

## THIAZOLE TRPML1 AGONISTS AND USES THEREOF

## CROSS-REFERENCE

**[0001]** This application claims the benefit of U.S. Provisional Application Serial No. 63/618,506 filed January 8, 2024; which is hereby incorporated by reference in its entirety.

## BACKGROUND OF THE INVENTION

**[0002]** TRPML1, also named Mucolipin-1, is a ligand-gated cation channel expressed mostly in intracellular organelles like the late endosome and lysosome of many mammalian cells. This channel is member of the large family of Transient receptor potential (TRP) channels and has, with TRPML2 and TRPML3, two close analogues. Loss-of-function mutations in the gene encoding for TRPML1, the 12,000 base pair gene MCOLN-1 located in human chromosome 19p13, are the direct cause of Type IV mucopolidosis (MLIV), an autosomal recessive lysosomal storage disease.

**[0003]** At the molecular level, TRPML1 is a  $\text{Ca}^{2+}$ -permeable, non-selective cation channel formed of four six-transmembrane spanning proteins each of 580 amino acids. The channel opens upon binding of its endogenous ligand phosphatidylinositol-3,5-bisphosphate ( $\text{PtdIns}(3,5)\text{P}_2$ ) to its pore region. Channel activity is modulated by pH and  $\text{PtdIns}(4,5)\text{P}_2$  levels. TRPML1 is an inwardly rectifying channel permeable to different mono- and divalent cations, including  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ , and  $\text{Fe}^{2+}$ . Its N-terminal AP1 sequence targets the channel to the lysosome while a C-terminal AP2 sequence is responsible for intracellular trafficking and internalization. In addition, TRPML1 has four putative N-linked glycosylation sites in its luminal loop between TM1 and 2. It is reported that TRPML channels can be formed as homo-tetramers (e.g., TRPML1, TRPML2, and TRPML3) but also in some cases as hetero-tetramers where one channel is composed of different members of the TRPML family.

**[0004]** TRPML1 is found in all mammalian tissues with highest expression levels in brain, spleen, liver, kidney, and heart. Expression is found in many cell types, including neurons, myeloid cells, macrophages, microglia, podocytes, and muscle cells. TRPML1 is involved in function of late endosome / lysosomes (LEs), more specifically in protein trafficking, lysis, and autophagy.

**[0005]** Lysosomes are organelles filled with hydrolytic enzymes, characterized by a low luminal pH of about 5, a high luminal  $\text{Ca}^{2+}$  concentration of about 0.5 mM, and a membrane polarization of about +60 mV.

**[0006]** TRPML1 in LEs is reported to be responsible for the formation of transport vesicles, and it is required for the reformation of lysosomes from LE hybrid organelles and autolysosomes, mostly due to its  $\text{Ca}^{2+}$  permeability. TRPML1 is likely also important for iron release from the lysosome after degradation of iron-binding proteins like cytochrome C. In addition, TRPML1 is reported to regulate autophagy, probably in an mTOR-independent manner, by promoting TFEB translocation to the nucleus via calcineurin activation.

## SUMMARY OF THE INVENTION

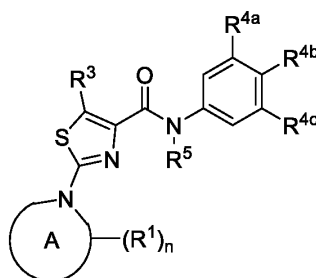
[0007] In Type IV mucopolipidosis (MLIV), the lack of functional TRPML1 leads to severe intellectual disability, motor deficits, retinal degeneration, and systemic symptoms leading to a strongly reduced life expectancy. Cells from MLIV patients show increased autophagosomes, accumulation of lysofusicin, and lipid accumulation in the lysosomes.

[0008] Failure of TRPML1-dependent autophagosome-lysosome fusion is also thought to impair clearance of apoptotic neurons by macrophages and microglia cells. Experimental results suggest involvement of TRPML1 in neurodegenerative diseases like Alzheimer's and amyotrophic lateral sclerosis (ALS). For example, Alzheimer's disease related loss-of-function mutations in presenilin 1 lead to dysregulation of lysosomal  $\text{Ca}^{2+}$  homeostasis via TRPML1 modulation. On the other side, over-expression of TRPML1 in rodent Alzheimer's models reduced neuronal apoptosis and rescued memory impairments. Pharmacological activation of TRPML1 showed similar effects, clearing accumulated sphingolipids and A $\beta$  peptides from lysosomes. In another study TRPML1 activation was sufficient to upregulate lysosomal exocytosis, rescue defective  $\alpha$ -syn secretion and prevent  $\alpha$ -syn accumulation in iPSC-derived dopaminergic neurons from patients expressing mutant PARK9. Similarly, TRPML1 activation rescued motor neurons from death and ER stress induced by the cycad neurotoxin beta-methylamino-L-alanine, L-BMAA as a model for ALS.

[0009] Therefore, it is desired to develop TRPML1 modulators to rescue impaired lysosomal function and cellular autophagy in neurodegenerative diseases.

[0010] Despite widespread interest for several years across the pharmaceutical industry, currently described small molecule TRPML1 agonists are not optimized for functional activity and drug like properties. Consequently, there is still an unmet need for compounds which can efficiently stimulate TRPML1 and that can be delivered to the different target organs which are sites of any TRPML1-mediated pathology.

[0011] Disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (I) as disclosed herein.

[0012] Also disclosed herein is a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable excipient.

[0013] Also disclosed herein is a method of treating a TRPML1-mediated disorder or disease in a subject in need thereof, the method comprising administering a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

### INCORPORATION BY REFERENCE

[0014] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

### DETAILED DESCRIPTION OF THE INVENTION

#### Definitions

[0015] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the invention may be practiced without these details. In other instances, well-known structures have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments. Unless the context requires otherwise, throughout the specification and claims which follow, the word “comprise” and variations thereof, such as, “comprises” and “comprising” are to be construed in an open, inclusive sense, that is, as “including, but not limited to.” Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed invention.

[0016] Reference throughout this specification to “some embodiments” or “an embodiment” means that a particular feature, structure, or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearances of the phrases “in one embodiment” or “in an embodiment” in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments. Also, as used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the content clearly dictates otherwise. It should also be noted that the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise.

[0017] The terms below, as used herein, have the following meanings, unless indicated otherwise:

[0018] “Oxo” refers to =O.

[0019] “Amino” refers to -NH<sub>2</sub>.

[0020] “Hydroxy” refers to -OH.

[0021] “Carboxyl” refers to -COOH.

[0022] “Alkyl” refers to a straight-chain or branched-chain saturated hydrocarbon monoradical having from one to about ten carbon atoms, more preferably one to six carbon atoms. Examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-

dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl and hexyl, and longer alkyl groups, such as heptyl, octyl and the like. Whenever it appears herein, a numerical range, such as “C<sub>1</sub>-C<sub>6</sub> alkyl,” means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated. In some embodiments, the alkyl is a C<sub>1</sub>-C<sub>10</sub> alkyl. In some embodiments, the alkyl is a C<sub>1</sub>-C<sub>6</sub> alkyl. In some embodiments, the alkyl is a C<sub>1</sub>-C<sub>5</sub> alkyl. In some embodiments, the alkyl is a C<sub>1</sub>-C<sub>4</sub> alkyl. In some embodiments, the alkyl is a C<sub>1</sub>-C<sub>3</sub> alkyl. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted, for example, with one or more oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl, and the like. In some embodiments, the alkyl is independently optionally substituted with one or more oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, the alkyl is independently optionally substituted with one or more halogen, -CN, -OH, or -OMe. In some embodiments, the alkyl is independently optionally substituted with halogen.

**[0023]** “Alkenyl” refers to a straight-chain or branched-chain hydrocarbon monoradical having one or more carbon-carbon double-bonds and having from two to about ten carbon atoms, more preferably two to about six carbon atoms. The group may be in either the *cis* or *trans* or *Z* or *E* conformation about the double bond(s) and should be understood to include both isomers. Examples include, but are not limited to, ethenyl (-CH=CH<sub>2</sub>), 1-propenyl (-CH<sub>2</sub>CH=CH<sub>2</sub>), isopropenyl [-C(CH<sub>3</sub>)=CH<sub>2</sub>], butenyl, 1,3-butadienyl and the like. Whenever it appears herein, a numerical range, such as “C<sub>2</sub>-C<sub>6</sub> alkenyl,” means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkenyl” where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkenyl group may be optionally substituted, for example, with one or more oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl, and the like. In some embodiments, the alkenyl is independently optionally substituted with one or more oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, the alkenyl is independently optionally substituted with one or more halogen, -CN, -OH, or -OMe. In some embodiments, the alkenyl is independently optionally substituted with halogen.

**[0024]** “Alkynyl” refers to a straight-chain or branched-chain hydrocarbon monoradical having one or more carbon-carbon triple-bonds and having from two to about ten carbon atoms, more preferably from two to about six carbon atoms. Examples include, but are not limited to, ethynyl, 2-propynyl, 2-butyne, 1,3-butadiynyl and the like. Whenever it appears herein, a numerical range, such as “C<sub>2</sub>-C<sub>6</sub> alkynyl,” means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkynyl” where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkynyl group may be optionally substituted, for example, with one or more oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, or

heteroaryl, and the like. In some embodiments, the alkynyl is independently optionally substituted with one or more oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, the alkynyl is independently optionally substituted with one or more halogen, -CN, -OH, or -OMe. In some embodiments, the alkynyl is independently optionally substituted with halogen.

**[0025]** “Alkylene” refers to a straight or branched divalent hydrocarbon chain. Unless stated otherwise specifically in the specification, an alkylene group may be optionally substituted, for example, with one or more oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl, and the like. In some embodiments, the alkylene is independently optionally substituted with one or more oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, the alkylene is independently optionally substituted with one or more halogen, -CN, -OH, or -OMe. In some embodiments, the alkylene is independently optionally substituted with halogen.

**[0026]** “Alkoxy” refers to a radical of the formula -Oalkyl where alkyl is defined as above. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted, for example, with one or more oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl, and the like. In some embodiments, the alkoxy is independently optionally substituted with one or more halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, the alkoxy is independently optionally substituted with one or more halogen, -CN, -OH, or -OMe. In some embodiments, the alkoxy is independently optionally substituted with halogen.

**[0027]** “Aryl” refers to a radical derived from a hydrocarbon ring system comprising 6 to 30 carbon atoms and at least one aromatic ring. The aryl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the aryl is bonded through an aromatic ring atom) or bridged ring systems. In some embodiments, the aryl is a 6- to 10-membered aryl. In some embodiments, the aryl is a 6-membered aryl (phenyl). Aryl radicals include, but are not limited to, anthracenyl, naphthyl, phenanthrenyl, azulenyl, phenyl, chrysenyl, fluoranthenyl, fluorenyl, as-indacenyl, s-indacenyl, indanyl, indenyl, phenalenyl, phenanthrenyl, pleiadenyl, pyrenyl, and triphenylenyl. Unless stated otherwise specifically in the specification, an aryl may be optionally substituted, for example, with one or more halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl, and the like. In some embodiments, the aryl is independently optionally substituted with one or more halogen, methyl, ethyl, -CN, -COOH, -COOMe, -CF<sub>3</sub>, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, the aryl is independently optionally substituted with one or more halogen, methyl, ethyl, -CN, -CF<sub>3</sub>, -OH, or -OMe. In some embodiments, the aryl is independently optionally substituted with halogen.

**[0028]** “Cycloalkyl” refers to a partially or fully saturated, monocyclic, or polycyclic carbocyclic ring, which may include fused (when fused with an aryl or a heteroaryl ring, the cycloalkyl is bonded through a non-aromatic ring atom), spiro, and/or bridged ring systems. In some embodiments, the cycloalkyl is

fully saturated. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms (e.g., C<sub>3</sub>-C<sub>15</sub> fully saturated cycloalkyl or C<sub>3</sub>-C<sub>15</sub> cycloalkenyl), from three to ten carbon atoms (e.g., C<sub>3</sub>-C<sub>10</sub> fully saturated cycloalkyl or C<sub>3</sub>-C<sub>10</sub> cycloalkenyl), from three to eight carbon atoms (e.g., C<sub>3</sub>-C<sub>8</sub> fully saturated cycloalkyl or C<sub>3</sub>-C<sub>8</sub> cycloalkenyl), from three to six carbon atoms (e.g., C<sub>3</sub>-C<sub>6</sub> fully saturated cycloalkyl or C<sub>3</sub>-C<sub>6</sub> cycloalkenyl), from three to five carbon atoms (e.g., C<sub>3</sub>-C<sub>5</sub> fully saturated cycloalkyl or C<sub>3</sub>-C<sub>5</sub> cycloalkenyl), or three to four carbon atoms (e.g., C<sub>3</sub>-C<sub>4</sub> fully saturated cycloalkyl or C<sub>3</sub>-C<sub>4</sub> cycloalkenyl). In some embodiments, the cycloalkyl is a 3- to 10-membered fully saturated cycloalkyl or a 3- to 10-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 3- to 6-membered fully saturated cycloalkyl or a 3- to 6-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 5- to 6-membered fully saturated cycloalkyl or a 5- to 6-membered cycloalkenyl. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls include, for example, adamantyl, norbornyl, decalyl, bicyclo[3.3.0]octyl, bicyclo[4.3.0]nonyl, cis-decalyl, trans-decalyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, and bicyclo[3.3.2]decyl, bicyclo[1.1.1]pentyl, bicyclo[3.1.0]hexyl, bicyclo[3.1.1]heptyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, Spiro[4.2]heptyl, spiro[4.3]octyl, spiro[5.2]octyl, spiro[3.3]heptyl, and spiro[5.3]nonyl. Partially saturated cycloalkyls include, for example cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Unless stated otherwise specifically in the specification, a cycloalkyl is independently optionally substituted, for example, with one or more oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl, and the like. In some embodiments, a cycloalkyl is independently optionally substituted with one or more oxo, halogen, methyl, ethyl, -CN, -COOH, -COOMe, -CF<sub>3</sub>, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, a cycloalkyl is independently optionally substituted with one or more oxo, halogen, methyl, ethyl, -CN, -CF<sub>3</sub>, -OH, or -OMe. In some embodiments, the cycloalkyl is independently optionally substituted with halogen.

**[0029]** “Halo” or “halogen” refers to bromo, chloro, fluoro or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro. In some embodiments, halogen is chloro.

**[0030]** “Haloalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 2-fluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

**[0031]** “Haloalkoxy” refers to -O-haloalkyl, with haloalkyl as defined above.

**[0032]** “Hydroxyalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more hydroxyls. In some embodiments, the alkyl is substituted with one hydroxyl. In some embodiments, the alkyl is substituted with one, two, or three hydroxyls. Hydroxyalkyl includes, for example, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, or hydroxypentyl. In some embodiments, the hydroxyalkyl is hydroxymethyl.

**[0033]** “Aminoalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more amines. In some embodiments, the alkyl is substituted with one amine. In some embodiments, the alkyl is

substituted with one, two, or three amines. Aminoalkyl includes, for example, aminomethyl, aminoethyl, aminopropyl, aminobutyl, or aminopentyl. In some embodiments, the aminoalkyl is aminomethyl.

**[0034]** “Deuteroalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more deuteriums. In some embodiments, the alkyl is substituted with one deuterium. In some embodiments, the alkyl is substituted with one, two, or three deuteriums. In some embodiments, the alkyl is substituted with one, two, three, four, five, or six deuteriums. Deuteroalkyl includes, for example,  $\text{CD}_3$ ,  $\text{CH}_2\text{D}$ ,  $\text{CHD}_2$ ,  $\text{CH}_2\text{CD}_3$ ,  $\text{CD}_2\text{CD}_3$ ,  $\text{CHDCD}_3$ ,  $\text{CH}_2\text{CH}_2\text{D}$ , or  $\text{CH}_2\text{CHD}_2$ . In some embodiments, the deuteroalkyl is  $\text{CD}_3$ .

**[0035]** “Heteroalkyl” refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a  $\text{C}_1$ - $\text{C}_6$  heteroalkyl wherein the heteroalkyl is comprised of 1 to 6 carbon atoms and one or more atoms other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus, or combinations thereof wherein the heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a  $\text{C}_1$ - $\text{C}_6$  heteroalkyl wherein the heteroalkyl is comprised of 1 to 6 carbon atoms and one or two atoms selected from the group consisting of oxygen, nitrogen, and sulfur wherein the heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. Examples of such heteroalkyl are, for example,  $-\text{CH}_2\text{OCH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{OCH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$ ,  $-\text{CH}(\text{CH}_3)\text{OCH}_3$ ,  $-\text{CH}_2\text{NHCH}_3$ ,  $-\text{CH}_2\text{N}(\text{CH}_3)_2$ ,  $-\text{CH}_2\text{CH}_2\text{NHCH}_3$ , or  $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ . Unless stated otherwise specifically in the specification, a heteroalkyl is independently optionally substituted for example, with one or more oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl, and the like. In some embodiments, a heteroalkyl is independently optionally substituted with one or more oxo, halogen, methyl, ethyl,  $-\text{CN}$ ,  $-\text{CF}_3$ ,  $-\text{OH}$ ,  $-\text{OMe}$ ,  $-\text{NH}_2$ , or  $-\text{NO}_2$ . In some embodiments, a heteroalkyl is independently optionally substituted with one or more oxo, halogen, methyl, ethyl,  $-\text{CN}$ ,  $-\text{CF}_3$ ,  $-\text{OH}$ , or  $-\text{OMe}$ . In some embodiments, the heteroalkyl is independently optionally substituted with halogen.

**[0036]** “Heterocycloalkyl” refers to a 3- to 24-membered partially or fully saturated ring radical comprising 2 to 23 carbon atoms and from one to 8 heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, silicon, and sulfur. In some embodiments, the heterocycloalkyl is fully saturated. In some embodiments, the heterocycloalkyl is C-linked. In some embodiments, the heterocycloalkyl is N-linked. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heterocycloalkyl comprises one to three nitrogens. In some embodiments, the heterocycloalkyl comprises one or two nitrogens. In some embodiments, the heterocycloalkyl comprises one nitrogen. In some embodiments, the heterocycloalkyl comprises one nitrogen and one oxygen. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with an aryl or a heteroaryl ring, the heterocycloalkyl is bonded through a non-aromatic ring

atom), spiro, or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heterocycloalkyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Representative heterocycloalkyls include, but are not limited to, heterocycloalkyls having from two to fifteen carbon atoms (e.g., C<sub>2</sub>-C<sub>15</sub> fully saturated heterocycloalkyl or C<sub>2</sub>-C<sub>15</sub> heterocycloalkenyl), from two to ten carbon atoms (e.g., C<sub>2</sub>-C<sub>10</sub> fully saturated heterocycloalkyl or C<sub>2</sub>-C<sub>10</sub> heterocycloalkenyl), from two to eight carbon atoms (e.g., C<sub>2</sub>-C<sub>8</sub> fully saturated heterocycloalkyl or C<sub>2</sub>-C<sub>8</sub> heterocycloalkenyl), from two to seven carbon atoms (e.g., C<sub>2</sub>-C<sub>7</sub> fully saturated heterocycloalkyl or C<sub>2</sub>-C<sub>7</sub> heterocycloalkenyl), from two to six carbon atoms (e.g., C<sub>2</sub>-C<sub>6</sub> fully saturated heterocycloalkyl or C<sub>2</sub>-C<sub>6</sub> heterocycloalkenyl), from two to five carbon atoms (e.g., C<sub>2</sub>-C<sub>5</sub> fully saturated heterocycloalkyl or C<sub>2</sub>-C<sub>5</sub> heterocycloalkenyl), or two to four carbon atoms (e.g., C<sub>2</sub>-C<sub>4</sub> fully saturated heterocycloalkyl or C<sub>2</sub>-C<sub>4</sub> heterocycloalkenyl). Examples of such heterocycloalkyl radicals include, but are not limited to, aziridinyl, azetidiny, oxetanyl, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazoliny, imidazolidiny, isothiazolidiny, isoxazolidiny, morpholiny, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidiny, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidiny, quinuclidiny, thiazolidiny, tetrahydrofuryl, trithianyl, tetrahydropyranly, thiomorpholiny, thiomorpholiny, 1-oxo-thiomorpholiny, 1,1-dioxo-thiomorpholiny, 1,3-dihydroisobenzofuran-1-yl, 3-oxo-1,3-dihydroisobenzofuran-1-yl, methyl-2-oxo-1,3-dioxol-4-yl, and 2-oxo-1,3-dioxol-4-yl. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides, and the oligosaccharides. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e., skeletal atoms of the heterocycloalkyl ring). In some embodiments, the heterocycloalkyl is a 3- to 8-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 4- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 8-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 4- to 6-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered heterocycloalkenyl. Unless stated otherwise specifically in the specification, a heterocycloalkyl is independently optionally substituted, for example, with one or more oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the heterocycloalkyl is independently optionally substituted with one or more oxo, halogen, methyl, ethyl, -CN, -COOH, -COOMe, -CF<sub>3</sub>, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, the heterocycloalkyl is independently optionally

substituted with one or more halogen, methyl, ethyl, -CN, -CF<sub>3</sub>, -OH, or -OMe. In some embodiments, the heterocycloalkyl is independently optionally substituted with halogen.

**[0037]** “Heteroaryl” refers to a 5- to 14-membered ring system radical comprising one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, and sulfur, and at least one aromatic ring. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heteroaryl comprises one to three nitrogens. In some embodiments, the heteroaryl comprises one or two nitrogens. In some embodiments, the heteroaryl comprises one nitrogen. In some embodiments, the heteroaryl is C-linked. In some embodiments, the heteroaryl is N-linked. The heteroaryl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the heteroaryl is bonded through an aromatic ring atom) or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. In some embodiments, the heteroaryl is a 5- to 10-membered heteroaryl comprising 1, 2, or 3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur. In some embodiments, the heteroaryl is a 5- to 6-membered heteroaryl comprising 1, 2, or 3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur. In some embodiments, the heteroaryl is a 6-membered heteroaryl comprising 1, 2, or 3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur. In some embodiments, the heteroaryl is a 5-membered heteroaryl comprising 1, 2, or 3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothieryl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, isothiazolyl, imidazolyl, indazolyl, indolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indoliziny, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e., thienyl). Unless stated otherwise specifically in the specification, a heteroaryl is independently optionally substituted, for example, with one or more halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl, and the like. In some embodiments, the heteroaryl is independently optionally substituted with one or more halogen, methyl, ethyl, -CN, -COOH, -COOMe, -CF<sub>3</sub>, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, the heteroaryl is independently optionally substituted with one or more halogen, methyl,

ethyl, -CN, -CF<sub>3</sub>, -OH, or -OMe. In some embodiments, the heteroaryl is independently optionally substituted with halogen.

**[0038]** The term “optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, “optionally substituted alkyl” means either “alkyl” or “substituted alkyl” as defined above. Further, an optionally substituted group may be un-substituted (e.g., -CH<sub>2</sub>CH<sub>3</sub>), fully substituted (e.g., -CF<sub>2</sub>CF<sub>3</sub>), mono-substituted (e.g., -CH<sub>2</sub>CH<sub>2</sub>F) or substituted at a level anywhere in-between fully substituted and mono-substituted (e.g., -CH<sub>2</sub>CHF<sub>2</sub>, -CH<sub>2</sub>CF<sub>3</sub>, -CF<sub>2</sub>CH<sub>3</sub>, -CFHCHF<sub>2</sub>, etc.).

**[0039]** The term “one or more” when referring to an optional substituent means that the subject group is independently optionally substituted with one, two, three, or four, or more substituents. In some embodiments, the subject group is independently optionally substituted with one, two, three, or four substituents. In some embodiments, the subject group is independently optionally substituted with one, two, or three substituents. In some embodiments, the subject group is independently optionally substituted with one or two substituents. In some embodiments, the subject group is independently optionally substituted with one substituent. In some embodiments, the subject group is independently optionally substituted with two substituents. In some embodiments, the subject group is independently optionally substituted with three substituents.

**[0040]** An “effective amount” or “therapeutically effective amount” refers to an amount of a compound administered to a mammalian subject, either as a single dose or as part of a series of doses, which is effective to produce a desired therapeutic effect.

