

ULK INHIBITORS AND METHODS OF USE THEREOF

CROSS-REFERENCE

[0001] This application claims priority to U.S. Provisional Application Number 63/549,108 filed February 2, 2024, and U.S. Provisional Application Number 63/716,893 filed November 6, 2024, the contents of each of which are incorporated herein by reference in their entireties.

BACKGROUND

[0001] Autophagy is a process that enables cells to recycle cellular organelles, proteins, stored lipids, glucagon, and other materials for the purpose of generating nutrients under periods of stress. These cellular contents are recycled by engulfment in vesicles called autophagosomes. Autophagosomes subsequently merge with lysosomes that degrade the autophagosomal contents for recycling of nutrients to the cell. Tumor cells are prone to activate autophagy, as these cells have a high metabolic demand, experience cellular stress, and frequently are in hypoxic environments with limited blood flow and nutrient supply. Moreover, chemotherapy and targeted anti-cancer therapies have been shown to induce autophagy as a treatment resistance mechanism, and combination of autophagy inhibition (by genetic loss of function mutations in autophagy genes or by pharmacologic means) with chemotherapeutic regimens has been shown to suppress tumor growth and trigger tumor cell apoptosis to a greater extent than single agent chemotherapy.

[0002] Mutant Ras proteins drive approximately 30 percent of all human cancers – including 95 percent of pancreatic cancers, 45 percent of colorectal cancers, and 30% of lung cancers, and treatment of these mutant Ras cancers is currently an area of high unmet medical need. Mutant Ras cancers are highly proliferative and depend on basal levels of autophagy for survival, suggesting that inhibition of autophagy in these “autophagy addicted” cancers is a viable therapeutic approach.

[0003] Currently, the most widely used autophagy inhibitors are chloroquine and hydroxychloroquine, which are well-known anti-malarial agents. These anti-malarials have been thought to block autophagy by being sequestered in the lysosomal compartment, raising the pH of these lysosomes and thereby inactivating proteases that degrade and recycle nutrients. These anti-malarial agents have multiple mechanisms of action beyond inhibiting lysosomes and are known to induce retinopathies in patients. Hence there is a need for more targeted agents which selectively block autophagy and do not exhibit the toxicities of these anti-malarial agents. ULK1 kinase is the initiating protein of autophagy and is a serine/threonine kinase. The ULK1 kinase complex is activated in response to cellular stress including nutrient deprivation and energy

depletion. Nutrient deprivation activates ULK kinase activity through inhibition of mTORC1, and energy depletion activates ULK kinase activity through activation by AMP-activated protein kinase AMPK. Importantly, kinase dead mutants of ULK kinase block initiation of canonical autophagy, suggesting that small molecule inhibitors of ULK kinase activity would be able to block autophagy.

[0004] Further mechanistic studies have shown that genetic deletion of ULK1 inhibits autophagy in cancer cells, relieving FOX3A turn-over and upregulation of the pro-apoptotic protein PUMA. In addition to classical activation of canonical autophagy, ULK1 kinase activity has been shown to be required for Bcl-2-L-13 mediated mitophagy (autophagy of damaged mitochondria). ULK1 and ULK2 kinases have also been demonstrated to rewire cancer cell glucose metabolism which favors increases in the reducing agent NADPH leading to a reduction in toxic reactive oxygen species (ROS). ULK inhibitors may also find utility in blocking these noncanonical pro-tumoral activities of ULK.

[0005] Autophagy is also upregulated in host cells and tissues in cancer. Autophagy in pancreatic tissue stellate cells was demonstrated to support tumor growth. Pancreatic stellate cells were shown to support pancreatic cancer tumor metabolism through autophagic alanine secretion. Inhibition of host tissue autophagy was demonstrated to lead to a depletion in circulating arginine (a required amino acid for tumor metabolism and growth) through liver - mediated increases in arginase secretion. Activation of ULK1 kinase was also shown to inactivate the STING pathway in immune cells through inhibitory phosphorylation of STING, mediating a negative feedback mechanism for limiting an innate immune cell response mediated by interferons. Thus, not only is autophagy activated in tumor cells (cancer cell autonomous), but also in other cells in the tumor microenvironment or host tissues (cancer cell nonautonomous) to support tumor survival and growth.

[0006] Mutant Ras cancers are addicted to autophagy. In pancreatic cancer, mutant Ras signals predominantly through the MAP kinase pathway. Mutant Ras activates RAF kinases, which in turn activate MEK kinases, which finally activate ERK kinases: mutant Ras → RAF → MEK → ERK. Despite mutant Ras signaling through the MAP kinase pathway, inhibitors of this pathway have provided no or little clinical benefit in clinical trials when used as single agents. It has been recently reported that inhibition of the MAP kinase pathway induces autophagy as a compensatory adaptive stress response resistance mechanism. When MEK inhibitors were combined with the autophagy inhibitor hydroxychloroquine, there was synergistic activity leading to regression of a number of mutant Ras or mutant BRAF cancers. Similarly, when ERK inhibitors were combined with the autophagy inhibitor hydroxychloroquine or chloroquine, there was synergistic activity leading to inhibition of mutant

Ras pancreatic cancers. It has been demonstrated that genetic depletion of RAF kinases (CRAF and BRAF) led to synergistic anti-tumor activity in mutant Ras cancer cell lines when autophagy was also genetically depleted. In composite, recent publications highlight that dual inhibition of the RAS/MAPK pathway and the autophagy pathway in mutant Ras cancers is a promising treatment regimen for patients with mutant Ras cancers. It has also been demonstrated that other targeted therapies and chemotherapeutic agents activate tumor autophagy as a resistance mechanism; hence there is rationale for combining such targeted therapeutics or chemotherapeutic agents with inhibitors of autophagy.

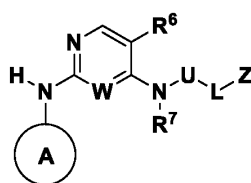
[0007] It has also been demonstrated that tumor driver receptor tyrosine kinases (RTKs) can modulate autophagy, and that inhibitors of RTKs also activate autophagy through the same mTORC1 and AMP kinase pathways as do inhibitors of mutant RAS or RAF. Inhibitors of mutant oncogenic KIT kinase, inhibitors of oncogenic EGFR kinase, and inhibitors of oncogenic FLT3 kinase are known to activate autophagy as an adaptive stress response resistance mechanism.

[0008] There is a need for new targeted therapies which inhibit autophagy and can be used in combination with RTK/RAS/MAPK pathway inhibitors, chemotherapeutic agents, and/or other targeted therapeutics.

SUMMARY

[0009] Described herein are compounds that are inhibitors of autophagy, pharmaceutical compositions, and their use as agents in the treatment of disorders such as cancer, processes for their preparation, and pharmaceutical compositions containing them as an active ingredient. Such pharmaceutical compositions may comprise the compound as the sole active agent or in combination with other active agents in the presence of a pharmaceutically acceptable excipient. In an embodiment, the described compounds are inhibitors of ULK kinase activity, including ULK1 and ULK2 activity.

[00010] For example, compounds provided herein may be described as represented by Formula (I):



Formula (I)

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:
A is selected from the group consisting of cycloalkyl and heterocyclyl;

W is selected from the group consisting of N and CH;

U is selected from the group consisting of C(=O), alkyl, and heterocyclyl, or U is absent, or wherein U and R⁷ taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 10 atoms in the ring structure;

5 L is selected from the group consisting of a bond, alkyl, cycloalkyl, and heterocyclyl;

Z is selected from the group consisting of H, cyano, -N(R⁸)SO₂R⁹, -N(R⁸)C(=O)R⁹, -N(R¹⁸)SO₂NR¹⁹R²⁸, -SO₂R²⁹, -S(O)(=NH)-R¹⁰, and optionally substituted heterocyclyl, wherein the optionally substituted heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of R³¹,

10 or wherein two occurrences of R³¹ taken together with the carbon atoms to which they are attached form an optionally substituted ring having 5 to 8 atoms in the ring structure;

R⁶ is selected from the group consisting of halogen, cyano, alkyl, haloalkyl, cycloalkyl, and heterocyclyl;

R⁷ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

15 R⁸ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

R⁹ is selected from the group consisting of amino, alkyl, cycloalkyl, and heterocyclyl, or wherein R⁸ and R⁹ taken together with the nitrogen and sulfur or carbon atoms to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure;

20 R¹⁰ is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

R¹⁸ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

R¹⁹ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

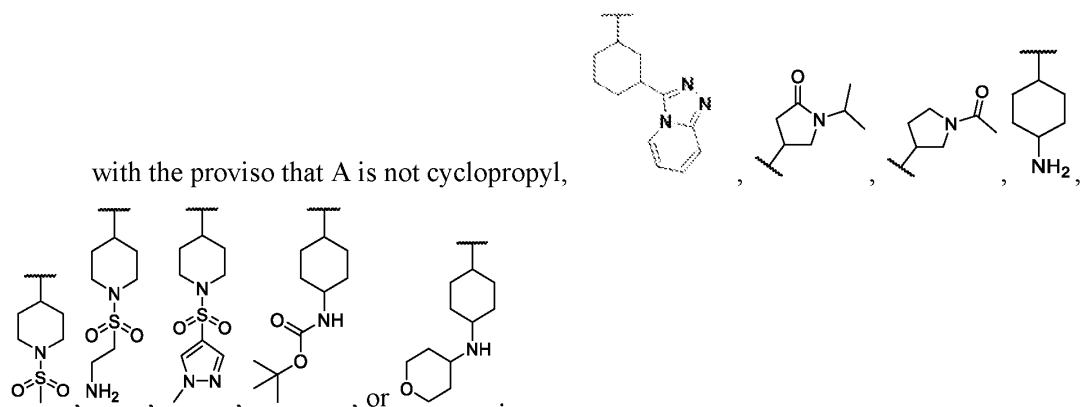
R²⁸ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl, or wherein R¹⁸ and R²⁸ taken together with the nitrogen atoms to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure, or wherein R¹⁹ and R²⁸ taken together with the nitrogen atom to which they are attached

25 form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure;

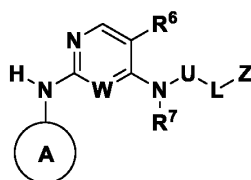
R²⁹ is selected from the group consisting of amino, alkyl, cycloalkyl, and heterocyclyl; and

30 R³¹ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, at each occurrence, is optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone, sulfonamide, heterocyclyl, or heteroaryl,



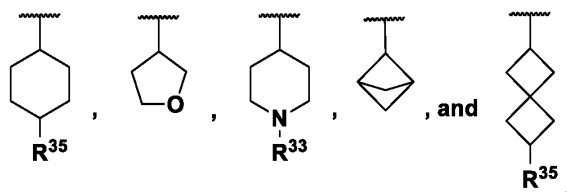
[00011] Also provided herein, in some embodiments, is a compound represented by Formula (II):



Formula (II)

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

A is selected from the group consisting of



- 10 wherein each occurrence of R^{33} is independently selected from the group consisting of H, alkyl, haloalkyl, cycloalkyl, and heterocyclyl, and each occurrence of R^{35} is independently selected from the group consisting of H, halogen, and alkyl;

W is selected from the group consisting of N and CH;

- 15 U is selected from the group consisting of C(=O), alkyl, and heterocyclyl, or U is absent, or wherein U and R^7 taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 10 atoms in the ring structure;

L is selected from the group consisting of a bond, alkyl, cycloalkyl, and heterocyclyl;

- 20 Z is selected from the group consisting of H, cyano, $-N(R^8)SO_2R^9$, $-N(R^8)C(=O)R^9$, $-N(R^{18})SO_2NR^{19}R^{28}$, $-SO_2R^{29}$, $-S(O)(=NH)-R^{10}$, and optionally substituted heterocyclyl, wherein the optionally substituted heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of R^{31} ;

or wherein two occurrences of R³¹ taken together with the carbon atoms to which they are attached form an optionally substituted ring having 5 to 8 atoms in the ring structure;

R⁶ is selected from the group consisting of halogen, cyano, alkyl, haloalkyl, cycloalkyl, and heterocyclyl;

5 R⁷ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

R⁸ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

R⁹ is selected from the group consisting of amino, alkyl, cycloalkyl, and heterocyclyl,

or wherein R⁸ and R⁹ taken together with the nitrogen and, sulfur or carbon atoms to which they are attached, form an optionally substituted heterocyclyl ring having from 4 to 6

10 atoms in the ring structure;

R¹⁰ is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

R¹⁸ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

R¹⁹ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

R²⁸ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl,

15 or wherein R¹⁸ and R²⁸ taken together with the nitrogen atoms to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure,

or wherein R¹⁹ and R²⁸ taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure;

R²⁹ is selected from the group consisting of amino, alkyl, cycloalkyl, and heterocyclyl;

20 and

R³¹ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, at each occurrence, is optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone, sulfonamide, heterocyclyl, or heteroaryl.

[00012] In another embodiment, described herein is a pharmaceutical composition comprising a compound described herein (*e.g.*, a compound of Formula (I), Formula (Ia), or Formula (II), or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, as described herein) and a pharmaceutically acceptable carrier or excipient.

[00013] In another embodiment, provided herein is a method of treating a tumor in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein or pharmaceutically acceptable salts, enantiomers, stereoisomers, or tautomers thereof, or of a pharmaceutical composition described herein.

[00014] In another embodiment, provided herein is a method of treating a cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein or pharmaceutically acceptable salts, enantiomers, stereoisomers, or tautomers thereof, or of a pharmaceutical composition described herein.

5 [00015] In another embodiment, provided herein is a method of treating a disorder selected from the group consisting of gastrointestinal stromal tumors, esophageal cancers, gastric cancers, melanomas, gliomas, glioblastomas, gynecological cancers (e.g., ovarian cancers, cervical cancers, uterine cancers, vaginal cancers, and vulvar cancers), bladder cancers, pancreatic cancers, prostate cancers, lung cancers, breast cancers, renal cancers, hepatic cancers, 10 osteosarcomas, Ewing sarcoma, multiple myelomas, leukemias, cancers that are metastatic to bone, papillary thyroid carcinomas, non-small cell lung cancer, colorectal cancers, acute myeloid leukemia, relapsed acute myeloid leukemia, refractory acute myeloid leukemia, myelodysplastic syndrome, acute lymphocytic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, myeloproliferative neoplasms, and mantle cell lymphoma in a patient in need thereof, 15 comprising administering to the patient a therapeutically effective amount of a compound described herein or pharmaceutically acceptable salts, enantiomers, stereoisomers, or tautomers thereof, or of a pharmaceutical composition described herein.

[00016] In some embodiments, the method further comprises administering to the patient one or more additional therapeutic agents.

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DETAILED DESCRIPTION

[00017] The features and other details of the disclosure will now be more particularly described. Certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and as understood by a person of skill in the art. Unless defined otherwise, all technical and scientific 25 terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

Definitions

[00018] The definitions set forth in this application are intended to clarify terms used throughout this application.

30 [00019] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the subject matter herein belongs. As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated in order to facilitate the understanding of the present disclosure.

[00020] As used herein, the singular forms "a," "an," and "the" encompass plural references unless the context clearly indicates otherwise. The terms "comprising," "including," and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

5 **[00021]** As used herein, the term "herein" means the entire application.

[00022] As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, and the Handbook of Chemistry and Physics, 75th Ed. 1994. 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., Smith, M. B. and March, J., eds. John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

10 **[00023]** When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents, positions of substituents and/or variables are permissible only if such combinations result in stable compounds.

15 **[00024]** As used herein, the terms "optional" or "optionally" mean that the subsequently described event or circumstance may occur or may not occur, and that the description includes instances where the event or circumstance occurs as well as instances in which it does not. For example, "optionally substituted alkyl" refers to the alkyl may be substituted as well as where the alkyl is not substituted.

20 **[00025]** It is understood that substituents and substitution patterns on the disclosed compounds can be selected by one of ordinary skilled person in the art to result chemically stable compounds which can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure result.

25 **[00026]** As used herein, the term "optionally substituted" refers to the replacement of one to six hydrogen atoms in a given structure with the radical of a specified substituent including, but not limited to: hydroxyl, hydroxyalkyl, alkoxy, halogen, alkyl, aryl, cycloalkyl, heterocyclyl, amino, aminoalkyl, cyano, haloalkyl, haloalkoxy, -OC(=O)-CH₂-Oalkyl. Preferably, "optionally substituted" refers to the replacement of one to four hydrogen atoms in a given structure with the

substituents mentioned above. More preferably, one to three hydrogen atoms are replaced by the substituents as mentioned above. It is understood that the substituent can be further substituted.

[00027] As used herein, the term “substituted” refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *e.g.*, which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched, and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this application, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms.

[00028] Substituents can include any substituents described herein, for example, such substituents, if not otherwise specified, can include, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, a heteroaralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), -CF₃, -CN, and the like. Unless specifically stated as “unsubstituted,” references to chemical moieties herein are understood to include substituted variants. For example, reference to an “aryl” group or moiety implicitly includes both substituted and unsubstituted variants.

[00029] As used herein, the term “alkyl” refers to a straight chained or branched non-aromatic hydrocarbon which is completely saturated. Typically, a straight chained or branched alkyl group has from 1 to about 20 carbon atoms, preferably from 1 to about 10, *e.g.*, may be C₁-C₁₀alkyl or *e.g.*, C₁-C₆alkyl unless otherwise defined. Examples of straight chained and branched alkyl groups include, but are not limited to, methyl, ethyl, 1-propyl (n-propyl), 2-propyl, n-butyl,

sec-butyl, tertbutyl, 1-pentyl, 2-pentyl, 3-pentyl, neo-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 1-octyl, 2-octyl, 3-octyl or 4-octyl and the like. Moreover, the term “alkyl” used throughout the specification, examples, and claims is intended to include both “unsubstituted alkyls” and “substituted alkyls”, the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. The

5 “alkyl” group may be optionally substituted.

[00030] The term “C_x-C_y” when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. For example, the term “C_x-C_y” refers to substituted or unsubstituted

10 saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from x to y carbons in the chain, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc. C₀ alkyl indicates a hydrogen where the group is in a terminal position, a bond if internal.

[00031] As used herein, the term “hydrocarbyl” refers to a group that is bonded through a carbon atom that does not have a =O or =S substituent, and typically has at least one carbon-hydrogen bond and a primarily carbon backbone but may optionally include heteroatoms. Thus, groups like methyl, ethoxyethyl, 2-pyridyl, and trifluoromethyl are considered to be hydrocarbyl for the purposes of this application, but substituents such as acetyl (which has a =O substituent on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not.

15 Hydrocarbyl groups include, but are not limited to aryl, heteroaryl, carbocycle, heterocyclyl, alkyl, alkenyl, alkynyl, and combinations thereof. The “hydrocarbyl” group may be optionally substituted.

[00032] As used herein, the term “alkoxy” refers to a straight or branched, saturated aliphatic (alkyl) hydrocarbon radical bonded to an oxygen atom that is attached to a core structure. Preferably, alkoxy groups have one to six carbon atoms, *i.e.*, may be C₁-C₆ alkoxy. Examples of alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, 3-methyl butoxy and the like. The “alkoxy” group may be optionally substituted.

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[00033] As used herein, the term “alkoxyalkyl” refers to an alkyl group (as defined above) substituted with an alkoxy group and may be represented by the general formula alkyl-O-alkyl. Examples of alkoxyalkyl groups include but are not limited to methyl-O-ethylene-, ethyl-O-ethylene-. The “alkoxyalkyl” group may be optionally substituted.

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[00034] As used herein, the term “haloalkyl” refers to alkyl group (as defined above) is substituted with one or more halogens. A monohaloalkyl radical, for example, may have a chlorine, bromine, iodine, or fluorine atom. Dihalo and polyhaloalkyl radicals may have two or

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more of the same or different halogen atoms. Examples of haloalkyl include, but are not limited to, chloromethyl, dichloromethyl, trichloromethyl, dichloroethyl, dichloropropyl, fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, and the like. The “haloalkyl” group may be optionally substituted.

[00035] As used herein, the term “haloalkoxy” refers to radicals wherein one or more of the hydrogen atoms of the alkoxy group are substituted with one or more halogens. Representative examples of “haloalkoxy” groups include, but not limited to, difluoromethoxy (-OCHF₂), trifluoromethoxy (-OCF₃), or trifluoroethoxy (-OCH₂CF₃). The “haloalkoxy” group may be optionally substituted.

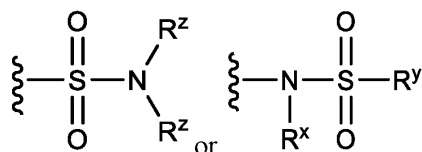
[00036] As used herein, the term “aryl” includes substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably the ring is a 5- to 7-membered ring, more preferably a 6-membered ring. The term “aryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (fused rings) wherein at least one of the rings is aromatic. *e.g.*, the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyls. The term “fused” means that the second ring is attached or formed by having two adjacent atoms in common with the first ring. The term “fused” is equivalent to the term “condensed”. Examples of aryl groups include but are not limited to phenyl, naphthyl, phenanthryl, phenol, aniline, or indanyl and the like. Unless otherwise specified, all aryl groups described herein may be optionally substituted.

[00037] As used herein, the terms “polycyclyl”, “polycycle”, and “polycyclic” refer to two or more rings (*e.g.*, cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyls) in which one or more atoms are common to two adjoining rings, *e.g.*, the rings are “fused rings”. Each of the rings of the polycycle can be substituted or unsubstituted. In certain embodiments, each ring of the polycycle contains from 3 to 10 atoms in the ring, preferably from 5 to 7.

[00038] As used herein, the term “acyl” refers to a group -C(=O)-R^w wherein R^w is optionally substituted alkyl. Examples of “acyl” include, but are not limited to, instances where R^w is C₁-C₁₀alkyl (C₁-C₁₀acyl) or C₁-C₆alkyl (C₁-C₆acyl). In some embodiments, each occurrence of the optionally substituted substituent is independently selected from the group consisting of H, OH, alkoxy, cyano, F, and amino. Additional examples of “acyl” include -C(=O)-CH₃, -C(=O)-CH₂-CH₃, -C(=O)-CH₂-CH₂-CH₃, or -C(=O)-CH(CH₃)₂.

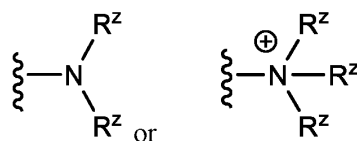
[00039] As used herein, the term “formyl” refers to a group -C(=O)H.

[00040] As used herein, the term “sulfonamide” and “sulfonamido” is represented by:



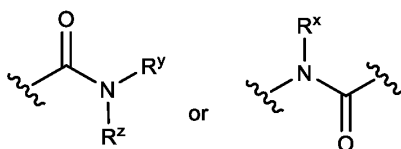
wherein R^x , R^y and R^z , at each occurrence, independently represents a hydrogen, optionally substituted hydrocarbyl group, or R^z groups taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure which may be optionally substituted.

[00041] As used herein, the terms “amine” and “amino” refer to both unsubstituted and substituted amines and salts thereof, *e.g.*, a moiety that can be represented by:



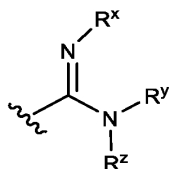
wherein R^z independently represent a hydrogen or optionally substituted hydrocarbyl group, or R^z groups are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure which may be optionally substituted.

[00042] As used herein, the terms “amide” and “amido” each refer to a group represented by:



wherein R^x , R^y , and R^z each independently represents a hydrogen or optionally substituted hydrocarbyl group, or R^y and R^z are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure which may be optionally substituted.

[00043] As used herein, the term “amidine” refers to a group represented by



wherein R^x , R^y , and R^z each independently represents a hydrogen or optionally substituted hydrocarbyl group, or R^y , and R^z groups are taken together with the N atom to which they are

attached complete a heterocycle having from 4 to 8 atoms in the ring structure which may be optionally substituted.

[00044] As used herein, the term “aminoalkyl” refers to an alkyl group substituted with an amino group.

5 **[00045]** As used herein, the term “amidoalkyl” refers to an alkyl group substituted with an amido group.

[00046] As used herein, the term “cyanoalkyl” refers to an alkyl group substituted with a cyano group.

10 **[00047]** As used herein, the term “alkylthio” refers to a thiol group substituted with an alkyl group and may be represented by the general formula alkyl-S-

[00048] As used herein, the term “thioalkyl” refers to an alkyl group substituted with a thiol group.

[00049] As used herein, the term “hydroxyalkyl” refers to an alkyl group substituted with a hydroxy group.

15 **[00050]** As used herein, the term “cycloalkyl” alone or in combination with other term(s) refers to a cyclic hydrocarbon which is completely saturated. “Cycloalkyl” includes monocyclic, bicyclic, and tricyclic rings. Typically, a monocyclic cycloalkyl group has from 3 to about 10 carbon atoms, more typically 3 to 8 carbon atoms (*e.g.*, C₃-C₁₀cycloalkyl or *e.g.*, C₃-C₆cycloalkyl unless otherwise defined. Examples of monocyclic cycloalkyls include
20 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. The second ring of a bicyclic cycloalkyl or, the second or third rings of a tricyclic cycloalkyl, may be selected from saturated, unsaturated and aromatic rings. Cycloalkyl includes bicyclic and tricyclic molecules in which one, two or three or more atoms are shared between the two rings. The term “fused cycloalkyl” refers to a bicyclic or tricyclic cycloalkyl in which each of the rings shares two
25 adjacent atoms with the other ring. The second ring of a fused bicyclic cycloalkyl or, the second or third rings of a fused tricyclic cycloalkyl, may be selected from saturated, unsaturated, and aromatic rings. A “cycloalkenyl” group is a cyclic hydrocarbon containing one or more double bonds. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxys, alkylthios, aminoalkyls, carbonyl-substituted alkyls, -CF₃, -CN, and the like. A cycloalkyl may alternatively
30 be polycyclic with more than two rings. Examples of polycyclic cycloalkyls include bridged, fused, and spirocyclic carbocyclyls.

[00051] As used herein, the term “cycloalkylalkyl” refers to an alkyl group substituted with a cycloalkyl group.

35 **[00052]** As used herein, the terms “carbocycle,” or “carbocyclic” include bicyclic or tricyclic rings in which one, two or three or more atoms are shared between the two rings. The

term “fused carbocycle” refers to a bicyclic carbocycle in which each of the rings shares two adjacent atoms with the other ring. Each ring of a fused carbocycle may be selected from saturated, unsaturated and aromatic rings. In an exemplary embodiment, an aromatic ring, *e.g.*, phenyl, may be fused to a saturated or unsaturated ring, *e.g.*, cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, is included in the definition of carbocyclic. Exemplary “carbocycles” include cyclopentane, cyclohexane, bicyclo[2.2.1]heptane, 1,5-cyclooctadiene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]oct-3-ene, naphthalene and adamantane. Exemplary fused carbocycles include decalin, 4,5- naphthalene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]octane, 4,5,6,7-tetrahydro-1H-indene and bicyclo[4.1.0]hept-3-ene. “Carbocycles” may be substituted at any one or more positions capable of bearing a hydrogen atom.

[00053] As used herein, the term “cyano” refers to -CN group.

[00054] As used herein, the term “hydroxy” or “hydroxyl” refers to -OH group.

[00055] As used herein, the term “halo” or “halogen” alone or in combination with other term(s) means chloro, fluoro, bromo, and iodo.

[00056] As used herein, the term “heteroatom” refers an atom of any element other than carbon or hydrogen. Exemplary heteroatoms are nitrogen (N), oxygen (O), sulfur (S), and silicon (Si).

[00057] As used herein, the terms “heterocyclyl”, “heterocycloalkyl”, “heterocycle”, and “heterocyclic” refer to a non-aromatic, saturated or partially saturated, including monocyclic, polycyclic (*e.g.*, bicyclic, tricyclic) bridged, or fused, ring system of 3 to 15 member having at least one heteroatom or heterogroup selected from O, N, S, S(O), S(O)₂, NH or C(O) with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. Examples of “heterocyclyl” include, but are not limited to azetidiny, oxetanyl, imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, 1,4-dioxanyl, dioxidothiomorpholinyl, oxapiperazinyl, oxapiperidinyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiophenyl, dihydropyranyl, indolinyl, indolinylmethyl, 2-azabicyclo[2.2.2]octanyl, azocinyl, chromanyl, xanthenyl and N-oxides thereof. Attachment of a heterocycloalkyl substituent can occur via either a carbon atom or a heteroatom. A heterocycloalkyl group can be optionally substituted with one or more suitable groups by one or more aforesaid groups. Preferably “heterocyclyl” refers to 5- to 6-membered ring selected from the group consisting of azetidiny, oxetanyl, imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, 1,4-dioxanyl and N-oxides thereof. More preferably,

“heterocyclyl” includes azetidiny, pyrrolidinyl, morpholinyl and piperidinyl. All heterocyclyl are optionally substituted by one or more aforesaid groups.

[00058] As used herein, the term “heteroaryl” refers to substituted or unsubstituted aromatic single ring structures, preferably 5- to 7-membered rings, more preferably 5- to 6-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The term “heteroaryl” also refers to substituted or unsubstituted aromatic or partly aromatic ring systems containing at least one heteroatom and having two or more cyclic rings (bicyclic, tricyclic, or polycyclic), containing 8 to 20 ring atoms, suitably 5 to 10 ring atoms, which may be linked covalently, or fused in which two or more atoms are common to two adjoining rings wherein at least one of the rings is heteroaromatic, *e.g.*, the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. The rings may contain an N or S atom, wherein the N or S atom is optionally oxidized, or the N atom is optionally quaternized. All heteroaryls are optionally substituted. Any suitable ring position of the heteroaryl moiety may be covalently linked to a defined chemical structure. Examples of heteroaryl include, but are not limited to: furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, cinnoliny, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzofuranyl, benzothienyl, benzotriazinyl, phthalazinyl, thianthrene, dibenzofuranyl, dibenzothienyl, benzimidazolyl, indolyl, isoindolyl, indazolyl, quinoliny, isoquinoliny, quinazoliny, quinoxaliny, puriny, pteridinyl, 9H-carbazolyl, alpha-carboline, indoliziny, benzoisothiazolyl, benzoxazolyl, pyrrolopyridyl, furopyridiny, puriny, benzothiadiazolyl, benzoxadiazolyl, benzotriazolyl, benzotriadiazolyl, 7-azaindolyl, 7-azaindolyl, pyrrolopyridiny, pyrrolopyrimidinyl, oxazolonepyridiny, oxazolonepyrimidinyl, imidazolonepyridiny, imidazolonepyrimidinyl, pyrazolopyridiny, pyrazolopyrimidinyl, tetrahydronaphthyridiny, tetrahydropyridolpyriminy, dihydronaphthyridinonyl, naphthyridinonyl, oxazinanonepyridiny, oxazinanonepyrimidinyl, carbazolyl, dibenzothienyl, acridiny and the like.

[00059] As used herein, the terms “sulfone” or “sulfonyl” refer to the group $-S(O)_2-R^{6d}$ wherein R^{6d} represents an optionally substituted hydrocarbyl.

[00060] As used herein, within a ring, refers to a single or double bond, as valency permits and which results in the formation of a stable ring moiety.

[00061] The compounds of the disclosure may contain one or more chiral centers and, therefore, exist as stereoisomers. The term “stereoisomers” when used herein consist of all enantiomers or diastereomers. These compounds may be designated by the symbol “R” or “S,” depending on the configuration of substituents around the stereogenic carbon atom, but the

skilled artisan will recognize that a structure may denote a chiral center implicitly. These compounds may also be designated by “(+)” and “(-)” based on their optical rotation properties. The presently described compounds encompasses various stereoisomers of these compounds and mixtures thereof. Mixtures of enantiomers or diastereomers may be designated by the symbol “(±)” in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

[00062] Individual enantiomers and diastereomers of the disclosed compounds can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, (3) direct separation of the mixture of optical enantiomers on chiral liquid chromatographic columns or (4) kinetic resolution using stereoselective chemical or enzymatic reagents. Racemic mixtures can also be resolved into their component enantiomers by well-known methods, such as chiral-phase liquid chromatography or crystallizing the compound in a chiral solvent. Stereoselective syntheses, a chemical or enzymatic reaction in which a single reactant forms an unequal mixture of stereoisomers during the creation of a new stereocenter or during the transformation of a pre-existing one, are well known in the art. Stereoselective syntheses encompass both enantio- and diastereoselective transformations and may involve the use of chiral auxiliaries. For examples, see Carreira and Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH: Weinheim, 2009.

