teva); ixabepilone (semi-synthetic analog of epothilone B, microtubule inhibitor, tubulin-based antimetabolic, Ixempra®, Bristol-Myers Squibb); nelarabine (prodrug of deoxyguanosine analog, nucleoside metabolic inhibitor, Arranon®, Novartis); clorafabine (prodrug of ribonucleotide reductase inhibitor, competitive inhibitor of deoxycytidine, Clolar®, Sanofi-Aventis); and trifluridine and tipiracil (thymidine-based nucleoside analog and thymidine phosphorylase inhibitor, Lonsurf®, Taiho Oncology).

[00621] In some embodiments, one or more other therapeutic agent is a kinase inhibitor or VEGF-R antagonist. Approved VEGF inhibitors and kinase inhibitors useful in the present invention include: bevacizumab (Avastin®, Genentech/Roche) an anti-VEGF monoclonal antibody; ramucirumab (Cyramza®, Eli Lilly), an anti-VEGFR-2 antibody and ziv-aflibercept, also known as VEGF Trap (Zaltrap®; Regeneron/Sanofi). VEGFR inhibitors, such as regorafenib (Stivarga®, Bayer); vandetanib (Caprelsa®, AstraZeneca); axitinib (Inlyta®, Pfizer); and lenvatinib (Lenvima®, Eisai); Raf inhibitors, such as sorafenib (Nexavar®, Bayer AG and Onyx); dabrafenib (Tafinlar®, Novartis); and vemurafenib (Zelboraf®, Genentech/Roche); MEK inhibitors, such as cobimetanib (Cotellic®, Exelexis/Genentech/Roche); trametinib (Mekinist®, Novartis); Bcr-Abl tyrosine kinase inhibitors, such as imatinib (Gleevec®, Novartis); nilotinib (Tasigna®, Novartis); dasatinib (Sprycel®, BristolMyersSquibb); bosutinib (Bosulif®, Pfizer); and ponatinib (Inclusig®, Ariad Pharmaceuticals); Her2 and EGFR inhibitors, such as gefitinib (Iressa®, AstraZeneca); erlotinib (Tarceeva®, Genentech/Roche/Astellas); lapatinib (Tykerb®, Novartis); afatinib (Gilotrif®, Boehringer Ingelheim); osimertinib (targeting activated EGFR, Tagrisso®,

AstraZeneca); and brigatinib (Alunbrig®, Ariad Pharmaceuticals); c-Met and VEGFR2 inhibitors, such as cabozantinib (Cometriq®, Exelexis); and multikinase inhibitors, such as sunitinib (Sutent®, Pfizer); pazopanib (Votrient®, Novartis); ALK inhibitors, such as crizotinib (Xalkori®, Pfizer); ceritinib (Zykadia®, Novartis); and alectinib (Alecenza®, Genentech/Roche); Bruton's tyrosine kinase inhibitors, such as ibrutinib (Imbruvica®, Pharmacyclics/Janssen); and Flt3 receptor inhibitors, such as midostaurin (Rydapt®, Novartis).

[00622] Other kinase inhibitors and VEGF-R antagonists that are in development and may be used in the present invention include tivozanib (Aveo Pharmaceuticals); vatalanib (Bayer/Novartis); lucitanib (Clovis Oncology); dovitinib (TKI258, Novartis); Chiauauib (Chipscreen Biosciences); CEP-11981 (Cephalon); linifanib (Abbott Laboratories); neratinib (HKI-272, Puma Biotechnology); radotinib (Supect®, IY5511, Il-Yang Pharmaceuticals, S. Korea); ruxolitinib (Jakafi®, Incyte Corporation); PTC299 (PTC Therapeutics); CP-547,632 (Pfizer); foretinib (Exelexis, GlaxoSmithKline); quizartinib (Daiichi Sankyo) and motesanib (Amgen/Takeda).

[00623] In another embodiment, the present invention provides a method of treating organ transplant rejection or graft vs. host disease comprising administering to a patient in need thereof a provided compound and one or more additional therapeutic agents selected from a steroid, cyclosporin, FK506, rapamycin, a hedgehog signaling inhibitor, a BTK inhibitor, a JAK/pan-JAK inhibitor, a TYK2 inhibitor, a PI3K inhibitor, and a SYK inhibitor.

[00624] In another embodiment, the present invention provides a method of treating or lessening the severity of a disease comprising administering to a patient in need thereof a provided compound and a BTK inhibitor, wherein the disease is selected from inflammatory bowel disease, arthritis, systemic lupus erythematosus (SLE), vasculitis, idiopathic thrombocytopenic purpura (ITP), rheumatoid arthritis, psoriatic arthritis, osteoarthritis, Still's disease, juvenile arthritis, diabetes, myasthenia gravis, Hashimoto's thyroiditis, Ord's thyroiditis, Graves' disease, autoimmune thyroiditis, Sjogren's syndrome, multiple sclerosis, systemic sclerosis, Lyme neuroborreliosis, Guillain-Barre syndrome, acute disseminated encephalomyelitis, Addison's disease, opsoclonus-myoclonus syndrome, ankylosing spondylosis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hepatitis, autoimmune gastritis, pernicious anemia, celiac disease, Goodpasture's syndrome, idiopathic thrombocytopenic purpura, optic neuritis, scleroderma, primary biliary cirrhosis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, psoriasis, alopecia universalis, Behcet's disease, chronic fatigue, dysautonomia, membranous glomerulonephropathy, endometriosis, interstitial cystitis, pemphigus vulgaris, bullous pemphigoid, neuromyotonia, scleroderma, vulvodynia, a hyperproliferative disease, rejection of transplanted organs or tissues, Acquired Immunodeficiency

Syndrome (AIDS, also known as HIV), type 1 diabetes, graft versus host disease, transplantation, transfusion, anaphylaxis, allergies (e.g., allergies to plant pollens, latex, drugs, foods, insect poisons, animal hair, animal dander, dust mites, or cockroach calyx), type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, and atopic dermatitis, asthma, appendicitis, atopic dermatitis, asthma, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, Crohn's disease, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, ulcerative colitis, uveitis, vaginitis, vasculitis, or vulvitis, B-cell proliferative disorder, e.g., diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia, splenic marginal zone lymphoma, multiple myeloma (also known as plasma cell myeloma), non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmacytoma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, mantle cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, or lymphomatoid granulomatosis, breast cancer, prostate cancer, or cancer of the mast cells (e.g., mastocytoma, mast cell leukemia, mast cell sarcoma, systemic mastocytosis), bone cancer, colorectal cancer, pancreatic cancer, diseases of the bone and joints including, without limitation, rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome, systemic sclerosis, osteoporosis, bone cancer, bone metastasis, a thromboembolic disorder, (e.g., myocardial infarct, angina pectoris, reocclusion after angioplasty, restenosis after angioplasty, reocclusion after aortocoronary bypass, restenosis after aortocoronary bypass, stroke, transitory ischemia, a peripheral arterial occlusive disorder, pulmonary embolism, deep venous thrombosis), inflammatory pelvic disease, urethritis, skin sunburn, sinusitis, pneumonitis, encephalitis, meningitis, myocarditis, nephritis, osteomyelitis, myositis, hepatitis, gastritis, enteritis, dermatitis, gingivitis, appendicitis, pancreatitis, cholecystitis, agammaglobulinemia, psoriasis, allergy, Crohn's disease, irritable bowel syndrome, ulcerative colitis, Sjogren's disease, tissue graft rejection, hyperacute rejection of transplanted organs, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), autoimmune polyglandular disease (also known as autoimmune polyglandular

syndrome), autoimmune alopecia, pernicious anemia, glomerulonephritis, dermatomyositis, multiple sclerosis, scleroderma, vasculitis, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome, atherosclerosis, Addison's disease, Parkinson's disease, Alzheimer's disease, diabetes, septic shock, systemic lupus erythematosus (SLE), rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, osteoarthritis, chronic idiopathic thrombocytopenic purpura, Waldenstrom macroglobulinemia, myasthenia gravis, Hashimoto's thyroiditis, atopic dermatitis, degenerative joint disease, vitiligo, autoimmune hypopituitarism, Guillain-Barre syndrome, Behcet's disease, scleroderma, mycosis fungoides, acute inflammatory responses (such as acute respiratory distress syndrome and ischemia/reperfusion injury), and Graves' disease.

[00625] In another embodiment, the present invention provides a method of treating or lessening the severity of a disease comprising administering to a patient in need thereof a provided compound and a PI3K inhibitor, wherein the disease is selected from a cancer, a neurodegenerative disorder, an angiogenic disorder, a viral disease, an autoimmune disease, an inflammatory disorder, a hormone-related disease, conditions associated with organ transplantation, immunodeficiency disorders, a destructive bone disorder, a proliferative disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), liver disease, pathologic immune conditions involving T cell activation, a cardiovascular disorder, and a CNS disorder.

[00626] In another embodiment, the present invention provides a method of treating or lessening the severity of a disease comprising administering to a patient in need thereof a provided compound and a PI3K inhibitor, wherein the disease is selected from benign or malignant tumor, carcinoma or solid tumor of the brain, kidney (e.g., renal cell carcinoma (RCC)), liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina, endometrium, cervix, testis, genitourinary tract, esophagus, larynx, skin, bone or thyroid, sarcoma, glioblastomas, neuroblastomas, multiple myeloma or gastrointestinal cancer, especially colon carcinoma or colorectal adenoma or a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, adenoma, adenocarcinoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small-cell lung carcinoma, lymphomas, (including, for example, non-Hodgkin's Lymphoma (NHL) and Hodgkin's lymphoma (also termed Hodgkin's or Hodgkin's disease)), a mammary carcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, or a leukemia, diseases include Cowden syndrome, Lhermitte-Duclos disease and Bannayan-Zonana syndrome, or diseases in which the PI3K/PKB pathway is aberrantly activated, asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe

asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection, acute lung injury (ALI), adult/acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy, bronchitis of whatever type or genesis including, but not limited to, acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis, pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis, Loffler's syndrome, eosinophilic, pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma and eosinophil-related disorders affecting the airways occasioned by drug-reaction, psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphigus, epidermolysis bullosa acquisita, conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or etiology, including autoimmune hematological disorders (e.g. hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia), systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), endocrine ophthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy, restenosis, cardiomegaly, atherosclerosis, myocardial infarction, ischemic stroke and congestive heart failure, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and cerebral ischemia, and neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity and hypoxia.

[00627] In some embodiments, one or more other therapeutic agent is a phosphatidylinositol 3 kinase (PI3K) inhibitor. In some embodiments, a PI3K inhibitor is selected from idelalisib (Zydelig®, Gilead), alpelisib (BYL719, Novartis), taselisib (GDC-0032, Genentech/Roche); pictilisib (GDC-0941, Genentech/Roche); copanlisib (BAY806946, Bayer); duvelisib (formerly IPI-145, Infinity

Pharmaceuticals); PQR309 (Piquar Therapeutics, Switzerland); and TGR1202 (formerly RP5230, TG Therapeutics).

[00628] The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a cancer, an autoimmune disorder, a proliferative disorder, an inflammatory disorder, a neurodegenerative or neurological disorder, schizophrenia, a bone-related disorder, liver disease, or a cardiac disorder. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. Compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein 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 the present invention 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.

[00629] Pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00630] 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, 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 can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00631] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00632] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00633] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00634] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00635] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound 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, for example,

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 may also comprise buffering agents.

[00636] Solid compositions of a similar type may also 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. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, 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 may also 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.

[00637] The active compounds can also 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 may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, 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.

[00638] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also

contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00639] According to one embodiment, the invention relates to a method of inhibiting protein kinase activity or degrading a protein kinase in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[00640] According to another embodiment, the invention relates to a method of inhibiting or degrading STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, or STAT6, or a mutant thereof, activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[00641] The term “biological sample”, as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00642] Inhibition and/or degradation of a STAT protein, or a protein selected from STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, or STAT6, or a mutant thereof, activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

[00643] Another embodiment of the present invention relates to a method of degrading a protein kinase and/or inhibiting protein kinase activity in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound.

[00644] According to another embodiment, the invention relates to a method of degrading and/or inhibiting one or more of STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, or STAT6, or a mutant thereof, activity in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound. In other embodiments, the present invention provides a method for treating a disorder mediated by one or more of STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, or STAT6, or a mutant thereof, in a patient in need thereof, comprising the step of administering to said patient a compound according to the present invention or pharmaceutically acceptable composition thereof. Such disorders are described in detail herein.

[00645] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents

that are normally administered to treat that condition, may also be present in the compositions of this invention. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as “appropriate for the disease, or condition, being treated.”

[00646] A compound of the current invention may also be used to advantage in combination with other antiproliferative compounds. Such antiproliferative compounds include, but are not limited to aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active compounds; alkylating compounds; histone deacetylase inhibitors; compounds which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibitors; mTOR inhibitors; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; matrix metalloproteinase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; compounds used in the treatment of hematologic malignancies; compounds which target, decrease or inhibit the activity of Flt-3; Hsp90 inhibitors such as 17-AAG (17-allylaminogeldanamycin, NSC330507), 17-DMAG (17-dimethylaminoethylamino-17-demethoxy-geldanamycin, NSC707545), IPI-504, CNF1010, CNF2024, CNF1010 from Conforma Therapeutics; temozolomide (Temodal®); kinesin spindle protein inhibitors, such as SB715992 or SB743921 from GlaxoSmithKline, or pentamidine/chlorpromazine from CombinatoRx; MEK inhibitors such as ARRY142886 from Array BioPharma, AZD6244 from AstraZeneca, PD181461 from Pfizer and leucovorin.

[00647] The term "aromatase inhibitor" as used herein relates to a compound which inhibits estrogen production, for instance, the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to steroids, especially atamestane, exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane is marketed under the trade name Aromasin™. Formestane is marketed under the trade name Lentaron™. Fadrozole is marketed under the trade name Afema™. Anastrozole is marketed under the trade name Arimidex™. Letrozole is marketed under the trade names Femara™ or Femar™. Aminoglutethimide is marketed under the trade name Orimeten™. A combination of the invention comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, such as breast tumors.

[00648] In some embodiments, one or more other therapeutic agent is an mTOR inhibitor, which inhibits cell proliferation, angiogenesis and glucose uptake. In some embodiments, an mTOR inhibitor is everolimus (Afinitor®, Novartis); temsirolimus (Torisel®, Pfizer); and sirolimus (Rapamune®, Pfizer).

[00649] In some embodiments, one or more other therapeutic agent is an aromatase inhibitor. In some embodiments, an aromatase inhibitor is selected from exemestane (Aromasin®, Pfizer); anastrozole (Arimidex®, AstraZeneca) and letrozole (Femara®, Novartis).

[00650] The term "antiestrogen" as used herein relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. Tamoxifen is marketed under the trade name Nolvadex™. Raloxifene hydrochloride is marketed under the trade name Evista™. Fulvestrant can be administered under the trade name Faslodex™. A combination of the invention comprising a chemotherapeutic agent which is an antiestrogen is particularly useful for the treatment of estrogen receptor positive tumors, such as breast tumors.

[00651] The term "anti-androgen" as used herein relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide (Casodex™). The term "gonadorelin agonist" as used herein includes, but is not limited to abarelix, goserelin and goserelin acetate. Goserelin can be administered under the trade name Zoladex™.

[00652] The term "topoisomerase I inhibitor" as used herein includes, but is not limited to topotecan, gimatecan, irinotecan, camptothecin and its analogues, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148. Irinotecan can be administered, e.g. in the form as it is marketed, e.g. under the trademark Camptosar™. Topotecan is marketed under the trade name Hycamtin™.

[00653] The term "topoisomerase II inhibitor" as used herein includes, but is not limited to the anthracyclines such as doxorubicin (including liposomal formulation, such as Caelyx™), daunorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophyllotoxines etoposide and teniposide. Etoposide is marketed under the trade name Etopophos™. Teniposide is marketed under the trade name VM 26-Bristol. Doxorubicin is marketed under the trade name Acridin™ or Adriamycin™. Epirubicin is marketed under the trade name Farmorubicin™. Idarubicin is marketed under the trade name Zavedos™. Mitoxantrone is marketed under the trade name Novantron.

[00654] The term "microtubule active agent" relates to microtubule stabilizing, microtubule destabilizing compounds and microtubulin polymerization inhibitors including, but not limited to taxanes, such as paclitaxel and docetaxel; vinca alkaloids, such as vinblastine or vinblastine sulfate, vincristine or vincristine sulfate, and vinorelbine; discodermolides; cochicine and epothilones and derivatives thereof. Paclitaxel is marketed under the trade name Taxol™. Docetaxel is marketed under the trade name

Taxotere™. Vinblastine sulfate is marketed under the trade name Vinblastin R.P™. Vincristine sulfate is marketed under the trade name Farmistin™.

[00655] The term "alkylating agent" as used herein includes, but is not limited to, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel). Cyclophosphamide is marketed under the trade name Cyclostin™. Ifosfamide is marketed under the trade name Holoxan™.

[00656] The term "histone deacetylase inhibitors" or "HDAC inhibitors" relates to compounds which inhibit the histone deacetylase and which possess antiproliferative activity. This includes, but is not limited to, suberoylanilide hydroxamic acid (SAHA).

[00657] The term "antineoplastic antimetabolite" includes, but is not limited to, 5-fluorouracil or 5-FU, capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists such as pemetrexed. Capecitabine is marketed under the trade name Xeloda™. Gemcitabine is marketed under the trade name Gemzar™.

[00658] The term "platin compound" as used herein includes, but is not limited to, carboplatin, cisplatin, cisplatinum and oxaliplatin. Carboplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark Carboplat™. Oxaliplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark Eloxatin™.

[00659] The term "Bcl-2 inhibitor" as used herein includes, but is not limited to compounds having inhibitory activity against B-cell lymphoma 2 protein (Bcl-2), including but not limited to ABT-199, ABT-731, ABT-737, apogossypol, Ascenta's pan-Bcl-2 inhibitors, curcumin (and analogs thereof), dual Bcl-2/Bcl-xL inhibitors (Infinity Pharmaceuticals/Novartis Pharmaceuticals), Genasense (G3139), HA14-1 (and analogs thereof; see WO2008118802), navitoclax (and analogs thereof, see US7390799), NH-1 (Shenayng Pharmaceutical University), obatoclax (and analogs thereof, see WO2004106328), S-001 (Gloria Pharmaceuticals), TW series compounds (Univ. of Michigan), and venetoclax. In some embodiments the Bcl-2 inhibitor is a small molecule therapeutic. In some embodiments the Bcl-2 inhibitor is a peptidomimetic.

[00660] The term "compounds targeting/decreasing a protein or lipid kinase activity; or a protein or lipid phosphatase activity; or further anti-angiogenic compounds" as used herein includes, but is not limited to, protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, such as a) compounds targeting, decreasing or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as compounds which target, decrease or inhibit the activity of PDGFR, especially compounds which inhibit the PDGF receptor, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib, SU101, SU6668 and GFB-111; b) compounds targeting, decreasing or inhibiting the activity of the fibroblast growth factor-receptors (FGFR); c) compounds targeting, decreasing or inhibiting the activity

of the insulin-like growth factor receptor I (IGF-IR), such as compounds which target, decrease or inhibit the activity of IGF-IR, especially compounds which inhibit the kinase activity of IGF-I receptor, or antibodies that target the extracellular domain of IGF-I receptor or its growth factors; d) compounds targeting, decreasing or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors; e) compounds targeting, decreasing or inhibiting the activity of the Axl receptor tyrosine kinase family; f) compounds targeting, decreasing or inhibiting the activity of the Ret receptor tyrosine kinase; g) compounds targeting, decreasing or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, such as imatinib; h) compounds targeting, decreasing or inhibiting the activity of the C-kit receptor tyrosine kinases, which are part of the PDGFR family, such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine kinase family, especially compounds which inhibit the c-Kit receptor, such as imatinib; i) compounds targeting, decreasing or inhibiting the activity of members of the c-Abl family, their gene-fusion products (e.g. BCR-Abl kinase) and mutants, such as compounds which target decrease or inhibit the activity of c-Abl family members and their gene fusion products, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib or nilotinib (AMN107); PD180970; AG957; NSC 680410; PD173955 from ParkeDavis; or dasatinib (BMS-354825); j) compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK/pan-JAK, FAK, PDK1, PKB/Akt, Ras/MAPK, PI3K, SYK, TYK2, BTK and TEC family, and/or members of the cyclin-dependent kinase family (CDK) including staurosporine derivatives, such as midostaurin; examples of further compounds include UCN-01, safingol, BAY 43-9006, Bryostatin 1, Perifosine; Ilmofofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; isochinoline compounds; FTIs; PD184352 or QAN697 (a P13K inhibitor) or AT7519 (CDK inhibitor); k) compounds targeting, decreasing or inhibiting the activity of protein-tyrosine kinase inhibitors, such as compounds which target, decrease or inhibit the activity of protein-tyrosine kinase inhibitors include imatinib mesylate (Gleevec™) or tyrphostin such as Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin); l) compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR₁ ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, such as EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, CP 358774, ZD 1839, ZM 105180; trastuzumab (Herceptin™), cetuximab (Erbix™), Iressa, Tarceva, OSI-774, CI-1033, EKB-

569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives; m) compounds targeting, decreasing or inhibiting the activity of the c-Met receptor, such as compounds which target, decrease or inhibit the activity of c-Met, especially compounds which inhibit the kinase activity of c-Met receptor, or antibodies that target the extracellular domain of c-Met or bind to HGF, n) compounds targeting, decreasing or inhibiting the kinase activity of one or more JAK family members (JAK1/JAK2/JAK3/TYK2 and/or pan-JAK), including but not limited to PRT-062070, SB-1578, baricitinib, pacritinib, momelotinib, VX-509, AZD-1480, TG-101348, tofacitinib, and ruxolitinib; o) compounds targeting, decreasing or inhibiting the kinase activity of PI3 kinase (PI3K) including but not limited to ATU-027, SF-1126, DS-7423, PBI-05204, GSK-2126458, ZSTK-474, buparlisib, pictrelisib, PF-4691502, BYL-719, dactolisib, XL-147, XL-765, and idelalisib; and; and q) compounds targeting, decreasing or inhibiting the signaling effects of hedgehog protein (Hh) or smoothened receptor (SMO) pathways, including but not limited to cyclopamine, vismodegib, itraconazole, erismodegib, and IPI-926 (saridegib).

[00661] Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are e.g. inhibitors of phosphatase 1, phosphatase 2A, or CDC25, such as okadaic acid or a derivative thereof.

[00662] In some embodiments, one or more other therapeutic agent is a growth factor antagonist, such as an antagonist of platelet-derived growth factor (PDGF), or epidermal growth factor (EGF) or its receptor (EGFR). Approved PDGF antagonists which may be used in the present invention include olaratumab (Lartruvo®, Eli Lilly). Approved EGFR antagonists which may be used in the present invention include cetuximab (Erbix®, Eli Lilly); necitumumab (Portrazza®, Eli Lilly), panitumumab (Vectibix®, Amgen); and osimertinib (targeting activated EGFR, Tagrisso®, AstraZeneca).

[00663] The term “PI3K inhibitor” as used herein includes, but is not limited to compounds having inhibitory activity against one or more enzymes in the phosphatidylinositol-3-kinase family, including, but not limited to PI3K α , PI3K γ , PI3K δ , PI3K β , PI3K-C2 α , PI3K-C2 β , PI3K-C2 γ , Vps34, p110- α , p110- β , p110- γ , p110- δ , p85- α , p85- β , p55- γ , p150, p101, and p87. Examples of PI3K inhibitors useful in this invention include but are not limited to ATU-027, SF-1126, DS-7423, PBI-05204, GSK-2126458, ZSTK-474, buparlisib, pictrelisib, PF-4691502, BYL-719, dactolisib, XL-147, XL-765, and idelalisib.

[00664] The term “BTK inhibitor” as used herein includes, but is not limited to compounds having inhibitory activity against Bruton's Tyrosine Kinase (BTK), including, but not limited to AVL-292 and ibrutinib.

[00665] The term “SYK inhibitor” as used herein includes, but is not limited to compounds having inhibitory activity against spleen tyrosine kinase (SYK), including but not limited to PRT-062070, R-343, R-333, Excellair, PRT-062607, and fostamatinib

[00666] Further examples of BTK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO2008039218 and WO2011090760, the entirety of which are incorporated herein by reference.

[00667] Further examples of SYK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO2003063794, WO2005007623, and WO2006078846, the entirety of which are incorporated herein by reference.

[00668] Further examples of PI3K inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO2004019973, WO2004089925, WO2007016176, US8138347, WO2002088112, WO2007084786, WO2007129161, WO2006122806, WO2005113554, and WO2007044729 the entirety of which are incorporated herein by reference.

[00669] Further examples of JAK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO2009114512, WO2008109943, WO2007053452, WO2000142246, and WO2007070514, the entirety of which are incorporated herein by reference.

[00670] Further anti-angiogenic compounds include compounds having another mechanism for their activity, e.g. unrelated to protein or lipid kinase inhibition e.g. thalidomide (Thalomid™) and TNP-470.

[00671] Examples of proteasome inhibitors useful for use in combination with compounds of the invention include, but are not limited to bortezomib, disulfiram, epigallocatechin-3-gallate (EGCG), salinosporamide A, carfilzomib, ONX-0912, CEP-18770, and MLN9708.

[00672] Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are e.g. inhibitors of phosphatase 1, phosphatase 2A, or CDC25, such as okadaic acid or a derivative thereof.

[00673] Compounds which induce cell differentiation processes include, but are not limited to, retinoic acid, α - γ - or δ -tocopherol or α - γ - or δ -tocotrienol.

[00674] The term cyclooxygenase inhibitor as used herein includes, but is not limited to, Cox-2 inhibitors, 5-alkyl substituted 2-arylamino-phenylacetic acid and derivatives, such as celecoxib (Celebrex™), rofecoxib (Vioxx™), etoricoxib, valdecoxib or a 5-alkyl-2-arylamino-phenylacetic acid, such as 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid, lumiracoxib.

[00675] The term "bisphosphonates" as used herein includes, but is not limited to, etridronic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid. Etridronic acid is marketed under the trade name Didronel™. Clodronic acid is marketed under the trade name Bonefos™. Tiludronic acid is marketed under the trade name Skelid™. Pamidronic acid is marketed under the trade name Aredia™. Alendronic acid is marketed under the trade name Fosamax™. Ibandronic acid is marketed under the trade name Bondranat™. Risedronic acid is marketed under the trade name Actonel™. Zoledronic acid

is marketed under the trade name Zometa™. The term "mTOR inhibitors" relates to compounds which inhibit the mammalian target of rapamycin (mTOR) and which possess antiproliferative activity such as sirolimus (Rapamune®), everolimus (Certican™), CCI-779 and ABT578.

[00676] The term "heparanase inhibitor" as used herein refers to compounds which target, decrease or inhibit heparin sulfate degradation. The term includes, but is not limited to, PI-88. The term "biological response modifier" as used herein refers to a lymphokine or interferons.

[00677] The term "inhibitor of Ras oncogenic isoforms", such as H-Ras, K-Ras, or N-Ras, as used herein refers to compounds which target, decrease or inhibit the oncogenic activity of Ras; for example, a "farnesyl transferase inhibitor" such as L-744832, DK8G557 or R115777 (Zarnestra™). The term "telomerase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of telomerase. Compounds which target, decrease or inhibit the activity of telomerase are especially compounds which inhibit the telomerase receptor, such as telomestatin.

[00678] The term "methionine aminopeptidase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of methionine aminopeptidase. Compounds which target, decrease or inhibit the activity of methionine aminopeptidase include, but are not limited to, bengamide or a derivative thereof.

[00679] The term "proteasome inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of the proteasome. Compounds which target, decrease or inhibit the activity of the proteasome include, but are not limited to, Bortezomib (Velcade™,); carfilzomib (Kyprolis®, Amgen); and ixazomib (Ninlaro®, Takeda), and MLN 341.

[00680] The term "matrix metalloproteinase inhibitor" or ("MMP" inhibitor) as used herein includes, but is not limited to, collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, e.g. hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat (BB-2516), prinomastat (AG3340), metastat (NSC 683551) BMS-279251, BAY 12-9566, TAA211, MMI270B or AAJ996.

[00681] The term "compounds used in the treatment of hematologic malignancies" as used herein includes, but is not limited to, FMS-like tyrosine kinase inhibitors, which are compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, 1-β-D-arabinofuransylcytosine (ara-c) and bisulfan; and ALK inhibitors, which are compounds which target, decrease or inhibit anaplastic lymphoma kinase.

[00682] Compounds which target, decrease or inhibit the activity of FMS-like tyrosine kinase receptors (Flt-3R) are especially compounds, proteins or antibodies which inhibit members of the Flt-3R receptor kinase family, such as PKC412, midostaurin, a staurosporine derivative, SU11248 and MLN518.

[00683] The term "HSP90 inhibitors" as used herein includes, but is not limited to, compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90; degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteasome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins or antibodies which inhibit the ATPase activity of HSP90, such as 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors.

[00684] The term "antiproliferative antibodies" as used herein includes, but is not limited to, trastuzumab (Herceptin™), Trastuzumab-DM1, erbitux, bevacizumab (Avastin™), rituximab (Rituxan®), PRO64553 (anti-CD40) and 2C4 Antibody. By antibodies is meant intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.

[00685] For the treatment of acute myeloid leukemia (AML), compounds of the current invention can be used in combination with standard leukemia therapies, especially in combination with therapies used for the treatment of AML. In particular, compounds of the current invention can be administered in combination with, for example, farnesyl transferase inhibitors and/or other drugs useful for the treatment of AML, such as Daunorubicin, Adriamycin, Ara-C, VP-16, Teniposide, Mitoxantrone, Idarubicin, Carboplatinum and PKC412.

[00686] Other anti-leukemic compounds include, for example, Ara-C, a pyrimidine analog, which is the 2'-alpha-hydroxy ribose (arabinoside) derivative of deoxycytidine. Also included is the purine analog of hypoxanthine, 6-mercaptopurine (6-MP) and fludarabine phosphate. Compounds which target, decrease or inhibit activity of histone deacetylase (HDAC) inhibitors such as sodium butyrate and suberoylanilide hydroxamic acid (SAHA) inhibit the activity of the enzymes known as histone deacetylases. Specific HDAC inhibitors include MS275, SAHA, FK228 (formerly FR901228), Trichostatin A and compounds disclosed in US 6,552,065 including, but not limited to, N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)-ethyl]- amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof and N-hydroxy-3-[4-[(2-hydroxyethyl){2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof, especially the lactate salt. Somatostatin receptor antagonists as used herein refer to compounds which target, treat or inhibit the somatostatin receptor such as octreotide, and SOM230. Tumor cell damaging approaches refer to approaches such as ionizing radiation. The term "ionizing radiation" referred to above and hereinafter means ionizing radiation that occurs as either electromagnetic rays (such as X-rays and gamma rays) or particles (such as alpha and beta particles). Ionizing radiation is provided in, but not limited to, radiation therapy and is known in the art. See Hellman,

Principles of Radiation Therapy, Cancer, in Principles and Practice of Oncology, Devita et al., Eds., 4th Edition, Vol. 1, pp. 248-275 (1993).

[00687] Also included are EDG binders and ribonucleotide reductase inhibitors. The term “EDG binders” as used herein refers to a class of immunosuppressants that modulates lymphocyte recirculation, such as FTY720. The term “ribonucleotide reductase inhibitors” refers to pyrimidine or purine nucleoside analogs including, but not limited to, fludarabine and/or cytosine arabinoside (ara-C), 6-thioguanine, 5-fluorouracil, cladribine, 6-mercaptopurine (especially in combination with ara-C against ALL) and/or pentostatin. Ribonucleotide reductase inhibitors are especially hydroxyurea or 2-hydroxy-1H-isoindole-1,3-dione derivatives.

[00688] Also included are in particular those compounds, proteins or monoclonal antibodies of VEGF such as 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine succinate; AngiostatinTM; EndostatinTM; anthranilic acid amides; ZD4190; ZD6474; SU5416; SU6668; bevacizumab; or anti-VEGF antibodies or anti-VEGF receptor antibodies, such as rhuMab and RHUFab, VEGF aptamer such as Macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgG1 antibody, Angiozyme (RPI 4610) and Bevacizumab (AvastinTM).

[00689] Photodynamic therapy as used herein refers to therapy which uses certain chemicals known as photosensitizing compounds to treat or prevent cancers. Examples of photodynamic therapy include treatment with compounds, such as VisudyneTM and porfimer sodium.

[00690] Angiostatic steroids as used herein refers to compounds which block or inhibit angiogenesis, such as, e.g., anecortave, triamcinolone, hydrocortisone, 11- α -epihydrocortisol, cortexolone, 17 α -hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone and dexamethasone.

[00691] Implants containing corticosteroids refers to compounds, such as fluocinolone and dexamethasone.

[00692] Other chemotherapeutic compounds include, but are not limited to, plant alkaloids, hormonal compounds and antagonists; biological response modifiers, preferably lymphokines or interferons; antisense oligonucleotides or oligonucleotide derivatives; shRNA or siRNA; or miscellaneous compounds or compounds with other or unknown mechanism of action.

[00693] The compounds of the invention are also useful as co-therapeutic compounds for use in combination with other drug substances such as anti-inflammatory, bronchodilatory or antihistamine drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. A compound of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered

separately, before, simultaneously with or after the other drug substance. Accordingly the invention includes a combination of a compound of the invention as hereinbefore described with an anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substance, said compound of the invention and said drug substance being in the same or different pharmaceutical composition.

[00694] Suitable anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone dipropionate, fluticasone propionate, ciclesonide or mometasone furoate; non-steroidal glucocorticoid receptor agonists; LTB₄ antagonists such LY293111, CGS025019C, CP-195543, SC-53228, BIIL 284, ONO 4057, SB 209247; LTD₄ antagonists such as montelukast and zafirlukast; PDE4 inhibitors such cilomilast (Ariflo® GlaxoSmithKline), Roflumilast (Byk Gulden), V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering- Plough), Arofyline (Almirall Prodesfarma), PD189659 / PD168787 (Parke-Davis), AWD-12- 281 (Asta Medica), CDC-801 (Celgene), SeICID(TM) CC-10004 (Celgene), VM554/UM565 (Vernalis), T-440 (Tanabe), KW-4490 (Kyowa Hakko Kogyo); A_{2a} agonists; A_{2b} antagonists; and beta-2 adrenoceptor agonists such as albuterol (salbutamol), metaproterenol, terbutaline, salmeterol fenoterol, procaterol, and especially, formoterol and pharmaceutically acceptable salts thereof. Suitable bronchodilatory drugs include anticholinergic or antimuscarinic compounds, in particular ipratropium bromide, oxitropium bromide, tiotropium salts and CHF 4226 (Chiesi), and glycopyrrolate.

[00695] Suitable antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride, activastine, astemizole, azelastine, ebastine, epinastine, mizolastine and tefenadine.

[00696] Other useful combinations of compounds of the invention with anti-inflammatory drugs are those with antagonists of chemokine receptors, e.g. CCR-1, CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 and CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, particularly CCR-5 antagonists such as Schering-Plough antagonists SC-351125, SCH- 55700 and SCH-D, and Takeda antagonists such as N-[[4-[[[6,7-dihydro-2-(4-methylphenyl)-5H-benzo-cyclohepten-8-yl]carbonyl]amino]phenyl]-methyl]tetrahydro-N,N-dimethyl-2H-pyran-4-aminium chloride (TAK-770).

[00697] The structure of the active compounds identified by code numbers, generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications).

[00698] A compound of the current invention may also be used in combination with known therapeutic processes, for example, the administration of hormones or radiation. In certain embodiments, a provided compound is used as a radiosensitizer, especially for the treatment of tumors which exhibit poor sensitivity to radiotherapy.

[00699] A compound of the current invention can be administered alone or in combination with one or more other therapeutic compounds, possible combination therapy taking the form of fixed combinations or the administration of a compound of the invention and one or more other therapeutic compounds being staggered or given independently of one another, or the combined administration of fixed combinations and one or more other therapeutic compounds. A compound of the current invention can besides or in addition be administered especially for tumor therapy in combination with chemotherapy, radiotherapy, immunotherapy, phototherapy, surgical intervention, or a combination of these. Long-term therapy is equally possible as is adjuvant therapy in the context of other treatment strategies, as described above. Other possible treatments are therapy to maintain the patient's status after tumor regression, or even chemopreventive therapy, for example in patients at risk.

[00700] Those additional agents may be administered separately from an inventive compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another normally within five hours from one another.

[00701] As used herein, the term “combination,” “combined,” and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a compound of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising a compound of the current invention, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[00702] The amount of both an inventive compound and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, compositions of this invention should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of an inventive compound can be administered.

[00703] In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound of this invention may act synergistically. Therefore, the amount of additional therapeutic agent in such compositions will be less than that required in a monotherapy utilizing only that therapeutic agent. In such compositions a dosage of between 0.01 – 1,000 µg/kg body weight/day of the additional therapeutic agent can be administered.

[00704] The amount of one or more other therapeutic agent present in the compositions of this invention may be no more than the amount that would normally be administered in a composition comprising that

therapeutic agent as the only active agent. Preferably the amount of one or more other 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. In some embodiments, one or more other therapeutic agent is administered at a dosage of about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95% of the amount normally administered for that agent. As used herein, the phrase “normally administered” means the amount an FDA approved therapeutic agent is provided for dosing per the FDA label insert.

[00705] The compounds of this invention, or pharmaceutical compositions thereof, may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition comprising a kinase inhibitor. Implantable devices coated with a compound of this invention are another embodiment of the present invention.

Exemplary Immuno-Oncology agents

[00706] In some embodiments, one or more other therapeutic agent is an immuno-oncology agent. As used herein, the term “an immuno-oncology agent” refers to an agent which is effective to enhance, stimulate, and/or up-regulate immune responses in a subject. In some embodiments, the administration of an immuno-oncology agent with a compound of the invention has a synergic effect in treating a cancer.

[00707] An immuno-oncology agent can be, for example, a small molecule drug, an antibody, or a biologic or small molecule. Examples of biologic immuno-oncology agents include, but are not limited to, cancer vaccines, antibodies, and cytokines. In some embodiments, an antibody is a monoclonal antibody. In some embodiments, a monoclonal antibody is humanized or human.

[00708] In some embodiments, an immuno-oncology agent is (i) an agonist of a stimulatory (including a co-stimulatory) receptor or (ii) an antagonist of an inhibitory (including a co-inhibitory) signal on T cells, both of which result in amplifying antigen-specific T cell responses.

[00709] Certain of the stimulatory and inhibitory molecules are members of the immunoglobulin super family (IgSF). One important family of membrane-bound ligands that bind to co-stimulatory or co-inhibitory receptors is the B7 family, which includes B7-1, B7-2, B7-H1 (PD-L1), B7-DC (PD-L2), B7-H2 (ICOS-L), B7-H3, B7-H4, B7-H5 (VISTA), and B7-H6. Another family of membrane bound ligands that bind to co-stimulatory or co-inhibitory receptors is the TNF family of molecules that bind to cognate TNF

receptor family members, which includes CD40 and CD40L, OX-40, OX-40L, CD70, CD27L, CD30, CD30L, 4-1BBL, CD137 (4-1BB), TRAIL/Apo2-L, TRAILR1/DR4, TRAILR2/DR5, TRAILR3, TRAILR4, OPG, RANK, RANKL, TWEAKR/Fn14, TWEAK, BAFFR, EDAR, XEDAR, TACI, APRIL, BCMA, LT β R, LIGHT, DcR3, HVEM, VEGI/TL1A, TRAMP/DR3, EDAR, EDA1, XEDAR, EDA2, TNFR1, Lymphotoxin α /TNF β , TNFR2, TNF α , LT β R, Lymphotoxin α 1 β 2, FAS, FASL, RELT, DR6, TROY, NGFR.

[00710] In some embodiments, an immuno-oncology agent is a cytokine that inhibits T cell activation (e.g., IL-6, IL-10, TGF- β , VEGF, and other immunosuppressive cytokines) or a cytokine that stimulates T cell activation, for stimulating an immune response.