**[0041]** “Treatment” of an individual (e.g., a mammal, such as a human) or a cell is any type of intervention used in an attempt to alter the natural course of the individual or cell. In some embodiments, treatment includes administration of a pharmaceutical composition subsequent to the initiation of a pathologic event or contact with an etiologic agent and includes stabilization of the condition (e.g., condition does not worsen) or alleviation of the condition.

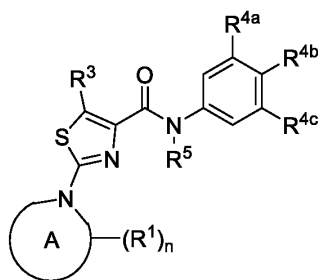
**[0042]** “Synergy” or “synergize” refers to an effect of a combination that is greater than additive of the effects of each component alone at the same doses.

**[0043]** As used herein, a “disease or disorder associated with TRPML1” or, alternatively, “a TRPML1-mediated disease or disorder” means any disease or other deleterious condition in which TRPML1, or a mutant thereof, is known or suspected to play a role.

## Compounds

**[0044]** Described herein are compounds, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof useful in the treatment of a TRPML1-mediated disease or disorder.

**[0045]** Disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (I),

wherein:

Ring A is heterocycloalkyl;

each R<sup>1</sup> is independently deuterium, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, -L-cycloalkyl, or -L-heterocycloalkyl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R;

or two R<sup>1</sup> on the same atom are taken together to form an oxo;

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

R<sup>3</sup> is C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R;

R<sup>4a</sup> is hydrogen, deuterium, halogen, -CN, -NO<sub>2</sub>, -OH, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, cycloalkyl, or heterocycloalkyl;

R<sup>4b</sup> is -OR<sup>a</sup>, -O-cycloalkyl, -O-heterocycloalkyl, -NR<sup>c</sup>R<sup>d</sup>, -NR<sup>b</sup>-cycloalkyl, -NR<sup>b</sup>-heterocycloalkyl, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, cycloalkyl, or heterocycloalkyl; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R; and

R<sup>4c</sup> is deuterium, halogen, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, cycloalkyl, or heterocycloalkyl;

R<sup>5</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, cycloalkyl, or heterocycloalkyl;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R<sup>c</sup> and R<sup>d</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl,

C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, -L-cycloalkyl, -

L-heterocycloalkyl, -L-aryl, or -L-heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R; or R<sup>c</sup> and R<sup>d</sup> are taken together with the atom to which they are attached to form a heterocycloalkyl independently optionally substituted with one or more R; and

L is absent or C<sub>1</sub>-C<sub>3</sub>alkylene independently optionally substituted with one or more R;

each R is independently deuterium, halogen, -CN, -OH, -S(=O)C<sub>1</sub>-C<sub>3</sub>alkyl, -S(=O)<sub>2</sub>C<sub>1</sub>-C<sub>3</sub>alkyl, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHC<sub>1</sub>-C<sub>3</sub>alkyl, -S(=O)<sub>2</sub>N(C<sub>1</sub>-C<sub>3</sub>alkyl)<sub>2</sub>, -NH<sub>2</sub>, -NHC<sub>1</sub>-C<sub>3</sub>alkyl, -N(C<sub>1</sub>-C<sub>3</sub>alkyl)<sub>2</sub>, -C(=O)C<sub>1</sub>-C<sub>3</sub>alkyl, -C(=O)OH, -C(=O)OC<sub>1</sub>-C<sub>3</sub>alkyl, -C(=O)NH<sub>2</sub>, -C(=O)NHC<sub>1</sub>-C<sub>3</sub>alkyl, -C(=O)N(C<sub>1</sub>-C<sub>3</sub>alkyl)<sub>2</sub>, C<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>1</sub>-C<sub>3</sub>alkoxy, C<sub>1</sub>-C<sub>3</sub>haloalkyl, C<sub>1</sub>-C<sub>3</sub>deuteroalkyl, C<sub>1</sub>-C<sub>3</sub>haloalkoxy, C<sub>1</sub>-C<sub>3</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>3</sub>aminoalkyl, C<sub>1</sub>-C<sub>3</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 3- to 6-membered heterocycloalkyl; wherein each cycloalkyl and heterocycloalkyl is independently optionally substituted with one or more halogen;

or two R on the same atom form an oxo.

**[0046]** In some embodiments of a compound of Formula (I), R<sup>4a</sup> is hydrogen, deuterium, halogen, -CN, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of a compound of Formula (I), R<sup>4a</sup> is hydrogen, halogen, -OH, or C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of a compound of Formula (I), R<sup>4a</sup> is hydrogen or halogen. In some embodiments of a compound of Formula (I), R<sup>4a</sup> is hydrogen. In some embodiments of a compound of Formula (I), R<sup>4a</sup> is C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of a compound of Formula (I), R<sup>4a</sup> is halogen. In some embodiments of a compound of Formula (I), R<sup>4a</sup> is -OH.

**[0047]** In some embodiments of a compound of Formula (I), R<sup>4a</sup> is -F or -Cl. In some embodiments of a compound of Formula (I), R<sup>4a</sup> is -F. In some embodiments of a compound of Formula (I), R<sup>4a</sup> is -Cl.

**[0048]** In some embodiments of a compound of Formula (I), R<sup>4a</sup> is -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, or -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>. In some embodiments of a compound of Formula (I), R<sup>4a</sup> is -CH<sub>3</sub>. In some embodiments of a compound of Formula (I), R<sup>4a</sup> is -CH<sub>2</sub>CH<sub>3</sub>. In some embodiments of a compound of Formula (I), R<sup>4a</sup> is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>.

**[0049]** In some embodiments of a compound of Formula (I), R<sup>4b</sup> is deuterium, halogen, -CN, -OH, -OR<sup>a</sup>, -O-cycloalkyl, -O-heterocycloalkyl, -NR<sup>c</sup>R<sup>d</sup>, -NR<sup>b</sup>-cycloalkyl, -NR<sup>b</sup>-heterocycloalkyl, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, cycloalkyl, heterocycloalkyl is independently optionally substituted with one or more R.

**[0050]** In some embodiments of a compound of Formula (I), R<sup>4b</sup> is -OR<sup>a</sup>, -O-cycloalkyl, -O-heterocycloalkyl, -NR<sup>c</sup>R<sup>d</sup>, -NR<sup>b</sup>-cycloalkyl, or heterocycloalkyl, wherein each cycloalkyl and heterocycloalkyl is independently optionally substituted with one or more R.

**[0051]** In some embodiments of a compound of Formula (I), R<sup>4b</sup> is -O-cycloalkyl or heterocycloalkyl, wherein each cycloalkyl and heterocycloalkyl is independently optionally substituted with one or more R.

**[0052]** In some embodiments of a compound of Formula (I), R<sup>4b</sup> is -O-cycloalkyl independently optionally substituted with one or more R.

[0053] In some embodiments of a compound of Formula (I),  $R^{4b}$  is -O-cycloalkyl. In some embodiments of a compound of Formula (I),  $R^{4b}$  is -O-cycloalkyl wherein the cycloalkyl is monocyclic cycloalkyl. In some embodiments of a compound of Formula (I),  $R^{4b}$  is -O-cycloalkyl wherein the cycloalkyl is bicyclic cycloalkyl.

[0054] In some embodiments of a compound of Formula (I),  $R^{4b}$  is heterocycloalkyl independently optionally substituted with one or more R.

[0055] In some embodiments of a compound of Formula (Ia),  $R^{4b}$  is heterocycloalkyl. In some embodiments of a compound of Formula (I),  $R^{4b}$  is 3- to 10-membered heterocycloalkyl. In some embodiments of a compound of Formula (I),  $R^{4b}$  is 5- to 10-membered heterocycloalkyl. In some embodiments of a compound of Formula (I),  $R^{4b}$  is 5- to 8-membered heterocycloalkyl.

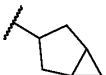
[0056] In some embodiments of a compound of Formula (I),  $R^{4b}$  is ; wherein Ring B is cycloalkyl and m is 0-4.

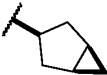
[0057] In some embodiments of a compound of Formula (I),  $R^{4b}$  is ; wherein Ring B is monocyclic cycloalkyl and m is 0-4.

[0058] In some embodiments of a compound of Formula (I),  $R^{4b}$  is ; wherein Ring B is bicyclic cycloalkyl and m is 0-4.

[0059] In some embodiments of a compound of Formula (I), m is 0-4. In some embodiments of a compound of Formula (I), m is 0-3. In some embodiments of a compound of Formula (I), m is 0-2. In some embodiments of a compound of Formula (I), m is 0 or 1. In some embodiments of a compound of Formula (I), m is 1 or 2. In some embodiments of a compound of Formula (I), m is 0. In some embodiments of a compound of Formula (I), m is 1. In some embodiments of a compound of Formula (I), m is 2. In some embodiments of a compound of Formula (I), m is 3. In some embodiments of a compound of Formula (I), m is 4.

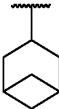
[0060] In some embodiments of a compound of Formula (I),  $R^{4b}$  is ; wherein Ring

B is . In some embodiments of a compound of Formula (I),  $R^{4b}$  is ; wherein

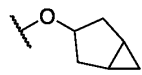
Ring B is . In some embodiments of a compound of Formula (I),  $R^{4b}$  is ;

wherein Ring B is .

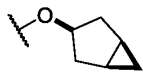
[0061] In some embodiments of a compound of Formula (I),  $R^{4b}$  is ; wherein Ring

B is .

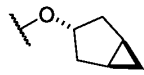
[0062] In some embodiments of a compound of Formula (I),  $R^{4b}$  is



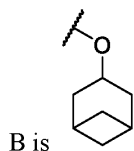
embodiments of a compound of Formula (I),  $R^{4b}$  is



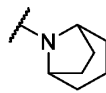
of Formula (I),  $R^{4b}$  is



[0063] In some embodiments of a compound of Formula (I),  $R^{4b}$  is  $-O-B-(R)_m$ ; wherein Ring



[0064] In some embodiments,  $R^{4b}$  is

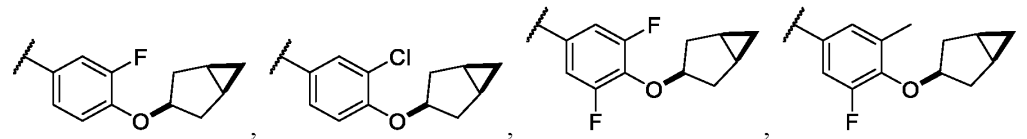
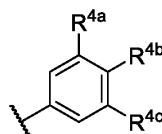


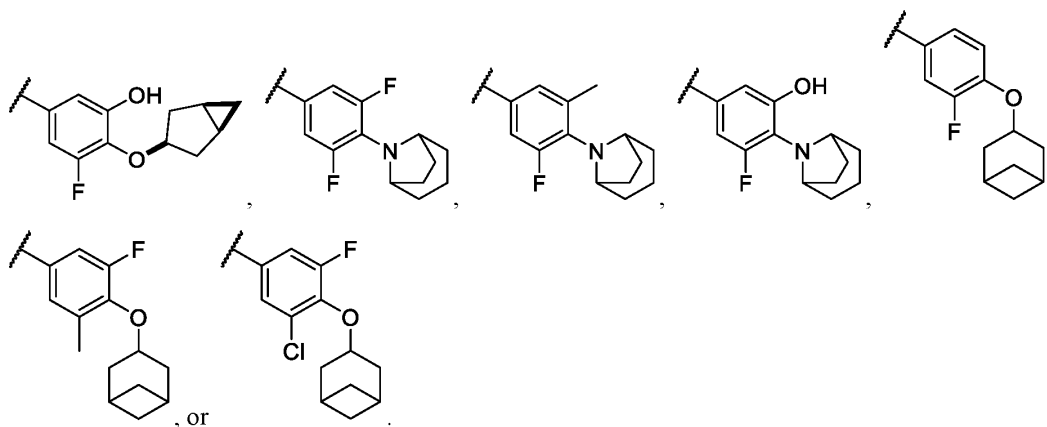
[0065] In some embodiments of a compound of Formula (I),  $R^{4c}$  is halogen, -OH, or  $C_1$ - $C_6$ alkyl. In some embodiments of a compound of Formula (I),  $R^{4c}$  is halogen or  $C_1$ - $C_6$ alkyl. In some embodiments of a compound of Formula (I),  $R^{4c}$  is -OH. In some embodiments of a compound of Formula (I),  $R^{4c}$  is  $C_1$ - $C_6$ alkyl.

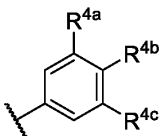
[0066] In some embodiments of a compound of Formula (I),  $R^{4c}$  is -F or -Cl. In some embodiments of a compound of Formula (I),  $R^{4c}$  is -F. In some embodiments of a compound of Formula (I),  $R^{4c}$  is -Cl.

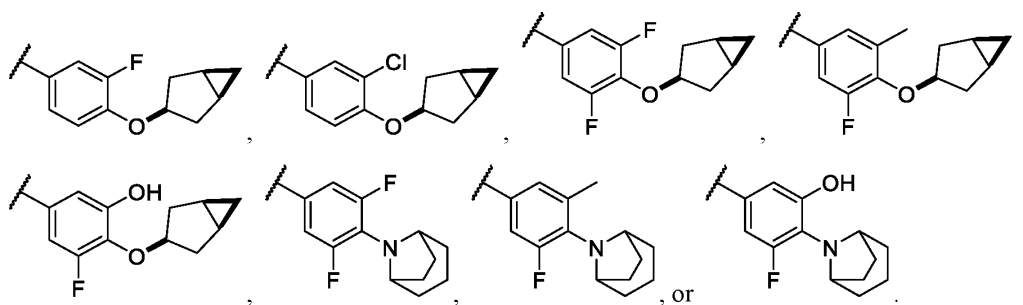
[0067] In some embodiments of a compound of Formula (I),  $R^{4c}$  is -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, or -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>. In some embodiments of a compound of Formula (I),  $R^{4c}$  is -CH<sub>3</sub>. In some embodiments of a compound of Formula (I),  $R^{4c}$  is -CH<sub>2</sub>CH<sub>3</sub>. In some embodiments of a compound of Formula (I),  $R^{4c}$  is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>.

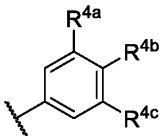
[0068] In some embodiments of a compound of Formula (I),

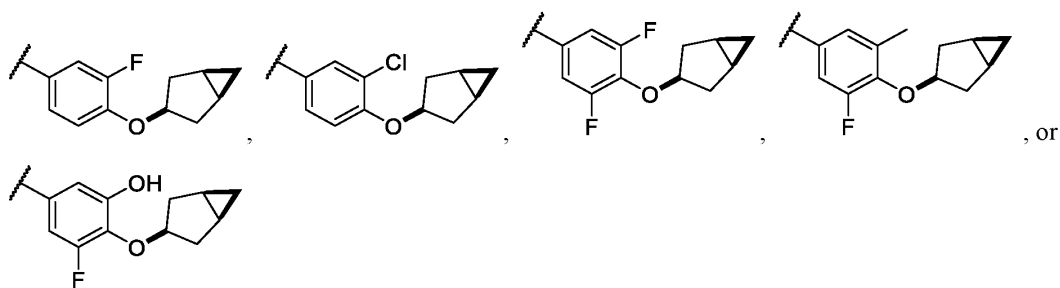


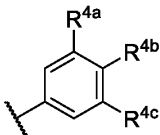


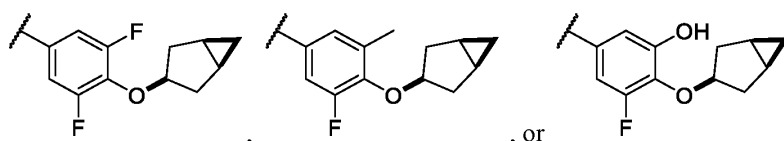
[0069] In some embodiments of a compound of Formula (I),  is



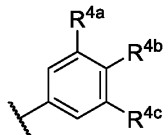
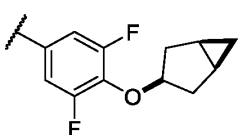
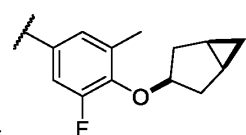
[0070] In some embodiments of a compound of Formula (I),  is

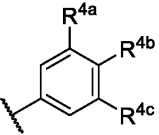
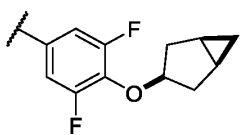


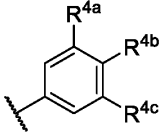
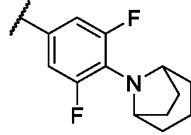
[0071] In some embodiments of a compound of Formula (I),  is

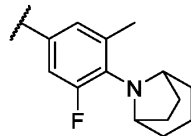
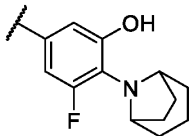


. In some embodiments of a

compound of Formula (I),  is  or . In some

embodiments of a compound of Formula (I),  is .

[0072] In some embodiments of a compound of Formula (I),  is .

, or .

[0073] In some embodiments of a compound of Formula (I), Ring A is 3- to 10-membered heterocycloalkyl comprising one, two, or three heteroatoms selected from oxygen, nitrogen, and sulfur.

[0074] In some embodiments of a compound of Formula (I), Ring A is 3- to 8-membered heterocycloalkyl comprising one, two, or three heteroatoms selected from oxygen, nitrogen, and sulfur.

[0075] In some embodiments of a compound of Formula (I), Ring A is 3- to 6-membered heterocycloalkyl comprising one or two heteroatoms selected from oxygen, nitrogen, and sulfur.

[0076] In some embodiments of a compound of Formula (I), Ring A is 4- to 6-membered heterocycloalkyl comprising one or two heteroatoms selected from oxygen, nitrogen, and sulfur.

[0077] In some embodiments of a compound of Formula (I), Ring A is 4- to 5-membered heterocycloalkyl comprising one or two heteroatoms selected from oxygen, nitrogen, and sulfur.

[0078] In some embodiments of a compound of Formula (I), Ring A is 5- to 6-membered heterocycloalkyl comprising one or two heteroatoms selected from oxygen, nitrogen, and sulfur.

[0079] In some embodiments of a compound of Formula (I), Ring A is 3- to 10-membered heterocycloalkyl comprising one, two, or three heteroatoms selected from oxygen and nitrogen.

[0080] In some embodiments of a compound of Formula (I), Ring A is 3- to 8-membered heterocycloalkyl comprising one, two, or three heteroatoms selected from oxygen and nitrogen.

[0081] In some embodiments of a compound of Formula (I), Ring A is 3- to 6-membered heterocycloalkyl comprising one or two heteroatoms selected from oxygen and nitrogen.

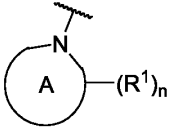
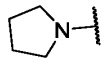
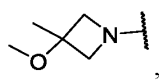
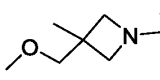
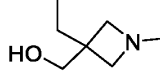
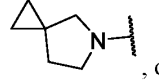
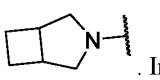
[0082] In some embodiments of a compound of Formula (I), Ring A is 4- to 6-membered heterocycloalkyl comprising one or two heteroatoms selected from oxygen and nitrogen.

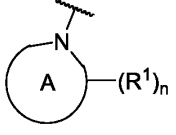
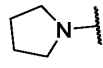
[0083] In some embodiments of a compound of Formula (I), Ring A is 4- to 5-membered heterocycloalkyl comprising one or two heteroatoms selected from oxygen and nitrogen.

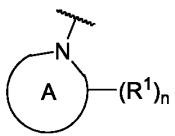
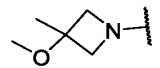
- [0084] In some embodiments of a compound of Formula (I), Ring A is 5- to 6-membered heterocycloalkyl comprising one or two heteroatoms selected from oxygen and nitrogen.
- [0085] In some embodiments of a compound of Formula (I), Ring A is 3- to 10-membered heterocycloalkyl comprising one, two, or three heteroatoms that are nitrogen.
- [0086] In some embodiments of a compound of Formula (I), Ring A is 3- to 8-membered heterocycloalkyl comprising one, two, or three heteroatoms that are nitrogen.
- [0087] In some embodiments of a compound of Formula (I), Ring A is 3- to 6-membered heterocycloalkyl comprising one or two heteroatoms that are nitrogen.
- [0088] In some embodiments of a compound of Formula (I), Ring A is 4- to 6-membered heterocycloalkyl comprising one or two heteroatoms that are nitrogen.
- [0089] In some embodiments of a compound of Formula (I), Ring A is 4- to 5-membered heterocycloalkyl comprising one or two heteroatoms that are nitrogen.
- [0090] In some embodiments of a compound of Formula (I), Ring A is 5- to 6-membered heterocycloalkyl comprising one or two heteroatoms that are nitrogen.
- [0091] In some embodiments of a compound of Formula (I), Ring A is a monocyclic heterocycloalkyl.
- [0092] In some embodiments of a compound of Formula (I), Ring A is a 3- to 6-membered monocyclic heterocycloalkyl comprising one or two heteroatoms selected from oxygen, nitrogen, and sulfur.
- [0093] In some embodiments of a compound of Formula (I), Ring A is a 4- to 6-membered monocyclic heterocycloalkyl comprising one or two heteroatoms selected from oxygen, nitrogen, and sulfur.
- [0094] In some embodiments of a compound of Formula (I), Ring A is a 4- to 5-membered monocyclic heterocycloalkyl comprising one or two heteroatoms selected from oxygen, nitrogen, and sulfur.
- [0095] In some embodiments of a compound of Formula (I), Ring A is a 3- to 6-membered monocyclic heterocycloalkyl comprising one or two heteroatoms selected from oxygen and nitrogen.
- [0096] In some embodiments of a compound of Formula (I), Ring A is a 4- to 6-membered monocyclic heterocycloalkyl comprising one or two heteroatoms selected from oxygen and nitrogen.
- [0097] In some embodiments of a compound of Formula (I), Ring A is a 4- to 5-membered monocyclic heterocycloalkyl comprising one or two heteroatoms selected from oxygen and nitrogen.
- [0098] In some embodiments of a compound of Formula (I), Ring A is a 3- to 6-membered monocyclic heterocycloalkyl comprising one or two heteroatoms that are nitrogen.
- [0099] In some embodiments of a compound of Formula (I), Ring A is a 4- to 6-membered monocyclic heterocycloalkyl comprising one or two heteroatoms that are nitrogen.
- [00100] In some embodiments of a compound of Formula (I), Ring A is a 4- to 5-membered monocyclic heterocycloalkyl comprising one or two heteroatoms that are nitrogen.