[00063] The disclosure also embraces isotopically labeled compounds which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. For example, a compound of the disclosure may have one or more H atom replaced with deuterium.

[00064] As used herein, “deuterated” mean that at least one hydrogen atom is replaced by deuterium. In any sample of a deuterated compound, some discrete molecules of the compound will likely have hydrogen, rather than deuterium, at the specified position. However, the percent of molecules of the deuterated compound which have deuterium at the specified position will be much greater than would naturally occur. The deuterium at the deuterated position is enriched.

[00065] A compound described herein can be formulated as a pharmaceutical composition using a pharmaceutically acceptable carrier and administered by a variety of routes. In some embodiments, such compositions are for oral administration. In some embodiments, compositions formulated for oral administration are provided as tablets. In some embodiments, such compositions are for parenteral (by injection) administration. In some embodiments, such compositions are for transdermal administration. In some embodiments, such compositions are for topical administration. In some embodiments, such compositions are for intravenous (IV) administration. In some embodiments, such compositions are for intramuscular (IM) administration. Such pharmaceutical compositions and processes for preparing them are well known in the art. See, *e.g.*, REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (A. Gennaro, et al., eds., 19th ed., Mack Publishing Co., 1995).

[00066] “Pharmaceutically or pharmacologically acceptable” include molecular entities and compositions that do not produce an adverse, allergic, or other untoward reaction when administered to an animal, or a human, as appropriate. For human administration, preparations should meet sterility, pyrogenicity, and general safety and purity standards as required by FDA Office of Biologics standards.

[00067] The term “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” as used herein refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

[00068] The term “pharmaceutical composition” as used herein refers to a composition comprising at least one compound as disclosed herein formulated together with one or more pharmaceutically acceptable carriers.

[00069] The term “pharmaceutically acceptable salt(s)” as used herein refers to salts of acidic or basic groups that may be present in compounds used in the compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, including, but not limited to, malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate,

benzenesulfonate, *p*-toluenesulfonate and pamoate (i.e., 1,1'-methylene-*bis*-(2-hydroxy-3-naphthoate)) salts.

[00070] “Disease,” “disorder,” and “condition” are used interchangeably herein.

[00071] “Individual,” “patient,” or “subject” are used interchangeably herein and include
5 any animal, including mammals, including mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and humans. The compounds described herein can be administered to a mammal, such as a human, but can also be administered to other mammals such as an animal in need of veterinary treatment, *e.g.*, domestic animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.*,
10 rats, mice, guinea pigs, and the like). The mammal treated in the methods described herein is desirably a mammal in which treatment of a disorder described herein is desired, such as a human.

[00072] A “combination therapy” as used herein is a treatment that includes the administration of two or more therapeutic agents, *e.g.*, a compound of Formula (I), Formula (Ia),
15 or Formula (II), or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, and an additional therapeutic agent described herein, to a patient in need thereof.

[00073] A “RAS/MAPK pathway inhibitor” is an inhibitor of the RAS/MAPK signaling pathway. Inhibitors of this pathway include Ras inhibitors (*e.g.*, AMG-510 (sotorasib), MRTX849 (adagrasib), GDC-6036, MRTX-1133, RMS-9805, RMC-6291, and RMC-6236, and
20 pharmaceutically acceptable salts thereof), RAF inhibitors (*e.g.*, LY3009120, LXH254, RAF709, dabrafenib, vemurafenib, encorafenib, DCC-3084, belvarafenib, KIN-2787, and VS-6766, and pharmaceutically acceptable salts thereof), MEK inhibitors (*e.g.*, trametinib, selumetinib, cobimetinib, and binimetinib, and pharmaceutically acceptable salts thereof), and ERK inhibitors (*e.g.*, ulixertinib, SCH772984, LY3214996, ravoxertinib, VX-11e, ERAS-007,
25 and ASTX-029, and pharmaceutically acceptable salts thereof). The terms “RAS/MAPK pathway inhibitor” and “RAS/MAPK kinase inhibitor” are used interchangeably herein.

[00074] A “RTK pathway inhibitor” is an inhibitor of the RTK (Receptor Tyrosine Kinase) signaling pathway. Inhibitors of this pathway include KIT inhibitors (*e.g.*, ripretinib, avapritinib, sunitinib, AZD3229 (NB003), THE-630, imatinib, midostaurin, bezuclastinib,
30 olverembatinib (HQP1351), famitinib, IDRX-42 (M4205), elenestinib, BLU-808, IDRX-73, SLRN-517, THB335, pexidartinib, and regorafenib, and pharmaceutically acceptable salts thereof), EGFR inhibitors (*e.g.*, erlotinib, gefitinib, osimertinib, cetuximab, and pharmaceutically acceptable salts thereof), PDGFR α inhibitors (*e.g.*, avapritinib, JNJ10198409, crenolanib, ponatinib, and pharmaceutically acceptable salts thereof), VEGFR inhibitors (*e.g.*, regorafenib
35 and pazopanib, and pharmaceutically acceptable salts thereof), FLT3 inhibitors (*e.g.*,

midostaurin, lestaurtinib, ponatinib, tandutinib, quizartinib, crenolanib, and gilteritinib), BCR-Abl inhibitors (*e.g.*, imatinib, nilotinib, and dasatinib, and pharmaceutically acceptable salts thereof), and an ALK inhibitor (*e.g.*, lorlatinib, and alectinib, and pharmaceutically acceptable salts thereof).

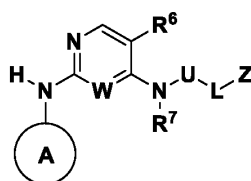
- 5 [00075] “Therapeutically effective amount” includes the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by the researcher, veterinarian, medical doctor, or other clinician. A compound described herein, *e.g.*, the compound of Formula (I), Formula (Ia), or Formula (II), or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, is administered
- 10 in therapeutically effective amounts to treat a condition described herein. Alternatively, a therapeutically effective amount of a compound is the quantity required to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in the prevention of or a decrease in the symptoms associated with the condition.

- [00076] As used herein, “treating” includes any effect, *e.g.*, lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder and the like.
- 15

- [00077] As used herein, “compounds of the disclosure”, comprise compounds of Formula (I) Formula (Ia), and Formula (II), or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof.
- 20

Compounds

- [00078] In some embodiments, provided herein is a compound represented by Formula (I):



Formula (I)

- 25 or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:
- A is selected from the group consisting of cycloalkyl and heterocyclyl;
 - W is selected from the group consisting of N and CH;
 - U is selected from the group consisting of C(=O), alkyl, and heterocyclyl, or U is absent, or wherein U and R⁷ taken together with the nitrogen atom to which they are attached

30 form an optionally substituted heterocyclyl ring having from 4 to 10 atoms in the ring structure;

 - L is selected from the group consisting of a bond, alkyl, cycloalkyl, and heterocyclyl;

Z is selected from the group consisting of H, cyano, $-N(R^8)SO_2R^9$, $-N(R^8)C(=O)R^9$, $-N(R^{18})SO_2NR^{19}R^{28}$, $-SO_2R^{29}$, $-S(O)(=NH)-R^{10}$, and optionally substituted heterocyclyl, wherein the optionally substituted heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of R^{31} ,

5 or wherein two occurrences of R^{31} taken together with the carbon atoms to which they are attached form an optionally substituted ring having 5 to 8 atoms in the ring structure;

R^6 is selected from the group consisting of halogen, cyano, alkyl, haloalkyl, cycloalkyl, and heterocyclyl;

R^7 is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

10 R^8 is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

R^9 is selected from the group consisting of amino, alkyl, cycloalkyl, and heterocyclyl,

or wherein R^8 and R^9 taken together with the nitrogen and sulfur or carbon atoms to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure;

15 R^{10} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

R^{18} is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

R^{19} is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

R^{28} is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl,

20 or wherein R^{18} and R^{28} taken together with the nitrogen atoms to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure,

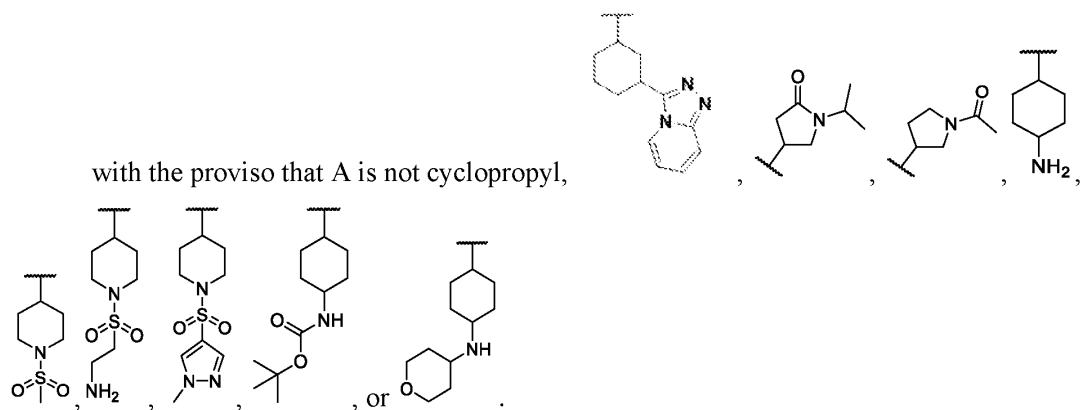
or wherein R^{19} and R^{28} taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure;

R^{29} is selected from the group consisting of amino, alkyl, cycloalkyl, and heterocyclyl; and

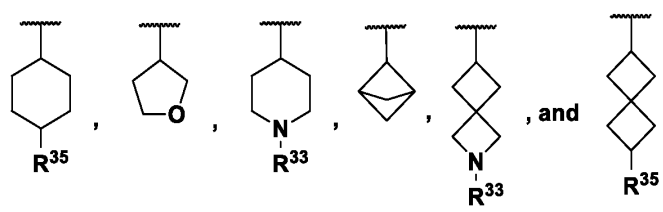
25 R^{31} is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, at each occurrence, is optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone, sulfonamide, heterocyclyl, or heteroaryl,

30

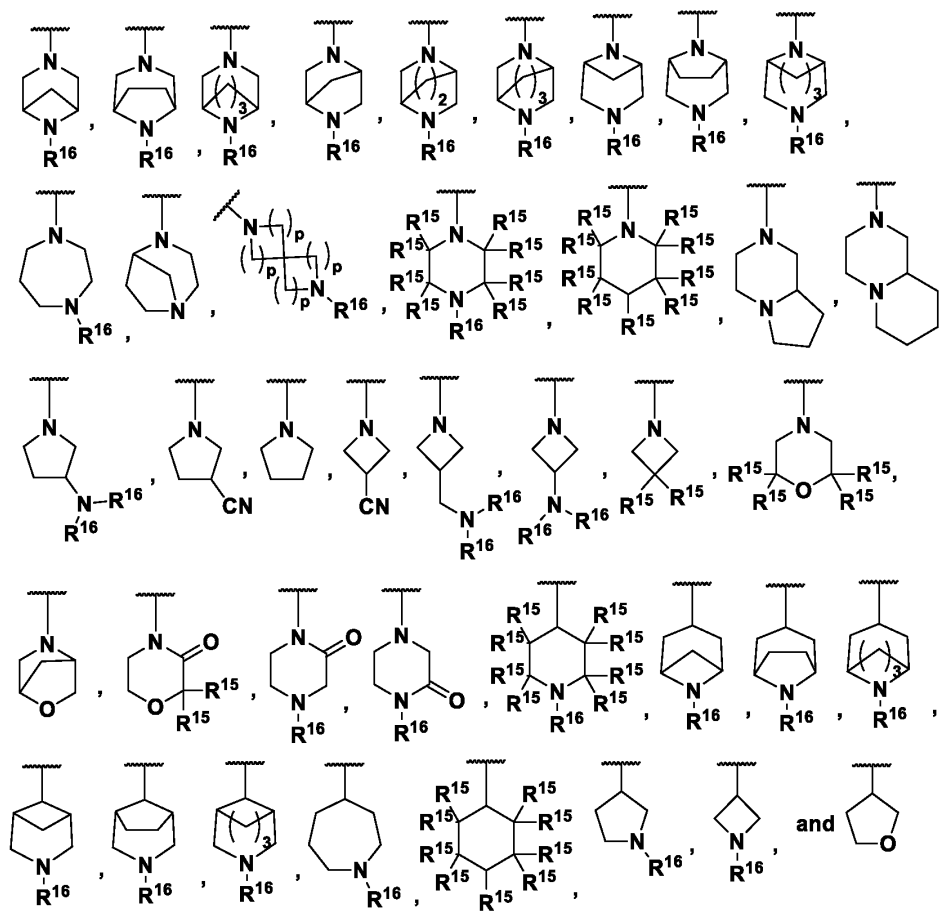


[00079] In some embodiments, A is selected from the group consisting of



- 5 wherein each occurrence of R^{33} is independently selected from the group consisting of H, alkyl, haloalkyl, cycloalkyl, and heterocyclyl, and each occurrence of R^{35} is independently selected from the group consisting of H, halogen, alkyl, and heterocyclyl.

[00080] In some embodiments, R^{35} and R^{33} , each individually, is selected from the group consisting of



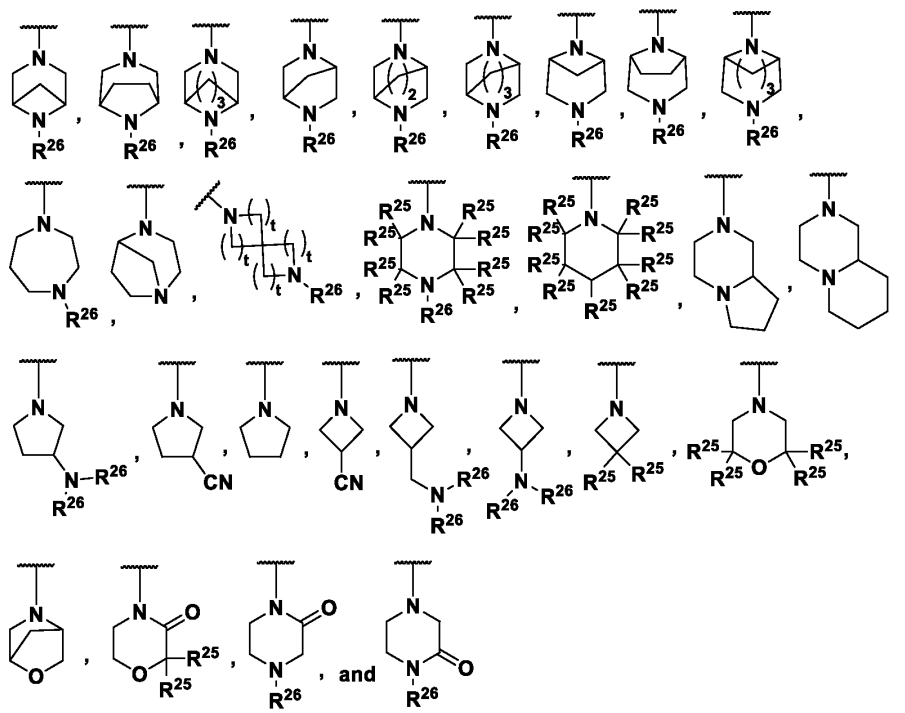
wherein R¹⁵, at each occurrence, is independently selected from the group consisting of H, halogen, amino, cyano, alkyl, cycloalkyl, and heterocyclyl, or wherein two R¹⁵, taken together with the carbon atom to which they are attached form an optionally substituted ring having from 4 to 6 atoms in the ring structure;

R¹⁶, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl, or wherein two R¹⁶, taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure; and

10 p , at each occurrence, is independently 1, 2, or 3;

wherein the alkyl, cycloalkyl, or heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone, sulfonamide, heterocyclyl, or heteroaryl.

[00081] The In some embodiments, R^{15} , at each occurrence, is independently selected from the group consisting of



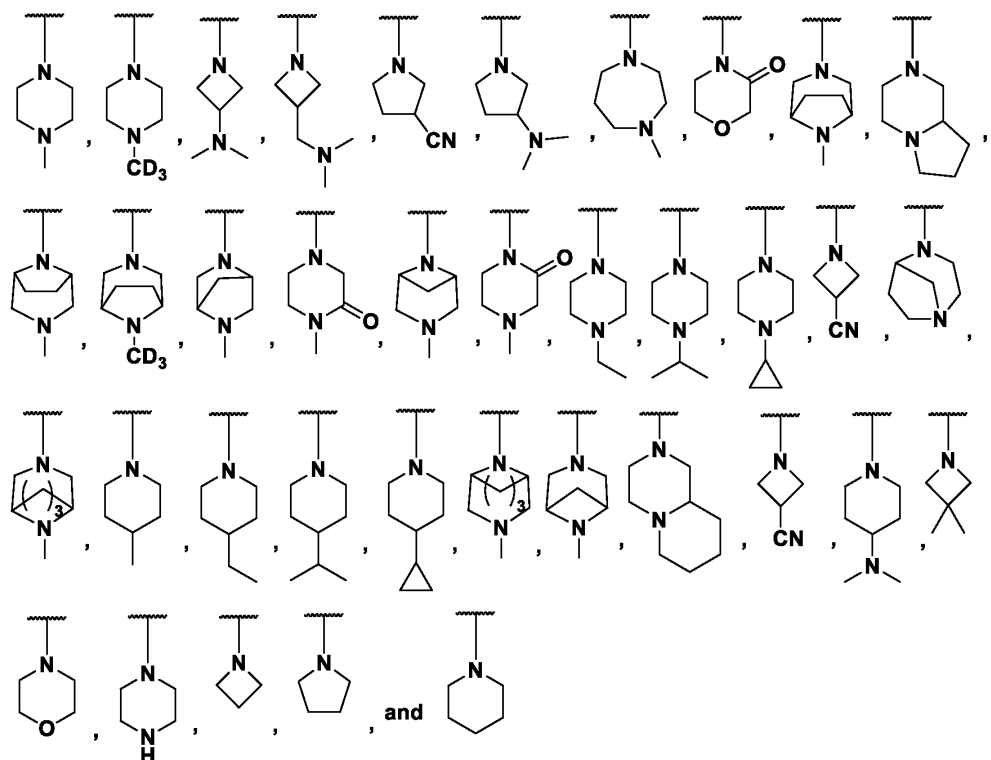
wherein R^{25} , at each occurrence, is independently selected from the group consisting of H, halogen, amino, cyano, alkyl, cycloalkyl, and heterocyclyl, or wherein two R^{25} , taken together with the carbon atom to which they are attached form an optionally substituted ring having from 4 to 6 atoms in the ring structure;

R^{26} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl, or wherein two R^{26} , taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure; and

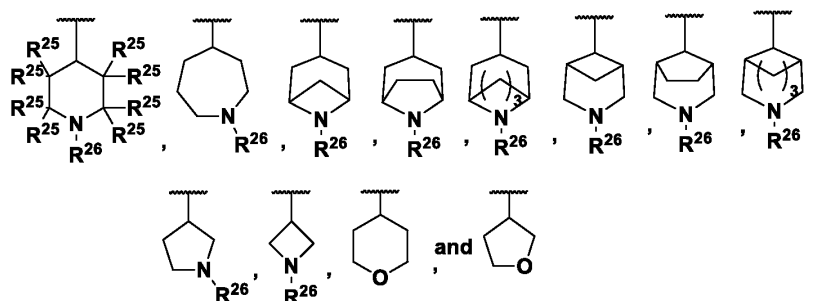
t, at each occurrence, is independently 1, 2, or 3;

wherein the alkyl, cycloalkyl, or heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone, sulfonamide, heterocyclyl, or heteroaryl.

[00082] In some embodiments, R^{15} is selected from the group consisting of



[00083] In some embodiments, R^{16} is selected from the group consisting of H, alkyl, alkylamino, cycloalkyl,



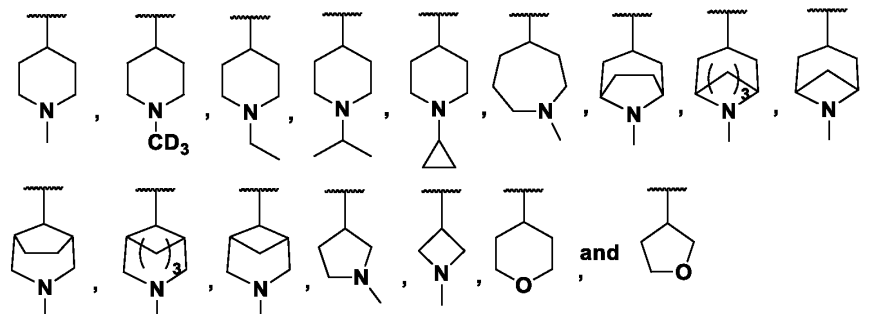
5 wherein R^{25} , at each occurrence, is independently selected from the group consisting of H, halogen, amino, cyano, alkyl, cycloalkyl, and heterocyclyl, or wherein two R^{25} , taken together with the carbon atom to which they are attached form an optionally substituted ring having from 4 to 6 atoms in the ring structure; and

10 R^{26} is independently selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

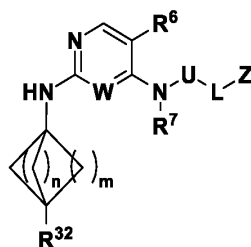
wherein the alkyl, cycloalkyl, or heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, hydroxyalkyl,

cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone, sulfonamide, heterocyclyl, or heteroaryl.

[00084] In some embodiments, R^{16} is selected from the group consisting of



5 [00085] In some embodiments, also provided herein is a compound of Formula (Ia):



Formula (Ia)

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

- 10 W is selected from the group consisting of N and CH;
- U is selected from the group consisting of $C(=O)$, alkyl, and heterocyclyl, or U is absent, or wherein U and R^7 taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 10 atoms in the ring structure;
- L is selected from the group consisting of a bond, alkyl, cycloalkyl, and heterocyclyl;
- 15 Z is selected from the group consisting of H, substituted heterocyclyl, cyano, - $N(R^8)SO_2R^9$, - $N(R^8)C(=O)R^9$, - $N(R^{18})SO_2NR^{19}R^{28}$, - SO_2R^{29} , and - $S(O)(=NH)-R^{10}$, wherein the optionally substituted heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of R^{31} ,
- or wherein two occurrences of R^{31} taken together with the carbon atoms to which they
- 20 are attached form an optionally substituted ring having 5 to 8 atoms in the ring structure;
- R^6 is selected from the group consisting of halogen, cyano, alkyl, cycloalkyl, and heterocyclyl;
- R^7 is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;
- R^8 is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

R⁹ is selected from the group consisting of amino, alkyl, cycloalkyl, and heterocyclyl, or wherein R⁸ and R⁹ taken together with the nitrogen and sulfur or carbon atoms to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure;

- 5 R¹⁰ is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;
 R¹⁸ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;
 R¹⁹ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;
 R²⁸ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl,
 or wherein R¹⁸ and R²⁸ taken together with the nitrogen atoms to which they are attached
 10 form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure,
 or wherein R¹⁹ and R²⁸ taken together with the nitrogen atom to which they are attached
 form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure;
 and

- R²⁹ is selected from the group consisting of amino, alkyl, cycloalkyl, and heterocyclyl;
 15 R³¹ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;
 R³² is selected from the group consisting of H, halogen, alkyl, cycloalkyl, heterocyclyl,
 aryl and heteroaryl;

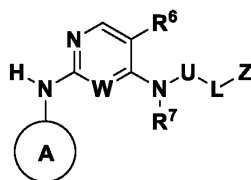
- wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, at each occurrence, is
 optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl,
 20 cycloalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy,
 hydroxyalkyl, cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone,
 sulfonamide, heterocyclyl, or heteroaryl;

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

n is 0, 1, 2, or 3;

- 25 wherein both m and n are not simultaneously 0.

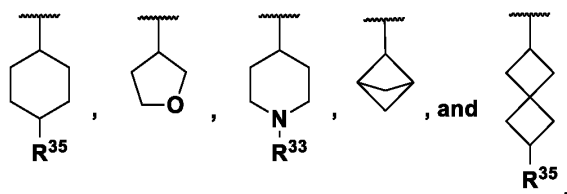
[00086] Also provided herein, in some embodiments, is a compound represented by
 Formula (II):



Formula (II)

- 30 or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

A is selected from the group consisting of



- wherein each occurrence of R³³ is independently selected from the group consisting of H, alkyl, haloalkyl, cycloalkyl, and heterocyclyl, and each occurrence of R³⁵ is independently selected
- 5 from the group consisting of H, halogen, and alkyl;

W is selected from the group consisting of N and CH;

U is selected from the group consisting of C(=O), alkyl, and heterocyclyl, or U is absent, or wherein U and R⁷ taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 10 atoms in the ring structure;

- 10 L is selected from the group consisting of a bond, alkyl, cycloalkyl, and heterocyclyl;

Z is selected from the group consisting of H, cyano, -N(R⁸)SO₂R⁹, -N(R⁸)C(=O)R⁹, -N(R¹⁸)SO₂NR¹⁹R²⁸, -SO₂R²⁹, -S(O)(=NH)-R¹⁰, and optionally substituted heterocyclyl, wherein the optionally substituted heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of R³¹,

- 15 or wherein two occurrences of R³¹ taken together with the carbon atoms to which they are attached form an optionally substituted ring having 5 to 8 atoms in the ring structure;

R⁶ is selected from the group consisting of halogen, cyano, alkyl, haloalkyl, cycloalkyl, and heterocyclyl;

R⁷ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

- 20 R⁸ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

R⁹ is selected from the group consisting of amino, alkyl, cycloalkyl, and heterocyclyl,

or wherein R⁸ and R⁹ taken together with the nitrogen and, sulfur or carbon atoms to which they are attached, form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure;

- 25 R¹⁰ is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

R¹⁸ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

R¹⁹ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

R²⁸ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl,

- or wherein R¹⁸ and R²⁸ taken together with the nitrogen atoms to which they are attached
- 30 form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure,

or wherein R^{19} and R^{28} taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure;

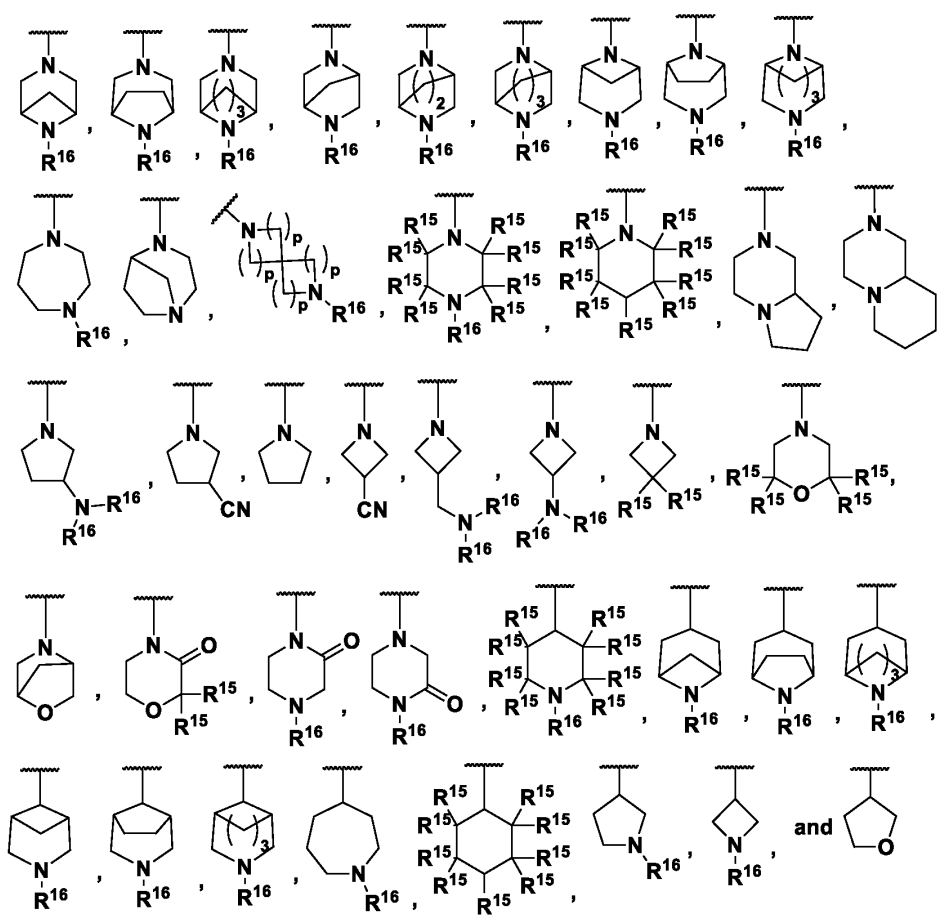
R^{29} is selected from the group consisting of amino, alkyl, cycloalkyl, and heterocyclyl;

and

5 R^{31} is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, at each occurrence, is optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone, 10 sulfonamide, heterocyclyl, or heteroaryl.

[00087] In some embodiments, R^{35} and R^{33} , each individually, is selected from the group consisting of



wherein R^{15} , at each occurrence, is independently selected from the group consisting of 15 H, halogen, amino, cyano, alkyl, cycloalkyl, and heterocyclyl, or wherein two R^{15} , taken together

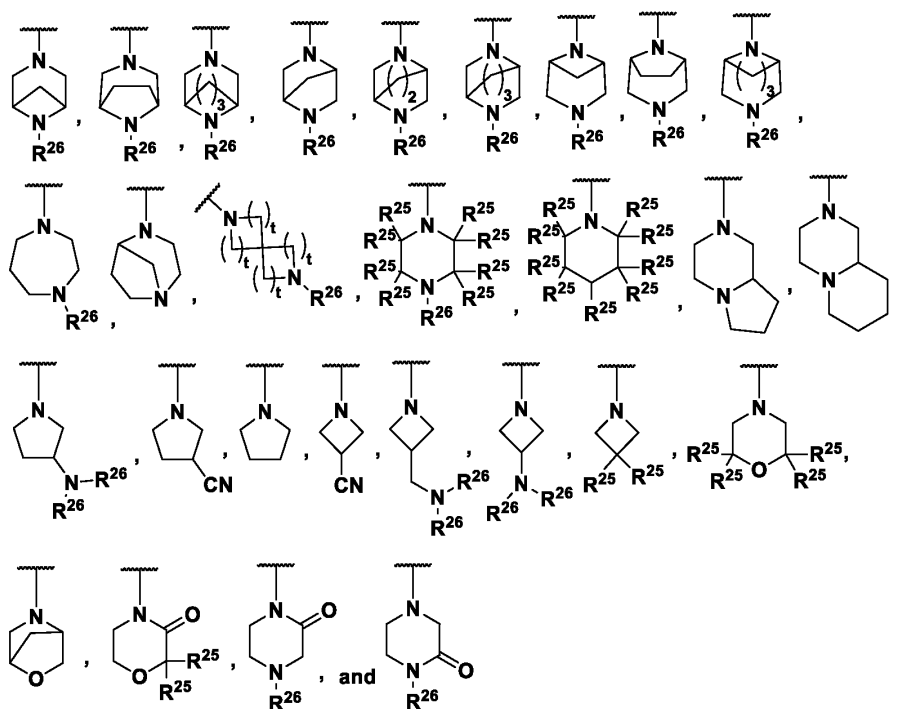
with the carbon atom to which they are attached form an optionally substituted ring having from 4 to 6 atoms in the ring structure;

R^{16} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl, or wherein two R^{16} , taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure; and

p, at each occurrence, is independently 1, 2, or 3;

wherein the alkyl, cycloalkyl, or heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone, sulfonamide, heterocyclyl, or heteroaryl.