[00711] In some embodiments, a combination of a compound of the invention and an immuno-oncology agent can stimulate T cell responses. In some embodiments, an immuno-oncology agent is: (i) an antagonist of a protein that inhibits T cell activation (e.g., immune checkpoint inhibitors) such as CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, TIM-3, Galectin 9, CEACAM-1, BTLA, CD69, Galectin-1, TIGIT, CD113, GPR56, VISTA, 2B4, CD48, GARP, PD1H, LAIR1, TIM-1, and TIM-4; or (ii) an agonist of a protein that stimulates T cell activation such as B7-1, B7-2, CD28, 4-1BB (CD137), 4-1BBL, ICOS, ICOS-L, OX40, OX40L, GITR, GITRL, CD70, CD27, CD40, DR3 and CD28H.

[00712] In some embodiments, an immuno-oncology agent is an antagonist of inhibitory receptors on NK cells or an agonists of activating receptors on NK cells. In some embodiments, an immuno-oncology agent is an antagonists of KIR, such as lirilumab.

[00713] In some embodiments, an immuno-oncology agent is an agent that inhibits or depletes macrophages or monocytes, including but not limited to CSF-1R antagonists such as CSF-1R antagonist antibodies including RG7155 (WO11/70024, WO11/107553, WO11/131407, WO13/87699, WO13/119716, WO13/132044) or FPA-008 (WO11/140249; WO13169264; WO14/036357).

[00714] In some embodiments, an immuno-oncology agent is selected from agonistic agents that ligate positive costimulatory receptors, blocking agents that attenuate signaling through inhibitory receptors, antagonists, and one or more agents that increase systemically the frequency of anti-tumor T cells, agents that overcome distinct immune suppressive pathways within the tumor microenvironment (e.g., block inhibitory receptor engagement (e.g., PD-L1/PD-1 interactions), deplete or inhibit Tregs (e.g., using an anti-CD25 monoclonal antibody (e.g., daclizumab) or by ex vivo anti-CD25 bead depletion), inhibit metabolic enzymes such as IDO, or reverse/prevent T cell energy or exhaustion) and agents that trigger innate immune activation and/or inflammation at tumor sites.

[00715] In some embodiments, an immuno-oncology agent is a CTLA-4 antagonist. In some embodiments, a CTLA-4 antagonist is an antagonistic CTLA-4 antibody. In some embodiments, an antagonistic CTLA-4 antibody is YERVOY (ipilimumab) or tremelimumab.

[00716] In some embodiments, an immuno-oncology agent is a PD-1 antagonist. In some embodiments, a PD-1 antagonist is administered by infusion. In some embodiments, an immuno-oncology agent is an antibody or an antigen-binding portion thereof that binds specifically to a Programmed Death-1 (PD-1) receptor and inhibits PD-1 activity. In some embodiments, a PD-1 antagonist is an antagonistic PD-1 antibody. In some embodiments, an antagonistic PD-1 antibody is OPDIVO (nivolumab), KEYTRUDA (pembrolizumab), or MEDI-0680 (AMP-514; WO2012/145493). In some embodiments, an immuno-oncology agent may be pidilizumab (CT-011). In some embodiments, an immuno-oncology agent is a recombinant protein composed of the extracellular domain of PD-L2 (B7-DC) fused to the Fc portion of IgG1, called AMP-224.

[00717] In some embodiments, an immuno-oncology agent is a PD-L1 antagonist. In some embodiments, a PD-L1 antagonist is an antagonistic PD-L1 antibody. In some embodiments, a PD-L1 antibody is MPDL3280A (RG7446; WO2010/077634), durvalumab (MEDI4736), BMS-936559 (WO2007/005874), and MSB0010718C (WO2013/79174).

[00718] In some embodiments, an immuno-oncology agent is a LAG-3 antagonist. In some embodiments, a LAG-3 antagonist is an antagonistic LAG-3 antibody. In some embodiments, a LAG3 antibody is BMS-986016 (WO10/19570, WO14/08218), or IMP-731 or IMP-321 (WO08/132601, WO009/44273).

[00719] In some embodiments, an immuno-oncology agent is a CD137 (4-1BB) agonist. In some embodiments, a CD137 (4-1BB) agonist is an agonistic CD137 antibody. In some embodiments, a CD137 antibody is urelumab or PF-05082566 (WO12/32433).

[00720] In some embodiments, an immuno-oncology agent is a GITR agonist. In some embodiments, a GITR agonist is an agonistic GITR antibody. In some embodiments, a GITR antibody is BMS-986153, BMS-986156, TRX-518 (WO006/105021, WO009/009116), or MK-4166 (WO11/028683).

[00721] In some embodiments, an immuno-oncology agent is an indoleamine (2,3)-dioxygenase (IDO) antagonist. In some embodiments, an IDO antagonist is selected from epacadostat (INCB024360, Incyte); indoximod (NLG-8189, NewLink Genetics Corporation); capmanitib (INC280, Novartis); GDC-0919 (Genentech/Roche); PF-06840003 (Pfizer); BMS:F001287 (Bristol-Myers Squibb); Phy906/KD108 (Phytoceutica); an enzyme that breaks down kynurenine (Kynase, Kyn Therapeutics); and NLG-919 (WO09/73620, WO009/1156652, WO11/56652, WO12/142237).

[00722] In some embodiments, an immuno-oncology agent is an OX40 agonist. In some embodiments, an OX40 agonist is an agonistic OX40 antibody. In some embodiments, an OX40 antibody is MEDI-6383 or MEDI-6469.

[00723] In some embodiments, an immuno-oncology agent is an OX40L antagonist. In some embodiments, an OX40L antagonist is an antagonistic OX40 antibody. In some embodiments, an OX40L antagonist is RG-7888 (WO06/029879).

[00724] In some embodiments, an immuno-oncology agent is a CD40 agonist. In some embodiments, a CD40 agonist is an agonistic CD40 antibody. In some embodiments, an immuno-oncology agent is a CD40 antagonist. In some embodiments, a CD40 antagonist is an antagonistic CD40 antibody. In some embodiments, a CD40 antibody is lucatumumab or dacetuzumab.

[00725] In some embodiments, an immuno-oncology agent is a CD27 agonist. In some embodiments, a CD27 agonist is an agonistic CD27 antibody. In some embodiments, a CD27 antibody is varlilumab.

[00726] In some embodiments, an immuno-oncology agent is MGA271 (to B7H3) (WO11/109400).

[00727] In some embodiments, an immuno-oncology agent is abagovomab, adecatumumab, afutuzumab, alemtuzumab, anatumomab mafenatox, apolizumab, atezolimab, avelumab, blinatumomab, BMS-936559, catumaxomab, durvalumab, epacadostat, epratuzumab, indoximod, inotuzumab ozogamicin, intelumumab, ipilimumab, isatuximab, lambrolizumab, MED14736, MPDL3280A, nivolumab, obinutuzumab, ocaratuzumab, ofatumumab, olatatumab, pembrolizumab, pidilizumab, rituximab, ticilimumab, samalizumab, or tremelimumab.

[00728] In some embodiments, an immuno-oncology agent is an immunostimulatory agent. For example, antibodies blocking the PD-1 and PD-L1 inhibitory axis can unleash activated tumor-reactive T cells and have been shown in clinical trials to induce durable anti-tumor responses in increasing numbers of tumor histologies, including some tumor types that conventionally have not been considered immunotherapy sensitive. See, e.g., Okazaki, T. *et al.* (2013) *Nat. Immunol.* 14, 1212–1218; Zou *et al.* (2016) *Sci. Transl. Med.* 8. The anti-PD-1 antibody nivolumab (Opdivo®, Bristol-Myers Squibb, also known as ONO-4538, MDX1106 and BMS-936558), has shown potential to improve the overall survival in patients with RCC who had experienced disease progression during or after prior anti-angiogenic therapy.

[00729] In some embodiments, the immunomodulatory therapeutic specifically induces apoptosis of tumor cells. Approved immunomodulatory therapeutics which may be used in the present invention include pomalidomide (Pomalyst®, Celgene); lenalidomide (Revlimid®, Celgene); ingenol mebutate (Picato®, LEO Pharma).

[00730] In some embodiments, an immuno-oncology agent is a cancer vaccine. In some embodiments, the cancer vaccine is selected from sipuleucel-T (Provenge®, Dendreon/Valeant Pharmaceuticals), which

has been approved for treatment of asymptomatic, or minimally symptomatic metastatic castrate-resistant (hormone-refractory) prostate cancer; and talimogene laherparepvec (Imlygic®, BioVex/Amgen, previously known as T-VEC), a genetically modified oncolytic viral therapy approved for treatment of unresectable cutaneous, subcutaneous and nodal lesions in melanoma. In some embodiments, an immuno-oncology agent is selected from an oncolytic viral therapy such as pexastimogene devacirepvec (PexaVec/JX-594, SillaJen/formerly Jennerex Biotherapeutics), a thymidine kinase- (TK-) deficient vaccinia virus engineered to express GM-CSF, for hepatocellular carcinoma (NCT02562755) and melanoma (NCT00429312); pelareorep (Reolysin®, Oncolytics Biotech), a variant of respiratory enteric orphan virus (reovirus) which does not replicate in cells that are not RAS-activated, in numerous cancers, including colorectal cancer (NCT01622543); prostate cancer (NCT01619813); head and neck squamous cell cancer (NCT01166542); pancreatic adenocarcinoma (NCT00998322); and non-small cell lung cancer (NSCLC) (NCT 00861627); enadenotucirev (NG-348, PsiOxus, formerly known as ColoAd1), an adenovirus engineered to express a full length CD80 and an antibody fragment specific for the T-cell receptor CD3 protein, in ovarian cancer (NCT02028117); metastatic or advanced epithelial tumors such as in colorectal cancer, bladder cancer, head and neck squamous cell carcinoma and salivary gland cancer (NCT02636036); ONCOS-102 (Targovax/formerly Oncos), an adenovirus engineered to express GM-CSF, in melanoma (NCT03003676); and peritoneal disease, colorectal cancer or ovarian cancer (NCT02963831); GL-ONC1 (GLV-1h68/GLV-1h153, Genelux GmbH), vaccinia viruses engineered to express beta-galactosidase (beta-gal)/beta-glucuronidase or beta-gal/human sodium iodide symporter (hNIS), respectively, were studied in peritoneal carcinomatosis (NCT01443260); fallopian tube cancer, ovarian cancer (NCT 02759588); or CG0070 (Cold Genesys), an adenovirus engineered to express GM-CSF, in bladder cancer (NCT02365818).

[00731] In some embodiments, an immuno-oncology agent is selected from JX-929 (SillaJen/formerly Jennerex Biotherapeutics), a TK- and vaccinia growth factor-deficient vaccinia virus engineered to express cytosine deaminase, which is able to convert the prodrug 5-fluorocytosine to the cytotoxic drug 5-fluorouracil; TG01 and TG02 (Targovax/formerly Oncos), peptide-based immunotherapy agents targeted for difficult-to-treat RAS mutations; and TILT-123 (TILT Biotherapeutics), an engineered adenovirus designated: Ad5/3-E2F-delta24-hTNF α -IRES-hIL20; and VSV-GP (ViraTherapeutics) a vesicular stomatitis virus (VSV) engineered to express the glycoprotein (GP) of lymphocytic choriomeningitis virus (LCMV), which can be further engineered to express antigens designed to raise an antigen-specific CD8⁺ T cell response.

[00732] In some embodiments, an immuno-oncology agent is a T-cell engineered to express a chimeric antigen receptor, or CAR. The T-cells engineered to express such chimeric antigen receptor are referred to as a CAR-T cells.

[00733] CARs have been constructed that consist of binding domains, which may be derived from natural ligands, single chain variable fragments (scFv) derived from monoclonal antibodies specific for cell-surface antigens, fused to endodomains that are the functional end of the T-cell receptor (TCR), such as the CD3-zeta signaling domain from TCRs, which is capable of generating an activation signal in T lymphocytes. Upon antigen binding, such CARs link to endogenous signaling pathways in the effector cell and generate activating signals similar to those initiated by the TCR complex.

[00734] For example, in some embodiments the CAR-T cell is one of those described in U.S. Patent 8,906,682 (June; hereby incorporated by reference in its entirety), which discloses CAR-T cells engineered to comprise an extracellular domain having an antigen binding domain (such as a domain that binds to CD19), fused to an intracellular signaling domain of the T cell antigen receptor complex zeta chain (such as CD3 zeta). When expressed in the T cell, the CAR is able to redirect antigen recognition based on the antigen binding specificity. In the case of CD19, the antigen is expressed on malignant B cells. Over 200 clinical trials are currently in progress employing CAR-T in a wide range of indications. [<https://clinicaltrials.gov/ct2/results?term=chimeric+antigen+receptors&pg=1>].

[00735] In some embodiments, an immunostimulatory agent is an activator of retinoic acid receptor-related orphan receptor γ (ROR γ t). ROR γ t is a transcription factor with key roles in the differentiation and maintenance of Type 17 effector subsets of CD4⁺ (Th17) and CD8⁺ (Tc17) T cells, as well as the differentiation of IL-17 expressing innate immune cell subpopulations such as NK cells. In some embodiments, an activator of ROR γ t is LYC-55716 (Lycera), which is currently being evaluated in clinical trials for the treatment of solid tumors (NCT02929862).

[00736] In some embodiments, an immunostimulatory agent is an agonist or activator of a toll-like receptor (TLR). Suitable activators of TLRs include an agonist or activator of TLR9 such as SD-101 (Dynavax). SD-101 is an immunostimulatory CpG which is being studied for B-cell, follicular and other lymphomas (NCT02254772). Agonists or activators of TLR8 which may be used in the present invention include motolimod (VTX-2337, VentiRx Pharmaceuticals) which is being studied for squamous cell cancer of the head and neck (NCT02124850) and ovarian cancer (NCT02431559).

[00737] Other immuno-oncology agents that may be used in the present invention include urelumab (BMS-663513, Bristol-Myers Squibb), an anti-CD137 monoclonal antibody; varlilumab (CDX-1127, Celldex Therapeutics), an anti-CD27 monoclonal antibody; BMS-986178 (Bristol-Myers Squibb), an anti-OX40 monoclonal antibody; lirilumab (IPH2102/BMS-986015, Innate Pharma, Bristol-Myers Squibb), an

anti-KIR monoclonal antibody; monalizumab (IPH2201, Innate Pharma, AstraZeneca) an anti-NKG2A monoclonal antibody; andecaliximab (GS-5745, Gilead Sciences), an anti-MMP9 antibody; MK-4166 (Merck & Co.), an anti-GITR monoclonal antibody.

[00738] In some embodiments, an immunostimulatory agent is selected from elotuzumab, mifamurtide, an agonist or activator of a toll-like receptor, and an activator of ROR γ t.

[00739] In some embodiments, an immunostimulatory therapeutic is recombinant human interleukin 15 (rhIL-15). rhIL-15 has been tested in the clinic as a therapy for melanoma and renal cell carcinoma (NCT01021059 and NCT01369888) and leukemias (NCT02689453). In some embodiments, an immunostimulatory agent is recombinant human interleukin 12 (rhIL-12). In some embodiments, an IL-15 based immunotherapeutic is heterodimeric IL-15 (hetIL-15, Novartis/Admune), a fusion complex composed of a synthetic form of endogenous IL-15 complexed to the soluble IL-15 binding protein IL-15 receptor alpha chain (IL15:sIL-15RA), which has been tested in Phase 1 clinical trials for melanoma, renal cell carcinoma, non-small cell lung cancer and head and neck squamous cell carcinoma (NCT02452268). In some embodiments, a recombinant human interleukin 12 (rhIL-12) is NM-IL-12 (Neumedicines, Inc.), NCT02544724, or NCT02542124.

[00740] In some embodiments, an immuno-oncology agent is selected from those described in Jerry L. Adams et al., “Big opportunities for small molecules in immuno-oncology,” Cancer Therapy 2015, Vol. 14, pages 603-622, the content of which is incorporated herein by reference in its entirety. In some embodiments, an immuno-oncology agent is selected from the examples described in Table 1 of Jerry L. Adams et al. In some embodiments, an immuno-oncology agent is a small molecule targeting an immuno-oncology target selected from those listed in Table 2 of Jerry L. Adams ET. AL. In some embodiments, an immuno-oncology agent is a small molecule agent selected from those listed in Table 2 of Jerry L. Adams et al.

[00741] In some embodiments, an immuno-oncology agent is selected from the small molecule immuno-oncology agents described in Peter L. Toogood, “Small molecule immuno-oncology therapeutic agents,” Bioorganic & Medicinal Chemistry Letters 2018, Vol. 28, pages 319-329, the content of which is incorporated herein by reference in its entirety. In some embodiments, an immuno-oncology agent is an agent targeting the pathways as described in Peter L. Toogood.

[00742] In some embodiments, an immuno-oncology agent is selected from those described in Sandra L. Ross et al., “Bispecific T cell engager (BiTE®) antibody constructs can mediate bystander tumor cell killing”, PLoS ONE 12(8): e0183390, the contents of which is incorporated herein by reference in its entirety. In some embodiments, an immuno-oncology agent is a bispecific T cell engager (BiTE®) antibody construct. In some embodiments, a bispecific T cell engager (BiTE®) antibody construct is a CD19/CD3

bispecific antibody construct. In some embodiments, a bispecific T cell engager (BiTE®) antibody construct is an EGFR/CD3 bispecific antibody construct. In some embodiments, a bispecific T cell engager (BiTE®) antibody construct activates T cells. In some embodiments, a bispecific T cell engager (BiTE®) antibody construct activates T cells, which release cytokines inducing upregulation of intercellular adhesion molecule 1 (ICAM-1) and FAS on bystander cells. In some embodiments, a bispecific T cell engager (BiTE®) antibody construct activates T cells which result in induced bystander cell lysis. In some embodiments, the bystander cells are in solid tumors. In some embodiments, the bystander cells being lysed are in proximity to the BiTE®-activated T cells. In some embodiment, the bystander cells comprises tumor-associated antigen (TAA) negative cancer cells. In some embodiment, the bystander cells comprise EGFR-negative cancer cells. In some embodiments, an immuno-oncology agent is an antibody which blocks the PD-L1/PD1 axis and/or CTLA4. In some embodiments, an immuno-oncology agent is an ex-vivo expanded tumor-infiltrating T cell. In some embodiments, an immuno-oncology agent is a bispecific antibody construct or chimeric antigen receptors (CARs) that directly connect T cells with tumor-associated surface antigens (TAAs).

Exemplary Immune Checkpoint Inhibitors

[00743] In some embodiments, an immuno-oncology agent is an immune checkpoint inhibitor as described herein.

[00744] The term “checkpoint inhibitor” as used herein relates to agents useful in preventing cancer cells from avoiding the immune system of the patient. One of the major mechanisms of anti-tumor immunity subversion is known as “T-cell exhaustion,” which results from chronic exposure to antigens that has led to up-regulation of inhibitory receptors. These inhibitory receptors serve as immune checkpoints in order to prevent uncontrolled immune reactions.

[00745] PD-1 and co-inhibitory receptors such as cytotoxic T-lymphocyte antigen 4 (CTLA-4, B and T Lymphocyte Attenuator (BTLA; CD272), T cell Immunoglobulin and Mucin domain-3 (Tim-3), Lymphocyte Activation Gene-3 (Lag-3; CD223), and others are often referred to as a checkpoint regulators. They act as molecular “gatekeepers” that allow extracellular information to dictate whether cell cycle progression and other intracellular signaling processes should proceed.

[00746] In some embodiments, an immune checkpoint inhibitor is an antibody to PD-1. PD-1 binds to the programmed cell death 1 receptor (PD-1) to prevent the receptor from binding to the inhibitory ligand PDL-1, thus overriding the ability of tumors to suppress the host anti-tumor immune response.

[00747] In one aspect, the checkpoint inhibitor is a biologic therapeutic or a small molecule. In another aspect, the checkpoint inhibitor is a monoclonal antibody, a humanized antibody, a fully human antibody, a

fusion protein or a combination thereof. In a further aspect, the checkpoint inhibitor inhibits a checkpoint protein selected from CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, B-7 family ligands or a combination thereof. In an additional aspect, the checkpoint inhibitor interacts with a ligand of a checkpoint protein selected from CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, B-7 family ligands or a combination thereof. In an aspect, the checkpoint inhibitor is an immunostimulatory agent, a T cell growth factor, an interleukin, an antibody, a vaccine or a combination thereof. In a further aspect, the interleukin is IL-7 or IL-15. In a specific aspect, the interleukin is glycosylated IL-7. In an additional aspect, the vaccine is a dendritic cell (DC) vaccine.

[00748] Checkpoint inhibitors include any agent that blocks or inhibits in a statistically significant manner, the inhibitory pathways of the immune system. Such inhibitors may include small molecule inhibitors or may include antibodies, or antigen binding fragments thereof, that bind to and block or inhibit immune checkpoint receptors or antibodies that bind to and block or inhibit immune checkpoint receptor ligands. Illustrative checkpoint molecules that may be targeted for blocking or inhibition include, but are not limited to, CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, GAL9, LAG3, TIM3, VISTA, KIR, 2B4 (belongs to the CD2 family of molecules and is expressed on all NK, $\gamma\delta$, and memory CD8⁺ ($\alpha\beta$) T cells), CD160 (also referred to as BY55), CGEN-15049, CHK 1 and CHK2 kinases, A2aR, and various B-7 family ligands. B7 family ligands include, but are not limited to, B7- 1, B7-2, B7-DC, B7-H1, B7-H2, B7-H3, B7-H4, B7-H5, B7-H6 and B7-H7. Checkpoint inhibitors include antibodies, or antigen binding fragments thereof, other binding proteins, biologic therapeutics, or small molecules, that bind to and block or inhibit the activity of one or more of CTLA-4, PDL1, PDL2, PD1, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD 160 and CGEN-15049. Illustrative immune checkpoint inhibitors include Tremelimumab (CTLA-4 blocking antibody), anti-OX40, PD-L1 monoclonal Antibody (Anti-B7-H1; MEDI4736), MK-3475 (PD-1 blocker), Nivolumab (anti-PD1 antibody), CT-011 (anti-PD1 antibody), BY55 monoclonal antibody, AMP224 (anti-PDL1 antibody), BMS- 936559 (anti-PDL1 antibody), MPLDL3280A (anti-PDL1 antibody), MSB0010718C (anti-PDL1 antibody), and ipilimumab (anti-CTLA-4 checkpoint inhibitor). Checkpoint protein ligands include, but are not limited to PD-L1, PD-L2, B7-H3, B7-H4, CD28, CD86 and TIM-3.

[00749] In certain embodiments, the immune checkpoint inhibitor is selected from a PD-1 antagonist, a PD-L1 antagonist, and a CTLA-4 antagonist. In some embodiments, the checkpoint inhibitor is selected from the group consisting of nivolumab (Opdivo®), ipilimumab (Yervoy®), and pembrolizumab (Keytruda®). In some embodiments, the checkpoint inhibitor is selected from nivolumab (anti-PD-1

antibody, Opdivo®, Bristol-Myers Squibb); pembrolizumab (anti-PD-1 antibody, Keytruda®, Merck); ipilimumab (anti-CTLA-4 antibody, Yervoy®, Bristol-Myers Squibb); durvalumab (anti-PD-L1 antibody, Imfinzi®, AstraZeneca); and atezolizumab (anti-PD-L1 antibody, Tecentriq®, Genentech).

[00750] In some embodiments, the checkpoint inhibitor is selected from the group consisting of lambrolizumab (MK-3475), nivolumab (BMS-936558), pidilizumab (CT-011), AMP-224, MDX-1105, MEDI4736, MPDL3280A, BMS-936559, ipilimumab, lirlumab, IPH2101, pembrolizumab (Keytruda®), and tremelimumab.

[00751] In some embodiments, an immune checkpoint inhibitor is REGN2810 (Regeneron), an anti-PD-1 antibody tested in patients with basal cell carcinoma (NCT03132636); NSCLC (NCT03088540); cutaneous squamous cell carcinoma (NCT02760498); lymphoma (NCT02651662); and melanoma (NCT03002376); pidilizumab (CureTech), also known as CT-011, an antibody that binds to PD-1, in clinical trials for diffuse large B-cell lymphoma and multiple myeloma; avelumab (Bavencio®, Pfizer/Merck KGaA), also known as MSB0010718C), a fully human IgG1 anti-PD-L1 antibody, in clinical trials for non-small cell lung cancer, Merkel cell carcinoma, mesothelioma, solid tumors, renal cancer, ovarian cancer, bladder cancer, head and neck cancer, and gastric cancer; or PDR001 (Novartis), an inhibitory antibody that binds to PD-1, in clinical trials for non-small cell lung cancer, melanoma, triple negative breast cancer and advanced or metastatic solid tumors. Tremelimumab (CP-675,206; Astrazeneca) is a fully human monoclonal antibody against CTLA-4 that has been studied in clinical trials for a number of indications, including: mesothelioma, colorectal cancer, kidney cancer, breast cancer, lung cancer and non-small cell lung cancer, pancreatic ductal adenocarcinoma, pancreatic cancer, germ cell cancer, squamous cell cancer of the head and neck, hepatocellular carcinoma, prostate cancer, endometrial cancer, metastatic cancer in the liver, liver cancer, large B-cell lymphoma, ovarian cancer, cervical cancer, metastatic anaplastic thyroid cancer, urothelial cancer, fallopian tube cancer, multiple myeloma, bladder cancer, soft tissue sarcoma, and melanoma. AGEN-1884 (Agenus) is an anti-CTLA4 antibody that is being studied in Phase 1 clinical trials for advanced solid tumors (NCT02694822).

[00752] In some embodiments, a checkpoint inhibitor is an inhibitor of T-cell immunoglobulin mucin containing protein-3 (TIM-3). TIM-3 inhibitors that may be used in the present invention include TSR-022, LY3321367 and MBG453. TSR-022 (Tesaro) is an anti-TIM-3 antibody which is being studied in solid tumors (NCT02817633). LY3321367 (Eli Lilly) is an anti-TIM-3 antibody which is being studied in solid tumors (NCT03099109). MBG453 (Novartis) is an anti-TIM-3 antibody which is being studied in advanced malignancies (NCT02608268).

[00753] In some embodiments, a checkpoint inhibitor is an inhibitor of T cell immunoreceptor with Ig and ITIM domains, or TIGIT, an immune receptor on certain T cells and NK cells. TIGIT inhibitors that

may be used in the present invention include BMS-986207 (Bristol-Myers Squibb), an anti-TIGIT monoclonal antibody (NCT02913313); OMP-313M32 (Oncomed); and anti-TIGIT monoclonal antibody (NCT03119428).

[00754] In some embodiments, a checkpoint inhibitor is an inhibitor of Lymphocyte Activation Gene-3 (LAG-3). LAG-3 inhibitors that may be used in the present invention include BMS-986016 and REGN3767 and IMP321. BMS-986016 (Bristol-Myers Squibb), an anti-LAG-3 antibody, is being studied in glioblastoma and gliosarcoma (NCT02658981). REGN3767 (Regeneron), is also an anti-LAG-3 antibody, and is being studied in malignancies (NCT03005782). IMP321 (Immutep S.A.) is an LAG-3-Ig fusion protein, being studied in melanoma (NCT02676869); adenocarcinoma (NCT02614833); and metastatic breast cancer (NCT00349934).

[00755] Checkpoint inhibitors that may be used in the present invention include OX40 agonists. OX40 agonists that are being studied in clinical trials include PF-04518600/PF-8600 (Pfizer), an agonistic anti-OX40 antibody, in metastatic kidney cancer (NCT03092856) and advanced cancers and neoplasms (NCT02554812; NCT05082566); GSK3174998 (Merck), an agonistic anti-OX40 antibody, in Phase 1 cancer trials (NCT02528357); MEDI0562 (Medimmune/AstraZeneca), an agonistic anti-OX40 antibody, in advanced solid tumors (NCT02318394 and NCT02705482); MEDI6469, an agonistic anti-OX40 antibody (Medimmune/AstraZeneca), in patients with colorectal cancer (NCT02559024), breast cancer (NCT01862900), head and neck cancer (NCT02274155) and metastatic prostate cancer (NCT01303705); and BMS-986178 (Bristol-Myers Squibb) an agonistic anti-OX40 antibody, in advanced cancers (NCT02737475).

[00756] Checkpoint inhibitors that may be used in the present invention include CD137 (also called 4-1BB) agonists. CD137 agonists that are being studied in clinical trials include utomilumab (PF-05082566, Pfizer) an agonistic anti-CD137 antibody, in diffuse large B-cell lymphoma (NCT02951156) and in advanced cancers and neoplasms (NCT02554812 and NCT05082566); urelumab (BMS-663513, Bristol-Myers Squibb), an agonistic anti-CD137 antibody, in melanoma and skin cancer (NCT02652455) and glioblastoma and gliosarcoma (NCT02658981).

[00757] Checkpoint inhibitors that may be used in the present invention include CD27 agonists. CD27 agonists that are being studied in clinical trials include varlilumab (CDX-1127, Celldex Therapeutics) an agonistic anti-CD27 antibody, in squamous cell head and neck cancer, ovarian carcinoma, colorectal cancer, renal cell cancer, and glioblastoma (NCT02335918); lymphomas (NCT01460134); and glioma and astrocytoma (NCT02924038).

[00758] Checkpoint inhibitors that may be used in the present invention include glucocorticoid-induced tumor necrosis factor receptor (GITR) agonists. GITR agonists that are being studied in clinical trials

include TRX518 (Leap Therapeutics), an agonistic anti-GITR antibody, in malignant melanoma and other malignant solid tumors (NCT01239134 and NCT02628574); GWN323 (Novartis), an agonistic anti-GITR antibody, in solid tumors and lymphoma (NCT 02740270); INCAGN01876 (Incyte/Agenus), an agonistic anti-GITR antibody, in advanced cancers (NCT02697591 and NCT03126110); MK-4166 (Merck), an agonistic anti-GITR antibody, in solid tumors (NCT02132754) and MEDI1873 (Medimmune/AstraZeneca), an agonistic hexameric GITR-ligand molecule with a human IgG1 Fc domain, in advanced solid tumors (NCT02583165).

[00759] Checkpoint inhibitors that may be used in the present invention include inducible T-cell co-stimulator (ICOS, also known as CD278) agonists. ICOS agonists that are being studied in clinical trials include MEDI-570 (Medimmune), an agonistic anti-ICOS antibody, in lymphomas (NCT02520791); GSK3359609 (Merck), an agonistic anti-ICOS antibody, in Phase 1 (NCT02723955); JTX-2011 (Jounce Therapeutics), an agonistic anti-ICOS antibody, in Phase 1 (NCT02904226).

[00760] Checkpoint inhibitors that may be used in the present invention include killer IgG-like receptor (KIR) inhibitors. KIR inhibitors that are being studied in clinical trials include lirilumab (IPH2102/BMS-986015, Innate Pharma/Bristol-Myers Squibb), an anti-KIR antibody, in leukemias (NCT01687387, NCT02399917, NCT02481297, NCT02599649), multiple myeloma (NCT02252263), and lymphoma (NCT01592370); IPH2101 (1-7F9, Innate Pharma) in myeloma (NCT01222286 and NCT01217203); and IPH4102 (Innate Pharma), an anti-KIR antibody that binds to three domains of the long cytoplasmic tail (KIR3DL2), in lymphoma (NCT02593045).

[00761] Checkpoint inhibitors that may be used in the present invention include CD47 inhibitors of interaction between CD47 and signal regulatory protein alpha (SIRPa). CD47/SIRPa inhibitors that are being studied in clinical trials include ALX-148 (Alexo Therapeutics), an antagonistic variant of (SIRPa) that binds to CD47 and prevents CD47/SIRPa-mediated signaling, in phase 1 (NCT03013218); TTI-621 (SIRPa-Fc, Trillium Therapeutics), a soluble recombinant fusion protein created by linking the N-terminal CD47-binding domain of SIRPa with the Fc domain of human IgG1, acts by binding human CD47, and preventing it from delivering its “do not eat” signal to macrophages, is in clinical trials in Phase 1 (NCT02890368 and NCT02663518); CC-90002 (Celgene), an anti-CD47 antibody, in leukemias (NCT02641002); and Hu5F9-G4 (Forty Seven, Inc.), in colorectal neoplasms and solid tumors (NCT02953782), acute myeloid leukemia (NCT02678338) and lymphoma (NCT02953509).

[00762] Checkpoint inhibitors that may be used in the present invention include CD73 inhibitors. CD73 inhibitors that are being studied in clinical trials include MEDI9447 (Medimmune), an anti-CD73 antibody, in solid tumors (NCT02503774); and BMS-986179 (Bristol-Myers Squibb), an anti-CD73 antibody, in solid tumors (NCT02754141).

[00763] Checkpoint inhibitors that may be used in the present invention include agonists of stimulator of interferon genes protein (STING, also known as transmembrane protein 173, or TMEM173). Agonists of STING that are being studied in clinical trials include MK-1454 (Merck), an agonistic synthetic cyclic dinucleotide, in lymphoma (NCT03010176); and ADU-S100 (MIW815, Aduro Biotech/Novartis), an agonistic synthetic cyclic dinucleotide, in Phase 1 (NCT02675439 and NCT03172936).

[00764] In some embodiments, STAT3 inhibition/degradation can significantly enhance CDN-induced STING signaling and antitumor immunity (Pei et al., *Can. Lett.* 2019, 450:110).

[00765] Checkpoint inhibitors that may be used in the present invention include CSF1R inhibitors. CSF1R inhibitors that are being studied in clinical trials include pexidartinib (PLX3397, Plexxikon), a CSF1R small molecule inhibitor, in colorectal cancer, pancreatic cancer, metastatic and advanced cancers (NCT02777710) and melanoma, non-small cell lung cancer, squamous cell head and neck cancer, gastrointestinal stromal tumor (GIST) and ovarian cancer (NCT02452424); and IMC-CS4 (LY3022855, Lilly), an anti-CSF-1R antibody, in pancreatic cancer (NCT03153410), melanoma (NCT03101254), and solid tumors (NCT02718911); and BLZ945 (4-[2((1R,2R)-2-hydroxycyclohexylamino)-benzothiazol-6-yl]oxy]-pyridine-2-carboxylic acid methylamide, Novartis), an orally available inhibitor of CSF1R, in advanced solid tumors (NCT02829723).

[00766] Checkpoint inhibitors that may be used in the present invention include NKG2A receptor inhibitors. NKG2A receptor inhibitors that are being studied in clinical trials include monalizumab (IPH2201, Innate Pharma), an anti-NKG2A antibody, in head and neck neoplasms (NCT02643550) and chronic lymphocytic leukemia (NCT02557516).

[00767] In some embodiments, the immune checkpoint inhibitor is selected from nivolumab, pembrolizumab, ipilimumab, avelumab, durvalumab, atezolizumab, or pidilizumab.

EXEMPLIFICATION

General Synthetic Methods

[00755] The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade. If not mentioned otherwise, all evaporations were performed under reduced pressure, preferably between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials was confirmed by standard analytical methods, e.g., microanalysis and spectroscopic characteristics, e.g., MS, IR, NMR. Abbreviations used are those conventional in the art.

[00756] All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesis the compounds of the present invention were either commercially available

or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21). Further, the compounds of the present invention can be produced by organic synthesis methods known to one of ordinary skill in the art as shown in the following examples.

[00757] All reactions were carried out under nitrogen or argon unless otherwise stated.

[00758] Proton NMR (^1H NMR) was conducted in deuterated solvent. In certain compounds disclosed herein, one or more ^1H shifts overlap with residual proteo solvent signals; these signals have not been reported in the experimental provided hereinafter.

Analytical instruments

LCMS	Shimadzu UFLC MS: LCMS-2020
	Agilent Technologies 1200 series MS: Agilent Technologies 6110
	Agilent Technologies 1200 series MS: LC/MSD VL
NMR	BRUKER AVANCE III/400; Frequency (MHz) 400.13; Nucleus: ^1H ; Number of Transients: 8
Prep-HPLC	Gilson GX-281 systems: instruments GX-A, GX-B, GX-C, GX-D, GX-E, GX-F, GX-G and GX-H
GCMS	SHIMADZU GCMS-QP2010 Ultra
Analytical cSFC	Agilent Technologies 1290 Infinity
Prep-cSFC	Waters SFC Prep 80

[00759] For acidic LCMS data: LCMS was recorded on an Agilent 1200 Series LC/MSD or Shimadzu LCMS2020 equipped with electro-spray ionization and quadrupole MS detector [ES+ve to give MH^+] and equipped with Chromolith Flash RP-18e 25*2.0 mm, eluting with 0.0375 vol% TFA in water (solvent A) and 0.01875 vol% TFA in acetonitrile (solvent B). Other LCMS was recorded on an Agilent 1290 Infinity RRLLC attached with Agilent 6120 Mass detector. The column used was BEH C18 50*2.1 mm, 1.7 micron. Column flow was 0.55 ml/min and mobile phase are used (A) 2 mM Ammonium Acetate in 0.1% Formic Acid in Water and (B) 0.1 % Formic Acid in Acetonitrile.

[00760] For basic LCMS data: LCMS was recorded on an Agilent 1200 Series LC/MSD or Shimadzu LCMS 2020 equipped with electro-spray ionization and quadrupole MS detector [ES+ve to give MH^+] and equipped with Xbridge C18, 2.1X50 mm columns packed with 5 mm C18-coated silica or Kinetex EVO

C18 2.1X30mm columns packed with 5 mm C18-coated silica, eluting with 0.05 vol% $\text{NH}_3 \cdot \text{H}_2\text{O}$ in water (solvent A) and acetonitrile (solvent B).

[00761] HPLC Analytical Method: HPLC was carried out on X Bridge C18 150*4.6 mm, 5 micron. Column flow is 1.0 ml /min and mobile phase are used (A) 0.1 % Ammonia in water and (B) 0.1 % Ammonia in Acetonitrile.

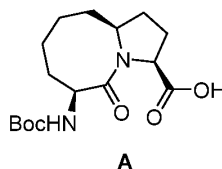
[00762] Prep HPLC Analytical Method: The compound was purified on Shimadzu LC-20AP and UV detector. The column used was X-BRIDGE C18 (250*19)mm, 5 μ . Column flow was 16.0 ml/min. Mobile phase used was (A) 0.1% Formic Acid in Water and (B) Acetonitrile. Basic method used was (A) 5mM ammonium bicarbonate and 0.1% NH_3 in Water and (B) Acetonitrile or (A) 0.1% Ammonium Hydroxide in Water and (B) Acetonitrile. The UV spectra were recorded at 202nm & 254nm.

[00763] NMR Method: The ^1H NMR spectra were recorded on a Bruker Ultra Shield Advance 400 MHz/5 mm Probe (BBFO). The chemical shifts are reported in part-per-million.