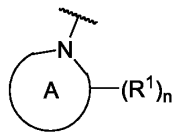
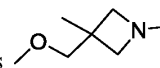
- [00101] In some embodiments of a compound of Formula (I), Ring A is an azetidiny, pyrrolidinyl, piperidinyl, morpholinyl, or piperazinyl. In some embodiments of a compound of Formula (I), Ring A is an azetidiny or pyrrolidinyl. In some embodiments of a compound of Formula (I), Ring A is a pyrrolidinyl or piperidinyl. In some embodiments of a compound of Formula (I), Ring A is an azetidiny. In some embodiments of a compound of Formula (I), Ring A is a pyrrolidinyl.
- [00102] In some embodiments of a compound of Formula (I), Ring A is a bicyclic heterocycloalkyl.
- [00103] In some embodiments of a compound of Formula (I), Ring A is a 6- to 10-membered bicyclic heterocycloalkyl comprising one or two heteroatoms selected from oxygen, nitrogen, and sulfur.
- [00104] In some embodiments of a compound of Formula (I), Ring A is a 6- to 8-membered bicyclic heterocycloalkyl comprising one or two heteroatoms selected from oxygen, nitrogen, and sulfur.
- [00105] In some embodiments of a compound of Formula (I), Ring A is a 6- to 10-membered bicyclic heterocycloalkyl comprising one or two heteroatoms selected from oxygen and nitrogen.
- [00106] In some embodiments of a compound of Formula (I), Ring A is a 6- to 8-membered bicyclic heterocycloalkyl comprising one or two heteroatoms selected from oxygen and nitrogen.
- [00107] In some embodiments of a compound of Formula (I), Ring A is a 6- to 10-membered bicyclic heterocycloalkyl comprising one or two heteroatoms that are nitrogen.
- [00108] In some embodiments of a compound of Formula (I), Ring A is a 6- to 8-membered bicyclic heterocycloalkyl comprising one or two heteroatoms that are nitrogen.
- [00109] In some embodiments of a compound of Formula (I), each R<sup>1</sup> is independently halogen, -CN, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, or C<sub>1</sub>-C<sub>6</sub>heteroalkyl.
- [00110] In some embodiments of a compound of Formula (I), each R<sup>1</sup> is independently -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>heteroalkyl.
- [00111] In some embodiments of a compound of Formula (I), each R<sup>1</sup> is independently -OR<sup>a</sup> or C<sub>1</sub>-C<sub>6</sub>alkyl.
- [00112] In some embodiments of a compound of Formula (I), each R<sup>1</sup> is independently -OR<sup>a</sup> or C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl.
- [00113] In some embodiments of a compound of Formula (I), each R<sup>1</sup> is independently -OR<sup>a</sup> or C<sub>1</sub>-C<sub>6</sub>heteroalkyl.
- [00114] In some embodiments of a compound of Formula (I), each R<sup>1</sup> is -OR<sup>a</sup>.
- [00115] In some embodiments of a compound of Formula (I), each R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub>alkyl.
- [00116] In some embodiments of a compound of Formula (I), each R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl.
- [00117] In some embodiments of a compound of Formula (I), each R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub>heteroalkyl.
- [00118] In some embodiments of a compound of Formula (I), each R<sup>1</sup> independently is -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, -OCH<sub>3</sub>, -CH<sub>2</sub>OCH<sub>3</sub>, or -CH<sub>2</sub>OH. In some embodiments of a compound of Formula (I), R<sup>1</sup> is -CH<sub>3</sub>. In some embodiments of a compound of Formula (I), R<sup>1</sup> is -CH<sub>2</sub>CH<sub>3</sub>. In some embodiments of a

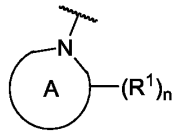
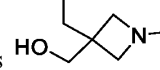
compound of Formula (I),  $R^1$  is  $-\text{OCH}_3$ . In some embodiments of a compound of Formula (I),  $R^1$  is  $-\text{CH}_2\text{OCH}_3$ . In some embodiments of a compound of Formula (I),  $R^1$  is  $-\text{CH}_2\text{OH}$ .

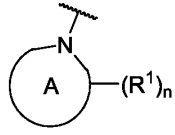
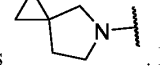
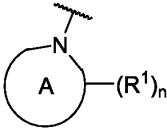
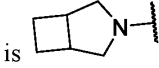
[00119] In some embodiments of a compound of Formula (I),  is , , , , , or . In some embodiments

of a compound of Formula (I),  is . In some embodiments of a compound of

Formula (I),  is . In some embodiments of a compound of Formula (I),

 is . In some embodiments of a compound of Formula (I),

 is . In some embodiments of a compound of Formula (I),

 is . In some embodiments of a compound of Formula (I),  is .

[00120] In some embodiments of a compound of Formula (I),  $n$  is 0, 1, 2, or 3. In some embodiments of a compound of Formula (I),  $n$  is 0, 1, or 2. In some embodiments of a compound of Formula (I),  $n$  is 1 or 2. In some embodiments of a compound of Formula (I),  $n$  is 0 or 1. In some embodiments of a compound of Formula (I),  $n$  is 0. In some embodiments of a compound of Formula (I),  $n$  is 1. In some embodiments of a compound of Formula (I),  $n$  is 2. In some embodiments of a compound of Formula (I),  $n$  is 3.

[00121] In some embodiments of a compound of Formula (I),  $R^3$  is  $\text{C}_1\text{-C}_6$ alkyl or  $\text{C}_1\text{-C}_6$ haloalkyl. In some embodiments of a compound of Formula (I),  $R^3$  is  $\text{C}_1\text{-C}_6$ haloalkyl. In some embodiments of a compound of Formula (I),  $R^3$  is  $\text{C}_1\text{-C}_6$ alkyl. In some embodiments of a compound of Formula (I),  $R^3$  is  $-\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{F}$ , or  $-\text{CH}_2\text{CF}_3$ . In some embodiments of a compound of Formula (I),  $R^3$  is  $-\text{CH}_2\text{CH}_2\text{F}$  or  $-\text{CH}_2\text{CF}_3$ . In some embodiments of a compound of Formula (I),  $R^3$  is  $-\text{CH}_2\text{CH}_3$ . In some embodiments of a compound of Formula (I),  $R^3$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$ . In some embodiments of a

compound of Formula (I),  $R^3$  is  $-\text{CH}_2\text{CH}_2\text{F}$ . In some embodiments of a compound of Formula (I),  $R^3$  is  $-\text{CH}_2\text{CF}_3$ .

**[00122]** In some embodiments of a compound of Formula (I),  $R^5$  is hydrogen. In some embodiments of a compound of Formula (I),  $R^5$  is hydrogen,  $\text{C}_1\text{-C}_6$ alkyl, or  $\text{C}_1\text{-C}_6$ haloalkyl. In some embodiments of a compound of Formula (I),  $R^5$  is hydrogen or  $\text{C}_1\text{-C}_6$ alkyl. In some embodiments of a compound of Formula (I),  $R^5$  is  $\text{C}_1\text{-C}_6$ alkyl.

**[00123]** In some embodiments of a compound disclosed herein, each  $R^a$  is independently  $\text{C}_1\text{-C}_6$ alkyl,  $\text{C}_1\text{-C}_6$ haloalkyl,  $\text{C}_1\text{-C}_6$ deuteroalkyl,  $\text{C}_1\text{-C}_6$ hydroxyalkyl,  $\text{C}_1\text{-C}_6$ aminoalkyl,  $\text{C}_1\text{-C}_6$ heteroalkyl, -L-cycloalkyl, or -L-heterocycloalkyl; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each  $R^a$  is independently  $\text{C}_1\text{-C}_6$ alkyl,  $\text{C}_1\text{-C}_6$ haloalkyl,  $\text{C}_1\text{-C}_6$ deuteroalkyl,  $\text{C}_1\text{-C}_6$ hydroxyalkyl,  $\text{C}_1\text{-C}_6$ aminoalkyl,  $\text{C}_1\text{-C}_6$ heteroalkyl; wherein each alkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each  $R^a$  is independently  $\text{C}_1\text{-C}_6$ alkyl,  $\text{C}_1\text{-C}_6$ haloalkyl, or  $\text{C}_1\text{-C}_6$ deuteroalkyl; wherein each alkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each  $R^a$  is independently  $\text{C}_1\text{-C}_6$ alkyl or  $\text{C}_1\text{-C}_6$ haloalkyl; wherein each alkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each  $R^a$  is independently  $\text{C}_1\text{-C}_6$ alkyl independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each  $R^a$  is independently  $\text{C}_1\text{-C}_6$ haloalkyl independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each  $R^a$  is independently  $\text{C}_1\text{-C}_6$ alkyl,  $\text{C}_1\text{-C}_6$ haloalkyl, or  $\text{C}_1\text{-C}_6$ deuteroalkyl. In some embodiments of a compound disclosed herein, each  $R^a$  is independently  $\text{C}_1\text{-C}_6$ alkyl or  $\text{C}_1\text{-C}_6$ haloalkyl. In some embodiments of a compound disclosed herein, each  $R^a$  is independently  $\text{C}_1\text{-C}_6$ alkyl. In some embodiments of a compound disclosed herein, each  $R^a$  is independently  $\text{C}_1\text{-C}_6$ haloalkyl.

**[00124]** In some embodiments of a compound disclosed herein,  $R^a$  is  $-\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_3$ , or  $-\text{CH}_2\text{CH}_2\text{CH}_3$ . In some embodiments of a compound disclosed herein,  $R^a$  is  $-\text{CH}_3$ . In some embodiments of a compound disclosed herein,  $R^a$  is  $-\text{CH}_2\text{CH}_3$ . In some embodiments of a compound disclosed herein,  $R^a$  is  $-\text{CH}_2\text{CH}_2\text{CH}_3$ .

**[00125]** In some embodiments of a compound disclosed herein, each  $R^b$  is independently hydrogen,  $\text{C}_1\text{-C}_6$ alkyl,  $\text{C}_1\text{-C}_6$ haloalkyl,  $\text{C}_1\text{-C}_6$ deuteroalkyl,  $\text{C}_1\text{-C}_6$ hydroxyalkyl,  $\text{C}_1\text{-C}_6$ aminoalkyl,  $\text{C}_1\text{-C}_6$ heteroalkyl, -L-cycloalkyl, or -L-heterocycloalkyl; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each  $R^b$  is independently hydrogen,  $\text{C}_1\text{-C}_6$ alkyl,  $\text{C}_1\text{-C}_6$ haloalkyl,  $\text{C}_1\text{-C}_6$ deuteroalkyl,  $\text{C}_1\text{-C}_6$ hydroxyalkyl,  $\text{C}_1\text{-C}_6$ aminoalkyl,  $\text{C}_1\text{-C}_6$ heteroalkyl; wherein each alkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each  $R^b$  is independently hydrogen,  $\text{C}_1\text{-C}_6$ alkyl,  $\text{C}_1\text{-C}_6$ haloalkyl, or  $\text{C}_1\text{-C}_6$ deuteroalkyl; wherein each alkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each  $R^b$  is independently hydrogen,  $\text{C}_1\text{-C}_6$ alkyl or  $\text{C}_1\text{-C}_6$ haloalkyl; wherein each alkyl is

independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>haloalkyl independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, or C<sub>1</sub>-C<sub>6</sub>deuteroalkyl. In some embodiments of a compound disclosed herein, each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of a compound disclosed herein, each R<sup>b</sup> is independently hydrogen or C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of a compound disclosed herein, each R<sup>b</sup> is independently hydrogen or C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of a compound disclosed herein, each R<sup>b</sup> is hydrogen. In some embodiments of a compound disclosed herein, each R<sup>b</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl.

**[00126]** In some embodiments of a compound disclosed herein, each R<sup>c</sup> and R<sup>d</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, -L-cycloalkyl, or -L-heterocycloalkyl; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each R<sup>c</sup> and R<sup>d</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl; wherein each alkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, or C<sub>1</sub>-C<sub>6</sub>deuteroalkyl; wherein each alkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each R<sup>c</sup> and R<sup>d</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl or C<sub>1</sub>-C<sub>6</sub>haloalkyl; wherein each alkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each R<sup>c</sup> and R<sup>d</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each R<sup>c</sup> and R<sup>d</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub>haloalkyl independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each R<sup>c</sup> and R<sup>d</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, or C<sub>1</sub>-C<sub>6</sub>deuteroalkyl. In some embodiments of a compound disclosed herein, each R<sup>c</sup> and R<sup>d</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of a compound disclosed herein, each R<sup>c</sup> and R<sup>d</sup> are independently hydrogen or C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of a compound disclosed herein, each R<sup>c</sup> and R<sup>d</sup> are independently hydrogen or C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of a compound disclosed herein, each R<sup>c</sup> and R<sup>d</sup> are hydrogen. In some embodiments of a compound disclosed herein, each R<sup>c</sup> and R<sup>d</sup> are independently C<sub>1</sub>-C<sub>6</sub>alkyl.

**[00127]** In some embodiments of a compound disclosed herein, R<sup>c</sup> and R<sup>d</sup> are taken together with the atom to which they are attached to form a heterocycloalkyl independently optionally substituted with one or more R.

**[00128]** In some embodiments of a compound disclosed herein, L is absent. In some embodiments of a compound disclosed herein, L is C<sub>1</sub>-C<sub>3</sub>alkylene independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, L is C<sub>1</sub>-C<sub>3</sub>alkylene. In some embodiments of a

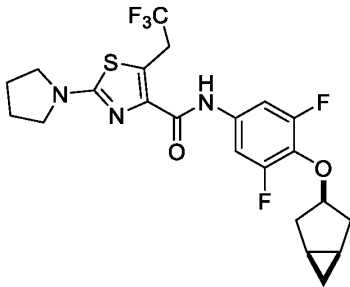
compound disclosed herein, L is C<sub>1</sub>alkylene. In some embodiments of a compound disclosed herein, L is C<sub>2</sub>alkylene. In some embodiments of a compound disclosed herein, L is C<sub>3</sub>alkylene. In some embodiments of a compound disclosed herein, L is -CH<sub>2</sub>-. In some embodiments of a compound disclosed herein, L is -CH<sub>2</sub>CH<sub>2</sub>-. In some embodiments of a compound disclosed herein, L is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-.

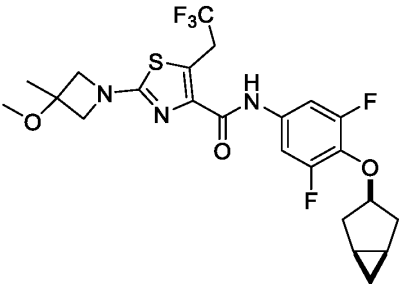
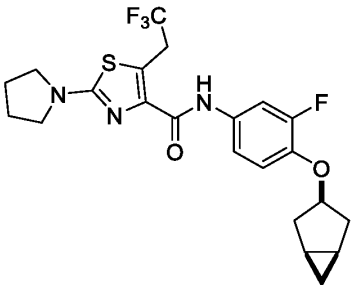
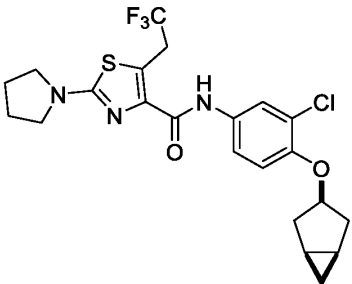
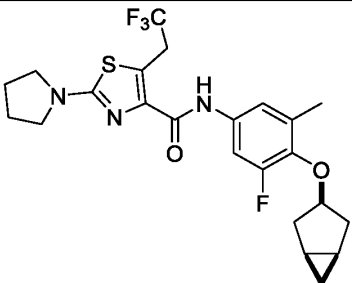
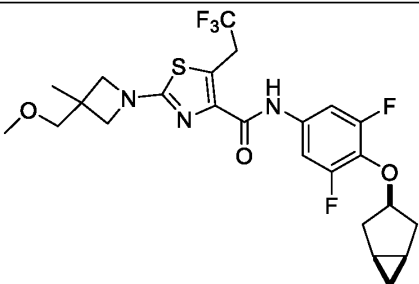
**[00129]** In some embodiments of a compound disclosed herein, each R is independently deuterium, halogen, -CN, -OH, -NH<sub>2</sub>, -NHC<sub>1-3</sub>alkyl, -N(C<sub>1-3</sub>alkyl)<sub>2</sub>, -C(=O)C<sub>1-3</sub>alkyl, -C(=O)OH, -C(=O)OC<sub>1-3</sub>alkyl, -C(=O)NH<sub>2</sub>, -C(=O)NHC<sub>1-3</sub>alkyl, -C(=O)N(C<sub>1-3</sub>alkyl)<sub>2</sub>, C<sub>1-3</sub>alkyl, C<sub>1-3</sub>alkoxy, C<sub>1-3</sub>haloalkyl, C<sub>1-3</sub>deuteroalkyl, C<sub>1-3</sub>haloalkoxy, C<sub>1-3</sub>hydroxyalkyl, C<sub>1-3</sub>aminoalkyl, or C<sub>1-3</sub>heteroalkyl; or two R on the same atom form an oxo. In some embodiments of a compound disclosed herein, each R is independently deuterium, halogen, -CN, -OH, -NH<sub>2</sub>, -NHC<sub>1-3</sub>alkyl, -N(C<sub>1-3</sub>alkyl)<sub>2</sub>, C<sub>1-3</sub>alkyl, C<sub>1-3</sub>alkoxy, C<sub>1-3</sub>haloalkyl, C<sub>1-3</sub>deuteroalkyl, C<sub>1-3</sub>haloalkoxy, C<sub>1-3</sub>hydroxyalkyl, C<sub>1-3</sub>aminoalkyl, or C<sub>1-3</sub>heteroalkyl; or two R on the same atom form an oxo. In some embodiments of a compound disclosed herein, each R is independently deuterium, halogen, -CN, -OH, -NH<sub>2</sub>, -NHC<sub>1-3</sub>alkyl, -N(C<sub>1-3</sub>alkyl)<sub>2</sub>, C<sub>1-3</sub>alkyl, C<sub>1-3</sub>alkoxy, or C<sub>1-3</sub>haloalkyl; or two R on the same atom form an oxo. In some embodiments of a compound disclosed herein, each R is independently deuterium, halogen, C<sub>1-3</sub>alkyl, C<sub>1-3</sub>alkoxy, or C<sub>1-3</sub>haloalkyl; or two R on the same atom form an oxo. In some embodiments of a compound disclosed herein, each R is independently deuterium, halogen, C<sub>1-3</sub>alkyl, or C<sub>1-3</sub>haloalkyl. In some embodiments of a compound disclosed herein, each R is independently deuterium, halogen, or C<sub>1-3</sub>alkyl. In some embodiments of a compound disclosed herein, each R is independently halogen or C<sub>1-3</sub>alkyl. In some embodiments of a compound disclosed herein, each R is independently halogen. In some embodiments of a compound disclosed herein, each R is independently C<sub>1-3</sub>alkyl.

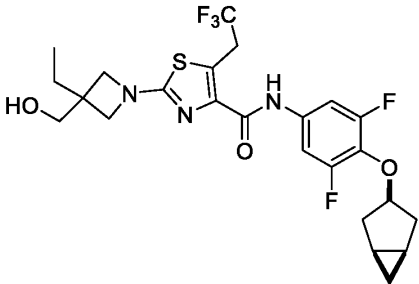
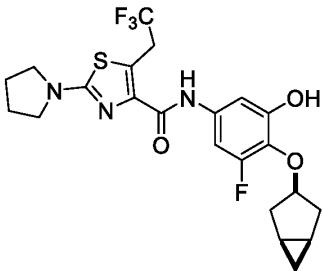
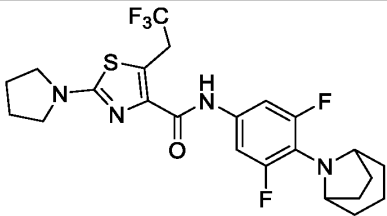
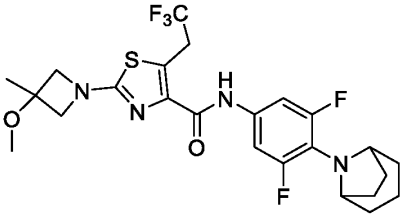
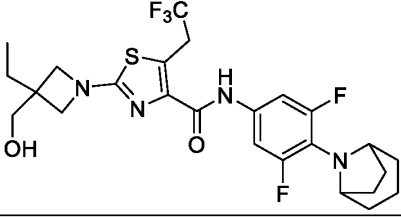
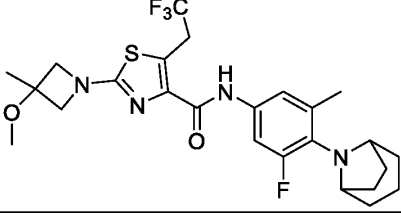
**[00130]** Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

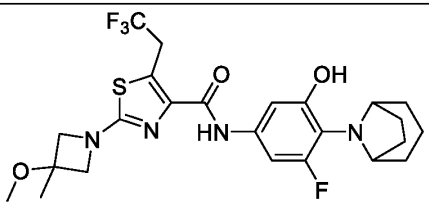
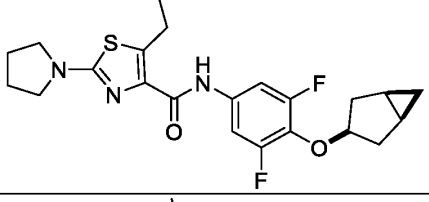
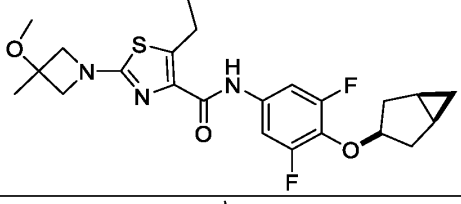
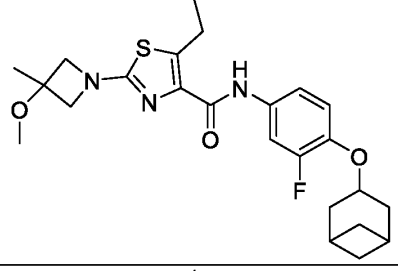
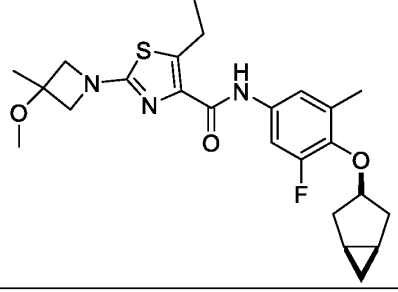
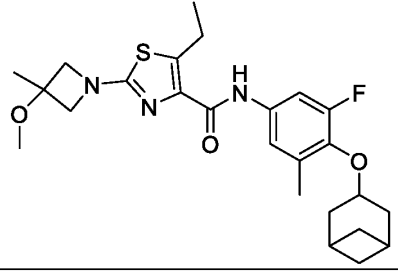
**[00131]** In some embodiments, the compound is selected from a compound found in **Table 1**.