[00088] The In some embodiments, R^{15} , at each occurrence, is independently selected from the group consisting of



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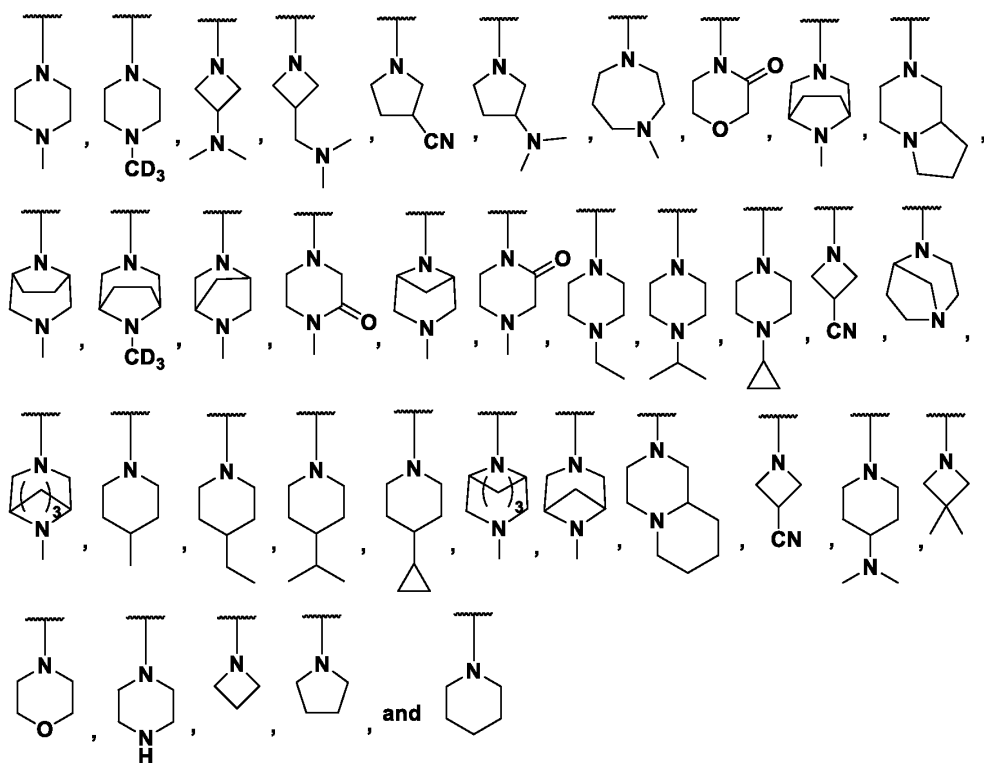
wherein R^{25} , at each occurrence, is independently selected from the group consisting of H, halogen, amino, cyano, alkyl, cycloalkyl, and heterocyclyl, or wherein two R^{25} , taken together with the carbon atom to which they are attached form an optionally substituted ring having from 4 to 6 atoms in the ring structure;

R^{26} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl, or wherein two R^{26} , taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure; and

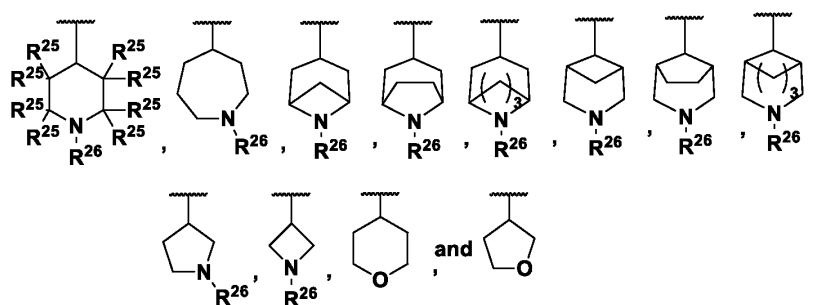
5 t, at each occurrence, is independently 1, 2, or 3;

wherein the alkyl, cycloalkyl, or heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone, sulfonamide, heterocyclyl, or heteroaryl.

[00089] In some embodiments, R^{15} is selected from the group consisting of



[00090] In some embodiments, R^{16} is selected from the group consisting of H, alkyl, alkylamino, cycloalkyl,

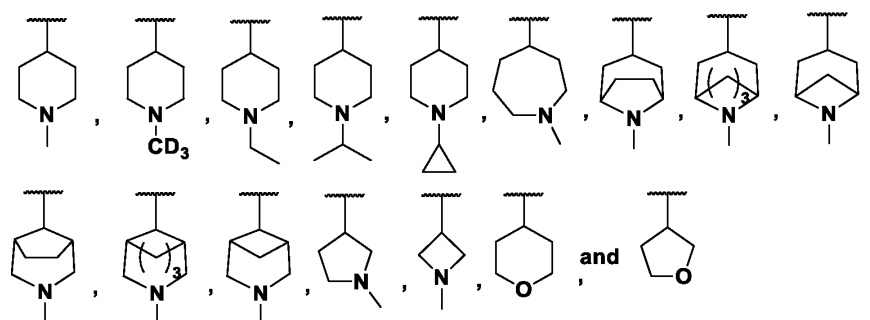


wherein R^{25} , at each occurrence, is independently selected from the group consisting of H, halogen, amino, cyano, alkyl, cycloalkyl, and heterocyclyl, or wherein two R^{25} , taken together with the carbon atom to which they are attached form an optionally substituted ring having from 4 to 6 atoms in the ring structure; and

R^{26} is independently selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

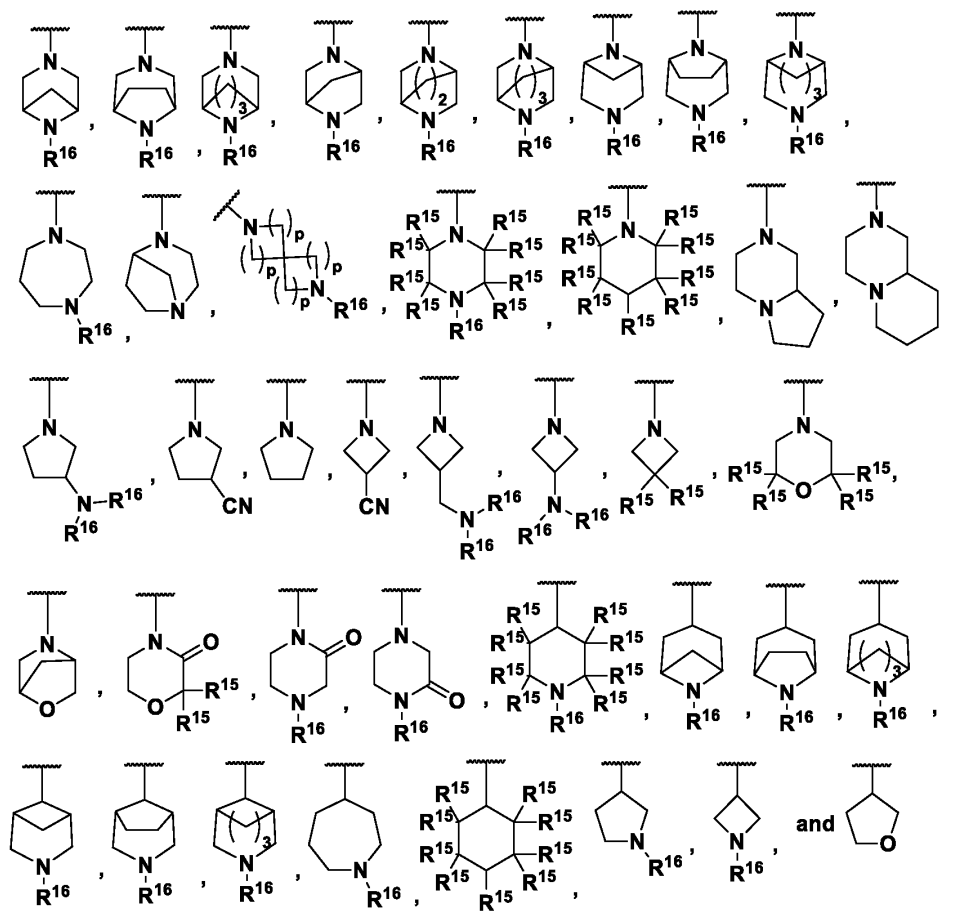
wherein the alkyl, cycloalkyl, or heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone, sulfonamide, heterocyclyl, or heteroaryl.

[00091] In some embodiments, R^{16} is selected from the group consisting of



[00092] In some embodiments, m is 1 and n is 0. In other embodiments, m is 2 and n is 0. In some embodiments, m is 3 and n is 0. In some embodiments, m is 1 and n is 1.

[00093] In some embodiments, R^{32} is selected from the group consisting of H, halogen, alkyl, cycloalkyl, heterocyclyl, and heteroaryl.



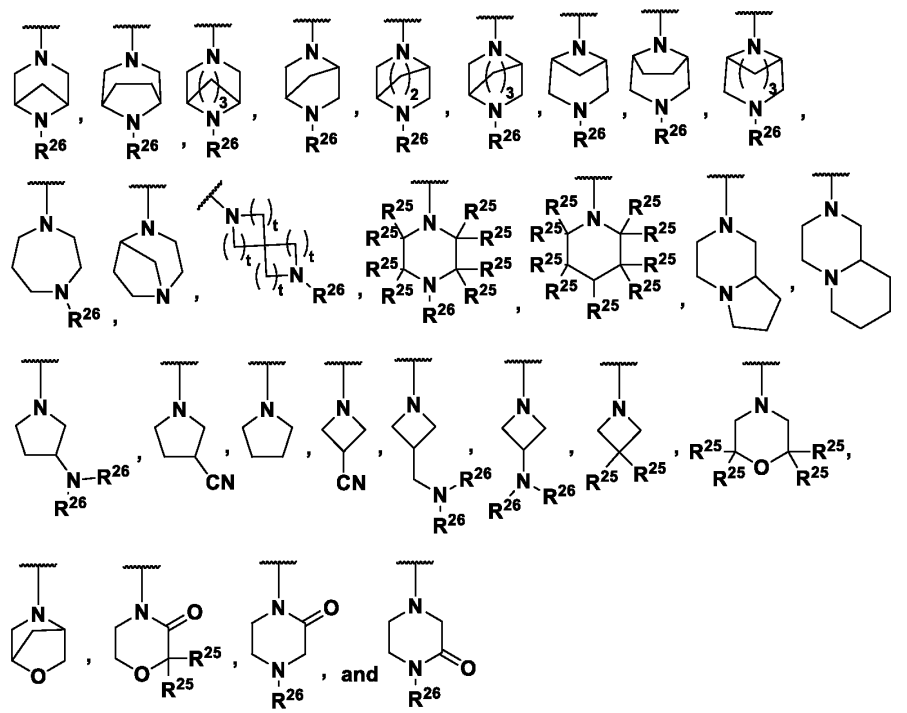
wherein R^{15} , at each occurrence, is independently selected from the group consisting of H, halogen, amino, cyano, alkyl, cycloalkyl, and heterocyclyl, or wherein two R^{15} , taken together with the carbon atom to which they are attached form an optionally substituted ring having from 4 to 6 atoms in the ring structure;

R^{16} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl, or wherein two R^{16} , taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure; and

p, at each occurrence, is independently 1, 2, or 3;

wherein the alkyl, cycloalkyl, or heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone, sulfonamide, heterocyclyl, or heteroaryl.

[00097] In some embodiments, R^{15} , at each occurrence, is independently selected from the group consisting of



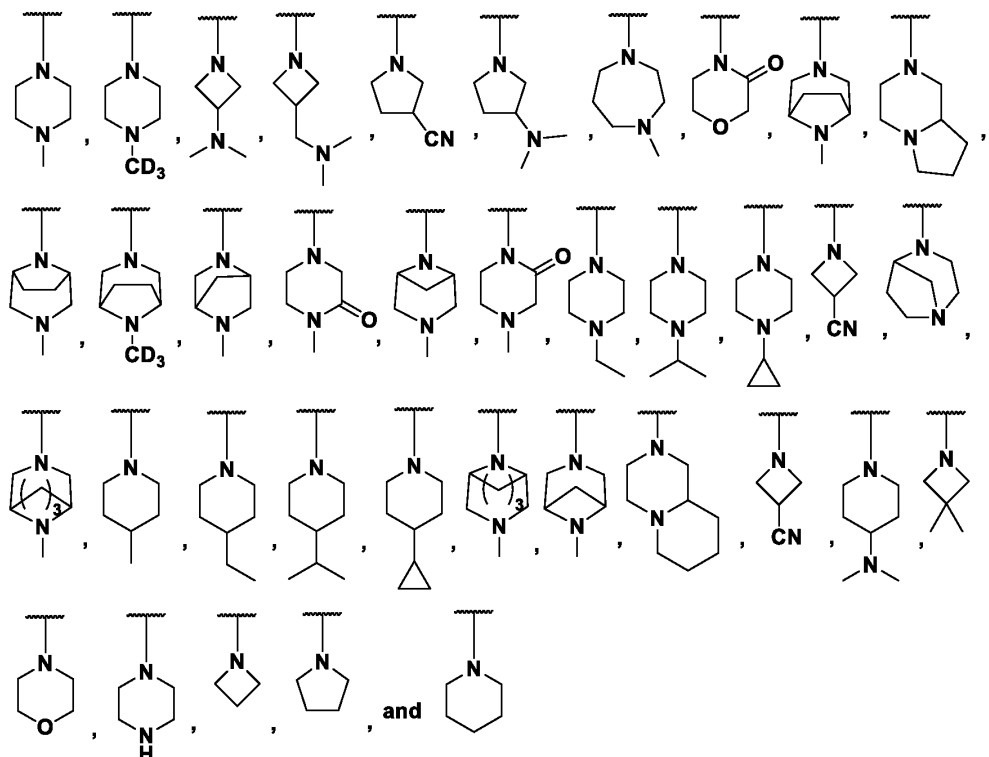
wherein R^{25} , at each occurrence, is independently selected from the group consisting of H, halogen, amino, cyano, alkyl, cycloalkyl, and heterocyclyl, or wherein two R^{25} , taken together with the carbon atom to which they are attached form an optionally substituted ring having from 4 to 6 atoms in the ring structure;

R^{26} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl, or wherein two R^{26} , taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure; and

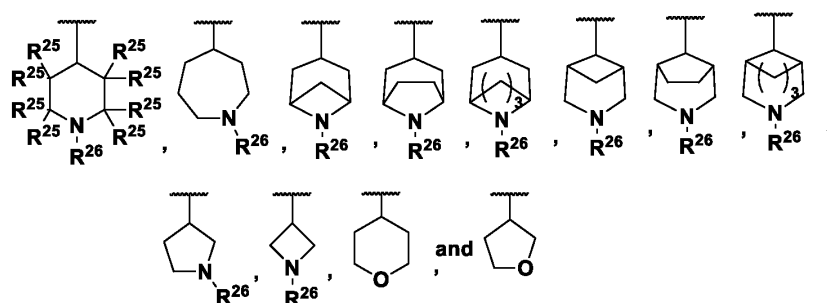
t , at each occurrence, is independently 1, 2, or 3;

wherein the alkyl, cycloalkyl, or heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone, sulfonamide, heterocyclyl, or heteroaryl.

[00098] In some embodiments, R^{15} is selected from the group consisting of



[00099] In some embodiments, R^{16} is selected from the group consisting of H, alkyl, alkylamino, cycloalkyl,



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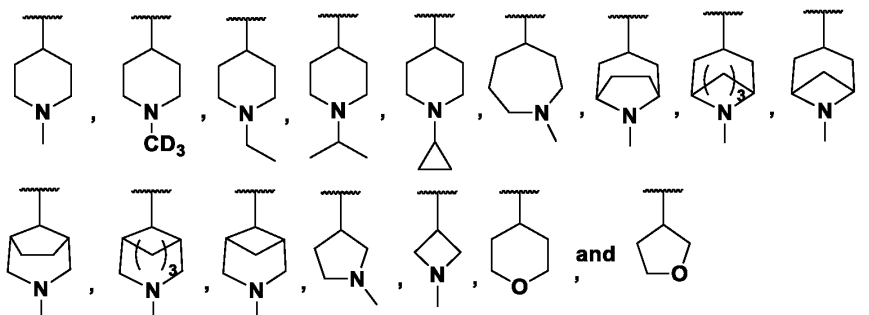
wherein R^{25} , at each occurrence, is independently selected from the group consisting of H, halogen, amino, cyano, alkyl, cycloalkyl, and heterocyclyl, or wherein two R^{25} , taken together with the carbon atom to which they are attached form an optionally substituted ring having from 4 to 6 atoms in the ring structure; and

10 R^{26} is independently selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

wherein the alkyl, cycloalkyl, or heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl, cycloalkyl,

cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone, sulfonamide, heterocyclyl, or heteroaryl.

[000100] In some embodiments, R^{16} is selected from the group consisting of



5

[000101] In some embodiments, W is N. In other embodiments, W is CH.

[000102] In some embodiments, R^6 is selected from the group consisting of halogen, cyano, haloalkyl, and cycloalkyl. In some embodiments, R^6 is selected from the group consisting of Cl,

Br, CN, CF_3 , and . In some embodiments, R^6 is CF_3 .

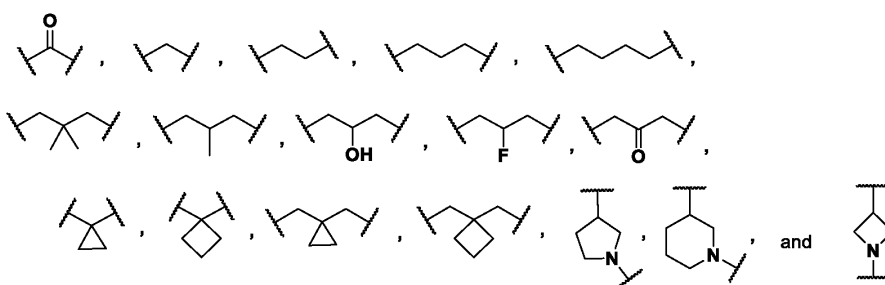
10 [000103] In some embodiments, R^7 is H.

[000104] In some embodiments, U is absent.

[000105] In some embodiments, U is selected from the group consisting of $C(=O)$, alkyl, and heterocyclyl.

15 [000106] In some embodiments, U is selected from the group consisting of alkyl and heterocyclyl.

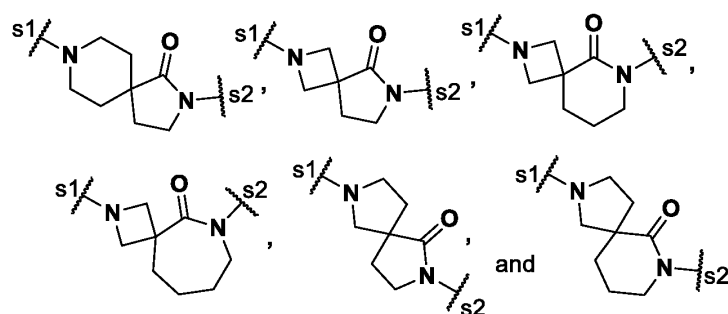
[000107] In some embodiments, U is selected from the group consisting of



20 [000108] In some embodiments, U and R^7 taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 8 atoms in the ring structure. In some embodiments, U and R^7 taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure. In some embodiments, U and R^7 taken together with the nitrogen

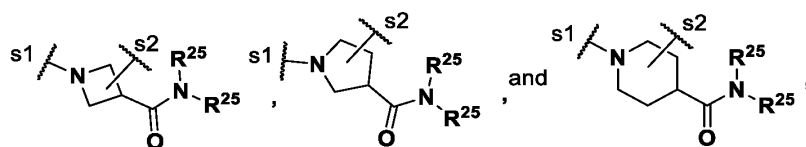
atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 atoms in the ring structure. In some embodiments, U and R⁷ taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 5 atoms in the ring structure. In some embodiments, U and R⁷ taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 6 atoms in the ring structure.

[000109] In some embodiments, U and R⁷ taken together with the nitrogen atom to which they are attached is selected from the group consisting of



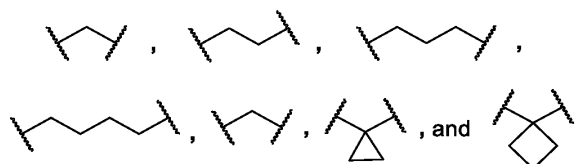
10 wherein s1 is the site attached to the ring containing N and W and s2 is the site attached to L-Z. In some embodiments, L is a bond and Z is H.

[000110] In some embodiments, U and R⁷ taken together with the nitrogen atom to which they are attached is selected from the group consisting of



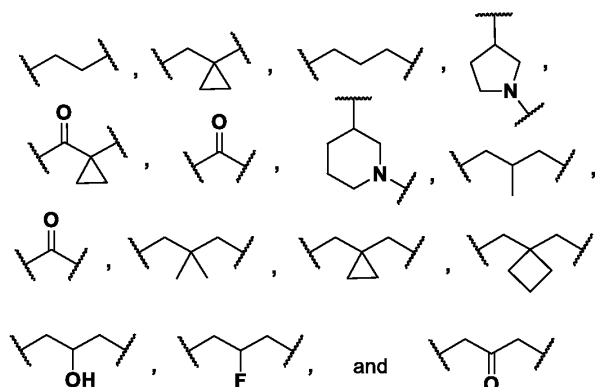
15 wherein s1 is the site attached to the ring containing N and W and s2 is the site attached to L-Z, and wherein each occurrence of R²⁵ is independently selected from the group consisting of H, and alkyl. In some embodiments, L is a bond and Z is H.

[000111] In some embodiments, L is selected from the group consisting of a bond and alkyl. In some embodiments, L is selected from the group consisting of a bond,



In some embodiments, L is a bond.

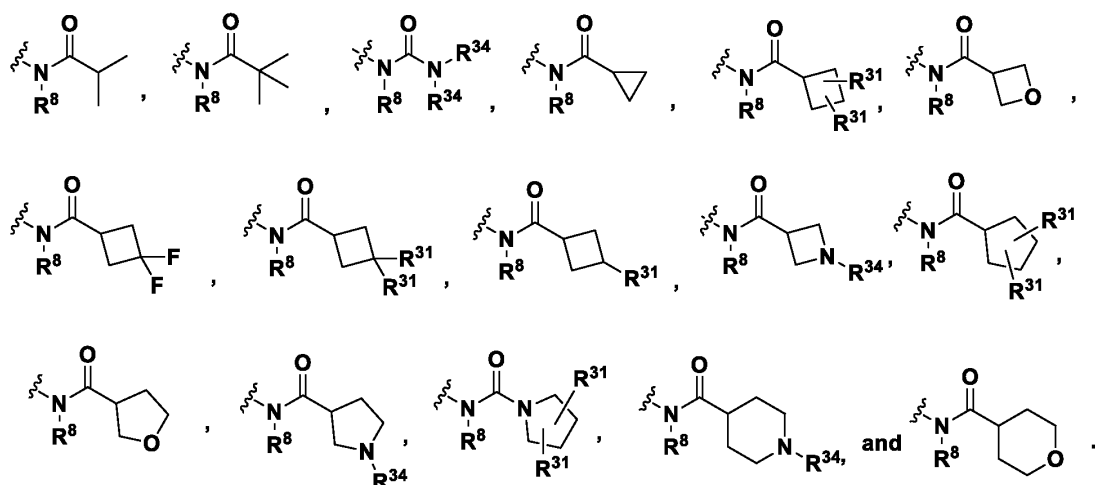
[000112] In some embodiments, U-L is selected from the group consisting of



[000113] In some embodiments, L is a bond, and Z is H.

5 **[000114]** In some embodiments, Z is selected from the group consisting of $-\text{N}(\text{R}^8)\text{SO}_2\text{R}^9$, $-\text{N}(\text{R}^8)\text{C}(=\text{O})\text{R}^9$, and $-\text{N}(\text{R}^{18})\text{SO}_2\text{NR}^{19}\text{R}^{28}$.

[000115] In some embodiments, $N(R^8)C(=O)R^9$ is selected from the group consisting of:



wherein R³⁴ is selected from the group consisting of H, alkyl and cycloalkyl.

10 **[000116]** In some embodiments, R⁸ is selected from the group consisting of H, and alkyl;
 R⁹ is selected from the group consisting of amino, alkyl, and cycloalkyl,
 or wherein R⁸ and R⁹ taken together with the nitrogen and sulfur or carbon atoms to
 which they are attached form an optionally substituted heterocyclcyl ring having from 4 to 6
 atoms in the ring structure;

15 R¹⁸ is selected from the group consisting of H, and alkyl;

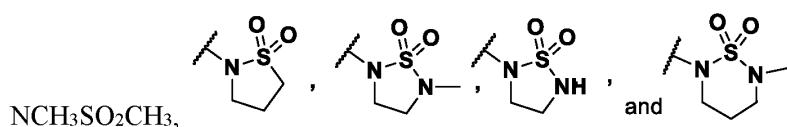
R¹⁹ is selected from the group consisting of H, and alkyl; and

R²⁸ is selected from the group consisting of H, and alkyl,

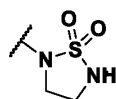
or wherein R¹⁸ and R²⁸ taken together with the nitrogen atoms to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure,

- 5 or wherein R¹⁹ and R²⁸ taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure.

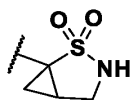
[000117] In some embodiments, Z is selected from the group consisting of NHSO₂NH₂, NHSO₂CH₃, NHSO₂-cyclopropyl, NCH₃SO₂-cyclopropyl, NHC(O)CH₃, NCH₃SO₂N(CH₃)₂,

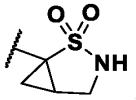


- 10 [000118] In some embodiments, Z is selected from the group consisting of NHSO₂NH₂, NHSO₂CH₃, NHC(O)CH₃, NCH₃SO₂CH₃, and



[000119] In some embodiments, Z is selected from the group consisting of cyano and



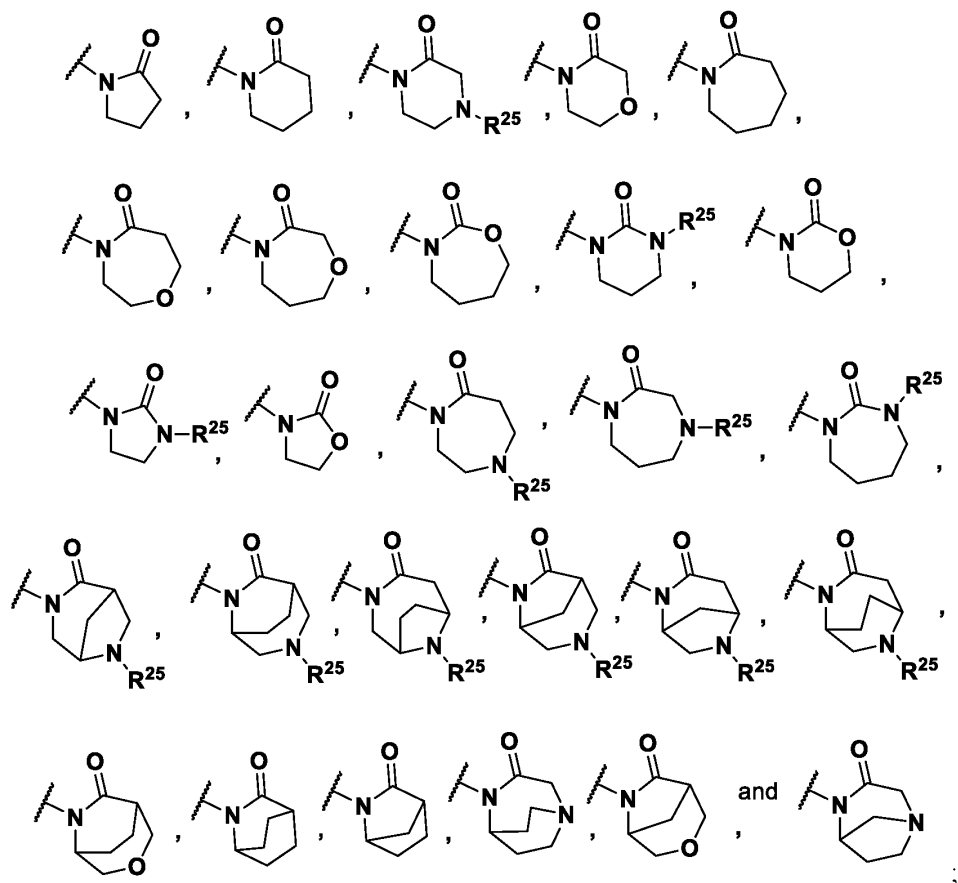
- 15 [000120] In some embodiments, Z is .

[000121] In some embodiments, Z is selected from the group consisting of -SO₂R²⁹ and -S(O)(=NH)-R¹⁰.

- [000122] In some embodiments, R²⁹ is selected from the group consisting of alkyl, cycloalkyl, and amino. In some embodiments, R²⁹ is selected from the group consisting of CH₃,
20 CH₂CH₃, CH(CH₃)₂, CH₂CH(CH₃)₂, NH₂, and NHCH₃. In some embodiments, R²⁹ is selected from the group consisting of CH₃, and NH₂.

[000123] In some embodiments, R¹⁰ is CH₃.

[000124] In some embodiments, Z is a substituted heterocyclyl selected from the group consisting of

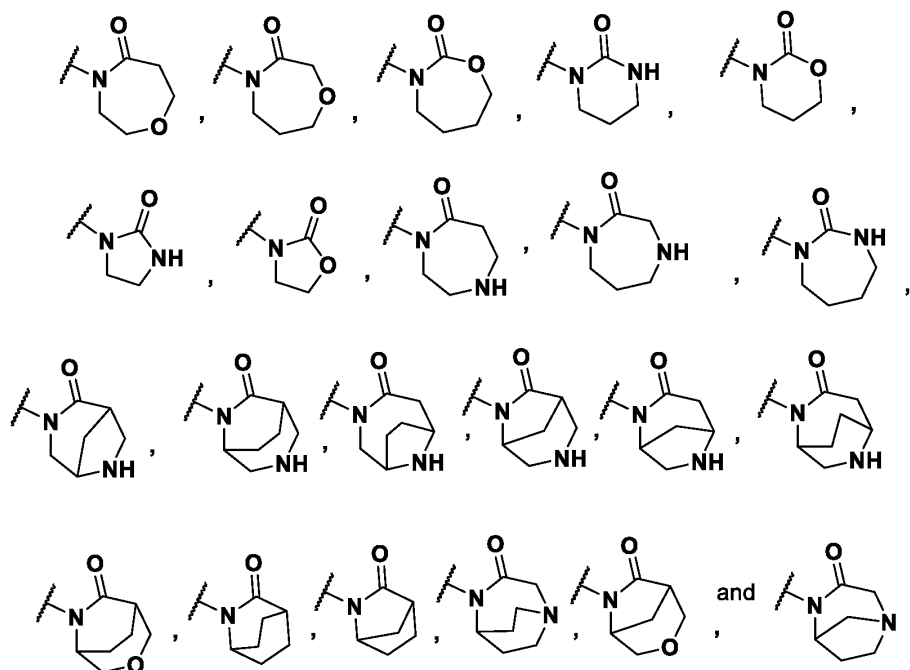


wherein R^{25} is selected from the group consisting of H, alkyl, deuterated alkyl, haloalkyl, cycloalkyl, and heterocyclyl.

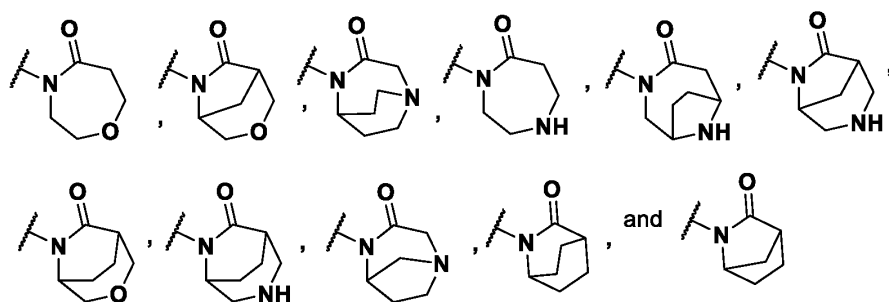
[000125] In some embodiments, wherein R^{25} is selected from the group consisting of H, alkyl, and cycloalkyl.

[000126] In some embodiments, R^{25} is selected from the group consisting of H, and CH_3 .