[00764] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present invention, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

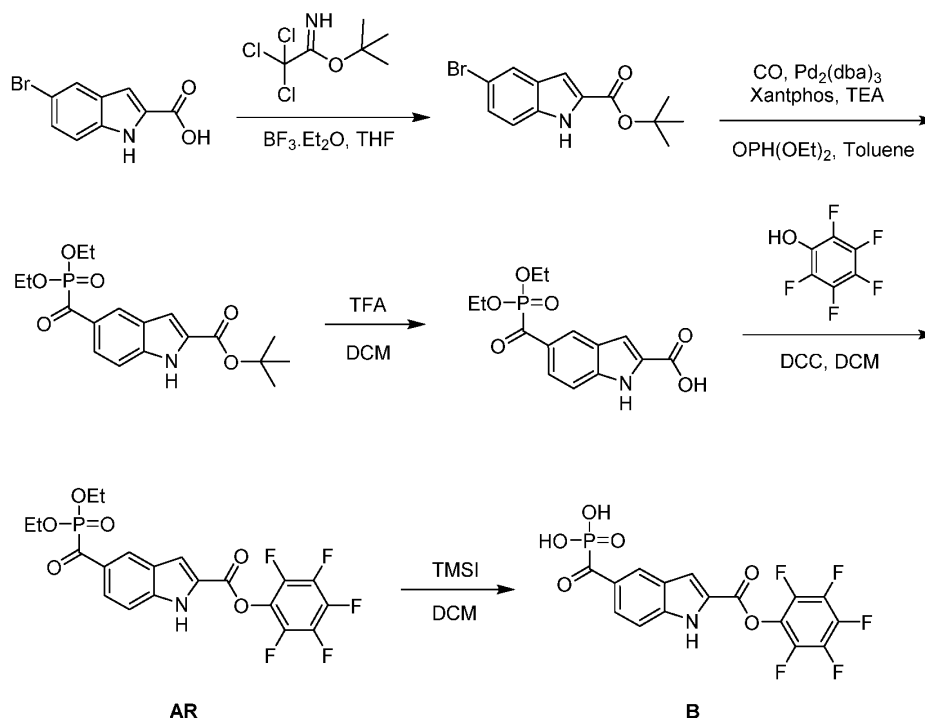
Intermediates:

[00768] (3*S*,6*S*,10*aS*)-6-[(tert-butoxycarbonyl)amino]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azocine-3-carboxylic acid (Intermediate A)



[00757] (3*S*,6*S*,10*aS*)-6-[(tert-butoxycarbonyl)amino]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azocine-3-carboxylic acid was synthesized as described in Sun, Haiying; Nikolovska-Coleska, Zaneta; Lu, Jianfeng; Meagher, Jennifer L.; Yang, Chao-Yie; Qiu, Su; Tomita, York; Ueda, Yumi; Jiang, Sheng; Krajewski, Krzysztof; Roller, Peter P.; Stuckey, Jeanne A.; Wang, Shaomeng, *Journal of the American Chemical Society*, Volume: 129, Issue: 49, Pages: 15279-15294 and WO 2007/130626, the content of each of which is herein incorporated by reference.

[00758] 2-(2,3,4,5,6-pentafluorophenoxycarbonyl)-1*H*-indole-5-carboxylphosphonic acid (Intermediate B) and 2,3,4,5,6-pentafluorophenyl 5-[(diethoxyphosphoryl)carbonyl]-1*H*-indole-2-

carboxylate (Intermediate AR)**[00759]** Step 1 - *Tert*-butyl 5-bromo-1H-indole-2-carboxylate

[00760] To a stirred solution of 5-bromo-1H-indole-2 carboxylic acid (20.00 g, 83.31 mmol, CAS# 7254-19-5) in THF (250.00 mL) was added *tert*-butyl 2,2,2-trichloroethanimidate (45.51 g, 208.29 mmol) in portions at 25 °C under nitrogen atmosphere. To the above mixture was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2.36 g, 16.66 mmol) dropwise over 10 min at 0 °C. The resulting mixture was stirred for overnight at rt. On completion, the reaction was quenched with saturated aq. Na_2CO_3 (200 mL) and diluted with water (100 mL). The mixture was then extracted with EtOAc (3×100 mL), the combined organic layers were washed with water (3×100 mL), and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluted with PE/EtOAc (20 / 1), to afford the title compound (22.8 g, 92% yield) as a light yellow solid; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.90 (s, 1H), 7.86 (d, $J = 1.9$ Hz, 1H), 7.42 (d, $J = 8.8$ Hz, 1H), 7.36 (dd, $J = 8.8, 1.9$ Hz, 1H), 7.03 (dd, $J = 2.2, 0.9$ Hz, 1H), 1.57 (s, 9H); LC/MS (ESI, m/z): $[(M - 1)]^- = 293.9, 295.9$.

[00761] Step 2 - *Tert*-butyl 5-((diethoxyphosphoryl)carbonyl)-1H-indole-2-carboxylate

[00762] To a stirred mixture of *tert*-butyl 5-bromo-1H-indole-2-carboxylate (20.00 g, 67.53 mmol) in toluene (300.00 mL) were added $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (3.5 g, 3.4 mmol), XantPhos (1.96 g, 3.38 mmol) and

TEA (6.84 g, 67.53 mmol) in turns at rt. The reaction system was degassed under vacuum and purged with CO several times and stirred under CO balloon (~1 atm) at 25 °C for 10 min. Then diethylphosphonate (9.32 g, 67.53 mmol) was added to above mixture and the resulting mixture was stirred for 4 h at 90 °C under CO atmosphere. On completion, the reaction mixture was filtered and the filter cake was washed with DCM (3 × 15 mL). The filtrate was concentrated under reduced pressure and the crude product was purified by reverse phase flash with the following conditions (Column: Spherical C18, 20~40 μ m, 330 g; Mobile Phase A: Water (0.05%FA), Mobile Phase B: ACN; Flow rate: 80 mL/min; Gradient (B%): 5%~5%, 8 min; 40%~70%, 30 min; 95%, 5 min; Detector: 254 nm; Rt: 35 min.) to afford the title compound (18 g, 70%yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.28 (s, 1H), 8.76 (d, *J* = 1.7 Hz, 1H), 7.97 (dd, *J* = 8.9, 1.7 Hz, 1H), 7.63-7.57 (m, 1H), 7.37-7.34 (m, 1H), 4.23-4.15 (m, 4H), 1.58 (s, 9H), 1.29 (t, *J* = 7.0 Hz, 6H); LC/MS (ESI, *m/z*): [(M + 1)]⁺ = 382.1.

[00763] Step 3 - 5-((Diethoxyphosphoryl)carbonyl)-1H-indole-2-carboxylic acid

[00764] To a stirred solution of *tert*-butyl 5-[(diethoxyphosphoryl)carbonyl]-1H-indole-2-carboxylate (55.00 g, 144.22 mmol) in DCM (1100 mL) was added TFA (500 mL) dropwise at rt and the resulting mixture was stirred for 2 h at rt under nitrogen atmosphere. On completion, the resulting mixture was concentrated under reduced pressure. The residue was triturated with Et₂O (1000 mL) to afford the title compound (46 g, 98% yield) as a light brown solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.36 (s, 1H), 8.78 (d, *J* = 1.7 Hz, 1H), 7.96 (dd, *J* = 8.9, 1.7 Hz, 1H), 7.61-7.55 (m, 1H), 7.39 (dd, *J* = 2.1, 0.9 Hz, 1H), 4.21-4.18 (m, 4H), 1.29 (t, *J* = 7.0 Hz, 6H); LC/MS (ESI, *m/z*): [(M + 1)]⁺ = 326.1.

[00765] Step 4 - 2,3,4,5,6-pentafluorophenyl 5-[(diethoxyphosphoryl)carbonyl]-1H-indole-2-carboxylate (Intermediate AR)

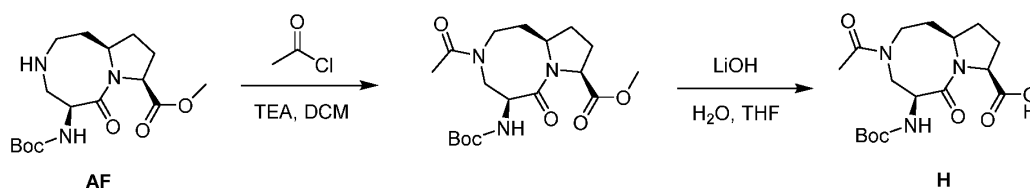
[00766] To a stirred solution of 5-[(diethoxyphosphoryl)carbonyl]-1H-indole-2-carboxylic acid (100.00 g, 307.45 mmol) and pentafluorophenol (84.89 g, 461.17 mmol) in DCM (1.50 L) was added DCC (95.15 g, 461.17 mmol) at rt under air atmosphere. The resulting mixture was stirred overnight at rt under nitrogen atmosphere. On completion, the resulting mixture was filtered and the filter cake was washed with DCM (3 × 100 mL). The filtrate was then concentrated under reduced pressure to 300 mL of DCM and the mixture was diluted with hexane (1 L). The precipitated solids were collected by filtration and washed with hexane (3 × 100 mL) to afford the title compound (150 g, contains trace amount of DCU) as a light yellow solid.

[00767] Step 5 - 2-(2,3,4,5,6-pentafluorophenoxy carbonyl)-1H-indole-5-carboxylphosphonic acid

[00768] To a stirred solution of 2,3,4,5,6-pentafluorophenyl 5-[(diethoxyphosphoryl)carbonyl]-1H-indole-2-carboxylate (65.00 g, 132.30 mmol) in anhydrous DCM (1300 mL) was added TMSI (79.42 g, 396.90 mmol) dropwise at rt under Argon atmosphere. The resulting mixture was stirred for 30 min at rt under Argon atmosphere. On completion, the mixture was concentrated under reduced pressure. The residue

was then dissolved in dry MeCN (500 mL), then sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (50 mL) was dropwise into the solution until the dark brown solution changed to light yellow and a precipitate was generated. The suspension was filtered and the filter cake was washed with ACN/water (10/1, 50 mL, three times) and collected. The collected solid was triturated with Et_2O (500 mL) to afford the title compound (45 g, 78 %) as an off-white solid. LCMS (ESI, m/z): $(M + 1)^+$ 434.0.

[00769] (5*S*,8*S*,10*aR*)-3-acetyl-5-[(*tert*-butoxycarbonyl)amino]-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocine-8-carboxylic acid (Intermediate H)



[00770] Step 1 - Methyl (5*S*,8*S*,10*aR*)-3-acetyl-5-[(*tert*-butoxycarbonyl)amino]-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocine-8-carboxylate

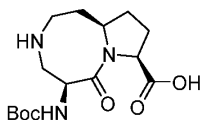
[00771] To a solution of methyl (5*S*,8*S*,10*aR*)-5-[(*tert*-butoxycarbonyl)amino]-6-oxo-octahydro-1*H*-pyrrolo[1,2-*a*][1,5]diazocine-8-carboxylate (4.44 g, 13.01 mmol, Intermediate AF) in DCM (50.00 mL) were added TEA (3.95 g, 39.02 mmol) and acetyl chloride (1.53 g, 19.51 mmol) at 0 °C, then the mixture was stirred at rt for 3 hours. The reaction was quenched by the addition of sat. NaHCO_3 (100 mL) and the resulting mixture was extracted with DCM (5 x 100 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography (column, C18 silica gel; mobile phase, CH_3CN in water (plus 10 mmol/L NH_4HCO_3), 25% to 40% gradient in 15 min; Detector, UV 220/254 nm) to give the title compound as a light yellow solid (4.55 g, 91% yield): ^1H NMR (400 MHz, CDCl_3) δ 5.84 (d, J = 6.4 Hz, 1H), 4.50 (t, J = 8.6 Hz, 2H), 4.17-4.13 (m, 1H), 3.97-3.83 (m, 2H), 3.77 (s, 3H), 3.42-3.28 (m, 1H), 3.21 (dd, J = 14.3, 10.7 Hz, 1H), 2.42-2.33 (m, 1H), 2.30 (s, 3H), 2.24-1.97 (m, 3H), 1.90 -1.72 (m, 2H), 1.44 (s, 9H). LC/MS (ESI, m/z): $[(M + 1)]^+ = 384.1$.

[00772] Step 2 - (5*S*,8*S*,10*aR*)-3-acetyl-5-[(*tert*-butoxycarbonyl)amino]-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocine-8-carboxylic acid

[00773] To a stirred solution of methyl (5*S*,8*S*,10*aR*)-3-acetyl-5-[(*tert*-butoxycarbonyl)amino]-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocine-8-carboxylate (4.5 g) in THF (50.0 mL) was added H_2O (50.0 mL) and LiOH (5.29 g, 221 mmol) in portions at rt and the resulting mixture was stirred for 16 h. The mixture was acidified to pH 6 with aqueous HCl (1 M). The precipitated solids were collected by filtration and washed with water (2 x 10.0 mL). Then it was dried in vacuum to give the title compound as a white solid. (300 MHz, CDCl_3) δ 5.87 (d, J = 6.9 Hz, 1H), 4.67-4.65 (m, 1H), 4.54 (t, J = 8.3 Hz, 1H), 4.29-4.25 (m,

1H), 3.95-3.77 (m, 2H), 3.68-3.63 (m, 3H), 3.35 (t, $J = 12.5$ Hz, 1H), 2.36-2.34 (m, 2H), 2.23 (s, 3H), 2.01-1.98 (s, 1H), 1.84-1.80 (m, 1H), 1.45 (s, 9H). LC/MS (ESI, m/z): $[(M + 1)]^+ = 370.2$.

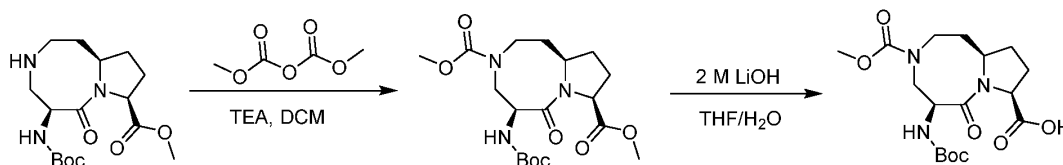
[00774] (5*S*,8*S*,10*aR*)-5-[(*tert*-butoxycarbonyl)amino]-6-oxo-octahydro-1*H*-pyrrolo[1,2-*a*][1,5]diazocine-8-carboxylic acid (Intermediate AF)



AF

[00775] (5*S*,8*S*,10*aR*)-5-[(*tert*-butoxycarbonyl)amino]-6-oxo-octahydro-1*H*-pyrrolo[1,2-*a*][1,5]diazocine-8-carboxylic acid was synthesized as described in WO2011050068 A2 2011-04-28.

[00776] (5*S*,8*S*,10*aR*)-5-[(*tert*-butoxycarbonyl)amino]-3-(methoxycarbonyl)-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocine-8-carboxylic acid (Intermediate AW)



AF

AW

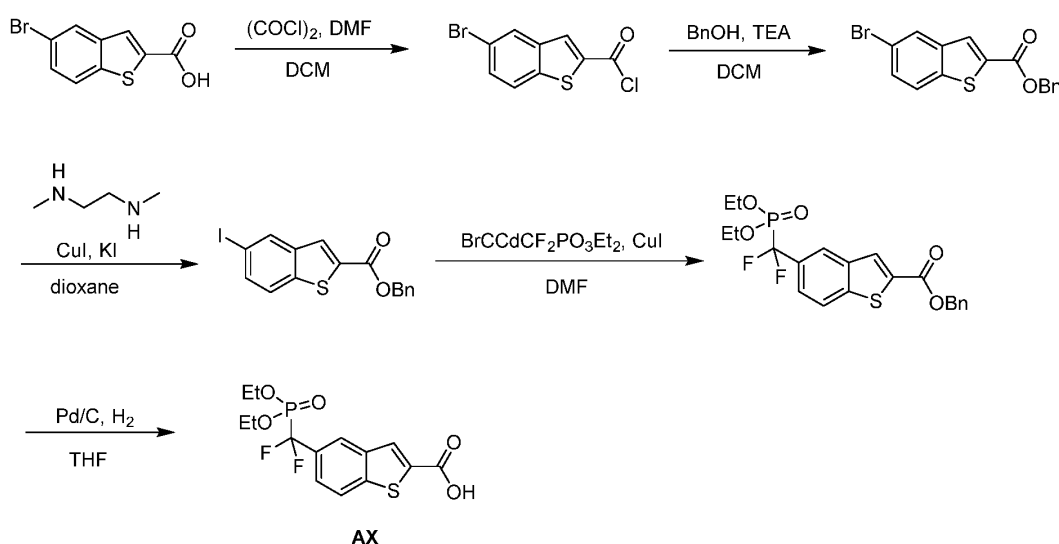
[00777] Step 1 - 3,8-dimethyl (5*S*,8*S*,10*aR*)-5-[(*tert*-butoxycarbonyl)amino]-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocine-3,8-dicarboxylate

[00778] To a stirred solution of methyl (5*S*,8*S*,10*aR*)-5-[(*tert*-butoxycarbonyl)amino]-6-oxo-octahydro-1*H*-pyrrolo[1,2-*a*][1,5]diazocine-8-carboxylate (10.00 g, 29.29 mmol, Intermediate AF) and TEA (5.93 g, 58.58 mmol) in DCM (200 mL) was added methyl methylumyl dicarbonate (5.85 g, 43.94 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred for 2 h at rt under nitrogen atmosphere. On completion, the resulting mixture was quenched with water (200 mL) then the reaction mixture was extracted with CH_2Cl_2 (2 x 200 mL). The combined organic layers were washed with brine (3 x 200 mL), and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure to afford the title compound (13 g, 79% yield) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 5.60-5.56 (m, 1H), 4.59-4.54 (m, 1H), 4.50-4.44 (m, 1H), 4.23-4.16 (m, 1H), 4.08-3.80 (m, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.64-3.37 (m, 2H), 3.31-3.24 (m, 1H), 2.37-2.31 (m, 1H), 2.15-2.07 (m, 1H), 2.05-1.89 (m, 2H), 1.89-1.78 (m, 2H), 1.42 (s, 9H). LC/MS (ESI, m/z): $[(M + H)]^+ = 400.2$.

[00779] Step 2 - (5*S*,8*S*,10*aR*)-5-[(*tert*-butoxycarbonyl)amino]-3-(methoxycarbonyl)-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocine-8-carboxylic acid

[00780] To a stirred solution of 3,8-dimethyl (5*S*,8*S*,10*aR*)-5-[(*tert*-butoxycarbonyl)amino]-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocine-3,8-dicarboxylate (13.00 g) in THF (30 mL) was added LiOH (3.90 g, 162.7 mmol) at rt and the mixture was stirred for 2 h at rt. On completion, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography (Column, Welflash TM C18-1, 20-40 μ m, 330 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient 20 % to 50 % B in 30 min; Flow rate: 80 mL/min; Detector: 220/254nm; desired fractions were collected at 38% B) and concentrated under reduced pressure to afford the title compound (10.3 g, 82% yield) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 5.95-5.55 (m, 1H), 4.70-4.64 (m, 1H), 4.53-4.49 (m, 1H), 4.25-4.21 (m, 1H), 3.96-3.78 (m, 1H), 3.73 (s, 3H), 3.63-3.30 (m, 3H), 2.39-2.32 (m, 1H), 2.27-2.07 (m, 2H), 2.07-1.66 (m, 3H), 1.42 (s, 9H).

[00781] 5-((diethoxyphosphoryl)difluoromethyl)benzo[b]thiophene-2-carboxylic acid (Intermediate AX)



[00782] Step 1 -5-bromo-1-benzothiophene-2-carbonyl chloride

[00783] To a stirred solution of 5-bromo-1-benzothiophene-2-carboxylic acid (60 g, 233 mmol, CAS# 7312-10-9) in DCM (2000 mL) was added (COCl)₂ (44.43 g, 350 mmol) and DMF (2 mL, 25.91 mmol) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at rt under nitrogen atmosphere. On completion, the resulting mixture was concentrated under reduced pressure to afford the title compound (50 g, 78% yield).

[00784] Step 2 - Benzyl 5-bromo-1-benzothiophene-2-carboxylate

[00785] To a stirred solution of 5-bromo-1-benzothiophene-2-carbonyl chloride (80 g, 290 mmol) and

TEA (80.71 mL, 580.7 mmol) in DCM (4000 mL) was added phenylmethanol (47.09 g, 435 mmol) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 16 h at rt under nitrogen atmosphere. On completion, the reaction mixture was quenched with sat. NH_4Cl (aq.) (300 mL) at 0 °C and the mixture was extracted with CH_2Cl_2 (3 x 400 mL). The combined organic layers were washed with brine (3 x 500 mL), and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1), to afford the title compound (80 g, 79% yield) as a light yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.49-8.41 (m, 1H), 8.22-8.15 (m, 1H), 7.96-7.88 (m, 1H), 7.85-7.79 (m, 1H), 7.51-7.46 (m, 2H), 7.45-7.37 (m, 3H), 5.44-5.33 (m, 2H); LC/MS (ESI, m/z): $[(\text{M} + \text{H})]^+ = 347.5, 349.5$.

[00786] Step 3 - benzyl 5-iodo-1-benzothiophene-2-carboxylate

[00787] A 400 mL sealed bottle equipped with a magnetic stirring bar was filled with argon before adding benzyl 5-bromo-1-benzothiophene-2-carboxylate (10 g, 29 mmol), CuI (548.48 mg, 2.88 mmol), NaI (8.59 g, 57.3 mmol), methyl[2-(methylamino)ethyl]amine (2 mL, 0.576 mmol,) and dioxane (150 mL). The reaction system was charged with argon for another three times, then the mixture was stirred at 110 °C for 16 h. On completion, the reaction system was cooled to rt and quenched with ammonium chloride aqueous solution. The reaction mixture was then extracted with EtOAc (500 mL x 3), washed with brine, dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. The residual crude product was purified by flash column chromatography (PE:EA = 10:1) to afford the title compound (9 g, 79% yield) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.58-8.51 (m, 1H), 8.36-8.31 (m, 1H), 7.91-7.82 (m, 1H), 7.85-7.78 (m, 1H), 7.51-7.46 (m, 2H), 7.45-7.37 (m, 3H), 5.29-5.21 (m, 2H). GC/MS (ESI, m/z): $[(\text{M})]^+ = 394.0$.

[00788] Step 4 - Benzyl 5-[(diethoxyphosphoryl)difluoromethyl]-1-benzothiophene-2-carboxylate

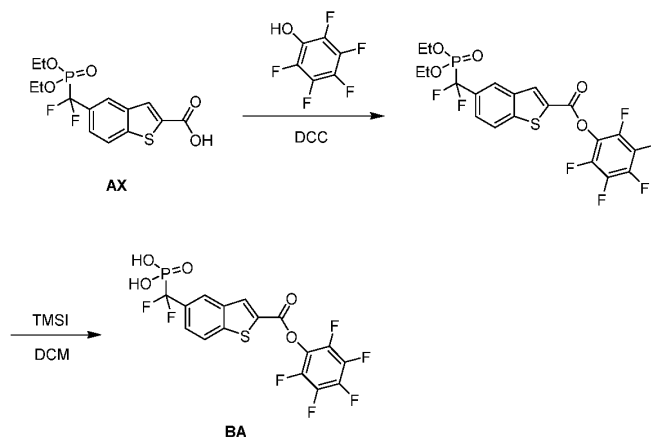
[00789] To a solution of diethyl bromodifluoromethylphosphonate (13.48 g, 50.48 mmol) in DMF (30 mL) was added cadmium (10.01 g, 89.03 mmol) at 25 °C and the mixture was stirred at 25 °C for 4 h under N_2 atmosphere. The unreacted cadmium was then removed by filtration under N_2 atmosphere, and the filtrate was treated with CuCl (5.05 g, 50.99 mmol) and benzyl 5-iodo-1-benzothiophene-2-carboxylate (10.00 g, 25.37 mmol) at rt. The resulting mixture was stirred for 20 h at 25 °C under nitrogen atmosphere. On completion the reaction was quenched with sat. NH_4Cl (aq.) (500 mL) at rt and the resulting mixture was extracted with EtOAc (3 x 800 mL). The combined organic layers were washed with brine (8 x 300 mL), and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 μm , 330 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 20% - 95% B in 30 min; Flow rate: 80 mL/min; Detector: 220/254 nm; desired fractions were collected at 95% B) and concentrated

under reduced pressure to afford the title compound (9 g, 78% yield) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.21-8.14 (m, 2H), 7.99-7.92 (m, 1H), 7.76-7.70 (m, 1H), 7.51-7.47 (m, 2H), 7.46-7.35 (m, 3H), 5.45-5.39 (m, 2H), 4.30-4.11 (m, 4H), 1.39-1.28 (m, 6H); LC/MS (ESI, *m/z*): $[(\text{M} + \text{H})]^+ = 455.2$.

[00790] Step 5 - 5-[(diethoxyphosphoryl)difluoromethyl]-1-benzothiophene-2-carboxylic acid

[00791] To a solution of benzyl 5-[(diethoxyphosphoryl)difluoromethyl]-1-benzothiophene-2-carboxylate (9.00 g, 19.80 mmol) in MeOH (100 mL) was added Pd/C (716.62 mg, 6.73 mmol) under nitrogen atmosphere. The reaction system was degassed under vacuum and purged with H_2 several times. Then the mixture was hydrogenated under H_2 balloon (~ 1 atm) at 25 $^\circ\text{C}$ for 16 h. After completion of the reaction, Pd/C was filtered off through celite and the filter cake was washed with MeOH (3 x 100 mL). The corresponding filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 μm , 330 g; Eluent A: Water (10 mmol/L FA); Eluent B: ACN; Gradient: 20% - 55% B in 30 min; Flow rate: 80 mL/min; Detector: 220/254 nm; desired fractions were collected at 48% B) and concentrated under reduced pressure to afford the title compound (5.5g, 76% yield) as a white solid (100 mg, 49%) as a white solid. ^1H NMR (300 MHz, DMSO-*d*₆) δ 13.67 (s, 1H), 8.31-8.20 (m, 3H), 7.64-7.52 (m, 1H), 4.22-4.01 (m, 4H), 1.32-1.18 (m, 6H); LC/MS (ESI, *m/z*): $[(\text{M} + \text{H})]^+ = 365.3$.

[00792] Difluoro[2-(2,3,4,5,6-pentafluorophenoxycarbonyl)-1-benzothiophen-5-yl]methylphosphonic acid (Intermediate BA)



[00793] Step 1 - 2,3,4,5,6-pentafluorophenyl 5-[(diethoxyphosphoryl)difluoromethyl]-1-benzothiophene-2-carboxylate

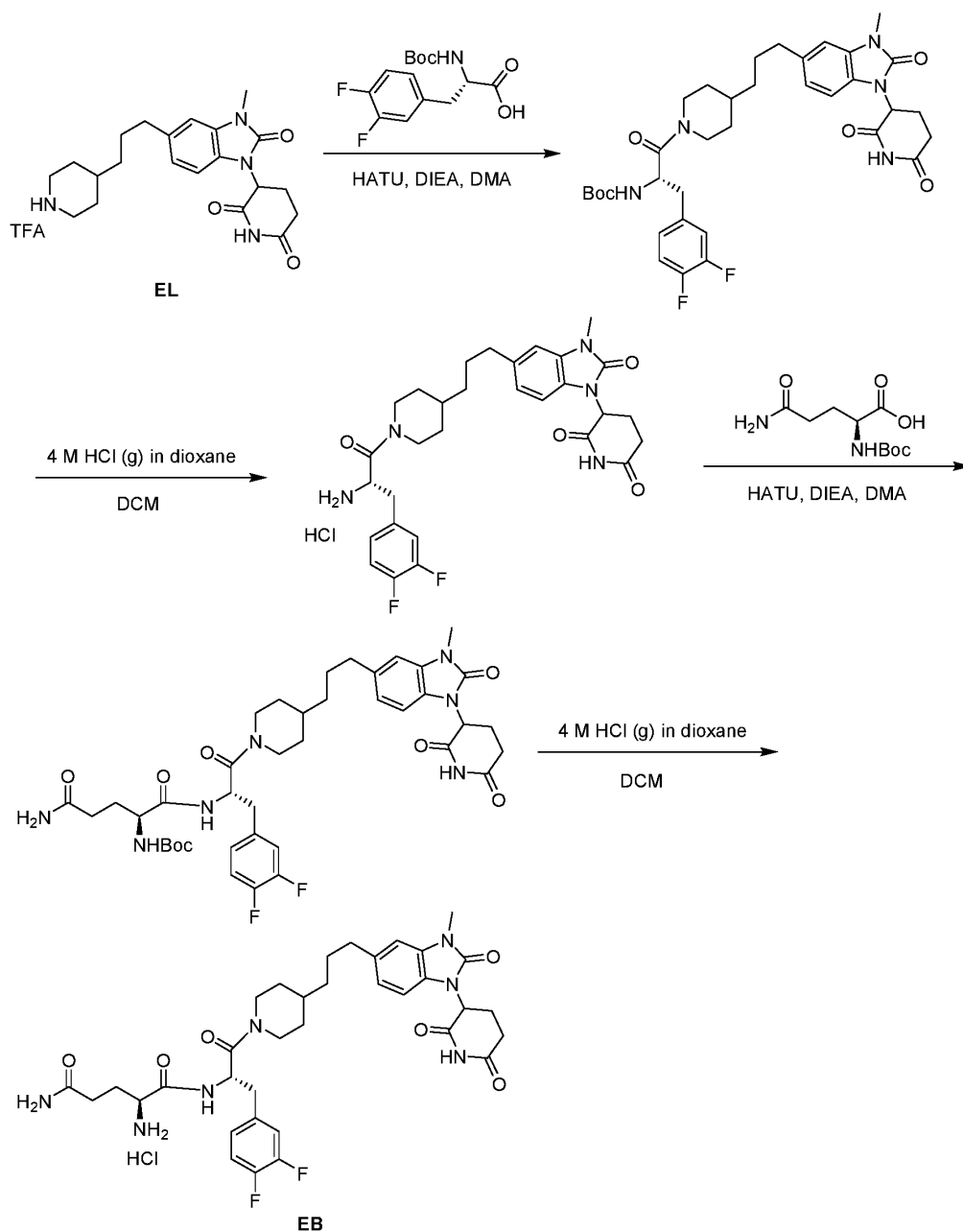
[00794] To a stirred mixture of 5-[(diethoxyphosphoryl)difluoromethyl]-1-benzothiophene-2-carboxylic acid (1.0 g, 2.74 mmol, Intermediate AX) and pentafluorophenol (0.56 g, 3.04 mmol) in DCM (15 mL) was added DCC (0.85 g, 4.12 mmol) at rt under nitrogen atmosphere. The resulting mixture was

stirred for 2 h at rt under nitrogen atmosphere. On completion, the resulting mixture was filtered and the filter cake was washed with DCM (3 x 100 mL). The filtrate was concentrated under reduced pressure and the resulting mixture was suspended in hexanes (500 mL). The precipitated solids were collected by filtration and washed with hexanes (3 x 50 mL) to afford the title compound (900 mg, 62% yield) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.35-8.28(m, 1H), 8.26-8.20(m, 1H), 8.15-8.09(m, 1H), 7.78-7.64 (m, 1H), 4.21-3.99 (m, 4H), 1.35-1.21 (m, 6H). LC/MS (ESI, m/z): [(M + H)]⁺ = 531.5.

[00795] Step 2 - difluoro[2-(2,3,4,5,6-pentafluorophenoxy)carbonyl]-1-benzothiophen-5-yl]methylphosphonic acid as a white solid

[00796] To a stirred solution of 2,3,4,5,6-pentafluorophenyl 5-[(diethoxyphosphoryl)difluoromethyl]-1-benzothiophene-2-carboxylate (900 mg, 1.70 mmol) in DCM (15 mL) was added TMSI (1697 mg, 8.49 mmol) dropwise at 25 °C under nitrogen atmosphere. The resulting mixture was stirred for 15 min at 25 °C under nitrogen atmosphere. On completion, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 μm, 330 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 15% - 75% B in 30 min; Flow rate: 90 mL/min; Detector: 220/254 nm; desired fractions were collected at 65% B) and concentrated under reduced pressure to afford the title compound (600 mg, 75% yield) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.61-8.55 (m, 1H), 8.38-8.31 (m, 1H), 8.21-8.14 (m, 1H), 7.88-7.81 (m, 1H). LC/MS (ESI, m/z): [(M + H)]⁺ = 475.5.

[00797] (2*S*)-2-amino-*N*-[(2*S*)-3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]pentanediamide (Intermediate EB)



[00798] Step 1 - *Tert*-butyl *N*-[(2*S*)-3-(3,4-difluorophenyl)-1-(4-[3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl]piperidin-1-yl)-1-oxopropan-2-yl]carbamate

[00799] To a stirred solution of 3-[3-methyl-2-oxo-5-[3-(piperidin-4-yl)propyl]-1,3-benzodiazol-1-yl]piperidine-2,6-dione trifluoroacetate (1.00 g, 2.38 mmol, Intermediate EL) and (2*S*)-2-[(*tert*-

butoxycarbonyl)amino]-3-(3,4-difluorophenyl)propanoic acid (0.79 g, 2.61 mmol, CAS# 198474-90-7) in DMA (10.00 mL) were added HATU (1.17 g, 3.09 mmol) and TEA (0.96 g, 9.49 mmol) at 25 °C under nitrogen atmosphere and the reaction mixture was stirred for 1 hr. On completion, the residue was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 µm, 120 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 30% - 80% B in 25 min; Flow rate: 65 mL/min; Detector: 220/254 nm; desired fractions were collected at 75% B and concentrated under reduced pressure) to afford the title compound (1.1 g, 69% yield) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.38-8.33 (m, 1H), 7.11-6.81 (m, 6H), 6.80-6.69 (m, 1H), 5.50-5.42 (m, 1H), 5.26-5.21 (m, 1H), 4.85-4.80 (m, 1H), 4.58-4.52 (m, 1H), 3.81-3.75 (m, 1H), 3.45 (s, 3H), 3.06-2.71 (m, 6H), 2.67-2.43 (m, 3H), 2.29-2.17 (m, 1H), 1.79-1.53 (m, 4H), 1.42 (s, 9H), 1.29-1.01 (m, 3H), 0.96-0.68 (m, 1H); LC/MS (ESI, *m/z*): [(M + H)]⁺ = 668.3.

[00800] Step 2 - 3-[5-(3-[1-[(2*S*)-2-amino-3-(3,4-difluorophenyl)propanoyl]piperidin-4-yl]propyl)-3-methyl-2-oxo-1,3-benzodiazol-1-yl]piperidine-2,6-dione hydrochloride

[00801] To a stirred solution of *tert*-butyl *N*-[(2*S*)-3-(3,4-difluorophenyl)-1-(4-[3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl]piperidin-1-yl)-1-oxopropan-2-yl]carbamate (1.10 g, 1.65 mmol) in DCM (10.00 mL) was added HCl (gas) in 1,4-dioxane (10.00 mL) at rt under nitrogen atmosphere and the reaction mixture was stirred for 2 hr. On completion, the reaction mixture was concentrated under vacuum to afford the title compound (900 mg, 90% yield) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.31-7.21 (m, 2H), 7.14-6.89 (m, 4H), 5.40-5.28 (m, 1H), 4.74-4.64 (m, 1H), 4.51-4.46 (m, 1H), 3.77-3.58 (m, 1H), 3.42 (s, 3H), 3.20-2.54 (m, 9H), 2.22-2.12 (m, 1H), 1.81-1.39 (m, 5H), 1.35-0.97 (m, 3H), 0.91-0.69 (m, 1H); LC/MS (ESI, *m/z*): [(M + H)]⁺ = 568.7.

[00802] Step 3 - *Tert*-butyl *N*-[(1*S*)-3-carbamoyl-1-[[[(2*S*)-3-(3,4-difluorophenyl)-1-(4-[3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl]piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl}propyl]carbamate

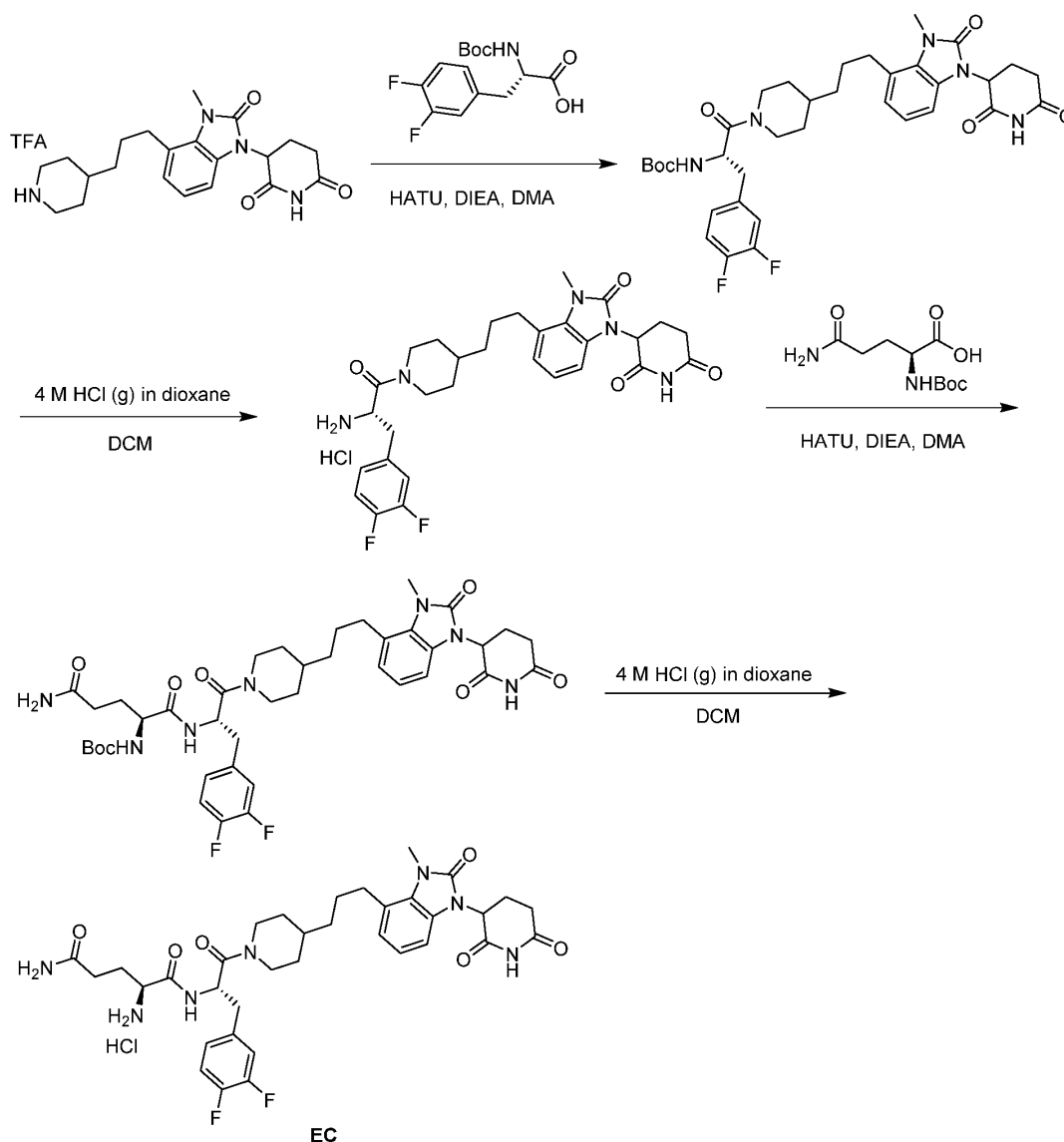
[00803] To a stirred solution of 3-[5-(3-{1-[(2*S*)-2-amino-3-(3,4-difluorophenyl)propanoyl]piperidin-4-yl}propyl)-3-methyl-2-oxo-1,3-benzodiazol-1-yl]piperidine-2,6-dione hydrochloride (900 mg, 1.49 mmol) and (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-4-carbamoylbutanoic acid (366.9 mg, 1.49 mmol) in DMA (10.00 mL) were added HATU (736.42 mg, 1.937 mmol) and TEA (603.02 mg, 5.960 mmol) at 25 °C under nitrogen atmosphere and the reaction mixture was stirred for 1 hr. On completion, the reaction mixture was concentrated under reduced pressure. Then the residue was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 µm, 330 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 20% - 70% B in 25 min; Flow rate: 90 mL/min; Detector: 220/254 nm; desired fractions were collected at 65% B and concentrated under reduced pressure) to afford the title compound (1 g, 84% yield)

as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.53-9.28 (m, 1H), 7.89-7.75 (m, 1H), 7.08-6.95 (m, 2H), 6.96-6.64 (m, 6H), 6.31-6.15 (m, 1H), 5.63-5.50 (m, 1H), 5.39-5.18 (m, 1H), 5.13-5.00 (m, 1H), 4.50 (d, *J* = 12.8 Hz, 1H), 4.25-4.07 (m, 1H), 3.86-3.71 (m, 1H), 3.45 (s, 3H), 3.05-2.39 (m, 8H), 2.30-2.21 (m, 3H), 2.11-1.95 (m, 4H), 1.71-1.62 (m, 3H), 1.42 (s, 9H), 1.29-0.96 (m, 3H), 0.99-0.79 (m, 1H); LC/MS (ESI, *m/z*): [(M + H)]⁺ = 796.6.