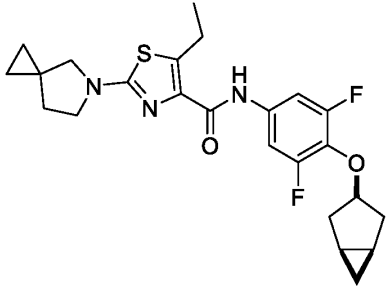
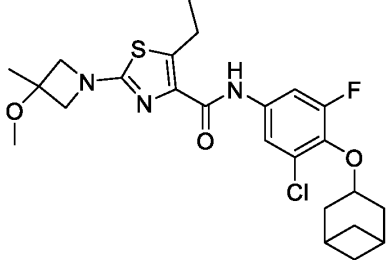
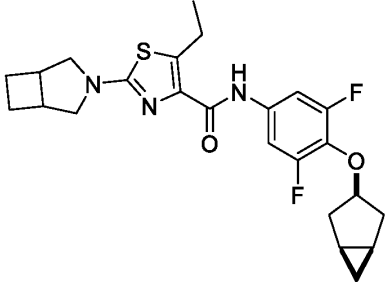
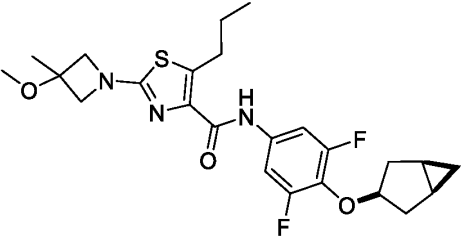
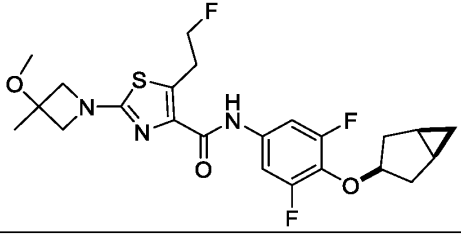
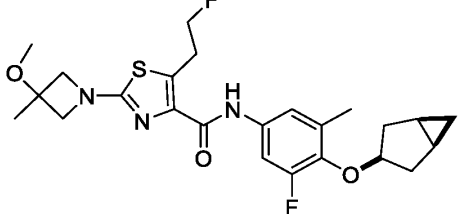
Table 1

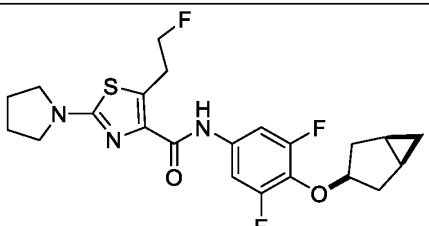
| Ex. | Structure                                                                           | Name                                                                                                                      |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| 1   |  | N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-2-(pyrrolidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide |

| Ex. | Structure                                                                           | Name                                                                                                                                              |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| 2   |    | N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-2-(3-methoxy-3-methylazetidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide         |
| 3   |    | N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3-fluorophenyl)-2-(pyrrolidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide                             |
| 4   |   | N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3-chlorophenyl)-2-(pyrrolidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide                             |
| 5   |  | N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3-fluoro-5-methylphenyl)-2-(pyrrolidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide                    |
| 6   |  | N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-2-(3-(methoxymethyl)-3-methylazetidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide |

| Ex. | Structure                                                                           | Name                                                                                                                                               |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| 7   |    | N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-2-(3-ethyl-3-(hydroxymethyl)azetidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide   |
| 8   |    | N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3-fluoro-5-hydroxyphenyl)-2-(pyrrolidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide                    |
| 9   |   | N-(4-(8-azabicyclo[3.2.1]octan-8-yl)-3,5-difluorophenyl)-2-(pyrrolidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide                        |
| 10  |  | N-(4-(8-azabicyclo[3.2.1]octan-8-yl)-3,5-difluorophenyl)-2-(3-methoxy-3-methylazetidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide        |
| 11  |  | N-(4-(8-azabicyclo[3.2.1]octan-8-yl)-3,5-difluorophenyl)-2-(3-ethyl-3-(hydroxymethyl)azetidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide |
| 12  |  | N-(4-(8-azabicyclo[3.2.1]octan-8-yl)-3-fluoro-5-methylphenyl)-2-(3-methoxy-3-methylazetidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide   |

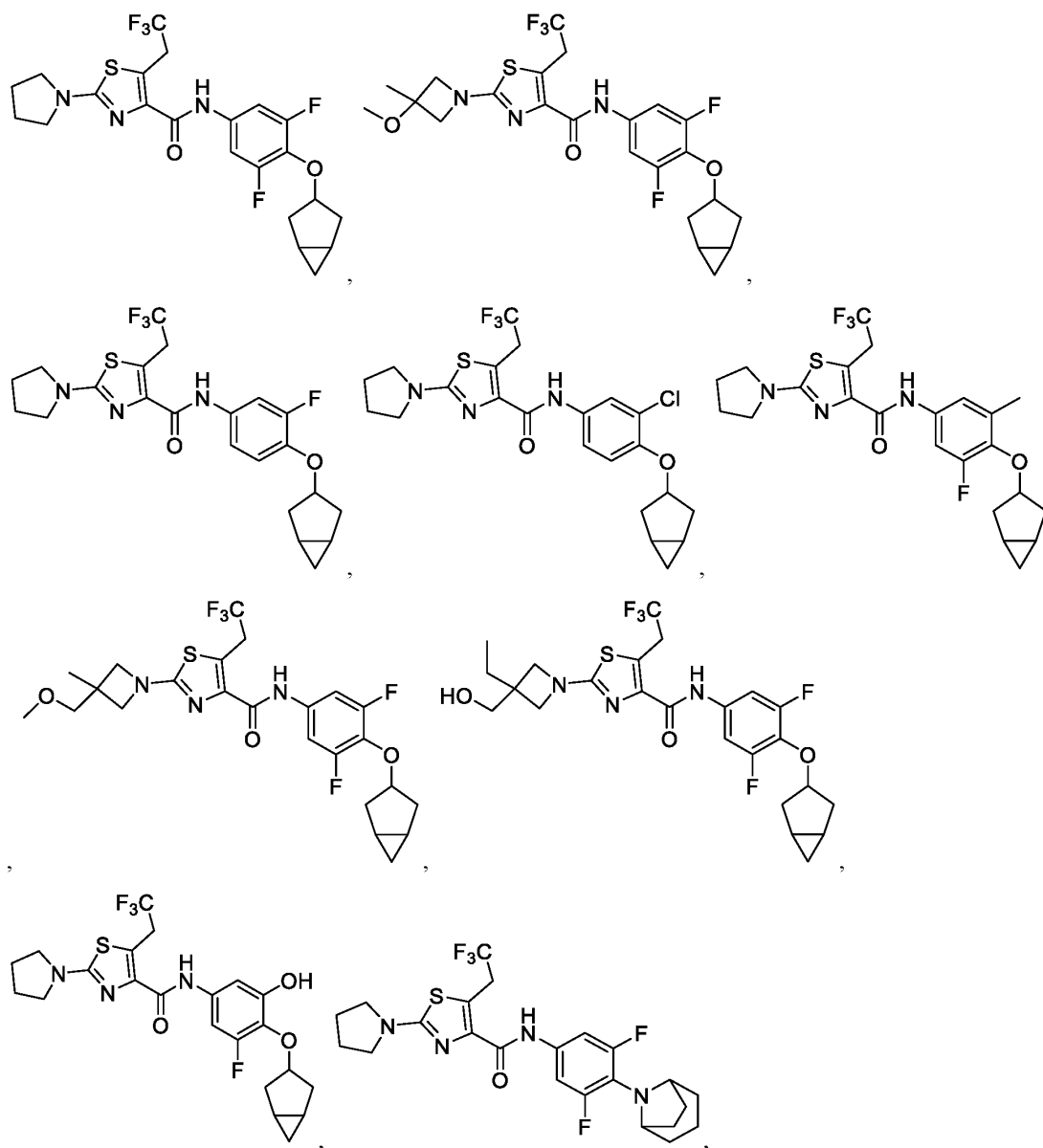
| Ex. | Structure                                                                           | Name                                                                                                                                              |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| 13  |    | N-(4-(8-azabicyclo[3.2.1]octan-8-yl)-3-fluoro-5-hydroxyphenyl)-2-(3-methoxy-3-methylazetidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide |
| 14  |    | N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-5-ethyl-2-(pyrrolidin-1-yl)thiazole-4-carboxamide                                          |
| 15  |    | N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-5-ethyl-2-(3-methoxy-3-methylazetidin-1-yl)thiazole-4-carboxamide                          |
| 16  |   | N-(4-(bicyclo[3.1.1]heptan-3-yloxy)-3-fluorophenyl)-5-ethyl-2-(3-methoxy-3-methylazetidin-1-yl)thiazole-4-carboxamide                             |
| 17  |  | N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3-fluoro-5-methylphenyl)-5-ethyl-2-(3-methoxy-3-methylazetidin-1-yl)thiazole-4-carboxamide                     |
| 18  |  | N-(4-(bicyclo[3.1.1]heptan-3-yloxy)-3-fluoro-5-methylphenyl)-5-ethyl-2-(3-methoxy-3-methylazetidin-1-yl)thiazole-4-carboxamide                    |

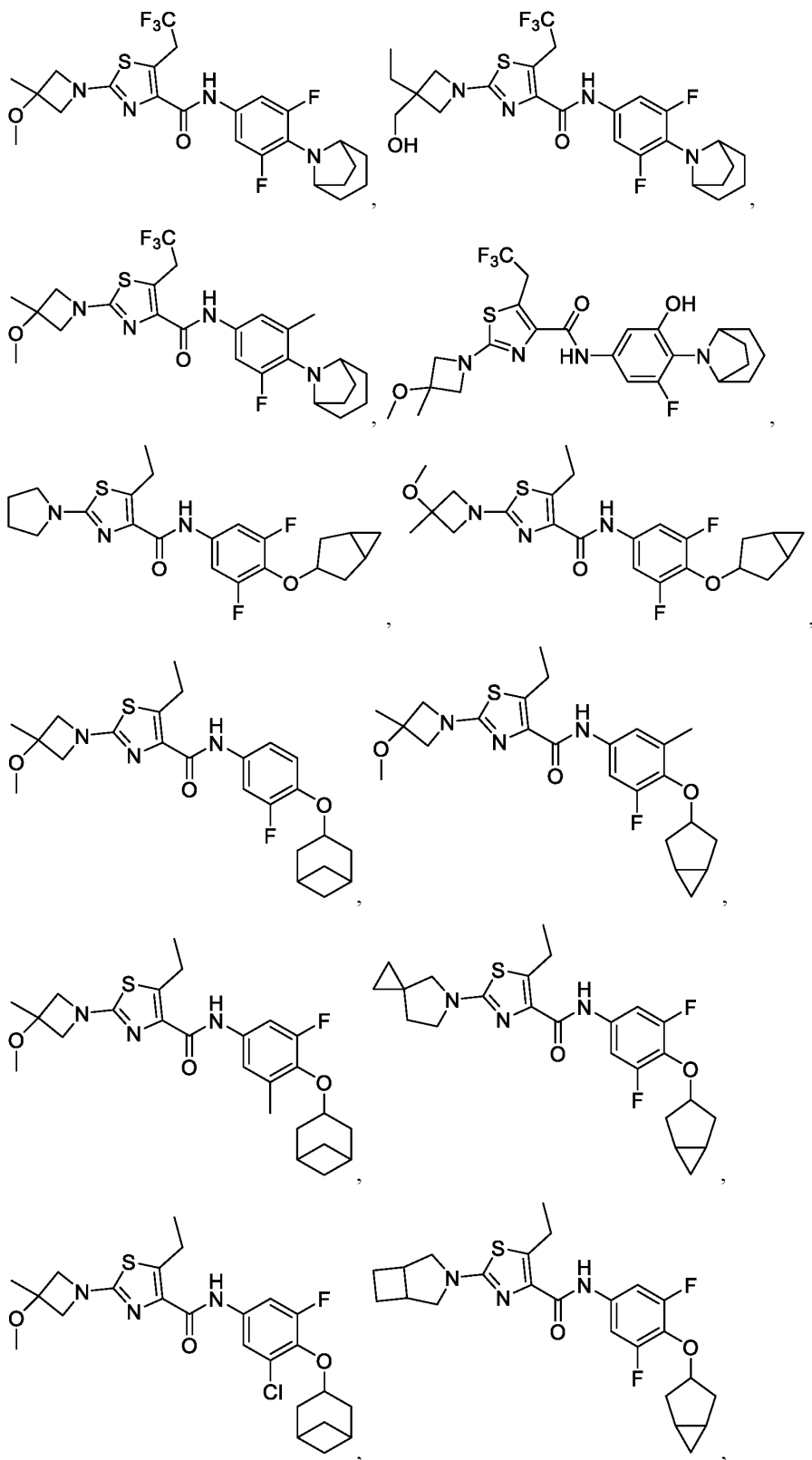
| Ex. | Structure                                                                           | Name                                                                                                                                    |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| 19  |    | N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-5-ethyl-2-(5-azaspiro[2.4]heptan-5-yl)thiazole-4-carboxamide                     |
| 20  |    | N-(4-(bicyclo[3.1.1]heptan-3-yloxy)-3-chloro-5-fluorophenyl)-5-ethyl-2-(3-methoxy-3-methylazetidin-1-yl)thiazole-4-carboxamide          |
| 21  |   | N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-2-(3-azabicyclo[3.2.0]heptan-3-yl)-5-ethylthiazole-4-carboxamide                 |
| 22  |  | N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-2-(3-methoxy-3-methylazetidin-1-yl)-5-propylthiazole-4-carboxamide               |
| 23  |  | N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-5-(2-fluoroethyl)-2-(3-methoxy-3-methylazetidin-1-yl)thiazole-4-carboxamide      |
| 24  |  | N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3-fluoro-5-methylphenyl)-5-(2-fluoroethyl)-2-(3-methoxy-3-methylazetidin-1-yl)thiazole-4-carboxamide |

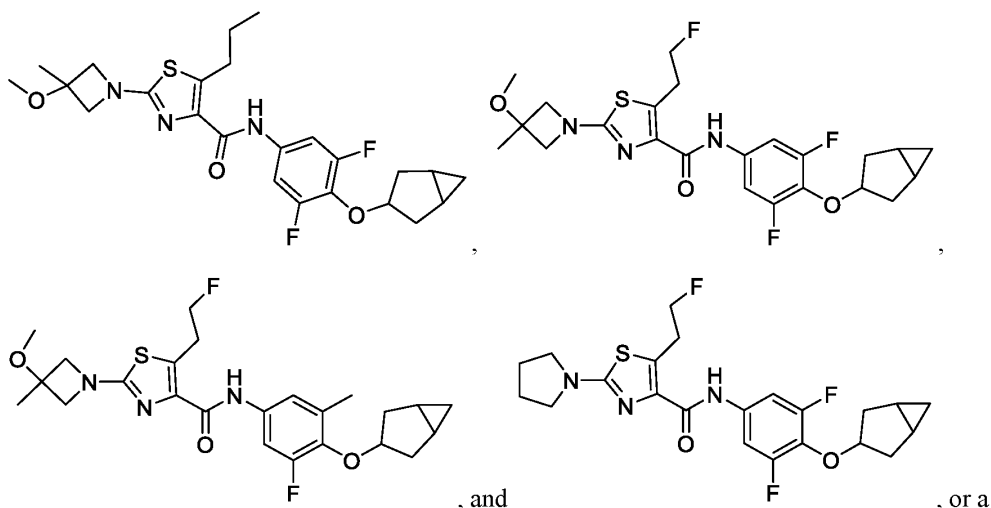
| Ex. | Structure                                                                         | Name                                                                                                               |
|-----|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| 25  |  | N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-5-(2-fluoroethyl)-2-(pyrrolidin-1-yl)thiazole-4-carboxamide |

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

[00132] In some embodiments, the compound is selected from the group consisting of:







pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

### Further Forms of Compounds Disclosed Herein

#### *Isomers/Stereoisomers*

**[00133]** In some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the corresponding mixtures thereof. In some situations, the compounds described herein possess one or more chiral centers and each center independently exists in the R configuration or S configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred. In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization.

#### *Labeled compounds*

**[00134]** In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein

include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact 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 compounds disclosed herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chlorine, such as  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^{17}\text{O}$ ,  $^{31}\text{P}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{18}\text{F}$ , and  $^{36}\text{Cl}$ , respectively. Compounds described herein, and the pharmaceutically acceptable salts, solvates, or stereoisomers thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds, for example those into which radioactive isotopes, such as  $^3\text{H}$  and  $^{14}\text{C}$ , are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e.,  $^3\text{H}$  and carbon-14, i.e.,  $^{14}\text{C}$ , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavy isotopes, such as deuterium, i.e.,  $^2\text{H}$ , produces certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. In some embodiments, one or more hydrogen in a compound disclosed herein has been replaced by a deuterium atom. In some embodiments, one or more alkyl substituents in a compound disclosed herein has been replaced by a deuterioalkyl substituents.

**[00135]** In some embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

*Pharmaceutically acceptable salts*

**[00136]** In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

**[00137]** In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds disclosed herein, or a solvate, or stereoisomer thereof, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

**[00138]** Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral, organic acid or inorganic base, such salts including, but not limited to, acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, gluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate,

glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate,  $\gamma$ -hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate metaphosphate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-naphthalenesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylate, undecanoate, and xylenesulfonate.

**[00139]** Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid and muconic acid. In some embodiments, other acids, such as oxalic, while not in themselves pharmaceutically acceptable, are employed in the preparation of salts useful as intermediates in obtaining the compounds disclosed herein, solvate, or stereoisomer thereof and their pharmaceutically acceptable acid addition salts.

**[00140]** In some embodiments, those compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, sulfate, of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate,  $N^+(C_1-C_4 \text{ alkyl})_4$  hydroxide, and the like.

**[00141]** Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they contain. In some embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

*Solvates*

[00142] In some embodiments, the compounds described herein exist as solvates. The invention provides for methods of treating diseases by administering such solvates. The invention further provides for methods of treating diseases by administering such solvates as pharmaceutical compositions.

[00143] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed with pharmaceutically acceptable solvents, such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of the compounds described herein can be conveniently prepared or formed during the processes described herein. By way of example only, hydrates of the compounds described herein can be conveniently prepared from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran or methanol. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

#### *Tautomers*

[00144] In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. Tautomers are compounds that are interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and one or more adjacent double bonds. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. All tautomeric forms of the compounds disclosed herein are contemplated. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH.

#### **Method of Treatment**

[00145] Provided herein are methods for treating TRPML1-mediated disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound disclosed herein effective to reduce or prevent said disorder in the subject, in combination with at least one additional agent for the treatment of said disorder that is known in the art. Certain embodiments provide therapeutic compositions comprising at least one compound disclosed herein in combination with one or more additional agents for the treatment of TRPML1-mediated disorders.

[00146] Also, provided herein are compounds for use in the manufacture of a medicament for the treatment of a TRPML1 mediated disease. Further provided herein is a method of treatment of a disease mediated by TRPML1 activity, in a mammalian subject, which comprises administering a therapeutically effective amount of a compound disclosed herein.

[00147] TRPML1-mediated diseases include proliferative disorders, such as cancers, inflammatory disorders, pain, neurodegenerative disorders, cognitive and psychiatric disorders, and other diseases as disclosed below.

[00148] TRPML1-mediated disorder or disease is aging, bone diseases, cardiovascular diseases, congenital developmental disorders, eye diseases, hematological and solid malignancies, infectious diseases, inflammatory diseases, liver diseases, metabolic diseases, neurological or neurodegenerative

diseases, pancreatitis, renal diseases, skeletal muscle disorders, obesity, lysosomal storage diseases, hypertrophic cardiomyopathy, dilated cardiomyopathy, inclusion body myositis, Paget's disease, or pulmonary diseases.

**[00149]** In some embodiments, the TRPML1-mediated disorder or disease is Aicardi-Goutières syndrome, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), ataxia-telangiectasia, autism spectrum disorders, Batten disease, bipolar disorder, cerebral ataxia, Charcot-Marie-Tooth variant diseases, Chronic Wasting disease, corticobasal degeneration, corticobasal syndrome, bovine spongiform encephalopathy, Creutzfeldt-Jacob disease, Danon disease, Duchenne muscular dystrophy, exotic ungulate encephalopathy, Fabre disease, Fatal Familial insomnia, Friedreich ataxia, Feline spongiform encephalopathy, Fragile X, frontal temporal dementia, Gaucher disease, Gerstmann-Straussler-Scheinker disease, Giant axonal neuropathy, GM1 and GM2 gangliosidosis, Huntington's disease, Infantile Refsum disease, JUNQ and IPOD, Krabbe's disease, Kuru, Leukoencephalopathy, Lewy Body dementia, locomotor ataxia, Lyme disease, Machado Joseph disease, major depressive disorder, MPS-III, mucopolidosis, multiple sulfatase deficiency, multiple systems atrophy, myofibrillar myopathies, myotonic dystrophy, Niemann-Pick disease, neuronal ceroid lipofuscinosis, Parkinson's disease, Parkinsonism, Pick's disease, polyglutamine diseases, Pompe disease, pontocerebellar hypoplasia, prion diseases, progressive nuclear palsy, progressive Supranuclear palsy, pyruvate dehydrogenase deficiency, Sandhoff disease, schizophrenia, scrapie, Shy-Drager syndrome, spinal muscular atrophy, spinocerebellar ataxias, sporadic familial insomnia, subacute degeneration of the spinal cord, subacute sclerosing panencephalitis, Tay-Sachs disease, transneuronal degeneration, tuberous Sclerosis, Spinocerebellar Ataxia's, or vascular dementia.

**[00150]** In some embodiments, the TRPML1-mediated disorder or disease is age-related macular degeneration, non-alcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), non-alcoholic fatty liver disease (NAFLD), retinal cell degeneration in glaucoma, retinitis pigmentosa, acute kidney injury, atherosclerosis, Crohn's disease, diabetic nephropathy, female infertility, H. pylori infections, hypochlorhydria, pancreatitis, retinal detachment, type 2 diabetes mellitus, ulcerative colitis, or sarcopenia.

**[00151]** The compounds disclosed herein are useful for the treatment of neurodegenerative disorders of various origins such as Alzheimer's disease and other dementia conditions such as Lewy body dementia, fronto-temporal dementia and other tauopathies; amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease and other parkinsonian syndromes; Huntington's disease; HIV-induced neuroinflammation; essential tremors; other spinocerebellar degenerations, neuropathies such as Charcot-Marie-Tooth neuropathy and other TRPML1-mediated diseases such as Type IV mucopolidosis (MLIV). The compounds disclosed herein are also useful for the treatment of neurological conditions such as epilepsy including simple partial seizure, complex partial seizure, secondary generalized seizure, further including absence seizure, myoclonic seizure, clonic seizure, tonic seizure, tonic clonic seizure, and atonic seizure, and for prevention and treatment of status epilepticus (SE).

**[00152]** The compounds disclosed herein are also useful for the treatment of cognitive disorders and of psychiatric disorders. Psychiatric disorders include, and are not limited to major depression, dysthymia, mania, bipolar disorder (such as bipolar disorder type I, bipolar disorder type II), cyclothymic disorder, rapid cycling, ultradian cycling, mania, hypomania, schizophrenia, schizophreniform disorders, schizoaffective disorders, personality disorders, attention disorders with or without hyperactive behavior, delusional disorders, brief psychotic disorders, shared psychotic disorders, psychotic disorder due to a general medical condition, substance-induced psychotic disorders or a psychotic disorder not otherwise specified, anxiety disorders such as generalized anxiety disorder, panic disorders, post-traumatic stress disorder, impulse control disorders, phobic disorders, dissociative states. The compounds disclosed herein are also useful for the treatment of smoking addiction, drug addiction, or alcoholism. The compounds disclosed herein are particularly useful for the treatment of bipolar disorders, psychosis, anxiety, or addiction.

**[00153]** The compounds disclosed herein are useful in the prevention or treatment of neuroinflammation and CNS damage induced by HIV infection and of HIV-associated neurocognitive deficits. The compounds disclosed herein are useful in the prevention or treatment of neuropathic pain. Neuropathic pain syndromes include, and are not limited to: chemotherapy-induced peripheral neuropathy, diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; neuralgia, such as post-herpetic neuralgia and trigeminal neuralgia, Morton's neuralgia, causalgia; and pain resulting from physical trauma, amputation, phantom limb, cancer, toxins or chronic inflammatory conditions; central pain such as the one observed in thalamic syndromes, mixed central and peripheral forms of pain such as complex regional pain syndromes (CRPS) also called reflex sympathetic dystrophies.

**[00154]** The compounds disclosed herein are also useful for the treatment of pain, including chronic pain. Chronic pain includes, and is not limited to, chronic pain caused by inflammation or an inflammatory-related condition, osteoarthritis, rheumatoid arthritis, acute injury or trauma, upper back pain or lower back pain (resulting from systematic, regional or primary spine disease such as radiculopathy), bone pain (due to osteoarthritis, osteoporosis, bone metastasis or unknown reasons), pelvic pain, spinal cord injury-associated pain, cardiac chest pain, non-cardiac chest pain, central post-stroke pain, myofascial pain, sickle cell pain, cancer pain, Fabry's disease, AIDS pain, geriatric pain or pain caused by headache, temporomandibular joint syndrome, gout, fibrosis or thoracic outlet syndromes, in particular rheumatoid arthritis and osteoarthritis.

**[00155]** The compounds disclosed herein are also useful in the treatment of acute pain caused by acute injury, illness, sport-medicine injuries, carpal tunnel syndrome, burns, musculoskeletal sprains and strains, musculotendinous strain, cervicobrachial pain syndromes, dyspepsia, gastric ulcer, duodenal ulcer, dysmenorrhea, endometriosis, or surgery (such as open heart or bypass surgery), post-operative pain, kidney stone pain, gallbladder pain, gallstone pain, obstetric pain, or dental pain.

**[00156]** The compounds disclosed herein are also useful in the treatment of headaches such as migraine, tension type headache, transformed migraine or evolutive headache, cluster headache, as well

as secondary headache disorders, such as the ones derived from infections, metabolic disorders or other systemic illnesses and other acute headaches, paroxysmal hemicrania and the like, resulting from a worsening of the above mentioned primary and secondary headaches.

**[00157]** The compounds disclosed herein are also useful in the treatment of diseases such as vertigo, tinnitus, muscle spasm, and other disorders including and not limited to cardiovascular diseases (such as cardiac arrhythmia, cardiac infarction or angina pectoris, hypertension, cardiac ischemia, cerebral ischemia) endocrine disorders (such as acromegaly or diabetes insipidus) diseases in which the pathophysiology of the disorder involves excessive or hypersecretory or otherwise inappropriate cellular secretion of an endogenous substance (such as catecholamine, a hormone or a growth factor).

**[00158]** The compounds disclosed herein are also useful in the selective treatment of liver disease, such as inflammatory liver diseases, for example chronic viral hepatitis B, chronic viral hepatitis C, alcoholic liver injury, primary biliary cirrhosis, autoimmune hepatitis, liver fibrosis, non-alcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), non-alcoholic fatty liver disease (NAFLD), and liver transplant rejection.