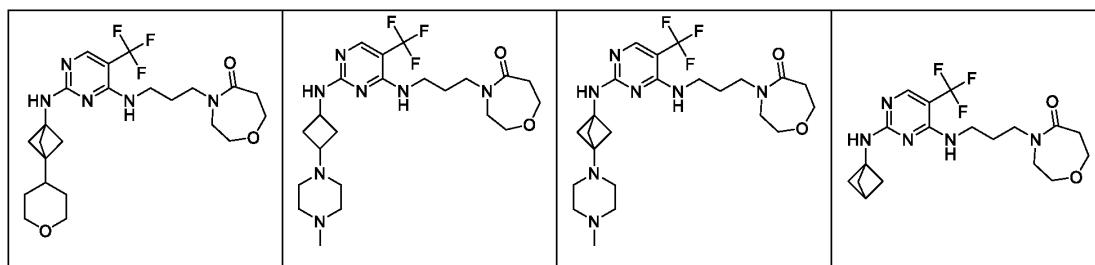
[000127] In some embodiments, Z is a substituted heterocyclyl selected from the group consisting of

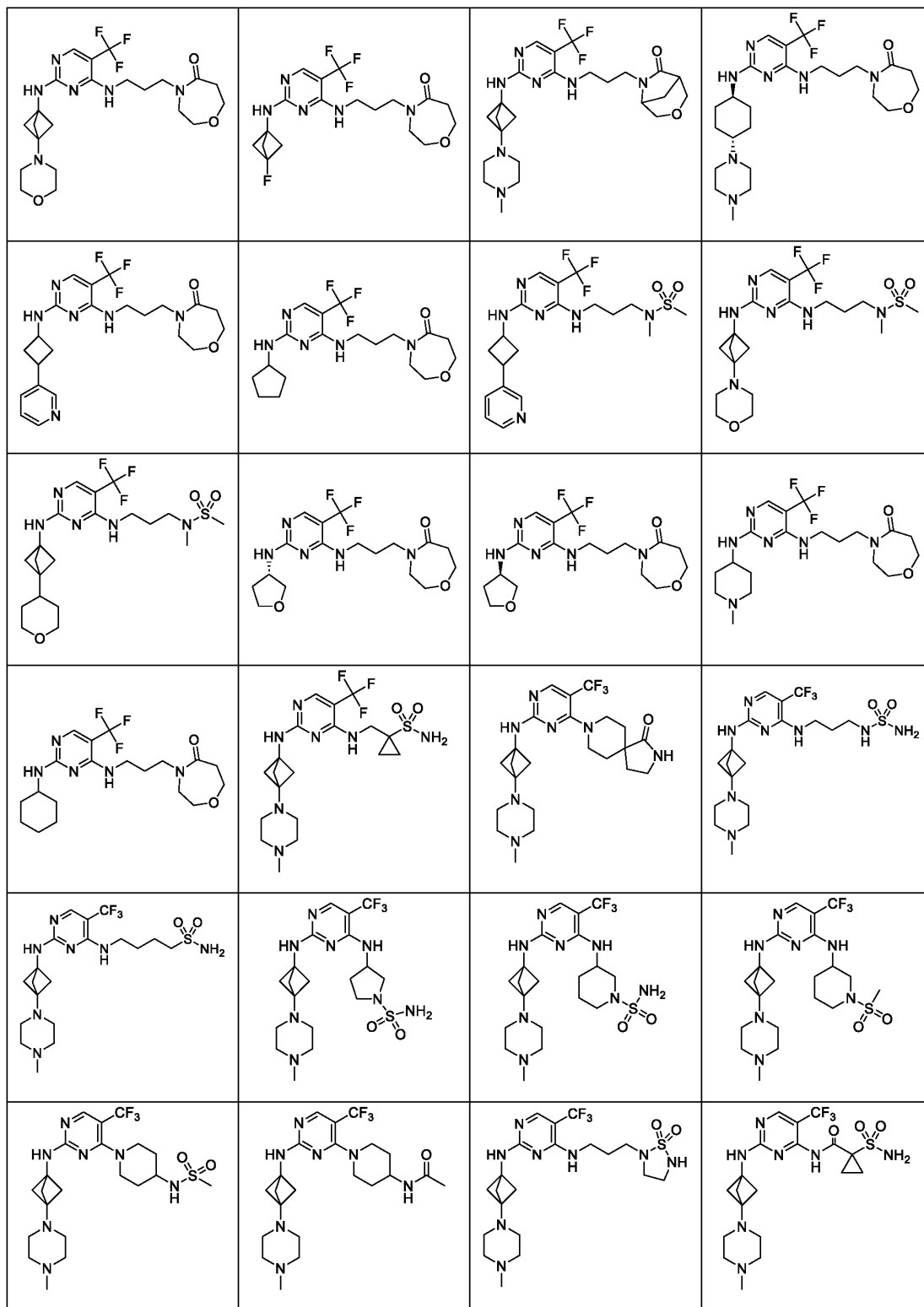


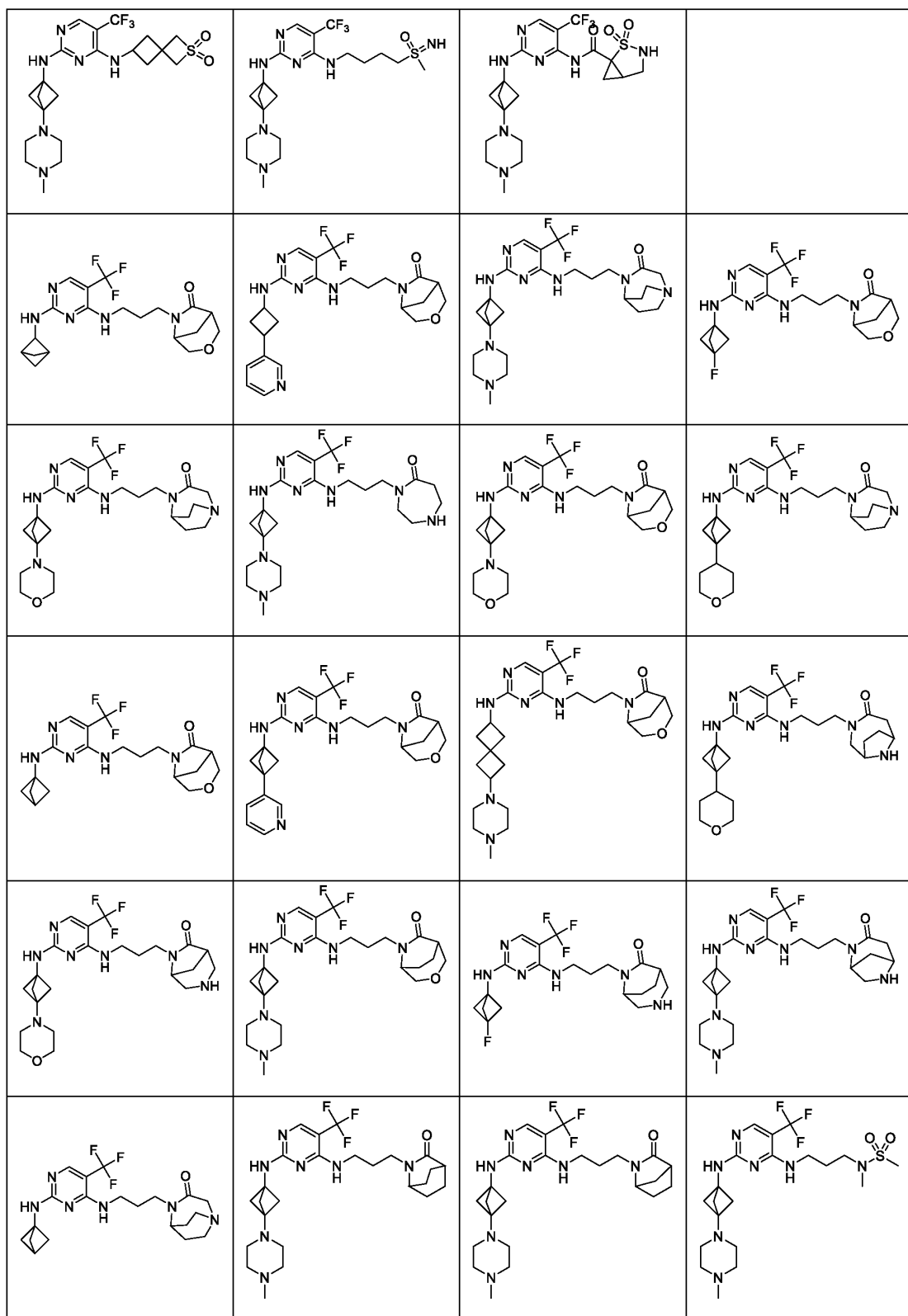
[000128] In some embodiments, Z is a substituted heterocyclyl selected from the group consisting of

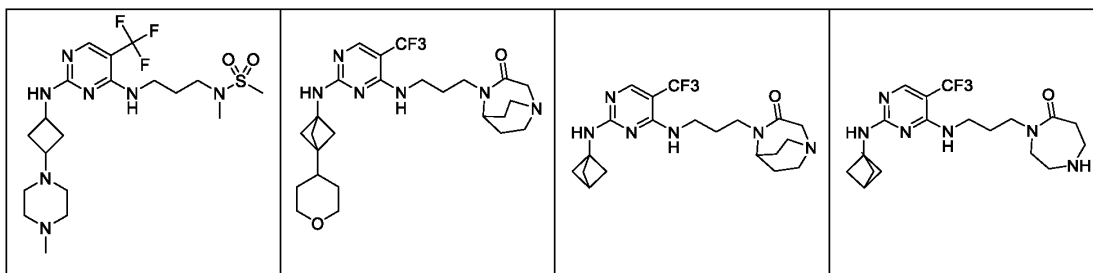


- 5 [000129] Also provided herein, in some embodiments, is a compound selected from the group consisting of:



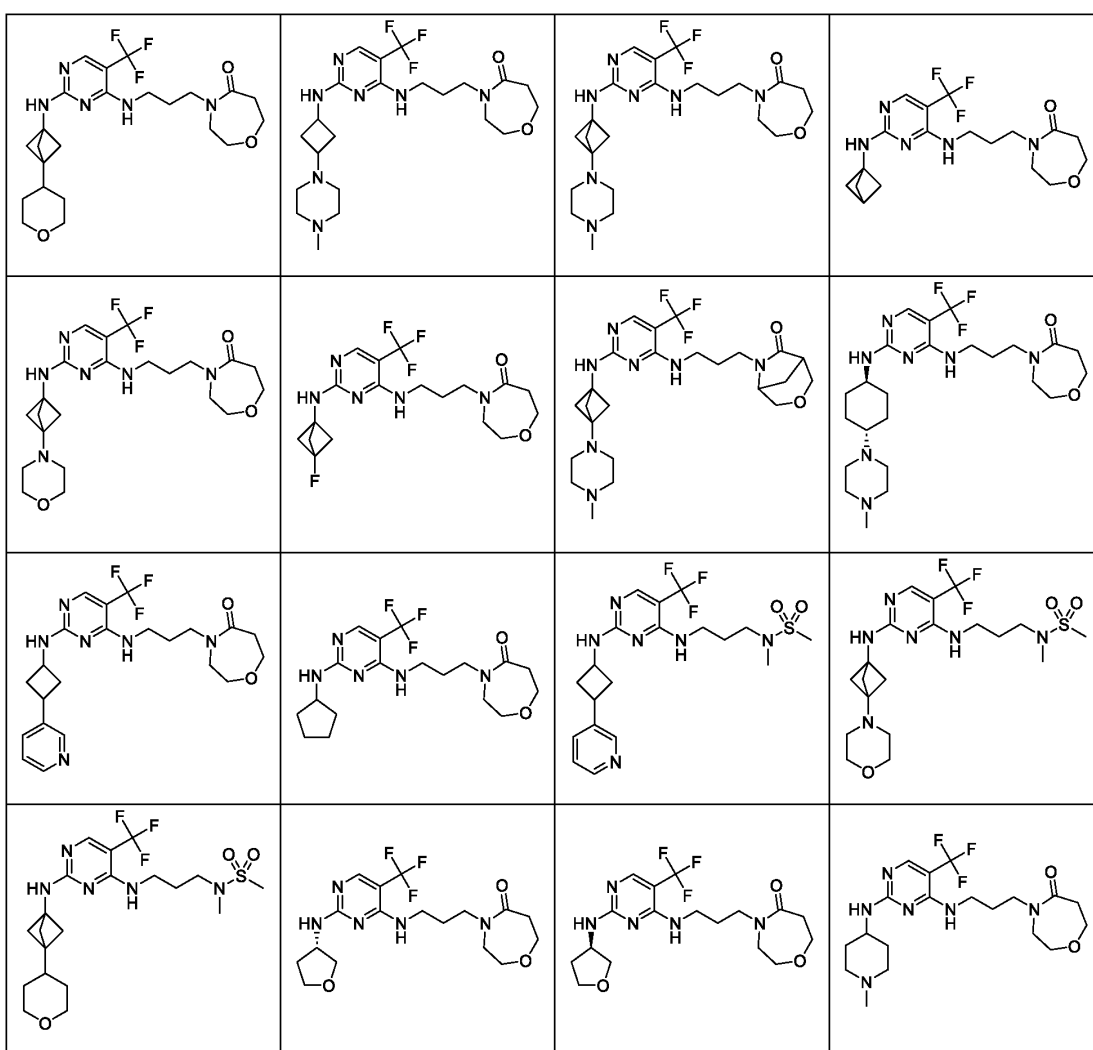


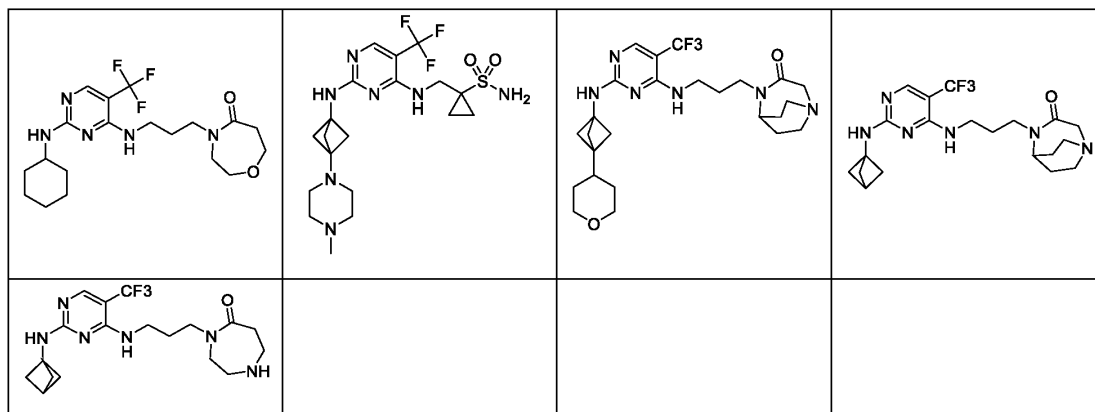




and pharmaceutically acceptable salts, enantiomers, stereoisomers, and tautomers thereof.

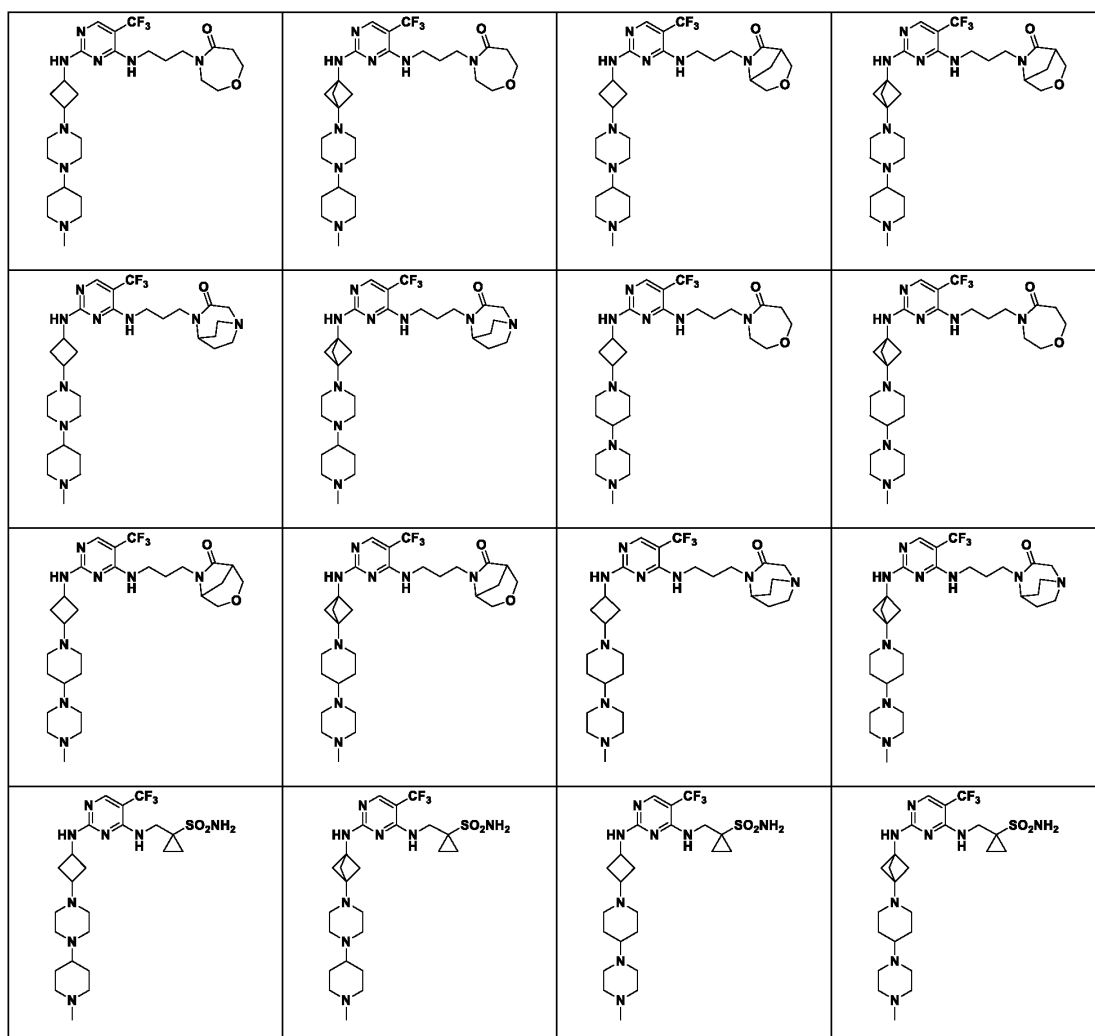
[000130] In some embodiments, a compound disclosed herein is selected from the group consisting of:





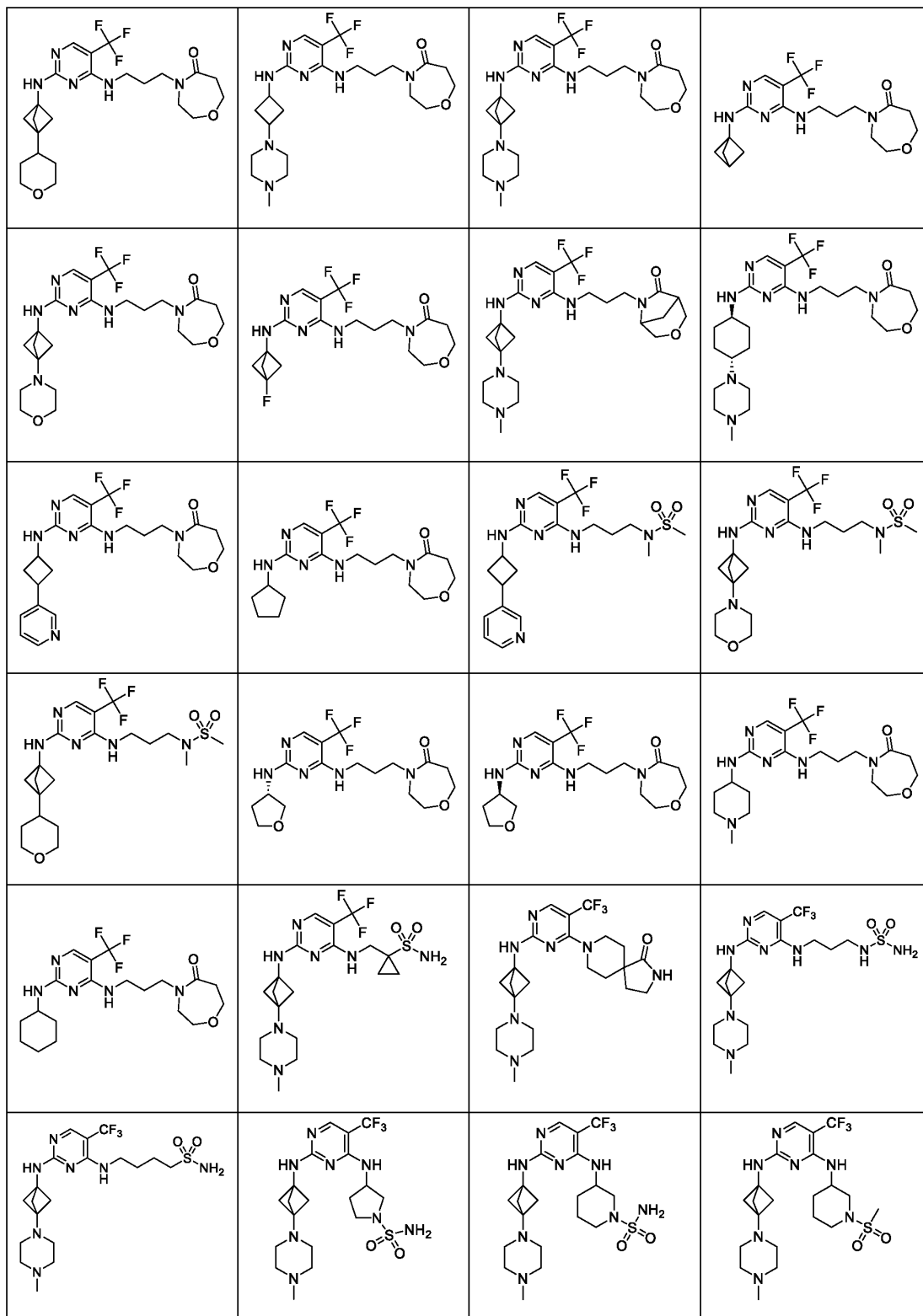
and pharmaceutically acceptable salts, enantiomers, stereoisomers, and tautomers thereof.

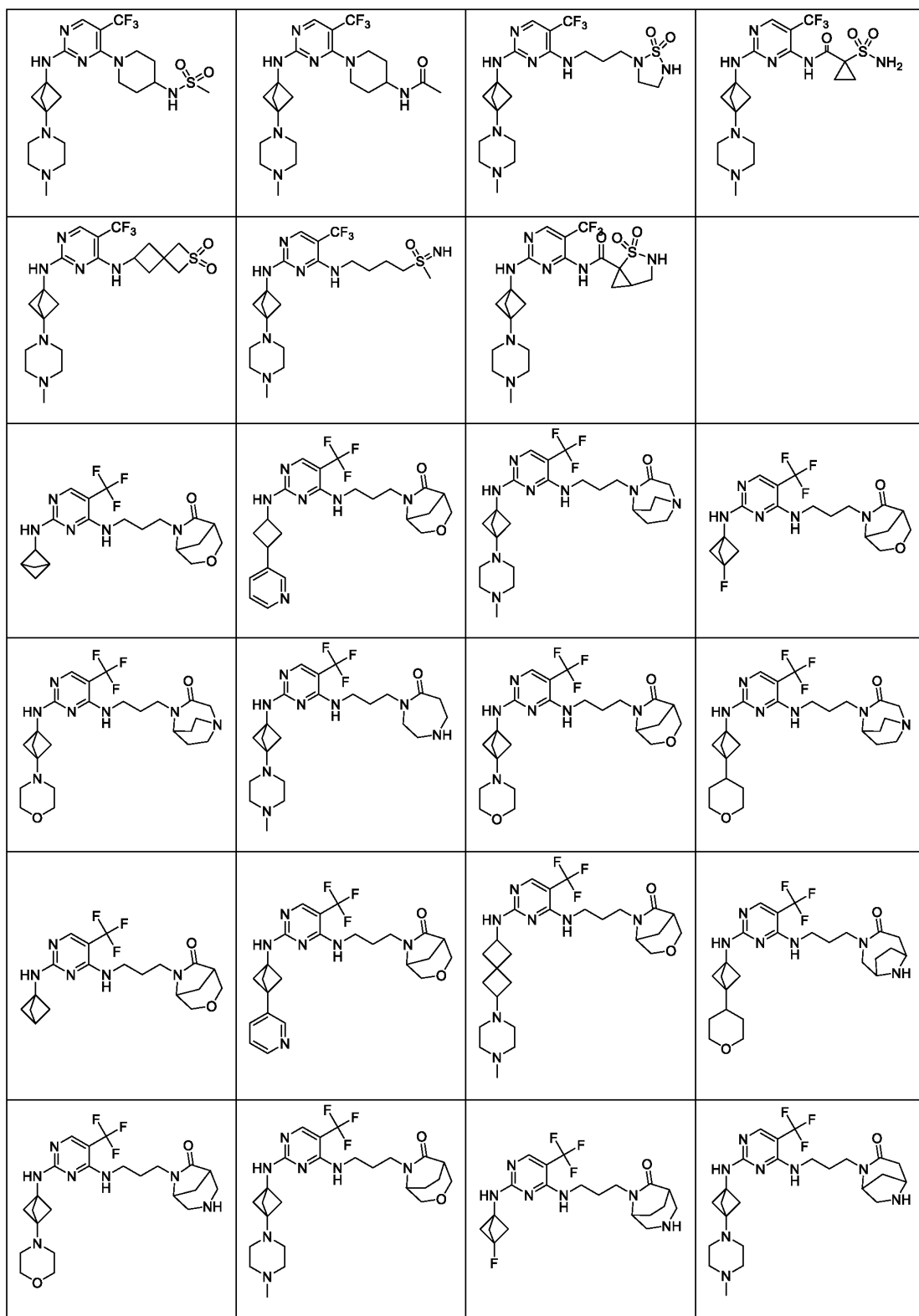
[000131] Also provided herein, in some embodiments, is a compound selected from the group consisting of:

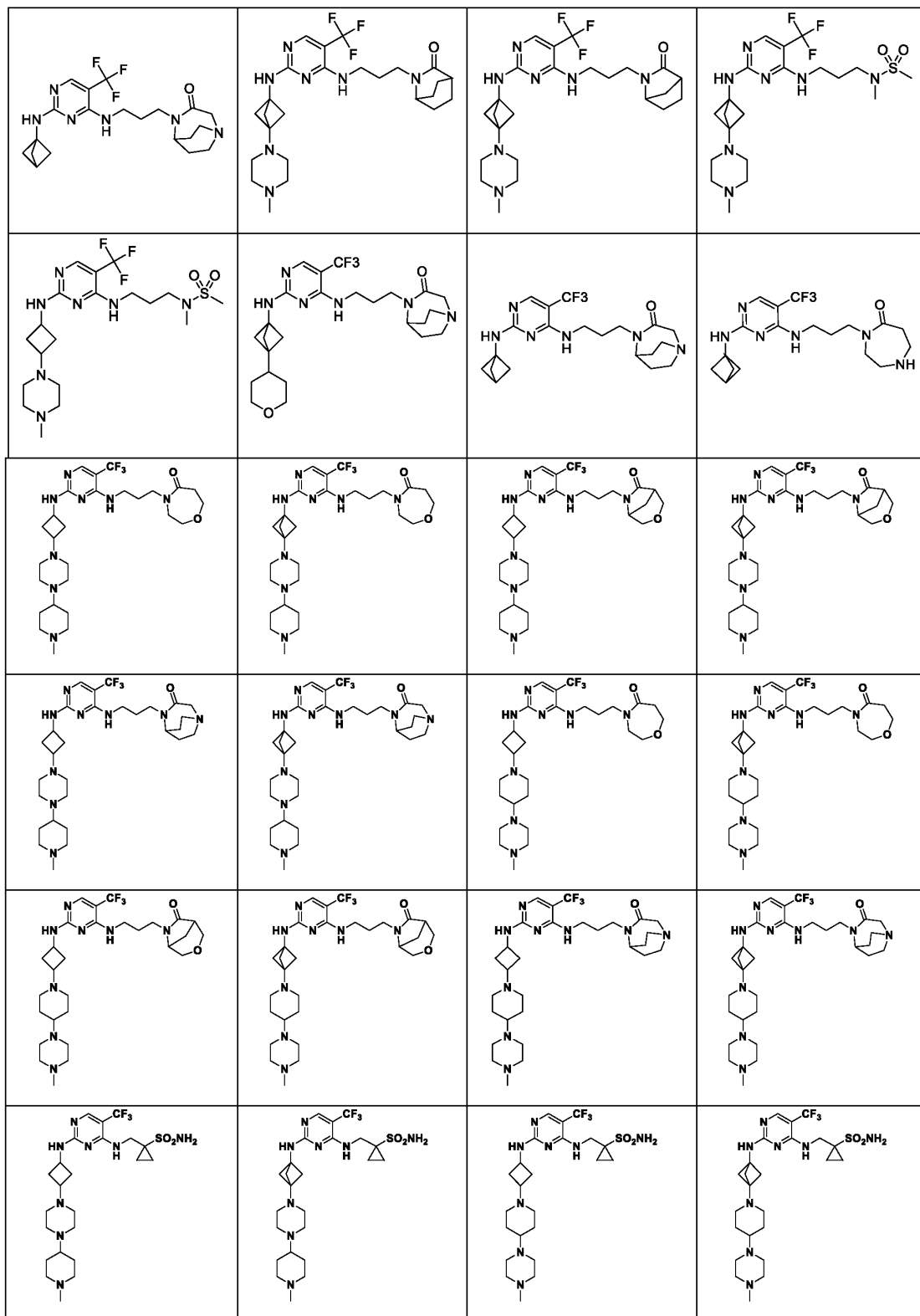


and pharmaceutically acceptable salts, enantiomers, stereoisomers, and tautomers thereof.

[000132] Also provided herein, in some embodiments, is a compound selected from the group consisting of:







and pharmaceutically acceptable salts, enantiomers, stereoisomers, and tautomers thereof.

Methods of Treatment

[000133] Compounds described herein (*e.g.*, compounds of Formula (I), Formula (Ia), and Formula (II), or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof) can act as inhibitors of autophagy useful in the treatment of a disorder in a patient in
5 need thereof. The disorder, for example, can be a tumor, *e.g.*, a solid tumor. The disorder may also be cancer.

[000134] Exemplary disorders also include gastrointestinal stromal tumors, esophageal cancers, gastric cancers, melanomas, gliomas, glioblastomas, gynecological cancers (*e.g.*, ovarian cancers, cervical cancers, uterine cancers, vaginal cancers, and vulvar cancers), bladder
10 cancers, pancreatic cancers, prostate cancers, lung cancers, breast cancers, renal cancers, hepatic cancers, osteosarcomas, Ewing sarcoma, multiple myelomas, leukemias, cervical carcinomas, cancers that are metastatic to bone, papillary thyroid carcinomas, non-small cell lung cancer, colorectal cancers, acute myeloid leukemia, relapsed acute myeloid leukemia, refractory acute myeloid leukemia, myelodysplastic syndrome, acute lymphocytic leukemia, chronic lymphocytic
15 leukemia, chronic myeloid leukemia, myeloproliferative neoplasms, and mantle cell lymphoma. A cancer treated by the methods described herein may be a metastatic cancer.

[000135] In some embodiments, the compounds described herein are useful for the treatment of cancers caused by RAS mutation. In some embodiments, the cancer is caused by a KRAS mutation. In some embodiments, the cancer has additional mutations in tumor suppressor
20 proteins, including mutations in TP53, PTEN, CDN2A/INK4A, p16, or STAG2. In some embodiments, these additional mutations occur in one or more of TP53, PTEN, CDN2A/INK4A, p16, or STAG2. In some embodiments, the cancer is pancreatic ductal adenocarcinoma. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is colorectal. In some embodiments, the cancer is acute myeloid leukemia.

[000136] In some embodiments, determination of cellular inhibition of autophagy by compounds described herein is determined by monitoring of autophagic flux, for instance by monitoring inhibition of autophagy-mediated clearance of mCherry/GFP-LC3 fusion protein. In some embodiments, determination of cellular inhibition of autophagy by compounds described herein is determined by monitoring of accumulation of autophagic proteins such as p62 or LC-3.
25 In some embodiments, determination of cellular inhibition of autophagy by compounds described herein is determined by decreased clearance of luciferase-tagged LC3 protein. In some embodiments, determination of cellular inhibition of autophagy by compounds described herein is determined by monitoring decreases in cellular autophagosomes, for instance by measurement of fluorescent puncta with the autophagosome marker Cyto-ID.

[000137] In some embodiments, cellular inhibition of ULK kinase by compounds described herein is determined by inhibition of phosphorylation of cellular ULK substrates including ATG13, ATG14, Beclin 1, or STING either in tumor cells or in non-tumor host tissues. In some embodiments, cellular inhibition of ULK kinase by compounds described herein is determined in
5 host tissues including immune cells.