[00804] Step 4 - (2*S*)-2-amino-*N*-[(2*S*)-3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]pentanediamide hydrochloride

[00805] To a stirred solution of *tert*-butyl *N*-[(1*S*)-3-carbamoyl-1-{(2*S*)-3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl}propyl]carbamate (1 g, 1 mmol,) in dioxane (10 mL, 120 mmol) was added HCl (gas) in 1,4-dioxane (10 mL, 200 mmol) at rt under nitrogen atmosphere and the reaction mixture was stirred for 2 hr. On completion, the reaction mixture was concentrated under vacuum to afford the title compound (900 mg, 98% yield) as a light yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.26-7.14 (m, 2H), 7.10-6.90 (m, 4H), 5.37-5.30 (m, 1H), 5.14-5.04 (m, 1H), 4.49-4.38 (m, 1H), 4.04-3.84 (m, 2H), 3.44-3.40 (m, 3H), 3.11-2.89 (m, 4H), 2.88-2.36 (m, 7H), 2.22-1.94 (m, 3H), 1.76-1.05 (m, 8H), 0.85-0.64 (m, 1H); LC/MS (ESI, *m/z*): [(M + H)]⁺ = 696.2.

[00806] (2*S*)-2-amino-*N*-[(2*S*)-3-(3,4-difluorophenyl)-1-(4-[3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]propyl]piperidin-1-yl)-1-oxopropan-2-yl]pentanediamide (Intermediate EC)



[00807] Step 1 - Tert-butyl N-[(2S)-3-(3,4-difluorophenyl)-1-(4-[3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]propyl]piperidin-1-yl)-1-oxopropan-2-yl]carbamate

[00808] To a stirred solution of 3-[3-methyl-2-oxo-4-[3-(piperidin-4-yl)propyl]-1,3-benzodiazol-1-yl]piperidine-2,6-dione; trifluoroacetaldehyde (1.00 g, 2.38 mmol, Intermediate EM) and (2S)-2-[(tert-butoxycarbonyl)amino]-3-(3,4-difluorophenyl)propanoic acid (0.72 g, 2.39 mmol, CAS# 198474-90-7) in DMA (10.00 mL) were added HATU (1.17 g, 3.09 mmol) and TEA (0.96 g, 9.48 mmol) at 25 °C under nitrogen atmosphere and the reaction mixture was stirred for 1 h. On completion, the reaction mixture was

concentrated under reduced pressure. Then the residue was purified by reverse phase flash chromatography with the following conditions: Column: WelFlash TM C18-I, 20-40 μ m, 120 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 25% - 85% B in 25 min; Flow rate: 65 mL/min; Detector: 220/254 nm; desired fractions were collected at 73% B and concentrated under reduced pressure) to afford the title compound (1.1g, 69% yield) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.36-8.33 (m, 1H), 7.11-6.81 (m, 6H), 6.80-6.69 (m, 1H), 5.48-5.44 (m, 1H), 5.26-5.21 (m, 1H), 4.88-4.81 (m, 1H), 4.56-4.51 (m, 1H), 3.81-3.75 (m, 1H), 3.48-3.42 (m, 3H), 3.06-2.71 (m, 6H), 2.67-2.43 (m, 3H), 2.29-2.17 (m, 1H), 1.79-1.53 (m, 4H), 1.42 (s, 9H), 1.29-1.01 (m, 3H), 0.96-0.68 (m, 1H); LC/MS (ESI, m/z): $[(\text{M} + \text{H})]^+ = 668.3$.

[00809] Step 2 - 3-[4-(3-{1-[(2*S*)-2-amino-3-(3,4-difluorophenyl)propanoyl]piperidin-4-yl}propyl)-3-methyl-2-oxo-1,3-benzodiazol-1-yl]piperidine-2,6-dione hydrochloride

[00810] To a stirred solution of *tert*-butyl *N*-[(2*S*)-3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]carbamate (1.10 g, 1.65 mmol) in dioxane (10.00 mL, 118.04 mmol) was added HCl (gas) in 1,4-dioxane (10.00 mL, 175.1 mmol) at rt under nitrogen atmosphere and the mixture was stirred for 2 h. On completion, the reaction mixture was concentrated under vacuum to afford the title compound (900 mg, 90% yield) as a white solid. ^1H NMR (400 MHz, Methanol-*d*₄) δ 7.31-7.21 (m, 2H), 7.14-6.89 (m, 4H), 5.40-5.28 (m, 1H), 4.74-4.64 (m, 1H), 4.51-4.47 (m, 1H), 3.77-3.58 (m, 1H), 3.71-3.64 (m, 3H), 3.20-2.54 (m, 9H), 2.22-2.12 (m, 1H), 1.81-1.39 (m, 5H), 1.35-0.97 (m, 3H), 0.91-0.69 (m, 1H); LC/MS (ESI, m/z): $[(\text{M} + \text{H})]^+ = 568.7$.

[00811] Step 3 - *Tert*-butyl *N*-[(1*S*)-3-carbamoyl-1-{[(2*S*)-3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl}propyl]carbamate

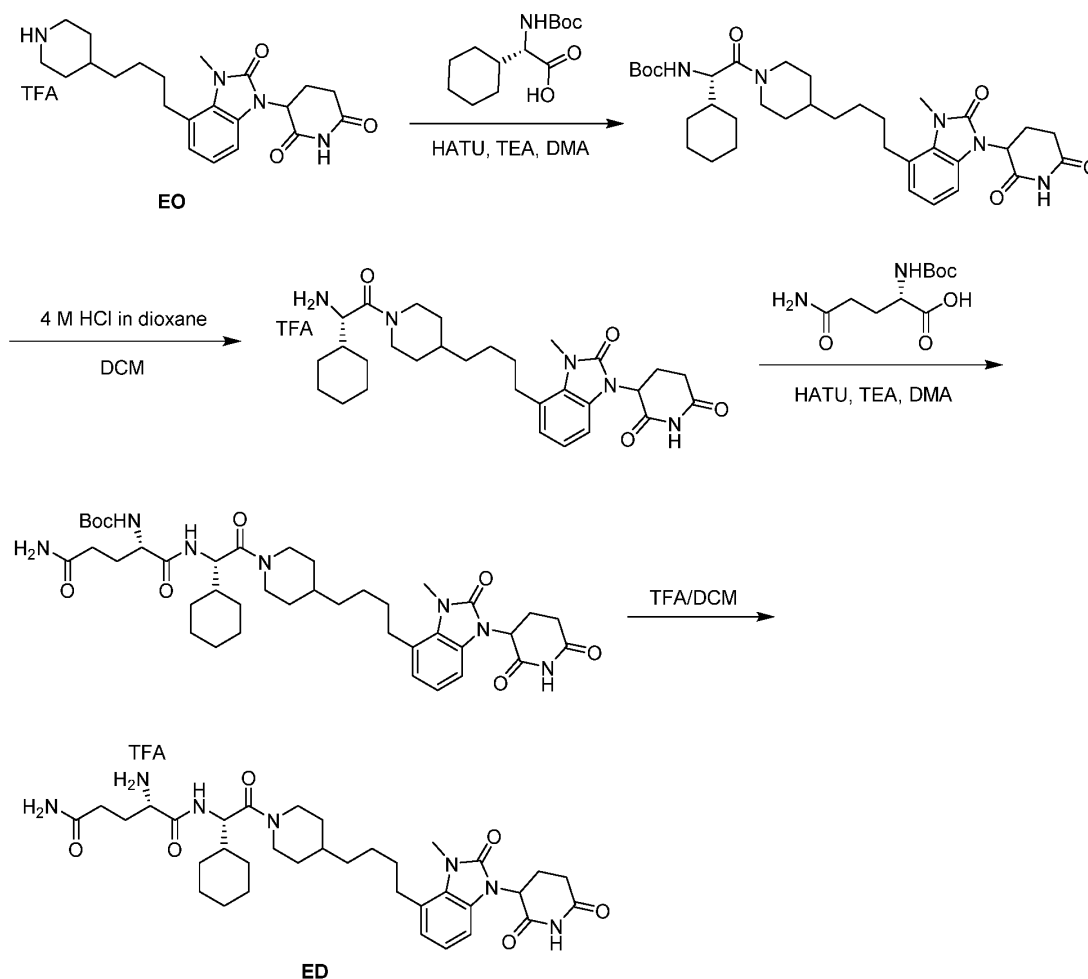
[00812] To a stirred solution of 3-[4-(3-{1-[(2*S*)-2-amino-3-(3,4-difluorophenyl)propanoyl]piperidin-4-yl}propyl)-3-methyl-2-oxo-1,3-benzodiazol-1-yl]piperidine-2,6-dione hydrochloride (900 mg, 1.49 mmol) and (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-4-carbamoylbutanoic acid (366.89 mg, 1.490 mmol) in DMA (10 mL, 110 mmol) were added HATU (736.42 mg, 1.937 mmol) and TEA (603.02 mg, 5.959 mmol) at rt under nitrogen atmosphere and the reaction mixture was stirred for 1 h. On completion, the reaction mixture was concentrated under reduced pressure. Then the residue was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 μ m, 300 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 20% - 70% B in 25 min; Flow rate: 90 mL/min; Detector: 220/254 nm; desired fractions were collected at 65% B and concentrated under reduced pressure) to afford the title compound (1 g, 84% yield) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.53-9.28 (m, 1H), 7.88-7.81 (m,

1H), 7.06-7.01 (m, 2H), 6.96-6.64 (m, 6H), 6.28-6.23 (m, 1H), 5.61-5.56 (m, 1H), 5.39-5.18 (m, 1H), 5.11-5.04 (m, 1H), 4.55-4.50 (m, 1H), 4.21-4.18 (m, 1H), 3.79-3.74 (m, 1H), 3.63 (s, 3H), 3.51-3.40 (m, 3H), 3.05-2.39 (m, 8H), 2.11-1.95 (m, 4H), 1.71-1.62 (m, 3H), 1.42 (s, 9H), 1.29-0.96 (m, 3H), 0.99-0.79 (m, 1H); LC/MS (ESI, m/z): [(M + H)]⁺ = 796.6.

[00813] Step 4 - (2S)-2-amino-N-[(2S)-3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]pentanediamide hydrochloride

[00814] To a stirred solution of *tert*-butyl *N*-[(1*S*)-3-carbamoyl-1-{[(2*S*)-3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl}propyl]carbamate (1 g, 1 mmol) in dioxane (10 mL, 120 mmol) was added HCl (gas) in 1,4-dioxane (10 mL, 120 mmol) at rt under nitrogen atmosphere and the reaction mixture was stirred for 2 h. On completion, the reaction mixture was concentrated under vacuum to afford the title compound (900 mg, 98% yield) as a light yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.26-7.14 (m, 2H), 7.10-6.90 (m, 4H), 5.37-5.33 (m, 1H), 5.14-5.04 (m, 1H), 4.49-4.38 (m, 1H), 4.04-3.84 (m, 2H), 3.46-3.40 (m, 3H), 3.11-2.89 (m, 4H), 2.88-2.36 (m, 7H), 2.22-1.94 (m, 3H), 1.76-1.05 (m, 8H), 0.85-0.64 (m, 1H); LC/MS (ESI, m/z): [(M + H)]⁺ = 696.2.

[00815] (2S)-2-amino-N-[(1S)-1-cyclohexyl-2-(4-{4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]butyl}piperidin-1-yl)-2-oxoethyl]pentanediamide (Intermediate ED)



[00816] Step 1 - *Tert*-butyl *N*-[(1*S*)-1-cyclohexyl-2-(4-{4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]butyl}piperidin-1-yl)-2-oxoethyl]carbamate

[00817] To a stirred solution of 3-{3-methyl-2-oxo-4-[5-(piperidin-4-yl)pentyl]-1,3-benzodiazol-1-yl}piperidine-2,6-dione trifluoroacetate (2.8 g, 5.5 mmol, Intermediate EO) and (*S*)-[(*tert*-butoxycarbonyl)amino](cyclohexyl)acetic acid (1.55 g, 6.03 mmol, CAS# 109183-71-3) in DMA (25 mL) were added TEA (3.81 mL, 27.4 mmol) and HATU (2.50 g, 6.58 mmol) in turns at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at rt under nitrogen atmosphere. On completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography (Column, Welflash TM C18-1, 20-40 μ m, 330 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient 15% to 45% B in 30 min; Flow rate: 80 mL/min; Detector: 220/254 nm; desired fractions were collected at 38% B and concentrated under reduced pressure) to afford the title compound

(2.26 g, 65% yield) as a yellow oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.41 (s, 1H), 6.97 (t, $J = 7.8$ Hz, 1H), 6.87 (d, $J = 7.6$ Hz, 1H), 6.66 (d, $J = 7.8$ Hz, 1H), 5.40 (t, $J = 8.6$ Hz, 1H), 5.21 (dd, $J = 12.5, 5.3$ Hz, 1H), 4.59-4.55 (m, 1H), 4.50-4.45 (m, 1H), 4.05-3.94 (m, 2H), 3.65 (s, 3H), 3.12-2.86 (m, 4H), 2.86-2.62 (m, 2H), 2.59-2.53 (m, 1H), 2.25-2.11 (m, 1H), 1.85-1.58 (m, 9H), 1.54-1.39 (m, 12H), 1.36-1.22 (m, 3H), 1.17-0.99 (m, 6H); LC/MS (ESI, m/z): $[(M + H)]^+ = 638.4$.

[00818] Step 2 - 3-[4-(4-{1-[(2*S*)-2-amino-2-cyclohexylacetyl]piperidin-4-yl}butyl)-3-methyl-2-oxo-1,3-benzodiazol-1-yl]piperidine-2,6-dione trifluoroacetate

[00819] To a stirred solution of *tert*-butyl *N*-[(1*S*)-1-cyclohexyl-2-(4-{4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]butyl}piperidin-1-yl)-2-oxoethyl]carbamate (2.26 g, 3.54 mmol) in DCM (40 mL) was added TFA (8 mL) dropwise at rt under nitrogen atmosphere. The resulting mixture was stirred for 1 h at rt under nitrogen atmosphere. On completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by trituration with Et₂O (20 mL) and the precipitated solids were dried under vacuum to afford the title compound (2.48 g) as a yellow semi-solid. LC/MS (ESI, m/z): $[(M + H)]^+ = 538.4$.

[00820] Step 3 - *Tert*-butyl *N*-[(1*S*)-3-carbamoyl-1-{[(1*S*)-1-cyclohexyl-2-(4-{4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]butyl}piperidin-1-yl)-2-oxoethyl]carbamoyl}propyl]carbamate

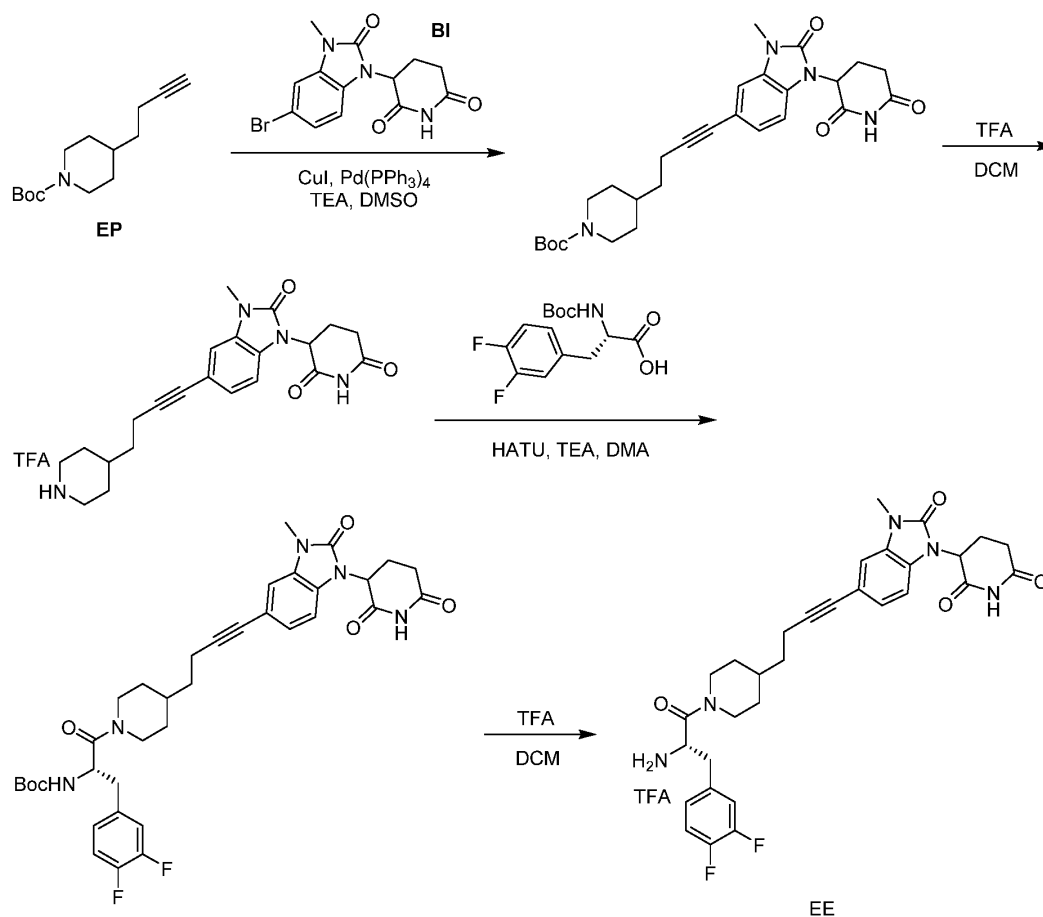
[00821] To a stirred solution of 3-[4-(4-{1-[(2*S*)-2-amino-2-cyclohexylacetyl]piperidin-4-yl}butyl)-3-methyl-2-oxo-1,3-benzodiazol-1-yl]piperidine-2,6-dione trifluoroacetate (2.48 g, 3.901 mmol) and (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-4-carbamoylbutanoic acid (1.06 g, 4.29 mmol, CAS# 13726-85-7) in DMA (20 mL) were added TEA (2.71 mL, 19.5 mmol) and HATU (1.78 g, 4.68 mmol) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at rt under nitrogen atmosphere. On completion, the reaction mixture was concentrated under reduced pressure. Then the residue was purified by reverse flash chromatography (column, Welflash TM C18-1, 20-40 μm , 330 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient 25% to 55% B in 30 min; Flow rate: 80 mL/min; Detector: 220/254 nm; desired fractions were collected at 54% B and concentrated under reduced pressure) to afford the title compound (2.6 g, 87.01%) as a yellow solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.01-8.75 (m, 1H), 7.19 (d, $J = 9.0$ Hz, 1H), 6.99 (td, $J = 7.8, 4.2$ Hz, 1H), 6.89 (dt, $J = 7.9, 1.4$ Hz, 1H), 6.76-6.60 (m, 2H), 5.89-5.68 (m, 1H), 5.40-5.21 (m, 1H), 4.82-4.79 (m, 1H), 4.60-4.56 (m, 1H), 4.20-4.18 (m, 1H), 4.03-3.98 (m, 1H), 3.68 (s, 3H), 3.07-3.01 (m, 1H), 2.99-2.84 (m, 4H), 2.84-2.69 (m, 2H), 2.64-2.53 (m, 1H), 2.43-2.16 (m, 3H), 2.02-1.97 (m, 2H), 1.89-1.57 (m, 10H), 1.52-1.42 (m, 12H), 1.38-0.91 (m, 9H); LC/MS (ESI, m/z): $[(M + H)]^+ = 766.4$.

[00822] Step 4 - (2*S*)-2-amino-*N*-[(1*S*)-1-cyclohexyl-2-(4-{4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-

oxo-1,3-benzodiazol-4-yl]butyl}piperidin-1-yl)-2-oxoethyl]pentanediamide trifluoroacetate

[00823] To a stirred solution of *tert*-butyl *N*-[(1*S*)-3-carbamoyl-1-[(1*S*)-1-cyclohexyl-2-(4-{4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]butyl}piperidin-1-yl)-2-oxoethyl]carbamoyl}propyl]carbamate (2.6 g, 3.4 mmol) in DCM (50 mL) was added TFA (10 mL) dropwise at rt under nitrogen atmosphere. The resulting mixture was stirred for 2 h at rt under nitrogen atmosphere. On completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by trituration with Et₂O (20 mL) and the precipitated solids were dried under reduced pressure to the title compound (2 g) as a yellow semi-solid. LC/MS (ESI, *m/z*): [(*M* + *H*)]⁺ = 666.4.

[00824] 3-[5-(4-{1-[(2*S*)-2-amino-3-(3,4-difluorophenyl)propanoyl]piperidin-4-yl}but-1-yn-1-yl)-3-methyl-2-oxo-1,3-benzodiazol-1-yl]piperidine-2,6-dione (Intermediate EE)



[00825] Step 1 - *Tert*-butyl 4-[4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]but-3-yn-1-yl]piperidine-1-carboxylate

[00826] To a stirred solution of *tert*-butyl 4-(but-3-yn-1-yl)piperidine-1-carboxylate (4.00 g, 16.85 mmol, Intermediate EP) in DMSO (30.00 mL) and TEA (10.00 mL) were added 3-(5-bromo-3-methyl-2-oxo-1,3-benzodiazol-1-yl)piperidine-2,6-dione (5.70 g, 16.9 mmol, Intermediate BI), CuI (0.32 g, 1.7 mmol) and Pd(PPh₃)₄ (1.95 g, 1.69 mmol) in turns at rt under nitrogen atmosphere. The resulting mixture was stirred for 4 h at 80 °C under nitrogen atmosphere. On completion, the reaction mixture was allowed to cool down to rt. The resulting mixture was concentrated under reduced pressure to remove excess TEA. Then to the residue was added FA (3 mL) and the resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL), the combined organic layers were washed with brine (8 x 50 mL), and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂ / MeOH (60:1), to afford the title compound (3.8 g, 46% yield) as a brown solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.29 (s, 1H), 7.15 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.07 (d, *J* = 1.4 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 5.21 (dd, *J* = 12.6, 5.4 Hz, 1H), 4.19-4.04 (m, 2H), 3.44 (s, 3H), 2.99-2.93 (m, 1H), 2.89-2.85 (m, 1H), 2.81-2.65 (m, 3H), 2.47 (t, *J* = 6.9 Hz, 2H), 2.30-2.19 (m, 1H), 1.76-1.72 (m, 2H), 1.64-1.66 (m, 3H), 1.48 (s, 9H), 1.21-1.10 (m, 2H); LC/MS (ESI, *m/z*): [(M + H)]⁺ = 495.3.

[00827] Step 2 - 3-{3-Methyl-2-oxo-5-[4-(piperidin-4-yl)but-1-yn-1-yl]-1,3-benzodiazol-1-yl}piperidine-2,6-dione trifluoroacetate

[00828] To a stirred solution of *tert*-butyl 4-{4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]but-3-yn-1-yl}piperidine-1-carboxylate (2.4 g, 4.9 mmol) in DCM (15.00 mL) was added TFA (3.00 mL) dropwise at rt under air atmosphere. The resulting mixture was stirred for 1 h at rt under air atmosphere. On completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by trituration with Et₂O (2 x 50 mL) to afford the title compound (2.5 g, 94% yield) as a light brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.11 (s, 1H), 8.71 (s, 1H), 8.39 (s, 1H), 7.23 (s, 1H), 7.10 (s, 2H), 5.38 (dd, *J* = 12.8, 5.4 Hz, 1H), 3.34 (s, 3H), 3.28 (d, *J* = 12.7 Hz, 2H), 2.95-2.81 (m, 2H), 2.78-2.59 (m, 2H), 2.47 (t, *J* = 7.2 Hz, 2H), 2.10-1.98 (m, 1H), 1.92-1.83 (m, 2H), 1.73-1.69 (m, 1H), 1.54 (q, *J* = 7.2 Hz, 2H), 1.40-1.27 (m, 2H). LC/MS (ESI, *m/z*): [(M + H)]⁺ = 395.3.

[00829] Step 3 - *Tert*-butyl N-[(2S)-3-(3,4-difluorophenyl)-1-(4-[4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]but-3-yn-1-yl]piperidin-1-yl)-1-oxopropan-2-yl]carbamate

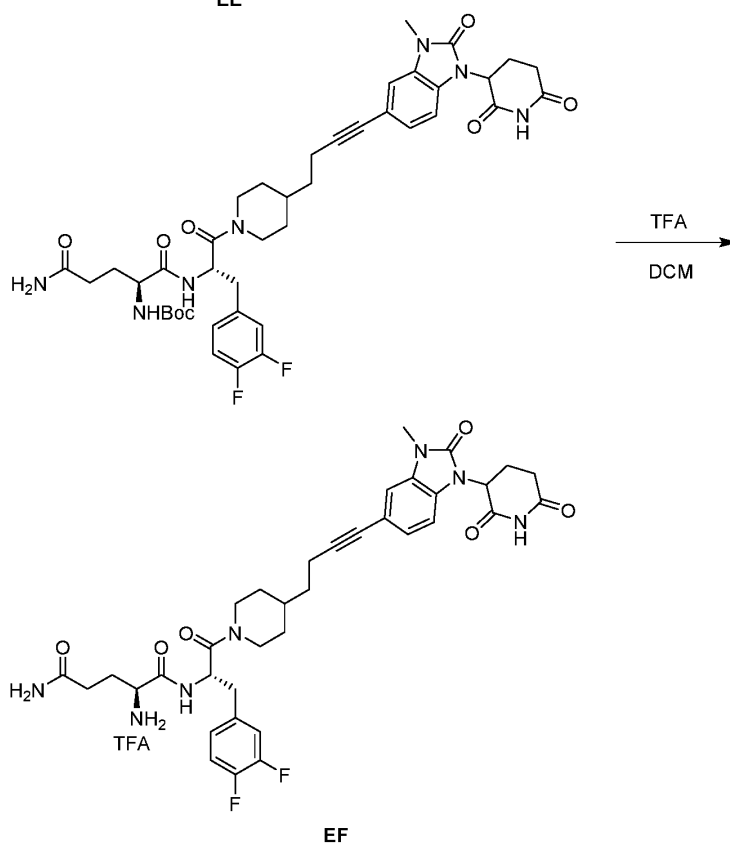
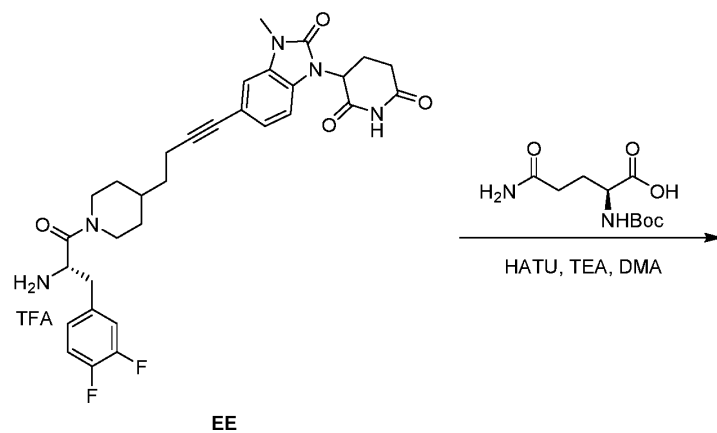
[00830] To a stirred solution of 3-[3-methyl-2-oxo-5-[4-(piperidin-4-yl)but-1-yn-1-yl]-1,3-benzodiazol-1-yl]piperidine-2,6-dione trifluoroacetate (2.3 g, 4.7 mmol) and (2S)-2-[(*tert*-butoxycarbonyl)amino]-3-(3,4-difluorophenyl)propanoic acid (1.69 g, 5.60 mmol, CAS# 198474-90-7) in DMA (15 mL) were added TEA (2.36 g, 23.4 mmol) and HATU (2.13 g, 5.60 mmol) in turns at rt under air atmosphere. The resulting mixture was stirred for 1 h at rt. On completion, the reaction mixture was

concentrated under reduced pressure. The residue was then purified by reverse phase flash chromatography (Column: WelFlash™ C18-I, 20-40 μ m, 330 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 35% - 65% B in 25 min; Flow rate: 80 mL/min; Detector: 220/254 nm; desired fractions were collected at 60 % B and concentrated under reduced pressure) to afford the title compound (2.3 g, 73% yield) as a light brown solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.57-8.51 (m, 1H), 7.17-7.09 (m, 1H), 7.09-7.05 (m, 2H), 7.03-6.86 (m, 2H), 6.74 (d, J = 8.1 Hz, 1H), 5.57-5.43 (m, 1H), 5.22 (dd, J = 12.7, 5.4 Hz, 1H), 4.86-4.82 (m, 1H), 4.58 (d, J = 13.2 Hz, 1H), 3.80 (t, J = 16.1 Hz, 1H), 3.43 (s, 3H), 3.06-2.95 (m, 2H), 2.95-2.83 (m, 3H), 2.77-2.73 (m, 1H), 2.68-2.50 (m, 2H), 2.46-2.41 (m, 2H), 2.26-2.22 (m, 1H), 1.79 (d, J = 13.5 Hz, 1H), 1.74-1.66 (m, 2H), 1.58-1.48 (m, 2H), 1.42 (s, 9H), 1.16-1.05 (m, 1H). LC/MS (ESI, m/z): $[(M + H)]^+ = 678.2$.

[00831] Step 4 - 3-[5-(4-{1-[(2S)-2-amino-3-(3,4-difluorophenyl)propanoyl]piperidin-4-yl}but-1-yn-1-yl)-3-methyl-2-oxo-1,3-benzodiazol-1-yl]piperidine-2,6-dione trifluoroacetate

[00832] To a stirred solution of *tert*-butyl *N*-[(2S)-3-(3,4-difluorophenyl)-1-(4-{4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]but-3-yn-1-yl}piperidin-1-yl)-1-oxopropan-2-yl]carbamate (2.3 g, 3.4 mmol) in DCM (15.00 mL) was added TFA (3.00 mL) dropwise at rt under air atmosphere. The resulting mixture was stirred for 1 h at rt under air atmosphere. On completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by trituration with Et₂O (2 x 60 mL) to afford the title compound (2.3 g, 90% yield) as a light brown solid. ^1H NMR (400 MHz, DMSO-*d*₆) δ 11.11 (s, 1H), 8.16 (d, J = 22.8 Hz, 4H), 7.51-7.29 (m, 2H), 7.21 (s, 1H), 7.11-7.07 (m, 2H), 5.38 (dd, J = 12.8, 5.4 Hz, 1H), 4.69-4.43 (m, 2H), 4.39-4.35 (m, 1H), 3.88-3.75 (m, 1H), 3.43-3.36 (m, 2H), 3.01-2.88 (m, 4H), 2.75-2.59 (m, 2H), 2.45-2.41 (m, 2H), 2.04-2.00 (m, 2H), 1.80-1.72 (m, 1H), 1.68-1.56 (m, 2H), 1.54-1.50 (m, 1H), 1.42-1.38 (m, 1H), 1.04-0.94 (m, 1H). LC/MS (ESI, m/z): $[(M + H)]^+ = 578.5$.

[00833] (2S)-2-amino-*N*-[(2S)-3-(3,4-difluorophenyl)-1-(4-{4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]but-3-yn-1-yl}piperidin-1-yl)-1-oxopropan-2-yl]pentanediamide
(Intermediate EF)



[00834] Step 1 - *Tert*-butyl *N*-[(1*S*)-3-carbamoyl-1-[(2*S*)-3-(3,4-difluorophenyl)-1-(4-{4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]but-3-yn-1-yl}piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl]propyl]carbamate

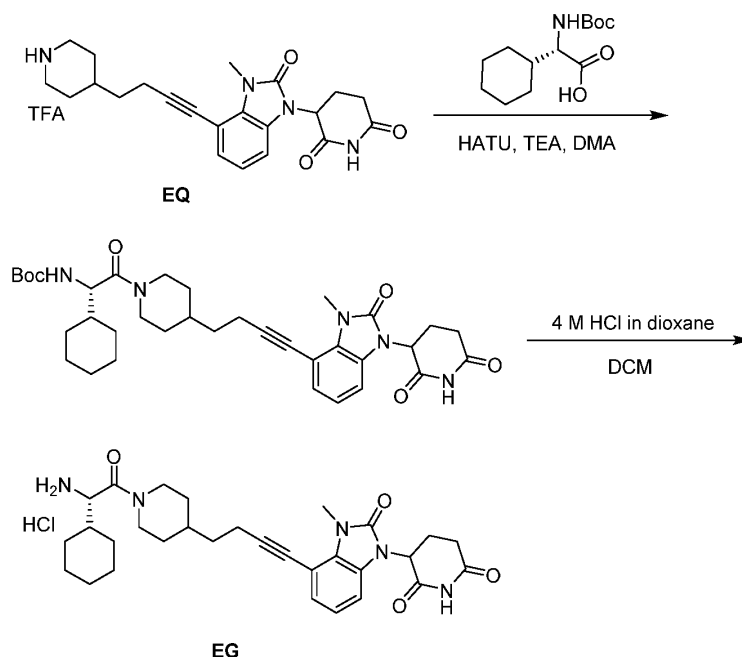
[00835] To a stirred solution of 3-[5-(4-{1-[(2*S*)-2-amino-3-(3,4-difluorophenyl)propanoyl]piperidin-

4-yl}but-1-yn-1-yl)-3-methyl-2-oxo-1,3-benzodiazol-1-yl]piperidine-2,6-dione trifluoroacetate (2.3 g, 3.4 mmol, Intermediate EE) and (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-4-carbamoylbutanoic acid (1.01 g, 4.09 mmol, CAS# 13726-85-7) in DMA (15 mL) were added TEA (1.72 g, 17.0 mmol) and HATU (1.55 g, 4.09 mmol) in turns at rt under air atmosphere. The resulting mixture was stirred for 1 h at rt under air atmosphere. On completion, the reaction mixture was concentrated under reduced pressure. Then the residue was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 μ m, 330 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 35% - 65% B in 25 min; Flow rate: 80 mL/min; Detector: 220/254 nm; desired fractions were collected at 51 % B and concentrated under reduced pressure) to afford the title compound (1.83 g, 67% yield) as a light brown solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.29-9.19 (m, 1H), 7.73 (s, 1H), 7.14-7.08 (m, 1H), 7.09-6.96 (m, 3H), 6.93-6.89 (m, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.64 (s, 1H), 6.15 (s, 1H), 5.54-5.52 (m, 1H), 5.35-5.20 (m, 1H), 5.10-5.03 (m, 2H), 4.53 (d, *J* = 12.8 Hz, 1H), 4.17 (s, 1H), 3.81 (s, 1H), 3.41 (s, 3H), 3.01-2.82 (m, 3H), 2.76-2.62 (m, 1H), 2.54-2.50 (m, 1H), 2.41 (q, *J* = 6.9 Hz, 2H), 2.25-2.21 (m, 3H), 1.97-1.93 (m, 2H), 1.78-1.74 (m, 1H), 1.71-1.61 (m, 2H), 1.56-1.50 (m, 1H), 1.50-1.44 (m, 2H), 1.42 (s, 9H), 1.17-1.07 (m, 1H), 0.92-0.88 (m, 1H). LC/MS (ESI, *m/z*): [(M + H)]⁺ = 806.4.

[00836] Step 2 - (2*S*)-2-amino-*N*-[(2*S*)-3-(3,4-difluorophenyl)-1-(4-{4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]but-3-yn-1-yl}piperidin-1-yl)-1-oxopropan-2-yl]pentanediamide trifluoroacetate

[00837] To a stirred solution of *tert*-butyl *N*-[(1*S*)-3-carbamoyl-1-[(2*S*)-3-(3,4-difluorophenyl)-1-(4-{4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]but-3-yn-1-yl}piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl]propyl]carbamate (1.8 g, 2.2 mmol) in DCM (3.00 mL) was added TFA (1.00 mL) dropwise at rt under air atmosphere. The resulting mixture was stirred for 1 h at rt under air atmosphere. On completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by trituration with Et₂O (2 x 10 mL) to afford the title compound (1.6 g, 89% yield) as a light brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.10 (s, 1H), 8.87 (t, *J* = 6.4 Hz, 1H), 8.18 (s, 3H), 7.44 (s, 1H), 7.42-7.27 (m, 1H), 7.22 (s, 1H), 7.11-7.07 (m, 3H), 6.98 (d, *J* = 7.9 Hz, 1H), 5.75-5.65 (s, 2H), 5.38 (dd, *J* = 12.8, 5.4 Hz, 1H), 5.00-4.96 (m, 1H), 4.35 (d, *J* = 12.5 Hz, 1H), 3.95 (t, *J* = 15.3 Hz, 1H), 3.85-3.81 (m, 1H), 3.34 (s, 3H), 3.05-2.92 (m, 1H), 2.90-2.86 (m, 2H), 2.74-2.54 (m, 3H), 2.43 (q, *J* = 7.9 Hz, 2H), 2.26-2.22 (m, 2H), 2.06-2.02 (m, 1H), 1.93-1.89 (m, 2H), 1.75-1.58 (m, 2H), 1.49-1.45 (m, 2H), 1.05-0.98 (m, 1H), 0.85-0.75 (m, 1H). LC/MS (ESI, *m/z*): [(M + H)]⁺ = 706.4.

[00838] 3-[4-(4-{1-[(2*S*)-2-amino-2-cyclohexylacetyl] piperidin-4-yl} but-1-yn-1-yl)-3-methyl-2-oxo-1,3-benzodiazol-1-yl] piperidine-2,6-dione (Intermediate EG)



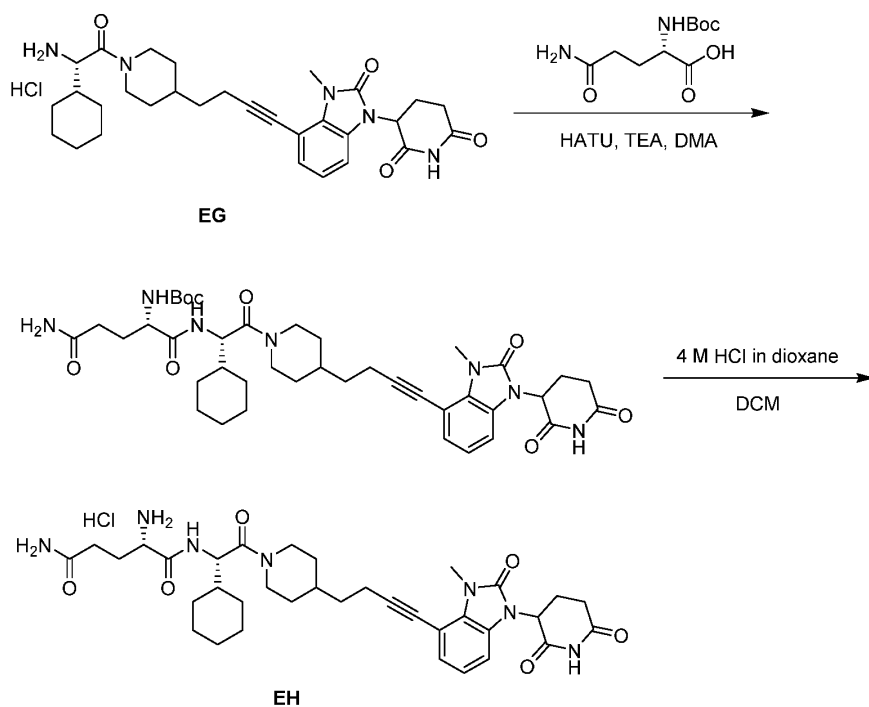
[00839] Step 1- *Tert*-butyl *N*-[(1*S*)-1-cyclohexyl-2-(4-{4-[1-(2, 6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1, 3-benzodiazol-4-yl] but-3-yn-1-yl} piperidin-1-yl)-2-oxoethyl] carbamate

[00840] To a stirred solution of 3-{3-methyl-2-oxo-4-[4-(piperidin-4-yl) but-1-yn-1-yl]-1,3-benzodiazol-1-yl} piperidine-2,6-dione trifluoroacetate (4 g, 8.122 mmol, Intermediate EQ) and (*S*)-[(*tert*-butoxycarbonyl) amino] (cyclohexyl) acetic acid (2.30 g, 8.934 mmol, CAS# 109183-71-3) in DMA (30.00 mL) were added TEA (5.64 mL, 40.6 mmol) and HATU (3.71 g, 9.75 mmol) at 0 °C under nitrogen atmosphere. The resulting mixture was then stirred for 1 h at 25 °C under nitrogen atmosphere. On completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography (Column: WelFlash™ C18-I, 20-40 μm, 330 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 40%-80% B in 40 min; Flow rate: 80 mL/min; Detector: 220/254 nm; desired fractions were collected at 69% B and concentrated under reduced pressure) to afford the title compound (3.9 g, 76% yield) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.46 (s, 1H), 7.11 (d, *J* = 7.9 Hz, 1H), 6.96 (t, *J* = 7.9 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 5.44-5.39 (m, 1H), 5.25-5.17 (m, 1H), 4.67-4.61 (m, 1H), 4.53-4.46 (m, 1H), 4.07-4.04 (m, 1H), 3.77 (s, 3H), 3.18-2.98 (m, 1H), 2.97-2.68 (m, 3H), 2.68-2.57 (m, 1H), 2.56-2.44 (m, 2H), 2.29-2.15 (m, 1H), 1.95-1.60 (m, 11H), 1.43 (s, 9H), 1.33-0.95 (m, 7H); LC/MS (ESI, *m/z*): [(*M* + *H*)]⁺ = 634.3.