**[00159]** The compounds disclosed herein inhibit inflammatory processes affecting all body systems. Therefore, they are useful in the treatment of inflammatory processes of the musculoskeletal system of which the following is a list of examples but it is not comprehensive of all target disorders: arthritic conditions such as ankylosing spondylitis, cervical arthritis, fibromyalgia, gout, juvenile rheumatoid arthritis, lumbosacral arthritis, osteoarthritis, osteoporosis, psoriatic arthritis, rheumatic disease; disorders affecting skin and related tissues: eczema, psoriasis, dermatitis and inflammatory conditions such as sunburn; disorders of the respiratory system: asthma, allergic rhinitis and respiratory distress syndrome, lung disorders in which inflammation is involved such as asthma and bronchitis; chronic obstructive pulmonary disease; disorders of the immune and endocrinological systems: periarthritis nodosa, thyroiditis, aplastic anaemia, scleroderma, myasthenia gravis, multiple sclerosis and other demyelinating disorders, encephalomyelitis, sarcoidosis, nephritic syndrome, Bechet's syndrome, polymyositis, gingivitis.

**[00160]** The compounds disclosed herein are also useful in the treatment of gastrointestinal (GI) tract disorders such as inflammatory bowel disorders (IBD) including but not limited to ulcerative colitis, Crohn's disease, ileitis, proctitis, celiac disease, enteropathies, microscopic or collagenous colitis, eosinophilic gastroenteritis, or pouchitis resulting after proctocolectomy and post ileonatal anastomosis, and irritable bowel syndrome including any disorders associated with abdominal pain and/or abdominal discomfort such as pylorospasm, nervous indigestion, spastic colon, spastic colitis, spastic bowel, intestinal neurosis, functional colitis, mucous colitis, laxative colitis and functional dyspepsia; but also for treatment of atrophic gastritis, gastritis varioliforme, ulcerative colitis, peptic ulceration, pyrosis, and other damage to the GI tract, for example, by *Helicobacter pylori*, gastroesophageal reflux disease, gastroparesis, such as diabetic gastroparesis; and other functional bowel disorders, such as non-ulcerative dyspepsia (NUD); pancreatitis, emesis, diarrhea, visceral inflammation, and hypochlorhydria.

**[00161]** The compounds disclosed herein are also useful in the treatment of disorders of the genito-urinary tract such as overactive bladder, prostatitis (chronic bacterial and chronic nonbacterial prostatitis), prostatic dysplasia, interstitial cystitis, urinary incontinence, and benign prostatic hyperplasia, annexes, pelvic inflammation, Bartholin'sitis and vaginitis. In particular, overactive bladder and urinary incontinence.

**[00162]** The compounds disclosed herein are also useful in the treatment of renal disorders including diabetic nephropathy, renal allograft rejection, infectious renal diseases, IgA nephropathy, fibrotic kidney disease, lupus nephritis, glomerulonephritis, acute kidney injury, and renal carcinoma.

**[00163]** The compounds disclosed herein are also useful in the treatment of ophthalmic diseases such as retinitis, retinitis pigmentosa, retinopathies, uveitis, acute injury to the eye tissue, age-related macular degeneration, glaucoma, retinal cell degeneration in glaucoma, conjunctivitis, and retinal detachment.

**[00164]** The compounds disclosed herein are also useful in the treatment of eating disorders such as anorexia nervosa including the subtypes restricting type and binge-eating/purging type; bulimia nervosa including the subtypes purging type and non-purging type; obesity; compulsive eating disorders; binge eating disorder; and eating disorder not otherwise specified.

**[00165]** The compounds disclosed herein are also useful in the treatment of allergic dermatitis, hyper-responsiveness of the airway, chronic obstructive pulmonary disease (COPD), bronchitis, septic shock, Sjögren's syndrome, glomerulonephritis, atherosclerosis, growth, and metastases of malignant cells, myeloblastic leukemia, diabetes (type 2 diabetes mellitus), meningitis, osteoporosis, burn injury, ischemic heart disease, stroke, peripheral vascular disease, varicose veins, glaucoma, and female infertility.

**[00166]** In some embodiments, the compounds and pharmaceutical compositions of the present disclosure are useful in the treatment or prevention of progression of cancer. In some embodiments, the cancer is a hematologic malignancy or solid tumor. Hematologic malignancies include leukemias, lymphomas, multiple myeloma, and subtypes thereof. Lymphomas can be classified various ways, often based on the underlying type of malignant cell, including Hodgkin's lymphoma (often cancers of Reed-Sternberg cells, but also sometimes originating in B cells; all other lymphomas are non-Hodgkin's lymphomas), B-cell lymphomas, T-cell lymphomas, mantle cell lymphomas, Burkitt's lymphoma, follicular lymphoma, and others as defined herein and known in the art.

**[00167]** B-cell lymphomas include, but are not limited to, diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL) /small lymphocytic lymphoma (SLL), and others as defined herein and known in the art.

**[00168]** T-cell lymphomas include T-cell acute lymphoblastic leukemia/lymphoma (T-ALL), peripheral T-cell lymphoma (PTCL), T-cell chronic lymphocytic leukemia (T-CLL) Sezary syndrome, and others as defined herein and known in the art.

**[00169]** Leukemias include acute myeloid (or myelogenous) leukemia (AML), chronic myeloid (or myelogenous) leukemia (CML), acute lymphocytic (or lymphoblastic) leukemia (ALL), chronic lymphocytic leukemia (CLL) hairy cell leukemia (sometimes classified as a lymphoma) and others as defined herein and known in the art.

[00170] Plasma cell malignancies include lymphoplasmacytic lymphoma, plasmacytoma, and multiple myeloma.

[00171] Solid tumors include melanomas, neuroblastomas, gliomas or 5 carcinomas such as tumors of the brain, head and neck, breast, lung (e.g., non-small cell lung cancer, NSCLC), reproductive tract (e.g., ovary), upper digestive tract, pancreas, liver, renal system (e.g., kidneys), bladder, prostate and colorectum.

[00172] Besides being useful for human treatment, certain compounds and formulations disclosed herein may also be useful for veterinary treatment of companion animals, exotic animals, and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

### Dosing

[00173] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation and/or dose ranging clinical trial.

[00174] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the compounds are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00175] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, in specific embodiments, the dosage, or the frequency of administration, or both, is reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain embodiments, however, the patient requires intermittent or daily treatment on a long-term basis upon any recurrence of symptoms.

[00176] The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight, sex) of the subject or host in need of treatment, but nevertheless is determined according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated.

### Routes of Administration

[00177] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical

administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

**[00178]** In certain embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long-acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other embodiments, the drug is delivered in a targeted drug delivery system, for example, in a liposome coated with organ specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended-release formulation, or in the form of an intermediate-release formulation. In some embodiments, the compound described herein is administered topically.

#### **Pharmaceutical Compositions/Formulations**

**[00179]** The compounds described herein are administered to a subject in need thereof, either alone or in combination with pharmaceutically acceptable carriers, excipients, or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. In one embodiment, the compounds disclosed herein may be administered to animals. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal, and topical routes of administration.

**[00180]** In another aspect, provided herein are pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and at least one pharmaceutically acceptable excipient. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable excipients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), herein incorporated by reference for such disclosure.

**[00181]** In some embodiments, the pharmaceutically acceptable excipient is selected from carriers, binders, filling agents, suspending agents, flavoring agents, sweetening agents, disintegrating agents, dispersing agents, surfactants, lubricants, colorants, diluents, solubilizers, moistening agents, plasticizers, stabilizers, penetration enhancers, wetting agents, anti-foaming agents, antioxidants, preservatives, and any combinations thereof.

**[00182]** The pharmaceutical compositions described herein are administered to a subject by appropriate administration routes, including, but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), intranasal, buccal, topical, rectal, or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, liquids, gels, syrups, elixirs, slurries, suspensions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid oral dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, powders, dragees, effervescent formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

**[00183]** Pharmaceutical compositions including compounds described herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof are manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or compression processes.

**[00184]** Pharmaceutical compositions for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents are added, such as the cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. In some embodiments, dyestuffs or pigments are added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

**[00185]** Pharmaceutical compositions that are administered orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In some embodiments, stabilizers are added.

**[00186]** Pharmaceutical compositions for parental use are formulated as infusions or injections. In some embodiments, the pharmaceutical composition suitable for injection or infusion includes sterile aqueous solutions, or dispersions, or sterile powders comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, the pharmaceutical composition comprises a liquid carrier. In some embodiments, the liquid carrier is a solvent or liquid dispersion medium comprising, for example, water, saline, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic

glyceryl esters, and any combinations thereof. In some embodiments, the pharmaceutical compositions further comprise a preservative to prevent growth of microorganisms.

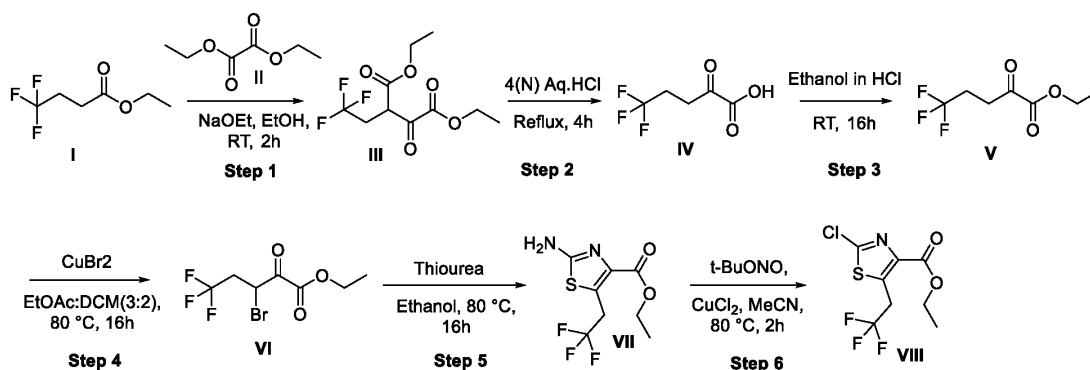
### Combination

**[00187]** Disclosed herein are methods of treating a TRPML1-mediated disorder or disease using a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, in combination with an additional therapeutic agent.

**[00188]** In some embodiments, the additional therapeutic agent is administered at the same time as the compound disclosed herein. In some embodiments, the additional therapeutic agent and the compound disclosed herein are administered sequentially. In some embodiments, the additional therapeutic agent is administered less frequently than the compound disclosed herein. In some embodiments, the additional therapeutic agent is administered more frequently than the compound disclosed herein. In some embodiments, the additional therapeutic agent is administered prior than the administration of the compound disclosed herein. In some embodiments, the additional therapeutic agent is administered after the administration of the compound disclosed herein.

## EXAMPLES

### Scheme 1: Preparation of ethyl 2-chloro-5-(2,2,2-trifluoroethyl)thiazole-4-carboxylate (VIII)



**[00189] Step 1:** To a stirred solution of ethyl 4,4,4-trifluorobutanoate, **I** (200 g, 1176.47 mmol) in ethanol (1540 mL) was added diethyl oxalate, **II** (239.45 mL, 1764.70 mmol) followed by addition of NaOEt (21%) (457 mL, 1411.76 mmol) via a dropping funnel and stirred for 2 h at RT. After completion [Monitored by TLC 20 % EtOAc/Hexane, *R<sub>f</sub>*-0.2, (KMnO<sub>4</sub> active)], reaction mixture was concentrated under reduced pressure. Resultant crude was diluted with water (700 mL) and washed by EtOAc (3x 300 mL). Aqueous part was separated, acidified by 3(N) aq. HCl, and extracted by EtOAc (500 mL x 3). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to afford crude diethyl 2-oxo-3-(2,2,2-trifluoroethyl) succinate, **III** (200 g, 63%) as colorless liquid.

**[00190] Step 2:** Solution of diethyl 2-oxo-3-(2,2,2-trifluoroethyl) succinate, **III** (200 g, 740.74 mmol) in 4(N) aqueous HCl solution (2L) was allowed to reflux [110 °C] for 4 h. The reaction was monitored by TLC [20 % EtOAc in hexane (KMnO<sub>4</sub> active)]. The reaction mixture was brought to RT, excess NaCl was added to the reaction mixture and extracted by EtOAc (4x 800 mL). The organic part was dried over sodium sulfate and concentrated under reduced pressure to afford crude 5,5,5-trifluoro-2-oxopentanoic acid, **IV** (130 g, crude compound) as light brown liquid, this was used for the next step without further purification.

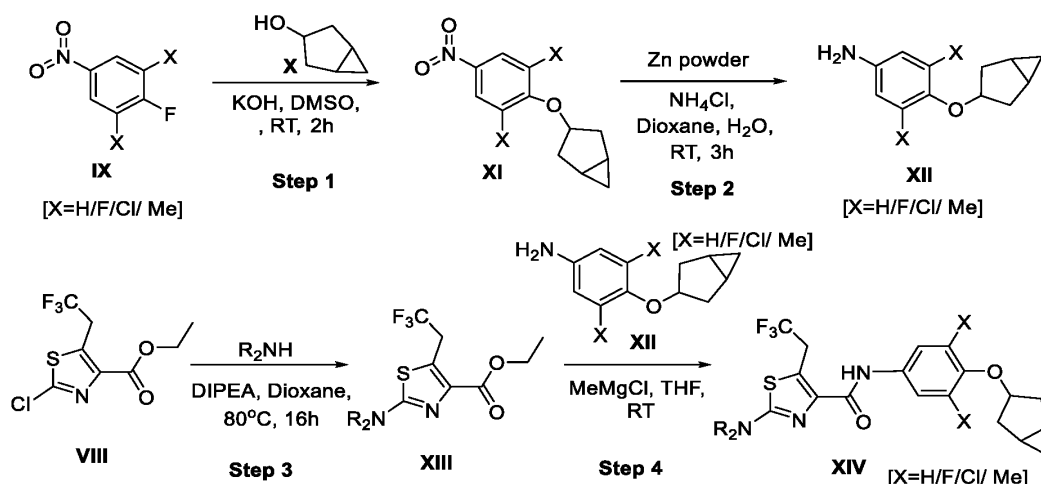
**[00191] Step 3:** Solution of 5,5,5-trifluoro-2-oxopentanoic acid, **IV** (130 g, 764.70 mmol, 1eq.) in ethanolic HCl (1300 mL) was allowed to stir at RT for 16 h. After completion [monitored by TLC (20 % EtOAc /Hexane), *R<sub>f</sub>*-0.3], reaction mixture was concentrated under reduced pressure. Resultant crude was purified by column chromatography using silica Gel under gradient elution of 0-15 % EtOAc/Hexane to afford ethyl 5,5,5-trifluoro-2-oxopentanoate, **V** (95 g, ~85% pure) as colorless liquid.

**[00192] Step 4:** To a stirred solution of ethyl 5,5,5-trifluoro-2-oxopentanoate, **V** (200 g, 1010 mmol) in EtOAc : DCM (3:2) [8200 mL (40 % wt/vol)] was added CuBr<sub>2</sub> (450.5 g, 2020 mmol) and heated to 80 °C for 16 h. The reaction was monitored by TLC in 20 % EtOAc/Hexane (*R<sub>f</sub>*-0.2, UV inactive, KMnO<sub>4</sub> active) and after completion reaction mixture was filtered through sintered funnel, filtrate was concentrated under reduced pressure. The crude was dissolved by DCM (1 L) and filtered through celite bed, resultant filtrate was dried over sodium sulfate and concentrated under reduced pressure to afford crude ethyl 3-bromo-5,5,5-trifluoro-2-oxopentanoate, **VI** (260 g, 93%) as a brown liquid.

**[00193] Step 5:** To a stirred solution of ethyl 3-bromo-5,5,5-trifluoro-2-oxopentanoate, **VI** (5 g, 18.116 mmol) in ethanol (100 mL) was added thiourea (6.1 g, 81.522 mmol) and reaction mixture was heated to 80 °C for 16 h. After completion [monitored by TLC [30 % EtOAc/Hexane, *R<sub>f</sub>* - 0.4)], reaction mixture was concentrated under reduced pressure. Resultant crude was diluted with water, basified with saturated NaHCO<sub>3</sub> solution and extracted with ethyl acetate (3 x 600 mL), washed by brine solution. The organic part was dried over sodium sulfate and concentrated under reduced pressure. The crude was purified by column chromatography using silica (100-200 mesh) under gradient elution of 50% EtOAc/Hexane to afford ethyl 2-amino-5-(2,2,2-trifluoroethyl)thiazole-4-carboxylate, **VII** (2.5 g, 54%) as an off white solid.

**[00194] Step 6:** To a stirred solution of CuCl<sub>2</sub> (1.5 g, 11.8 mmol) in acetonitrile (50 mL) was added t-BuONO (2.5 mL, 19.7 mmol) and heated to 50 °C for 30 min. Then ethyl 2-amino-5-(2,2,2-trifluoroethyl)thiazole-4-carboxylate, **VII** (2.5 g, 9.8 mmol) was suspended in 20 mL of acetonitrile and added to the reaction mixture at same temperature and allowed to stir at 80 °C for 1.5 h. After completion [monitored by TLC (30 % EtOAc/Hexane, *R<sub>f</sub>*-0.6)], reaction mixture was concentrated under reduced pressure and was diluted in EtOAc (500 mL) and water (500 mL), filtered through celite bed. The organic part was separated and washed with brine solution (400 mL). Then organic layer was dried over sodium sulfate and concentrated under reduced pressure, resultant crude was purified by column chromatography using silica (100-200 mesh) under gradient elution of 0-5% EtOAc/Hexane to afford ethyl 2-chloro-5-(2,2,2-trifluoroethyl)thiazole-4-carboxylate, **VIII** as pale yellow liquid (2 g, 74%).

**Scheme 2: General conditions for preparation of example of the general formula specified by structure XIV (Examples 1-7):**



**[00195] Step 1:** To a stirred solution of **IX** (1.0 eq.) and cis bicyclo[3.1.0]hexan-3-ol, **X** (1.2 eq.) in DMSO (3 mL/mmol), was added KOH (3.0 eq.). The reaction was stirred for 2 h at RT. After completion [Monitored by TLC], the resultant reaction mixture was partitioned between EtOAc and water. Organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude was purified through flash column chromatography using EtOAc in hexane as an eluent to afford products of general structure **XI**.

**[00196] Step 2:** To a stirred solution of **XI** (1 eq.) in 1,4-dioxane:water (5:1) (20 mL/g **XI**) was added zinc dust (7 eq.) along with ammonium chloride (7 eq.) at 0 °C. It was then stirred for 3 h at RT. After completion [Monitored by TLC], reaction mixture was filtered through a glass sintered. The filtrate was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resultant crude was purified by flash column chromatography using EtOAc in hexane to afford products of general structure **XII**.

**[00197] Step 3:** To a stirred solution of intermediate (**VIII**) (1.0 eq.) and DIPEA (3.0 eq.) in dioxane (3 mL/mmol) was added  $\text{R}_2\text{NH}$  (1.1 eq.) and resultant reaction mixture was allowed to stir at 80 °C for 16 h. After completion [Monitored by TLC], reaction mixture was concentrated under reduced pressure to remove dioxane. Resultant crude was purified through column chromatography using EtOAc in hexane as an eluent to afford products of general structure **XIII**.

**[00198] Step 4:** To a stirred solution of ester **XIII** (1.0 eq.) and amine **XII** (1.0 eq.) in dry THF (30 mL/g), was added MeMgCl (3M in THF, 2.4 eq.) dropwise and was stirred for 1 h at RT. The reaction was monitored by TLC. After completion reaction mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  solution and extracted with EtOAc and washed with water. Organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Resultant crude was purified by column chromatography using EtOAc in hexane as an eluent to afford products of general structure **XIV**.

**Example 1**

[00199] Example 1 was synthesized utilizing the procedures outlined in scheme 2 wherein compound IX was 3,4,5-trifluoronitrobenzene in step 1 and pyrrolidine as the amine in step 3, to provide N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-2-(pyrrolidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide (110 mg, 56%).

**Example 2**

[00200] Example 2 was synthesized utilizing the procedures outlined in scheme 2 wherein compound IX was 3,4,5-trifluoronitrobenzene in step 1 and 3-methoxy-3-methylazetidine hydrochloride as the amine in step 3, to provide N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-2-(3-methoxy-3-methylazetidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide (125 mg, 60%).

**Example 3**

[00201] Example 3 was synthesized utilizing the procedures outlined in scheme 2 wherein compound IX was 3,4-difluoronitrobenzene in step 1 and pyrrolidine as the amine in step 3, to provide N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3-fluorophenyl)-2-(pyrrolidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide (70 mg, 45%).

**Example 4**

[00202] Example 4 was synthesized utilizing the procedures outlined in scheme 2 wherein compound IX was 2-chloro-1-fluoro-4-nitrobenzene in step 1 and pyrrolidine as the amine in step 3, to provide N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3-chlorophenyl)-2-(pyrrolidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide (90 mg, 57%).

**Example 5**

[00203] Example 5 was synthesized utilizing the procedures outlined in scheme 2 wherein compound IX was 1,2-difluoro-3-methyl-5-nitrobenzene in step 1 and pyrrolidine as the amine in step 3, to provide N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3-fluoro-5-methylphenyl)-2-(pyrrolidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide (90 mg, 57%).

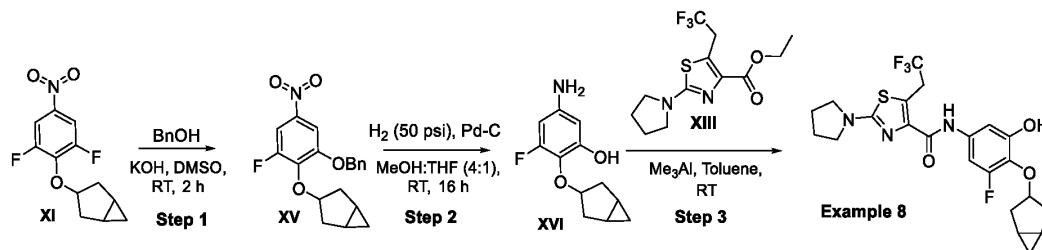
**Example 6**

[00204] Example 6 was synthesized utilizing the procedures outlined in scheme 2 wherein compound IX was 3,4,5-trifluoronitrobenzene in step 1 and 3-(methoxymethyl)-3-methylazetidine hydrochloride as the amine in step 3, to provide N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-2-(3-(methoxymethyl)-3-methylazetidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide (52 mg, 22%).

**Example 7**

[00205] Example 7 was synthesized utilizing the procedures outlined in scheme 2 wherein compound IX was 3,4,5-trifluoronitrobenzene in step 1 and (3-ethylazetidin-3-yl)methanol hydrochloride as the amine in step 3, to provide N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-2-(3-ethyl-3-(hydroxymethyl)azetidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide (19 mg, 14%).

**Example 8****Scheme 3:**

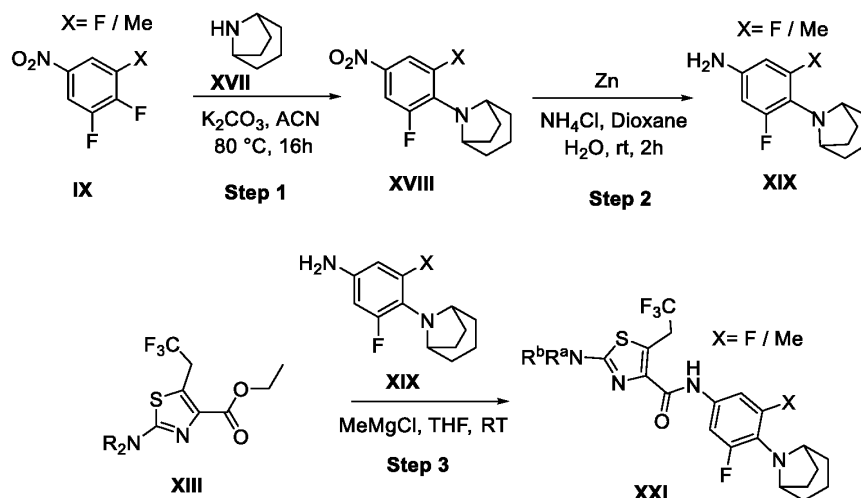


**[00206] Step 1:** To a stirred solution of **XI** (1g, 3.92 mmol) and KOH dust (0.61 g, 10.98 mmol) in DMSO (5 mL) was added BnOH (0.8 mL, 3.92 mmol) and stirred for 2 h at rt. After completion [Monitored by TLC], reaction mixture was partitioned between EtOAc and water. Organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resultant crude was purified through silica column chromatography (2% EtOAc in hexane) to afford product (850 mg, 63%) as pale yellow liquid **XV**.