[000138] In some embodiments, in vivo inhibition of autophagy by compounds described herein is determined by inhibition of phosphorylation of cellular ULK substrates including ATG13, ATG14, Beclin 1, or STING either in tumor cells or in non-tumor host tissues. In some
10 embodiments, in vivo inhibition of ULK kinase by compounds described herein is determined in host tissues including immune cells. In some embodiments, the in vivo inhibition of autophagic flux by compounds described herein can be used as a pharmacodynamic model for monitoring the kinetics and extent of such ULK inhibition. In some embodiments, in vivo inhibition of ULK
15 kinase by compounds described herein is determined in pancreatic cancer-bearing animals. In some embodiments, in vivo inhibition of ULK kinase by compounds described herein is determined in lung cancer-bearing animals. In some embodiments, in vivo inhibition of ULK kinase is determined in colorectal cancer-bearing animals. In some embodiments, in vivo
20 inhibition of autophagy by compounds described herein is determined by inhibition of autophagic flux in tumor cells, or in non-tumor host tissues by monitoring inhibition of autophagosome formation, or by accumulation of autophagic proteins such as p62 or LC-III. In some embodiments, in vivo inhibition of autophagy is determined in host tissues including
immune cells. In some embodiments, the in vivo inhibition of autophagic flux can be used as a pharmacodynamic model for monitoring the kinetics and extent of such ULK inhibition.

[000139] In some embodiments, inhibition of autophagy and anti-tumor activity by compounds described herein are evaluated in xenograft studies utilizing human RAS mutant cell
25 lines in immunocompromised mice, for instance in SCID or nude mice. In some embodiments, inhibition of autophagy and anti-tumor activity by compounds described herein are evaluated in xenograft studies utilizing human RAS mutant patient-derived tumor xenografts (PDXs) in immunocompromised mice, for instance in SCID or nude mice. In some embodiments, xenograft
30 studies include evaluation of compounds described herein in pancreatic cancer models. In some embodiments, xenograft studies include evaluation of compounds described herein in lung cancer models. In some embodiments, xenograft studies include evaluation of compounds described herein in colorectal cancer models. In some embodiments, xenograft studies include
evaluation of compounds described herein in acute myeloid leukemia models. In some
35 embodiments, inhibition of autophagy and anti-tumor activity by compounds described herein are evaluated in syngeneic murine genetically engineered models (GEMs) of mutant RAS

cancers. In some embodiments, inhibition of autophagy and anti-tumor activity by compounds described herein are evaluated in the murine GEM syngeneic orthotopic pancreatic cancer model known as the KPC model (LSL-Kras^{G12D/+};LSL-Trp53^{R172H/+};Pdx-1-Cre) or variants of the KPC model.

5 [000140] In some embodiments, compounds described herein will be evaluated in xenograft or GEM cancer models in combination with a MEK inhibitor. In some embodiments, compounds described herein will be evaluated in xenograft or GEM cancer models in combination with a RAF inhibitor. In some embodiments, compounds described herein will be evaluated in xenograft or GEM cancer models in combination with an ERK inhibitor. In some
10 embodiments, compounds described herein will be evaluated in xenograft or GEM cancer models in combination with a RAS G12C direct inhibitor.

[000141] In some embodiments, inhibition of autophagy and anti-tumor activity by compounds described herein is evaluated in immunocompetent murine cancer models to assess an immunomodulatory component to the mechanism of action of ULK inhibitors. In some
15 embodiments, the immunocompetent murine model is the murine GEM syngeneic orthotopic pancreatic cancer model known as the KPC model (LSL-Kras^{G12D/+};LSL-Trp53^{R172H/+};Pdx-1-Cre) or variants of the KPC model. In some embodiments, immunomodulatory properties of compounds described herein are evaluated in combination with a MEK inhibitor. In some
20 embodiments, immunomodulatory properties of compounds described herein are evaluated in combination with a RAF inhibitor. In some embodiments, immunomodulatory properties of compounds described herein are evaluated in combination with an ERK inhibitor. In some
embodiments, immunomodulatory properties of compounds described herein are evaluated in combination with a RAS G12C direct inhibitor.

[000142] In some embodiments, the immunomodulatory component of ULK inhibition is
25 an enhanced innate immune response. In some embodiments, the immunomodulatory component of ULK inhibition is an enhanced adaptive immune response. In some embodiments, the immunomodulatory component of ULK inhibition is an enhanced activity of antigen-presenting cells. In some embodiments, the immunomodulatory component of ULK inhibition is an enhanced anti-tumor activity of myeloid cells including macrophages. In some embodiments, the
30 immunomodulatory component of ULK inhibition is an enhanced anti-tumor activity of Natural Killer cells. In some embodiments, the immunomodulatory component of ULK inhibition is an enhanced activity of effector T Cells, including cytotoxic T Cells.

[000143] In an embodiment, provided herein is a method of treating a disorder described herein that includes: administering a therapeutically effective amount of compound described
35 herein in a patient in need thereof, and during or after the course of administration (*e.g.*, at

discrete time points, such as one week, two weeks, or on month after initial administration of a contemplated compound) detecting the engagement of the compound with an ULK kinase, wherein detecting comprises contacting a sample obtained from the patient (including but not limited to a tumor, blood, saliva, or tissue) with a phospho-ATG13 antibody ELISA assay to
5 detect inhibition of ULK kinase activity, *e.g.*, based on the level of phospho-ATG13 in the sample. In some embodiments, a contemplated method comprises optionally contacting a sample obtained from the patient (including but not limited to a tumor, blood, saliva, or tissue) prior to administration of the compound with a phospho-ATG13 antibody ELISA assay, and comparing the level of phospho-ATG13 in the sample obtained prior to administration with the level of
10 phospho-ATG13 in the sample obtained during or after the course of administration. In some embodiments, the phospho-ATG13 is p-S318ATG13.

[000144] In an embodiment, provided herein is a method of treating a disorder described herein that includes: administering a therapeutically effective amount of compound described herein in a patient in need thereof, and during or after the course of administration (*e.g.*, at
15 discrete time points, such as one week, two weeks, or on month after initial administration of a contemplated compound) detecting the engagement of the compound with an ULK kinase, wherein detecting comprises contacting a sample obtained from the patient (including but not limited to a tumor, blood, saliva, or tissue) with a phospho-ATG14 antibody ELISA assay to detect inhibition of ULK kinase activity, *e.g.*, based on the level of phospho-ATG14 in the
20 sample. In some embodiments, a contemplated method comprises optionally contacting a sample obtained from the patient (including but not limited to a tumor, blood, saliva, or tissue) prior to administration of the compound with a phospho-ATG14 antibody ELISA assay, and comparing the level of phospho-ATG14 in the sample obtained prior to administration with the level of phospho-ATG14 in the sample obtained during or after the course of administration. In some
25 embodiments, the phospho-ATG14 is p-ATG14 Ser29.

[000145] In an embodiment, provided herein is a method of treating a disorder described herein that includes: administering a therapeutically effective amount of compound described herein in a patient in need thereof, and during or after the course of administration (*e.g.*, at
30 discrete time points, such as one week, two weeks, or on month after initial administration of a contemplated compound) detecting the engagement of the compound with an ULK kinase, wherein detecting comprises contacting a sample obtained from the patient (including but not limited to a tumor, blood, saliva, or tissue) with a p62 antibody ELISA assay to detect inhibition of ULK kinase activity, *e.g.*, based on the level of p62 in the sample. In some embodiments, a contemplated method comprises optionally contacting a sample obtained from the patient
35 (including but not limited to a tumor, blood, saliva, or tissue) prior to administration of the

compound with a p62 antibody ELISA assay, and comparing the level of p62 in the sample obtained prior to administration with the level of p62 in the sample obtained during or after the course of administration.

5 [000146] In an embodiment, provided herein is a method of treating a disorder described herein that includes: administering a therapeutically effective amount of compound described herein in a patient in need thereof, and during or after the course of administration (*e.g.*, at discrete time points, such as one week, two weeks, or on month after initial administration of a contemplated compound) detecting the engagement of the compound with an ULK kinase, wherein detecting comprises contacting a sample obtained from the patient (including but not
10 limited to a tumor, blood, saliva, or tissue) with a pBeclin antibody ELISA assay to detect inhibition of ULK kinase activity, *e.g.*, based on the level of pBeclin in the sample. In some embodiments, a contemplated method comprises optionally contacting a sample obtained from the patient (including but not limited to a tumor, blood, saliva, or tissue) prior to administration of the compound with a pBeclin antibody ELISA assay, and comparing the level of pBeclin in
15 the sample obtained prior to administration with the level of pBeclin in the sample obtained during or after the course of administration.

[000147] The compounds provided herein may be administered to patients (animals and humans) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. It will be appreciated that the dose required for use in any particular application will vary from
20 patient to patient, not only with the particular compound or composition selected, but also with the route of administration, the nature of the condition being treated, the age and condition of the patient, concurrent medication or special diets then being followed by the patient, and other factors which those skilled in the art will recognize, with the appropriate dosage ultimately being at the discretion of the attendant physician. For treating clinical conditions and diseases noted
25 above, a compound provided herein may be administered orally, subcutaneously, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. Parenteral administration may include subcutaneous injections, intravenous or intramuscular injections or infusion techniques.

30 [000148] Treatment can be continued for as long or as short a period as desired. The compositions may be administered on a regimen of, for example, one to four or more times per day. A suitable treatment period can be, for example, at least about one week, at least about two weeks, at least about one month, at least about six months, at least about 1 year, or indefinitely. A treatment period can terminate when a desired result is achieved.

Combination Therapy

[000149] Compounds described herein, *e.g.*, a compound of Formula (I), Formula (Ia), and Formula (II), or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, as defined herein, can be administered in combination with one or more additional therapeutic agents to treat a disorder described herein, such as a cancer described herein. For example, provided in the present disclosure is a pharmaceutical composition comprising a compound described herein, *e.g.*, a compound of Formula (I), Formula (Ia), and Formula (II), or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, as defined herein, one or more additional therapeutic agents, and a pharmaceutically acceptable excipient.

In some embodiments, a compound of Formula (I), Formula (Ia), and Formula (II), or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, as defined herein and one additional therapeutic agent is administered. In some embodiments, a compound of Formula (I), Formula (Ia), and Formula (II), or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, as defined herein and two additional therapeutic agents are administered. In some embodiments, a compound of Formula (I), Formula (Ia), and Formula (II), or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, as defined herein and three additional therapeutic agents are administered. Combination therapy can be achieved by administering two or more therapeutic agents, each of which is formulated and administered separately. For example, a compound of Formula (I), Formula (Ia), and Formula (II), or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, as defined herein and an additional therapeutic agent can be formulated and administered separately. Combination therapy can also be achieved by administering two or more therapeutic agents in a single formulation, for example a pharmaceutical composition comprising a compound of Formula (I), Formula (Ia), and Formula (II), or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, as one therapeutic agent and one or more additional therapeutic agents. For example, a compound of Formula (I), Formula (Ia), and Formula (II), or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, as defined herein and an additional therapeutic agent can be administered in a single formulation. Other combinations are also encompassed by combination therapy. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or weeks of each other. In some cases even longer intervals

are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so.

[000150] Combination therapy can also include two or more administrations of one or more of the agents used in the combination using different sequencing of the component agents. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, *e.g.*, in the order X-Y-X, X-X-Y, Y-X-Y, Y-Y-X, X-X-Y-Y, etc.

[000151] Combination therapy can also include two or more administrations of one or more of the agents used in the combination using different routes of administration. Each of the one or more of the agents may be independently administered orally, subcutaneously, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. Parenteral administration may include subcutaneous injections, intravenous or intramuscular injections or infusion techniques.

[000152] In some embodiments, the one or more additional therapeutic agent that may be administered in combination with a compound described herein (*e.g.*, Formula (I), Formula (Ia), and Formula (II), or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof) can be a RTK pathway inhibitor, a MAP kinase pathway inhibitor, a PI3K inhibitor, an mTOR inhibitor, an immunomodulatory agent, or a chemotherapeutic agent, or any combination thereof.

[000153] In some embodiments, the additional therapeutic agent is a RTK pathway inhibitor. Such RTK pathway inhibitors include, for example, KIT inhibitors, EGFR inhibitors, PDGFR α inhibitors, VEGFR inhibitors, anti-VEGF therapeutics, BCR-Abl inhibitors, and ALK inhibitors.

[000154] Exemplary KIT inhibitors include, but are not limited, to ripretinib, avapritinib, sunitinib, AZD3229 (NB003), THE-630, imatinib, midostaurin, bezuclastinib, olverembatinib (HQP1351), famitinib, IDRX-42 (M4205), elenestinib, BLU-808, IDRX-73, SLRN-517, THB335, DCC-3009, pexidartinib, and regorafenib, and pharmaceutically acceptable salts thereof. In some embodiments, the KIT inhibitor is selected from the group consisting of ripretinib, avapritinib, sunitinib, AZD3229 (NB003), THE-630, imatinib, midostaurin, bezuclastinib, olverembatinib (HQP1351), famitinib, IDRX-42 (M4205), elenestinib, BLU-808, IDRX-73, SLRN-517, THB335, pexidartinib, and regorafenib, and pharmaceutically acceptable salts thereof.

- [000155] Exemplary EGFR inhibitors include, but are not limited to, cetuximab, osimertinib, gefitinib, lapatinib, erlotinib, dacomitinib, neratinib, and afatinib, and pharmaceutically acceptable salts thereof.
- [000156] Exemplary PDGFR α inhibitors include, but are not limited to, ripretinib, 5 JNJ10198409, crenolanib, and avapritinib, and pharmaceutically acceptable salts thereof.
- [000157] Exemplary VEGFR inhibitors include, but are not limited to, regorafenib, axitinib, lenvatinib, cabozantinib, sorafenib, sunitinib, vandetinib, nintedanib, tivozanib, and pazopanib, and pharmaceutically acceptable salts thereof. Exemplary anti-VEGF therapeutics include bevacizumab.
- 10 [000158] Exemplary BCR-Abl inhibitors include, but are not limited to, imatinib, nilotinib, dasatinib, bosutinib, and ponatinib, and asciminib, and pharmaceutically acceptable salts thereof.
- [000159] Exemplary ALK inhibitors include, but are not limited to, lorlatinib, brigatinib, ceritinib, crizotinib, and alectinib, and pharmaceutically acceptable salts thereof.
- [000160] Exemplary FLT3 inhibitors include, but are not limited to, midostaurin, 15 lestaurtinib, ponatinib, tandutinib, quizartinib, crenolanib, and gilteritinib, and pharmaceutically acceptable salts thereof.
- [000161] In some embodiments, the additional therapeutic agent is a MAP kinase pathway inhibitor. Such MAP kinase pathway inhibitors include, for example, MEK inhibitors, ERK inhibitors, RAF inhibitors, and Ras inhibitors.
- 20 [000162] Exemplary MEK inhibitors include, but are not limited to, trametinib, selumetinib, cobimetinib, binimetinib, avutometinib, mirdametinib, pimasertib, refametinib, and pelitinib, and pharmaceutically acceptable salts thereof. In some embodiments, the MEK inhibitor is selected from the group consisting of trametinib, selumetinib, cobimetinib, binimetinib, mirdametinib, and VS-6766, and pharmaceutically acceptable salts thereof.
- 25 [000163] Exemplary ERK inhibitors include, but are not limited to, ulixertinib, SCH772984, LY3214996, ravoxertinib, VX-11e, ERAS-007, and ASTX-029, and pharmaceutically acceptable salts thereof.
- [000164] Exemplary RAF inhibitors include, but are not limited to, LY3009120, LXH254 (naporafenib), RAF709, KIN-2787 (exarafenib), dabrafenib, vemurafenib, encorafenib, 30 tovorafenib, PLX8394, agerafenib, lifirafenib, belvarafenib, uplarafenib, JZP815, BDTX-4933, and DCC-3084, and pharmaceutically acceptable salts thereof. In some embodiments, the RAF inhibitor is selected from the group consisting of LY3009120, LXH254, RAF709, dabrafenib, vemurafenib, belvarafenib, KIN-2787, VS-6766, encorafenib, JZP815, and DCC-3084, and pharmaceutically acceptable salts thereof.

[000165] Exemplary Ras inhibitors include, but are not limited to, sotorasib (AMG-510), adagrasib (MRTX849), LY3537982, opnurasib, divarasil (GDC-6036), fulzerasil, MRTX-1133, JAB-21822, GFH925, ELI-002, RMC-6236, ASP3082, YL-17231, QTX3034, RMC-9805, HRS-4642, RMC-8839, INCB161734, and RMC-6291, and pharmaceutically acceptable salts thereof. In some embodiments, the Ras inhibitor is selected from the group consisting of AMG-510, MRTX849, GDC-6036, MRTX-1133, RMC-9805, RMC-6291, RMC-6236, LY3537982, opnurasib, divarasil, and pharmaceutically acceptable salts thereof.

[000166] In some embodiments, the Ras inhibitor is a KRAS inhibitor, for example, a KRAS G12C inhibitor, a KRAS G12D inhibitor, or a pan-KRAS inhibitor.

[000167] In some embodiments, the additional therapeutic agent is a PI3K inhibitor, an AKT inhibitor, or an mTOR inhibitor.

[000168] Exemplary PI3K inhibitors include, but are not limited to, alpelisib, LY294002, idelalisib, duvelisib, copanlisib, umbralisib, and omipalisib, and pharmaceutically acceptable salts thereof.

[000169] Exemplary mTOR inhibitors include, but are not limited to, rapamycin, everolimus, temsirolimus, PF04691502, and PP242, and pharmaceutically acceptable salts thereof.

[000170] Exemplary AKT inhibitors include, but are not limited to, ipatasertib, and capivasertib, and pharmaceutically acceptable salts thereof.

[000171] The compounds described herein may be administered in combination with other therapeutic agents known to treat cancers. Such other therapeutic agents include radiation therapy, anti-tubulin agents, DNA alkylating agents, DNA synthesis-inhibiting agents, DNA intercalating agents, anti-estrogen agents, anti-androgens, steroids, anti-EGFR agents, kinase inhibitors, mTOR inhibitors, PI3 kinase inhibitors, AKT inhibitors, cyclin-dependent kinase inhibitors, CD4/CD6 kinase inhibitors, topoisomerase inhibitors, Histone Deacetylase (HDAC) inhibitors, DNA methylation inhibitors, anti-HER2 agents, anti-angiogenic agents, proteasome inhibitors, PARP inhibitors, cell cycle regulating kinase inhibitors, thalidomide, lenalidomide, antibody-drug-conjugates (ADCs), immunotherapeutic agents including immunomodulating agents, targeted therapeutic agents, cancer vaccines, and CAR-T cell therapy.

[000172] In an embodiment, the additional therapeutic agents can be chemotherapeutic agents including but not limited to an anti-tubulin agents (for example, paclitaxel, paclitaxel protein-bound particles for injectable suspension including nab-paclitaxel, eribulin, docetaxel, ixabepilone, vincristine, auristatins, or maytansinoids), vinorelbine, DNA-alkylating agents (including cisplatin, carboplatin, oxaliplatin, cyclophosphamide, ifosfamide, temozolomide), DNA intercalating agents or DNA topoisomerase inhibitors (including anthracyclines such as

doxorubicin, pegylated liposomal doxorubicin, daunorubicin, idarubicin, mitoxantrone, or epirubicin, camptothecins such as topotecan, irinotecan, or exatecan), 5-fluorouracil, capecitabine, cytarabine, decitabine, 5-aza cytidine, gemcitabine and methotrexate.

[000173] In some embodiments, the additional therapeutic agent is selected from the group consisting of anti-tubulin agents, vinorelbine, DNA-alkylating agents, DNA intercalating agents, 5-fluorouracil, capecitabine, cytarabine, decitabine, 5-azacytidine, gemcitabine, irinotecan, and methotrexate.

[000174] In some embodiments, the additional therapeutic agents can be kinase inhibitors including but not limited to erlotinib, gefitinib, neratinib, afatinib, osimertinib, lapatanib, crizotinib, brigatinib, ceritinib, alectinib, lorlatinib, everolimus, temsirolimus, abemaciclib, LEE011, palbociclib, cabozantinib, sunitinib, pazopanib, sorafenib, regorafenib, sunitinib, axitinib, dasatinib, imatinib, ripretinib, avapritinib, JNJ10198409, nilotinib, idelalisib, ibrutinib, BLU-285, BLU-667, Loxo 292, larotrectinib, crenolanib, gilteritinib, and quizartinib, anti-estrogen agents including but not limited to tamoxifen, fulvestrant, anastrozole, letrozole, and exemestane, anti-androgen agents including but not limited to abiraterone acetate, enzalutamide, nilutamide, bicalutamide, flutamide, cyproterone acetate, steroid agents including but not limited to prednisone and dexamethasone, PARP inhibitors including but not limited to neraparib, olaparib, talazoparib, and rucaparib, topoisomerase I inhibitors including but not limited to irinotecan, camptothecin, exatecan, and topotecan, topoisomerase II inhibitors including but not limited to anthracyclines, etoposide, etoposide phosphate, and mitoxantrone, Histone Deacetylase (HDAC) inhibitors including but not limited to vorinostat, romidepsin, panobinostat, valproic acid, and belinostat, DNA methylation inhibitors including but not limited to DZNep and 5-aza-2'-deoxycytidine, proteasome inhibitors including but not limited to bortezomib and carfilzomib, thalidomide, lenalidomide, pomalidomide, biological agents including but not limited to trastuzumab, ado-trastuzumab, pertuzumab, cetuximab, panitumumab, ipilimumab, tremelimumab, anti-PD-1 agents including pembrolizumab, nivolumab, pidilizumab, and Cemiplimab, anti-PD-L1 agents including atezolizumab, avelumab, durvalumab and BMS-936559, anti-angiogenic agents including bevacizumab and aflibercept, and antibody-drug-conjugates (ADCs) including DM1, DM4, MMAE, MMAF, or camptothecin payloads, brentuximab vedotin and trastuzumab emtansine, radiotherapy, therapeutic vaccines including but not limited to sipuleucel-T.

[000175] In some embodiments, the additional therapeutic agents can be immunomodulatory agents including but not limited to anti-PD-1 or anti-PDL-1 therapeutics including pembrolizumab, nivolumab, atezolizumab, durvalumab, BMS-936559, avelumab, or dostarlimab, anti-TIM3 (anti-HAVcr2) therapeutics including but not limited to TSR-022 or

- MBG453, anti-LAG3 therapeutics including but not limited to relatlimab, LAG525, or TSR-033, anti-4-1BB (anti-CD37, anti-TNFRSF9), CD40 agonist therapeutics including but not limited to SGN-40, CP-870,893 or RO7009789, anti-CD47 therapeutics including but not limited to Hu5F9-G4, anti-CD20 therapeutics, anti-CD38 therapeutics, STING agonists including but not limited to ADU-S100, MK-1454, ASA404, or amidobenzimidazoles, anthracyclines including but not limited to doxorubicin or mitoxanthrone, hypomethylating agents including but not limited to azacytidine or decitabine, other immunomodulatory therapeutics including but not limited to epidermal growth factor inhibitors, statins, metformin, angiotensin receptor blockers, thalidomide, lenalidomide, pomalidomide, prednisone, or dexamethasone.
- 10 **[000176]** In some embodiments, the additional therapeutic agent is an immunomodulatory agent. In some embodiments, the immunomodulatory agent is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, BMS-936559, avelumab, cetuximab, TSR-022, MBG453, relatlimab, LAG525, TSR-033, SGN-40, CP-870,893, RO7009789, Hu5F9-G4, ADU-S100, MK-1454, ASA404, doxorubicin, mitoxanthrone, azacytidine, decitabine, statins, metformin, thalidomide, lenalidomide, pomalidomide, prednisone, dexamethasone, and dostarlimab, and pharmaceutically acceptable salts thereof.
- [000177]** In some embodiments, the additional therapeutic agent is selected from a luteinizing hormone-releasing hormone (LHRH) analog, including goserelin and leuprolide.
- [000178]** In some embodiments, the additional therapeutic agent is selected from the group consisting of selected from the group consisting of everolimus, trabectedin, abraxane, TLK 286, AV-299, DN-101, pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, pemetrexed, erlotinib, dasatinib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etv, nolatrexed, azd2171, batabulin, ofatumumab, zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111, 131-I-TM-601, ALT-110, BIO 140, CC 8490, cilengitide, gimatecan, IL13-PE38QQR, INO 1001, IPdR₁ KRX-0402, lucanthone, LY 317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311, romidepsin, ADS-100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, irinotecan, liposomal doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709, seliciclib, PD0325901, AZD-6244, capecitabine, L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)-ethyl]benzoyl]-, disodium salt, heptahydrate, camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrozole, exemestane, letrozole, DES(diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11, CHIR-258,); 3-[5-(methylsulfonylpiperadinemethyl)-indolyl]-

quinolone, vatalanib, AG-013736, AVE-0005, goserelin acetate, leuprolide acetate, triptorelin
 pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate,
 raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714, TAK-165, HKI-
 272, erlotinib, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-166, GW-
 5 572016, Ionafernib, BMS-214662, tipifarnib; amifostine, NVP-LAQ824, suberoyl analide
 hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib, KR951,
 aminoglutethimide, arnsacrine, anagrelide, L-asparaginase, Bacillus Calmette-Guerin (BCG)
 vaccine, bleomycin, buserelin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin,
 cladribine, clodronate, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin,
 10 diethylstilbestrol, epirubicin, fludarabine, fludrocortisone, fluoxymesterone, flutamide,
 gemcitabine, gleevac, hydroxyurea, idarubicin, ifosfamide, imatinib, leuprolide, levamisole,
 lomustine, mechlorethamine, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin,
 mitotane, mitoxantrone, nilutamide, octreotide, oxaliplatin, pamidronate, pentostatin,
 plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, teniposide, testosterone,
 15 thalidomide, thioguanine, thiotepa, tretinoin, vindesine, 13-cis-retinoic acid, phenylalanine
 mustard, uracil mustard, estramustine, altretamine, floxuridine, 5-deoxyuridine, cytosine
 arabinoside, 6-mecaptopurine, deoxycoformycin, calcitriol, valrubicin, mithramycin, vinblastine,
 vinorelbine, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291, squalamine,
 endostatin, SU5416, SU6668, EMD121974, interleukin-12, IM862, angiostatin, vitaxin,
 20 droloxifene, idoxifene, spironolactone, finasteride, cimitidine, trastuzumab, denileukin diftitox,
 gefitinib, bortezomib, irinotecan, topotecan, doxorubicin, docetaxel, vinorelbine, bevacizumab
 (monoclonal antibody) and erbitux, cremophor-free paclitaxel, epithilone B, BMS-247550,
 BMS-310705, droloxifene, 4-hydroxytamoxifen, pipendoxifene, ERA-923, arzoxifene,
 fulvestrant, acolbifene, lasofoxifene, idoxifene, TSE-424, HMR-3339, ZK186619, PTK787/ZK
 25 222584, VX-745, PD 184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-
 23573, RAD001, ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684,
 LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, erythropoietin,
 granulocyte colony-stimulating factor, zoledronate, prednisone, cetuximab, granulocyte
 macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-2a,
 30 pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L-asparaginase, lenalidomide,
 gemtuzumab, hydrocortisone, interleukin-11, dexrazoxane, alemtuzumab, all-transretinoic acid,
 ketoconazole, interleukin-2, megestrol, immune globulin, nitrogen mustard, methylprednisolone,
 ibritumomab tiuxetan, androgens, decitabine, hexamethylmelamine, bexarotene, tositumomab,
 arsenic trioxide, cortisone, editronate, mitotane, cyclosporine, liposomal daunorubicin, Edwina-
 35 asparaginase, strontium 89, casopitant, netupitant, an NK-1 receptor antagonists, palonosetron,

aprepitant, diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone, methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, sspgfilgrastim, erythropoietin, epoetin alfa and darbepoetin alfa, ipilimumab, vemurafenib, MRTX849, MRTX1133, AMG510, GDC-6036, 5 RMC-9805, RMC-6291, RMC-6236, belvarafenib, KIN-2787, ERAS-007, ASTX-029, and mixtures thereof.

Pharmaceutical Compositions and Kits

[000179] Another aspect of this disclosure provides pharmaceutical compositions comprising compounds as disclosed herein formulated together with a pharmaceutically acceptable carrier or excipient. In particular, the present disclosure provides pharmaceutical 10 compositions comprising compounds as disclosed herein formulated together with one or more pharmaceutically acceptable carriers or excipients. These formulations include those suitable for oral, rectal, topical, buccal, parenteral (*e.g.*, subcutaneous, intramuscular, intradermal, or intravenous) rectal, vaginal, or aerosol administration, although the most suitable form of 15 administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used. For example, disclosed compositions may be formulated as a unit dose, and/or may be formulated for oral or subcutaneous administration.

[000180] Exemplary pharmaceutical compositions may be used in the form of a 20 pharmaceutical preparation, for example, in solid, semisolid, or liquid form, which contains one or more of the compounds described herein, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral, or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, 25 and any other form suitable for use. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

[000181] For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical carrier, *e.g.*, conventional tableting ingredients such as corn 30 starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, *e.g.*, water, to form a solid preformulation composition containing a homogeneous mixture of a compound provided herein, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the

composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills, and capsules.

[000182] In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more

5 pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain

10 silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules,

15 tablets and pills, the compositions may also comprise buffering agents. 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 sugars, as well as high molecular weight polyethylene glycols and the like.

[000183] A tablet may be made by compression or molding, optionally with one or more

20 accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage

25 forms, such as dragees, capsules, pills, and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

[000184] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous, or organic solvents, or mixtures thereof, and powders.

30 Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the subject composition, 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,

35 propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ,

olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

5 [000185] Suspensions, in addition to the subject composition, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[000186] Formulations for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing a subject composition with one or more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a
10 suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent.

[000187] Dosage forms for transdermal administration of a subject composition include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable
15 carrier, and with any preservatives, buffers, or propellants which may be required.

[000188] The ointments, pastes, creams, and gels may contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

20 [000189] Powders and sprays may contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays may additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[000190] Compositions and compounds of the present disclosure may alternatively be
25 administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (*e.g.*, fluorocarbon propellant) suspension could be used. Sonic nebulizers may be used because they minimize exposing the agent to shear, which may result in degradation of the compounds contained in the subject compositions. Ordinarily, an aqueous aerosol is made by formulating an aqueous
30 solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronic, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars, or sugar alcohols. Aerosols generally are
35 prepared from isotonic solutions.

[000191] Pharmaceutical compositions of the present disclosure suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[000192] Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions described herein include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. Proper fluidity may be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[000193] In another embodiment, provided are enteral pharmaceutical formulations including a disclosed compound and an enteric material, and a pharmaceutically acceptable carrier or excipient thereof. Enteric materials refer to polymers that are substantially insoluble in the acidic environment of the stomach, and that are predominantly soluble in intestinal fluids at specific pHs. The small intestine is the part of the gastrointestinal tract (gut) between the stomach and the large intestine, and includes the duodenum, jejunum, and ileum. The pH of the duodenum is about 5.5, the pH of the jejunum is about 6.5 and the pH of the distal ileum is about 7.5.

[000194] Accordingly, enteric materials are not soluble, for example, until a pH of about 5.0, of about 5.2, of about 5.4, of about 5.6, of about 5.8, of about 6.0, of about 6.2, of about 6.4, of about 6.6, of about 6.8, of about 7.0, of about 7.2, of about 7.4, of about 7.6, of about 7.8, of about 8.0, of about 8.2, of about 8.4, of about 8.6, of about 8.8, of about 9.0, of about 9.2, of about 9.4, of about 9.6, of about 9.8, or of about 10.0. Exemplary enteric materials include cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methacrylate-methylmethacrylate-chlorotrimethylammonium ethyl

acrylate copolymer, natural resins such as zein, shellac and copal colophonium, and several commercially available enteric dispersion systems (*e.g.*, Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, and Aquateric). The solubility of each of the above materials is either known or is readily determinable *in vitro*. The foregoing is a list of possible materials, but one of skill in the art with the benefit of the disclosure would recognize that it is not comprehensive and that there are other enteric materials that would meet the objectives described herein.