[00841] Step 2 - 3-[4-(4-{1-[(2*S*)-2-amino-2-cyclohexylacetyl] piperidin-4-yl} but-1-yn-1-yl)-3-methyl-2-oxo-1, 3-benzodiazol-1-yl] piperidine-2, 6-dione hydrochloride

[00842] To a stirred mixture of *tert*-butyl *N*-[(1*S*)-1-cyclohexyl-2-(4-{4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl] but-3-yn-1-yl} piperidin-1-yl)-2-oxoethyl] carbamate (3.9 g, 6.2 mmol) in DCM (30.00 mL) was added a solution of 4 M HCl (gas) in 1,4-dioxane (20.00 mL) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at rt under nitrogen atmosphere. On completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by trituration with Et₂O (50.00 mL) to afford the title compound (3.6 g, 98% yield) as an off-white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.20-7.12(m, 2H), 7.10-7.06 (m, 2H), 5.43-5.35 (m, 1H), 4.67-4.48 (m, 1H), 4.38-4.32 (m, 1H), 4.09-3.93 (m, 1H), 3.81 (s, 3H), 3.27-3.19 (m, 1H), 3.06-2.75 (m, 4H), 2.67-2.60 (m, 2H), 2.29-2.21 (m, 1H), 2.05-1.59 (m, 11H), 1.51-1.06 (m, 7H); LC/MS (ESI, *m/z*): [(M + H)]⁺=534.5.

[00843] (2*S*)-2-amino-N1-[(1*S*)-1-cyclohexyl-2-(4-(4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1*H*-benzo[d]imidazol-5-yl)but-3-yn-1-yl)piperidin-1-yl)-2-oxoethyl]pentanediamide
(Intermediate EH)



[00844] Step 1 - *Tert*-butyl *N*-[(1*S*)-3-carbamoyl-1-[(1*S*)-1-cyclohexyl-2-(4-{4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl] but-3-yn-1-yl} piperidin-1-yl)-2-oxoethyl] carbamoyl} propyl] carbamate

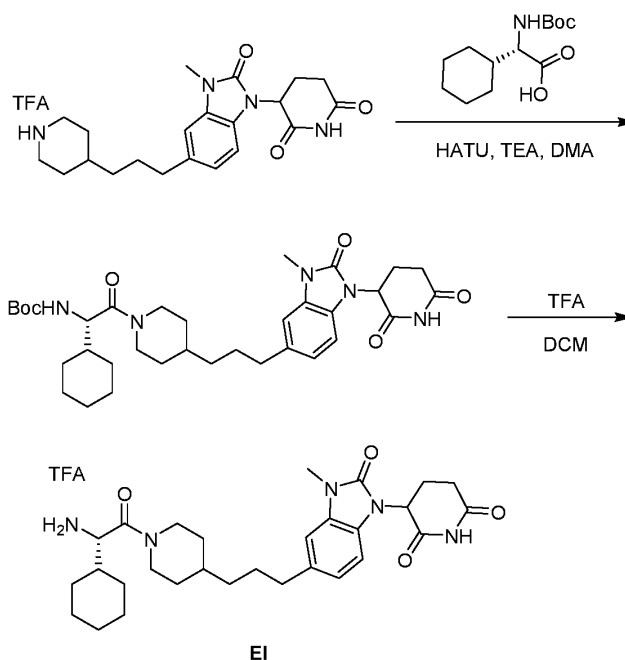
[00845] To a stirred solution of 3-[4-(4-{1-[(2*S*)-2-amino-2-cyclohexylacetyl] piperidin-4-yl} but-1-yn-1-yl)-3-methyl-2-oxo-1,3-benzodiazol-1-yl] piperidine-2,6-dione hydrochloride (3.6 g, 6.31 mmol,

Intermediate EG) and (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-4-carbamoylbutanoic acid (1.87 g, 7.58 mmol, CAS# 13726-85-7) in DMA (30.00 mL) were added TEA (3.19 g, 31.6 mmol) and HATU (2.88 g, 7.58 mmol) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 25 °C under nitrogen atmosphere. On completion, the reaction mixture was concentrated under reduced pressure to remove TEA. The residue was purified by reverse flash chromatography (Column: WelFlash TM C18-I, 20-40 µm, 330 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 30%-65% B in 30 min; Flow rate: 80 mL/min; Detector: 220/254 nm; desired fractions were collected at 60% B and concentrated under reduced pressure) to afford the title compound (4.3 g, 89% yield) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.70-9.43 (m, 1H), 7.49-7.40 (m, 2H), 7.12-7.07 (m, 1H), 6.89-6.70 (m, 3H), 6.15 (s, 1H), 5.59-5.53 (m, 1H), 5.47-5.26 (m, 1H), 4.82-4.76 (m, 1H), 4.64-4.58 (m, 1H), 4.27-3.96 (m, 2H), 3.77 (s, 3H), 3.12-3.02 (m, 1H), 2.99-2.84 (m, 2H), 2.83-2.55 (m, 2H), 2.56-2.46 (m, 2H), 2.36-2.13 (m, 3H), 2.02-1.53 (m, 12H), 1.42 (s, 9H), 1.32-0.90 (m, 7H); LC/MS (ESI, m/z): [(M + H)]⁺ = 762.5.

[00846] Step 2 - (2*S*)-2-Amino-*N*-[(1*S*)-1-cyclohexyl-2-(4-{4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1, 3-benzodiazol-4-yl] but-3-yn-1-yl} piperidin-1-yl)-2-oxoethyl] pentanediamide hydrochloride

[00847] To a stirred mixture of *tert*-butyl *N*-[(1*S*)-3-carbamoyl-1-[(1*S*)-1-cyclohexyl-2-(4-{4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1, 3-benzodiazol-4-yl] but-3-yn-1-yl} piperidin-1-yl)-2-oxoethyl] carbamoyl} propyl] carbamate (2.1 g, 2.8 mmol) in DCM (20.00 mL) was added a solution of 4 M HCl (gas) in 1,4-dioxane (15.00 mL) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at rt under nitrogen atmosphere. On completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by trituration with Et₂O (30.00 mL) to afford the title compound (2 g, 99% yield) as an off-white solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.11 (s, 1H), 8.77-8.57 (m, 1H), 8.36 (broad, 3H), 7.54-7.49 (m, 1H), 7.27-6.87 (m, 1H), 5.58-5.27 (m, 2H), 4.72-4.56 (m, 1H), 4.51-4.29 (m, 1H), 4.00-3.85 (m, 1H), 3.67 (s, 3H), 3.50-3.29 (m, 1H), 3.19-2.81 (m, 2H), 2.80-2.56 (m, 4H), 2.27-2.20 (m, 2H), 2.08-2.01 (m, 1H), 1.95-1.82 (m, 2H), 1.82-1.37 (m, 12H), 1.34-0.84 (m, 9H); LC/MS (ESI, m/z): [(M + H)]⁺ = 662.3.

[00848] 3-[5-(3-{1-[(2*S*)-2-amino-2-cyclohexylacetyl]piperidin-4-yl}propyl)-3-methyl-2-oxo-1,3-benzodiazol-1-yl]piperidine-2,6-dione (Intermediate EI)



[00849] Step 1 - *Tert*-butyl *N*-[(1*S*)-1-cyclohexyl-2-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-2-oxoethyl]carbamate

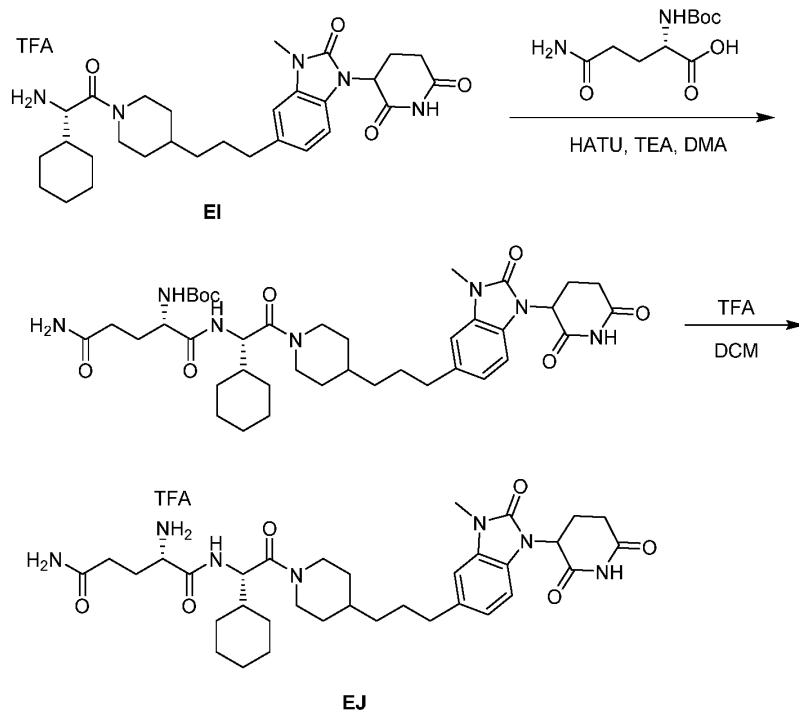
[00850] To a stirred solution of 3-{3-methyl-2-oxo-5-[3-(piperidin-4-yl)propyl]-1,3-benzodiazol-1-yl}piperidine-2,6-dione (1.688 g, 4.390 mmol, Intermediate EL) and (*S*)-[(*tert*-butoxycarbonyl)amino](cyclohexyl)acetic acid (899.8 mg, 3.497 mmol, CAS# 109183-71-3) in DMA (13 mL) were added TEA (1.8 g, 18 mmol) and HATU (1.6 g, 4.2 mmol) in turns at rt. The resulting mixture was stirred for 1 h at rt. On completion, the residue was purified by reverse phase flash chromatography (Column: WelFlash™ C18-I, 20-40 μ m, 330 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 25%-65% B in 25 min; Flow rate: 80 mL/min; Detector: 220/254 nm; desired fractions were collected at 50% B and concentrated under reduced pressure) to afford the title compound (2.3 g, 84% yield) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.32 (s, 1H), 6.93-6.83 (m, 2H), 6.75-6.71 (m, 1H), 5.42-5.38 (m, 2H), 5.23 (dd, J = 12.6, 5.4 Hz, 2H), 4.59-4.56 (m, 1H), 4.49-4.46 (m, 1H), 4.03-3.96 (m, 1H), 3.45 (s, 3H), 3.11-3.00 (m, 1H), 2.97-2.93 (m, 1H), 2.90-2.71 (m, 2H), 2.67-2.63 (m, 2H), 2.58-2.55 (m, 1H), 2.30-2.20 (m, 1H), 1.75-1.79 (m, 4H), 1.66-1.69 (m, 2H), 1.58-1.51 (m, 2H), 1.44 (s, 9H), 1.34-1.37 (m, 2H), 1.25-1.21 (m, 1H), 1.19-0.99 (m, 7H). LC/MS (ESI, m/z): $[(M + H)]^+ = 624.4$.

[00851] Step 2 - 3-[5-(3-{1-[(2*S*)-2-amino-2-cyclohexylacetyl]piperidin-4-yl}propyl)-3-methyl-2-oxo-1,3-benzodiazol-1-yl]piperidine-2,6-dione

[00852] To a stirred solution of *tert*-butyl *N*-[(1*S*)-1-cyclohexyl-2-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-

3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-2-oxoethyl]carbamate (2.334 g, 3.742 mmol) in DCM (20.00 mL) was added TFA (4 mL) dropwise at rt and the resulting mixture was stirred for 30 min. On completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by trituration with Et₂O (2 x 10 mL) to afford the title compound (2.3 g, 99% yield) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.73 (s, 1H), 7.96 (s, 3H), 6.92-6.87 (m, 2H), 6.77 (s, 1H), 6.32 (s, 3H), 5.30-5.26 (m, 1H), 4.56-4.52 (m, 2H), 4.34-4.30 (m, 1H), 3.78-3.74 (m, 1H), 3.46 (s, 3H), 3.08-3.04 (m, 1H), 2.94-2.90 (m, 1H), 2.69-2.65 (m, 4H), 2.27-2.24 (m, 1H), 1.85-1.78 (m, 4H), 1.75-1.66 (m, 9H), 1.36-1.23 (m, 4H). LC/MS (ESI, *m/z*): [(M + H)]⁺ = 524.2.

[00853] (2*S*)-2-amino-*N*-[(1*S*)-1-cyclohexyl-2-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-2-oxoethyl]pentanediamide (Intermediate EJ)



[00854] Step 1 - *Tert*-butyl *N*-[(1*S*)-3-carbamoyl-1-{[(1*S*)-1-cyclohexyl-2-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-2-oxoethyl]carbamoyl}propyl]carbamate

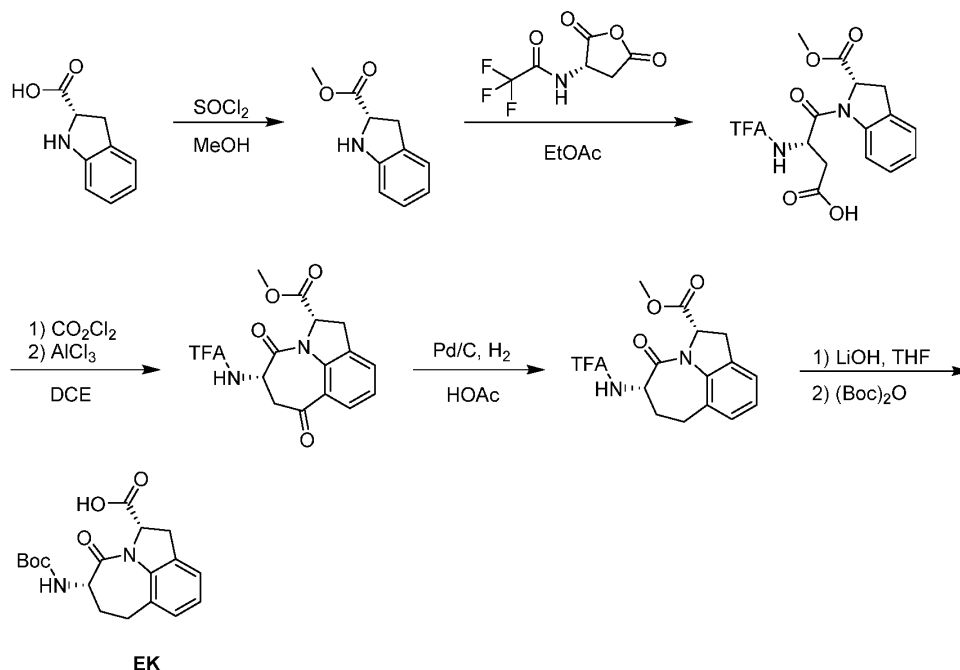
[00855] To a stirred solution of 3-[5-(3-{1-[(2*S*)-2-amino-2-cyclohexylacetyl]piperidin-4-yl}propyl)-3-methyl-2-oxo-1,3-benzodiazol-1-yl]piperidine-2,6-dione (2.322 g, 4.434 mmol, Intermediate EI) and (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-4-carbamoylbutanoic acid (1.09 g, 4.434 mmol, CAS# 13726-85-7) in DMA (20.00 mL) were added TEA (2.24 g, 22.1 mmol) and HATU (2.02 g, 5.32 mmol) in turns at rt.

The resulting mixture was stirred for 1 h at rt. On completion, the reaction mixture was concentrated under reduced pressure. Then the residue was purified by reverse phase flash chromatography (Column: WelFlash™ C18-I, 20-40 μ m, 330 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 25%-55% B in 25 min; Flow rate: 80 mL/min; Detector: 220/254 nm; desired fractions were collected at 50% B and concentrated under reduced pressure) to afford the title compound (2.115 g, 64% yield) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.51-9.39 (m, 1H), 7.87-7.77 (m, 2H), 7.04-6.97 (m, 2H), 6.89-6.82 (m, 2H), 6.80-6.72 (m, 2H), 5.60-5.55 (m, 2H), 5.39-5.30 (m, 2H), 5.30-5.21 (m, 2H), 4.54-4.46 (m, 2H), 4.22-4.15 (m, 2H), 3.45 (s, 3H), 2.93-2.85 (m, 10H), 2.66-2.58 (m, 4H), 2.29-2.18 (m, 3H), 2.01-1.87 (m, 2H), 1.66-1.58 (m, 4H), 1.42 (s, 9H), 1.31-1.00 (m, 3H). LC/MS (ESI, *m/z*): [(M + H)]⁺ = 752.4.

[00856] Step 2 - (2*S*)-2-amino-*N*-[(1*S*)-1-cyclohexyl-2-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-2-oxoethyl]pentanediamide

[00857] To a stirred solution of *tert*-butyl *N*-[(1*S*)-3-carbamoyl-1-{[(1*S*)-1-cyclohexyl-2-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-2-oxoethyl]carbamoyl}propyl]carbamate (2.115 g, 2.813 mmol) in DCM (20 mL) was added TFA (4 mL, 50 mmol) dropwise at rt and the mixture was stirred for 30 min. On completion, the reaction mixture was concentrated under reduced pressure to afford the title compound (1.8 g, 99% yield) as a white solid. ^1H NMR (400 MHz, DMSO-*d*₆) δ 11.07 (s, 1H), 8.62-8.53 (m, 2H), 8.14-8.10 (m, 3H), 7.44-7.40 (m, 2H), 7.05-6.95 (m, 3H), 6.90-6.83 (m, 2H), 5.34 (dd, *J* = 12.8, 5.3 Hz, 1H), 4.68-4.59 (m, 2H), 4.39-4.33 (m, 1H), 4.05-3.96 (m, 1H), 3.90-3.84 (m, 1H), 3.46 (s, 3H), 3.10-2.96 (m, 1H), 2.96-2.84 (m, 2H), 2.78-2.69 (m, 1H), 2.67-2.63 (m, 1H), 2.62-2.58 (m, 4H), 2.26-2.15 (m, 2H), 1.89-1.85 (m, 1H), 1.69-1.59 (m, 8H), 1.27-0.97 (m, 6H), 0.88-0.86 (m, 1H). LC/MS (ESI, *m/z*): [(M + H)]⁺ = 652.4.

[00858] (2*S*,11*S*)-11-[(*tert*-butoxycarbonyl)amino]-12-oxo-1-azatricyclo[6.4.1.0^{4,13}]trideca-4(13),5,7-triene-2-carboxylic acid (Intermediate EK)



[00859] Step 1 - Methyl (2S)-2,3-dihydro-1H-indole-2-carboxylate

[00860] To a stirred solution of (2S)-2,3-dihydro-1H-indole-2-carboxylic acid (500.00 g, 3064.2 mmol, CAS# 79815-20-6) in MeOH (7.50 L) was added SOCl₂ (333.43 mL, 2802.6 mmol) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 65 °C under nitrogen atmosphere. On completion, the reaction mixture was allowed to cool down to rt. Then the reaction mixture was concentrated under vacuum. The residue was dissolved in DCM (3000 mL) then neutralized to pH 7 with saturated NaHCO₃ (aq.). The resulting mixture was extracted with CH₂Cl₂ (3 x 1500 mL). The combined organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound (500 g, 92% yield) as a brown oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.15-7.04 (m, 2H), 6.81-6.72 (m, 2H), 4.42 (dd, *J* = 10.2, 5.5 Hz, 1H), 3.78 (s, 3H), 3.44-3.34 (m, 2H); LC/MS (ESI, *m/z*): [(M + H)]⁺ = 178.1.

[00861] Step 2 - (3S)-4-[(2S)-2-(methoxycarbonyl)-2,3-dihydroindol-1-yl]-4-oxo-3-(2,2,2-trifluoroacetamido)butanoic acid

[00862] To a stirred mixture of methyl (2S)-2,3-dihydro-1H-indole-2-carboxylate (400.00 g, 2257.3 mmol) in was added *N*-[(3S)-2,5-dioxoxolan-3-yl]-2,2,2-trifluoroacetamide (524.16 g, 2483.028 mmol, CAS# 777-33-3) in EtOAc (3.00 L) dropwise for 3 hours at rt under nitrogen atmosphere. The resulting mixture was stirred for overnight hour at rt under nitrogen atmosphere. On completion, the reaction mixture was washed with water (2 x 1 L) and dried over anhydrous Na₂SO₄. The combined organic layer was

concentrated under reduced pressure to afford the title compound (800 g, 91% yield) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.57 (s, 1H), 9.99 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.30-7.20 (m, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 5.32 (dd, *J* = 10.6, 1.9 Hz, 1H), 5.03-4.98 (m, 1H), 3.68-3.65 (m, 1H), 3.64 (s, 3H), 3.21-3.17 (m, 1H), 3.03-2.98 (m, 1H), 2.74-2.67 (m, 1H); LC/MS (ESI, *m/z*): [(M - H)]⁻ = 387.2.

[00863] Step 3 - Methyl (2*S*,11*S*)-9,12-dioxo-11-(2,2,2-trifluoroacetamido)-1-azatricyclo[6.4.1.0⁴[4,13]]trideca-4,6,8(13)-triene-2-carboxylate

[00864] To a solution of (3*S*)-4-[(2*S*)-2-(methoxycarbonyl)-2,3-dihydroindol-1-yl]-4-oxo-3-(2,2,2-trifluoroacetamido)butanoic acid (15.00 g, 38.63 mmol) in DCE (250.00 mL) was added DMF (0.30 mL, 4.1 mmol) followed by oxalyl chloride (4.44 mL, 35.0 mmol). The mixture was then stirred at 25 °C for 20 min then cooled to 0 °C. After 5 min, to the mixture was added in one batch AlCl₃ (20.60 g, 154.5 mmol). The mixture was stirred at 0 °C for 5 min, then at 25 °C for 2 h, then placed in a pre-heated oil bath (50 °C) and stirred for 16 h under nitrogen atmosphere. An additional amount of AlCl₃ (5.15 g, 38.6 mmol) was added and stirred at 50 °C for another 3.5 h. On completion, the reaction mixture was cooled to rt then poured into ice water (0.6 L), then DCM (0.5L) and water (0.3 L) was added. The resulting mixture was filtered and the filter cake was washed with DCM (3 x 100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by trituration with ether (300 mL). The resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE : EtOAc (20:1 to 8:1) to afford the title compound (4 g, 28% yield) as a brown solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 5.8 Hz, 1H), 7.52-7.47 (m, 1H), 7.29-7.23 (m, 1H), 5.46 (dd, *J* = 10.8, 2.5 Hz, 1H), 4.94-4.89 (m, 1H), 3.80 (s, 3H), 3.68-3.63 (m, 1H), 3.37-3.20 (m, 3H); LC/MS (ESI, *m/z*): [(M - H)]⁻ = 369.1.

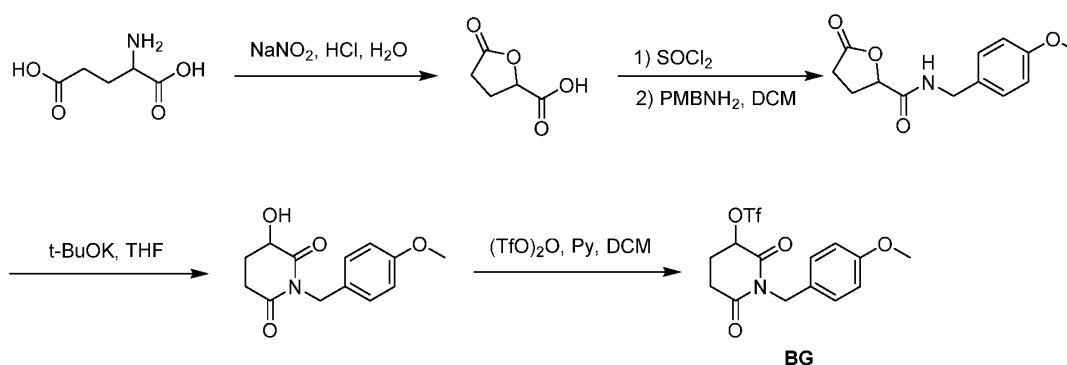
[00865] Step 4 - (2*S*,11*S*)-12-oxo-11-(2,2,2-trifluoroacetamido)-1-azatricyclo[6.4.1.0⁴[4,13]]trideca-4,6,8(13)-triene-2-carboxylate

[00866] To a solution of methyl (2*S*,11*S*)-9,12-dioxo-11-(2,2,2-trifluoroacetamido)-1-azatricyclo[6.4.1.0⁴[4,13]]trideca-4,6,8(13)-triene-2-carboxylate (42.00 g, 113.4 mmol) in HOAc (1000.00 mL) was added Pd/C (10 wt%, 10 g) in a pressure tank. The mixture was then hydrogenated at rt under 60 psi of hydrogen pressure for 72 h. On completion, the reaction mixture was filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (20:1), to afford the title compound (24.8 g, 61% yield) as a yellow solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.92 (s, 1H), 7.19-7.01 (m, 3H), 5.38-5.26 (m, 1H), 4.48-4.44 (m, 1H), 3.78 (s, 3H), 3.57-3.50 (m, 1H), 3.46-3.41 (m, 1H), 3.26-3.15 (m, 2H), 2.48-2.43 (m, 1H), 2.29-2.14 (m, 1H); LC/MS (ESI, *m/z*): [(M + H)]⁺ = 357.2.

[00867] Step 5 - (2*S*,11*S*)-11-[(*tert*-butoxycarbonyl)amino]-12-oxo-1-azatricyclo[6.4.1.0⁴[4,13]]trideca-4(13),5,7-triene-2-carboxylic acid

[00868] A solution of methyl (2*S*,11*S*)-12-oxo-11-(2,2,2-trifluoroacetamido)-1-azatricyclo[6.4.1.0⁴[4,13]]trideca-4(13),5,7-triene-2-carboxylate (50.00 g, 140.3 mmol) and LiOH (16.80 g, 701.7 mmol) in THF (300.00 mL)/H₂O (300.00 mL) was stirred for 3 h at rt under nitrogen atmosphere. The solution was neutralized to pH 10 with HCl (2 M). To the above solution was added Boc₂O (33.03 mL, 151.4 mmol) dropwise at rt. The resulting mixture was stirred for additional overnight at rt. On completion, the resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with water (200 mL). The precipitated solids were collected by filtration and washed with water (3 x 30 mL) and dried under reduced pressure to afford the title compound (35 g, 72% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.85 (s, 1H), 7.13-7.09 (m, 2H), 7.08-7.04 (m, 1H), 7.00-6.95 (m, 1H), 5.03 (dd, *J* = 11.1, 2.6 Hz, 1H), 4.10-4.01 (m, 1H), 3.58-3.41 (m, 1H), 3.19-2.91 (m, 3H), 2.14-1.91 (m, 2H), 1.40 (s, 9H); LC/MS (ESI, *m/z*): [(*M* + *H*)]⁺ = 347.2.

[00869] [1-[(4-Methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl] trifluoromethanesulfonate (Intermediate BG)



[00870] Step 1 - 5-Oxotetrahydrofuran-2-carboxylic acid

[00871] To a solution of 2-aminopentanedioic acid (210 g, 1.43 mol, CAS# 617-65-2) in H₂O (800 mL) and HCl (12 M, 210 mL) was added a solution of NaNO₂ (147 g, 2.13 mol) in H₂O (400 mL) at -5 °C. The mixture was stirred at 15 °C for 12 hrs. On completion, the mixture was concentrated and then dissolved in EA (500 mL) and filtered and washed with EA (3 X 100 mL). The filtrate and washed solution were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give the title compound (200 g, crude) as yellow oil. ¹H NMR (400MHz, CDCl₃) δ 6.43 (s, 1H), 5.02 - 4.95 (m, 1H), 2.67 - 2.38 (m, 4H)

[00872] Step 2 - N-[(4-methoxyphenyl)methyl]-5-oxo-tetrahydrofuran-2-carboxamide

[00873] To 5-oxotetrahydrofuran-2-carboxylic acid (120 g, 922 mmol) was added SOCl₂ (246 g, 2.07

mol) at 0 °C slowly. The mixture was stirred at 85 °C for 3 hrs, and then the mixture was stirred at 15 °C for 6 hrs. The mixture was concentrated *in vacuo*. The residue was dissolved in dry DCM (1 L) at 0 °C under N₂. After that a solution of Et₃N (187 g, 1.84 mol) and 4-methoxybenzylamine (101 g, 738 mmol) in DCM (400 mL) was added, then the mixture was stirred at 15 °C for 3 hrs. On completion, water (600 mL) was added and the mixture was extracted with DCM (3 X 300mL). The combined organic phase was washed with 0.5 M HCl (500 mL), brine (500 mL), dried over with anhydrous sodium sulfate and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash silica gel chromatography (PE: EA = 1:1) to give the title compound (138 g, 60% yield) as a yellow solid. ¹H NMR (400MHz, CDCl₃) δ 7.22 - 7.20 (d, *J* = 8.0, 1H), 6.89 - 6.87 (d, *J* = 8.0, 1H), 4.90 - 4.86 (m, 1H), 4.47 - 4.4.36 (m, 2H) 3.81 (s, 3H), 2.67 - 2.64 (m, 1H), 2.59 - 2.54 (m, 2H), 2.40 - 2.38 (m, 1H); LC-MS (ESI⁺) *m/z* 272.0 (M+Na)⁺.

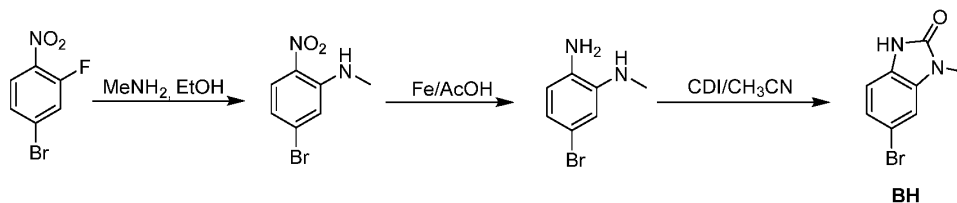
[00874] Step 3 - 3-Hydroxy-1-[(4-methoxyphenyl)methyl]piperidine-2,6-dione

[00875] A solution of N-[(4-methoxyphenyl)methyl]-5-oxo-tetrahydrofuran-2-carboxamide (138 g, 553 mmol) in anhydrous THF (1500 mL) was cooled to -78 °C. Then, t-BuOK (62.7 g, 559 mmol) in a solution of anhydrous THF (1000 mL) was added dropwise slowly at -78 °C under nitrogen atmosphere. The resulting reaction mixture was stirred at -40 °C for 1 hr. On completion, the reaction mixture was quenched with saturated NH₄Cl solution (100 mL). The mixture was extracted with ethyl acetate (3 X 1500 mL). The combined organic layer was washed with brine (300 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE: EA = 1:1) to give the title compound (128 g, 92% yield) as a white solid. ¹H NMR (400MHz, CDCl₃) δ 7.39 - 7.32 (m, 2H), 6.89 - 6.81 (m, 2H), 4.91 (s, 2H), 4.17 - 4.11 (m, 1H), 3.80 (s, 3H), 3.54 (s, 1H), 2.98 - 2.87 (m, 1H), 2.73 - 2.60 (m, 1H), 2.26 - 2.20 (m, 1H), 1.80 (dq, *J* = 4.8, 13.1 Hz, 1H).

[00876] Step 4 - [1-[(4-Methoxyphenyl) methyl]-2,6-dioxo-3-piperidyl] trifluoromethanesulfonate

[00877] To a solution of 3-hydroxy-1-[(4-methoxyphenyl) methyl] piperidine-2, 6-dione (43.0 g, 173 mmol) and pyridine (27.3 g, 345 mmol) in DCM (500 mL) was added trifluoromethylsulfonyl trifluoromethanesulfonate (73.0 g, 258 mmol) dropwise at 0 °C. The mixture was stirred at -10°C for 1.5 hours under N₂. On completion, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (PE: EA = 20:1/8:1) to give the title compound (45.0 g, 68% yield) as light yellow gum. ¹H NMR (400MHz, CDCl₃) δ 7.36 (d, *J* = 8.4 Hz, 2H), 6.85 - 6.82 (m, 2H), 5.32 - 5.28 (m, 1H), 4.91 (s, 2H), 3.79 (s, 3H), 3.02 - 2.97 (m, 1H), 2.79 - 2.74 (m, 1H), 2.41 - 2.35 (m, 2H).

[00878] 5-Bromo-3-methyl-1H-benzimidazol-2-one (Intermediate BH)



[00879] Step 1 - 5-Bromo-N-methyl-2-nitro-aniline

[00880] 4-bromo-2-fluoro-1-nitro-benzene (230 g, 1.05 mol, CAS#321-23-3) was added to a solution of methylamine in tetrahydrofuran (2 M, 1.51 L). The mixture was stirred at 15 °C for 10 minutes. On completion, the mixture was diluted with H₂O (250 mL) and extracted with EtOAc (3 X 300 mL). The combined organic layers were washed with brine (300 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the title compound (200 g, 83% yield) as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ 8.22 (s, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.16 (d, *J* = 1.6 Hz, 1H), 6.82 (dd, *J* = 8.4, 1.6 Hz, 1H), 2.95 (d, *J* = 4.8 Hz, 3H).

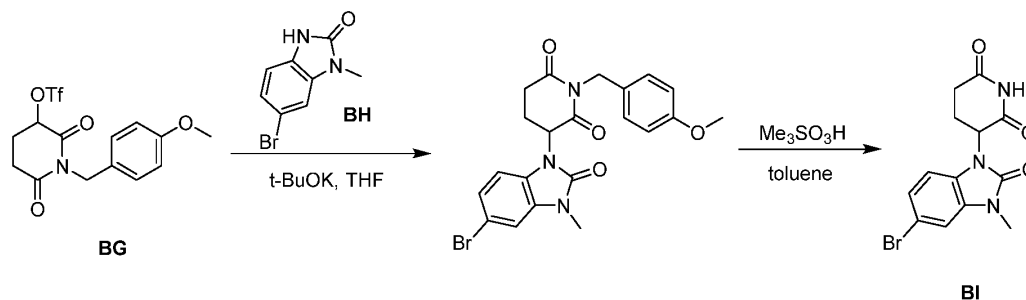
[00881] Step 2 - 4-Bromo-N2-methyl-benzene-1,2-diamine

[00882] To a mixture of 5-bromo-N-methyl-2-nitro-aniline (200 g, 865 mmol) in EtOAc (1 L) and H₂O (500 mL) was added AcOH (1.00 L). The mixture was warmed to 50 °C, and then Fe (174 g, 3.11 mol) was added to the reaction mixture. After that, the reaction mixture was stirred at 80 °C for 6 hours. On completion, the mixture was filtered through celite. The filtrate was *concentrated in vacuo* and the residue was diluted with H₂O (250 mL) and extracted with EtOAc (3 X 300 mL). The combined organic layers were washed with aq. NaHCO₃ and brine (300 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash silica gel chromatography to give the title compound (130 g, 75% yield) as black oil. ¹H NMR (400MHz, DMSO-*d*₆) δ 6.55 - 6.52 (m, 1H), 6.48 - 6.45 (m, 1H), 6.43 - 6.42 (m, 1H), 4.89 - 4.88 (m, 1H), 4.61 (s, 2H), 2.70 (d, *J* = 4.0 Hz, 3H).

[00883] Step 3 - 5-Bromo-3-methyl-1H-benzimidazol-2-one

[00884] To a solution of 4-bromo-N2-methyl-benzene-1,2-diamine (110 g, 547 mmol) in CH₃CN (1.3 L) was added CDI (177 g, 1.09 mol). The mixture was stirred at 80 °C for 6 hours under N₂. On completion, the mixture was concentrated *in vacuo*. The mixture was diluted with H₂O (1.0 L) and filtered. The filter cake was washed with water (3 X 200 mL) and dried *in vacuo* to give the title compound (106 g, 85% yield) as a white solid. ¹H NMR (400MHz, DMSO-*d*₆) δ 11.00 (s, 1H), 7.33 (s, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 3.27 (s, 3H).

[00885] 3-(5-bromo-3-methyl-2-oxo-benzimidazol-1-yl)piperidine-2,6-dione (3-(5-bromo-3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidine-2,6-dione) (Intermediate BI)



[00886] Step 1 - 3-(5-Bromo-3-methyl-2-oxo-benzimidazol-1-yl)-1-[(4-methoxyphenyl)methyl]piperidine-2,6-dione

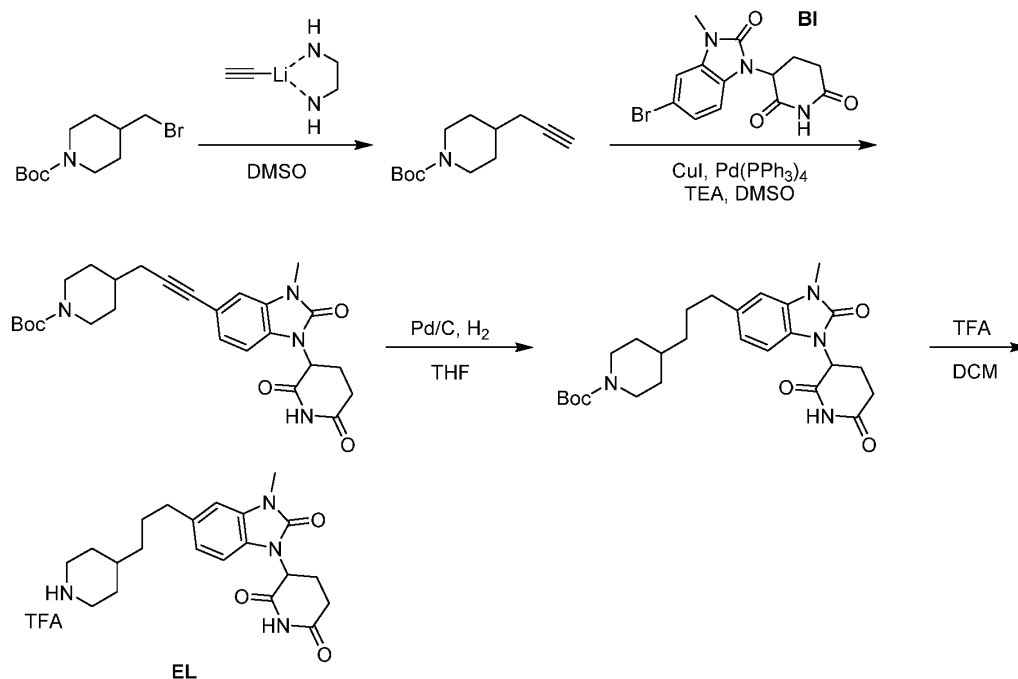
[00887] To a solution of 5-bromo-3-methyl-1H-benzimidazol-2-one (4.90 g, 21.6 mmol, Intermediate BH) in THF (300 mL) was added t-BuOK (3.63 g, 32.3 mmol) at 0 °C. The mixture was stirred at 0-10°C for 1 hour under N₂. Then a solution of [1-[(4-methoxyphenyl) methyl]-2, 6-dioxo-3-piperidyl] trifluoromethanesulfonate (9.87 g, 25.9 mmol, Intermediate BG) in THF (100 mL) was added to the reaction mixture at 0-10°C over 30 minutes. The mixture was stirred at 0-10°C for 30 minutes under N₂. An additional solution of [1-[(4-methoxyphenyl) methyl]-2, 6-dioxo-3-piperidyl] trifluoromethanesulfonate (2.47 g, 6.47 mmol) in THF (20 mL) was added to the reaction mixture at 0-10°C dropwise. The mixture was then stirred at 0-10°C for another 30 minutes under N₂. On completion, the reaction was quenched with water (400 mL) and extracted with EA (3 X 200 mL). The combined organic layer was concentrated *in vacuo*. The residue was triturated with EA (80 mL) and filtered. The filter cake was collected and dried *in vacuo* to give the title compound (6.70 g, 67% yield) as light yellow solid. The filtrate was also concentrated *in vacuo* and the residue was purified by column chromatography to give another batch title compound (1.80 g, 18% yield) as light yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ 7.47 (d, *J* = 1.6 Hz, 1H), 7.21 - 7.16 (m, 3H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.55 - 5.51 (m, 1H), 4.84 - 4.73 (m, 2H), 3.72 (s, 3H), 3.33 (s, 3H), 3.04 - 3.00 (m, 1H), 2.83 - 2.67 (m, 2H), 2.07 - 2.05 (m, 1H).