**[00207] Step 2:** To a stirred solution of **XV** (850 mg, 2.47 mmol) in methanol (40 mL) was added 500 mg Pd/C and stirred under hydrogen atmosphere of 50 psi at rt for 16 h. After completion [Monitored with TLC], the reaction mixture was filtered through celite, concentrated under reduced pressure. The residue was then purified by flash column chromatography (20% EtOAc in hexane) to afford amine **XVI**, (450 mg, 81%) as brown liquid.

**[00208] Step 3:** To a stirred solution of **XIII** (150 mg, 0.487 mmol) and amine **XVI** (108.5 mg, 0.487 mmol) in dry toluene (10 mL), trimethylaluminum (2M in toluene, 0.8 mL, 1.70 mmol) dropwise at 0 °C, and the resultant reaction mixture was allowed to stir at rt for 2 h. After completion [Monitored with TLC/LCMS] the reaction mixture was quenched with saturated ammonium chloride solution and partitioned with EtOAc. Organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Resultant crude was purified by flash column chromatography (5% EtOAc in hexane) to afford **Example 8** (130 mg, 55 %).

Scheme 4: General procedure for the synthesis of examples of general structure XXI (Examples 9-12).



**[00209] Step 1:** To a stirred solution of compound IX (1.0 eq.) and potassium carbonate (2.0 eq.) in acetonitrile (3 mL/mmol) was added 8-azabicyclo[3.2.1]octane, XVII (1.1 eq.). The reaction mass was heated at 80 °C for 16 h. After completion [Monitored by TLC or LC-MS], reaction mixture was concentrated to remove volatiles. The crude reaction mixture was then diluted with EtOAc and washed with brine. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude material was purified through flash column chromatography using EtOAc/hexane as eluent to afford the intermediate compound XVIII.

**[00210] Step 2:** To a stirred solution of compound XVIII in 1,4-dioxane:water (5:1) was added zinc dust (7.0 eq.) followed by ammonium chloride (7.0 eq.) at 0 °C. It was then stirred for 2 h at rt. After completion [Monitored by TLC], the reaction mixture was filtered through a sintered glass. The filtrate was dried over anhydrous  $Na_2SO_4$ , concentrated under reduced pressure and purified through flash column chromatography using EtOAc-hexane as eluent to afford products of general structure XIX.

**[00211] Step 3:** To a stirred solution of ester XIII (1.0 eq.) and amine XIX (1.0 eq.) in dry THF (30 mL/g), was added MeMgCl (3M in THF, 2.4 eq.) dropwise and was stirred for 1 h at RT. The reaction was monitored by TLC. After completion reaction mixture was quenched with 1 N HCl and extracted with EtOAc and washed with water. Organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Resultant crude was purified by column chromatography to afford products of general structure XXI.

#### Example 9

**[00212]** Example 9 was synthesized utilizing the procedures outlined in scheme 4 wherein compound IX was 1,2,3-trifluoro-5-nitrobenzene in step 1 and pyrrolidine as the amine in step 3 (Scheme 2), to provide N-(4-(8-azabicyclo[3.2.1]octan-8-yl)-3,5-difluorophenyl)-2-(pyrrolidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide (80 mg, 48%)

**Example 10**

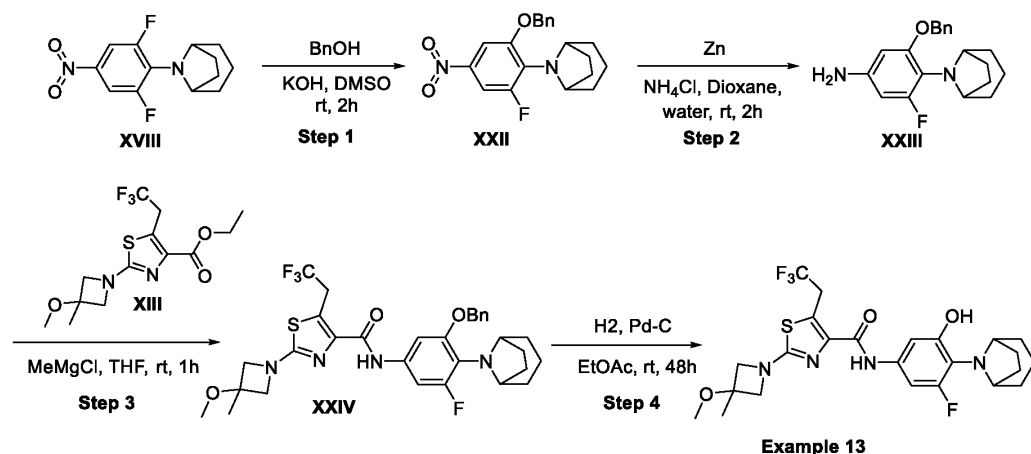
[00213] Example 10 was synthesized utilizing the procedures outlined in scheme 4 wherein compound **IX** was 1,2,3-trifluoro-5-nitrobenzene in step 1 and 3-methoxy-3-methylazetidine hydrochloride as the amine in step 3 (Scheme 2), to provide N-(4-(8-azabicyclo[3.2.1]octan-8-yl)-3,5-difluorophenyl)-2-(3-methoxy-3-methylazetidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide (60 mg, 38%).

**Example 11**

[00214] Example 11 was synthesized utilizing the procedures outlined in scheme 4 wherein compound **IX** was 1,2,3-trifluoro-5-nitrobenzene in step 1 and (3-ethylazetidin-3-yl)methanol hydrochloride as the amine in step 3 (Scheme 2), to provide N-(4-(8-azabicyclo[3.2.1]octan-8-yl)-3,5-difluorophenyl)-2-(3-ethyl-3-(hydroxymethyl)azetidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide (35 mg, 21%).

**Example 12**

[00215] Example 12 was synthesized utilizing the procedures outlined in scheme 4 wherein compound **IX** was 1,2-difluoro-3-methyl-5-nitrobenzene in step 1 and 3-methoxy-3-methylazetidine hydrochloride as the amine in step 3 (Scheme 2), to provide N-(4-(8-azabicyclo[3.2.1]octan-8-yl)-3-fluoro-5-methylphenyl)-2-(3-methoxy-3-methylazetidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide (60 mg, 38%).

**Example 13****Scheme 5:**

[00216] **Step 1:** To a stirred solution of benzyl alcohol (322 mg, 2.98 mmol), KOH dust (455 mg, 8.13 mmol) in DMSO (5 mL) was added 8-(2,6-difluoro-4-nitrophenyl)-8-azabicyclo[3.2.1]octane, **XVIII** (480 mg, 2.71 mmol) and stirred for 2 h at rt. After completion [Monitored by TLC], reaction mixture was partitioned between EtOAc and water. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resultant crude was purified through flash column chromatography using 5% EtOAc in hexane as an eluent to afford 8-(2-(benzyloxy)-6-fluoro-4-nitrophenyl)-8-azabicyclo[3.2.1]octane, **XXII** (590 mg, 61%) as yellow solid.

[00217] **Step 2:** To a stirred solution of 8-(2-(benzyloxy)-6-fluoro-4-nitrophenyl)-8-azabicyclo[3.2.1]octane, **XXII** (480 mg, 1.35 mmol) in 1,4-dioxane: water (6 mL, 5:1) was added zinc

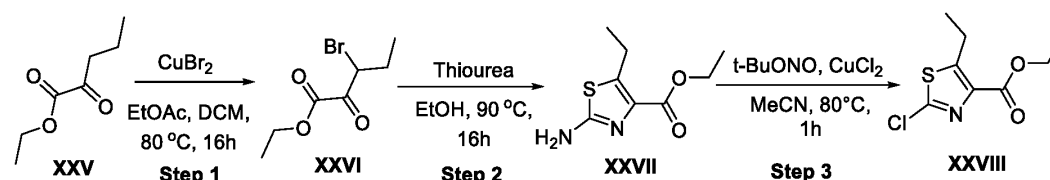
dust (425mg, 6.74 mmol) along with ammonium chloride (436 mg, 8.09 mmol) at 0 °C. It was then stirred for 2 h at rt. After completion [Monitored by TLC], reaction mixture was filtered through a glass sintered. The filtrate was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resultant crude was purified by flash column chromatography using 10% EtOAc in hexane to afford 3-(benzyloxy)-4-(8-azabicyclo[3.2.1]octan-8-yl)-5-fluoroaniline, **XXIII** (300 mg, 68%) as off white solid.

**[00218] Step 3:** To a stirred solution of ethyl 2-(3-methoxy-3-methylazetidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxylate, **XIII** (203.21 mg, 0.601 mmol) and 3-(benzyloxy)-4-(8-azabicyclo[3.2.1]octan-8-yl)-5-fluoroaniline, **XXIII** (200 mg, 0.613 mmol) in dry THF (10 mL) was added MeMgCl (3M in THF, 0.8 mL, 2.45 mmol) at rt and the resultant reaction mixture was allowed to stir at rt for 1h. After completion [Monitored with TLC/ LCMS], reaction mixture was quenched with saturated ammonium chloride solution and partitioned with EtOAc. Organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resultant crude was purified by flash column chromatography using 10% EtOAc in hexane to afford N-(3-(benzyloxy)-4-(8-azabicyclo[3.2.1]octan-8-yl)-5-fluorophenyl)-2-(3-methoxy-3-methylazetidin-1-yl)-5-(2,2,2-trifluoroethyl)oxazole-4-carboxamide, **XXIV** (150 mg, 40%) as an off-white solid.

**[00219] Step 4:** To a degassed solution of **XXIV** (150 mg, 0.24 mmol) in EtOAc (10 mL) Pd-C (10%, 50 mg) was added and the resultant reaction mixture was allowed to stir under hydrogen balloon pressure at rt for 48h. After completion [Monitored with TLC/ LCMS], reaction mixture was filtered and filtrate was concentrated under reduced pressure. The resultant crude was purified by preparative HPLC to afford N-(4-(8-azabicyclo[3.2.1]octan-8-yl)-3-fluoro-5-hydroxyphenyl)-2-(3-methoxy-3-methylazetidin-1-yl)-5-(2,2,2-trifluoroethyl)thiazole-4-carboxamide, **Example 13** (30 mg, 22%).

#### Preparation of intermediate ethyl 2-chloro-5-ethylthiazole-4-carboxylate (**XXVIII**):

##### Scheme 6:



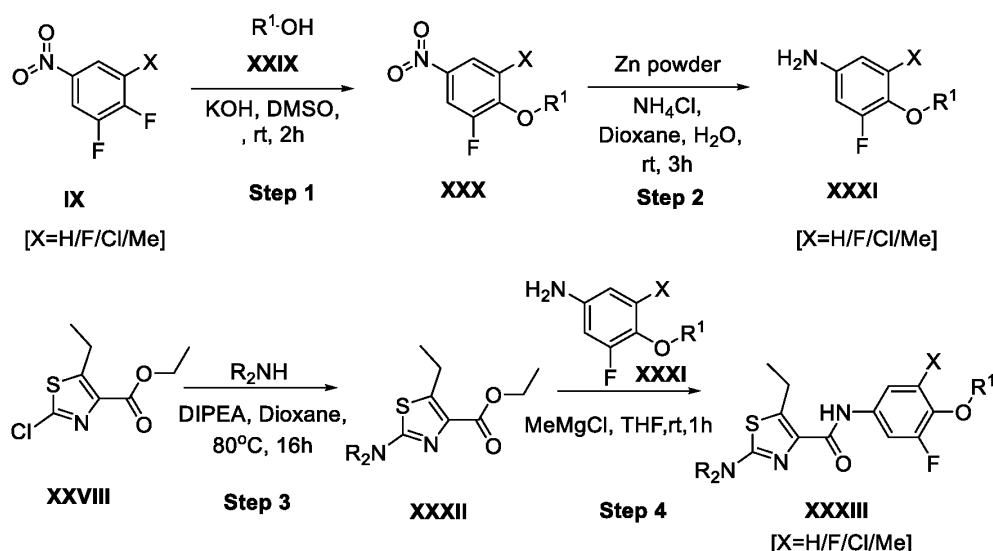
**[00220] Step 1:** To a stirred solution of ethyl 2-oxopentanoate, **XXV** (150 g, 1.04 mol) in EtOAc: DCM mixture (6000 mL, 3:2) was added CuBr<sub>2</sub> (464.58 g, 2.08 mol) and reaction mixture was heated to 80 °C for 16 h. After completion [monitored by TLC (20 % EtOAc/Hexane), *R<sub>f</sub>* 0.3 (KMnO<sub>4</sub> active)], reaction was filtered through sintered funnel and the filtrate was dried over sodium sulfate and concentrated under reduced pressure to obtain crude compound. The crude was purified by column chromatography using silica under gradient elution of 20 % EtOAc/Hexane to afford ethyl 3-bromo-2-oxopentanoate, **XXVI** as a brown liquid (160 g, 68.86 %).

**[00221] Step 2:** To a stirred solution of ethyl 3-bromo-2-oxopentanoate, **XXVI** (10.5 g, 47.3 mmol) in ethanol (150 mL) was added thiourea (14.38 g, 189.2 mmol). The reaction was heated to 90 °C for 16 h.

After completion [Monitored by TLC 20 % EtOAc/Hexane,  $R_f$ -0.2], reaction mixture was concentrated under reduced pressure. Resultant crude was diluted with ethyl acetate (500 mL), washed by saturated solution of  $\text{NaHCO}_3$  (1x200 mL) and brine solution (1x 200 mL). The organic part was dried over sodium sulfate and concentrated under reduced pressure to obtain crude compound. The crude was triturated by 70 % n-pentane in diethyl ether solution three times to get pure ethyl 2-amino-5-ethylthiazole-4-carboxylate, **XXVII** as an off white solid (7 g, 74%).

**[00222] Step 3:** To a stirred solution of  $\text{CuCl}_2$  (4.5 g, 33.7 mmol) in acetonitrile (60 mL) was added *tert*-Butyl nitrite (5.5 mL, 53.5 mmol) heated to 50 °C for 15 min. Then into the solution, ethyl 2-amino-5-ethylthiazole-4-carboxylate, **XXVII** (7.0 g, 33 mmol) dissolved in acetonitrile (30 mL) was added and the reaction mixture was heated to 80 °C and stirred for 1h. After completion [monitored by TLC (10 % EtOAc/Hexane,  $R_f$  - 0.4)], reaction mixture was concentrated under reduced pressure. The mixture was diluted in EtOAc (2000 mL) and water (1000 mL) and filtered through celite bed. The organic part was separated and washed by brine solution (1x 500 mL), dried over sodium sulfate, and concentrated under reduced pressure. The resultant crude was purified by column chromatography using silica under gradient elution of 0-10% EtOAc/Hexane to afford ethyl 2-chloro-5-ethylthiazole-4-carboxylate, **XXVIII** as a pale yellow gum (5.5 g, 75.82%).

**Scheme 7: General conditions for preparation of example of the general formula specified by structure XXXIII (Examples 14-21):**



**[00223] Step 1.** To a stirred solution of **IX** (1.0 eq.) and **XXIX** (1.2 eq.) in DMSO (3 mL/mmol), was added KOH (3.0 eq.). The reaction was stirred for 2 h at rt. After completion [Monitored by TLC], the resultant reaction mixture was partitioned between EtOAc and water. Organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude was purified through flash column chromatography using EtOAc in hexane as an eluent to afford desired product **XXX**.

**[00224] Step 2:** To a stirred solution of **XXX** (1 eq.) in 1,4-dioxane:water (5:1) (20 mL/g **XXX**) was added zinc dust (7 eq.) along with ammonium chloride (7 eq.) at 0 °C. It was then stirred for 3 h at rt.

After completion [Monitored by TLC], reaction mixture was filtered through a glass sintered. The filtrate was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resultant crude was purified by flash column chromatography using EtOAc in hexane to afford the pure **XXXI**.

**[00225] Step 3:** To a stirred solution of **XXVIII** (1.0 eq.) and DIPEA (3.0 eq.) in dioxane (3 mL/mmol) was added  $R_2NH$  (1.1 eq.) and resultant reaction mixture was allowed to stir at room temperature for 16 h. After completion [Monitored by TLC], reaction mixture was concentrated under reduced pressure to remove dioxane. The resultant crude was purified by flash column chromatography using EtOAc in hexane to afford the pure **XXXII**.

**[00226] Step 4:** To a stirred solution of **XXXII** (1.0 eq.) and **XXXI** (1.0 eq.) in dry THF (30 mL/g), was added MeMgCl (3M in THF, 2.4 eq.) dropwise and was stirred for 1h at RT. The reaction was monitored by TLC. After completion reaction mixture was quenched with 1 N HCl and extracted with EtOAc and washed with water. Organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Resultant crude was purified by column chromatography to afford examples of the general structure **XXXIII**.

#### Example 14

**[00227]** Example 14 was synthesized utilizing the procedures outlined in scheme 7 wherein compound **IX** was 1,2,3-trifluoro-5-nitrobenzene, using cis bicyclo[3.1.0]hexan-3-ol as the alcohol in step 1 and pyrrolidine as the amine in step 3, to provide N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-5-ethyl-2-(pyrrolidin-1-yl)thiazole-4-carboxamide (140 mg, 82%).

#### Example 15

**[00228]** Example 15 was synthesized utilizing the procedures outlined in scheme 7 wherein compound **IX** was 1,2,3-trifluoro-5-nitrobenzene, using cis bicyclo[3.1.0]hexan-3-ol as the alcohol in step 1 and 3-methoxy-3-methylazetidine hydrochloride as the amine in step 3, to provide N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-5-ethyl-2-(3-methoxy-3-methylazetidin-1-yl)thiazole-4-carboxamide (36 mg, 22%).

#### Example 16

**[00229]** Example 16 was synthesized utilizing the procedures outlined in scheme 7 wherein compound **IX** was 3,4-difluoronitrobenzene, using bicyclo[3.1.1]heptan-3-ol as the alcohol in step 1 and 3-methoxy-3-methylazetidine hydrochloride as the amine in step 3, to provide N-(4-(bicyclo[3.1.1]heptan-3-yloxy)-3-fluorophenyl)-5-ethyl-2-(3-methoxy-3-methylazetidin-1-yl)thiazole-4-carboxamide (90 mg, 54%).

#### Example 17

**[00230]** Example 17 was synthesized utilizing the procedures outlined in scheme 7 wherein compound **IX** was 1,2-difluoro-3-methyl-5-nitrobenzene, using cis bicyclo[3.1.0]hexan-3-ol as the alcohol in step 1 and 3-methoxy-3-methylazetidine hydrochloride as the amine in step 3, to provide N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3-fluoro-5-methylphenyl)-5-ethyl-2-(3-methoxy-3-methylazetidin-1-yl)thiazole-4-carboxamide (66 mg, 40%).

**Example 18**

[00231] Example 18 was synthesized utilizing the procedures outlined in scheme 7 wherein compound **IX** was 1,2-difluoro-3-methyl-5-nitrobenzene, using bicyclo[3.1.1]heptan-3-ol as the alcohol in step 1 and 3-methoxy-3-methylazetidine hydrochloride as the amine in step 3, to provide N-(4-(bicyclo[3.1.1]heptan-3-yloxy)-3-fluoro-5-methylphenyl)-5-ethyl-2-(3-methoxy-3-methylazetidin-1-yl)thiazole-4-carboxamide (64 mg, 38%).

**Example 19**

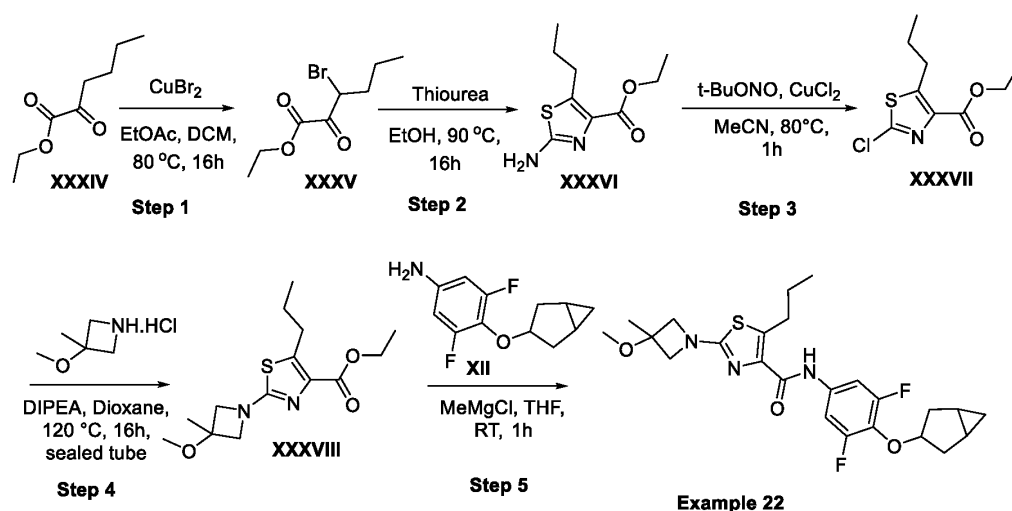
[00232] Example 19 was synthesized utilizing the procedures outlined in scheme 7 wherein compound **IX** was 1,2,3-trifluoro-5-nitrobenzene, using cis bicyclo[3.1.0]hexan-3-ol as the alcohol in step 1 and 5-azaspiro[2.4]heptane as the amine in step 3, to provide N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-5-ethyl-2-(5-azaspiro[2.4]heptan-5-yl)thiazole-4-carboxamide (45 mg, 17%).

**Example 20**

[00233] Example 20 was synthesized utilizing the procedures outlined in scheme 7 wherein compound **IX** was 1-chloro-2,3-difluoro-5-nitrobenzene, using bicyclo[3.1.1]heptan-3-ol as the alcohol in step 1 and 3-methoxy-3-methylazetidine hydrochloride as the amine in step 3, to provide N-(4-(bicyclo[3.1.1]heptan-3-yloxy)-3-chloro-5-fluorophenyl)-5-ethyl-2-(3-methoxy-3-methylazetidin-1-yl)thiazole-4-carboxamide (84 mg, 47%).

**Example 21**

[00234] Example 21 was synthesized utilizing the procedures outlined in scheme 7 wherein compound **IX** was 1,2,3-trifluoro-5-nitrobenzene, using cis bicyclo[3.1.0]hexan-3-ol as the alcohol in step 1 and 3-azabicyclo[3.2.0]heptane as the amine in step 3, to provide N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-2-(3-azabicyclo[3.2.0]heptan-3-yl)-5-ethylthiazole-4-carboxamide (25 mg, 38%).

**Example 22****Scheme 8:**

[00235] **Step 1:** To a stirred solution of ethyl 2-oxohexanoate, **XXXIV** (5 g, 31.65 mmol) in EtOAc: DCM mixture (250 mL, 3:2) was added CuBr<sub>2</sub> (14.1 g, 63.29 mmol) and reaction mixture was heated to

80 °C for 16 h. After completion [monitored by TLC (10 % EtOAc /Hexane), *R<sub>f</sub>*-0.3 (KMnO<sub>4</sub> active)], reaction was filtered through sintered funnel and the filtrate was dried over sodium sulfate and concentrated under reduced pressure to obtain crude compound. The crude was purified by column chromatography using silica under gradient elution of 10 % EtOAc/Hexane to afford ethyl 3-bromo-2-oxohexanoate, **XXXV** as a brown liquid (7.5 g, 99 %).

**[00236] Step 2:** To a stirred solution of ethyl 3-bromo-2-oxohexanoate, **XXXV** (7.5 g, 31.78 mmol) in ethanol (150 mL) was added thiourea (6.04 g, 79.45 mmol). The reaction was heated to 90 °C for 16 h. After completion [Monitored by TLC 20 % EtOAc/Hexane, *R<sub>f</sub>*-0.1], reaction mixture was concentrated under reduced pressure. Resultant crude was diluted with ethyl acetate (100 mL), washed by saturated solution of NaHCO<sub>3</sub> (1x200 mL) and brine solution (1x 100 mL). The organic part was dried over sodium sulfate and concentrated under reduced pressure to obtain crude compound. The crude was triturated by 70 % n-pentane in diethyl ether solution three times to get pure ethyl 2-amino-5-propylthiazole-4-carboxylate, **XXXVI** as an off white solid (5 g, 73%).