[000195] Advantageously, described herein are kits for use by a *e.g.*, a consumer in need of treatment of cancer. Such kits include a suitable dosage form such as those described above and instructions describing the method of using such dosage form to mediate, reduce or prevent inflammation. The instructions would direct the consumer or medical personnel to administer the dosage form according to administration modes known to those skilled in the art. Such kits could advantageously be packaged and sold in single or multiple kit units. An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

[000196] It may be desirable to provide a memory aid on the kit, *e.g.*, in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, *e.g.*, as follows "First Week, Monday, Tuesday, . . . etc. . . . Second Week, Monday, Tuesday, . . . " etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of a first compound can consist of one tablet or capsule while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

EXAMPLES

[000197] The compounds described herein can be prepared in a number of ways based on the teachings contained herein and synthetic procedures known in the art. In the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be chosen to be the conditions standard for that reaction, unless otherwise indicated. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule should be compatible with the reagents and reactions proposed. Substituents not compatible with the reaction conditions will be apparent to one skilled in the art, and alternate methods are therefore indicated. The starting materials for the examples are either commercially available or are readily prepared by standard methods from known materials.

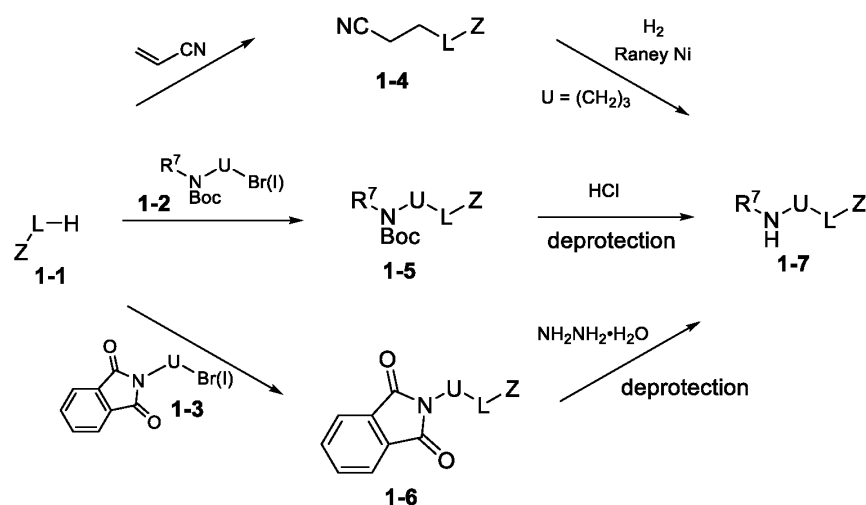
[000198] The following abbreviations are used in this disclosure and have the following definitions: "ADP" is adenosine diphosphate, "Adbrettphos-Pd-G3" is [2-(di-1-adamantylphosphino)-2',4',6'-triisopropyl-3,6-dimethoxybiphenyl][2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate, "Boc" is *tert*-butylcarbonate, "DCM" is dichloromethane, "DIEA" is *N,N*-diisopropylethylamine, "DMF" is *N,N*-dimethylformamide, "DMSO" is dimethylsulfoxide, "ESI" is electrospray ionization, "Et₂O" is diethylether, "EtOAc" is ethyl acetate, "EtOH" is ethanol, "GST" is glutathione S-transferase, "h" is hour or hours, "H₂" is hydrogen gas, "HCl" is hydrochloric acid, "Hex" is hexanes, "H₂O" is water, "IC₅₀" is half maximal inhibitory concentration, "MeCN" is acetonitrile, "MeOH" is methanol, "MgSO₄" is magnesium sulfate, "MHz" is megahertz, "min" is minute or minutes, "MS" is mass spectrometry, "NADH" is nicotinamide adenine dinucleotide, "NaH" is sodium hydride, "NaHCO₃" is sodium bicarbonate, "Na₂SO₄" is sodium sulfate, "NH₄Cl" is ammonium chloride, "NMR" is nuclear magnetic resonance, "PBS" is phosphate buffered saline, "Pd/C" is palladium on carbon, "rt" is room temperature which is also known as "ambient temp," which will be understood to consist of a range of normal laboratory temperatures ranging from 15-25 °C, "sat'd" is saturated, "TEA" is triethylamine, "TFA" is trifluoroacetic acid, and "THF" is tetrahydrofuran.

30 General Chemistry

[000199] Exemplary compounds described herein are available by the general synthetic methods illustrated in the Schemes below, Intermediate preparations, and the accompanying Examples.

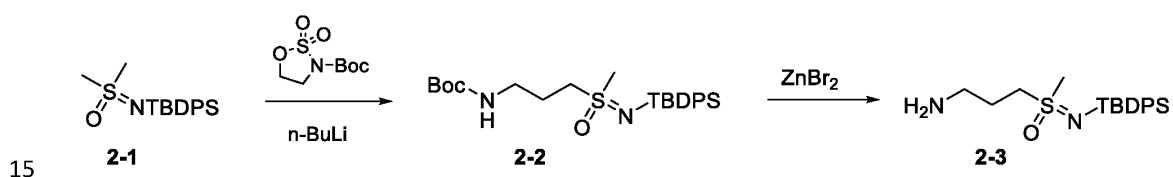
Synthetic Schemes

Scheme 1



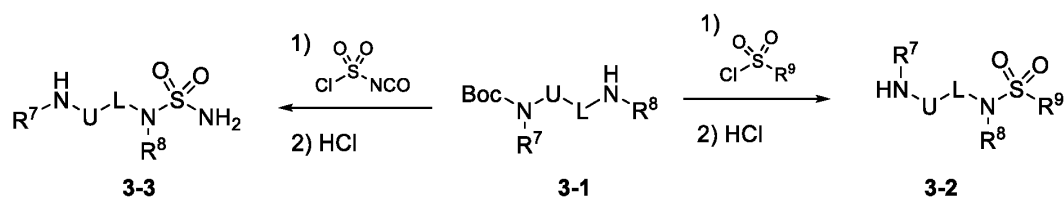
[000200] Scheme 1 illustrates an exemplary preparation of intermediate 1-7. Treatment of
 5 commercially available Z-L-H, 1-1 with acrylonitrile in the presence of base such as Triton B
 affords 1-4. Raney Ni catalyzed hydrogenation of 1-4 affords 1-7 (U = (CH₂)₃). In another
 embodiment, amines 1-1 react with bromides or iodides 1-2 (commercially available or
 synthesized by those skilled in the art) in the presence of base such as NaH or *tert*-BuOK to afford
 1-5. The Boc protecting group of 1-5 may be removed upon exposure to acid such as HCl or TFA
 10 to afford 1-7. In another embodiment, amines 1-1 react with bromides or iodides 1-3
 (commercially available or synthesized by those skilled in the art) in the presence of base such as
 NaH to afford 1-6. Hydrazinolysis of 1-6 with NH₂NH₂ affords 1-7.

Scheme 2



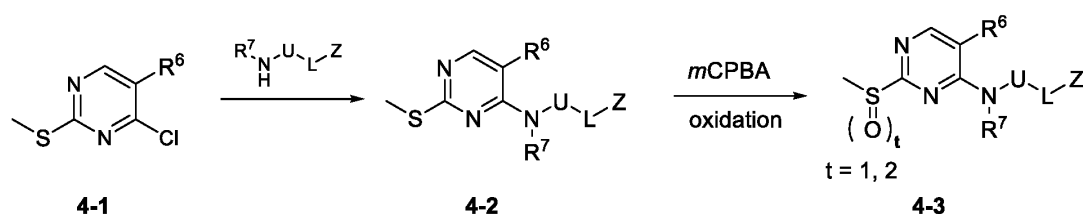
[000201] Scheme 2 illustrates an exemplary preparation of intermediate 2-3. ((*tert*-
 15 Butyldiphenylsilyl)imino)dimethyl-λ⁶-sulfanone 2-1 reacts with *tert*-butyl 1,2,3-oxathiazolidine-
 3-carboxylate 2,2-dioxide in the presence of base such as *n*-BuLi to afford *tert*-butyl (3-(*N*-(*tert*-
 butyldiphenylsilyl)-S-methylsulfonimidoyl)propyl)carbamate 2-2 which can be treated with
 20 ZnBr₂ to remove Boc group to afford (3-aminopropyl)((*tert*-butyldiphenylsilyl)imino)(methyl)-
 λ⁶-sulfanone 2-3.

Scheme 3



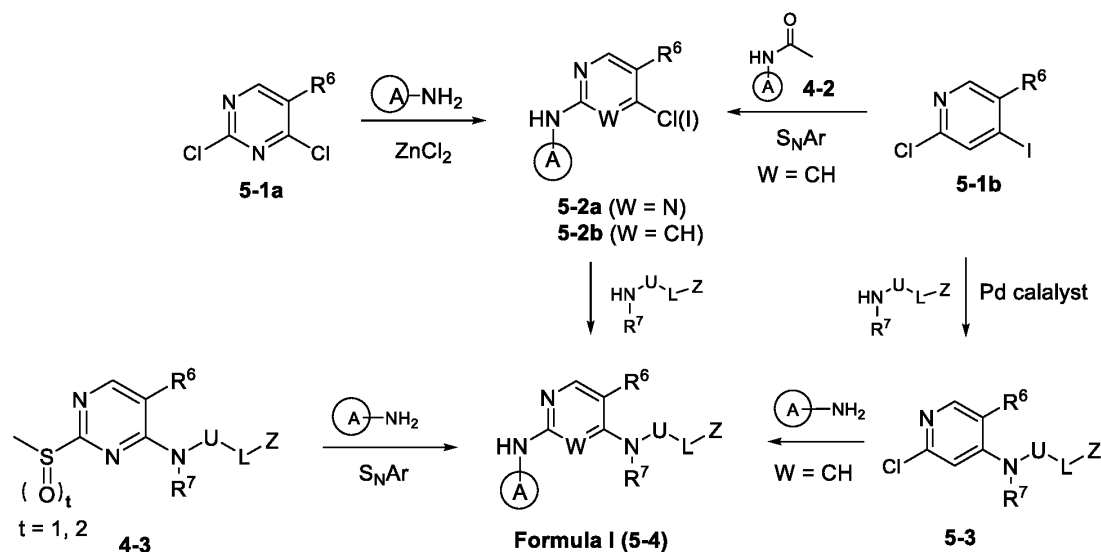
[000202] Scheme 3 illustrates an exemplary preparation of intermediates **3-2** and **3-3**. Diamines **3-1** (commercially available or synthesized by those skilled in the art) react with sulfonyl chloride R⁹SO₂Cl followed by deprotection with HCl to afford **3-2**. In another embodiment, diamines **3-1** (commercially available or synthesized by those skilled in the art) react with chlorosulfonyl isocyanate followed by deprotection with HCl to afford **3-3**.

Scheme 4



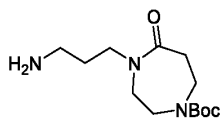
[000203] Scheme 4 illustrates an exemplary preparation of intermediates **4-3**. Compounds **4-1** (commercially available or synthesized by those skilled in the art) can be reacted with amines Z-L-U-NR⁷H (commercially available or synthesized by those skilled in the art, see schemes 1, 2, and 3) in the presence of base such as DIEA to afford **4-2**. Oxidation of **4-2** with *m*CPBA affords a mixture of sulfoxides and sulfones **4-3** (t = 1, 2).

Scheme 5



[000204] Scheme 4 illustrates an exemplary preparation of compounds of Formula I (5-4, W = N, CH). Compounds of Formula I (5-4, W = N, CH) can be prepared from four different intermediates, 4-3, 5-2a, 5-2b, and 5-3. Compounds 5-1a (commercially available or synthesized by those skilled in the art) reacts with amines A-NH₂ (commercially available or synthesized by those skilled in the art) in the presence of ZnCl₂ at temperature lower than 10 °C followed by SFC purification to afford 5-2a. S_NAr of compounds 5-2a with amines Z-L-U-NR⁷H (commercially available or synthesized by those skilled in the art, see schemes 1, 2, and 3) at elevated temperature in aprotic solvent such as 1,4-dioxane affords compounds of Formula I (5-4, W = N). Chlorides 5-1b (W = CH) react with 4-2 (commercially available or synthesized by those skilled in the art) in the presence of base such as NaH to afford 5-2b (W = CH). Intermediates 5-2b (W = CH) react with amines Z-L-U-NR⁷H (commercially available or synthesized by those skilled in the art) under Buchwald reaction conditions to afford compounds of Formula I (5-4, W = CH). In another embodiment, compounds 5-1b react with amines Z-L-U-NR⁷H (commercially available or synthesized by those skilled in the art) under Buchwald reaction conditions to afford 5-3 which can be reacted with amines A-NH₂ (commercially available or synthesized by those skilled in the art) to afford compounds of Formula I (5-4, W = CH). Compounds 4-3 react with amines A-NH₂ (commercially available or synthesized by those skilled in the art) by a nucleophilic substitution reaction, typically performed in an aprotic solvent at temperatures ranging from ambient temp to 150 °C to afford compounds of Formula I (5-4, W = N).

Preparation of intermediate **A1**: *tert*-butyl 4-(3-aminopropyl)-5-oxo-1,4-diazepane-1-carboxylate

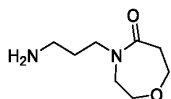


[000205] A solution of *tert*-butyl 5-oxo-1,4-diazepane-1-carboxylate (17.5 g, 82 mmol) and benzyl(trimethyl)ammonium;hydroxide (3.71 mL, 8.2 mmol, 40% purity) in DMF (700 mL) was added prop-2-enenitrile (10.8 mL, 163 mmol). The mixture was stirred at 52 °C for 5 h and then the reaction mixture was concentrated under reduced pressure. The reaction mixture was diluted with H₂O (10 mL), filtered and the filtrate was extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0% to 40% EtOAc/pet-ether) to obtain *tert*-butyl 4-(2-cyanoethyl)-5-oxo-1,4-diazepane-1-carboxylate (21.3 g, 44%) as a brown solid. ¹H NMR (400 MHz, CDCl₃): δ 3.56-3.63 (m, 4H), 3.46-3.56 (m, 4H), 2.56-2.64 (m, 4H), 1.40 (s, 9H); LC-MS (ESI) m/z: 212.1 (M+H⁺).

[000206] A suspension of *tert*-butyl 4-(2-cyanoethyl)-5-oxo-1,4-diazepane-1-carboxylate (5.0 g, 18.7 mmol) in MeOH (120 mL) was treated with Raney Ni (1.6 g, 1.87 mmol) and 28% NH₄OH (5.2 mL, 37.4 mmol). The mixture was stirred under H₂ under 50 Psi at rt for 15 h. The reaction was filtered and the filtrate was concentrated to give *tert*-butyl 4-(3-aminopropyl)-5-oxo-1,4-diazepane-1-carboxylate (**A1**, 4.8 g, 75%) as a brown solid. ¹H NMR (400 MHz, CDCl₃): δ 3.56 (d, J = 4.4 Hz, 4H), 3.47 (m, 2H), 3.36-3.41 (m, 2H), 2.66 (m, 4H), 1.63 (m, 2H), 1.46 (s, 9H); LC-MS (ESI) m/z: 272.2 (M+H⁺).

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Preparation of intermediate **A2**: 4-(3-aminopropyl)-1,4-oxazepan-5-one



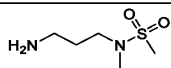
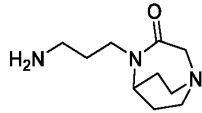
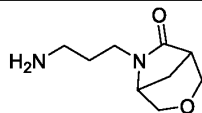
[000207] A solution of 1,4-oxazepan-5-one (10 g, 87 mmol) in dry THF (400 mL) at 0 °C was treated with sodium hydride (3.0 g, 130 mmol) portion wise under nitrogen atmosphere. The reaction mixture was stirred for 15 min at 0 °C then *tert*-butyl (3-bromopropyl) carbamate (21 g, 87 mmol) was added. The solution was continued stirred from 0 °C rt for 16 h. The reaction mixture was quenched with saturated solution of NH₄Cl (200 mL) and then the solution was extracted with EtOAc (2 x 150 mL). The combined organic extract was washed with brine (150 mL), dried over anhydrous Na₂SO₄, and filtered under reduced pressure. The crude was purified by silica gel column chromatography (40 to 50 % EtOAc/hexane, 15 CV's) to obtain *tert*-butyl (3-(5-oxo-1,4-oxazepan-4-yl)propyl) carbamate (12 g, 50 % yield) as yellow liquid. The product was dissolved in DCM (50 mL) and treated with 4 N HCl in 1,4-dioxane (4 eq). The mixture was stirred

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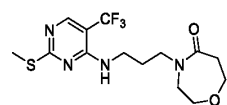
at rt for 3 h and concentrated, dried under high vacuum to obtain 4-(3-aminopropyl)-1,4-oxazepan-5-one HCl salt (**A2**, 100 % yield). ¹H NMR (400 MHz, DMSO-d₆): δ 8.09 (brs, 3H), 3.62 (m, 4H), 3.49 (m, 2H), 3.35 (t, J = 6.8 Hz, 2H), 2.73 (m, 2H), 2.62 (t, J = 4.8 Hz, 2H), 1.78 (m, 2H); LC-MS (ESI) m/z: 173.2 (M+H⁺).

5

[000208] The following compounds are prepared essentially by method of preparation intermediates **A1** and **A2**.

Ex No	Product	Yield (%)	¹ H NMR (400 MHz, DMSO-d ₆): δ	LC-MS (m/z: M+H ⁺)
A3		crude	4.98 (br s, 1H), 3.14-3.27 (m, 4H), 2.85 (s, 3H), 2.81 (s, 3H), 1.75 (m, 2H), 1.44 (s, 9H).	211.1
A4	 HCl salt	32	11.93 (s, 1H), 8.15 (s, 3H), 4.08 (s, 2H), 3.86 (m, 1H), 3.44 (t, J = 6.8 Hz, 2H), 3.26-3.40 (m, 4H), 2.74 (m, 2H), 2.09-2.23 (m, 4H), 1.82 (m, 2H).	198.2
A5	 HCl salt	56	7.94 (br s, 3H), 3.86 (d, J = 2.6 Hz, 1H), 3.24 (m, 1H), 2.88 (m, 1H), 2.71 (m, 2H), 2.60 (dd, J = 1.6, 4.0 Hz, 1H), 1.66-1.83 (m, 5H), 1.52 (m, 1H), 1.27-1.35 (m, 2H).	185.2

Preparation of intermediate **B1**: 4-(3-((2-(methylthio)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-1,4-oxazepan-5-one

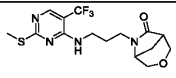
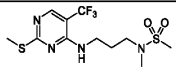
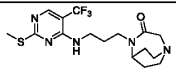
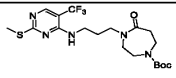
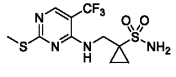


[000209] A solution of 4-(3-aminopropyl)-1,4-oxazepan-5-one hydrochloride (**A2**, 3.0 g, 17.4 mmol) in DMF (60 mL) was treated with DIEA (15.5 ml, 87.2 mmol) at 0 °C and stirred for 15 min. Then 4-chloro-2-(methylthio)-5-(trifluoromethyl) pyrimidine (6.0 g, 26.2 mmol) was added and stirring continued from 0 °C to rt for 16 h. The reaction mixture was quenched with ice water (120 mL) and extracted with EtOAc (3x). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (40 to 50 % EtOAc/hexanes) to obtain 4-(3-((2-(methylthio)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-1,4-oxazepan-5-one (**B1**, 3.0 g, 47%) as yellow liquid. ¹H NMR (400 MHz, DMSO-d₆): δ 8.27 (s, 1H), 7.53 (br t, J = 5.6 Hz, 1H), 3.66-3.68 (m, 2H), 3.63-3.66 (m, 2H), 3.46-

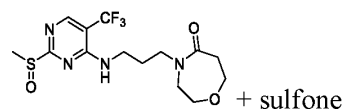
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3.51 (m, 2H), 3.41-3.45 (m, 2H), 3.33-3.36 (m, 2H), 2.60-2.67 (m, 2H), 2.48 (s, 3H), 1.69 (m, 2H); LC-MS (ESI) m/z: 365.1 (M+H⁺).

[000210] The following compounds are prepared essentially by method of preparation
5 intermediate **B1**.

Ex No	Product	Yield (%)	¹ H NMR (400 MHz, DMSO-d ₆): δ	MS (m/z: M+H ⁺)
B2		76	8.26 (s, 1H), 7.55 (t, J = 5.9 Hz, 1H), 3.66-3.72 (m, 2H), 3.63 (m, 1H), 3.39-3.57 (m, 5H), 2.98 (m, 1H), 2.47 (s, 3H), 2.28 (m, 1H), 2.20 (m, 1H), 1.89 (m, 1H), 1.65-1.83 (m, 2H).	377.0
B3		75	8.26 (s, 1H), 7.46 (t, J = 5.6 Hz, 1H), 3.45-3.50 (m, 2H), 3.07 (t, J = 6.8 Hz, 2H), 2.85 (s, 3H), 2.74 (s, 3H), 2.47 (s, 3H), 1.77-1.84 (m, 2H).	359.0
B4		78	8.26 (s, 1H), 7.58 (t, J = 6.0 Hz, 1H), 3.54 (s, 2H), 3.40-3.50 (m, 3H), 3.34 (t, J = 6.5 Hz, 2H), 2.86 (m, 4H), 2.47 (s, 3H), 1.93-2.05 (m, 2H), 1.85 (m, 2H), 1.71 (h, J = 6.5 Hz, 2H).	390.0
B5		66	8.25 (s, 1H), 7.52 (br t, J = 5.6 Hz, 1H), 3.39-3.48 (m, 8H), 3.29-3.31 (m, 2H), 2.53-2.60 (m, 2H), 2.47 (s, 3H), 1.69 (m, 2H), 1.39 (s, 9H).	464.2
B6		67		343.0

Preparation of intermediate **C1**: 4-(3-((2-(methylsulfinyl)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-1,4-oxazepan-5-one

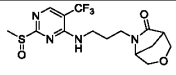
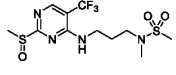
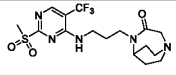
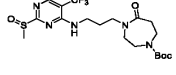
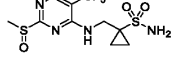


10 **[000211]** A solution of 4-(3-((2-(methylthio)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-1,4-oxazepan-5-one (**B1**, 3.0 g, 8.2 mmol) in DCM (60 mL) at 0 °C, *m*CPBA (2.0 g, 11.5 mmol) was added and stirred from 0 °C to rt for 3 h. The reaction mixture was washed with sat'd NaHCO₃ (aq). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to obtain a mixture of 4-(3-((2-(methylsulfinyl)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-1,4-oxazepan-5-one and 4-(3-((2-

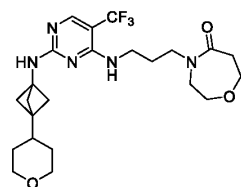
15

(methylsulfonyl)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-1,4-oxazepan-5-one (3.0 g, 95%, 9:1) as light yellow semi-solid. ¹H NMR (400 MHz, DMSO-d₆): δ 8.59 (s, 1H), 7.94 (br s, 1H), 3.60 (m, 4H), 3.45 (m, 4H), 3.36 (m, 2H), 2.88 (s, 3H), 2.63 (m, 2H), 1.70 (m, 2H); LC-MS (ESI) m/z: 381.3 (M+H⁺) and 397.3.

- 5 **[000212]** The following compounds are prepared essentially by method of preparation intermediate C1.

Ex No	SM	Product	Yield (%)	¹ H NMR (400 MHz, DMSO-d ₆): δ	MS (m/z: M+H ⁺)
C2	B2	 + sulfone	100	No Data	393.2 415.2
C3	B3	 + sulfone	86	8.57 (d, J = 1.1 Hz, 1H), 7.91 (t, J = 5.7 Hz, 1H), 3.51 (m, 2H), 3.07 (t, J = 7.0 Hz, 2H), 2.83 (s, 3H), 2.83 (s, 3H), 2.73 (s, 3H), 1.82 (m, 2H).	375.0 391.0
C4	B4	 + sulfone	crude		422.2
C5	B5	 + sulfone	72		480.2
C6	B6	 + sulfone	77	8.62 (d, J = 1.0 Hz, 1H), 7.87 (m, 1H), 7.80 (t, J = 5.9 Hz, 1H), 7.52 (t, J = 8.1 Hz, 1H), 7.01 (s, 2H), 4.06 (dd, J = 5.9, 14.8 Hz, 1H), 3.95 (dd, J = 5.9, 14.6 Hz, 1H), 2.83 (s, 3H), 1.00-1.18 (m, 4H).	359.0

Preparation of Example 1: 4-(3-((2-((3-(tetrahydro-2H-pyran-4-yl)bicyclo[1.1.1]pentan-1-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-1,4-oxazepan-5-one

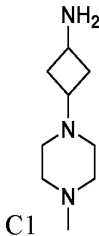
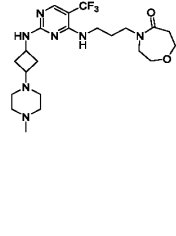
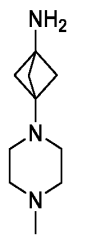
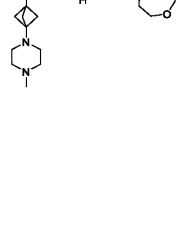
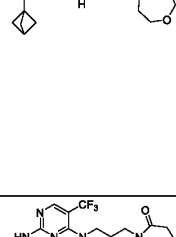
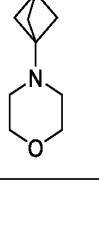


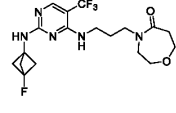
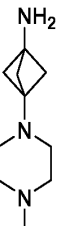
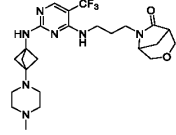
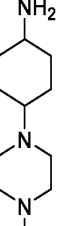
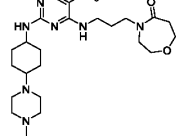
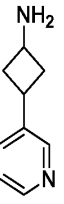
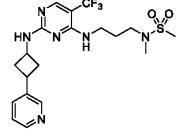
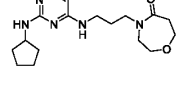
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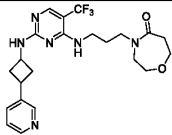
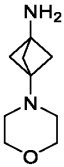
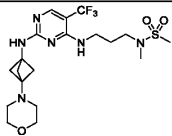
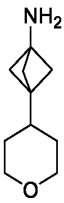
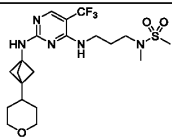
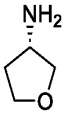
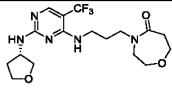
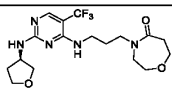
[000213] A solution of 3-(tetrahydro-2H-pyran-4-yl)bicyclo[1.1.1]pentan-1-amine hydrochloride (0.027 g, 0.13 mmol) and 4-(3-((2-(methylsulfinyl)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-1,4-oxazepan-5-one (**C1**, 0.050 g, 0.13 mmol) in DMSO (1 mL) was treated with DIEA (one drop, 3 eq). The reaction mixture was heated to 50 °C overnight. The reaction was

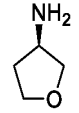
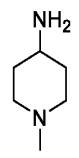
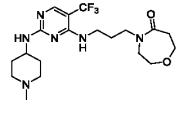
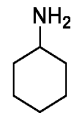
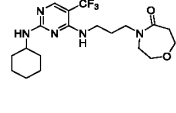
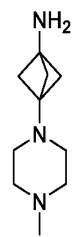
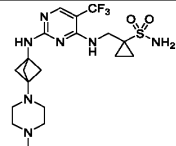
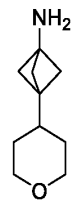
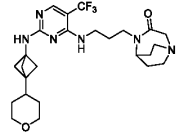
cooled to rt and then diluted with water. The solids were collected to obtain 4-(3-((2-((3-(tetrahydro-2H-pyran-4-yl)bicyclo[1.1.1]pentan-1-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-1,4-oxazepan-5-one (**1**, 0.038 g, 60%) as a beige solid. ¹H NMR (400 MHz, DMSO-d₆): δ 7.97 (s, 1H), 7.89 (s, 1H), 6.92 (s, 1H), 3.77-3.88 (m, 2H), 3.63 (m, 4H), 3.45 (m, 2H), 3.31-3.39 (m, 2H), 3.24 (dt, J = 2.1, 11.8 Hz, 2H), 2.58-2.68 (m, 2H), 1.83 (s, 6H), 1.81-1.85 (br m, 1H), 1.54-1.68 (m, 4H), 1.44 (br d, J = 12.4 Hz, 2H), 1.12 (m, 2H); MS (ESI) m/z: 484.2 (M+H⁺).

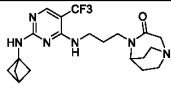
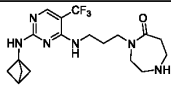
[000214] The following compounds are prepared essentially by method of preparation example 1.