[00888] Step 2 - 3-(5-Bromo-3-methyl-2-oxo-benzimidazol-1-yl)piperidine-2,6-dione

[00889] To a mixture of 3-(5-bromo-3-methyl-2-oxo-benzimidazol-1-yl)-1-[(4-methoxyphenyl)methyl] piperidine-2,6-dione (8.50 g, 18.6 mmol) in toluene (50 mL) was added methanesulfonic acid (33.8 g, 351 mmol, 25 mL) at room temperature (15 °C). The mixture was stirred at 120 °C for 2 hours. On completion, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was poured into ice/water (200 mL), and extracted with EA (3 X 100 mL). The combined organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was triturated with EA (80 mL) and filtered. The filtrate cake was collected and dried *in vacuo* to give the title compound (4.20 g, 67% yield) as off-white solid. ¹H NMR (400MHz, DMSO-*d*₆)

δ 11.12 (s, 1H), 7.47 (d, $J = 2.0$ Hz, 1H), 7.22 (d, $J = 8.4$ Hz, 1H), 7.10 (d, $J = 8.4$ Hz, 1H), 5.40 - 5.35 (m, 1H), 2.34 (s, 3H), 2.92 - 2.88 (m, 1H), 2.71 - 2.60 (m, 2H), 2.03 - 1.99 (m, 1H).

[00890] 3-[3-methyl-2-oxo-5-[3-(piperidin-4-yl)propyl]-1,3-benzodiazol-1-yl]piperidine-2,6-dione
(Intermediate EL)



[00891] Step 1 - *Tert*-butyl 4-(prop-2-yn-1-yl) piperidine-1-carboxylate

[00892] To a stirred solution of *tert*-butyl 4-(bromomethyl) piperidine-1-carboxylate (25 g, 89.867 mmol, CAS# 158407-04-6) in DMSO (250 mL) was added lithium acetylide ethylenediamine complex (12.14 g, 134.8 mmol, CAS# 6867-30-7) at 0 °C under nitrogen atmosphere. The resulting mixture was then stirred for 2 h at 25 °C under nitrogen atmosphere. On completion, the reaction mixture was acidified to pH 5 with 2 M HCl (aq.). The resulting mixture was then extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (3 x 100 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (20:1), to afford the title compound (15 g, 75% yield) as a colorless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 4.19-4.08 (m, 1H), 3.47-3.42 (m, 2H), 3.34-3.29 (m, 1H), 2.76-2.67 (m, 1H), 2.22-2.13 (m, 2H), 1.87-1.74 (m, 2H), 1.69-1.59 (m, 1H), 1.48 (s, 9H), 1.29-1.12 (m, 2H); LC/MS (ESI, *m/z*): [(M + H)]⁺ = 224.2.

[00893] Step 2 - *Tert*-butyl 4-[3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-

yl]prop-2-yn-1-yl]piperidine-1-carboxylate

[00894] To a stirred solution of *tert*-butyl 4-(prop-2-yn-1-yl)piperidine-1-carboxylate (4.19 g, 18.8 mmol) and 3-(5-bromo-3-methyl-2-oxo-1,3-benzodiazol-1-yl)piperidine-2,6-dione (6.34 g, 18.8 mmol, Intermediate BI) in DMSO (30.00 mL) and TEA (10 mL) were added Pd(PPh₃)₄ (2.17 g, 1.88 mmol) and CuI (0.36 g, 1.88 mmol) at rt under nitrogen atmosphere. The resulting mixture was purged with nitrogen 3 times and the mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. On completion, the mixture was allowed to cool down to room temperature. Then the reaction mixture was filtered and the filter cake was washed with MeCN (3 x 100 mL). The filtrate was concentrated under reduced pressure. The residue was then purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 µm, 330 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 35%-60% B in 30 min; Flow rate: 80 mL/min; Detector: 220/254 nm; desired fractions were collected at 50% B and concentrated under reduced pressure) to afford the title compound (2.18 g, 24% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.10 (s, 1H), 7.24 (s, 1H), 7.12-7.07 (m, 2H), 5.76 (s, 1H), 5.43-5.33 (m, 1H), 3.97 (d, *J* = 13.1 Hz, 2H), 3.34 (s, 3H), 2.97-2.83 (m, 1H), 2.81-2.76 (m, 1H), 2.74-2.58 (m, 2H), 2.40 (d, *J* = 6.5 Hz, 2H), 2.10-1.98 (m, 1H), 1.81-1.72 (m, 2H), 1.71-1.63 (m, 1H), 1.40 (s, 9H), 1.23-1.09 (m, 2H); LC/MS (ESI, *m/z*): [(M + H)]⁺ = 481.2.

[00895] Step 3 - *Tert*-butyl 4-[3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl]piperidine-1-carboxylate

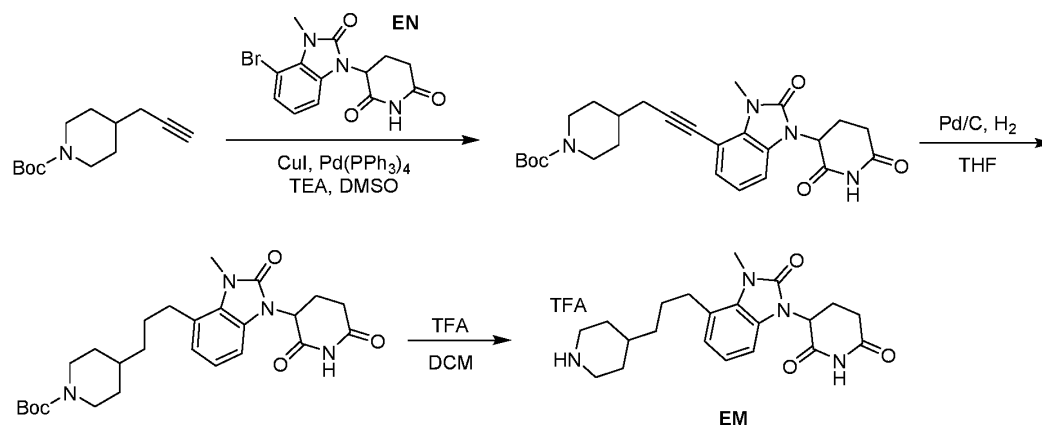
[00896] To a solution of *tert*-butyl 4-[3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]prop-2-yn-1-yl]piperidine-1-carboxylate (2.18 g, 4.54 mmol) in THF (20 mL) was added Pd/C (0.05 g, 0.5 mmol) under nitrogen atmosphere. The reaction system was degassed under vacuum and purged with H₂ several times. Then the reaction mixture was hydrogenated under H₂ balloon (~1 atm) at 25 °C for 2 h. After completion of the reaction, Pd/C was filtered off through celite. The filter cake was washed with MeOH (3 x 20 mL). The corresponding filtrate was concentrated under reduced pressure to provide the title compound (1.87 g, 83% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.07 (s, 1H), 7.05-6.96 (m, 2H), 6.90-6.83 (m, 1H), 5.38-5.29 (m, 1H), 3.91 (d, *J* = 13.0 Hz, 2H), 3.65-3.57 (m, 1H), 3.33 (s, 3H), 2.98-2.84 (m, 1H), 2.78-2.56 (m, 5H), 2.06-1.94 (m, 1H), 1.82-1.71 (m, 1H), 1.68-1.52 (m, 4H), 1.39 (s, 9H), 1.29-1.19 (m, 2H), 1.02-0.87 (m, 2H); LC/MS (ESI, *m/z*): [(M + H)]⁺ = 485.2.

[00897] Step 4 - 3-[3-Methyl-2-oxo-5-[3-(piperidin-4-yl)propyl]-1,3-benzodiazol-1-yl]piperidine-2,6-dione trifluoroacetate

[00898] To a stirred solution of *tert*-butyl 4-[3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl]piperidine-1-carboxylate (1.87 g, 3.86 mmol) in DCM (20.00 mL) was added TFA (10.00 mL) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 25 °C under

nitrogen atmosphere. On completion, the reaction mixture was concentrated under reduced pressure. The residue was then purified by trituration with Et₂O (100.00 mL) to afford the title compound (2.0 g, 97% yield) as a light brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.07 (s, 1H), 7.04-6.99 (m, 2H), 6.89-6.86 (m, 1H), 5.39-5.29 (m, 1H), 3.33 (s, 3H), 3.25 (d, *J* = 12.5 Hz, 2H), 2.97-2.76 (m, 3H), 2.76-2.56 (m, 4H), 2.05- 1.97 (m, 1H), 1.86-1.72 (m, 2H), 1.68-1.46 (m, 3H), 1.34-1.15 (m, 5H); LC/MS (ESI, *m/z*): [(M + H)]⁺ = 385.2.

[00899] 3-[3-methyl-2-oxo-4-[3-(piperidin-4-yl)propyl]-1,3-benzodiazol-1-yl]piperidine-2,6-dione
(Intermediate EM)



[00900] Step 1 - *Tert*-butyl 4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]prop-2-yn-1-yl}piperidine-1-carboxylate

[00901] To a stirred solution of *tert*-butyl 4-(prop-2-yn-1-yl)piperidine-1-carboxylate (4.19 g, 18.8 mmol) and 3-(4-bromo-3-methyl-2-oxo-1,3-benzodiazol-1-yl)piperidine-2,6-dione (6.34 g, 18.8 mmol, Intermediate EN) in DMSO (30.00 mL) and TEA (10 mL) were added Pd(PPh₃)₄ (2.17 g, 1.88 mmol) and CuI (0.36 g, 1.9 mmol) in turns at rt under nitrogen atmosphere. The resulting mixture was purged with nitrogen 3 times, then the resulting mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. On completion, the mixture was allowed to cool down to rt. The resulting mixture was filtered and the filter cake was washed with MeCN (3 x 100 mL). Then the filtrate was concentrated under reduced pressure. The solution was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 μ m, 330 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 30%-60% B in 30 min; Flow rate: 80 mL/min; Detector: 220/254 nm; desired fractions were collected at 50% B and concentrated under reduced pressure) to afford the title compound (4.01 g, 44% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.12 (s, 1H), 7.26-7.23 (m, 1H), 7.19-7.16 (m, 1H), 7.01-6.99 (m, 1H), 5.40-5.36 (m, 1H), 3.96 (d, *J* = 13.2 Hz, 2H), 3.64 (s, 3H), 2.94-2.83 (m, 3H), 2.69-2.64 (m, 3H), 2.07-2.01 (m, 2H), 1.78-1.70

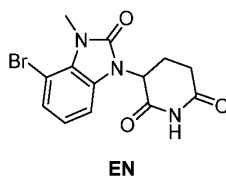
(m, 3H), 1.39 (s, 9H), 1.23-1.13 (m, 2H); LC/MS (ESI, m/z): $[(M + H)]^+ = 481.2$.

[00902] Step 2 - *Tert*-butyl 4-[3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]propyl]piperidine-1-carboxylate

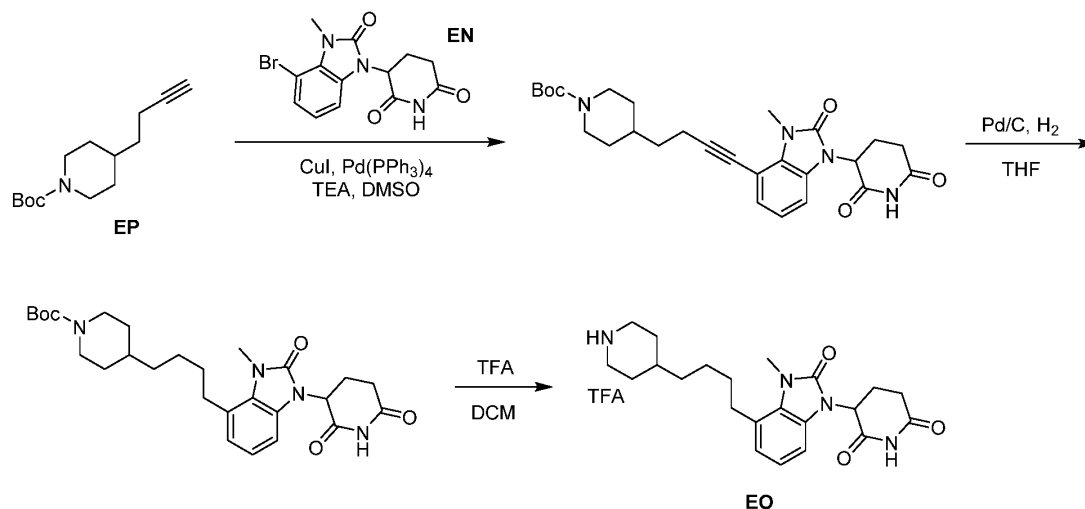
[00903] To a solution of *tert*-butyl 4-[3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]prop-2-yn-1-yl]piperidine-1-carboxylate (1.61 g, 3.35 mmol) in THF (20.00 mL) was added Pd/C (0.04 g, 0.3 mmol) under nitrogen atmosphere. The reaction system was degassed under vacuum and purged with H₂ several times, then the reaction mixture was hydrogenated under H₂ balloon (~1 atm) at 25 °C for 2 h. After completion of the reaction, Pd/C was filtered off through celite. The filter cake was washed with MeOH (3 x 100 mL). The corresponding filtrate was concentrated under reduced pressure to provide the title compound (1.69 g, 99% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.07 (s, 1H), 6.99-6.92 (m, 2H), 6.89-6.84 (m, 1H), 5.42-5.30 (m, 1H), 3.91 (d, *J* = 12.9 Hz, 2H), 3.54 (s, 3H), 2.91-2.83 (m, 3H), 2.75-2.58 (m, 4H), 2.04-1.94 (m, 1H), 1.69-1.55 (m, 4H), 1.47-1.40 (m, 1H), 1.38 (s, 9H), 1.35-1.28 (m, 2H), 1.03-0.88 (m, 2H). LC/MS (ESI, m/z): $[(M + H)]^+ = 485.2$

[00904] Step 3: 3-[3-methyl-2-oxo-4-[3-(piperidin-4-yl)propyl]-1,3-benzodiazol-1-yl]piperidine-2,6-dione trifluoroacetate To a stirred solution of *tert*-butyl 4-[3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]propyl]piperidine-1-carboxylate (1.69 g, 3.49 mmol) in DCM (20.00 mL) was added TFA (10.00 mL) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 25 °C under nitrogen atmosphere. On completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by trituration with Et₂O (60.00 mL) to afford the title compound (2.38 g) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.08 (s, 1H), 6.99-6.95 (m, 2H), 6.91-6.85 (m, 1H), 5.41-5.32 (m, 1H), 3.55 (s, 3H), 3.25 (d, *J* = 12.5 Hz, 2H), 2.95-2.58 (m, 7H), 2.06-1.95 (m, 1H), 1.86-1.77 (m, 2H), 1.68-1.50 (m, 3H), 1.39-1.18 (m, 5H); LC/MS (ESI, m/z): $[(M + H)]^+ = 385.2$.

[00905] 3-(4-bromo-3-methyl-2-oxo-1,3-benzodiazol-1-yl)piperidine-2,6-dione (Intermediate EN) (CAS# 2304754-51-4, experimental preparation from WO 2020264499 A1)



[00906] 3-{3-methyl-2-oxo-4-[4-(piperidin-4-yl)butyl]-1,3-benzodiazol-1-yl}piperidine-2,6-dione (Intermediate EO)



[00907] Step 1 - *Tert*-butyl 4-[4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]but-3-yn-1-yl]piperidine-1-carboxylate

[00908] To a stirred solution of *tert*-butyl 4-(but-3-yn-1-yl)piperidine-1-carboxylate (4.50 g, 19.0 mmol, Intermediate EP) and 3-(4-bromo-3-methyl-2-oxo-1,3-benzodiazol-1-yl)piperidine-2,6-dione (6.41 g, 19 mmol, Intermediate EN) in DMSO (26.00 mL) and TEA (9 mL) were added CuI (0.36 g, 1.9 mmol) and Pd(PPh₃)₄ (2.19 g, 1.90 mmol) in turns at rt under nitrogen atmosphere. The resulting mixture was stirred for 4 h at 80 °C under nitrogen atmosphere. On completion, the mixture was allowed to cool down to rt. The resulting mixture was concentrated under reduced pressure to remove excess TEA. Then to the residue was added FA (3 mL) and the resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with EtOAc (3 x 400 mL). The combined organic layers were washed with brine (4 x 100 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1), to afford the title compound (3.8 g, 41% yield) as a brown solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.27 (s, 1H), 7.13 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.98 (t, *J* = 7.9 Hz, 1H), 6.73 (dd, *J* = 7.9, 1.1 Hz, 1H), 5.21 (dd, *J* = 12.4, 5.3 Hz, 1H), 4.16-4.09 (m, 2H), 3.79 (s, 3H), 3.02-2.91 (m, 1H), 2.88-2.83 (m, 1H), 2.81-2.62 (m, 3H), 2.52 (t, *J* = 6.9 Hz, 2H), 2.27-2.15 (m, 1H), 1.74-1.71 (m, 2H), 1.67-1.55 (m, 3H), 1.48 (s, 9H), 1.22-1.12 (m, 2H); LC/MS (ESI, *m/z*): [(M + H)]⁺ = 495.3.

[00909] Step 2 - *tert*-butyl 4-{4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]butyl}piperidine-1-carboxylate

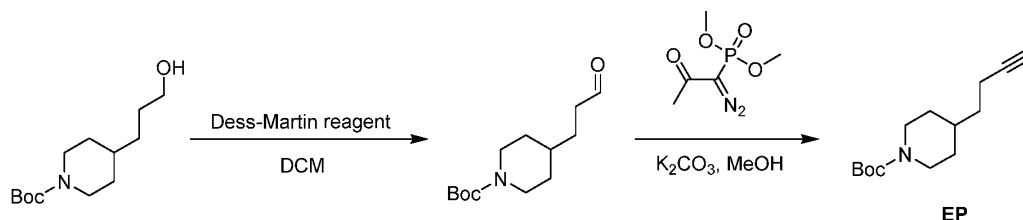
[00910] To a stirred solution of *tert*-butyl 4-{4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]but-3-yn-1-yl}piperidine-1-carboxylate (3 g, 6 mmol) in THF (60 mL) was added Pd/C

(0.06 g, 0.6 mmol) at rt under nitrogen atmosphere. The reaction system was degassed under vacuum and purged with H₂ several times, then the mixture was hydrogenated under H₂ balloon (1 atm) at rt for 3 h. After completion of the reaction, Pd/C was filtered off through celite. The filter cake was washed with THF (3 x 20 mL). The corresponding filtrate was concentrated under reduced pressure to afford the title compound (2.4 g, 79% yield) as a yellow solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.37 (s, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 6.90 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.68 (dd, *J* = 7.8, 1.1 Hz, 1H), 5.23 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.19-4.06 (m, 2H), 3.68 (s, 3H), 3.00-2.88 (m, 3H), 2.87-2.82 (m, 1H), 2.81-2.62 (m, 3H), 2.24-2.18 (m, 1H), 1.73-1.61 (m, 4H), 1.53-1.37 (m, 12H), 1.29-1.26 (m, 2H), 1.16-1.04 (m, 2H); LC/MS (ESI, *m/z*): [(M + H)]⁺ = 499.3.

[00911] Step 3 - 3-{3-methyl-2-oxo-4-[4-(piperidin-4-yl)butyl]-1,3-benzodiazol-1-yl}piperidine-2,6-dione trifluoroacetate

[00912] To a stirred solution of *tert*-butyl 4-[4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]butyl]piperidine-1-carboxylate (2.40 g, 4.81 mmol) in DCM (40.00 mL) was added TFA (8.00 mL) dropwise at rt. The resulting mixture was then stirred for 1 h at rt under nitrogen atmosphere. On completion, the reaction mixture was concentrated under reduced pressure to afford the title compound (2.8 g) as a yellow semi-solid. LC/MS (ESI, *m/z*): [(M + H)]⁺ = 399.3.

[00913] *Tert*-butyl 4-(but-3-yn-1-yl) piperidine-1-carboxylate (Intermediate EP)



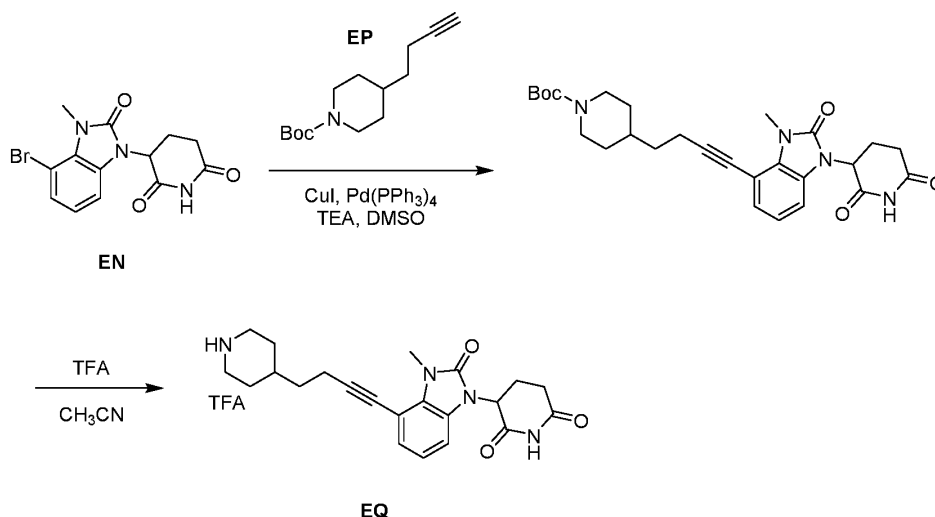
[00914] Step 1 - *Tert*-butyl 4-(3-oxopropyl) piperidine-1-carboxylate

[00915] To a stirred solution of *tert*-butyl 4-(3-hydroxypropyl) piperidine-1-carboxylate (5.00 g, 20.5 mmol, CAS# 156185-63-6) in DCM (30.00 mL) was added Dess-Martin reagent (10.46 g, 24.66 mmol) at 0 °C under nitrogen atmosphere. The resulting mixture was then stirred for 2 h at 25 °C under nitrogen atmosphere. On completion, the reaction mixture was quenched with sat. aq. Na₂SO₃ (50 mL). The resulting mixture was extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were washed with brine (3 x 200 mL), and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with (PE/EtOAc 5:1), to afford the title compound (4.13 g, 83% yield) as a colorless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.78 (t, *J* = 1.7 Hz, 1H), 4.12-4.07 (m, 2H), 2.72-2.62 (m, 2H), 2.52-2.44 (m, 2H), 1.69-1.54 (m, 4H), 1.45 (s, 9H), 1.43-1.34 (m, 1H), 1.18-1.02 (m, 2H); LC/MS (ESI, *m/z*): [(M + H - 56)]⁺ = 186.2.

[00916] Step 2 - *Tert*-butyl 4-(but-3-yn-1-yl) piperidine-1-carboxylate

[00917] To a stirred mixture of *tert*-butyl 4-(3-oxopropyl) piperidine-1-carboxylate (4.13 g, 17.1 mmol) and K₂CO₃ (4.73 g, 34.2 mmol) in MeOH (30.00 mL) was added seyferth-gilbert reagent (3.62 g, 18.8 mmol, CAS# 90965-06-3) dropwise at 0 °C under nitrogen atmosphere. Then the resulting mixture was stirred for 2 h at 25 °C under nitrogen atmosphere. On completion, the reaction mixture was filtered and the filter cake was washed with MeOH (3 x 30 mL). The filtrate was concentrated under reduced pressure. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with (PE/EtOAc 15:1), to afford the title compound (3.25 g, 80% yield) as a yellow oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 4.21-3.97 (m, 2H), 2.69 (t, *J* = 12.8 Hz, 2H), 2.29-2.17 (m, 2H), 1.95 (t, *J* = 2.7 Hz, 1H), 1.72-1.63 (m, 2H), 1.63-1.52 (m, 1H), 1.52-1.47 (m, 2H), 1.45 (s, 9H), 1.18-1.00 (m, 2H); LC/MS (ESI, *m/z*): [(M + H - 56)]⁺=182.2.

[00918] 3-{3-methyl-2-oxo-4-[4-(piperidin-4-yl) but-1-yn-1-yl]-1,3-benzodiazol-1-yl} piperidine-2,6-dione (Intermediate EQ)



[00919] Step 1 - *Tert*-butyl 4-[4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]but-3-yn-1-yl]piperidine-1-carboxylate

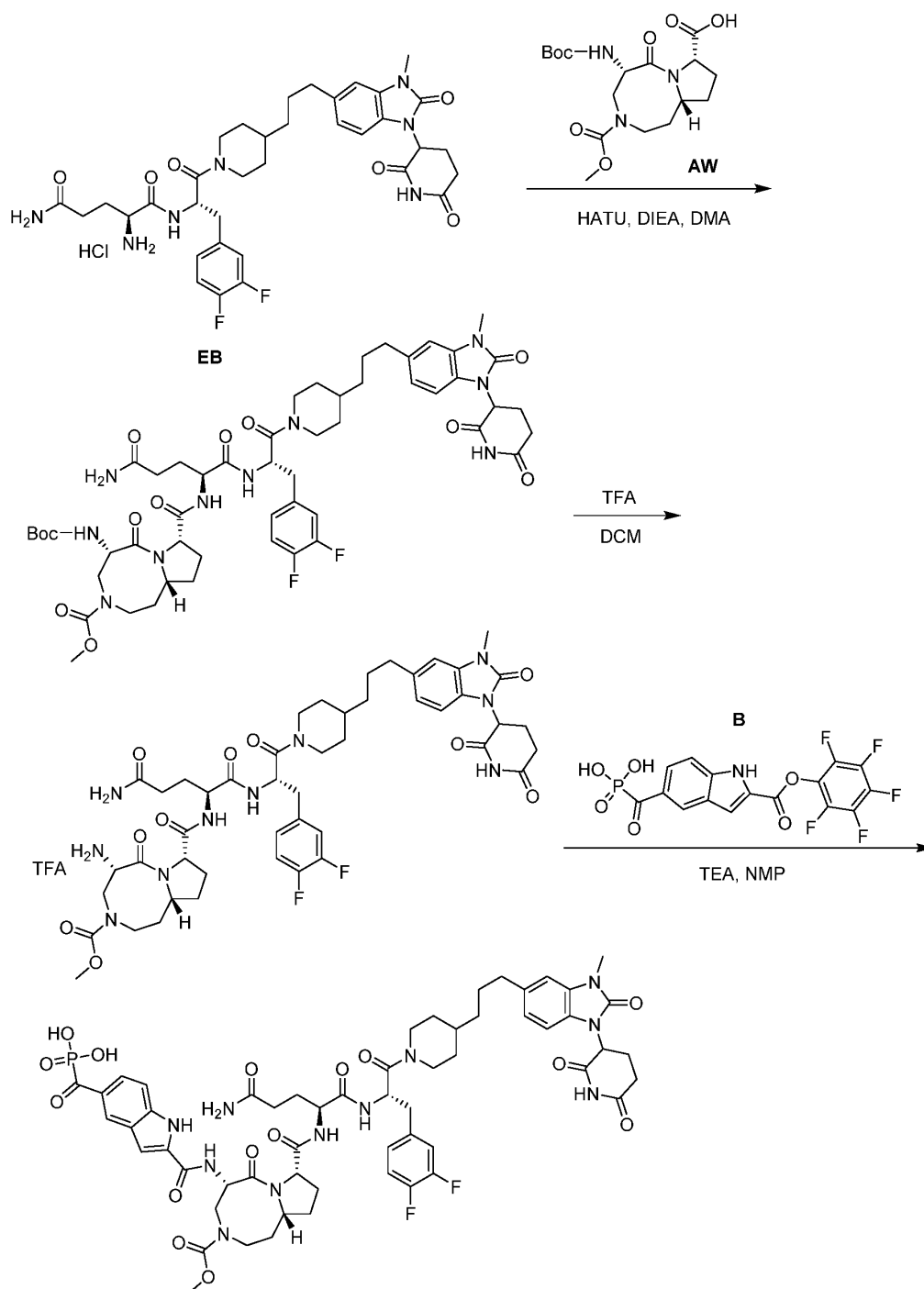
[00920] To a stirred solution of *tert*-butyl 4-(but-3-yn-1-yl)piperidine-1-carboxylate (4.50 g, 19.0 mmol, Intermediate EP) and 3-(4-bromo-3-methyl-2-oxo-1,3-benzodiazol-1-yl)piperidine-2,6-dione (6.41 g, 19.0 mmol, Intermediate EN) in DMSO (26.00 mL) and TEA (13 mL) were added CuI (0.36 g, 1.9 mmol) and Pd(PPh₃)₄ (2.19 g, 1.90 mmol) in turns at rt under nitrogen atmosphere. The resulting mixture was then stirred for 4 h at 85 °C under nitrogen atmosphere. On completion, the reaction mixture was allowed to cool down to rt, then it was concentrated under reduced pressure. The resulting mixture was diluted with water

(200 mL) and extracted with EtOAc (3 x 400 mL). The combined organic layers were washed with brine (4 x 100 mL), then dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1), to afford the title compound (3.8 g, 41% yield) as a brown solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.27 (s, 1H), 7.13 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.98 (t, *J* = 7.9 Hz, 1H), 6.73 (dd, *J* = 7.9, 1.1 Hz, 1H), 5.21 (dd, *J* = 12.4, 5.3 Hz, 1H), 4.16-4.12 (m, 2H), 3.79 (s, 3H), 3.01-2.90 (m, 1H), 2.88-2.84 (m, 1H), 2.81-2.66 (m, 3H), 2.52 (t, *J* = 6.9 Hz, 2H), 2.26-2.17 (m, 1H), 1.76-1.71 (m, 2H), 1.64-1.59 (m, 2H), 1.52-1.44 (m, 10H), 1.21-1.12 (m, 2H); LC/MS (ESI, *m/z*): [(M + H)]⁺ = 495.3.

[00921] Step 2 - 3-{3-methyl-2-oxo-4-[4-(piperidin-4-yl) but-1-yn-1-yl]-1,3-benzodiazol-1-yl} piperidine-2,6-dione trifluoroacetate

[00922] To a solution of *tert*-butyl 4-[4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-4-yl]but-3-yn-1-yl]piperidine-1-carboxylate (3.00 g, 6.07 mmol) in ACN (60.00 mL) was added TFA (10.00 mL) dropwise at rt. The resulting mixture was stirred for additional 1 h at rt. On completion, the resulting mixture was concentrated under vacuum. The residue was then purified by trituration with Et₂O to give the title compound (2.8 g, 91% yield) as a yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.15-7.01 (m, 3H), 5.40-5.30 (m, 1H), 3.77 (s, 3H), 3.45-3.41 (m, 2H), 3.06-2.99 (m, 2H), 2.96-2.73 (m, 3H), 2.61 (t, *J* = 7.2 Hz, 2H), 2.24-2.13 (m, 1H), 2.11-2.01 (m, 2H), 1.93-1.79 (m, 1H), 1.91-1.82 (m, 2H), 1.55-1.38 (m, 2H); LC/MS (ESI, *m/z*): [(M + H)]⁺ = 395.3.

Example 1 (Method 1): Synthesis of 2-[[[(5*S*,8*S*,10*aR*)-8-[[[(1*S*)-3-carbamoyl-1-[(2*S*)-3-(3,4-difluorophenyl)-1-(4-[3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl]piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl]propyl]carbamoyl]-3-(methoxycarbonyl)-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocin-5-yl]carbamoyl]-1*H*-indole-5-carbonylphosphonic acid (I-5)



[00923] Step 1 - Methyl (5*S*,8*S*,10*aR*)-5-[(*tert*-butoxycarbonyl)amino]-8-{[(1*S*)-3-carbamoyl]-1-{[(2*S*)-

3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl}propyl]carbamoyl}-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocine-3-carboxylate

[00924] To a stirred solution of (2*S*)-2-amino-*N*-[(2*S*)-3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]pentanediamide hydrochloride (100 mg, 0.137 mmol, Intermediate EB) and (5*S*,8*S*,10*aR*)-5-[(*tert*-butoxycarbonyl)amino]-3-(methoxycarbonyl)-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocine-8-carboxylic acid (57.90 mg, 0.151 mmol, Intermediate AW) in DMA (1 mL) were added HATU (67.51 mg, 0.178 mmol) and TEA (55.28 mg, 0.548 mmol) at 25 °C under nitrogen atmosphere. The resulting mixture was then stirred for 1 h at 25 °C under nitrogen atmosphere. On completion, the reaction mixture was concentrated under reduced pressure. The residue was then purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 μ m, 120 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 30% - 70% B in 30 min; Flow rate: 65 mL/min; Detector: 220/254 nm; desired fractions were collected at 55% B and concentrated under reduced pressure) to afford the title compound (78 mg, 54% yield) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.11-9.00 (m, 1H), 8.83-8.72 (m, 1H), 7.25-7.15 (m, 2H), 7.08-6.94 (m, 3H), 6.93-6.80 (m, 4H), 6.76 (d, *J* = 8.0 Hz, 1H), 5.97-5.65 (m, 2H), 5.33-5.19 (m, 1H), 5.08-4.96 (m, 1H), 4.83-4.67 (m, 1H), 4.58-4.14 (m, 4H), 3.77 (s, 3H), 3.44 (d, *J* = 3.1 Hz, 3H), 3.30-3.10 (m, 1H), 3.05-2.72 (m, 6H), 2.70-2.48 (m, 4H), 2.45-2.06 (m, 12H), 1.89-1.76 (m, 3H), 1.71-1.50 (m, 4H), 1.45 (s, 9H), 1.34-1.01 (m, 2H); LC/MS (ESI, *m/z*): [(M + H)]⁺ = 1063.6.

[00925] Step 2 - Methyl (5*S*,8*S*,10*aR*)-5-amino-8-[(1*S*)-3-carbamoyl-1-{[(2*S*)-3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl}propyl]carbamoyl}-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocine-3-carboxylate trifluoroacetate

[00926] To a stirred solution of methyl (5*S*,8*S*,10*aR*)-5-[(*tert*-butoxycarbonyl)amino]-8-[(1*S*)-3-carbamoyl-1-{[(2*S*)-3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl}propyl]carbamoyl}-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocine-3-carboxylate (78 mg, 0.073 mmol) in DCM (2.00 mL) was added TFA (1 mL) at 25 °C under nitrogen atmosphere and the mixture was stirred for 1 h. On completion, the reaction mixture was concentrated under vacuum to afford the title compound (70 mg, 90% yield) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.11-9.00 (m, 1H), 8.83-8.72 (m, 1H), 7.25-7.15 (m, 2H), 7.08-6.94 (m, 5H), 6.93-6.80 (m, 4H), 6.76 (d, *J* = 8.0 Hz, 1H), 5.97-5.65 (m, 2H), 5.33-5.19 (m, 1H), 5.08-4.96 (m, 1H), 4.83-4.67 (m, 1H), 4.58-4.14 (m, 4H), 3.77 (s, 3H), 3.44 (d, *J* = 3.1 Hz, 3H), 3.30-3.10 (m, 1H), 3.05-2.72 (m, 6H), 2.70-2.48 (m, 4H), 2.45-2.06 (m, 12H), 1.89-1.76 (m, 3H), 1.71-1.50 (m, 4H),

1.34-1.01 (m, 2H); LC/MS (ESI, m/z): $[(M + H)]^+ = 963.7$.

[00927] Step 3 - 2-[[[(5*S*,8*S*,10*aR*)-8-[[[(1*S*)-3-carbamoyl-1-[[[(2*S*)-3-(3,4-difluorophenyl)-1-(4-[3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl]piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl]propyl]carbamoyl]-3-(methoxycarbonyl)-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocin-5-yl]carbamoyl]-1*H*-indole-5-carbonyl]phosphonic acid

[00928] To a stirred solution of methyl (5*S*,8*S*,10*aR*)-5-amino-8-[[[(1*S*)-3-carbamoyl-1-[[[(2*S*)-3-(3,4-difluorophenyl)-1-(4-[3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl]piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl]propyl]carbamoyl]-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocine-3-carboxylate; trifluoroacetaldehyde (120.00 mg, 0.113 mmol) and 2-(2,3,4,5,6-pentafluorophenoxy)carbonyl)-1*H*-indole-5-carbonyl]phosphonic acid (98.44 mg, 0.226 mmol, Intermediate B) in NMP (2.00 mL) was added TEA (114.44 mg, 1.131 mmol) at 25 °C under nitrogen atmosphere. The resulting mixture was then stirred for 2 h at 25 °C under nitrogen atmosphere. On completion, the reaction mixture was concentrated under reduced pressure. Then the residue was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 μ m, 120 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 20% - 50% B in 25 min; Flow rate: 65 mL/min; Detector: 220/254 nm; desired fractions were collected at 41% B and concentrated under reduced pressure) to afford the title compound (26.4 mg, 19% yield) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.08-12.03 (m, 1H), 11.08 (s, 1H), 8.80 (s, 1H), 8.77-8.70 (m, 1H), 8.23-8.10 (m, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.96 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 6.7 Hz, 1H), 7.35-7.08 (m, 3H), 7.08-6.94 (m, 3H), 6.86 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.78-6.68 (m, 1H), 5.34 (dd, *J* = 12.8, 5.4 Hz, 1H), 5.02-4.82 (m, 2H), 4.43-4.11 (m, 4H), 3.96-3.76 (m, 2H), 3.70-3.60 (m, 3H), 3.59-3.52 (m, 2H), 3.52-3.48 (m, 2H), 3.45 (s, 3H), 3.44-3.39 (m, 3H), 2.90-2.81 (m, 3H), 2.79-2.70 (m, 1H), 2.70-2.55 (m, 3H), 2.18-1.94 (m, 5H), 1.91-1.53 (m, 10H), 1.49-1.43 (m, 1H), 1.27-1.08 (m, 2H), 1.05-0.83 (m, 1H), 0.80-0.44 (m, 1H); LC/MS (ESI, m/z): $[(M + H)]^+ = 1215.4$.

Table 2: Compounds synthesized via Method 1, where the corresponding amines and acids were coupled in Step 1.