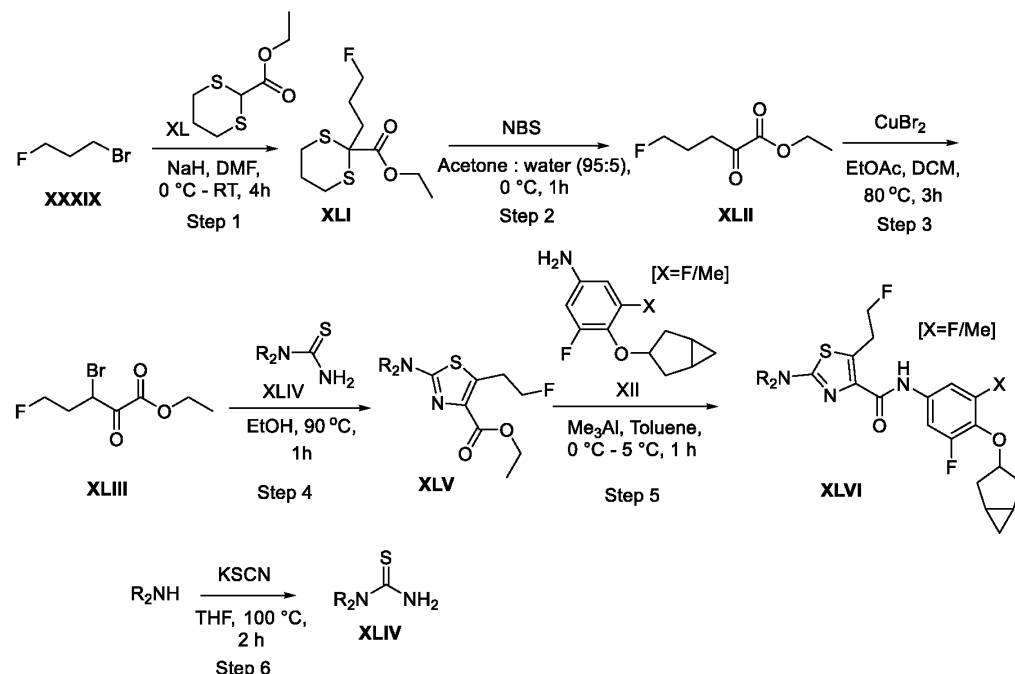
**[00237] Step 3:** To a stirred solution of CuCl<sub>2</sub> (3.19 g, 23.83 mmol) in acetonitrile (200 mL) was added *tert*-Butyl nitrite (4.53 mL, 37.85 mmol) heated to 50 °C for 30 min. Then into the solution, ethyl 2-amino-5-propylthiazole-4-carboxylate, **XXXVI** (5 g, 23.36 mmol) dissolved in acetonitrile (50 mL) was added and the reaction mixture was heated to 80 °C and stirred for 1h. After completion [monitored by TLC (30 % EtOAc/Hexane, *R<sub>f</sub>*- 0.8)], reaction mixture was concentrated under reduced pressure. The mixture was diluted in EtOAc (200 mL) and water (100 mL) and filtered through celite bed. The organic part was separated and washed by brine solution (1x200 mL), dried over sodium sulfate, and concentrated under reduced pressure. The resultant crude was purified by column chromatography using silica under gradient elution of 0-5% EtOAc/Hexane to afford ethyl 2-chloro-5-propylthiazole-4-carboxylate, **XXXVII** as a colorless liquid (4.4 g, 80%).

**[00238] Step 4:** To a stirred solution of ethyl 2-chloro-5-propylthiazole-4-carboxylate, **XXXVII** (500 mg, 2.15 ) and DIPEA (1.1 mL, 6.44 mmol) in dioxane (5 mL) in a sealed tube, was added amine, 3-methoxy-3-methylazetidine hydrochloride (383.69 mg, 2.57 mmol) and resultant reaction mixture was allowed to stir at 120 °C for 16 h. Then [Monitored by TLC] reaction mixture was concentrated under reduced pressure to remove dioxane. Resultant crude was purified through column chromatography using 30 % EtOAc in hexane as eluent to afford ethyl 2-(3-methoxy-3-methylazetidin-1-yl)-5-propylthiazole-4-carboxylate, **XXXVIII** (400 mg, 62%) as a colorless sticky.

**[00239] Step 5:** To a stirred solution of ethyl 2-(3-methoxy-3-methylazetidin-1-yl)-5-propylthiazole-4-carboxylate **XXXVIII** (200 mg, 0.67 mmol) and 4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluoroaniline **XII** (151 mg, 0.67 mmol) in dry THF (10 mL), was added MeMgCl (0.15 mL of 3M in THF solution) dropwise and was stirred for 1h at room temperature. The reaction was monitored by TLC. After completion reaction mixture was quenched with saturated ammonium chloride solution, extracted with EtOAc (100 mL), and washed with water (100 mL). Organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Resultant crude was purified by column chromatography using 10 % EtOAc in hexane as eluent to afford N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-

3,5-difluorophenyl)-2-(3-methoxy-3-methylazetidin-1-yl)-5-propylthiazole-4-carboxamide, **Example 22** (100 mg, 31%).

**Scheme 9: General procedure for the synthesis of examples of general structure XLVI (Examples 23-25).**



**[00240] Step 1:** To a solution of **XXXIX** (20 g, 143 mmol) and **XL** (18.23 g, 94.96 mmol) in DMF (150 mL) was added NaH (5.7 g) at  $0^\circ\text{C}$  and then it was allowed to warm up to room temperature gradually for a duration about 4h. After completion of reaction [Monitored by TLC (KMnO<sub>4</sub> stain)] cold water (1L) was added and extracted with ethyl acetate (2x500 mL). Combined organic layer was washed with brine solution, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuo to obtain the crude, which was purified on silica gel flash chromatography (2% EtOAc in hexane) to afford ethyl 2-(3-fluoropropyl)-1,3-dithiane-2-carboxylate, **XLI** (20 g, 83%) as colorless liquid.

**[00241] Step 2:** Solution of **XLI** (20 g, 79.36 mmol) in acetone 400 mL (5mL/mmol) was added dropwise over 5 minutes to a stirred suspension of N-bromosuccinimide (98.88 g, 555.55 mmol) in acetone/water 1.6 L (95/5, v/v, 3 mL/mmol) at  $0^\circ\text{C}$ . The reaction mixture was stirred at the same temperature for 1 hour, while the progress of the reaction was monitored by thin layer chromatography, and then aqueous sodium sulphite was added. the mixture was stirred until the color faded from the organic layer. Diluted with a mixture of methylene chloride/hexane (1/1, v/v, 1 L) and was washed with aq. 5% NaHCO<sub>3</sub> solution (500 mLx2), water (500 mL x 2), phases were separated and dried over magnesium sulfate. The solvent was removed under reduced pressure to obtain the crude, which was purified on silica gel flash chromatography (10% EtOAc in hexane) to afford ethyl 5-fluoro-2-oxopentanoate, **XLII** (9 g, 70%) as colorless liquid.

**[00242] Step 3:** To the solution of ethyl 5-fluoro-2-oxopentanoate, **XLII** (11g, 67.90 mmol) in ethyl acetate (330 mL) and DCM (220 mL) was added CuBr<sub>2</sub> (37.85 g, 169.75 mmol) and the resultant reaction mixture was allowed to stir at 80 °C for 3 h. After completion [Monitored by TLC (KMnO<sub>4</sub> stain)], the reaction mixture was filtered through celite and filtrate part was concentrated to afford the crude. Purification of the residue was carried out by silica gel column chromatography (5% EtOAc in hexane) to obtain desired product ethyl 3-bromo-5-fluoro-2-oxopentanoate, **XLIII** (12 g, 73%) as a colorless liquid.

**[00243] Step 4:** To the stirred solution **XLIII** (1 eq.) in ethanol (40 mL/g **XLIII**) was added thiourea derivative, **XLIV** (2 eq.) at room temperature and then it was heated to 90 °C for 1 h. After completion [Monitored by TLC, LC-MS], reaction mixture was concentrated to remove ethanol. The crude reaction mixture was then treated with saturated aqueous solution of NaHCO<sub>3</sub> (100 mL) and extracted with EtOAc (2x 100 mL). Organic layer was washed with water (2x 100 mL) and was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Purification of the residue was carried out by silica gel column chromatography (EtOAc in hexane) to afford products of general structure **XLV**.

**[00244] Step 5:** To a stirred solution of **XLV** (1.0 eq.) in dry toluene (30 mL/g **XLV**), **XII** (1.0 eq.) was added followed by drop wise addition of trimethylaluminum (2M in toluene, 4.0 eq.) at 0 °C and the resultant reaction mixture was allowed to stir at rt for 1 h. After completion [Monitored with TLC/LCMS] the reaction mixture was quenched with saturated ammonium chloride solution and partitioned with EtOAc. Organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resultant crude product was purified by flash column chromatography to afford products of general structure **XLVI**.

**Step 6:** To the stirred suspension of R<sub>2</sub>NH.HCl (1 eq.) in THF (10 mL/g) was added KSCN (1 eq.) (for pyrrolidine 4M HCl in dioxane solution 1 eq. was used) at room temperature and stirred for 30 min. Then it was heated to 100°C for 2 h and cooled to RT and then MeOH was added into the reaction mixture. The reaction mixture was filtered and was concentrated to obtain the desired product, **XLIV** (crude), which was used without purification.

#### Example 23

**[00245]** Example 23 was synthesized utilizing the procedures outlined in scheme 9 wherein 3-methoxy-3-methylazetidine-1-carbothioamide was used in step 4 and 4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluoroaniline was used as the amine in step 5, to provide N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-5-(2-fluoroethyl)-2-(3-methoxy-3-methylazetidin-1-yl)thiazole-4-carboxamide (25 mg, 10%).

#### Example 24

**[00246]** Example 24 was synthesized utilizing the procedures outlined in scheme 9 wherein 3-methoxy-3-methylazetidine-1-carbothioamide was used in step 4 and 4-(bicyclo[3.1.0]hexan-3-yloxy)-3-fluoro-5-methylaniline was used as the amine in step 5, to provide N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3-fluoro-5-methylphenyl)-5-(2-fluoroethyl)-2-(3-methoxy-3-methylazetidin-1-yl)thiazole-4-carboxamide (26 mg, 11%).

**Example 25**

**[00247]** Example 25 was synthesized utilizing the procedures outlined in scheme 9 wherein pyrrolidine-1-carbothioamide was used in step 4 and 4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluoroaniline was used as the amine in step 5, to provide N-(4-(bicyclo[3.1.0]hexan-3-yloxy)-3,5-difluorophenyl)-5-(2-fluoroethyl)-2-(pyrrolidin-1-yl)thiazole-4-carboxamide (40 mg, 13%).

**[00248]** Table 2 shows analytical data for the compounds disclosed herein.

**Table 2**

| Ex. | NMR                                                                                                                                                                                                                                                                                                                                                                                            | [M+H]  | Rt (min) | LCMS Method |
|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|----------|-------------|
| 1   | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 10.02 (s, 1H), 7.64 (d, 2H, J = 10.48 Hz), 4.72 (bs, 1H), 4.36 - 4.29 (m, 2H), 3.46 (bs, 4H), 2.09 - 1.90 (m, 8H), 1.33 (bs, 2H), 0.69 (bs, 1H), 0.48 (bs, 1H).                                                                                                                                                                           | 488.3  | 3.84     | Method B    |
| 2   | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.98 (s, 1H), 7.63 (d, 2H, J = 10.2 Hz), 4.72 - 4.65 (m, 1H), 4.56 (t, 2H, J = 5.76 Hz), 4.04 (d, 2H, J = 8.56 Hz), 3.90 (d, 2H, J = 8.56 Hz), 3.55 (t, 1H, J = 5.72 Hz), 3.49 (t, 1H, J = 5.76 Hz), 3.21 (s, 3H), 2.09 - 2.06 (m, 2H), 1.93 - 1.89 (m, 2H), 1.47 (s, 3H), 1.34 - 1.32 (m, 2H), 0.69 - 0.68 (m, 1H), 0.50 - 0.47 (m, 1H). | 518.3  | 3.85     | Method B    |
| 3   | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.83 (s, 1H), 7.72 - 7.68 (m, 1H), 7.46 - 7.44 (m, 1H), 7.07 (t, 1H, J = 9.2 Hz), 4.91 (t, 1H, J = 10.92 Hz), 4.38 - 4.30 (m, 2H), 3.47 - 3.44 (m, 4H), 2.19 - 2.15 (m, 2H), 2.01 - 1.98 (m, 4H), 1.9 - 1.86 (m, 2H), 1.34-1.31 (m, 2H), 0.56 - 0.53 (m, 1H), 0.49 - 0.44 (m, 1H).                                                        | 470.1  | 2.49     | Method G    |
| 4   | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.83 (s, 1H), 7.90 - 7.89 (m, 1H), 7.63 - 7.61 (m, 1H), 7.04 - 7.02 (m, 1H), 4.96 (t, 1H, J = 6.48 Hz), 4.39 - 4.3 (m, 2H), 3.47 - 3.44 (m, 4H), 2.21 - 2.18 (m, 2H), 2.01 - 1.98 (m, 4H), 1.89 - 1.85 (m, 2H), 1.35 - 1.33 (m, 2H), 0.67 - 0.65 (m, 1H), 0.47 - 0.46 (m, 1H).                                                            | 486.1  | 2.69     | Method G    |
| 5   | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.81 (s, 1H), 7.61 - 7.57 (m, 1H), 7.38 (s, 1H), 4.61 (t, 1H, J = 6.48 Hz), 4.38 - 4.3 (m, 2H), 3.47 - 3.44 (m, 4H), 2.2 (s, 3H), 2.09 - 2.06 (m, 2H), 2.01 - 1.93 (m, 6H), 1.34 - 1.31 (m, 2H), 0.72 - 0.69 (m, 1H), 0.54 - 0.53 (m, 1H).                                                                                                | 484.3  | 3.68     | Method E    |
| 6   | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 10.05 (s, 1H), 7.63 - 7.60 (m, 2H), 4.74 (t, 1H, J = 6.24 Hz), 4.37 - 4.29 (m, 2H), 3.94 (d, 2H, 7.84 Hz), 3.74 (d, 2H, J = 7.8 Hz), 3.3 (s, 3H), 3.28 (s, 2H), 2.09 - 2.07 (m, 2H), 1.94 - 1.90 (m, 2H), 1.34 - 1.3 (m, 5H), 0.69 - 0.68 (m, 1H), 0.50 - 0.47 (m, 1H).                                                                   | 532.5  | 2.6      | Method B    |
| 7   | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 10.07 (s, 1H), 7.63 - 7.60 (m, 2H), 4.97 - 4.95 (m, 1H), 4.73 - 4.71 (m, 1H), 4.35 - 4.29 (m, 2H), 3.88 (d, 2H, 8 Hz), 3.73 (d, 2H, Hz), 3.47 - 3.45 (m, 2H), 2.06 - 2.07 (m, 2H), 1.93 - 1.90 (m, 2H), 1.66 - 1.62 (m, 2H), 1.34 - 1.31 (m, 2H), 0.89 (t, 6H, J = 7.3 Hz), 0.69 - 0.68 (m, 1H), 0.48 - 0.47 (m, 1H).                     | 542.3  | 3.68     | Method G    |
| 8   | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.83 (s, 1H), 9.74 (s, 1H), 7.30 (d, 1H, J = 1.8 Hz), 7.07 - 7.04 (m, 1H), 4.76 (t, 1H, J = 6.2 Hz), 4.37 - 4.29 (m, 2H), 3.46 - 3.43 (m,                                                                                                                                                                                                 | 486.33 | 3.58     | Method B    |

| Ex. | NMR                                                                                                                                                                                                                                                                                                                                                                                                              | [M+H]  | Rt (min) | LCMS Method |
|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|----------|-------------|
|     | 4H), 2.01 - 1.88 (m, 8H), 1.29 - 1.26 (m, 2H), 0.85 - 0.82 (m, 1H), 0.45 - 0.4 (m, 1H).                                                                                                                                                                                                                                                                                                                          |        |          |             |
| 9   | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.88 (s, 1H), 7.51 - 7.48 (m, 1H), 7.46 (s, 1H), 4.37 - 4.29 (m, 2H), 4.00 (bs, 2H), 3.47 - 3.44 (m, 4H), 2.01 - 1.99 (m, 4H), 1.93 - 1.90 (m, 2H), 1.77 - 1.70 (m, 5H), 1.50 - 1.42 (m, 3H).                                                                                                                                                               | 501.2  | 2.96     | Method G    |
| 10  | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.92 (s, 1H), 7.51 - 7.44 (m, 2H), 4.39 - 4.31 (m, 2H), 4.07 (d, 2H, J = 8.72 Hz), 4.00 (bs, 2H), 3.94 (d, 2H, J = 8.76 Hz), 3.21 (s, 3H), 1.93 - 1.90 (m, 2H), 1.80 - 1.87 (m, 5H), 1.50 - 1.41 (m, 6H).                                                                                                                                                   | 531.2  | 4.08     | Method G    |
| 11  | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.91 (s, 1H), 7.50 - 7.46 (m, 2H), 4.97 (t, 1H, J = 5.28 Hz), 4.35 - 4.3 (m, 2H), 3.99 (bs, 2H), 3.88 (d, 2H, J = 8 Hz), 3.73 (d, 2H, J = 8 Hz), 3.47 - 3.45 (m, 2H), 1.93 - 1.90 (m, 2H), 1.77 - 1.62 (m, 7H), 1.50 - 1.41 (m, 3H), 0.89 (t, 3H, J = 7.36 Hz).                                                                                             | 545.1  | 3.85     | Method G    |
| 12  | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.73 (s, 1H), 7.46 (dd, 1H, J = 2.27 Hz & 18.04 Hz), 7.22 (s, 1H), 4.40 - 4.32 (m, 2H), 4.07 (d, 2H, J = 8.76 Hz), 3.93 (d, 2H, J = 8.73 Hz), 3.62 (bs, 2H), 3.21 (s, 3H), 2.31 (s, 3H), 1.94 - 1.93 (m, 2H), 1.83 - 1.80 (m, 2H), 1.73 - 1.68 (m, 3H), 1.55 - 1.47 (m, 6H).                                                                                | 527.4  | 3.8      | Method B    |
| 13  | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.65 (s, 1H), 9.30 (s, 1H), 7.18 (s, 1H), 6.99 - 6.95 (m, 1H), 4.37 - 4.31 (m, 2H), 4.06 (d, 2H, J = 8.72 Hz), 3.93 (d, 2H, J = 8.68 Hz), 3.88 (bs, 2H), 3.21 (s, 3H), 1.92 - 1.90 (m, 2H), 1.82 - 1.79 (m, 2H), 1.69 - 1.66 (m, 3H), 1.50 - 1.47 (m, 4H), 1.42 - 1.39 (m, 2H).                                                                             | 529.5  | 3.14     | Method B    |
| 14  | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.84 (s, 1H), 7.64 (d, 2H, J = 10.76 Hz), 4.72 (t, 1H, J = 6.12 Hz), 3.42 (bs, 4H), 3.13 - 3.07 (m, 2H), 2.08 - 2.06 (m, 2H), 1.98 - 1.90 (m, 6H), 1.33 - 1.32 (m, 2H), 1.20 (t, 3H, J = 7.28 Hz), 0.69 (bs, 1H), 0.48 (bs, 1H).                                                                                                                            | 434.3  | 3.53     | Method B    |
| 15  | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.89 (s, 1H), 7.63 - 7.60 (m, 2H), 4.71 (bs, 1H), 4.02 (d, 2H, J = 8.32 Hz), 3.89 (d, 2H, J = 8.32 Hz), 3.20 (s, 3H), 3.11 - 3.10 (m, 2H), 2.09 - 2.06 (m, 2H), 1.93 - 1.90 (m, 2H), 1.46 (s, 3H), 1.32 (bs, 2H), 1.20 (t, 3H, J = 7.12 Hz), 0.69 (bs, 1H), 0.47 (bs, 1H).                                                                                  | 464.3  | 3.85     | Method B    |
| 16  | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.67 (s, 1H), 7.74 (dd, 1H, J = 2.44, 13.64 Hz), 7.45 (d, 1H, J = 1.92 Hz), 7.16 (t, 1H, J = 9.28 Hz), 4.91 - 4.88 (m, 1H), 4.02 - 4.00 (d, 2H, 8.56 Hz), 3.89 (d, 2H, J = 8.64 Hz), 3.21 (s, 3H), 3.13 - 3.09 (m, 2H), 2.42 - 2.32 (m, 4H), 1.88 - 1.87 (m, 2H), 1.85 - 1.84 (m, 2H), 1.52 - 1.47 (m, 4H), 1.41 - 1.39 (m, 1H), 1.20 (t, 3H, J = 7.44 Hz). | 460.36 | 4.09     | Method E    |
| 17  | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.64 (s, 1H), 7.61 - 7.57 (m, 1H), 7.34 (s, 1H), 4.59 (t, 1H, J = 6.2 Hz), 4.02 (d, 2H, J = 8.48 Hz), 3.88 (d, 2H, J = 8.44 Hz), 3.20 (s, 3H), 3.14 - 3.08 (m, 2H), 2.19 (s, 3H), 2.09 - 2.06 (m, 2H), 1.96 - 1.92 (m, 2H), 1.46 (s, 3H), 1.32 (bs, 2H), 1.20 (t, 3H, J = 7.36 Hz), 0.71 - 0.70 (m, 1H), 0.52 - 0.51 (m, 1H).                               | 460.2  | 2.49     | Method G    |

| Ex. | NMR                                                                                                                                                                                                                                                                                                                                                                                                                | [M+H] | Rt (min) | LCMS Method |
|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|----------|-------------|
| 18  | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.65 (s, 1H), 7.62 - 7.58 (m, 1H), 7.36 (s, 1H), 4.59 - 4.55 (m, 1H), 4.02 (d, 2H, J = 8.56 Hz), 3.89 (d, 2H, J = 8.68 Hz), 3.21 (s, 3H), 3.14 - 3.09 (m, 2H), 2.34 - 2.28 (m, 4H), 2.24 (s, 3H), 2.09 - 2.07 (m, 1H), 1.96 - 1.89 (m, 3H), 1.53 - 1.47 (m, 4H), 1.36 - 1.32 (m, 1H), 1.20 (t, 3H, J = 7.44 Hz)..                                             | 474.4 | 2.92     | Method E    |
| 19  | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.83 (s, 1H), 7.64 - 7.61 (m, 2H), 4.72 (t, 1H, J = 6.32 Hz), 3.59 (t, 2H, J = 6.76 Hz), 3.37 (s, 2H), 3.13 - 3.08 (m, 2H), 2.08 - 2.05 (m, 2H), 1.95 - 1.9 (m, 4H), 1.34 - 1.31 (m, 2H), 1.23 - 1.16 (m, 3H), 0.71 - 0.62 (m, 5H), 0.50 - 0.47 (m, 1H).                                                                                                      | 460.2 | 3.2      | Method B    |
| 20  | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.89 (s, 1H), 7.81 - 7.76 (m, 2H), 4.70 - 4.67 (m, 1H), 4.02 (d, 2H, J = 8.48 Hz), 3.89 (d, 2H, J = 8.44 Hz), 3.20 (s, 3H), 3.14 - 3.08 (m, 2H), 2.34 - 2.28 (m, 4H), 2.07 - 1.92 (m, 7H), 1.60 - 1.56 (m, 1H), 1.47 (s, 3H), 1.33 - 1.29 (m, 1H), 1.20 (t, 3H, J = 7.36 Hz).                                                                                 | 494.1 | 4.42     | Method G    |
| 21  | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.89 (s, 1H), 7.68 - 7.61 (m, 2H), 4.73 (t, 1H, J = 6.28 Hz), 3.62 (d, 2H, J = 10.72 Hz), 3.32 (bs, 2H), 3.15 - 3.10 (m, 2H), 3.06 (bs, 2H), 2.10 - 2.06 (m, 2H), 1.94 - 1.90 (m, 2H), 1.75 - 1.67 (m, 2H), 1.34 - 1.32 (m, 2H), 1.23 - 1.16 (m, 3H), (s, 3H), 0.71 - 0.68 (m, 1H), 0.50 - 0.47 (m, 1H).                                                      | 459.9 | 3.88     | Method B    |
| 22  | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.86 (s, 1H), 7.62 - 7.56 (m, 2H), 4.7 (t, 1H, J = 9.08 Hz), 3.99 (d, 2H, J = 8.56 Hz), 3.86 (d, 2H, J = 8.64 Hz), 3.18 (s, 3H), 3.07 (t, 2H, J = 7.36 Hz), 2.07 - 2.04 (m, 2H), 1.91 - 1.87 (m, 2H), 1.58 - 1.52 (m, 2H), 1.44 (s, 3H), 1.31 - 1.28 (m, 2H), 0.9 (t, 3H, J = 7.36 Hz), 0.65 - 0.65 (m, 1H), 0.47 - 0.45 (m, 1H).                             | 478.4 | 2.42     | Method B    |
| 23  | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.98 (s, 1H), 7.63 - 7.61 (m, 2H), 4.72 - 4.65 (m, 2H), 4.56 - 4.54 (m, 1H), 4.04 (d, 2H, J = 8.72 Hz), 3.90 (d, 2H, J = 8.72 Hz), 3.55 (t, 1H, J = 5.72 Hz), 3.49 (t, 1H, J = 5.72 Hz), 3.21 (s, 3H), 2.10 - 2.07 (m, 2H), 1.94 - 1.90 (m, 2H), 1.48 (s, 3H), 1.34 - 1.31 (m, 2H), 0.70 - 0.67 (m, 1H), 0.50 - 0.45 (m, 1H).                                 | 482.3 | 3.7      | Method B    |
| 24  | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.71 (s, 1H), 7.61 - 7.57 (m, 1H), 7.36 (s, 1H), 4.67 (t, 1H, J = 5.88 Hz), 4.58 - 4.53 (m, 2H), 4.03 (d, 2H, J = 8.6 Hz), 3.90 (d, 2H, J = 8.6 Hz), 3.56 (t, 1H, J = 5.88 Hz), 3.50 (t, 1H, J = 5.88 Hz), 3.21 (s, 3H), 2.20 (s, 3H), 2.11 - 2.06 (m, 2H), 1.96 - 1.93 (m, 2H), 1.47 (s, 3H), 1.34 - 1.31 (m, 2H), 0.72 - 0.69 (m, 1H), 0.53 - 0.50 (m, 1H). | 478.4 | 3.69     | Method B    |
| 25  | <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 9.90 (s, 1H), 7.64 - 7.61 (m, 2H), 4.73 (t, 1H, J = 6.32), 4.68 (t, 1H, J = 5.88 Hz), 4.56 (t, 1H, J = 5.92 Hz), 3.55 (t, 1H, J = 5.92 Hz), 3.48 - 3.42 (m, 5H), 2.1 - 2.09 (m, 2H), 2.00 - 1.9 (m, 6H), 1.34 - 1.31 (m, 2H), 0.71 - 0.68 (m, 1H), 0.49 - 0.46 (m, 1H).                                                                                       | 451.7 | 2.57     | Method E    |