Ex No	SM	Product	Yield (%)	¹ H NMR (400 MHz, DMSO-d ₆): δ	MS (m/z: M+H ⁺)
2			36	8.00 (m, 1H), 7.61 (m, 1H), 6.84 (m, 1H), 4.22 (m, 1H), 3.64 (m, 4H), 3.43-3.50 (m, 2H), 2.60-2.67 (m, 2H), 2.12-2.43 (m, 13H), 2.05 (br s, 2H), 1.72 (m, 3H).	486.2
3			28	7.98 (br s, 2H), 6.94 (br s, 1H), 3.61-3.68 (m, 4H), 3.44-3.50 (m, 2H), 3.23-3.41 (br m, 4H), 2.60-2.68 (m, 2H), 2.30-2.45 (br m, 8H), 2.20 (s, 3H), 1.98 (s, 3H), 1.93-2.02 (br m, 2H), 1.90 (m, 1H), 1.60-1.70 (br m, 2H).	498.2
4			82	7.88-8.06 (m, 2H), 6.90 (br s, 1H), 3.58-3.66 (m, 4H), 3.45 (m, 2H), 3.34-3.42 (m, 2H), 3.33 (m, 2H), 2.58-2.67 (m, 2H), 2.41 (d, J = 4.2 Hz, 1H), 2.03 (s, 6H), 1.55-1.72 (m, 2H).	400.0
5			27	8.00 (br s, 1H), 6.99 (br s, 1H), 3.62-3.69 (m, 3H), 3.57-3.62 (m, 4H), 3.43-3.52 (m, 2H), 3.26-3.43 (m, 6H), 2.58-2.72 (m, 2H), 2.35-2.45 (br m, 4H), 2.02 (s, 6H), 1.56-1.76 (br m, 2H).	485.2

6	C1 		8	8.09 (s, 1H), 8.01 (s, 1H), 6.98 (s, 1H), 3.63 (dd, J = 6.5, 3.4 Hz, 4H), 3.46 (t, J = 4.3 Hz, 2H), 3.38 (d, J = 5.7 Hz, 1H), 3.34 (d, J = 6.3 Hz, 1H), 2.69 – 2.54 (m, 2H), 2.35 (d, J = 2.2 Hz, 6H), 1.66 (s, 2H).	418.2
7	C2 		8	8.17 (s, 1H), 7.98 (d, J = 8.9 Hz, 1H), 6.96 (s, 1H), 3.59-3.74 (m, 3H), 3.53 (d, J = 10.4 Hz, 1H), 3.31-3.50 (m, 4H), 2.99 (dt, J = 6.2, 13.2 Hz, 1H), 2.38 (br s, 7H), 2.28 (d, J = 3.4 Hz, 1H), 2.19 (s, 5H), 1.98 (s, 6H), 1.88 (d, J = 10.6 Hz, 1H), 1.63-1.83 (m, 2H).	510.2
8	C1 		24	7.92-8.04 (br m, 1H), 7.25 (br m, 0.7H), 6.97 (br m, 0.3H), 6.88 (br m, 0.7H), 6.75 (br m, 0.3H), 3.93 (br m, 1H), 3.56-3.68 (m, 4H), 3.45 (m, 2H), 3.35 (br m, 4H), 2.65-2.98 (br m, 8H), 2.61 (m, 2H), 2.30-2.45 (br m, 2H), 1.92 (m, 1H), 1.41-1.91 (br m, 10H), 1.24 (m, 1H).	514.2
9	C3 		6	8.50 (s, 1H), 8.40 (dd, J = 1.6, 4.7 Hz, 1H), 7.99 (s, 1H), 7.82 (d, J = 6.1 Hz, 1H), 7.74 (dt, J = 8.0, 2.1 Hz, 1H), 7.30-7.38 (m, 1H), 4.45 (d, J = 31.7 Hz, 1H), 3.58 (s, 1H), 3.38 (d, J = 6.8 Hz, 3H), 3.04 (dd, J = 6.6, 13.2 Hz, 3H), 2.83 (d, J = 12.1 Hz, 3H), 2.73 (d, J = 2.5 Hz, 1H), 2.67 (s, 2H), 2.37-2.47 (m, 2H), 1.77 (s, 3H).	459.2
10	C1 		96	8.03 (br s, 0.3H), 7.96 (s, 0.7H), 7.31 (m, 0.7H), 7.09 (m, 0.3H), 6.86 (m, 0.7H), 6.74 (br m, 0.3H), 4.05-4.27 (br m, 1H), 3.59-3.68 (m, 4H), 3.42-3.50	402.2

				(m, 2H), 3.29-3.41 (m, 4H), 2.57-2.69 (m, 2H), 1.79-1.94 (br m, 2H), 1.57-1.74 (m, 4H), 1.40-1.50 (s, 4H).	
11	C1 		48	8.49 (d, J = 10.1 Hz, 1H), 8.39 (td, J = 4.5, 1.6 Hz, 1H), 7.98 (d, J = 6.2 Hz, 1H), 7.59-7.84 (m, 2H), 7.34 (dt, J = 4.9, 8.6 Hz, 1H), 6.75-6.97 (m, 1H), 4.24-4.55 (m, 1H), 3.48-3.77 (m, 5H), 3.46 (s, 1H), 3.14-3.42 (m, 8H), 2.53-2.72 (m, 2H), 2.43 (m, 1H), 1.96-2.19 (m, 1H), 1.55-1.78 (m, 1H).	465.2
12	C3 		11	7.99 (s, 1H), 3.54-3.61 (m, 4H), 3.44 (s, 2H), 3.08 (t, J = 6.9 Hz, 2H), 2.84 (s, 3H), 2.74 (s, 3H), 2.36 (t, J = 4.6 Hz, 4H), 1.99 (s, 6H), 1.69-1.86 (m, 2H).	479.2
13	C3 		35	7.97 (s, 1H), 7.90 (s, 1H), 6.78 (s, 1H), 3.76-3.91 (m, 2H), 3.42 (s, 2H), 3.24 (td, J = 2.0, 11.7 Hz, 2H), 3.06 (t, J = 6.9 Hz, 2H), 2.83 (s, 3H), 2.72 (s, 3H), 1.83 (s, 6H), 1.76 (q, J = 7.0 Hz, 2H), 1.62 (m, 1H), 1.45 (d, J = 12.4 Hz, 2H), 1.12 (m, 2H).	478.2
14	C1 		80	8.04 (br s, 0.3H), 8.00 (br s, 0.7H), 7.57 (br m, 0.7H), 7.34 (br m, 0.3H), 6.95 (br m, 0.7H), 6.82 (br m, 0.3H), 4.26-4.45 (br m, 1H), 3.84-3.91 (m, 1H), 3.76-3.84 (m, 1H), 3.66-3.74 (m, 1H), 3.60-3.66 (m, 4H), 3.52 (m, 1H), 3.43-3.48 (m, 2H), 3.32-3.41 (m, 4H), 2.57-2.67 (m, 2H), 2.09 (m, 1H), 1.86 (m, 1H), 1.59-1.75 (br m, 2H).	404.2
15	C1		95	8.04 (br s, 0.3H), 8.00 (br s, 0.7H), 7.57 (br m, 0.7H), 7.34 (br m, 0.3H), 6.95	404.2

				(br m, 0.7H), 6.82 (br m, 0.3H), 4.26-4.45 (br m, 1H), 3.84-3.91 (m, 1H), 3.76-3.84 (m, 1H), 3.66-3.74 (m, 1H), 3.60-3.66 (m, 4H), 3.52 (m, 1H), 3.43-3.48 (m, 2H), 3.32-3.41 (m, 4H), 2.57-2.67 (m, 2H), 2.09 (m, 1H), 1.86 (m, 1H), 1.59-1.75 (br m, 2H).	
16	C1 		96	8.02 (br s, 0.4H), 7.95 (s, 0.6H), 7.21 (br m, 0.6H), 7.00 (br m, 0.4H), 6.86 (br m, 0.6H), 6.75 (br m, 0.4H), 3.60-3.69 (m, 5H), 3.43-3.51 (m, 2H), 3.28-3.38 (m, 4H), 2.67-2.78 (m, 2H), 2.57-2.67 (m, 2H), 2.15 (s, 3H), 1.84-1.99 (m, 2H), 1.70-1.83 (m, 2H), 1.56-1.70 (m, 2H), 1.40-1.55 (m, 2H).	431.2
17	C1 		95	8.01 (br s, 0.4H), 7.94 (br s, 0.6H), 7.17 (br m, 0.6H), 6.95 (br m, 0.4H), 6.85 (br m, 0.6H), 6.72 (br m, 0.4H), 3.56-3.78 (m, 5H), 3.40-3.50 (m, 2H), 3.27-3.40 (m, 4H), 2.57-2.68 (m, 2H), 1.75-1.92 (br m, 2H), 1.50-1.74 (br m, 5H), 1.00-1.35 (m, 5H).	416.2
18	C6 		66	8.16 (s, 1H), 8.10 (s, 1H), 8.03 (s, 1H), 7.09 (s, 1H), 6.60 (s, 1H), 4.02 (br m, 2H), 2.38 (br s, 8H), 2.19 (s, 3H), 1.97 (s, 6H), 1.16 (m, 2H), 0.88 (m, 2H).	476.2
19	C4 		29	7.98 (br s, 1H), 7.90 (br s, 1H), 7.03 (s, 1H), 3.85 (m, 2H), 3.55 (s, 2H), 3.22-3.50 (m, 9H), 2.79-2.93 (m, 3H), 1.98 (dd, J = 7.4, 14.3 Hz, 2H), 1.85 (s, 6H), 1.59-1.74 (m, 3H), 1.41-1.50 (m, 2H), 1.14 (m, 2H).	509.2

20	C4 		36	7.97 (d, J = 16.9 Hz, 2H), 7.00 (s, 1H), 3.55 (s, 2H), 3.46 (m, 1H), 3.32-3.42 (m, 4H), 2.78-2.94 (m, 4H), 2.42 (s, 1H), 2.05 (s, 6H), 1.91-2.01 (m, 2H), 1.80-1.89 (m, 2H), 1.70 (m, 2H).	425.2
21	C5  HCl		26	9.34 (s, 1H), 7.97 (s, 1H), 6.93 (s, 1H), 3.40 (m, 10H), 2.42 (m, 2H), 2.10 (m, 10H), 1.64 (s, 2H).	399.2

Biochemical assay for ULK1 (SEQ. ID NO: 1)

[000215] Activity of ULK1 kinase was determined spectroscopically using a coupled pyruvate kinase/lactate dehydrogenase assay that continuously monitors the ATP hydrolysis-dependent oxidation of NADH (*e.g.*, Schindler *et al.* Science (2000) 289: 1938-1942). Assays were conducted in 384-well plates (100 μ L final volume) using 0.1 nM ULK1 (from Beryllium), 0.075 mM peptide substrate (YANWLAASIYLDGKKK), 1.5 units pyruvate kinase, 2.1 units lactate dehydrogenase, 1 mM phosphoenol pyruvate, 0.28 mM NADH and 1 mM ATP in assay buffer (100 mM Tris, pH 7.5, 15 mM MgCl₂, 0.5 mM DTT, 0.004% (w/v) BSA, and 0.004% Triton X-100). Inhibition of ULK1 was measured by adding serial diluted test compound (final assay concentration of 1% DMSO). A decrease in absorption at 340 nm was monitored continuously for 6 h at 30 °C on a multi-mode microplate reader (BioTek). The reaction rate was calculated using the 2-3 h time frame. The reaction rate at each concentration of compound was converted to percent inhibition using controls (*i.e.*, reaction with no test compound and reaction with a known inhibitor) and IC₅₀ values were calculated using software routines in Prism (GraphPad software).

ULK1 protein sequence (residues 1-283; SEQ. ID NO: 1)

MEPGRGGTETVGKFEFSRKDLIGHGAFVVFVKGRHRAAHDLEVAVKCINKKNLAKSQT
 LLGKEIKILKELKHENIVALYDFQEMANSVYLVMEYCNGGDLADYLHAMRTLSEDTRL
 FLQQIAGAMRLLHSKGIIHRDLKPQNILLSNPAGRRANPNSIRVKIADFGFARYLQSNMM
 AATLCGSPMYMAPEVIMSQHYDGKADLWSIGTIVYQCLTGKAPFQASSPQDLRLFYEK
 NKTLVPTIPRETSAPLRQLLLALLQRNHKDRMDFDEFFHHPFLDASPS

Biochemical assay for ULK2 (SEQ. ID NO: 2)

[000216] Activity of ULK2 kinase was determined spectroscopically using a coupled pyruvate kinase/lactate dehydrogenase assay that continuously monitors the ATP hydrolysis-dependent oxidation of NADH (*e.g.*, Schindler *et al.* Science (2000) 289: 1938-1942). Assays

5 were conducted in 384-well plates (100 mL final volume) using 1 nM ULK2 (Signal Chem U02-11G), 200 mM ULKtide, 1.5 units pyruvate kinase, 2.1 units lactate dehydrogenase, 1 mM phosphoenol pyruvate, 0.28 mM NADH and 1 mM ATP in assay buffer (100 mM Tris, pH 7.5, 15 mM MgCl₂, 0.5 mM DTT, 0.1% octyl-glucoside, 0.002% (w/v) BSA, and 0.002% Triton X-100). Inhibition of ULK2 was measured by adding serial diluted test compound (final assay

10 concentration of 1% DMSO). A decrease in absorption at 340 nm was monitored continuously for 6 h at 30 °C on a multi-mode microplate reader (BioTek). The reaction rate was calculated using the 2-3 h time frame. The reaction rate at each concentration of compound was converted to percent inhibition using controls (*i.e.*, reaction with no test compound and reaction with a known inhibitor) and IC₅₀ values were calculated by fitting a four-parameter sigmoidal curve to the data

15 using Prism (GraphPad software).

ULK2 protein sequence (residues 1-306 with N-terminal GST and His tag; SEQ. ID NO: 2)

MSPILGYWKIKGLVQPTRLLEYLEEKYEEHLYERDEGDKWRNKKFELGLEFPNLPYYI
DGDVKLTQSMAIRYIADKHNMLGGCPKERAIEISMLEGAVLDIRYGVSR IAYS KDFETL

20 KVDFLSKLPEMLKMFEDRLCHKTYLNGDHVTHPDFMLYDALDVVLYMDPMLCLDAFPK
LVCFKKR IEAIPQIDKYLKSSKYIAWPLQGWQATFGGGDHPPKSDLEVLFQGPEFMEVV
GDFEYSKRDLVGHGAFVVFGRHRQKTDWEVAIKSINKKNLSKSKILLGKEIKILKEL
QHENIVALYDVQELPNSVFLVMEYCNGGDLADYLQAKGTLSED TIRVFLHQIAAAMRIL
HSKGIIHRDLKPQNILLSYANRRKSSVSGIRIKIADFGFARYLHSNMMAATLCGSPMYMA

25 PEVIMSQHYDAKADLWSIGTVIYQCLVGKPPFQANSPQDLRMFYEKNRSLMPSIPRETSP
YLANLLLGLLQRNQKDRMDFEAFFSHPFLEQGPVKKSCPVPVPMYSGSVSGSSCGSSPS
CRFASHHHHHH

Table 1. Inhibition of biochemical activity of ULK1 and ULK2 kinases by exemplary compounds.

Ex No	ULK1	ULK2	Ex No	ULK1	ULK2
1	+		16	+	
2	+++	+	17	++	+
3	++++	++	18	+	
4	+++	++	19	+	
5	++	+	20	++	+ ⁵
6	++	+	21	+	
7	++++	++			
8	+++	+			
9	++++	++			
10	+				
11	+				
12	+				
13	+				
14	+++	+			
15	+				

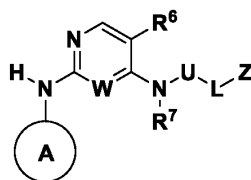
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[000217] For Table 1, “++++” refers to an IC₅₀ less than or equal to 100 nM; “+++” refers to an IC₅₀ greater than 100 nM and less than or equal to 500 nM; “++” refers to an IC₅₀ greater than 500 nM and less than or equal to 1000 nM; and “+” refers to an IC₅₀ greater than 1000 nM.

CLAIMS

What is claimed:

1. A compound represented by Formula (I):



Formula (I)

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

A is selected from the group consisting of cycloalkyl and heterocyclyl;

W is selected from the group consisting of N and CH;

- 10 U is selected from the group consisting of C(=O), alkyl, and heterocyclyl, or U is absent, or wherein U and R⁷ taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 10 atoms in the ring structure;

L is selected from the group consisting of a bond, alkyl, cycloalkyl, and heterocyclyl;

- 15 Z is selected from the group consisting of H, cyano, -N(R⁸)SO₂R⁹, -N(R⁸)C(=O)R⁹, -N(R¹⁸)SO₂NR¹⁹R²⁸, -SO₂R²⁹, -S(O)(=NH)-R¹⁰, and optionally substituted heterocyclyl, wherein the optionally substituted heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of R³¹,

or wherein two occurrences of R³¹ taken together with the carbon atoms to which they are attached form an optionally substituted ring having 5 to 8 atoms in the ring structure;

- 20 R⁶ is selected from the group consisting of halogen, cyano, alkyl, haloalkyl, cycloalkyl, and heterocyclyl;

R⁷ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

R⁸ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

R⁹ is selected from the group consisting of amino, alkyl, cycloalkyl, and heterocyclyl,

- 25 or wherein R⁸ and R⁹ taken together with the nitrogen and, sulfur or carbon atoms to which they are attached, form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure;

R¹⁰ is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

R¹⁸ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

- 30 R¹⁹ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

R²⁸ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl,

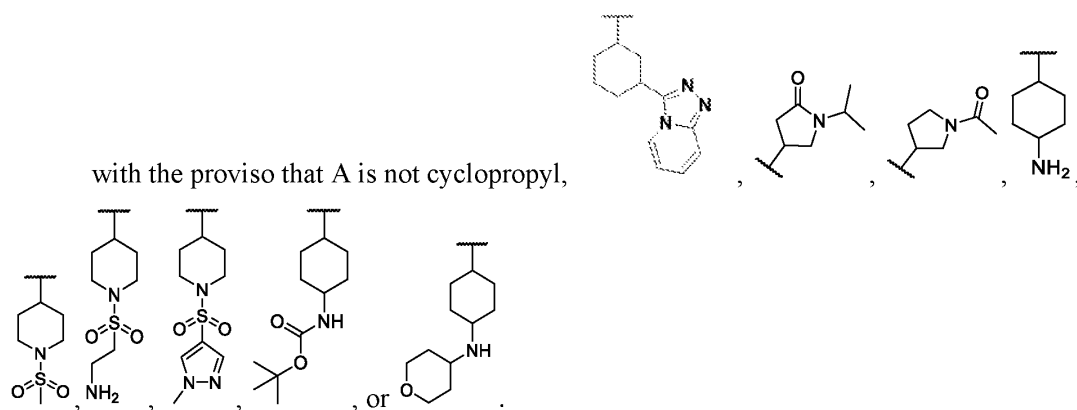
or wherein R^{18} and R^{28} taken together with the nitrogen atoms to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure,

or wherein R^{19} and R^{28} taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure;

- 5 R^{29} is selected from the group consisting of amino, alkyl, cycloalkyl, and heterocyclyl; and

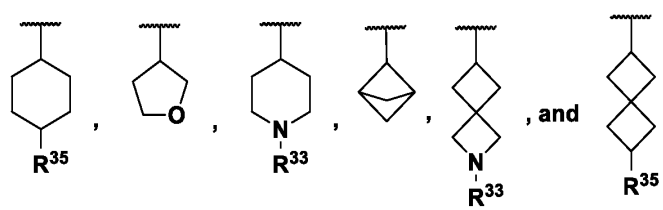
R^{31} is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

- wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, at each occurrence, is optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone, sulfonamide, heterocyclyl, or heteroaryl,



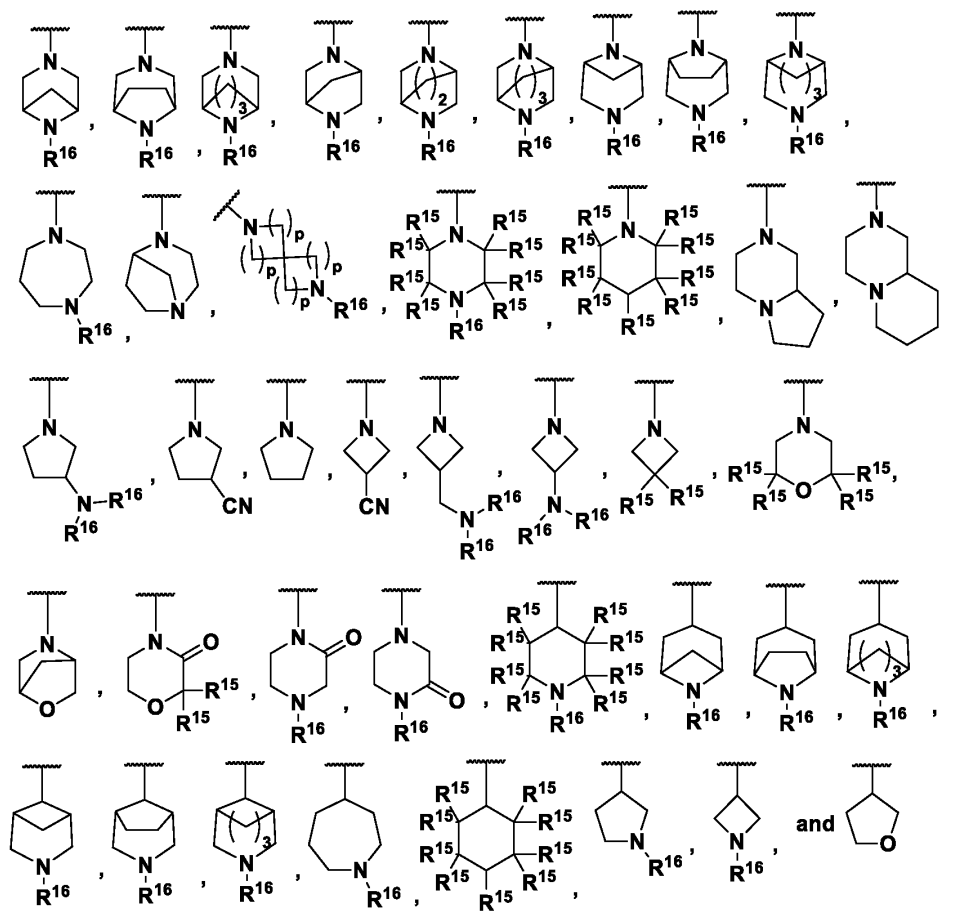
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2. The compound of claim 1, wherein A is selected from the group consisting of



- wherein each occurrence of R^{33} is independently selected from the group consisting of H, alkyl, haloalkyl, cycloalkyl, and heterocyclyl, and each occurrence of R^{35} is independently selected from the group consisting of H, halogen, alkyl, and heterocyclyl.

3. The compound of claim 2, wherein R^{35} and R^{33} , each individually, is selected from the group consisting of

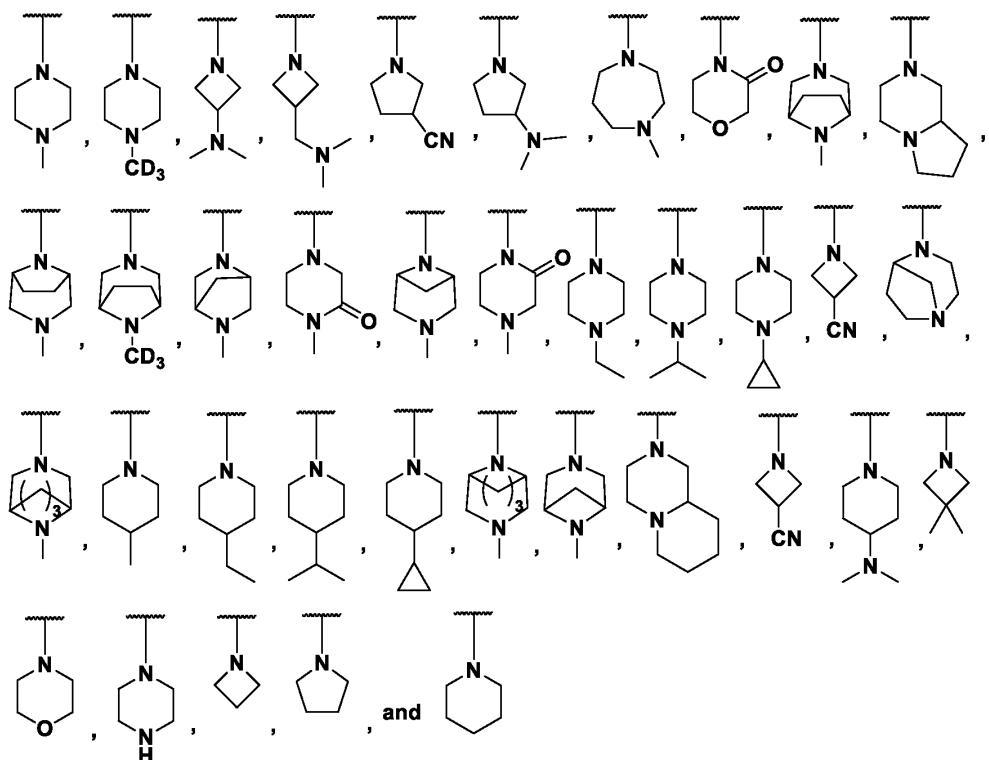


wherein R¹⁵, at each occurrence, is independently selected from the group consisting of H, halogen, amino, cyano, alkyl, cycloalkyl, and heterocyclyl, or wherein two R¹⁵, taken together with the carbon atom to which they are attached form an optionally substituted ring having from 4 to 6 atoms in the ring structure;

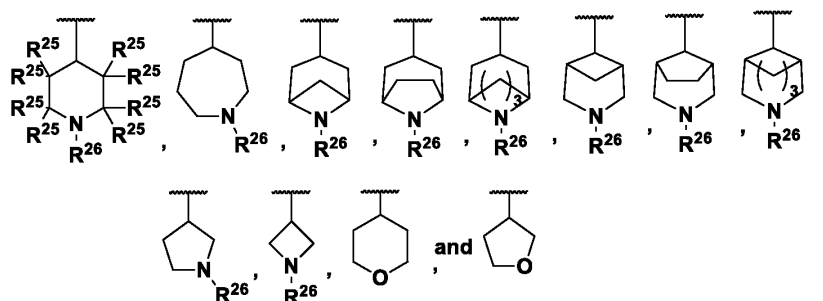
R¹⁶, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl, or wherein two R¹⁶, taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure; and

10 p , at each occurrence, is independently 1, 2, or 3;

wherein the alkyl, cycloalkyl, or heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone, sulfonamide, heterocyclyl, or heteroaryl.



6. The compound of claim 3, wherein R^{16} is selected from the group consisting of H, alkyl, alkylamino, cycloalkyl,



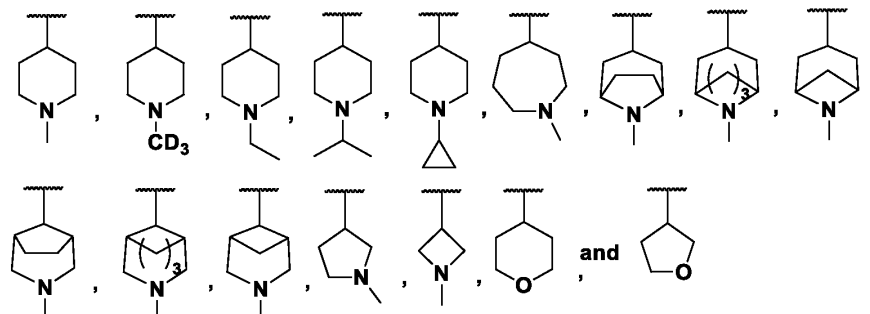
5 wherein R^{25} , at each occurrence, is independently selected from the group consisting of H, halogen, amino, cyano, alkyl, cycloalkyl, and heterocyclyl, or wherein two R^{25} , taken together with the carbon atom to which they are attached form an optionally substituted ring having from 4 to 6 atoms in the ring structure; and

10 R^{26} is independently selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

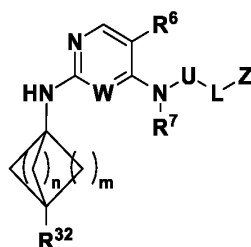
wherein the alkyl, cycloalkyl, or heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, hydroxyalkyl,

cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone, sulfonamide, heterocyclyl, or heteroaryl.

7. The compound of claim 6, wherein R¹⁶ is selected from the group consisting of



5 8. A compound represented by Formula (Ia):



Formula (Ia)

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

10 W is selected from the group consisting of N and CH₃;

U is selected from the group consisting of C(=O), alkyl, and heterocyclyl, or U is absent, or wherein U and R⁷ taken together with the nitrogen atom to which they are attached

form an optionally substituted heterocyclyl ring having from 4 to 10 atoms in the ring structure;

L is selected from the group consisting of a bond, alkyl, cycloalkyl, and heterocyclyl;

15 Z is selected from the group consisting of H, substituted heterocyclyl, cyano, $-(R^8)SO_2R^9$, $-N(R^8)C(=O)R^9$, $-N(R^{18})SO_2NR^{19}R^{28}$, $-SO_2R^{29}$, and $-S(O)(=NH)-R^{10}$, wherein the optionally substituted heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of R^{31} ,

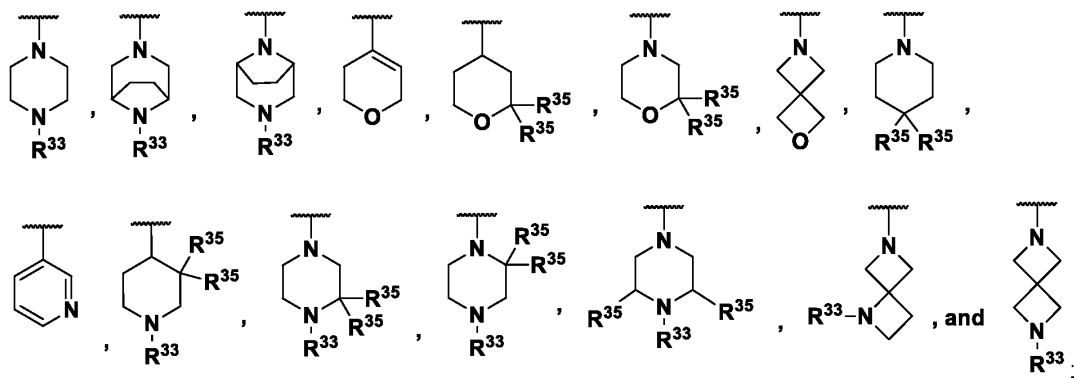
or wherein two occurrences of R³¹ taken together with the carbon atoms to which they
20 are attached form an optionally substituted ring having 5 to 8 atoms in the ring structure;

R⁶ is selected from the group consisting of halogen, cyano, alkyl, cycloalkyl, and heterocyclyl;

R⁷ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

- R⁸ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;
R⁹ is selected from the group consisting of amino, alkyl, cycloalkyl, and heterocyclyl,
or wherein R⁸ and R⁹ taken together with the nitrogen and sulfur or carbon atoms to
which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6
5 atoms in the ring structure;
R¹⁰ is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;
R¹⁸ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;
R¹⁹ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;
R²⁸ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl,
10 or wherein R¹⁸ and R²⁸ taken together with the nitrogen atoms to which they are attached
form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure,
or wherein R¹⁹ and R²⁸ taken together with the nitrogen atom to which they are attached
form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure;
and
15 R²⁹ is selected from the group consisting of amino, alkyl, cycloalkyl, and heterocyclyl;
R³¹ is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;
R³² is selected from the group consisting of H, halogen, alkyl, cycloalkyl, heterocyclyl,
aryl and heteroaryl;
wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, at each occurrence, is
20 optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl,
cycloalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy,
hydroxyalkyl, cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone,
sulfonamide, heterocyclyl, or heteroaryl;
m is 0, 1, 2, or 3; and
25 n is 0, 1, 2, or 3;
wherein both m and n are not simultaneously 0.
9. The compound of claim 8, wherein m is 1 and n is 0.
10. The compound of claim 8, wherein m is 2 and n is 0.
11. The compound of claim 8, wherein m is 3 and n is 0.
30 12. The compound of claim 8, wherein m is 1 and n is 1.
13. The compound of any one of claims 8-12, wherein R³² is selected from the group
consisting of H, halogen, alkyl, cycloalkyl, heterocyclyl, and heteroaryl.

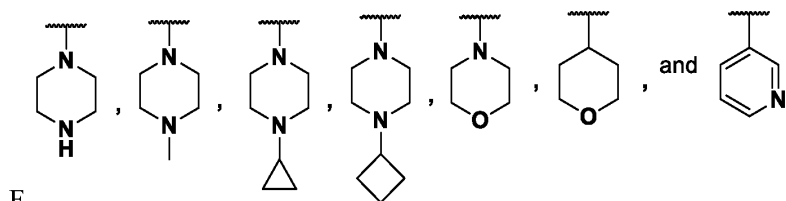
14. The compound of any one of claims 8-13, wherein R^{32} is selected from the group consisting of H, halogen,



wherein each occurrence of R^{33} is independently selected from the group consisting of H, alkyl, haloalkyl, cycloalkyl, and heterocyclyl, and each occurrence of R^{35} is independently selected from the group consisting of H, halogen, and alkyl, or wherein two occurrences of R^{35} taken together with the carbon atom to which they are attached form a cycloalkyl.

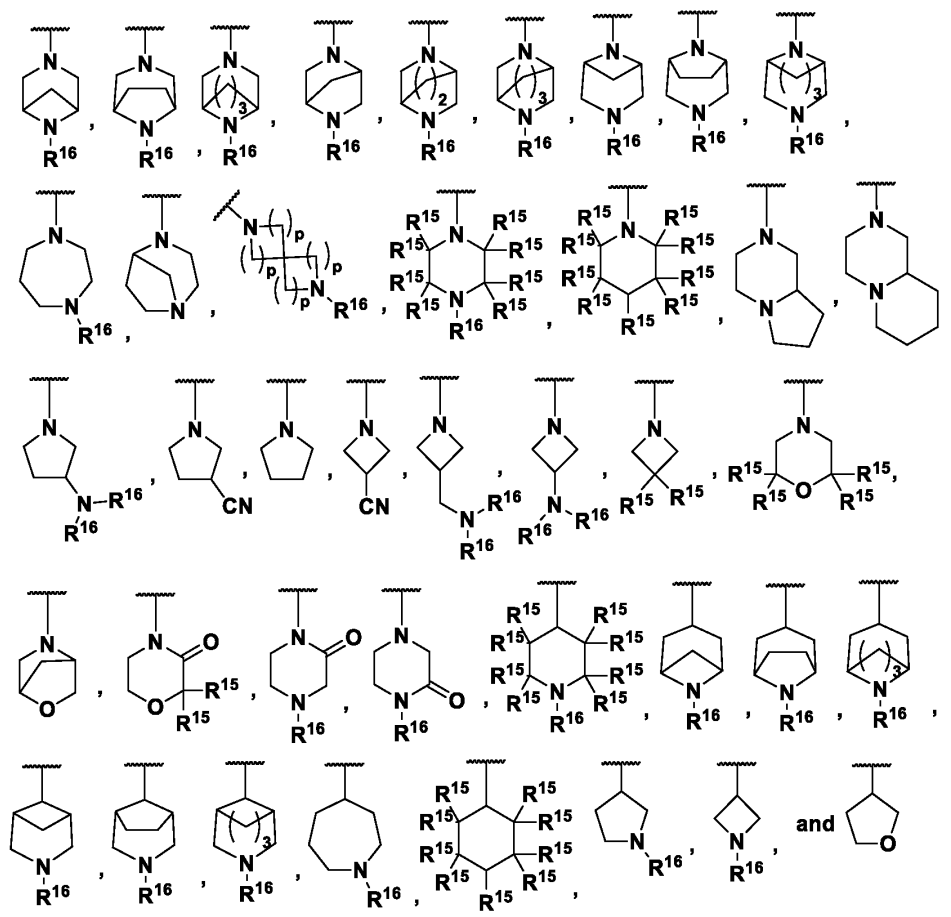
15. The compound of claim 14, wherein R^{33} is selected from the group consisting of H, alkyl, and cycloalkyl, and R^{35} at each occurrence is H.