I-# ^a	Step 1 Amine	Step 1 Acid	Step 3 Carboxylate	LC/MS (ESI, m/z) (M + H) ⁺	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ
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I-1	EF	AW	BA	1263.4	11.10 (s, 1H), 8.93 (dd, $J = 28.1$, 7.3 Hz, 1H), 8.31 (d, $J = 5.9$ Hz, 1H), 8.32-8.06 (m, 4H), 7.61 (d, $J = 8.6$ Hz, 1H), 7.34-7.20 (m, 3H), 7.11-7.07 (m, 2H), 6.71 (d, $J = 13.9$ Hz, 1H), 5.37 (dd, $J = 12.8$, 5.4 Hz, 1H), 4.98-4.84 (m, 2H), 4.44-4.29 (m, 3H), 4.30-4.23 (m, 2H), 4.22-4.14 (m, 2H), 3.99-3.73 (m, 2H), 3.69-3.61 (m, 3H), 3.59-3.40 (m, 5H), 2.97-2.87 (m, 2H), 2.90-2.77 (m, 1H), 2.75-2.71 (m, 1H), 2.65-2.61 (m, 1H), 2.45-2.41 (m, 3H), 2.12-2.01 (m, 6H), 1.82-1.79 (m, 3H), 1.72-1.69 (m, 7H), 1.51-1.40 (m, 2H), 1.09-0.92 (m, 1H), 0.85-0.81 (m, 1H), 0.63-0.60 (m, 1H)
I-4	EF	AW	B	1224.7	12.07-12.03 (m, 1H), 11.13 (s, 1H), 8.81 (s, 1H), 8.72 (dd, $J = 28.0$, 7.5 Hz, 1H), 8.22-8.16 (m, 1H), 8.09 (d, $J = 7.8$ Hz, 1H), 8.00-7.91 (m, 1H), 7.52-7.42 (m, 2H), 7.34-7.20 (m, 3H), 7.11-7.07 (m, 2H), 6.71 (d, $J = 13.9$ Hz, 1H), 5.37 (dd, $J = 12.8$, 5.4 Hz, 1H), 4.98-4.84 (m, 2H), 4.44-4.29 (m, 3H), 4.30-4.23 (m, 2H), 4.22-4.14 (m, 2H), 3.99-3.73 (m, 2H), 3.69-3.61 (m, 3H), 3.59-3.40 (m, 5H), 2.97-2.87 (m, 2H), 2.90-2.77 (m, 2H), 2.75-2.71 (m, 1H), 2.65-2.61 (m, 1H), 2.45-2.41 (m, 3H), 2.12-2.01 (m, 6H), 1.82-1.79 (m, 3H), 1.72-1.69 (m, 7H), 1.51-1.40 (m, 1H), 1.09-0.92 (m, 1H), 0.85-0.81 (m, 1H), 0.63-0.60 (m, 1H)
I-6	EC	AW	B	1214.4	12.08-12.05 (d, $J = 11.8$ Hz, 1H), 11.09 (s, 1H), 8.80 (s, 1H), 8.75-8.64 (m, 1H), 8.21-8.13 (m, 1H), 8.08 (d, $J = 7.9$ Hz, 1H), 7.96 (d, $J = 8.8$ Hz, 1H), 7.53 (d, $J = 8.8$ Hz, 1H), 7.47-7.36 (m, 1H), 7.33-7.23 (m, 2H), 7.21-7.10 (m, 1H), 7.08-7.02 (m, 1H), 6.99-6.92 (m, 2H), 6.90-6.83 (m, 1H), 6.77-6.69 (m, 1H), 5.41-5.32 (m, 1H), 5.01-4.86 (m, 2H), 4.44-4.23 (m, 3H), 4.20-4.14 (m, 1H), 3.95-3.78 (m, 2H), 3.69-3.62 (m, 3H), 3.59-3.51 (m, 4H), 3.45 (s, 3H), 2.95-2.60 (m, 8H), 2.17-1.95 (m, 5H), 1.91-1.55 (m, 10H), 1.51-1.46 (m, 1H), 1.33-1.19 (m, 2H), 1.09-0.80 (m, 1H), 0.77-0.48 (m, 1H)
I-7	EF	H	B	1208.7	12.22 (s, 1H), 11.13 (s, 1H), 8.81 (s, 1H), 8.48-8.42 (m, 1H), 8.26-8.14 (m, 3H), 7.95 (d, $J = 8.8$ Hz, 1H), 7.51 (d, $J = 8.9$ Hz, 1H), 7.46 (s, 1H), 7.35-7.21 (m, 4H), 7.10-7.06 (m, 3H), 6.76-6.74 (m, 1H), 5.40-5.36 (m, 1H), 5.04-5.00 (m, 1H), 4.98 – 4.89 (m, 2H), 4.47-4.30 (m, 1H), 4.30-4.14 (m, 1H), 3.90-3.86 (m, 1H), 3.78-3.62 (m, 1H), 3.32-3.26 (m, 3H), 2.99-2.86 (m, 2H), 2.86-2.69 (m, 1H), 2.71-2.65 (m, 1H), 2.66-2.62 (m, 1H), 2.63-2.58 (m, 1H), 2.45-2.40 (m, 2H), 2.12-2.08 (m, 3H), 2.06-1.95 (m, 8H), 1.82-1.78 (m, 1H), 1.75-1.66 (m, 10H), 1.50-1.46 (m, 1H), 1.44-1.40 (m, 1H), 0.98-0.94 (m, 2H), 0.83-0.78 (m, 1H)

I-8	EB	H	B	1198.6	12.16-12.04 (m, 1H), 11.25-11.19 (m, 1H), 8.80 (s, 1H), 8.49-8.42 (m, 1H), 8.20-8.03 (m, 2H), 7.99-7.95 (m, 1H), 7.56-7.51 (m, 1H), 7.48-7.42 (m, 1H), 7.33-7.16 (m, 3H), 7.08-6.95 (m, 3H), 6.91-6.61 (m, 2H), 5.36-5.33 (m, 1H), 5.08-4.83 (m, 2H), 4.47-4.12 (m, 4H), 3.91-3.87 (m, 2H), 3.81-3.79 (m, 2H), 3.51-3.41 (m, 1H), 3.28-3.23 (m, 1H), 2.98-2.74 (m, 4H), 2.74-2.55 (m, 4H), 2.36-2.19 (m, 2H), 2.17-1.91 (m, 7H), 1.87-1.71 (m, 3H), 1.68-1.51 (m, 5H), 1.51-1.37 (m, 1H), 1.27-1.09 (m, 2H), 1.05-0.80 (m, 1H), 0.78-0.49 (m, 1H)
I-9	EC	H	B	1199.0	12.93-11.96 (m, 1H), 11.10 (s, 1H), 8.92-8.88 (m, 1H), 8.55-8.11 (m, 2H), 8.11-7.73 (m, 2H), 7.66-7.39 (m, 2H), 7.35-7.15 (m, 3H), 7.11-6.64 (m, 5H), 5.40-5.36 (m, 1H), 5.05-4.87 (m, 2H), 4.46-4.10 (m, 5H), 3.98-3.60 (m, 4H), 3.58-3.54 (m, 3H), 3.40-3.21 (m, 2H), 3.00-2.78 (m, 5H), 2.75-2.57 (m, 2H), 2.25-1.88 (m, 8H), 1.88-1.39 (m, 10H), 1.35-1.10 (m, 2H), 1.05-0.44 (m, 2H)
I-10	EF	H	BA	1247.4	11.10 (s, 1H), 9.06-8.60 (m, 1H), 8.34 (d, $J=5.1$ Hz, 1H), 8.21-8.04 (m, 4H), 7.62-7.58 (m, 1H), 7.35-7.25 (m, 2H), 7.23-7.20 (m, 2H), 7.12-7.02 (m, 3H), 6.73-6.68 (m, 1H), 5.37 (dd, $J=12.9, 5.4$ Hz, 1H), 5.01-4.96 (m, 2H), 4.45-4.30 (m, 3H), 4.27-4.13 (m, 1H), 3.94-3.82 (m, 1H), 3.71-3.68 (m, 2H), 3.37-3.34 (m, 3H), 2.99-2.88 (m, 2H), 2.87-2.77 (m, 1H), 2.76-2.66 (m, 1H), 2.66-2.59 (m, 1H), 2.58-2.52 (m, 2H), 2.46-2.42 (m, 2H), 2.19-2.04 (m, 3H), 2.04-1.90 (m, 7H), 1.81-1.67 (m, 9H), 1.52-1.39 (m, 2H), 1.26-1.22 (m, 1H), 1.06-0.96 (m, 1H), 0.82-0.78 (m, 1H), 0.63-0.60 (m, 1H)
I-12	EB	A	B	1155.7	12.02 (s, 1H), 11.08 (s, 1H), 8.82-8.78 (m, 1H), 8.64-8.61 (m, 1H), 8.23-8.02 (m, 2H), 7.97-7.94 (m, 1H), 7.55-7.50 (m, 1H), 7.45-7.42 (m, 1H), 7.32-7.20 (m, 2H), 7.18-7.14 (m, 1H), 7.09-6.95 (m, 3H), 6.88-6.85 (m, 1H), 6.74 (s, 1H), 5.41-5.28 (m, 1H), 5.06-4.86 (m, 2H), 4.38-4.23 (m, 3H), 4.24-4.15 (m, 1H), 3.91-3.87 (m, 1H), 3.57-3.43 (m, 4H), 3.12-3.06 (m, 1H), 2.96-2.83 (m, 3H), 2.77-2.63 (m, 2H), 2.62-2.55 (m, 3H), 2.13-1.98 (m, 5H), 1.94-1.74 (m, 7H), 1.73-1.39 (m, 10H), 1.29-1.11 (m, 3H), 1.08-0.82 (m, 1H), 0.77-0.44 (m, 1H)
I-13	EC	EK	B	1175.3	12.07 (s, 1H), 11.10 (s, 1H), 8.99-8.91 (m, 1H), 8.83 (s, 1H), 8.27-8.08 (m, 2H), 8.02-7.93 (m, 1H), 7.57-7.44 (m, 2H), 7.30-7.18 (m, 3H), 7.14-7.09 (m, 2H), 7.03-6.94 (m, 4H), 6.90-6.86 (m, 1H), 6.76 (s, 1H), 5.49-5.24 (m, 1H), 5.16-5.09 (m, 1H), 4.96-4.82 (m, 1H), 4.73-4.62 (m, 1H), 4.38-4.26 (m, 1H), 4.19-4.10 (m, 1H), 3.92-3.75 (m, 1H), 3.49-3.42 (m, 5H), 3.17-3.13 (m, 1H), 3.00-2.57 (m, 9H), 2.26-2.21 (m, 2H), 2.11-1.93 (m, 3H), 1.87-1.13 (m, 11H), 1.05-0.60 (m, 2H), 0.47-0.35 (m, 1H)

I-15	EJ	AW	BA	1209.5	11.07 (s, 2H), 8.97-8.89 (m, 1H), 8.33-8.29 (m, 2H), 8.13-8.09 (m, 3H), 7.71-7.69 (m, 2H), 7.62-7.59 (m, 2H), 7.15 (s, 1H), 7.01-6.98 (m, 2H), 6.89-6.85 (m, 2H), 6.74-6.68 (m, 2H), 5.33 (dd, $J = 12.8, 5.3$ Hz, 2H), 4.91-4.87 (m, 2H), 4.61-4.57 (m, 2H), 4.41-4.37 (m, 2H), 4.26-4.22 (m, 3H), 3.99-3.96 (m, 2H), 3.86-3.82 (m, 2H), 3.68-3.62 (m, 4H), 3.43 (s, 3H), 2.98-2.85 (m, 2H), 2.62-2.58 (m, 5H), 2.13-2.09 (m, 1H), 1.84-1.82 (m, 3H), 1.64-1.59 (m, 14H), 1.21-1.26 (m, 6H)
I-16	EH	AW	BA	1219.6	11.11 (s, 1H), 8.93 (dd, $J = 21.9, 7.2$ Hz, 1H), 8.38-7.99 (m, 4H), 7.82-7.67 (m, 1H), 7.65-7.55 (m, 1H), 7.29-6.89 (m, 4H), 6.72 (d, $J = 9.2$ Hz, 1H), 5.40-5.36 (m, 1H), 4.89-4.85 (m, 1H), 4.72-4.52 (m, 2H), 4.49-4.13 (m, 4H), 4.09-3.74 (m, 2H), 4.08-4.02 (m, 3H), 3.73 (s, 3H), 4.10-3.76 (m, 2H), 3.12-2.56 (m, 3H), 2.31-1.37 (m, 26H), 1.37-0.81 (m, 9H)
I-17^b	ED	AW	BA	1123.6	11.10 (s, 1H), 8.90-8.84 (m, 1H), 8.33-8.14 (m, 2H), 8.09-8.02 (m, 2H), 7.74-7.67 (m, 1H), 7.64-7.58 (m, 1H), 7.40-7.10 (m, 2H), 7.02-6.82 (m, 3H), 6.78-6.67 (m, 1H), 5.43-5.31 (m, 1H), 4.89 (m, 1H), 4.66-4.54 (m, 1H), 4.47-4.39 (m, 2H), 4.31-4.10 (m, 2H), 4.05-3.89 (m, 2H), 3.89-3.75 (m, 2H), 3.73-3.60 (m, 5H), 3.59-3.51 (m, 6H), 3.04-2.79 (m, 5H), 2.76-2.57 (m, 2H), 2.28-1.94 (m, 5H), 1.94-1.80 (m, 3H), 1.80-1.42 (m, 12H), 1.48-1.32 (m, 2H), 1.32-1.13 (m, 3H), 1.12-1.02 (m, 2H), 1.02-0.81 (m, 3H)
I-18	EJ	AW	B	1170.5	12.09-12.02 (m, 2H), 11.09-11.05 (m, 2H), 8.83-8.78 (m, 2H), 8.75-8.69 (m, 1H), 8.68-8.59 (m, 1H), 8.24-8.17 (m, 2H), 7.99-7.92 (m, 2H), 7.73-7.67 (m, 2H), 7.56-7.50 (m, 2H), 7.49-7.42 (m, 3H), 7.23-7.14 (m, 2H), 7.06-6.96 (m, 4H), 6.90-6.84 (m, 3H), 6.76-6.69 (m, 3H), 5.38-5.29 (m, 3H), 4.96 (s, 1H), 4.62-4.57 (m, 2H), 4.46-4.33 (m, 3H), 4.32-4.27 (m, 4H), 4.24-4.17 (m, 1H), 4.01-3.95 (m, 2H), 3.91-3.81 (m, 2H), 3.69-3.62 (m, 3H), 3.32 (s, 3H), 2.99-1.96 (m, 1H), 2.92-2.84 (m, 1H), 2.77-2.69 (m, 1H), 2.67-2.57 (m, 4H), 2.18-2.05 (m, 1H), 1.88-1.84 (m, 1H), 1.26-1.22 (m, 2H), 1.15-1.15 (m, 2H), 0.98-0.91 (m, 4H)
I-19	EH	AW	B	1180.7	12.01-11.90 (m, 1H), 11.11 (s, 1H), 8.85 (s, 1H), 8.76-8.59 (m, 1H), 8.31-8.13 (m, 1H), 7.96 (d, $J = 8.7$ Hz, 1H), 7.80-7.63 (m, 1H), 7.44-7.39 (m, 2H), 7.25-6.92 (m, 4H), 6.74-6.70 (m, 1H), 5.38 (dd, $J = 12.7, 5.4$ Hz, 1H), 4.96-4.93 (m, 1H), 4.62-4.58 (m, 1H), 4.43-4.38 (m, 2H), 4.35-4.13 (m, 3H), 4.03-3.99 (m, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 3.60-3.40 (m, 6H), 3.10-2.96 (m, 3H), 2.95-2.84 (m, 1H), 2.78-2.56 (m, 2H), 2.23-1.98 (m, 6H), 1.94-1.45 (m, 14H), 1.28-0.80 (m, 9H)

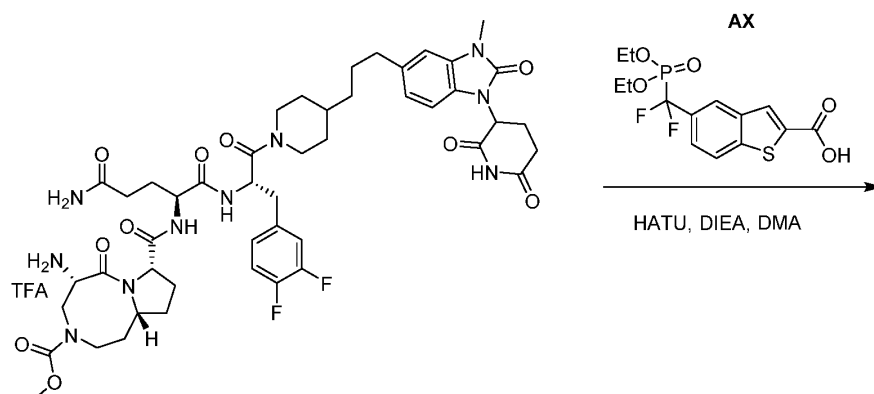
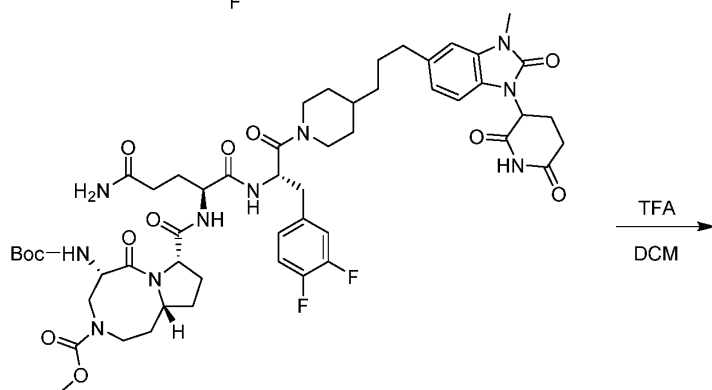
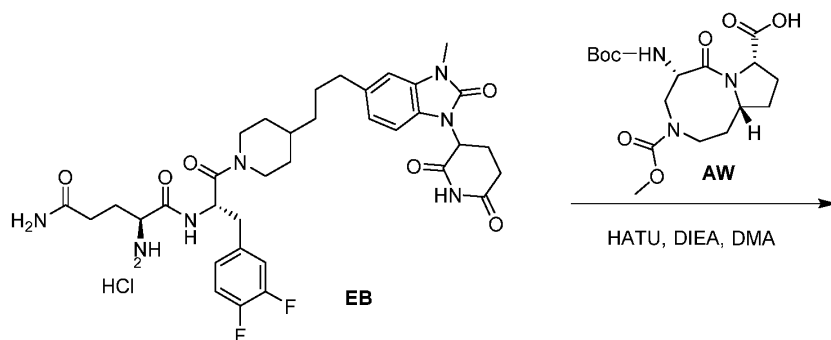
I-20	ED	AW	B	1184.7	12.04-11.87 (m, 1H), 11.10 (s, 1H), 8.84 (s, 1H), 8.77-8.60 (m, 1H), 8.28-8.19 (m, 1H), 8.05-7.91 (m, 1H), 7.78-7.71 (m, 1H), 7.50-7.38 (m, 2H), 7.35-7.12 (m, 2H), 7.02-6.81 (m, 3H), 6.77-6.64 (m, 1H), 5.41-5.38 (m, 1H), 4.97-4.93 (m, 1H), 4.65-4.59 (m, 1H), 4.45-4.18 (m, 4H), 4.16-4.07 (m, 3H), 4.02-3.79 (m, 4H), 3.70-3.63 (m, 6H), 3.02-2.90 (m, 3H), 2.69-2.61 (m, 1H), 2.60-2.56 (m, 1H), 2.30-1.85 (m, 9H), 1.76-1.49 (m, 12H), 1.44-1.36 (m, 3H), 1.30-1.06 (m, 6H), 1.03-0.82 (m, 4H)
I-27^b	ED	H	B	1168.6	12.15-12.01 (m, 1H), 11.09 (s, 1H), 8.86-8.70 (m, 1H), 8.49-8.41 (m, 1H), 8.31-8.18 (m, 1H), 8.21-8.11 (m, 1H), 7.99-7.92 (m, 1H), 7.81-7.69 (m, 1H), 7.55-7.41 (m, 2H), 7.28-7.21 (m, 1H), 6.99-6.92 (m, 2H), 6.91-6.82 (m, 1H), 6.78-6.71 (m, 1H), 5.41-5.35 (m, 1H), 5.06-4.87 (m, 1H), 4.67-4.53 (m, 1H), 4.50-4.29 (m, 3H), 4.29-4.13 (m, 2H), 4.04-3.80 (m, 3H), 3.78-3.58 (m, 2H), 3.54 (s, 3H), 3.35-3.21 (m, 2H), 3.03-2.80 (m, 4H), 2.74-2.58 (m, 1H), 2.22 (s, 3H), 2.16-2.04 (m, 4H), 2.04-1.94 (m, 2H), 1.92-1.86 (m, 2H), 1.81-1.44 (m, 14H), 1.42-1.34 (m, 2H), 1.31-1.18 (m, 2H), 1.18-1.02 (m, 3H), 1.03-0.79 (m, 4H)
I-28	EJ	H	B	1154.5	11.99 (s, 1H), 11.07 (s, 1H), 8.91 (s, 1H), 8.42-8.38 (m, 1H), 8.29-8.25 (m, 1H), 7.98-7.96 (m, 1H), 7.75-7.71 (m, 1H), 7.45-7.35 (m, 2H), 7.25 (s, 1H), 7.06-6.97 (m, 2H), 6.89-6.85 (m, 1H), 6.78 (s, 1H), 5.33 (dd, $J = 12.5, 5.6$ Hz, 1H), 5.03-4.98 (m, 1H), 4.62-4.58 (m, 1H), 4.47-4.43 (m, 1H), 4.39-4.34 (m, 1H), 4.25-4.21 (m, 2H), 4.01-3.97 (m, 1H), 3.74-3.70 (m, 1H), 3.31 (s, 3H), 2.90-2.82 (m, 10H), 2.65-2.60 (m, 2H), 2.21-2.08 (m, 1H), 2.00-1.84 (m, 1H), 1.66-1.60 (m, 12H), 1.27-1.22 (m, 3H), 1.12-1.08 (m, 13H), 0.98-0.90 (m, 4H)
I-29	EH	H	B	1164.7	12.25-11.89 (m, 1H), 11.11 (s, 1H), 8.81 (s, 1H), 8.51-8.13 (m, 2H), 7.97 (d, $J = 8.8$ Hz, 1H), 7.82-7.63 (m, 1H), 7.48-7.44 (m, 2H), 7.35-7.15 (m, 1H), 7.11 (d, $J = 7.8$ Hz, 1H), 7.06 (dd, $J = 7.9, 1.3$ Hz, 1H), 6.99 (t, $J = 7.8$ Hz, 1H), 6.84-6.63 (m, 1H), 5.38 (dd, $J = 12.7, 5.4$ Hz, 1H), 5.09-4.88 (m, 1H), 4.70-4.53 (m, 1H), 4.53-4.12 (m, 4H), 4.12-3.68 (m, 2H), 3.65 (s, 3H), 3.13-2.95 (m, 2H), 2.95-2.79 (m, 3H), 2.79-2.55 (m, 4H), 2.22 (s, 3H), 2.11-1.94 (m, 2H), 1.94-1.34 (m, 21H), 1.33-0.77 (m, 9H)
I-30	EJ	H	BA	1171.5	11.09 (s, 1H), 8.90 (s, 1H), 8.76-8.69 (m, 1H), 8.45-8.38 (m, 2H), 8.29-8.25 (m, 1H), 8.23-8.19 (m, 2H), 7.77-7.73 (m, 1H), 7.28-7.24 (m, 1H), 7.23-7.20 (m, 1H), 7.06-6.97 (m, 4H), 6.90-6.83 (m, 2H), 6.81-6.77 (m, 1H), 5.36-5.32 (m, 1H), 5.00-4.96 (m, 1H), 4.61-4.57 (m, 1H), 4.45-4.35 (m, 2H), 4.24-4.20 (m, 2H), 4.01-3.97 (m, 1H), 3.92-3.84 (m, 1H), 3.72-3.67 (m, 2H), 3.32 (s, 3H), 3.03-2.95 (m, 1H), 2.93-2.83 (m, 2H), 2.77-2.66 (m, 2H), 2.62-2.57 (m, 3H), 2.22-2.16 (m, 2H), 2.12-2.08 (m, 3H), 2.02-1.98 (m,

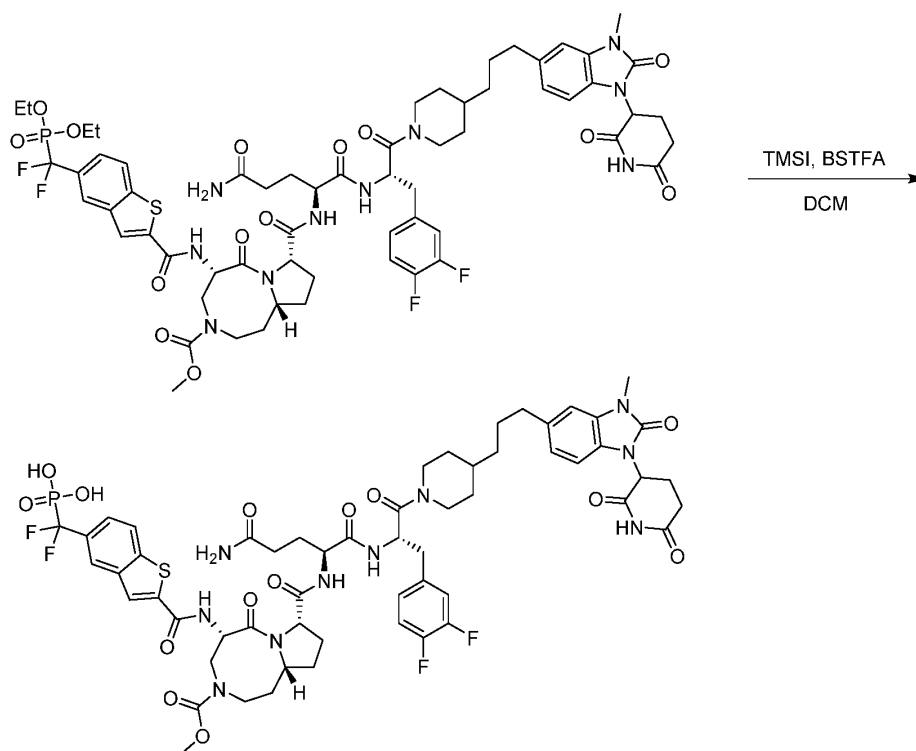
					1H), 1.91-1.87 (m, 2H), 1.64-1.61 (m, 12H), 1.26-1.22 (m, 3H), 1.12-1.08 (m, 3H), 0.99-0.96 (m, 3H), 0.90-0.86 (m, 1H)
I-31	EH	H	BA	1181.6	11.11 (s, 1H), 9.15-8.86 (m, 1H), 8.70 (d, $J = 6.8$ Hz, 1H), 8.39 (s, 1H), 8.33-8.07 (m, 3H), 7.82-7.66 (m, 1H), 7.22 (d, $J = 19.0$ Hz, 1H), 7.15-6.95 (m, 3H), 6.86-6.63 (m, 1H), 5.38 (dd, $J = 12.7, 5.4$ Hz, 1H), 5.11-4.81 (m, 2H), 4.62-4.59 (m, 1H), 4.51-4.33 (m, 2H), 4.33-4.16 (m, 2H), 4.02-4.00 (m, 1H), 3.92-3.85 (m, 1H), 3.77-3.68 (m, 2H), 3.64 (s, 3H), 3.12-2.97 (m, 1H), 2.95-2.82 (m, 1H), 2.78-2.57 (m, 4H), 2.17 (s, 3H), 2.12-1.97 (m, 2H), 1.97-1.46 (m, 21H), 1.26-1.02 (m, 5H), 1.03-0.88 (m, 4H)
I-32	ED	H	BA	1185.6	11.10 (s, 1H), 9.12-8.64 (m, 2H), 8.40 (s, 1H), 8.33-8.06 (m, 3H), 7.79-7.65 (m, 1H), 7.35-7.11 (m, 2H), 7.00-6.82 (m, 3H), 6.80-6.64 (m, 1H), 5.41-5.30 (m, 1H), 5.03-4.82 (m, 1H), 4.69-4.54 (m, 1H), 4.51-4.12 (m, 4H), 4.10-3.79 (m, 2H), 3.77-3.51 (m, 5H), 3.06-2.80 (m, 4H), 2.80-2.55 (m, 3H), 2.26-2.15 (m, 3H), 2.14-2.08 (m, 3H), 2.06-1.80 (m, 5H), 1.81-1.47 (m, 14H), 1.46-1.32 (m, 2H), 1.32-0.77 (m, 10H)

^aReactions were run at rt for 1-16 hrs. TEA could also be used as a base in Step 2. Compounds were purified under standard conditions such as reverse flash chromatography under a variety of conditions.

^bDeprotection with 4 M HCl in dioxane and DCM at rt for 2 hr.

Example 2 (Method 2): Synthesis of (2-{{(5*S*,8*S*,10*aR*)-8-{{(1*S*)-3-carbamoyl-1-{{(2*S*)-3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl}propyl]carbamoyl}-3-(methoxycarbonyl)-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocin-5-yl]carbamoyl}-1-benzothiophen-5-yl)difluoromethylphosphonic acid (I-2)





[00929] Step 1- Methyl (5*S*,8*S*,10*aR*)-5-[(*tert*-butoxycarbonyl)amino]-8-{[(1*S*)-3-carbamoyl-1-{[(2*S*)-3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl}propyl]carbamoyl}-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocine-3-carboxylate

[00930] To a stirred solution of (2*S*)-2-amino-*N*-[(2*S*)-3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]pentanediamide hydrochloride (100 mg, 0.137 mmol, Intermediate EB) and (5*S*,8*S*,10*aR*)-5-[(*tert*-butoxycarbonyl)amino]-3-(methoxycarbonyl)-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocine-8-carboxylic acid (52.64 mg, 0.137 mmol, Intermediate AW) in DMA (1 mL, 10 mmol) were added HATU (67.51 mg, 0.178 mmol) and TEA (0.09 mL, 0.7 mmol) at 25 °C under nitrogen atmosphere and the reaction was stirred for 1 hr at rt. On completion, the reaction mixture was concentrated under reduced pressure. Then the residue was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 µm, 120 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 25% - 65% B in 25 min; Flow rate: 65 mL/min; Detector: 220/254 nm; desired fractions were collected at 45% B and concentrated under reduced pressure) to afford the title compound (90 mg, 62% yield) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.04-8.89 (m, 1H), 8.71-8.61 (m, 1H), 7.51-6.38 (m, 1H), 7.25-7.15 (m, 1H), 7.12-6.92

(m, 3H), 6.92-6.69 (m, 5H), 5.91-5.58 (m, 1H), 5.36-5.16 (m, 1H), 5.10-4.95 (m, 1H), 4.84-4.68 (m, 1H), 4.67-4.05 (m, 4H), 3.77 (s, 3H), 3.44 (s, 3H), 3.29-3.13 (m, 1H), 3.05-2.73 (m, 7H), 2.66-2.08 (m, 10H), 1.99-1.52 (m, 9H), 1.45 (s, 9H), 1.32-0.98 (m, 4H), 0.87-0.21 (m, 2H); LC/MS (ESI, m/z): [(M + H)]⁺ = 1063.4.

[00931] Step 2 - Methyl (5*S*,8*S*,10*aR*)-5-amino-8-{[(1*S*)-3-carbamoyl-1-{[(2*S*)-3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl}propyl]carbamoyl}-6-oxo-octahydropyrrolo[1,2-a][1,5]diazocine-3-carboxylate trifluoroacetate

To a stirred solution of methyl (5*S*,8*S*,10*aR*)-5-[(*tert*-butoxycarbonyl)amino]-8-{[(1*S*)-3-carbamoyl-1-{[(2*S*)-3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl}propyl]carbamoyl}-6-oxo-octahydropyrrolo[1,2-a][1,5]diazocine-3-carboxylate (90 mg, 0.09 mmol) in DCM (3.60 mL) was added TFA (1.80 mL) at 25 °C under nitrogen atmosphere and the reaction mixture was stirred for 1 h. On completion, the reaction mixture was concentrated under vacuum to afford the title compound (80 mg, 89% yield) as a light brown solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.14-6.96 (m, 3H), 6.96-6.77 (m, 3H), 5.26-5.18 (m, 1H), 5.08-4.97 (m, 1H), 4.29-4.16 (m, 1H), 4.15-4.03 (m, 1H), 3.81-3.76 (m, 3H), 3.44 (s, 3H), 3.03-2.82 (m, 4H), 2.78-2.47 (m, 9H), 2.42-2.01 (m, 10H), 1.99-1.54 (m, 7H), 1.52-1.01 (m, 5H), 0.97-0.28 (m, 2H); LC/MS (ESI, m/z): [(M + H)]⁺ = 963.9.

[00932] Step 3 - Methyl (5*S*,8*S*,10*aR*)-8-{[(1*S*)-3-carbamoyl-1-{[(2*S*)-3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl}propyl]carbamoyl}-5-{5-[(diethoxyphosphoryl)difluoromethyl]-1-benzothiophene-2-amido}-6-oxo-octahydropyrrolo[1,2-a][1,5]diazocine-3-carboxylate

[00933] To a stirred solution of methyl (5*S*,8*S*,10*aR*)-5-amino-8-{[(1*S*)-3-carbamoyl-1-{[(2*S*)-3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl}propyl]carbamoyl}-6-oxo-octahydropyrrolo[1,2-a][1,5]diazocine-3-carboxylate trifluoroacetate (80 mg, 0.08 mmol) and 5-[(diethoxyphosphoryl)difluoromethyl]-1-benzothiophene-2-carboxylic acid (27.47 mg, 0.075 mmol, Intermediate AX) in DMA (2.00 mL) were added HATU (37.27 mg, 0.098 mmol) and TEA (0.06 mL, 0.430 mmol) at 25 °C under nitrogen atmosphere and the reaction mixture was stirred for 1 h. On completion, the reaction mixture was concentrated under reduced pressure. Then the residue was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 μm, 120 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 25% - 55% B in 30 min; Flow rate: 65 mL/min; Detector: 220/254 nm; desired fractions were collected at 40% B and concentrated under reduced pressure) to afford

the title compound (70 mg, 71% yield) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.26-8.14 (m, 2H), 8.12-8.06 (m, 1H), 7.68-7.64 (m, 1H), 7.21-7.08 (m, 2H), 7.07-6.91 (m, 4H), 5.47-5.26 (m, 1H), 5.17-4.99 (m, 2H), 4.48-4.35 (m, 3H), 4.33-4.09 (m, 5H), 3.99-3.86 (m, 2H), 3.84-3.74 (m, 3H), 3.71-3.47 (m, 2H), 3.44 (s, 3H), 3.07-2.51 (m, 8H), 2.44-1.94 (m, 8H), 1.92-1.41 (m, 8H), 1.38-1.27 (m, 6H), 1.20-1.15 (m, 4H), 1.05-0.24 (m, 2H); LC/MS (ESI, m/z): [(M + H)]⁺ = 1309.5.

[00934] Step 4 - (2-[(5*S*,8*S*,10*aR*)-8-[(1*S*)-3-carbamoyl-1-[(2*S*)-3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl]propyl]carbamoyl]-3-(methoxycarbonyl)-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocin-5-yl]carbamoyl]-1-benzothiophen-5-yl)difluoromethylphosphonic acid

[00935] To a stirred solution of methyl (5*S*,8*S*,10*aR*)-8-[(1*S*)-3-carbamoyl-1-[(2*S*)-3-(3,4-difluorophenyl)-1-(4-{3-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-1,3-benzodiazol-5-yl]propyl}piperidin-1-yl)-1-oxopropan-2-yl]carbamoyl]propyl]carbamoyl]-5-{5-[(diethoxyphosphoryl)difluoromethyl]-1-benzothiophene-2-amido}-6-oxo-octahydropyrrolo[1,2-*a*][1,5]diazocine-3-carboxylate (70 mg, 0.05 mmol) and TMSI (53.49 mg, 0.265 mmol) in DCM (1 mL) was added trimethylsilyl 2,2,2-trifluoro-*N*-(trimethylsilyl)ethanecarboximidate (68.81 mg, 0.267 mmol) at 25 °C under nitrogen atmosphere and the reaction mixture was stirred for 10 min. On completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography (Column: WelFlash TM C18-I, 20-40 μm, 120 g; Eluent A: Water (plus 10 mmol/L FA); Eluent B: ACN; Gradient: 20% - 45% B in 30 min; Flow rate: 65 mL/min; Detector: 220/254 nm; desired fractions were collected at 43% B and concentrated under reduced pressure) to afford the title compound (16.2 mg, 23% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.08 (s, 1H), 8.99-8.94 (m, 1H), 8.35-8.25 (m, 1H), 8.19-8.00 (m, 4H), 7.62-7.56 (m, 1H), 7.34-7.08 (m, 3H), 7.06-6.95 (m, 3H), 6.89-6.84 (m, 1H), 6.77-6.66 (m, 1H), 5.39-5.27 (m, 1H), 4.96-4.82 (m, 2H), 4.42-4.09 (m, 5H), 3.97-3.73 (m, 2H), 3.69-3.60 (m, 3H), 3.58-3.37 (m, 3H), 2.99-2.83 (m, 3H), 2.82-2.55 (m, 5H), 2.20-1.94 (m, 6H), 1.91-1.35 (m, 12H), 1.27-1.08 (m, 2H), 1.07-0.85 (m, 1H), 0.81-0.68 (m, 1H), 0.64-0.45 (m, 1H); LC/MS (ESI, m/z): [(M + H)]⁺ = 1254.1.

Table 3: Compounds synthesized via Method 2, where the corresponding amines and acids were coupled in Step 1; and the correspond acid was coupled in Step 3.

I-# ^a	Step 1 Amine	Step 1 Acid	Step 3 Acid	LC/MS (ESI, m/z) (M + H) ⁺	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ
I-3	EC	AW	AX	1253.4	11.09 (s, 1H), 8.99-8.93 (m, 1H), 8.34-8.25 (m, 1H), 8.20-8.01 (m, 4H), 7.65-7.60 (m, 1H), 7.34-7.20 (m, 2H), 7.19-7.10 (m, 1H), 7.08-6.92 (m, 3H), 6.89-6.83 (m, 1H), 6.76-6.71 (m, 1H),

					5.40-5.32 (m, 1H), 4.95-4.89 (m, 2H), 4.42-4.12 (m, 4H), 3.97-3.75 (m, 5H), 3.73-3.61 (m, 7H), 2.97-2.73 (m, 7H), 2.69-2.64 (m, 1H), 2.15-1.93 (m, 5H), 1.92-1.39 (m, 11H), 1.34-1.13 (m, 2H), 1.09-0.79 (m, 1H), 0.75-0.48 (m, 1H)
I-11	EB	A	AX	1195	11.08 (s, 1H), 8.88-8.84 (m, 1H), 8.35-8.31 (m, 1H), 8.21-7.97 (m, 4H), 7.62-7.59 (m, 1H), 7.33-7.19 (m, 2H), 7.18-7.14 (m, 1H), 7.08-6.96 (m, 3H), 6.88-6.85 (m, 1H), 6.75-6.73 (m, 1H), 5.35-5.31 (m, 1H), 4.99-4.86 (m, 2H), 4.41-4.23 (m, 3H), 4.22-4.12 (m, 1H), 3.92-3.87 (m, 1H), 3.25-3.19 (m, 2H), 2.98-2.73 (m, 4H), 2.73-2.54 (m, 5H), 2.14-1.95 (m, 5H), 1.88-1.81 (m, 7H), 1.71-1.36 (m, 11H), 1.22-1.18 (m, 2H), 1.05-0.91 (m, 1H), 0.75-0.46 (m, 1H)
I-14	EC	EK	AX	1214.5	11.09 (s, 1H), 9.13 (d, $J = 7.8$ Hz, 1H), 8.36-8.27 (m, 1H), 8.24-8.18 (m, 2H), 8.16-8.08 (m, 2H), 7.62 (d, $J = 8.6$ Hz, 1H), 7.30-7.14 (m, 3H), 7.12-7.07 (m, 2H), 7.04-6.95 (m, 4H), 6.89-6.83 (m, 1H), 6.78-6.72 (m, 1H), 5.40-5.34 (m, 1H), 5.15-5.08 (m, 1H), 4.95-4.89 (m, 1H), 4.66-4.59 (m, 1H), 4.35-4.24 (m, 1H), 4.19-4.12 (m, 1H), 3.88-3.82 (m, 1H), 3.57-3.50 (m, 2H), 3.49-3.44 (m, 2H), 3.15-3.06 (m, 4H), 2.99-2.80 (m, 7H), 2.67-2.59 (m, 3H), 2.31-2.18 (m, 2H), 2.09-1.98 (m, 3H), 1.85-1.73 (m, 1H), 1.71-1.52 (m, 5H), 1.51-1.39 (m, 1H), 1.30-1.15 (m, 2H), 1.06-0.90 (m, 1H), 0.77-0.61 (m, 1H)

^aStep 1 was run anywhere from 3-12 h at rt. Step 2 was run anywhere from 1-4 h at rt. Other deprotection agents, like TFA, can also be employed. Step 3 was run anywhere from 1-2 h at rt. TEA in NMP could also be used for the coupling in place of HATU.