**LCMS methods****Method B**

**[00249]** The HPLC measurement was performed using Waters Acquity H Class UPLC comprising a quaternary pump with degasser, a sample manager, a column oven (set at 50 °C), a diode-array detector DAD and a column as specified in the respective methods below. Flow from the column was split to a MS spectrometer. The MS detector (Waters SQ Detector 2) was configured with an electrospray ionization source. Mass spectra were acquired by scanning from 160 to 1200 in 0.20 second. The capillary needle voltage was 3.50 kV in positive and negative ionization mode and the source temperature was maintained at 150 °C. Nitrogen was used as the desolvation gas, the flow was 750 L/Hour. Data acquisition was performed with Mass Lynx 4.2 Software. Reversed phase HPLC was carried out on a Waters Acquity BEH C8 column (1.7 µm, 50 x 2.1 mm) with a flow rate of 0.800 ml/min. Two mobile phases were used, mobile phase A: 0.05% HCOOH in water; mobile phase B: 0.05% HCOOH in ACN: Water (90:10)], and they were employed to run a gradient conditions from 5% B for 0.75 minutes, from 5% to 25% in 0.75 minutes, and from 25 % to 95 % in 1.50 minutes, 95 % B for 1.00 minutes and 5% B in 0.50 minutes and hold these conditions for 0.60 minutes in order to re-equilibrate the column (Total Run Time 5.10 minutes). An injection volume of 0.5 µl was used.

**Method E**

**[00250]** The HPLC measurement was performed using Shimadzu HPLC comprising a binary pump with degasser, a sample manager a dual channel UV detector and a column as specified in the respective methods below. Flow from the column was split to a MS spectrometer. The MS detector (Applied Biosystems API2000/2000 Trap) was configured with an electrospray ionization source. Mass spectra were acquired by scanning from 100 to 800 in 0.40 second. The ion spray voltage 5500 V in positive and 4500 V in negative ionization mode and the source temperature was maintained at 300 °C and Deculturing Potential 8-50 V depending on compound. Data acquisition was performed with Analyst 1.6.3 Software. Reversed phase HPLC was carried out on a Waters Xbridge C18/ Agilent Zorbax C18 column (5 µm, 50 x 4.6 mm) with a flow rate of 1.20 ml/min. Two mobile phases were used, mobile phase A: 10mm Ammonium Acetate in water; mobile phase B: ACN, and they were employed to run a gradient conditions from 10 % B to 30 % B in 1.50 minutes, and from 30 % to 90 % in 1.50 minutes, 90 % B for 1.00 minutes and 10 % B in 1.00 minutes and hold these conditions for 0.10 minutes. Pre run Equilibration Time 0.50 min (Total Run Time 5.10 minutes). An injection volume of 1 µl to 3 µl was used (Depending on the sample concentration).

**Method G**

**[00251]** The HPLC measurement was performed using Waters Acquity H Class UPLC comprising a quaternary pump with degasser, a sample manager, a column oven (set at 50 °C), a diode-array detector DAD and a column as specified in the respective methods below. Flow from the column was split to a MS spectrometer. The MS detector (Waters SQ Detector 2) was configured with an electrospray ionization source. Mass spectra were acquired by scanning from 160 to 1200 in 0.20 second. The capillary needle voltage was 3.50 kV in positive and negative ionization mode and the source

temperature was maintained at 150 °C. Nitrogen was used as the desolvation gas, the flow was 750 L/Hour. Data acquisition was performed with Mass Lynx 4.2 Software. Reversed phase HPLC was carried out on a Waters Xbridge C18 column (3.5 µm, 50 x 3 mm) with a flow rate of 1.20 ml/min. Two mobile phases were used, mobile phase A: 5 mM NH<sub>4</sub>OAc in water; mobile phase B: 5 mM NH<sub>4</sub>OAc in ACN: Water (90:10)], and they were employed to run a gradient conditions from 5 % B for 0.75 minutes, from 5 % to 15 % in 0.50 minutes, from 15 % to 70 % in 1.25 minutes and from 70% to 98 % in 1.25 minutes, 98 % B for 0.50 minutes and 5 % B in 0.25 minutes and hold these conditions for 0.60 minutes in order to re-equilibrate the column (Total Run Time 5.10 minutes). An injection volume of 0.5 µl was used.

#### Example A: Cellular TRPML1 Assay

##### Cell line

[00252] The final clone for the TRPML1 assay is HEK T-REx/GCaMP6f/TRPML1. GCaMP6f is a genetically encoded calcium indicator that is stably expressed in this cell line and used as a fluorescent read-out.

##### Assay protocol

[00253] Experiments were performed in 384 MTP format. Cells are seeded at 15000 cells/well in 20 µl/well of Optimum + 0.5% FBS without selection antibiotics. Twenty-four hours later, cells are assayed for the response to various compounds using the Ca<sup>2+</sup> sensitive GCaMP6f protein stably expressed in the cells as readout.

[00254] The experiment was performed in a 384-well format according to the following procedures:

- 24 h after seeding, the cells were pre-incubated at room temperature for about 10 min.
- Started the experiment at the FLIPR<sup>TETRA</sup> by injecting 10 µL/w of 3x concentrated test compounds and controls in Ca<sup>2+</sup> free Tyrode's buffer. Monitored the kinetic response over a period of 300 seconds.
- Final DMSO concentration: 0.5%

[00255] Data from FLIPR<sup>TETRA</sup> measurements were analyzed with the Genedata Screener<sup>®</sup> software.

##### Data analysis

|                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Compound</b>   | Calculate the Kinetic Response Value (KRV) as:                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>% Activity</b> | $\frac{(MAX_{CA} - \text{Baseline})}{\text{Baseline}} = \frac{[(\max(\text{sec}5 \dots 290) - \text{mean}(\text{sec}1 \dots \text{sec}2)) / \text{mean}(\text{sec}1 \dots \text{sec}2)]}{\text{mean}(\text{sec}1 \dots \text{sec}2)}$ <p>Normalize the KRV to the median (&lt;&gt;) of Neutral and Stimulator control wells:</p> $\text{Activity} [\%]_{Ago} = 100 * \left( \frac{x - < \text{NeutralControls} >}{< \text{Stimulator Controls} > - < \text{NeutralControls} >} \right)$ |

**Example B: TFEB Translocation Assay****Reporter and Cell line**

[00256] Reporter TFEB: the reporter is fused to a sequence of monomeric red fluorescent protein.

[00257] The reporter TFEB have been stably expressed in U2OS cell line and used as read-out.

**Assay protocol**

[00258] Experiments were performed in 384 MTP well format. Cells were seeded in 384-w at a density of 4000 cells/well in 20 µl/well complete growth medium without antibiotics. Twenty-four hours later, cells were treated with compounds and incubated for further 2 hours. Then the cells were imaged and assayed for the response to various compounds using the reporter for TFEB expressed in the cells as readout.

[00259] The experiments were performed in a 384-well format according to the following procedure:

- 24 h after seeding, cell culture medium was carefully removed and replaced with 20 µl of Opti-MEM (30' incubation at 37 °C before compound addition).
- Then, cells were incubated with compounds diluted in Opti-MEM + 0.015% Tween 80 at the desired concentration, with the reference molecule (agonist) Torin-1 at a top concentration of 1 µM (max signal), and with the other reference molecule (agonist) MLSA-5 at top concentration of 20 µM for 2 hours at 37°C and 5% CO<sub>2</sub>. The final percentage of DMSO was 0.5% in all the conditions.
- Staining of the nuclei was obtained by incubating the cells with 24 µM/well of Hoechst 3342 in standard Tyrode's buffer for 15 min at RT.
- Then the cells were fixed with PFA 4% for 30 min at RT.
- After three washes with standard Tyrode's buffer, samples were acquired by recording two fluorescence emission channels (DS-red and blue) at 20X magnification and with at least 3 fields of view per well in an Operetta CLS microscope (PerkinElmer).
- Image analysis was performed by using Harmony software (PerkinElmer). The image analysis involved the following steps: flat-field illumination correction, nuclei segmentation, cytoplasm segmentation and calculation of intensity fluorescence in the cytosol and nuclei compartments. Measurements of signal intensity ratio (nucleus to cytoplasm) was used to obtain information on the effects of compounds on the TFEB translocation.
- Data from image analysis measurements were finally loaded and analyzed for normalization and fitting procedures in Genedata Screener© software.

**Data analysis**

[00260] Feature: Mean translocation ratio (mean/well)

[00261] Data normalization: Stimulator - Neutral control

[00262] Normalization results are expressed as "activity %," meaning that our values are placed on an equivalent scale in order to make them comparable across plates. The GeneData Screener method used herein normalizes the median of the Stimulator control wells (Torin-1) to 100% and the median of the Neutral control wells (DMSO) to 0%.

$$Activity[\%] = 100 * (x - \text{Min}) / (\text{Max} - \text{Min})$$

[00263] The data from example A and example B is found in Table 3.

Table 3. Activity of TRPML1 agonists

| Ex. | TRPML1 FLIPR pEC <sub>50</sub> | TFEB Translocation pEC <sub>50</sub> |
|-----|--------------------------------|--------------------------------------|
| 1   | A                              | A                                    |
| 2   | A                              | A                                    |
| 3   | B                              |                                      |
| 4   | C                              |                                      |
| 5   | B                              |                                      |
| 6   | A                              |                                      |
| 7   | B                              | A                                    |
| 8   | C                              |                                      |
| 9   | A                              | A                                    |
| 10  | A                              |                                      |
| 11  | B                              |                                      |
| 12  | B                              | A                                    |
| 13  | B                              |                                      |
| 14  | B                              | A                                    |
| 15  | B                              | A                                    |
| 16  | B                              | A                                    |
| 17  | A                              |                                      |
| 18  | B                              |                                      |
| 19  | A                              |                                      |
| 20  | B                              | A                                    |
| 21  | B                              | A                                    |
| 22  | A                              |                                      |
| 23  | B                              | A                                    |
| 24  | B                              | A                                    |
| 25  | B                              |                                      |

A = between less than 9.0 and more than or equal to 7.0

B = between less than 7.0 and more than or equal to 6.0

C = between less than 6.0 and more than or equal to 5.0

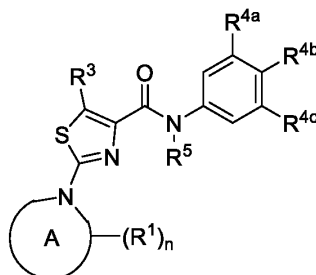
D = between less than 5.0 and more than or equal to 4.0

NT = not tested

## CLAIMS

## WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (I).

wherein:

Ring A is heterocycloalkyl;

each  $R^1$  is independently deuterium, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, -L-cycloalkyl, or -L-heterocycloalkyl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R;

or two  $R^1$  on the same atom are taken together to form an oxo;

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

$R^3$  is C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R;

$R^{4a}$  is hydrogen, deuterium, halogen, -CN, -NO<sub>2</sub>, -OH, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, cycloalkyl, or heterocycloalkyl;

$R^{4b}$  is -OR<sup>a</sup>, -O-cycloalkyl, -O-heterocycloalkyl, -NR<sup>c</sup>R<sup>d</sup>, -NR<sup>b</sup>-cycloalkyl, -NR<sup>b</sup>-heterocycloalkyl, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, cycloalkyl, or heterocycloalkyl; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R; and

$R^{4c}$  is deuterium, halogen, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, cycloalkyl, or heterocycloalkyl;

$R^5$  is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, cycloalkyl, or heterocycloalkyl;

each  $R^a$  is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each  $R^b$  is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, -L-cycloalkyl, -L-heterocycloalkyl,

-L-aryl, or -L-heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R<sup>c</sup> and R<sup>d</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl,

C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R<sup>c</sup> and R<sup>d</sup> are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R; and

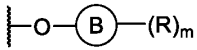
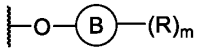
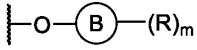
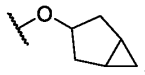
L is absent or C<sub>1</sub>-C<sub>3</sub>alkylene independently optionally substituted with one or more R;

each R is independently deuterium, halogen, -CN, -OH, -S(=O)C<sub>1</sub>-C<sub>3</sub>alkyl, -S(=O)<sub>2</sub>C<sub>1</sub>-C<sub>3</sub>alkyl, -

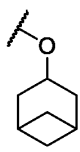
S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHC<sub>1</sub>-C<sub>3</sub>alkyl, -S(=O)<sub>2</sub>N(C<sub>1</sub>-C<sub>3</sub>alkyl)<sub>2</sub>, -NH<sub>2</sub>, -NHC<sub>1</sub>-C<sub>3</sub>alkyl, -N(C<sub>1</sub>-C<sub>3</sub>alkyl)<sub>2</sub>, -C(=O)C<sub>1</sub>-C<sub>3</sub>alkyl, -C(=O)OH, -C(=O)OC<sub>1</sub>-C<sub>3</sub>alkyl, -C(=O)NH<sub>2</sub>, -C(=O)NHC<sub>1</sub>-C<sub>3</sub>alkyl, -C(=O)N(C<sub>1</sub>-C<sub>3</sub>alkyl)<sub>2</sub>, C<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>1</sub>-C<sub>3</sub>alkoxy, C<sub>1</sub>-C<sub>3</sub>haloalkyl, C<sub>1</sub>-C<sub>3</sub>deuteroalkyl, C<sub>1</sub>-C<sub>3</sub>haloalkoxy, C<sub>1</sub>-C<sub>3</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>3</sub>aminoalkyl, C<sub>1</sub>-C<sub>3</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 3- to 6-membered heterocycloalkyl; wherein each cycloalkyl and heterocycloalkyl is independently optionally substituted with one or more halogen;

or two R on the same atom form an oxo.

2. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein R<sup>4a</sup> is hydrogen, deuterium, halogen, -CN, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl.
3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein R<sup>4a</sup> is hydrogen, halogen, -OH, or C<sub>1</sub>-C<sub>6</sub>alkyl.
4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein R<sup>4a</sup> is hydrogen or halogen.
5. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein R<sup>4a</sup> is hydrogen.
6. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein R<sup>4a</sup> is C<sub>1</sub>-C<sub>6</sub>alkyl.
7. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein R<sup>4a</sup> is halogen.
8. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein R<sup>4a</sup> is -OH.
9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein R<sup>4b</sup> is deuterium, halogen, -CN, -OH, -OR<sup>a</sup>, -O-cycloalkyl, -O-heterocycloalkyl, -NR<sup>c</sup>R<sup>d</sup>, -NR<sup>b</sup>-cycloalkyl, -NR<sup>b</sup>-heterocycloalkyl, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>deuteroalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, cycloalkyl, heterocycloalkyl is independently optionally substituted with one or more R.

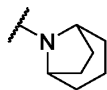
10. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein  $R^{4b}$  is  $-OR^a$ ,  $-O$ -cycloalkyl,  $-O$ -heterocycloalkyl,  $-NR^cR^d$ ,  $-NR^b$ -cycloalkyl, or heterocycloalkyl, wherein each cycloalkyl and heterocycloalkyl is independently optionally substituted with one or more R.
11. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein  $R^{4b}$  is  $-O$ -cycloalkyl or heterocycloalkyl, wherein each cycloalkyl and heterocycloalkyl is independently optionally substituted with one or more R.
12. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein  $R^{4b}$  is  $-O$ -cycloalkyl independently optionally substituted with one or more R.
13. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein  $R^{4b}$  is heterocycloalkyl independently optionally substituted with one or more R.
14. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein  $R^{4b}$  is ; wherein Ring B is cycloalkyl and m is 0-4.
15. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein  $R^{4b}$  is ; wherein Ring B is monocyclic cycloalkyl and m is 0-4.
16. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein  $R^{4b}$  is ; wherein Ring B is bicyclic cycloalkyl and m is 0-4.
17. The compound of any one of claims 14-16, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein m is 0-2.
18. The compound of any one of claims 14-16, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein m is 0 or 1.
19. The compound of any one of claims 14-16, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein m is 1 or 2.
20. The compound of any one of claims 14-16, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein m is 0.
21. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein  $R^{4b}$  is .

22. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, solvate, or



stereoisomer thereof, wherein R<sup>4b</sup> is

23. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, solvate, or



stereoisomer thereof, wherein R<sup>4b</sup> is

24. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein R<sup>4c</sup> is halogen, -OH, or C<sub>1</sub>-C<sub>6</sub>alkyl.
25. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein R<sup>4c</sup> is halogen.
26. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein R<sup>4c</sup> is -OH.
27. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein R<sup>4c</sup> is C<sub>1</sub>-C<sub>6</sub>alkyl.
28. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein Ring A is monocyclic heterocycloalkyl.
29. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein Ring A is an azetidiny, pyrrolidinyl, piperidinyl, morpholinyl, or piperazinyl.
30. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein Ring A is a pyrrolidinyl or piperidinyl.
31. The compound of any one of claims 1-30, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein Ring A is a pyrrolidinyl.
32. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein Ring A is an azetidiny.
33. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein Ring A is a bicyclic heterocycloalkyl.
34. The compound of any one of claims 1-33, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -CN, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, or C<sub>1</sub>-C<sub>6</sub>heteroalkyl.
35. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>heteroalkyl.
36. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -OR<sup>a</sup> or C<sub>1</sub>-C<sub>6</sub>alkyl.

37. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -OR<sup>a</sup> or C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl.
38. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -OR<sup>a</sup> or C<sub>1</sub>-C<sub>6</sub>heteroalkyl.
39. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein n is 0, 1, or 2.
40. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein n is 1 or 2.
41. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein n is 2.
42. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein n is 0.
43. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein R<sup>3</sup> is C<sub>1</sub>-C<sub>6</sub>alkyl or C<sub>1</sub>-C<sub>6</sub>haloalkyl.
44. The compound of any one of claims 1-43, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein R<sup>3</sup> is C<sub>1</sub>-C<sub>6</sub>haloalkyl.
45. The compound of any one of claims 1-43, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein R<sup>3</sup> is C<sub>1</sub>-C<sub>6</sub>alkyl.
46. The compound of any one of claims 1-43, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein R<sup>3</sup> is -CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>F, or -CH<sub>2</sub>CF<sub>3</sub>.
47. The compound of any one of claims 1-46, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein R<sup>5</sup> is hydrogen.
48. A compound, selected from a compound found in the specification and in Table 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.
49. A pharmaceutical composition comprising a compound of any one of claims 1-48, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable excipient.
50. A method of treating a TRPML1-mediated disorder or disease; the method comprising administering a therapeutically effective amount of a compound of any one of claims 1-48, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.
51. The method of claim 50, wherein the TRPML1-mediated disorder or disease is aging, bone diseases, cardiovascular diseases, congenital developmental disorders, eye diseases, hematological and solid malignancies, infectious diseases, inflammatory diseases, liver diseases, metabolic diseases, neurological or neurodegenerative diseases, pancreatitis, renal diseases, skeletal muscle disorders, obesity, lysosomal storage diseases, hypertrophic cardiomyopathy, dilated cardiomyopathy, inclusion body myositis, Paget's disease, or pulmonary diseases.
52. The method of claim 50, wherein the TRPML1-mediated disorder or disease is Aicardi-Goutières syndrome, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), ataxia-telangiectasia, autism

spectrum disorders, Batten disease, bipolar disorder, cerebral ataxia, Charcot-Marie-Tooth variant diseases, chronic wasting disease, corticobasal degeneration, corticobasal syndrome, bovine spongiform encephalopathy, Creutzfeldt-Jacob disease, Danon disease, Duchenne muscular dystrophy, exotic ungulate encephalopathy, Fabre disease, Fatal Familial insomnia, Friedreich ataxia, Feline spongiform encephalopathy, Fragile X, frontal temporal dementia, Gaucher disease, Gerstmann-Straussler-Scheinker disease, Giant axonal neuropathy, GM1 and GM2 gangliosidosis, Huntington's disease, Infantile Refsum disease, JUNQ and IPOD, Krabbe's disease, Kuru, Leukoencephalopathy, Lewy Body dementia, locomotor ataxia, Lyme disease, Machado Joseph disease, major depressive disorder, MPS-III, mucopolysaccharidosis, multiple sulfatase deficiency, multiple systems atrophy, myofibrillar myopathies, myotonic dystrophy, Niemann-Pick disease, neuronal ceroid lipofuscinosis, Parkinson's disease, Parkinsonism, Pick's disease, polyglutamine diseases, Pompe disease, pontocerebellar hypoplasia, prion diseases, progressive nuclear palsy, progressive Supranuclear palsy, pyruvate dehydrogenase deficiency, Sandhoff disease, schizophrenia, scrapie, Shy-Drager syndrome, spinal muscular atrophy, spinocerebellar ataxias, sporadic familial insomnia, subacute degeneration of the spinal cord, subacute sclerosing panencephalitis, Tay-Sachs disease, transneuronal degeneration, tuberous Sclerosis, Spinocerebellar Ataxia's, or vascular dementia.

53. The method of claim 50, wherein the TRPML1-mediated disorder or disease is age-related macular degeneration, non-alcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), non-alcoholic fatty liver disease (NAFLD), retinal cell degeneration in glaucoma, retinitis pigmentosa, acute kidney injury, atherosclerosis, Crohn's disease, diabetic nephropathy, female infertility, H. pylori infections, hypochlorhydria, pancreatitis, retinal detachment, type 2 diabetes mellitus, ulcerative colitis, or sarcopenia.