16. The compound of claim 14 or 15, wherein R^{32} is selected from the group consisting of H,



F,

17. The compound of any one of claims 8-16, wherein R^{32} is selected from the group consisting of



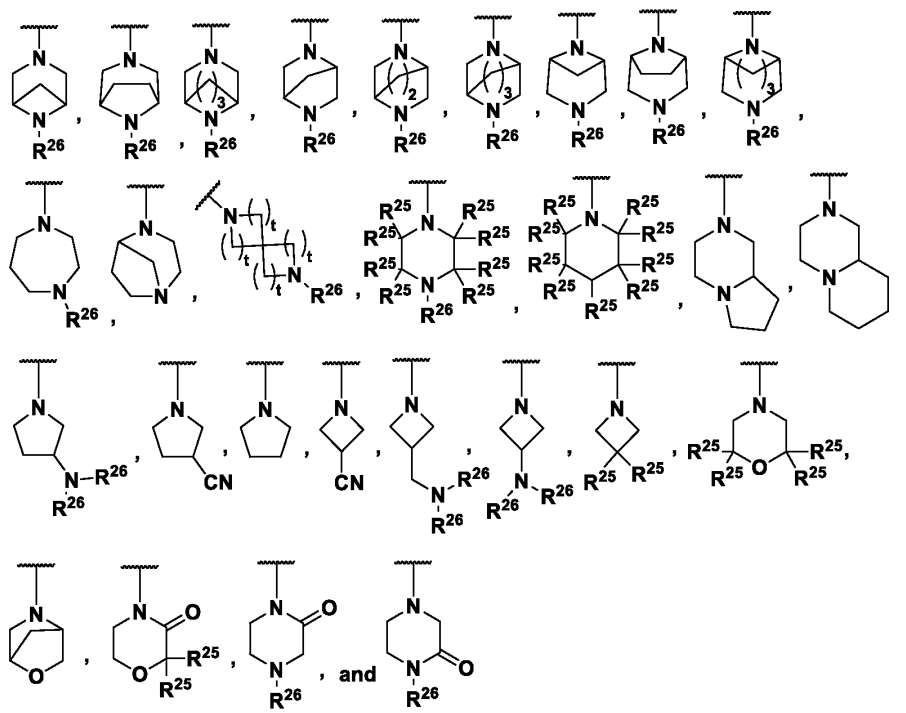
wherein R^{15} , at each occurrence, is independently selected from the group consisting of H, halogen, amino, cyano, alkyl, cycloalkyl, and heterocyclyl, or wherein two R^{15} , taken together with the carbon atom to which they are attached form an optionally substituted ring having from 4 to 6 atoms in the ring structure;

R^{16} , at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl, or wherein two R^{16} , taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure; and

p, at each occurrence, is independently 1, 2, or 3;

wherein the alkyl, cycloalkyl, or heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone, sulfonamide, heterocyclyl, or heteroaryl.

18. The compound of claim 17, wherein R¹⁵, at each occurrence, is independently selected from the group consisting of



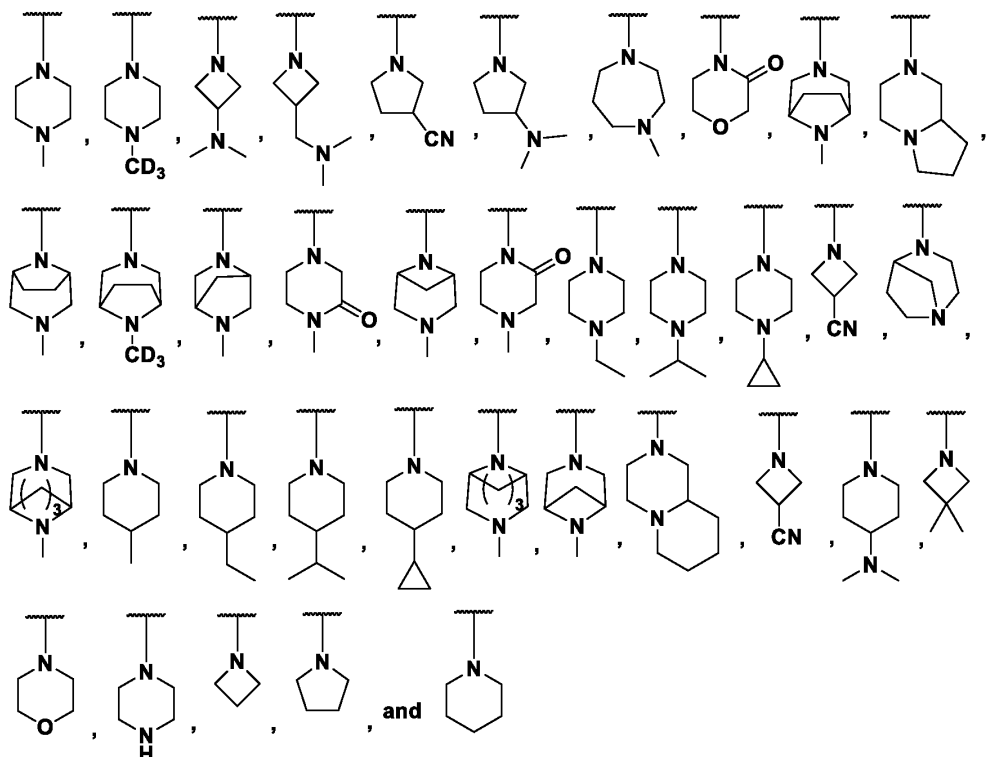
wherein R²⁵, at each occurrence, is independently selected from the group consisting of H, halogen, amino, cyano, alkyl, cycloalkyl, and heterocyclyl, or wherein two R²⁵, taken together with the carbon atom to which they are attached form an optionally substituted ring having from 4 to 6 atoms in the ring structure;

R²⁶, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl, or wherein two R²⁶, taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure; and

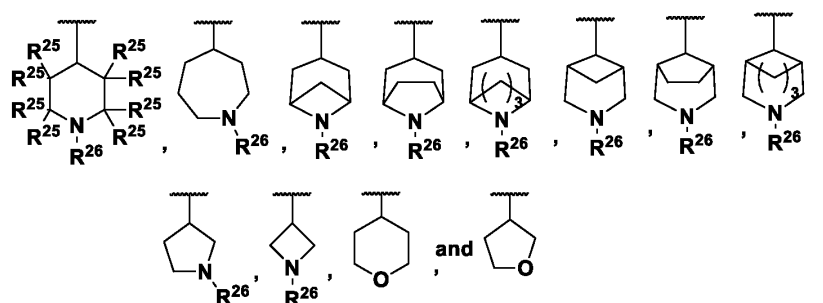
t, at each occurrence, is independently 1, 2, or 3;

wherein the alkyl, cycloalkyl, or heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone, sulfonamide, heterocyclyl, or heteroaryl.

19. The compound of claim 18, wherein R^{15} is selected from the group consisting of



20. The compound of claim 17, wherein R^{16} is selected from the group consisting of H, alkyl, alkylamino, cycloalkyl,



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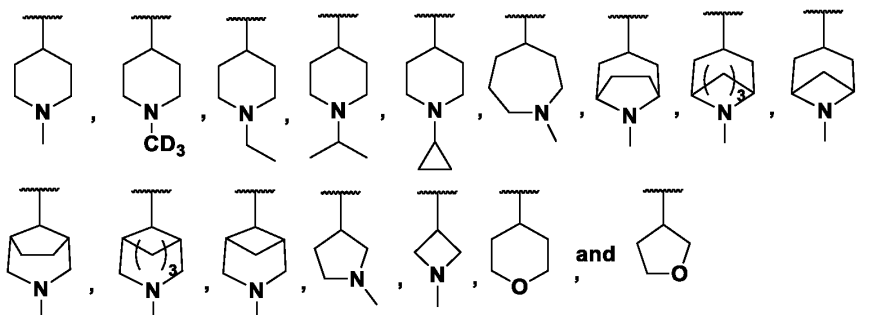
wherein R^{25} , at each occurrence, is independently selected from the group consisting of H, halogen, amino, cyano, alkyl, cycloalkyl, and heterocyclyl, or wherein two R^{25} , taken together with the carbon atom to which they are attached form an optionally substituted ring having from 4 to 6 atoms in the ring structure; and

- 10 R^{26} is independently selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl;

wherein the alkyl, cycloalkyl, or heterocyclyl, at each occurrence, is optionally substituted with one or more independent occurrences of halogen, alkyl, haloalkyl, cycloalkyl,

cycloalkylalkyl, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, oxo, amino, alkylamino, amide, acyl, carbamoyl, sulfone, sulfonamide, heterocyclyl, or heteroaryl.

21. The compound of claim 20, wherein R^{16} is selected from the group consisting of



5

22. The compound of any one of claims 1-21, wherein W is N.

23. The compound of any one of claims 1-21, wherein W is CH.

24. The compound of any one of claims 1-23, wherein R^6 is selected from the group consisting of halogen, cyano, haloalkyl, and cycloalkyl.

10 25. The compound of any one of claims 1-24, wherein R^6 is selected from the group

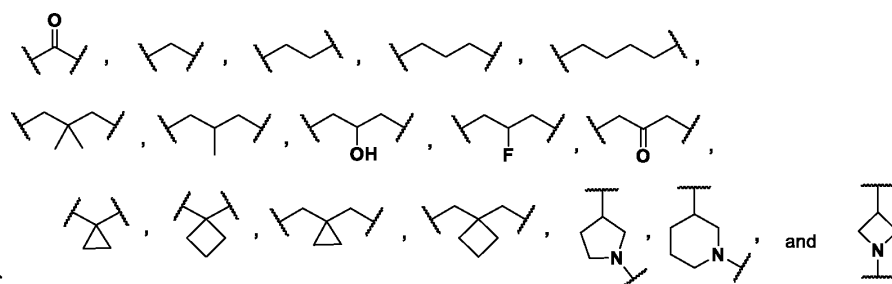
consisting of Cl, Br, CN, CF_3 , and

26. The compound of any one of claims 1-25, wherein R^6 is CF_3 .

27. The compound of any one of claims 1-26, wherein R^7 is H.

15 28. The compound of any one of claims 1-27, wherein U is selected from the group consisting of alkyl and heterocyclyl.

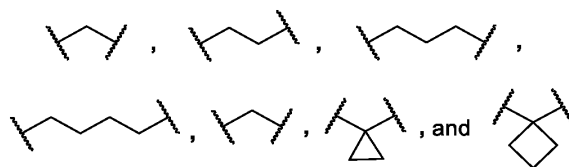
29. The compound of any one of claims 1-28, wherein U is selected from the group



consisting of

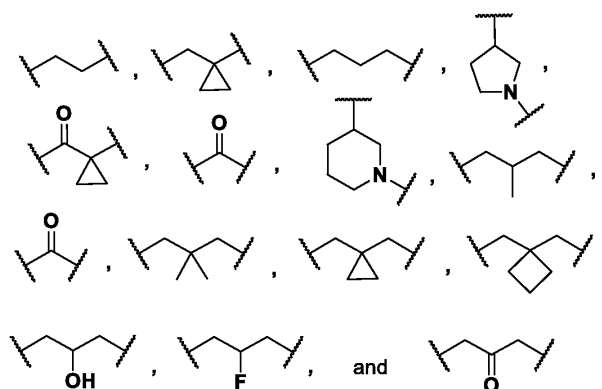
30. The compound of any one of claims 1-29, wherein L is selected from the group consisting of a bond and alkyl.

31. The compound of any one of claims 1-30, wherein L is selected from the group consisting of a bond,



32. The compound of any one of claims 1-31, wherein L is a bond.

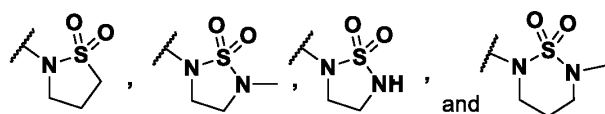
5 33. The compound of any one of claims 1-31, wherein U-L is selected from the group consisting of



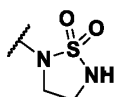
34. The compound of any one of claims 1-33, wherein Z is selected from the group consisting of $-N(R^8)SO_2R^9$, $-N(R^8)C(=O)R^9$, and $-N(R^{18})SO_2NR^{19}R^{28}$.

10 35. The compound of any one of claims 1-34, wherein
 R^8 is selected from the group consisting of H, and alkyl;
 R^9 is selected from the group consisting of amino, and alkyl,
or wherein R^8 and R^9 taken together with the nitrogen and sulfur or carbon atoms to
which they are attached form an optionally substituted heterocyclyl ring having from 4 to 6
15 atoms in the ring structure;
 R^{18} is selected from the group consisting of H, and alkyl;
 R^{19} is selected from the group consisting of H, and alkyl; and
 R^{28} is selected from the group consisting of H, and alkyl,
or wherein R^{18} and R^{28} taken together with the nitrogen atoms to which they are attached
20 form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure,
or wherein R^{19} and R^{28} taken together with the nitrogen atom to which they are attached
form an optionally substituted heterocyclyl ring having from 4 to 6 atoms in the ring structure.

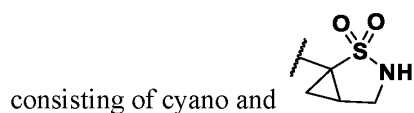
36. The compound of any one of claims 1-35, wherein Z is selected from the group consisting of NHSO_2NH_2 , NHSO_2CH_3 , NHSO_2 -cyclopropyl, NCH_3SO_2 -cyclopropyl, NHC(O)CH_3 , $\text{NCH}_3\text{SO}_2\text{N(CH}_3)_2$, $\text{NCH}_3\text{SO}_2\text{CH}_3$,



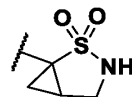
37. The compound of any one of claims 1-36, wherein Z is selected from the group consisting of NHSO_2NH_2 , NHSO_2CH_3 , NHC(O)CH_3 , $\text{NCH}_3\text{SO}_2\text{CH}_3$, and



38. The compound of any one of claims 1-33, wherein Z is selected from the group



39. The compound of any one of claims 1-33, and 38, wherein Z is



40. The compound of any one of claims 1-33, wherein Z is selected from the group consisting of $-\text{SO}_2\text{R}^{29}$ and $-\text{S(O)(=NH)-R}^{10}$.

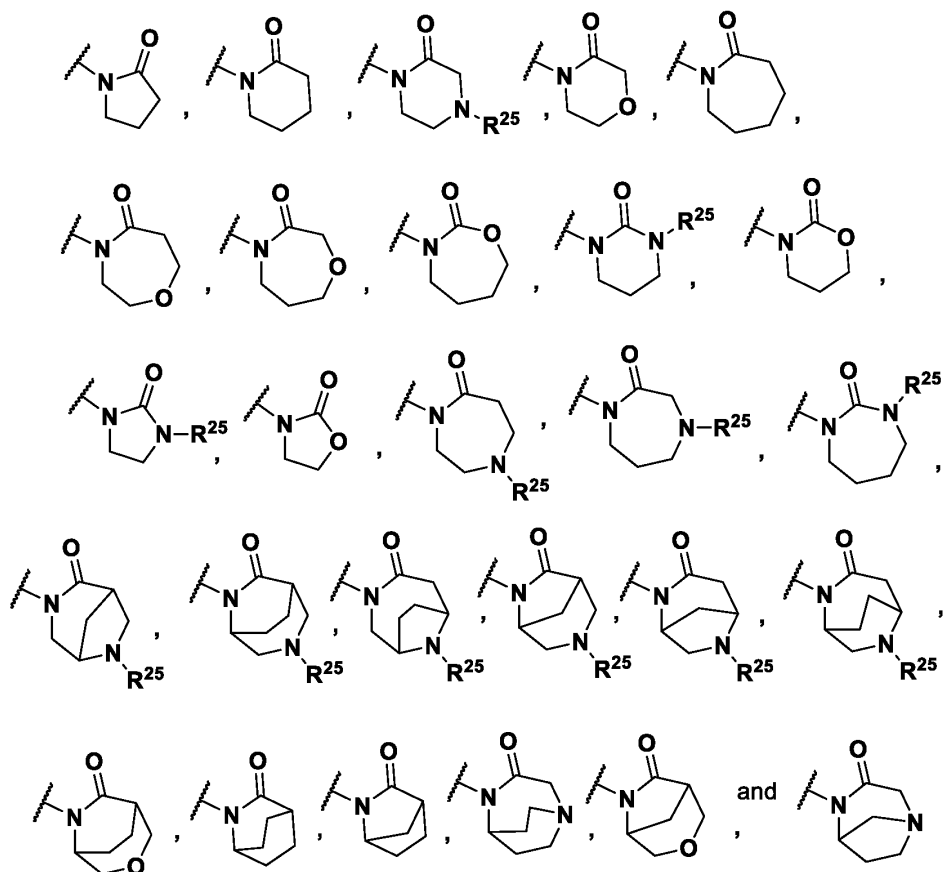
41. The compound of any one of claims 1-33, and 40, wherein R^{29} is selected from the group consisting of alkyl, cycloalkyl, and amino.

42. The compound of any one of claims 1-33, and 40-41, wherein R^{29} is selected from the group consisting of CH_3 , CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, NH_2 , and NHCH_3 .

43. The compound of any one of claims 1-33, and 40-42, wherein R^{29} is selected from the group consisting of CH_3 , and NH_2 .

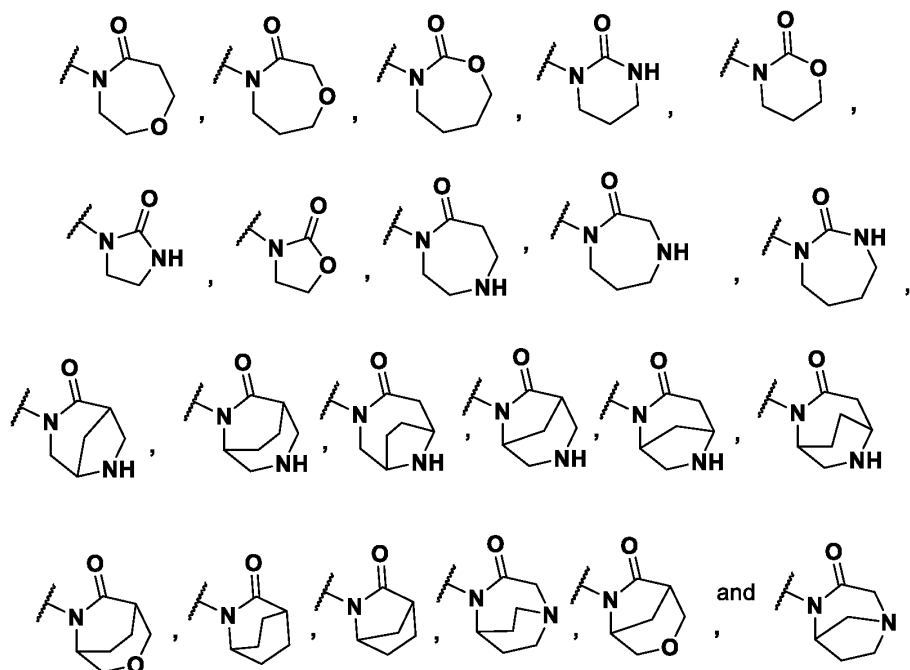
44. The compound of any one of claims 1-33, and 40, wherein R^{10} is CH_3 .

45. The compound of any one of claims 1-33, wherein Z is a substituted heterocyclyl selected from the group consisting of

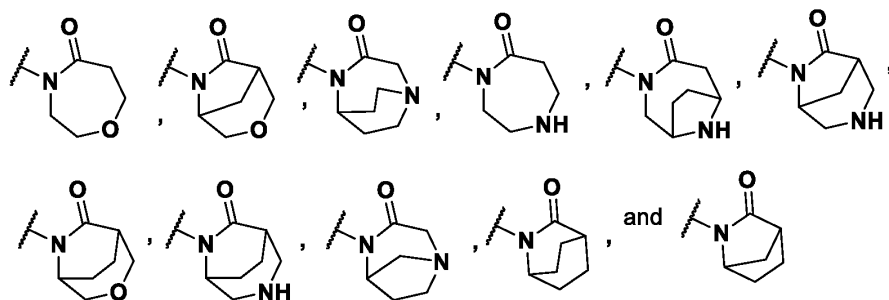


wherein R^{25} is selected from the group consisting of H, alkyl, haloalkyl, cycloalkyl, and heterocyclyl.

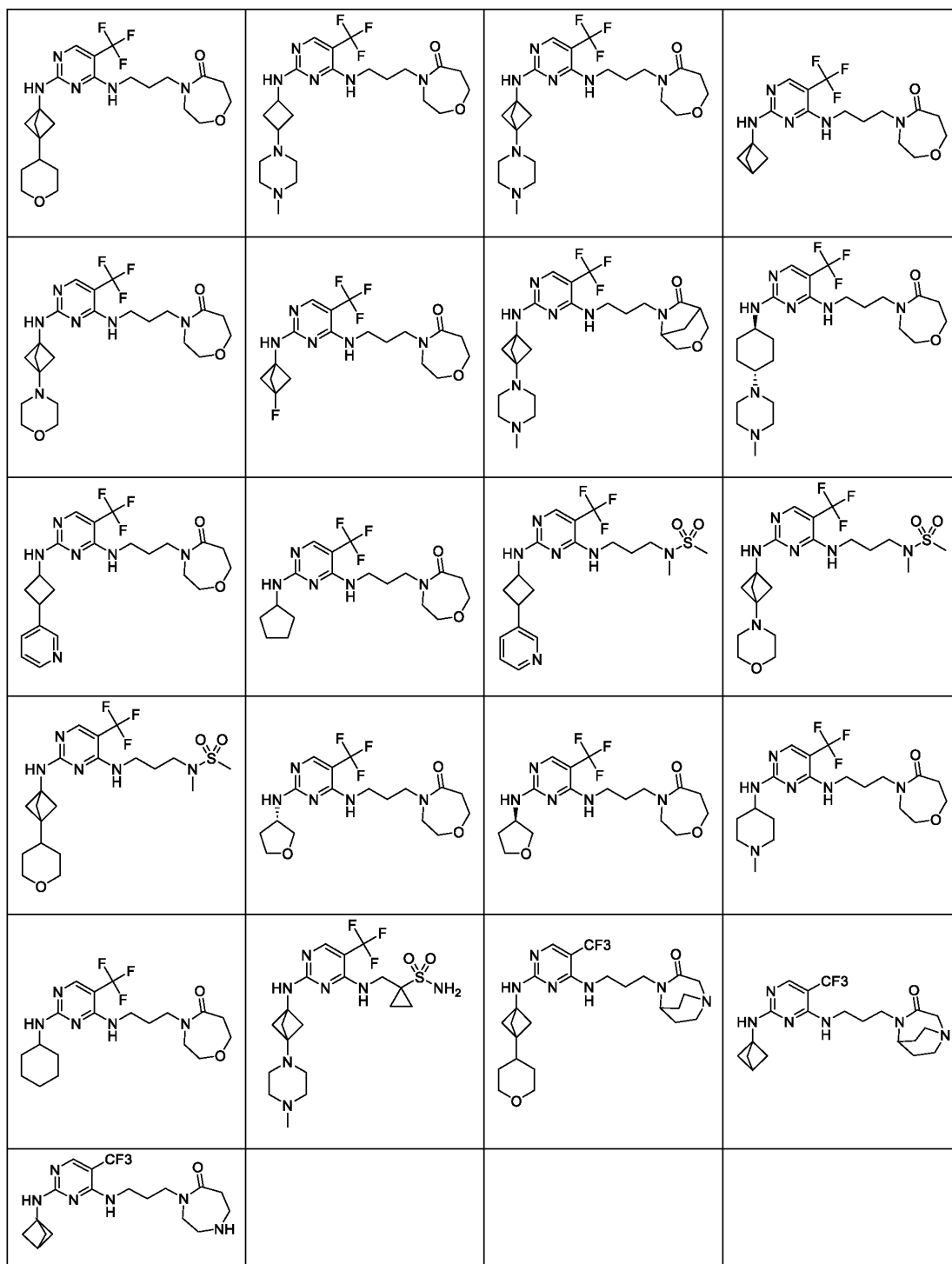
46. The compound of claim 45, wherein R^{25} is selected from the group consisting of H, alkyl,
 5 and cycloalkyl.
47. The compound of claim 45 or 46, wherein R^{25} is selected from the group consisting of H, and CH_3 .
48. The compound of any one of claims 1-33, and 45-47, wherein Z is a substituted heterocyclyl selected from the group consisting of



49. The compound of any one of claims 1-33, and 45-48, wherein Z is a substituted heterocyclyl selected from the group consisting of

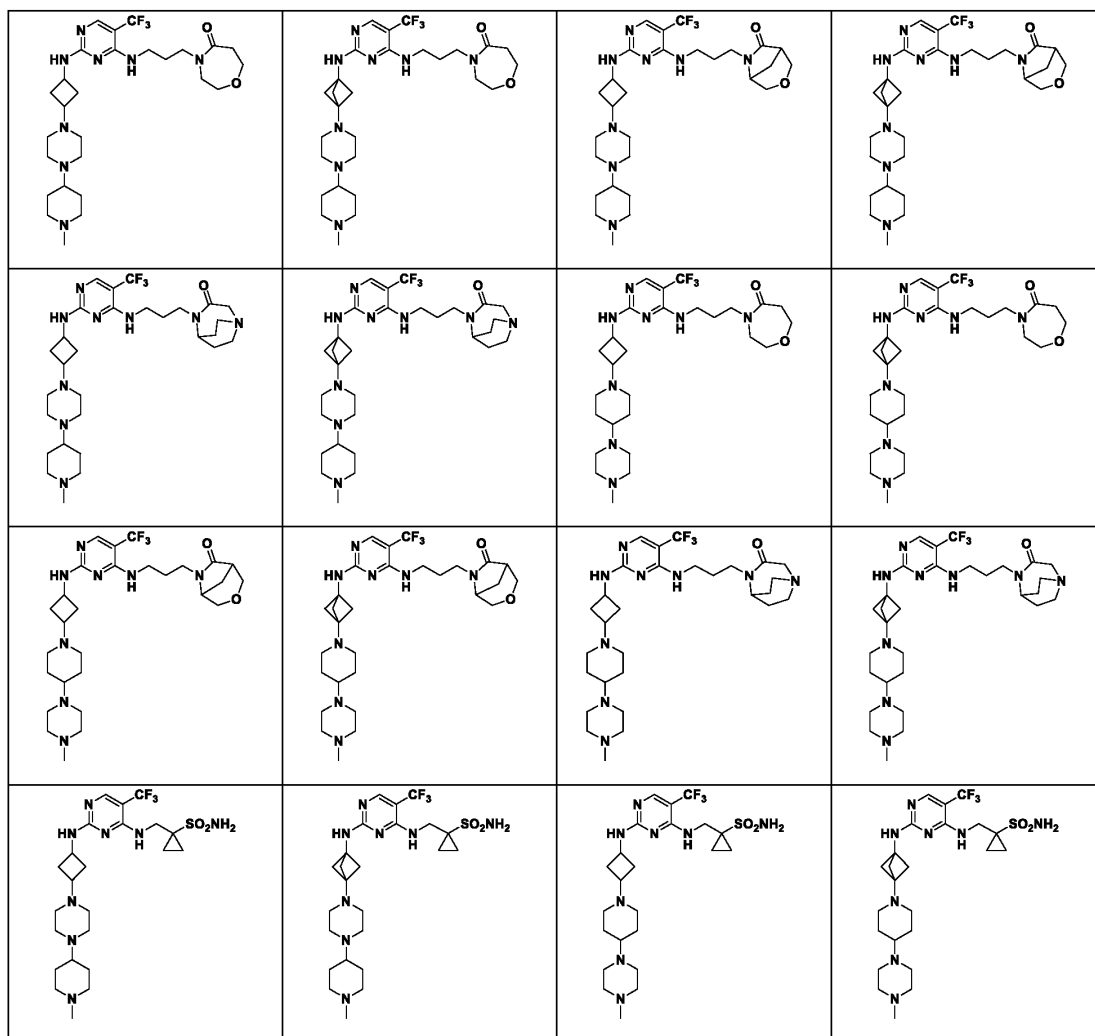


50. A compound selected from the group consisting of:



and pharmaceutically acceptable salts, enantiomers, stereoisomers, and tautomers thereof.

51. A compound selected from the group consisting of:



52. A pharmaceutical composition comprising the compound according to any one of claims 1-51, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

53. A method of treating a disease or disorder in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-51, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 52.

54. The method of claim 53, wherein the disease or disorder is cancer.

55. The method of claim 54, wherein the cancer is selected from the group consisting of gastrointestinal stromal tumors, esophageal cancer, gastric cancer, melanomas, gliomas, glioblastomas, gynecological cancers (*e.g.*, ovarian cancer, cervical cancer, uterine cancer, vaginal cancer, and vulvar cancer), bladder cancer, pancreatic cancer, prostate cancer, lung

cancers, breast cancers, renal cancers, hepatic cancers, osteosarcomas, Ewing sarcoma, multiple myelomas, cancers that are metastatic to bone, papillary thyroid carcinoma, non-small cell lung cancer, colorectal cancer, acute myeloid leukemia, relapsed acute myeloid leukemia, refractory acute myeloid leukemia, myelodysplastic syndrome, acute lymphocytic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, myeloproliferative neoplasms, and mantle cell lymphoma.

56. The method of any one of claims 53-55, further comprising administering to the patient one or more additional therapeutic agents.

57. The method of claim 56, wherein the one or more additional therapeutic agents is selected from the group consisting of a MAP kinase pathway inhibitor, an EGFR inhibitor, a KIT inhibitor, a FLT3 inhibitor, and a combination thereof.

58. The method of claim 57, wherein the MAP kinase pathway inhibitor is selected from the group consisting of a MEK inhibitor, an ERK inhibitor, a RAF inhibitor, and a Ras inhibitor, and a combination thereof.

59. The method of claim 58, wherein the MEK inhibitor is selected from the group consisting of trametinib, selumetinib, cobimetinib, binimetinib, avutometinib, mirdametinib, pimasertib, refametinib, and pelitinib, and pharmaceutically acceptable salts thereof.

60. The method of claim 58, wherein the ERK inhibitor is selected from the group consisting of ulixertinib, SCH772984, LY3214996, ravoxertinib, and VX-11e, and pharmaceutically acceptable salts thereof.

61. The method of claim 58, wherein the RAF inhibitor is selected from the group consisting of LY3009120, LXH254 (naporafenib), RAF709, KIN-2787 (exarafenib), dabrafenib, vemurafenib, encorafenib, tovorafenib, PLX8394, agerafenib, lifirafenib, belvarafenib, uplarafenib, JZP815, BDTX-4933, and DCC-3084, and pharmaceutically acceptable salts thereof.

62. The method of claim 58, wherein the Ras inhibitor is selected from the group consisting of sotorasib (AMG-510), adagrasib (MRTX849), LY3537982, opnurasib, divarasib (GDC-6036), fulzerasib, MRTX-1133, JAB-21822, GFH925, ELI-002, RMC-6236, ASP3082, YL-17231, QTX3034, RMC-9805, HRS-4642, RMC-8839, INCB161734, and RMC-6291, and pharmaceutically acceptable salts thereof.

63. The method of claim 57, wherein the EGFR inhibitor is selected from the group consisting of cetuximab, osimertinib, gefitinib, lapatinib, erlotinib, dacomitinib, neratinib, and afatinib, and pharmaceutically acceptable salts thereof.

64. The method of claim 57, wherein the KIT inhibitor is selected from the group consisting of ripretinib, avapritinib, sunitinib, AZD3229 (NB003), THE-630, imatinib, midostaurin,

bezuclastinib, olverembatinib (HQP1351), famitinib, IDRX-42 (M4205), elenestinib, BLU-808, IDRX-73, SLRN-517, THB335, DCC-3009, pexidartinib, and regorafenib, and pharmaceutically acceptable salts thereof.

65. The method of claim 57, wherein the FLT3 inhibitor is selected from the group
5 consisting of midostaurin, lestaurtinib, ponatinib, tandutinib, quizartinib, and gilteritinib, and pharmaceutically acceptable salts thereof.

66. The method of claim 56, wherein the additional therapeutic agent is a chemotherapeutic agent.

67. The method of claim 66, wherein the chemotherapeutic agent is a selected from the group
10 consisting of anti-tubulin agents, vinorelbine, DNA-alkylating agents, DNA intercalating agents, 5-fluorouracil, capecitabine, cytarabine, decitabine, 5-aza cytidine, gemcitabine, and methotrexate.