Example 3. HiBiT Assay Protocol

[00936] Compound preparation and Cell seeding: The transfected A549 cells were harvested from dish into cell culture medium and cell numbers counted. Cells were diluted with culture medium to the desired density and 30 μ L of cell suspension (about 2000 cells/well) were added into each well of a 384-well cell culture plate as designated and transferred into 37°C 5% CO₂ incubator for 24 h. Compounds were dissolved to 10 mM stock solution and 12 μ L of the stock solution was transferred to a 384 LDV-plate. 3 fold, 10-point dilution was performed by transferring 4 μ L compound into 8 μ L DMSO using a TECAN (EVO200) liquid handler. 30 μ L of diluted compound from compound source plate was transferred into the cell plate as designated by using Echo550 and transferred into 37°C 5% CO₂ incubator for 24 h.

[00937] Detection: Plates were removed from incubators and equilibrated at room temperature for 15 minutes. Nano-Glo Hibit Lytic Detection reagent (Promega Cat# N3040) was thawed and equilibrated to room temperature before the experiment. 30 μ L of Nano-Glo Hibit Lytic Detection reagent was added into each well to be detected. The plates were held at room temperature for 10 min followed by reading on

EnSpire.

[00938] Data analysis: The remaining activity was calculated following the formula: Remaining Activity(%)=100% × (Lumsample-LumNC)/(LumPC-LumNC). Calculate the IC50 by fitting the curve using Xlfit (v5.3.1.3), equation 201: fit = (A+((B-A)/(1+((x/C)^D))))); A: Bottom; B: Top; C: IC50; and D: Slope.

[00939] STAT3 HiBiT degradation results for compounds of the invention are presented in **Table 4**. The letter codes for STAT3 DC50 include: A (<0.05 μM), B (0.05 – 0.2 μM), C (0.2 – 1.0 μM), and D (>1.0 μM).

Table 4. STAT3 HiBiT Degradation Results

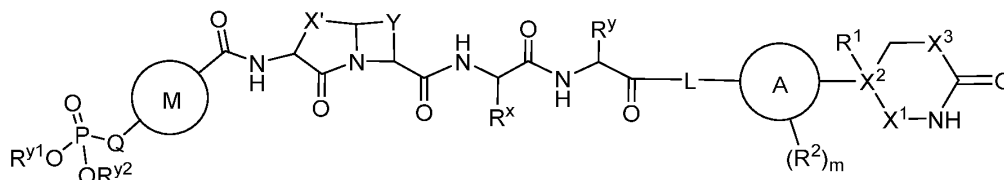
I-#	Cell: STAT3 HiBit A549 degradation 24h GMean External Abs- DC50 (nM)	I-11	B
I-1	A	I-12	C
I-2	A	I-13	C
I-3	A	I-14	D
I-4	C	I-15	C
I-5	B	I-16	C
I-6	C	I-17	C
I-7	C	I-18	C
I-8	D	I-19	C
I-9	C	I-20	C
I-10	B	I-27	D
		I-28	D
		I-29	D
		I-30	D
		I-31	B
		I-32	C

[00940] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

CLAIMS

We claim:

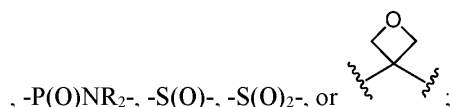
1. A compound of formula **I-bbb**:



I-bbb

or a pharmaceutically acceptable salt thereof, wherein:

X¹ is a bivalent moiety selected from a covalent bond, -CR₂-, -C(O)-, -C(S)-, -CR(CF₃)-, -P(O)OR-, -P(O)R-



X² is a carbon atom or silicon atom;

X³ is a bivalent moiety selected from -CR₂-, -NR-, -O-, -S-, or -SiR₂-;

R¹ is hydrogen, halogen, -CN, -OR, -SR, -S(O)R, -S(O)₂R, -NR₂, -P(O)(OR)₂, -P(O)NR₂OR, -P(O)(NR₂)₂, -Si(OH)₂R, -Si(OH)R₂, -SiR₃, or an optionally substituted C₁₋₄ aliphatic;

each R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

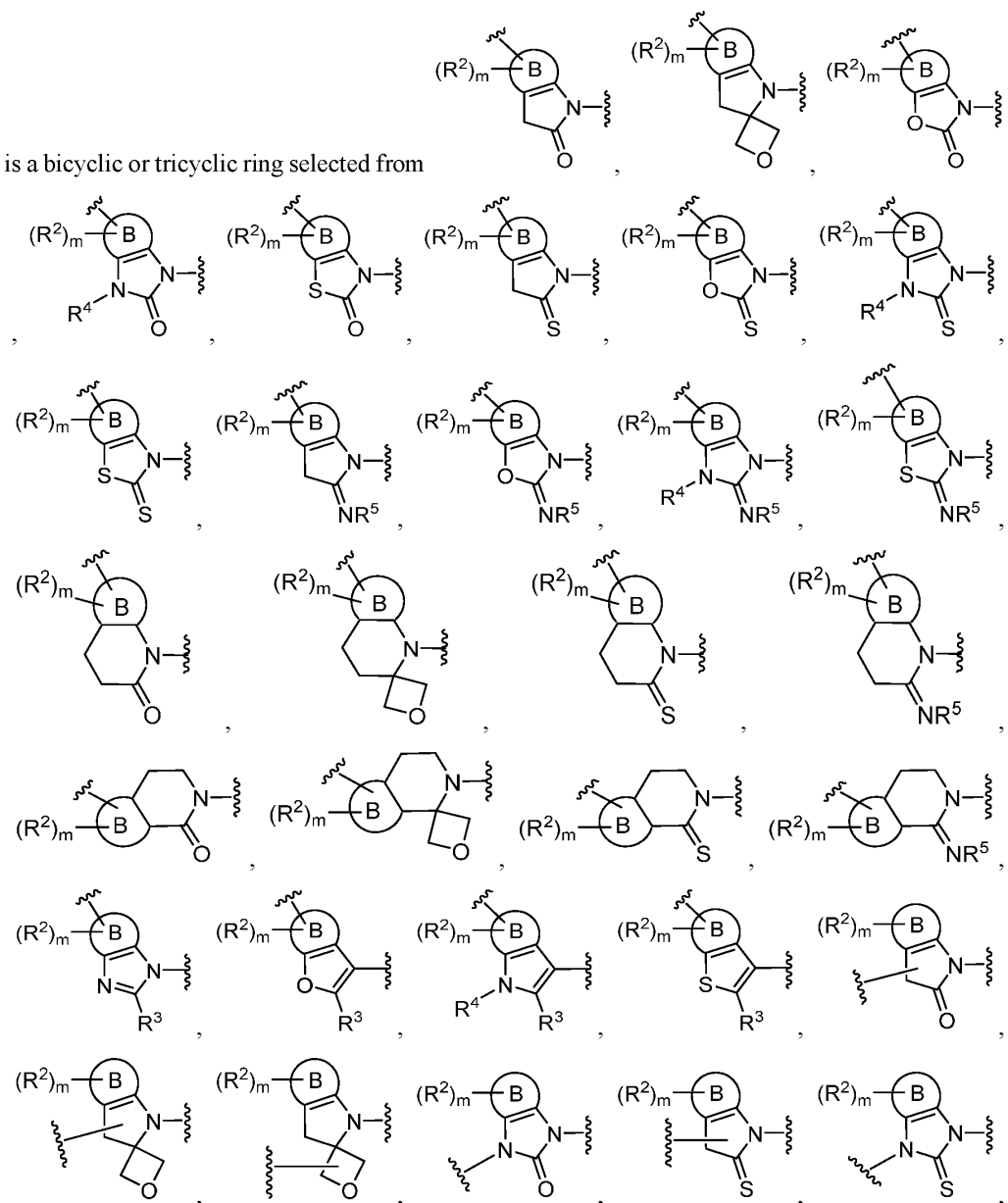
two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in addition to the carbon or nitrogen from which the two R groups are attached, independently selected from nitrogen, oxygen, and sulfur;

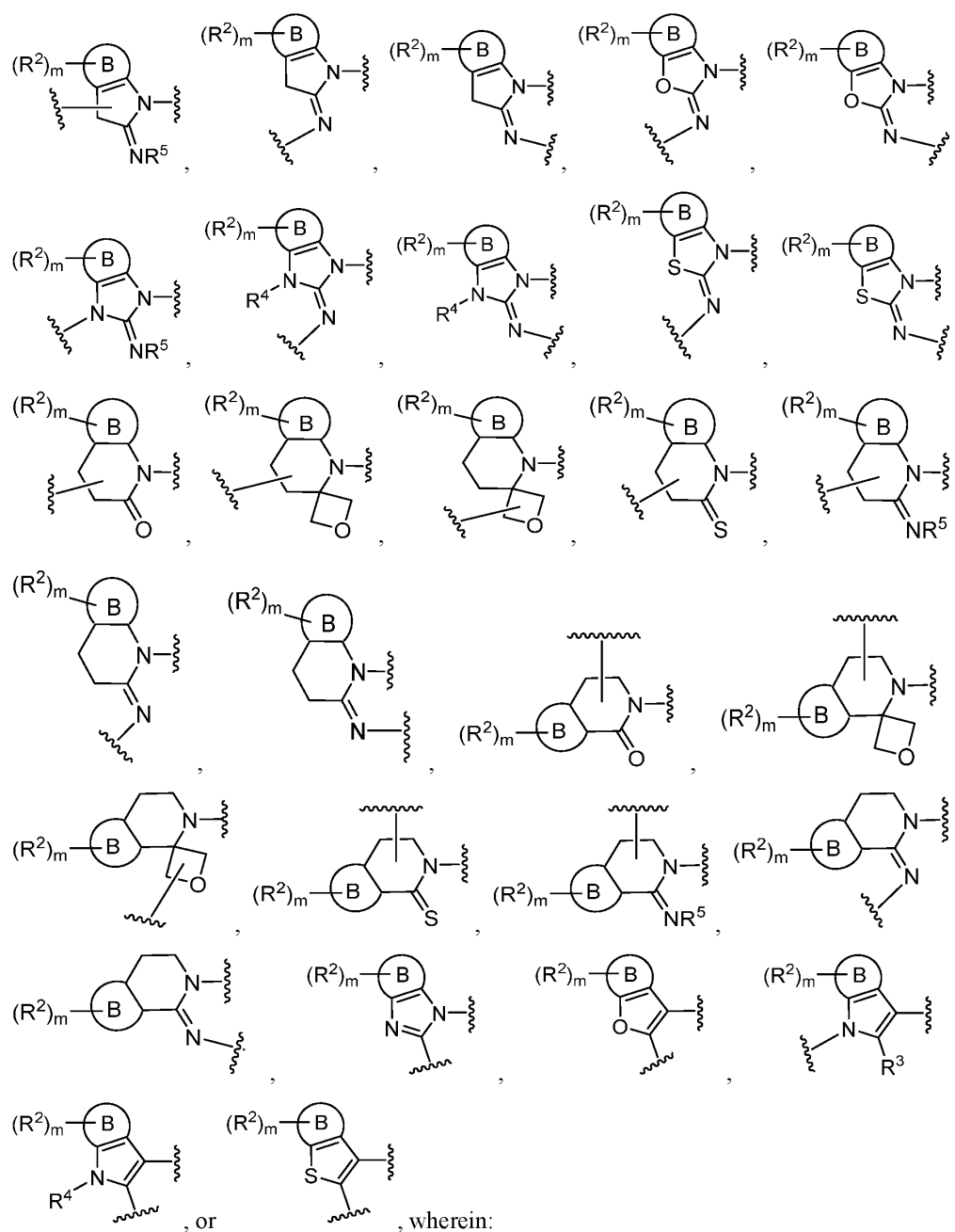
each R² is independently hydrogen, R⁶, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -SiR₃, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)NROR, -CR₂NRC(O)R, -CR₂NRC(O)NR₂, -OC(O)R, -OC(O)NR₂, -OP(O)R₂, -OP(O)(OR)₂, -OP(O)(OR)NR₂, -OP(O)(NR₂)₂, -NRC(O)OR, -NRC(O)R, -NRC(O)NR₂, -NRS(O)₂R, -NP(O)R₂, -NRP(O)(OR)₂, -NRP(O)(OR)NR₂, -NRP(O)(NR₂)₂, or -NRS(O)₂R;

each R⁶ and R^A is independently an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7

membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring A is a bicyclic or tricyclic ring selected from





Ring B is a fused ring selected from benzo, 5-6 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5 to 7-membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from

nitrogen, oxygen, or sulfur;

R^3 is selected from hydrogen, halogen, -OR, -NR₂, or -SR;

each R^4 is independently hydrogen, R^6 , halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)NROR, -OC(O)R, -OC(O)NR₂, -NRC(O)OR, -NRC(O)R, -NRC(O)NR₂, or -NRS(O)₂R;

R^5 is hydrogen, C₁₋₄ aliphatic, or -CN;

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

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C₁₋₂₀ hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, -CRF-, -CF₂-, -C(O)-, -S-, -S(O)-, -S(O)₂-, -SiR₂-, -Si(OH)R-, -Si(OH)₂-, -P(O)OR-, -P(O)R-, or -P(O)NR₂-, wherein:

each -Cy- is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

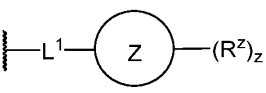
X' is an optionally substituted -(CH₂)_x-, wherein 1-2 methylenes of X is optionally replaced with a bivalent group selected from -NR-, -N(COR)-, -N(CO₂R)-, -N(SO₂R)-, -N(CONR₂)-, and -N(SO₂NR₂)-, wherein:

x is 1, 2, 3, 4, or 5;

Y is an optionally substituted -(CH₂)_y-, wherein:

y is 1, 2, or 3;

R^x is hydrogen, R^A , -(CR₂)₁₋₃OCONR₂, or -(CR₂)₁₋₃CONR₂;

R^y is hydrogen, R^A , or 

L^1 is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-5} hydrocarbon chain, wherein 0-3 methylene units of L^1 are independently replaced by $-O-$, $-NR-$, $-CRF-$, $-CF_2-$, $-C(O)-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

Ring Z is a ring selected from phenyl, naphthyl, a 5-10 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^z is hydrogen, R^A , halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)NROR$, $-CR_2NRC(O)R$, $-CR_2NRC(O)NR_2$, $-OC(O)R$, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-NRC(O)OR$, $-NRC(O)R$, $-NRC(O)NR_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, or $-NRS(O)_2R$;

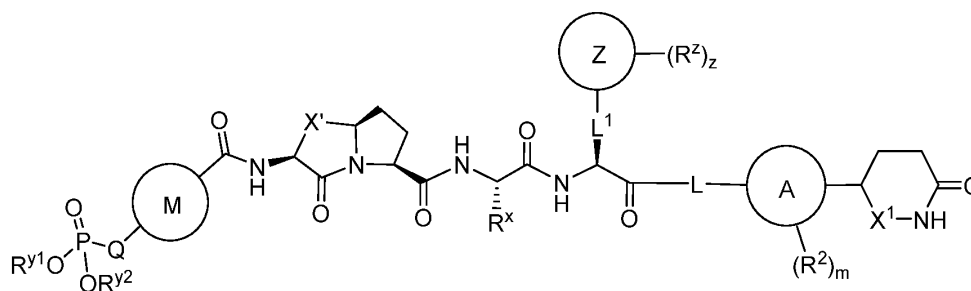
z is 0, 1, 2, 3, or 4;

Ring M is an optionally substituted bivalent ring selected from phenylenyl, naphthylenyl, a 5-10 membered heteroarylenyl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclylenyl or heterocyclylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

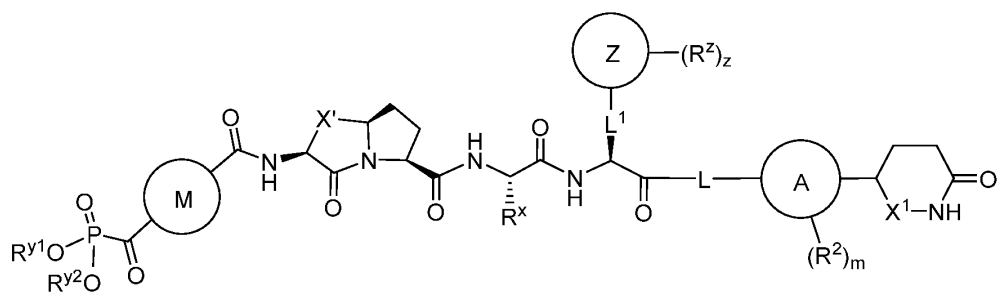
Q is a bivalent moiety selected from $-O-$, $-CR_2-$, $-CF_2-$, $-CFR-$, $-C(O)-$, $-OCR_2-$, and $-C(S)-$; and

R^{y1} and R^{y2} are each independently hydrogen, R^A , $-CH_2CO_2R$, or $-CH_2OCO_2R$.

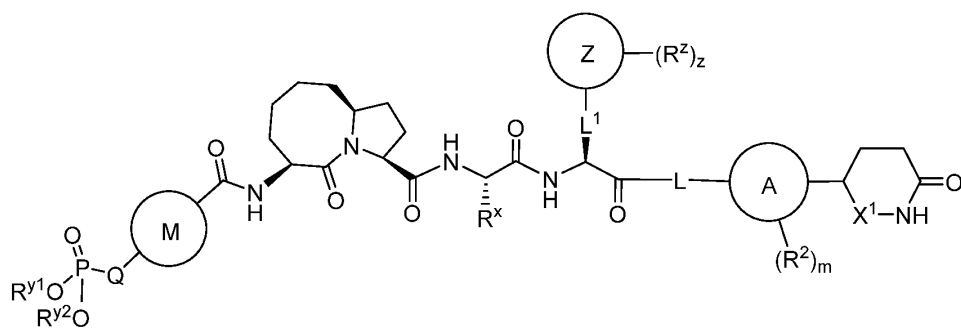
2. The compound of claim 1, wherein said compound is of any one of the following formulae:



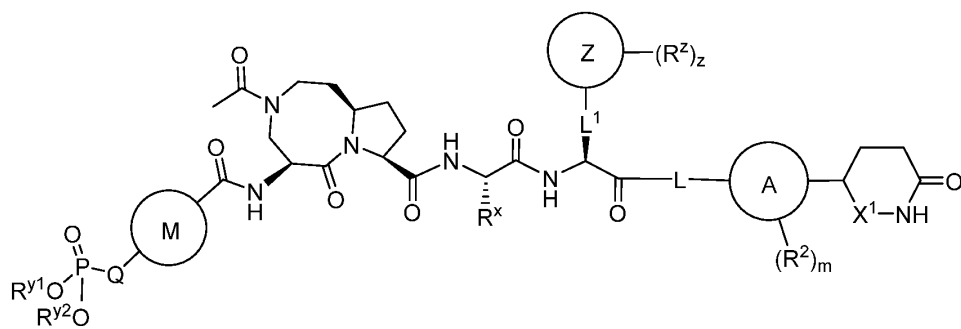
I-bbb-1



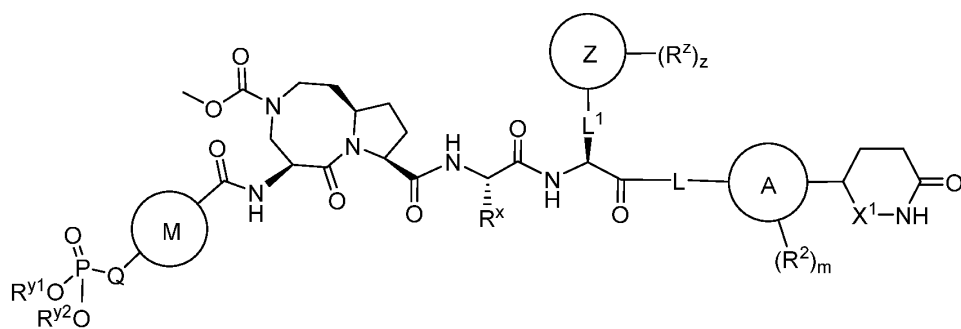
I-bbb-2



I-bbb-3



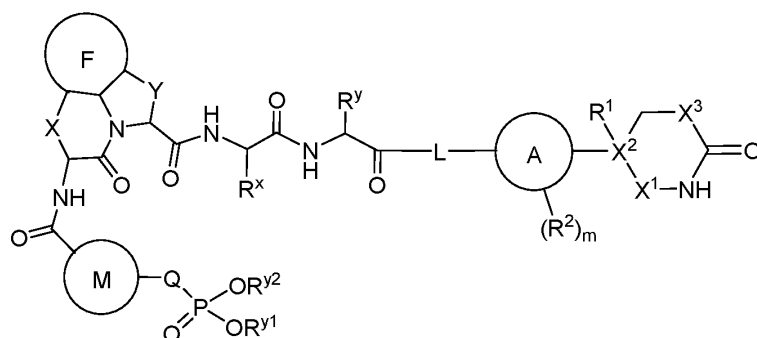
I-bbb-4



I-bbb-5

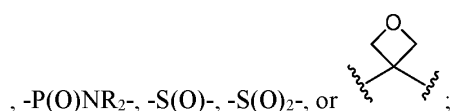
or a pharmaceutically acceptable salt thereof.

3. A compound of formula **I-ddd**:

**I-ddd**

or a pharmaceutically acceptable salt thereof, wherein:

X¹ is a bivalent moiety selected from a covalent bond, -CR₂-, -C(O)-, -C(S)-, -CR(CF₃)-, -P(O)OR-, -P(O)R-



X² is a carbon atom or silicon atom;

X³ is a bivalent moiety selected from -CR₂-, -NR-, -O-, -S-, or -SiR₂-;

R¹ is hydrogen, halogen, -CN, -OR, -SR, -S(O)R, -S(O)₂R, -NR₂, -P(O)(OR)₂, -P(O)NR₂OR, -P(O)(NR₂)₂, -Si(OH)₂R, -Si(OH)R₂, -SiR₃, or an optionally substituted C₁₋₄ aliphatic;

each R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

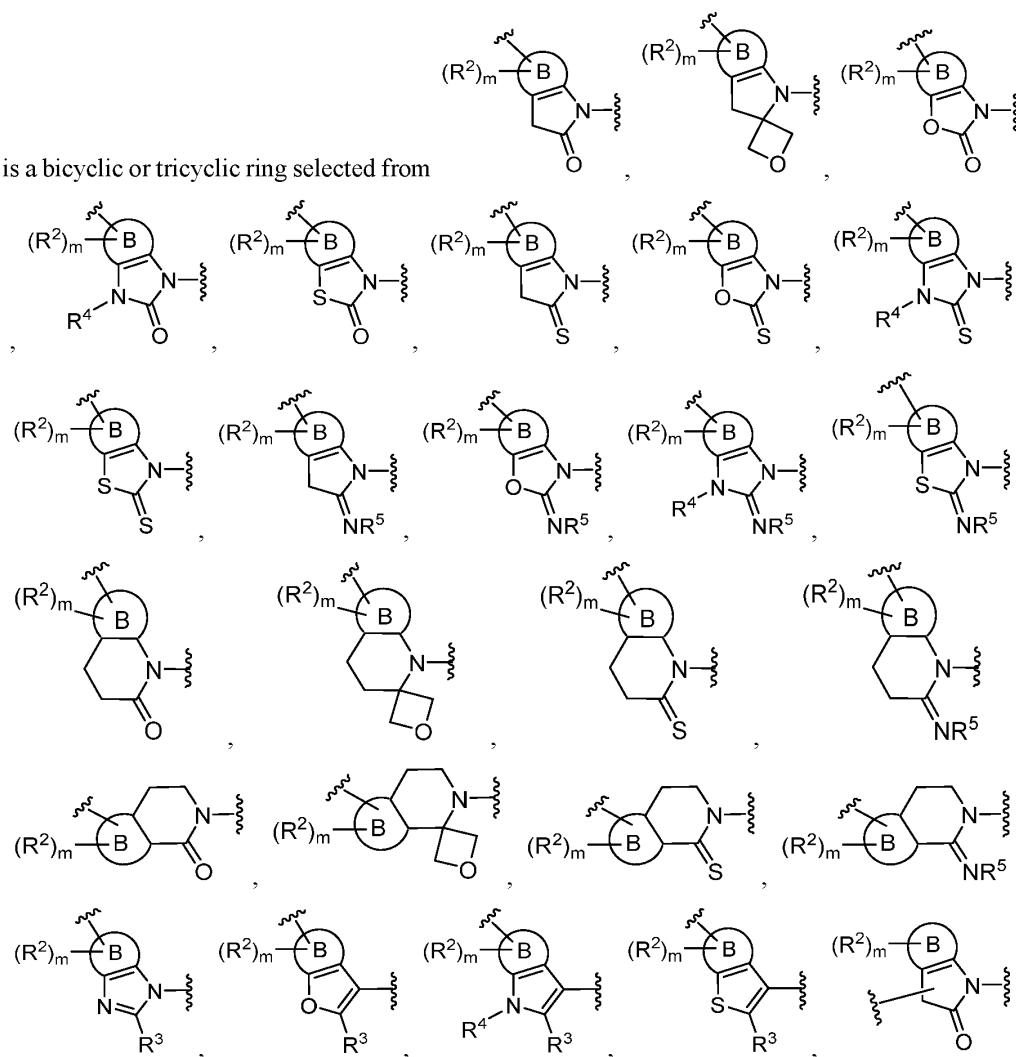
two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in addition to the carbon or nitrogen from which the two R groups are attached, independently selected from nitrogen, oxygen, and sulfur;

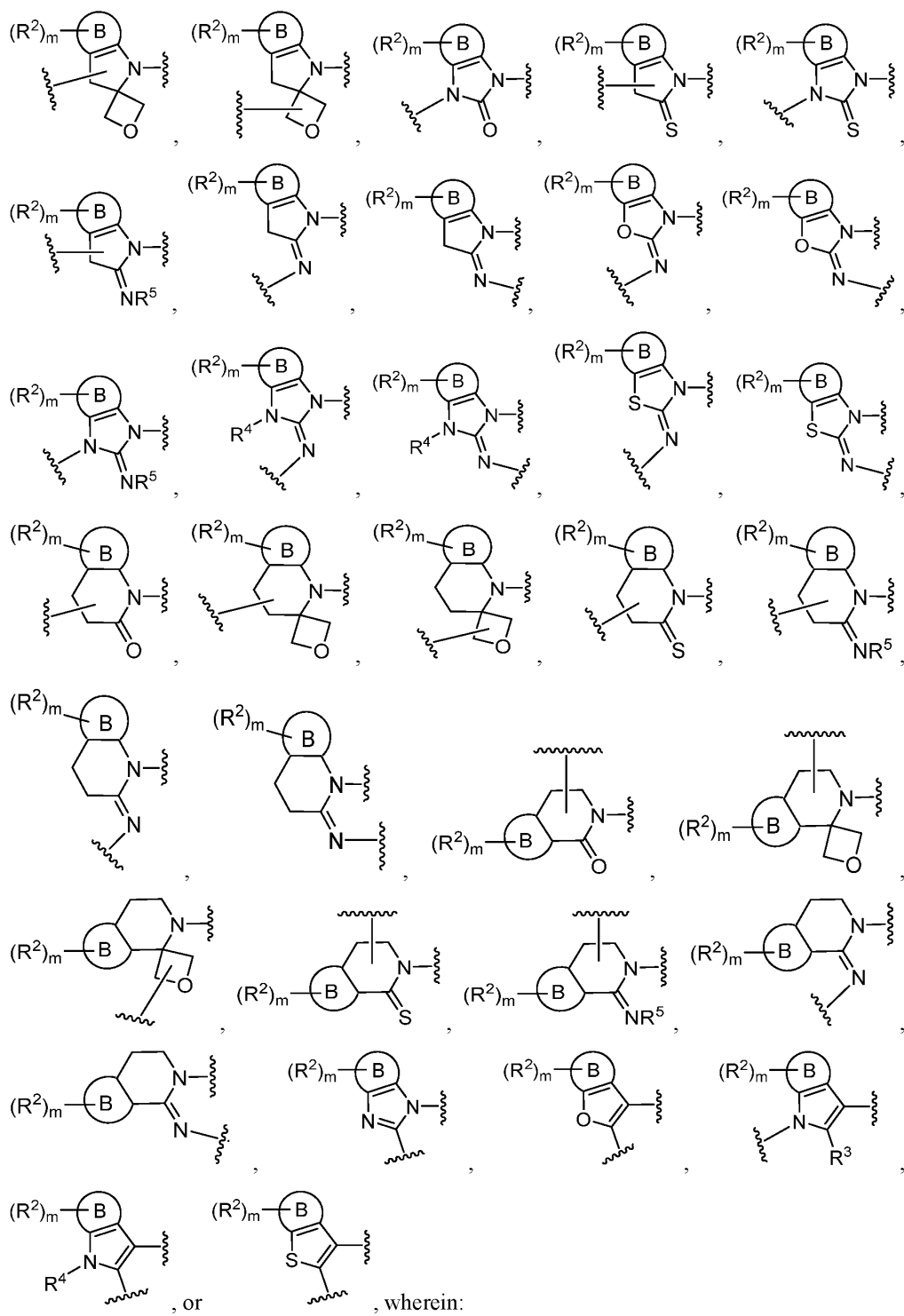
each R² is independently hydrogen, R⁶, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -SiR₃, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)NROR, -CR₂NRC(O)R, -

$\text{CR}_2\text{NRC(O)NR}_2$, $-\text{OC(O)R}$, $-\text{OC(O)NR}_2$, $-\text{OP(O)R}_2$, $-\text{OP(O)(OR)}_2$, $-\text{OP(O)(OR)NR}_2$, $-\text{OP(O)(NR}_2)_2$, $-\text{NRC(O)OR}$, $-\text{NRC(O)R}$, $-\text{NRC(O)NR}_2$, $-\text{NRS(O)}_2\text{R}$, $-\text{NP(O)R}_2$, $-\text{NRP(O)(OR)}_2$, $-\text{NRP(O)(OR)NR}_2$, $-\text{NRP(O)(NR}_2)_2$, or $-\text{NRS(O)}_2\text{R}$;

each R^6 and R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring A is a bicyclic or tricyclic ring selected from





Ring B is a fused ring selected from benzo, 5-6 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5 to 7-membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R³ is selected from hydrogen, halogen, -OR, -NR₂, or -SR;

each R⁴ is independently hydrogen, R⁶, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)NROR, -OC(O)R, -OC(O)NR₂, -NRC(O)OR, -NRC(O)R, -NRC(O)NR₂, or -NRS(O)₂R;

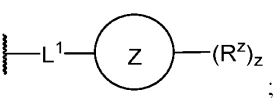
R⁵ is hydrogen, C₁₋₄ aliphatic, or -CN;

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

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C₁₋₂₀ hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, -CRF-, -CF₂-, -C(O)-, -S-, -S(O)-, -S(O)₂-, -SiR₂-, -Si(OH)R-, -Si(OH)₂-, -P(O)OR-, -P(O)R-, or -P(O)NR₂-, wherein:

each -Cy- is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclenyl, a 4-7 membered saturated or partially unsaturated heterocyclenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^x is hydrogen, R^A, -(CR₂)₁₋₃OCONR₂, or -(CR₂)₁₋₃CONR₂;

R^y is hydrogen, R^A, or ;

L¹ is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C₁₋₅ hydrocarbon chain, wherein 0-3 methylene units of L¹ are independently replaced by -O-, -NR-, -CRF-, -CF₂-, -C(O)-, -S-, -S(O)-, or -S(O)₂-;

Ring Z is a ring selected from phenyl, naphthyl, a 5-10 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^z is hydrogen, R^A , halogen, -CN, -NO₂, -OR, -SR, -NR₂, -SiR₃, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)NROR, -CR₂NRC(O)R, -CR₂NRC(O)NR₂, -OC(O)R, -OC(O)NR₂, -OP(O)R₂, -OP(O)(OR)₂, -OP(O)(OR)NR₂, -OP(O)(NR₂)₂, -NRC(O)OR, -NRC(O)R, -NRC(O)NR₂, -NRS(O)₂R, -NP(O)R₂, -NRP(O)(OR)₂, -NRP(O)(OR)NR₂, -NRP(O)(NR₂)₂, or -NRS(O)₂R;

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

Ring F is an optionally substituted fused ring selected from a 6-membered aryl, a 5-6 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

X is an optionally substituted -(CH₂)_x-, wherein:

x is 0, 1, 2, or 3;

Y is an optionally substituted -(CH₂)_y-, wherein:

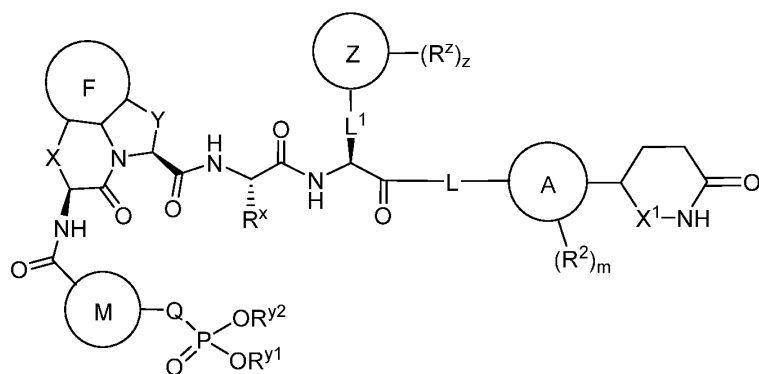
y is 0, 1, 2, or 3;

Ring M is an optionally substituted bivalent ring selected from phenylenyl, naphthylenyl, a 5-10 membered heteroarylenyl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclylenyl or heterocyclylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

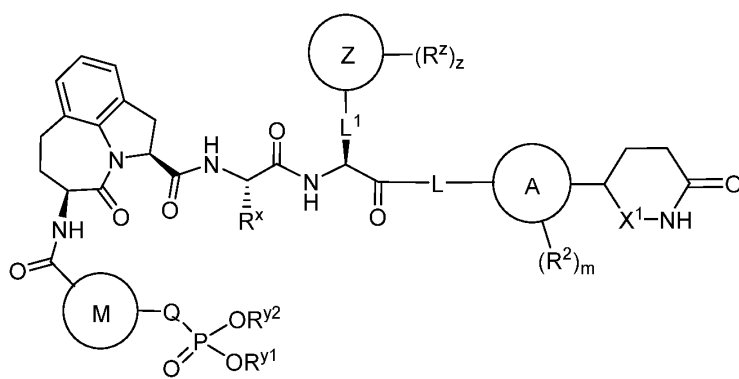
Q is a bivalent moiety selected from -O-, -CR₂-, -CF₂-, -CFR-, -C(O)-, -OCR₂-, and -C(S)-; and

R^{y1} and R^{y2} are each independently hydrogen, R^A , -CH₂CO₂R, or -CH₂OCO₂R.

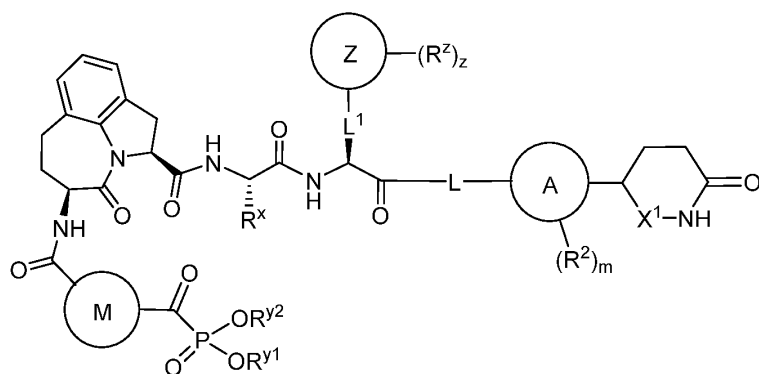
4. The compound of claim 3, wherein said compound is any one of the following formula:



I-ddd-1



I-ddd-2



I-ddd-3

or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1-4, wherein Ring B is a fused ring selected from benzo or 5-6 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

6. The compound of any one of claims 1-5, wherein R^x is $-(CH_2)_{1-3}OCONR_2$, or $-(CH_2)_{1-3}CONR_2$;
7. The compound of any one of claims 1-6, wherein Ring Z is a ring selected from phenyl, a 5-6 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5-6 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;
8. The compound of any one of claims 1-7, wherein Ring M is an optionally substituted bivalent ring selected from phenylenyl, naphthylenyl, a 5-10 membered heteroarylenyl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclenyl or heterocyclenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;
9. The compound of any one of claims 1-8, wherein Q is a bivalent moiety selected from $-CF_2-$ and $-C(O)-$.
10. The compound of any one of claims 1-9, wherein R^{y1} and R^{y2} are each independently hydrogen, $-CH_2CO_2R$, or $-CH_2OCO_2R$.
11. The compound of any one of claims 1-10, wherein said compound is selected from any one of the compounds depicted in **Table 1**, or a pharmaceutically acceptable salt thereof.
12. A pharmaceutical composition comprising a compound according to any one of claims 1-11, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.
13. The pharmaceutical composition according to claim 12, further comprising an additional therapeutic agent.
14. A method of degrading STAT3 protein in a patient or biological sample comprising administering to said patient, or contacting said biological sample with a compound according to any one of claims 1-11, or a pharmaceutical composition thereof.

15. A method of treating an STAT3-mediated disorder, disease, or condition in a patient comprising administering to said patient a compound according to any one of claims 1-11, or a pharmaceutical composition thereof.

16. The method according to claim 15, further comprising administration of an additional therapeutic agent.

17. The method according to claim 15, wherein the STAT3-mediated disorder, disease or condition is selected from a cancer, a neurodegenerative disease, a viral disease, an autoimmune disease, an inflammatory disorder, a hereditary disorder, a hormone-related disease, a metabolic disorder, a condition associated with organ transplantation, an immunodeficiency disorder, a destructive bone disorder, a proliferative disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, liver disease, a pathologic immune condition involving T cell activation, a cardiovascular disorder, and a CNS disorder.

18. The method according to claim 17, wherein the cancer is selected from glioma, breast cancer, prostate cancer, head and neck squamous cell carcinoma, skin melanomas, ovarian cancer, malignant peripheral nerve sheath tumors (MPNST), pancreatic cancer, non-small cell lung cancer, urothelial cancer, liver cancer, bile duct cancer, kidney cancer, colon cancer, esophageal cancer, gastric cancer, gastrointestinal stromal tumors, and hematological malignancies include lymphomas, leukemias, myelomas, myeloproliferative neoplasms and myelodysplastic syndromes.

19. The method according to claim 17, wherein autoimmune disease is selected from systemic sclerosis, idiopathic pulmonary fibrosis, inflammatory bowel disease, atopic dermatitis, rheumatoid arthritis, acute graft versus host disease, chronic graft versus host disease, and tissue fibrosis diseases.

20. The method according to claim 18, wherein the hematologic malignancy is selected from large granular lymphocytic (LGL) leukemia (T and NK cell), cutaneous T cell lymphoma (CTCL), peripheral T cell lymphomas (PTCL), anaplastic large-cell lymphoma (ALCL), diffuse large B cell lymphoma (DLBCL), acute myelogenous leukemia, multiple myeloma, and myelofibrosis.